Acoustic Startle Response as a Prognostic Tool for Traumatic Brain Injury

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Abstract

Traumatic Brain Injury (TBI) is a leading cause of death and disability in military and civilian populations. TBI can occur from a number of insults - such as blunt force, blast impact, or penetrating wounds - all associated with acute cognitive and sensory symptoms. The Acoustic Startle Reflex (ASR) is a brain-stem mediated, tri-synaptic response to acoustic stimuli involving involuntary contraction of major muscle groups. Previous studies have demonstrated that this response is suppressed following the fluid-percussion model of traumatic brain injury (TBI). The possibility exists that the suppression of this response could be exploited for prognostic purposes.

Introduction

Reliable metrics capable of diagnosing and tracking TBI severity are limited (1). This unmet need inhibits physician ability to affectively treat patients. Most efforts into meeting this need have focused on proteinaceous and small-molecule biomarkers which elevate in the blood serum following TBI (2). However, we propose that the acoustic startle response (ASR) – a preserved defensive reflex (3) – may have diagnostic and prognostic measurement value. Here, we exposed rats to a well-established model of TBI and tracked alterations in ASR amplitude and latency. Previous studies have reported suppression of the ASR following TBI up to 21 days (4). Here, we report that the ASR amplitude partially recovers after week 4, yet fails to approach pre-injury values at 14 weeks. Suppression of ASR latency is also displayed, yet no trend of recovery was seen. Further, our ongoing study aims to discover histopathological correlates of TBI severity and degree of ASR suppression (amplitude and latency) on an individual rat basis for prognostic applications.

Methods and Materials

We exposed Sprague-Dawley rats to the controlled cortical impact (CCI) model of TBI. ASR was measured before the injury (baseline) and at 9 time points after the TBI (From Day 1 to 14 weeks) in ventilated startle chambers where a white noise burst (110 dB, 40ms, inter-trial interval between 30 and 45s, 30 trials) was presented. Rats were perfused and the tissue are currently being processed for histological evaluation of the impact and peri-impact areas, relevant brain stem regions (caudal pontine reticular nucleus), secondary cell death, and inflammation.

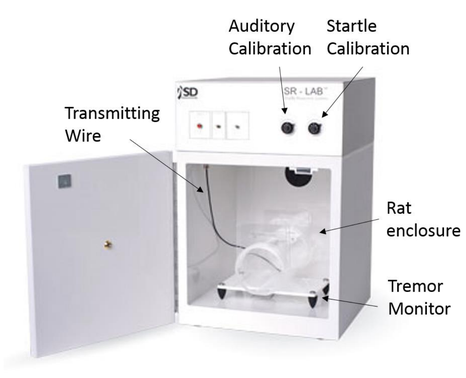

Figure 1 - Left: Experimental set up for controlled cortical impact (CCI) model of traumatic brain injury. Piston induces damage in right motor cortex. Right: Acoustic startle response (ASR) apparatus used to measure reflex includes auditory and startle response calibration controls, a rat enclosure which sits atop a tremor monitor, and a transmitting wire which feeds to receiving computer. (SanDiego Instruments).

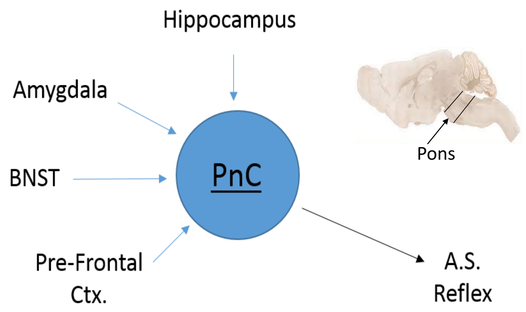

Figure 2 - Left: The caudal pontine reticular nucleus (PnC) is centrally responsible for the acoustic startle reflex (A.S. reflex). A number of brain regions modulate the PnC including the Hippocampus, Amygdala, Bed Nucleus Stria Terminalis (BNST), and the Prefrontal Cortex, among others. Upper right: The pons, an anterior group of brainstem nuclei, is shown ventral to the cerebellum (sagittal section).

Results

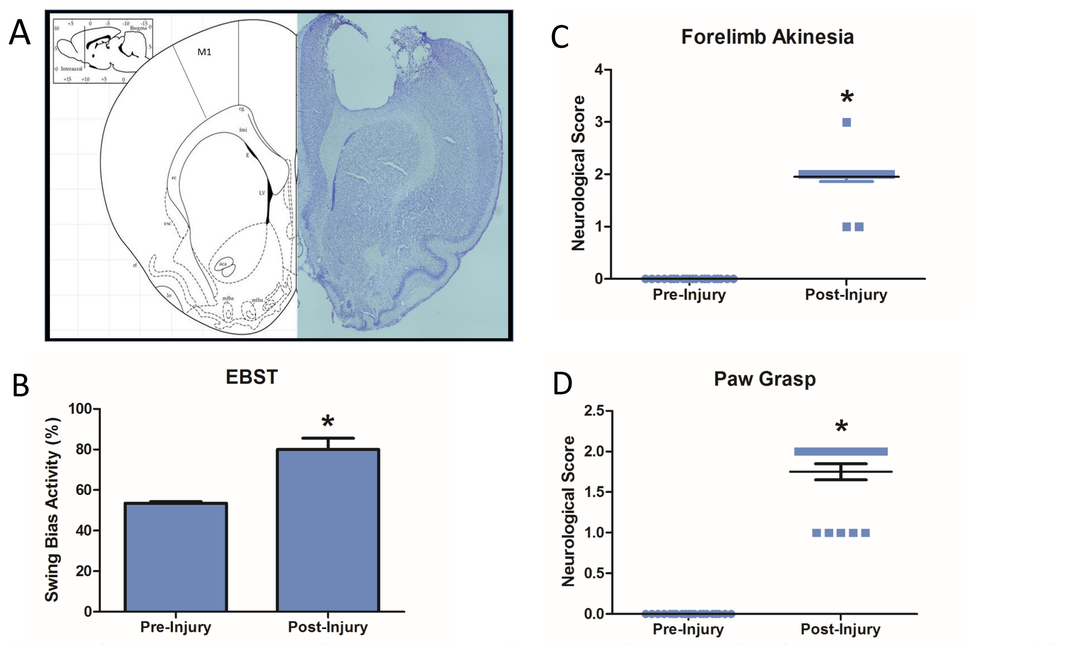

Figure 3. A) Impact area as revealed by Cresyl violet staining. Figure shows TBI-induced injury on M1 motor cortex of the ipsilateral hemisphere. B-D TBI-induced motor deficits were evaluated by using elevated body Swing test (EBST, B), Forelimb Akinesia (C) and Paw Grasp (D) tests. B) Effect of TBI on elevated body swing test (EBST) bias demonstrating neurological deficits resultant from injury. C) Forelimb Akinesia test demonstrating motor/neurological deficits after injury. D) Paw Grasp test demonstrating motor-neurological deficits after TBI. *P<0.05 in unpaired t-test

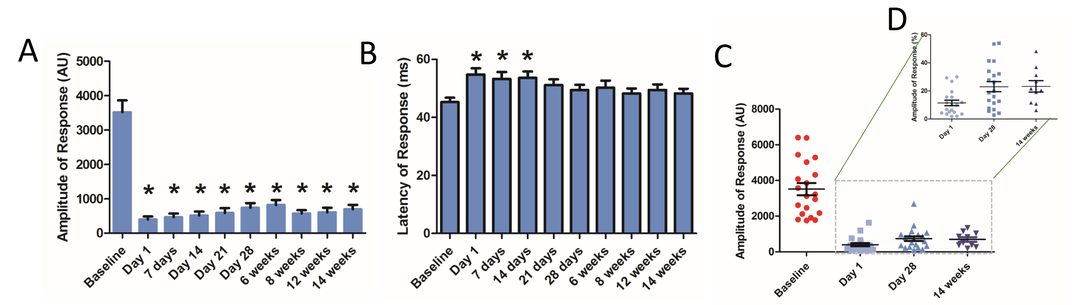

Figure 4 – TBI-induced suppression of Acoustic Startle Reflex. Amplitude. A) Suppression of the ASR was observed after TBI as revealed by an intense decrease in the amplitude of response in all time points when compared to the baseline ($P<0.0001$ versus baseline, one-way ANOVA and Bonferroni's post-test). B) An increase in the latency of response was observed at Day 1, 7 and 14 ($P<0.01$, 0.05 and 0.05, respectively). C) and D). Variability in the amplitude of startle responses before (C) and after injury (D). Data represented as mean ± SEM (percentage of baseline).

Discussion

- We demonstrated that severe TBI-induced suppression of ASR for at least 14 weeks post-injury as revealed by the decrease in both amplitude and latency of response.
- A correlation between TBI severity and ASR suppression could facilitate the diagnostic of TBI and may provide a prognostic value, allowing a convenient method of measuring TBI severity, as well as an outcome assay for potential treatments in the clinic.
- Additional behavioral and histological analyses may reveal specifics about the pathophysiological manifestations of TBI on sensory-motor integration.

Future Directions

- Histological analysis to evaluate the size of impact area and number of live cells in the peri-impact area.
- Histological and Immunohistochemical evaluation of neuronal loss and inflammation in cortical and subcortical underlying the acoustic startle response and its modulation

Acknowledgements

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