Acute Amantadine Enhances the Benefits of Delayed and Abbreviated Environmental Enrichment in a Pediatric Traumatic Brain Injury Model

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Abstract:

Environmental enrichment (EE) accelerates motor and spatial learning after traumatic brain injury (TBI), with benefits observed across different age groups. While EE is typically introduced immediately after TBI, this approach is not clinically feasible, as rehabilitation often begins post-critical care. Given the importance of early intervention for recovery, this study explored the potential of amantadine (AMT) as a bridge therapy prior to EE. AMT was chosen based on preclinical evidence supporting its use in adult TBI, suggesting it may also be effective for pediatric TBI. Hypothesis: Bridging EE with AMT will increase motor and cognitive benefits beyond that of EE alone. Methods: Anesthetized post-natal day 21 male rats received a cortical impact of moderate severity (2.5 mm impact) or sham injury. Rats were housed in standard (STD) conditions for one week and administered either AMT (10 mg/kg) or saline vehicle (1 mL/kg) intraperitoneally for 7 days. EE (6-hr/day) began on day 8 for the bridge and continuous EE groups. Motor and cognitive performance was assessed on days 8-12 and 14-21, respectively. The data were analyzed by repeated measures analysis of variance and Newman-Keuls post-hoc. Results: Bridging EE with AMT facilitated motor recovery vs. vehicle-treated STD-housed rats ($p<0.05$) and provided additional benefits in the acquisition of spatial learning over EE alone ($p<0.05$), which supports the hypothesis. Bridging EE with AMT did not provide additional benefits in memory retention compared to EE alone ($p>0.05$). Between the STD-housed rats, the AMT-treated group performed better on both tasks vs. the STD-only group ($p<0.05$). Conclusions and significance: Bridging EE with AMT did provide additional benefit to cognitive recovery, but the limit of an additive effect to just one behavioral measure may be due to a sub-optimal dose of AMT and warrants a dose-response study.