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Research report

The histamine H_3-receptor inverse agonist Pitolisant improves fear memory in mice

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HIGHLIGHTS

- Pitolisant is a novel H_3 receptor inverse agonist used to treat narcoleptic patients.
- We show that Pitolisant improved consolidation in the fear conditioning task in mice.
- Dizocilpine impaired consolidation and reconsolidation in this task.
- Pitolisant completely reversed the memory deficits induced by dizocilpine.
- Pitolisant may be useful to treat cognitive deficits in humans.

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ABSTRACT

Numerous studies have demonstrated that brain histamine plays a crucial role in learning and memory and histamine H_3 receptor inverse agonists (H_3R inverse agonists) have been proposed to treat cognitive disorders. Pitolisant (BF2.649, 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride) was the first H_3R inverse agonist that has been tested in human trials and is well tolerated. The present study investigated whether Pitolisant (0.625–20 mg/kg, i.p.) improves consolidation and reconsolidation processes in the fear conditioning task in female C57BL/6J mice. We also tested whether Pitolisant reverses memory deficits induced by the non-competitive N-methyl-D-aspartate (NMDA) antagonist dizocilpine (MK-801). Our results indicate that post-training systemic injections of Pitolisant facilitated consolidation of contextual fear memory and reversed amnesia induced by an i.p. injection of 0.12 mg/kg dizocilpine. In addition, none of the doses of Pitolisant we have tested after reactivation (reexposure to the context in which training took place 48 h earlier) affected reconsolidation, whereas dizocilpine disrupted it. However, Pitolisant was able to reverse the deficit in reconsolidation induced by 0.12 mg/kg dizocilpine. The present results are the first demonstration that Pitolisant is effective in improving consolidation processes in the fear condition task and add further evidence to its potential for treating cognitive disorders.

1. Introduction

Pitolisant (BF2.649 or tiprolisant) is a promising new medication that enhances wakefulness and reduces excessive daytime sleep in patients suffering from narcolepsy [1,2]. Animal studies have demonstrated that the wake promoting effects of Pitolisant result from an increased activity of histaminergic neurons in the brain [1,3]. Histamine is an important biogenic amine involved in many cognitive functions such as vigilance, learning and memory. Interestingly, several drugs that activate histaminergic transmission have cognitive enhancing properties and can potentially reverse learning disorders associated with Alzheimer's disease [4]. Pitolisant is a selective inverse agonist for the histamine H_3 receptor and enhances histaminergic activity in the brain of mice [3]. However, its effects on memory processes have poorly been investigated and its therapeutic potential to alleviate cognitive problems in humans is unknown.

Neurons that synthetize histamine are exclusively located in the tuberomamillary nucleus (TMN), a region located in the posterior part of the hypothalamus. Histaminergic neurons send their fibers to almost all brain areas including the amygdala and the nucleus basalis magnocellularis (NBM), two cortical areas involved in memory processes essential to consolidate adverse events [5,6]. Histamine is synthesized from L-histidine by the enzyme histidine decarboxylase (HDC) and its effects are mediated by four histamine receptors in the brain: the histamine H_1, H_2, H_3 and H_4 receptors (H_1R, H_2R, H_3R and H_4R). H_1R and H_2R

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are mainly postsynaptic excitatory receptors whereas H_3R and H_4R are inhibitory receptors coupled to $G_{i/o}$ proteins [7,8]. H_3R were originally described as presynaptic autoreceptors located on histaminergic axons and their activation inhibits the release and synthesis of histamine [9]. Nevertheless, later studies have found that most H_3R are inhibitory heteroreceptors located on non-histaminergic axons. Their activation can inhibit the synthesis and release of various neurotransmitters such as gamma-aminobutyric acid (GABA), acetylcholine, glutamate, dopamine and norepinephrine [4,7,10].

Pharmacological manipulations that increase brain histaminergic activity generally facilitate memory consolidation in various learning tasks (see [11] for a review). Consolidation refers to the process that stabilizes a memory trace after acquisition of a new information. Immediately after the acquisition phase, the memory trace is fragile and labile and is gradually converted into a lasting trace that is stable over time [12]. During the consolidation phase, memories are susceptible to disruption when amnesic treatments are applied shortly after learning such as electroconvulsive shocks [13]. Glutamate transmission and in particular N-methyl-D-aspartate (NMDA) receptors play a critical role in consolidation of fear memories since the blockade of NMDA receptors impairs memory consolidation [14] whereas NMDA receptor activation facilitates consolidation [15]. In addition, other neurotransmitter systems like histamine can facilitate the consolidation of memories [16]. The systemic injection of H_3R inverse agonists improve consolidation in the inhibitory avoidance test [17], the social memory test [18,19], the two-trail place recognition task [20] and the fear conditioning task [14].

Memory formation is a dynamic process. When a memory is briefly reactivated, it can return in a labile state and requires then a process of stabilization to be able to return in long term memory again and not be forgotten [21,22]. During this memory process called reconsolidation, the duration of exposure to the original learning context is an important determinant of subsequent memory processing. A short exposure to the context results in reconsolidation whereas a longer exposure leads to extinction [23]. Nader et al. [24] showed that memory reconsolidation can be disrupted in rats when a protein-synthesis inhibitor is injected in the amygdala after a brief reactivation of the fear memory. As for consolidation, NMDA receptors play an important function in reconsolidation processes [25]. The blockade of NMDA receptors with dizocilpine impairs memory reconsolidation in the fear conditioning task [14,26]. Inversely, activation of these receptors with the partial agonist D-cycloserine facilitates reconsolidation in the same task [26]. Other neurotransmitter systems such as β-adrenergic signaling could be implicated in reconsolidation. It has been shown that the β-adrenergic receptor antagonist propranolol injected systemically disrupted reconsolidation of appetitive memories [27]. Additionally, propranolol and the β-adrenergic receptor agonist isoproterenol microinjected into the amygdala respectively impaired and enhanced reconsolidation in the fear conditioning task [28]. The role of histamine transmission is practically unknown in reconsolidation processes. In our laboratory, we have previously demonstrated that thioperamide can block the deficit in reconsolidation produced by dizocilpine in the fear conditioning test [14].

Only one study has investigated whether Pitolisant has cognitive enhancing properties. Ligneau et al. [3] have shown that the intraperitoneal (i.p.) administration of Pitolisant improves working memory measured with the two-trial object recognition task in mice. The purpose of the present study is to further investigate the effects of Pitolisant on memory processes using the fear conditioning test. A first set of experiments examined whether i.p. injections of Pitolisant can improve consolidation of a contextual fear memory in mice. Therefore, different doses of Pitolisant were injected immediately after the training session alone or in combination with dizocilpine. A second set of experiments tested the effects of various doses of Pitolisant on reconsolidation. Two days after acquisition of the fear memory, mice were briefly reexposed to the learning context (reactivation session) and were then injected with Pitolisant alone or in combination with dizocilpine.

2. Materials and methods

2.1. Animals

For the whole study, 252 naïve female C57BL/6J mice, born in the central animal farm of the University of Liège, were employed. One week before the start of each experiment, mice were individually housed in transparent polycarbonate cages (15 cm $L \times 33$ cm $W \times 13$ cm H). Water and food (standard pellets, Carfil Quality BVDA, Oud-Turnhout, Belgium) were available *ad libitum* during the whole study. At the beginning of the experiment, mice were 10–12 weeks old and weighed 18–22 g. The animal room was maintained on a 12 h light–dark cycle (lights on at 8.00 am) with an ambient temperature of 20–22 °C. All procedures were carried out during the light phase between 9:00 am and 2:00 pm. All experimental protocols have been approved by the ethic committee on animal experimentation of the University of Liège in accordance with the recommendations of the European Community Council for the Ethical Treatment of Animals (EEC Council Directive No. 86/609) and the Guidelines approved by the European Commission (No. 2007/526/CE).

2.2. Drugs

Dizocilpine maleate (MK-801) was purchased from Sigma–Aldrich (Bornem, Belgium) and Pitolisant maleate (BF2.649) from Tocris Bioscience (Bristol, United Kingdom). Substances were prepared daily and dissolved in sterile 0.9% saline in order to deliver final doses of 0.12 mg/kg dizocilpine and 0.625, 1.25, 2.5, 5, 10 or 20 mg/kg Pitolisant. All solutions were administered through the intraperitoneal (i.p.) route in a volume of 10 ml/kg (0.01 ml/g body weight). A control treatment consisted of an equal volume of saline solution.

2.3. Behavioral apparatus

An automated rodent conditioning system (MED Associates Inc., St. Albans, VT, USA, ENV-307W-TH) was used to study contextual fear conditioning of each mice (for a detailed description see Charlier and Tirelli [14]). Conditioned freezing was measured in two identical conditioning chambers (24 cm $L \times 20$ cm $W \times 21.5$ cm H) enclosed in sound-attenuating cubicles with ventilation fans (emitting a background noise of 69 dB). The walls and the ceiling were constructed of clear Plexiglas. The front was a horizontally hinged door. The floor of each chamber consisted of 23 stainless steel rods (3 mm in diameter, 8 mm apart). The chambers were illuminated by a single house light, mounted in the top centre of the right wall, and were cleaned with 10% ethanol after utilization. A software program controlled a shock scrambler that delivered the footshock (US) through the floor rods. Stimuli presentation and data recording from both boxes were controlled by a MED-PC program *via* a specific interface. Freezing was defined as a total absence of movements (except those related to respiratory movements) and was measured in terms of percent time spent in that posture during the experimental session.

2.4. Experimental procedure

The conditioning procedure was similar to that of previous studies [14,29]. Briefly, before the start of each experiment, mice were habituated to handling and injected with a saline solution. Prior to each experimental session, mice were weighed in the colony room and returned into their individual home cage. Then, mice each left in their individual home cage were placed on a cart and conducted to the testing room. Mice were tested less than 3 min later. Immediately thereafter, mice were injected with the appropriate treatment, replaced in their home cage and returned to the colony room.

The contextual fear conditioning comprised two basic phases: the training session (acquisition) and the memory retention test session (recall). Training consisted in placing the mouse in the test chamber (whose context provided the CS) where it was left undisturbed for 2 min (pre-shock period). After this period, the mouse received two moderate footshocks (28 s apart, 2 s duration, 0.25 mA intensity; US). Then, it remained in the chamber for an additional 30 s (post-shock period). Freezing posture was recorded during both pre- and post-shock periods. On the retention test session, which took place 72 h after the training session, the mouse was replaced in the training chamber for a 5 min test period during which conditioned freezing was recorded. In the experiments studying reconsolidation, a reactivation session was performed 48 h after the training session and 24 h prior to the retention session. This session consisted in exposing the mouse to the training chamber for a short period of 2 min during which freezing was recorded without any footshock being delivered.

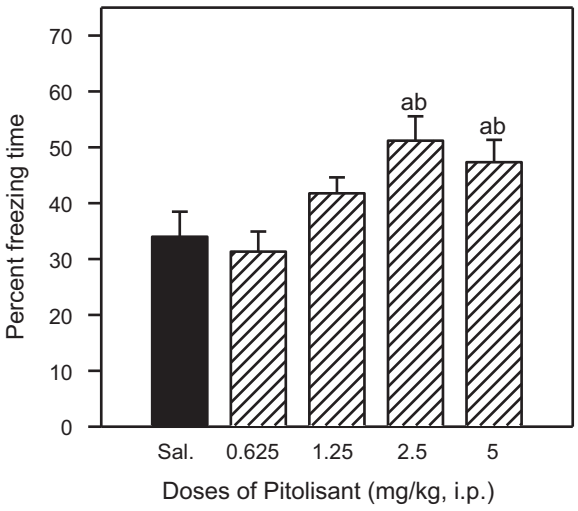

Fig. 1. Effects of the histamine H_3R inverse agonist Pitolisant on consolidation of a contextually-conditioned fear memory in C57BL/6J mice. Mice were trained under two foot-shocks that induced reliable freezing behavior. The drug (at one of the four doses) or saline ($n = 12$) was injected i.p. immediately after completion of training. The retention test took place 72 h later. Memory performance on the retention test was expressed in terms of percent time spent freezing. Columns represent means ± standard error of the mean (vertical bars). (a) Value significantly different from that of the saline group at $p < 0.015$ (2.5 mg/kg) or $p < 0.048$ (5 mg/kg), (b) Value significantly different from that of the 0.625 mg/kg Pitolisant group at $p < 0.01$ (2.5 mg/kg) or $p < 0.05$ (5 mg/kg), as yielded by post-ANOVA Newman–Keuls tests.

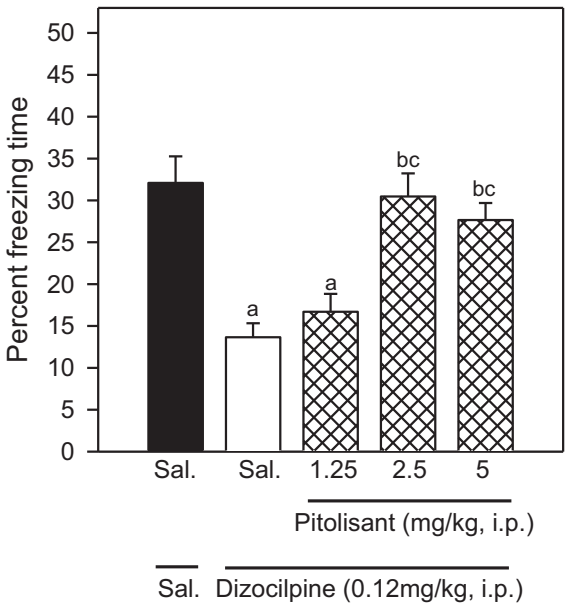

Fig. 2. Effects of Pitolisant on dizocilpine-induced deficit in consolidation of a contextually-conditioned fear memory in C57BL/6J mice. Mice were trained under two foot-shocks that induced reliable freezing behavior. Dizocilpine (0.12 mg/kg) and Pitolisant (at one of the three possible doses) were injected i.p. a few seconds apart and immediately after training. The control groups received saline twice or dizocilpine plus saline ($n = 12$). The retention test was performed 72 h later. Memory performance was expressed in terms of percent time spent freezing. Columns represent means ± standard error of the mean (vertical bars). (a) Value significantly different from that of the saline-plus-saline group (all comparisons at $p < 0.001$), (b) value significantly different from that of the dizocilpine-plus-saline group (all comparisons at $p < 0.001$), (c) value significantly different from that of the group treated with dizocilpine (0.12 mg/kg) and Pitolisant (1.25 mg/kg) (all comparisons at $p < 0.001$), as yielded by post-ANOVA Newman–Keuls tests.

The psychopharmacological effects of Pitolisant were revealed on the retention test session, the drugs being injected immediately after the training session in the consolidation experiments (Experiments 1 and 2) or after the reactivation session in the reconsolidation experiments (Experiments 3 and 4). In Experiment 1, five independent groups of 12 mice were each injected with saline, 0.625, 1.25, 2.5 or 5 mg/kg Pitolisant. In Experiment 2, where the potential effects of Pitolisant on dizocilpine-induced amnesia were evaluated, four groups of 12 mice were injected with 0.12 mg/kg dizocilpine a few seconds before receiving saline, 1.25, 2.5 or 5 mg/kg Pitolisant, a fifth group receiving saline twice. Experiment 3 comprised six groups of 10 mice that received saline, 1.25, 2.5, 5, 10 or 20 mg/kg Pitolisant. Finally, Experiment 4, which evaluated the effects of Pitolisant on dizocilpine-induced deficit in reconsolidation, involved five groups of 12 mice that were injected with 0.12 mg/kg dizocilpine prior to receiving saline, 2.5, 5, 10 or 20 mg/kg Pitolisant, a fifth group being injected with saline twice.

2.5. Data analysis

The reliability of the effects was evaluated using fixed model one-way analyses of variance (ANOVA), in which the mean scores of conditioned freezing (percent time spent in freezing posture) on the retention test were considered as the dependent variable and the experimental groups as the independent variable. In case of significant effect, relevant between mean differences were assessed using the Newman–Keuls *post hoc* test. The data and analyses of freezing scores on the training and reactivation sessions were not presented in Section 3, the corresponding levels being graphically and statistically undistinguishable across groups. Significance was always set at $p < 0.05$.

3. Results

3.1. Effect of Pitolisant on consolidation

Fig. 1 shows the effects of Pitolisant on consolidation of a contextual fear conditioning (Experiment 1). The freezing values derived from the groups having received the two highest doses of this H_3R inverse agonist (2.5 or 5 mg/kg) were significantly greater than that of the saline group, from which the effect induced by the two lower doses of Pitolisant did not statistically differ. This profile of effects was supported by the one-way ANOVA ($F_{(4,55)} = 4.71$, $p < 0.002$) and subsequent Newman–Keuls *post hoc* tests.

3.2. Effect of Pitolisant on dizocilpine-induced deficit in consolidation

Fig. 2 presents the interactive effects of dizocilpine and Pitolisant administered directly after the training session on conditioned freezing consolidation (Experiment 2). The values derived from the two groups that received 2.5 or 5 mg/kg Pitolisant after dizocilpine were significantly greater than that of the group treated with dizocilpine plus saline, reaching the levels of the control group that received saline twice. This pattern of effects was revealed by the one-way ANOVA ($F_{(4,55)} = 12.02$, $p < 0.000$) and Newman–Keuls tests (2.5 mg/kg at $p < 0.001$ or 5 mg/kg at $p < 0.001$). Furthermore, the decrease in memory performance in mice treated with dizocilpine plus saline was significant at $p < 0.001$. This effect was also observed in the group injected with dizocilpine plus 1.25 mg/kg Pitolisant at $p < 0.001$, indicating that this low dose was unable to reverse the amnesia induced by the antagonist of the NMDR.

3.3. Effect of Pitolisant on reconsolidation

Fig. 3 represents conditioned freezing on the retention test in mice having received one of the five doses of Pitolisant (1.25–20 mg/kg) immediately after the reactivation session (Experiment 3). There was no significant change in memory performance in any of the five groups, which exhibited similar values. This absence of efficacy is corroborated by the one-way ANOVA ($F_{(5,54)} = 0.34$, $p > 0.88$).

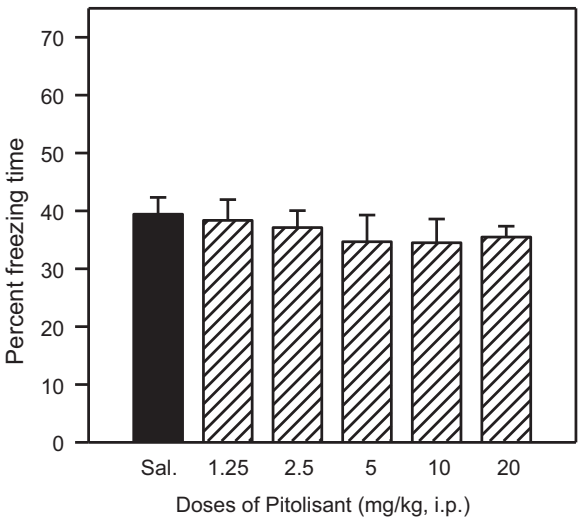

Fig. 3. Effects of Pitolisant on reconsolidation of a contextually-conditioned fear memory in C57BL/6J mice. Mice were trained under two foot-shocks that induce reliable freezing behavior. Forty-eight hours later, Pitolisant (at one of the five possible doses) or saline were given i.p. immediately after a reactivation session ($n = 10$). The retention test was conducted 24 h later and memory performance was expressed in terms of percent time spent freezing. Columns represent means ± standard error of the mean (vertical bars). There were no statistical significant drug effects.

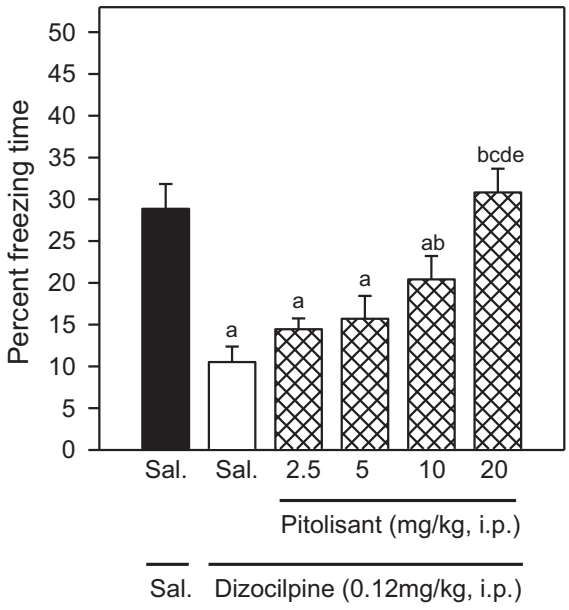

Fig. 4. Effects of Pitolisant on dizocilpine-induced deficit in reconsolidation of a contextually-conditioned fear memory in C57BL/6J mice. Mice were trained under two foot-shocks that induced reliable freezing behavior. Forty-eight hours later, mice received i.p. injections of dizocilpine (0.12 mg/kg) and Pitolisant (at one of the four possible doses) a few seconds apart and immediately after a reactivation session. The control groups received saline twice or dizocilpine plus saline ($n = 12$). The retention test was performed 24 h later and memory performance was expressed in terms of percent time spent freezing. Columns represent means ± standard errors of the mean (vertical bars). (a) Value significantly different from that of the saline-plus-saline group (all comparisons at $p < 0.05$), (b) value significantly different from that of the dizocilpine-plus-saline group (all comparisons at $p < 0.05$), (c) value significantly different from that of the group treated with dizocilpine (0.12 mg/kg) and Pitolisant (2.5 mg/kg) at $p < 0.001$, (d) value significantly different from that of the group treated with dizocilpine (0.12 mg/kg) and Pitolisant (5 mg/kg) at $p < 0.001$, (e) value significantly different from that of the group treated with dizocilpine (0.12 mg/kg) and Pitolisant (10 mg/kg) at $p < 0.05$, as yielded by post-ANOVA Newman–Keuls tests.

3.4. *Effect of Pitolisant on dizocilpine-induced deficit in reconsolidation*

Fig. 4 depicts the interactive effects of dizocilpine and Pitolisant administered after the reactivation session on conditioned freezing measured on the retention test (Experiment 4). The value derived from the group treated with the highest dose of Pitolisant (20 mg/kg) right after dizocilpine (0.12 mg/kg) was significantly greater than that of all other groups treated this NMDR antagonist and reached the levels of the control group that had received saline twice. This profile of effects was supported by the one-way ANOVA ($F_{(5,66)} = 10.75$, $p < 0.001$) and Newman–Keuls tests (all comparisons at $p < 0.001$). Interestingly, 10 mg/kg Pitolisant induced an intermediate effect. Specifically, the values of this group was significantly lower than that of the group treated with saline twice ($p < 0.05$) while being higher than that of the group injected with dizocilpine plus saline ($p < 0.05$). Note that the lowest doses of Pitolisant (2.5 and 5 mg/kg) failed to reverse the memory reconsolidation deficit induced by dizocilpine (respectively $p > 0.26$ and $p > 0.31$).

4. Discussion

The current study replicates our previous findings showing that the blockade of H_3R improves consolidation processes in the fear conditioning task [14]. In agreement with what we had observed with thioperamide, the i.p. administration of Pitolisant after the conditioning trial facilitated consolidation of contextual fear memory. In addition, post-training injection of the NMDA antagonist dizocilpine impaired consolidation, an effect that was completely reversed by the administration of Pitolisant. In other experiments, Pitolisant, dizocilpine or the combination of these drugs were injected after the reactivation session to evaluate whether Pitolisant affects reconsolidation mechanisms. Pitolisant did not alter reconsolidation when injected alone but it was able to completely prevent the deficit in reconsolidation induced by dizocilpine.

Ligneau et al. [3] demonstrated that Pitolisant improves working memory in the two-trial object recognition task in mice. The present study shows that i.p. injections of Pitolisant also enhance consolidation in the contextual fear conditioning paradigm. These results are in agreement with previous experiments demonstrating that the systemic injection of H_3R inverse agonists facilitates memory consolidation in the passive avoidance task [17], the social memory test [18,19] and the two-trail place recognition task [20]. Together, these data indicate that H_3R inverse agonists have beneficial effects on different aspects of memory but the neuronal mechanisms underlying these effects are still unclear. Previous studies in rats have demonstrated that the basolateral amygdala (BLA) and the hippocampus are involved in the consolidation of adverse events such as fear memory [5,30,31]. However, these brain regions are unlikely to be the sites through which i.p. injections of thioperamide and Pitolisant improve consolidation processes in the fear conditioning task (Charlier and Tirelli [14]; present results). Thioperamide microinjected in the BLA impairs consolidation of fear memory in rats [32]. Procognitive effects are observed in the fear conditioning paradigm when H_3R of the BLA or the hippocampus are activated rather than blocked [32–34], an observation opposite to the results obtained after systemic injections of thioperamide or Pitolisant (Charlier and Tirelli [14]; present results).

Many studies have shown that the NBM plays a central role in memory consolidation of information acquired in the fear conditioning task [6,35]. Benetti et al. [36] found that thioperamide microinjected into the NBM improves consolidation of contextual fear memory in rats. These results are in agreement with our experiments showing that systemic administration of thioperamide or Pitolisant facilitates consolidation in C57BL/6J mice (Charlier and

Tirelli [14]; present results). Evidence suggests that H_3R inverse agonists improve memory consolidation in the fear conditioning paradigm through the activation of H_2R in the NBM [36]. The local administration of H_3R inverse agonists such as thioperamide into the NBM increases histamine release in this brain region through the blockade of H_3 autoreceptors located on histaminergic fibers [37]. Moreover, the procognitive effects of thioperamide on consolidation of fear memory were prevented by the intra-NBM administration of the H_2R antagonist zolantidine [36]. Therefore, Benetti et al. [36] have proposed that thioperamide improves consolidation of contextual fear memory because this compound increases histamine release in the NBM through the blockade of H_3 autoreceptors. According to their hypothesis, increased levels of endogenous histamine activate postsynaptic H_2R in the NBM. The results of the present study show that Pitolisant has the same procognitive effects on consolidation processes in the fear conditioning task than thioperamide [14]. Thus, the neuronal mechanisms proposed by Benetti et al. [36] to explain the action of thioperamide on contextual fear memory might also be valid for the results with have obtained with Pitolisant. In the future, it might be interesting to investigate whether the procognitive effects of systemic injections of thioperamide and Pitolisant on consolidation can be reversed by the intracerebral injection of an H_2R antagonist in the NBM.

The current study shows that Pitolisant improves consolidation, but not reconsolidation, when injected alone in the fear conditioning task, an observation consistent with our previous study conducted with thioperamide [14]. Other studies have found that certain experimental manipulations exert differential effects on consolidation and reconsolidation processes in the fear conditioning test and suggest that these mnemonic processes are qualitatively and quantitatively distinct [38]. For example, thioperamide administered locally in the BLA impairs consolidation, but not reconsolidation, of contextual fear memory in rats [32,39]. Moreover, Lee et al. [31] have reported a double dissociation in the molecular mechanisms that underlie consolidation and reconsolidation in the contextual fear conditioning paradigm by infusing antisense oligodeoxynucleotides into the hippocampus of rats. They have demonstrated that brain-derived neurotrophic factor (BDNF), but not the transcription factor Zif268, is required for consolidation. Conversely, Zif268, but not BDNF, is recruited for reconsolidation. These results suggest that we have reported differential effects of H_3R inverse agonists (thioperamide and Pitolisant) on consolidation and reconsolidation in the fear conditioning task probably because distinct neuronal mechanisms underlie these mnemonic processes. Consequently, our data indicate that histaminergic pathways essentially contribute to neuronal circuits involved in consolidation of aversive events.

In agreement with our previous study conducted with thioperamide [14], Pitolisant blocked the deficits in consolidation and reconsolidation induced by dizocilpine (Experiments 2 and 4). The neuronal mechanisms that mediate the ability of thioperamide and Pitolisant to improve memory consolidation when injected alone are not necessarily the same than those involved in their ability to prevent dizocilpine-induced amnesia. In addition to the mechanism proposed above to explain how Pitolisant ameliorates consolidation *per se*, other neural mechanisms might be involved in its actions on amnesia produced by dizocilpine. Histamine can potentiate NMDA receptors by interacting with an allosteric site located on these receptors [40]. In cultured hippocampal cells, histamine enhanced NMDA receptor-mediated transmission [41] and this histamine–NMDA interaction could mediate the ability of histamine to reverse dizocilpine-induced amnesia [42]. Since NMDA receptors play an important function in both consolidation and reconsolidation processes, it is possible that thioperamide and Pitolisant reversed dizocilpine-induced amnesia in our studies through direct activation of NMDA receptors by histamine released by these H_3R inverse agonists. It is important to note that elevated levels of histamine in the brain and H_3R inverse agonists can confer neuroprotection in various animal models of neurotoxicity (see Bhowmik et al. [43] for a review). Thus, the ability of Pitolisant to attenuate dizocilpine-induced amnesia in our experiments could also result from a neuroprotective action.

In summary, the present study demonstrates that Pitolisant improves consolidation in the fear conditioning task in mice. Additionally, this histaminergic drug reverses the deficits in consolidation and reconsolidation induced by dizocilpine. However, reconsolidation processes were not affected when Pitolisant was injected alone immediately after the reactivation session. As suggested by Tiligada et al. [4], our results indicate that Pitolisant could be useful for the treatment of cognitive deficits associated with Alzheimer's disease. Together, the present study highlights the need to further investigate the procognitive effects of Pitolisant in animal models and to test whether this compound could be useful in the treatment of cognitive deficits in human clinical trials.

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