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5-hydroxytryptamine_{1A} (5-HT_{1A}) receptor agonists: a decade of empirical evidence supports their use as an efficacious therapeutic strategy for brain trauma

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Abstract

Traumatic brain injury (TBI) is a significant and enduring health care issue with limited treatment options. While several pre-clinical therapeutic approaches have led to enhanced motor and/or cognitive performance, the benefits of these treatments have not translated to the clinic. One plausible explanation is that the therapies may not have been rigorously evaluated, thus rendering the bench-to-bedside leap premature and subsequently unsuccessful. An approach that has undergone considerable empirical research after TBI is pharmacological targeting of 5-HT_{1A} receptors with agonists such as repinotan HCl, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), and buspirone. The goal of this review is to integrate and interpret the findings from a series of studies that evaluated the efficacy of 5-HT_{1A} receptor agonists on functional, histological, and molecular outcome after acquired brain injury. The overwhelming consensus of this exhaustive review is that a decade of empirical evidence supports their use as an efficacious therapeutic strategy for brain trauma.

Keywords

5-HT_{1A} receptor agonists; behavioral outcome; controlled cortical impact; functional recovery; hippocampus; learning and memory; Morris water maze; serotonin_{1A}; traumatic brain injury

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Introduction

Traumatic brain injury (TBI) affects an estimated 10 million people worldwide (Hyder et al., 2007). Many suffer significant neurological disabilities (Sosin et al., 1995; Thurman et al., 1999; Langlois et al., 2004; Selassie et al., 2008; Faul et al., 2010) that preclude their ability to remain self-sufficient. Moreover, 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 (Langlois et al., 2004; Faul et al., 2010). Accordingly, if individuals who sustain a TBI are to once again become integrated and productive members of society, the identification, refinement, and effective implementation of treatment strategies capable of producing neurobehavioral and cognitive recovery after TBI is essential.

Numerous therapeutic approaches have been conducted after experimental TBI and many of them have shown significant improvement in locomotor and cognitive performance, as well as decreases in histological damage (see excellent reviews by Kokiko and Hamm, 2007; Bales et al., 2009; Wheaton et al., 2009; Garcia et al., 2011). However, these interventions have not translated to the clinic (Doppenberg et al., 2004; Menon, 2009). One plausible explanation is that the therapies may not have been rigorously evaluated at the bench, thus rendering the bench-to-bedside leap premature and consequently unsuccessful. An approach that has undergone considerable empirical research after TBI is pharmacological targeting of 5-HT_{1A} receptors with agonists such as repinotan HCl, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), and buspirone.

5-HT_{1A} receptors are the most studied and best-characterized of the fourteen 5-HT receptor subtypes (Barnes and Sharp, 1999). They are abundantly expressed in key brain regions that subserve learning and memory, such as the cortex and hippocampus, and thus play a prominent role in cognition (Barnes and Sharp, 1999; Meneses 1999; Meneses and Perez-Garcia, 2007). 5-HT_{1A} receptors are also susceptible to neuronal damage induced by TBI or other CNS injuries (De Vry et al., 1997, 1998) and thus it is plausible that these receptors could be an important and potentially efficacious therapeutic target to investigate after TBI. Indeed, the limited, albeit, persuasive studies in this comprehensive review show that manipulating this system confers significant cognitive and histological benefits after brain trauma.

The primary objective of this review is to integrate the current literature based on experiential studies evaluating 5-HT_{1A} receptor agonists for their effect on cognitive, motor, histological and/or molecular outcome after brain trauma. The secondary goal is to invigorate interest in this still understudied, but efficacious therapeutic approach for TBI. The importance of evaluating therapies that act on the 5-HT neurotransmitter system is that to date only the partial dopamine₂ (D₂) receptor agonist amantadine has shown some promise translating from bench-to-bedside when administered in the subacute phase after severe TBI (Giacino et al., 2012). Clearly, additional research is necessary to discover potential pharmacotherapies that may treat the debilitating consequences of TBI. As this comprehensive review shows, a decade of experiential evidence supports the use of 5-HT_{1A} receptor agonists as an efficacious therapeutic strategy for brain injury.

Using the specific key-terms “traumatic brain injury” AND “serotonin $1A$ ” 27 articles were identified by PubMed. Refining the search to “traumatic brain injury” AND “5-HT $1A$ receptor agonists”, yielded 17 articles of which 7 were specific to TBI. The same terms in Scopus returned 23 and 13 articles, respectively, with 13 specific to TBI (including the 7 from PubMed). Finally, after reviewing the bibliographies of the papers that were exclusive to TBI, an additional 2 papers were identified that fit the criteria of brain trauma, albeit not “traumatic” per se. These 2 papers focused on acute subdural hematomas (ASDH) and were included because hematomas are the most common mass lesions after TBI (Alessandri et al., 1999). Hence, the review focuses on 15 papers, of which 14 are experimental and 1 is clinical. All studies are described in the body and briefly summarized in Table 1.

The overwhelming majority of the studies described in this review followed two basic therapeutic approaches; the first was an early and single (i.e., acute) treatment after TBI, and the second was delayed and provided over multiple days (i.e., chronic). In some instances, the therapeutic approaches were also combined with environmental enrichment (EE) to determine additive or synergistic effects in a rehabilitative setting.

Acute administration

Repinotan HCl

The first TBI study to evaluate the potential protective effects of a 5-HT $1A$ receptor agonist was conducted by Kline and colleagues who provided a 4-hr continuous infusion of repinotan (previously labeled BAY x3702) at a dose of 10 μ g/kg/hr (i.v.) commencing 5 min after a controlled cortical impact (CCI) injury of moderate severity. Evidence of neuroprotection was operationally defined as an amelioration of functional outcome and an attenuation of histopathology (Kline et al., 2001). The data revealed that the repinotan-treated TBI group acquired spatial learning significantly faster than the vehicle controls as demonstrated by shorter times to locate the hidden platform in a Morris water maze (MWM) task (Kline et al., 2001). Moreover, repinotan also attenuated hippocampal CA $1/3$ neuronal loss and decreased cortical lesion volume. No motor differences were observed as both the repinotan and vehicle-treated brain injured groups recovered beam-balance and beam-walking ability at the same rate. The lack of motor differences between treatment groups may be attributable to the relatively quick recovery of gross motor function.

Repinotan has also been shown to confer neuroprotection in ASDH brain injury models produced by injecting non-heparinized autologous blood into the subdural space (Alessandri et al., 1999; Mauler and Horváth, 2005). Alessandri and colleagues reported that repinotan (i.e., BAY X3702; 0.01 mg/kg or 0.003 mg/kg) conferred significant histological neuroprotection when injected 15 min prior to ASDH and then continuously for an additional 4-hrs. Specifically, the repinotan-treated rats had significantly smaller cortical lesion volumes compared to the vehicle-treated controls (Alessandri et al., 1999). In a second ASDH study, Mauler and Horváth administered repinotan as bolus intravenous injections immediately after surgery and again at 2 hr and 4 hr (10 μ g/kg and 100 μ g/kg), or as a continuous 4-hr intravenous infusion (0.1 μ g/kg, 1 μ g/kg, 10 μ g/kg, 100 μ g/kg, 300 μ g/kg, and 1000 μ g/kg). The data showed a significant decrease in infarct volume after the repeated dosing regimen with no differences among doses. Furthermore, when repinotan was

provided as a continuous infusion, infarct volumes were decreased at all but the lowest and highest doses, with the 1 µg/kg and 10 µg/kg doses conferring the greatest efficacy (Mauler and Horváth, 2005).

8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT)

To further evaluate the efficacy of acute administration of a 5-HT_{1A} receptor agonist after TBI, Kline and co-workers (2002b) designed a dose-response study where one of three single doses of 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT; 0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg, i.p.) was administered 15 min after TBI or sham injury. The data showed that only the middle dose of 8-OH-DPAT attenuated hippocampal cell loss and facilitated spatial learning in the MWM. The lowest and highest doses did not differ from one another or from the vehicle control, suggesting that 8-OH-DPAT has a narrow therapeutic profile, just as observed with repinotan after ASDH. Such a narrow effective dose range has also been reported in non-TBI models of cognition (Meneses, 1999; Meneses and Perez-Garcia, 2007). Moreover, the 8-OH-DPAT-treated groups exhibited a rapid, mild, and transient hypothermic response, which was more robust (i.e., 34.42 ± 0.56) in the dose that conferred the benefits. Hence, the interpretation of the behavioral and histological results were tempered somewhat because hypothermia has been reported in numerous TBI studies to confer neuroprotection (Bramlett et al., 1995; Clark et al., 1996; Dixon et al., 1998; Bayir et al., 2003), even at a relatively mild level of 36 °C as reported by Clifton and colleagues (1991).

Hence, to rule out the potential contribution of hypothermia and confirm the potential benefits produced by 8-OH-DPAT, a follow up study was conducted where the experimental design effectively controlled for the 8-OH-DPAT-induced hypothermia. Briefly, two separate 8-OH-DPAT-treated groups (0.5 mg/kg, which was the effective dose of the previous study) were utilized with the difference being that one was allowed to spontaneously cool as in the previous study and the other was actively kept at the normothermic range of 37 ± 0.5 °C with a heating fan. Both 8-OH-DPAT-treated groups performed significantly better in the acquisition of spatial learning and memory retention vs. the vehicle treated controls, but did not differ from one another despite a rapid (15 min), mild (34.4–34.9 °C), and transient (~1 h) hypothermic effect in the unmanaged group. Moreover, both groups displayed a significant reduction in CA₃ cell loss and cortical lesion volume versus the vehicle group. These data demonstrated unequivocally that the beneficial effects conferred by a single systemic administration of 8-OH-DPAT after CCI injury were not mediated by concomitant hypothermia (Kline et al., 2004a).

In contrast, a study evaluating molecular changes after brain trauma produced by a closed head weight drop found that hypothermia induced by 8-OH-DPAT increased Bcl-2 expression while decreasing Bax and caspase-3 expression. A decrease in TUNEL positive cells was also attributed to the mild hypothermic effect as the 8-OH-DPAT control group that remained normothermic did not exhibit the same effect (Mao et al., 2013). The benefits attributed to temperature in this study versus those of Kline and colleagues (2002b, 2004a) may be due to differences in brain injury or outcomes evaluated. Furthermore, although the dose of 8-OH-DPAT, route, and time of administration was similar between the studies,

hypothermia was reported to occur later in the Mao study with peak lows reported at 2 hr after injury, whereas following CCI injury the lowest temperature was recorded at 30 min after drug administration. An additional study from the Kline group also showed a rapid and mild hypothermic effect that was not correlated with functional improvement after TBI (Yelleswarapu et al., 2012).

While the four studies described thus far demonstrate significant benefits after an early and single systemic administration of 8-OH-DPAT, the 15 min time to treat may not be clinically ideal. Therefore, to evaluate the efficacy of 8-OH-DPAT in a more realistic time frame, Cheng and colleagues (2007) designed a study to determine whether the therapeutic window of efficacy could be extended. Briefly, the optimal dose of 8-OH-DPAT (0.5 mg/kg, i.p.) determined from the previous studies was provided at 15 min, 1 hr, and 2 hr after TBI or sham injury and neurobehavioral and cognitive effects were compared to the vehicle-treated controls. As in the previous studies (Kline et al., 2002b, 2004a; Yelleswarapu et al., 2012), 8-OH-DPAT administered 15 min after TBI produced a significant benefit in the MWM task vs. the vehicle-treated control group. However, neither the 1-hr nor 2-hr delayed 8-OH-DPAT treatment groups differed from the vehicle group. These data suggest that in addition to a narrow dose response as described previously, a single systemic administration of 8-OH-DPAT also has a narrow therapeutic window for conferring neuroprotection.

Delayed and chronic administration

An alternative therapeutic strategy to neuroprotection is restoration. The acute drug administration studies focused on preventing further deleterious effects of TBI-induced excitotoxicity. And while they are effective, it is not always feasible to administer treatments to TBI patients within the limited narrow therapeutic window elucidated in the previous section. Hence, there is a need to evaluate therapies that can be administered in a delayed fashion. However, as just elucidated, delaying treatment following a single administration of 8-OH-DPAT is ineffective (Cheng et al., 2007). This realization suggests that delaying treatment may require chronic exposure. Therefore, the following section focuses on studies assessing the efficacy of the 5-HT_{1A} receptor agonists, 8-OH-DPAT and buspirone, when administration was delayed and chronic.

8-OH-DPAT

Expanding on the early-and-single administration studies showing a benefit with 8-OH-DPAT, Cheng and colleagues (2008) sought to evaluate the potential efficacy of this pharmacotherapy when it was delayed by 24 hr after TBI and provided once daily for 19 days. A semblance of a dose response curve that included the dose that was optimal in the single administration studies was used (0.5 mg/kg), as was a lower dose (0.1 mg/kg) to account for the potential effects of daily treatments. The hypothesis was that either of the two doses would improve functional outcome after a TBI. The data showed that the delayed and chronic regimen of 8-OH-DPAT did improve spatial learning and memory. Specifically, the lower dose was significantly better than both the vehicle control group and the higher 8-OH-DPAT dose, which incidentally was the optimal dose in the acute studies (Kline et al., 2002b, 2004a; Yelleswarapu et al., 2012). Moreover, the higher dose of 8-OH-DPAT

exhibited a trend for worse performance in the MWM. This finding reiterates that 8-OH-DPAT has a narrow dose-response profile.

Buspirone

In a subsequent study evaluating chronic 5-HT_{1A} receptor agonist treatments, Olsen and colleagues (2012) focused on buspirone with the rationale being that it is widely used clinically to treat anxiety and depression, and thus if effective could facilitate bench-to-bedside translatability as safety and tolerability issues are well known (Chew and Zafonte, 2009). When designing the experiment, the authors remained cognizant of the narrow dose efficacy of 5-HT_{1A} receptor agonists and hence included and evaluated a thorough dose response profile. Twenty-four hr after a cortical impact injury of moderate severity, five doses of buspirone (0.01, 0.05, 0.1, 0.3, and 0.5 mg/kg) or vehicle were administered once daily for 19 days. The data revealed that the 0.3 mg/kg dose significantly improved cognitive performance as assessed in the MWM. Specific improvements were observed in both the time and distance to locate the escape platform, as well as percent time spent in the target quadrant during a probe trial that measures memory retention. Indeed, for the probe assessment, the 0.3 mg/kg dose did not differ from the non-injured sham controls. Additionally, histological benefits (i.e., reduced cortical lesion volumes) were also seen in the 0.3 mg/kg group relative to the vehicle-treated and other buspirone dose groups. These findings again support the therapeutic efficacy of 5-HT_{1A} receptor agonists after TBI despite a narrow therapeutic dose range.

Combination therapies: 5-HT_{1A} receptor agonists plus environmental enrichment

The significant benefits reported with the 5-HT_{1A} receptor agonists 8-OH-DPAT and buspirone after TBI are robust. However, TBI patients also receive prescribed rehabilitation after discharge from critical care and hence the following studies were designed to mimic the clinic where patients would receive a pharmacotherapy while undergoing neurorehabilitation. Environmental enrichment (EE) has been shown to confer significant neurobehavioral and histological benefits after TBI and is thus considered a preclinical model of neurorehabilitation (for comprehensive reviews, see Bondi et al., 2014a,b). It was hypothesized that the combination of 5-HT_{1A} receptor agonists and rehabilitation would produce greater benefits than either therapy alone.

Acute 8-OH-DPAT plus EE

Similar to the previous studies assessing an early single systemic administration of 8-OH-DPAT after TBI (Kline et al., 2002b, 2004a; Yelleswarapu et al., 2012), there was a significant benefit in cognitive performance vs. the vehicle-treated controls. Additionally, as has been shown in numerous studies, EE also conferred improvements in the acquisition of spatial learning (Hamm et al., 1996; Passineau et al., 2001; Sozda et al., 2010; de Witt et al., 2011; Cheng et al., 2012; Bondi et al., 2014a,b). Moreover, when 8-OH-DPAT was followed by continuous EE the acquisition of spatial learning was significantly improved, demonstrating that combining the therapies was more efficacious than 8-OH-DPAT alone (Kline et al., 2007a). However, a caveat to this finding is that the groups receiving EE alone or in combination with 8-OH-DPAT did not differ from one another.

Delayed and chronic 8-OH-DPAT or buspirone plus EE

To evaluate the potential additive or synergistic benefits of delayed and chronic treatment with 5-HT_{1A} receptor agonists combined with EE, two separate studies evaluating each pharmacotherapy were conducted. With the exception of the inclusion of EE, which was initiated immediately after TBI and continued for the duration of the study, all experimental parameters were identical to those previously reported for the CCI injury chronic studies already discussed (Cheng et al., 2008; Olsen et al., 2012). The findings showed that both 8-OH-DPAT and EE attenuated hippocampal CA₃ and choline acetyltransferase-positive (ChAT⁺) medial septal cell loss. Both therapies also facilitated motor recovery as well as learning and memory retention. There were no reported advantages to combining the two therapies in the behavioral endpoints, but there were significantly more sparing of ChAT⁺ cells in the combination group versus either treatment alone. This finding suggests that the combination of 8-OH-DPAT and EE conferred additive neuroprotective benefits (Kline et al., 2010).

In the buspirone plus EE study, the behavioral results were similar to those described for the combination 8-OH-DPAT and EE study. Briefly, motor and cognitive recovery was enhanced in the buspirone-treated group housed in standard conditions as well as in those receiving EE. EE on its own also facilitated functional recovery, which is consistent with several other studies (Bondi et al., 2014a,b). Hippocampal CA₃ cell loss was reduced in both EE groups, regardless of combined treatment, but not with buspirone or vehicle alone. No differences were revealed between the buspirone treated group receiving EE and the EE alone group, suggesting that the combination of treatments was not more robust than either alone (Kline et al., 2012).

Pediatric TBI: delayed and chronic buspirone plus EE

TBI is not confined to adults. Indeed, children make up one of the higher risk groups with approximately 475,000 under the age of 15 acquiring a TBI each year (Faul et al., 2010). Over 37,000 of the young patients are hospitalized and 2,600 do not survive the initial insult. These sobering statistics make TBI the leading cause of death and disability in the pediatric population (Keenan et al., 2004; Langlois et al., 2004; Babikian and Asarnow, 2009). Of the survivors, it is conservatively estimated that 50% demonstrate cognitive, physical, and psychosocial deficits (Anderson et al., 2001; Hawley et al., 2004; Babikian and Asarnow, 2009). The overwhelming deleterious effects of TBI in a group that may be impacted for decades warrants the evaluation of potentially efficacious therapies.

Because of its promising ameliorative effects in adult models of TBI (Kline et al., 2012; Olsen et al., 2012), buspirone was provided alone and in combination with EE after pediatric TBI of moderate severity. The authors sought to test the hypothesis that, like in the adult model, buspirone and EE would attenuate histological damage and enhance spatial learning and memory after cortical impact injury. The hypothesis was elaborated on further by predicting that the combination would be more efficacious than either therapeutic approach individually. To test the hypotheses, two experiments were conducted. In the first experiment, three doses of buspirone were provided to determine the optimal dose that would subsequently be combined with EE in the second experiment (Monaco et al., 2014).

The data from the first experiment showed that the middle dose of buspirone (0.1 mg/kg) enhanced MWM performance relative to vehicle and the two other doses of buspirone (0.08 mg/kg and 0.3 mg/kg). The middle dose also reduced lesion size compared to the vehicle control group. The findings from experiment 2 showed that EE significantly enhanced spatial learning and reduced lesion size vs. the standard housed controls. Furthermore, the combination of buspirone and EE led to markedly better performance in the water maze task relative to the buspirone and EE treatments alone, which supported the hypothesis of an additive effect with the two treatments (Monaco et al., 2014).

Clinical TBI

Repinotan

To date, there has been only one randomized, double-blind, placebo controlled clinical study evaluating the safety and potential efficacy of repinotan after TBI. Four groups of severe TBI patients (80% male with a mean age of 37.6 years) received one of three doses of repinotan (0.5, 1.25, and 2.5 mg/day) or placebo by continuous i.v. infusion for 7 days commencing 24 hr after injury (Öhman et al., 2001). No adverse effects were reported with repinotan. Regarding clinical efficacy, the lower and higher doses conferred more favorable outcomes than the middle dose, which did not differ from placebo. However, no statistical differences were revealed and thus the three repinotan groups were pooled. Overall, 60% of the repinotan-treated patients exhibited good outcome or moderate disability relative to the placebo-control group. While the difference between the groups was not statistically significant, the preliminary results do demonstrate the potential for efficacy with repinotan, and perhaps other 5-HT_{1A} receptor agonists, after TBI.

Discussion

The unanimous findings from this comprehensive literature review are that 5-HT_{1A} receptor agonists administered after adult or pediatric brain trauma confer histological protection and facilitate neurobehavioral and cognitive recovery. Importantly, the benefits are observed even when treatment is delayed (Cheng et al., 2008; Olsen et al., 2012), which effectively extends the therapeutic window. However, delaying treatment required a chronic administration paradigm as only studies employing such an experimental design revealed cognitive and histological benefits, whereas delaying a single treatment by even an hour after TBI was ineffective (Cheng et al., 2007). This finding speaks to potential mechanisms associated with acute and single vs. delayed and chronic treatment strategies. The results also revealed that lower doses may be necessary when the treatments are provided chronically, as higher doses tended to exacerbate the impairment (Cheng et al., 2008). Moreover, it was shown that combining 5-HT_{1A} receptor agonists with a pre-clinical model of neurorehabilitation (i.e., EE) conferred neuroprotection in adult rats (Kline et al., 2010) and facilitated cognition in a pediatric model (Monaco et al., 2014). These unequivocal positive findings in preclinical models of TBI combined with the favorable results of a clinical study (Öhman et al., 2001) provide the impetus for further investigation into the role of the 5-HT_{1A} receptor agonists, alone and in combination with rehabilitation, in cognitive and neural protection after brain trauma.

Several potential mechanisms for the benefits mediated by repinotan HCl, 8-OH-DPAT, and buspirone after TBI are possible. Furthermore, the mechanisms may differ for acute (i.e., early and single) vs. chronic (delayed and multiple) administration paradigms whereas early is protective and delayed is typically reparative. The protective hypothesis for acute administration is confirmed by the data showing that only the treatment at 15 minutes after TBI was effective. When treatment was delayed by 1-hr or 2-hr after TBI the effects were no different than vehicle (Cheng et al., 2007). The neuroprotective effect parallels the well documented glutamate surge that occurs within minutes after TBI and returns to basal levels by 1-hr (Faden et al., 1989; Palmer et al., 1993; Rose et al., 2002), suggesting that the benefits of acute 8-OH-DPAT treatment may be mediating its benefits, at least in part, by reducing excitotoxicity. The attenuation of excitotoxicity may have occurred by neuronal hyperpolarization via the activation of G-protein coupled inwardly rectifying K⁺ channels (Prehn et al., 1991; Andrade, 1992) and decreased glutamate release after brain trauma (De Vry et al., 1997; Mauler et al., 2001). Moreover, 5-HT_{1A} receptor agonism may exert neuroprotection by direct interaction with voltage-gated Na⁺ channels to reduce Na⁺ influx (Melena et al., 2000).

The reduction in excitotoxicity may account for the replicable decrease in hippocampal cell loss and reduced cortical lesion volume seen in the ASDH and cortical impact studies (Allesandri et al., 1999; Kline et al., 2001, 2002b, 2004a, 2007b, 2010b, 2012; Mauler et al., 2005; Olsen et al., 2012; Monaco et al., 2014) as well as the decreases in Bax, caspase-3, and TUNEL expression following diffuse brain injury (Mao et al., 2013). Delayed treatment also confers significant protection against TBI-induced hippocampal cell loss and lesion expansion (Kline et al., 2010, 2012; Olsen 2012; Monaco et al., 2014). Moreover, the protective effects can be augmented when 5-HT_{1A} receptor agonism is combined with neurorehabilitation as demonstrated by greater sparing of ChAT⁺ cells (Kline et al., 2010) and additive effects on cognitive performance in pediatric rats (Monaco et al., 2014). It is noteworthy that additive behavioral effects were only observed in the pediatric TBI model. A plausible explanation for the increased efficacy of the combination treatments in this age group is enhanced sensitivity to EE resulting from a burst of synaptogenesis and subsequent changes in synaptic efficiency associated with memory processing (Teyler et al., 1989).

Additional potential mechanisms of 5-HT_{1A} receptor agonist mediated histological and behavioral improvement may include the complex interaction with various neurotransmitter systems. It is known that the 5-HT_{1A} receptor subtype interacts with the cholinergic and dopaminergic neurotransmission (Fujii et al., 1997; Barnes and Sharp, 1999; Meneses 1999; Koyama et al., 1999; Meneses and Perez-Garcia, 2007). Cholinergic neurotransmission may have been restored after TBI as ChAT⁺ cell detection in the medial septum, which was used to gauge the integrity of cholinergic neurons projecting to the hippocampus, was protected by 8-OH-DPAT. This histological protection also correlated with enhanced MWM performance. Moreover, non-TBI studies have also shown that 5-HT_{1A} receptor agonists protect basal forebrain cholinergic neurons from NMDA neurotoxicity, which subsequently translates to reduced behavioral dysfunction (Harkany et al., 2001; Oosterink et al., 2003). Several studies have shown that dopamine (DA) neurotransmission plays a substantive role in spatial learning and memory (Kokiko and Hamm, 2007; Bales et al., 2009; Wheaton et al., 2009; Garcia et al., 2011). The alteration in dopaminergic neurotransmission after TBI

(McIntosh et al., 1994; Yan et al., 2002; Massucci et al., 2004; Wagner et al., 2005; Bales et al., 2009) may have also been restored with 5-HT_{1A} receptor agonists as they are known to increase dopamine levels in regions considered essential for cognitive processing such as the prefrontal cortex and hippocampus (Barnes and Sharp, 1999; Sakaue et al., 2000). Moreover, treatment with D₂ receptor agonists like bromocriptine or methylphenidate enhance cognitive outcome and limit hippocampal cell loss after experimental and clinical TBI (Plenger et al., 1996; Kline et al, 2000, 2002a, 2004b, Phelps et al., 2015), whereas D₂ receptor antagonists such as the antipsychotics haloperidol and risperidone negatively impact cognitive outcome (Kline et al., 2007b, 2008, Hoffman et al., 2008; Phelps et al., 2015).

Conclusion

While the findings from the reviewed studies illustrate the efficacy of 5-HT_{1A} receptor agonists after experimental brain trauma, and modestly in clinical TBI, a caveat is that these pharmacotherapies have a narrow effective dose response and an equally tight therapeutic window after acute treatment. However, these potential challenges can be overcome with well-designed clinical studies where doses and therapeutic windows are carefully determined for optimal motor and cognitive benefit. Indeed, this is a practice that should be routine for all therapeutic interventions. While all three 5-HT_{1A} receptor agonists conferred significant benefits in the preclinical studies, buspirone is the only one of the three that is currently used as a treatment for anxiety and depression, as well as other neuropsychiatric disorders, and therefore, safety and side effect profiles in humans are already known.

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Highlights

- 5-HT_{1A} receptor agonists facilitate cognitive recovery after experimental TBI
- 5-HT_{1A} receptor agonists confer neuroprotection after experimental TBI
- The benefits of 5-HT_{1A} receptor agonists are seen when administered acutely and chronically as well as in adult and pediatric models of TBI
- Some benefits of 5-HT_{1A} receptor agonists can be augmented when combined with a preclinical model of neurorehabilitation (i.e., environmental enrichment)
- The 5-HT_{1A} receptor agonist buspirone is used in other CNS disorders and thus translation to the clinic can be expedited when further studies show it to be beneficial

Table 1Summary of studies evaluating 5-HT_{1A} receptor agonists after brain trauma

Treatment Conditions	Histopathology	Behavioral/Physiological Effects	Reference
5-HT _{1A} receptor agonists: acute administration (adult male rats)			
Repinotan (BAY X 3702): i.v. infusion (0.003 or 0.01 mg/kg/hr) 15 min prior to-and-continuing for 4 hr after ASDH		<ul style="list-style-type: none"> Not applicable ↓ cortical lesion volume in repinotan-treated vs. VEH, with no dose differences 	Alessandri et al., 1999
Repinotan: i.v. infusion (10 µg/kg/hr) 5 min - 4 hr after CCI		<ul style="list-style-type: none"> ↑ spatial learning in repinotan-treated vs. VEH ↑ CA_{1,3} neuron sparing and ↓ cortical lesion in repinotan-treated vs. VEH 	Kline et al., 2001
8-OH-DPAT: single i.p. injection (0.1, 0.5, or 1.0 mg/kg) 15 min after CCI		<ul style="list-style-type: none"> Mild hypothermia induced by 8-OH-DPAT ↑ MWM performance in 8-OH-DPAT (0.5 mg/kg) vs. VEH ↑ CA₃ neuron sparing in 8-OH-DPAT (0.5 mg/kg) vs. VEH 	Kline et al., 2002b
8-OH-DPAT: single i.p. injection (0.5 mg/kg) 15 min after CCI		<ul style="list-style-type: none"> Mild hypothermia induced by 8-OH-DPAT ↑ spatial learning in 8-OH-DPAT-treated normothermia and hypothermia groups vs. VEH ↑ CA₃ neuron sparing and ↓ cortical lesion in 8-OH-DPAT vs. VEH 	Kline et al., 2004a
Repinotan: i.v. infusion (10 µg/kg or 100 µg/kg) 0, 2, and 4 hr after ASDH 4 hr continuous i.v. infusion (0.1, 1, 10, 100, 300, or 1000 µg/kg/h) beginning immediately after ASDH		<ul style="list-style-type: none"> Not applicable ↓ infarct volumes after repeated repinotan dosing, with no dose differences ↓ infarct volumes after continuous repinotan infusion in all but lowest and highest doses vs. VEH 	Mauler et al., 2005
8-OH-DPAT: single i.p. injection (0.5 mg/kg) 15 min, 1 hr, or 2 hr after CCI		<ul style="list-style-type: none"> ↑ motor and MWM improvement in the 8-OH-DPAT group treated at 15 min, but not at 1 hr or 2 hr vs. VEH Not applicable 	Cheng et al., 2007
8-OH-DPAT: single i.p. injection (0.5 mg/kg) 15 min after CCI; WAY100635 + 8-OH-DPAT: single i.p. injections (0.5 mg/kg and 0.5 mg/kg, 15 min prior and 15 min after CCI; SB269970 + 8-OH-DPAT: single i.p. injections (2 mg/kg and 0.5 mg/kg) 15 min prior and 15 min after CCI, respectively		<ul style="list-style-type: none"> ↑ spatial learning in 8-OH-DPAT and 8-OH-DPAT + WAY100635 groups vs. VEH Not applicable 	Yelleswarapu et al., 2012
8-OH-DPAT: single i.p. injection (0.5 mg/kg) 15 min after closed head weight drop injury		<ul style="list-style-type: none"> Mild hypothermia induced by 8-OH-DPAT ↑ Bcl-2 expression vs. vehicle 	Mao et al., 2013

Treatment Conditions	Histopathology	Behavioral/Physiological Effects	Reference
		<ul style="list-style-type: none"> ↓ Bax and caspase-3 expression vs. vehicle ↓ TUNEL staining (i.e., apoptosis) vs. vehicle 	
5-HT _{1A} receptor agonists: delayed and chronic administration (adult male rats)			
8-OH-DPAT: once daily i.p. injections (0.1 or 0.5 mg/kg) 24 hr after CCI for 19 d	<ul style="list-style-type: none"> ↑ motor and MWM improvement in 8-OH-DPAT 0.1 mg/kg vs. 0.5 mg/kg and VEH ↑ motor impairment in 8-OH-DPAT (0.5 mg/kg) vs. VEH 	<ul style="list-style-type: none"> Not applicable 	Cheng et al., 2008
Buspirone: once daily i.p. injections (0.01, 0.05, 0.1, 0.3, or 0.5 mg/kg) 24 hr after CCI for 19 d	<ul style="list-style-type: none"> ↑ MWM improvement in buspirone (0.3 mg/kg) vs. other doses and VEH ↑ motor impairment in buspirone 0.5 mg/kg vs. 0.3 mg/kg 	<ul style="list-style-type: none"> ↓ cortical lesion volume in buspirone (0.3 mg/kg) vs. other doses and VEH 	Olsen et al., 2012
5-HT _{1A} receptor agonists combined with environmental enrichment (adult male rats)			
8-OH-DPAT: single i.p. injection (0.5 mg/kg) beginning 15 min after CCI EE: initiated immediately after CCI and provided continuously for 19 d	<ul style="list-style-type: none"> ↑ motor performance in 8-OH-DPAT + EE and VEH+ EE vs. VEH + STD ↑ MWM performance in all treatment groups vs. VEH + STD controls 	<ul style="list-style-type: none"> ↑ CA₃ neuron sparing in all treatment groups vs. VEH + STD controls No difference in CA₃ neuron sparing in 8-OH-DPAT + EE vs. VEH + EE 	Kline et al., 2007a
8-OH-DPAT: once daily i.p. injections (0.1 mg/kg) 24 hr after CCI for 19 d EE: initiated immediately after CCI and provided continuously for 19 d	<ul style="list-style-type: none"> ↑ motor and MWM performance in all treatment groups vs. VEH + STD controls No MWM differences between 8-OH-DPAT + EE and VEH + EE 	<ul style="list-style-type: none"> ↑ CA₃ neuron sparing in all treatment groups vs. VEH + STD controls ↓ TBI-induced ChAT + cell loss in all treatment groups vs. VEH + STD controls ↓ TBI-induced ChAT + cell loss in 8-OH-DPAT + EE vs. VEH + EE 	Kline et al., 2010
Buspirone: once daily i.p. injections (0.3 mg/kg) 24 hr after CCI for 19 d EE: initiated immediately after CCI and provided continuously for 19 d	<ul style="list-style-type: none"> ↑ motor and MWM performance in all treatment groups vs. VEH + STD controls No MWM differences between buspirone + EE and VEH + EE 	<ul style="list-style-type: none"> ↑ CA₃ neuron sparing in all treatment groups vs. VEH + STD controls No difference in CA₃ neuron survival in buspirone + EE vs. VEH + EE 	Kline et al., 2012
5-HT _{1A} receptor agonists combined with environmental enrichment (pediatric male rats)			

Treatment Conditions	Histopathology	Behavioral/Physiological Effects	Reference
Exp. 1 (STD housing). Buspirone: once daily i.p. injections (0.08, 0.1, or 0.3 mg/kg) 24 hr after CCI for 16 d Exp. 2 (EE housing). Buspirone: once daily i.p. injections (0.1 mg/kg) 24 hr after CCI for 16 d. EE: initiated after weaning (PND 28) and provided continuously for 1 wk		<ul style="list-style-type: none"> • ↑ MWM performance in the buspirone (0.1 mg/kg) + STD group vs. two other doses and VEH [Exp. 1] • ↑ spatial learning in all treatment groups vs. VEH + STD controls [Exp. 2] • ↑ spatial learning in buspirone + EE vs. buspirone + STD and VEH + EE 	<ul style="list-style-type: none"> • ↓ cortical lesion volume in buspirone (0.1 mg/kg) + STD vs. VEH + STD group [Exp. 1] • ↓ cortical lesion volume in all treatment groups vs. VEH + STD [Exp. 2]
5-HT _{1A} receptor agonists: TBI patients			
Repinotan (BAY X 3702): i.v. continuous infusion (0.5, 1.25, or 2.5 mg/day) from 24 hr to 7d after TBI		<ul style="list-style-type: none"> • Good outcome or moderate disability in repinotan-treated vs. placebo controls (60% vs. 50%) • ↑ outcome in the low (0.5 mg) and high (2.5 mg) doses vs. medium (1.25 mg) • No adverse physiological effects 	<ul style="list-style-type: none"> • Not applicable
			Öhman et al, 2001