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Spontaneous recovery of traumatic brain injury-induced functional deficits is not hindered by daily administration of lorazepam

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Abstract

Agitation and aggression are common sequelae of traumatic brain injury (TBI) and pose a challenge to physicians and other health providers during acute patient care and subsequent neurorehabilitation. Antipsychotic drugs (APDs) are routinely administered to manage TBI patients displaying such maladaptive behaviors despite several clinical and preclinical studies demonstrating that they hinder recovery. A potentially viable alternative to APDs may be the benzodiazepines, which have differing mechanisms of action. Hence, the aim of the study was to test the hypothesis that lorazepam (LOR) would not impede recovery after TBI. Anesthetized adult male rats received a cortical impact or sham injury and then were intraperitoneally administered LOR (0.1 mg/kg, 1.0 mg/kg, or 2.0 mg/kg) or vehicle (VEH; 1 mL/kg) commencing 24-h after surgery and once daily for 19 days. Motor and cognitive outcomes were assessed on post-operative days 1–5 and 14–19, respectively. No differences were revealed among the four sham control groups and thus they were pooled into one inclusive SHAM group. The SHAMs performed better than all TBI groups on all assessments ($p < 0.05$). Regarding TBI, the 2.0 mg/kg LOR group performed better than the VEH and 0.1 mg/kg or 1.0 mg/kg LOR groups on every task ($p < 0.05$); no differences were observed among the latter three groups on any endpoint ($p > 0.05$). Overall, these preclinical behavioral data support the hypothesis and reveal a therapeutic benefit with the higher dose of LOR. The findings suggest that LOR may be an alternative, to APDs, for

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controlling agitation without compromising spontaneous recovery and perhaps could afford a dual benefit by also promoting therapeutic efficacy.

Keywords

Beam-walk; 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 [1] that yields significant neurological disabilities and negatively impacts quality of life [2–8]. The financial burden resulting from medical and rehabilitative care, as well as diminished productivity, is estimated to be greater than \$76.5 billion per year [2,3]. In addition to motor and cognitive dysfunction, which include, but are not limited to, postural and balance deficits as well as memory loss, impulsivity, poor executive function, and learning impairments [9–11], TBI induces agitation and aggression, with the former afflicting as many as 70% [12–15] and the latter affecting 34% of the clinical TBI population [16,17]. Moreover, these maladaptive behaviors may hamper acute medical care and subsequent neurorehabilitation [18].

To manage these behavioral dysfunctions, antipsychotic drugs (APDs) are routinely administered [12,18–23] with the intent to provide safety for both the patient and staff [18,20,24], as well as, to allow for greater patient participation in rehabilitation [25]. While haloperidol (HAL), which is a D₂ receptor antagonist, is effective in reducing the agitation [18,26,27], it hinders recovery as shown by several clinical studies [12,18–23]. Rao and colleagues (1985) showed that HAL extended the duration of post-traumatic amnesia in a group with severe traumatic closed head injury [28]. HAL has also been reported to induce neuroleptic malignant syndrome in a TBI patient [29]. Moreover, HAL reduced the degree of cognitive improvement after its discontinuation, suggesting long-term cognitive deficits with its use [22].

Persistent cognitive deficits have also been reported in pre-clinical studies assessing HAL and risperidone [30]. Specifically, HAL has been shown to halt the acquisition of spatial learning and memory as demonstrated by significantly slower and less learning over time vs. vehicle-treated controls [31,32]. These findings, in parallel with data showing that D₂ receptor agonists, such as bromocriptine and methylphenidate, enhance the recovery process [30,33–36] demonstrate that typical and atypical APDs are impairing functional recovery after TBI likely due to D₂ receptor antagonism mediated perturbations.

Despite the APD-induced deleterious effects on neurobehavior and cognition, some form of post-injury sedation is necessary to manage disruptive patients. Management of symptoms is critical to ensure patient and staff safety [18,20,24] as well as thorough patient evaluation and treatment. In the longer term, reducing agitation may facilitate optimal participation in neurorehabilitation [25]. Hence, alternative pharmacological treatments that may reduce agitation and/or aggression without compromising spontaneous recovery are warranted.

A potentially viable alternative to APDs may be the benzodiazepines, which have differing mechanisms of action. Lorazepam (LOR), for example, is a member of the classical benzodiazepine drug family that includes diazepam [37–40]. Benzodiazepines are positive allosteric modulators of GABA receptors and have no D₂ antagonism properties [37,38,40,41]. Because the mechanism of action for LOR differs from that of HAL and risperidone, it is hypothesized that LOR would not impede motor and cognitive recovery when provided chronically after TBI. While several excellent reviews and studies exist discussing the use and efficacy of benzodiazepines in general [42–44] and LOR specifically [26,45–49] to manage agitation after clinical brain injury, there are no experimental studies evaluating LOR after experimental TBI. Hence, the current study was designed to investigate a dose response of LOR on neuromotor and cognitive performance after cortical impact injury in rats. The rationale is that LOR, if innocuous to motor and cognitive recovery after TBI with doses that produce sedation, may be considered as a viable alternative to typical and atypical APDs after brain trauma.

2. Materials and methods

2.1. Subjects

Sixty-seven adult male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 300–325 g on the day of surgery were housed in ventilated polycarbonate cages and maintained in a temperature (21 ± 1 °C) and light controlled (on 0700–900) environment with food and water available *ad libitum*. The rats were acclimated to the colony for one week and then underwent a single day of beam-walk training until able to traverse the entire length of the beam (100 cm) within 5 s. Fully trained rats were then randomly assigned to one of four TBI or one of four sham groups where they received one of three doses of LOR (0.1 mg/kg, 1.0 mg/kg, or 2.0 mg/kg) or vehicle (VEH; 1.0 mL/kg). All experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh. Every attempt was made to limit the number of rats used and to minimize suffering.

2.2. Surgery

A surgical level of anesthesia was induced and maintained with inspired concentrations of 4% and 2% isoflurane, respectively, in 2:1 N₂O:O₂ in a vented anesthesia chamber. Following endotracheal intubation, the rats were secured in a stereotaxic frame and mechanically ventilated. Utilizing aseptic techniques, a 6-mm craniotomy was made in the right hemisphere between bregma and lambda and from midline to the coronal ridge, using a high-speed dental drill. A controlled cortical impact (CCI) of 2.8 mm tissue deformation at 4 m/sec produced an injury of moderate severity as previously described [30–32,50–54]. Sham control rats underwent all anesthetic and surgical manipulations except the impact. Anesthesia was discontinued immediately after CCI or sham injury and the incision was promptly closed with nylon sutures. The rats were subsequently extubated and acute neurological evaluations were performed.

2.3. Acute neurological evaluation

Return of the righting reflex was determined by the time required to turn from the supine to prone position three consecutive times and was assessed immediately after the cessation of anesthesia.

2.4. Drug administration

LOR was purchased from Tocris Bioscience (Bristol, UK) and was prepared daily by dissolving in 1:1 dimethyl sulfoxide and physiological saline, which served as the VEH. LOR or a comparable volume of VEH was administered intraperitoneally beginning 24 h after CCI or sham injury and once daily until all behavioral evaluations were completed (i.e., post-operative day 19). On the days when behavioral assessments were conducted, treatments were administered immediately after testing by an experimenter unaware of group conditions. The exception to this paradigm was to determine if the doses utilized were sufficient to induce sedation, which would be necessary to reduce agitation and aggression clinically. In this instance, a sub-set of rats were administered LOR (2.0 mg/kg) or VEH and 1-h later swim speed was evaluated in the water maze. The route of administration was selected based on previous studies from our laboratory [30–32,51] and the LOR doses were selected from both the literature [55–58] and the aforementioned pilot study from our laboratory. Clinical doses are in a range of 2–4 mg/kg for control of agitation and aggression in adults [49] and 0.1–4 mg/kg for status epilepticus in pediatric patients [59,60].

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

Established beam-balance and beam-walk tasks were used to assess motor function. Briefly, the beam-balance task consists of placing the rat on an elevated and narrow beam (1.5 cm wide) and recording the time it remains on for a maximum of 60 s. The beam-walk task, modified from that originally devised by Feeney and colleagues (1982) [61], consists of training/assessing rats using a negative-reinforcement paradigm to escape a bright light (situated directly over the start point) and white noise by traversing an elevated narrow beam (2.5 × 100 cm) and entering a darkened goal box. The adverse stimuli (light and noise) were terminated when the rat entered the goal box, which served as reinforcement for completing the task. Performance was assessed by recording the elapsed time to traverse the beam. Rats were tested for beam-balance and beam-walk performance prior to surgery to establish a baseline measure and again on post-operative days 1–5. Testing consisted of three trials (60 s allotted time with an inter-trial interval of 30 s) per day on each task. If a rat was unable to traverse the entire length of the beam the maximum allowed time of 60 s was recorded. The average daily scores for each rat were used in the statistical analyses.

2.6. Cognitive function: acquisition of spatial learning and memory

Spatial learning was assessed in a water maze task demonstrated to be sensitive to cognitive function/dysfunction after TBI [30–32,51,62–66]. The maze was a plastic pool (180 cm diameter, 60 cm high) filled with tap water ($21 \pm 1^\circ\text{C}$) to a depth of 28 cm and was situated in a room with salient 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 south-west quadrant and held constant for each rat. Acquisition of spatial learning was initiated on post-operative day

14 and continued until day 18. The paradigm consisted of providing a block of four daily trials for five consecutive days to locate the platform when it was submerged 2 cm below the water surface (i.e., invisible to the rat). On 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 cognitive performance. 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 (4-min inter-trial interval). 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 (i.e., 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. The percent time spent in the target quadrant was used in the statistical analysis. All data including swim speed were obtained using the ANY-maze video tracking software (Stoelting, Wood Dale, IL).

2.7. Data analyses

Statistical analyses were performed on behavioral data collected by observers blinded to treatment conditions using StatView 5.0.1 (Abacus Concepts, Inc., Berkeley, CA). The motor and cognitive data were analyzed by repeated-measures analysis of variance (ANOVA). The acute neurological assessment, probe trial, visible platform, and swim speed were analyzed by one-factor ANOVAs. When the ANOVA showed a significant effect, 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 were considered significant when p values were ≤ 0.05 .

3. Results

There were no significant differences among the four sham groups in any outcome measure and thus they were pooled into one inclusive SHAM group. Five rats from the TBI groups (2 from both the LOR 0.1 mg/kg and 1.0 mg/kg groups and 1 from the VEH treated group) were excluded from the study because of an inability to locate the visible platform, which may be indicative of visual acuity deficits that could manifest as a potential confound given the need to clearly visualize the cues located on the walls to acquire spatial learning. Hence, the statistical analyses were conducted on 62 rats and the final group sizes were as follows: TBI+ LOR (0.1 mg/kg; $n = 10$), TBI+ LOR (1.0 mg/kg; $n = 9$), TBI + LOR (2.0 mg/kg; $n = 14$), TBI + VEH (1.0 mL/kg; $n = 9$), Sham + LOR (0.1 mg/kg; $n = 5$), Sham + LOR (1.0 mg/kg; $n = 5$), Sham + LOR (2.0 mg/kg; $n = 5$), Sham + VEH (1.0 mL/kg; $n = 5$).

3.1. Acute neurological evaluation

No significant difference was revealed among the TBI groups for righting reflex latency (range = 343.0 ± 14.1 s to 393.2 ± 15.4 s) following the cessation of anesthesia [$p > 0.05$]. As expected, the SHAM controls exhibited significantly shorter righting reflex times relative to the TBI groups (109.4 ± 11.1 s to 125.6 ± 12.1 s; $p < 0.0001$). The lack of differences in this acute neurological index indicates that injury severity was similar among the TBI groups.

3.2. Sedative observation (water maze swim speed assessment after LOR treatment)

Swim speed was significantly reduced in the LOR-treated group relative to VEH controls. Specifically, the group administered LOR 1-h prior to assessment in the water maze had a mean swim speed of 16.4 ± 2.5 cm/sec, while those provided LOR after behavioral assessment exhibited an average speed of 30.5 ± 0.6 cm/sec ($p < 0.05$). Although evaluating agitation was not the goal of the current study, the data show that the dose of LOR used was sufficient to induce sedation, which is necessary to attenuate agitation and thus may have clinical relevance.

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

All groups were able to balance on the beam for the allotted 60 s prior to surgery (Fig. 1). After surgery, the repeated-measures ANOVA revealed significant Group [$F_{4,57} = 16.162$, $p < 0.0001$] and Day [$F_{5,285} = 88.970$, $p < 0.0001$] differences, as well as a significant Group $\times$ Day interaction [$F_{20,285} = 12.075$, $p < 0.0001$]. The post-hoc analysis revealed that the SHAM controls, which were able to balance for the full 60 s were significantly better than all TBI groups [$p < 0.05$]. The TBI + LOR (2.0 mg/kg) was different from the TBI + VEH [$p < 0.05$], but did not differ from the TBI + LOR (0.1 mg/kg or 1.0 mg/kg) groups [$p > 0.05$], which also did not differ from one another [$p > 0.05$]. Regarding beam-walk performance, no significant differences were observed among any of the groups in the time to traverse the beam prior to surgery (Fig. 2). However, after surgery, the repeated-measures ANOVA revealed significant Group [$F_{4,57} = 145.471$, $p < 0.0001$] and Day [$F_{5,285} = 224.486$, $p < 0.0001$] differences, as well as a significant Group $\times$ Day interaction [$F_{20,285} = 21.340$, $p < 0.0001$]. Like the beam-balance findings, the post-hoc analysis revealed that the SHAM group was significantly better than all TBI groups [$p < 0.05$]. Additionally, the TBI + LOR (2.0 mg/kg) was markedly better than all other TBI groups, regardless of treatment or dose [$p < 0.05$]. No difference was revealed between the TBI + LOR (0.1 mg/kg and 1.0 mg/kg) groups [$p > 0.05$], nor between them and the TBI + VEH group [$p > 0.05$].

3.4. Cognitive function: acquisition of spatial learning and memory

The repeated measures ANOVA revealed significant Group [$F_{4,57} = 19.126$, $p < 0.0001$] and Day [$F_{4,228} = 13.319$, $p < 0.0001$] differences. The post-hoc test revealed that the SHAM control group was superior to all TBI groups in learning the escape platform [$p < 0.05$; Fig. 3]. Additionally, the TBI + LOR (2 mg/kg) group performed better over the five days of training relative to the TBI + VEH and TBI + LOR (0.1 mg/kg) groups [$p < 0.05$]. The TBI + LOR (1.0 mg/kg) group did not differ from any of the TBI groups, regardless of treatment or dose [$p > 0.05$]. Analysis of the probe trial (i.e., memory retention) data did not reveal a

significant overall Group effect [$F_{4,57} = 1.841$, $p = 0.13$]. The visible platform data showed no differences between the SHAM and TBI +LOR (2 mg/kg) groups [$p > 0.05$], but both reached the goal quicker than all other TBI groups [$p < 0.05$]. Lastly, the ANOVA for swim speed revealed a significant group $F_{4,57} = 2.590$, $p = 0.0461$ difference, which according to the post-hoc test was due to the TBI + LOR (1.0 mg/kg) group swimming faster than the SHAM controls (33.4 ± 1.5 cm/sec vs. 28.0 ± 0.9 cm/sec) ($p < 0.05$; Fig. 4).

4. Discussion

We investigated the effects of LOR, a benzodiazepine, on neurobehavioral recovery and spatial learning acquisition and memory retention after CCI injury in rats. The hypothesis that LOR would not impede motor and cognitive recovery when provided chronically after TBI was supported. As expected, the sham groups did not differ from one another regardless of treatment or dose, which indicates there was no effect of chronic LOR in uninjured controls. Support for the hypothesis, however, was derived from the data showing that none of the three doses of LOR were different from the VEH-treated controls in any endpoint. Moreover, the TBI group receiving 2.0 mg/kg of LOR exhibited enhanced motor and cognitive performance relative to the injured VEH-treated group. These findings are further supported by the fact that all TBI rats received equivalent levels of injury and anesthesia as indicated by the acute neurological data.

The beneficial effect of LOR (2.0 mg/kg) is not without intrigue as previous studies from our laboratory [30–32,51] and others [61,67,68] have shown impediments to recovery with sedative drugs, such as the APDs HAL and risperidone. It has been suggested that the deleterious effects exerted by these APDs may be due to antagonism of D_2 receptors, as other therapies that have no such mechanism, such as the third generation APD, aripiprazole, do not negatively impact recovery after TBI. The lack of negative effects with aripiprazole may be due to its mechanisms of action, which include D_2 and $5-HT_{1A}$ receptor agonism [69–73]. Moreover, D_2 receptor agonists, such as methylphenidate and bromocriptine and $5-HT_{1A}$ receptor agonists, such as buspirone and 8-OH-DPAT, robustly enhance functional outcome after CCI injury [30,33–36,50,53,62,63,74–79].

LOR, however, is a benzodiazepine and like classical benzodiazepines it does not directly innervate GABA receptors, as they are typically positive allosteric modulators (PAMs), which increase the efficacy of endogenous GABA. PAMs typically increase Cl^- pore opening duration as well as frequency [40,41,80]. However activation must be induced by neurotransmitter binding (i.e., endogenous GABA). Directly targeting GABA receptors via agonist or antagonist approaches may be too indiscriminate [40]. However, allosteric modulation of the GABA system, utilizing an endogenous approach may potentiate improved homeostasis. As such, modulation of the GABAergic system utilizing intrinsic neurotransmission may improve functional recovery after TBI [81–83].

There are, however, conflicting reports of the utility of benzodiazepines following TBI. The dichotomy of benzodiazepine function suggests either a detrimental or beneficial outcome within a TBI context. Studies indicate that the benzodiazepine families of drugs are potentially harmful to cognitive recovery [84,85]. Specifically, benzodiazepines have been

shown to alter GABA_A receptor mediated responses to TBI [82,87–89]. In direct contrast, studies conducted by O'Dell and colleagues and Dash et al. suggest that the enhancement of GABAergic neurotransmission improves functional outcomes after TBI [82,90]. These findings of improved performance are bolstered by the current data as 2.0 mg/kg of LOR enhanced neurobehavioral and cognitive performance, possibly by allosteric modulation of perturbed GABAergic systems following injury. A potential explanation for these findings may be the disinhibition of tonal dopaminergic down regulation after injury [33,91]. Dopamine release in the post-injury time frame may be intrinsically linked to GABAergic modulation as numerous studies have shown inhibitory tonal influence on dopaminergic neurons [92–94].

5. Conclusion

In summary, the findings from this original pharmacological and behavioral endeavor into the use of LOR after a CCI injury in adult male rats clearly shows that unlike APDs with D₂ antagonistic properties, functional recovery was not hindered. Indeed, the higher dose of LOR enhanced outcome relative to VEH-treated controls. Moreover, the beneficial dose was also shown in a pilot study to provide substantial sedation as evidenced by a 50% reduction in swim speed relative to VEH-controls. These findings suggest that LOR, because of its sedative effect, may have some benefit for alleviating TBI-induced agitation and aggression without compromising spontaneous recovery. Moreover, with the correct dose, LOR may benefit outcome.

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Fig. 1.

Mean ($\pm$ S.E.M.) time (sec) balancing on an elevated narrow beam prior to, and after, TBI or sham injury. There were no significant differences among the sham groups and thus the data were pooled (SHAM). * $p < 0.05$ vs. TBI + VEH. ** $p < 0.05$ vs. all TBI groups, regardless of treatment. No other comparisons were significant.

Fig. 2.

Mean ($\pm$ S.E.M.) time (sec) to traverse an elevated narrow beam after TBI or sham injury.

There were no significant differences among the sham groups and thus the data were pooled (SHAM). * $p < 0.05$ vs. TBI+ VEH. ** $p < 0.05$ vs. all TBI groups, regardless of treatment.

No other comparisons were significant.

Fig 3.

Mean ($\pm$ S.E.M.) time (sec) to locate a hidden and visible platform in the water maze. There were no significant differences among the sham groups and thus the data were pooled (SHAM). For the hidden platform assessments, $*p < 0.05$ vs. TBI + VEH and TBI + LOR (0.1 mg/kg). $**p < 0.05$ vs. all TBI groups, regardless of treatment. No other comparisons were significant. For the visible platform assessment, $*p < 0.05$ vs. TBI + VEH and TBI + LOR (0.1 mg/kg) and $**p < 0.05$ vs. all TBI groups, except the TBI + LOR (2 mg/kg). No other comparisons were significant.