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Research report

The blockade of the serotoninergic receptors 5-HT5A, 5-HT6 and 5-HT7 in the basolateral amygdala, but not in the hippocampus facilitate the extinction of fear memory

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ABSTRACT

Extinction is the learned inhibition of retrieval. It is the mainstay of exposure therapy, which is widely used to treat drug addiction, phobias and fear-related pathologies such as post-traumatic stress disorder. The serotonin (5-HT) system is positioned to modulate the extinction circuitry via ascending 5-HT projections that innervate certain brain structures including the hippocampus and the basolateral amygdala (BLA). The most recently described serotoninergic receptors 5-HT5A, 5-HT6, 5-HT7 affect different memory processes and so are putative therapeutic targets for disorders related to cognition; however, their role in the extinction of contextual fear conditioning (CFC) has not been studied yet. Here we investigate the role of these receptors in the CA1 region of the hippocampus and the BLA in the extinction of CFC. For this, male rats were implanted with cannulae in the CA1 or in the BLA region through which they received immediately or 3 h after extinction training of CFC infusions of SB699551 (10 μg/side), 5-HT5A antagonist; WAY-208466 (0.04 μg/side), 5-HT6 agonist; SB-271046A (10 μg/side), 5-HT6 antagonist; AS-19 (5 μg/side), 5-HT7 agonist; SB-269970 (5 μg/side), 5-HT7 antagonist. After 24 h, animals were submitted to a 3 min extinction test. Results show that the infusion immediately after extinction training of 5-HT5A, 5-HT6 and 5-HT7 antagonists, and 3 h after extinction training of 5-HT5A and 5-HT7 antagonists in the BLA region, but not in CA1, facilitates the extinction of CFC memory.

1. Introduction

Fear memories are essential to survival. However, their expression out of context can lead to anxiety, phobias or to the incapacitating condition known as post-traumatic stress disorder (PTSD) [1]. One of the main options of treatment for these disorders is exposure therapy, which is based on the extinction learning of fear memories [2,3].

Extinction is the inhibition of retrieval of a previously acquired memory through overlapping of a new memory [4]. One way to study the extinction memory is through the Pavlovian fear conditioning in which subjects are presented to a neutral conditioned stimulus (CS), paired with an aversive unconditioned stimulus (US), leading to a conditioned fear response (CR). The continuous presentation of the CS without the US will lead to the gradual decrease, or extinction, of the CR [2,3]. It is well documented that fear extinction process requires the CA1 region of the hippocampus and the basolateral amygdala (BLA) [5–7].

The serotonin (5-HT) system is positioned to modulate the extinction circuitry via ascending 5-HT projections arising from midbrain raphe nuclei that innervate certain brain structures including the BLA, the hippocampus, the medial prefrontal cortex and the bed nucleus of the stria terminalis [8]. Research has largely focused on the role of 5-HT1A, 5-HT2 and 5-HT3 serotoninergic receptors on fear extinction [9]. However, the role of other 5-HT receptors on the extinction have not been broadly explored. For example, the most recently described serotoninergic receptors 5-HT5A, 5-HT6 and 5-HT7 affect different mechanisms of memory in several behavioral tasks, such as water maze, novel object recognition, T-maze, hole-board and fear conditioning [10–13], however, their roles on the extinction of contextual fear conditioning (CFC) have not been studied so far. Furthermore, recent

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studies have demonstrated an involvement of these receptors in pathophysiological processes, such as Alzheimer's disease and schizophrenia, thus highlighting their therapeutic possibilities [14–21].

The clinical application of extinction reinforces the need to better understand its processes, especially those related to its modulation by pharmacological agents [2,5,9,22]. Serotonergic dysfunctions are known to be implicated in the pathogenesis of anxiety related pathologies [23] and there is a general endorsement by clinical practice guidelines of selective serotonin reuptake inhibitors (SSRIs) as first-line agents in treating these disorders [24], howsoever, the mechanisms through which the therapeutic effect takes place and if it is related to extinction have not been properly explored.

Therefore, here we investigate whether the most recently described serotoninergic receptors, 5-HT5A, 5-HT6 and 5-HT7 in the CA1 region of the hippocampus and in the BLA participate on the consolidation of extinction of CFC, through local administration of agonists and antagonists of these receptors. Two different time points of infusion were chosen in order to investigate the time of action of these receptors in the consolidation of extinction. The time points of infusion were chosen based on previous works which have shown that memory formation and cAMP rat hippocampal production in passive avoidance learning task have been detected immediately or 3 h following training [25] and that these three serotoninergic receptors in the CA1 region of the hippocampus are involved in the consolidation and/or reconsolidation of CFC memory when agonists or antagonists were infused immediately or 3 h after consolidation or reconsolidation of CFC memory [26].

2. Materials and methods

2.1. Animals

Male *Wistar* rats (CrlCembe:WI; 3 months-old, 300–330 g) purchased from Centro de Modelos Biologicos Experimentais (CeMBE) of the Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, were housed four to a cage and kept with free access to food and water, under a 12-h light/dark cycle (lights on at 7:00 a.m.) and temperature of the animals' room maintained at 22–23 °C. All experimental procedures were performed in accordance with Animal Committee on Ethics in the Care and Use of Laboratory Animals of the Pontifical Catholic University of Rio Grande do Sul.

2.2. Surgery

Under deep anesthesia (75 mg/kg ketamine plus 10 mg/kg xylazine; intraperitoneally) animals were bilaterally implanted with stainless steel 22gauge guide cannulae aimed 1 mm above the CA1 region of the dorsal hippocampus (anterior, −4.2 mm; lateral, ± 3.0 mm; ventral, −1.8 mm; from bregma) or the BLA (anterior, −2.4 mm; lateral, ± 5.1 mm; ventral, −7.5 mm; from bregma) and fixed to the skull with dental acrylic [27]. Animals could recover from surgery for 7 days and then were handled once a day for 3 consecutive days before experimental procedures.

2.3. Contextual fear conditioning apparatus

The CFC apparatus was a chamber within a ventilated sound-attenuating box (Panlab®, Barcelona, Spain) with aluminum walls (35 × 35 × 35 cm), a transparent plastic front lid and a floor of parallel stainless-steel grid bars connected to a device to deliver the foot shocks. The chamber was cleaned with 70% ethanol and completely dried between the sessions for each animal. Freezing behavior (defined as the absence of all visible movement except for respiratory-related movements) was scored and converted into a percentage of time.

2.4. Behavioral procedure

On Day 1 (CFC training session), animals were placed into the conditioning chamber for 2 min. Then three electrical foot shocks (0.5 mA, 2 s) were delivered with a 30 s interval between them. Animals were removed from the conditioning chamber 30 s after the last foot shock and placed back in their home cages. On Day 2, animals were placed in the same conditioning chamber for a 20 min CFC extinction training (Ext Tr), without the foot shocks. On Day 3, animals were placed once more in the same apparatus for a 3 min extinction test (Ext Test) without foot shocks. After Ext Tr, animals were randomly divided in vehicle (Veh) or drug groups. Drug administration into the CA1 region of the hippocampus or into the BLA occurred immediately or 3 h after the extinction session.

2.5. Pharmacological treatments

The animals were gently restrained by hand, and an infusion needle (30 gauge) was fitted tightly into the guides, extending 1 mm from the tip of the guide cannulae. The infusion needle was attached to a polyethylene tubing (PE10, Plastics One) connected to a 10 µl Hamilton syringe, and infusion was performed at a rate of 1.0 µl/60 s. The infusion needle was left in place for one additional minute after the infusion in order to minimize backflow, and then carefully withdrawn and placed on the other side. All treatments were bilateral. The drugs were freshly dissolved in sterile saline 0.9% and the drugs and doses used were SB-699551 (10 µg/side), 5-HT5A antagonist [16,28]; WAY-208466 (0.04 µg/side), 5-HT6 agonist [26]; SB-271046A (10 µg/side), 5-HT6 antagonist [29]; AS-19 (5 µg/side), 5-HT7 agonist [30]; SB-269970 (5 µg/side), 5-HT7 antagonist [28,31], infused in a volume of 1.0 µl per side into the CA1 region and 0.5 µl per side into the BLA. The drug doses were chosen according to previous studies [26,32–34].

2.6. Cannulae placements

Correct cannulae placements were verified 2 to 4 days after the end of the last behavioral procedure. Animals were infused with a 4% methylene blue solution over 30 s into the CA1 region of the dorsal hippocampus (1.0 µl/side) and BLA (0.5 µl/side) at the coordinates mentioned above. After 30 min, the animals were sacrificed by excess anesthesia and the brains were removed and kept in 10% formalin. The extension of the spread of the dye was considered to represent an estimation of the amount of drug infused. Cannula placement was considered correct when the spread was ≤ 1 mm from the intended infusion site; this occurred in 98% of the animals.

2.7. Statistical analysis

The obtained data were expressed as mean ± SEM and analyzed statistically by unpaired *t*-test or one-way ANOVA followed by Bonferroni test using GraphPad Prism software. Differences between groups below $p < 0.05$ were considered statistically significant.

3. Results

3.1. Participation of the 5-HT5A receptors on the extinction of the contextual fear conditioning memory

As shown in Fig. 1, animals that received the antagonist of the 5-HT5A receptors, SB-699551 (10 µg/side), into the CA1 region of the hippocampus immediately (Fig. 1A) or 3 h (Fig. 1B) after the extinction training (Ext Tr), exhibited similar levels of freezing to the Veh group during the extinction test (Ext Test) (unpaired *t*-test: Fig. 1A, SB-699551-Veh $t_{(10)} = 1.583$, $p > 0.5$; Fig. 1B, SB-699551-Veh $t_{(11)} = 0.267$, $p > 0.5$). On the other hand, animals that received infusions of SB- 699551 (10 µg/side) into the BLA immediately (Fig. 1C)

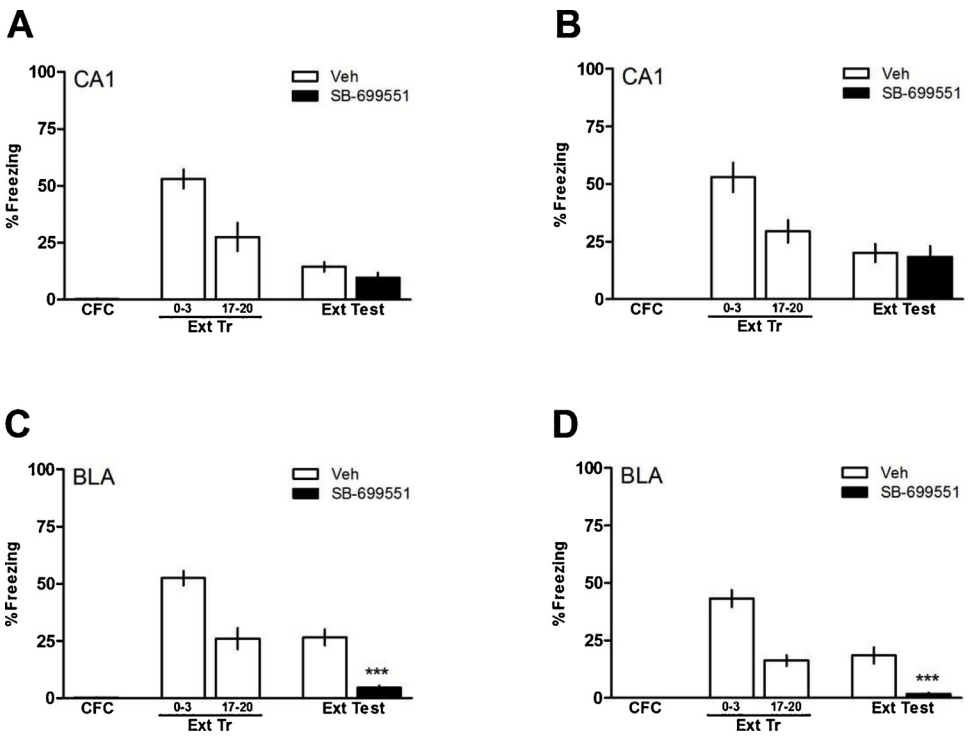

Fig. 1. Participation of the 5-HT5A receptors of the CA1 region of the hippocampus and BLA on the extinction of CFC. Animals were trained in the CFC task. After 24 h, animals were submitted to an extinction training session (Ext Tr) and received bilateral intra-CA1 infusion immediately (A) or 3 h (B) later or intra-BLA infusion immediately (C) or 3 h (D) later of Veh (saline 0.9%) or SB-699551 (10 μg/side). Twenty-four hours later, animals were subjected to a 3-min Ext Test. The figure shows the percentage of time spent freezing in the first 2 min of the CFC, in the first 3 min and last 3 min of the Ext Tr and in the Ext Test. Data are presented as mean ± SEM of the percentage of time spent freezing. ***p < 0.001 for SB-699551 vs. Veh group on the extinction test. Unpaired *t*-test; n = 6–9 animals per group.

or 3 h (Fig. 1D) after the Ext Tr, exhibited lower levels of freezing than the Veh group during the Ext Test (unpaired *t*-test: Fig. 1C, SB-699551-Veh $t_{(16)} = 6.206$, $p < 0.001$; Fig. 1D, SB-699551-Veh $t_{(14)} = 4.738$, $p < 0.001$). These results indicate that the blockade of 5-HT5A receptors in the BLA but not in the CA1 region of the hippocampus modulates the extinction of the CFC memory facilitating this process.

3.2. Participation of the 5-HT6 receptors in the extinction of the contextual fear conditioning memory

As shown in Fig. 2, animals that received the agonist of the 5-HT6 receptors, WAY-208466 (0.04 μg/side) or the antagonist of the 5-HT6 receptors, SB271046 (10 μg/side), intra-CA1 immediately (Fig. 2A) or 3 h (Fig. 2B) after the Ext Tr exhibited similar levels of freezing as the Veh group during the Ext Test (one-way ANOVA: Fig. 2A, $F_{(2,15)} = 1.075$, Veh-WAY-208466 ($p > 0.05$), Veh-SB-271046 ($p > 0.05$); Fig. 2B, $F_{(2,18)} = 0.04851$, Veh-WAY-208466 ($p > 0.05$),

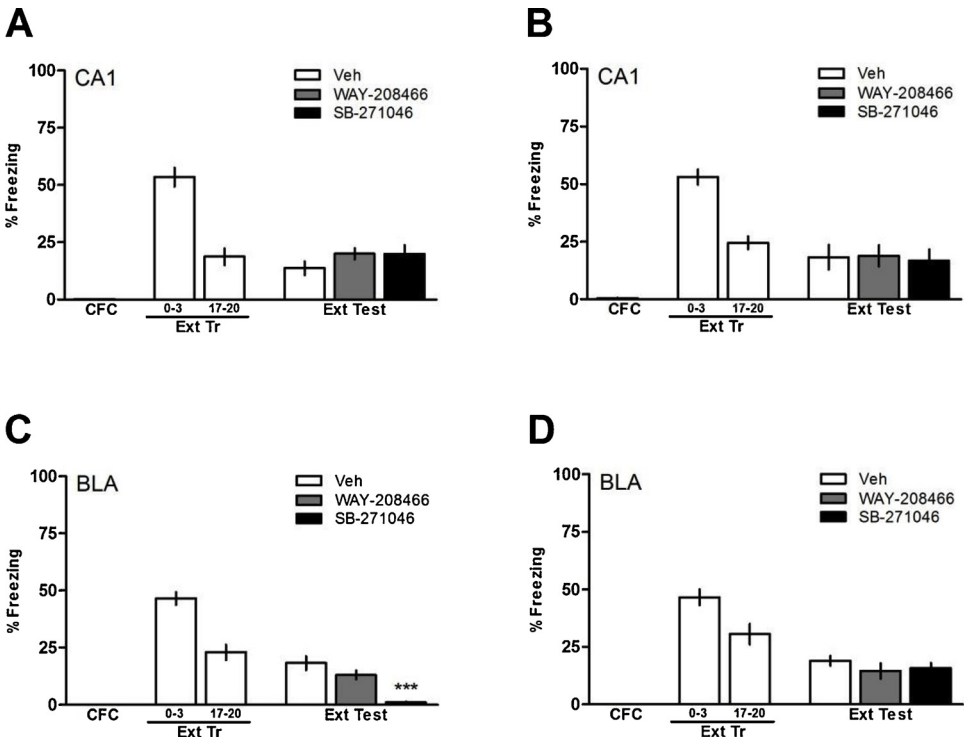

Fig. 2. Participation of the 5-HT6 receptors of the CA1 region of the hippocampus and BLA on the extinction of CFC. Animals were trained in the CFC task. After 24 h, animals were submitted to an extinction training session (Ext Tr) and received bilateral intra-CA1 infusion immediately (A) or 3 h (B) later or intra-BLA infusion immediately (C) or 3 h (D) later of Veh (saline 0.9%), WAY-208466 (0.04 μg/side) or SB-271046 (10 μg/side). Twenty-four hours later, animals were subjected to a 3-min Ext Test. The figure shows the percentage of time spent freezing in the first 2 min of the CFC, in the first 3 min and last 3 min of the Ext Tr and in the Ext Test. Data are presented as mean ± SEM of the percentage of time spent freezing. ***p < 0.001 for SB-271046 *vs.* Veh group on the extinction test. Bonferroni-test after one-way ANOVA; n = 5–8 animals per group.

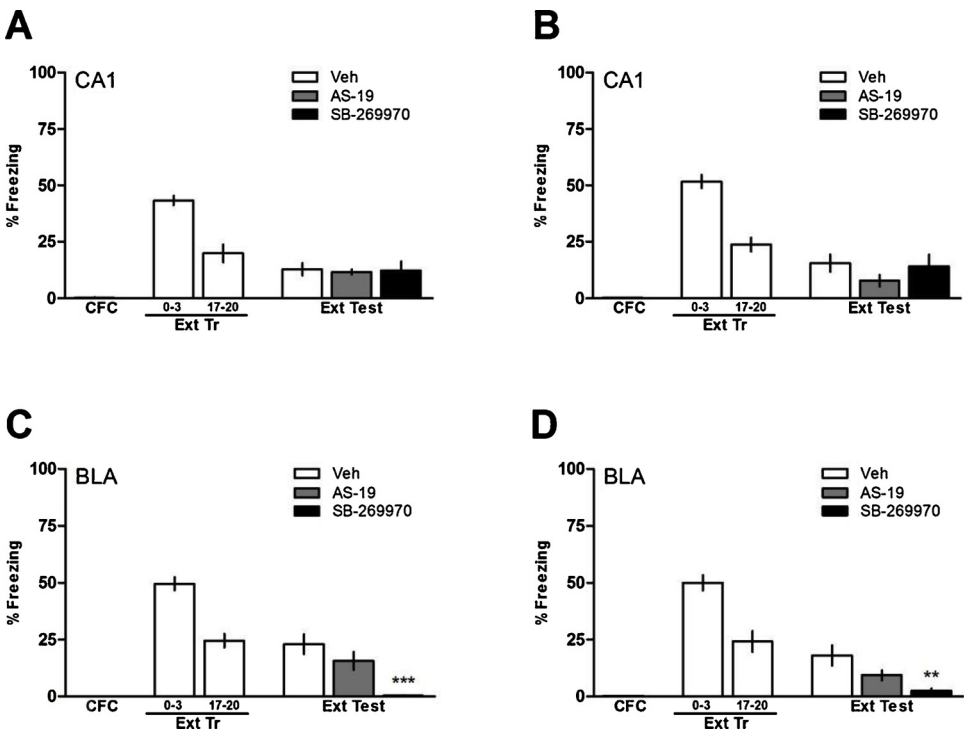

Fig. 3. Participation of the 5-HT7 receptors of the CA1 region of the hippocampus and BLA on the extinction of CFC. Animals were trained in the CFC task. After 24 h, animals were submitted to an extinction training session (Ext Tr) and received bilateral intra-CA1 infusion immediately (A) or 3 h (B) later or intra-BLA infusion immediately (C) or 3 h (D) later of Veh (saline 0.9%) or AS-19 (5 μg/side) or SB-269970 (5 μg/side). Twenty-four hours later, animals were subjected to a 3-min Ext Test. The figure shows the percentage of time spent freezing in the first 2 min of the CFC, in the first 3 min and last 3 min of the Ext Tr and in the Ext Test. Data are presented as mean ± SEM of the percentage of time spent freezing. $^{**}p < 0.01$ and $^{***}p < 0.001$ for SB-269970 *vs.* Veh group on the extinction test. Bonferroni-test after one-way ANOVA; n = 5–9 animals per group.

VehSB-271046 ($p > 0.05$)). Likewise, animals that received WAY-208466 (0.04 μg/side) intra-BLA immediately (Fig. 2C) or 3 h (Fig. 2D) after the Ext Tr exhibited similar levels of freezing as the Veh group during the Ext Test (one-way ANOVA: Fig. 2C, $F_{(2,19)} = 16.11$, Veh-WAY-208466 ($p > 0.05$); Fig. 2D, $F_{(2,16)} = 0.774$, Veh-WAY-208466 ($p > 0.05$)). Although, animals that received SB-271046 (10 μg/side), into the BLA, immediately (Fig. 2C) after the Ext Tr exhibited lower levels of freezing than the Veh group during the Ext Test (one-way ANOVA: Fig. 2C, $F_{(2,19)} = 16.11$, Veh-SB-271046 ($p < 0.001$)). When the SB-271046 (10 μg/side) was infused 3 h after the extinction training (Fig. 2D) the animals exhibited similar levels of freezing as the Veh group during the Ext Test (one-way ANOVA: Fig. 2D, $F_{(2,16)} = 0.774$, Veh-SB-271046 ($p > 0.05$)). These results indicate that the blockade of 5-HT6 receptors in the BLA but not in the CA1 region of the hippocampus modulates the extinction of the CFC memory facilitating this process.

3.3. Participation of the 5-HT7 receptors in the extinction of the contextual fear conditioning memory

As demonstrated in Fig. 3, animals that received the agonist of the 5-HT7 receptors, AS-19 (5 μg/side) or the antagonist of the 5-HT7 receptors, SB269970 (5 μg/side), intra-CA1 immediately (Fig. 3A) or 3 h (Fig. 3B) after the Ext Tr exhibited similar levels of freezing as the Veh group during the Ext Test (one-way ANOVA: Fig. 3A, $F_{(2,19)} = 0.02506$, Veh-AS-19 ($p > 0.05$), Veh-SB269970 ($p > 0.05$); Fig. 3B, $F_{(2,22)} = 1.036$, Veh-AS-19 ($p > 0.05$), Veh-SB-269970 ($p > 0.05$)). Likewise, animals that received AS-19 (5 μg/side), intra-BLA immediately (Fig. 3C) or 3 h (Fig. 3D) after the Ext Tr exhibited similar levels of freezing as the Veh group during the Ext Test (one-way ANOVA: Fig. 3C, $F_{(2,21)} = 9.501$, Veh-AS-19 ($p > 0.05$); Fig. 3D, $F_{(2,20)} = 7.589$, Veh-AS-19 ($p > 0.05$)). However, animals that received the SB-269970 (5 μg/side), into the BLA, immediately (Fig. 3C) or 3 h (Fig. 3D) after the Ext Tr exhibited lower levels of freezing than the Veh group during the Ext Test (one-way ANOVA: Fig. 3C, $F_{(2,21)} = 9.501$, Veh-SB-269970 ($p < 0.001$); Fig. 3D, $F_{(2,20)} = 7.589$, Veh-SB269970 ($p < 0.01$)).

These results indicate that the blockade of 5-HT7 receptors in the BLA but not in the CA1 region of the hippocampus modulates the extinction of the CFC memory facilitating this process.

4. Discussion

Concerning whether the CA1 and BLA serotoninergic 5-HT5A, 5-HT6 and 5-HT7 receptors play a role in extinction of CFC memory, our findings show that the blockade of these receptors in the BLA but not in the CA1 region of the hippocampus favors the consolidation of extinction of CFC memory in different time frames. The BLA is a crucial brain structure in processing aversive memory and extinction [1]. Modulation and storage are not necessarily mutually exclusive functions, and many studies believe that the BLA exerts both [25,35,36]. It operates to a certain extent in parallel with the CA1 region in memory processing [1,37], but there is evidence that BLA promotes learning, such as inhibitory avoidance, independently of hippocampus by increasing the emotional value of the training [38]. Animals treated with 5,7-dihydroxytryptamine (a serotonin-depleting agent) injected into the BLA showed increased duration of social interaction time, suggestive of reduced anxiety-like behavior, reduced acquisition of fear during conditioning and reduced fear retrieval [39].

5-HT transporter knockout (5-HTTKO) mice have increased extracellular 5-HT levels and an impairment on retrieval of fear extinction in comparison to wild-type controls [40,41]. In addition, 5-HTTKO mice showed anomalous dendritic spine density in the principal neurons of the BLA [42]. Furthermore, serotonergic terminal lesions in the amygdala induced by local injection of 5,7-dihydroxytryptamine attenuated memory-dependent fear accessed by conditioned fear and enhanced the retrieval of extinction memory [43]. In summary, these studies support the negative correlation between 5-HT levels and consolidation of extinction seen in our results, seeing that the infusion of 5-HT5A, 5-HT6 and 5HT7 antagonists in the BLA was able to reduce freezing expression, thus facilitating the consolidation of extinction. Furthermore, the results obtained don't seem to be related to dysfunctions in locomotor and exploratory activity due to the drugs used, as it has already been accessed by previous studies [16,44–48].

Despite the important role played by the CA1 region of the hippocampus in the consolidation of extinction [1,5] and the substantial

expression of 5-HT5A, 5-HT6 and 5-HT7 receptors in this region [13,49–51] the infusion of both agonist and antagonist of these receptors do not affect this process. Schmidt et al (2017) showed the role of these receptors in the consolidation and/or reconsolidation of CFC memory with the same drugs, doses, time points and infusion procedure done in this study [26]. Liu et al. (2015) injected WAY-208466 (1.5, 3 and 6 μg/rat) intra dorsal hippocampus to study depressive-like behaviors [52], Perez-García & Meneses (2008) used AS-19 (1 μg/side) intra CA1 to verify the role of the 5-HT7 in autoshaping learning and cAMP accumulation [53] and while Jafari-Sabet et al. (2019) infused AS-19 (0.25, 0.5 and 1 μg/mouse) to better elucidate the cross state-dependent learning between 8-OH-DPAT and/or AS-19 and Muscimol [54]. Other than that, most studies of above-mentioned 5-HT receptors agonists and antagonists have been using peripheral administration only or infused in other brain regions, such as prelimbic cortex [46,55], BLA [56,57], dorsal raphe nucleus, locus coeruleus, basal forebrain or dorsolateral tegmental nucleus [58] and lateral ventricle [59]. Therefore, there is no previous information which may indicate its specific effects when administered directly into the CA1 region in CFC extinction memory. This data suggests that these receptors in the CA1 region of the hippocampus might hold an influence on many emotional-related memories but is not specifically related to the consolidation of extinction memory itself, at least it was not seen using this specific drugs, doses and time points.

Further research is clearly necessary to better explore the manipulation of the serotoninergic system, once studies on 5-HT receptors are still hampered by the lack of selective binders, especially agonists. The 5-HT5A receptor still lacks an acknowledged agonist, while 5-HT7 agonists such as AS-19 used in this experiment appear to have low *in vivo* agonist potencies [30,51]. This might explain the absence of agonist responses in both structures in this study, but it is also important to highlight that the lack of effect could be related to the drug doses. In addition, more studies should be conducted to better elucidate the function of the 5-HT5A, 5-HT6 and 5-HT7 serotoninergic receptors in the CA1 region and perhaps other hippocampal regions during extinction consolidation.

The 5-HT5A receptor is supposed to hold an inhibitory role, since the deletion of this receptor's gene results in an unexpected increase in inhibitory 5-HT1A currents [34]. According to Kassai et al. (2012), SB-699551-A, a 5HT5A antagonist, presented an anxiolytic-like influence in behavior, while A843277, another 5-HT5A antagonist, showed an antidepressant-like property [16]. Also, Yamazaki et al. (2014, 2015) demonstrated that 5-HT5A antagonists could ameliorate memory and cognitive impairments associated with age and scopolamine-induced memory deficit in animal models of schizophrenia [19,20]. It was also described that the systemic administration of 5-HT5A antagonist impaired short- and long-term memory in an associative learning task [10]. Here we demonstrate that the administration of a 5-HT5A antagonist in the BLA immediately or 3 h after extinction session leads to an improvement of extinction memory of CFC, unlike what is seen in reconsolidation and in CA1 region of the hippocampus, for instance, in which the blockade of 5-HT5A caused an impairment in the reconsolidation of CFC memory [26]. This pattern highlights the fact that consolidation, reconsolidation and extinction have some similarities but the time course, the brain structures and molecular mechanisms involved might differ [1]. Still, considering that so far there are no selective 5-HT5A receptors agonists, further studies with selective 5-HT5A compounds in behavioral tasks are necessary [60].

The 5-HT6 receptor is almost exclusively located in the central nervous system, which is a significant indicator of their important role in the regulation of several brain activities, such as cognition and memory [12,61]. Our results demonstrate that the administration of 5-HT6 antagonist in the BLA immediately after extinction session led to an improvement on extinction memory, which corroborate previous works showing that 5-HT6 receptor antagonists enhanced cognitive properties in different memories tasks in aged rat [11] and with scopolamine-induced deficits [62–66]. It also broadens interesting possibilities of drug development for the treatment of Alzheimer's disease [67] and schizophrenia [68]. However, there are discrepant results in the literature related to the 5-HT6 receptor and memory [26,69–71]. One of the possible explanation to the paradoxical effects of 5-HT6 receptor agonists and antagonists is that the agonists act on the few 5-HT6 receptors located directly on the cholinergic and glutamatergic neurons, receiving only a little tonic serotonergic input, whereas the antagonists may act on the 5-HT6 receptor located in the upstream inhibitory GABAergic interneurons, receiving 5-HT input that disinhibits acetylcholine and glutamate release [66]. It is also important to consider that these differences could be related to the use of different antagonists, experimental conditions and instruments for measuring behavior [72]. Furthermore, the 5-HT6 receptor antagonist has a more time-limited impact than the 5-HT5A and 5-HT7 receptors antagonists.

The 5-HT7 receptor is one of the most recently discovered receptor subtypes for 5-HT. The similar expression and distribution of mRNA and proteins for 5-HT7 receptors in the limbic structures supports the notion that they play a role in the regulation of functions like mood, memory processing, and emotional association with memory [73]. Indeed, Schmidt and collaborators verified that the blockade of 5-HT7 receptors facilitated the consolidation and reconsolidation of CFC memory [26]. In the present study, the findings of 5-HT7 receptors were similar to those demonstrated here for 5-HT5A, indicating that the antagonism of 5-HT7 receptors improves the extinction of the CFC memory on the BLA but not the CA1 region of the hippocampus. It has been suggested that the amygdala may be an important sensorimotor interface for both context- and tone-dependent fear conditioning [13] and is consistent with the hypothesis that the 5-HT7 receptor ligands can also improve contextual learning and memory through a mechanism independent of the hippocampus [21]. Furthermore, the highest density of this receptor in the hippocampus was observed in the CA3 region and the dentate gyrus, areas known to be involved in the response to changes in the environment [74]. 5-HT7 activation in the CA3 area enhances hyperpolarization induced cation current [75], which decreases excitatory post-synaptic potentials thus reducing neuronal excitability. The blockade of this inhibitory effect of the 5-HT7 receptor may explain the beneficial effects of its antagonists on cognition and memory [76]. Another possible explanation is that the 5-HT7 receptors may interact functionally with other 5-HT receptors and change the valence of their behavioral actions. Stiedl et al. (2015) described interactions between 5-HT7 and 5-HT1A receptors, including 5-HT1A autoreceptors, which may alter the function of both [77]. In addition, hippocampal infusion of 8-OHDPAT, a dual 5-HT1A and 5-HT7 receptor agonist, impaired passive avoidance through hippocampal 5-HT1A receptor activation, while 5-HT7 receptor appears to facilitate memory processes in a broader cortico-limbic network and not the hippocampus alone [30].

5. Conclusion

The antagonism of 5-HT5A, 5-HT6 and 5-HT7 receptors in BLA is beneficial for the consolidation of extinction memory in different timepoints, an effect not seen in the CA1 region of the dorsal hippocampus. Specific time-related effects of serotonin on extinction unfold new prospects regarding the operation of this system and widens the range of possible therapeutic approaches, begetting new evidences in memory research that encourage new lines of investigation.

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