An empirical evaluation of a bridge therapy with amantadine and environmental enrichment after controlled cortical impact injury in adult male rats

Rachel A. Bittner, Vincent J. Vozzella, Eleni H. Moschonas, B.S., Jeffrey P. Cheng, B.S., Corina O. Bondi, Ph.D., and Anthony E. Kline, Ph.D.

Physical Medicine & Rehabilitation, Safar Center for Resuscitation Research, Critical Care Medicine, Psychology, Neurobiology, and Center for Neuroscience, University of Pittsburgh, Pittsburgh, PA

PURPOSE

Environmental enrichment (EE) has been shown to facilitate motor recovery and hasten spatial learning and memory when provided after traumatic brain injury (TBI). These effects are observed in both male and female rats, as well as adults and postnatal neonates. Historically, EE has been provided immediately and continuously after TBI but this paradigm is not clinically relevant as rehabilitation is typically not initiated until after clinical recovery, which may be several days. Moreover, once rehabilitation is prescribed it is for only a few hours per day. However, it is important to begin treating the injured brain as soon as possible to optimize recovery. Hence, the goal of this study was to administer amantadine (AMT), which has been shown to exert benefits when provided chronically 1-3, as a bridge therapy before commencing EE. We hypothesized that a bridge therapy with AMT followed by delayed environmental EE would confer better motor and cognitive benefits than AMT or EE alone.

METHODS

Surgery: Forty anesthetized adult male rats received either a controlled cortical impact (2.5 mm, 40 g) to the right hemisphere or a sham injury as previously described.4,5

Drug administration: 24 h post-injury the rats were randomized and either given AMT (10 or 20 mg/kg) or VEH (1 mL/kg) by intraperitoneal injection for 7 days (bridge).

Environmental enrichment: Rats were put in EE on post-operative days 8-19 once a day for 6 hours then returned to standard housing.

Behavioral evaluation: Motor function was evaluated using a well-validated beam test on post-operative days 7-11. Briefly, the beam-walk score consisted of recording the number of left (i.e. injury to the right hemisphere, thus affecting the left hindlimb) foot steps at the rat attempted to traverse the wooden beam (see rating scale in Fig. 1). Cognitive function was assessed with a Morris water maze test on days 14-19. Specifically, the cognitively task consisted of providing 2 trials per day in which the rat was allowed 120 s to find a platform submerged below the water surface. The probe test measures memory retention and consists of measuring the time the rat spent in the target quadrant as well as the time the rat spent swimming in the target quadrant from the previous training trials.

Histology: Coronal sections (3um) at 1 mm intervals will be stained using Cresyl violet. Lesion volume and hippocampal cells will be quantified.

RESULTS

(A) Beam-walk measures how quickly the rat can traverse the beam as well as how effective the walking is based on the number of foot steps. (B) Morris water maze assesses spatial learning with a spatial learning task and platform.

EE rats. Note the enlarged learning space with hidden platform allowing the rats to move from one level to another as well as gain exercise. Also note the variety of stimuli objects. Housing 10 rats per cage together attained alleviation.

Mean (±S.E.M.) time (sec) to find the hidden and visible platforms after TBI or sham injury: *p < 0.05 vs. TBI + VEH + STD and TBI + AMT (10 mg/kg); **p < 0.5 vs. TBI + VEH + STD. *p < 0.5 vs. all TBI groups.

DISCUSSION

➢ A rehab-intensive EE paradigm improved cognitive and motor performance in all groups.

➢ Bridging EE with AMT yielded better cognitive recovery than EE-alone.

➢ The data show that EE does not have to be implemented immediately or continuously after TBI to be effective.

➢ 10 mg/kg AMT was ineffective on its own as there were no differences in motor and cognitive function between the AMT (10 mg/kg) + STD and VEH + STD groups.

➢ 20 mg/kg AMT improved cognition over the VEH + STD and AMT (10 mg/kg) + STD groups.

CONCLUSIONS

Bridging EE with the higher doses of AMT conferred better cognitive benefits (acquisition of spatial learning) than either EE or AMT alone, which supports our hypothesis.

REFERENCES


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