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Low Dose Methylphenidate Modulates Risky Decision Making and Prefrontal Catecholamine Regulation in a Sex-Dependent Manner Following Repeated Mild Traumatic Brain Injury

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Head trauma impairs higher-order decision making processes mediated within the prefrontal cortex (PFC) of the brain and often leads to increased risk-taking behavior. Mild forms of TBI (mTBI), often labeled concussion, account for over 75% of reported TBI cases. Although many individuals including athletes and military personnel experience repeated mild traumatic brain injuries (rmTBIs), the consequences of sustaining multiple traumatic events and whether effects are sex-dependent remain elusive. Additionally, there are no FDA-approved treatments for rmTBI. The catecholamine neurotransmitters, dopamine (DA) and norepinephrine (NE), modulate the PFC's actions and require precise regulation for optimal processing. Imbalances in catecholamine function have been associated with TBI and are theorized to underlie TBI-induced increases in risky decision making. The psychostimulant, methylphenidate (MPH), elevates catecholamine levels by blocking DA and NE reuptake transporters (NET). Due to MPH's efficacy in reducing impulsive and risky behavior in patients with attention deficit hyperactivity disorder (ADHD), it has been considered as a potential therapy for alleviating similar neurocognitive symptoms following TBI. However, it is unknown how MPH can influence risk/reward decision making and levels of catecholamine regulatory proteins within specific PFC subregions following rmTBIs. Here we used a closed head-controlled cortical impact model to induce up to 3 mTBIs, the probabilistic discounting task of risky decision making, and western blotting to determine the effects of chronic low-dose MPH (0.5 and 2 mg/kg, i.p.) on risky behavior and catecholamine regulatory protein levels within specific PFC subregions following rmTBI in male and female rats. Our results show that rmTBI alone increases risky choice preference in saline-treated females, but not males. MPH prevented injury-induced risky choice behavior in females for up to 3 weeks post-rmTBI. Conversely, MPH promoted risky choice behavior in rmTBI males. Within the medial PFC, expression levels of packaging protein vesicular monoamine transporter (VMAT) were decreased in both male and female saline-treated rmTBI groups. MPH treatment normalized VMAT levels in injured females, but not injured males. Within the orbitofrontal cortex, VMAT and NET were decreased in the MPH-treated rmTBI males only. Our results suggest that females are more susceptible to rmTBI-induced behavioral disruption and rmTBI reduces transporter levels within regions of the PFC. In addition, MPH treatment produces restorative benefits in females, but exaggerates pathological outcomes in males. This study is the first to reveal a potential sex-specific psychostimulant therapeutic strategy for rmTBI-induced risky behavior and neuropathological outcomes.

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