THE DEXTROAMPHETAMINE RESPONSE IN HUMAN SUBJECTS: A PSYCHOLOGICAL, PSYCHOPHYSIOLOGICAL AND NEUROENDOCRINE STUDY.

by

David Jacobs, M.B., BS. F.R.A.N.Z.C.P.

Department of Psychiatry.

University of Adelaide.

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PART I.

An investigation of the roles of the dopamine and noradrenaline pathways in dextroamphetamine induced arousal.

PART II.

The response of the neuroendocrine system to dextroamphetamine: effects of dopaminergic or noradrenergic blockade.

PART III.

Dextroamphetamine induced arousal as a pharmacological model for mild mania.

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SUMMARY

Noradrenaline and dopamine have been implicated in the pathogenesis of affective disorders. Our understanding of these disorders should therefore be enhanced by clarification of the roles of the noradrenaline and dopamine pathways within the central nervous system. An ideal agent for such research is dextroamphetamine sulphate as it acts by the release of noradrenaline and dopamine at specific sites in the CNS. Dextroamphetamine alters psychological and biological functioning in normal subjects in a manner that resembles affective illness. Its effects on neuroendocrine responses have been used in research on affective illness.

The aims of this study were to examine: (1) the psychological, psychophysiological and neuroendocrine responses to dextroamphetamine; and (2) the roles of central noradrenaline and dopamine pathways in these responses by using specific centrally acting blocking drugs. These have been achieved by examining the changes induced in normal human volunteers by a single oral 20 mg dose of dextroamphetamine and by observing the effects on these responses by pretreatment with either the selective alpha-1-noradrenergic receptor blocker thymoxamine or the selective dopamine receptor blocker pimozide.

Experiments were randomised, placebo controlled and double blind. Subjective changes were measured using visual

analogue rating scales. Psychophysiological measures included pulse rate, blood pressure and skin conductance. The neuroendocrine responses measured were: plasma cortisol and serum prolactin, growth hormone (GH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH). Plasma dextroamphetamine levels were assayed to confirm that changes observed were not the result of pharmacokinetic effects of the blocking drugs.

Dextroamphetamine increased subjective arousal and produced a concomitant rise in pulse rate, blood pressure and skin conductance. These responses were attenuated by dopamine blockade (pimozide) and enhanced by noradrenergic blockade (thymoxamine). These findings imply that dopamine pathways are involved in the promotion of arousal, with noradrenergic pathways exerting a modulatory role.

Dextroamphetamine was found to stimulate the release of cortisol, prolactin TSH, LH and FSH but not GH. The interaction of the blocking drugs on the neuroendocrine response to dextroamphetamine imply that dopamine pathways are stimulatory in the release of LH and FSH, are inhibitory in the release of prolactin and TSH, and have no effect on cortisol release. They may play a dual role in the regulation of GH release. Noradrenaline pathways may be stimulatory in LH release, inhibitory in the release of cortisol GH and TSH, and not involved in prolactin and FSH release. The complexity of control of secretion of these

hormones mean that the significance of dextroamphetamine induced changes in neuroendocrine functioning in patients with affective disorder must be interpreted with care.

The response to a single dose of 20mg of dextroamphetamine in normal volunteers would appear to be a useful model for mania since: (1) the range of subjective responses to dextroamphetamine which were observed, were similar to the symptoms which are commonly seen in mania; (2) both the physiological and neuroendocrine effects of dextroamphetamine were the same as those reported to occur in mania; (3) the response to the dopamine receptor blocking drug pimozide is similar in the two conditions.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text.

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GENERAL INTRODUCTION

The series of investigations to be described were undertaken with the aim of furthering our understanding of the pathogenesis of affective disorder. Noradrenaline (Schildkraut, 1965) and dopamine (Silverstone, 1978) have both been implicated in the biology of affective disorder but their precise roles remain unclear. The first objective was to investigate the relative contributions of the dopamine and noradrenaline pathways to the psychological, psychophysiological and neuroendocrine response to dextroamphetamine in human subjects. The second was to determine how similar the arousal response to oral dextroamphetamine in normal subjects is to mild mania in terms of clinical picture, psychobiological profile and pharmacology. In other words could amphetamine induced arousal in normals be used as a pharmacological model for mania?

The response to the amphetamine group of drugs has been well documented since their introduction earlier this century. They influence psychological state and behaviour in human subjects; they elevate mood, heighten arousal and increase activity in ways that resemble some forms of psychiatric disease, especially mania. Their effect on the neuroendocrine system has not been so closely studied. Nevertheless the neuroendocrine response to amphetamine has been studied in order to examine the activity of the catecholamine pathways in affective disorder.

i. The catecholamine pathways.

Pharmacological experimentation is a potentially valuable tool for investigating the function of the central nervous system in intact subjects and for examining the roles of the individual neurotransmitter pathways in various types of psychological and biological activity. Dextroamphetamine is particularly suited to examine the catecholamine pathways in this context as it acts as an indirect agonist in both the dopamine and noradrenaline pathways (Carlsson, 1970; Scheel-Kruger, 1972; Groves and Rebec, 1976).

As far as pharmacological experimentation is concerned, the administration of a pharmacological agonist or antagonist alone in the resting state, may provoke such small changes that they are difficult to measure. Further information about a neurotransmitter system can be gained by studying the interactions between the effects of the agonist and specific pharmacological antagonists. In the present series of studies, the effects on the responses to dextroamphetamine of specific blocking drugs have been examined. The underlying assumption is that if a response to dextroamphetamine is attenuated by a blocker, that response is probably initiated in the first place through activation of the particular pathway the blocker is thought to inhibit. Conversely, if the blocker enhances the amphetamine response, then the original response may be due to suppression of the neurotransmitter in the pathway the blocker is thought to block.

As far as psychopharmacological investigation of the catecholamine pathways are concerned, while there are a number of specific pharmacological agonists and antagonist of dopamine that are available, there are few noradrenergic agonist drugs. Amphetamine derivatives remain one of the few centrally acting agents known to stimulate, post synaptic noradrenergic receptors.

Although there is considerable evidence that the catecholamines dopamine and noradrenaline are involved in psychobiological function, uncertainty exists about their particular roles in humans. Recent evidence from animal experiments, has demonstrated that the dopamine pathways play an important role in motor function, motivation and arousal, sensory - motor integration and the control of neuroendocrine function (Iversen, 1980; Checkley, 1981; Ungerstedt et al, 1982; Iversen and Alpert, 1983). In humans, dopamine pathways are involved in mood and arousal in normal subjects (Jonsson, 1972; Silverstone et al, 1980) and in Parkinson´s disease Hornykiewicz, 1978; Ungerstedt et al, 1983), schizophrenia (Snyder et al, 1974) and mania (Silverstone and Cookson, 1982).

Earlier investigators proposed that noradrenaline pathways were responsible for the alerting influences of the reticular activating system and were directly involved in conditions of altered mood (Schildkraut and Kety, 1967; Fuxe et al, 1970; Snyder, 1975). Schildkraut (1965) proposed that a relative lack of catecholamines, particularly

noradrenaline, was correlated with depression and an excess with mania. Intensive studies of the noradrenergic pathways over the past decade in experimental animals has failed to confirm that the noradrenergic pathways play these roles. What this research has suggested is that the noradrenergic pathways are involved in the control of hypothalamic function and the neuroendocrine system, in learning, and in the animal's response to stimuli (Mason, 1980, 1981, 1983; Clark, 1979; Robbins, 1984). The role of the noradrenergic pathways in human psychobiological functioning remains less clear.

ii. A model for mania.

Research into the neurological aspects of psychological functioning and behaviour is limited by the innaccessibility and complexity of the brain. Most of our knowledge of the action of central catecholamine pathways comes from studies using experimental animals. These experiments are frequently invasive in nature. Extrapolation of behaviour from one species to another is difficult, and one cannot assume that the central neurotransmitter systems have the same function in different animal species. Animal studies are also limited because one cannot directly investigate the mental state. The development of a non-invasive technique for the study of catecholamine function in normal human beings where experimental conditions can be controlled, would provide a significant advance in research.

Pharmacological models have provided a useful avenue of

scientific investigation in psychiatry, in particular by providing a stimulus for the generation of new hypotheses which can, in turn, be tested in the disease state. If a human model of psychiatric illness fulfills the necessary criteria for validity, it would act as a valuable tool for further psychobiological research into mania.

PART I

AN INVESTIGATION OF THE ROLES OF THE DOPAMINE AND NORADRENALINE PATHWAYS IN DEXTROAMPHETAMINE AROUSAL IN HUMAN SUBJECTS

Introduction

INTRODUCTION

1.1. Introduction

Dextroamphetamine produces a consistent elevation of mood and arousal in humans. Its pharmacological action provides a method of comparing the roles of the different catecholamine pathways in mood and arousal since dextroamphetamine has been shown in experimental animals to release newly formed dopamine and noradrenaline presynaptically, thereby acting as an indirect dopaminergic and noradrenergic agonist. We know that the dopamine and noradrenaline pathways are involved in mood and arousal both in health and disease, but their precise roles remain uncertain. Indeed some earlier assumptions about the functions of these pathways have required re-evaluation in the light of recent advances.

Following a review of amphetamine arousal in humans, a detailed review of the structure and function of the central catecholamine pathways will be given. Previous efforts to elucidate the relative roles of the dopamine and noradrenaline pathways in psychological functioning in both experimental animals and human subjects are examined. The introduction to Part I will conclude by reviewing the clinical pharmacology of the two blocking drugs used.

1.2. Amphetamine Arousal in Humans

1.2.1. Historical review

Amphetamine was first manufactured and studied by Gordon Alles in the late 1920´s and early 1930´s as part of a search for an ephedrine-like drug for the treatment of asthma; the natural source of ephedrine (the plant ephedra vulgaris), having been exhausted. Alles found that phenyl-iso-propylamine (amphetamine) was an effective substitute (Alles and Prinzmetal, 1933; Leake, 1970). Experimenting on himself, Alles found that the isomer dextroamphetamine had significant mood elevating effects (Leake, 1970). Very early reports had suggested that the drug was without significant subjective effects (Miller and Piness, 1928, see also the comprehensive review by Silverstone and Wells, 1980).

Psychological and behavioural effects of amphetamine were increasingly reported shortly after its clinical introduction. Prinzmetal and Bloomberg (1935) reported that it was effective in the treatment of narcolepsy and that overdosage caused insomnia. The drug´s anorectic action was observed in passing by Prinzmetal and Bloomberg (1935) and by Peoples and Guttman (1936). The latter reported that amphetamine had significant effects on the pulse rate and blood pressure of subjects as well as their mood and talkativeness. In open trials, Nathanson (1937) and Davidoff and Reifenstein (1937) found that amphetamine

caused an elevation in mood and reduced fatigue. Both normal subjects and a variety of patients suffering different psychiatric disorders participated in these early studies.

The general consensus view which emerged was that amphetamine had a significant central nervous system stimulatory effect with relatively little peripheral stimulation. An oral dose of 10 to 20 mg led to euphoria, exhilaration and, in some subjects, irritability, lessening of fatigue, increased energy and capacity for work and increased talkativeness. The drug reduced the symptoms of narcolepsy and caused insomnia and anorexia. Davidoff and Reifenstein (1937) reported irritability and restlessness as a common accompaniment. However, dullness, forgetfulness, drowsiness, depression, delirium or hallucinations were reported by some subjects.

The ability of amphetamine drugs to reduce fatigue and sleep lead to their widespread use in World War Two by British, German and Japanese servicemen (Leake 1970). This ability too, together with their efficacy in improving endurance capability and hence athletic performance, led to their use by some athletes and their subsequent banning (Silverstone and Wells, 1980).

Interest in the amphetamine drugs continued into the post war period. Levine et al, (1948), in an open study on patients with a variety of psychiatric illnesses, reported similar findings to the earlier studies. They found that

intravenous methyl amphetamine produced wakefulness, elimination of fatigue, increased talkativeness and restlessness. Hypomanic patients and tense patients, however, became more relaxed and one became drowsy, whereas psychotic symptoms tended to worsen. Similar findings were reported by Lassagna and his colleagues (Lassagna et al, 1955) in studies using a subcutaneous injection of amphetamine sulphate.

Later controlled studies, which used a variety of measuring instruments, confirmed these earlier open studies which relied largely on anecdotal reports. An oral dose of either 10 or 20 mg of dextroamphetamine sulphate caused a rise in mood and arousal as measured by the profile of mood states and linear mood scale (Smith and Davis, 1977), a modified adjective checklist (Brown et al, 1978) and visual analogue scales (Silverstone et al, 1983). In addition to the elevation of subjective mood and arousal, amphetamine drugs give rise to anorexia and reduced food intake (Silverstone and Kyriakedes, 1982; Silverstone et al, 1983). As far as psychophysiological measures are concerned, amphetamine causes a rise in pulse rate, blood pressure and skin conductance (Martin et al, 1971; Zahn et al, 1975; 1981; Morselli et al, 1978; Goldstein et al, 1983; Nurnberger et al, 1984) and administration leads to a rise in the secretion of cortisol and changes in the secretion of the different anterior pituitary hormones (See Part II).

However the response to amphetamine is variable. As early

as 1937 Davidoff and Reifenstein (1937) commented on the variability of the psychophysiological responses. In some subjects drowsiness and a reduction in alertness is noted (Tecce and Cole, 1974). Checkley (1978) commented on the variability of the subjective response to amphetamine. This variability can be demonstrated in a number of measures and appears to be influenced by the time that has elapsed since the drug was administered - which presumably reflects differences in blood levels (Tecce and Cole, 1974). Other factors which influence response to amphetamine are age (Rapoport et al, 1980), and psychoticism and neuroticism scores on the Eysenck Personality Inventory (Claridge and Birchall, 1973).

1.2.2. Clinical uses

Amphetamine derivatives have been used in a diversity of clinical situations since their introduction over fifty years ago (Silverstone and Wells, 1980). Their effect on sleep led to their being used in the treatment of narcolepsy for which purpose they are still prescribed. Their anorectic action lead to their widespread use in the treatment of obesity. Levine et al, (1948) reported that subjects, and in particular psychiatric patients, became more talkative. This observation led to its use in psychiatry as an abreactant, often in conjunction with a barbiturate (Slater and Roth, 1969). Amphetamine derivatives, as well as another stimulant methylphenidate, were found to be effective in the treatment of hyperkinetic syndrome (Arnold et al, 1972) for which they have been extensively prescribed in the USA. The treatment seems to be without long term benefit however and subject to a variety of different risks (Barcley, 1977).

In spite of their mood elevating effect, amphetamine drugs have not proved particularly useful as antidepressant agents. Checkley (1978) demonstrated that the mood elevating and antidepressant effects of methyl amphetamine were different in that the latter effect was a more delayed one. Fawcett and Siomopoulos (1971) proposed that a positive response to dextroamphetamine generally predicted that a depressed patient would respond to imipramine, a finding which has been confirmed more recently (Van Kammen

and Murphy, 1978). There is also some evidence that dextroamphetamine may have a role as an antidepressant in patients who fail to respond to conventional antidepressant regimes (Ward and Lampe, 1982). The value of amphetamine compounds as therapeutic agents though has been overshadowed by their use as recreational drugs.

1.2.3. Amphetamine abuse

In the post war period, abuse of amphetamine drugs was widespread. In 1958 Connell reported that heavy amphetamine usage was associated with a paranoid psychosis which was very similar to paranoid schizophrenia (Connell, 1958). The psychosis could be reproduced experimentally (Bell, 1973) and similarities were noticed with behaviour observed in animals receiving high doses of amphetamine (Ellinwood, 1967; Ellinwood et al, 1973; Ellison and Eison, 1983). The psychosis is accompanied by marked stereotypy, insomnia, alertness, hypersexuality, fear, suspiciousness, increased vigilance, and hallucinations (particularly visual and tactile). There is, however, a relative absence of formal thought disorder (Bell, 1973). In other words, there are significant differences between the phenomena of amphetamine psychosis and paranoid schizophrenia. This has not deterred researchers using amphetamine induced psychosis as a model for schizophrenia (Snyder, 1973). The "model psychosis" has played an important role in the formulation of the dopamine hypothesis of schizophrenia (Snyder, 1972; Snyder et al, 1974).

1.2.4. Experimental use

Because of the serious psychological and social sequelae of their abuse, amphetamines have been withdrawn from clinical use. Under strictly controlled conditions however, they still have a valuable and established role in psychopharmacological research. As they give a reasonably reproduceable response, psychologically and biologically, they have been used in a diversity of approaches to study psychiatric illnesses. Thus the drugs have been used as a model for psychiatric illness (Snyder, 1973; Robbins and Sahakian, 1980; Jacobs, 1983) (see Part III), in an attempt to establish a pharmacological marker for the treatment of depression (Fawcett and Siomopoulos, 1971) and to investigate the neuroendocrine system in Affective Illness (see Part II). As amphetamine drugs in moderate doses act by the release of both noradrenaline and dopamine from the presynaptic neurone (see 1.2.5.), they have been used to study the relative roles of the dopamine and noradrenaline pathways in different behaviours in experimental animals and in psychological and neuroendocrine functioning in humans. This will be discussed in detail in the relevant sections that follow.

1.2.5. The pharmacology of amphetamine

Amphetamine derivatives are readily absorbed from the gastrointestinal tract and are little affected by first pass hepatic metabolism (Innes and Nickerson, 1975). They rapidly enter the brain and are found in high concentrations there. Peak plasma levels occur two to three hours after oral administration.

A substantial part of elimination is via excretion unchanged in the urine. As amphetamine has a pKa value of 9.93, elimination is greatly facilitated by acid urine. Some is metabolized in the liver by p-hydroxylation or n-demethylation, deamination and conjugation. The plasma half life (urine pH 6 - 7.5) is approximately ten hours (Shepherd et al, 1968; Innes and Nickerson, 1975; Checkley, 1982[a]).

Dextroamphetamine exerts its effect by the release of newly formed dopamine and noradrenaline from the presynaptic neurone (Carlsson, 1970; Scheel-Kruger, 1972; Chiueh and Moore, 1975; Groves and Rebec, 1976; Moore, 1977), a conclusion reached by the following observations. The release is associated with an increase in the concentration of the metabolites of dopamine and noradrenaline formed extracellularly (3-methoxytyramine and normetanephrine); at the same time, there is a drop of intracellular dopamine and noradrenaline levels (Carlsson, 1970).

Amphetamine causes a release of dopamine and noradrenaline

in reserpine sensitized animals, suggesting that the site of release is primarily extragranular (Hansson, 1967; Carlsson, 1970; Moore, 1977). Furthermore, release is blocked by prior administration of alpha methylparatyrosine, providing further evidence that dopamine and noradrenaline are released from a newly formed, readily releasable, catecholamine pool (Carlsson, 1970; Scheel-Kruger, 1972). At higher doses, amphetamine can exert an inhibitory action on the re-uptake pump but this mechanism is generally considered to be of secondary importance (Carlsson, 1970; Scheel-Kruger, 1972; Feigenbaum et al, 1982). At higher doses still, re-uptake of serotonin may also be inhibited (Groves and Rebec, 1976). The amphetamines appear to have no direct stimulatory action on receptors, nor do they have any inhibitory effect on monoamine oxidase, as was earlier proposed (Carlsson, 1970).

The neuronal response to dextroamphetamine is reported to be biphasic (Rebec and Segal, 1978), with very low doses reducing the activity of noradrenaline and dopamine neurones presumably by preferential action presynaptically (Engberg and Svensson, 1979; Huang and Maas, 1981). At higher doses it acts postsynaptically. At doses used in the experiment to be described, it is unlikely that presynaptic receptor influences are important.

1.3. Central Catecholamine Pathways

1.3.1. Introduction

In recent years extensive investigations using experimental animals, have implicated a wide range of functions for the dopaminergic and noradrenergic neurotransmitter systems. This review will focus on research studies that investigate the role of the catecholamine neurotransmitter systems in changes in mood and arousal from the psychological and psychophysiological perspective. Their role in neuroendocrine functioning will be considered in Part II and in psychiatric disease with particular reference to mania in Part III. This review will give greater weight to studies in humans since it cannot be assumed that the neurophysiology of these pathways and their role in psychobiological functioning is directly comparable between experimental animals and humans.

1.3.2. History

Sir Henry Dale (1938) reported that the first steps towards an understanding of the function of noradrenaline occurred in 1894. Dr George Oliver had invented an instrument to measure the diameter of arteries through the unbroken skin. While experimenting on his son, he observed that subcutaneous injections of extracts of calf´s suprarenal gland caused narrowing of the radial artery. Dr Oliver was initially unsuccessful in impressing the physiologist Professor Edward Schafer with his finding until he was able to persuade the professor to inject some of the extract into an anaesthetised dog from which he had been recording the arterial blood pressure. To Professor Schafer´s surprise the extract caused a profound rise in blood pressure. Elliott (1904) verified an observation that the response to the extract from the calf´s suprarenal gland resembled the effect of stimulating the sympathetic nervous system. He identified adrenaline as the active ingredient and proposed that sympathetic nerves act by release of adrenaline (or its immediate precursor).

Following the classical work of the Nobel prize winner Loewi (1922) which demonstrated the chemical transmitter action of acetylcholine, several workers turned their attention to the sympathetic nervous system. Cannon and Rosenblueth (1933) found evidence that a sympathetic transmitter existed, that it was probably not adrenaline, and that it existed in two forms which they called Sympathin

E and I, respectively. They felt that the transmitter may be ambifunctional but combined with different "receptive substances" in the effector cell. (Eventually it became established that there were not two forms of transmitter substance but two different types of receptors, the alpha and beta adrenoceptor [Ahlquist, 1948]).

Doubts began to grow that the transmitter substance released with sympathetic nerve stimulation was adrenaline. Dale himself expressed this doubt as early as 1910 (Barger and Dale, 1910) in view of the differential effects of various amines. Nevertheless he proposed that those nerve fibres or impulses transmitting their effect by adrenaline (or something very like it) be called "adrenergic". According to Dale, his use of the term did not include the transmitting substance or the effector cell. Von Euler (1947) also questioned the evidence that adrenaline was the substance released on sympathetic nerve stimulation. In research for which he was awarded the Nobel prize Von Euler found that the action of adrenergic nerve fibre extract more closely resembled the action of noradrenaline (Sympathin E). He believed that Sympathin I may be adrenaline. Noradrenaline and adrenaline were identified in the brain and assumed by Von Euler to occur in the cerebral vascular motor nerves.

Vogt (1954) mapped the concentration of both noradrenaline and adrenaline in the various sections of the brain. She showed that noradrenaline had a specific pattern of

distribution in the brain strongly suggesting that it played a specialised role in brain function. The areas of highest concentration included the hypothalamus and other sites where the sympathetic nervous system was believed to be represented centrally.

As it was known that dopamine is the precursor of noradrenaline, it had been anticipated that dopamine would also be found in the central nervous system. It was surprising then when dopamine was discovered at relatively high concentrations at sites other than those of high noradrenaline concentration, eg, the caudate nucleus, putamen and substantia nigra (Carlsson et al, 1958).

1.3.3. Neuroanatomy

In the 1960's experimental techniques such as the histochemical fluorescence technique (Falck et al, 1962), were developed to give detailed mapping of the catecholamine neurones within the central nervous system and their associated pathways in animals, particularly the rat (Dahlstrom and Fuxe, 1965). The precision of mapping has been improved subsequently by supplementary techniques such as producing lesions steriotaxically or by injection of 6 hydroxydopamine (Fuxe et al, 1970; Ungerstedt, 1971) and more recently by the development of microfluorescent techniques and autoradiographic tracings (for reviews see Moore and Bloom, 1979; Clark, 1979; Robbins and Everitt, 1982). By these means, two major ascending noradrenergic pathways have been identified, the locus coeruleus noradrenergic system, the major component of which is the dorsal noradrenergic pathway (DNP), and the ventral tegmental pathway (VTP). Four major dopamine pathways have also been described.

a. The noradrenaline pathways

Three ascending pathways originate from the locus coeruleus. The largest, the DNP, ascends through the mesencephalon, ventral and lateral to the periaquaductal grey. A second smaller pathway ascends within the central grey as part of the dorsal longitudinal fasciculus, and a third ascends through the ventral tegmental tract to join the median forebrain bundle. The DNP turns ventrally at the

level of the fasciculus retroflexus to join the dorsal portion of the median forebrain bundle at the level of the hypothalamus. Fibres leave the tract to innervate the thalamus and epithalamus. The DNP ascends as part of the median forebrain bundle with fibres leaving to join, on the one hand, the ansa peduncularis - ventral amygdaloid system to innervate the amygdala and ventral hippocampus, and, on the other hand, the mammilothalamic tract to innervate the anterior thalamus. At the level of the caudal septum the DNP fibres in the median forebrain bundle break up into five main groups. These fibres enter the fornix, the stria medullaris, stria terminalis and cingulum or continue as the median forebrain bundle. These pathways innervate the hippocampal formation, habenula, amygdaloid complex, neocortex and olefactory tubercle. Innervation is largely ipsilateral (Ungerstedt, 1971; Jacobowitz, 1978; Moore and Bloom, 1979; Clark, 1979; Robbins and Everitt, 1982). See figure 1.1.

Pathways also project laterally from the locus coeruleus to innervate the molecular layer of the cerebellar cortex and descending fibres innervate the sensory nuclei of the lower brain stem (Moore and Bloom, 1979; Robbins and Everitt, 1982).

The second ascending noradrenergic pathway is the ventral tegmental pathway (VTP). It arises from cells scattered throughout the medulla and pons, in particular, the lateral reticular nucleus, the ventrolateral medullary area and

subcoerular group, the axons forming a plexus rather than a discrete bundle or tract. They enter the VTP through, and ventral to, the decussation of the superior cerebellar peduncle, then disperse amongst the catecholamine radiation to join the median forebrain bundle in the mesencephalon before ascending to the diencephalon. Ascending fibres of the VTP mix with its descending fibres and with the ascending fibres of the locus coeruleus noradrenergic system. Fibres have a wide distribution within the mesencephalon and diencephalon, but in contrast to the locus coeruleus system, projections of the VTP are restricted to subcortical areas. The pathways innervate, largely ipsilaterally, the whole of the hypothalamus, the lateral septal nucleus and ventral amygdaloid nucleus as well as some brain stem nuclei, including the substantia nigra and ventral tegmental area and the midbrain raphe nuclei (Ungerstedt, 1971; Moore and Bloom, 1979; Robbins and Everitt, 1982). See figure 1.1.

b. The dopamine pathways

Dopamine neurons in the CNS are involved in a number of different systems; the nigrostriatal, mesolimbic and mesocortical, tuberoinfundibular, retinal and medullary. The dopamine neurones in the mesencephalon give rise to the nigrostriatal, mesolimbic and mesocortical tracts and probably form a continuous crescentic cluster of cells rather than being separated as previously thought (Iversen and Fray, 1982; Iversen and Alpert, 1983). Axons arising

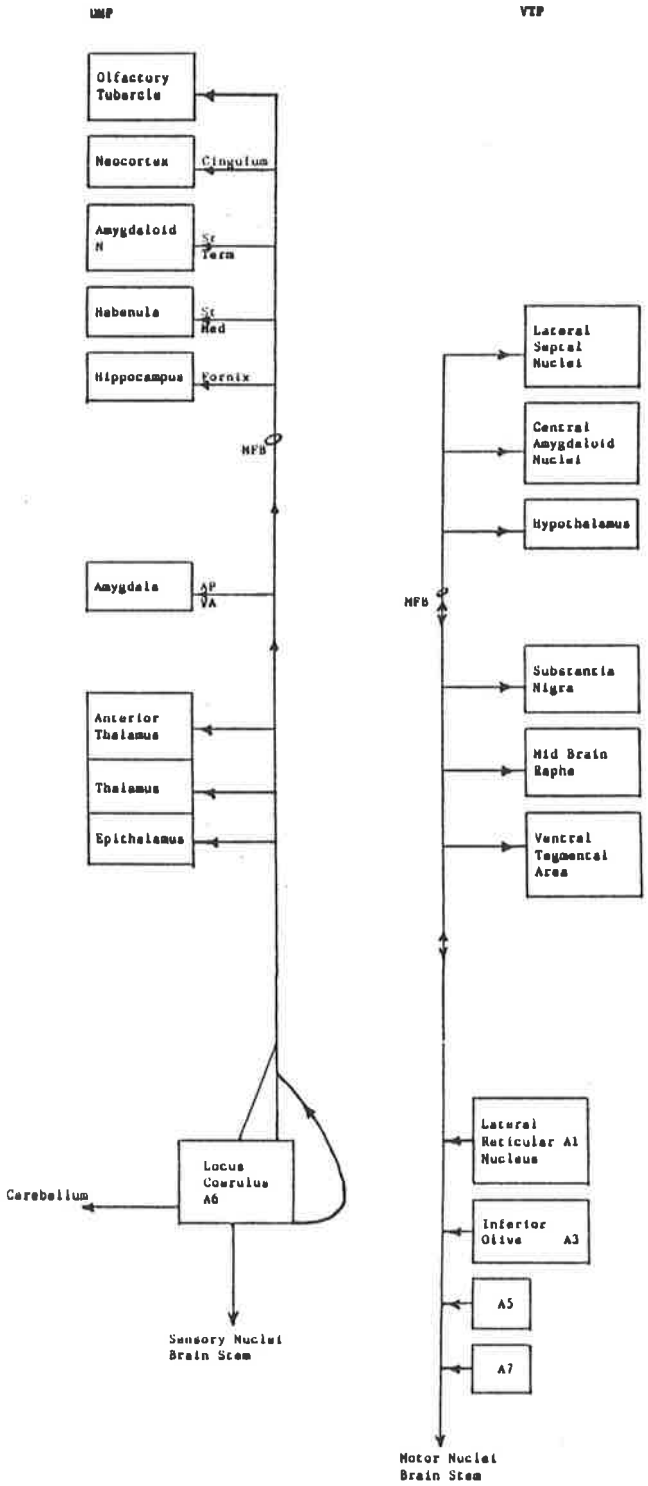

Figure 1.1 Schematic representation of the central noradrenergic pathways.

DNP	Dorsal noradrenergic pathway.
VTP	Ventral tegmental pathway.
MFB	Median forebrain bundle.
St Term	Stria terminalis.
St Med	Stria medullaris.
APUA	Ansa peduncularis ventral amygdaloid tract.

from the substantia nigra and ventral tegmental area, run via the median forebrain bundle in the lateral hypothalamus and innervate the caudate putamen, nucleus accumbens, septal and amygdaloid nuclei, and the medial frontal cortex (Fuxe et al, 1970; Ungerstedt, 1971; Robbins and Everett, 1982; Iversen and Fray, 1982; Iversen and Alpert, 1983).

The three pathways are now known to be highly functionally integrated. The most lateral dopamine neurones in the zona compacta of the substantia nigra project to the striatum and the most medial, in the ventral tegmentum, to the frontal cortex and limbic structures. However lateral A10 neurones project to the medial striatum while medial A9 neurones project to limbic areas. Furthermore there are feedback circuits. The nucleus accumbens neurones receiving dopamine inputs, have efferents to the zona reticularis in the substantia nigra. Efferent fibres from the medial cortex project to the same region of the nucleus accumbens that receive inputs from fibres from the A10 region. The caudate nucleus also receives efferents from the motor cortex and the limbic component of the dopamine system as well as efferents from the hippocampus (Iversen and Alpert, 1983). (see figure 1.2).

The tuberoinfundibular pathway consists of a short band of fibres that connect the arcuate and periventricular nuclei of the hypothalamus to the median eminence (Fuxe et al, 1970; Robbins and Everitt, 1982).

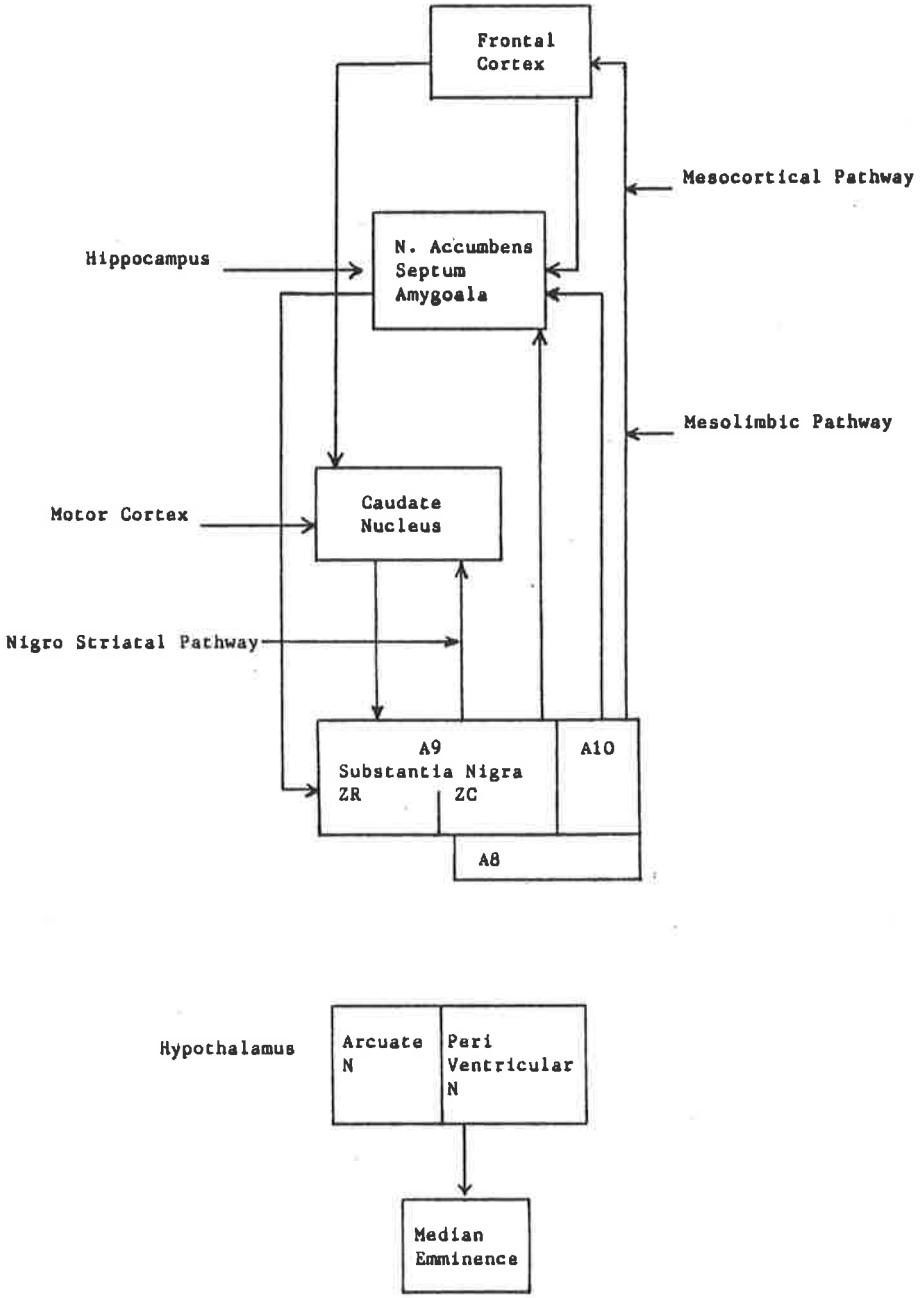

Figure 1.2 Schematic representation of the central dopamine pathways.

ZR Zona reticularis.
ZC Zona compacta.

1.3.4. Neurophysiology of the catecholamines

a. Neurotransmitters

Both dopamine and noradrenaline fulfill the criteria for a neurotransmitter in the central nervous system (Iversen, 1979; Siggins, 1979; Van Dongen, 1981). In addition to acting as synaptic neurotransmitters, both dopamine and noradrenaline may act as non-synaptic neurotransmitters and neurohormones. In the tuberoinfundibular-median eminence system for example, dopamine is released into the portal pituitary blood and acts as pituitary inhibitory factor (Muller et al, 1977[a]). Van Dongen (1981) concluded that noradrenaline acts as a synaptic and non-synaptic neurotransmitter and that noradrenaline released from the locus coeruleus into the ventricle might act as a CSF hormone.

b. Receptors

The final component of the synaptic neurotransmitter mechanism is the receptor. Recent work has expanded our knowledge in this aspect of the synapse to the extent that we are now obliged to reconsider earlier hypotheses regarding the mode of action of psychotrophic drugs. This in turn has meant a re-evaluation of hypotheses relating to the functioning of the neurotransmitter pathways based on the effects of these drugs and, as a consequence, theories of the nature of psychiatric illnesses based on pharmacological evidence.

i. Alpha and beta adrenoceptors

Ahlquist (1948) compared the effect of different sympathomimetic amines on a variety of physiological functions and concluded that there were two different adrenergic receptors, one essentially excitatory and the other inhibitory (with the important exception of myocardial excitation). As there seemed to be only one adrenergic mediating substance he concluded that two different receptors were involved (the alpha and beta adrenoceptor) rather than the two forms of sympathin (E or I) proposed earlier. The subsequent search for and discovery of effective beta adrenergic blocking drugs has been a milestone in the treatment of hypertension.

ii. Pre- and postsynaptic receptors.

Until the beginning of the last decade it was generally assumed that adrenoceptors were located only on the membrane of the postsynaptic structures. Since then, evidence has accumulated that adrenoceptors are also located on the outer surface of adrenoceptor vacuosities. These have become known as presynaptic receptors. They modulate stimulus evoked transmitter release. Presynaptic receptors are present for both the alpha and beta noradrenergic systems (Strombom, 1975; Langer, 1978; 1981; Dubocovich, 1984) and the dopamine pathways (Roth, 1984; Rebec, 1984).

Noradrenaline receptors

The different noradrenergic receptors are now classified pharmacologically, based on differential effects by selective agonists and antagonists, and by receptor binding studies as alpha 1 and alpha 2 or beta 1 and beta 2 receptors.

Alpha 1 noradrenergic receptors (or adrenoceptors) are postsynaptic in nature and, peripherally at least, mediate an excitatory response in the synapse. The alpha 2 adrenoceptors are generally presynaptic (but may also be post synaptically located). The presynaptic alpha 2 adrenoceptors are inhibitory, producing their effect by reducing the amount of noradrenergic stimulation in the synapse. The postsynaptic alpha 2 receptors may be excitatory, for example, in their involvement in the control of cardiovascular function (Dubocovich, 1984).

Beta receptors are similarly subdivided into postsynaptic (or beta 1) adrenoceptors and presynaptic (beta 2) adrenoceptors. Beta 2 receptors can be postsynaptically situated and provide positive feedback.

Three of the four subtypes of adrenergic receptors are linked (peripherally at least) to the same biochemical effector, the adenylate cyclase system, which in turn influences the cellular levels of adenosine 3 5 monophosphate (cyclic AMP). Beta 1 and beta 2 receptors stimulate adenylate cyclase whereas the alpha 2 receptor

inhibits it. Alpha 1 receptors increase intracellular calcium levels. The drugs which are active at noradrenergic receptors and which can be classified as affecting alpha 1 or alpha 2, beta 1 or beta 2 receptors either as adrenergic agonists or antagonists are listed in table 1.1. (Langer, 1978; 1981; Motulsky and Insel, 1982; Lefkowitz et al, 1984; Sulser, 1984).

Table 1.1.

Receptor	alpha 1	alpha 2	beta 1	beta 2
Location	post-synaptic	pre-post-non-synaptic	post-synaptic	pre-post-non-synaptic
Mechanism	increase intra-cellular Ca ions	inhibition adenylate cyclase (not CNS)	stimulation adenylate cyclase	stimulation adenylate cyclase
Agonist	phenyl-ephrine	clonidine	iso-prenaline	salbutamol adrenaline
Antagonist	thymoxamine prazosin	yohimbine	propranolol	propranolol

Noradrenergic agonist and antagonist drugs.

It is not certain how this classification is related to the human central nervous system. The drugs described are not as specific in their action at pre- or postsynaptic sites as is often assumed. Clonidine, for example, is generally considered to be a presynaptic alpha noradrenergic agonist, but it also has a postsynaptic action on some functions (flexor reflex activity, motor activity and perhaps blood pressure)(Strombom, 1975; Anden et al, 1976;

Kobinger, 1978; Langer, 1978; 1981; Velley et al, 1982). Clonidine sedation would appear to be via presynaptic alpha 2 receptor stimulation (Monti, 1982). Clonidine tends to exert more of a postsynaptic than presynaptic action with increasing doses as does yohimbine, which is usually regarded as a presynaptic noradrenergic antagonist (Anden et al, 1976; 1982).

Dopamine receptors

Dopamine receptors have also been subclassified. Firstly dopamine receptors in the central nervous system may be either pre- or postsynaptically situated. Presynaptic inhibitory autoreceptors for example may be stimulated by low doses of apomorphine which in turn cause a decrease in motor activity in experimental animals. Higher doses preferentially stimulate postsynaptic receptors (Strombom, 1975; Nagy et al, 1978; Rebec, 1984; Roth, 1984). In addition, dopamine receptors have been divided into two subtypes, the D1 and D2 receptors, depending on the presence or absence of adenylate cyclase linkage. The D2 site (or butyrophenone site) may be more closely linked with dopamine induced behaviour, Parkinson's disease and psychological dysfunction than the D1 site (Creese and Snyder, 1978; Schachter et al, 1980; Offermeier and Van Rooyen, 1982; Stoof and Kebabian, 1984; Rebec, 1984). The presynaptic receptors have been designated D3 and D4 receptors, the latter being those located presynaptically on cortico

striatal glutamate nerve fibres (Ungerstedt et al, 1982).

A second system of classification has been proposed by Cools and Van Rossum (1980)(Cools 1981). They categorise dopamine receptors into the excitatory neostriatal DAE and the inhibitory mesolimbic DAI receptors (the latter being regulated by mesolimbic alpha-like noradrenergic receptors).

iii. Adaptive changes in receptors.

Adaptive changes may occur in the receptors when changes in neurotransmitter activity occur over a period of time, for example following sustained drug usage or following a lesion of the relevant pathways. Generally speaking, heightened activity of the synapse and increased receptor stimulation (for example using an agonist drug) is followed by reduction in transmitter synthesis and turnover, via activation of presynaptic receptors (see previous section) or down regulation of the receptor. Reduced synaptic activity (as caused for example by an antagonist drug or following a lesion in the pathway) is associated with heightened sensitivity of the receptor. Adaptive receptor changes occur at presynaptic as well as postsynaptic receptors and are associated with changes in the receptor's affinity for the neurotransmitter, or the number of receptors (receptor density)(Byland, 1979; Resine, 1981; Sulser, 1984; Rebec, 1984).

Appreciation of these changes has lead to a re-evaluation

of the action of drugs in the treatment of psychiatric illnesses, for example the antidepressants in depressive illness (Leonard, 1982; Sulser, 1984). Chronic administration of antidepressants and ECT induce a subsensitivity of the noradrenaline sensitive adenylate cyclase, linked to down regulation of beta adrenoceptors; whilst some also cause down regulation of the alpha 2 receptors (Garcia-Sevilla et al, 1981; Sulser, 1984). Down regulation of the dopamine autoreceptor may also be important in the therapeutic effect of antidepressants and ECT (Antelman et al, 1982).

As the downgrading of receptors with prolonged antidepressant therapy correlates with the delayed therapeutic response, the original hypothesis for the role of the catecholamine in affective illness (Schildkraut, 1965; 1973) must be reappraised (Maas and Huang, 1980; Sulser, 1984).

The experiment reported in this thesis deals with changes following acute drug administration. Although subjects presented at least weekly for four sessions, three using active drugs, it is unlikely that receptor changes would have developed with such a regime.

iv. Current views on catecholamine neurophysiology

Noradrenaline

Developments over the last five years suggest that the function of both the noradrenergic and dopaminergic pathways are more complex than previously considered. The work of Bloom (1978; 1980) and his colleagues (Moore and Bloom, 1979; Aston-Jones and Bloom, 1981) is especially relevant in this context. These workers have used iontophoretically applied noradrenaline to show that noradrenaline usually slows the firing rate of cells in the cerebellar cortex, hippocampus, lateral geniculate body and cerebral cortex. However even though noradrenaline usually inhibits spontaneous discharge, the response to certain sensory inputs may be increased by noradrenaline. For example, the relative signal to noise ratio of responses by cells in the auditory cortex to vocalisations is increased because noradrenaline produces a greater suppression of spontaneous activity than the response to vocalisation. Locus coeruleus stimulation can increase the discharge of hippocampal cells to a conditioned stimulus. Bloom has proposed that noradrenaline pathways and the arborisation of axons, act to set the background tonal activity of an area in a "bias adjusting" or modulatory way. He suggests this may be relevant in attributing reinforcing value to sensations on the one hand, and in influencing the animals' ability to distinguish between relevant and irrelevant stimuli on the other. The DNP may suppress vegetative functions while

enhancing activity concerned with processing salient external stimuli (Aston -Jones and Bloom, 1981). Bloom proposes: "Such a functional system would add a valuable adjunct to the vocabulary of cellular communication signals by which neurones communicate" (Bloom, 1977; 1978). Similar proposals have been put forward by other workers (Woodward et al, 1979; Rogawski and Aghajanian, 1980; 1982).

Dopamine and noradrenaline interaction

Recent evidence of an interaction between the dopamine and noradrenaline pathways has added further complexity to the situation. Antelman and Cagguilla (1977) have proposed that it may be profitable to consider an interactive relationship between the two pathways. They cite a variety of examples that point to such an interaction and propose that the effect of noradrenaline is dependent on an intact dopamine system and that the potentiation or depression of behaviour by noradrenergic pathways depends on activational features in the environment. They suggest that in normal functioning, noradrenaline exerts an indirect modulatory influence on the dopamine system and regulates its function. When the activity of the noradrenergic pathways is diminished and the organism is stressed, facilitation of dopamine mediated behaviour is likely. In conditions of minimal stress or activation, diminished function of the noradrenaline neurones will either have no effect or will depress function.

A modulatory role by the noradrenergic pathways was also proposed by Bloom (1977; 1978) (see above). Other writers have since described neuroanatomical, neurochemical and pharmacological evidence giving support to the possibility of an interaction between dopamine and noradrenaline. Cools and Van Rossum (1980) and Cools (1981), give anatomical and neurochemical evidence for such an interaction. They report that dopamine receptors are functionally different in the nucleus accumbens from the caudate nucleus. The inhibitory DAI neurones in the nucleus accumbens differ from the DAE neurones in being directly controlled by alpha noradrenergic receptors.

There is biochemical and neurophysiological evidence of an interaction of dopamine and noradrenaline neurones though their precise nature and behavioural consequences remain unclear (Lloyd, 1978; Iversen, 1980). Robbins and Everitt (1982) reviewed the evidence for an interaction between the pathways as proposed by Antelman and Cagguilla. They described a variety of biochemical and pharmacological difficulties encountered in confirming the Antelman and Cagguilla hypothesis experimentally. They conclude that "there would appear to be sufficient behavioural neuroanatomical and pharmacological evidence to justify considerable effort in discerning the relationship between them (the noradrenergic and dopaminergic systems) as this may considerably inform our understanding of the control mechanisms underlying many forms of behaviour." Robbins

(1984) more recently proposed a two tiered interaction between the two systems coordinating the response to stress (see above).

Kostowski and his colleagues (Kostowski, 1979; Plaznik and Kostowski, 1983) have provided further evidence of a dopamine noradrenaline interaction in the central nervous system. However they suggest that the noradrenergic system should not be regarded as a unified system because there is evidence that the function of the VTP and the DNP have inhibitory and facilitatory effects respectively, on the dopamine pathways.

c. The role of the catecholamine pathways in psychobiological functioning

i. Noradrenergic pathways

Early ideas

As the intracerebral connections of the noradrenergic pathways were worked out, other evidence about them started to accumulate from lesion studies in experimental animals and from pharmacological studies in experimental animals and in humans. By the end of the 1960's, the psychobiological function of the noradrenergic pathways appeared to be reasonably well established (Schildkraut and Kety, 1967; Fuxe et al, 1970). Schildkraut and Kety suggested that noradrenaline played a role in anxiety and arousal. They drew attention to the similarity between the effects of intravenous noradrenaline and the physiological responses to arousal and anger, as well as to observations that anxious, hyperactive or aroused individuals excreted high levels of noradrenaline and its metabolites. Pharmacological studies indicated that catecholamine depletion (by reserpine or alpha methylparatyrosine) led to sedation or depression whilst stimulation of catecholamine pathways (by amphetamine or antidepressants) led to elation or to relief of depression. Schildkraut and Kety conjectured that there was a direct relationship between noradrenaline and elevation of

arousal, anger and mood.

The catecholamine hypothesis of affective illness was proposed by Schildkraut (1965). He hypothesised that "some if, not all depressions, are associated with an absolute or relative deficiency of catecholamines, particularly noradrenaline, at functionally important adrenergic receptor sites of the brain. Elation conversely may be associated with an excess of such amines."

Fuxe et al (1970) proposed a similar role for noradrenaline in alertness and hyperactivity. They reviewed evidence from neurophysiological and pharmacological studies in experimental animals and concluded that alertness reflected activity in the DNP, whereas autonomic functioning and aggression reflected activity of the VTP. Locomotor activity and exploratory behaviour, they suggested, involved the activity of both noradrenergic and dopaminergic pathways.

Confirmatory evidence for a similar role for the catecholamines in humans seemed to come from a detailed comparison of the relative efficacy of dextro versus laevo amphetamine in inducing arousal and alertness (Snyder, 1972; 1973). Dextroamphetamine appeared much more active than laevoamphetamine in preventing reuptake, and promoting the release of noradrenaline from the presynaptic neurone, whereas the two isomers appeared equally active in promoting the release of dopamine. Snyder therefore argued that, where the two isomers exerted a similar clinical or

behavioural effect, this was due to an action on dopamine pathways (paranoid psychosis). Those responses where dextroamphetamine was considerably more potent (eg alerting and mood elevating) reflected noradrenergic activity.

Other investigators have subsequently challenged both the behavioural and biochemical bases for these conclusions. For example Smith and Davis (1977) were unable to replicate the psychological differences in response to dextro or laevo amphetamine in a carefully standardised experiment.

Feigenbaum et al (1982) reported that no preferential reuptake inhibition of either dopamine or noradrenaline could be demonstrated and that reuptake inhibition was a minor action of amphetamine drugs compared with catecholamine release (Feigenbaum and Yanai, 1983). Other biochemical studies have demonstrated that dextro and laevo amphetamine are equipotent in influencing the activity of noradrenergic pathways but that laevoamphetamine is relatively less effective than dextroamphetamine in dopamine pathways (Bunney et al, 1975). This would give an interpretation opposite to that originally proposed by Snyder.

As mentioned in section 1.3.4.b. recent evidence on the changes in catecholamine receptors have cast some doubt on interpretations from pharmacological sources on the role of the catecholamines in affective illness.

Conclusions based on the different levels of catecholamine

and their metabolites in the plasma urine and CSF are confounded by continuing uncertainty about the central and peripheral effects of noradrenaline. Studies comparing the level of noradrenaline and its metabolites cannot differentiate between central and peripheral activity and between primary and secondary phenomena (Post and Goodwin, 1973).

These issues have led to a reappraisal of the role of the noradrenergic pathways in psychobiological functioning.

Recent trends - animal studies

Over the past ten years or so we have seen that many of the behaviours previously linked with noradrenergic functions are now established as dopaminergic behaviours. Mesolimbic dopamine pathways are thought to be involved with locomotor activity, behavioural motivation and arousal. Striatal dopamine pathways are involved in the initiating and sequencing of voluntary movement and sensory-motor integration, while the mesofrontal dopamine pathways are involved with organized and focused behaviour, for example, responding to interioceptive stimuli (Iversen, 1980; Ungerstedt et al, 1982; Iversen and Fray, 1982). See section 1.3.4.b.

Thus activation of behaviour seems to depend on central dopamine mechanisms. The dorsal noradrenergic pathway (DNP) may be involved in the organization of a coordinated

response to stress over a range of different behaviours and functions (Robbins, 1984). Robbins proposes a two tiered system of interaction between dopamine and noradrenaline, an upper and lower arousal mechanism. The lower (dopamine mechanism) responds to intensive arousing stimuli, while the upper noradrenergic mechanism compensates for sub- or supra-optimal activity of the lower mechanism.

The role of noradrenergic pathways in other psychobiological and behavioural activaties has come under scrutiny as well. For example, evidence is emerging from studies in experimental animals, that the noradrenergic pathways have a role in learning, more specifically in extinction rather than in the acquisition of behaviour. DNP lesioned animals also show increased distractability (Mason, 1980; 1981; 1983). Considerable research into this area has led Mason to propose that the DNP has a role in the animal being able to filter and ignore irrelevant information (Mason, 1980; 1981; 1983; McNaughton and Mason, 1980; Iversen, 1980; Robbins, 1984).

Noradrenergic pathways have been shown to be involved in the development of visual plasticity (Robbins, 1984) and they also probably have an inhibitory role in aggression (McNaughton and Mason, 1980). They are involved in the regulation of eating behaviour, sexual behaviour (McNaughton and Mason, 1980), sleep (Gillin et al, 1978[a]; Monti, 1980), seizure control (McNaughton and Mason, 1980) and homeostasis via the hypothalamo anterior pituitary system

(Muller et al, 1977[a]; Robbins and Everitt, 1982).

Recent studies - human

As mentioned earlier the notion that the noradrenergic pathways were primarily involved in changes in mood, arousal and in affective illness needs reconsideration.

Considerable uncertainty still remains whether a direct relationship between arousal, anxiety and noradrenergic functioning exists or whether the proposal that the noradrenergic pathways exert a modulatory role on the activity of dopamine pathways is more appropriate.

Recent pharmacological studies using human subjects have failed to resolve the issue. Clonidine, an alpha 2 noradrenergic agonist, and yohimbine, an alpha 2 noradrenergic antagonist are sedating and alerting respectively when given to normal subjects (Monti, 1980; Sievers et al, 1981; Hoehn - Saric, 1982; Charney et al, 1983; 1984). Charney et al (1983; 1984) for example, report that yohimbine increased symptoms of nervousness, panic, restlessness and blood pressure but interestingly, caused a parallel increase in ratings of drowsiness. They suggest that anxiety and panic may reflect increased sensitivity to augmented noradrenergic function and that impaired presynaptic neuronal regulation may exist with panic disorder. Some doubt remains, however about how much the action of clonidine and yohimbine rests on involvement of

presynaptic compared with postsynaptic receptors in the central or peripheral nervous system (Strombom, 1975; Anden, 1976; 1982).

The postsynaptic alpha and beta noradrenergic antagonists, thymoxamine and propranolol, seem to be without clear or consistent central effects in normal subjects (Jacobs and Silverstone, unpublished; Lader and Tyrer, 1972). Propranolol's effects on the somatic symptoms of anxiety are likely to be peripherally mediated (Lader and Tyrer, 1972; Gottschalk et al, 1974).

Other pharmacological studies are confounded by the lack of specific action of the drugs used and by variability in response. Most antidepressant drugs, for example, have as a primary action the prevention of the re-uptake into the presynaptic neurone of noradrenaline and other neurotransmitter substances namely serotonin, dopamine and acetylcholine (Silverstone and Turner, 1982). In addition to sedation and reducing the symptoms of panic and anxiety (Sheenan et al, 1980), antidepressants elevate mood in depressed patients and may precipitate mania (Wehr and Goodwin, 1979). Doubt has been raised as to whether these changes reflect adaptive changes by pre- or post synaptic receptors over the period of time before the drugs exert their therapeutic action (Maas and Huang, 1980; Waldmeier, 1981; Leonard, 1982; Sulser, 1984)(see section 1.3.4.b)

Psychiatric disorders

The role of noradrenaline in psychological disease also remains uncertain. As will be described subsequently (Part III) a central role for dopamine has emerged in mania.

As far as anxiety states are concerned, it is possible that noradrenaline has a central nervous system as well as peripheral nervous system role. As mentioned earlier, the role of peripheral noradrenergic receptors is demonstrated in the clinical efficacy of propranolol (Gottschalk et al, 1974). The effects of clonidine and yohimbine are likely to involve central receptors too but in a manner that remains to be resolved (Dollery et al, 1975; Jouvent et al, 1980; Hoehn-Saric, 1982; Charney et al, 1983; 1984)(see above).

Even the central role of noradrenaline in the depressive phase of affective illness has come under criticism. The catecholamine hypothesis (Schildkraut, 1965) stated that depression was associated with a relative lack or hypofunction of the noradrenergic synapse. The hypothesis was proposed before the recent work on adaptive receptor changes were known. Antidepressant drugs after continuous therapy, cause a down regulation of postsynaptic beta adrenoceptors and alpha 2 presynaptic adrenoceptors and hence may exert their therapeutic action by lowering the activity of noradrenergic pathways, implying relative hyperactivity of the pathways in depression (Waldmeier, 1981; Reisine, 1981; Leonard, 1982; Sulser, 1984; Sulser et al, 1984) (see 1.3.4.b.)

Although it has been assumed that dopamine plays a pre-eminent role in the pathogenesis of schizophrenia (Matthysse, 1974), Hornykiewicz (1982) proposed that the role of noradrenaline in schizophrenia had been underestimated. The work by Mason and his colleagues (McNaughton and Mason, 1979; Mason, 1980; 1981; 1983) suggests that the DNP has a role in selective attention. In the rat forebrain, noradrenaline depletion leads to increased distractability, a perseveration of inappropriate behaviour (or a resistance to extinction) and an apparent failure to filter out irrelevant stimuli. Mason points out that there may be a similarity between these observations and the perseveration of inappropriate response patterns in schizophrenic patients. Increased attention to irrelevant stimuli is also observed in schizophrenic patients. The abnormalities of a perceptual filter mechanism seen with schizophrenic patients may correspond to those seen in experimental animals with noradrenaline pathway lesions. Alterations in attention and the ability to filter irrelevant stimuli, may provide a biological explanation of the schizophrenic´s abnormal ideas and hallucinations (Mason, 1981).

ii. Dopaminergic pathways.

Animal studies

The role of the dopamine pathways in motor activity has been demonstrated using lesion studies and pharmacological methods. From the pharmacological perspective, dopamine precursors or agonists, for example L Dopa, methylphenidate, apomorphine and amphetamine, have an activating action in experimental animals (Randrup and Munkvad, 1966; Costall and Naylor, 1974; Iversen and Iversen, 1975; Fray et al, 1980; Nickolson, 1981; Rebec, 1984), provided that the dosage is high enough that the drug acts predominantly at post synaptic receptors (Rebec and Segal, 1978; Rebec, 1984). Activation is attenuated by the neuroleptics whose common action is dopamine blockade (Murphy and Redmond, 1975; Groves and Rebec, 1976; Ljungberg and Ungerstedt, 1978).

Looking at amphetamine in particular, the increase in locomotor activity that follows a relatively low dose of amphetamine, involves dopamine neurones in the nucleus accumbens whilst the stereotypy which follows high doses involves dopamine neurones in the caudate nucleus (Kelly et al, 1975; Groves and Rebec, 1976; Robbins and Everitt, 1982).

Confirmatory evidence for the role of the dopamine pathways in the initiation and coordination of motor behaviour came from the discovery that degeneration of the nigrostriatal dopamine neurones was associated with

Parkinson´s disease and that symptoms could be reversed by L dopa (Hornykiewicz, 1978; Ungerstedt et al, 1982). Dopamine pathways appeared to be involved in mental functions in view of the efficacy of the neuroleptic drugs in the treatment of schizophrenia and mania (Fuxe et al, 1970; Snyder et al, 1974; Silverstone and Turner, 1982). Dopamine pathways seemed also to be involved in the control of anterior pituitary hormone secretion, temperature regulation and emesis (Fuxe et al, 1970; Muller et al, 1977[a]; Silverstone and Turner, 1982). Further studies, particularly those involving chemical ablative techniques, imply that dopamine pathways are important in the organisation of the different types of responses that contribute to motivation (Robbins and Everitt, 1982).

As described earlier (1.3.3.b.), the nigrostriatal mesolimbic and mesocortical pathways have now been shown to form closely integrated circuits with nucleus accumbens - substantia nigral, corticostriatal and corticolimbic connections. Ablative lesions of the nigrostriatal system are associated with sensory motor neglect (Iversen and Alpert, 1983; Ungerstedt et al, 1982). The neglect appears to reflect a lack of attention to exterioceptive cues (Iversen, 1980). A bilateral lesion causes total sensory motor neglect, even to food and water (Iversen and Fray, 1982; Ungerstedt et al, 1982; Iversen and Alpert, 1983). Iversen and Fray (1982) suggest that the dopaminergic input in the striatum facilitates the integration of sensory flow with motor responses, via the cortex.

Lesions in the mesolimbic pathways on the other hand attenuate the amphetamine induced increase in locomotor activity and, in unstimulated animals, cause a fall in spontaneous activity. Animals are unable to respond to change. This area therefore is probably associated with motivational (interioceptive) stimuli, i.e. affective, reinforcing or aversive stimuli processed by the hypothalamo-limbic system (Iversen and Fray, 1982; Ungerstedt et al, 1982; Iversen and Alpert, 1983), with adaptive behaviour depending on integration of both pathways.

The cortical dopamine pathways form part of the integrated dopamine circuits via the corticostriatal and corticolimbic pathways. Dopamine neurones in the anterior cortex receive sensory information from other cortical areas which is integrated and transmitted to the striatum and limbic system (Iversen and Fray, 1982; Ungerstedt et al, 1982; Iversen and Alpert, 1983).

Human behaviour

Earlier predictions were that noradrenaline would emerge as the major alerting catecholamine in humans (Schildkraut, 1965; Fuxe et al, 1970)(see earlier). Over the last decade however, the role of dopamine in human psychological and behavioural functioning has become increasingly clear.

Drugs which enhance dopaminergic activity by increasing precursor load (L Dopa), by releasing dopamine into the synapse (Methylphenidate, amphetamine), or by acting as direct dopamine agonists (bromocriptine), may increase mood and activity. They may also reverse depression and precipitate mania (Murphy et al, 1973; Murphy and Redmond, 1975; Randrup et al, 1975; Gerner et al, 1976; Silverstone, 1978). On the other hand, drugs which suppress the activity of dopaminergic pathways, either by inhibition of synthesis (alpha methylparatyrosine) or by dopamine receptor blocking action (neuroleptics) cause sedation and reduce the hyperactivity of mania (Randrup et al, 1975; Silverstone, 1978).

The role of dopamine pathways in motor behaviour is clearly demonstrated in Parkinson´s Disease where there is a degeneration of substantia nigra neurones and the nigrostriatal tract accompanied by gross depletion of striatal dopamine. The defect may be reversed, in part at least, by the dopamine precursor L Dopa (Hornykiewicz, 1978; Ungerstedt et al, 1982). In addition to the bradykinesia and other motor symptoms, depression is a common symptom of Parkinson´s disease (Randrup et al, 1975).

Psychiatric disorder

Dopamine pathways are believed to have a role in the pathogenesis of schizophrenia (Snyder, 1972; 1973; Snyder et al, 1974; Matthysse, 1974), though their involvement may not be as close as first proposed. The original dopamine hypothesis was based on the observation that all antipsychotic neuroleptics have dopamine blocking activity and the drugs' capacity to block dopamine activity was directly related to the drugs' antipsychotic potential (Snyder, 1973). Further support was produced by studies of the schizophrenia-like psychosis induced by high or prolonged doses of amphetamine (Bell, 1965; Ellinwood, 1967; Snyder, 1972; 1973). Snyder (1972) reasoned that dopamine was involved because dextro- and laevo- amphetamine were equipotent in causing re-uptake inhibition and release of dopamine and in inducing the paranoid psychosis. Furthermore, neuroleptics were able to inhibit the presentation of amphetamine psychosis (Connell, 1958).

The role of dopamine and noradrenaline in the biology of mania will be covered in detail in Part III.

iii. Evidence for dopamine - noradrenaline interaction.

Some writers have proposed that the noradrenaline dopamine stress response system may be central to certain psychiatric and neurological disorders. This may apply in particular to affective illness (both mania and depression), schizophrenia and Parkinson's disease and therefore that the pathways should not be considered in isolation (Iversen, 1980; Hornykiewicz, 1982; Plaznik and Kostowski, 1983).

As described earlier (1.3.4.b), neuroanatomical and neurophysiological evidence exists for an interaction between the two catecholamine pathways, with the direction of noradrenergic modulation of the dopamine pathways being dependent on the degree of arousal present. Thus, noradrenergic stimulation would facilitate the activity of the dopamine pathways in the unaroused state, but inhibit them in the aroused condition (Antelman and Cagguilla, 1977; Iversen, 1980; Robbins and Everitt, 1982; Robbins, 1984).

To date, the question of an interaction between dopamine and noradrenaline pathways has not been directly tested in human subjects. Some pharmacological data may be interpreted as supporting this hypothesis. Blocking noradrenaline synthesis, by giving a dopamine beta hydroxylase inhibitor, accentuates the psychotic symptoms of aroused manic patients (Sack and Goodwin, 1974). Amphetamine drugs have differential effects depending on the state of arousal. Amphetamine drugs in moderate doses may accentuate arousal and mood in normal individuals (Silverstone et al,

1983), in depressed patients (Fawcett and Siomopoulos, 1971; Ward and Lampe, 1982), and may precipitate mania (Gerner et al, 1976) or cause a schizophreniform paranoid psychosis (Bell, 1965; Ellinwood, 1967). On the other hand, they may produce sedation in normal subjects (Tecce and Cole, 1974), reduce the symptoms of anxiety in obsessive-compulsive patients (Insel et al, 1983), attenuate the symptoms of mania (Beckman and Heinemann, 1976) and reduce the symptoms in some schizophrenic patients (Van Kammen et al, 1982). Thus the sedating effect of amphetamine in conditions of relative hyperarousal might reflect the amphetamine induced stimulation of noradrenergic pathways exerting a modulating influence on an overactive dopamine system.

1.4. Previous Attempts to Elucidate the Relative Roles of the Dopamine and Noradrenaline Pathways in Amphetamine Arousal

1.4.1. Experimental animals

The effects on experimental animals of amphetamine derivatives have been widely studied and have served as a major pharmacological tool in researching the catecholamine pathways.

In experimental animals lower doses of amphetamine derivatives, when given acutely, cause an increase in arousal and locomotor activity. In higher doses they produce stereotyped behaviours (Iversen and Iversen, 1975; Groves and Rebec, 1976).

There is strong evidence to suggest that the increase in locomotor activity is due to the stimulation of dopamine pathways and that the site of action is the nucleus accumbens (Kelly et al, 1975; Iversen and Fray, 1982). The locomotor effect may be blocked by alpha methylparatyrosine but not by a dopamine beta hydroxylase inhibitor (Hollister et al, 1974). It is also blocked by dopamine blocking drugs but it is either not blocked, or only partially blocked, by noradrenaline blocking drugs (Rolinski and Scheel-Kruger, 1973; Moore, 1977). Noradrenergic involvement in the increase in locomotor activity induced by dextroamphetamine remains controversial however. Roberts et al (1975) report that a lesion in the dopaminergic nigrostriatal pathway

attenuated dextroamphetamine induced locomotor activity whereas a lesion in both noradrenergic pathways failed to influence the activity. However in a more recent study Kostowski et al (1982) report some attenuation of dextroamphetamine locomotor activity by similar lesions in the noradrenaline pathways. If noradrenaline is involved, its role seems to be of secondary importance (Groves and Rebec, 1976). Indeed reducing noradrenergic activity was reported by Ungerstedt (1971) to increase amphetamine induced behaviour, suggesting that the pathways may play a modulatory role.

Dopamine pathways are primarily involved in amphetamine induced stereotypy with no evidence of an involvement of noradrenaline pathways (Lal and Sourkes, 1972; Groves and Rebec, 1976). The site of action appears to be in the caudate nucleus (Kelly et al, 1975).

Experimental animals have been used to study other amphetamine induced behaviours. These include anorexia and aberrant behaviour following prolonged high doses of the drug.

Amphetamine drugs produce anorexia in experimental animals as they do in humans. Earlier evidence implicating the dopamine pathways (Hollister et al, 1975) must be reviewed in the light of evidence that only the anorectic effect of high doses of amphetamine was blocked by neuroleptics (Samanin et al, 1978; Burridge and Blundell, 1979). This suggested that dopamine blockade might be exerting an effect

on the general behaviour of the animal, rather than a direct action on anorexia. Lesions in the VTP however prevented dextroamphetamine anorexia (Samanin et al, 1978). Leibowitz (1984) has observed that the anorexia induced by intrahypothalamic injections of amphetamine was attenuated by beta noradrenergic and dopamine blockers. In man, on the other hand, dopamine blockers do not appear to effect dextroamphetamine induced anorexia (Silverstone et al, 1980), but thymoxamine may attenuate it (Jacobs and Silverstone, in preparation).

Experimental animals have also been exposed to continuous high doses of amphetamine drugs in an effort to produce a model psychosis similar to that induced in humans. In animals exposed to dextroamphetamine by implanted slow release pellets, the stereotypy phase is followed by a period of relative inactivity and then by a phase in which the animal displays aberrant social behaviour (Ellison and Eison, 1983). The authors describe "parasitotic" and often "hallucinatory like behaviour" as well as increased vigilance. The latter phase appears to be associated with irreversible alterations of dopaminergic innervation of the caudate nucleus.

1.4.2. Human subjects

There is strong evidence that the elevation of mood and alertness are dependent on dextroamphetamine's ability to stimulate dopamine receptors rather than noradrenergic receptors. The elevation of mood following intravenous racemic amphetamine was blocked by alpha methylparatyrosine (Jonsson et al, 1971), pimozide, and to a lesser extent, chlorpromazine, whereas thioridazine, or propranolol were ineffective (Jonsson, 1972; Gunne et al, 1972). Phenoxybenzamine slightly increased the response to amphetamine (Gunne et al, 1972). It should be noted that pimozide has a more specific dopaminergic blocking action than the other neuroleptics used in these experiments (Anden et al, 1970; Pinder et al, 1976).

Pimozide was also found to attenuate the stimulant action of an oral dose of dextroamphetamine as measured by the visual analogue rating scale (Silverstone et al, 1980). Pimozide similarly blocked the sleep changes induced by an intravenous dose of dextroamphetamine in normal subjects (Gillin et al, 1978[b]). Intramuscular haloperidol was reported to attenuate behavioural excitation induced by intravenous dextroamphetamine, but both intravenous propranolol and thymoxamine were without effect (Nurnberger et al, 1984). Neither haloperidol or pimozide however, altered the rise in pulse rate or blood pressure induced by intravenous dextroamphetamine (Rosenblatt et al, 1979; Nurnberger et al, 1984).

The paranoid psychosis, induced by high or continuous usage of amphetamine derivatives has been regarded as being due to the drugs´ stimulant effect on dopamine pathways (Snyder, 1972; 1973). See section 1.3.4.c.

1.5. Catecholamine Receptor Blocking Drugs

1.5.1. Introduction

As has already been stated amphetamine drugs act as indirect dopaminergic and noradrenergic agonists. Consequently, specific catecholamine blocking drugs can be used to study the relative roles of the two pathways in the amphetamine response. Attenuation of the response by blocking a specific neurotransmitter pathway implies that response was dependent on that pathway, whereas accentuation of the response implies that the pathways concerned were exerting an inhibitory or modulatory action. In the experiment to be described two catecholamine blocking drugs were used, Pimozide and Thymoxamine. Pimozide is a relatively specific dopamine blocking drug (see below) whereas thymoxamine has relatively specific blocking action at the alpha 1 noradrenergic sites (see below).

1.5.2. Pimozide

a. Pharmacology

Pimozide is one of the diphenylbutylpiperidine group of drugs and is used as a neuroleptic drug. In both animals and humans, it is readily absorbed after oral administration and readily reaches the central nervous system. Biological half life for liver, blood and brain is about five to six hours. In the brain, highest concentrations are found in the caudate nucleus and the pituitary gland. The pharmacological effects are probably due to the unchanged drug. It is metabolised mainly by oxidative dealkylation and excreted in the urine and faeces. In human subjects, the plasma half life is eighteen hours (see Pinder et al, 1976).

b. Mechanism of action

Pimozide appears to selectively block central dopamine receptors rather than noradrenaline receptors (Anden et al, 1970) and is effective in blocking dopamine agonist behaviour in experimental animals (Pinder et al, 1976). Although, in an in vitro study, pimozide caused an inhibition of noradrenaline sensitive cyclic AMP in limbic forebrain tissue (Blumberg et al, 1975), it causes only slight changes in the level of endogenous noradrenaline (Pinder et al, 1976). Pimozide has been widely used in pharmacological research as a selective dopamine receptor blocking drug. It is generally without significant

peripheral action on the autonomic nervous system or the cardiovascular system.

For these reasons pimozide would appear to be the most specific and suitable dopamine agonist to use for pharmacological investigation. Other neuroleptics have significant noradrenergic or cholinergic blocking action (McKay, 1982).

c. Uses in psychiatry

Earlier reports suggested that pimozide may be particularly efficacious in patients suffering from chronic schizophrenia who are relatively inert as it lacked the marked sedative action of other neuroleptics (Pinder et al, 1976). It has, however, also been found to be effective in psychotic illness with agitation, especially in mania. Indeed pimozide appeared to have a more specific antimanic action than chlorpromazine (Cookson et al, 1981). It is effective, too, in acute schizophrenia (Silverstone et al, 1984) and has been recommended in monosymptomatic delusional psychosis (Munro, 1980).

1.5.3. Thymoxamine

The search for a suitable postsynaptic alpha noradrenergic blocking drug has been more difficult. Some alpha noradrenergic blocking drugs have a preferential action at presynaptic sites (yohimbine, phentolamine), are comparatively toxic (phenoxybenzamine), or are less specific in their action (chlorpromazine)(Nickerson and Collier, 1975; Drew et al, 1979; Anden et al, 1976; 1982).

a. Pharmacology

Thymoxamine, the thymyl ester of alkylamine, has alpha-adrenoceptor blocking action. Its clinical uses are in the treatment of asthma, labyrinthine ischaemia and peripheral vascular disease, and as an agent to induce miosis in ophthalmology. Little information is available about its pharmacokinetic properties.

b. Mechanism of action

Thymoxamine, together with its metabolites, deacetylthymoxamine and N-demethyldeacetylthymoxamine, has a relatively specific competitive alpha-adrenoceptor blocking activity with no beta-adrenoceptor blocking or serotonin blocking action (Birmingham and Szolcsanyi, 1965; Creuzet et al, 1980; Roquebert et al, 1981[a]). Birmingham and Szolcsanyi (1965) report that thymoxamine has mild antihistamine properties as well. Thymoxamine's alpha-adrenoceptor blocking activity is at post synaptic rather than presynaptic receptor sites as it was not

effective in reversing a variety of clonidine induced changes as distinct from yohimbine and phentolamine (Drew, 1976; Drew et al, 1979; Roquebert et al, 1981[b]).

Thymoxamine's activity within the central nervous system can be implied as intravenous thymoxamine reduced the increased tendon jerk induced by methylamphetamine (Phillips et al, 1973), attenuated the rise of ACTH following methylamphetamine Rees et al, 1970) and increased REM sleep (Oswald et al, 1975). There is no record of the clinical use of thymoxamine in psychiatric illness.

Methods

METHODS

1.6. Introduction

Four experiments were performed in all. Two studies were designed to investigate the effect of prior dopaminergic blockade by pimozide, or prior alphanoradrenergic blockade by thymoxamine, on the responses in normal volunteers to 20 mg of oral dextroamphetamine. In both of these experiments twelve subjects presented on four occasions. In addition, two further studies were performed to investigate the effects of the two blocking drugs alone with four subjects being used in each. Subjects in these studies presented on three occasions.

In describing the procedures, the different experiments are designated as follows.

Experiment A: Pimozide alone.

Experiment B: Pimozide and dextroamphetamine.

Experiment C: Thymoxamine alone.

Experiment D: Thymoxamine and dextroamphetamine.

All measures, psychological, psychophysiological and neuroendocrine were performed in each group. The results from the occasion in experiments B and D in which dextroamphetamine was given alone (placebo blocker -

dextroamphetamine 20 mg) have been pooled and compared to the placebo only occasion (placebo blocker - placebo dextroamphetamine) from these two experiments.

Part I will describe the results of the psychological and psychophysiological tests.

Part II will consider neuroendocrine aspects, both of the dextroamphetamine response alone and the effect of dopamine and noradrenaline blockade; further details of relevant methodology will be given in that section.

Part III will examine the pooled results to compare the effects of dextroamphetamine alone with the phenomena and psychophysiological concomitants of mild mania. Further relevant methodological details will be given in Part III.

All experiments were conducted in the Academic Unit of Human Psychopharmacology, St Bartholomews and the London Hospitals situated at the German Hospital in London (United Kingdom).

1.7. Subjects

All the subjects who participated were young men, aged 17 - 31 years and were either students or professional and all but one were white. The study was canvassed by word of mouth. They were paid ten pounds sterling for each attendance.

Prior to participation volunteers presented for a screening interview conducted by the investigator. At this interview a history of prior and current physical health and prior and current psychological health was elicited. A detailed review of prior or current drug usage (prescribed, unprescribed or illicit) was conducted. A thorough physical examination was carried out reviewing all systems with particular reference to the cardiovascular system. Height and weight were recorded. Subjects completed an Eysenck Personality Inventory.

The nature of the study was discussed in detail with the subjects who were acquainted with the drugs used and potential risks. Subjects were familiarised with the schedule of the experiment and the routine that would be followed. They were acquainted with the laboratory and experimental equipment that would be used. Seven subjects interviewed were denied admission to the study as they gave a history of past or current drug and alcohol misuse (two), past psychological difficulties (two), or evidence on physical examination of poor health (three).

One subject was discharged from the study after he experienced nausea on the first experimental run. In retrospect this seemed an idiosyncratic reaction to thymoxamine and was the only discomfort encountered by any of the subjects.

1.7.1. Subject profiles

Details of subjects (means +- SEM) are summarised in table 1.2.

TABLE 1.2.

Experiment	A	B	C	D
Drug combination	PMZ alone	PMZ +dAMP	TMX alone	TMX +dAMP
number	4	12	4	12
mean age (years)	23.3 (+-2.6)	23.3 (+-4.2)	24.8 (+-4.0)	24.6 (+-3.4)
mean height (cm)	179.9 (+-5.9)	181.2 (+-5.7)	179.9 (+-5.9)	181.5 (+-5.5)
mean weight (kg)	68.6 (+-9.9)	71.5 (+-5.5)	69.5 (+-10.4)	69.5 (+-7.3)
EPI mean E score	13.5 (+-5.7)	14.6 (+-4.6)	11.0 (+-3.7)	13.8 (+-4.6)
mean N score	6.5 (+-1.7)	6.3 (+-3.3)	9.3 (+-4.1)	8.5 (+4.4)

Details of subjects used.

1.7.2. Instructions to subjects

After the evaluation interview, subjects presented on four evenings, at least seven days apart. They were instructed to avoid tea, coffee, tobacco or alcohol in the twenty-four hours prior to the experiment. If, for any reason, prescribed drugs had been recommended during the experimental period, attendance was postponed (e.g. on one occasion a subject used a nasal decongestant for a cold).

Subjects fasted after breakfast apart from drinking fruit juice and water during the day. They presented to the laboratory in the late afternoon when the recording apparatus was connected, the drugs administered and the experiment commenced.

During the experiment subjects sat alone and could read or watch television. The design of the department enabled the experimenter to run the equipment in a separate room. At the conclusion of the experiment a meal was provided and the subject was taken home.

1.8. Measurements

All psychological and psychophysiological measures were taken and the data analysed by the experimenter. Analysis of plasma samples for dextroamphetamine levels was conducted by Servier Laboratories London, whilst the analyses of plasma cortisol and serum anterior pituitary hormone levels were undertaken in the department of Clinical Endocrinology, St Bartholomew's Hospital, London.

1.8.1. Psychological measures

A number of criteria had to be considered when selecting the most appropriate measurement of changes of mental state. Any measure of mental state is essentially subjective in nature. As one aim of the study involved comparing the response to dextroamphetamine with the phenomena of mania, flexibility in selecting appropriate dimensions was necessary.

It was intended that measures of mental state be recorded at half hourly intervals which required that the test be easily repeated and rapidly administered.

The test had to be of proven sensitivity, reliability and validity. In this experimental design the visual analogue rating scale was found to fulfil the above criteria rather than one of the mood adjective checklists (MacKay, 1980). Visual analogue rating scales (Aitken, 1969; Aitken and Zeally, 1970; Maxwell, 1978) are sensitive and accurate

rating scales particularly for within subject comparisons of change and were considered most appropriate for the needs of this experiment.

Visual analogue rating scales were used to investigate changes within an individual over time. As raw scores were not used there was no valid reason in this circumstance to expose the data to any particular transformation, eg, log e (Bond and Lader, 1974) or arcsine (Aitken and Zeally, 1970) beyond the conversion of scores to a change from a reference zero time (Maxwell 1978). Change scores were subject to within subject statistical comparison.

The dimensions studied were as follows:

Mood.

I feel very miserable - I feel very happy.

I feel very placid - I feel very irritable and angry.

Arousal.

I feel very drowsy - I feel very alert.

I feel mentally slowed - I feel that my mind is racing very fast.

I feel very restful and physically inactive - I feel very restless and fidgety.

I feel lethargic / I feel full of energy.

Subjects were asked to rate the quality of of their previous night's sleep on the morning after attendance on a 5 point scale (very well - very badly).

Comments made by the subjects either during the experiment or afterwards, were recorded as were any other observations considered relevant by the experimenter.

1.8.2. Psychophysiological measures

Although subjective measures of mental state using visual analogue scales are flexible, sensitive and allow repeated measures of change over a period of time, the fact that they are a subjective measure requires that ideally, they should not be used in isolation in psychopharmacological studies.

A variety of objective psychophysiological measures reflecting arousal - sedation have been found sufficiently sensitive to detect changes following drug administration (Lader, 1975).

Arousal was determined in this experiment by the following measures:

a. Pulse rate.

b. Blood pressure.

c. Skin galvanometry.

   i. Skin conductance levels.

   ii. Number of spontaneous fluctuations in skin conductance.

Changes in plasma cortisol which were also measured in this experiment have been used in other studies to reflect changes in arousal. In this study however, changes in plasma cortisol were not used to study arousal; rather the

effect of pimozide or thymoxamine pretreatment on plasma cortisol secretion was considered along with other studies examining the catecholamine control of cortisol secretion. See Part II.

Pulse rate and systolic blood pressure can give a sensitive objective measure of arousal (Lader, 1975). However, as drugs used in this experiment have peripheral catecholaminergic activity, changes recorded may reflect peripheral rather than central action.

a. Pulse rate

In the pilot study pulse rate was recorded graphically using a digital pulse recorder. However as this instrument gave an audible click which could give the subject feedback about the effect of the medication he may have taken, it was felt preferable to measure the pulse rate manually. The radial pulse was counted for one minute every thirty minutes throughout the experiment.

b. Blood pressure

Systolic and diastolic blood pressure was recorded every thirty minutes throughout the experiment using a mercury sphygmomanomometer. Diastolic blood pressure was taken at the point the sounds became muffled.

c. Skin Galvanometry

Skin galvanometry allows an accurate objective measure of background arousal. The sweat glands, although acting under

the control of the sympathetic nervous system, are unique in that the control is cholinergic (Venables and Christie, 1980). Thus changes in catecholamine functioning measured by skin galvanometry are more likely to reflect central rather than peripheral changes during the experiment (Lader, 1975).

The measures of arousal using skin galvanometry in this experiment were the skin conductance level and the number of spontaneous fluctuations in skin conductance. The methodology followed that described by Lader and Wing (1966) and Lader (1975).

Newly made silver-silver chloride electrodes were used. Each was 11 mm in diameter (95 square mm) and set in a recessed plastic holder with a depth of 1 mm to allow packing of conductive medium. Electrodes were replaced if the silver chloride coating was damaged. The conductive medium was .05 molar KCL prepared in an agar paste (Venables and Christie 1973).

Subjects washed their hands without soap on arrival.

A unipolar electrode placement was used. After the area was inspected for cuts or scars a circular foam cornplaster was applied to the palmar surface of the thumb centering on the thumb print whorl. This ensured a constant surface area of skin 9.5 mm in diameter and an area of 71 square mm. The recess of the active electrode and the well of the corn plaster was packed with conductive medium and the electrode secured firmly in place with micro-pore dressing. An

inactive electrode was applied to the anterior surface of the forearm which had been carefully abraded with an emery board using the same conducting medium.

Skin resistance was measured using a Servioscribe recorder for five minutes every thirty minutes, fifteen minutes after measures of visual analogue scale ratings, pulse and blood pressure were made and blood samples taken. Skin resistance (Kilohms) was recorded graphically for five minutes. The mean of five measures at one minute intervals was calculated, converted to a measure of the skin conductance level (Micromhos) and logged (Lader and Wing, 1966; Lader, 1975). Log conversion of the skin conductance level is customary practice and has been validated by Venables and Christie (1980).

A second reliable measure of arousal derived from the skin galvanometric reading was the number of spontaneous fluctuations in skin conductance (Lader and Wing, 1966; Lader, 1975). Those spontaneous fluctuations greater than .003 Log Micromhos that occurred in a forty second period in every minute of the five minute recording was counted and the mean for a forty second period calculated.

1.8.3. Blood Samples

At 1700 hours, after basal readings were taken, a venous cannula was inserted into a forearm vein (scalp vein cannula 21 gauge). This was kept patent, initially and after each blood sample was drawn, by a 0.05 ml injection of heparin diluted in normal saline (100 units in 1 ml). Immediately prior to the dextroamphetamine dose and hourly thereafter blood was collected in lithium heparin tubes, centrifuged immediately and the supernatant plasma stored at minus 20 degrees centigrade for plasma dextroamphetamine estimation. Plasma dextroamphetamine levels were assayed by Servier Laboratories (Dr. Bruce Campbell) using a gas chromatographic method (Campbell 1969).

Further blood samples were collected thirty minutes prior to the dextroamphetamine dose, immediately prior to the dextroamphetamine dose, and hourly thereafter. It was collected in lithium heparin tubes and centrifuged immediately, or placed in glass tubes and centrifuged after clotting, and the supernatant plasma or serum was stored at minus 20 degrees centigrade for estimation of plasma cortisol and serum prolactin, growth hormone, thyroid stimulating hormone, follicle stimulating hormone and luteinizing hormone. Samples were assayed at the Department of Clinical Endocrinology, St Bartholomews Hospital (Professor Lesley Rees) by the fluorimetric method for free 11 hydroxy corticosteroids or by the double radio-immuno assay method for the other hormones. See Part II.

1.8.4. Recording schedule

Psychological and psychophysiological measurements were commenced at 1700 hours and repeated at half hourly intervals until 2200 hours. The skin galvanometric measures were performed fifteen minutes after the other measures. Blood samples were taken at 1730 hrs, and at 1800, and repeated hourly thereafter.

1.9. Drugs Used

1.9.1. Pilot studies

Pilot studies were conducted in an open manner to investigate the optimum doses, routes of administration and timing of the dosage schedules. These experiments revealed that using oral dextroamphetamine 20 mg rather than 10 mg gave a more reproducible rise in arousal and mood as measured by visual analogue scales, the maximal rise being recorded two to three hours after the dextroamphetamine dosage. It was not felt ethically justified to expose the subjects to parenteral dextroamphetamine.

Dopamine blockade

Two alternative methods of dopamine blockade were considered:

(a) Intravenous droperidol given immediately prior to dextroamphetamine.

(b) Pimozide given orally 2 hours prior to the dextroamphetamine dosage.

Intravenous droperidol at a dose of 0.5 mg when given alone or just prior to a dosage of 20 mg of dextroamphetamine, caused marked discomfort in the subjects. Subjects reported such anxiety, dysphoria and irritability that they were reluctant to continue.

Pimozide on the other hand caused no subjective discomfort. Both doses (2 mg and 4 mg) caused a rise in prolactin two to four hours after the dosage, with that following 4 mg being significantly greater than that following 2 mg. In order that the maximal dopamine blockade by pimozide would coincide with the peak response to dextroamphetamine, it was decided that pimozide should be given two hours prior to amphetamine.

Alphanoradrenergic Blockade

Thymoxamine was chosen as the preferred noradrenergic blocking drug, as it is a relatively selective alpha 1 postsynaptic noradrenergic antagonist. It is available in both parenteral and oral form. Intravenous thymoxamine was given either immediately prior to dextroamphetamine or ninety minutes after the dextroamphetamine, at a dose of 0.1 mg per kilogram. Oral thymoxamine was given at a dose of 80 or 160 mg one hour prior to dextroamphetamine. The oral route proved the more suitable.

1.9.2. Experimental design

In experiments A and C, when the effects of the blocking drugs alone were investigated, both doses of the active drugs or their placebo were administered at 1700 hours and measurements were taken for the three combinations for the following five hours.

In both Experiments B and D, dextroamphetamine 20 mgs or its placebo was given at 1800 hours. In Experiment B, either 2 or 4 mg of pimozide or pimozide placebo was given at 1600 hours. In Experiment D, either 80 or 160 mg of thymoxamine or thymoxamine placebo was given at 1700 hours. Thus there were four drug combinations for each experiment. See table 1.3.

TABLE 1.3.

Experiment B		Experiment D	
1600hr	1800hr	1700hr	1800hr
PMZ Placebo	dAMP Placebo	TMX Placebo	dAMP Placebo
PMZ Placebo	dAMP 20mg	TMX Placebo	dAMP 20mg
PMZ 2mg	dAMP 20mg	TMX 80mg	dAMP 20mg
PMZ 4mg	dAMP 20mg	TMX 160mg	dAMP 20mg

Dosage schedule for dextroamphetamine, pimozide and thymoxamine used in experiments B and D.

All drugs were given in a double blind manner. The schedules were randomised using a Latin square design.

1.10. Statistical Analysis

The data for all dimensions was converted to change scores by subtracting each value from the value scored by the subject at the commencement of the experiment, thereby allowing within subject statistical comparison. Two reference times were considered. Values just prior to the dose of dextroamphetamine or its placebo (1800 hours) was used to gauge the effect of the blocking drugs on the response to dextroamphetamine. Data was also assessed using an earlier reference time for change scores (1700 hours), this being one hour prior to the dextroamphetamine dosage. This latter reference time was used in order to expose any changes in basal state recordings caused by the blocking drugs occurring prior to the dextroamphetamine dose and thereby influencing reference values.

In experiments B and D the change scores with the three active dextroamphetamine combinations were compared with the placebo blocker - placebo dextroamphetamine combination. In a like manner, the placebo blocker - dextroamphetamine 20mg combination was compared with the active blocker - dextroamphetamine 20mg combination to determine the effect of the blocker on dextroamphetamine response. Subjective data (ie, that arising out of measures of changes in mental state using the visual analogue ratings scales) in experiments B and D were exposed to statistical analysis using the nonparametric Wilcoxon paired rank difference test for each time measurement. As the numbers were so small in

experiments A and C, Student's t test for matched pairs was used.

Differences between means of changes of all other data were tested using Student's t test for matched pairs. Statistical significance was taken at $P < .05$. Probability was calculated using the two tailed test.

1.11. Ethical Matters and Informed Consent

The protocol of the experiment was presented to, and approved by, the Ethics Committee, St. Bartholomews' Hospital teaching group. Informed consent was given by all subjects who participated in the experiment. Subjects were excluded from participation if it was felt there may be some risk involved.

Results

RESULTS

1.12. Dextroamphetamine Induced Arousal: Psychological and Psychophysiological Aspects

1.12.1. Introduction

Results from experiments B and D in which dextroamphetamine was given alone (placebo blocker - dextroamphetamine 20 mg) have been pooled and compared with placebo only (placebo blocker - placebo dextroamphetamine), thus giving 24 subjects in all.

All data has been converted to change scores. Graphical presentation will show differences of mean change scores from the placebo combination unless placebo conditions were exerting a significant influence. As the direction of response can be anticipated from earlier studies, the one tailed test for estimating statistical significance was used.

1.12.2. Results

The mean plasma levels of dextroamphetamine are seen in figure 1.3. The maximum levels occurred between 2 and 4 hours after administration.

Psychological data

The elevation of visual analogue scale ratings of happiness and irritability was quite modest. See figure 1.4. The elevation of different ratings of arousal however, with the exception of restlessness, was much more marked; the rise in ratings was statistically significant at virtually all recording times. See figure 1.5.

The dextroamphetamine dosage also influenced the subjects' sleep during the night following the experiment. The difference in the five point scale measuring impaired sleep was +2.1, ($P < .01$).

Pyschophysiological data

Dextroamphetamine induced a significant rise when compared with placebo in all measures apart from diastolic blood pressure and log skin conductance levels. The differences in mean changes in pulse rate and systolic blood pressure were highly significant after one hour. See figure 1.6. Placebo conditions affected log skin conductance levels only. Dextroamphetamine, in comparison, produced a modest rise in levels 2.5 hours after administration. On the other hand the number of spontaneous fluctuations in skin

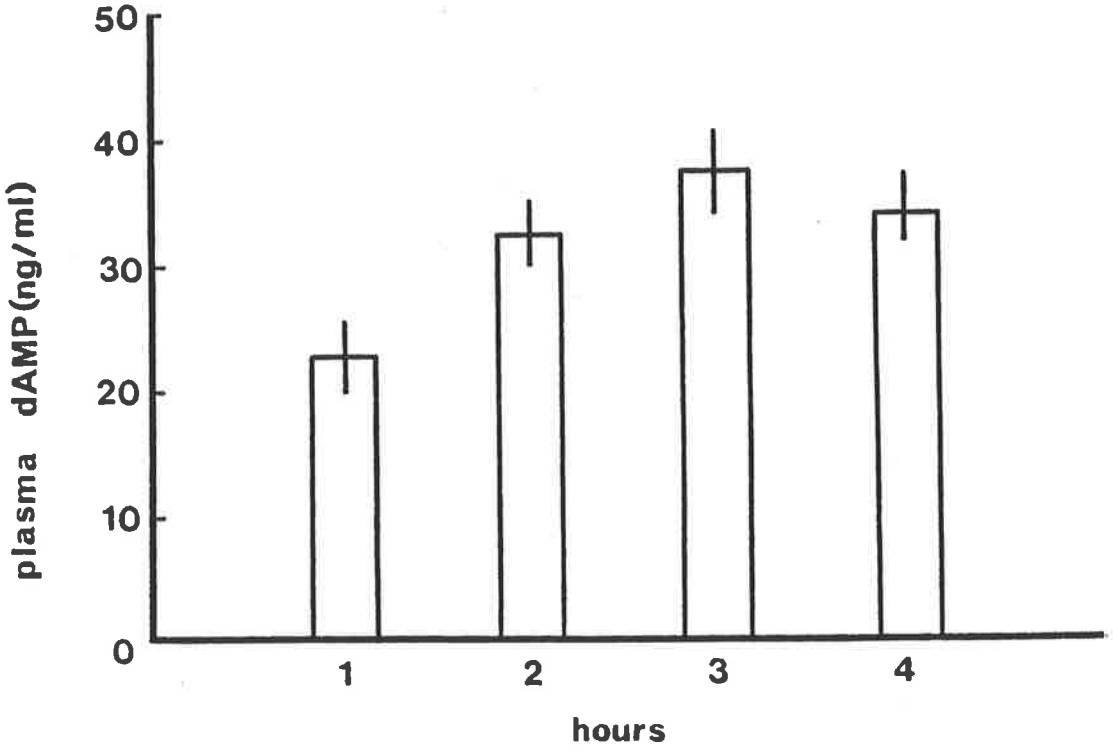

Figure 1.3 Mean (± SEM) plasma dAMP levels (ng/ml) following oral dAMP 20mg at 0 (1800) hours (18 subjects).

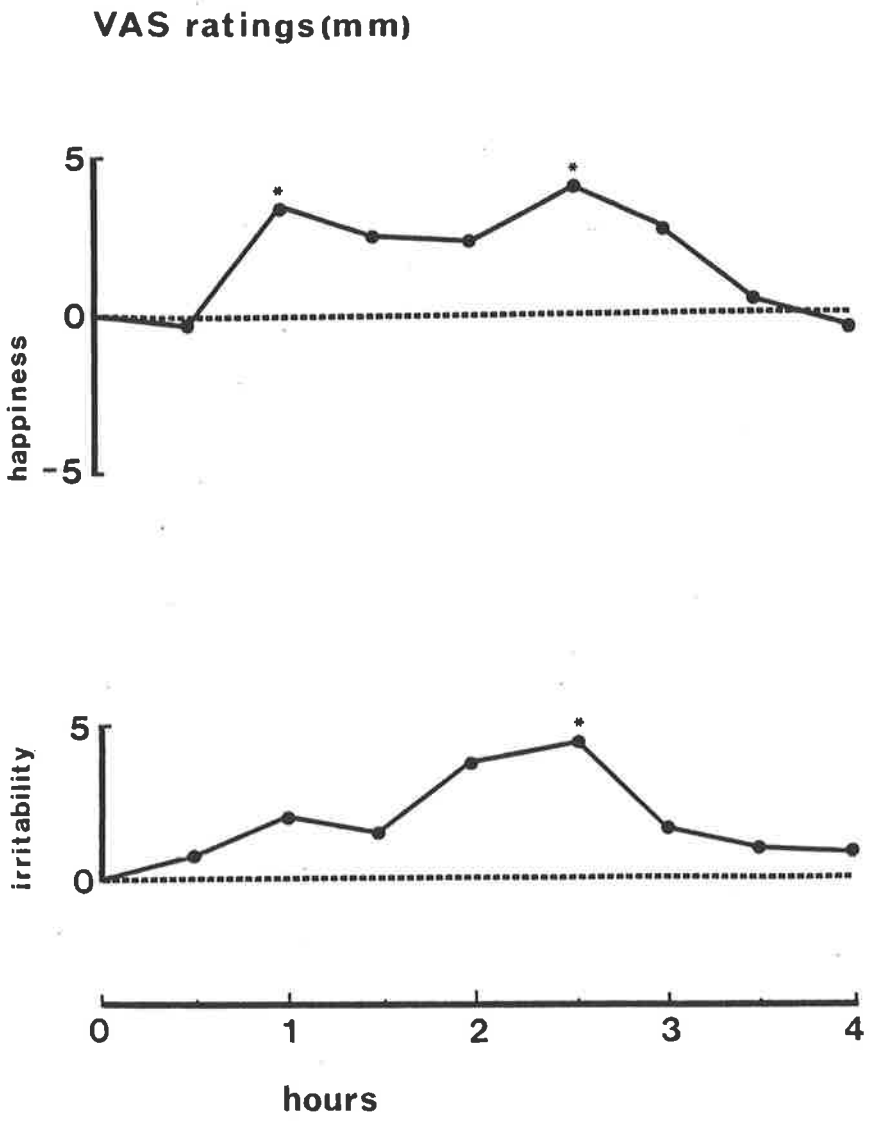

Figure 1.4 Difference in mean changes in VAS ratings (0 - 100mm) from placebo (x axis) in the miserable - happy and placid - irritable dimensions following oral dAMP 20mg given at 0 (1800) hours:

Difference versus placebo. *P <.05

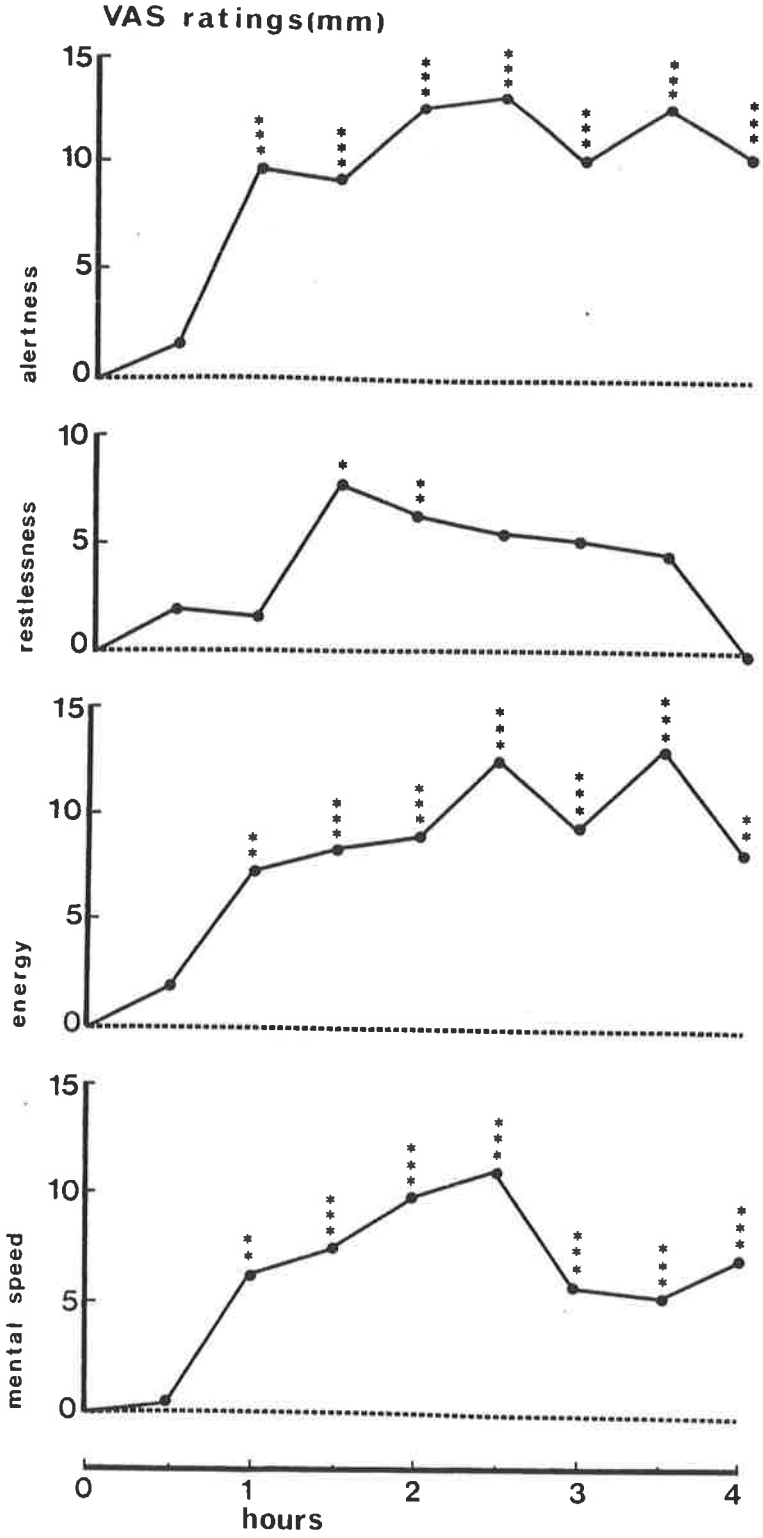

Figure 1.5 Difference in mean changes in VAS ratings (0 - 100mm) from placebo (x axis) in the drowsy-alert, restful-restless, lethargic-energetic and mentally slowed-mind racing dimensions following oral dAMP 20mg given at 0 (1800) hours.

Difference versus placebo. *P < .05 **P < .02 **P < .01

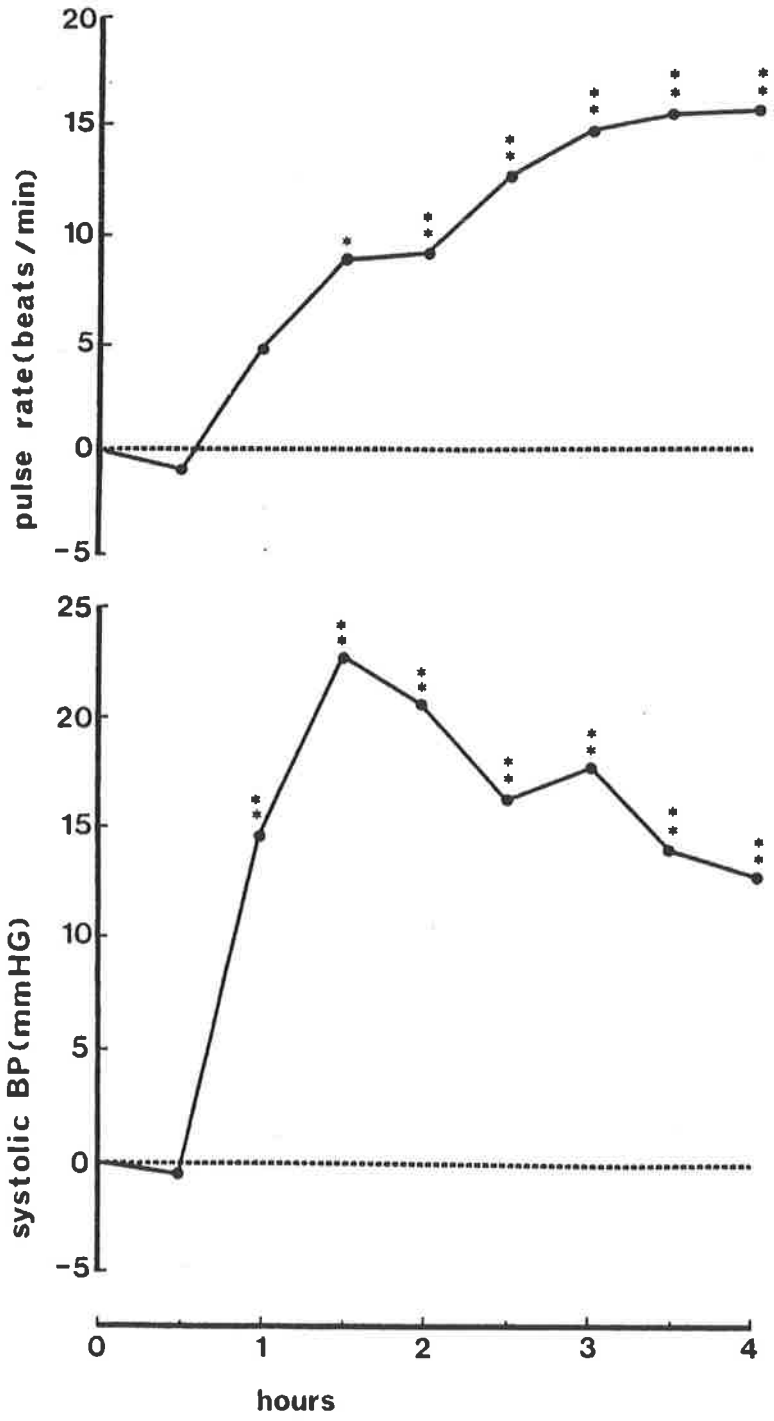

Figure 1.6 Difference in mean changes in pulse rate (beats/min) and systolic blood pressure (mm Hg) from placebo (x axis) following oral dAMP 20mg given at 0 (1800) hours:

Difference versus placebo. *P < .0025 **P < .001

conductance was increased by dextroamphetamine administration, particularly in the latter part of the study period. See figure 1.7.

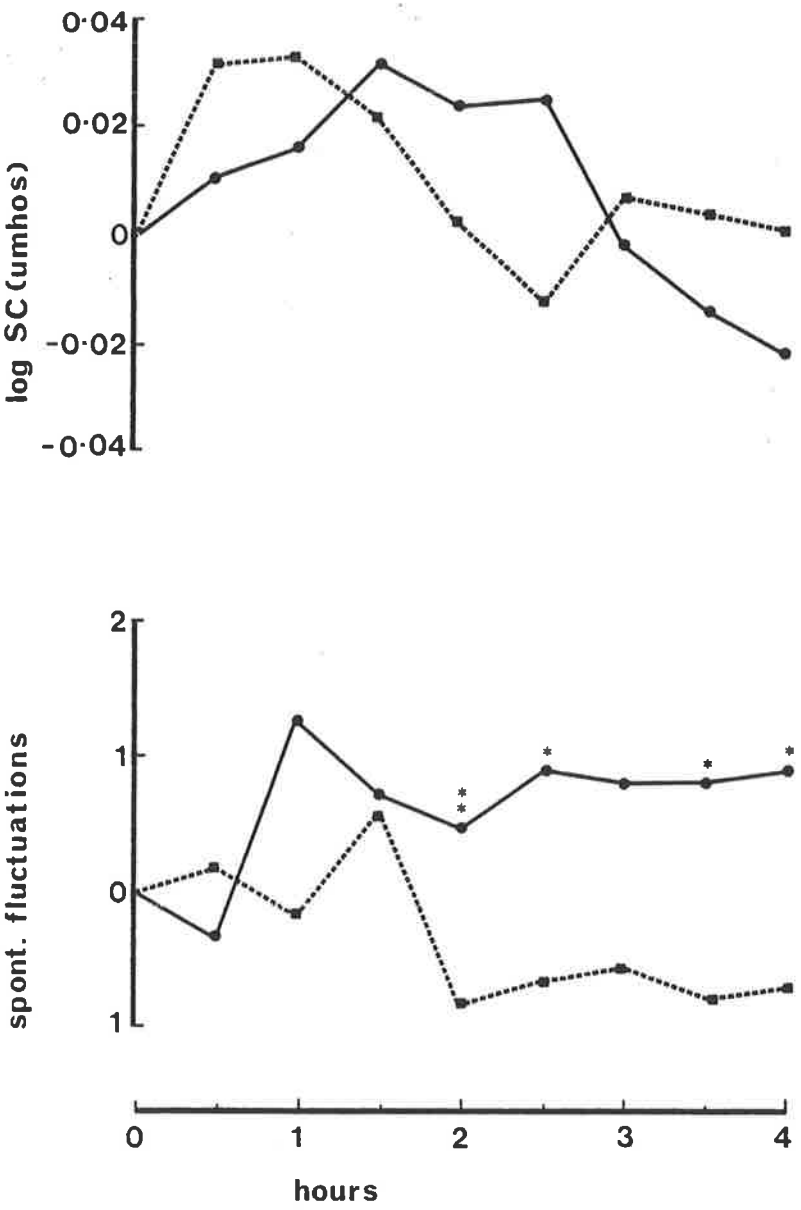

Figure 1.7 Mean changes in log SC (μmhos) and the number of spontaneous fluctuations in skin conductance following oral dAMP 20mg given at 0 (180 0) hours.

placebo

dAMP 20mg

Difference versus placebo. *P < .05 **P < .025

1.12.3. Discussion

The increase in ratings of mood and arousal and in most of the psychophysiological measures used, by dextroamphetamine 20 mg, is generally consistent with other studies.

The considerable difference in degree of subjective response comparing mood with arousal ratings is surprising and not reported in other studies (Smith and Davis, 1977; Silverstone et al, 1983), though less mood than arousal changes were observed by Silverstone et al (1980).

Increased irritability and happiness are to a degree oppositional. Checkley (1978) when studying the mood elevating and antidepressant effect of methylamphetamine, commented that mental state changes following amphetamine may be mixed over time or even at the same time, which may affect measurement using analogue scales.

The increases in most psychophysiological measures are likewise consistent with other studies (Martin et al, 1971; Morselli et al, 1978; Goldstein et al, 1983; Nurnberger et al, 1984). Other workers have similarly reported either a modest or no clear increase in skin conductance levels following dextroamphetamine (Zahn et al, 1975; 1981; Rapoport et al, 1980). The variability of response is demonstrated when skin conductance levels following dextroamphetamine in experiments B and D are compared. Skin conductance levels were significantly accentuated when compared with placebo in experiment B but not in experiment

D. See 1.13.4.b. and 1.14.4.b.

Although increases in pulse rate and systolic blood pressure may reflect peripheral activity of dextroamphetamine, changes in skin conductance measures are more likely to reflect central changes in arousal. Skin conductance changes are mediated by a cholinergic sympathetic pathway (Venables and Christie, 1980). Dextroamphetamine appears to have no direct action on cholinergic neurones (Moore, 1977).

The marked elevation of arousal induced by dextroamphetamine 20 mg given orally, measured both psychologically and psychophysiologically, implies that stimulation of catecholamine receptors in this study was occurring at post synaptic rather than at presynaptic sites. The latter may occur when a very low dose of amphetamine is given. See introduction Part III (1.2.5.).

The results in this section will be reconsidered in Part III when the response to dextroamphetamine will be compared with the known phenomena, psychobiological changes and pharmacological correlates of mild mania.

1.13. The Role of the Dopamine Pathways in Dextroamphetamine Induced Arousal

1.13.1. Introduction

This section reviews the results of experiments B and D in which the effects of pretreatment by pimozide on the psychological and psychophysiological response to oral dextroamphetamine were measured. The effects of pimozide when given alone and the possible effects of pimozide on the pharmacokinetics of dextroamphetamine will be considered first.

All data has been converted to change scores, with the reference time being 1800 hours. Graphical presentation of data will normally show differences of mean changes in scores from the placebo - placebo combination, unless placebo conditions were exerting an influence. Graphs will only be presented in those dimensions where a substantial effect was recorded. The effect of pimozide 2 mg will not be demonstrated graphically if its influence was similar to the higher dose. Tables provide data at the times of maximum response to dextroamphetamine and the time of maximum influence by pimozide. Tabulated measures include +- Standard Error Measurement. It can be assumed that the influences of the drugs at other times are similar unless otherwise stated in the text. Statistical probability was estimated using the 2 tailed test.

1.13.2. Results

a. Pimozide alone

i. Psychological measures

Mood

Pimozide alone produced no consistent response in the four subjects in the visual analogue scale ratings of happiness or arousal.

Arousal

In the various dimensions reflecting arousal and hyperactivity, pimozide 4 mg tended to elevate ratings in the mental speed dimension and both doses elevated scores in the restlessness dimensions. No changes reached statistical significance.

ii. Psychophysiological measures

Cardiovascular measures

Both doses of pimozide tended to reduce pulse rate and diastolic blood pressure but increase systolic blood pressure. Though the pattern of responses was reasonably consistent over time, only one reading reached statistical significance - diastolic blood pressure at 4.5 hours -6.2(+-1.2) mm HG, $P < .02$.

Skin galvanometry

Log skin conductance levels were modestly elevated following placebo alone. Both doses of pimozide lead to a noticeable drop in log skin conductance levels which increased during the experiment. This reached statistical significance in the last hour following pimozide 2 mg and in the last hour and a half following pimozide 4 mg. See figure 1.8. The differences from placebo at four hours were: pimozide 2 mg -0.40(+-0.09) and pimozide 4 mg -0.41(+-0.09), $P < .025$, and at four and a half hours: pimozide 2 mg -0.53(+-0.08) and pimozide 4 mg -0.41(+-0.05), $P < .01$.

No consistent changes were observed in the number of spontaneous fluctuations in skin conductance.

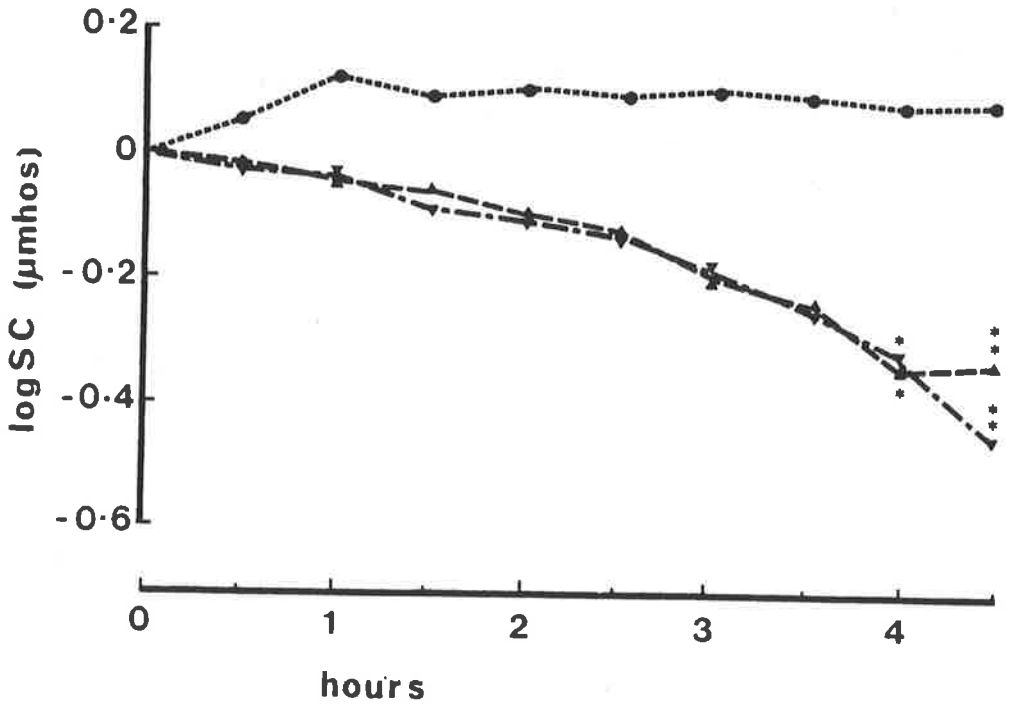

Figure 1.8 Mean changes in log SC (μmhos) following PMZ 2mg, PMZ 4mg given at 0 (1800) hours.

placebo
PMZ 2mg
PMZ 4mg

Difference versus placebo. *P <.025 **P <.01

b. Pharmacokinetic study

Neither dose of pimozide significantly affected serum dextroamphetamine levels indicating that any alterations of the dextroamphetamine response due to pimozide were not reflecting changes in the pharmacokinetics of dextroamphetamine. See figure 1.9.

Mean (+-SEM) area under the curve estimates are as follows:

dAMP 20 mg: 89.5(+-10.2)

PMZ 2 mg +
dAMP 20 mg: 81.3(+-11.7)

PMZ 4 mg +
dAMP 20 mg: 89.0(+-8.3)

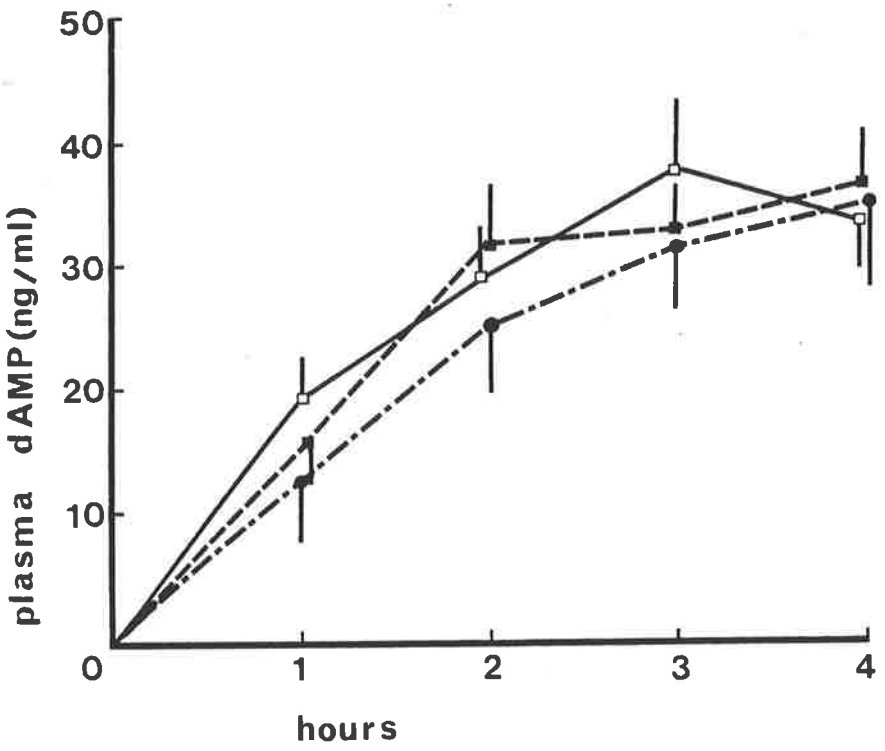

Figure 1.9 Mean (± SEM) plasma (ng/ml) following pretreatment by pimozide given 2 hours prior to the dAMP dosage given at 0 hours:

PMZ placebo - dAMP 20mg
PMZ 2mg - dAMP 20mg
PMZ 4mg - dAMP 20mg

c. The influence of pimozide pretreatment on the response to dextroamphetamine.

i. Psychological measures

Mood scales

The 12 subjects in experiment B recorded only a modest rise in the miserable - happy and placid - irritable dimensions, when dextroamphetamine 20 mg alone is compared with the placebo - placebo combination; the rise did not reach statistical significance. Pretreatment with either dose of pimozide failed to cause any consistent change to the dextroamphetamine response.

Arousal

Dextroamphetamine 20mg alone when compared with placebo caused a significant rise in the mean changes in visual analogue scale ratings in the drowsy - alert and lethargy - energetic, dimensions only. The rise in the restful - restless and mentally slow - mind racing dimensions were modest and failed to reach statistical significance.

Pretreatment with the higher dose of pimozide given two hours prior to dextroamphetamine, evoked a small drop in some parameters, and a small apparent rise in the drowsy - alert dimension, none of which reached statistical significance (See Table 1.4.). The changes in the energy and restlessness dimensions are graphically illustrated in figures 1.10 and 1.11.

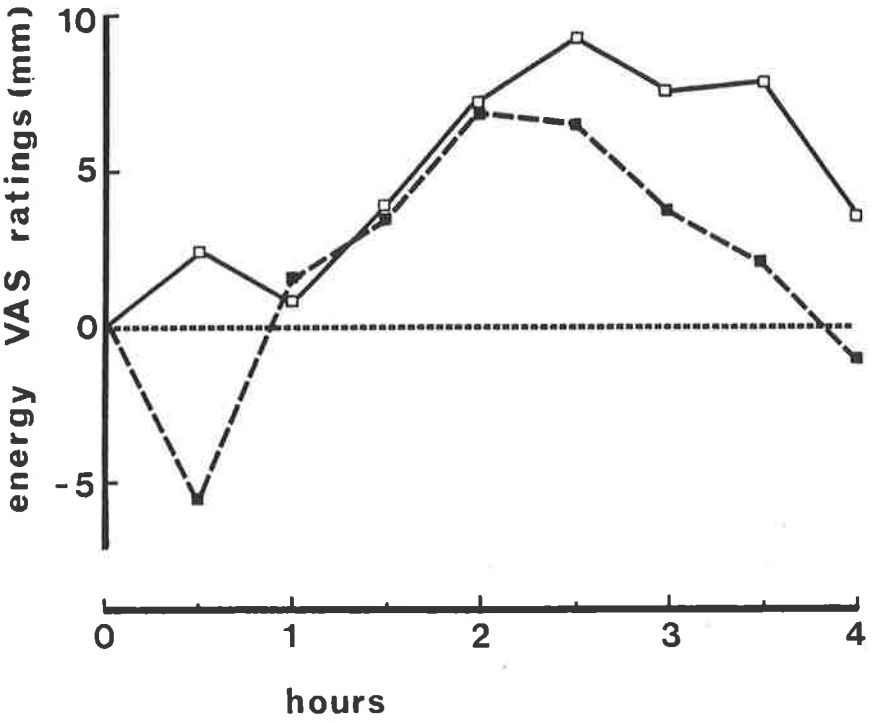

Figure 1.10 Differences in mean changes in VAS ratings (0 - 100mm) from the PMZ placebo - dAMP placebo combination (x axis) on the lethargic - energetic dimension demonstrating the effect of PMZ 4mg 2 hours earlier on the response to oral dAMP 20mg given at 0 (1800) hours.

PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

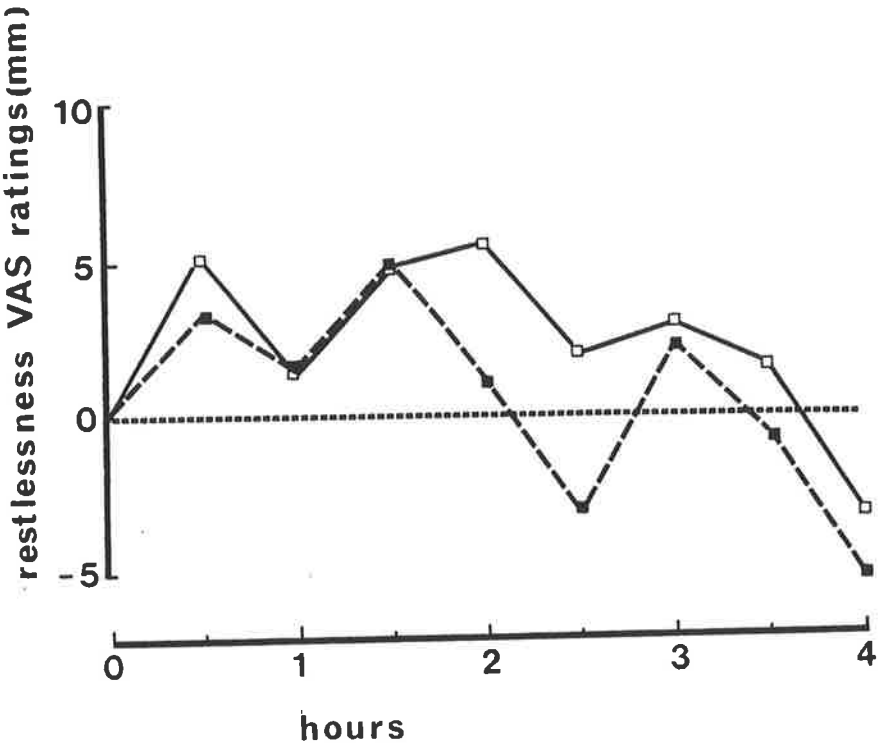

Figure 1.11 Differences in mean changes in VAS ratings (0 - 100mm) from the PMZ placebo - dAMP placebo combination (x axis) in the restful - restless dimension demonstrating the effect of PMZ 4mg given 2 hours earlier on the response to oral dAMP 20mg given at 0 (1800) hours.

PMZ placebo - dAMP 20mg

PMZ 4mg - dAMP 20mg

Table 1.4. Arousal Ratings

Dimension	PMZ Plac dAMP Plac	PMZ Plac dAMP 20mg	PMZ 2mg dAMP 20mg	PMZ 4mg dAMP 20mg
drowsy - alert		**	**	*
2h	-3.1	+8.7	+16.4	+16.6
4h	+0.8	+7.0	* +9.3	+6.3
lethargy - energy		*		
2.5h	-0.2	+9.0	+4.7	+6.4
3.5h	-0.9	* +7.0	+2.9	+1.1
ment.slow - mind racing				
1h	+2.1	+5.7	+5.3	+1.8
2.5h	+0.5	+11.0	+9.3	* +13.5
restful - restless				
2h	+1.8	+7.4	+8.7	+3.1
2.5h	+3.4	+5.4	+5.5	+0.3

Mean changes from 1800 hours at the times of maximum response to dextroamphetamine and at the time of maximum influence by pimozide pretreatment. * $P < .05$, ** $P < .02$, comparing the active drug combinations with placebo - placebo.

There was no consistent change in the alteration of dextroamphetamine induced sleep response by pimozide.

The data were also analysed to investigate whether pimozide was exerting any sedative action within two hours of its administration (that is before the dextroamphetamine dose) thereby influencing the reference value for comparing change. When 1700 hours was used as the reference time for comparing changes, a mild drop is seen in the drowsy - alert scores by 1800 hours (See Figure 1.12). Although this effect

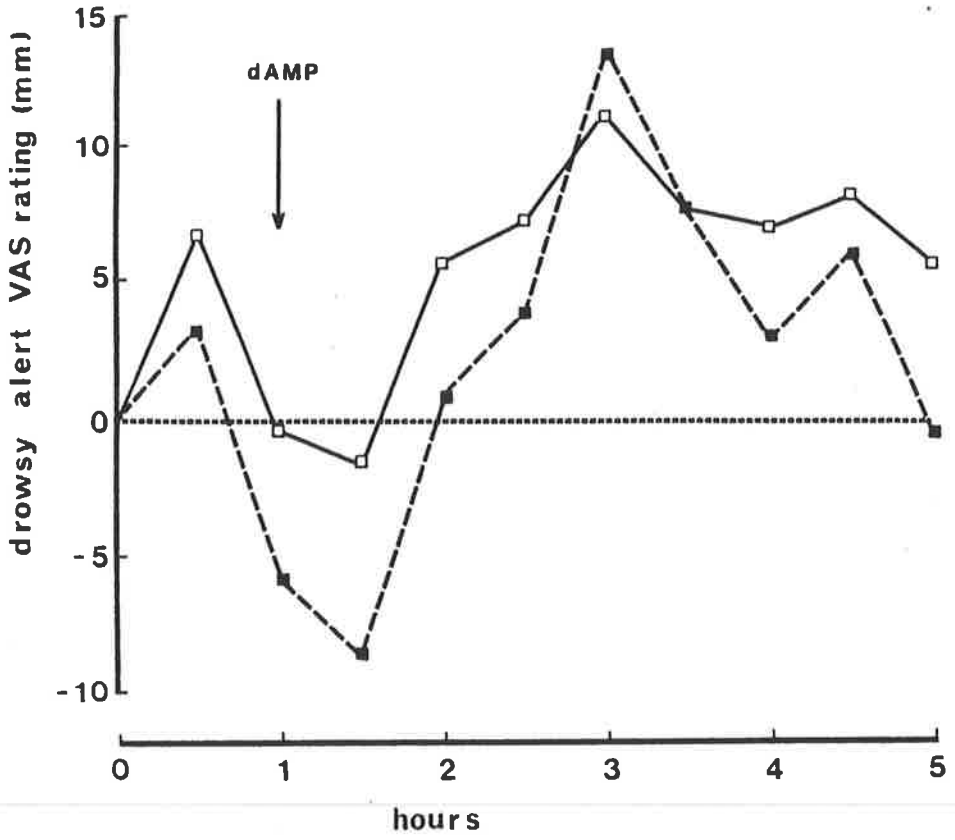

Figure 1.12 Differences in mean changes (0 = 1700 hours) in VAS ratings (0 - 100mm) from the PMZ placebo - dAMP placebo combination (x axis) in the drowsy - alert dimension demonstrating the effect of PMZ 4mg given 2 hours earlier (1600 hours) on the response to oral dAMP 20mg given at 1 (1800) hours:

PMZ placebo - dAMP 20mg

PMZ 4mg - dAMP 20mg

does not reach statistical significance, it can be seen that using this time for comparison in the drowsy - alert dimension pimozide pretreatment causes a late, modest non-significant fall in arousal. Altering the reference time for comparison of changes with the other dimensions did not influence the results.

ii. Psychophysiological Measures

In the twelve subjects in Experiment B, dextroamphetamine administration led to a significant rise in pulse and systolic blood pressure when compared with the placebo - placebo combination. The rise was maximal at two-and-a-half hours after administration. Diastolic blood pressure was not affected by dextroamphetamine nor was any pimozide effect demonstrable in these subjects.

The larger dose of pimozide pretreatment significantly reduced the increase in pulse rate induced by dextroamphetamine. For example at 2.5 hours the difference between the pimozide 4 mg - dextroamphetamine 20 mg and pimozide placebo - dextroamphetamine 20 mg was -7.6(+-2.3) beats /min ($P < .01$). See figure 1.13. Pimozide pretreatment did not appear to influence the systolic blood pressure response to dextroamphetamine. (It should be noted however that if the earlier time for comparison of changes [1700] is used, pimozide pretreatment did modestly but significantly reduce systolic blood pressure, the maximum effect being 2 hours after the dextroamphetamine dose {-4.8[+-2.3] mm HG, $P < .05$}).

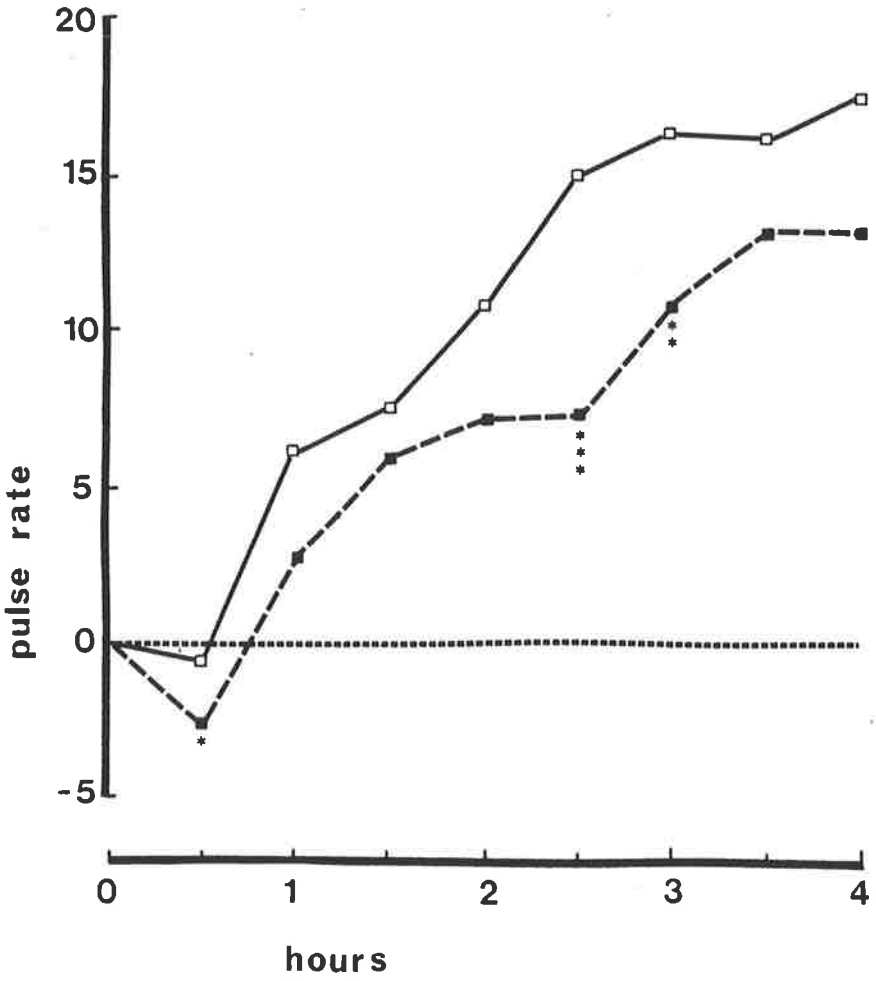

Figure 1.13 Differences in mean changes in pulse rate (beats/minute) from the PMZ placebo - dAMP placebo combination (x axis) demonstrating the effect of PMZ 4mg given 2 hours earlier on the response to oral dAMP 20mg given at 0 (1800) hours:

PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

Difference induced by PMZ on the dAMP response.
*P < .05 **P < .02 ***P < .01

The means of change scores (+- SEM) at the times of the maximum dextroamphetamine response and maximum influence by pimozide are listed in table 1.5.

Table 1.5. Cardiovascular Measures

Dimension	PMZ Plac dAMP Plac	PMZ Plac dAMP 20mg	PMZ 2mg dAMP 20mg	PMZ 4mg dAMP 20mg
pulse (beats/min)		***	***	*
2.5h	-1.4(+-1.6)	+13.6(+-2.4)	+10.6(+-1.7)	+6.0(+-1.7)
		***	***	***
4h	-1.3(+-1.5)	+16.1(+-3.4)	+11.9(+-2.7)	+11.9(+-2.0)
systolic BP mm HG		***	***	*
3h	+2.0(+-1.6)	+21.9(+-2.7)	+18.2(+-2.4)	+23.4(+-2.4)

Mean changes (+- SEM) from 1800 hours at the times of maximum response to dextroamphetamine and the maximum influence by pimozide (when different). * P <.05, ** P <.01, *** P <.001, comparing the active drug combinations with placebo - placebo.

Skin galvanometry

There was a rise in log skin conductance levels following placebo. Dextroamphetamine 20 mg significantly accentuated this rise and this accentuation was attenuated in a dose related manner by pimozide. See table 1.6. This is graphically illustrated in figures 1.14 and 1.15; the latter using differences of means of change scores clearly reveals the effect of pimozide on the dextroamphetamine response.

Table 1.6. Skin galvanometry

Drug condition	PMZ Plac dAMP Plac	PMZ Plac dAMP 20mg	PMZ 2mg dAMP 20mg	PMZ 4mg dAMP 20mg
log SC umhos means of changes				
1945h	+0.071 (+-.044)	+0.143 (+-.047)	+0.087 (+-.035)	+0.058 (+-.035)
diff from plac - plac		+0.072 (+-.035)	+0.016 (+-.033)	-0.010 (+-.043)
means of changes				
2015h	+0.059 (+-.055)	+0.134 (+-.049)	+0.081 (+-.041)	+0.064 (+-.040)
diff from plac - plac		+0.07 (+-.041)	+0.022 (+-.047)	+0.055 (+-.058)

Mean changes and differences from the placebo - placebo combination in log skin conductance levels (umhos) at the times of maximum response to dextroamphetamine and the maximum influence by pimozide.

The maximum influence by pimozide pretreatment on the dextroamphetamine induced changes in log skin conductance levels was at 1945 hours; -0.085(+-0.037) umhos, $P < .05$.

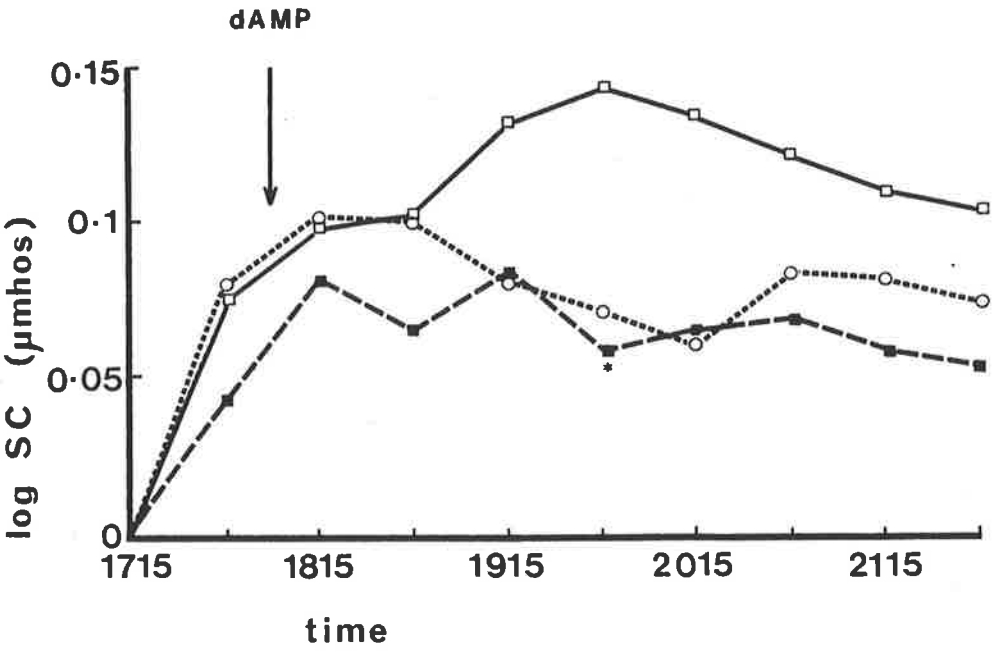

Figure 1.14 Mean changes in log SC (μmhos) in the response to oral dAMP 20mg given at 1800 hours following PMZ given at 1600 hours:

PMZ placebo - dAMP placebo
PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

Difference induced by PMZ 4mg pretreatment on the dAMP response.
*P < .05

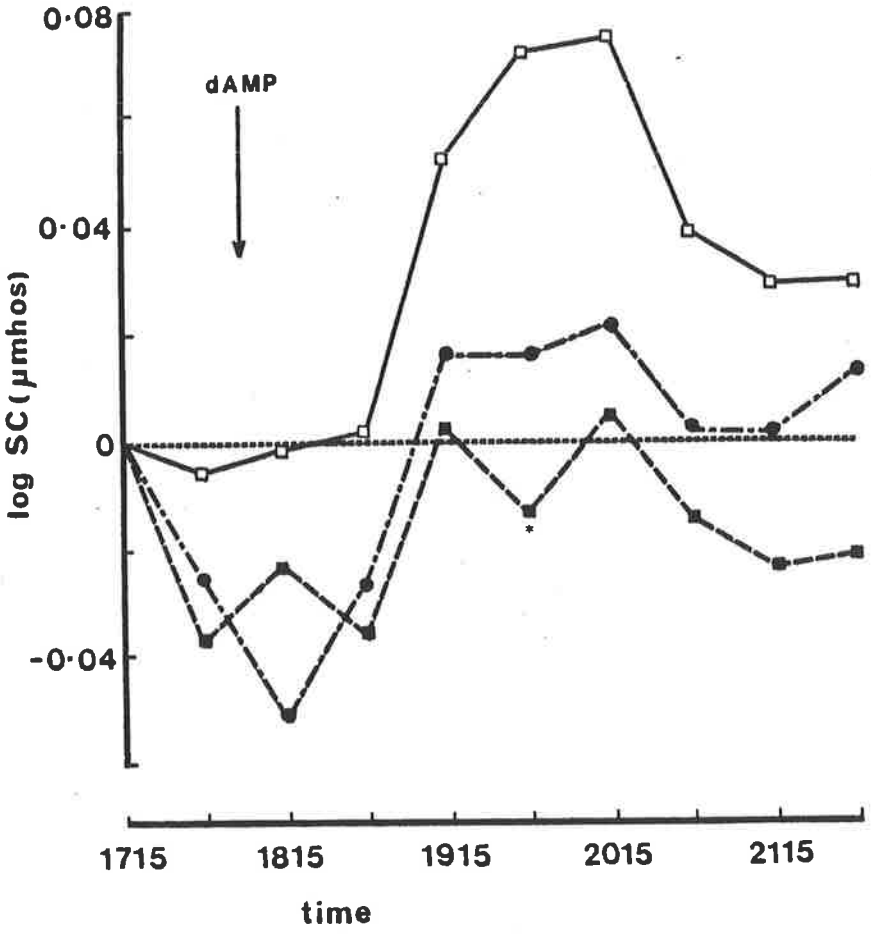

Figure 1.15 Differences in mean changes in log SC (µmhos) from the PMZ placebo - dAMP placebo combination (x axis) in the response to oral dAMP 20mg given at 1800 hours following PMZ 2mg and PMZ 4mg given at 1600 hours:

PMZ placebo - dAMP 20mg
PMZ 2mg - dAMP 20mg
PMZ 4mg - dAMP ·20mg

Difference induced by PMZ pretreatment on the dAMP response.
*P < .05

The number of spontaneous fluctuations in skin conductance did not change after placebo. Mean changes in scores (+-SEM) are recorded in table 1.7. and illustrated graphically in figure 1.16. Dextroamphetamine 20 mg produced a significant rise in the number of spontaneous fluctuations when compared with the placebo - placebo conditions at most readings. This rise was attenuated in part by pimozide, particularly by the higher dose. The maximum influence by pimozide was at three hours; -2.20(+0-.85), P <.025.

Table 1.7. Spontaneous fluctuations

Drug conditions	PMZ Plac dAMP Plac	PMZ Plac dAMP 20mg	PMZ 2mg dAMP 20mg	PMZ 4mg dAMP 20mg
spont. fluct no.				
2.5h	-0.3(+-0.67)	+1.5(+-1.0) **	+0.3(+-0.9)	-0.7(+-1.0)
3h	-0.7(+-0.5)	+1.9(+-0.8) **	+1.3(+-1.0)	+1.4(+-1.0)

Mean changes (+-SEM) in the number of spontaneous fluctuations in skin conductance, from 1800 hours, at the times of maximum response to dextroamphetamine 20mg and maximum influence by pimozide pretreatment. * P<.05, ** P<.01, comparing the active drug combinations with placebo - placebo.

In summary, the only demonstrable effect of pimozide alone was a reduction in log skin conductance levels. Pimozide pretreatment did not affect plasma dextroamphetamine levels.

The effect of pimozide pretreatment on the dextroamphetamine response measured by psychological ratings was modest with some tendency to reduce ratings; no effect

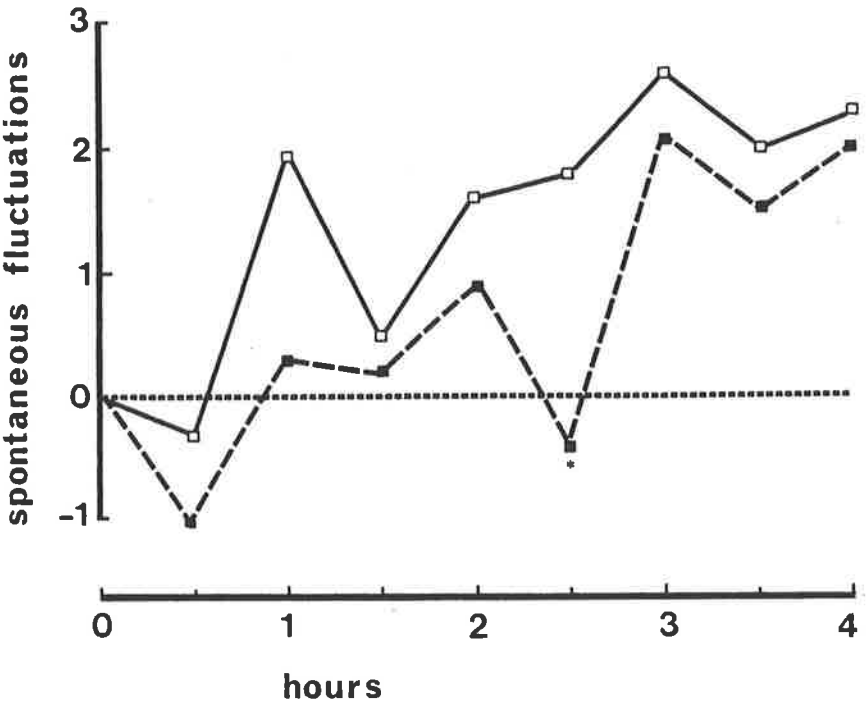

Figure 1.16 Differences in mean changes in the number of spontaneous fluctuations in skin conductance from the PMZ placebo - dAMP placebo combination (x axis) demonstrating the effect of PMZ 4mg given 2 hours earlier on the response to oral dAMP given at 0 hours:

PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

*P < .05

was statistically significant. Pimozide pretreatment did, however, reduce dextroamphetamine arousal measured psychophysiologically; reducing pulse rate systolic blood pressure, log skin conductance levels and the number of spontaneous fluctuations in skin conductance. This effect is particularly apparent if an earlier time for estimation of change values was used.

1.13.3. Discussion

Pimozide when given alone had little consistent effect on the various psychological ratings or psychophysiological measures apart from skin conductance levels. This may be a reflection of some sedating action of the drug.

This study failed to demonstrate any effect by pimozide on dextroamphetamine induced mood changes and thus did not replicate the findings of Jonsson (1972). In that study pimozide blocked the mood elevating effect of very high doses of intravenous dextroamphetamine.

The visual analogue scale ratings of the different arousal - hyperactivity dimensions demonstrated the stimulatory action by dextroamphetamine. Pimozide tended to reduce this but this trend failed to reach statistical significance. Pimozide failed to influence significantly the rating of the quality of sleep during the night following the experiment. However pimozide pretreatment lead to a drop in the psychophysiological measures of the dextroamphetamine response.

Neither Rosenblatt et al (1979) nor Nurnberger et al (1984) were able to demonstrate an attenuation of the cardiovascular response to intravenous dextroamphetamine by pimozide or the related dopamine blocker haloperidol. In the latter study though, haloperidol attenuated the rise in subjective arousal.

The site of action of pimozide on cardiovascular measures

is unclear, however the reduction in skin conductance measures presumably reflects a central action. As mentioned earlier, skin conductance changes are mediated by cholinergic sympathetic fibres (Venables and Christie, 1980). Pimozide is a specific centrally acting dopamine blocking drug and like dextroamphetamine has no direct action on cholinergic neurones (Pinder et al, 1976; MacKay, 1982).

Taking all these results together, it seems reasonable to suggest that dopamine blockade by pimozide attenuated in part at least, the arousal response to dextroamphetamine, implying that such dextroamphetamine induced changes involve dopamine pathways.

These findings are in keeping with previous studies investigating the effect of pimozide on the dextroamphetamine response. Jonsson (1972) reported that pimozide attenuated the mood elevating effect of a large intravenous dose of dextroamphetamine, this attenuation being more specific than that induced by chlorpromazine or thioridazine (Gunne et al, 1972).

Silverstone et al (1980) reported that pimozide attenuated subjective arousal as measured by visual analogue scales in normal young women. In that study the mood elevating effect of dextroamphetamine was too small for an attenuating effect to be measured. In a similar manner Gillin et al (1978[b]) reported that pimozide reduced the sleep-reducing effect induced by dextroamphetamine (not replicated in the present

study).

Although the effect of other neuroleptics on the dextroamphetamine response have not been widely studied in humans, they have been extensively studied in experimental animals. For example, the ability of a drug to block dextroamphetamine induced motor activity and stereotypy, is used as a biological measure of the drugs' potential as a neuroleptic agent (Janssen et al, 1965). Dopamine blockade or interruption of the dopamine pathways selectively attenuates dextroamphetamine induced hyperactivity. (See Introduction 1.4.)

The results of this experiment taken in conjunction with findings of similar experiments both using experimental animals and human studies give further confirmation that dopamine blockade attenuates the arousal and mood elevating effects of dextroamphetamine.

From this can be implied that dopamine pathways are directly involved in arousal in experimental animals and in arousal and mood in humans. This is in keeping with evidence from animal experiments investigating the role of the dopamine pathways using lesions and pharmacological procedures. The findings are also in keeping with other, predominantly pharmacological, studies in humans, which point to the dopamine pathways being involved in states of elevated mood and hyperactivity in both health and disease. See introduction 1.3.4.c.

The role of the dopamine pathways in mania will be discussed in detail in Part III.

1.14. The Role of Noradrenergic Pathways in Dextroamphetamine Induced Arousal

1.14.1. Introduction

This section will review the results of experiments C and D which investigated the effect of pretreatment by thymoxamine on the psychological and psychophysiological responses to dextroamphetamine. The effects of thymoxamine when given alone and the question of whether thymoxamine influences the pharmacokinetics of dextroamphetamine will be considered first.

All data has been converted to change scores. The reference time for change scores is 1800 hours (just prior to the administration of dextroamphetamine or its placebo) unless otherwise specified.

Graphs will be presented only for those dimensions that demonstrated significant changes. When the effects of the smaller dose of thymoxamine were similar to, but quantitatively smaller than the higher dose, they have not been illustrated. When the effect was in a different direction to that induced by the higher dose, the results are shown. In order to make the graphical presentation clearer, data arising from the placebo conditions have only been presented in those cases when placebo exerted an

influence on the results. Rather the data has been presented graphically as differences in the mean changes from the placebo - placebo combination (thereby making the placebo - placebo response the X axis).

All statistical probabilities were calculated either using the Willcoxon paired rank difference test or Student´s t test, using the two tailed test.

1.14.2. Results

a. Thymoxamine alone

i. Psychological measures

Neither dose of thymoxamine produced any consistent change in the miserable - happy dimension. In the irritability ratings, the higher dose tended to elevate, and the lower dose to reduce the scores but neither of these changes reached statistical significance.

Of the different visual analogue scale ratings of arousal and hyperactivity only those scores in the drowsy - alert dimension were elevated by the higher dose of thymoxamine (see figure 1.17.). No consistent change was manifest by either dose of thymoxamine in the other ratings of arousal.

ii. Psychophysiological measures

80 mg of thymoxamine tended to reduce pulse rate and systolic blood pressure while the higher dose lead to a small increase, though again neither change reached statistical significance. The higher dose of thymoxamine reduced diastolic blood pressure and this reached statistical significance at 1 and 4.5 hours, -6.3(+-1.7) and -7.3(+-1.7) mm HG, $P < .05$. See figure 1.18.

Log skin conductance was the only measure in which placebo conditions exerted an influence. The levels were increased after placebo and this rise was attenuated by both doses of thymoxamine. The number of spontaneous fluctuations on the

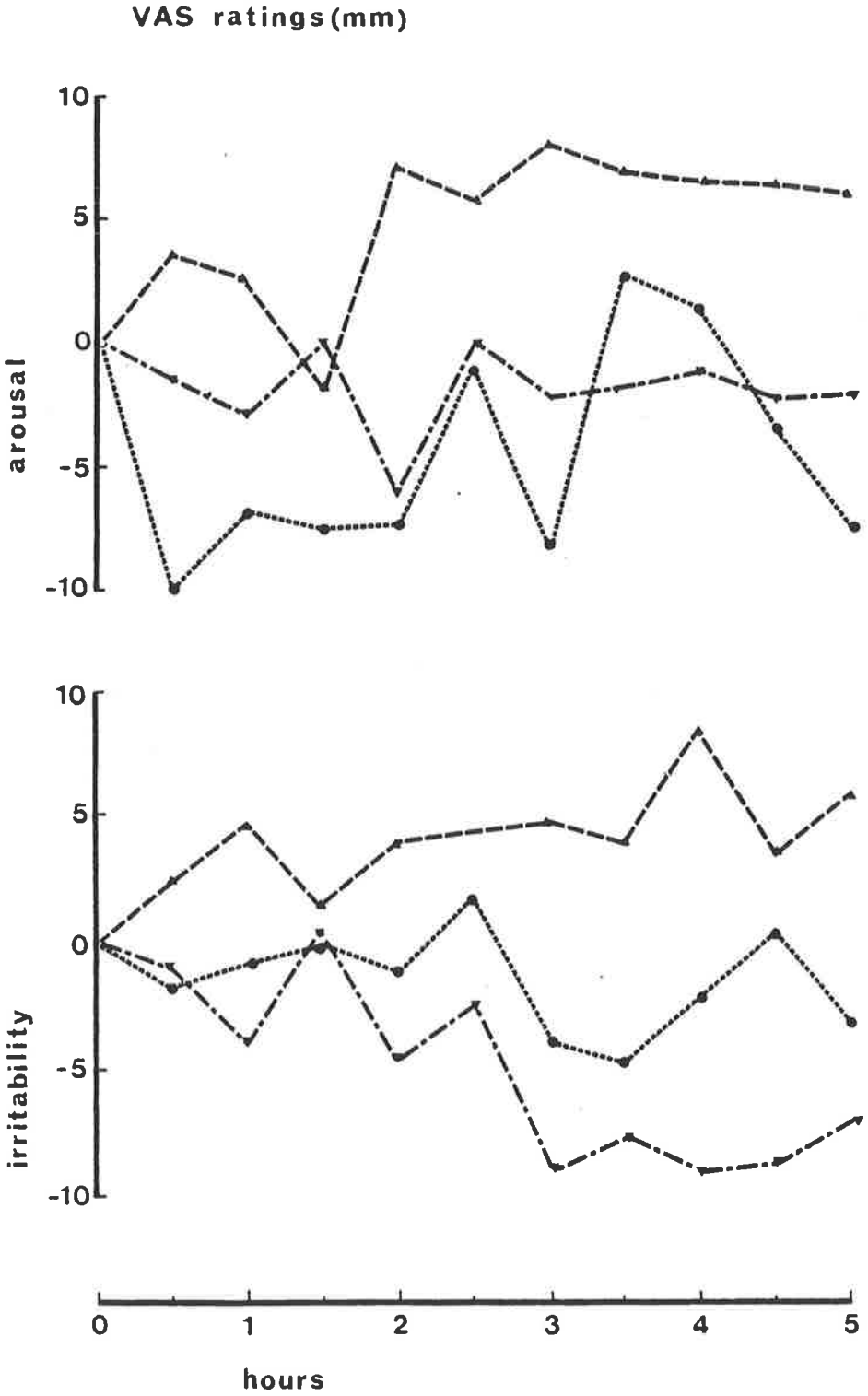

Figure 1.17 Mean changes in VAS ratings (0 - 100mm) in drowsy - alert and placid - irritable dimensions following TMX 80mg and TMX 160mg given at 0 hours:

placebo

TMX 80mg

TMX 160mg

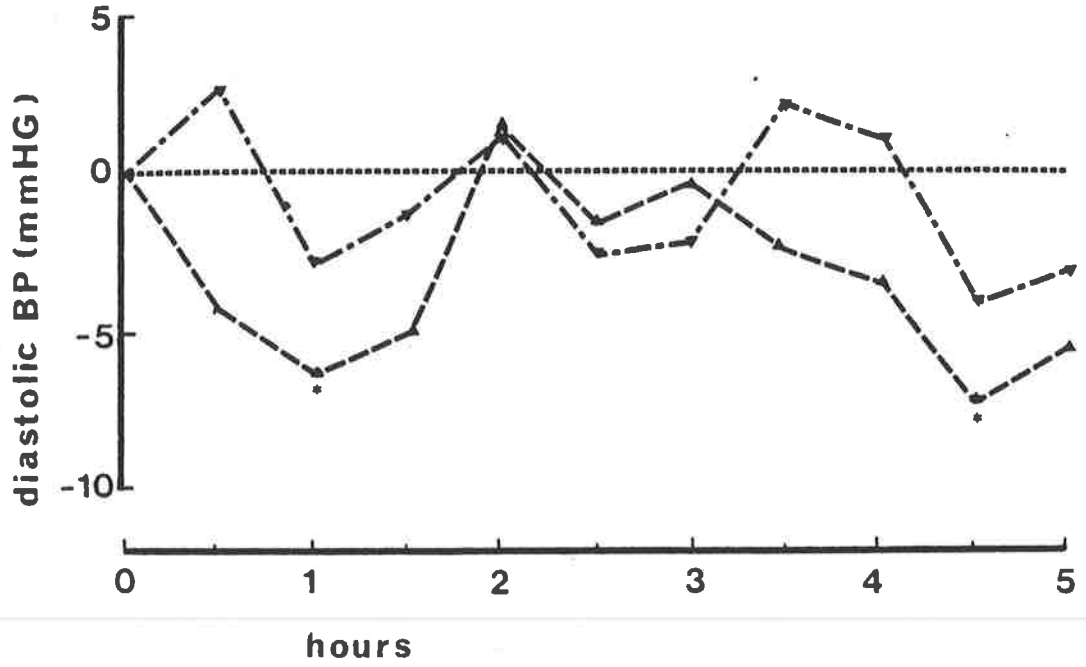

Figure 1.18 Differences in mean changes in diastolic BP (mm Hg) from placebo (x axis) following TMX 80mg and TMX 160mg given at 0 hours:

TMX 80mg

TMX 160mg

Difference versus placebo. *P < .05

other hand tended to rise following both doses of thymoxamine. The relative drop in skin conductance levels and the rise in spontaneous fluctuations measures both failed to reach statistical significance. See figure 1.19.

b. Pharmacokinetic study

Neither dose of thymoxamine significantly affected serum levels of dextroamphetamine indicating that changes induced by thymoxamine in the dextroamphetamine response were not due to changes in the pharmacokinetics of dextroamphetamine. (See figure 1.20.).

Estimates of the areas under the curve (+-SEM) are as follows.

dAmp 20mg: 120.5 (+- 10.3)

TMX 80m +
dAMP 20mg: 105.6 (+-7.1)

TMX 160mg +
dAMP 20mg: 129.0 (+-5.7)

Unfortunately some assay samples were lost. When estimates using matching pairs are compared, no effect by either dose of blocking drug is apparent.

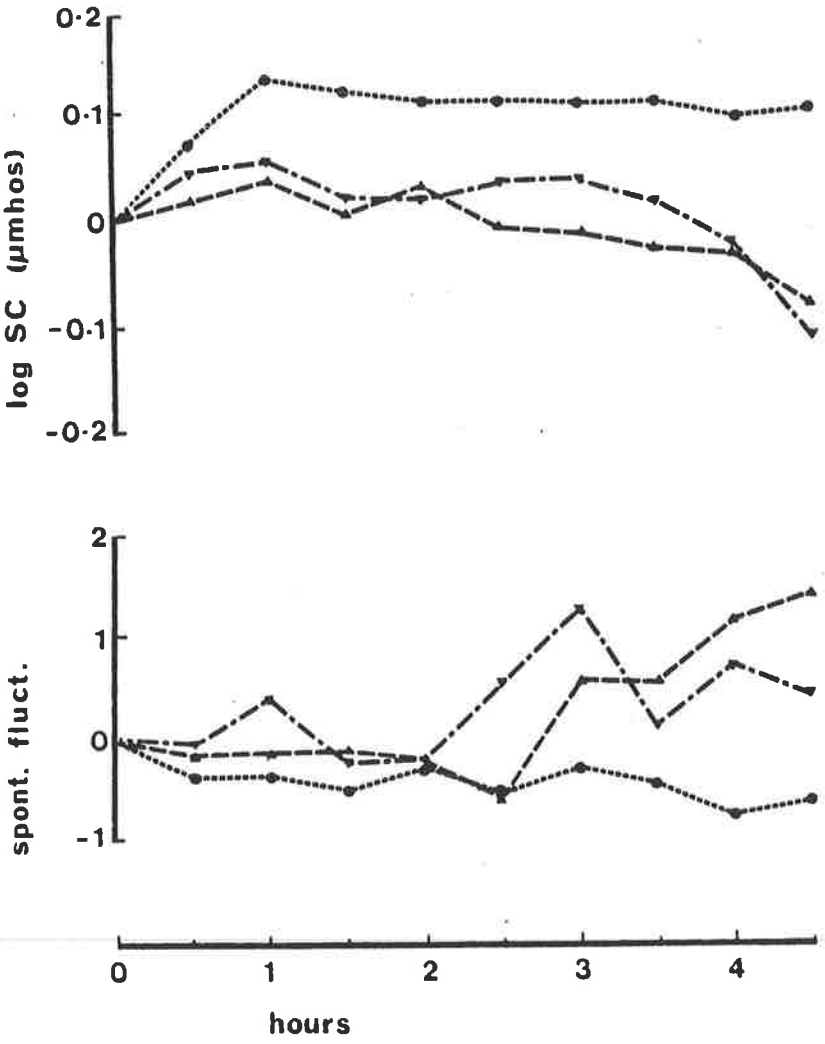

Figure 1.19 Mean changes in log SC (μmhos) and in the number of spontaneous fluctuations in skin conductance following TMX 80mg and TMX 160mg given at 0 hours:

placebo ●·····

TMX 80mg ▼-·-·-

TMX 160mg ▲——

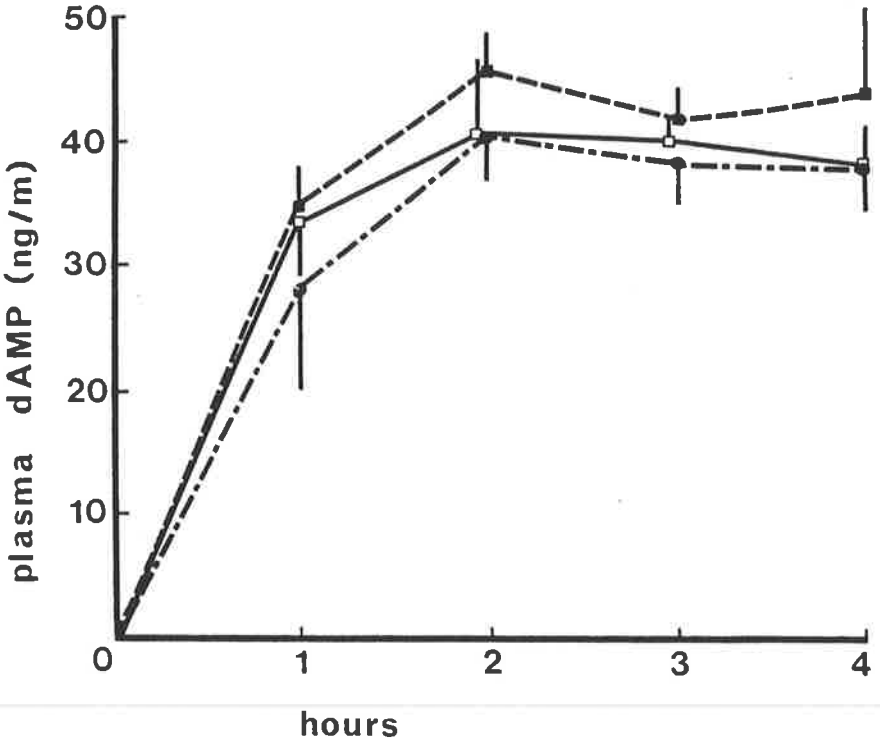

Figure 1.20 Mean (± SEM) plasma dAMP (ng/ml) following pretreatment by thymoxamine given 1 hour prior to the dAMP dosage given at 0 hours (6 subjects):

TMX placebo - dAMP 20mg
TMX 80mg - dAMP 20mg
TMX 160mg - dAMP 20mg

c. The influence of thymoxamine pretreatment on the response to dextroamphetamine

i. Psychological measures

Mood

In Experiment D dextroamphetamine 20 mg led to a modest rise in happiness and irritability ratings when compared with the placebo - placebo combination, though the response was variable (See table 1.8.).

Table 1.8.

Dimension	TMX Plac -dAMP Plac	TMX Plac -dAMP 20mg	TMX 80mg -dAMP 20mg	TMX 160mg -dAMP 20mg
miserable-happy				
2.5h	-1.7	+1.4	+4.0	+2.6
3.5h	-0.6	-0.9	-2.5	+1.5
placid-irritable				
2.5h	-5.4	+2.6	+4.6	+6.6*
3h	-3.6	-3.2	+6.6	+5.7*

VAS ratings of mood dimensions at the times of the maximum response to dAMP and the maximum influence of TMX pretreatment.
* $P<.05$ comparing the active drug combination with the placebo - placebo combination.

The increased irritability following dextroamphetamine 20 mg when compared with the placebo - placebo combination was maximal at 2.5 hours (+8.0, $P < .1$). Thymoxamine 160 mg pretreatment caused a significant increase in irritability compared with the placebo - placebo combination at 2.5 and 3 hours and compared with the placebo - dextroamphetamine 20

mg combination at 3 hours (+8.9, P <.02). See figure 1.21.

Arousal

Dextroamphetamine 20 mg when given alone, caused a rise in the visual analogue scale ratings in the four dimensions reflecting arousal; drowsy - alert, physically inactive - restless, mentally slowed- mind racing, and lethargy - energy. See table 1.9.

TABLE 1.9.

Dimension	TMX Plac dAMP Plac	TMX Plac dAMP 20mg	TMX 80mg dAMP 20mg	TMX 160mg dAMP 20mg
drowsy - alert				
1.5h	-2.5	+8.3**	+9.3**	+15.0***
2.5h	-6.2	+12.2**	+10.0***	+9.6**
restful-restless				
1h	-1.7	+0.2	+6.9	+13.7***
1.5h	-4.1	+6.0	+8.7*	+13.0***
lethargy - energy				
3h	-5.6	+5.6	+11.1	+6.7***
3.5h	-7.6	+10.4***	+5.1	+6.9***
ment. slowed -mind racing				
1h	-2.4	+5.1	+6.7*	+11.4***
2.5h	-2.5	+9.3*	+6.7*	+8.5**

VAS ratings of arousal dimensions at the times of the maximum response to dAMP and the maximum response by TMX pretreatment. *P<.05, **P<.02, ***P<.01, comparing active drug with the placebo - placebo combination.

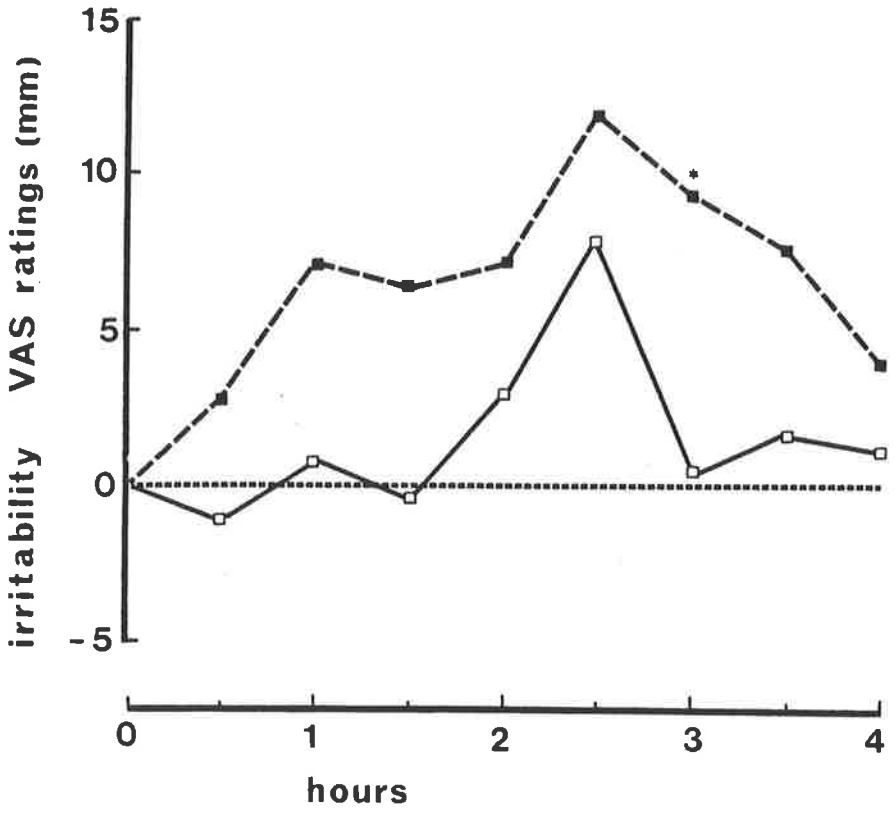

Figure 1.21 Differences in mean changes in VAS ratings (1 - 100mm) from the TMX placebo - dAMP placebo combination (x axis) in the placid - irritable dimension demonstrating the effect of TMX 160mg given 1 hour earlier on the response to oral dAMP 20mg given at 0 hours:

TMX placebo - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX pretreatment on the dAMP response.
*P < .02

Prior treatment with thymoxamine, particularly the higher dose, caused an elevation in ratings when compared with the placebo - placebo combination. 160 mg thymoxamine pretreatment lead to a significant accentuation of the dextroamphetamine response in the restlessness dimension only, maximal at one hour (+13.5, $P < .05$). See figure 1.22.

Thymoxamine pretreatment did not alter the reduction in sleep induced by dextroamphetamine.

ii. Psychophysiological measures

Cardiovascular measures

In the measures of pulse rate, systolic and diastolic blood pressure, dextroamphetamine administration led to a rise in scores when compared with placebo. The maximal difference from placebo occurs at different times, namely four hours (pulse), two hours (systolic blood pressure) and at one and a half hours (diastolic blood pressure). Thymoxamine pretreatment led to a modest rise in both blood pressure measures and a mild drop in pulse rate, none of which reached statistical significance. The values at the time of the maximal change induced by dextroamphetamine and of the maximal difference induced by thymoxamine pretreatment are given in Table 1.10.

A likely peripheral effect of thymoxamine makes it difficult to interpret these changes in terms of alteration in central arousal.

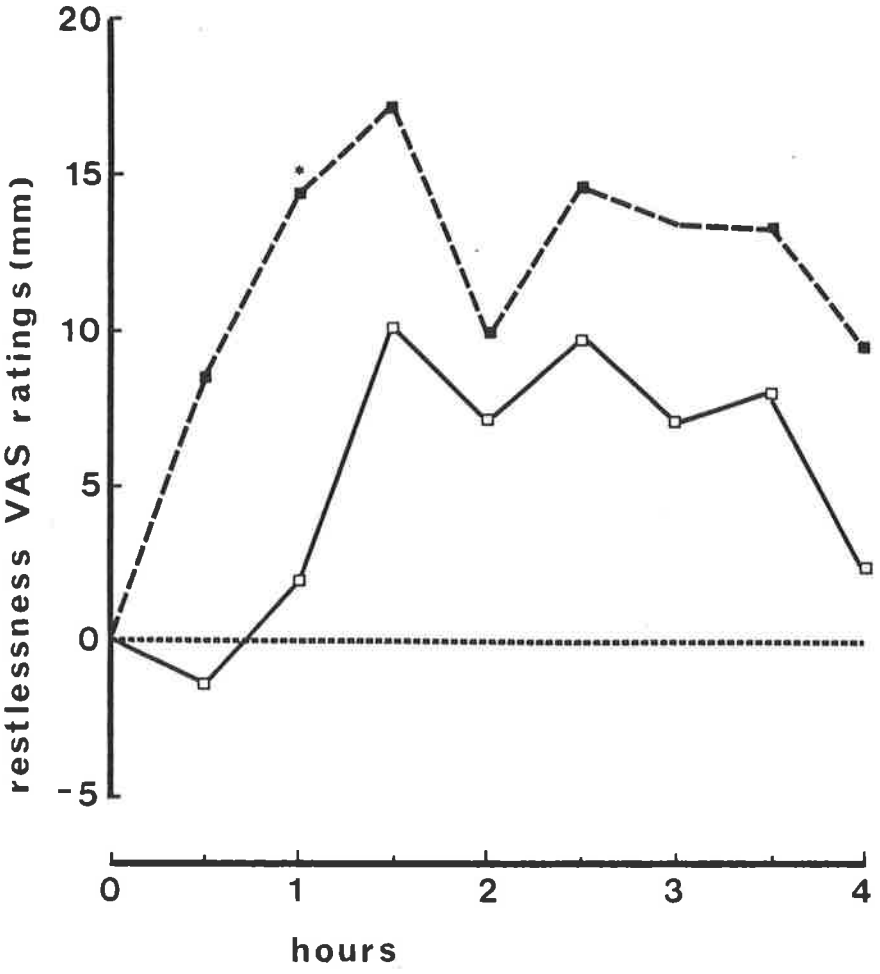

Figure 1.22 Differences in mean changes in VAS ratings (0 - 100mm) from the TMX placebo - dAMP placebo combination (x axis) in the restful - restless dimension demonstrating the effect of TMX 160mg given 1 hour earlier on the response to oral dAMP 20mg given at 0 hours:

TMX placebo - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX pretreatment on the dAMP response.
*P < .05

Table 1.10. Cardiovascular measures.

Dimension	TMX Plac dAMP Plac	TMX Plac dAMP 20mg	TMX 80mg dAMP 20mg	TMX 160mg dAMP 20mg
pulse (beats/min)		*	**	*
2.5h	-1.2(+-1.3)	+8.7(+-3.1)	+9.7(+-3.2)	+4.6(+-2.5)
		**	***	***
4h	-1.4(+-1.3)	+13.0(+-3.7)	+12.4(+-3.0)	+7.8(+-2.0)
systolic - BP mm HG		***	***	***
2h	+5.0(+-2.5)	+24.9(+-2.8)	+28.3(+-2.5)	+23.1(+-2.9)
		*	*	***
3.5h	+2.1(+-2.0)	+15.3(+-2.3)	+21.3(+-2.3)	+20.0(+-3.1)
diastolic BP mm HG		*		**
1.5h	+2.7(+-1.7)	+8.6(+-2.4)	+5.8(+-2.4)	+9.5(+-2.8)
3.5h	+3.6(+-1.7	+1.4(+-2.0)	+3.4(+-1.5)	+6.4(+-2.6)

Means of change scores (+-SEM) from 1800hr at the times of maximum response to dAMP and the maximum influence by TMX pretreatment. *P<.05, **P<.01, ***P<.001 comparing the active drug combination with the placebo - placebo combination.

Galvanometric measures

In Experiment D, skin conductance levels were affected by the placebo conditions of the experiment, an effect most clear when the reference time for change scores is 1715 hours (see figure 1.23). Dextroamphetamine 20 mg did not influence the skin conductance level when compared with the placebo - placebo conditions. Both doses of thymoxamine caused an augmentation of the skin conductance level when

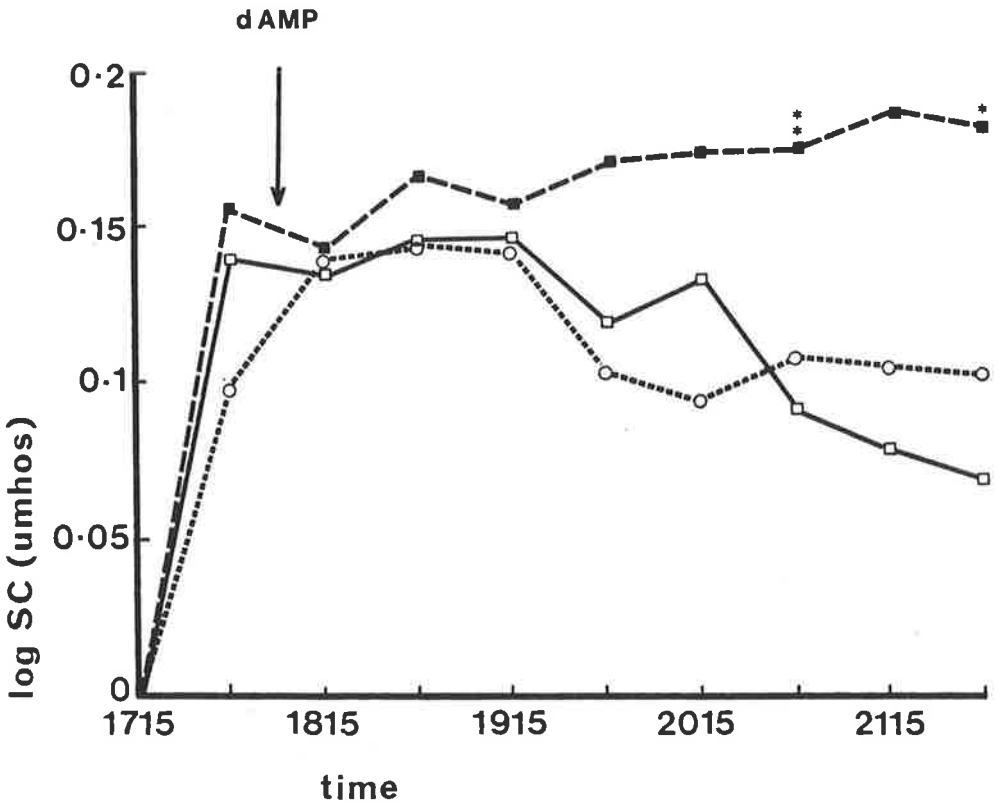

Figure 1.23 Mean changes in log SC (μmhos) in the response to oral dAMP 20mg given at 1800 hours following TMX given at 1700 hours:

TMX placebo - dAMP placebo
TMX placebo - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX pretreatment on the dAMP response.
*P <.05 **P <.025

compared with that induced by dextroamphetamine alone. The differences were maximal in the last hour of recordings. The differences between the thymoxamine 160 mg - dextroamphetamine 20 mg and the thymoxamine placebo - dextroamphetamine 20 mg combinations at 2045 and 2145 hours were +0.083(+-0.031) and +0.112(+-0.048) umhos (P <.02 and <.05. respectively). See table 1.11. These changes are illustrated graphically in figure 1.24 in which the differences of the mean changes in log skin conductance levels from the placebo - placebo conditions are portrayed.

TABLE 1.11. Skin conductance levels.

log SC umhos	TMX plac dAMP plac	TMX plac dAMP 20mg	TMX 80mg dAMP 20mg	TMX 160mg dAMP 20mg
2015h	+0.093 (+-0.040)	+0.131 (+-.031)	+0.134 (+-.052)	+0.173 (+-.02)
diff from plac - plac		+0.380 (+-.054)	+0.041 (+-.051)	+0.080 (+-.047)
2145h	+0.102 (+-.047)	+0.068 (+-.044)	+0.158 (+-.047)	+0.180 (+-.025)
diff from plac - plac		-0.340 (+-.051)	+0.056 (+-.049)	+0.078 (+-.055)

Means of changes (+-SEM) in log skin conductance levels (umhos) from 1715h at the times of maximum response to dAMP and the maximum influence by TMX.

The number of spontaneous fluctuations in skin conductance data on the other hand, did not reveal any response to the placebo conditions of the experiment. The increase in the number of spontaneous fluctuations by dextroamphetamine 20 mg when compared with the placebo - placebo combination did not reach statistical significance. Thymoxamine

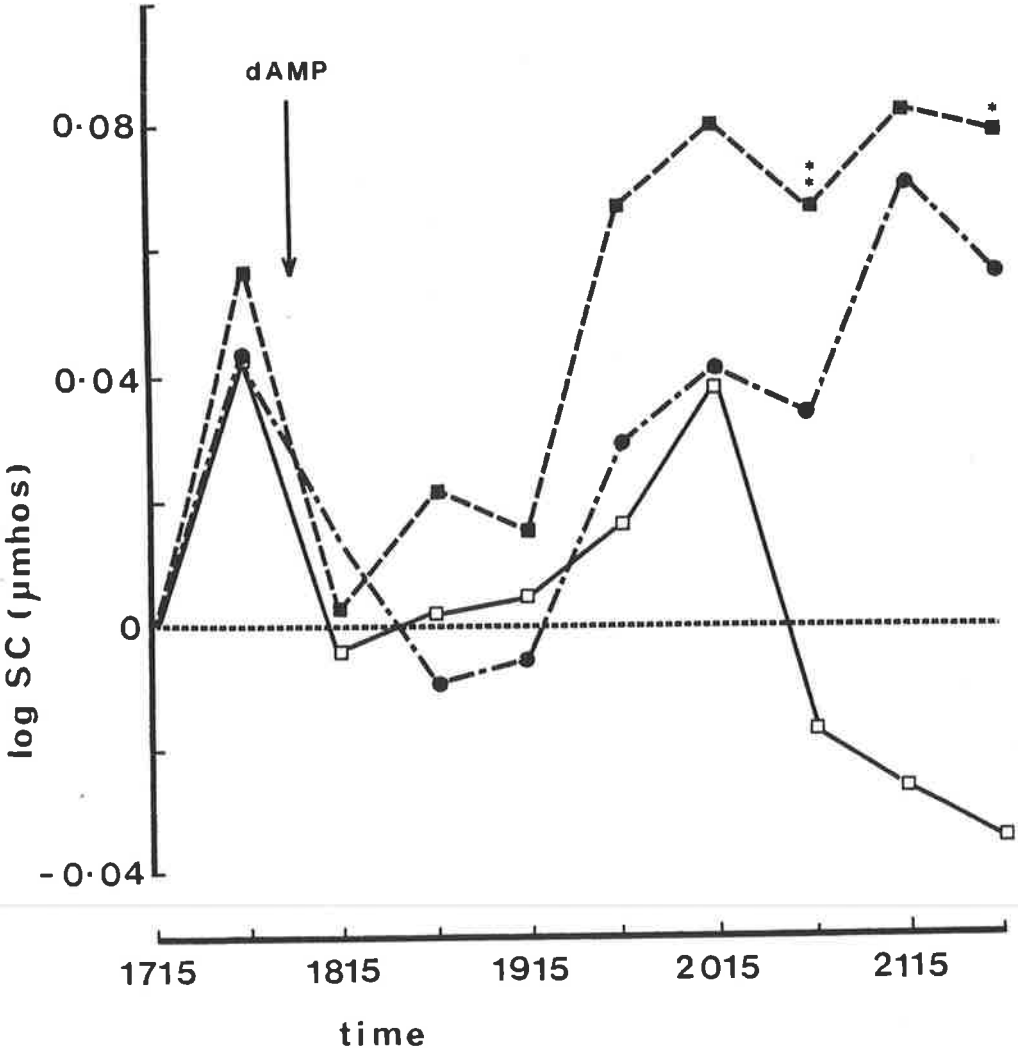

Figure 1.24 Differences in mean changes in log SC (μmhos) from the TMX placebo - dAMP placebo combination (x axis) in the response to oral dAMP 20mg given at 1800 hours following TMX 80mg and TMX 160mg given at 1700 hours:

TMX placebo - dAMP 20mg
TMX 80mg - dAMP 20mg
TMX 160mg - dAMP 20mg

Differences induced by TMX pretreatment on the dAMP response.
*P < .05 **P < .025

pretreatment lead to a dose related rise in the number of spontaneous fluctuations, maximal in the last hours of recording. The changes of means and differences from the placebo - placebo combination are given in table 1.12. and demonstrated graphically in figure 1.25.

Table 1.12. Spontaneous fluctuations in skin conduntance.

spont. fluct. no.	TMX Plac dAMP Plac	TMX Plac dAMP 20mg	TMX 80mg dAMP 20mg	TMX 160mg dAMP 20mg
3h	-0.4(+-1.0)	-0.2(+-0.8)	+1.1(+-1.4)	+1.6(+-0.6)
diff from plac - plac		+0.2(+-1.4)	+1.5(+-1.8)	+2.0(+-1.0)
4h	-0.3(+-0.6)	+0.7(+-0.9)	+2.6(+-1.3)	+2.8(+-1.1)
diff from plac - plac		+1.0(+-1.2)	+2.9(+-1.1) *	+3.1(+-1.2) *

Means of changes (+-SEM) in the number of spontaneous fluctuations in skin conductance at the times of maximum response to dAMP and the maximum influence by TMX. *P<.05.

The difference in the number of spontaneous fluctuations in skin conductance between the thymoxamine 160 mg - dextroamphetamine 20 mg and the placebo thymoxamine placebo - dextroamphetamine 20 mg at 3 and four hours were +1.8(+-0.5) and 2.1(+-1.2), (P <.01 and P <.1 respectively).

In all these experiments thymoxamine appeared to exert a dose related response, with the influence of the smaller dose of thymoxamine being in the same direction but of less intensity than the higher dose. Change scores were also estimated using the reference time of 1700 hours (just prior

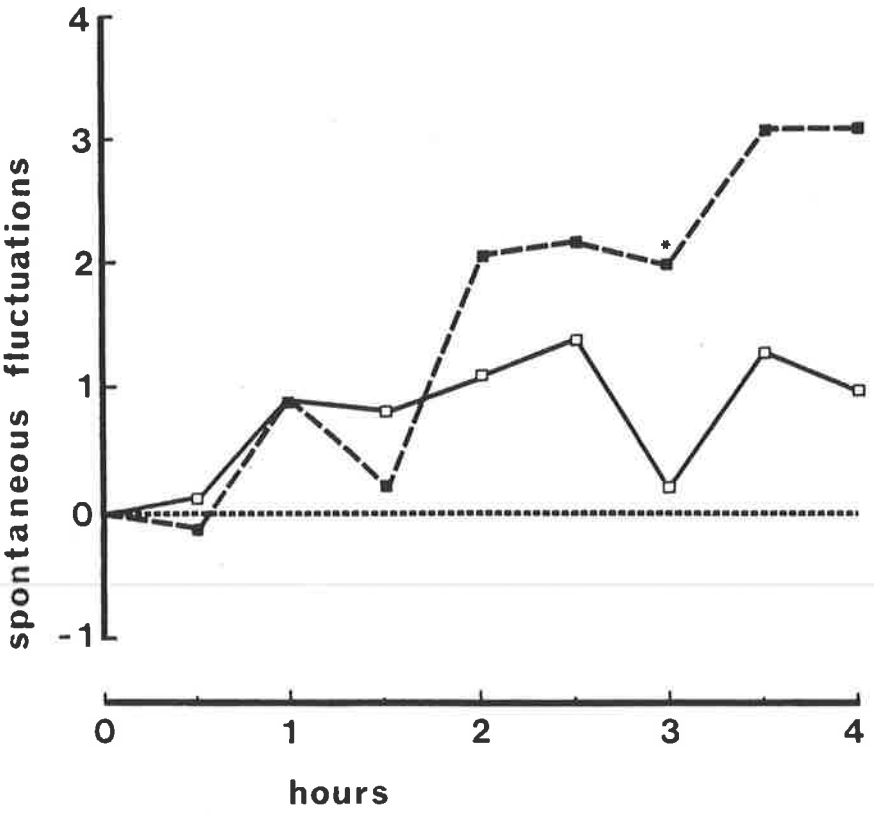

Figure 1.25 Differences in mean changes in the number of spontaneous fluctuations in skin conductance compared with the TMX placebo - dAMP placebo combination (x axis) demonstrating the effect of TMX 80mg given 1 hour earlier on the response to oral dAMP 20mg given at 0 hours:

TMX placebo - dAMP 20mg
TMX 160mg - dAMP 20mg

Differences induced by TMX pretreatment on the dAMP response.
*P < .01

to the thymoxamine dose) in the different measures, in an attempt to detect any early alteration in scores prior to dextroamphetamine. In doing so it was observed that thymoxamine 80 mg but not 160 mg caused a rapid drop in readings in the first hour in the miserable - happy, drowsy - alert visual analogue scale ratings and in the number of spontaneous fluctuations in skin conductance. In these dimensions, using the earlier reference time for estimating change values, pretreatment by thymoxamine 80 mg attenuated the dextroamphetamine response. This reached statistical significance in the two visual analogue rating scales. See figure 1.26.

In summary, no consistent effect could be discerned from data when thymoxamine was given alone. Thymoxamine appeared not to influence plasma dextroamphetamine levels. Thymoxamine pretreatment, particularly with the higher dose, significantly accentuated the dextroamphetamine response psychologically (as seen in irritability and restlessness ratings) and psychophysiologically. The latter effect was particularly clear in the skin conductance data. The smaller dose of thymoxamine may have exerted a rapid sedating action, within the first hour, which may have influenced the reference values for estimating change values prior to dextroamphetamine administration.

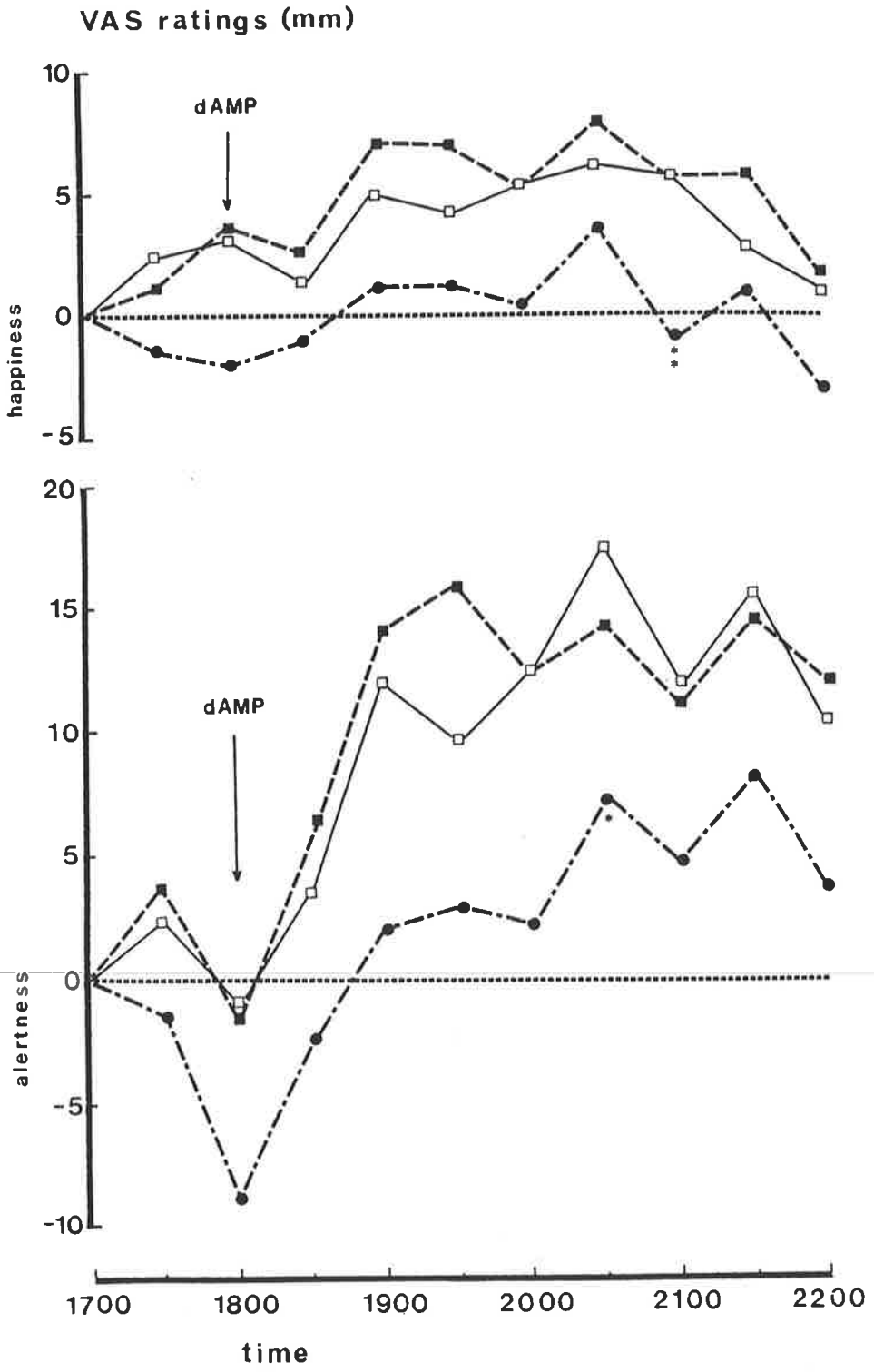

Figure 1.26 Differences in mean changes (0= 1700 hours) in VAS ratings (0 - 100mm) from the TMX placebo - dAMP placebo combination (x axis) in the miserable - happy and drowsy - alert dimensions, demonstrating the effect of TMX 80mg and TMX 160mg given at 1700 hours on the response to oral dAMP 20mg given at 1800 hours.

TMX placebo - dAMP 20mg
TMX 80mg - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX on the dAMP response. *P < .05
**P < .01

1.14.3. Discussion

Regrettably little is known of the pharmacokinetics of thymoxamine when give orally. As it is reported to be relatively poorly absorbed orally, two substantial doses were used, twice and four times the recommended dose for peripheral vasodilation (40 mg). Thymoxamine alone at this dosage level caused no deleterious effects apart from in one subject who suffered nausea and vomiting. This response in retrospect was likely to be an idiosyncratic response to thymoxamine. He was discharged from the experiment. No other subject was aware of discomfort from thymoxamine either when given alone or in combination with dextroamphetamine.

Thymoxamine has been shown to be active in the central nervous system after administration as it effects REM sleep (Oswald et al, 1975), the dextroamphetamine influence of the knee jerk (Phillips et al, 1973) and the secretion of cortisol and growth hormone stimulated by methylamphetamine (Rees et al, 1970).

It is difficult to draw firm conclusions from the the results of the study of thymoxamine alone. As the numbers are small, real trends may not have emerged or those that did emerge are likely to be apparent rather than real. In two of the subjective dimensions the higher dose of thymoxamine tended to elevate the scores. This trend was also suggested in its effect on pulse rate and systolic blood pressure. None of these changes reached statical

significance. The effect of thymoxamine in reducing diastolic blood pressure presumably reflected its peripheral vasodilator activity. There were no consistent changes in the skin conductance measures. One would have expected a sedative effect by thymoxamine, reflecting a stimulatory role by the noradrenergic pathways in the unaroused state. A sedative effect by intravenous thymoxamine was observed by Nurnberger et al (1984).

Overall the effect of oral thymoxamine pretreatment, particularly the higher dose, on the response to oral dextroamphetamine in normal human subjects, was to augment the response. This was observed in different visual analogue scale ratings, particularly irritability and restlessness and in the skin galvanometric measures. The smaller dose may have partially attenuated the dextroamphetamine response in some measures. It would seem reasonable to conclude that these changes reflect central actions of the drug.

These finding are contrary to those of Nurnberger et al (1984) who reported that intravenous thymoxamine did not influence the psychological or the cardiovascular system response to intravenous dextroamphetamine.

Conclusions are difficult to draw from the effects of thymoxamine pretreatment on the cardiovascular response to dextroamphetamine. The small differences observed following thymoxamine pretreatment are more likely to reflect the sum of both its central and peripheral actions. A peripheral

vasodilatory action by thymoxamine was not evident in experiment D in which no fall in diastolic blood pressure was measured.

There can be several explanations for the effect of thymoxamine on the dextroamphetamine response observed in this study. Firstly, the accentuation of irritability and arousal may have been a consequence of nausea or gastrointestinal irritation induced by thymoxamine. Only one subject, however, complained of discomfort and was discharged from the experiment. No clear subjective or objective measure of discomfort could be detected using thymoxamine alone. It is worth noting that the higher dose of thymoxamine attenuated the anorectic effect of amphetamine. If similar gastrointestinal discomfort to the lone subject who demonstrated nausea was experienced by other subjects, the anorectic action of dextroamphetamine would have been accentuated.

A second possibility is that thymoxamine may exert a differential action at pre or postsynaptic receptors depending on dose. Some drugs active at alpha noradrenergic receptor sites are not specific in their action, and may influence other receptors with increasing doses (Anden et al, 1976; 1982; Langer, 1981). If this were so with thymoxamine, this might explain why the higher dose had an augmenting effect on dextroamphetamine induced arousal whereas the smaller dose may have exerted a sedating effect. The lower dose of thymoxamine might act primarily

by blocking postsynaptic alpha noradrenergic receptors whilst the higher dose may have acted preferentially at presynaptic receptors. In other words at higher doses it may exert a yohimbine like effect. In animals studies however, thymoxamine and its metabolites appear to exert their noradrenergic blocking effects primarily at the postsynaptic alpha noradrenergic receptor sites with no evidence of significant activity at presynaptic sites (Drew, 1976; Drew et al, 1979; Roquebert et al, 1981[b]). To date there is no evidence that the preference between pre- and postsynaptic sites of action alters with the dose of thymoxamine.

Finally, the accentuation of the mood and arousal response to dextroamphetamine may be induced by thymoxamine exerting a central post synaptic alpha noradrenergic receptor blocking action. This would imply that these pathways may be involved in an inhibitory manner, at least in the aroused (dopamine hyperactive) state. In order to confirm or refute this latter conjecture, further studies using other alpha blockers would be required.

It has been clearly established that the arousal and activating effects of dextroamphetamine in experimental animals and the mood elevating and alerting effects of amphetamine drugs in human subjects reflects activation of dopamine pathways (Jonsson, 1972; Gunne et al, 1972; Rolinski and Scheel-Kruger, 1973; Hollister et al, 1974; Roberts et al, 1975; Groves and Rebec, 1976; Moore, 1977;

Gillin et al, 1978[b]; Silverstone et al, 1980). (See Introduction 1.4.). This is confirmed by the results in the study described earlier in which the specific dopamine blocker pimozide attenuated, in part at least, the alerting effects of dextroamphetamine, particularly as manifest in objective measures of central arousal.

The role of the noradrenergic pathways in the response to dextroamphetamine has not been studied to such an extensive degree. Hollister et al (1974) comment that the earlier animal studies investigating the effect of a dopamine beta hydroxylase inhibitor on the dextroamphetamine response which reported attenuation of response, failed to take into account the sedative action of the drug used. Attenuation of response could not replicated in their subsequent studies.

Other animal studies using either lesions in the noradrenergic pathways or pharmacological blockade, reported either no effect or a relatively small attenuating effect on amphetamine arousal (Mantegazza et al, 1968; Rolinski and Scheel-Kruger, 1973; Roberts et al, 1975; Groves and Rebec, 1976; Kostowski et al, 1982). Ungerstedt (1971) observed that noradrenergic blockade may accentuate amphetamine induced behaviour.

As far as studies using human volunteers are concerned, Jonsson (1972) reported that noradrenergic blockade of the response to intravenous dextroamphetamine led to no effect or a slight accentuation of mood (see also Gunne et al,

1972). Nurnberger et al (1984) reported that neither intravenous thymoxamine nor propranolol influenced the alerting or cardiovascular response to intravenous dextroamphetamine.

It had been generally assumed that noradrenergic pathways exert a stimulatory role in both animals and human subjects (Schildkraut and Kety, 1967; Fuxe et al, 1970; Snyder, 1973). These conclusions were reached following observations that peripherally administered noradrenaline gave rise to the flight and fight response. States of hyperactivity seemed to be associated with higher levels of noradrenaline and its metabolites. Lesions of the noradrenergic pathways appeared to give results consistent with this view. Furthermore, drugs which cause depletion of monoamines gave rise to hypoactivity in animals and depression in humans, which could be reversed by drugs which act to increase the synaptic concentration of the monoamines, in particular, noradrenaline (for example, the tricyclic antidepressants). Furthermore, the different degree of arousal and hyperactivity following dextro- or laevo- amphetamine seemed to reflect their assumed relative action metabolically.

More recent evidence on the nature and functioning of the noradrenergic pathways from a variety of sources has caused these earlier hypotheses to be re-evaluated. (See detailed review in the Introduction, 1.3.4.c.). For example, noradrenaline given peripherally does not cross the blood brain barrier and it is now known that the peripheral action

of noradrenaline is an important component of anxiety. Blocking beta noradrenergic activity peripherally has a significant effect on anxiety and arousal (Lader and Tyrer, 1972; Gottschalk et al, 1974). Drugs like reserpine and the tricyclic antidepressants, influence a wide variety of neurotransmitter systems. Furthermore, the antidepressant effect of tricyclic antidepressants seems to depend on adaptive changes in the relevant receptors rather than a simple increase in the concentration of neurotransmitter in the synapse. Indeed, by interpreting such receptor changes, some workers have concluded that depression may be a reflection of too great noradrenergic activity rather than too little (Maas and Huang, 1980; Waldmeier, 1981). The role of the noradrenergic pathways from interpretation based on the relative alerting actions of dextro- and laevo-amphetamine have likewise been challenged by more recent research on their neuropharmacological action (Bunney et al, 1975; Feigenbaum et al, 1982; Feigenbaum and Yanai, 1983).

Further pharmacological evidence for an alerting role by noradrenaline pathways has been suggested by the fact that clonidine, a central alpha 2 noradrenergic agonist, is sedating (Anden et al, 1976; Langer, 1978; Siever et al, 1981) whereas the alpha 2 antagonist, yohimbine, is alerting and causes anxiety in normal subjects (Charney et al, 1983; 1984). Doubt remains, however, about the proportion of pre- or postsynaptic alpha noradrenergic receptors in the central nervous system. There is also evidence that both clonidine and yohimbine are active at postsynaptic alpha 2 receptor

sites, particularly at higher doses (Anden et al, 1976; 1982).

Recent data from a variety of animal studies suggests that the noradrenergic pathways exert a bias adjusting or modulatory role and that they interact with intact dopamine pathways in a manner dependant upon the state of arousal (Antelman and Cagguilla, 1977; Bloom 1978; Woodward et al, 1979; Kostowski, 1979; Kostowski et al, 1982; Iversen, 1980; Robbins, 1984) (See detailed review in the Introduction 1.3.4.c.).

There appears to be no previous experiments described testing these issues in humans.

The findings in this study, that alpha noradrenergic pathways appear to exert an inhibitory action on dextroamphetamine induced arousal, though they may be stimulatory in the non-aroused state, is in keeping their emergent role in the literature. They probably exert a central modulatory action; a specific interaction occuring between the dopamine and noradrenaline pathways is likely, the interaction being dependent on the state of arousal (Antelman and Cagguilla, 1977; Robbins and Everitt, 1982; Robbins, 1984).

If this hypothesis proves correct, it would help to explain a variety of pharmacological findings that have previously appeared to be inconsistent. For example, although tricyclic antidepressants exert an antidepressant

effect usually after treatment for several weeks, in the short term (presumably at the time when they are acting as indirect monoamine, and, in particular, noradrenergic agonists) they are sedating and exert an anxiolytic effect, (Sheenan, 1980). Amphetamine derivatives can have diverse effects. In normal subjects they can cause a mixed mood response (Checkley, 1980) and sedation (Tecce and Cole, 1974). One explanation for the sedation may be that it is a manifestation of amphetamine's action predominantly on presynaptic receptors at lower doses as sedation tends to occur shortly after the drug is given, presumably when the concentrations are still relatively low (Tecce and Cole, 1974, Maas and Huang, 1980). Amphetamine is also known to be sedating in various aroused and hyperactive patients, eg, in hyperactive children (Arnold et al, 1972), manic patients (Kulcsar, 1966; Beckman and Heinmann, 1976) and some schizophrenic patients (Van Kammen et al, 1982). It is quite possible that in these situations of hyperarousal, amphetamines exert a sedative action via increased activity of the noradrenergic pathways. According to the dopamine - noradrenaline interaction hypothesis, such increased noradrenergic activity in the presence of increased activity in the dopamine pathways, would modulate that increased activity.

In conclusion, compared with the dopaminergic component of the response to dextroamphetamine, which appears to be stimulatory, the alphanoradrenergic component of the dextroamphetamine response may be inhibitory. This in

keeping with evidence in the literature of a dopaminergic noradrenergic interaction, which is likely to be dependent on the state of arousal of the individual. If it can be confirmed, this finding gives evidence of a modulatory, or bias adjusting role, of noradrenergic pathways proposed from animal studies.

PART II

THE RESPONSE OF THE NEUROENDOCRINE SYSTEM TO DEXTROAMPHETAMINE: EFFECTS OF DOPAMINERGIC AND NORADRENERGIC BLOCKADE

2.1. General Introduction

We have seen how the relative roles of noradrenaline and dopamine can be examined in the heightened state of arousal produced by dextroamphetamine. In this, and other states of increased arousal, there is frequently a concomitant increase in secretion of one or more pituitary hormones. It was therefore of interest to examine the relative roles of noradrenaline and dopamine in these changes in hormonal activity brought about by dextroamphetamine.

The living brain is a uniquely inaccessible organ to study. The neuroendocrine system allows an indirect avenue of objective study of brain functioning, particularly hypothalamic functioning, as the hormones released are now relatively easily measured. Furthermore there is an intimate relationship between the neuroendocrine system, psychological status and psychiatric illness.

As part of its role in maintaining homeostasis the neuroendocrine system is responsive to the psychological as well as physical status of the animal, showing many adaptive responses to stress. Furthermore, abnormalities in neuroendocrine functioning can be associated with changes in psychological status and behaviour. Examples include the psychological sequelae of thyrotoxicosis and myxoedema, Cushing´s disease and Addison´s disease, hyperprolactinaemia and acromegaly as well as the sequelae of peripheral

endocrine disease, for example, phaeochromocytoma and parathyroid disease (Lishman, 1978).

Considerable interest has been directed towards correlating changes in neuroendocrine functioning with both normal psychobiological status and psychiatric illness. This has led to the development of the dexamethasone suppression test and the TSH response to TRH test as biological state markers in major affective disorder (Carroll et al, 1981; Carroll, 1982; Kirkegaard et al, 1975; 1978). In addition other researchers have investigated the neuroendocrine response to pharmacological challenge in affective disorder in an effort to enlarge our understanding of the biology of these conditions. Pharmacological challenge of the neuroendocrine system is necessary as many anterior pituitary hormone levels in the physiologically basal state are so low, that it is difficult to measure and compare differences. Accordingly a variety of stimulatory procedures have been adopted.

Amphetamine derivatives have been used for this purpose since Besser et al (1969) demonstrated a rise in plasma cortisol and growth hormone following intravenous methylamphetamine. Subsequently, neuroendocrine stimulation by amphetamine derivatives have been used in two avenues of psychoneuroendocrinological research.

Firstly, researchers have used a challenge by amphetamine derivatives to study the functioning of the neuroendocrine system and indirectly the hypothalamus, in psychiatric

illness. Amphetamine drugs were used because of their action in stimulating central catecholamine pathways; these pathways were known to be involved in regulating anterior pituitary hormone release and in psychiatric disorders. These studies lead to the discovery of an abnormal response in serum cortisol, and possibly growth hormone, to amphetamine derivatives in patients suffering from affective disorder when compared with normal volunteers or upon recovery (Checkley and Crammer, 1977; Langer et al, 1976; Checkley, 1979; Sachar et al, 1980; Arato et al, 1983).

These authors observed that amphetamine derivatives induce cortisol and growth hormone release but that that release is reduced in affective disorder. As noradrenergic pathways were presumed to mediate in the secretion of both these hormones, the results of these studies have been taken to imply abnormalities of the noradrenergic pathways in affective disorder (Langer et al, 1976; Checkley, 1980; 1982[b]; Siever et al, 1981). Clearly it is essential to determine the nature and direction of the neuroendocrine response to amphetamine in normal volunteers before inferences can be made of the relative response in affective disorder.

Uncertainty persists however over the consistency of the growth hormone and prolactin response to amphetamine derivatives by normal subjects. Different responses are described under different experimental conditions. (See 2.3.1.)

The responses of TSH, LH and FSH to dextroamphetamine have not been directly studied in human subjects.

The second area of concern which is raised by studies using pharmacological challenge to investigate neuroendocrine functioning and hence the biology of affective disorder, is that the roles of the dopamine and noradrenaline pathways in the control of release of some of the different anterior pituitary hormones in humans are yet to be resolved.

The dopaminergic and noradrenergic pathways play an important role in the control of secretion of the different elements of the neuroendocrine system. The catecholamine control of anterior pituitary hormone secretion has been intensively studied in different animal species, using both in vitro and in vivo techniques. The control of some of the anterior pituitary hormones in humans have been relatively well studied, others less so. There are interspecies differences though; the control of secretion in humans often differs from other animals. It seems likely from recent research findings that the catecholamine control of anterior pituitary hormones is more complex than first imagined.

Thus, a second avenue of neuroendocrine research can make use of the known action of amphetamine derivatives to provide a pharmacological procedure to compare the relative roles of the dopamine and noradrenaline pathways in the control of the release of the anterior pituitary hormones.

Pharmacological techniques are one of the methods available for studying the catecholamine control of human pituitary functioning. The effects on basal secretion of the hormones by pharmacological agonists and antagonists alone may be so small that differences are difficult to detect. Experiments gain validity if the response to an agonist can be influenced by a specific pharmacological antagonist. Attenuation of response would imply that the pathway is involved in a stimulatory manner whilst accentuation of the response implies, on the other hand, an inhibitory relationship. However, although a number of relatively specific dopaminergic and noradrenergic antagonists and dopaminergic agonists exist, amphetamine derivatives are one of the few suitable noradrenergic agonists that act centrally. As amphetamines act as indirect dopamine and noradrenaline agonists, (see introduction Part I) blockade of either catecholamine allows a direct comparison of the relative roles of the two pathways in the secretion of the hormone being studied. This pharmacological procedure has been widely used to investigate the comparative roles of the dopaminergic and noradrenergic pathways in psychological functioning. (See Part I. 1.2.5.). This approach was pioneered in neuroendocrine research by Rees et al (1970) to investigate the role of alpha and beta noradrenergic pathways in the control of cortisol and growth hormone secretion.

2.2. Methodology

a. Subjects, drugs and experimental design

The subjects and drugs used and experimental design have been described in detail in Part I.

b. Blood samples

AT 1700 hours a venous cannula was inserted into a forearm vein (scalp vein cannula 21 gauge). This was kept patent initially and after each blood sample was drawn, by a 0.05ml. injection of heparin diluted in normal saline (100 units in 1 ml). Immediately prior to the administration of dextroamphetamine and hourly thereafter, a 10 ml blood sample was taken and transferred to a lithium heparin tube, immediately centrifuged and the supernatant plasma stored at minus 20 degrees centigrade for plasma dextroamphetamine and cortisol estimations.

A further 15 ml of blood was transferred to glass tubes thirty minutes before dextroamphetamine (1730 hours), and again immediately before (1800 hours), and hourly thereafter. Immediately after clotting, it was centrifuged and the supernatant serum stored at minus 20 degrees centigrade for estimation of serum prolactin (PRL), growth hormone (GH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH). PLasma cortisol and serum samples were assayed by the Department of

Clinical Endocrinology, St Bartholomew's Hospital London (Professor Lesley Rees).

c. Hormone assays

i. Plasma cortisol was assayed by the fluorimetric method for the estimation of free 11 hydroxy corticosteroids in plamsa (Mattingly, 1962). All the samples of each hormone were assayed in the same batch.

Sensitivity:

Lower end sensitivity: 80 - 90 n.moles / litre

Normal range, 0900hr: 200 - 600 n.moles / litre

2300hr: <200 n.moles / litre

Interassay coefficients:

Cortisol	100%	fluorescence
Corticosterone	25%	(negligible in humans)
Cortisone	0%	
Tetrahydrocortisol	5%	
11 - deoxycortisol	2%	
Oestradiol	23%	(only important in urine specimens)

The other hormones were assayed by the double radioimmunoassay method.

ii. Prolactin: The assay of Thorner et al (1977) was employed modified by using the First International Reference Preparation (MRC75/504) as standard. The assay range was 60 - 4000 mU/L and the mean interassay coefficient of variation was 10.3%.

iii. Growth Hormone was assayed by the radioimmunoassay method of Castracane et al (1984). The assay range was 1 - 50 mU/L and the mean coefficient of variation was 9.1%.

iv. Thyroid Stimulating Hormone: The North Thames Region Immunoassay Unit method was used with MRC68/38 as standard. Assay range was 1 - 50 mU/L and the mean interassay coefficient of variation was 9.7%.

v. Luteinizing Hormone and Follicle Stimulating Hormone: These assays used antisera kindly given by Professor W. R. Butt (Butt et al, 1975). LH standard was MRC68/40, the assay range was 1 - 50 U/L and the mean interassay coefficient of variation was 8.7%. The FSH standard was MRC69/104, the assay range was 0.2 - 25 U/L and the mean interassay coefficient of variation was 9.4%. Both used a second antibody separation procedure.

d. Data analysis

Hormone levels that fell outside the assay range were given as the limits for assays.

Plasma and serum levels were converted to an incremental value by subtracting each reading from the level at 1800 hours. The net incremental hormone responses represent the differences between hormone change levels after the active drugs is compared with the placebo combination. This required some modification in the case of growth hormone. Basal (pre - dextroamphetamine) levels of each hormone for

each drug combination in each experimental group were comparable apart from growth hormone. Here some subjects appeared to have exhibited a surge of secretion in the basal state. Accordingly, those subjects who showed a secretion of growth hormone, in the sample prior to dextroamphetamine, greater than 5 mU/L, were excluded from the data analysis.

The total hormone release over the four hour period was estimated by calculating the area beneath the curve, using the trapezoid method, for each subject's incremental response for each hormone with each drug combination.

In order to estimate the effect of dextroamphetamine challenge to the neuroendocrine system, changes in hormone secretion following dextroamphetamine alone (placebo blocker - dextroamphetamine 20 mg) were compared with those following placebo alone (placebo blocker - placebo dextroamphetamine) in the 24 subjects who participated in experiments B and D.

Statistical analyses were calculated using Student's t test for matched pairs. Statistical significance was taken as $P < .05$ using the two tail test.

Results are expressed graphically as the mean hormone increment (+- standard error measure) above or below the 1800 hour reference value for each sampling time. In order to simplify the graphs, mean (+-SEM) net incremental levels will be illustrated when placebo values were not influencing secretion (making placebo levels the x axis). The effect of

the smaller dose of the blocking drug will not usually be illustrated as the response was generally in a similar direction but to a lesser degree than the higher dose. The effect of Thymoxamine 80 mg will be illustrated if a dose response relationship was not observed.

2.3. The Response of the Neuroendocrine System to Dextroamphetamine

2.3.1. Literature review

Amphetamine drugs have been widely used to study the functioning of the neuroendocrine system in human subjects since Besser et al (1969) observed a stimulatory response in cortisol and growth hormone levels. Their use in animal experiments have not been so numerous. Animal experiments have shown, for example, that amphetamine drugs cause a drop and a reversal of the reserpine induced increase in prolactin secretion (Meltzer et al, 1979; Clemens et al, 1980; Gudelsky, 1981), but have little effect on resting prolactin levels (Meltzer et al, 1982). Amphetamine reduces the stress induced rise in ACTH (Van Loon, 1971; Muller et al, 1977[a]). Monkeys show an increase in TSH secretion following dextroamphetamine (Morley et al, 1980). Mice on the other hand had elevated T3 and T4 levels but not TSH levels following amphetamine suggesting a peripheral site of action (Melander et al, 1976).

In human subjects the response of cortisol, prolactin and growth hormone to amphetamine derivatives have been examined both in normal subjects and in patients suffering different psychiatric diseases. This will be discussed by considering each anterior pituitary hormone in turn.

a. ACTH - Cortisol

Activation of the pituitary adrenal axis occurs with stress following a variety of physical or psychological stimuli. The cortisol response may be particularly responsive to psychological stimuli (Martin et al, 1977; Rees, 1977).

Besser et al (1969) observed that the plasma cortisol levels in normal young men rose significantly following both intravenous methylamphetamine and oral dextroamphetamine, the response being most pronounced in the evening.

In depressive illness the cortisol response to intravenous methylamphetamine was found to be lower when patients were depressed than after recovery (Checkley and Crammer, 1977; Checkley, 1979). The authors propose that this finding supports the hypothesis that there is a functional deficiency of noradrenaline at some central adrenergic receptors. Sachar et al (1980) furthermore reported that intravenous dextroamphetamine given to depressed patients, significantly suppressed elevated morning cortisol levels.

b. Prolactin

Prolactin secretion is stimulated by stressful stimuli, particularly physical stimuli, for example anaesthesia and surgery (Martin et al, 1977; Thorner, 1977).

The reported response by serum prolactin to amphetamines in normal human subjects has been varied, with some authors

reporting a rise and others a fall. Halbreich et al (1981) and Nurnberger et al (1981) both demonstrated an increase in prolactin secretion following amphetamine, with Halbreich et al (1981) noting that the rise was apparent in young men in the evening but not in post menopausal women. A fall in serum prolactin secretion following amphetamine was reported by Wells et al (1978), DeLeo et al (1983) and Dommisse et al (1984).

The prolactin response to dextroamphetamine has also been studied in psychiatric illness. In both depressed patients (Slater et al, 1976) and schizophrenic patients (Van Kammen et al, 1978) an elevation of secretion was reported.

c. Growth hormone

Growth hormone secretion responds to stress. Secretion is increased by surgery, exercise, hypoglycaemia and pyrogen administration (Cryer and Daughaday, 1977; Johnson, 1982). The responsiveness to psychological stress in humans is not so clear. For example prolonged environmental stress is associated with growth failure (Martin et al, 1977). The stress response in experimental animals appears to be species specific (Martin et al, 1977).

Generally growth hormone levels are increased by amphetamine derivatives though the response is variable and depends on a variety of experimental conditions. Besser et al (1969) reported that intravenous methylamphetamine, but not oral dextroamphetamine, gave a rise in serum growth

hormone levels. Rees et al (1970) likewise demonstrated an increase in growth hormone secretion following intravenous methylamphetamine, but oral dextroamphetamine produced a fall (personal communication). Intravenous dextro- and laevo- amphetamine were reported to be equipotent in stimulating the release of growth hormone (Langer and Matussek, 1977). Halbreich et al (1980) reported that growth hormone response to intravenous dextroamphetamine was significantly less in postmenopausal women than young men. Young men had a higher response in the morning than the evening with the reverse being observed in the older women. In hyperkinetic children Aarskog et al (1977) reported a rise in growth hormone following oral dextroamphetamine maximal at sixty minutes which was only measurable then and at ninety minutes. This rise was attenuated after the children had been treated for five months with methylphenidate. Long term treatment of hyperactivity in children by dextroamphetamine may cause growth retardation (Safer and Allen, 1972), possibly by reducing growth hormone secretion. Intravenous dextroamphetamine had no effect on growth hormone in acromegalic patients (Muller et al, 1977[a]).

Amphetamine derivatives have been used to study growth hormone secretion in psychiatric patients. Langer et al (1976) reported a reduced response to intravenous amphetamine in endogenously depressed patients, and an enhanced response in neurotic depressives, with the response in schizophrenic and alcoholic patients not differing from

that seen in normal subjects. The authors interpret their observation as further evidence for the noradrenergic deficiency hypothesis in some patients with affective disorder. Checkley and Crammer (1977) on the other hand reported that the increase in growth hormone secretion following intravenous methylamphetamine was the same when the patients were depressed or recovered. In a subsequent study, Checkley (1979) reported that the increase in growth hormone secretion following intravenous methylamphetamine was similar in both endogenously and reactively depressed patients and in patients with other psychiatric diagnoses.

d. TSH

The anterior pituitary adrenal axis, prolactin and growth hormone have been generally regarded as being responsive to stress. Less is known of the response by other anterior pituitary hormones to stress. TSH secretion is specifically stimulated by cold exposure. The relationship of psychological stress and the anterior pituitary thyroid axis is not clear. Hyperthyroidism has long been considered a disease which may be induced by psychological stress though there is no scientific evidence for this (Morley, 1981). Physical stress on the other hand tends to suppress thyroid function in experimental animals and humans (Martin et al, 1977; Morley, 1981).

Morley et al (1980) observed that four patients who had abused amphetamine, had elevated T4 levels and symptoms of hyperthyroidism. Thyroid function returned to normal on

withdrawal from amphetamine. There appears to have been no direct study measuring changes in TSH secretion in human subjects following acute amphetamine administration.

e. LH and FSH

The response by LH and FSH to stress remains uncertain. LH secretion is stimulated by auditory stimuli in both experimental animals and humans (Beardwood, 1982). Inhibition of LH and FSH secretion by the stress of starvation (for example in anorexia nervosa) is well known (Beumont and Russell, 1982).

There appears to be no study measuring changes in gonadotrophin secretion in humans following amphetamines.

2.3.2. Results

a. Cortisol

Dextroamphetamine 20 mg caused a significant rise in plasma cortisol secretion whereas there was a steady fall after placebo (as expected due to the known diurnal rhythm of cortisol). See Figure 2.1. The net incremental rise in plasma cortisol following dextroamphetamine was statistically significant at all times throughout the experiment, being greatest at two hours when the difference was + 351.4(+-41.6) nmols/l, ($P<.001$).

The mean (+-SEM) estimates of the area under the curve measures are as follows:

Placebo:	-358.9(+-93.4)
dAMP 20 mg:	+470.0(+-67.6)
difference:	+828.0(+-106.4) ($P<.001$)

b. Prolactin

Serum prolactin rose significantly following dextroamphetamine administration. See figure 2.2. No change in serum prolactin secretion followed placebo. The rise was maximal at three hours when the difference between active and placebo dextroamphetamine was +62.1(+-28.2), mU/L ($P<.05$).

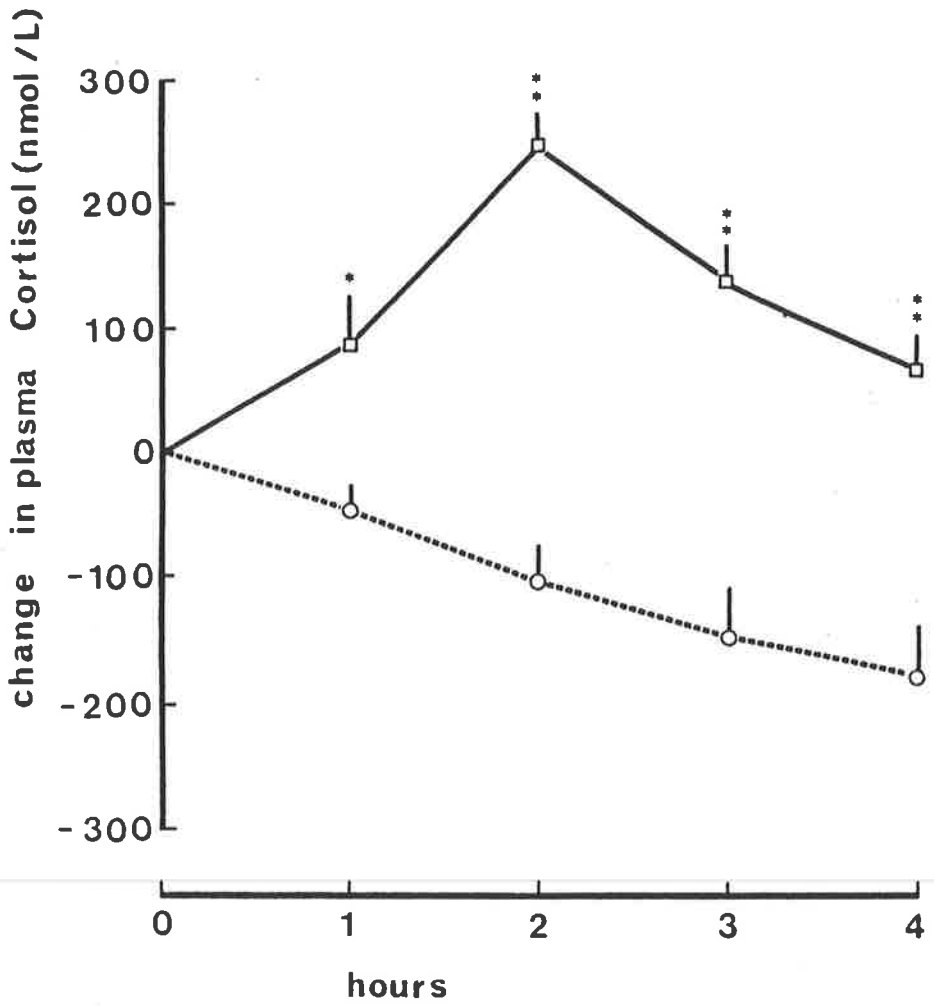

Figure 2.1 Mean (± SEM) incremental plasma cortisol (nmol/L) from 0 (1800) hours:

placebo ·····○·····

dAMP 20mg ——□——

Difference versus placebo. *P <.005 **P <.001

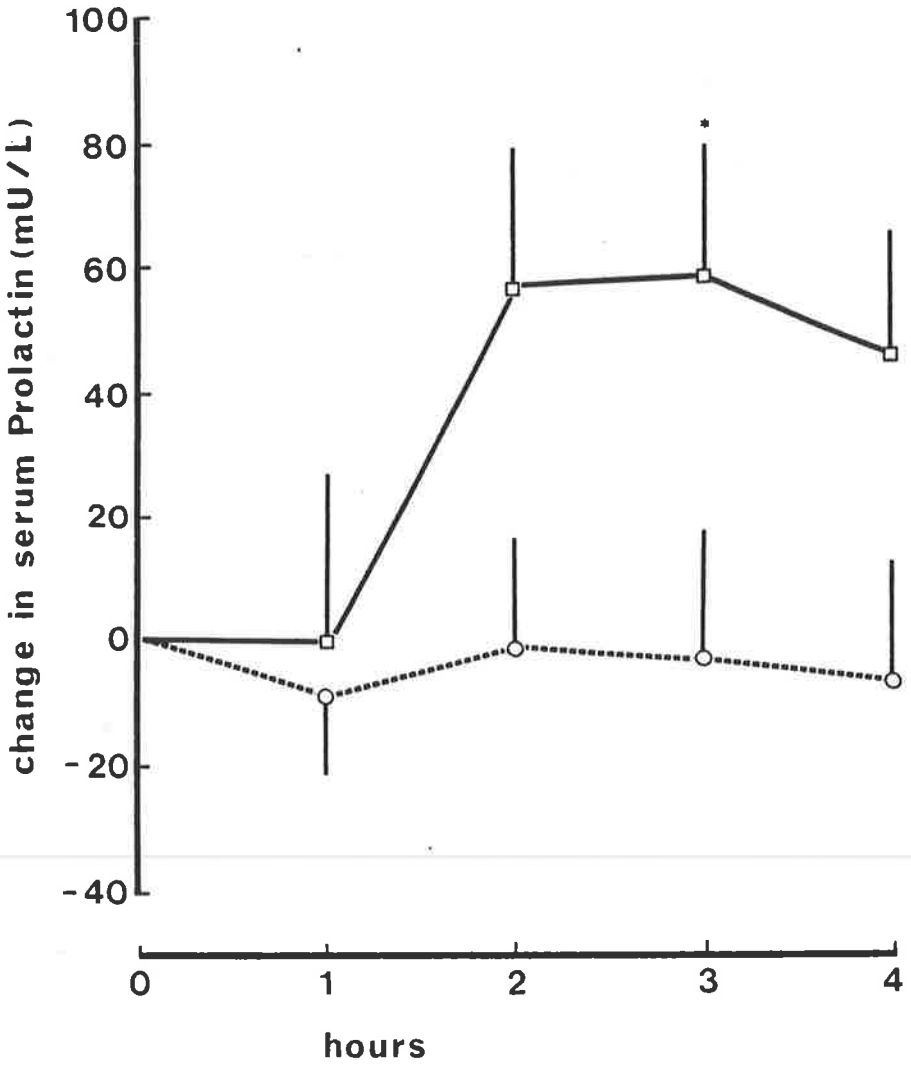

Figure 2.2 Mean (± SEM) incremental serum prolactin (mU/L) from 0 (1800) hours:

placebo
dAMP 20mg

Difference versus placebo. *P < .05

The mean (+-SEM) estimates for the areas under the curves measures are as follows.

Placebo: -2.3(+-49.5)

dAMP 20 mg: +137.3(+-44.6)

difference: +139.5(+-69.2) (P <.1)

c. Growth Hormone

There was a late, sustained increase in growth hormone secretion following placebo compared with an early nonsustained rise in serum growth hormone following dextroamphetamine. The increase in serum growth hormone levels following placebo administration, reached statistical significance at two, three, and four hours when compared with the pre - dextroamphetamine level. Incremental serum growth hormone levels following placebo (n=20) at these times were, +10.5(+-2.6) +8.7(+-4.0) and +10(+-2.8) mU/L; P<.001, <.05 and <.01 respectively (see figure 2.3).

The increase in growth hormone secretion following dextroamphetamine was particularly evident in the first two hours when the mean (+-SEM) incremental levels were; +9.9(+-3.7) and +6.4(+-2.6) mU/L; P<.02 and <.05 respectively. The small increase in secretion induced by the active drug when compared with placebo at one hour failed to reach statistical significance. Dextroamphetamine 20mg however appeared to reduce the growth hormone response when compared with placebo in the latter part of the study. The net incremental growth hormone levels at three and four

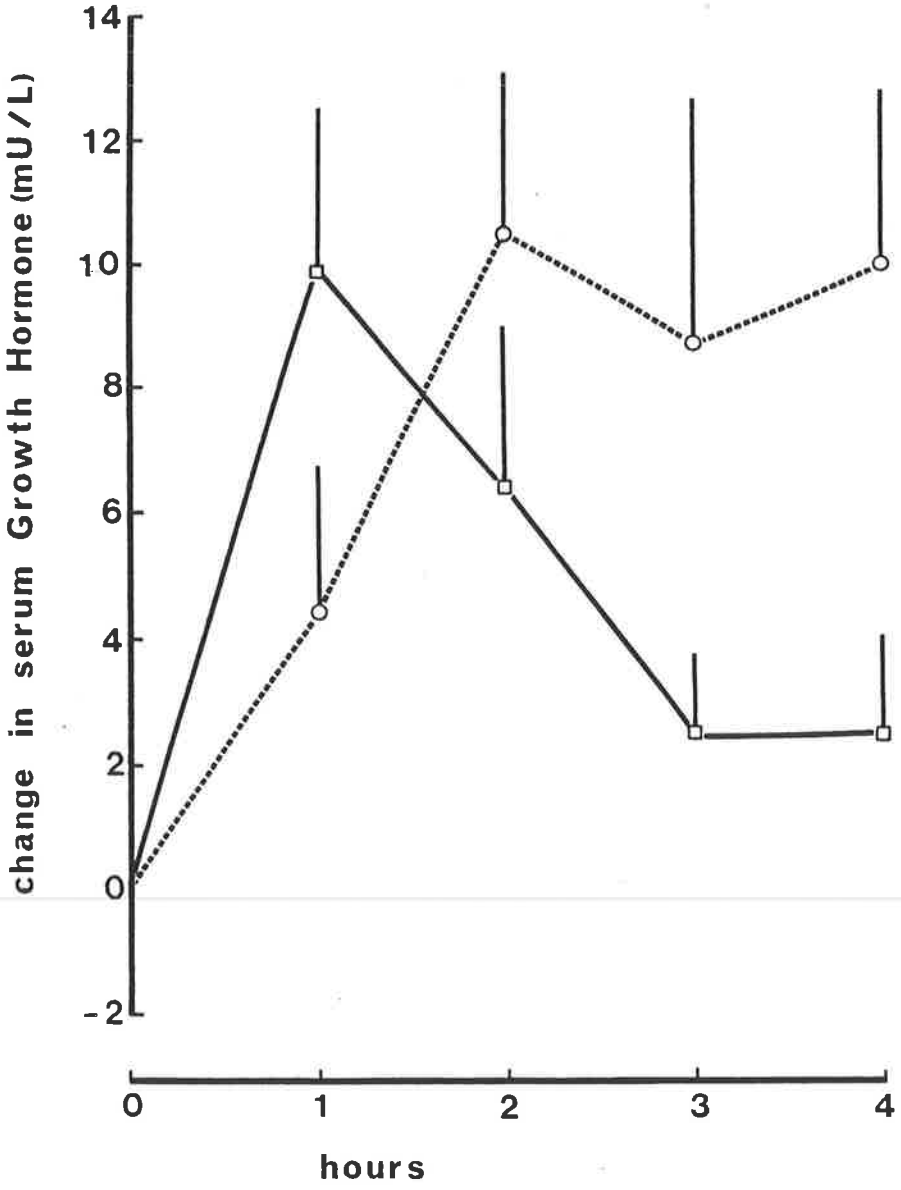

Figure 2.3 Mean (± SEM) incremental serum growth hormone (mU/L) from 0 (1800) hours:

placebo ○----------

dAMP 20mg □——————

hours (using matched paired data only, n=13), were -3.9(+-2.05) and -9.0(+-9.8) mU/L, (P <.1). (The difference at four hours reached statistical significance using the Wilcoxon paired rank difference test [P <.05]).

Estimates of the mean (+-SEM) areas beneath the curves are as follows: (data from matching pairs only N=13)

Placebo: +16.1(+-3.9)
dAMP 20mg: +10.7(+-2.1)
difference: -5.5(+-3.1) (P<.1)

d. TSH

Dextroamphetamine 20 mg led to a rise in TSH secretion when compared with placebo. See Figure 2.4. There was no change after placebo alone. The effect of dextroamphetamine was maximal at two hours, +0.41(+-0.19) mU/L, (P <.05).

Estimates of the areas under the curve are as follows:

Placebo: +0.14(+-0.22)
dAMP 20 mg: +0.78(+-0.30)
difference: +0.63(+-0.36) (p <.1)

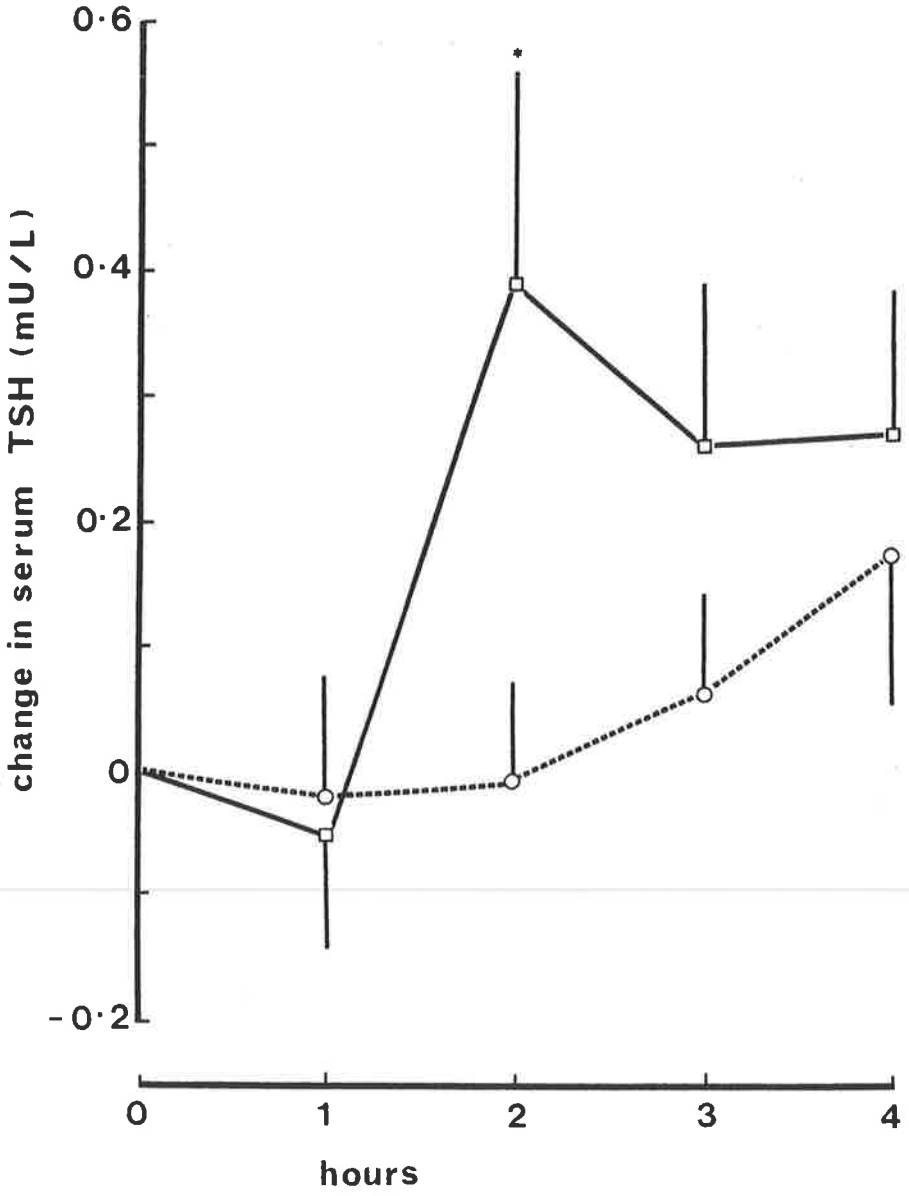

Figure 2.4 Mean (± SEM) incremental TSH (mU/L) from 0 (1800) hours:

placebo ○----------

dAMP 20mg □——————

Difference versus placebo. *P <.05

e. Gonadotrophins

The effect of dextroamphetamine 20 mg compared with placebo on LH and FSH release is shown in Figures 2.5. and 2.6. No change was manifest after placebo in either experiment. With both hormones the increase in secretion induced by dextroamphetamine was maximal at two hours, the net incremental LH (mean +-SEM): +2.54(+-0.68) U/L (P <.005) and net incremental FSH: +0.71 (+-0.2) U/L (P <.005).

Estimates of the areas under the curves are as follows:

LH:

Placebo:	-0.9(+-1.4)	
dAMP 20 mg:	+4.9(+-1.2)	
difference:	+5.9(+-1.8)	(P <.005)

FSH:

Placebo:	-0.3(+-0.3)	
dAMP 20 mg:	+1.3(+-0.4)	
difference:	+1.6(+-0.5)	(P <.005)

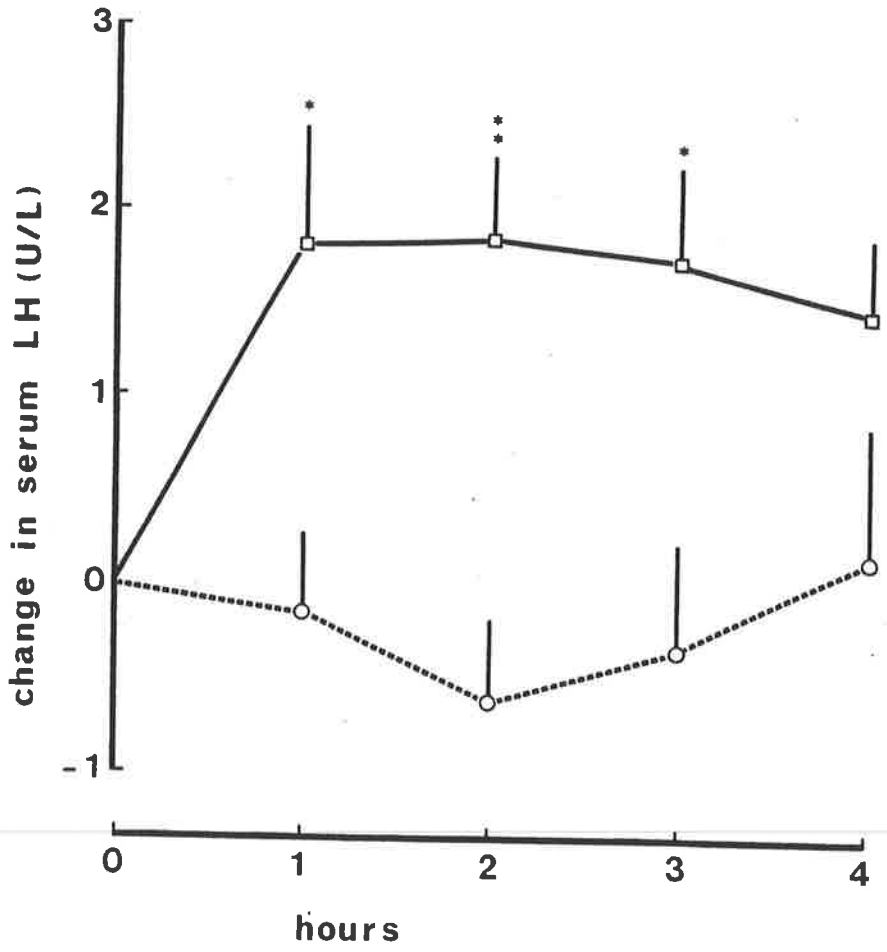

Figure 2.5 Mean (± SEM) incremental LH(U/L) from 0 (1800) hours:

placebo ○----------

dAMP 20mg □———————

Difference versus placebo. *P <.025 **P <.005

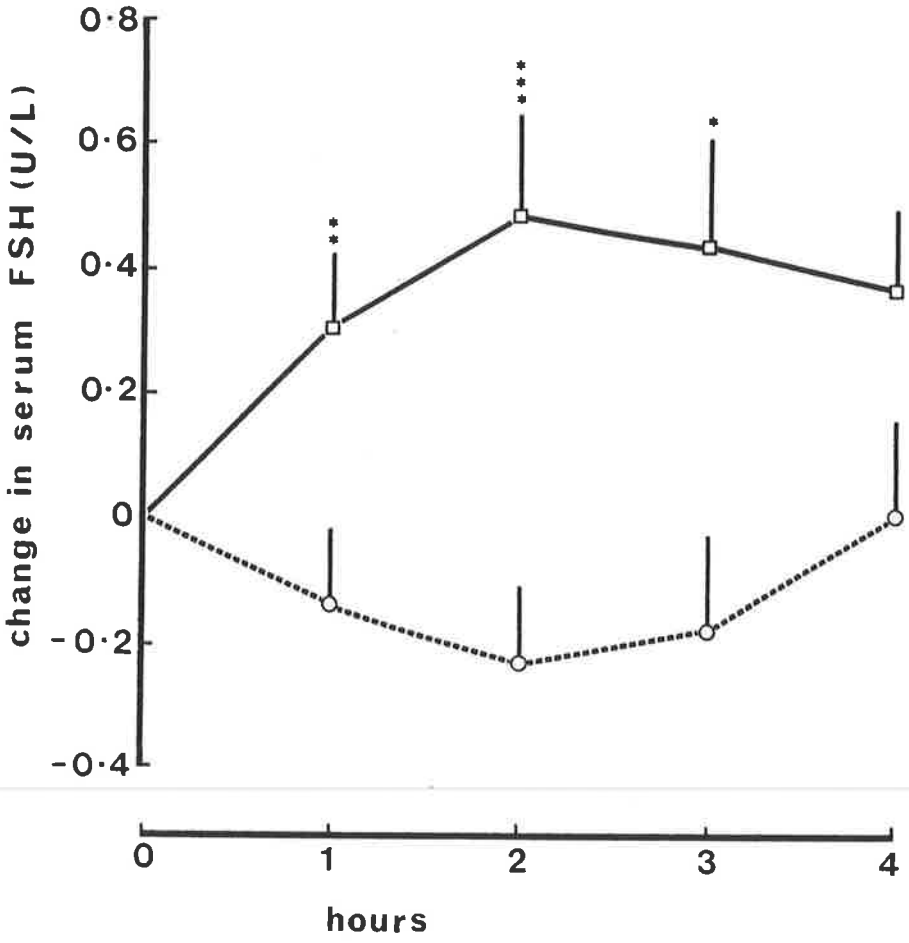

Figure 2.6 Mean (± SEM) incremental FSH (U/L) from 0 (1800) hours:

placebo

dAMP 20mg

Difference versus placebo. *P < .02 **P < .01 ***P < .005

2.3.3. Discussion

Oral dextroamphetamine 20 mg stimulated the secretion of plasma cortisol and serum prolactin, TSH, LH and FSH. This study appears to be the first to directly measure the effect of dextroamphetamine on TSH, LH or FSH in normal human subjects, though Morley et al (1980) proposed a central stimulatory action by amphetamine on thyroid activity.

No change in hormone secretion was observed in the above after placebo with the exception of cortisol with which the expected fall in levels associated with the evening component of its diurnal variation was observed. The placebo conditions did significantly influence growth hormone secretion however.

Many pharmacological studies of neuroendocrine function are conducted in the morning. This study was conducted in the late afternoon - early evening. Due to the duration of the experiment (over six hours) sufficient subjects who could take this amount of time away from work were simply not available. As the anterior pituitary hormones are secreted with a specific diurnal pattern, these results may not be directly comparable with other studies conducted in the morning.

It has been assumed that measuring plasma cortisol levels gives a satisfactory estimate of ACTH secretion (Besser et al, 1969; Ganong, 1980). Besser et al (1969), for example, demonstrated in two subjects that the rise in cortisol

secretion following intravenous methylamphetamine was mirrored by a similar rise in ACTH. The work of Fehm et al (1984) casts some doubt on this assumption however. They were unable to demonstrate a corresponding rise in ACTH secretion with the methylamphetamine induced rise in plasma cortisol levels although ACTH levels increased in association with increased cortisol levels following insulin induced hypoglycaemia. Further studies will be required to resolve this question. This observation casts doubt on the inferences drawn from studies investigating the cortisol response to amphetamine in patients with affective disorder on the activity of the central noradrenergic pathways in depression.

The response of prolactin to dextroamphetamine 20 mg in this study confirms the observations of some earlier investigations using normal subjects, or psychiatric patients (Slater et al, 1976; Van Kammen et al, 1978; Halbreich et al, 1980). This is in contrast to Wells et al (1978) and DeLeo et al (1983) who reported a fall in serum prolactin secretion, a response which might be expected in view of dextroamphetamine's potent indirect dopamine agonist action. The rise observed in the present study, and that of others, remains to be explained.

The growth hormone response to oral dextroamphetamine where dextroamphetamine, if anything, appeared to reduce the increase of secretion following placebo is also difficult to explain. Growth hormone secretion can be stimulated by a

variety of physiological and pharmacological stimuli. Experimentally these have included hypoglycaemia, exercise, stress, sleep, arginine, glucagon, vasopressin and a range of other pharmacological stimulants (Checkley, 1980; Martin, 1980). It is possible that as the subjects had fasted for eight hours prior to presentation in this study, the rise seen following placebo may have been secondary to lowered blood glucose levels or to the stress from venipuncture.

The growth hormone response to amphetamine derivatives seems to be variable. Although many studies report a rise in secretion, this depends on which amphetamine derivative was used, dose, route of administration, age of subjects, time of day, and presence of other stimulatory factors. (See literature review 2.3.1.). Other studies suggest that oral dextroamphetamine has little stimulatory action on growth hormone secretion. Besser et al (1969) for example, reported that although intravenous methylamphetamine caused a rise in growth hormone, oral dextroamphetamine in the evening did not. Rees et al (1970) described only a modest rise in growth hormone following intravenous methylamphetamine while oral dextroamphetamine caused a fall (personal communication).

The variable response of serum growth hormone to amphetamine derivatives and to different experimental conditions, may account for the the differing reports of the growth hormone response to amphetamine derivatives in psychiatric patients (Langer et al, 1976; Checkley and

Crammer, 1977; Checkley, 1979). In none of these studies was a placebo comparison made. The results of the present study indicate how necessary it is to include a placebo control. Furthermore this study indicates that inferences about the role of the catecholamine pathways in affective disorder, from observations of the response by depressed patients to amphetamine drugs (Langer et al, 1976; Langer and Matussek, 1977) may be unfounded.

In conclusion, oral dextroamphetamine would appear to be a satisfactory stimulus for challenging anterior pituitary hormone secretion (with the exception of growth hormone) both for the purpose of investigating cortisol and anterior pituitary function in psychiatric illness and the investigation of neuroendocrine functioning in health or disease. It is apparent that the procedure must be carefully standardised as the response can vary with the dose and route of administration, as well as other experimental conditions. This is particularly obvious when measuring the growth hormone response to challenge by an amphetamine derivative.

2.4. Effects of Prior Dopaminergic and Noradrenergic Blockade on the Neuroendocrine Response to Dextroamphetamine

2.4.1. Introduction

This study was conducted to investigate the roles of the dopamine and noradrenaline pathways on the secretion of the different anterior pituitary hormones.

As mentioned earlier a variety of techniques have been employed to study the role of the catecholamine pathways in neuroendocrine functioning, in particular in experimental animals, and to a varying degree in human subjects. As interspecies differences occurs with some hormones, the literature review will concentrate on studies using human subjects.

With a number of the hormones, pharmacological challenge of their secretion has been performed in patients suffering from affective disorder as a method of exploring the biology of this condition. affective disorders. These studies will be reviewed. The conclusions drawn from these studies on the functioning of the catecholamine pathways in affective disorder will be considered in the light of the results of the current experiment and other similar studies that have investigated the action of these pathways in human anterior pituitary hormone secretion.

A literature review, the results of the experiment

conducted and discussion will be presented for each hormone in turn, with the exception of LH and FSH which will be considered together.

2.4.2. ACTH - Cortisol

a. Literature review

ACTH, a 39 residue peptide, is under excitatory control by the hypothalamus via corticotrophin releasing factor. It is inhibited by the negative feedback effects of cortisol (Martin et al, 1977; Ganong, 1980). Neurotransmitter regulation of ACTH appears to be at the hypothalamic rather than the anterior pituitary level (Ganong, 1980). Cortisol is released from the adrenal cortex under excitatory control of ACTH.

As ACTH is comparatively difficult to measure directly by radioimmuno assay, most in vivo studies assay glucocorticoid (cortisol) output, which has been assumed to provide a satisfactory index of ACTH secretion (Ganong, 1980). However there is recent evidence that the cortisol level can be affected independently; for example the cortisol rise following methylamphetamine may not be associated with a corresponding rise in ACTH secretion (Fehm et al, 1984).

i. The role of dopamine pathways in ACTH and cortisol release

Dopamine pathways do not appear to be involved in the control of ACTH release in experimental animals (Muller et al, 1977[a]) or in cortisol release in man (Collu et al, 1975; Willcox et al, 1975; Leebaw et al, 1978; Checkley, 1980).

ii. The role of noradrenaline pathways in ACTH and cortisol release

In vitro studies

Earlier in vitro evidence suggested that corticotrophin releasing factor was stimulated by acetylcholine (nicotinic) and inhibited by alphanoradrenergic influences (Jones et al, 1976; Buckingham and Hodges, 1979). This view has been disputed by Fehm et al (1980) who observed that noradrenaline stimulated corticotrophin releasing factor, an effect which was blocked by phentolamine.

Animal studies

Evidence from animal studies suggest that alphanoradrenergic pathways may exert an inhibitory role in the regulation of ACTH release, particularly stress-induced release (Martin et al, 1977; Muller et al, 1977[a]; Ganong, 1980). Muller et al (1977[a]) in a comprehensive review of different experiments in animals in which a variety of procedures had been used, concluded that noradrenergic pathways appeared to have an inhibitory role in ACTH release, particularly in rats and dogs.

Ganong (1980) demonstrated that clonidine caused an inhibition of stress induced ACTH secretion and concluded that noradrenaline acts postsynaptically to inhibit

corticotrophin releasing hormone secretion. Furthermore Ganong et al (1982) gave evidence that in dogs, this inhibition occurs at post synaptic alpha 2 receptors.

Studies in humans

An inhibitory role for the alpha noradrenergic system on stress induced ACTH secretion has been proposed by Lancranjan et al (1979[a]) following the finding that guanfacine, an alpha adrenoceptor agonist reduced ACTH secretion stimulated by insulin-induced hypoglycaemia; a finding consistent with that of Wilcox et al (1975) that noradrenaline infusion decreased ACTH and cortisol levels.

The bulk of evidence from human studies in which a variety of different experimental procedures have been used (Rees et al, 1970; Nakai et al, 1973; Jezova-Repcekova et al, 1979; Checkley, 1980) suggests that ACTH and cortisol secretion is under stimulatory alpha noradrenergic control and inhibitory beta noradrenergic control. For example, the rise in cortisol secretion following IM methylamphetamine was attenuated by thymoxamine and accentuated by propranolol (Rees et al, 1970).

iii. The anterior pituitary axis and affective disorder

Cortisol levels are elevated in depressed patients, particularly in the evening, and these levels return to normal following recovery (Checkley, 1980; 1982[b]; Johnson,

1982). Many endogenously depressed and manic patients show a failure of suppression of cortisol secretion following dexamethasone, which usually returns to normal upon recovery (Graham et al, 1982; Carroll et al, 1982; Johnson, 1982). These observations however do not allow any inference about the role of the catecholamine pathways in affective disorder.

The cortisol response to insulin induced hypoglycaemia is reported to be reduced in endogenous depression, an effect that may be mediated by alpha noradrenergic pathways (Siever et al, 1981). The cortisol response to methylamphetamine is decreased in patients with endogenous depression but returns to normal following recovery (Checkley and Crammer, 1977; Checkley, 1979). The authors proposed that this observation supported the hypothesis of alpha noradrenergic hypofunction in some patients with endogenous depression.

b. Results

i. The effects of the blocking drugs alone

Pimozide

Pimozide induced a dose related non significant fall with the difference from placebo following pimozide 4 mg being, -184.8(+-66.3) nmols / litre, (P <.1) at 3 hours. See figure 2.7.

The estimates of the areas under the curve are as follows:

Placebo: -195.1(+-224.5)

PMZ 2 mg: -403.0(+-80.4)

PMZ 4 mg: -796.8(+-149.2)

net incremental area under the curve following PMZ 4 mg: -601.6(+-338.9), P <.2.

Thymoxamine

Thymoxamine also induced a relative fall in cortisol levels when compared with placebo which was most noticeable at one hour when the differences were as follows:

Thymoxamine 80 mg: -107(+-48.5) nmols / litre, P <.2

Thymoxamine 160 mg: -82.8(+-55.7) nmols / litre, P <.3

See figure 2.8.

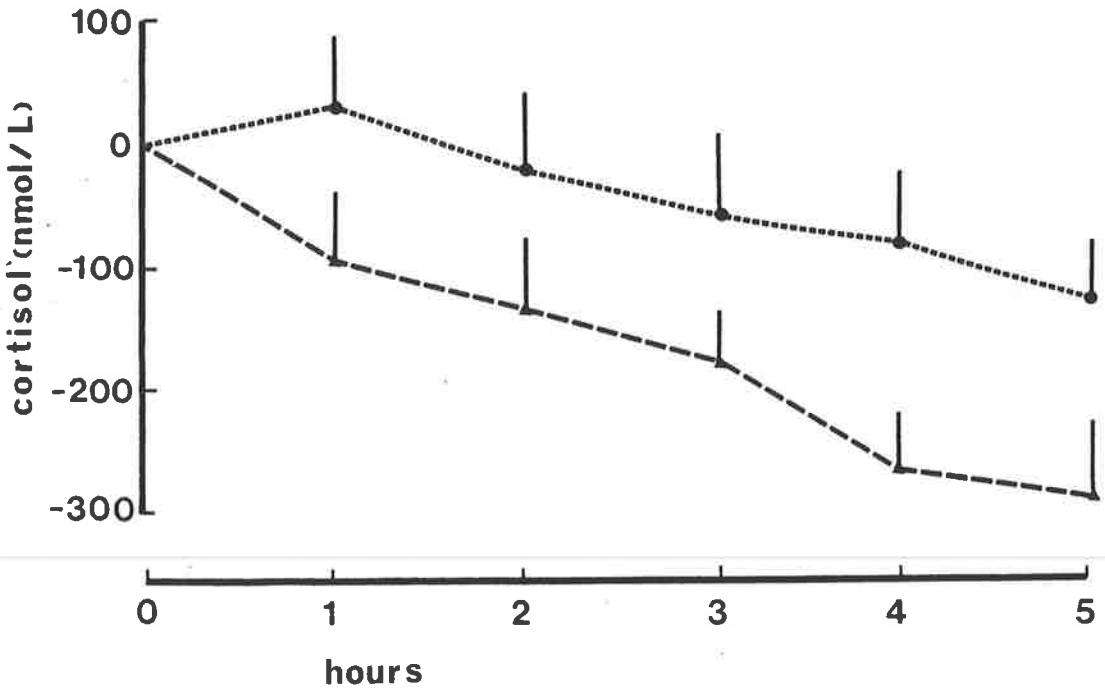

Figure 2.7 Mean (± SEM) incremental plasma cortisol (nmol/L):

placebo ●·····

PMZ 4mg ▲– – – –

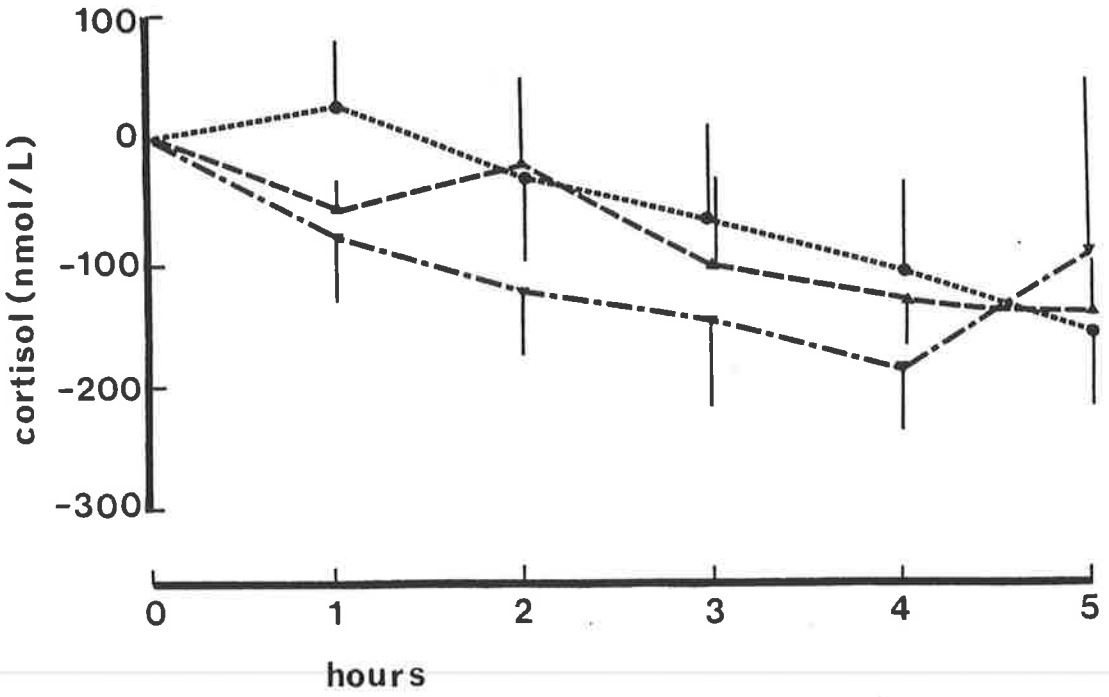

Figure 2.8 Mean (± SEM) incremental plasma cortisol (umol/L):

placebo ●·····

TMX 80mg ▼—·—·—

TMX 160mg ▲— — —

Estimates of area under the curve measures are as follows:

Placebo: -278.1(+-260.7)

TMX 80 mg: -556.0(+-239.9)

TMX 160 mg: -353.1(+-176.0)

net incremental area under the curve following TMX 160 mg: -278.1(+-132.1), P <.2.

ii. The effects of pimozide and thymoxamine pretreatment on the neuroendocrine response to oral dextroamphetamine

In both experiments B and D plasma cortisol levels fell steadily throughout, reflecting the diurnal drop in cortisol secretion in the evening. Dextroamphetamine induced a significant rise in plasma cortisol secretion at all times apart from 1 hour in experiment B.

Pimozide pretreatment was without influence on the cortisol response to dextroamphetamine. See figure 2.9.

Area under the curve estimates are as follows:

Placebo: -384.5(+-176.6)

dAMP 20 mg: +616.6(+-83.7)

PMZ 2 mg + dAMP 20 mg: +586.0(+-82.9)

PMZ 4 mg + dAMP 20 mg: +540.6(+-58.9)

Thymoxamine pretreatment, on the other hand, had an inconsistent effect. The 80 mg pretreatment dosage caused

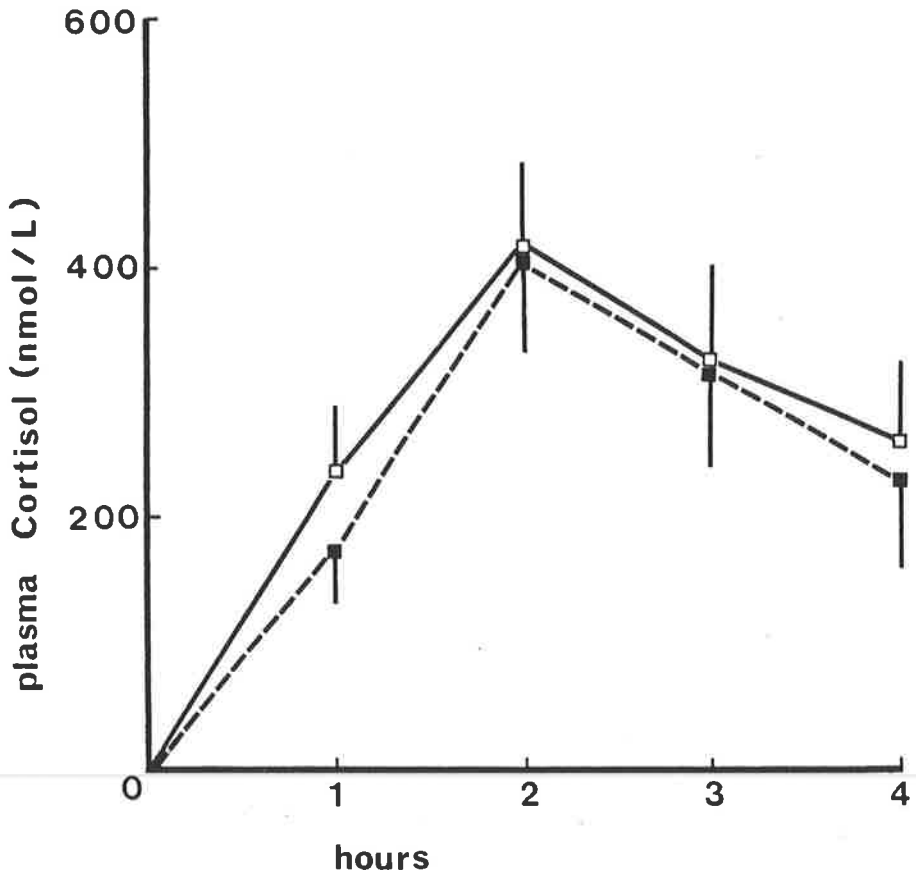

Figure 2.9 Mean (± SEM) net incremental plasma cortisol (nmol/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of PMZ 4mg given 2 hours earlier:

PMZ placebo - dAMP 20mg

PMZ 4mg - dAMP 20mg

an accentuation of the increase in cortisol secretion induced by dextroamphetamine which reached statistical significance at one and two hours. The differences between the means plasma cortisol levels following the thymoxamine 80 mg - dextroamphetamine 20 mg and thymoxamine placebo - dextroamphetamine 20 mg combination were +102.3(+-41.5) nmols/litre ($P < .05$) and +116.3(+-37) nmols/litre ($P < .01$) at one and two hours respectively. See figure 2.10. Pretreatment by the higher dose of thymoxamine tended to reduce the cortisol response to dextroamphetamine, though only modestly and late. The maximum attenuation was at 4 hours when the difference between the mean levels following the thymoxamine 160 mg - dextroamphetamine 20 mg and thymoxamine placebo - dextroamphetamine 20 mg combination was -42.1(+-28.4) nmols/litre ($P < .2$).

Area under the curve estimates are as follows:

placebo: -256.5(+-101.2)

dAMP 20 mg: +323.3(+-90.4)

TMX 80 mg + dAMP 20 mg: +539.3(+-75.5)

TMX 160 mg + dAMP 20 mg: +264.6(+-86.7)

Net incremental changes following TMX 80 mg and TMX 160 mg pretreatment compared with dAMP alone: +216.0(+-96.6) ($P < .05$) and -58.8(+-82.4) (NS) respectively.

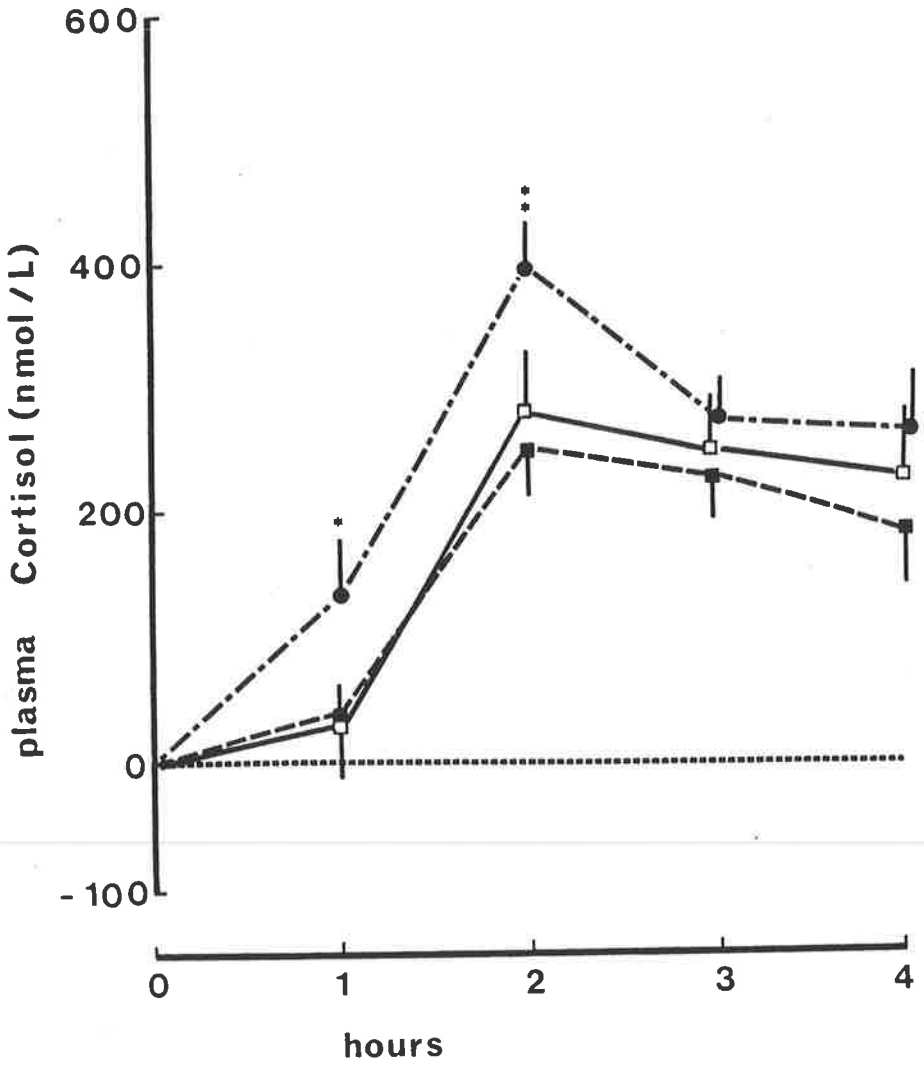

Figure 2.10 Mean (± SEM) net incremental plasma cortisol (nmol/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of TMX 80mg and TMX 160mg given 1 hour earlier:

TMX placebo - dAMP 20mg
TMX 80mg - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX on the dAMP response.
*P < .05 **P < .01

c. Discussion

The rise in cortisol levels following administration of oral dextroamphetamine is consistent with a variety of studies using amphetamine derivatives (Besser et al, 1969; Rees et al, 1970; Checkley, 1979). (See 2.1.). It had been assumed that this rise reflected an increase in ACTH secretion. As mentioned earlier (2.3.3.) the work of Fehm et al (1984) has cast doubt on this assumption. In their study, in contrast with the earlier study of Besser et al (1969), the rise in cortisol levels following intravenous methylamphetamine was not associated with a comparative rise in ACTH. Fehm et al (1984) conclude that the methylamphetamine induced rise in cortisol levels was independent of ACTH. Clearly, caution is required in interpreting the current results as reflecting ACTH activity rather than the effects on the secretion on cortisol secretion alone, until these questions are resolved.

Dopamine pathways

The absence of influence of pimozide on the dextroamphetamine stimulated increase in cortisol secretion implies no involvement of dopamine pathways in ACTH - cortisol secretion. The modest net drop in incremental plasma cortisol following pimozide alone may be a reflection of the drugs general sedating and anxiolytic effect and not a direct effect on the hypothalamo - adrenal axis.

Noradrenaline pathways

Oral thymoxamine given prior to dextroamphetamine did not produce the same effect as intravenous thymoxamine which attenuated the increase in plasma cortisol induced by intravenous methylamphetamine (Rees et al, 1970). The reason for this discrepancy is not clear. As both studies were conducted in the early evening, it cannot be due to the diurnal variation in cortisol secretion.

Furthermore no clear cut explanation for the difference in the effect of the two doses of thymoxamine can be given. One possible explanation is that thymoxamine may be exerting responses at either pre- or postsynaptic adrenoceptor sites depending on its dose. However, until it can be shown that thymoxamine has presynaptic alphanoradrenergic blocking activity, such a suggestion must remain conjectural.

A possible explanation for the reported differences in the effect of thymoxamine may depend on whether or not the response being measured is stress-related or not. The alpha noradrenergic pathways may inhibit corticotrophin releasing factor and stress-induced stimulation of ACTH, while exerting a physiologically stimulating role on the secretion of ACTH which is not stress related.

It is not possible to elucidate how much the rise in cortisol in this experiment was a stress response or due to the direct stimulation by the catecholamine pathways in the hypothalamus, anterior pituitary or at the level of the

adrenal cortex.

The role of the alpha noradrenergic pathways in the control of ACTH - cortisol secretion in humans therefore remains unresolved, with experimental evidence for both an excitatory and an inhibitory role. See literature review 2.4.2.a.

Affective illness

Pharmacological challenge investigating the cortisol response in depressive illness has been taken to imply central alpha noradrenergic hypofunction in endogenous depression (Checkley, 1980; 1982[b]; Siever et al, 1981; Johnson, 1982). Some of these conclusions have rested on the assumptions that changes in cortisol secretion reflected central activity in the hypothalamo anterior pituitary adrenal axis and that the alphanoradrenergic pathways exert a stimulatory action in the control of ACTH and cortisol release. It can be seen that these conclusions are open to question.

In conclusion, the results of this study give support to the view that dopamine pathways are not involved in the control of cortisol release in humans. As far as thymoxamine is concerned, the lack of a dose response relationship makes the findings difficult to interpret.

2.4.3. Prolactin

a. Literature review.

Prolactin secretion from the lactotroph appears to be released autonomously (Hall, 1984), but is under predominantly inhibitory control by the hypothalamus. Transection of the pituitary stalk causes a rise in prolactin secretion. The inhibitory control, via Prolactin Inhibitory Factor, involves the tuberoinfundibular dopamine system. There is considerable evidence that dopamine itself acts as the major physiological prolactin inhibitory factor, having a direct effect on the pituitary lactotroph (Muller et al, 1977[a]; Martin et al, 1977; Scanlon et al, 1979[a]; Gudelsky, 1981).

The same mechanism appears to act in humans (Besser et al, 1980).

i. The role of the dopamine pathways in the release of prolactin release

In vitro and animal studies

As mentioned above, there is good evidence that dopamine physiologically inhibits prolactin release. Dopamine neurones of the tuberoinfundibular system originate in the arcuate and periventricular nuclei of the hypothalamus and project axons to the external layer of the median eminence

where they terminate in close proximity to the hypophysial portal vessels. Dopamine released into the hypophysial portal vasculature has a direct acute inhibitory effect on the anterior pituitary lactotroph, inhibiting prolactin release (Muller et al, 1977[a]; Clemens et al, 1979; Gudelsky, 1981; Gudelsky et al, 1984). Increased dopamine levels over a period of time leads to a decrease in prolactin synthesis, an increase in prolactin degeneration and a reduction in cell division by the lactotroph (Cronin, 1982). This latter action is important in the clinical use of bromocriptine (a dopaminergic agonist) in the treatment of prolactin secreting tumours (Martin et al, 1977, Scanlon et al, 1979[a]). Increased prolactin levels in turn lead to an activation of tuberoinfundibular dopamine neurones and an increase in dopamine secretion in the median eminence (Moore and Johnston, 1982; Gudelsky 1981, Hall, 1984).

Oestrogens and progesterones appear to modulate the activity of the tuberoinfundibular dopamine neurones. Progesterone and oestradiol respectively increase or decrease the concentration of dopamine in the pituitary portal plasma (Gudelsky, 1981). In addition to interacting with the dopamine control of prolactin release, oestrogens may exert a direct stimulatory action on the lactotroph (Lloyd et al, 1973; Scanlon et al, 1979[a]).

Human studies

There is good evidence that the mechanism of controlling prolactin secretion by dopamine is the same in humans (Scanlon et al, 1979[a]; Besser et al, 1980). As mentioned above this is reflected in the clinical use of bromocriptine in the treatment of prolactin secreting pituitary adenomas.

ii. The role of noradrenergic pathways in the control of prolactin secretion

Animal studies

The role of the noradrenergic pathways in prolactin release remains to be clarified. In their comprehensive review Muller et al (1977[a]) report evidence that noradrenergic pathways may exert an inhibitory action on the resting secretion of prolactin as the alpha noradrenergic blocking drugs phentolamine and phenoxybenzamine, and the beta blocker propranolol increased serum prolactin levels in primates (Quadri et al 1976). Muller et al (1977[a]) propose too that betanoradrenergic pathways may exert a stimulatory action on tuberoinfundibular dopamine neurones.

Human studies

Few studies have been performed and the role of noradrenergic pathways in the control of prolactin release

in humans remains uncertain (Checkley, 1980). Lancranjan et al (1979[b]) reported that although neither clonidine or guanfacine (both alpha noradrenergic agonists) affected resting prolactin levels, guanfacine inhibited the prolactin rise following insulin induced hypoglycaemia.

Prolactin and affective disorders

Baseline prolactin levels have been reported to be within the normal range or elevated in patients with depression (Checkley, 1980; 1982[b]; Johnson, 1982). The prolactin response to TRH in depressed patients has been reported as being reduced or enhanced (Johnson, 1982). They may also show an augmented reduction of prolactin secretion following apomorphine challenge (Insel and Siever, 1981). Checkley (1980) concluded that evidence from studies investigating prolactin secretion in depression probably implies normal functioning of the dopamine receptors.

b. Results

i. The influence of the blocking drugs alone

Neither dose of thymoxamine exerted any influence on serum prolactin levels. Pimozide administration caused a dose related rise in serum prolactin secretion in the latter part of the experiment. See figure 2.11. At 5 hours post pimozide administration, the differences from placebo were;

pimozide 2 mg +335.0(+-81.8) mU/L, P <.05

pimozide 4 mg +997.0(+-138.5) mU/L, P <.01

Estimates of the mean (+-SEM) areas under the curve.

Pimozide:

placebo: +72.8(+-88.6)

PMZ 2 mg: +491.2(+-103.5)

PMZ 4 mg: +1476.2(+-539.8)

Net incremental levels following PMZ 4 mg: +1403.5(+-463.9), P <.1

Thymoxamine:

placebo: +98.4(+-70.5)

TMX 80 mg: +82.5(+-53.4)

TMX 160 mg: +107.5(+-84.9)

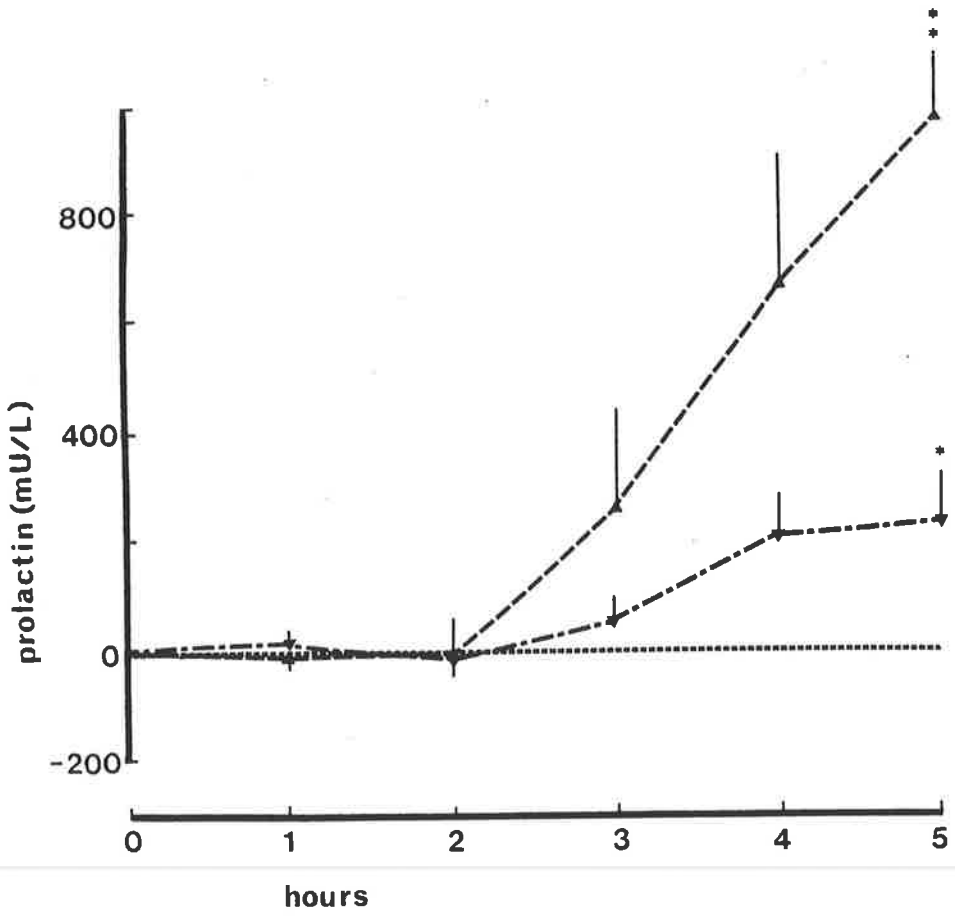

Figure 2.11 Mean (± SEM) net incremental serum prolactin (mU/L) following PMZ 2mg and PMZ 4mg:

PMZ 2mg

PMZ 4mg

Difference versus placebo. *P < .05 **P < .01

ii. The effects of pretreatment by pimozide and thymoxamine on the prolactin response to dextroamphetamine

Pimozide pretreatment led to a large dose related rise in serum prolactin levels. This increase was highly significant when one compares both pimozide pretreatment combinations with the placebo - placebo and placebo pimozide - dextroamphetamine 20 mg at all times (apart from the reading at one hour following pimozide 2 mg pretreatment). See figure 2.12. At 3 hours (5 hours post pimozide administration) the net incremental serum prolactin levels from placebo were:

Pimozide 2 mg pretreatment: +88.6(+-109.4) mU/L, $P < .001$

Pimozide 4 mg pretreatment: +1221.9(+-134.4) mU/L, $P < .001$

The net incremental serum prolactin levels compared with amphetamine alone at the same time were:

Pimozide 2 mg pretreatment: +827.4(+-133.9) mU/L, $P < .001$

Pimozide 4 mg pretreatment: +1160.8(+-135.1) mU/L, $P < .001$

The increase after 4 mg pimozide pretreatment was greater than after 2 mg and occurred earlier. At two hours the difference between the two was 401.3(+-148.6) mU/L, $P < .025$.

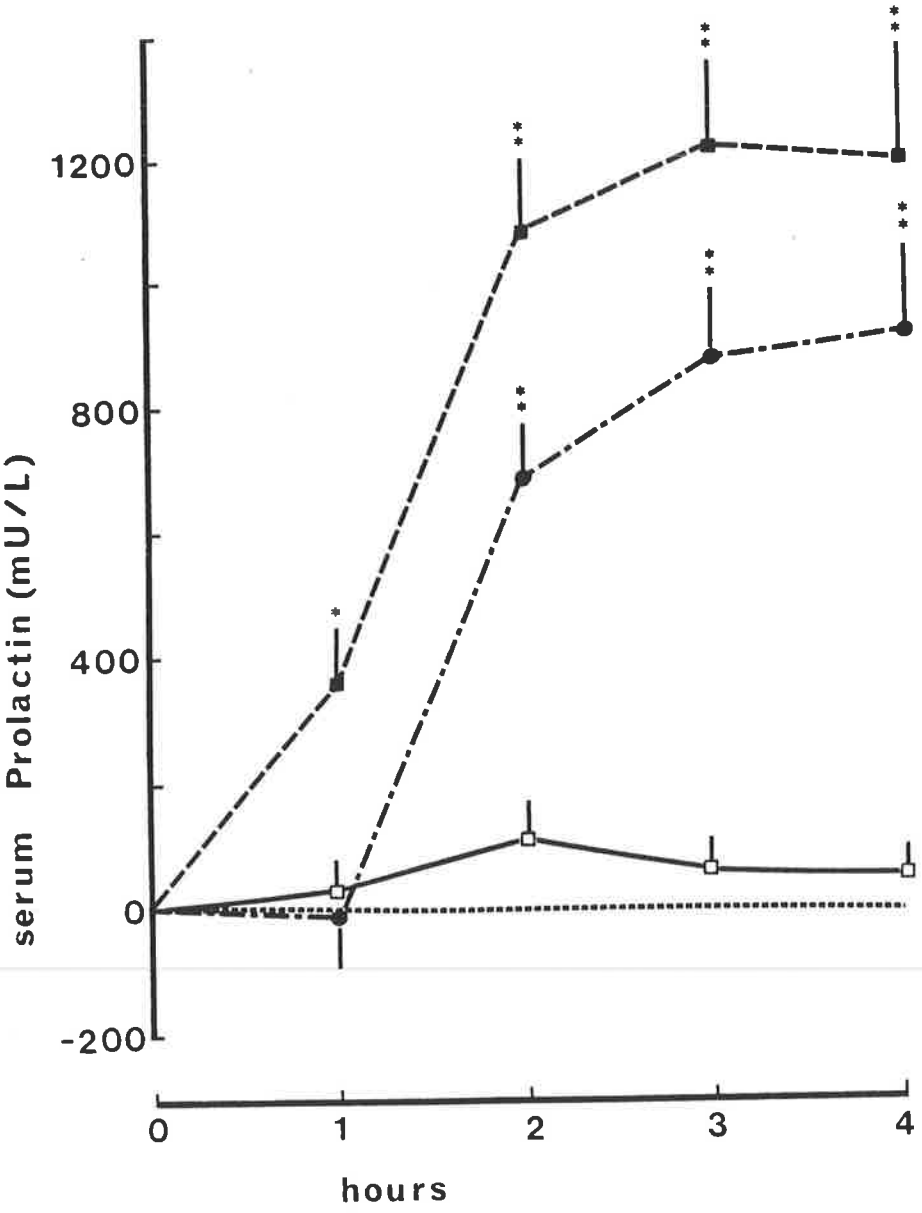

Figure 2.12 Mean (± SEM) net incremental serum prolactin (mU/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of PMZ 2mg and PMZ 4mg given 2 hours earlier:

PMZ placebo – dAMP 20mg
PMZ 2mg – dAMP 20mg
PMZ 4mg – dAMP 20mg

Difference induced by PMZ on the response to dAMP.
*P < .025 **P < .001

Estimates of the mean (+-SEM) areas under the curve are as follows:

Placebo: +10.7(+-100.3)

dAMP 20 mg: +208.3(+-68.3)

PMZ 2 mg +
dAMP 20 mg: +2037.0(+-259.8)

PMZ 4 mg +
dAMP 20 mg: +3094.5(+-252.4)

The increases in mean area under the curve following both doses of pimozide were highly significant ($P < .001$)

Thymoxamine pretreatment did not influence the small increase in serum prolactin induced by dextroamphetamine. See figure 2.13. The mean (+-SEM) area under the curve estimates are as follows.

placebo: -23.3(+-45.1)

dAMP 20 mg: +65.3(+-52.1)

TMX 80 mg +
dAMP 20 mg: +77.0(+-64.0)

TMX 160 mg +
dAMP 20 mg: +108.6(+-63.7)

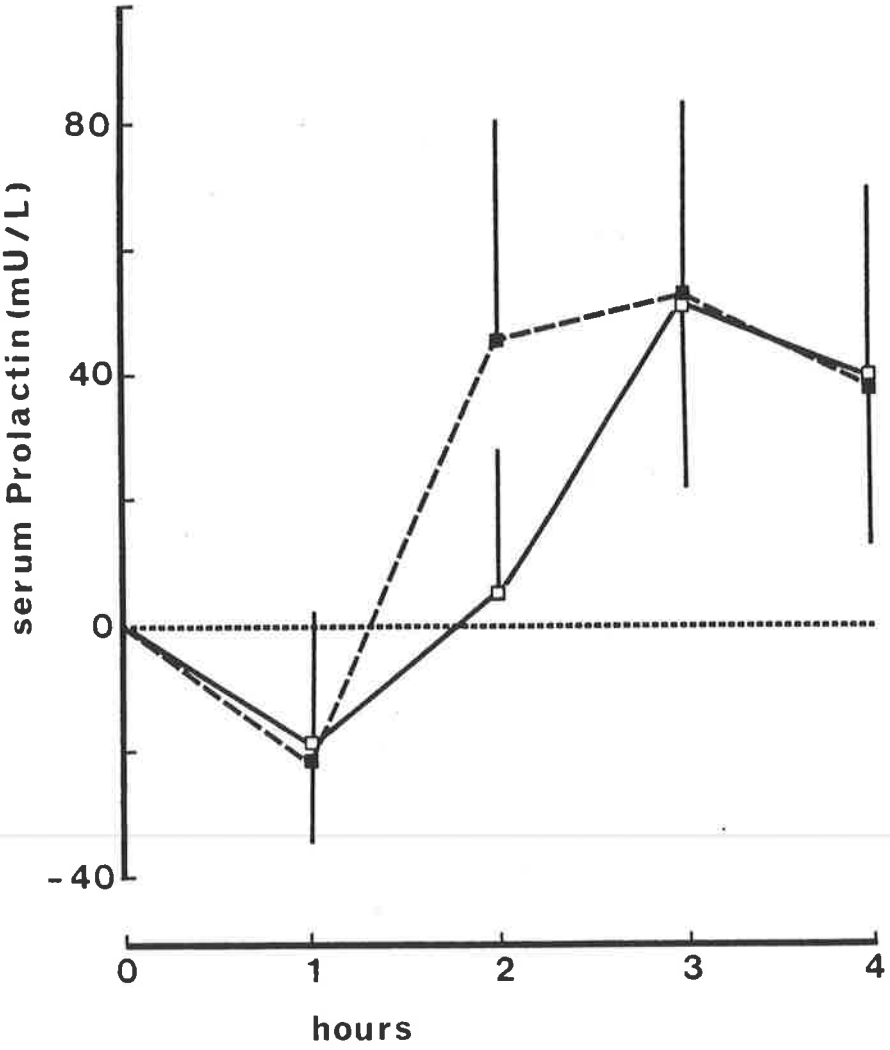

Figure 2.13 Mean (± SEM) net incremental serum prolactin (mU/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of TMX 160mg given 1 hour earlier:

TMX placebo - dAMP 20mg

TMX 160mg - dAMP 20mg

c. Discussion.

Dopamine blockade by Pimozide considerably increased the serum levels of prolactin in both the basal state and after dextroamphetamine. Thymoxamine pretreatment on the other hand was without any consistent effect. These findings are consistent with other studies investigating the role of the catecholamine pathways in prolactin release which demonstrate that the dopamine pathways act in an inhibitory manner in prolactin release and which imply that noradrenergic pathways are probably not involved.

A significant observation from the study investigating the effect of pimozide alone (figure 2.11.) is that dopamine blockade does not begin until at least 2 hours after oral pimozide. This is important in the interpretation of the influence by pimozide on dextroamphetamine induced arousal. Any reduction in arousal occurring 2 hours after pimozide (predextroamphetamine) observed in Part I of this study is not likely to be due to dopamine blockade.

The results do not influence conclusions about the activity of the catecholamine pathways in affective disorder from pharmacological challenge of neuroendocrine activity.

2.4.4. Growth hormone

a. Literature review

Growth hormone release from the somatotrophs in the anterior pituitary is under positive control from the hypothalamus via growth hormone releasing factor. The hypothalamus also secretes an inhibitory tetradecapeptide, growth hormone inhibitory factor or somatostatin (Cryer and Daughaday, 1977; Martin et al, 1977; Wass, 1983; Martin, 1983). Secretion of growth hormone in nonstressed humans is at basal levels, although significant fluctuations can occur with spontaneous surges of growth hormone secretion occurring at intervals regularly throughout the day. The largest peak is usually observed during the first two hours of sleep (Martin, 1983).

The catecholamine control of growth hormone secretion appears to be relatively complex and interspecies differences have been reported (Muller et al, 1977[a]).

i. The role of dopamine pathways in growth hormone secretion

Animal studies

In the rat, Muller et al (1977[b]), observed that dopamine pathways appeared to exert a stimulatory influence on growth hormone secretion in the new born rat but an inhibitory

influence in the adult. In the mouse dopamine pathways appear to be inhibitory (Muller et al, 1977[a]), while in the dog, haloperidol and pimozide reduced the growth hormone releasing effect of nomifensine (Casanueva et al, 1981) implying a stimulatory role for the dopamine pathways.

In baboons, intravenous dopamine infusion elevated growth hormone secretion, the elevation being suppressed by phentolamine. However, micro injections of dopamine into the hypothalamus lowered basal growth hormone levels (Steiner et al, 1978).

Human studies

Invitro studies using human pituitary cells demonstrated a suppression of growth hormone release from both normal and adenomatous cells by dopamine or bromocriptine which was blocked by haloperidol, metoclopramide and sulpiride (Ishibashi and Yamaji, 1984).

In vivo studies show a variable response by dopamine pathways on growth hormone release. Dopamine (Leebaw et al, 1978; Woolf et al, 1979; Ferrari et al, 1981) and the dopamine agonists, apomorphine (Lal et al, 1975), lergotrile and piribedal (Thorner et al, 1978) produce a rise in growth hormone, which can be blocked by the dopamine antagonists metoclopramide (Thorner et al, 1978) and chlorpromazine (Lal et al, 1975). (See also Scanlon et al, 1979[a]; Checkley, 1980). Pimozide reduced arginine and exercise induced growth

hormone release (Schwinn et al, 1976). On the other hand growth hormone secretion is increased by metoclopramide in hypogonadal and adolescent boys (Cohen et al, 1979 [a] and [b]).

While dopamine infusion, as mentioned above, stimulated growth hormone secretion, it inhibited the growth hormone response to insulin induced hypoglycaemia and L dopa (Leebaw et al, 1978; Woolf et al, 1979). Dopamine infusion, bromocriptine and L dopa give rise to a fall in growth hormone secretion in acromegaly (Muller et al, 1977[b]; Parkes et al, 1978; Roelfsema et al, 1978; Scanlon et al,1979[a]).

In the light of this apparently conflicting evidence, it has been suggested that dopamine pathways play a dual role in growth hormone release: stimulating basal growth hormone secretion but reducing stimulated growth hormone release (Leebaw et al, 1978; Scanlon et al, 1979[a]). Martin (1983) proposed that the inhibitory effect of dopamine is at the pituitary level.

ii. The role of noradrenergic pathways in growth hormone secretion

Animal studies

Most studies in animals suggest that the alpha noradrenergic system stimulates the release of growth hormone while the beta noradrenergic system is probably inhibitory.

Both Hypothalamic infusion and intravenous noradrenaline give an elevation of growth hormone secretion (Steiner et al, 1978; Martin, 1980) as does L dopa and clonidine, the rise induced by L dopa being blocked by phentolamine or phenoxybenzamine in dogs and baboons (Muller et al, 1977[a]; Martin, 1980). Phenoxybenzamine also completely inhibited growth hormone secretory episodes (Martin et al, 1980). Beta noradrenergic pathways either exert no effect or an inhibitory effect in different species (Muller et al, 1977[a]; Martin, 1983).

Human studies

Most evidence in human studies point to the alpha noradrenergic pathway acting in a stimulatory manner while the beta noradrenergic pathways exert an inhibitory action on growth hormone release.

Growth hormone secretion is increased by the alpha noradrenergic agonists clonidine (Lal et al, 1975) and guanfacine (Langranjan et al, 1979[b]). Stimulation of growth hormone secretion by L dopa, insulin induced hypoglycaemia, stress or exercise is blocked by alpha noradrenergic antagonists (Blackard and Heidingsfelder, 1968; Sachar et al, 1975; Jezova-Repakova et al, 1979; Scanlon et al, 1979[a]; Checkley, 1980; Martin, 1983).

Rees et al (1970), on the other hand, observed that the modest rise in growth hormone secretion following intravenous methylamphetamine was augmented by thymoxamine, though the difference did not reach statistical significance; propranolol had a greater effect significantly augmenting growth hormone secretion. Propranolol also has been reported to enhance the growth hormone release induced by glucagon, insulin induced hypoglycaemia, vasopressin and L dopa (Blackard and Heidingsfelder, 1968; Martin et al, 1983).

Growth hormone and affective disorder

A variety of pharmacological challenges have been performed to examine growth hormone secretion in affective disorder. The growth hormone response to hypoglycaemia is reported to be reduced in depressed and manic patients (Checkley, 1980; Johnson, 1982, Silverstone and Cookson, 1982). Some workers report an abnormal response to

amphetamine (Langer et al, 1976; Arato et al, 1983). Others have reported no difference between the depressed and non depressed state (Checkley and Crammer, 1977; Checkley, 1979). Both desipramine and clonidine challenge were reported to be associated with a diminished growth hormone response in depression (Laakman, 1980; Checkley, 1980; 1982[b]; Siever et al, 1981; Checkley et al, 1981; Honer et al, 1984). These findings have been taken to imply a deficiency of functioning of the alpha noradrenergic pathways in affective disorder (Langer and Matussek, 1977; Garver and Davis, 1979; Laakman, 1980; Checkley, 1982[b]).

The Growth hormone response to challenge by dopamine agonists including apomorphine and L dopa varies with some studies reporting no effect, a reduced or even an augmented effect in some depressed patients (Insel and Siever, 1981; Johnson, 1982; Checkley, 1982[b]).

b. Results.

i. Influence of the blocking drugs alone

The changes in serum growth hormone secretion induced by pimozide and thymoxamine alone are difficult to evaluate. In both experiments some subjects secreted a surge of growth hormone prior to the drugs' administration. Therefore the reference values for estimating changes in secretion were not comparable. If the subjects secreting more than 5 mU/L at base time are excluded, there is insufficient remaining data to draw any conclusions.

ii. Influence of blockade by pimozide and thymoxamine on the growth hormone response to dextroamphetamine

In both experiment B and D a rise in growth hormone secretion following placebo is evident. Dextroamphetamine administration appears to produce an early accentuation, followed by a later attenuation of this rise. These changes did not reach statistical significance. Pimozide pretreatment appeared to accentuate both the early rise and the late fall induced by dextroamphetamine. See figure 2.14 and table 2.I.

At one hour the net incremental serum growth hormone rise compared with placebo, following 2mg and 4 mg of pimozide pretreatment (matching pairs data only) were: +8.7(+-3.4) mU/L, and 19.1(+-7.0) mU/L, ($P < .05$), and at 3 hours; -6.3(+-4.5) mU/L (NS) and -10.0(+-3.7) mU/L, ($P < .05$) respectively.

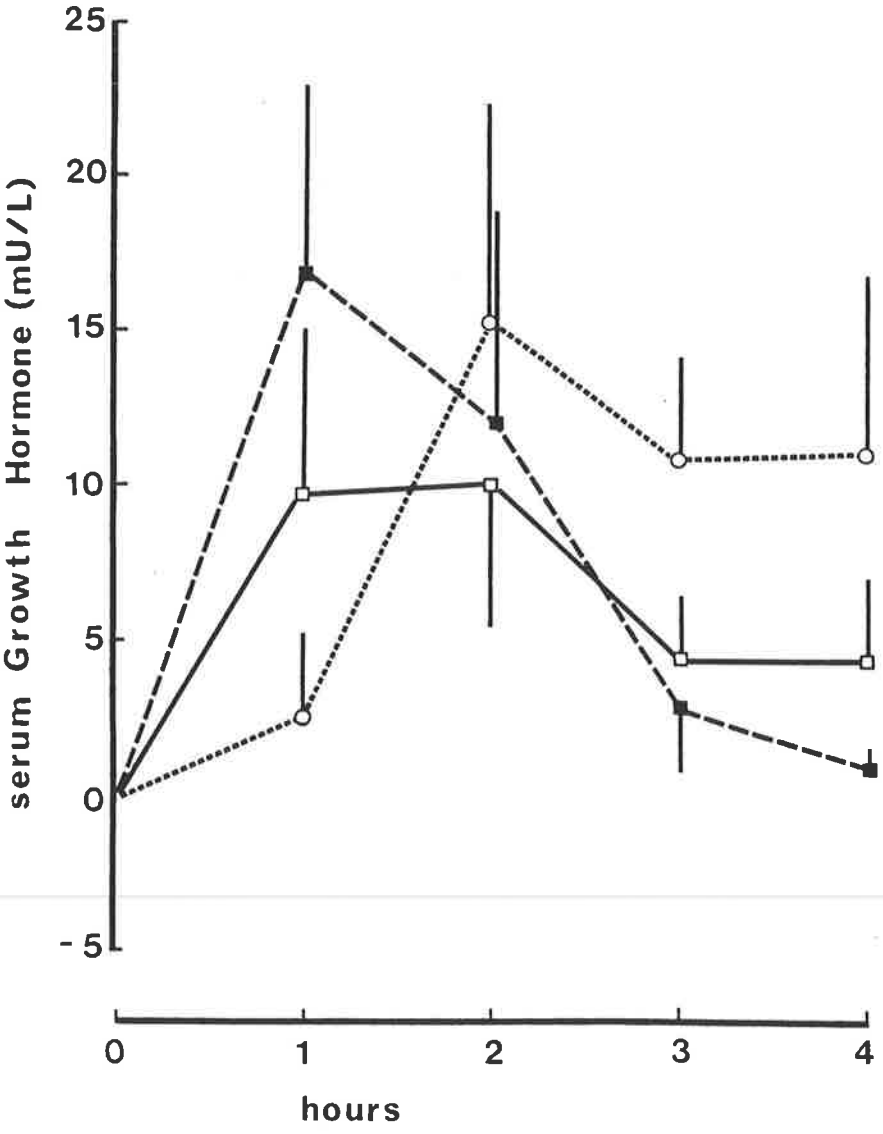

Figure 2.14 Mean (± SEM) incremental growth hormone (mU/L) demonstrating the response to oral dAMP 20mg given at 0 (1800) hours and the effect of PMZ 4mg given 2 hours earlier:

PMZ placebo - dAMP placebo

PMZ placebo - dAMP 20mg

PMZ 4mg - dAMP 20mg

The higher dose of pimozide in particular tended to augment the influence of dextroamphetamine on serum growth hormone secretion, with an accentuation of the dextroamphetamine induced rise at 2 hours and a decrease in secretion at 4 hours. Differences (matched paired data only) at these times were; +5.4(+-2.5) mU/L, ($P < .1$) and -4.8(+-3.9) mU/L, ($P < .3$) respectively.

Table 2.1

Time	PMZ Plac dAMP Plac	PMZ plac dAMP 20mg	PMZ 2mg dAMP 20mg	PMZ 4mg dAMP 20mg
1h (mean change)	+2.6(+-2.8)	+9.6(+-5.5)	+8.6(+-2.8)	+16.6(+-6.1)
diff from plac - plac matched prs	0	+4.7(+-3.7)	+8.7(+-3.4) *	+19.1(+-7.0) *
diff from plac - dAMP matched prs		0	-1.0(+-6.8)	+8.1(+-4.9)
2h (mean change)	+15.3(+-7.0)	+9.9(+-4.7)	+7.9(+-4.5)	+11.9(+-6.6)
diff from plac - plac matched prs	0	-2.3(+-4.5)	-8.2(+-8.4)	-8.2(+-7.4)
diff from plac - dAMP matched prs		0	+1.2(+-1.8)	+5.4(+-2.5)
3h (mean change)	+10.8(+-3.1)	+4.3(+-2.2)	+5.8(+-1.9)	+2.7(+-2.0)
diff from plac - plac matched prs	0	-4.4(+-2.7)	-6.3(+-4.5)	-10.0(+-3.7) *
diff from plac - dAMP matched prs		0	-2.1(+-3.4)	-1.8(+-4.1)
4h (mean change)	+10.9(+-5.6)	+4.2(+-2.7)	+2.2(+-1.1)	+0.9(+-0.7)
diff from plac - plac matched prs	0	-1.9(+-7.1)	-4.8(+-3.7)	-9.8(+-4.6)
diff from plac - dAMP matched prs		0	-2.9(+-4.1)	-4.8(+-3.9)

Incremental serum growth hormone levels together with difference data following PMZ pretreatment. * P <.05.

Estimates of the areas under the curves revealed no significant differences.

Thymoxamine pretreatment particularly the higher dose, augmented the early rise in growth hormone with the net incremental serum growth hormone levels compared with dextroamphetamine alone at 2 hours was, +13.3(+-5.5) mU/L, P <.05. See figure 2.15.

Mean (+-SEM) area under the curve estimates are as follows:

placebo: +21.3(+-5.9)

dAMP 20 mg: +8.2(+-2.3)

TMX 80 mg + dAMP 20 mg: +20.2(+-4.8)

TMX 160 mg + dAMP 20 mg: +26.5(+-5.1)

Difference TMX 160 mg - dAMP 20 mg v dAMP alone (matched pair data only, n=8): +14.2(+-4.6), P <.02.

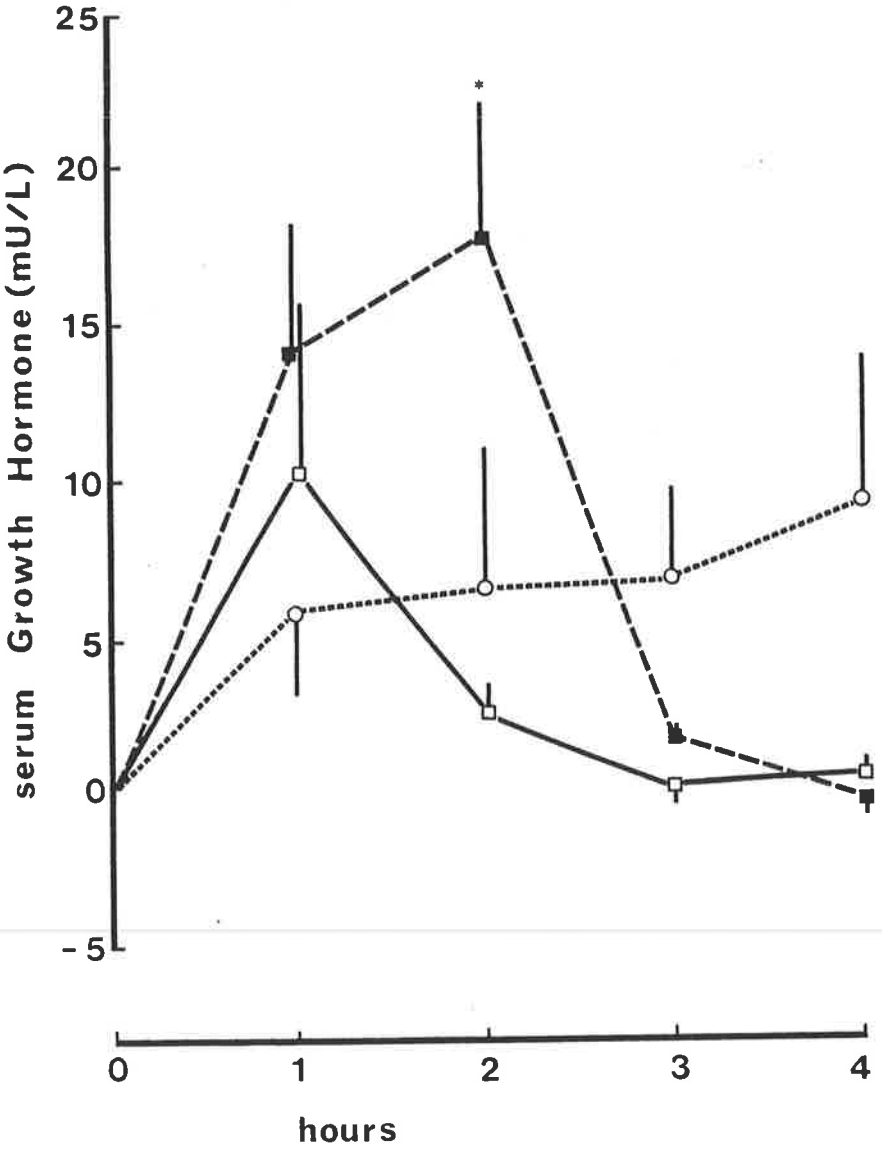

Figure 2.15 Mean (± SEM) incremental growth hormone (mU/L) demonstrating the response to oral dAMP 20mg given at 0 (1800) hours and the effect of TMX 160mg given 1 hour earlier:

TMX placebo - dAMP placebo
TMX placebo - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX on the dAMP response. *P < .05

c. Discussion.

It is difficult to make an interpretation of the role of catecholamine control of growth hormone secretion from these results. The possibly biphasic response by dextroamphetamine (an early stimulation followed by inhibition of secretion), might reflect an interaction of the influence of dextroamphetamine with other factors.

Dopamine pathways

The biphasic trends in growth hormone secretion following dextroamphetamine were augmented by pimozide pretreatment which failed to reach statistical significance, possibly as the number of matching pairs were too small. In view of these differential effects, it is possible that dopamine pathways exerted both excitatory and inhibitory influences on the dextroamphetamine response by growth hormone, and by implication, in the control of growth hormone release.

The role of the dopamine pathways in growth hormone release appears, from a review of the literature, to be complex with possibly an excitatory and inhibitory component to its action, both in experimental animals and in particular in humans. Scanlon et al (1979[a]) has proposed that perhaps the dopamine pathways play a dual role in growth hormone release in that they augment basal but reduce stimulated growth hormone release.

As dopamine infusion may effect both release and inhibition of release, an action outside the central nervous system as well as within the hypothalamus, appears to be involved (Muller et al, 1977[a]). The stimulatory effect of the dopamine pathways may be central, whereas the inhibitory effect of dopamine may be a direct effect on somatotrophs (Martin, 1983).

A dual action by the dopamine pathways on growth hormone release is not inconsistent with the findings in this study.

ii. The role of the noradrenergic pathways

Oral thymoxamine pretreatment, particularly the higher dose, increased net incremental serum growth hormone secretion when compared with the placebo-placebo combination or the placebo - dextroamphetamine combination. This suggests that the alpha noradrenergic pathways may have an inhibitory role in dextroamphetamine stimulated growth hormone release.

Similarly Rees et al (1970) reported an increase in growth hormone secretion following intravenous methyl amphetamine after intravenous thymoxamine pretreatment, though in that study the increase did not reach statistical significance. In the same experiment propranolol pretreatment significantly augmented the growth hormone response to intravenous methyl amphetamine.

Thymoxamine and its metabolites can block both alpha 1

adrenoceptors and histamine receptors. It is considered unlikely that its histamine blocking action is involved as histamine appears to be without influence in growth hormone release (Pontiroli et al, 1973).

Most experimental evidence to date, both in animals and humans, point to the alpha noradrenergic pathways being stimulatory and the beta noradrenergic pathways being inhibitory to growth hormone release. (See literature review 2.4.4.a).

It has been proposed that the site of noradrenergic stimulation of growth hormone release is within the central nervous system as release associated with extra hypothalamic (eg, amygdala) stimulation can be prevented by alpha noradrenergic blockade (Scanlon et al, 1979[a]; Martin, 1980). However as noradrenaline infusion and methoxamine can stimulate growth hormone release, it seems likely that there are some receptors outside the blood brain barrier in addition (Checkley, 1980).

The role of pre- or postsynaptic receptors are of particular relevance in clarifying the role of noradrenergic pathways in growth hormone release from pharmacological studies. For example, the noradrenergic agonists used in the studies in humans include both clonidine and guanfacine both of which are alpha 2 noradrenergic agonists (Doxey, 1979). These drugs may exert an action at either pre- or postsynaptic sites depending on the dosage and the function being investigated (Anden et al, 1976). This is important

because if the agonist used was in fact acting preferentially at presynaptic receptors, it would be exerting an inhibitory influence on the noradrenergic pathway. See Part I (1.3.4.b.).

This issue has been addressed in studies in experimental animals. Clonidine induced growth hormone secretion was blocked by yohimbine rather than prazosin or phenoxybenzamine in rats, implying an alpha 2 site of action (Eriksson et al, 1982). But as reserpine pretreatment did not abolish the clonidine response, Eriksson et al (1982) suggested that clonidine was acting at a postsynaptic alpha adrenoceptor site. In an extensive study investigating the relative roles of alpha 1 or alpha 2 adrenoceptors in growth hormone secretion in the rat, Krulich et al (1982) suggested that both pre and postsynaptic alpha noradrenergic receptors may be involved in the release of growth hormone with the alpha 1 receptor being inhibitory and the alpha 2 adrenoceptor involved in sustaining a tonic drive on secretion as well as pulsatile secretion.

Cella et al (1983) interpreted the findings of similar studies in the dog (which they believe more closely resembles the situation in humans), as showing that clonidine acts at presynaptically situated alpha 2 adrenoceptors, in stimulating the release of growth hormone. In their view clonidine, stimulated growth hormone release by inhibiting noradrenaline release onto postsynaptic sites, indicating that these postsynaptic

receptors were exerting an inhibitory action on the secretion of the hormone.

In a subsequent study Cella et al (1984) demonstrated, again in the dog, that activation of alpha 1 noradrenergic receptors was inhibitory to both tonic and stimulated growth hormone release.

If the previously noted rise in growth hormone following alpha noradrenergic stimulation in studies in humans, for example by clonidine, is manifest through an action by presynaptic stimulation, then noradrenaline may be exerting an inhibitory influence at postsynaptic sites. The results of this experiment and that of Rees et al (1970) would be in keeping with that.

It is important that these issues are resolved in the human situation. Clonidine has been used as a stimulant to test neuroendocrine and hence catecholamine activity in psychiatric illness. It has been reported that depressive patients showed a diminished response (Checkley et al, 1981; Sievers et al, 1982; Honer et al, 1984). This has been interpreted as reflecting a defect in function of central alpha noradrenergic receptors in depression.

Making inferences from other studies investigating noradrenergic function in affective disorder using pharmacological challenge is beset with problems. Changes in secretion following amphetamine are not always reproducible. Furthermore the effect of placebo conditions

must be considered. This appears to be particularly relevant when measuring the effect of amphetamine challenge. Finally, conclusions of hypo or hyper function of the noradrenergic pathways in depression, by investigating the growth hormone response to challenge of the alpha noradrenergic pathways, will require resolution of the question of whether they exert an inhibitory or excitatory action in growth hormone secretion in humans.

2.4.5. Thyrotrophin

a. Literature review

Thyrotrophin (TSH) secretion from the thyrotroph in the anterior pituitary is under positive control by the hypothalamus via thyrotrophin releasing hormone (TRH). TSH in turn stimulates the production and release of thyroxine and triiodothyronine (T4 and T3) which in turn exert a negative feedback on TSH release at the pituitary level (Martin et al, 1977; Scanlon et al,1979[a]).

i. The role of the dopamine pathways

Evidence from invitro, animal experiments as well as studies in humans, point to the dopamine pathways exerting an inhibitory influence on TSH release.

Invitro studies

TSH secretion from cultured cells was stimulated by dopamine antagonists (Hall and Meites, 1981) whereas dopamine itself reduced TSH release (Peters et al, 1983).

Animal studies

The dopamine agonists apomorphine, piribedal and bromocriptine have been observed to reduce TSH secretion in experimental animals (Muller et al, 1977[a]; Krulich et al,

1977; Krulich, 1982). Mueller et al (1976), reported that haloperidol blocked the effect of apomorphine. Apomorphine also reduced the cold stimulated rise in TSH secretion, an effect that was reversed by haloperidol, pimozide and sulpiride (Mannisto, 1981; Krulich, 1982).

Human studies

In humans, earlier studies investigating the role of dopamine pathways were inconclusive (Collu et al, 1975; Thorner et al, 1978). More recent studies have clearly established an inhibitory role for the dopamine pathways in TSH release (Scanlon et al, 1979[b]; Morley, 1981; Krulich, 1982). TSH release is stimulated by a variety of different dopamine blocking drugs including metoclopramide (Scanlon et al, 1977; 1979[a] and [b]; 1980[a] and [b]) and sulpiride (Massara et al, 1978[a]), haloperidol and pimozide (Delitala et al, 1981) while TSH secretion or the TSH response to TRH was inhibited by dopamine infusion (Scanlon et al, 1977; 1979[a]; Massara et al, 1978[b]; Leebaw et al, 1978). The stimulating response to dopamine blocking drugs is greater in hypothyroid patients (Scanlon et al, 1980[b]) and women (Scanlon et al, 1977; Massara et al, 1978[a]).

ii. The role of the noradrenaline pathways

Invitro studies

Noradrenaline causes a release of TRH from hypothalamic tissue (Grimm and Reichlin, 1973) and of TSH from pituitary - hypothalamo coincubations which can be blocked by the alpha noradrenergic blocker, phentolamine but not the beta blocker propranolol (Hall and Meites, 1981). Noradrenaline also caused a release from anterior pituitary cells alone (Peters et al, 1983).

Animal studies

Experiments in animals point to a stimulatory role for the alpha noradrenergic pathways in TSH release (Muller et al, 1977[a]; Krulich, 1982).

Basal TSH levels were found to be reduced by phentolamine and by dopamine beta hydroxylase inhibition (Krulich et al, 1977). Similarly the stimulatory response by TSH to cold in the rat was blocked by dopamine beta hydroxylase inhibition, phentolamine and phenoxybenzamine and augmented by clonidine (Krulich et al, 1977, Montoya et al, 1979). Krulich (1982) concludes that the noradrenergic pathways appear to act via the release of TRH.

Human studies

The role of the noradrenergic pathways in TSH release has been relatively little studied. Investigation of the influence of clonidine (Lal et al, 1975) or the influence of a variety of noradrenergic agonists and antagonists on the TSH response to TRH (Lauridsen et al, 1976) led to the conclusion that noradrenergic mechanisms were of little importance. Zgliczynski and Kaniewski, 1980) found that phentolamine but not propranolol reduced both basal TSH levels and the TSH response to TRH, implying a stimulatory role for the alpha noradrenergic pathways.

TSH and affective disorder

In some patients with either endogenous depression or mania, the TSH response to TRH is reduced (Kirkegaard et al, 1975; 1978; Johnson, 1982; Checkley, 1982[b]). These observations do not allow any conclusions about catecholamine activity to be drawn. Furthermore there appears to have been no direct study or pharmacological challenge of TSH secretion to investigate the roles of the catecholamines in affective disorder.

b. Results

i. The effect of the blocking drugs alone

Pimozide 4 mg caused a modest nonsignificant rise in TSH secretion. See figure 2.16. At 2 hours the difference from placebo was +0.7(+-1.04) mU/L.

Mean (+-SEM) estimates of the areas under the curve are as follows.

placebo: -0.21(+-1.20)
PMZ 2 mg: +0.25(+-0.17)
PMZ 4 mg: +1.38(+-1.24)

(Trends observed did not reach statistical significance)

Thymoxamine alone appeared not to influence TSH secretion.

ii. The effects of pimozide and thymoxamine blockade on the TSH response to dextroamphetamine

Pimozide 4 mg pretreatment accentuated the rise in serum TSH secretion induced by dextroamphetamine, whereas thymoxamine pretreatment attenuated it.

Pimozide 4 mg pretreatment caused a statistically significant increase in net incremental serum TSH secretion in all four readings. Differences in changes of means are as follows; +0.43(+-0.17) mU/L, +0.76(+-0.17) mU/L, +0.85(+-0.17) mU/L,and +0.75(+-0.16) mU/L (one hour $P < .05$ two, three, and four hours $P < .001$). Pimozide pretreatment

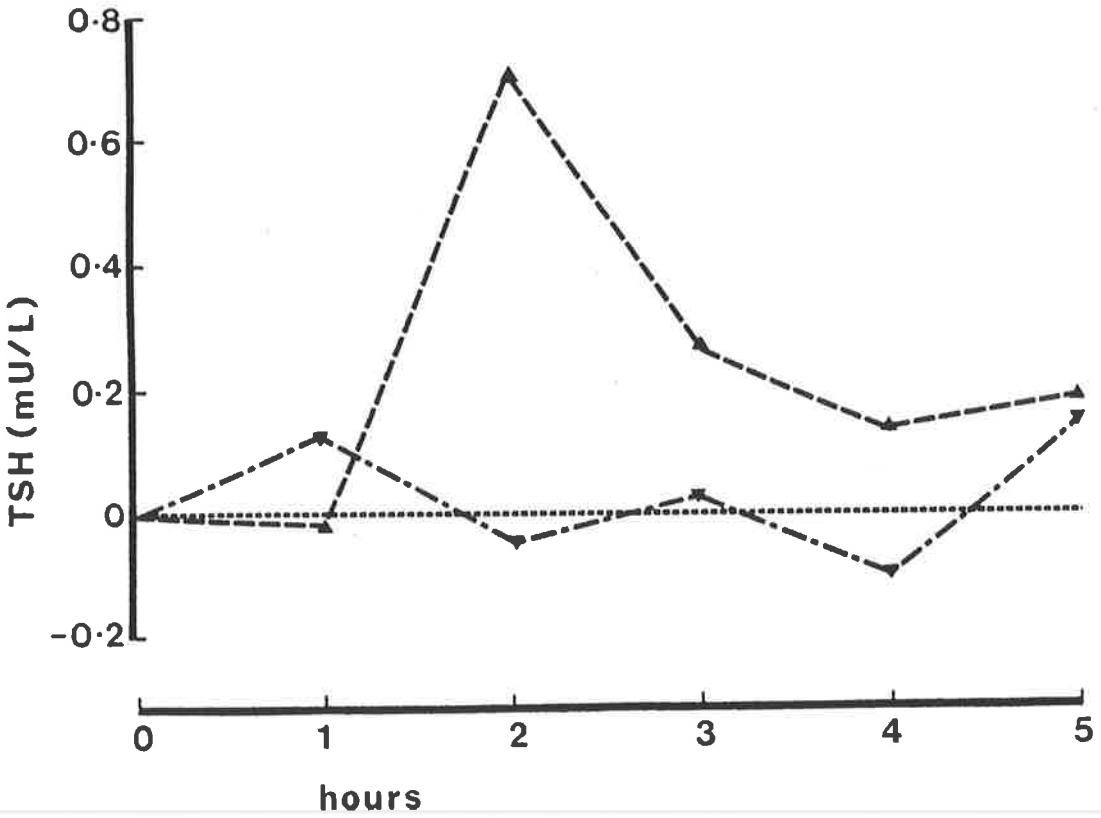

Figure 2.16 Mean (± SEM) net incremental TSH (mU/L) following PMZ 2mg and PMZ 4mg:

PMZ 2mg ▼—·—·—

PMZ 4mg ▲— — — —

accentuated the effect of dextroamphetamine on serum TSH, the net incremental serum TSH levels compared with dextroamphetamine alone was maximal at three hours (+-0.63[+-0.2 mU/L) (P <.01). See figure 2.17.

Estimates of the mean (+-SEM) areas under the curves are as follows:

placebo: -0.21(+-0.37)

dAMP 20 mg: +0.85(+-0.51)

PMZ 2 mg + dAMP 20 mg: +0.66(+-0.51)

PMZ 4 mg + dAMP 20 mg: +1.95(+-0.21)

Difference PMZ 4 mg - dAMP 20 mg v Placebo - dAMP 20 mg: 1.1(+-0.5), P <.05.

In experiment D the elevation of serum TSH secretion following dAMP was smaller than in Experiment B. Pretreatment with thymoxamine 160 mg, but not thymoxamine 80 mg, significantly reduced the TSH response to dextroamphetamine at three hours when the differences of changes of means were -0.28(+-0.11) mU/L (P <.025). See figure 2.18.

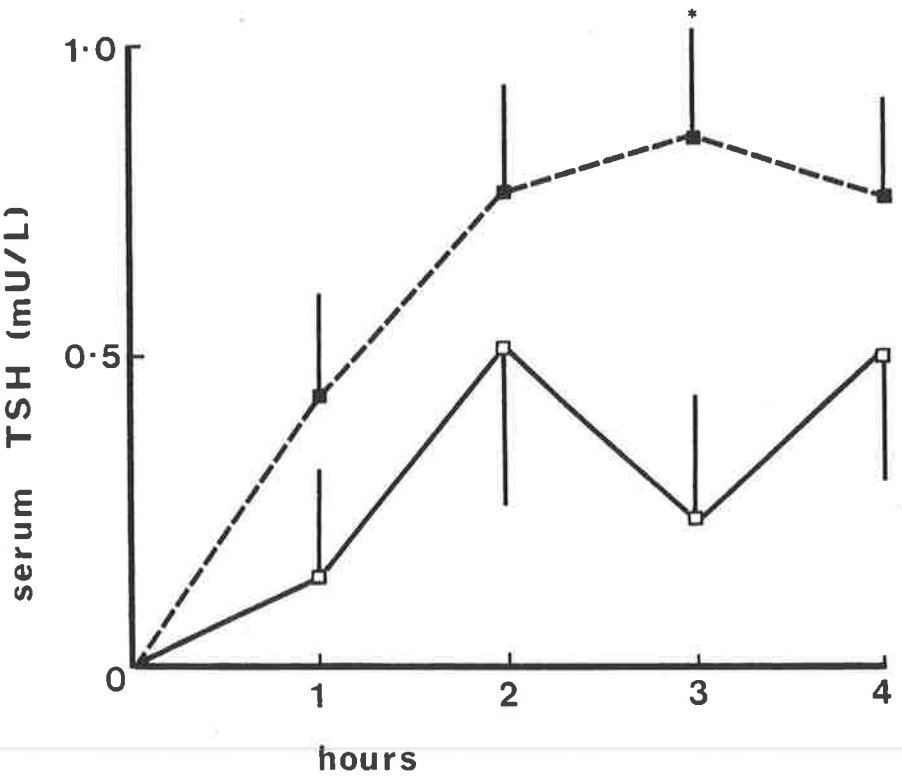

Figure 2.17 Mean (± SEM) net incremental serum TSH (mU/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of PMZ 4mg given 2 hours earlier:

PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

Difference induced by PMZ on the dAMP response. *P < .01

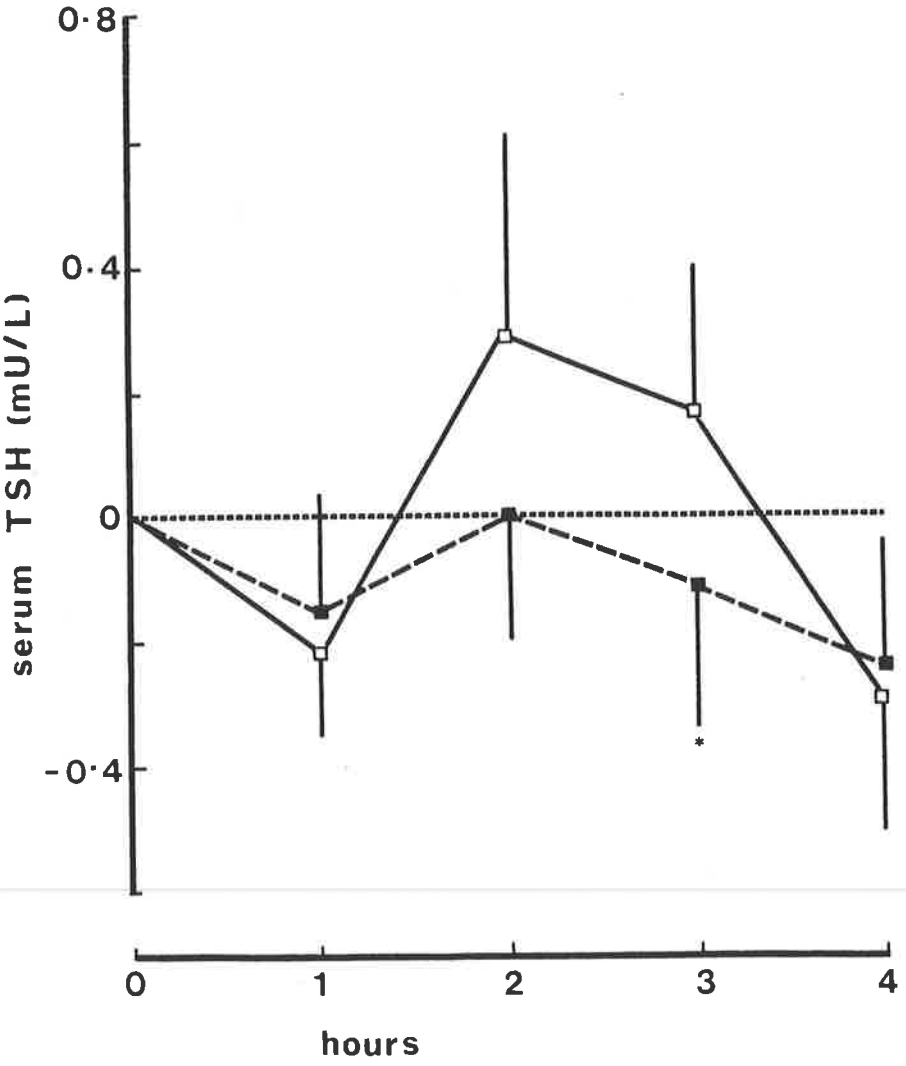

Figure 2.18 Mean (± SEM) net incremental serum TSH (mU/L) response to dAMP 20mg given at 0 (1800) hours demonstrating the effect of TMX 160mg given 1 hour earlier:

TMX placebo - dAMP 20mg
TMX 160mg - dAMP 20mg

Difference induced by TMX on the dAMP response. *P <.025

Estimates of mean (+-SEM) areas under the curve are as follows:

placebo: +0.42(+-0.23)

dAMP 20 mg: +0.66(+-0.36)

TMX 80 mg + dAMP 20 mg: +1.02(+-0.64)

TMX 160 mg + dAMP 20 mg: +0.18(+-0.41)

Difference TMX 160 mg - dAMP 20 mg v placebo - dAMP 20 mg: -0.48(+-0.29), P <.2

c. Discussion

The observed augmentation of the dextroamphetamine induced increase in TSH secretion by pimozide implies an inhibitory role for dopamine pathways, whilst the attenuation by thymoxamine implies a stimulatory role for the alphanoradrenergic pathways. These results confirm previous findings concerning the roles of the dopamine and noradrenaline in the control of TSH in euthyroid subjects.

Dopamine pathways

Considerable evidence has now accumulated demonstrating an inhibitory role of the dopamine pathways in TSH release from invitro studies and studies in experimental animals and human subjects.

As dopamine infusion can inhibit TSH release which may be reversed by domperidone, a site outside the blood brain barrier appears to be involved (Scanlon et al, 1979[a]). However recent evidence from experimental animals, also implicates a central level via the hypothalamic projections of the nigrostriatal dopamine system (Mannisto et al, 1981) or via inhibition of TRH release (Morley et al, 1981).

Noradrenergic pathways

Although the role of noradrenergic pathways in TSH release

has not been so extensively studied, particularly in human subjects, the alpha noradrenergic system appears to be stimulatory.

The question arises whether these pharmacological studies imply activity at pre- or post synaptic alpha noradrenergic receptors. Krulich et al (1977) reported that phenoxybenzamine (a specific alpha 1 noradrenergic blocker), but not phentolamine (a less specific noradrenergic blocker, active at both alpha 1 and alpha 2 sites) depressed TSH release in rats, implying involvement of postsynaptic alpha adrenoceptors. More recent investigation by Krulich and his colleagues (Krulich et al, 1982) into the role of the alpha 1 or alpha 2 receptors in the secretion of TSH in the rat conclude that the alpha 2 noradrenergic system is important in the stimulation of TSH release whilst the alpha 1 receptors are possibly inhibitory.

Studies in humans have not yet yielded sufficient information to allow any conclusions to be drawn about the roles of pre- or post synaptic adrenoceptors in TSH release. As thymoxamine and its metabolites have predominantly an alpha 1 noradrenergic blocking action (Drew, 1976; Drew et al, 1979; Roquebert et al, 1981[b]), the inhibition of TSH release by thymoxamine would suggest that the alpha 1 noradrenergic system is in part at least facilitatory in the release of TSH in man. The level of action of noradrenaline on the hypothalamo pituitary axis in TSH release is uncertain although there is evidence to

suggest it acts via the stimulation of TRH in the hypothalamus (Grimm and Reichlin, 1973).

Inference cannot be made as yet on the possible role of the catecholamine pathways in affective disorder as pharmacological challenge of TSH secretion in affective illness appears not to have been studied.

2.4.6. Gonadotrophins

a. Literature review

The gonadotrophins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), are released from the anterior pituitary under positive control of the hypothalamus via the influence of gonadotrophin releasing hormone (GnRH). GnRH, a decapeptide, is released in a pulsatile manner (Martin et al, 1977; Gallo, 1980). Indeed if GnRH is infused continuously, LH and FSH secretion is diminished. LH and to a less obvious extent, FSH, is also released in a pulsatile manner (Martin et al, 1977). GnRH appears, in primate species at least, to act in a permissive manner, priming gonadotrophin secretion by the pituitary cells to the influence of oestrogens, progesterone and testosterone (Belchetz, 1983). Sex steroids appear to exert a feedback influence primarily at the pituitary level. Oestrogen feedback on LH secretion may be either negative or positive depending on the phase of the menstrual cycle (Nakai et al, 1973) and oestradiol can also reduce the amplitude of LH release (Belchetz, 1983). Progesterone on the other hand appears to act centrally, slowing the frequency of GnRH secretory episodes in the luteal phase. Testosterone also slows LH pulses (Belchetz, 1983).

Most of the studies performed to date have been limited to subprimate species. Interspecies differences are apparent in the control of gonadotrophin secretion, however, and care

must be taken when extrapolating experimental evidence particularly from subprimate species to the human situation (Gallo, 1980; Belchetz, 1983).

Experimental work has been directed primarily towards an understanding of the release of LH rather than FSH. Control of FSH release is thought to be similar but not so dependent on catecholamines. The control of its release appears more dependent on other factors, eg, oestrogen negative feedback (Nillius, 1977).

i. The role of dopamine pathways in gonadotrophin secretion

Most experimental evidence points to the dopamine pathways being of secondary importance in gonadotrophin secretion. Their role, in the light of studies using experimental animals and humans, remain unclear.

Invitro studies

Invitro studies using rat hypothalamic tissue demonstrated that dopamine caused an increase in GnRH release which could be blocked by phentolamine and oestradiol (McCann et al, 1977). This observation together with an earlier finding that intraventricular dopamine caused LH release (Schneider and McCann, 1970[a] and [b]), led McCann and his colleagues to conclude that dopamine pathways were responsible for triggering GnRH release (McCann et al, 1977). Other studies

have confirmed a stimulatory effect of dopamine on GnRH release from hypothalamic tissue (Negro-Vilar et al, 1979; Robbins and Reichlin, 1982).

Animal studies

Although some studies suggest that the dopamine pathways play a stimulatory role in gonadotrophin release, including both the pulsatile release and the preovulatory surge, other studies imply either that there is no involvement or that they exert an inhibitory action. Indeed most evidence points to an inhibitory role (Muller et al, 1977[a]; Sawyer, 1979; Gallo, 1980; Barraclough and Wise, 1982) -- perhaps by axo-axonal influence in GnRH release in the median eminence (Sawyer and Clifton, 1980).

Barraclough and Wise (1982) conclude that one mechanism by which progesterone exerts its negative feedback is via suppressing hypothalamic noradrenaline and increasing dopamine activity thereby extinguishing LH and FSH surges.

Sarkar and Fink (1981) provide experimental evidence that in the rat, dopamine pathways may have a dual role in that the LH secretory surge could be inhibited or stimulated by dopamine, the former effect being blocked by pimozide or domperidone and the latter by haloperidol.

Studies in humans

Data from experiments in humans are likewise inconclusive. Leebaw et al (1978) report that dopamine infusion did not alter basal LH or FSH release but it blocked the incremental response of LH to GnRH in normal males. The FSH response to GnRH was unchanged.

Judd et al (1978) found in normal women that the inhibitory effect of dopamine infusion on LH and FSH secretion was substantial on day fourteen of the menstrual cycle, whereas the effect of dopamine infusion at other times of the cycle gave a small drop in LH only.

Martin et al (1981) also reported that dopamine infusion lowered LH levels and reduced spontaneous LH fluctuations in normal women.

Ferrari et al (1981) in a similar study, reported that dopamine infusion caused a drop in LH levels but not FSH levels in normal women and those with hyperprolactinaemia, amenorrhoea and ovarian disease.

Dopamine infusion also reduced the naloxone induced increments of LH in women in the mid luteal phase (Ropert et al, 1984).

Ho et al (1984) however reported no change in LH or FSH secretion in normals with dopamine infusion but a rise in secretion in hyperprolactinaemic patients. Connell et al (1984) likewise reported no alteration in LH secretion

following dopamine infusion in normals.

Experiments with dopamine agonists and antagonists have yielded similarly inconclusive results. The agonists lergotrile and apomorphine appear to be without influence on LH or FSH secretion (Lal et al, 1973; Thorner et al, 1978). Bromocriptine on the other hand has been reported to increase LH levels in a patient with hyperprolactinaemia (Porter et al, 1980). Martin et al (1981) also observed a slight increase in LH levels following bromocriptine in normal women and suggested that this might be due to a preferential stimulation of presynaptic receptors.

Collu et al (1975) reported that pimozide appeared to reduce the secretion of LH and testosterone in young men. Leppaluoto et al (1976) also reported a drop in midcycle LH (but not FSH) in normal women. Metoclopramide produced an abrupt increase in LH levels in women in the midluteal phase but not in the early or late follicular phase (Ropert et al, 1984).

Ho et al (1984) reported that monoiodotyrosine (which blocks central dopamine synthesis) did not alter LH or FSH release in normal subjects but it led to a release in hyperprolactinaemic women.

ii. The role of the noradrenergic pathways in gonadotrophin release

Invitro studies

In the invitro studies and the invivo studies using an intraventricular cannula, in which dopamine appeared to be exerting a stimulatory effect on GnRH release noradrenaline appeared to have no effect (Schneider and McCann, 1970[a] and [b]; McCann et al, 1977). Negro-Vilar et al (1979) observed that both noradrenaline and dopamine evoke the release of GnRH from median eminence fragments; these responses were blocked by phentolamine and pimozide respectively.

Animal studies

The bulk of evidence from animal studies since the pioneering work of Sawyer in the 1940's suggest that alpha noradrenergic pathways exert a primary physiological action in pulsatile gonadotropHin release and in the preovulatory surge. (Muller et al, 1977[a]; Sawyer, 1979; Sawyer and Clifton, 1980; Barraclough et al, 1984).

Extensive animal research, principally using the rat, has confirmed an excitatory role for the alpha noradrenergic pathways in gonadotrophin release via the central noradrenergic bundle, presumably via the release of GnRH.

This research has involved pharmacological approaches, injecting noradrenaline intraventricularly, making lesions and investigating the turnover rates of catecholamines (Muller et al, 1977[a]; Barraclough and Wise, 1982; Sawyer, 1979; Sawyer and Clifton, 1980; Gallo, 1980; Sarkar and Fink, 1981; Kinoshita et al, 1981; Barraclough et al, 1984).

Gallo (1980) proposed that in the rat there may be a dual noradrenergic control over episodic LH release, a dominant excitatory role and a less dominant noradrenergic system that can suppress pulsatile LH secretion. In a subsequent study, Gallo (1984) reported that the reduction in LH release following prolonged intraventricular infusion of noradrenaline was caused by a suppression of LH pulse frequency. Furthermore, the steroid background (or different stages of the menstrual cycle) of the animal appeared to determine the direction of GnRH and LH response to noradrenaline (Gallo, 1980).

Studies in humans

Few studies have been conducted investigating the role of the noradrenaline pathways in humans. Neither clonidine (Lal et al, 1973), nor guanfacine (Lancranjan and Marbach 1977), influenced gonadotrophin secretion. In a more recent study, neither phenoxybenzamine nor alpha methyldopa influenced naltrexone induced increase in pulsatile LH release (Veldhuis et al, 1983).

Fusaric acid, a dopamine beta hydroxylase inhibitor, was reported to reduce midcycle LH levels, (Leppaluoto et al, 1976), but it is not clear if this reflected its action of increasing dopamine or of lowering noradrenaline activity.

Gonadotrophins and affective disorder

Very few studies have been performed examining gonadotrophin release in affective disorder. Altman et al (1975) reported that LH secretion may be reduced in depressed patients which was taken to imply noradrenergic hypofunction in depression. This finding awaits duplication (Checkley, 1980).

c. Results.

i. The effects of the blocking drugs alone

Both pimozide and thymoxamine caused the serum levels of LH to drop. Neither thymoxamine or pimozide had any consistent effect on FSH secretion.

Pimozide

The effect of pimozide on LH secretion was greatest at 4 hours when the differences from placebo were as follows.

Pimozide 2 mg, -3.1(+-2.9) U/L (NS)

Pimozide 4 mg, -3.2(+-0.9) U/L, P <.05.

See figure 2.19. and table 2.2. There was some reduction in the mean areas under the curve of LH and FSH secretion following pimozide, the reduction in LH secretion reaching statistical significance.

Table 2.2.

LH	FSH
placebo: +4.0(+-2.1)	placebo: +0.40(+-2.10)
PMZ 2 mg: -6.6(+-5.4)	PMZ 2 mg: +0.34(+-2.38)
PMZ 4 mg: -3.0(+-2.5)	PMZ 4 mg: +0.06(+-0.68)

Mean (+-SEM) estimates of the areas under the curve of LH and FSH secretion following PMZ.
Difference (LH), PMZ 4 mg v placebo: -7.0(+-2.5), P <.1.

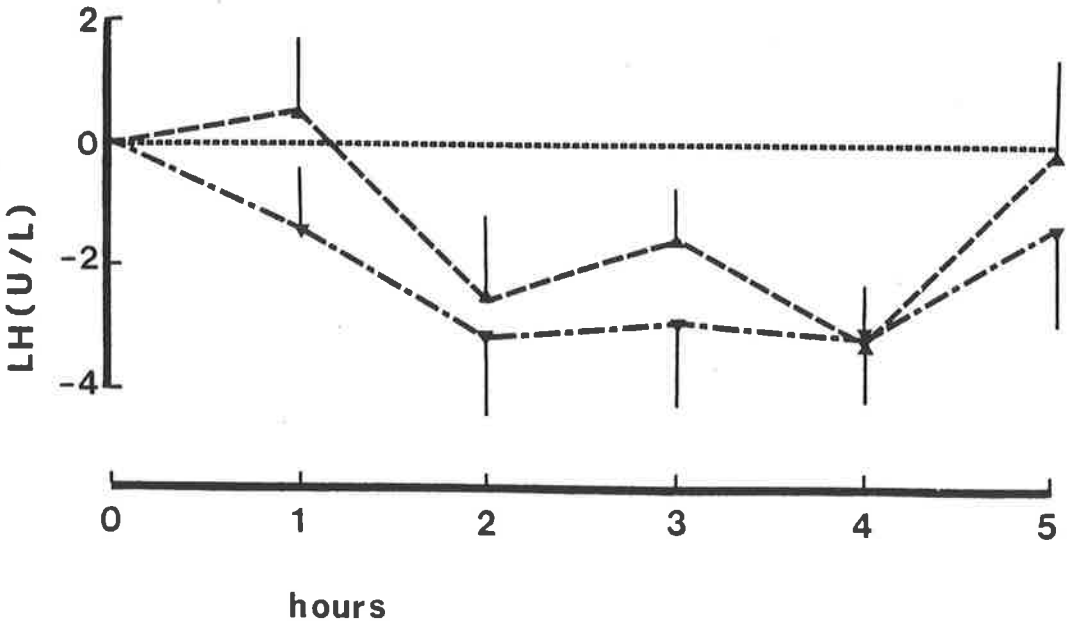

Figure 2.19 Mean (± SEM) net incremental serum LH (U/L) following PMZ 2mg and PMZ 4mg:

PMZ 2mg ▼-·-·-·-

PMZ 4mg ▲————

Thymoxamine

The effect of thymoxamine on LH secretion was not so consistent. The greatest effect by the higher dose was at 5 hours when the difference from placebo was -3.88(+-1.56) U/L (P <.1). See figure 2.20. The effect of thymoxamine on LH and FSH secretion as estimated by the mean areas under the curve are shown in table 2.3.

Table 2.3.

LH	FSH
placebo: +2.8(+-2.4)	placebo: -0.21(+-0.81)
TMX 80 mg: -1.0(+-6.3)	TMX 80 mg: -0.33(+-0.56)
TMX 160 mg: -0.5(+-5.2)	TMX 160 mg: -1.02(+-0.56)

Mean (+-SEM) estimates of the areas under the curve following TMX.

None of these differences were statistically significant.

ii. The effect of blockade by pimozide and thymoxamine on the LH and FSH response to dextroamphetamine

LH

Pimozide pretreatment led to an early dose-related reduction in the dextroamphetamine stimulated LH release. The differences in serum levels at 1 and 2 hours are given in table 2.4. and illustrated graphically in figure 2.21.

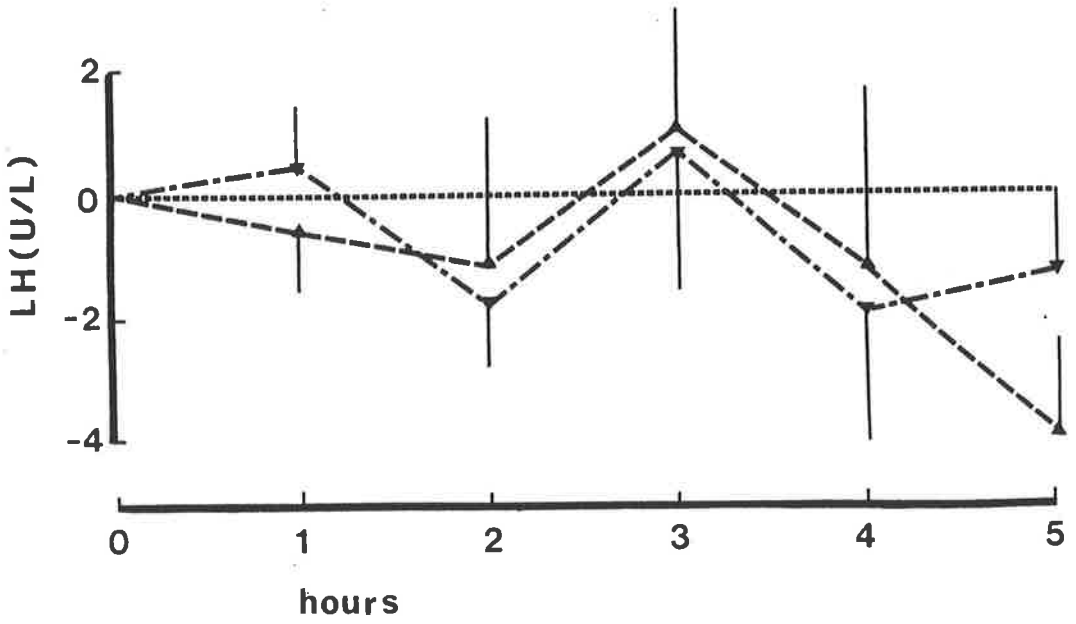

Figure 2.20 Mean (± SEM) net incremental serum LH (U/L) following TMX 80mg and TMX 160mg:

TMX 80mg

TMX 160mg

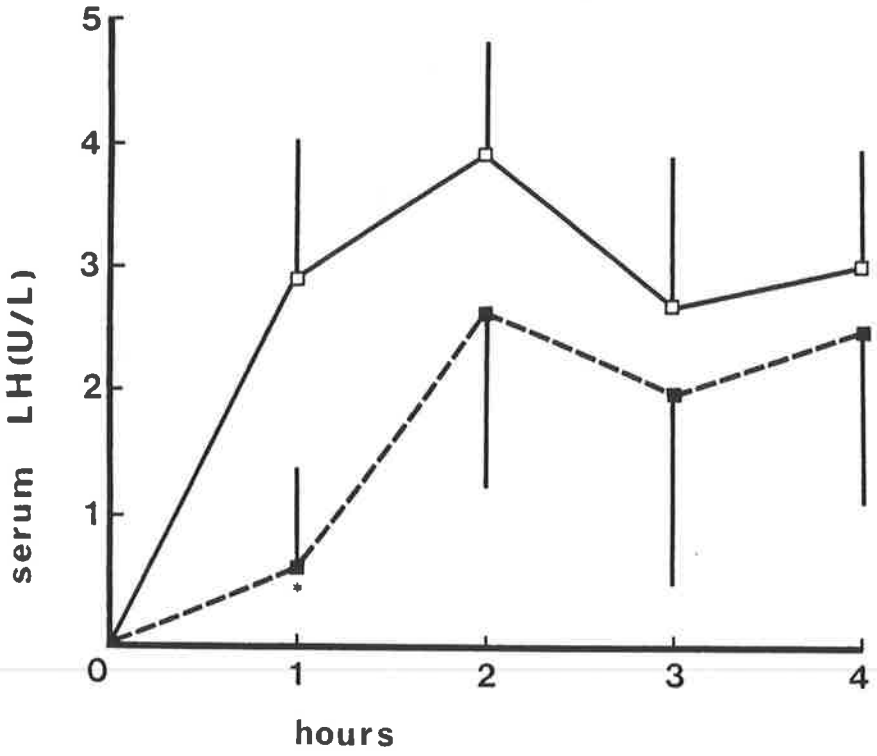

Figure 2.21 Mean (± SEM) net incremental LH (U/L) response to dAMP 20mg given at 0 (1800) hours demonstrating the effect of PMZ 4mg given 2 hours earlier:

PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

Difference induced by PMZ on the dAMP response. *P < .02

Table 2.4.

Time	PMZ Plac dAMP Plac	PMZ Plac dAMP 20mg	PMZ 2mg dAMP 20mg	PMZ 4mg dAMP 20mg
1h (change of means)	-0.29 (+-0.74)	+2.58 (+-0.76)	+1.18 (+-0.74)	+0.30 (+-0.49)
diff from plac - plac		+2.87* (+-1.12)	+1.47 (+-0.94)	+0.59 (+-0.81)
diff from plac - dAMP			-1.40* (+-0.56)	-2.28** (+-0.79)
2h (change of means)	-0.75 (+-0.75)	+3.15 (+-0.47)	+2.01 (+-0.41)	+1.93 (+-0.49)
diff from plac - plac		+3.90*** (+-0.94)	+2.76** (+-1.01)	+2.68 (+-1.45)
diff from plac - dAMP			-1.14 (+-0.58)	-1.22 (+-0.90)

Incremental (+-SEM) serum LH levels at 1 and 2 hours (0=1800hr), together with net incremental (+-SEM) levels compared with the placebo - placebo combination and placebo - dAMP 20mg combination
* P <.05, ** P <.025, *** P <.005.

Mean (+-SEM) estimates of areas under the curve:

Placebo: -1.87(+-2.37)

dAMP 20 mg: +7.70(+-1.37)

PMZ 2 mg + dAMP 20 mg: +5.38(+-1.41)

PMZ 4 mg + dAMP 20 mg: +4.47(+-1.99)

Difference, PMZ 4 mg - dAMP 20 mg v placebo - dAMP 20 mg; -3.23(+-1.52), P <.1.

Thymoxamine pretreatment, particularly at the higher dose, augmented the rise in LH secretion induced by dextroamphetamine, most markedly towards the end of the experiment. The net incremental serum LH levels induced by the thymoxamine 160 mg - dextroamphetamine 20 mg compared

with the placebo - placebo combination at 3 and 4 hours were +2.05(+-0.84) U/L and +2.72(+-0.88) U/L, P <.05 and P <.02 respectively. The differences induced by thymoxamine 160 mg pretreatment compared with the thymoxamine placebo - dextroamphetamine 20 mg combination at 3 and 4 hours were +1.26(+-0.69) U/L and +1.94(+-1.1) U/L, P <.1 and P <.2 respectively. See figure 2.22.

Estimates of the mean (+-SEM) areas under the curve:

placebo:	-0.20(+-1.63)
dAMP 20 mg:	+2.58(+-1.82)
TMX 80 mg + dAMP 20 mg:	+4.25(+-1.70)
TMX 160 mg + dAMP 20 mg:	+5.69(+-1.45)

(There were no statistically significant differences).

FSH

Pimozide pretreatment, particularly the higher dose, gave rise to an early reduction in the dextroamphetamine induced increase in FSH secretion. Thymoxamine on the other hand appeared to be without influence on FSH secretion. See figure 2.23. and 2.24.

The effect of pimozide pretreatment on the dextroamphetamine induced FSH response was maximal at 1 hour when the difference between increments in serum FSH was

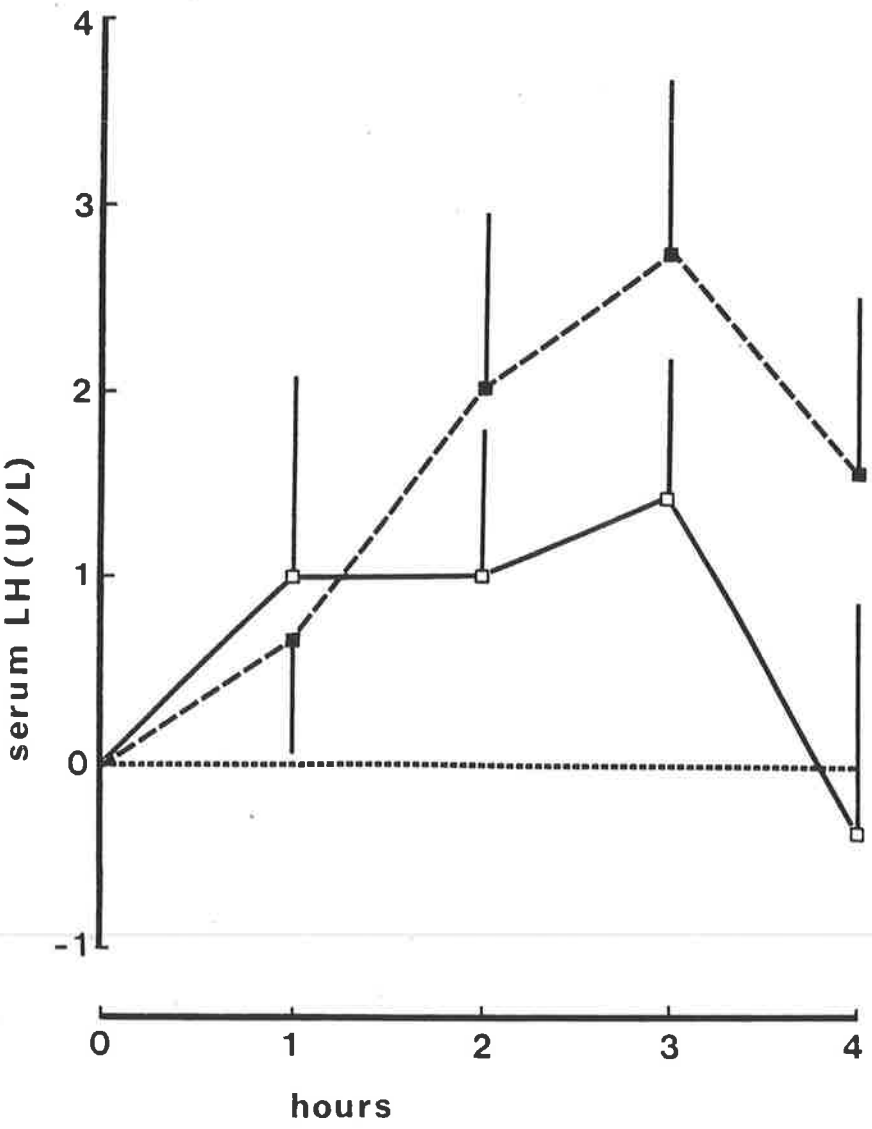

Figure 2.22 Mean (± SEM) net incremental serum LH (U/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of TMX 160mg given 1 hour earlier:

TMX placebo - dAMP 20mg

TMX 160mg - dAMP 20mg

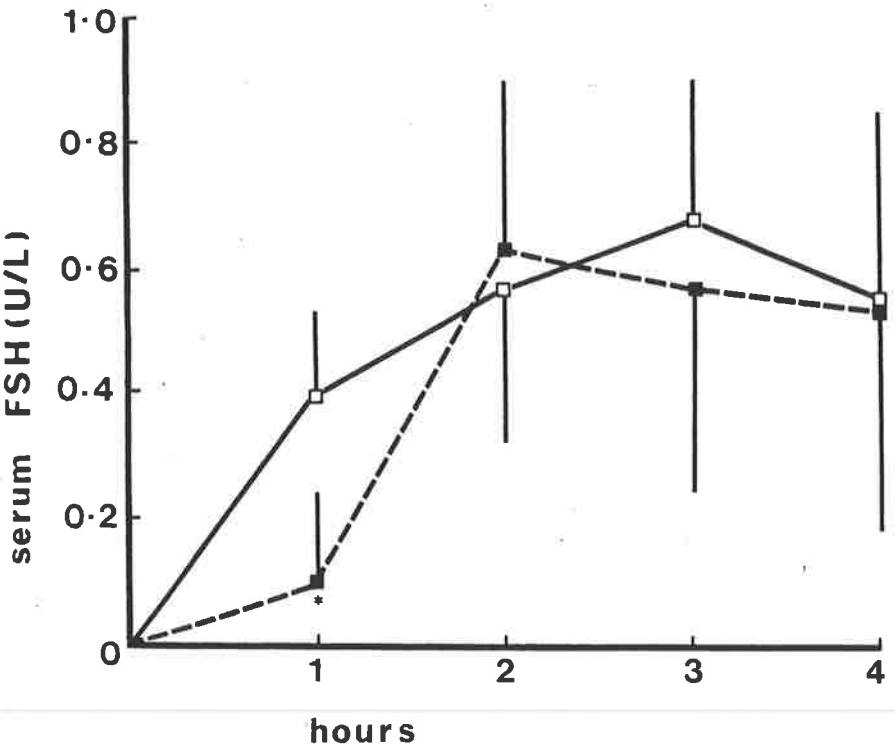

Figure 2.23 Mean (± SEM) net incremental serum FSH (U/L) response to dAMP 20mg given at 0 (1800) hours demonstrating the effect of PMZ 4mg given 2 hours earlier:

PMZ placebo - dAMP 20mg
PMZ 4mg - dAMP 20mg

Difference induced by PMZ 4mg on the dAMP response. *P $<$.05

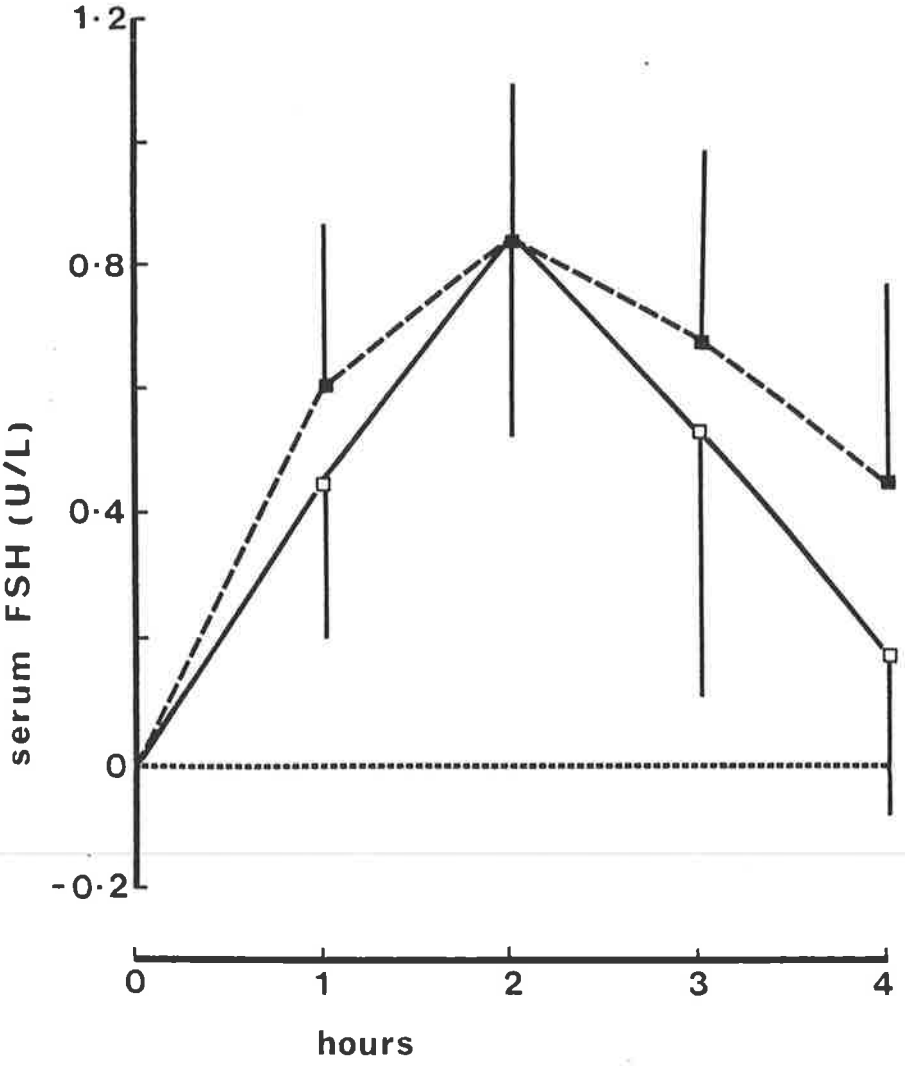

Figure 2.24 Mean (± SEM) net incremental serum FSH (U/L) response to oral dAMP 20mg given at 0 (1800) hours demonstrating the effect of TMX 160mg given 1 hour earlier:

TMX placebo - dAMP 20mg

TMX 160mg - dAMP 20mg

-0.29(+-0.12) U/L ($P < .05$).

Estimates of the areas under the curves did not demonstrate any significant changes induced by either blocking drug on the dextroamphetamine induced increase in FSH secretion.

c. Discussion.

Oral dextroamphetamine was an effective stimulant for the secretion of both LH and FSH.

Dopamine pathways

Pimozide pretreatment led to a fall in the dextroamphetamine induced rise in LH secretion, which is seen to a lesser degree in FSH secretion as well. This would imply that in human males, dopamine may have a stimulatory role in their release, particularly of LH. Furthermore pimozide appeared to cause a drop in the non-stimulated LH levels. This is consistent with the reports by Collu et al (1975) and Leppaluoto et al (1976).

Evidence from invitro or animal studies imply that dopamine has an inhibitory role in the release of LH. See literature review. Sarkar and Fink (1981) however report the apparent presence of two dopamine receptors that may be facilitatory or inhibitory in the release of LHRH and LH in the rat.

It is possible that the dopamine pathways may also play a dual role in humans. This would help to explain some of the apparently inconsistent experimental findings. Most of the experiments using dopamine infusion, report a fall in LH release, particularly in the mid luteal phase in normal women, as well as a fall in secretion in women with ovarian

disease (Judd et al, 1978; Ferrari et al, 1981; Martin et al, 1981). The LH response in patients with hyperprolactinaemia to dopamine infusion, was a fall in one series (Ferrari et al, 1981) and a rise in another (Ho et al, 1984).

The reported response to dopamine blockers likewise appears inconsistent. Pimozide caused a drop (Collu et al, 1975; Leppaluoto et al, 1976), while metoclopramide gave a rise in LH secretion (Ropert et al, 1984). The dopamine agonist bromocriptine was reported to cause a rise in LH secretion in a patient with hyperprolactinaemia (Porter et al, 1980) and in normal women (Martin et al, 1981).

Perhaps the central dopamine pathways in humans have a different effect from those outside the blood brain barrier.

An alternative explanation is that the dopamine pathways exert at least part of their action on LH secretion via their effect on prolactin secretion. As prolactin excess is known to be accompanied by reduced LH levels (Smith 1980), it is possible that the LH depressant effect of pimozide and the LH stimulant effect of bromocriptine and dopamine in hyperprolactinaemia is secondary to their influence in stimulating or inhibiting prolactin release.

The effect of the dopamine pathways on FSH release seems slight, if anything they would appear to exert a stimulatory action.

Noradrenaline pathways

In this study thymoxamine caused a modest accentuation of LH release and no effect on FSH release. This would imply an inhibitory role for the alphanoradrenergic pathways in basal LH release.

There is good evidence from animal studies to suggest that the alpha noradrenergic pathways facilitate LH release, both of the preovulatory release and surge and of basal secretion (Muller et al, 1977[a]; Sawyer, 1979; Sarkar and Fink, 1981; Barraclough and Wise, 1982; Barraclough et al, 1984) with some possibility of a secondary, less dominant, central noradrenergic system that inhibits LHRH and hence LH release (Gallo, 1980).

Control of FSH release has been thought to be similar, though not so influenced by changes in noradrenaline activity as is with LH release. FSH release appears to be more dependent on other factors, for example oestrogen negative feedback (Nillius, 1977).

Studies investigating the role of noradrenaline pathways in gonadotrophin release in humans are few. Neither the alpha noradrenergic agonists clonidine (Lal et al, 1973) nor guanfacine (Lancranjan and Marbach, 1977) nor the antagonist phenoxybenzamine (Veldhuis et al, 1983) influenced secretion. Clearly further studies are required before any conclusions on the role of the noradrenergic pathway on

gonadotrophin release in humans can be made.

There is insufficient experimental data to draw any conclusions about the role of catecholamine pathways in affective disorder using pharmacological challenge of gonadotrophin secretion. This lack of experimental investigation is surprising in view of the close relationship between affective illness and the reproductive system seen in puerperal depression and mania, and in the mood changes associated with menstruation and menopause.

2.4.7. Conclusions.

Pimozide and thymoxamine exerted different effects on the responses of the different anterior pituitary hormones to dextroamphetamine. The implied role of the catecholamine pathways in the hormonal response to dextroamphetamine can be compared with other experimental evidence for the role of the dopamine and noradrenaline pathways in the control of the secretion of these hormones.

The main findings of the present study can be summarized as follows.

Dopamine pathways do not appear to be involved in the control of cortisol secretion. The role of the alpha noradrenergic pathways is difficult to interpret as a dose response relationship was not observed following thymoxamine pretreatment. The most substantial effect, accentuation of cortisol secretion, might imply that they exert an inhibitory action.

As far as prolactin is concerned, as expected, dopamine pathways were shown to have an inhibitory action on prolactin release with the alpha noradrenergic pathways not being involved.

Conclusions about the role of the dopamine and noradrenaline pathways in dextroamphetamine induced growth hormone release are difficult to make from these results as other factors in the experiment influenced growth hormone

secretion. A case could be made for an enhancing and an inhibiting effect by the dopamine pathways and an inhibitory role for the alpha noradrenaline pathways.

A dual but opposing influence by the two catecholamine pathways was manifest in the release of TSH induced by dextroamphetamine administration. Dopamine pathways exerted an inhibitory action and the alpha noradrenergic pathways probably exerted a stimulatory action.

Conversely dopamine pathways appeared to be stimulatory in LH release whereas the alpha noradrenergic pathways are inhibitory.

The results suggest that the dopamine pathways may play a role, albeit a minor one, in stimulating the release of FSH.

These results are generally in keeping with other experimental evidence related to the role of the dopamine and alphanoradrenergic pathways in the control of the secretion of the different anterior pituitary hormones.

Experimental evidence for the role of the alpha noradrenergic pathways in cortisol secretion is conflicting. Although the bulk of evidence points to a stimulatory role in humans, other studies suggest an inhibitory action.

Controversy remains too, over the roles of the catecholamine pathways in growth hormone and LH release.

In recent years there has been increasing use of

pharmacological challenge to the neuroendocrine system in the investigation of the biology of a variety of psychiatric disorders. As far as affective disorder is concerned, the secretion of cortisol and growth hormone, and to a lesser degree prolactin, has been studied. Abnormalities may also exist in the secretion of TSH and LH in affective disorder.

In many of these studies, assumptions have been made regarding the central neurochemical control mechanisms involved in the control of anterior pituitary hormones in making hypotheses regarding the pathophysiology of affective illness. On the whole, workers have concluded that these investigations have demonstrated hypofunction of the alpha noradrenergic pathways and probably normal functioning of the dopamine pathways. The results of the present study indicate how complex these control mechanisms are likely to be, and therefore how cautious one must be in attempting to draw any firm conclusions.

PART III

DEXTROAMPHETAMINE INDUCED AROUSAL AS A PHARMACOLOGICAL MODEL FOR MILD MANIA.

3.1. Introduction

3.1.1. Introductory comments

Studying the biology of mania poses particular difficulties. The hyperactivity of patients suffering from the illness can make experimentation very difficult and it may be impossible for the patient, because of their lack of judgment when ill, to be able to give informed consent for scientific study. These problems become manifest when one reviews the literature on the biology of mania. There is a surprising lack of information on mania derived from studies on manic patients. Because mania can only be researched in manic patients with difficulty, other research strategies have to be considered.

Pharmacological models have provided a useful avenue of scientific investigation in psychiatry. They provide a stimulus for the generation of new hypotheses which can, in turn, be tested in the disease state. In the past, a variety of animal models have been proposed for the affective disorders but these suffer from a number of limitations. As animal studies do not allow any investigation of mental state, extrapolation to the human condition may be unwarranted. If a human model of mania can be developed which fulfils the necessary criteria for validity, it would act as a valuable tool for further psychobiological research into mania.

Since the introduction of amphetamine derivatives into clinical and research use, experimenters have described in detail the amphetamine response in humans. There are many similarities in the description of amphetamine arousal and the phenomena of mania. These similarities have been observed in the locomotor response to amphetamine derivatives in experimental animals (Robbins and Sahakian, 1980) as well as the psychological responses in humans (Gold and Byck, 1978).

The present study attempts to extend the comparison from the subjective and symptomatic level to the psychobiological and pharmacological levels.

It has been believed for some time that the catecholamines, dopamine and noradrenaline, play an important role in the biology of mania. In recent years the importance of dopamine has become increasingly clear in this connection, while that of noradrenaline is less so. Dextroamphetamine is believed to act by releasing newly formed dopamine and noradrenaline from the presynaptic neurone and preventing their reuptake (Carlsson, 1970; Scheel-Kruger, 1972; Chieuh and Moore, 1975; Groves and Rebec, 1976). See Part I. If dextroamphetamine can be shown to fulfil the criteria for a valid pharmacological model for mania, it would provide an avenue for investigating the possible roles of the dopamine and noradrenaline pathways in this condition.

The psychological and psychophysiological responses to oral dextroamphetamine have been presented in Part I and the neuroendocrine responses were presented in Part II. This section will compare some of these findings in detail with the known sequelae of mania.

3.1.2. Pharmacological models

a. Models in psychiatry

Opinions vary on the value of models in the study of psychiatric illness. Critics of animal models emphasise that no lesion or induced state in animals is homologous to any mental illness in humans; the uniqueness of the human experience, so much a feature of mental illness, being of necessity ignored (Shepherd et al, 1968). On the other hand, animal models have proved valuable in the study of the aetiology and nature of a range of illnesses as well as in the evaluation of new therapeutically active drugs. For example, behaviour therapy was developed from animal models of learning. Similarly the butyrophenone derivatives were introduced as neuroleptic drugs following examination of their effect on an amphetamine model of psychosis (Kumar, 1979).

Animal models, have the additional advantage that they afford the opportunity to carry out experimental procedures which would be ethically unacceptable in human subjects. Such models also allow control of and simplification of the experimental environment, thereby allowing more vigorous control of the variables to be tested (Robbins and Sahakian, 1980).

This greater control is obtained at a price; many models are an oversimplification of a complex situation. Furthermore it is unjustified to assume that brain function

is directly comparable in different species (Robbins and Sahakian, 1980). As a result, it is usually unwise to extrapolate the findings from one species to another.

In psychobiological research, the main value of models is to provide an experimental situation in which ideas can be tested in a simplified setting. The hypotheses so generated may, in turn, be tested in the human pathological state.

b. Criteria for acceptance of a model

A model of psychiatric illness should conform to a number of criteria before it can be considered a useful tool in psychobiological research. Four criteria were initially proposed by McKinney and Bunney (1969), (see also McKinney, 1974) to establish validity of a model illness. Three of these have gained general acceptance (Robbins and Sahakian, 1980). These three criteria are:

i. The model should exhibit close similarities in experiential and behavioural terms to the illness in question.

ii. It should have psychophysiological and biological correlates.

iii. It should respond to pharmacological manipulation in the same way as the naturally occurring condition (McKinney and Bunney, 1969; McKinney, 1974; Robbins and Sahakian, 1980).

The more the model satisfies these comparisons, the

greater its relevance to psychiatric research. The power of the model is further enhanced if matching can be established in features that are relatively specific to the illness in question.

Earlier writers cited a fourth criterion (McKinney and Bunney, 1969; McKinney, 1974), that the underlying neurobiological mechanisms in the model and in the illness in question should be the same. As the neurobiology of psychiatric illnesses is largely unknown, this criterion cannot usually be answered with any confidence. It is nevertheless an important question to keep in mind when considering if the model is of relevance to the illness in question. A pharmacological model is particularly useful if the known action of the drug used is similar to the pathophysiology in question, for example, if its mechanism of action involves the same neurotransmitter pathways that are thought to be involved in the illness being modelled.

c. Human versus Animal models

Despite the considerable experimental flexibility they allow, models of psychiatric illness using experimental animals suffer from two major disadvantages.

The first criterion of validity is difficult to satisfy. It requires that the model matches the illness in both experiential and behavioural terms but, psychiatric illness is described and diagnosed largely on a phenomenological basis. A knowledge of mental state is essential for any

real comparison and this of course is impossible in experimental animals. Even a comparison purely on behavioural terms is difficult to make as it is often difficult to know for certain what the animals' behaviour may mean (Kumar, 1979; Robbins and Sahakian, 1980).

The second major difficulty with animal models lies with the difficulty in extrapolating from one species to another. Not only are there major problems in assuming various behaviours are equivalent to those seen in humans, there are also clear differences between animals and humans in the structure and function of the central nervous system (Robbins and Sahakian, 1980).

A pharmacological model of a psychiatric illness using human subjects avoids these problems. However the main drawback with human studies is that ethical and practical considerations limit the range of experimental procedures that can be used. Nevertheless, noninvasive techniques are available which allow safe and meaningful experimentation. Furthermore research findings in animals gain in credibility if the underlying pharmacological model of psychiatric illness is supported by observing similar changes using normal human volunteers.

3.1.3. Phenomena of mania and the response to amphetamine

Mania as an illness goes under a number of names, all of which refer to the same condition. These names include the manic phase of bipolar affective illness, manic depressive psychosis, hypomania, major affective disorder, manic type. Kraepelin (reprint of 1921 English translation, 1976) in his classic study of Manic Depressive Insanity, described a variety of key symptoms of mania. He observed the presence of flight of ideas, fickle interest, grandiosity, heightened energy and mood, irritability, increased "busyness" and restlessness; he described the patients as "being a stranger to fatigue". These phenomena are still regarded as the key symptoms of the illness (Silverstone and Cookson, 1982).

Gibbons (1982) recently reviewed 4 studies from the last 15 years recording the frequency of manic symptoms. Those most frequently cited were: over talkativeness, overactivity, grandiosity, irritability, euphoria, insomnia, flights of ideas, lability, hostility and distractability.

Clinical diagnostic criteria published over the past decade have further helped to define the concept. There is a high degree of agreement between the different criteria that have been proposed (Feighner et al, 1972; ICD9, 1977: Spitzer et al, 1978; American Psychiatric Association, DSM-III, 1980). All require the presence of elation or irritability together with hyperactivity, distractability, overtalkativeness (sometimes amounting to pressure of speech), flights of ideas, grandiose ideas and social

dysfuntion (eg injudiciously spending money, promiscuity or disruption within the home or at work).

Many of the symptoms of mania resemble those produced by amphetamine drugs. From both anecdotal reports and more recently published controlled studies, there appears to be a close resemblance between the symptoms and signs observed in patients suffering mania and the phenomena observed following a single low dose of amphetamine.

Shortly after the introduction of amphetamine derivatives into clinical practice a number of central effects were noted. Reports of insomnia from amphetamine (benzadrine) overdosage and its efficacy in the treatment of narcolepsy (Prinzmetal and Bloomberg, 1935), were followed by observations of elevation of mood and reduced fatiguability in normal subjects. (Nathanson, 1937; Davidoff and Reifenstein, 1937). These earlier studies have been replicated by Levine et al (1948) and Lassagna et al (1955) who described elevation of mood or irritability, over-talkativeness, increase in motor activity and restlessness, a heightened sense of energy, alleviation of fatigue, anorexia, alertness and insomnia in their subjects.

Controlled experiments, despite some variability of response (Checkly, 1978), have confirmed that amphetamine in relatively low dosage gives a reproducible rise in mood and arousal, as measured in a variety of ways, including the Profile of Moods Scale and the Linear Mood scale (Smith and

Davies 1977), a modified Mood Adjective Checklist (Brown et al, 1978) and visual analogue rating scales (Silverstone et al, 1983). Higher or prolonged doses give rise to other phenomena (Ellinwood, 1967).

Mindful of the constraints in relating data from animal experimentation to an illness in humans, increase in activity following a relatively low dose of dextroamphetamine in experimental animals has been proposed as an animal model for mania. (Murphy, 1977; Robbins and Sahakian, 1980). A similarity was found between the amphetamine induced changes in the animals behaviour and that seen in mania.

3.1.4. Biological correlates of mania and dextroamphetamine

a. Biological changes in mania

i. Psychophysiological correlates.

Published reports of psychobiological changes occurring in mania are few because of the experimental difficulties of working with such patients. Nevertheless sufficient information has been obtained to suggest that there are significant changes in functioning during a manic episode. For example Lake et al (1982) demonstrated that manic patients had higher pulse rates and systolic blood pressures than a control group of healthy volunteers or depressed patients. Hemsley and Philips (1975) in a longitudinal study in one subject reported that manic episodes were associated with an increase in skin conductance levels.

There have also been some reports of observations on patients with a persisting 48 hour cycle bipolar affective illness. Jenner et al (1967) demonstrated that the manic phase was associated with increased weight and extracellular fluid and a drop in mean corpuscular volume. Pulse rate, skin resistance, thyroid function tests and urinary gonadotrophins all were unaffected. Bunney et al (1965) reported a drop in 17 hydroxycorticosteroids when the patient was manic and increased levels when the patient was depressed.

ii. Neuroendocrine correlates.

Anterior pituitary adrenocortical axis

A relationship between mania and the activity of the anterior pituitary - adrenocortical axis is suggested by the reports that euphoria may occur in patients with Cushings disease and in patients receiving systemic corticosteroids (Lishman, 1978; Hall et al, 1979). Although manic symptoms may be observed in patients with Cushings disease, they are relatively infrequent (Cohen, 1980). Studies in manic patients offer further support for these observations. For example, midnight levels of cortisol are higher in manic patients than in normal subjects (Cookson et al, 1983) and 46% of manic patients show an abnormal suppression response to dexamethasone (Graham et al, 1982).

Other hormones

There may also be some relationship between thyroid disease and mania. Kirkegaard et al (1978) have reported that manic patients exhibit a decrease in serum triiodothyronine levels and a reduced response of TSH to TRH. ALthough basal levels of gonadotrophins appear to be unaltered in mania, the risk of mania is relatively increased in the immediate post partum period (Dean and Kendell, 1981), a time when oestrogen levels are falling

dramatically. Oestrogen reduces dopamine activity; so a drop in oestrogen may be followed by a rapid relative increase in dopamine functioning which increases the risk of mania (Cookson, 1981). Growth Hormone appears to be unchanged in mania (Cookson et al, 1982; Silverstone and Cookson, 1982).

b. Biological correlates of amphetamine arousal

In a wide variety of experimental animals, amphetamine derivatives cause an increase in locomotor activity. In higher doses they produce stereotypy (Iversen and Iversen, 1975).

Studies investigating the psychophysiological response to dextroamphetamine in humans, report an elevation of blood pressure, pulse rate (Martin et al, 1971; Morselli et al, 1978; Nurnberger et al, 1984), skin conductance levels (Zahn et al, 1981) and contingent negative variation (Tecce and Cole, 1974). However just as the psychological response to amphetamine derivatives may be variable (see earlier) so too may there be variability in psychophysiological measures (Tecce and Cole, 1974; Rapoport et al, 1980).

Amphetamine derivatives have been used as stimulatory agents in the investigation neuroendocrine system functioning; both in the study of the catacholamine control of anterior pituitary hormone excretion (Rees et al, 1970), and as a stimulatory challenge in the investigation of neuroendocrine function in psychiatric illness. See Part

II. Amphetamine drugs are reported to stimulate the excretion of cortisol (Besser et al, 1969; Rees et al, 1970) and possibly TSH (Morley, 1981). The growth hormone (Besser et al, 1969) and prolactin response (Van Kammen et al, 1975) is usually stimulatory, the former depending upon experimental conditions. The response of the gonadotrophins to dextroamphetamine challenge as has been shown in Part II is also stimulatory.

3.1.5. Responses to pharmacological manipulation.

Neuroleptic drugs have proved a mainstay in the management of acute mania (Shaw, 1979). Both the sedating neuroleptics chlorpromazine and haloperidol (Shaw, 1979) and the less sedating drug pimozide (Cookson et al, 1981) have been shown to be effective. Lithium Carbonate, too, has proven efficacy both in the treatment of acute mania and, in particular, in prophylaxis (Silverstone and Turner, 1982).

Neuroleptics are also effective in reversing the effects of amphetamine derivatives. In fact, the ability to attenuate the stereotypy induced by amphetamine has been used as a biological measure of neuroleptic potential (Janssen et al, 1965). In humans pimozide has been shown to attenuate many of the responses to dextroamphetamine (Jonsson, 1972; Silverstone et al, 1980; Gillin et al, 1978[b]).

Similarly lithium carbonate has been shown to attenuate the response to amphetamine. In animals the locomotor stimulatory action of amphetamine drugs but not the amphetamine induced stereotypy was reversed by lithium carbonate pretreatment (Murphy, 1977; Iversen, 1980; Robbins and Sahakian, 1980). Lithium carbonate likewise attenuated the amphetamine induced arousal response in humans (Van Kammen and Murphy, 1975). Alpha methylparatyrosine, which blocks the synthesis of both catecholamines, reduced the symptoms of mania (Brodie et al, 1978) as well attenuating the response to amphetamine (Jonsson et al, 1971).

3.1.6. The role of dopamine and noradrenaline in the biology of mania

Schildkraut's (1965) catecholamine hypothesis of affective illness proposed that depression was associated with a relative deficit of catecholamines, particularly of noradrenaline, while mania was associated with a relative excess.

Over the past ten years however, a direct role of dopamine in the neurobiology of mania has become clearly established (Randrup and Munkvad, 1976; Silverstone, 1978; Post, 1980; Silverstone and Cookson, 1982). Although there is some uncertainty about changes in levels of dopamine and its metabolites in the blood and CSF of manic patients (Post, 1980), evidence from pharmacological studies is quite persuasive. Mania can be precipitated by L- dopa (Murphy et al, 1973) and dextroamphetamine (Gerner et al, 1976) (both of which can stimulate the activity of the noradrenergic and dopaminergic pathways). It can also be precipitated by the specific dopamine agonists piribedil and bromocriptine (Gerner et al, 1976; Brook and Cookson, 1978). Manic symptoms can be ameliorated by alpha methylparatyrosine (which blocks the formation of both noradrenaline and dopamine). Neuroleptic drugs have an antimanic action. Those with a more specific dopamine blocking action (eg. pimozide) have a more pronounced antimanic action than those neuroleptics with more mixed effect on the neurotransmitters, such as chlorpromazine (Cookson et al,

1981).

The evidence for a direct involvement of the dopamine pathways in the neurobiology of mania has overshadowed that of noradrenaline, the role of which has become increasingly uncertain. Levels of noradrenaline and noradrenergic metabolites (MPHG) are elevated in the blood, urine and CSF of manic patients (Post, 1980). It is unclear, however, whether these changes are secondary to the increase in arousal and motor activity (Post and Goodwin, 1973). Pharmacological evidence about the role of the noradrenaline pathways has unfortunately not helped to clarify the picture. L-dopa and amphetamine, which activate both catecholamine pathways can precipitate mania and manic symptoms may be reduced by alpha methylparatyrosine which also affects both catecholamine pathways. Tricyclic antidepressants are known to precipitate mania (Wehr and Goodwin, 1979) but they have a broad spectrum of effects on a number of central neurotransmitter pathways. If the formation of noradrenaline from dopamine is blocked by the dopamine beta hydroxylase inhibitor fusaric acid, there is a rise in dopamine and a drop in noradrenaline. This causes an accentuation of manic symptoms (Sack and Goodwin, 1974).

Manic symptoms are reduced by the alpha 2 noradrenergic agonist clonidine and rebound symptoms occur on withdrawal (Jouvent et al, 1980). Yohimbine an alpha 2 noradrenergic antagonist has been reported to precipitate mania (Price et al, 1984). The beta noradrenergic blocker propranolol, at

high doses, can ameliorate manic symptoms but as the non-noradrenergic blocking stereoisomer of propranolol also reduces manic symptoms, it is unlikely that the antimanic effect is via its betanoradrenergic action (Emrich et al, 1979).

In view of the uncertainty of the relative roles of the dopamine and noradrenaline pathways in mania, the effect of specific dopamine and noradrenaline blocking drugs on the manic like symptoms produced by amphetamine would be likely to shed some light on the problem.

3.2. Methods

The subjects, drugs used and experimental design are described in detail in Part I.

Different visual analogue rating scales dimensions were chosen to measure changes in the subjects mood, alertness and mental activity in those symptoms most frequently seen in manic patients ie. elation and irritability, arousal, restlessness, mental speed and energy. The impairment of sleep on the night following the experiment was rated by subjects on a 5 point scale the following day.

As the phenomena and psychophysiological sequelae of the amphetamine response alone were being investigated in this part of the study, data from experiments B and D were combined. Thus data from the placebo blocker - placebo dextroamphetamine combination from both experiments were combined as were the data from the placebo blocker - dextroamphetamine 20 mg combination. This gave a total of 24 subjects. Pharmacokinetic data as described in Part I was also combined giving 18 subjects in all, some samples from experiment D having been lost.

There is a paucity of information on the psychophysiological and biological concomitants of mania, preventing a detailed comparison with the response to dextroamphetamine. As mania appears to be associated with an elevation of pulse rate, systolic blood pressure and skin conductance levels and a rise in daytime plasma cortisol

levels (see introduction) these measures were chosen for comparison with the response to dextroamphetamine. Results from experiments B and D were again combined. The effect of pimozide on dextroamphetamine induced arousal, forming part of the pharmacological comparison of the two states, has been described in detail in Part I and will be briefly reviewed.

As in Part I and II, all data has been converted to change values from a reference level just prior to the dextroamphetamine dose at 1800 hours (the reference values were comparable within all dimensions). Mean changes in the subjective rating scales were analysed statistically using the Willcoxon signed rank difference test for pair differences. The differences in the mean changes in objective data were exposed to analysis using Student´s t test for matching pairs. As the direction of response can be anticipated, the one tail test for estimating statistical significance was used.

3.3. Results

3.3.1. A Phenomenological comparison

Oral dextroamphetamine 20 mg gave rise to an elevation in all the visual analogue rating scales reflecting the symptoms of mania. The subjects also rated their sleep the night following the experiment as being significantly disturbed.

The maximal changes for each visual analogue rating scale of the mood and hyperactivity parameters as well as the ratings of diminished sleep following placebo and dextroamphetamine 20 mg are shown in figure 3.1. All changes showed a statistically significant rise following dextroamphetamine administration, with the changes in the arousal - hyperactivity dimensions being higher and the difference reaching a higher degree of statistical significance than the mood scores. The maximum differences from placebo occurred at two and a half hours after dextroamphetamine administration for all measures apart from the restlessness dimension when the maximal change was at two hours.

The time of the maximal response to dextroamphetamine is comparable with the time of its peak serum level, which occurred between two and four hours after administration. See figure 3.2.

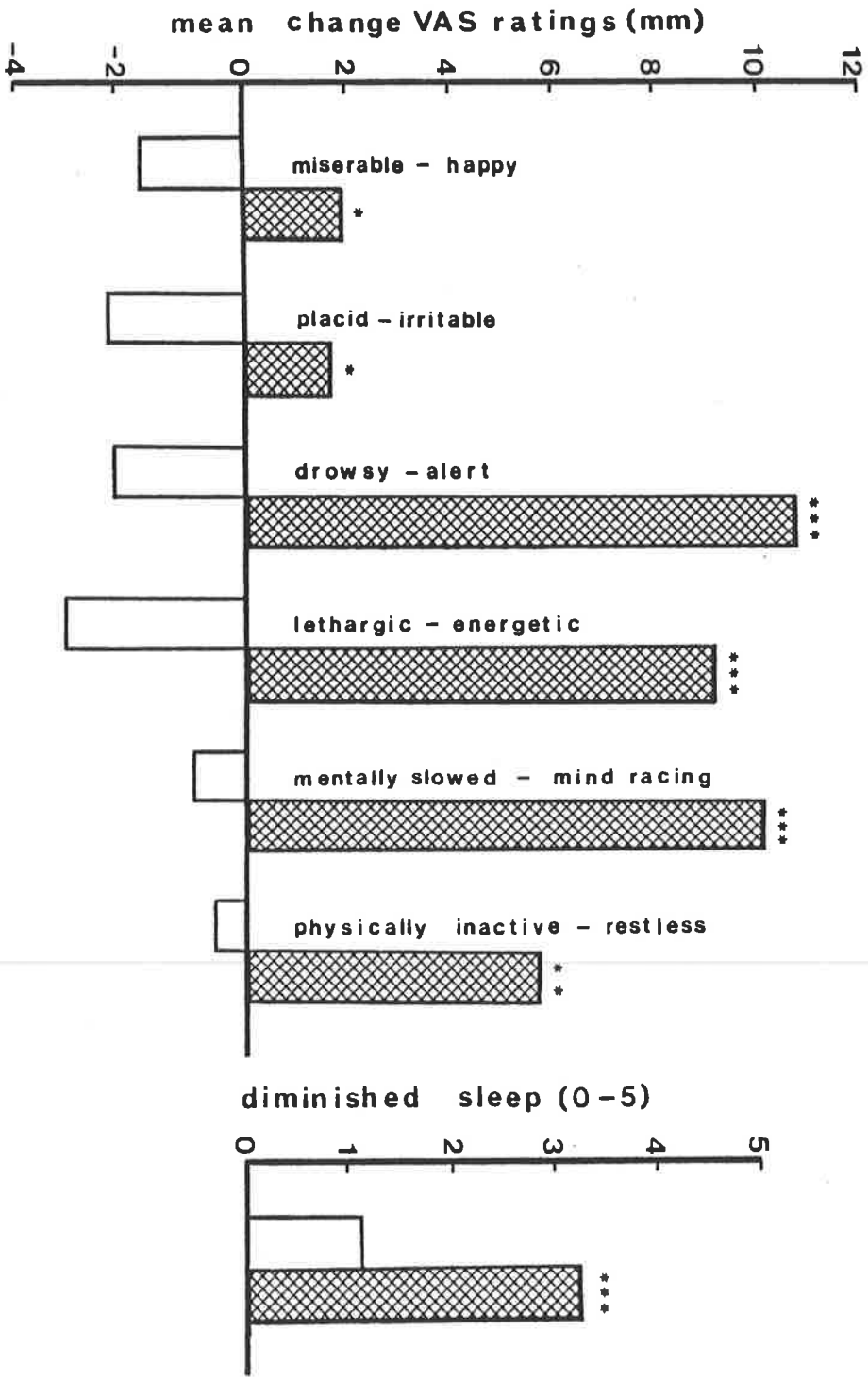

Figure 3.1 Mean changes in VAS ratings (0 - 100mm) following oral dAMP 20mg (maximal change shown) plus diminished sleep (0 - 5 scale):

placebo □ dAMP 20mg ▨

Difference versus placebo. *P < .05 **P < .02 ***P < .005

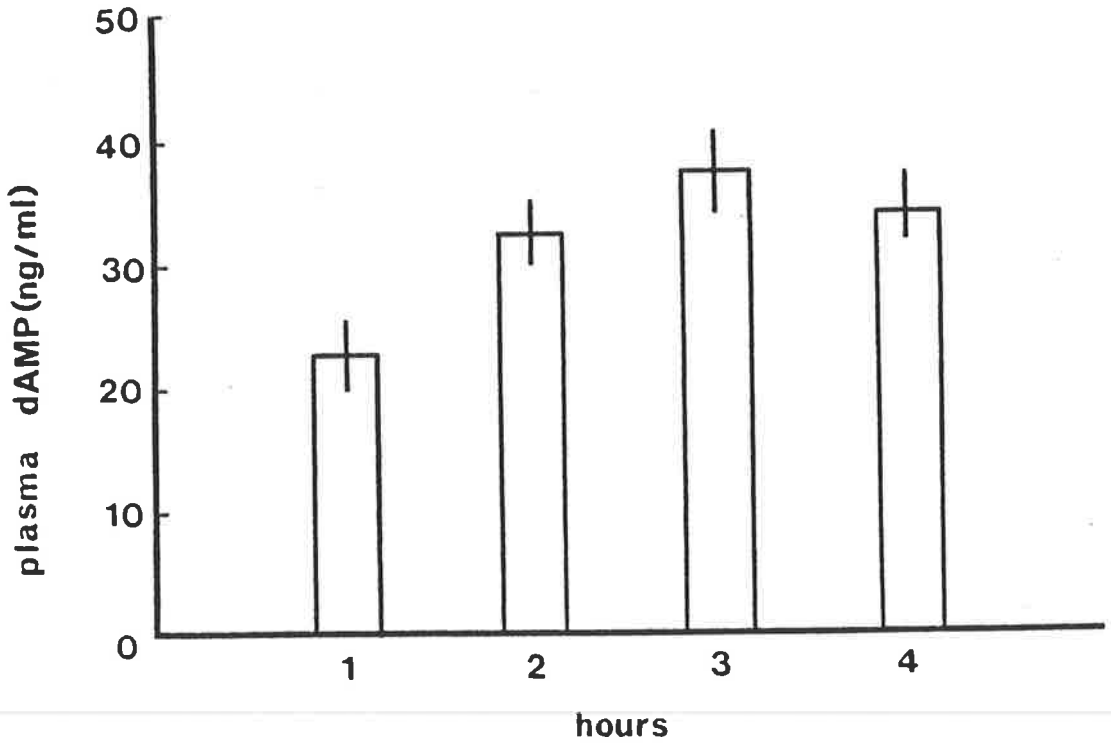

Figure 3.2 Mean (± SEM) plasma dAMP levels (ng/ml) following oral dAMP 20mg given at 0 (1800) hours:

The elevation in the arousal scores is accompanied by a reduction in the rating of the quality of sleep during the night following attendance. The difference from placebo in the scale diminished quality of sleep (5 point) was 2.1 ($P < .01$).

3.3.2. A psychophysiological comparison

Dextroamphetamine 20 mg led to an increase in all psychophysiological and biological measures. The time of maximal response was at two and a half hours.

The mean changes in pulse rate and systolic blood pressure along with those in log skin conductance levels and the number of spontaneous fluctuations in skin conductance at the time of maximal response are shown in figure 3.3. The mean changes (+-SEM) in pulse rate were +11.2(+-2.0) beats per minute following dextroamphetamine and -1.3(+-1.0) beats per minute following placebo; the difference being, +12.5(+-2.1) beats per minute, $P < .001$. The mean changes in systolic blood pressure at the same time were +19.4(+-1.3) mm Hg following dextroamphetamine and +3.4(+-1.5) mm Hg following placebo; the difference being +16.0(+-1.9) mm Hg, $P < .001$).

The changes in log skin conductance levels were similar in direction but the differences between placebo and dextroamphetamine failed to reach statistical significance. Thus at two and a half hours after the dextroamphetamine 20mg or its placebo, the mean change following dextroamphetamine was +0.025(+-0.024) micromhos compared to -0.012(+-0.021) micromhos following placebo; the difference being +0.042(+-0.030) micromhos, $P < .1$). The response in the number of spontaneous fluctuations in skin conductance at the same time was greater. The mean changes following dextroamphetamine 20mg was +0.88(+-0.65) and following

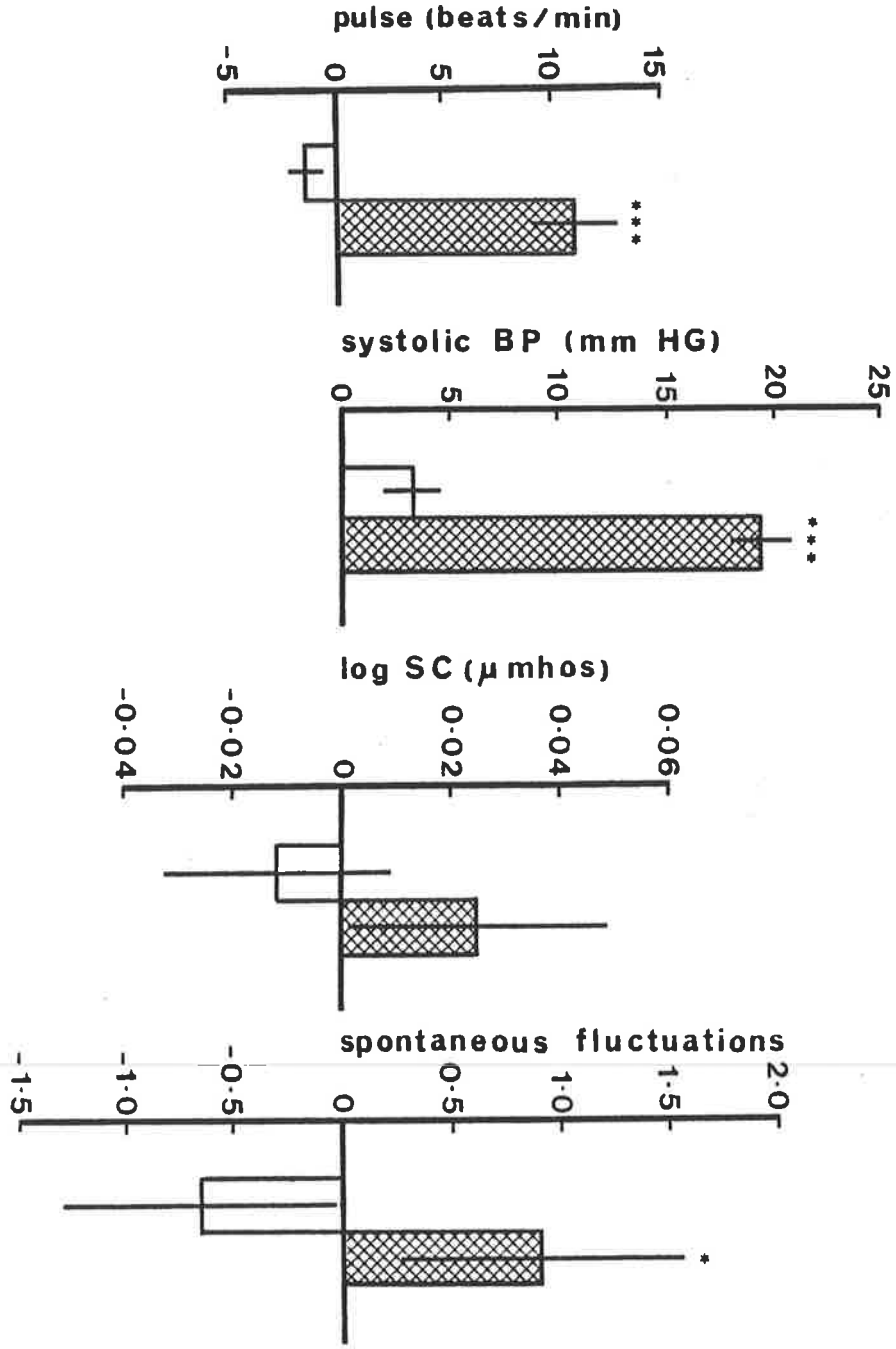

Figure 3.3 Mean changes (± SEM) in pulse rate systolic BP, log SC and number of spontaneous fluctuations at the maximal response following oral dAMP 20mg:

placebo □ dAMP ▨

Difference versus placebo. *P < .05 ***P < .001

placebo -0.65(+- 0.64) with the difference between the two drug regimes being +1.56(+- 0.81), P <.05.

Dextroamphetamine 20mg gave rise to an increase in mean plasma cortisol levels when compared with placebo in a response that reflects the rise in plasma dextroamphetamine levels. See figure 3.4. The maximal increase was at 2 hours with the mean changes in plasma cortisol from 1800 hrs rising from -102.3(+-29.3) nmols / litre following placebo, to 249.2(+-26.4) nmols / litre following dextroamphetamine. The difference between the two was +351.4(+-41.6), P <.001). See also Part II.

Thus the psychophysiological and biological changes following dextroamphetamine match those few changes that have been shown to be associated with mania.

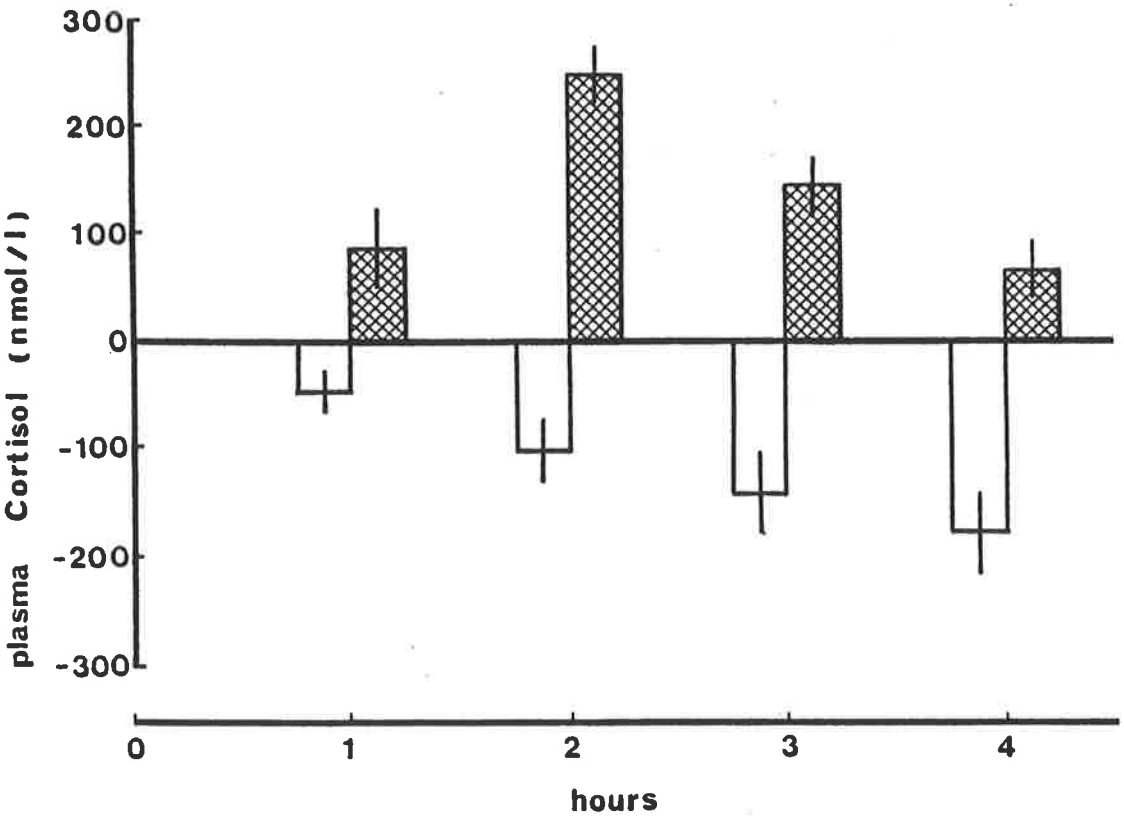

Figure 3.4 Mean changes (± SEM) in plasma cortisol (nmol/L) following oral dAMP given at 0 (1800) hours:

placebo ☐ dAMP ▨

3.3.3. A pharmacological comparison

Pimozide has been shown to be an effective and relatively selective drug in the treatment of mania (Post et al, 1980; Cookson et al, 1981).

The effect of pimozide on dextroamphetamine induced arousal has been described in detail in Part I and will be reviewed only briefly in this section.

Pimozide alone appeared not to influence subjective ratings or the psychophysiological data in any consistent manner. The sole exception was its effect on skin conductance levels where both doses of pimozide used caused a significant drop over 5 hours. In the 12 subjects in experiment B, dextroamphetamine 20 mg gave only a modest rise in elation and irritability and pimozide pretreatment failed to exert any significant change on them. The rise in visual analogue ratings of arousal, restlessness, mental speed and energy produced by dextroamphetamine was reduced by the higher dose of pimozide but this attenuation failed to reach statistical significance. See figure 3.5. (the reference time for change comparison of changes was 1700 hours in order to minimize any effects of pimozide on reference values). Pimozide pretreatment appeared not to influence the effect of dextroamphetamine on the quality of sleep in the night following the experiment either. Pretreatment by pimozide, particularly the higher dose, caused a statistically significant attenuation in the dextroamphetamine induced increase in pulse rate and

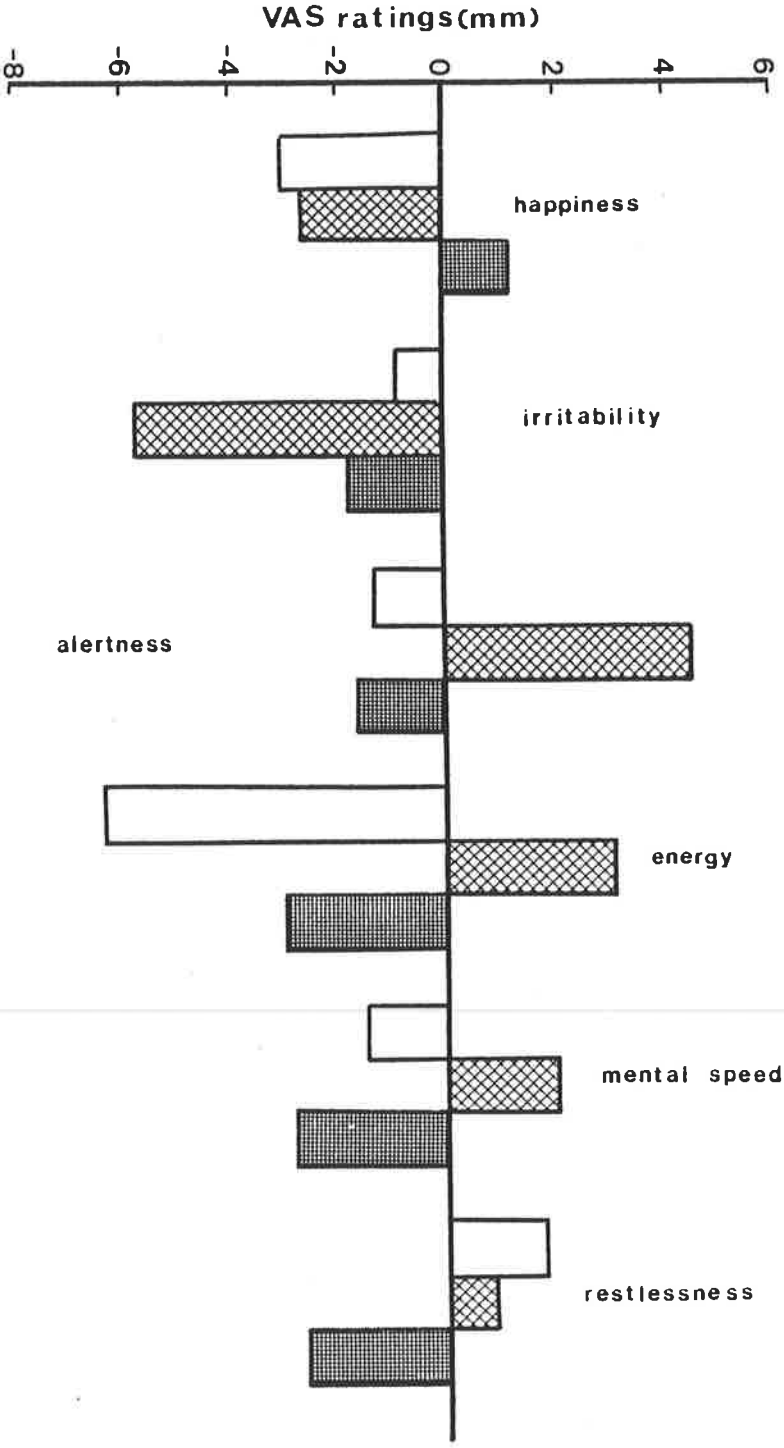

Figure 3.5 Mean changes in VAS ratings (0 - 100mm) in the miserable - happy, placid - irritable, drowsy - alert, lethargic - energetic, mentally slowed - mind racing, restful - restless dimensions from 1700 hours at the time of the maximal response by pimozide:

PMZ placebo - dAMP placebo

PMZ placebo - dAMP 20mg

PMZ 4mg - dAMP 20mg

systolic blood pressure, the rise skin conductance levels and the increased number of spontaneous fluctuations in skin conductance. See figure 3.6. (reference time for change values was 1700 hours).

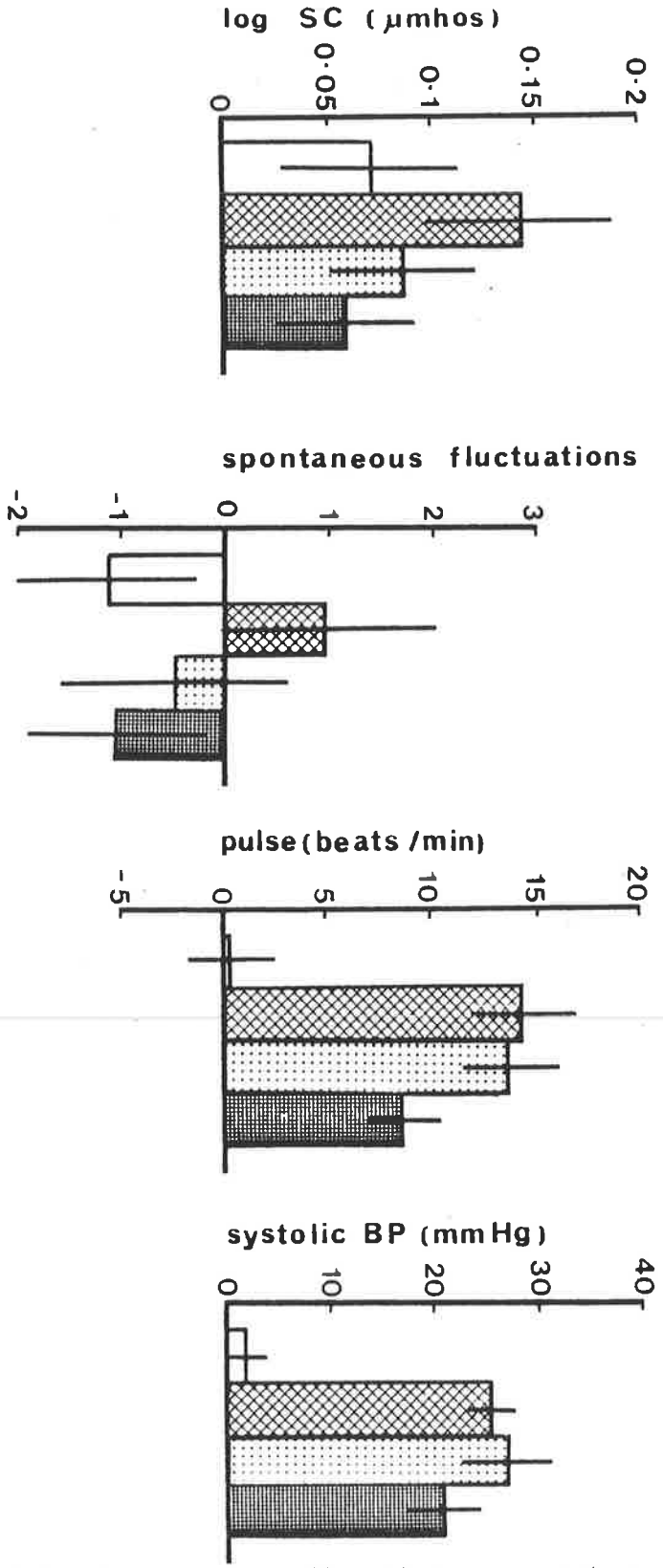

Figure 3.6 Mean changes (± SEM) in log SC (μmhos) and number of spontaneous fluctuations, pulse rate and systolic BP from 1700 hours at the time of the maximal dAMP response:

PMZ placebo - dAMP placebo

PMZ placebo - dAMP 20mg

PMZ 2mg - dAMP 20mg

PMZ 4mg - dAMP 20mg

3.4. Discussion

3.4.1. A phenomenonological comparison

An important feature of the use of a pharmacological model using human subjects, is that it allows a comparison between the phenomena of mania and the response to dextroamphetamine in terms of the mental state. As discussed earlier, such a comparison is only possible using a human model. In the early anecdotal reports of the subjective response to dextroamphetamine derivatives, many phenomena reminiscent of mania were described. In this regard one of the earliest reports by Davidoff and Reifenstein (1937) noted that oral racaemic amphetamine gave rise to insomnia, elevation of mood or increased agitation, over-talkativeness, increased motor activity and restlessness in normal subjects. Similar findings were described by Nathanson (1937) who reported that subjects frequently noted elation, lessened fatigue, talkativeness, increased energy. In some subjects a late effect of depression was observed. In subsequent open studies carried out in the 1950´s similar observations were made. These findings were confirmed in double-blind controlled studies of the psychological response to dextroamphetamine (Brown et al, 1978; Smith and Davis, 1977; Silverstone et al, 1983).

The most common features of mania are the symptoms of mood elevation and/or irritability, increased energy, physical

activity and restlessness, increased loquaciousness and repetitive speech, and alertness together with insomnia (Gibbons 1982). All are included in the various diagnostic criteria as being necessary for the diagnosis of mania (Feighner et al, 1972; ICD-9, 1977; Spitzer et al, 1978; American Psychiatric Association, DSM-III, 1980).

In the present study the action of dextroamphetamine on seven important mental state phenomena seen in mania was examined in normal subjects in a controlled and double-blind manner. The results clearly show a close correspondence between the symptomatology of mild mania and that following a single 20 mg oral dose of dextroamphetamine.

The effect by dextroamphetamine on the ratings of mood and irritability are much less than its effect on ratings measuring arousal and increased mental activity. Other studies (Smith and Davis, 1977; Silverstone et al, 1983) have not reported such a large difference between ratings of mood and arousal.

In a series of manic patients, Cookson (personal communication) observed an admixture of euphoria and irritability, neither of which was as prominent as an increase in symptoms such as restlessness and increased speed of thinking. These findings are similar to those in the current study.

In addition to the above findings, other similarities in mental state and behaviour have been observed between the

response to amphetamine derivatives and mania. Sometimes after a single dose, but more often after a higher dose or during withdrawal, symptoms of depression are reported (Connell, 1958; Ellinwood, 1967; Randrup et al, 1975). Schildkraut et al (1971) reports that while amphetamine addicts were still taking amphetamines "they were clinically hypomanic". Within twenty-four to forty-eight hours after stopping the drug they became depressed reaching a peak forty-eight to seventy-two hours after taking the last dose.

Normal subjects or addicts taking high or continuous doses of amphetamine drugs have revealed other phenomena. These have included behavioural and verbal stereotypies, increased energy and clarity of thinking, aggressiveness, heightened self-confidence and hypersexuality. Psychotic phenomena also occurred such as visual, tactile and auditory hallucinations and persecutory delusions (Bell, 1965; 1973; Ellinwood, 1967; Ellinwood et al, 1973). Although many workers have pointed to these phenomena as resembling paranoid schizophrenia (Snyder, 1972; 1973; Snyder et al, 1974), Ashcroft (1972) observed that stereotypic behaviour can be seen in manic patients. Furthermore the presence of hallucinations and paranoid delusions are not inconsistent with a diagnosis of mania. They are reported to occur relatively frequently in severe cases (Gibbons, 1982) and are usually mood congruent (American Psychiatric Association, DSM-III, 1980).

Checkley (1978) emphasised that the mental state changes with amphetamine derivatives are frequently mixed, not only showing differences over time but also at the same time, making measurement on a two-dimensional analogue scale difficult. Tecce and Cole (1974) report significant variability in the arousal response to dextroamphetamine when measured subjectively as well as using the psychophysiological measure of the contingent negative variation, particularly in the first hour after administration. Again mixed mood states of elation and depression, hyper- and hypoactivity are not inconsistent with the clinical picture of mania. The inconsistency of mood changes may account for the relatively low changes in the visual analogue scale ratings seen in the present experiment. It may also occur because the mood dimensions of happiness and irritability are to a degree opposing emotions.

3.4.2. A psychobiological comparison

The comparison of the response to dextroamphetamine and mania on psychophysiological and biological measures is made difficult because of the paucity of information about the physical sequelae of mania. A comprehensive literature search revealed very few parameters which had been shown to be altered in mania and which could also be used in an experimental comparison. The lack of psychophysiological and biological information reflects the very great difficulty posed by patients suffering from mania when scientific study in this area is attempted. Studying patients during and after their illness without the influence of medication is rarely possible. Leaving manic patients without active treatment for prolonged periods for the purpose of experimentation is not usually ethically appropriate, nor clinically desirable.

The reported findings with mania involve few patients and it is not certain how representative these findings might be. Kraepelin (reprint of 1921 English translation 1976) suggested that the pulse was raised or normal and that blood pressure also was raised, particularly in the more severe forms of mania. Studies in patients with a forty-eight hour cycle did not demonstrate changes of pulse with mania and although the patient was noticed to sweat more on manic days, there was no change in skin galvanometry (Jenner et al, 1967). Bunney et al (1965) demonstrated a negative correlation between mania and 17-hydroxycorticosteroid

levels.

More recent reports suggest that pulse and blood pressure are raised in manic patients (Lake et al, 1982) whilst a longitudinal report in one subject suggested that mania correlated with increasing skin conductance levels (Hemsley and Philips, 1975). Although this is barely satisfactory evidence for the basis of a psychophysiological comparison, it is the best that can be done in the circumstances.

Biologically there is evidence that cortisol is generally elevated in mania Cookson et al, 1980; Silverstone and Cookson, 1982). The pattern with the other anterior pituitary hormones in mania has not as yet been elucidated.

Both in the psychophysiological parameters and with plasma cortisol levels studied in this experiment, the response by normal subjects to dextroamphetamine closely matched those measures known to occur in mania.

3.4.3. A pharmacological comparison

Pimozide has been reported to exert an antimanic action, which may be more specific than other neuroleptics (Post et al, 1980; Cookson et al, 1981). In the experiment described in Part I, pimozide caused at most only a mild attenuation of the response to dextroamphetamine in some of the psychological dimensions with none of the changes reaching statistical significance. Pimozide reduced the rise in pulse rate and the rise in systolic blood pressure induced by dextroamphetamine. The effects on the cardiovascular system are difficult to interpret as it is not clear how much these changes are due to peripheral rather than central actions of the drugs.

Pimozide pretreatment caused a clear dose-related attenuation in the amphetamine induced rise in skin conductance measures suggesting that pimozide does attenuate the central effects of dextroamphetamine. Skin conductance changes are mediated by a cholinergic sympathetic pathway (Venables and Christie, 1980) and dextroamphetamine appears to have no direct action on cholinergic neurones (Moore, 1977). This is consistent with other studies that have demonstrated that pimozide attenuated the mood elevating effect of intravenous dextroamphetamine (Jonsson, 1972) and the alerting and sleep reducing effect of oral dextroamphetamine (Gillin et al, 1979[b]; Silverstone et al, 1980).

A comparison of the effects of other pharmacological

agents or challenges derived from the scientific literature also support the relevance of the model for mania. Alpha methylparatyrosine, which blocks the rate limited enzyme tyrosine hydroxylase concerned with the conversion of phenylalanine to dopa thereby reducing the formation of both dopamine and noradrenaline in the presynaptic neurone, was found to be effective in reducing the symptoms of mania (Brodie et al, 1971). This drug also attenuated the affective response to intravenous dextroamphetamine in human subjects (Jonsson et al, 1971).

Lithium carbonate has a major clinical role in the treatment of mania, both in reducing manic symptoms and as prophylaxis to prevent relapse (Cade, 1948; Schou, 1968; Shaw, 1979); it is therefore of interest that lithium carbonate has been reported as attenuating the arousal response to dextroamphetamine in normal subjects (Van Kammen and Murphy, 1975; Angrist and Gershon, 1979).

Considering the observations made in the present study together with those reported by other investigators, there appears to be close correspondence between the changes produced by a single dose of dextroamphetamine in normal volunteer subjects and those occurring during the course of a manic illness in the three criteria posed to validate the model. Indeed the amphetamine model clearly fulfils the three criteria required for a useful clinical model for mania. (See 3.1.2.b.)

i. Amphetamine produces a state in which there are close similarities in experiential and behavioural terms with those seen in mild mania.

ii. There are striking psychophysiological and biological correlates between amphetamine arousal and clinical mania.

iii. The response of both amphetamine arousal and mania to the dopamine receptor blocker pimozide are in a similar direction. The responses to lithium carbonate and alpha methylparatyrosine are similarly comparable.

See table 3.1.

Table 3.1.

Summary of results and cited references comparing the symptoms physical changes and responses to pharmacological challenge with the response to dextroamphetamine.

PARAMETER	MANIA	DEXTRO-AMPHETAMINE
Changes in Mental state		
elation	↑	↑
irritability	↑	↑
alertness	↑	↑
energy	↑	↑
restlessness	↑	↑
mental speed	↑	↑
sleep	↓	↓
Physical Changes		
pulse	↑ (a)	↑
systolic blood pressure	↑ (a)	↑
skin conductance	↑ (b)	↑
cortisol	↑ (c)	↑
Response to Pharmacological Challenge		
pimozide	↓ (d)	↓
lithium carbonate	↓ (e)	↓ (f)
alpha methylparatyrosine	↓ (g)	↓ (h)

(a) Lake et al, 1982 (b) Hemsley and Philips, 1975
(c) Cookson et al, 1982 (d) Cookson et al, 1981
(e) Schou, 1968 (f) Van Kammen and Murphy, 1975
(g) Brodie et al, 1971 (h) Jonsson et al, 1971

Hitherto amphetamine - induced states in humans have been almost exclusively regarded as a model for schizophrenia. This was based on the observation that when taken in high or prolonged dosage amphetamine produces a paranoid psychosis similar to paranoid schizophrenia (Connell, 1958; Bell, 1965; 1973; Ellinwood, 1967; Ellinwood et al, 1973; Snyder, 1972; 1973). However, as mentioned earlier, many of the symptoms described by individuals taking high doses of amphetamine drugs can be seen in more severe forms of mania. These include loquaciousness, restlessness, irritability and anger, increased self-confidence and grandiosity, stereotypy, hallucinations and delusions and withdrawal depression Ashcroft et al, 1965; 1972; Gibbons, 1982). At the time some workers pointed out that there were substantial differences between paranoid psychosis induced by amphetamine and schizophrenia (Bell, 1973; Snyder, 1973).

The comparison of the amphetamine induced psychosis with schizophrenia seems to have distracted workers from the rather obvious comparison between the response to a small dose of an amphetamine derivative and mild mania.

One possible reason for this may be that at the time comparisons were made between amphetamine psychosis and paranoid schizophrenia the distinction between schizophrenia and mania were not as clearly defined as they are now. Over the past fifteen years and particularly since the advent of the treatment for mania by lithium carbonate, the diagnostic criteria for the different psychoses have been sharpened.

Earlier criteria for schizophrenia, in particular those posed by Schneider, which were in general use until recently, have been found not to adequately distinguish mania from schizophrenia (Brockingham et al, 1978). Clinicians using the newer more refined diagnostic criteria, have found that many patients previously diagnosed as suffering paranoid schizophrenia should be reclassified as suffering mania and are successfully treated with lithium carbonate (Mellor, 1982).

3.4.4. Implications for the role of the catecholamine pathways in the biology of mania

The results obtained in the present study confirm that the response to a small dose of dextroamphetamine given orally to normal human subjects, fulfils a set of criteria which establishes that it may be a valid model for mild mania. The fourth criteria for a model of a psychiatric illness posed by McKinney and Bunney (1969) was that the model and disease share a common aetiology or mechanism of action. As the biological aetiology of mania is not known it was felt best to consider this criterion as a criterion of relevance rather than of validity.

The catecholamines are clearly involved in the pathogenesis of mania though their precise respective roles have yet to be determined. Earlier studies implicated a excess of activity of the noradrenergic pathways (Schildkraut, 1965; 1973). More recent evidence, particularly from pharmacological studies, strongly suggests that an elevation in the activity of dopamine pathways is of primary importance in the pathogenesis of mania (Randrup et al, 1975; Silverstone, 1978; Post, 1980; Silverstone and Cookson, 1982). The role of noradrenaline has become increasingly uncertain.

A model using dextroamphetamine is of relevance to allow further exploration of these questions, as amphetamine derivatives act as indirect agonists of both dopamine and noradrenaline centrally. (See 1.2.5.). As dextroamphetamine

induced symptoms are blocked by pimozide and other centrally acting dopamine blocking drugs, the model reinforces the possibility of a stimulatory role for dopamine pathways in mania.

In the investigation of the role of the alphanoradrenergic pathways in the dextroamphetamine response, pretreatment by thymoxamine, an alpha 1 postsynaptic noradrenergic antagonist, accentuated the response (see Part I). This was particularly manifest with the higher dose of thymoxamine and was demonstrable on both the psychological and psychophysiological effects of dextroamphetamine.

While the accentuating effect by thymoxamine on the dextroamphetamine response could reflect a blocking action on presynaptic alpha 2 adrenoceptors, ie. a yohimbine like action, there is no evidence to support such a view. It is more likely that the accentuation of the dextroamphetamine response by thymoxamine was due to its blocking action on postsynaptic receptors. If so, then a case can be made for the noradrenergic pathways (at least the alpha noradrenergic pathways) interacting with dopamine pathways in the regulation of arousal; the noradrenergic pathways being inhibitory in states of increased dopamine activity.

If this is so, it points the way to the possibility of a different approach to treatment.

Such a conclusion would be in keeping with the results of the study in which fusaric acid, a dopamine beta hydroxylase

inhibitor, was given to manic patients. This led to a rise in dopamine and a drop in noradrenaline and caused an exacerbation of symptoms (Sack and Goodwin, 1974).

Other studies investigating the role of the alpha noradrenergic pathways in mania have looked at clonidine and yohimbine, an agonist and antagonist respectively, at pre- and postsynaptic alpha 2 receptors (Anden et al, 1976; 1982; Langer, 1981). Clonidine administration reduced manic symptoms which may rebound on withdrawal (Youvent et al, 1980) whereas yohimbine may precipitate mania (Price et al, 1984). Interpretation of these results depend on whether the drugs are acting preferentially at pre- or postsynaptic sites within the central nervous system. Clearly other studies aimed at resolving these issues would be desirable.

3.4.5. Conclusion

It would appear reasonable to conclude that the response to a low dose of dextroamphetamine in normal human subjects fulfils the various criteria laid down for a valid model for mania as there is close correlation in the various criteria proposed. This gives credence to the use of dextroamphetamine as an animal model for mania (Murphy, 1978; Robbins and Sahakian, 1980). Furthermore, as dextroamphetamine acts as an indirect agonist for both dopamine and noradrenaline, it allows an opportunity to explore and compare the role of the two catecholamines in this disease. In so doing, the model reinforces the proposal that hyperfunction of the dopamine pathways is important in the biology of mania.

If we use oral dextroamphetamine as a model for mild mania to investigate the role of the alphanoradrenergic pathways in mania, results imply that the noradrenergic pathways may not be involved in the simple stimulatory role that had been previously assumed but that a more complex interactive relationship with the dopamine pathways exists.

As one of the main purposes in using models of illnesses in psychopharmacological research is in the generation of new research hypotheses, the model described promotes further investigation of the role of the noradrenergic pathways in the biology of mania.

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