Phosphodiesterase 4B2

The type 4 phosphodiesterase (PDE4) is the predominant PDE isozyme in various leukocytes and plays a key role in the regulation of inflammatory cell activation. There are four PDE4 subtypes (A, B, C, and D), and within each subtype, there are multiple variants. Very recently, we found in monocytes that PDE4B gene expression is selectively induced by lipopolysaccharide (LPS) and that the induction is inhibited by interleukin (IL)-10 and IL-4. In this study, we show that the PDE4B gene is constitutively expressed in neutrophils and that this expression remains unaffected by LPS or IL-10. PDE4B is the predominant subtype in neutrophils and in unstimulated or LPS-stimulated monocytes, and in these cells, the PDE4B2 variant is the only detectable molecular species of PDE4B. Therefore, PDE4B2 is the predominant PDE isoform in human neutrophils and monocytes, and its expression is regulated differently by these two cell types. Furthermore, leukocytes are the most dominant source of PDE4B2, suggesting that PDE4B2 is a relatively specific target for discovering anti-inflammatory drugs [1].

TBI results in decreased cAMP dependent pathway and reduced cAMP-response-element binding protein (CREB) activation, a critical pathway involved in learning and memory. TBI also acutely upregulates phosphodiesterase 4B2 (PDE4B2), which terminates cAMP signaling by hydrolyzing cAMP. We hypothesized that a subtype-selective PDE4B inhibitor could reverse the learning deficits induced by TBI. To test this hypothesis, adult male Sprague-Dawley rats received sham surgery or moderate parasagittal fluid-percussion brain injury. At 3 months postsurgery, animals were administered a selective PDE4B inhibitor or vehicle before cue and contextual fear conditioning, water maze training and a spatial working memory task. Treatment with the PDE4B inhibitor significantly reversed the TBI-induced deficits in cue and contextual fear conditioning and water maze retention. To further understand the underlying mechanisms of these memory impairments, we examined hippocampal long-term potentiation (LTP). TBI resulted in a significant reduction in basal synaptic transmission and impaired expression of LTP. Treatment with the PDE4B inhibitor significantly reduced the deficits in basal synaptic transmission and rescued LTP expression. The PDE4B inhibitor reduced tumor necrosis factor-α levels and increased phosphorylated CREB levels after TBI, suggesting that this drug inhibited molecular pathways in the brain known to be regulated by PDE4B. These results suggest that a subtype-selective PDE4B inhibitor is a potential therapeutic to reverse chronic learning and memory dysfunction and deficits in hippocampal synaptic plasticity following TBI.

SIGNIFICANCE STATEMENT: Currently, there are an estimated 3.2-5.3 million individuals living with disabilities from traumatic brain injury (TBI) in the United States, and 8 of 10 of these individuals report cognitive disabilities (Thurman et al., 1999; Lew et al., 2006; Zaloshnja et al., 2008). One of the molecular mechanisms associated with chronic cognitive disabilities is impaired cAMP signaling in the hippocampus. In this study, we report that a selective phosphodiesterase 4B (PDE4B) inhibitor reduces chronic cognitive deficits after TBI and rescues deficits in hippocampal long-term potentiation. These results suggest that PDE4B inhibition has the potential to improve learning and memory ability and overall functioning for people living with TBI [2].

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