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

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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.