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Neuron Restrictive Silencer Factor (NRSF/REST): A Novel Transcription Factor Regulating Cellular Reprogramming of 5-HT Neurons Following Traumatic Brain Injury

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Traumatic Brain Injury (TBI) is a large public health burden affecting over 3 million Americans annually. Mild TBI (mTBI)/concussion, the most common form of closed head injury, is associated with the development of neurologic sequalae including persistent headache, depression, anxiety, sleep disturbances, social withdrawal and/or PTSD, disorders linked to altered serotonin (5-HT) signaling. Clinically, serotonin reuptake inhibitors have poor efficacy rates in ameliorating the neuropsychiatric sequalae associated with TBI and the effects of mTBI on the function of the central 5-HT system are not well characterized. These problems are exacerbated by the current lack of any FDA-approved pharmacotherapeutics specifically aimed at treating TBI. We hypothesize that TBI results in defined alterations in central 5-HT neurotransmission that drive the generation of enduring symptoms associated with 5-HT signaling within the central nervous system (CNS). To test this hypothesis, adult C57Bl/6 mice were subjected to either a multimodal (acceleration-deceleration/blast) TBI paradigm or sham treatments followed by behavioral and/or molecular analyses 0-10 days post-injury (dpi). TBI acutely increased righting reflex times and resulted in significant reductions in sociability and social dominance, in the Crawley three chamber sociability assay and tube test for social dominance, respectively, 10 days post-injury (dpi). High performance liquid chromatography (HPLC) revealed increased total 5-HT and 5HIAA levels within the dorsal raphe nucleus (DRN) 10 dpi. RNA sequencing analysis utilized in combination with DRN samples from TBI or sham subjects revealed 197 differentially expressed gene transcripts, many of which are related to 5-HT metabolism, signaling and neuron identity. Using the EnrichR gene ontology tool, we sought to delineate potential upstream modulators of TBI-induced transcriptional regulation. Neuron Restrictive Silencer Factor (NRSF/REST) was identified as the most likely transcriptional regulator of differentially expressed transcripts closely associated with 5-HT neuron function and identified within our dataset. REST is a known epigenetic modifier and transcription factor, however it is entirely novel in the context of mammalian 5-HT neuron transcriptional regulation. Immunohistological co-labelling revealed significant increases in REST immunoreactivity within 5-HT neuron populations of the DRN elicited by injury. The current study provides evidence of a novel, injury-derived transcriptional repressor induced within 5-HT neurons following TBI, an effect associated with alterations in the expression of gene transcripts required for the identity, maintenance and function of 5-HT neurons within the CNS. Future studies will be aimed at determining whether REST may represent a novel therapeutic target for the amelioration of TBI-induced alterations in the 5-HT neuron transcriptome and subsequent behavioral and neurologic comorbidities associated with injury.

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