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Spontaneous recovery after controlled cortical impact injury is not impeded by intermittent administration of the antipsychotic drug risperidone

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Abstract

Several preclinical studies have reported that daily administration of the antipsychotic drug (APD) risperidone (RISP) impedes recovery after traumatic brain injury (TBI). However, it is not known whether intermittent dosing would produce similar deleterious effects. The relevance of providing APDs intermittently is that not all patients in rehabilitation require daily treatments to manage TBI-induced agitation. Hence, the goal of the current study was to test the hypothesis that intermittent (vs. daily) administration of RISP would be less disturbing to motor and cognitive recovery after TBI. Anesthetized adult male rats were subjected to either a cortical impact of moderate severity or sham injury and then were randomly assigned to groups receiving intraperitoneal injections of vehicle (VEH; 1.0 mL/kg) or RISP (0.45 mg/kg) 1x, 3x, or 7x per week until the completion of behavioral testing, which consisted of motor and cognitive assessments on post-operative days 1–5 and 14–19, respectively. The group receiving RISP 7x week exhibited greater motor and cognitive impairment compared to those receiving RISP 1x or

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3x per week, or VEH [$p < 0.05$]. Moreover, no differences were observed between the intermittent RISP groups vs. VEH [$p > 0.05$], which supports the hypothesis. A potential clinical ramification is that RISP may be safe to manage agitation after TBI, but only when used sparingly.

Keywords

antipsychotics; beam-walking; behavior; controlled cortical impact; functional recovery; learning and memory; Morris water maze; traumatic brain injury

1. Introduction

An estimated 10 million people worldwide incur a traumatic brain injury (TBI) each year, and according to predictions by the World Health Organization TBIs are on track to become the leading cause of death and disability worldwide by the year 2020 [1]. In the United States alone, there are over 2 million TBIs annually [2]. Cognitive dysfunction, which includes difficulties in memory, attention, and language are common and long lasting [2,3]. Indeed, it is estimated that 100,000 patients will experience long-term motor and cognitive disability [3].

In addition to the salient motor and cognitive deficits, TBI also leads to increased agitated and aggressive behavior [4–6]. These maladaptive behavioral symptoms are prevalent with some reports suggesting that up to 96% of TBI patients exhibit agitated behavior at some point during the acute recovery phase, while up to 75% display agitation while in rehabilitation [7–10]. Aggressive behavior is less common, but is still impactful as it affects approximately 11% of the TBI population [11].

Agitated TBI patients may resist treatment, become disruptive, and subsequently pose a physical risk to themselves or hospital staff, which hampers emergency care and subsequent rehabilitation [6,12–14]. Although non-pharmaceutical approaches, such as behavioral management and environmental controls (e.g., reducing noise and interruptions), have been used with some success, the administration of APDs is routine as they rapidly control agitation [6,15–17]. The use of APDs is not without controversy as several preclinical studies have shown them to exert deleterious effects on functional outcome [18–26]. It is possible that the duration of drug treatment may be compounding the issue as most of the reported studies provided daily administration of haloperidol or risperidone (RISP) [18–22]. However, a crucial point to consider is that TBI patients likely will not exhibit agitation or aggression every day and therefore do not necessitate daily administration. Therefore, the goal of the current study was to evaluate the effects of intermittent administration (3x or 1x per week) of the atypical APD RISP and to test the hypothesis that this paradigm would not impair motor and cognitive function to the same degree as the once daily (7x week) approach, which has been demonstrated previously with RISP as well as haloperidol [18–22].

2. Material and methods

2.1. Animals

Fifty-six adult male Sprague-Dawley rats (Harlan, Indianapolis, IN, USA) were housed in standard steel-wire mesh cages and maintained in a temperature ($21 \pm 1^\circ\text{C}$) and light (12:12 hr light:dark cycle with lights on at 7:00 a.m.) controlled environment with *ad libitum* rat chow and water. Experimental procedures began one week after acclimatization and were approved by the University of Pittsburgh's IACUC. Every attempt was made to limit the number of rats used and to minimize discomfort.

2.2. Surgery

Rats weighing 300–325 g on the day of surgery underwent surgical anesthesia, which was induced and maintained with inspired concentrations of 4% and 2% isoflurane, respectively, in a 2:1 ratio of $\text{N}_2\text{O}:\text{O}_2$. Following endotracheal intubation, the rats were secured in a stereotaxic frame and ventilated mechanically. Core body temperature was maintained at $37 \pm 0.5^\circ\text{C}$ with a heating blanket. Utilizing aseptic procedures, a midline scalp incision was made, the skin and fascia were reflected to expose the skull, and a craniectomy (6-mm in diameter) was made in the right hemisphere with a hand-held trephine. Subsequently, the impacting rod was extended and the impact tip (6 mm, flat) was centered and lowered until it touched the dura mater, then the rod was retracted and the impact tip was advanced 2.8 mm farther to produce a brain injury of moderate severity (2.8 mm tissue deformation at 4 m/sec). Immediately after the impact, anesthesia was discontinued, the incision was closed, and the rats were extubated and assessed for acute neurological outcome. Sham rats underwent similar surgical procedures, but were not subjected to the impact.

2.3. Acute neurological evaluation

Following termination of anesthesia, hind limb reflexive ability was assessed by gently squeezing the rats' paw and recording the time to elicit a withdrawal response. Return of the righting reflex was determined as the time required for a rat to turn from the supine to prone position. These natural reflexive responses are sensitive indicators of injury severity and anesthetic effects [18–22].

2.4. Drug administration

RISP (Research Diagnostics Inc., Flanders NJ) was prepared daily by dissolving in 1:1 dimethyl sulfoxide (DMSO)/saline, which also served as the vehicle (VEH). Following surgery, the rats were randomly assigned to the following group conditions: TBI + 7x week VEH (1 mL/kg; n=10), TBI + 7x week RISP (0.45 mg/kg; n=10), TBI + 3x week RISP (0.45 mg/kg; n=10), and TBI + 1x week RISP (0.45 mg/kg; n=10). Respective sham controls received the same treatments (n=4 per group). The dose for RISP was chosen based on several studies measuring functional brain injury outcome [18–21]. Treatments began 24 hr after cortical impact or sham surgery and were provided intraperitoneally *after* the daily behavioral assessments to circumvent sedative effects that may confound the results [19–22].

2.5. Motor performance: beam-balance and beam-walk

Motor function was assessed using well-established beam-balance and beam-walk tasks [18–22]. Performance on the beam-balance is assessed by recording the time (maximum of 60 sec per trial) that the rats can maintain their balance on an elevated narrow wooden beam (90 cm above floor level, 1.5 cm wide, and 34 cm in length). The beam-walk task, modified from that originally devised by Feeney and colleagues [24] and used extensively in our laboratory [18–22], consists of training/assessing rats using a negative-reinforcement paradigm to escape bright light and white noise by traversing an elevated narrow beam (90 cm above floor level, 2.5 cm wide, and 100 cm in length) and entering a darkened goal box at the opposite end. Performance on the beam-walk consists of recording time to traverse the beam as well as the distance traveled. The scoring criteria for distance traveled is based on a rating scale from 0 to 5, where 0 indicates an inability to ambulate beyond the start point, 1–4 corresponds to distal segments of 20, 40, 60, or 80 cm from the starting point, respectively, and 5 indicates traversal of the entire length of the beam (100 cm) and entrance into the goal box. Rats were trained prior to TBI or sham injury to perform the tasks without errors (i.e., maintain their balance for 60 sec and traverse the beam in under 5 sec). A baseline performance assessment was taken on the day of surgery. Performance was assessed on post-operative days 1–5 and consisted of three trials (60 sec allotted time per trial) per day on each task. The average daily scores for each subject were used in the statistical analyses.

2.6. Cognitive function: acquisition of spatial learning (time to platform)

A Morris water maze (MWM) task that is sensitive to TBI-induced cognitive dysfunction and subsequent recovery [27–30] was used to compare acquisition of spatial learning. The maze consisted of a plastic pool (180 cm diameter; 60 cm height) filled with water ($26 \pm 1^\circ\text{C}$) to a depth of 28 cm and was situated in a room with salient and permanent visual cues. The platform was a clear Plexiglas stand (10 cm diameter, 26 cm high) that was positioned 26 cm from the maze wall in the southwest quadrant of the maze and held constant throughout the study. Acquisition of spatial learning began on post-operative day 14 and consisted of providing a block of four daily trials (120 sec maximum, 4 min inter-trial interval) for five consecutive days (days 14–18 post-surgery) to locate the platform when it was submerged 2 cm below the water surface (i.e., invisible to the rat). On post-operative day 19 the platform was raised 2 cm above the water surface (i.e., visible to the rat) as a control procedure to determine the contributions of non-spatial factors (e.g., sensory-motor performance, motivation, and visual acuity) on MWM performance. Swim speed was also assessed on this day. For each daily block of trials, the rats were placed in the pool facing the wall at each of the four possible start locations (north, south, east, and west) in a randomized manner. Each trial lasted until the rat climbed onto the platform or until 120 sec had elapsed, whichever occurred first. All rats were required to remain on the platform for 30 sec before being placed in a heated incubator between trials (4-min inter-trial interval). The behavioral data were obtained using ANY-maze video tracking software, which in addition to determining time to the platform, also calculated swim speed and percent time in the target quadrant during the probe trial.

2.7. Cognitive function: memory retention

Memory retention was assessed on post-operative day 19 (i.e., one day after the final acquisition training session). During this test, the platform was removed from the pool and the rats were placed in the maze from the location point most distal to the quadrant where the platform was previously situated (i.e., “target quadrant”) and allowed to freely explore the pool for 30 sec. The percent time spent in the target quadrant was used in the statistical analysis.

2.8. Data analyses

Statistical analyses were performed on data collected by observers blinded to treatment conditions using StatView 5.0.1 software. The motor and cognitive data were analyzed by repeated-measures analysis of variance (ANOVA). The acute neurological data, probe trials, and swim speed were analyzed by one-factor ANOVAs. When the ANOVA revealed significant effects, the Newman-Keuls post hoc test was utilized to determine specific group differences. The results are expressed as the mean $\pm$ standard error of the mean (S.E.M.) and are considered significant when p values are < 0.05 .

3. Results

3.1

No significant differences were observed among the sham groups, regardless of treatment or number of administrations in any of the assessments and thus the data were pooled and analyzed as one group (denoted as “SHAM”).

3.2. Acute neurological evaluation

No significant differences were observed among the TBI groups in the time to recover the hind limb withdrawal reflex in response to a brief paw pinch (left range = 157.6 ± 2.4 sec to 166.3 ± 4.8 sec, $p > 0.05$; right range = 152.7 ± 2.4 sec to 165.2 ± 5.2 sec, $p > 0.05$) or the return of righting ability (range 376.7 ± 19.3 sec to 396.5 ± 21.1 sec, $p > 0.05$) following the cessation of anesthesia. The absence of significant differences among the groups suggests an equivalent level of injury and anesthesia.

3.3. Motor performance: beam-balance and beam-walk

Prior to surgery (baseline) all groups balanced on the beam for the full 60 sec on each of three trials. After surgery, the overall ANOVA revealed significant Group ($F_{4,51} = 9.204$, $p < 0.001$) and Day ($F_{5,225} = 54.791$, $p < 0.0001$) differences, as well as a significant Group x Day interaction ($F_{20,255} = 5.518$, $p < 0.0001$). The post-hoc test showed that all TBI groups balanced significantly less than the SHAM group ($p < 0.05$). There were no significant differences among the TBI groups (data not shown), regardless of treatment paradigm ($p > 0.05$).

No differences were revealed among the groups in beam-walk ability prior to surgery as all rats traversed the beam in under 4 sec (Fig. 1). Post-surgical repeated measures ANOVA showed significant Group ($F_{4,51} = 54.053$, $p < 0.0001$) and Day ($F_{5,255} = 166.68$, $p < 0.0001$) differences, as well as a significant Group x Day interaction ($F_{20,255} = 15.984$, $p <$

0.0001). All TBI groups were impaired relative to the SHAM group ($p < 0.05$), and the TBI + 7x RISP group was significantly slower than the TBI + 7x week VEH group ($p < 0.05$). Neither the TBI + 3x week RISP nor the TBI + 1x week RISP groups differed from the TBI + 7x week VEH control ($p > 0.05$).

Prior to surgery (baseline) all groups could traverse the entire length of the beam to earn a score of 5 (Fig. 2). After surgery, the overall ANOVA revealed significant Group ($F_{4,51} = 31.107$, $p < 0.001$) and Day ($F_{5,225} = 119.394$, $p < 0.0001$) differences, as well as a significant Group x Day interaction ($F_{20,255} = 11.101$, $p < 0.0001$). The post-hoc test showed that all TBI groups traversed significantly less than the SHAM group ($p < 0.05$) and that the TBI + 7x week RISP group was impaired vs. the TBI + 7x week VEH and TBI + 3x week RISP group ($p < 0.05$). Like the beam-walk traversal time data, neither the TBI + 3x week RISP nor the TBI + 1x week RISP groups differed from the TBI + 7x week VEH control ($p > 0.05$).

3.4. Cognitive function: acquisition of spatial learning (time to platform)

Repeated measures ANOVA for the MWM data revealed significant Group ($F_{4,51} = 22.433$, $p < 0.0001$) and Day ($F_{4,204} = 20.874$, $p < 0.0001$) differences, but no Group x Day interaction ($F_{16,204} = 1.508$, $p = 0.994$). The post-hoc analysis revealed that the SHAM control performed better than all TBI groups, regardless of treatment or number of treatments ($p < 0.05$). The analysis also revealed that spatial learning was significantly impeded in the TBI + 7x week RISP group vs. the TBI + 7x week VEH, TBI + 3x week RISP, and TBI + 1x week RISP groups ($p < 0.05$). Neither the TBI + 3x week RISP nor the TBI + 1x week RISP groups differed from the TBI + 7x week VEH control ($p > 0.05$; Fig. 3). No significant difference in swim speed (range = 27.3 ± 1.2 cm/sec to 29.4 ± 1.0 cm/sec) was observed among the TBI groups vs. SHAM controls ($p < 0.05$), but the SHAM group did locate the visible platform quicker than all TBI groups ($p < 0.05$).

3.5. Cognitive function: memory retention

Analysis of the probe data revealed a significant difference among the groups [$F_{4,51} = 5.927$, $p < 0.0001$]. The post-hoc analysis revealed that enhanced memory retention, as demonstrated by a greater percentage of the 30-sec allotted time spent in the target quadrant, was observed only in the SHAM controls ($p < 0.05$). No differences were observed among the TBI groups, regardless of treatment paradigm ($p > 0.05$; Fig. 4).

4. Discussion

Numerous preclinical studies have shown that chronic administration of APDs, such as haloperidol and RISP, block motor recovery, acquisition of spatial learning, and memory retention after brain trauma [18–26]. However, in most of the studies demonstrating a deleterious effect, the APDs were provided every day, mimicking the scenario in which a TBI patient is agitated constantly and thus receives treatment on a daily schedule. However, the reality is that many TBI patients are not continuously agitated, or aggressive, and thus do not require continuous APD treatment. Hence, the goal of this study was to determine whether a treatment paradigm that corresponds to a patient exhibiting occasional agitation

(i.e., intermittent) would still produce negative effects on recovery or whether the revised approach would be relatively safer. Our hypothesis was that the intermittent (3x week or 1x week) treatment with RISP would not produce negative effects to the same extent as the 7x week treatment paradigm.

In accord with previous studies [18–21], the once daily administration of RISP resulted in a significant delay in motor recovery and a robust disruption in the acquisition of spatial learning relative to the VEH-treated controls, which equates to an inhibition of spontaneous recovery. In contrast, and in support of the hypothesis, the intermittently-treated RISP groups did not differ from the VEH-treated control group, suggesting that spontaneous recovery after cortical impact injury was not impeded. Clinically, the data on dosing frequency of APDs is scarce, but Kisely and colleagues (2015) found no differences in psychotic symptoms or quality of life between two and four weekly doses of the APDs olanzapine, RISP, haloperidol, and fluphenazine [31]. This finding corresponds with the current study, and lends support for effective and safe intermittent administration paradigms.

Potential explanations for the deleterious effects of daily RISP on motor and cognitive performance are varied, but alterations in several neurotransmitter systems are viable possibilities. RISP exhibits affinity for dopamine D₂ receptors, where it acts as an antagonist. Additionally, chronic administration of RISP leads to alterations in cholinergic markers (i.e., decreased choline acetyltransferase) [32]. That disrupting these neurotransmitter systems leads to cognitive impairments has been well described in preclinical and clinical TBI studies [33–36]. Moreover, augmenting these neurotransmitter systems with D₂ receptor agonists, such as bromocriptine, amantadine, or methylphenidate, or the acetylcholinesterase inhibitor galantamine enhances cognitive performance [28,29,37–40]. RISP also has moderate affinity for the α_1 and α_2 adrenergic receptors [41]. Feeney and colleagues have shown that drugs that exert antagonistic effects on the noradrenergic system, such as haloperidol and clonidine, impede recovery after brain injury and can reinstate deficits (for excellent review see [42]).

5. Conclusion

APDs are routinely administered after TBI to control behavioral disturbances. The data showed that intermittent administration of RISP did not yield deleterious effects on motor or cognitive function after experimental TBI, which is in marked contrast to daily RISP. Moreover, no differences were observed between the intermittent RISP groups vs. VEH, which supports the hypothesis. A potential clinical ramification is that RISP may be safe to manage agitation after TBI, but only when used sparingly.

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Highlights

- Once daily administration of RISP for 19 days after TBI impeded motor and cognitive recovery
- Neither motor nor cognitive recovery differed between rats receiving intermittent RISP vs. VEH controls
- Spontaneous recovery after TBI is not impeded by intermittent administration RISP
- RISP may be safe to manage agitation after TBI, but only when used sparingly.

Fig. 1.

Mean ($\pm$ S.E.M.) time (sec) to traverse an elevated narrow beam prior to, and after, TBI or sham injury. There was no significant difference between the sham groups and thus they were pooled (SHAM). # $p < 0.05$ vs all TBI groups and * $p < 0.05$ vs. TBI + 7x week VEH. Neither TBI + 3x week RISP nor TBI + 1x week RISP differed from the TBI + 7x week VEH control, or from one another ($p > 0.05$).

Fig. 2.

Mean ($\pm$ S.E.M.) score for distance traveled along an elevated narrow beam prior to, and after, TBI or sham injury. There was no significant difference between the sham groups and thus they were pooled (SHAM). # $p < 0.05$ vs all TBI groups and * $p < 0.05$ vs. TBI + 7x week VEH. Neither TBI + 3x week RISP nor TBI + 1x week RISP differed from the TBI + 7x week VEH control, or from one another ($p > 0.05$).

Fig. 3.

Mean ($\pm$ S.E.M.) time (sec) to locate a hidden platform in the Morris water maze. There was no significant difference between the sham groups and thus they were pooled (SHAM). # $p < 0.05$ vs all TBI groups and * $p < 0.05$ vs. TBI + 7x week VEH, TBI + 3x week RISP, and TBI + 1x week RISP. Neither TBI + 3x week RISP nor TBI + 1x week RISP differed from the TBI + 7x week VEH control, or from one another ($p > 0.05$). No significant difference in swim speed was observed among the TBI groups vs. SHAM controls ($p > 0.05$), but the SHAM group did locate the visible platform quicker than all TBI groups ($p < 0.05$).

Fig. 4. Mean ($\pm$ S.E.M.) percentage of time spent in the target quadrant (i.e., where platform was previously located) after a single probe trial provided 19 days after TBI or sham injury. # $p < 0.05$ vs all TBI groups, which suggests enhanced memory retention. No significant differences were observed among the TBI groups, regardless of treatment paradigm ($p > 0.05$). The dotted line represents performance at the chance level (25%).