Acetylcholine and Posttraumatic Stress Disorder

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Signed Statement

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Dedication

To my four daughters,
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who were all born during the conduct of this research.

Abstract

Posttraumatic Stress Disorder (PTSD) is a psychiatric condition that can develop following exposure to a traumatic event involving actual or threatened death or serious injury. Responses include intense fear, helplessness or horror. Symptoms are characterised into clusters, described as re-experiencing, avoidance, and arousal. These symptoms, which are also evident in other conditions, have been associated with dysfunctions in the central acetylcholinergic system. Benefits from administering acetylcholinesterase inhibitors (AChEI) to people suffering these symptoms have been demonstrated. Donepezil hydrochloride, a reversible inhibitor of the enzyme acetylcholinesterase, is used in the treatment of conditions with difficulties in cognitive function, but has not been used in PTSD.

The aim of this thesis was to determine (1) whether there was a difference in the ACh system in people with PTSD and (2) whether administration of an AChEI would change the symtomatology.

IDEX (I^{123} iododexetimide) has been useful in imaging muscarinic-ACh receptors using Single Photon Emission Computerised Tomography (SPECT) and was utilised to investigate whether cholinergic activity in PTSD is altered. One hundred and sixty eight potential subjects were screened and eleven PTSD subjects were enrolled in the IDEX SPECT study. Three healthy non-PTSD control subjects also completed the study. Due to technical complications only the data obtained from eight PTSD and two control subjects was available for analysis. Imaging data for 2 further healthy non-PTSD control subjects were obtained from another study. Sixteen subjects were enrolled in the donepezil open label study (assessed at baseline, Week 2, 6 and 10). Nine PTSD subjects completed the 10-week trial and seven withdrew prematurely (at or after Week 2) due to side effects or a worsening of

PTSD symptoms.

For the IDEX SPECT study, a voxel-by-voxel statistical analysis of the PTSD subject group versus the control group showed both areas of reduced and increased IDEX uptake. Significant clusters in the PTSD group with a **reduced** IDEX uptake centred around the bilateral hippocampus, left insula and right precuneus, while **increased** IDEX uptake appeared in the caudate head.

For the donepezil study, in the per-protocol analysis (including only the 9 subjects that completed the protocol), all psychological assessments revealed a difference between the totals obtained at the Week 10 visit compared to those at the Baseline visit and the improvement was in the order of 51%. The intention-to-treat analysis (including all 16 subjects), a repeated measures Analysis of Variance (ANOVA) with a mixed models approach showed that all psychological measures demonstrated statistically significant benefits of the treatment. All subjects who completed the protocol recounted considerable improvement in their overall PTSD symptom profile, which covered symptoms in each of the three clusters.

The results of the IDEX SPECT study suggest that alterations in ACh binding in PTSD are evident and may begin to explain a part of the altered cognitive symptomatology apparent in this condition. The pilot open label donepezil trial provided some preliminary evidence that treatment with an AChEI can lessen the intrusions and distress associated with traumatic memories in people with PTSD.

List of Abbreviations

5-HT	Serotonin
^{99m}Tc-HMPAO	^{99m}-technetium-hexamethylpropyleneamineoxime
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase Inhibitor
AChE-E	Acetylcholinesterase - Erythrocytic
AChE-R	Acetylcholinesterase - Readthrough
AChE-S	Acetylcholinesterase - Synaptic
AD	Alzheimers Disease
ADAS-Cog	The Alzheimers Disease Assessment Scale - Cognitive Subscale
AINSE	Australian Institute of Nuclear Science and Engineering
ANOVA	Analysis of Variance
ANSTO	Australian Nuclear Science and Technology Organisation
CAPS	Clinician-Administered PTSD Scale for DSM-IV
CBT	Cognitive Behavioural Therapy
ChAT	Choline Acetyltransferase
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
CTN	Clinical Trial Notification

dbB	Diagonal Band of Broca
DLB	Lewy Body Dementia
DSM-IIIR	Diagnostic and Statistical Manual of Mental Disorders - Third Edition revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
E2020	Donepezil - an AChEI
EMDR	Eye Movement Desensitisation and Reprogramming
ENA-713	Rivastigmine - an AChEI
ERP	Event Related Potential
FBE	Full Blood Examination
FDG	Fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
FWHM	Full Width, Half Maximum
GABA	Gamma-Aminobutyric Acid
GHQ	General Health Questionnaire
HDB	Horizontal Limb of the Diagonal Band of Broca
HPA-axis	Hypothalamic - Pituitary - Adrenocortical Axis
ICD-10	International Classification of Diseases
IDEX	I^{123} Iododexetemide
IES	The Impact of Events Scale
IQ	Intelligence Quotient
K+	Potassium ions
LC	Locus Ceruleus
m-AChR	Muscarinic ACh Receptors
MBq	mega-Becquerel
MG	Myasthenia Gravis
MMSE	Mini-Mental State Examination

MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Medial Septal Nucleus
Na+	Sodium ions
n-AChRs	Nicotinic Acetylcholine Receptors
NART	The National Adult Reading Test - Second Edition
nbm	Nucleus Basalis of Meynert
NE	Noradrenaline
NWAHS	North West Adelaide Health Service
PCL-C	Posttraumatic Stress Disorder Check List - Civilian
PCL-M	Posttraumatic Stress Disorder Check List - Military
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PTSD	Posttraumatic Stress Disorder
rCBF	Regional Cerebral Blood Flow
SD	Standard Deviation
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SNS	Sympathetic Nervous System
SPECT	Single Photon Emission Computerised Tomography
SPM	Statistical Parametrical Map
SSRI	Selective Serotonin Reuptake Inhibitor
TGA	Therapeutic Goods Administration
TQEH	The Queen Elizabeth Hospital
VChAT	Vesicular Choline Acetyltransferase
VDB	Vertical Limb of the Diagonal Band of Broca
WHO	World Health Organization