Haloperidol, but Not Olanzapine, Impairs Cognitive Performance After Traumatic Brain Injury in Rats

ABSTRACT

Objective: Traumatic brain injury can cause a variety of impairments, including persistent alterations in personality, mood, and cognition. Antipsychotic agents are frequently used to treat pathologic behaviors in traumatic brain injury patients, but the influence of prolonged administration of such drugs on cognition after injury is unknown. The effects of two antipsychotic drugs on cognitive recovery after traumatic brain injury were assessed using the fluid percussion model in rats.

Design: The typical antipsychotic, haloperidol, and the third-generation antipsychotic, olanzapine, were administered via intraperitoneal injection beginning 24 hr after injury and continuing daily for the duration of the study. Morris water maze performance was assessed on days 11–15 postinjury.

Results: Haloperidol, an antagonist acting on D2-like dopamine receptors, exacerbated the cognitive deficits induced by injury, as injured rats treated with 0.30 mg/kg haloperidol performed worse in the Morris water maze than injured rats treated with vehicle.

Conclusions: Our results demonstrate the importance of the D2 receptor in cognitive recovery after traumatic brain injury. Also, the data illustrate that some classes of antipsychotic drugs may influence cognitive recovery, and further research is needed to determine the optimal pharmacologic treatment of aggression, agitation, and other pathologic behaviors in patients with traumatic brain injury.

Key Words: Traumatic Brain Injury, Dopamine, D2-like dopamine receptors, Haloperidol, Olanzapine, Antipsychotic Agents
Numerous and diverse impairments can result from traumatic brain injury (TBI), including persistent alterations in personality, mood, and cognition. A substantial number of TBI patients receive antipsychotic agents to treat psychosis, aggression, and other pathologic behaviors. However, the influence that prolonged administration of such drugs may have on other injury-induced sequelae, including cognition, remains largely unexplored.

Many of the pharmacologic agents used to treat various behavioral pathologies in TBI patients target dopamine (DA) neurotransmission. Experimental research indicates that the manipulation of DA neurotransmission after injury can affect the recovery process. For example, amphetamine has been shown to improve motor recovery, and l-deprenyl (a monoamine oxidase B inhibitor) facilitated cognitive recovery after brain injury in rats. The DA D2-like receptor agonist bromocriptine improved working and spatial memory performance after TBI in rats, indicating that potentiation of D2 receptor function may be beneficial. Further support for this hypothesis comes from a clinical study in which bromocriptine improved performance on prefrontal function tasks after TBI. Haloperidol blocks D2-like receptors and is among the medications most commonly utilized to treat agitation after head injury. Importantly, haloperidol blocked amphetamine’s beneficial effects on recovery after motor cortex ablation in cats and slowed recovery of motor function after motor cortex ablation in rats. Haloperidol also disrupted acquisition of the Morris water maze (MWM) task when injected into the rat accumbens. Further evidence that cognitive outcome may be affected by chronic DA antagonism comes from a recent study showing chronic treatment with haloperidol (90 days) disrupted MWM acquisition in normal rats. Thus, haloperidol’s potent antagonism of DA receptors may be detrimental to outcome after brain injury. Although there is experimental evidence that haloperidol is detrimental to recovery of motor function after cortical injury, the effects of haloperidol on recovery of cognitive function after TBI have not been investigated. Similarly, the atypical neuroleptic olanzapine has not been tested for its effect on cognitive recovery from TBI. Olanzapine has a diverse receptor binding profile, affecting norepinephrine, DA, histamine, muscarinic, and serotonin receptors. Chronic treatment with olanzapine (90 days) did not impair MWM acquisition in normal rats. Given that olanzapine is a less potent DA antagonist and affects different receptor systems than haloperidol, its effects on recovery after brain injury may differ from those of haloperidol.

The purpose of the present investigation was to test the effects of the chronic postinjury administration of olanzapine and haloperidol on both motor and cognitive recovery after TBI. Both of these drugs are among the antipsychotic agents used to treat psychosis, agitation, aggression, and other pathologic behaviors in TBI patients. Haloperidol is a traditional (typical), or first-generation, antipsychotic, whereas olanzapine is a third-generation antipsychotic. In patients with schizophrenia, third-generation antipsychotics such as olanzapine and clozapine are associated with improved cognition, fewer depressive and mood symptoms, and decreased risk of tardive dyskinesia (for a review, see Maguire). Perhaps this class of drug offers a better alternative to treat behavioral pathologies in TBI patients as well.

**METHODS**

**Subjects.** Adult (3-mo-old) male Sprague-Dawley rats (Hilltop Lab Animals, Scottsdale, PA) weighing 300–350 g were used. Animals were housed individually (at 20–22°C, with lights on from 06:00–18:00) with free access to food and water. All procedures followed the guidelines established in the *Guide for the Care and Use of Laboratory Animals* (United States Department of Health and Human Services) and were approved by our institutional animal care and use committee.

Originally, the experimental design included ten animals per treatment group for both olanzapine and haloperidol studies. However, the haloperidol study was terminated early because of a high rate of mortality in injured rats that received chronic haloperidol treatment. Thus, for the haloperidol study, the sample size ranges from two to ten animals per group, whereas for the olanzapine study, the sample size is ten animals per group.

**Drugs.** Haloperidol was purchased from Sigma-Aldrich (St. Louis, MO). Lilly Research Laboratories (Indianapolis, IN) provided olanzapine for the purposes of this study. Treatment with each drug was initiated 24 hr after TBI or sham injury and continued for the duration of the experiment (postinjury days [PIDs] 1–15). The 24-hr time point was chosen to avoid interfering with acute post-TBI cascades. Drug doses were chosen based on appropriate chronic dosing ranges, as presented in previous literature. Rats received daily intraperitoneal injections 1 hr before behavioral assessment. The following drugs and doses were evaluated:

**Haloperidol:**
- Injured + 0.30 mg/kg (n = 3)
- Injured + 0.10 mg/kg (n = 2)
- Injured + 0.03 mg/kg (n = 4)
- Injured + vehicle (saline) (n = 4)
- Sham + vehicle (n = 10)

**Olanzapine:**
- Injured + 3.0 mg/kg (n = 10)
- Injured + 1.0 mg/kg (n = 10)
- Injured + 0.3 mg/kg (n = 10)
- Injured + vehicle (saline) (n = 10)
- Sham + vehicle (n = 10)
**Fluid Percussion Injury.** TBI was produced by a lateral fluid percussion injury, previously described in detail by McIntosh et al. The device consists of a Plexiglas cylindrical reservoir, 60 cm in length and 4.5 cm in diameter, filled with double-distilled H2O. One end of the cylinder contains a rubber-covered Plexiglas piston mounted in O-rings. The opposite end of the cylinder has a 2-cm-long metal housing mounted with an extracranial pressure transducer (EPN-0300*-100A, Entran Devices, Fairfield, NJ). Fitted at the end of the metal housing is a 5-mm tube with a 2.6-mm-inner diameter male Luer-Loc fitting. This fitting was connected to a female Leur-Loc fitting that was chronically implanted over the exposed dura mater of the rat (described in Surgical Preparation and Injury). Injury was produced by the impact of a metal pendulum (4.54 kg) on the piston of the injury device. The impact injected a small volume of H2O into the closed cranial cavity, its pressure pulse was measured by the extracranial pressure transducer as atmospheric pressure and recorded on a storage oscilloscope (Tektronix 511, Tektronix, Beaverton, OR).

**Surgical Preparation and Injury.** Animals were surgically prepared under sodium pentobarbital anesthesia (60 mg/kg) 24 hr before fluid percussion or sham injury. Animals were placed in a stereotaxic frame, the scalp sagittally incised, and soft tissue displaced. A 4.8-mm-diameter craniotomy was performed over the right parietal cortex (5 mm from lambda, 5 mm from bregma, 4 mm from sagittal suture). Two nickel-plated screws were placed in burr holes 1 mm rostral to bregma and 1 mm rostral to lambda/1 mm medial to the lateral ridge. A modified 20-gauge Leur-Loc syringe hub (cut to 8 mm in length and 2.6 mm in inside diameter) was placed over the exposed, intact dura mater and bonded to the skull with cyanoacrylate adhesive and dental acrylic. After the acrylic hardened, the scalp was sutured closed over the injury tube, bacitracin applied to the incision, and the animal returned to its home cage.

At 24 hr after surgical preparation, animals were anesthetized with 4% isoflurane in a carrier gas of 70% N2O and 30% oxygen. The scalp was incised to expose the hub, the animal was anesthetized to the injury device, and a moderate (2.0 ± 0.1 atm) level of fluid percussion injury was delivered. Rats in the sham-injury groups were anesthetized and connected to the injury device, but no fluid pulse was delivered. The wound was sutured and neurologic assessments recorded (i.e., duration of suppression of pinna, paw, and righting reflexes). After the animals recovered, they were returned to the vivarium.

**Motor Assessment.** Motor function was assessed to ensure functional recovery of limbs and balance after surgical preparation and injury. Rats were trained on two motor tasks (i.e., beam balance and beam walk) before preparatory surgery (PID −1). Rats were then pre-assessed on PID 0 before injury to test for any possible motor effects related to preparatory surgery. Motor assessments occurred on PIDs 1–5 on beam-balance and beam-walk tasks.

The beam balance was used to assess the integrity of the vestibulomotor systems. Rats were placed on a suspended, narrow, wooden beam (1.5 cm in width), and the duration (not to exceed 60 sec) the rat was able to remain on the beam was measured. Rats received three consecutive trials each day on PIDs 1–5. The average of the three durations per day was used for statistical analysis.

Fine motor coordination was assessed with the beam-walk task. The rats were trained (on PID −1) to escape a bright light and loud white noise by walking along an elevated, 100-cm-long, 2.5-cm-wide wooden beam to enter a darkened goal box at the opposite end of the beam. Pegs (2 cm × 2 mm) were positioned on alternating sides of the beam 20 cm apart. During training and assessment, the rat was placed at one end of the beam near the light and noise. When the rat entered the goal box, the light and noise were turned off. The latency for the rat to reach the goal box (not to exceed 60 sec) was recorded. Rats received three consecutive trials each day on PIDs 1–5. The average of the three latencies per day was used for statistical analysis.

**Cognitive Assessment.** The MWM was used to assess cognitive performance. Each rat was placed in a large circular tank (180 cm in diameter by 45 cm in height) filled with thermostatically controlled, warm water (25–28°C) to a depth of 30 cm. The tank was located in a 2.5 × 2.5-m room with numerous extra-maze cues that remained constant throughout the experiments.

The procedure consisted of four trials per day on PIDs 11–15. Each day, the rat started a trial from each of four start locations (i.e., north, south, east, west). The order of the start positions was randomized for each animal on each day. The rat swam freely about the tank to find the hidden platform (2 cm below the water’s surface, 10 cm in diameter) and escape from the water. The latency to find the platform and the distance of the swim path was recorded. After finding the platform, animals remained there for 30 sec and then were removed from the maze and placed in a heated incubator for a 4-min intertrial interval. Animals that did not find the platform after 120 sec were placed on the platform for 30 sec and then removed from the maze. After the four trials were completed, animals were placed in a warming cage (26°C) until dry.
RESULTS

Haloperidol

**Neurologic Assessment.** Figure 1 shows the mean duration (in minutes) of suppression of the righting response after injury for all groups in the haloperidol study. There were no significant differences between the injured groups on this measure of injury severity.

**Figure 1:** The mean duration (in minutes) ± standard error of the mean of the suppression of the righting response after injury for all groups in the haloperidol study. There were no significant differences between the injured groups on this measure of injury severity.

Injured groups had a significant deficit on this task compared with sham-injured groups. Although injured animals treated with haloperidol demonstrated shorter durations on the beam-balance task, Duncan pair-wise group contrasts indicated that their performance did not differ significantly from injured animals treated with vehicle.

For the beam-walk task, shorter latencies indicate better performance. Figure 3 shows the mean beam-walk latency scores for the first 5 days after injury. A one-way ANOVA showed a significant effect of injury on beam-walk latency (F_{1,33} = 12.32, P < 0.001). Injured groups showed significantly impaired performance in comparison with sham-injured rats. However, as with the beam-balance task, there was no significant difference between the injured animals treated with haloperidol compared with injured animals treated with vehicle.

**Cognitive Assessment.** A shorter latency to find the goal platform indicates better performance in the MWM. Figure 4 illustrates the mean goal latency ± standard error of the mean (in seconds) in the MWM on

**Figure 2:** The mean beam-balance duration (in seconds) ± standard error of the mean for the first 5 days after injury for all groups in the haloperidol study. Injured groups had a significant deficit on this task compared with the sham-injured group. Haloperidol treatment did not significantly affect the performance of injured animals.
days 11–15 postinjury for all groups. A split-plot ANOVA (5 [group] × 5 [day]) comparing all groups revealed a significant effect of group on goal latency ($F_{4,18} = 15.66$, $P < 0.001$). Duncan pair-wise contrasts were performed to determine group differences. Sham-injured rats treated with vehicle performed significantly better in the MWM task than any of the injured groups. Injured rats treated with 0.3 mg/kg haloperidol performed significantly worse in the MWM task than rats treated with 0.0 or 0.1 mg/kg haloperidol. Thus, the highest dose of haloperidol tested exacerbated MWM deficits in injured animals. No significant difference between groups was found for swim speed (data not shown). It should be noted that because of unequal group sizes, the harmonic mean of the group sizes (harmonic mean sample size $= 3.488$) was used for the post hoc analysis.

**Olanzapine**

**Neurologic Assessment.** Figure 5 shows the mean duration (in minutes) of suppression of the righting response. A one-way ANOVA comparing injured rats with sham-injured rats produced a significant effect of injury on suppression of the righting reflex ($F_{1,50} = 45.33$, $P < 0.001$). However, Duncan post-ANOVA tests indicated that there was no significant difference among injured groups on the suppression of this reflex, indicating injured groups received an equivalent severity of injury.

**Motor Assessment.** For the beam-balance task, longer durations indicate better performance. The mean beam-balance durations (in seconds) for the first 5 days after injury are shown in Figure 6. A one-way ANOVA comparing injured rats with sham-injured rats yielded a significant effect of injury on beam-balance duration ($F_{1,50} = 6.01$, $P < 0.01$), indicating that injured groups had a significant deficit on this task compared with sham-injured rats. However, Duncan pair-wise group contrasts indicated that injured animals treated with olanzapine did not differ from injured animals treated with vehicle.

For the beam-walk task, shorter...
latencies indicate better performance. Figure 7 shows the mean beam-walk latency scores for the first 5 days after injury. A one-way ANOVA showed a significant effect of injury on beam-walk latency ($F_{1,50} = 30.70, P < 0.001$). Injured groups showed significantly impaired performance in comparison with sham-injured groups. However, as with the beam-balance task, there was no significant difference between injured animals treated with olanzapine and injured animals treated with vehicle.

Cognitive Assessment. A shorter latency to find the goal platform indicates better performance in the MWM. Figure 8 illustrates the mean goal latency (in seconds) in the MWM on days 11–15 postinjury for all groups. A split-plot ANOVA (5 [group] × 5 [day]) comparing all groups revealed a significant effect of group on goal latency ($F_{4,45} = 34.19, P < 0.0001$). Duncan pair-wise group contrasts indicated no significant difference in goal latency between injured groups treated with vehicle, 0.3, 1.0, or 3.0 mg/kg olanzapine. No significant difference between groups was found for swim speed (data not shown). Taken together, these results indicate that olanzapine did not affect the performance of injured animals in the MWM.

DISCUSSION

Haloperidol. Results of this study indicated that daily (15 days) postinjury administration of haloperidol was associated with enhanced impairments in cognitive performance of brain-injured rats after lateral fluid-percussion TBI. Haloperidol treatment did not significantly affect motor deficits in the current paradigm, although injured animals treated with 0.1 mg/kg or 0.3 mg/kg haloperidol did not perform as well as injured animals treated with vehicle in the beam-balance or beam-walk task. The tendency toward poorer motor performance is consistent with previous studies showing that haloperidol had detrimental effects on motor recovery after an ablation injury to the motor cortex.4,5 The lack of significance for the motor effects in the current paradigm may indicate that haloperidol can be especially detrimental when the motor cortex is selectively impaired, whereas motor impairment after a more diffuse injury in which the motor cortex is

Figure 5: The mean duration (in minutes) ± standard error of the mean of the suppression of the righting response after injury for all groups in the olanzapine study. There were no significant differences between the injured groups on this measure of injury severity.

Figure 6: The mean beam-balance duration (in seconds) ± standard error of the mean for the first 5 days after injury for all groups in the olanzapine study. Injured groups had a significant deficit on this task compared with the sham-injured group. Olanzapine treatment did not significantly affect the performance of injured animals.
relatively spared may not be as strongly influenced by treatment with the D2 antagonist.

Research has suggested that the suppression of dopaminergic function after injury may contribute to the impairment of behavioral function. For example, bromocriptine\(^7\) and amantadine\(^6\) have been shown to improve cognitive recovery after experimental TBI. If a depression of dopaminergic function is responsible for behavioral deficits observed after TBI, then pharmacologic interventions that further suppress catecholaminergic activity may enhance the deficits produced by brain injury. Our experimental results support this prediction: chronic postinjury administration of haloperidol impaired the recovery of cognitive performance in the MWM.

A significant limitation of the study is the small sample size. The haloperidol study was terminated because of a high mortality rate in animals treated with haloperidol. Many animals died from severe weight loss in the interval between injury and MWM assessment. However, the small sample size was sufficient for the MWM acquisition data to reveal statistically significant differences between groups. The lack of an appropriate dose response is likely because of the lack of sufficient sample size. Even so, the results suggest that the high dose of haloperidol used in the current study is detrimental to recovery of MWM acquisition performance.

**Olanzapine.** The 15 days of treatment with olanzapine did not affect the motor or MWM performance of brain-injured rats. Olanzapine is a member of a new class of neuroleptics, called third-generation agents.\(^1\)\(^2\) In the treatment of schizophrenic patients, this class of drugs has demonstrated benefits over second-generation agents such as risperidone and ziprasidone and over first-generation or traditional agents such as chlorpromazine and haloperidol. There may also be advantages to using third-generation agents to treat behavioral pathologies in TBI patients. Potentially because of its diverse binding profile, olanzapine did not exacerbate cognitive deficits after

**Figure 7:** The mean beam-walking latency (in seconds) ± standard error of the mean for the first 5 days after injury for all groups in the olanzapine study. Injured groups had a significant deficit on this task compared with the sham-injured group. Olanzapine treatment did not significantly affect the performance of either injured or sham-injured animals.

**Figure 8:** The mean latency (in seconds) ± standard error of the mean to reach the goal in the Morris water maze on days 11–15 after injury in the olanzapine study. Injured groups had a significant deficit on this task compared with the sham-injured group. Olanzapine treatment did not significantly affect the performance of injured animals.
TBI. This is an important area for future laboratory and clinical research.

**General Discussion.** Although antipsychotics are frequently used to treat various disturbances in TBI patients, the effects of such treatment on cognitive recovery and rehabilitation are unclear. Some clinical studies suggest that the use of neuroleptics may be detrimental to recovery. For example, case studies describe instances in which neuroleptic malignant syndrome is either induced or exacerbated by treatment with haloperidol. Another preliminary finding demonstrated an improvement in select areas of cognition after the discontinuation of antipsychotic treatment in TBI patients. Few controlled clinical trials specifically address the effects of antipsychotics on recovery of cognitive function. Because haloperidol is the most frequently prescribed medication to treat agitation after closed head injury, the cognitive effects of the drug warrant investigation. A variety of pharmacologic agents and strategies are available for the management of agitation and aggression, and there is currently no consensus as to the optimal treatment of posttraumatic agitation in head injury. The choice of treatment should depend on the cause of the maladaptive behavior. Although typical antipsychotics may be beneficial in treating aggression in patients with psychosis, conduct disorders, and mental retardation, atypical antipsychotics such as olanzapine may be more appropriate for patients with dementia, brain injury, and personality disorders.

The posttraumatic brain represents a complex system in which multiple neurotransmitter systems are altered. Our results lend support to the notion that the choice of pharmacologic agents to treat posttraumatic agitation and other pathologic behaviors may influence the cognitive recovery process. In our study, chronic treatment with haloperidol had a detrimental effect on cognitive recovery, whereas olanzapine treatment did not have an apparent effect. The mechanism or mechanisms responsible for the differences in outcome obtained with haloperidol and olanzapine are uncertain at present. Our results are consistent with a previous study showing cognitive deficits after treatment with haloperidol, but not olanzapine, in uninjured rats. Specifically, chronic treatment with haloperidol disrupted MWM acquisition when administered for 90 days, but not when administered for only 45 days. In contrast, olanzapine, when administered for 45 or 90 days, did not impair MWM performance. These findings, in combination with the results of the current studies (in which drugs were administered for only 15 days), suggest that the injured brain may have a lower threshold than the normal brain for potential cognitive deficits caused by chronic dosing with certain neuroleptics.

Haloperidol’s deleterious effects may be caused by the potent DA antagonism at the D2-like receptors, whereas olanzapine’s dopaminergic effects are less robust. DA is an important neurotransmitter for prefrontal function, and a decrease in dopaminergic neurotransmission can induce spatial memory deficits. Further, there is extensive evidence in laboratory and clinical studies that brain injury can result in a functional depression of catecholamine systems and that pharmacologic stimulation of these systems can enhance recovery. For example, two DA enhancing drugs, amantadine and L-deprenyl, improved MWM performance after TBI in rats. Also, the D2 agonist bromocriptine has shown beneficial effects in both clinical and experimental brain injury. Bromocriptine improved executive function in TBI patients in a double-blind, placebo-controlled clinical trial. It also attenuated working memory and spatial memory deficits, and lessened cell loss in hippocampal region CA3, in a study using the controlled cortical impact model of TBI in rats.

Alternatively, olanzapine’s interaction with the serotonin and muscarinic receptor systems may produce additional beneficial effects that are absent in haloperidol treatment. The roles of these neurotransmitter systems in the pathobiology of TBI are currently being investigated. Additional research will be required to determine why haloperidol impaired and olanzapine did not impair cognitive recovery from TBI. The results of the current study and other studies discussed here demonstrate the need for systematic research in this area to ensure that TBI patients receive appropriate pharmacotherapies to facilitate behavioral and cognitive recovery after injury.

**REFERENCES**


