Cognitive Impairment due to Traumatic Brain Injury: Investigation of the Cholinergic Hypothesis

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Introduction

Cognitive impairments are common consequences of traumatic brain injury (TBI). However, the neurobiological bases of impaired cognition due to TBI remain incompletely understood. In order to develop rational pharmacological, compensatory/behavioral, technological, and environmental therapies for such impairments and the disability they produce, a better understanding of the neurobiology of cognitive impairment due to TBI is required. Toward that end, we suggest that impairment of the hippocampally-mediated, cholinergically-dependent, pre-attentive process of sensory gating may, at least in part, underlie attention and memory impairments following TBI (1). Our cholinergic hypothesis of attention and memory impairment due to TBI states:

1) TBI results in dysfunction of hippocampal cholinergic systems
2) Hippocampal cholinergic dysfunction contributes to sensory gating impairments
3) Impaired sensory gating interfaces with the development of normal selective attention
4) Impaired selective attention interfaces with new learning
5) Impairments in attention and memory following TBI are, at least in part, a consequence of hippocampal cholinergic dysfunction.

The P50 evoked response to paired auditory stimuli (P50 ratio) reflects the function of a cholinergically-dependent inhibitory neuronal network in the hippocampus (2). Therefore, abnormal P50 physiology following TBI might serve as a putative marker of hippocampal cholinergic dysfunction in cognitively impaired TBI survivors. Volumetric MRI can quantitate alterations in the structure of the brain and hippocampus; disproportionate hippocampal volume loss in persons with abnormal P50 physiology following TBI would provide convergent structural and functional evidence consistent with the above hypothesis. Additionally, well-tolerated pro-cholinergic medications are widely available and may be used as a probe of the cholinergic system among persons with persistent symptoms of impaired auditory gating, attention, memory, and P50 physiology following TBI.

Methods

Subjects

For all studies presented here, participants were recruited from the Neuropsychiatry Clinic at University Hospital, via referral from physicians and neuropsychologists in the metropolitan Denver area, and through an advertisement placed in a Denver newspaper. Subjects reporting persistent problems with attention and memory for more than one year following a definable traumatic brain injury of at least mild severity (based on American Congress of Rehabilitation Medicine criteria, 1993) were sought. Telephone screening interviews were performed by the Neuropsychiatry Service Coordinator (JT) to establish eligibility for all of the studies described herein based on the following inclusion/exclusion criteria:

1) 18 - 60 years of age
2) History of clinically definite TBI
   a) non-penetrating (i.e., closed)
   b) not requiring neurological intervention
   c) post-traumatic amnesia of at least 15 minutes
   d) loss of consciousness was not a required element of the injury
3) TBI at least one year prior to study
4) No diagnosis of neurologic, psychiatric, or substance problems prior to injury
5) Absence of post-traumatic epilepsy
6) Immediate onset and persistence of symptoms of impaired auditory gating following TBI
7) No active mood, anxiety, or substance disorder at the time of study participation
8) Age and education adjusted Mini-Mental State Examination score (MMSE) ≥ 25% 12

Initial severity of TBI was based on duration of post-traumatic amnesia (PTA). PTA was selected for estimation of severity because this information could be derived from interview of patient/family, and other indices of severity such as the Glasgow Coma Scale score or the Galveston Orientation and Amnesia Test were not available for most subjects. Duration of PTA was based on patient/family interviews and/or review of medical records. Initial severity was operationally defined as mild (15' - 1 hr), moderate (1-24 hrs), severe (>24 hrs).

Experiment 1: P50 Recordings (1)

Hypothesis: Subjects with TBI and symptoms consistent with impaired auditory gating will be nonsuppressors of the P50 evoked waveform response to paired auditory stimuli.

Subjects: 20 persons with persistently impaired auditory gating, attention, and memory following TBI (mean age 42 ± 11 years) and 20 age, gender, and education matched non-impairment comparison subjects (mean age 40 ± 11 years).

P50 Recording Method

Auditory evoked potentials were assessed according to our previously described methods (Adler et al., 1993). Auditory stimuli were presented in pairs in a conditioning-testing design with a 0.5 second interpair interval and a 1 second inter-stimulus interval. A pulse stimulus of approximately 1 msec duration, amplified with a bandwidth between 20 and 12,000 Hz, was delivered through headphones. The intensity at the subject’s ear was set at 30 - 45 dB above hearing threshold. Three sets of average responses were constructed, each based on responses to 16 pairs of stimuli, and used to create an overall grand average of the conditioning and test P50 responses for each subject. The P50 wave was identified and measured in each of three sets of averages using a previously described computer algorithm (Nagamoto et al., 1989). The algorithm identified the conditioning P50 wave as the most positive peak between 40 and 80 msec after the first stimulus. The test P50 wave was identified as the most positive peak with a latency from the test stimulus within 10 msec of the latency of the conditioning P50 response. The amplitude of the test P50 wave divided by the amplitude of the conditioning P50 wave, expressed as a percentage and referred to here as the P50 ratio, was used as a measure of auditory gating.

Experiment 2: Volumetric MRI Analyses of the Hippocampus (4)

Hypothesis: Subjects with TBI and P50 nonsuppression will demonstrate reduced hippocampal volume on MRI of the brain.

Subjects: 10 persons with persistently impaired auditory gating, attention, and memory and abnormal P50 physiology following TBI and 10 age, gender, and education matched non-impairment comparison subjects.

Volumetric MRI Method

MRI of the brain was performed on a Phillips Gyroscan 1.5 T system. A standard head coil using a 3-tesla magnet was used. Coronal images of the head, with a TR/TE of 40/5 ms and a 40 degree flip-angle. A 256 x 256 matrix D spoiled gradient echo acquisition was used to obtain a series of 124, 1.7 mm thick, T1-weighted images of the entire brain. The first 10 slices were excluded to avoid the effects of the head coil. MRI data were transferred to a laptop computer and analyzed using the Data Language 3.0 (Research Systems, Boulder, CO). Intrarater reliabilities on total brain volume and hippocampal volumes were determined using a manual segmentation routine written in Interactive Digital Imaging and Analysis System (Dilas, Inc., Cambridge, MA). Specific volume measurements were performed for each of the following brain structures from the right hemisphere: the thalamus, basal ganglia, corpus callosum, lateral ventricle, left and right hippocampus, and left and right amygdala. Inter-rater reliability for the hippocampal volume measurement was .90. The volume of each structure was calculated using the Cavalieri method, and the right and left hippocampal volumes were averaged to obtain an overall hippocampal volume measure. The volumes were corrected for head size as a percentage of total brain volume. A series of one-way ANOVAs were conducted to assess differences between groups.

Results

Preparation of data files and statistical analysis were accomplished using SPSS for Windows statistical software (SPSS Inc., Chicago, IL). The analysis of variance (ANOVA) was performed using the Statistical Package for Social Sciences (SPSS for Windows, v. 10.0.6, Chicago, IL) to compare differences between groups for demographic and clinical variables. The Mann-Whitney U test was used to compare continuous variables with nonparametric distributions in some cases. The chi-square test was used to examine nominal variables as appropriate. A p value < .05 was considered significant.

Experiment 3: Pharmacology Probe Study

Hypothesis: Subjects with TBI and P50 nonsuppression will demonstrate relative normalization of P50 physiology during treatment with donepezil HCl (a cholinesterase inhibitor).

Subjects: 10 persons with persistently impaired auditory gating, attention, and memory and abnormal P50 physiology following TBI. For this study, all subjects had a GOS score of 5.

Study Design

Randomized, double-blind, placebo-controlled, crossover design. Group 1 received donepezil HCl 5 mg daily for six weeks, then donepezil 10 mg daily for six weeks, then crossed-over to placebo; two placebo phases of six weeks each followed thereafter. Group 2 received placebo for 12 weeks, followed by donepezil 5 mg daily for six weeks, and then donepezil 10 mg daily for six weeks. Placebo and donepezil were administered in identical fashion. P50 recordings were performed at baseline and at the end of each treatment phase.

Conclusions

These findings suggest that symptoms of impaired auditory gating following TBI are associated with abnormal P50 physiology and disproportionate hippocampal volume loss. Since it is known that P50 physiology reflects hippocampal cholinergic function, abnormal P50 physiology among individuals with the relevant symptom profile may serve as a useful clinical marker of hippocampal cholinergic dysfunction following TBI. Understanding the clinical symptoms associated with this physiologic disturbance may permit identification of individuals whose post-concussive symptoms may respond to treatment with pro-cholinergic medications, including the cholinesterase inhibitor donepezil HCl. Additional research is needed to determine if the P50 metric can facilitate identification of TBI survivors that may benefit from compensatory strategies, assistive technologies, and/or environmental interventions designed to improve multisensory sensory filtering and thereby enhance attention and memory.