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ORIGINAL ARTICLE

Serotonin 5-HT1A receptors modulate depression-related symptoms following mild traumatic brain injury in male adult mice

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Abstract

Traumatic brain injury is a complex phenomenon leading to neurological diseases and persistent disability that currently affects millions of people worldwide. Increasing evidence shows that a wide range of patients with mild traumatic brain injury (mTBI) suffer from depression during the initial stages of injury and the post-acute stages of recovery. However, the underlying mechanisms involved in depression following mTBI are still not fully understood. The aim of this study was to determine whether serotonin 5-hydroxytryptamine-1A (5-HT1A) receptor is involved in the regulation of depression-related behaviors following mild traumatic brain injury in mice. Mice with or without mTBI received intracerebroventricular injections of 5-HT1A receptor agonist (8-OH-DPAT) or antagonist (WAY-100635) for 5 days, then animals were subjected to behavioral tests. Four behavioral tests including novelty-suppressed feeding test, forced swim test, sucrose preference test and tail suspension test were used to evaluate depression-related symptoms in animals. Our results indicated that mTBI induction increased depression-like symptoms through altering serotonin 5-HT1A receptor activity in the brain. Activation of 5-HT1A receptor by a subthreshold dose of 8-OH-DPAT led to a significant decrease in depression-like behaviors, whereas blockade of 5-HT1A receptor by a subthreshold dose of WAY-100635 resulted in a considerable increase in depression-like phenotypes in mTBI-induced mice. The major strength of the present study is that depression-related symptoms were assessed in four behavioral tests. The present study supports the idea that disturbances in the function of serotonergic system in the brain following mTBI can play an important role in the regulation of depression-related behaviors.

Keywords SSRIs · Brain injury · Serotonin · 5-HT1A · Depression · Mice

Abbreviations

TBI	Traumatic brain injury
mTBI	Mild traumatic brain injury
SSRIs	Selective serotonin reuptake inhibitors
5-HT1A	5-hydroxytryptamine-1A
aCSF	Artificial cerebral spinal fluid
SEM	mean + standard error of the mean

Introduction

Traumatic brain injury (TBI) is a complex phenomenon leading to neurological diseases and persistent disability that currently affects millions of people worldwide (Hyder et al. 2007). Studies have shown that a wide range of patients with mild traumatic brain injury (mTBI) suffer from clinical symptoms at 1-year following injury and live with long-term TBI-induced neuropsychiatric disorders (Rutherford et al. 1979; Andersson et al. 2007). Depression disorder seems to be one of the most frequent psychiatric complications among patients who experienced mTBI (Fann et al. 2000, 2001; Rapoport et al. 2003; Silver et al. 2009; Lange et al. 2011). In line with

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this view, a significant correlation has been reported between TBI and the development of depression-related behaviors during the initial stages of injury and the post-acute stages of recovery (Deb et al. 1999; Kreutzer et al. 2001; Scholten et al. 2016).

The underlying mechanisms involved in TBI-induced depression are still not fully understood. However, the serotonergic system has been shown to play an important role in the regulation of neurobehavioral abnormalities after mTBI (Kline et al. 2001, 2002, 2004, 2007; Cheng et al. 2008; Kawa et al. 2015). For instance, more recently, we and others have demonstrated the effectiveness of selective serotonin reuptake inhibitors (SSRIs), a class of antidepressant drugs, in treating depression-related symptoms following TBI (Fann et al. 2000, 2017; Yue et al. 2017; Kosari-Nasab et al. 2018a). Substantial evidence from the past decades shows that abnormalities in the serotonin (5-hydroxytryptamine: 5-HT) neurotransmitter system can contribute to the development of depressive disorders (Carr and Lucki 2010, 2011). To date, seven distinct families of serotonin receptors (5-HT 1–7 receptors) with three subtypes (a, b, and c) in each family have been identified (Carr and Lucki 2010). Although, a number of these receptors have a pivotal role in the genesis of depression-related illnesses, the 5-HT 1A receptor subtype has been the most extensively investigated therapeutic target for antidepressant therapies (Kennett et al. 1987; Robinson et al. 1990; Artigas et al. 1996; Blier and Ward 2003; Kaufman et al. 2016). This receptor is widely distributed in different brain areas such as raphe nuclei, frontal cortex, septum, amygdala, hippocampus, and hypothalamus (Kanno et al. 2015). We recently showed that mTBI induction increases depression-related symptoms in mice (Kosari-Nasab et al. 2018a). This study set out to assess whether serotonin 5-HT1A receptor is involved in the regulation of depression-related behaviors brought about by mild traumatic brain injury in mice.

Materials and methods

Animals

Male NMRI mice (25–30 g; 10–11 weeks old) were obtained from the animal house of Pasteur Institute (Karaj, Iran). Mice were maintained in a room with temperature of 23.5 ± 0.5 °C and 12 h light/12 h dark cycle. Rodent chow and fresh tap water were provided ad libitum. Mice were housed in groups of 10 per cage (42 cm × 27 cm × 15 cm). All procedures were carried out under the recommended environments of the Guide for the Care and Use of Laboratory Animals of the National Institute of Health.

Brain injury

Traumatic brain injury was induced in NMRI mice as previously described by our group. Briefly, after anesthizing, animals were exposed to a concussive head injury device (Kosari-Nasab et al. 2018a). The head was directly placed on a sponge under a guide tube (diameter: 13 mm; height: 80 cm). A brass metal weight (50 g) was vertically dropped from height down the tube to deliver the impact to the right temporal area. Then animals were allowed to recover from anesthesia on a warming pad with 37 °C. Control animals (non-mTBI) only received the same procedure without being injured.

Stereotaxic surgery

Mice were anesthetized with a combination of ketamine hydrochloride (i.p. 50 mg/kg) and xylazine (4 mg/kg) ten days after mTBI induction as previously described (Kosari-Nasab et al. 2018c). Animals were placed in a stereotaxic instrument (Stoelting Co, USA) (Bashiri et al. 2018). A 26-gauge stainless-steel guide cannula was used to implant into the left lateral ventricle (anteroposterior: −0.34 mm; mediolateral: −1.0 mm; dorsal ventricular: 2 mm). Acrylic dental cement was used to fix the guid cannula on the skull. To keep the guid cannula free from debris and clogging, a 33-gauge stainless-steel stylet was inserted into the guide cannula. There was a10 days period for recovery from the surgery. The drugs (volume: 0.3 μl) were infused in the left lateral ventricle by a 1-μl Hamilton syringe connected to polyethylene tube during 60 s to avoid the possibility of reflux (Solati and Salari 2011).

Drugs and study design

8-OH-DPAT ((±)-8-Hydroxy-2-(dipropylamino) tetralin hydrobromide; Sigma, USA) and WAY-100635 (N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl] ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt; Sigma, USA) were dissolved in artificial cerebral spinal fluid (aCSF). The doses of 8-OH-DPAT (0.1 μg/mouse) and WAY-100635 (0.1 μg/mouse), per se ineffective on the forced swim test, were chosen based on previous studies (Jain et al. 2017) and from our previous pilot experiments. Animals were randomly divided into two cohorts with six subgroups of 10 mice in each group ($n = 10$): non-mTBI+aCSF, non-mTBI+8-OH-DPAT, non-mTBI+WAY-100635, mTBI+aCSF, mTBI+8-OH-DPAT and mTBI+WAY-100635. Four behavioral experiments were performed to assess depression-related behaviors in mice and each animal was tested only once. Animals daily received an intracerebroventricular injection of 8-OH-DPAT, WAY-100635 or aCSF for 5 days. Twenty-four or forty-eight hours after the last injection of drugs or vehicle, mice were subjected to behavioral tests. A summary of the

experimental design is shown in Fig. 1. There were two experiments and each cohort was used for one experiment. In experiment 1, animals were subjected to open field, novelty-suppressed feeding test, and forced swim test, while in experiment 2, animals were subjected to open field, sucrose preference test, and tail suspension test. A total of 148 mice were used in the present study. The tests were conducted in a quiet room during the light period (between 12:00–16:00 h). Animals were kept in the room for at least 1 h before the assessment.

Depression tests

Novelty-suppressed feeding test

The novelty-suppressed feeding test was performed as previously described (Kosari-Nasab et al. 2018b). This test shows that how animals respond to a conflict between the drive to eat and the fear of venturing in a novel and open environment. Animals were deprived of food but not water for 24 h. Three food pellets were placed in the center of a white open field (40 cm × 40 cm × 20 cm). To perform test, each mouse was placed in the corner of apparatus and the latency to start feeding was recorded during 10 min. To test whether feeding differences in animals were related to differences in hunger or motivation, the mice were returned to their cage and the home-cage food intake was measured for 10 min.

Locomotor activity

To avoid the confounding effect of locomotor activity in the forced swim test and tail suspicion test, prior to each test, mice were subjected to the open field test as previously described (Salari et al. 2018). A white wooden box (40 cm length, 40 cm width, 20 cm height) with 16 squares (10 × 10 cm) was used to assess the total line crossings (defined as all four paws crossing over the line) for 5 min trial period.

Forced swim test

The forced swim test was carried out as previously described by our group (Salari et al. 2015). Briefly, animals were placed into a transparent glass cylinder with 25 cm height and 10 cm diameter, filled with fresh tap water (25 ± 1 °C; 15 cm deep). The immobility was used as an index of behavioral despair. The total duration of immobility was recorded during the last 4-min of the 6-min testing period when the mice motionlessly floated on the water without struggling. Immediately after the test, mice were dried with towels, and allowed them to be fully dried by an electric heater for 20 min.

Sucrose preference test

This behavioral test was performed as previously described elsewhere (Amani et al. 2018). To train animlas and decrease reaction to the novelty, there were two identical water bottles on the cages for 3 days. Three days later, after 18 h food and water deprivation, two bottles containing 2% sucrose solution and fresh tap water were placed on the cages for 1 h. Immediately before and after the test, the amount of the sucrose solution or water consumed was meaured by weighing the bottles. The percentage of sucrose preference was considered as an indicator of anhedonia behavior.

Tail suspension test

The tail suspension test was performed as previously described (Salari and Amani 2017). A grey wooden box (40 cm × 30 cm × 20 cm) was used to evaluate the immobility during 5-min. Each mouse was individually suspended by the tail (2 cm from the end) using a clamp. The immobility behavior was considered when the animals were motionless.

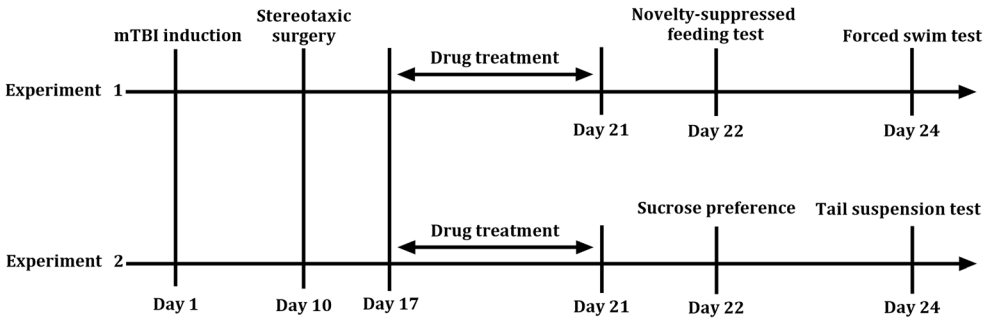

Fig. 1 Experimental design: In order to investigate the role of 5–HT1A receptor in the regulation of depression-related behaviors following mild traumatic brain injury (mTBI) in mice, animals received an intracerebroventricular administration of drugs including 5HT1A receptor agonist (8-OH-DPAT), antagonist (WAY-100635) or of vehicle (aCSF). Novelty-suppressed feeding test, forced swim test, sucrose preference test and tail suspension test were used to assess depression-like behaviors in mice. Ten animals were used in each group ($n = 10$)

Statistics

The SPSS software (IBM-Version-25) was used to analyze the data. The data were analyzed using two-way analysis of variance (ANOVA) with mTBI and drug as main factors. When there was a significant interaction, further analysis was carried out using Tukey's HSD post hoc tests for multiple comparisons. All data are presented as the mean + standard error of the mean (SEM). A p value less than 0.05 was considered statistically significant.

Results

Novelty-suppressed feeding test

A two-way ANOVA analysis revealed a main effect of mTBI [$F_{1,54} = 41.95$, $p < 0.001$] and drug treatment [$F_{2,54} = 8.84$, $p < 0.001$] for the latency to feed in the novelty-suppressed feeding test. A significant interaction was found between mTBI and drug treatment [$F_{2,54} = 12.61$, $p < 0.001$]. As illustrated in Fig. 2, *post-hoc* analysis showed that mTBI induction significantly increased the latency to feed [$p = 0.009$] in mice, as compared to non-mTBI mice. The analysis also indicated a significant decrease of the latency to feed [$p = 0.039$] in mTBI-induced mice following 8-OH-DPAT treatment. We found that WAY-100635 treatment significantly increased the latency to feed [$p = 0.013$] in mTBI-induced mice. These results show that a subthreshold dose of 8-OH-DPAT or WAY-100635 can alter depression-related behaviors in the novelty-suppressed feeding test.

Forced swim test

A two-way ANOVA indicated an overall main effect of mTBI [$F_{1,54} = 56.69$, $p < 0.001$] and drug administration [$F_{2,54} = 12.14$, $p < 0.001$] for the duration of immobility time. A significant interaction existed between mTBI and drug treatment [$F_{2,54} = 8.54$, $p = 0.001$]. As shown in Fig. 3a and b, *Post-hoc* analysis showed that mTBI induction resulted in a significant increase in the duration of immobility time [$p = 0.001$], compared to non-mTBI group. In addition, 8-OH-DPAT treatment considerably decreased the immobility time [$p = 0.025$] in mTBI-induced mice. WAY-100635 treatment also increased the immobility time [$p = 0.028$] following mTBI induction in mice. No significant change was observed in the locomotor activity of mice. These data indicate that activation or blockade of 5-HT1A receptors affects depression-like behavior in mTBI-induced mice in the forced swim test.

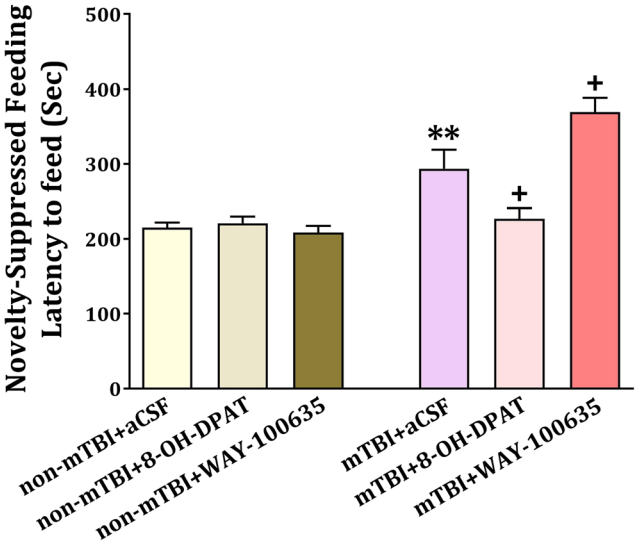

Fig. 2 Effects of intracerebroventricular administration of 5-HT1A receptor agonist (8-OH-DPAT) or antagonist (WAY-100635) following mTBI induction on depression-like behavior in the novelty-suppressed feeding test. Values are presented as mean + SEM. ($N = 10$) of latency to feed (sec). Significant differences: $^{**}p < 0.01$, compared to non-mTBI+aCSF group; $+p < 0.05$, compared to mTBI+aCSF group

Sucrose preference test

A two-way ANOVA analysis revealed a significant main effect of mTBI [$F_{1,54} = 36.57$, $p < 0.001$] and drug treatment [$F_{2,54} = 6.55$, $p = 0.003$] for the percentage of sucrose preference. A significant interaction was observed between mTBI and drug administration [$F_{2,54} = 9.89$, $p < 0.001$]. As can be seen from Fig. 4, the follow-up tests showed that mTBI induction in mice decreased the percentage of sucrose preference [$p = 0.011$] in comparison with non-mTBI animals. Moreover, WAY-100635 treatment was shown to decrease the percentage of sucrose preference [$p = 0.042$] in mTBI-induced mice. However, no significant alteration in the percentage of sucrose preference was found after 8-OH-DPAT treatment [$p = 0.098$] in mTBI-induced mice. These findings demonstrate that a subthreshold dose of 5-HT1A receptor agonist or antagonist might alter depression-related symptoms in mTBI-induced in the sucrose preference test.

Tail suspension test

A two-way ANOVA revealed an overall main effect of mTBI [$F_{1,54} = 52.16$, $p < 0.001$] and drug administration [$F_{2,54} = 11.24$, $p < 0.001$] for the immobility time. There was also a significant interaction between mTBI and drug treatment [$F_{2,54} = 12.21$, $p < 0.001$]. As shown in Fig. 5a and b, a significant increase was observed following mTBI induction in the immobility time [$p = 0.001$] in mice, as compared to non-mTBI animals. The analysis also indicated that 8-OH-DPAT treatment in mTBI-induced mice decreased the immobility time [$p =$

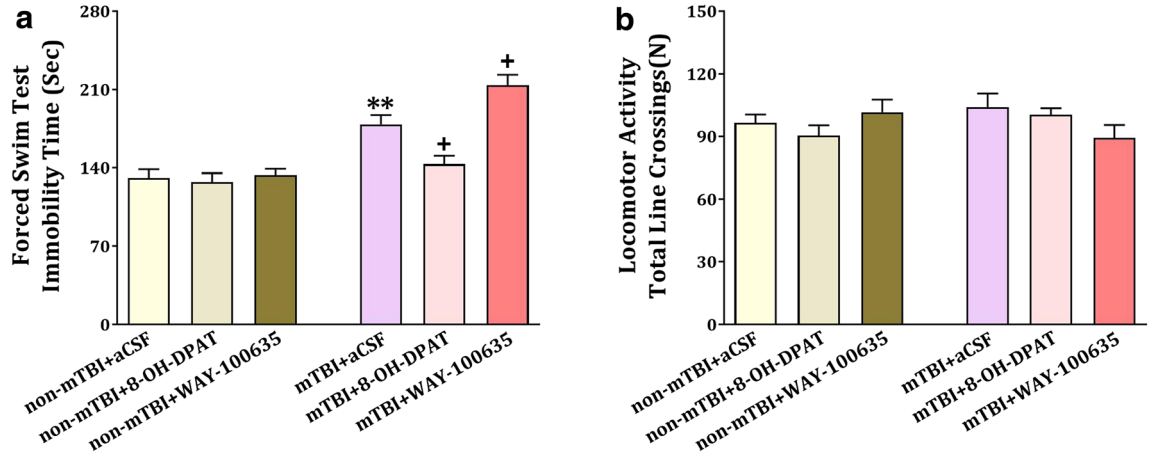

Fig. 3 Effects of intracerebroventricular administration of 5-HT1A receptor agonist (8-OH-DPAT) or antagonist (WAY-100635) following mTBI induction on depression-like behavior in the forced swim test (**a**) and locomotor activity in the open field (**b**). Values are presented as mean + SEM. ($N = 10$) of immobility time or total line crossings. Significant differences: $^{**}p < 0.01$, compared to non-mTBI+aCSF group; $+p < 0.05$, compared to mTBI+aCSF group

0.009]. In contrast, WAY-100635 treatment following mTBI induction significantly increased the immobility time [$p = 0.022$] in mice. No significant alteration was found in the locomotor activity of mice. These data indicate that a subthreshold dose of 8-OH-DPAT or WAY-100635 affects depressive-like behavior in mTBI-induced mice in the tail suspension test.

Discussion

Previous research has established that serotoninergic system is involved in affective disorders (Gardner and Boles 2011; Hale et al. 2012), hence, 5-HT1A receptors may constitute an attractive and potentially pharmacological intervention strategy for TBI-induced neuropsychiatric and neurocognitive deficits (Kline et al. 2001, 2002, 2004, 2007). In line with this, the present study demonstrated that the central activation of 5-HT1A receptors by a subthreshold dose of 8-OH-DPAT can significantly reduce depression-related symptoms following mTBI induction in mice. On the other hand, we found that the central blockade of 5-HT1A receptors by a subthreshold dose of WAY-100635 resulted in increased mTBI-induced depression-related behaviors in mice. These data clearly support the involvement of the 5-HT1A receptors in depression-related behaviors following mTBI. The role of monoaminergic system has previously been monitored following different types of TBI in rodents (Kline et al. 2001, 2002, 2004, 2007; Cheng et al. 2008). For example, a reduction of 5-HT was observed 6 days after unilateral-ventrolateral cortical lesions, while 5-hydroxyindoleacetic acid (5-HIAA; the primary metabolite of serotonin) was increased (Finklestein et al. 1983). Unilateral-focal cortical freezing was shown to bilaterally reduce 5-HT levels, whereas 5-HIAA was elevated (Pappius and Dadoun 1987). Indeed, this group later showed an increase in 5-HT synthesis in the cortex and hippocampus using the same model (Tsuiki et al. 1995). In another study, no alterations were found in 5-HT levels after TBI induction, while a reduction in the serotonin metabolite 5-HIAA was observed in the prefrontal cortex (Kawa et al. 2015). The considerable empirical research carried out within the field over the last two decades demonstrated that pharmacological targeting of 5-HT1A receptors with agonists such as repinotan HCl, 8-OH-DPAT and buspirone can be an efficacious therapeutic strategy for behavioral deficits and brain injuries following TBI (Cheng et al. 2016). Considering the fact that 5-HT1A receptors are abundantly expressed in the prefrontal cortex and hippocampus, key brain areas that are involved in depression-related disorders,

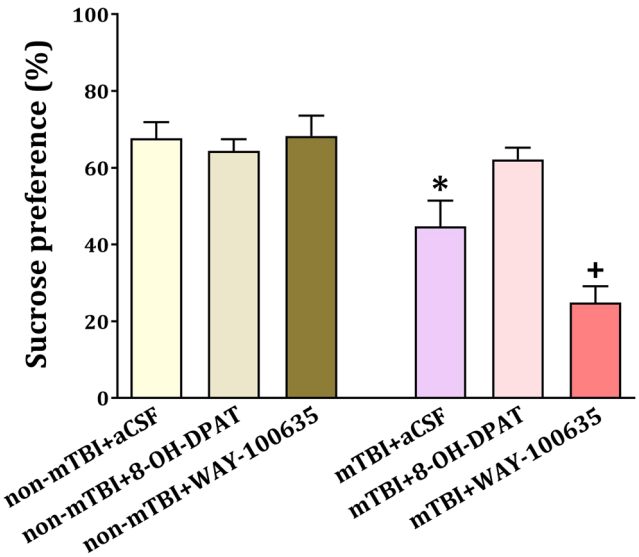

Fig. 4 Effects of intracerebroventricular administration of 5-HT1A receptor agonist (8-OH-DPAT) or antagonist (WAY-100635) following mTBI induction on depression-like behavior in the sucrose preference test. Values are presented as mean + SEM. ($N = 10$) of percentage of sucrose preference. Significant differences: $^{*}p < 0.05$, compared to non-mTBI+aCSF group; $+p < 0.05$, compared to mTBI+aCSF group

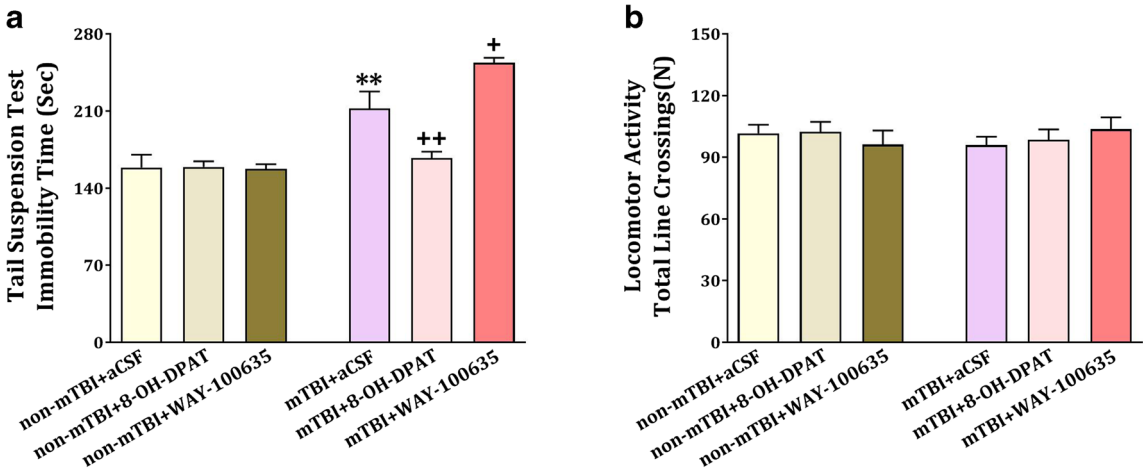

Fig. 5 Effects of intracerebroventricular administration of 5-HT1A receptor agonist (8-OH-DPAT) or antagonist (WAY-100635) following mTBI induction on depression-like behavior in the tail suspension test (**a**) and locomotor activity in the open field (**b**). Values are presented as mean + SEM. ($N = 10$) of immobility time or total line crossings. Significant differences: $^{**}p < 0.01$, compared to non-mTBI+aCSF group; $^{+}p < 0.05$ and $^{++}p < 0.01$, compared to mTBI+aCSF group

serotonin 5-HT1A receptors can be susceptible to damage induced by TBI or other central nervous system injuries (Cheng et al. 2016). For instance, it was shown that systemic 8-OH-DPAT treatment 15 min after TBI attenuated hippocampal cell loss and facilitated spatial learning in rats (Kline et al. 2002). Although, antidepressant effects of SSRIs after traumatic brain injury have been reported in humans and animal models (Fann et al. 2017; Yue et al. 2017), nevertheless, we did not find experimental evidence about the role of 5-HT1A receptor in the regulation of TBI-induced depression-like behaviors.

A considerable amount of clinical literature has established that deficits in 5-HT neurotransmission can lead to the development of major depression (Carr and Lucki 2010). Transient depressive symptoms have been shown in individuals with lowering of brain 5-HT (Moreno et al. 1999; Neumeister et al. 2004). The reduction of serotonin transporter sites was indicated in the prefrontal cortex of patients with depression disorder (Arango et al. 2002). In parallel with this finding, a significant reduction in the 5-HT1A receptor binding sites was found in deceased depressed patients (Stockmeier 2003). These data support the idea that decreased serotonin 5-HT 1A receptor activity could be a trait marker associated with major depression disorder in humans (Bhagwagar et al. 2004; Hirvonen et al. 2008). Mounting evidence demonstrates that 5-HT1A receptor agonists produce antidepressant-like effects in different behavioral tests such as forced swim test in rodents (Kostowski et al. 1992; Singh and Lucki 1993; Lucki et al. 1994; De Vry 1995; Blier and Ward 2003). In contrast, pretreatment with 5-HT1A antagonists have been shown to block the effects of 5-HT1A agonists in the forced swim test (Detke et al. 1995). In addition, the chronic treatment of 5-HT1A receptor agonist, 8-OH-DPAT, was found to increase neurogenesis and survival of neuronal cells in the hippocampus (Banasr et al. 2004). Several lines of preclinical data suggest that 5-HT1A receptor is a major regulator of 5-HT transmission in the brain because the presynaptic 5-HT1A receptor is involved in the regulation of neuronal discharge and negative feedback, whereas the postsynaptic 5-HT 1A receptor is abundantly expressed in the most important regions of the limbic system like hippocampus (Carr and Lucki 2010) which are involved in depression-related behaviors. Rodent studies have confirmed that activation of postsynaptic 5-HT1A receptors leads to behavioral changes similar to those of conventional antidepressant drugs (Lucki 1991). Interestingly, activation of 5-HT1A receptors has been shown to mediate the effects of antidepressants on neurogenesis in the hippocampus (Gould 1999; Malberg et al. 2000). Since postsynaptic 5-HT1A receptors are very important to the antidepressant response, it is conceivable that 8-OH-DPAT treatment reduced depression-like behaviors in mTBI-induced mice via postsynaptic 5-HT1A receptors. Taken together, our results support the idea that activation of 5-HT1A receptors could be an attractive and potentially efficacious therapeutic target to attenuate depression-related symptoms induced by mTBI. The major strength of the present study is that depression-related symptoms were assessed in four behavioral tests.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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