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Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury

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ABSTRACT

Antipsychotics are often administered to traumatic brain injured (TBI) patients as a means of controlling agitation, albeit the rehabilitative consequences of this intervention are not well known. Hence, the goal of this study was to evaluate the effects of risperidone (RISP) and haloperidol (HAL) on behavioral outcome after experimental TBI. Anesthetized rats received either a cortical impact or sham injury and then were randomly assigned to five TBI (RISP 0.045 mg/kg, RISP 0.45 mg/kg, RISP 4.5 mg/kg, HAL 0.5 mg/kg and VEHicle 1 mL/kg) and three Sham (RISP 4.5 mg/kg, HAL 0.5 mg/kg and VEH 1 mL/kg) groups. Treatments began 24 h after surgery and were provided once daily for 19 days. Behavior was assessed with established motor (beam-balance/walk) and cognitive (spatial learning/memory in a water maze) tasks on post-operative days 1–5 and 14–19, respectively. RISP and HAL delayed motor recovery, impaired the acquisition of spatial learning, and slowed swim speed relative to VEH in both TBI and sham groups. These data indicate that chronic administration of RISP and HAL impede behavioral recovery after TBI and impair performance in uninjured controls.

Whether resulting from falls or automobile and sports-related accidents, traumatic brain injury (TBI) is a significant public health care issue that affects approximately two million people in the United States each year. In addition to the plethora of secondary pathophysiological responses [10], TBI also induces motor and cognitive deficits [2,3,11–15]. Experimental studies aimed at enhancing recovery and/or alleviating these dysfunctions have focused on several therapeutic strategies [1,2,9,14]. Another approach has been to screen pharmacotherapies affecting the dopamine neurotransmitter system [4,12,15,25]. Several studies have shown that D_2 receptor agonists benefit functional and/or histological outcome after cortical injury [4,12,15,25]. However, less is known about the role of D_2 receptor antagonists on the recovery process. This issue is paramount because in addition to the physical and cognitive deficits, TBI induces other maladaptive behavioral responses such as agitation and aggression, which affect up to 50% of patients [23]. Because agitated patients disrupt healthcare and can be a physical risk to themselves and/or hospital staff [5,17,18], a common course of management is to provide antipsychotics such as risperidone (RISP) and haloperidol (HAL), which exert much of their effect by acting as high affinity D_2 receptor antagonists.

The few studies assessing the effects of antipsychotics have shown that in general these agents have deleterious consequences after TBI. Specifically, Feeney and colleagues showed that a single

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administration of HAL impaired the ability of rats to complete a beam-walking task after brain injury [6]. A similar outcome was reported in a follow-up study by Goldstein and Bullman [7]. A recent study from our laboratory showed that neither RISP nor HAL negatively impacted functional outcome when only a single administration was provided [13]. However, a significant reinstatement of motor and cognitive deficits was observed after 1 week of daily administrations [13]. In contrast to RISP and HAL, neither a single low dose of clozapine nor multiple doses of olanzapine, both of which have a lower affinity for D_2 receptors, have been reported to impact motor and cognitive performance after brain trauma [7,24].

The consequences of administering antipsychotics after TBI remain unclear and thus the aim of the current study is to provide more insight by reassessing the effects of RISP and HAL on functional recovery after experimental brain trauma. The current study differs from our prior report [13] by providing RISP and HAL once daily for the duration of behavioral testing. This approach will yield important data regarding the effect of chronic antipsychotic treatment in a rehabilitative-relevant paradigm.

Sixty-five adult male Sprague–Dawley rats weighing 300–325 g on the day of surgery were housed in standard steel-wire mesh cages and maintained in a temperature ($21 \pm 1\,^{\circ}C$) and light controlled (on 7:00 a.m. to 7:00 p.m.) environment with free access to food and water. After 1 week of acclimatization the rats underwent beam-walk training, which consisted of 4–5 trials to traverse a narrow beam, and then were prepared for surgery. Surgical procedures have been reported in detail elsewhere [11,12]. Briefly, isoflurane (4% in 2:1 N_2O/O_2) anesthetized rats were intubated, mechanically ventilated, and then subjected to either a right hemisphere controlled cortical impact (2.8 mm tissue deformation at 4 m/s) or sham injury. Core temperature was maintained at $37 \pm 0.5\,^{\circ}C$ during surgery. Following surgery, the rats were randomly assigned to the following groups: TBI + RISP (0.045 mg/kg; $n = 10$), TBI + RISP (0.45 mg/kg; $n = 10$), TBI + RISP (4.5 mg/kg; $n = 10$), TBI + HAL (0.5 mg/kg; $n = 10$), TBI + VEH (1 mL/kg; $n = 10$), Sham + RISP (4.5 mg/kg; $n = 5$), Sham + HAL (0.5 mg/kg; $n = 5$), and Sham + VEH (1 mL/kg; $n = 5$). RISP (Research Diagnostics, Flanders, NJ) and HAL (Sigma, St. Louis, MO) were prepared daily by dissolving in 1:1 dimethyl sulfoxide (DMSO)/saline (v/v), which also served as the VEH. Treatments began 24 h after surgery and were administered once daily (1 h prior to behavioral assessments; i.p.) for 19 days. The 0.45 mg/kg dose of RISP and the 0.5 mg/kg dose of HAL were chosen because these concentrations have been reported to be comparable to those used clinically to control psychosis [22]. Additionally, the 0.5 mg/kg dose of HAL is similar to that used in other TBI studies [6,7,24]. RISP concentrations 10-fold lower and 10-fold higher were also evaluated in an effort to establish a drug-induced behavioral response profile. All experimental procedures were approved by the Animal Care and Use Committee at the University of Pittsburgh and were conducted in accordance with the recommendations provided in the *Guide for the Care and Use of Laboratory Animals* (National Academy Press, 1996). Every attempt was made to limit the number of animals used and to minimize suffering.

Motor function was assessed with well-established beam-balance and beam-walk tasks [6,9,11,13]. Beam-balance consisted of placing the rat on an elevated narrow beam (1.5 cm wide) and recording the time it remained on for a maximum of 60 s. The beam-walk consisted of recording the elapsed time to traverse the beam. Testing was conducted immediately before surgery (to establish a baseline measure), as well as on post-operative days 1–5, and consisted of three trials (60 s allotted time with an inter-trial interval of 30 s) per day on each task. The average daily scores for each subject were used in the statistical analyses.

Spatial learning was assessed using a Morris water maze (MWM) task that is sensitive to cognitive function/dysfunction after TBI [8,11,12]. Briefly, the maze consisted of a plastic pool (180 cm diameter; 60 cm high) filled with tap water ($26 \pm 1\,^{\circ}C$) to a depth of 28 cm and was situated in a room with salient visual cues. The platform was a clear Plexiglas stand that was positioned in the southwest quadrant and held constant for each rat. Acquisition of spatial learning began on post-operative day 14 and consisted of providing a block of four daily trials (4-min inter-trial interval) for five consecutive days (14–18) to locate the platform when it was submerged 2 cm below the water surface (i.e., invisible to the rat). 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, east, south, and west) in a randomized manner. Each trial lasted until the rat climbed onto the platform or until 120 s had elapsed, whichever occurred first. Rats that failed to locate the goal within the allotted time were manually guided to it. All rats remained on the platform for 30 s before being placed in a heated incubator between trials. The times of the four daily trials for each rat were averaged and used in the statistical analyses. One day after the final acquisition training session (day 19), all rats were given a single probe trial to measure retention. Briefly, 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 s. Following the probe trial, a visible platform test was provided. The data were obtained using a spontaneous motor activity recording and tracking (SMART) system.

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 assessments and swim speed data were analyzed by one-factor ANOVAs. When the overall ANOVAs revealed a significant effect, the Bonferroni/Dunn post hoc test was used to determine specific group differences. The data are presented as the mean ± standard error (S.E.M.) and are considered significant at $p \leq 0.05$ or as determined by the Bonferroni/Dunn statistic after correcting for multiple comparisons.

No significant differences were observed among the TBI groups in hind limb withdrawal response latencies after a brief paw pinch [range 168.5 ± 5.3 s to 182.2 ± 6.1 s, $p > 0.05$] or for return of the righting reflex [range 404.5 ± 21.88 s to 448.1 ± 36.9 s, $p > 0.05$] after the cessation of anesthesia. The lack of significant differences with these acute neurological indices suggests that all TBI groups experienced an equivalent level of injury and anesthesia.

All rats balanced on the beam for the allotted 60 s prior to surgery. However, after the cortical impact significant impairments were detected in all TBI groups vs. Sham controls [$p < 0.05$]. Moreover, the TBI + RISP (4.5 mg/kg) group was significantly impaired relative to the TBI + VEH group [$p < 0.0001$]. No other TBI group comparisons revealed statistical differences [$p > 0.05$]. Similar to the beam-balance findings, there were also no significant beam-walking differences among groups prior to injury. However, as depicted in Fig. 1, all TBI groups receiving RISP and HAL were significantly impaired (i.e., took longer to traverse the beam) vs. the TBI + VEH group. Furthermore, both RISP (4.5 mg/kg) and HAL hindered the ability of sham controls as evidenced by longer traversal times for the Sham + RISP and Sham + HAL groups vs. the Sham + VEH group [$p < 0.0001$ and $p = 0.0008$, respectively].

The ANOVA for spatial learning revealed significant group [$F_{7,57} = 14.356$, $p < 0.0001$] and day [$F_{4,228} = 8.627$, $p < 0.0001$] differences, as well as a significant group × day interaction [$F_{28,228} = 1.610$, $p = 0.031$]. Specifically, all TBI groups were significantly impaired relative to the Sham + VEH controls. Moreover,

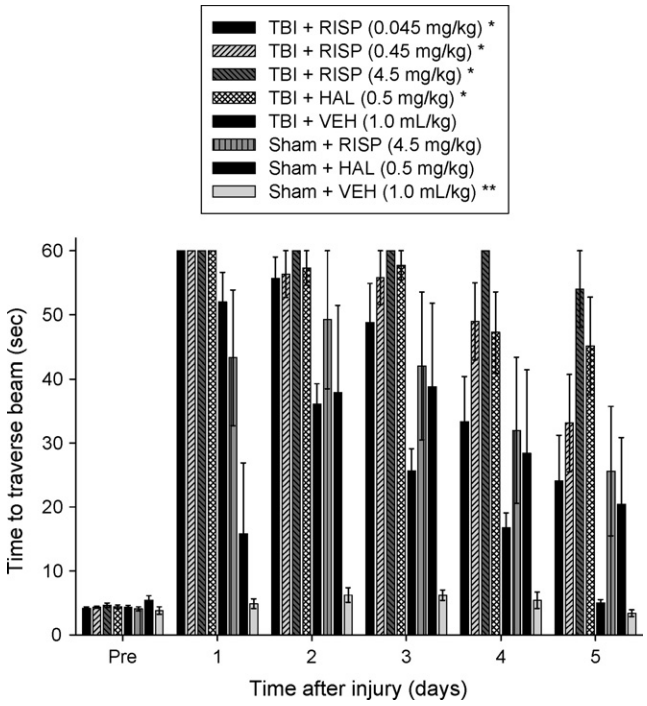

Fig. 1. Mean (±S.E.M.) time (s) to traverse a narrow beam prior to, and after, TBI or Sham injury. RISP (all doses) and HAL hindered the ability to recover TBI-induced motor deficits vs. VEH [$^{*}p < 0.05$]. All TBI and both the Sham + RISP and Sham + HAL groups were significantly impaired vs. the Sham + VEH group [$^{**}p < 0.05$].

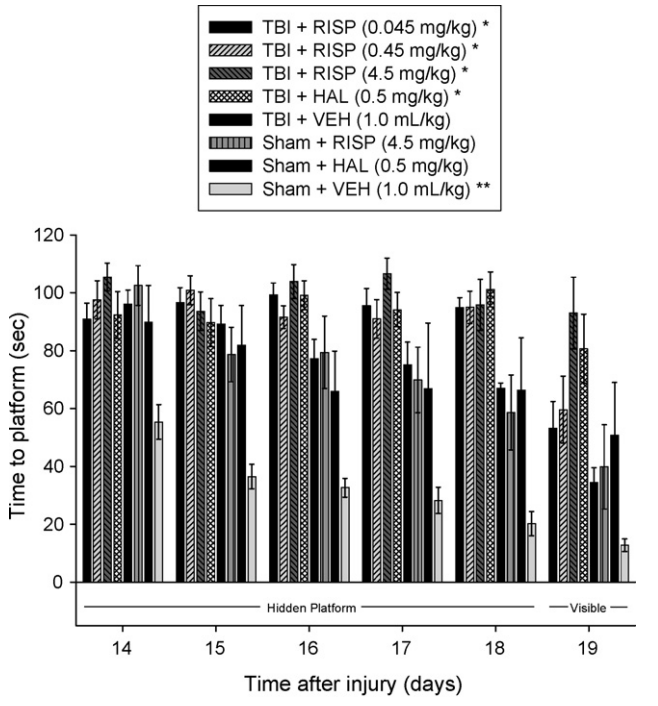

Fig. 2. Mean (±S.E.M.) time (s) to locate either a hidden (submerged) or visible (raised) platform in a water maze. RISP (all doses) and HAL hindered the ability to acquire spatial learning relative to VEH [$^{*}p < 0.05$]. All TBI and both the Sham + RISP and Sham + HAL groups were significantly impaired vs. the Sham + VEH group [$^{**}p < 0.05$]. The TBI + RISP (4.5 mg/kg) group also exhibited visible platform deficits vs. the TBI + VEH group [$p = 0.0002$].

all TBI groups receiving RISP and HAL were significantly impaired vs. the TBI + VEH group [$p < 0.0001$], but did not differ from one another [$p > 0.05$]. As depicted in Fig. 2, RISP (4.5 mg/kg) and HAL also impaired the ability of sham controls to learn the location of the escape platform as indicated by longer search times for the Sham + RISP and Sham + HAL groups vs. the Sham + VEH group [p's < 0.0001]. Neither the Sham + RISP nor Sham + HAL groups differed from the TBI + VEH group [$p = 0.55$ and $p = 0.19$, respectively] further attesting to drug-induced impairment in uninjured controls. Only the highest dose of RISP (4.5 mg/kg) showed a statistical impairment in visible platform performance relative to the TBI + VEH group [$p = 0.0002$], while both RISP and HAL differed from the Sham + VEH group [$p < 0.0001$ and $p = 0.0003$, respectively].

Analysis of memory retention revealed a significant difference among groups [$p < 0.0001$], which was attributed to the Sham + VEH group performing better than all other groups. Specifically, the Sham + VEH group spent 51.6 ± 6.6% of the allotted time searching in the target quadrant, whereas, all other groups performed either below or just slightly above chance level (means ± S.E.M. ranged from 18.9 ± 6.7% to 28.7 ± 2.8%). As shown in Fig. 3, swim speed was also significantly impaired in the RISP (except the 0.045 mg/kg dose) and HAL groups (range = 18.6 ± 3.7 cm/s to 24.2 ± 0.6 cm/s) vs. the Sham + VEH and TBI + VEH groups (32.7 ± 0.5 cm/s and 31.5 ± 1.0 cm/s, respectively) [$p < 0.0007$].

Agitation and aggression are common maladaptive behavioral sequelae of TBI. Emergency medicine clinicians must quickly assess and consider the differential diagnosis, which can only be done successfully with a manageable patient. However, because restraints frequently lead to injury and weakening of the therapeutic alliance, the use of antipsychotics has become increasingly prevalent even though the ramifications of this approach on the recovery process are not well defined. Similar challenges are also encountered by physiatrists or rehabilitation specialists. Therefore, this study sought to evaluate the effect of chronic administration of two com-

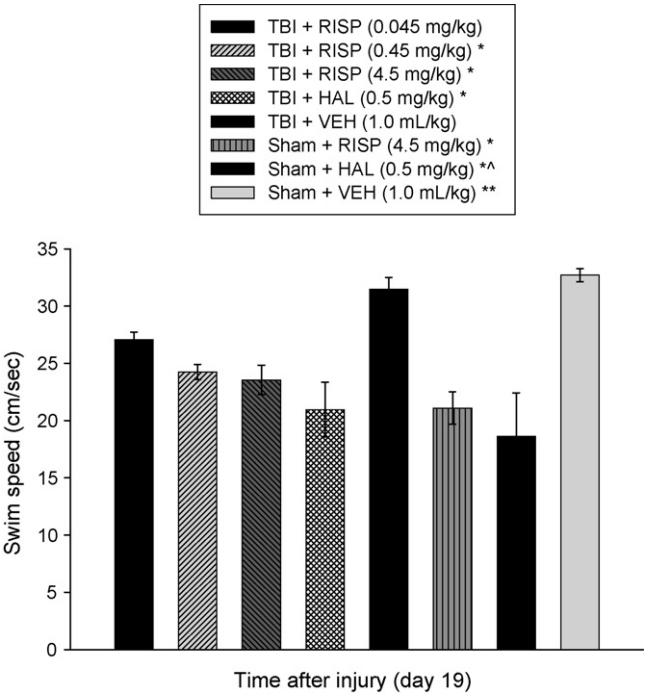

Fig. 3. Mean (±S.E.M.) swim speed (cm/s). A significant decrease in swim speed was observed in the TBI + RISP (0.45 and 4.5 mg/kg), TBI + HAL, Sham + RISP, and Sham + HAL groups vs. the TBI + VEH group [$^{*}p < 0.05$]. All groups, except the TBI + VEH, swam significantly slower than the Sham + VEH group [$^{**}p < 0.05$]. Lastly, the Sham + HAL group was significantly slower than the TBI + RISP (0.045 mg/kg) group [$^{\wedge}p < 0.05$].

monly used antipsychotics, RISP and HAL, on behavioral recovery after experimental TBI. The data show that all three doses of RISP (0.045, 0.45, and 4.5 mg/kg) and HAL (0.5 mg/kg) impeded the ability of brain injured rats to recover motor ability and to learn the location of a hidden platform in a water maze task, which is suggestive of cognitive impairment. The data further show that chronic administration of RISP and HAL to non-injured animals also impairs their ability to perform these tasks. Thus, the deleterious effects of chronic administration of RISP and HAL are not limited to TBI. RISP and HAL also decreased swim speed in both the TBI and sham control groups. Because performance in both the motor and water maze tasks is measured by time (i.e., to traverse the beam or to locate the platform, respectively), it is possible that the deleterious effects of RISP and HAL on behavioral outcome may be confounded by drug-induced sedation. This issue necessitates further study.

These findings are in accord with other brain trauma studies showing that antipsychotics can significantly alter behavior. Using a model of cortical ablation injury, Feeney and colleagues demonstrated that HAL impairs motor recovery [6]. The deleterious effect of a single administration of HAL was subsequently replicated by Goldstein and Bullman [7]. HAL has also been reported to impair cognitive performance when administered chronically after fluid percussion brain injury [24]. A recent study from our laboratory revealed that following a controlled cortical impact injury both a high dose of RISP (4.5 mg/kg) and HAL (0.5 mg/kg) reinstated motor and cognitive deficits when the treatments were provided for five consecutive days. However, the lower doses of RISP (0.045 or 0.45 mg/kg) did not significantly impact behavior. Taken together, the data from the previous and current studies suggest that in addition to timing and dosing, the duration of treatment is also an important determinant in whether behavioral outcome is compromised. This is especially true for RISP as HAL exerted a deleterious effect on behavior whether it was provided for 5 days [13] or 19 days.

As previously indicated, both RISP and HAL demonstrated high affinity for dopamine D_2 receptors, where they act as antagonists. This mechanism, combined with the plethora of data showing that TBI produces significant changes in dopaminergic neurotransmission [19,20] and the reports that D_2 receptor agonists improve functional outcome after brain trauma [4,12,15] suggest that the detrimental effect of RISP and HAL are mediated by their antagonism of D_2 receptors. Further support for this notion comes from studies showing that neither clozapine nor olanzapine, antipsychotics with a low affinity for D_2 receptors, negatively affect motor and cognitive performance [7,24].

The lack of detrimental effects on functional outcome after TBI with the atypical antipsychotics clozapine and olanzapine, which are partial 5-HT_{1A} receptor agonists, is intriguing and lend support for other serotonin-based therapies for treating TBI-induced agitation. Specifically, the 5-HT_{1A} receptor agonist buspirone has been reported to be effective in attenuating agitation after head injury [16]. Moreover, studies from our laboratory have shown that administering buspirone after cortical impact injury facilitates the acquisition of spatial learning and memory [21]. Hence, buspirone could potentially provide dual benefits for the TBI patient by reducing agitation and perhaps enhancing functional recovery. While the studies of buspirone and recovery of TBI-induced deficits are still in preclinical stages, this treatment would appear to be more efficacious than the alternative (i.e., RISP and HAL).

In conclusion, the data show that chronic administration of RISP and HAL impede motor recovery and the acquisition of spatial learning and memory after experimental TBI. These data have significant implications for clinical TBI because of the behavioral dysfunctions that occur, such as agitation and aggression, and that are often treated with antipsychotics. A limitation of the current study is that behavior was not reassessed after discontinuation of RISP and HAL and thus it is not known if the negative effect on behavioral recovery is transient (i.e., seen only during the period of drug administration), long-lasting, or permanent. However, based on a previous report from our laboratory where it was shown that the reinstatement of deficits produced by RISP and HAL were still present even after a 3-day drug washout period [13], it is likely that the deleterious effects will be persistent. Evaluating this issue, as well as the potential contribution of drug-induced sedation on behavioral outcome are logical and critical follow-up studies that will provide a more thorough understanding of the effects of antipsychotics on functional recovery after experimental TBI and may help guide clinical applications.

Conflict of interest

There are no conflicts of interest to report.

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