Post-Concussive Syndrome in Youth: GABAergic Effects of Melatonin

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The long-term goal of this line of research is to develop rational, biologically based evidence for the treatment of post-concussion syndrome (PCS) in children. The objective of this application is to examine the effect of melatonin on the symptoms of PCS and its neurobiology using integrated neurodiagnostic techniques in children. Overview: By the age of ten, more than 1 in 10 children will sustain a mild traumatic brain injury (mTBI), also known as concussion. Our research found that 1 in 7 school children with mTBI suffer PCS symptoms for three months or longer, and that annually over a 100 children in Canada have PCS for over a year. PCS is a constellation of clinical symptoms including physical (i.e. headaches), cognitive (i.e. memory), and behavioral disturbances. PCS is associated with significant morbidity in the child and his/her family, and yet there are no evidence-based medical treatments available. Furthermore, our neurobiological understanding of PCS is lacking, and routine clinical tests are not informative. Our recent uncontrolled study of treatment outcome in persistent PCS found that 83% of children reported a positive response to oral melatonin. Melatonin has several relevant mechanisms of action, including its GABAergic and neuroprotective effects. As an absence of overt clinical symptoms following mTBI does not always coincide with brain metabolic recovery, it is important to investigate persisting physiological disturbances when evaluating treatment options. Recent research suggests that the explanations for persistent PCS symptoms may be due to alterations in neurotransmission (including GABAergic cortical inhibition) and neuronal circuitry, particularly involving the dorsolateral prefrontal cortex (DLPFC).

We therefore have two specific aims: (1) To determine if treatment with melatonin improves PCS in children following mTBI. We hypothesize that the treatment of mTBI children with PCS with 3mg or 10mg of oral melatonin for 28 days will result in a decrease in PCS symptoms as compared with placebo. Effects will be dose-dependent and may be independent of sleep effects. Methods: A randomized double blind, placebo controlled trial (RCT); outcome measure is a PCS symptom questionnaire. A subsequent RCT will then be performed using the optimal melatonin dose at a second center. (2) To understand the neurophysiological mechanisms of pediatric PCS and assess any resultant effects of treatment with melatonin. We hypothesize that PCS in children will be associated with detectable neurophysiological changes in the brain i.e., PCS children will have decreased brain activation of the DLPFC, decreased fractional anisotropy values in white matter tracts, and abnormal GABAergic cortical inhibition. These changes will return towards normal as symptoms decrease. Methods: A case-controlled study within the RCT, using functional MRI and Transcranial Magnetic Stimulation to investigate the neurophysiological properties of pediatric mTBI before and after treatment; treatment groups from the RCT will be compared with two control groups: normal controls and asymptomatic mTBI children. Significance: This study has the potential to provide a safe and effective treatment for PCS and will provide valuable information about the neurophysiological properties of the brain associated with PCS following mTBI in children and how these change with symptom resolution. It will

also pioneer the adjunctive integrated neurodiagnostic techniques in treatment studies of mTBI in order to evaluate both the symptomatic and metabolic recovery of the brain.