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DIFFERENTIAL EFFECTS OF HISTAMINE H_3 RECEPTOR INVERSE AGONIST THIOPERAMIDE, GIVEN ALONE OR IN COMBINATION WITH THE N-METHYL-D-ASPARTATE RECEPTOR ANTAGONIST DIZOCILPINE, ON RECONSOLIDATION AND CONSOLIDATION OF A CONTEXTUAL FEAR MEMORY IN MICE

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Abstract—Albeit there is no doubt that histamine and its H_3 receptors participate in several aspects of learning and memory, such as memory consolidation, nothing is known about their potential involvement in memory reconsolidation. On the basis of previous reports of pro-cognitive effects of histamine H_3 receptor inverse agonists (which augment histamine release), we investigated to what extent the most representative of them, thioperamide, is able to facilitate reconsolidation of a contextually-conditioned fear memory in C57BL/6J mice. We also examined the effects of thioperamide on the stark disruptive effect that the non-competitive N-methyl-D-aspartate (NMDA) antagonist dizocilpine (MK-801) typically exerts on both reconsolidation and consolidation. Post-training systemic injections (i.p.) of thioperamide facilitated consolidation at 10 and 20 mg/kg and reversed amnesia induced by an i.p. injection of 0.12 mg/kg dizocilpine at 5, 10 and 20 mg/kg. Importantly, none of the five thioperamide doses (2.5, 5, 10, 20 and 30 mg/kg) given right after reactivation (reexposure to the context in which training took place 48 h earlier) affected reconsolidation, whereas all similarly given doses of dizocilpine (0.03, 0.06 and 0.12 mg/kg) disrupted it more or less equally. By contrast, thioperamide was able to unambiguously reverse the deficit in reconsolidation induced by 0.12 mg/kg dizocilpine at 10 and 20, but not 5 mg/kg. This is the first demonstration of an involvement of the interactive articulation between histamine and NMDA receptors in the mechanisms of memory reconsolidation, which seems to be indifferent to an increase of brain histamine per se. The results suggest a qualitatively different participation of histaminergic signalling in the mechanisms of reconsolidation and consolidation. The precise circuits within which these interactions take place are yet to be identified.

Key words: consolidation, reconsolidation, thioperamide, dizocilpine, histamine H3 receptor, NMDA receptor.

Histamine is secreted by neurons exclusively located in the hypothalamic tuberomammillary nucleus (TMN) projecting to various brain regions such as striatum, cortex, septum, hippocampus and amygdala. Its synthesis is realized by the enzyme histidine decarboxylase (HDC) and its actions on the brain are mediated mainly by the metabotropic receptors H_1, H_2, and H_3. H_1 and H_2 receptors are primarily located post-synaptically, their activation leading to excitatory effects. H_3 receptors, initially described as presynaptic auto-receptors regulating the release of histamine, can also function as hetero-receptors inhibiting the synthesis and release of various neurotransmitters such as GABA, dopamine, noradrenalin, serotonin or acetylcholine. The TMN also receives neurons from many brain areas such as the prefrontal cortex (glutamate), the basal forebrain (acetylcholine), the rostral raphe (serotonin), the ventrolatérale preoptic area (GABA) or the hypothalamus (orexin), which can provide excitatory or inhibitory inputs (Brown et al., 2001; Haas et al., 2008; Benarroch, 2010; Passani and Blandina, 2011).

Histamine is involved in many physiological and behavioural functions, including locomotion, thermoregulation, epilepsy, circadian rhythms, arousal and sleep, water and food intake, nociception, stress and anxiety and drug reward. There is also convincing evidence for a deep participation of histamine in the mechanisms of learning and memory (Haas et al., 2008; Benarroch, 2010; Berlin et al., 2011). More precisely, an increasing number of recent animal-model studies using not only classical imidazole-based but also several newly-synthesized non-imidazole histamine H_3 inverse agonists strongly suggest a promoting action of histamine release in several processes or aspects of learning and memory, like working memory, reference memory, acquisition or retrieval/recall (Huang et al., 2004; Gemkow et al., 2009; Bardgett et al., 2010; Brioni et al., 2011).

Consolidation is another major learning-and-memory process that has also received some attention in histamine psychopharmacology. This cognitive phenomenon refers to a process during which a labile trace, emerging after acquisition, is gradually stabilized and converted into a lasting trace resistant to any amnesic treatment (McGaugh and Roozendaal, 2009). Systemic, i.c.v. and intracerebral administrations of histamine or agents activating the release of histamine (H_3 receptor inverse agonists like thioperamide, A-304121 or ABT-239) often strengthen memory consolidation in aversively-reinforced instrumental tasks (De Almeida and Izquierdo, 1988; Prast et al., 1996; Flood et al., 1998; Ghi et al., 2001; Orsetti et al., 2001, 2002; Fox et al., 2003, 2005; Bernaerts et al., 2004; Da

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Abbreviations: ANOVA, analyses of variance; NMDA, N-methyl-D-aspartate; US, unconditioned stimulus.

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Silva et al., 2006). Additionally, histamine H_3 inverse agonists are able to reverse memory consolidation deficits induced by well-known amnesic agents, such as scopolamine and the N-methyl-D-aspartate (NMDA) antagonist dizocilpine, suggesting the participation of a functional interaction between histamine neurotransmission and both the acetylcholine or glutamate systems in the mechanisms of consolidation (Molinengo et al., 1999; Orsetti et al., 2001; Bernaerts et al., 2004).

More recently, memory reconsolidation has become the focus of cognitive and psychobiological studies. During this memory process, the brief retrieval of memory trace, stored in long-term memory, can induce the return to a labile state which is subject to change and requires de novo protein synthesis to occur (Przybyslawski and Sara, 1997; Tronson and Taylor, 2007). Recent studies have shown that the duration of exposure is an important determinant of subsequent memory processing, short exposure to the original learning context resulting in reconsolidation and longer exposure to the same context leading to extinction (Suzuki et al., 2004). Reconsolidation and consolidation share certain mechanisms occurring within the amygdala and the hippocampus, other mechanisms being specific to each process (Alberini, 2005; Tronson and Taylor, 2007; Nader and Einarsson, 2010). For instance, in the basolateral amygdala, protein synthesis is necessary for both processes, while the expression of the transcription factor CCAAT enhancer binding protein beta (C/EBPbeta) is essential only for reconsolidation; in the hippocampus, protein synthesis and C/EBPbeta are required only for consolidation, but not for reconsolidation, of a passive-avoidance fear-memory (Alberini, 2005). In others studies, both consolidation and reconsolidation did not occur without amygdala de novo protein synthesis (Nader and Einarsson, 2010). Lee and colleagues (2004) have reported a double dissociation between contextual fear conditioning consolidation and reconsolidation within the hippocampus, consolidation involving brain-derived neurotrophic factor (BDNF) but not the transcription factor Zif268, whereas reconsolidation recruits Zif268 but not BDNF.

The major neurotransmitters such as dopamine, noradrenalin, acetylcholine and GABA contribute to the underpinnings of both consolidation and reconsolidation, as indicated by several recent psychopharmacological studies (Tronson and Taylor, 2007; Diergaarde et al., 2008). Glutamate arguably constitutes the most profoundly-involved neurotransmitter in the mechanisms of consolidation and reconsolidation, both processes being consistently inhibited by antagonists or facilitated by positive modulators acting on the NMDA receptor (or its subunits) in a variety of learning-and-memory procedures in rats and mice (see reviews by Riedel et al., 2003; Morgado-Bernal, 2011). Note that reconsolidation can also be disrupted without consolidation being affected, as is the case for the positive modulator of the $GABA_A$ benzodiazepine-binding site midazolam and the beta-adrenergic antagonist propanolol, suggesting the possibility of a differential involvement of the corresponding receptor sites and neurotransmitters in these memory processes (Debiec and LeDoux, 2004; Bustos et al., 2006).

Curiously, there is practically no psychopharmacological study having investigated the potential participation of histamine, yet a major monoamine neurotransmitter, in the mechanisms of reconsolidation (Bucherelli et al., 2006). Here, we addressed that question in a series of experiments examining the effects of systemic administrations of the classic histamine H_3 receptor inverse agonist thioperamide (known to augment the release of histamine) on reconsolidation and consolidation of a contextual fear memory in mice. The establishment of such a memory, which depends on the integrity of the amygdaloid-hippocampal complex (Kim and Jung, 2006), relies on the pairing of a footshock (the unconditioned stimulus; US) with a circumscribed context that subsequently becomes a conditional stimulus (CS) eliciting on its own conditioned freezing (CR), the natural response to the initial foot-shock (UR) in rodents. As for many learning-and-memory procedures, both consolidation and reconsolidation of contextual fear memories can readily be disrupted or facilitated by systemic injections of NMDA antagonists or the partial NMDA agonist D-cycloserine, respectively (Suzuki et al., 2004; Lee et al., 2006; Camera et al., 2007). Since histamine H_3 inverse agonists can prevent the disruptive effects that NMDA receptor antagonists exert on consolidation of several cognitive tasks, as seen above, we also examined the interactive effects of thioperamide and the representative non-competitive NMDA antagonist dizocilpine (MK-801) on reconsolidation. To that end, thioperamide and dizocilpine dose–response curves were established in separate experiments for allowing the identification of optimal doses to be used in the interaction experiments.

EXPERIMENTAL PROCEDURES

Animals and housing

A total of 372 experimentally naive female C57BL/6J mice, born in the central animal farm of the University of Liège, were used (only once). Upon arrival in our animal colony, mice were housed individually in transparent polycarbonate cages (15 cm L×33 cm W×13 cm H) whose floor was lined with pine sawdust bedding. Food (standard pellets, Carfil Quality BVDA, Oud-Turnhout, Belgium) and tap water were available *ad libitum* during the whole experimentation and until their euthanasia, which took place a few weeks later. At the beginning of the experiment, mice were aged 10–12 weeks and weighted 18–22 g. The housing room was maintained on a 12:12 h light–dark cycle (lights on at 08.00 h) with an ambient temperature of 20–22 °C. All procedures were carried out during the light period of the light–dark cycle, between 9:00 and 14:00 h. The 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 (n° 2007/526/CE).

Drugs

Purchased from Sigma Aldrich, Bornem, Belgium, dizocilpine maleate (MK-801) and thioperamide maleate solutions were prepared fresh daily, both drugs being dissolved in sterile 0.9% saline in order to deliver final doses of 0.03, 0.06 or 0.12 mg/kg dizocilpine

and 2.5, 5, 10, 20 or 30 mg/kg thioperamide in a volume of 10 ml/kg (0.01 ml/g body weight), depending upon the experiment. The control treatment consisted of an equal volume of saline solution. All injections were given via the intra-peritoneal route (i.p.).

Behavioral apparatus

Conditioned freezing was acquired and its retention tested in two identical commercially-available chambers (MED Associates Inc., St. Albans, VT, USA, ENV-307W-TH) encased in sound-attenuating cubicles (MED Associates Inc., ENV-021M). Ventilation fans at the rear of the cubicles offered both air exchange and background noise (69 dB). The chambers were made of clear acrylic glass boards in the back and ceiling, and aluminium sheets on both sides, the front constituting a horizontally hinged door (24 cm L×20 cm W×21.5 cm H). Illumination was provided by a small white light mounted in the top centre of the right wall. The chamber floor consisted of 23 stainless-steel rods, each 3 mm in diameter and spaced 8 mm apart. A Programmable Microcontroller Constant Current Shock Source (MED Associates Inc., ENV-414) controlled a shock scrambler that delivered the footshock (US) through the floor rods. The floor covered the upper surface of a base platform that was mounted onto a precision force transducer that generated a voltage current proportionate to any platform displacement triggered by the mouse behavioural activity (Fitch et al., 2002; Nielsen and Crnic, 2002). Each platform was calibrated to a fixed displacement that produces a force of 1 g at a frequency of 2 Hz via the Threshold Activity Monitoring Software (MED Associates Inc., SOF-806). Stimuli presentation and data recording from both chambers were controlled by a MED-PC program (MED Associates Inc., SOF-735) via a specific interface (MED Associates Inc., DIG-716). Freezing posture was defined as a total absence of platform displacements, and thereby of movements (except respiration-related ones, obviously), and was measured in terms of percent time spent in that posture during the test session. The chambers were cleaned with a 10% ethanol solution after each individual testing.

Behavioral procedure

Our fear conditioning procedure was comparable to that often utilized in rodent studies (e.g. Bustos et al., 2006). Prior to each session, mice were weighted in the colony room and then conducted by pairs on a cart to the experimental room, while remaining in their home cage. Mice were tested less than 3 min later. Immediately thereafter, mice were injected with the appropriate treatment (within less than 45 s), replaced in their home cage and returned to the colony room within 4–5 min. The whole procedure, which involved two mice tested concomitantly, lasted a mere 15 min. The fear conditioning task comprised two basic phases: the training session (acquisition) and the memory retention test session (recall). On the training session, mice were placed into the test chamber (whose context provided the CS) and left there for a 2 min pre-shock period, which was followed by two moderate footshocks administered 28-s apart (2-s duration, 0.25-mA intensity; US) and by a 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, mice were replaced in the training chamber for a 5-min test period during which conditioned freezing was recorded. In the experiments dealing with reconsolidation, a reactivation session was performed 48 h after the training session and 24 prior to the retention session. The reactivation session consisted of exposing the mouse to the training chamber for a unique short session of 2 min during which its behaviour was recorded without any footshock being delivered. The psychopharmacological effects were revealed on the retention test session, the drugs being injected immediately after the training session in the consolidation experiments or after the reactivation session in the reconsolidation experiments.

Drug administration protocols

In the experiments concerning consolidation (Experiments 1, 2 and 3), all injections were given right after the training session. In Experiment 1, four independent groups of 12 mice each were injected with saline, 5, 10 or 20 mg/kg thioperamide, and in Experiment 2 four other groups of 12 mice received saline, 0.03, 0.06 or 0.12 mg/kg dizocilpine. In Experiment 3, where the potential effects of thioperamide 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, 5, 10 or 20 mg/kg thioperamide, a fifth group receiving saline twice.

In the experiments concerning memory reconsolidation (Experiments 4, 5 and 6), all injections were given right after the reactivation session. Experiment 4 comprised six groups of 12 mice that received saline, 2.5, 5, 10, 20 or 30 mg/kg thioperamide. Experiment 5, which comprised two sub-experiments, aimed at reproducing the disruptive effects of dizocilpine on reconsolidation in our laboratory setting. The first sub-experiment (Reactivation) involved four groups of 13 mice that were injected with saline, 0.03, 0.06 or 0.12 mg/kg dizocilpine immediately after reexposure to the training apparatus. The second sub-experiment (No reactivation) was designed to ascertain the specificity of the disruptive effects of dizocilpine found in the first sub-experiment. To that end, four groups of eight mice were injected with saline, 0.03, 0.06 or 0.12 mg/kg dizocilpine in the colony room without being exposed again to the testing apparatus, a procedure that did not allow memory reactivation to occur. Experiment 6, which aimed at evaluating the effects of thioperamide on dizocilpine-induced deficit in reconsolidation, involved four groups of 12 mice that were injected with 0.12 mg/kg dizocilpine a few seconds prior to receiving saline, 5, 10 or 20 mg/kg thioperamide, a fifth group being injected with saline twice.

Datal analysis

The reliability of the effects was evaluated by means of 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 compared between the groups. In case of significant effect, subsequent Tukey–HSD tests were performed to isolate the single between-mean significant differences. The critical level of statistical significance was conventionally set at $P<0.05$. For the sake of clarity and conciseness, the data and analyses dealing with freezing on the training and reactivation sessions were not presented in the Results section, the corresponding levels being graphically and statistically undistinguishable across groups.

RESULTS

Effects on consolidation

In Fig. 1, Panel B shows the effects of thioperamide on conditioned freezing consolidation (Experiment 1). The freezing values derived from the groups having received the two highest doses of the histamine H_3 inverse agonist (10 or 20 mg/kg) were significantly greater than that of the saline group, from which the effect induced by the lowest thioperamide dose did not statistically differ. Overall, thioperamide tended to induce a dose-dependent increase in memory performance, the values of the three drugged groups remaining statistically comparable. This profile of effects was supported by the one-way ANOVA ($F_{(3,44)}=5.81$,

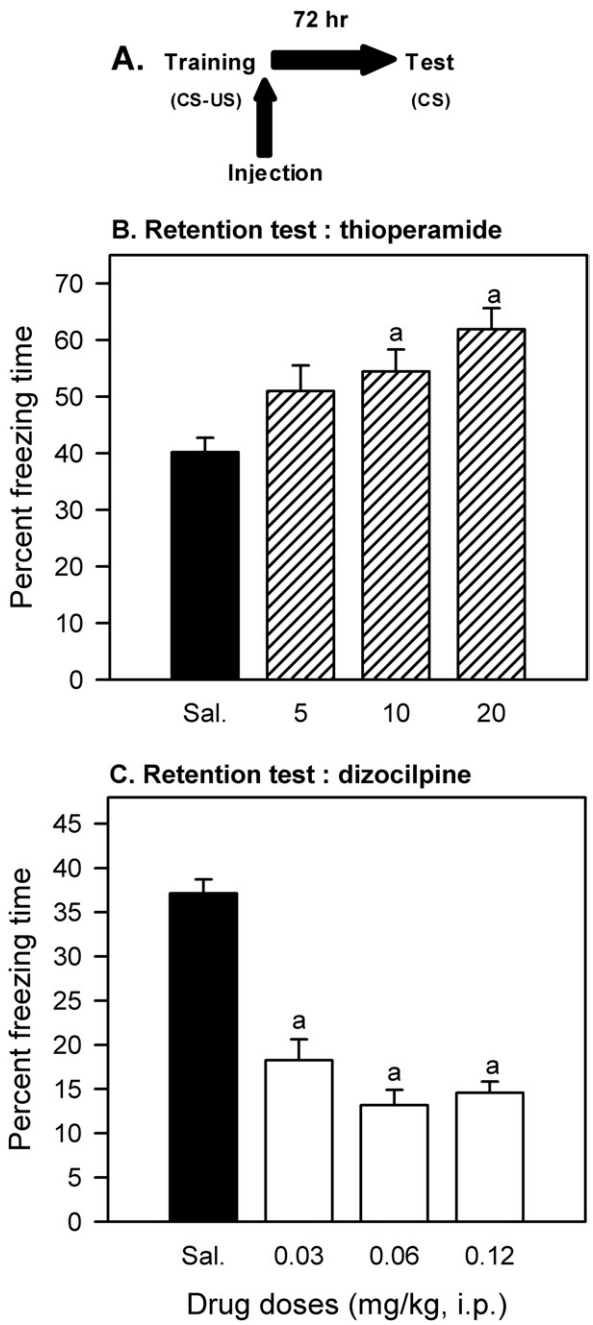

Fig. 1. Effects of the histamine H_3 inverse agonist thioperamide and the non-competitive NMDA antagonist dizocilpine on consolidation of a contextually-conditioned fear memory in C57BL/6J mice. (Panel A) Diagram explaining the protocol used in this experiment. Mice were trained under two foot-shocks (0.25 mA) that induced reliable freezing behaviour. The drug (at one of the three doses) or saline ($n=12$) was injected i.p. immediately after completion of training, a 5-min retention test taking place 72 h later. Memory performance was expressed in terms of percent time spent freezing (conditioned freezing response). (Panel B) Experiment 1: Memory performance on the retention test in thioperamide-treated mice ($n=12$). (Panel C) Experiment 2: Memory performance on the retention test in dizocilpine-treated mice ($n=12$). Columns represent means+standard error of the mean (vertical bars). a: values significantly different from that of the respective saline group at $P<0.048$ (10 mg/kg), $P<0.0012$ (20 mg/kg) or $P<0.0002$ (all dizocilpine groups), as yielded by post-ANOVA Tukey-HSD tests.

$P<0.002$) and subsequent Tukey–HSD tests (10 mg/kg at $P<0.048$ and 20 mg/kg at $P<0.0012$).

Panel C in Fig. 1 depicts the disruptive effects of dizocilpine on conditioned freezing consolidation (Experiment 2). The freezing values derived from the three groups having been injected with the NMDA antagonist were starkly smaller than the control value (saline), with no between-group obvious differences, a profile of effects that was supported by the one-way ANOVA ($F_{(3,44)}=39.13$, $P<0.0001$) and Tukey–HSD between-mean comparisons (all differences at $P<0.0002$).

Fig. 2 (Panel B) presents the interactive effects of thioperamide and dizocilpine administered immediately after training on conditioned freezing consolidation (Experi-

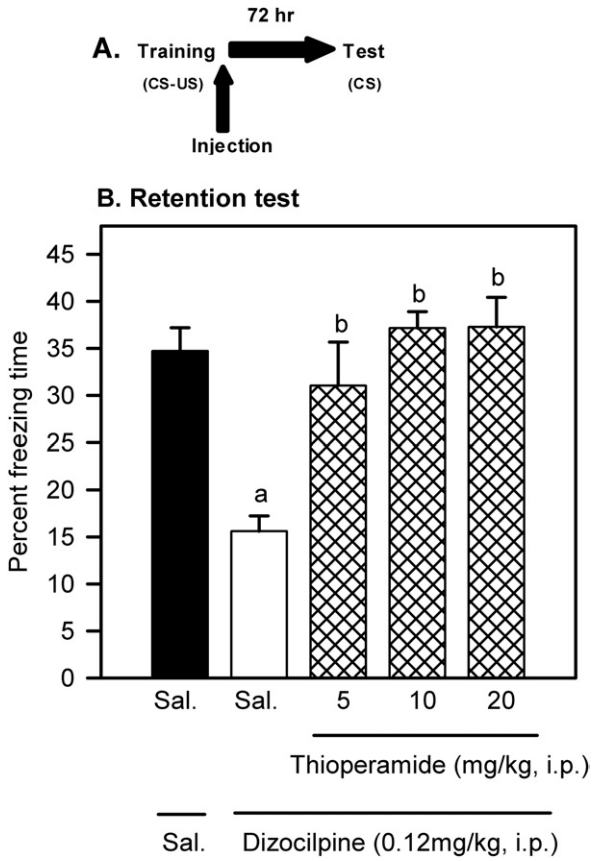

Fig. 2. Experiment 3: Effects of thioperamide on dizocilpine-induced deficit in consolidation of a contextually-conditioned fear memory in C57BL/6J mice. (Panel A) Diagram explaining the protocol used in this experiment. Mice were trained under two foot-shocks (0.25 mA) that induced reliable freezing behaviour. Dizocilpine (0.12 mg/kg) and thioperamide (at one of the three possible doses) were injected i.p. a few seconds apart and immediately after completion of training, a 5-min retention test taking place 72 h later. Memory performance was expressed in terms of percent time spent freezing (conditioned freezing response). The control groups received saline twice or dizocilpine plus saline. (Panel B) Interactive effects of dizocilpine and thioperamide on consolidation as revealed by memory performance on the retention test ($n=12$). Columns represent means+standard error of the mean (vertical bars). a: value significantly different from that of the saline-plus-saline group at $P<0.0004$, b: value significantly different from that of the saline-plus-dizocilpine group at $P<0.0043$ (5 mg/kg) or $P<0.0002$ (10 and 20 mg/kg), as yielded by post-ANOVA Tukey-HSD tests.

ment 3). The values derived from the three groups that received 5, 10 or 20 mg/kg thioperamide 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 (intact memory performance), as supported by the one-way ANOVA ($F_{(4,55)}=9.52$, $P<0.0001$) and Tukey–HSD tests (5 mg/kg at $P<0.0043$ or 10 and 20 mg/kg at $P<0.0002$). Note that the decrease in memory performance in mice having received 0.12 mg/kg dizocilpine plus saline was significant at $P<0.0004$.

Effects on reconsolidation

Fig. 3 (Panel B) represents conditioned freezing on the retention test in mice having received one of the five doses of thioperamide (2.5–30 mg/kg) immediately after the reactivation session (Experiment 4). There was no significant change in memory performance in any of the five groups, which exhibited comparable values, an unambiguous absence of efficacy is corroborated by the one-way ANOVA ($F_{(5,78)}=0.322$, $P>0.89$).

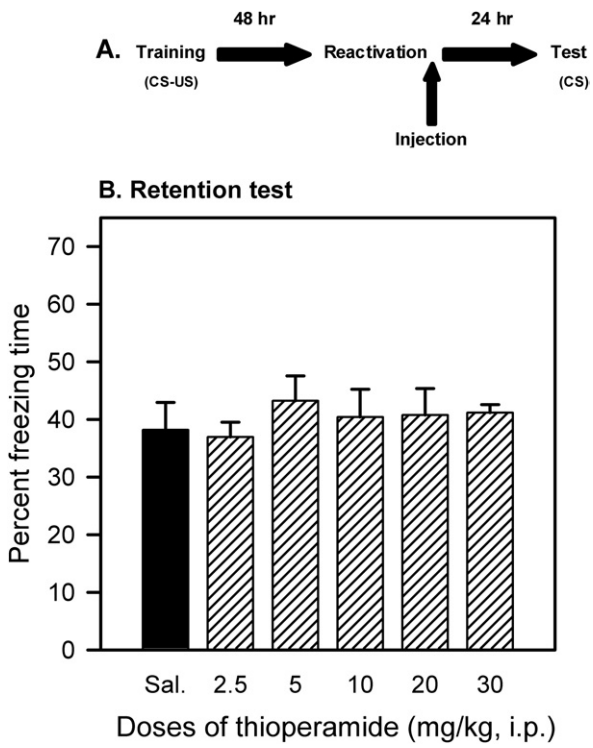

Fig. 3. Experiment 4: Effects of the histamine H_3 inverse agonist thioperamide on reconsolidation of a contextually-conditioned fear memory in C57BL/6J mice. (Panel A) Diagram describing the protocol used. Mice were trained under two foot-shocks (0.25 mA) that induce reliable freezing behaviour. Forty-eight hours later, thioperamide (at one of the five possible doses) or saline were given i.p. immediately after a 120-s reactivation session. A 5-min retention test was conducted 24 h later and memory performance was expressed in terms of percent time spent freezing (conditioned freezing response). (Panel B) Memory performance on the retention test in thioperamide-treated mice ($n=12$). Columns represent means+standard error of the mean (vertical bars). There were no visible drug effects.

Panel B in Fig. 4 depicts conditioned freezing on the retention test in mice having received one of the three doses of dizocilpine (0.03, 0.06 or 0.12 mg/kg) immediately after the reactivation session (Experiment 5, first sub-experiment). While being indistinguishable, the values from the three experimental groups having received 0.03, 0.06 or 0.12 mg/kg dizocilpine were significantly lower than that of the saline group, a profile of effects supported by the one-way ANOVA ($F_{(3,48)}=13.12$, $P<0.0001$) and post hoc Tukey-HSD tests (0.03 mg/kg at $P<0.0012$; 0.06 mg/kg at $P<0.0002$ and 0.12 mg/kg at $P<0.0003$). Panel C in Fig. 4 shows the mean levels of conditioned freezing on the retention test performed 24 h following the administration of 0.03, 0.06 and 0.12 mg/kg dizocilpine outside of the experimental context with the aim to control for the specificity of the effect reported in the first sub-experiment (Panel B). Such a specificity was ascertained since the four groups exhibited graphically undistinguishable levels of freezing, the one-way ANOVA yielding no significant between-group differences at all ($F_{(3,28)}=0.261$, $P>0.85$).

Fig. 5 (Panel B) depicts the interactive effects of thioperamide and dizocilpine administered after the reactivation session on conditioned freezing as measured on the retention test session (Experiment 6). The values derived from the groups having received the two higher doses of thioperamide (10 and 20 mg/kg) right after dizocilpine (0.12 mg/kg) were significantly greater than that of the group treated with dizocilpine plus saline (decreased memory retention), without however reaching the levels of the control group that had received saline twice (intact memory retention), as supported by the one-way ANOVA ($F_{(4,55)}=7.99$, $P<0.0001$) and Tukey-HSD tests (10 mg/kg value at $P<0.0055$ and 20 mg/kg value at $P<0.022$). Note that the value derived from the group having received the smallest dose of thioperamide (5 mg/kg) after dizocilpine remained significantly lower than that of the group having received saline twice (Tukey-HSD at $P<0.0016$), which was obviously significantly higher than that of the group treated with 0.12 mg/kg dizocilpine plus saline (Tukey-HSD at $P<0.0004$).

DISCUSSION

The present study brought about the following findings. Experiments 1 and 4 showed that histamine H_3 inverse agonist thioperamide convincingly facilitated memory consolidation but had no significant effect on reconsolidation of conditioned fear memory in mice, even at relatively high doses. By contrast, in Experiments 3 and 6 thioperamide readily abolished the disruption of both consolidation and reconsolidation induced by a representative dose of the non-competitive NMDA antagonist dizocilpine. The disruptive effects of dizocilpine per se were characterized prior to these experiments (Experiments 2 and 5), replicating and complementing previous comparable results obtained in rats and mice tested for contextual fear memories (Suzuki et al., 2004; Lee et al., 2006; Camera et al., 2007). Note that the dizocilpine effects on reconsolidation were specific

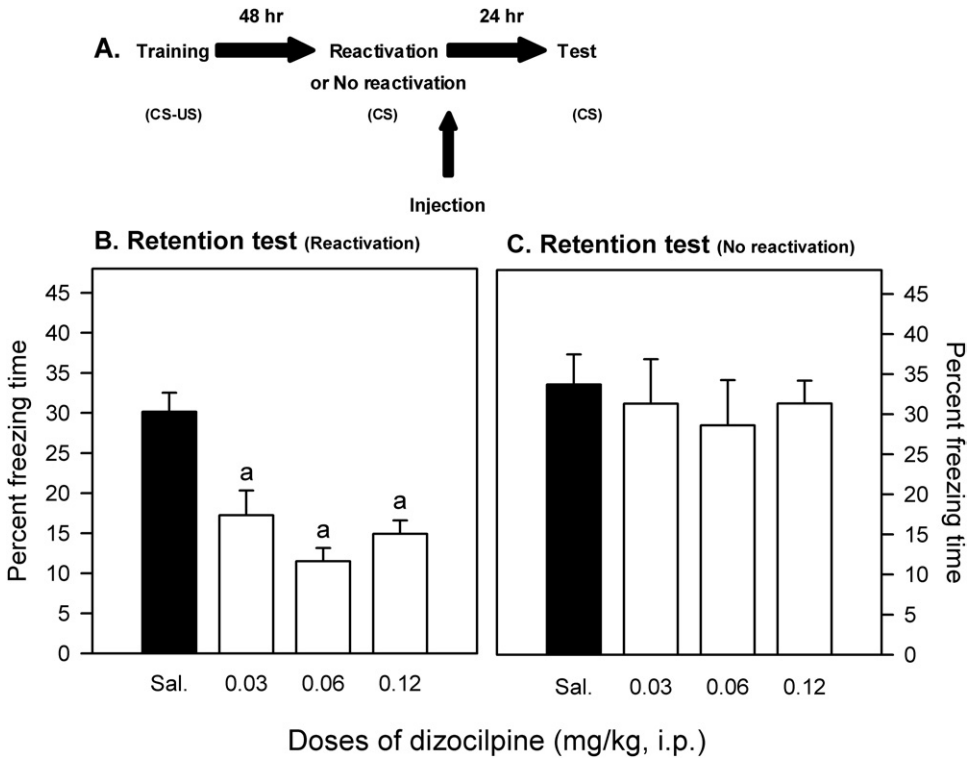

Fig. 4. Experiment 5: Effects of the NMDA antagonist dizocilpine on reconsolidation of a contextually-conditioned fear memory in C57BL/6J mice. (Panel A) Diagram describing the protocols used in the two sub-experiments that involved either a reactivation or no reactivation. Mice were trained under two foot-shocks (0.25 mA) that induce reliable freezing behaviour. Forty-eight hours later, dizocilpine (at one of the three doses) or saline were given i.p. immediately after a 120-s reactivation session ("Reactivation" sub-experiment) or in the colony room without reactivation ("No reactivation" sub-experiment), a 5-min retention test being conducted 24 h later. Memory performance was expressed in that test in terms of percent time spent freezing (conditioned freezing response). (Panel B) "Reactivation" sub-experiment: Memory performance on the retention test in mice having received dizocilpine right after a reactivation session (n=13). (Panel C) "No reactivation" sub-experiment: Memory performance on the retention test in mice having received dizocilpine without reactivation (n=8). Columns represent means+standard error of the mean (vertical bars). a: value significantly different from that of the saline group at $P<0.0012$ (0.03 mg/kg), $P<0.0002$ (0.06 mg/kg) or $P<0.0003$ (0.12 mg/kg), as yielded by post-ANOVA Tukey-HSD tests. There were no visible drug effects in the No reactivation sub-experiment.

since no effect at all was obtained when the drug was given outside of the test context.

The thioperamide-induced improvement of consolidation is the first that had been obtained using the contextual fear conditioning procedure in the mouse. A relevant previous study also reports similar effects in rats having received a systemic administration of proxyfan, an H_3 receptor protean agonist (Baldi et al., 2005). We have reproduced these results and observed a facilitation of fear-motivated passive avoidance after systemic injections of GT2231, another protean agonist, in the mouse (unpublished results). Given that protean agonists have a spectrum of activity ranging from full inverse agonism to full agonism depending on the level of the H_3 receptor constitutive activity, and that inverse agonists typically enhance consolidation in rodents (whatever the cognitive test), one can logically consider that proxyfan and GT2231 acted as full inverse agonists in those experiments (Arrang et al., 2007). In fact, the present data are in line with a number of studies in which post-training systemic injections of imidazole and non-imidazole histamine H_3 receptor inverse agonists facilitated the subsequent expression of passive-avoidance fear memories (which are partially related to Pavlovian conditioned fear) and non-aversive social- or place-recognition memories in mice and rats (Prast et al., 1996; Ghi et al., 1998; Molinengo et al., 1999; Orsetti et al., 2001; Fox et al., 2003, 2005; Bernaerts et al., 2004). As indicated in the introduction, the effects of systemic histaminergic compounds on reconsolidation have not been examined to date. In a study examining retrieval, that is thought to share some functional features with reconsolidation, H_3 receptor agonists injected prior to the retention test of a contextually conditioned fear response were found to deteriorate memory performance, an interference that was readily prevented by thioperamide (Yokoyama et al., 2009). The inefficacy of thioperamide on reconsolidation contrasts with the facilitation that many H_3 receptor inverse agonists typically exert not only on consolidation but also on acquisition and retrieval of aversively, positively and non-reinforced tasks in mice and rats (Meguro et al., 1995; Ghi et al., 1998; Yates et al., 1999; Fox et al., 2003, 2005; Esbenshade et al., 2005; Komater et al., 2005; Ligneau et al., 2007; Brioni et al., 2011).

Our thioperamide and dizocilpine interactive effects on consolidation extend to pure Pavlovian contextual fear conditioning, comparable to previous findings obtained in mice tested in passive avoidance task (Bernaerts et al., 2004). If such an interaction has not been reported previ-

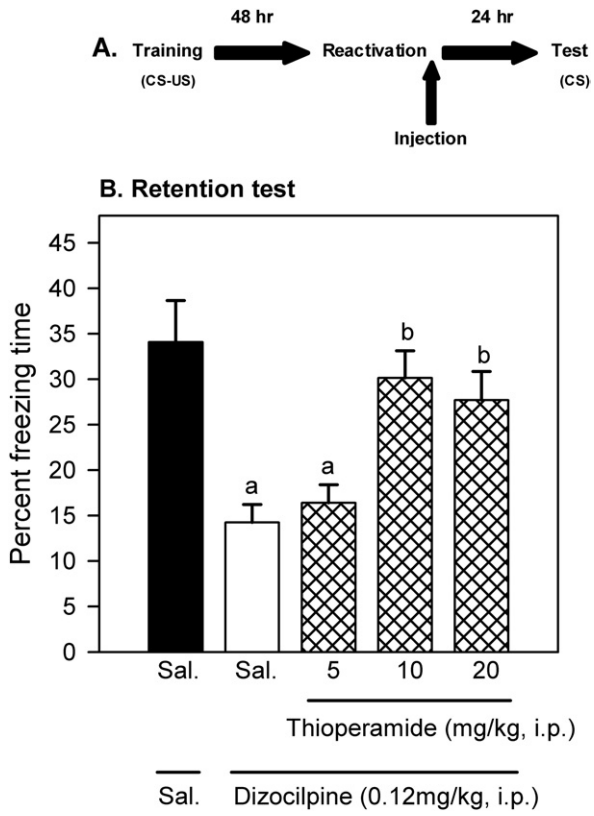

Fig. 5. Experiment 6: Effects of thioperamide on dizocilpine-induced deficit in reconsolidation of a contextually-conditioned fear memory in C57BL/6J mice. (Panel A) Diagram explaining the protocol used in this experiment. Mice were trained under two foot-shocks (0.25 mA) that induced reliable freezing behaviour. Forty-eight hours later, mice received i.p. injections of dizocilpine (0.12 mg/kg) and thioperamide (at one of the three possible doses) a few seconds apart and immediately after a 120-s reactivation session, a 5-min retention test taking place 24 h later. The control groups received saline twice or dizocilpine plus saline. Memory performance was expressed in terms of percent time spent freezing (conditioned freezing response). (Panel B) Interactive effects of dizocilpine and thioperamide on reconsolidation as revealed by memory performance on the retention test ($n=12$). Columns represent means+standard errors of the mean (vertical bars). a: value significantly different from that of the saline-plus-saline group at $P<0.0004$ (saline+dizocilpine) or $P<0.0016$ (5 mg/kg), b: value significantly different from that of the saline-plus-dizocilpine group at $P<0.0055$ (10 mg/kg) or $P<0.022$ (20 mg/kg), as yielded by post-ANOVA Tukey-HSD tests.

ously for reconsolidation, it has also been demonstrated for other memory phases like acquisition, retrieval and working memory in a variety of tasks (Chen et al., 1999; Orsetti et al., 2001; Huang et al., 2003, 2004; Nishiga and Kamei, 2003; Bardgett et al., 2009, 2010).

Taken together, our and some previous findings suggest that fear-memory reconsolidation and consolidation are underpinned by dissimilar histaminergic mechanisms while sharing common interactive histamine–NMDA mechanisms. Concerning the substrate of these mechanisms, a number of studies suggests that histamine signalling is involved in consolidation within both the hippocampus and the amygdala and in reconsolidation solely or mainly within the hippocampus. Note that owing to the enormous complexity of histamine networks and differential actions of histamine receptors, administration of comparable histaminergic drugs can induce both promoting and inhibitory cognitive effects, which anyway can only logically reflect some functional involvement of the manipulated sites (Passani et al., 2007). Specifically, thioperamide bilaterally infused into the basolateral amygdala after reactivation has been reported to remain without effect on the reconsolidation of contextual fear memory in the rat, as in the present study (Bucherelli et al., 2006). By contrast, consolidation of contextual fear memory was hampered by similar infusions of thioperamide and clobenpropit (another H_3 receptor inverse agonist) and improved by the H_3 agonist imetit (Passani et al., 2001; Cangioli et al., 2002). Consistent with these results, consolidation of active-avoidance fear memories can be ameliorated by post-acquisition infusions of H_1 receptor antagonists or H_3 receptor agonists into the nucleus basalis magnocellularis, a region strongly connected to the amygdala (Privou et al., 1999). As far as we know, the reconsolidation effects of hippocampal infusions of histaminergic drugs have not been examined yet. Nonetheless, consolidation of contextual and passive-avoidance fear memories have been reported to be enhanced following dorso-hippocampal infusions of H_3 receptor agonists in the rat (Giovannini et al., 2003; Da Silva et al., 2006). Consolidation can also be impaired by ventro-hippocampal infusions of histamine in rats tested in an active-avoidance fear conditioning procedure (Alvarez and Banzan, 2008). Additionally, infused into the medial septum, which strongly projects to the hippocampus via cholinergic and GABAergic septo-hippocampal neurons, thioperamide can facilitate and imetit can blunt, both the consolidation of a similar task (Flood et al., 1998). Several of the above-described effects were counteracted by systemic or local applications of H_1 or H_2 receptor antagonists.

The available results on the cognitive involvement of histamine–NMDA interactions within the amygdaloid–hippocampal complex concern exclusively retrieval, acquisition and working memory assessed in aversively and especially positively reinforced instrumental tasks in the rat. Nevertheless, one can reasonably conceive that these results also hold for both consolidation and reconsolidation. For instance, bilateral dorso-hippocampal infusions of NMDA receptor agonists attenuated the retrieval deficit of a radial-maze task induced by a systemic injection of an H_1 receptor antagonist, an effect that was exacerbated by an H_3 receptor agonist (Nakazato et al., 2000; Masuoka and Kamei, 2009; Masuoka et al., 2010). Conversely, bilateral ventral or dorsal hippocampal infusions of the H_3 receptor inverse agonist clobenpropit or histamine reduced radial-maze working memory deficits induced by systemic dizocilpine, and the effect of clobenpropit was reversed by an H_3 receptor agonist and an H_1 receptor antagonist (Huang et al., 2003, 2004; Xu et al., 2005). In one of the few studies having envisaged the concomitant manipulation of the basolateral amygdala and the ventral hippocampus, infusions of an H_1 receptor antagonist into both these sites impaired acquisition of a conditioned avoidance response,

an effect that was attenuated by hippocampal infusions of glutamate (Alvarez and Ruarte, 2004). At a neurochemical level, histamine–NMDA interactions have been evidenced in the hippocampus and the prefrontal cortex, no comparable information being available about how the amygdala could be involved in those interactions. For instance, histamine can amplify NMDA currents and synaptosomes glutamate release in cultured hippocampal neurons (see reviews by Brown et al., 2001; Haas et al., 2008). Importantly, histamine activation of NMDA receptors in synaptosomes has been shown to depend, at least partly, on an allosteric site located on these receptors, suggesting specific functions for the histamine–glutamate interactions (Burban et al., 2010; Hansen et al., 2010).

Such a framework of fragmented results made it difficult to propose a cogent explanation of the contrast between the efficacy of thioperamide on consolidation and its inefficacy on reconsolidation, except when combined with dizocilpine. All the more so as the histamine system is well-known to be functionally connected to most important neurotransmitter systems which are deeply involved in all phases of learning-and-memory mechanisms, albeit reconsolidation has been much less investigated in that regard (Diergaarde et al., 2008). In fact, we are left to countless speculative suggestions. For example, one can posit that reconsolidation of contextual fear memories normally involves higher intensity of histaminergic transmission than other memory processes like consolidation and thus requires greater doses of H_3 inverse agonists to be facilitated. In our experiments, the smallest dose of thioperamide (5 mg/kg) abrogated the disruptive effect of dizocilpine on consolidation but remained without effect on dizocilpine-induced disruption of reconsolidation. Also, the alleviating effects of the highest thioperamide doses (10 and 20 mg/kg) on dizocilpine-induced deficits in reconsolidation reached levels that tended to remain lower than the control levels (albeit the differences were far from being significant, see Fig. 5). This hypothesis is unlikely since *in vivo* cortical H_3 receptor occupancy by thioperamide can achieve quasi maximal levels at around 15 mg/kg (i.p.), our highest dose being 30 mg/kg thioperamide (Miller et al., 2009). Furthermore, in a study currently in progress in our laboratory, systemic injections of a large range of doses of highly brain-penetrating H_3 receptor inverse agonists yielded the same pattern of effects as those reported here for thioperamide.

One can also speculate that the hampered efficacy of both systemic and amygdalar administrations of thioperamide on reconsolidation (Bucherelli et al., 2006; present results) was due to relatively low H_3 receptor, or even H_1 and H_2 receptors, availabilities in specific but still undefined amygdalar circuits. However, there is no convincing evidence for the existence of particular amygdalar subareas with low densities in H_1, H_2 and especially H_3 receptors, although a few studies have reported that these receptors (binding and mRNA expression) are far from being evenly distributed over the amygdalar and hippocampal areas (Drutel et al., 2001; Pillot et al., 2002; Lozada et al., 2005).

In another scenario, the reduced efficacy of systemic post-reactivation thioperamide could have been induced by thioperamide itself via the parallel mobilization of a circuitry normally responsible for an inhibitory control of fear expression that would have hampered an otherwise facilitated reconsolidation, the final cognitive outcome remaining unchanged. Such a control can be conveyed by the pathways projecting from the medial prefrontal cortex to amygdalar circuits, which are thought to control the expression and the extinction of conditioned fear (Sotres-Bayon et al., 2004). According to recent models, during the recall of conditioned freezing, increased output of the lateral and basal nuclei of amygdala excites the central nuclei, thereby promoting fear expression via outputs to the brainstem. Fear is reduced by the parallel activation of the prefrontal cortex which in turn excites amygdalar intercalated inhibitory GABAergic neurons to attenuate the outputs of central nuclei (Sotres-Bayon et al., 2004; Kim and Jung, 2006). Since the prefrontal cortex deep layers are rich in H_1 and H_2 receptors, post-reactivation thioperamide-induced histamine release could have triggered these inhibitory pathways and amygdalar mechanisms involved in reconsolidation (Dai et al., 2007; Haas et al., 2008). Another hypothetical mechanism of concomitant neutralization of thioperamide-induced effect on reconsolidation could rely on a reduction of amygdalar ERK phosphorylation, whose activation within the amygdala has been shown to facilitate reconsolidation (Tronson and Taylor, 2007). Since H_3 receptor activation, which diminishes histamine release, can facilitate ERK phosphorylation in the amygdala (Arrang et al., 2007), one could speculate that thioperamide somewhat inhibited ERK phosphorylation cascade and thus failed to accentuate reconsolidation in our mice and Bucherelli and collaborators' rats (2006). Naturally, such a counteracting control could also be mediated by one or several neurotransmitters, via undefined circuitries inside or outside the amygdada, such as GABA, norepinephrine, serotonin or acethylcholine, some of which being known to be released by histamine and H_3 receptors in the amygdala, the nucleus basalis, the septum or the hippocampus (Brown et al., 2001; Haas et al., 2008; Passani et al., 2007).

It must be kept in mind that given that thioperamide and other H_3 inverse agonists are able to affect consolidation when infused into the amygdala, each of the above-described mechanistic scenarios necessarily implies that reconsolidation and consolidation to be subtended by distinct and specialized histaminergic circuits, which are far from being evidenced. Additionally, it is only by reactivating dizocilpine-blocked NMDAergic neurotransmission probably via the allosteric site located on the NMDA receptor that thioperamide-induced histamine released, at least in the hippocampus, would have somewhat rescued reconsolidation. Thus, histaminergic participation in reconsolidation would necessarily depend upon the occurrence of some changes in NMDA activity, whereas that involved in consolidation would not, both neurotransmitter systems acting individually as well as interactively on both cognitive processes. At first sight, these possibilities are not easy to

reconcile with the findings that NMDA receptor blockade can augment and metabotropic (mGlu) 2 receptor activation can mitigate histamine neuron activity in the mouse and rat prefrontal cortex and especially ventral hippocampus, histamine neurons expressing NMDA receptors (Faucard et al., 2006; Fell et al., 2010). One must admit that dizocilpne-induced histamine activation either occurs in brain areas that are not involved in memory mechanisms or it is not enough to be able to influence these processes in presence of an overwhelming NMDA receptor blockade.

In conclusion, to our knowledge the present findings show for the first time the existence of a functional histamine–NMDA/glutamate interaction underpinning contextual fear reconsolidation, which is not affected by the separate pharmacological activation of the histamine system. Contextual fear consolidation appeared to be readily facilitated by drug-induced histamine release both with and without drug-induced NMDA blockade. The exact mechanisms whereby H_3 receptors inverse agonists exert these differential effects have to wait further elucidation. In particular, it remains unknown how basolateral amygdala circuits could contribute to the histamine-NMDA underpinnings of reconsolidation. A manner to verify the hypothesis that amygdalar histamine is predominantly involved in the lack of effect of thioperamide on reconsolidation would be to repeat our reconsolidation experiment with an auditory fear conditioning procedure that is known to be far less hippocampus-dependent than contextual fear conditioning (Kim and Jung, 2006). In other words, if amygdalar histamine activity is not involved in reconsolidation processes, thioperamide or any other histaminergic interference with reactivation should not affect auditory fear memory or abrogate its disruption under NMDA blockade. Also, it would be fruitful to undertake studies comparing systematically the fear memory effects of post-acquisition (consolidation) or post-reactivation (reconsolidation) infusions into the hippocampus, the amygdala or both structures of histamine H_3 inverse agonists alone or in association with NMDA antagonists.

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