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Research report

The prototypical histamine H_3 receptor inverse agonist thioperamide improves multiple aspects of memory processing in an inhibitory avoidance task

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HIGHLIGHTS

- This study tested the effects of thioperamide on the different stages of memory.
- Memory performance was assessed with the inhibitory avoidance task in female mice.
- Our results show that thioperamide improved consolidation and retrieval processes.
- Thioperamide injected before the training session also enhanced memory performance.
- State-dependent effects did not alter the cognitive enhancing effects of thioperamide.

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ABSTRACT

Numerous studies have found that histamine plays a major role in memory and that the histamine H_3 receptor (H_3R) inverse agonist thioperamide improves cognitive performance in various animal models. However, little is known about the stages of memory that are specifically affected by thioperamide. The purpose of the present study was to investigate the effects of thioperamide on acquisition, consolidation and retrieval processes in a one-trial inhibitory avoidance task in female C57BL/6J mice. In addition, potential state-dependency effects were studied by injecting thioperamide before the training and the test sessions in order to induce similar physiological states during acquisition and retrieval. Our results indicate that post-training systemic administration of thioperamide facilitated consolidation. Moreover, the administration of thioperamide before the training session had no effect on latency to enter the black compartment during training but enhanced memory during the retention test. The administration of thioperamide before the retention test also increased performance, which indicates that this compound ameliorates memory retrieval. Finally, when animals received thioperamide before the training session and before the retention test, the cognitive enhancing effects of thioperamide were not significantly changed. Together, our results show that thioperamide improves cognitive performance in an inhibitory avoidance task through actions on different memory stages. Furthermore, inducing a similar physiological state with thioperamide during acquisition and retrieval do not significantly affect cognitive enhancement. Our results suggest that the blockade of H_3R can be helpful for the treatment of neuropsychiatric conditions characterized by deficits affecting several stages of memory processing.

1. Introduction

Since the discovery of the histamine H_3 receptor (H_3R) in 1983, compelling evidence has been accumulated demonstrating that H_3R inverse agonists improve memory in numerous animal models [1,2]. The cognitive enhancing properties of these compounds result from an increased activity of the histaminergic system and have been suggested to possess diverse therapeutic applications in multiple neuropsychiatric diseases such as Alzheimer's disease, schizophrenia and drug addiction [3,4]. Despite that the pro-cognitive effects of H_3R inverse agonists have been convincingly demonstrated and replicated, little is known about the specific memory processes that are affected by these compounds. Memory

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is considered as a dynamic process that has several stages, including acquisition, consolidation and retrieval [5]. In the inhibitory (also called passive) avoidance task, memory acquisition occurs when an animal initially placed in a white chamber steps through a black conditioning chamber where it receives an electric foot shock. Under these conditions, the animal learns an association between this context and the shock. During the consolidation phase, the memory underlying the context–shock association evolves gradually from a labile trace to a more fixed state [6]. During retrieval, the animal is returned to the white chamber, where the memory of the context–shock association is evaluated. In these conditions, the animal has the choice to enter the black chamber. The latency to leave the white chamber is used as an index of the strength of the context–shock association. As a result of the learning process, the animal typically spends more time in the white chamber before entering the black one than when it is placed in the white chamber for the first time [7].

Histamine releasing neurons are exclusively confined in the tuberomammillary nucleus (TM) located in the posterior hypothalamus, from where they innervate almost the whole brain and different parts of spinal cord . Histamine synthesis is executed by the enzyme histidine decarboxylase (HDC) converting L-histidine to histamine. The action of histamine in the brain is mediated by four histamine receptors (H_1R, H_2R, H_3R, H_4R). H_1R and H_2R are primarily located postsynaptically and their activation leads to excitatory effects. In contrast, H_3R and H_4R are inhibitory receptors coupled to Gi/o proteins [8,9]. The H_3R were initially described as presynaptic autoreceptors located on histaminergic neurons, where they play a negative feedback role on histamine synthesis and release [1,8]. However, H_3R can also function as heteroreceptors located on non-histaminergic neurons, and inhibit the synthesis and release of various neurotransmitters, such as dopamine, GABA, serotonin, glutamate or acetylcholine [8,10]. The H_3R displays a high level of constitutive activity and several H_3R inverse agonists such as thioperamide that were first considered as histamine H_3 receptor antagonists are actually histamine H_3 inverse agonists [11].

Since the beginning of the nineties, the role of H_3R has been studied in various physiological and biological functions, including water and food consumption, locomotion, anti-nociception, circadian rhythms, vigilance and cognition [8,10,12]. With regard to cognitive functions, numerous studies demonstrate a role for H_3R in social, spatial and fear memory consolidation [13–15]. On the other hand, the effects of histamine ligands on memory acquisition and retrieval are not clearly established or remain unknown. Most studies show that systemic administration of H_3R inverse agonists before the training trials can counteract genetically- or pharmacologically-induced deficits in memory acquisition [16–18]. However, there are few studies available about the effects of systemic injections of H_3 inverse agonists on intact rodents. Concerning the process of retrieval, the small number of results is inconsistent [19,14,20,21]. Finally, there is no study having systematically dissected the impact of H_3R inverse agonists on acquisition, consolidation and retrieval using the inhibitory avoidance task.

Clinical observations and experimental evidence indicate that some events can only be recalled when an individual is under the influence of the same drug that he has ingested at the time of the acquisition of these events [22,23]. This phenomenon called state-dependent learning has also been demonstrated in animals [24,25]. For example, it has been shown that alcohol injected to rats before the training session of an inhibitory avoidance task reduced performance during the retention test [25]. However, when alcohol was injected before both the training and the retention sessions, the memory deficit was no longer present. Thus, when the rats experienced the same drug state during acquisition and retention, memory performance was similar to rats that never received alcohol. This suggests that inducing a similar drug state during memory acquisition and memory retention would make recall optimal. State-dependency mechanisms have never been investigated directly in relation to the pro-cognitive effects of H_3R inverse agonists in an inhibitory avoidance task. However, Mattioli and co-workers have demonstrated that histidine induces a state-dependent memory retrieval deficit in mice mediated by histamine using a two-trial elevated plus-maze (EPM) procedure [26,27]. Their results suggest that compounds that increase brain histamine levels, like thioperamide, could induce a specific drug state capable of interfering with memory processing.

The main purpose of the present study was to clarify whether thioperamide, a prototypical H_3R inverse agonist, can affect the different stages of memory in an inhibitory avoidance procedure using female C57BL/6J mice. Thioperamide was injected systemically because H_3 inverse agonists have a therapeutic potential for the treatment of cognitive deficits in humans after oral administration although the memory stages specifically affected after the blockade of H_3 receptors are still unclear [28]. First, we conducted an experiment (Experiment 1) that investigated the effect of thioperamide on spontaneous locomotion in order to select doses that did not affect locomotor activity. Experiment 2 tested thioperamide in the EPM to determine whether the doses selected from Experiment 1 could modify anxiety levels of the mice. Previous results from our laboratory indicated that post-trial injection of thioperamide facilitates consolidation processes in male C57BL/6J mice in the inhibitory avoidance task [29]. Experiment 3 of the present study aimed at replicating these results in female mice. In Experiment 4, thioperamide was injected before the training session to test its effects on acquisition. To investigate the effects of thioperamide on memory retrieval, thioperamide was injected before the retention test in Experiment 5. Since the elevation of the histamine levels in the brain may induce a specific drug state capable of interfering with memory processing [26,27], a sixth experiment (Experiment 6) was designed to study whether injecting thioperamide before both the training session and the retention test could affect memory performance.

2. Material and methods

2.1. Animals

For the whole study, 185 naive females 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 × 33 cm W × 13 cm H). Water and food (standard pellets, Carfil Quality BVDA, Oud-Turnhout, Belgium) were available *ad libitum* during the whole experimentation. At the beginning of the experiments, 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 a.m.) with an ambient temperature of 20–22 °C. All procedures were carried out during the light phase between 9:00 a.m. and 2:00 p.m. 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

Thioperamide maleate was purchased from Sigma–Aldrich (Bornem, Belgium). Thioperamide was prepared daily and dissolved in sterile saline (NaCl 0.9%) in order to deliver final doses of 10 or 20 mg/kg. All solutions were administered through the intraperitoneal (i.p.) route in a final volume of 10 ml/kg (0.01 ml/g body weight). The choice of the doses and the time of injection were based on previous experiments performed in our laboratory [29,30]. Control animals received an equal volume of saline solution. The EPM and inhibitory avoidance experiments were performed double-blind and the experimenter was unaware of the solutions injected to the mice in Experiments 2–6.