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Scopolamine prevents retrograde memory interference between two different learning tasks

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ABSTRACT

Subjects exposed to learning experiences could store the new information through memory consolidation process. If consolidation is interfered by exposing the experimental subjects to another novel stimulus, memory of the first learning situation is sometimes disrupted. The cholinergic system is critically involved in acquisition of new information. Here, we use low doses of the muscarinic cholinergic receptor antagonist scopolamine (SCOP) to disrupt acquisition of new information, but sparing memory consolidation of previous memories. Mice were consecutively exposed to two learning situations: the inhibitory avoidance (IA) and the nose-poke habituation (NPH) tasks. The exposure of mice to the NPH task, after being trained in the IA apparatus, impairs consolidation of the avoidance memory in a manner related to the duration of the exposure to the NPH task. If the exposure to the NPH task occurred after reactivation of the avoidance memory, reconsolidation was impaired. Blockade of acquisition of the NPH task by SCOP allowed consolidation and reconsolidation of the avoidance memory. Results indicate that cholinergic system blockade by SCOP impairs acquisition but is less able to affect memory consolidation. The mere exposure and perception of a novel situation are not sufficient conditions to cause impairment of retention performance about previously learned information, but effective processing leading to acquisition of the NPH task information is necessary to cause the interference between both learning situations.

1. Introduction

When subjects are exposed to new experiences, the information acquired could be stored and eventually produce behavioral modifications. Once acquired, the information needs to be progressively strengthened over time through a consolidation process, during which memory is stabilized [1,2]. If the information processing were perturbed while consolidation is taking place, the storage could be affected and, as a consequence, the formation of the memory trace could be either enhanced or impaired.

Under physiological conditions, memory consolidation could be interfered by the presentation of novel learning situations [3–5] or by sleep deprivation [6]. The interference could be also produced through pharmacological manipulations, and the drugs administered exert their actions by modulating endogenous processes. In this sense, the administration of agonists or antagonists of neurotransmitter or hormonal receptors [7], protein synthesis inhibitors [8], transcription factors and their blockers [9] or protein kinase inhibitors [10], can produce either the enhancement or the impairment of memory consolidation.

Although it was traditionally accepted that once consolidation is complete memories become permanent [11], several studies have shown that when a well consolidated memory is reactivated, it again becomes sensitive to disruption [3,12–16]. Most treatments affecting memory consolidation when given after training are also able to disrupt memories when given after its reactivation. The period of sensitivity triggered after memory retrieval was named reconsolidation [13].

Novel events tend to attract attention and become more effectively encoded in memory than predictable events [17]. In primates, the exposure to different types of novelty has been related to activation of the hippocampus and nearby regions of the medial temporal lobe, and prefrontal cortex [18]. Activated areas correspond well to modulating connections of the nucleus basalis of Meynert, one of the main cholinergic projecting nuclei modulating overall cortical activity, implicated in learning and memory [19]. In rodents, cholinergic systems are preferentially activated by novel stimuli [20] and are necessary for consolidating memories about such novel stimuli in different species [16,21,22].

It has been suggested that high acetylcholine (ACh) levels are necessary for acquisition of new information, while low levels enable recall [23]. Thus, decreases in ACh levels or administration of muscarinic cholinergic antagonists such as scopolamine (SCOP), should impair acquisition, but should also be necessary for consolidation and retrieval. In fact, when SCOP is given after training,

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retention is affected only by high doses (more than 4 mg/kg), but not when low doses are administered [24]. However, when SCOP is administered before a learning trial, retention performance is impaired even at low doses [25,26]. If two novel learning tasks are sequentially acquired, low doses of SCOP could be used as a pharmacological tool to selectively impair the acquisition of the second learning situation, though without affecting either memory consolidation or reconsolidation of the first one.

The exposure of mice to a novel environment (a hole-board or an open field, for example), after being trained in the inhibitory avoidance task, impairs consolidation of the avoidance memory only if the novel context is perceived as new, but not if it is recognized as previously explored [3,4]. Similar results were obtained impairing memory reconsolidation, when the novel situation is presented after memory reactivation [3]. It was initially proposed that the novelty-induced retrograde interference was caused by the perception of the novel situation [3,4]. However, the ultimate reason for this impairment has not been elucidated yet, because presentation of novel stimuli affects a number of physiological processes, such as attention, stress, etc., besides learning. The present work attempts to separately assess the involvement of different memory processes triggered by the placement of mice on a hole-board (second novel learning situation) after the exposure to an inhibitory avoidance apparatus (first novel learning situation), in order to find the reason for the interference between both learning tasks.

2. Materials and methods

2.1. Experimental subjects

CF-1 male mice (FUCAL, Buenos Aires, Argentina) were used (age 45–60 days; weight 25–30 g). They were individually identified and housed in stainless-steel cages, 10–15 per cage. The mice were kept in a climatized animal room (21–23 °C) maintained on a 12 h light/dark cycle (lights on 06:00 h), with *ad libitum* access to dry food and tap water. Experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 80-23/96), and local regulations. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Behavioral procedures

2.2.1. Inhibitory avoidance (IA)

The avoidance behavior was studied in one-trial learning, step-through type, which utilizes the natural preference of mice for a dark environment. The apparatus consisted of a dark compartment (20 cm × 20 cm × 15 cm) with a stainless-steel grid floor and a sliding door opened in its front center communicating with a small illuminated platform (5 cm × 5 cm) attached to it and elevated 100 cm from the floor (conditioning context) [27]. The mice were not exposed to the apparatus before the learning trial. During training, each mouse was placed in the illuminated platform. As it stepped into the dark compartment received a footshock of 1.2 mA, 50 Hz, 1 s, that yields median retention scores at the ceiling [3,16]. The retention tests were performed at the times indicated for each experimental group. Thus, each mouse was placed on the platform again, and the step-through latency was recorded. The retention test was finished either when the mouse stepped into the dark compartment or failed to cross within 300 s. In the latter case the mouse was immediately removed from the platform and assigned a score of 300 s. In the retention test session the footshock was omitted.

2.2.2. Nose-poke habituation task (NPH)

The nose-poke habituation response was described and validated for rats [28] and for mice as experimental subjects [3,29]. The apparatus employed was a hole-board (Ugo Basile Mod. 6650, Comerio, Italy) made of a matte gray Perspex panel (40 cm × 40 cm × 22 cm) which has 16 flush mounted tubes of 3 cm i.d. Each tube has an infrared emitter and a diametrically opposed receiver connected to an automatic counter to register the number of nose-pokes into the holes.

During training, each mouse was placed at the center of the apparatus and the number of nose-pokes was automatically registered for 5 min. The retention test was performed 24 h later. Thus, mice were placed again on the apparatus and nose-pokes were registered for 5 min. The nose-poke behavior is expressed as nose-pokes/5 min. Differences in the number of nose-pokes between training and testing represents the memory of the task [3,28,29].

2.3. Drug administrations

Scopolamine (SCOP) (Sigma, St. Louis, MO, USA) was dissolved in saline solution immediately before its use and administered intraperitoneally (10 ml/kg). Controls received the same volume of saline solution (SS). Experiments were carried out in a blinded fashion with regard to drug treatments.

2.4. Experimental groups

The first experiment was aimed to determine the susceptibility of memory consolidation of the IA task to different duration of exposure to the NPH task. Six groups of mice ($n = 10$ mice/group) were trained in the IA task and immediately exposed or not to the NPH apparatus, for 3, 10, 30, 60 or 300 s. The mice were tested for retention in the IA apparatus 24 h after training.

The second experiment was aimed to find the minimum dose of SCOP impairing retention of the NPH task. Four groups of mice ($n = 15$ mice/group) were injected either with SS or SCOP (0.1, 0.5 or 1.0 mg/kg) and 20 min after it, mice were placed on the NPH for 5 min. Mice were placed again on the NPH apparatus 24 h later to perform the retention test. Short-term memory of the NPH task was also assessed in order to know whether the pre-training administration of SCOP affected acquisition or consolidation. Thus, two additional groups were trained following a similar protocol and injected with SS or SCOP (0.5 mg/kg), but memory of the NPH task was tested 1 h after training.

The next experiment was performed in order to determine the susceptibility of memory consolidation of the IA task to the administration of SCOP, and to find the dose range of this drug not impairing memory consolidation. Four groups of mice ($n = 15$ mice/group) were trained in the IA task and were given SS or SCOP (0.5, 1.0 or 5.0 mg/kg) immediately after training. Mice were tested for retention 24 h later.

To evaluate the susceptibility of reactivated memories to SCOP, and to find the dose range of this drug not disrupting memory reconsolidation, five groups of mice ($n = 10$ mice/group) were trained in the IA task. After the first retention test, performed 24 h later, mice received SS or SCOP (0.1, 0.5, 1.0 or 5.0 mg/kg) immediately after it, and were tested again 24 h later.

In the next experiment, mice were consecutively exposed to both learning tasks (IA and NPH). Four groups of mice ($n = 15$ mice/group) were trained in the IA task and immediately after it, the mice received SS or SCOP (0.5 mg/kg), and were returned to their home cages. They were placed for 5 min on the NPH apparatus 20 min later. Mice were tested in the IA task 24 h and 48 h after it, and 20 min later they were tested in the NPH task.

In the last experiment, mice were consecutively exposed to both learning tasks, but for testing influences on memory reconsolidation. Four groups of mice ($n = 10$ mice/group) were trained in the IA task. The first retention test was performed 24 h after training, and immediately after it, the mice were given SS or SCOP (0.1 mg/kg), and were returned to their home cages. They were placed for 5 min on

the NPH apparatus 20 min later. The mice were tested again in the IA task 24 h after it, and 20 min later they were tested in the NPH task.

2.5. Data analysis

Latencies to step-through either during the training or the retention test are expressed as medians and interquartile ranges. They were analyzed, when appropriate, with the non-parametric analysis of variance of Kruskal–Wallis, and the differences between groups were estimated by individual Mann–Whitney *U* test (two tailed) [30]. Data from the hole-board were analyzed by one-way ANOVA and expressed as mean ± SEM; post hoc analysis with the Newman–Keuls test was performed [31].

In all cases *P* values less than 0.05 were considered significant.

3. Results

Training step-through latencies differences among all the groups trained in the IA task were not significant ($H_{(22)} = 6.721$; $P > 0.05$).

3.1. Susceptibility of the avoidance memory to the new learning

After the training session in the IA task, the placement of mice on the NPH apparatus impaired retention performance in the IA task in a manner dependent on the time spent on the NPH task. That is, the larger the exposure, the greater the impairment. The minimum exposure to NPH needed to impair retention performance of the IA task was 60 s, but no significant impairment was seen when mice were exposed for 3, 10 or 30 s (Fig. 1).

During the first exposure to the NPH apparatus, it was found that mice took about 1–2 s to start moving, and 5 to 10 s to do the first nose-poke (data not shown). Hence, in the group exposed for 3 s, mice had not enough time to perform the first nose-poke, but in the 10 s-exposed group, all the mice explored at least one of the holes.

3.2. Effects of SCOP on retention of the NPH task

This experiment tested the effects of SCOP on the retention of the NPH task by injecting the drug 20 min before the learning trial (Fig. 2).

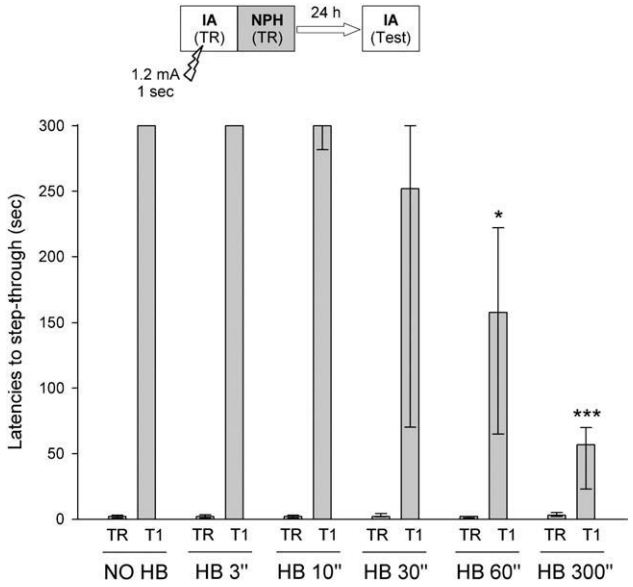

Fig. 1. Effect of the exposure to a NPH apparatus immediately after the training session in the IA apparatus. Each bar represents the median and interquartile range ($n = 10$ mice/group). IA: inhibitory avoidance; NPH: nose-poke habituation task; TR: training session. $^{*}p < 0.05$; $^{***}p < 0.001$, compared with the group not exposed to the NPH task.

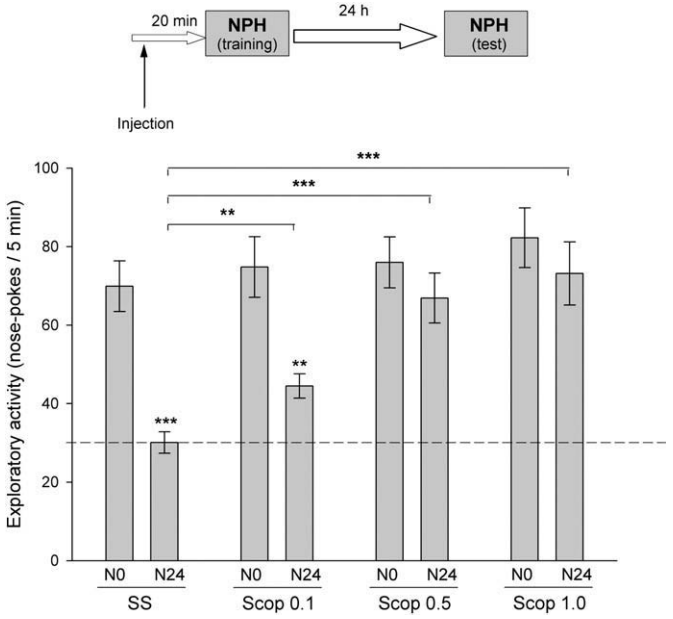

Fig. 2. Effects of SCOP on the NPH memory. SCOP (0.1–1.0 mg/kg) was administered 20 min before training and the test was performed 24 h later. Each bar represents the mean number of nose-pokes done in 5 min ± SEM. NPH: nose-poke habituation task; N0–N24: number of nose-pokes during training and the test, respectively. $n = 15$ mice/group. $^{**}p < 0.01$; $^{***}p < 0.001$, compared with performance in the training session of the same group or with the test of SS injected group.

In Fig. 2, the exploratory activity during training and testing is represented for each group. During the retention test, SS injected mice exhibited good retention performance, but animals injected with SCOP showed a dose-dependent impairment.

Short-term memory of the NPH task was impaired in animals receiving SCOP ($p < 0.05$, compared with the SS injected group, Table 1).

3.3. Effects of SCOP administered after training in the IA task

This experiment was aimed to test the influence of SCOP on memory consolidation of the IA task administering SCOP immediately after the training session. The results are shown in Fig. 3. Mice that received SS showed retention performance at the ceiling (300 s). The post-training impairing effect of SCOP on retention performance was only evident at a dose of 5 mg/kg ($p < 0.001$, compared with SS control group), but not for the doses of 0.5 and 1.0 mg/kg ($p > 0.05$, in both cases compared with SS control group).

3.4. Effects of SCOP administered after reactivation of the avoidance memory

In this experiment, SCOP was administered immediately after memory reactivation of the IA task to examine the effects of the drug

Table 1
Effects of SCOP on short-term memory of the NPH task.

Group	Exploratory activity during training (nose-pokes/5 min)	Exploratory activity during the test (nose-pokes/5 min)
SS	50.5 ± 5.0	20.4 ± 2.4 (***)
SCOP (0.5 mg/kg)	60.1 ± 5.2	56.8 ± 6.4 (ns)

SCOP (0.5 mg/kg) was administered 20 min prior to the first exposure to the NPH apparatus. The retention test was performed 1 h after the training session, in order to assess short-term memory of the NPH task. Data show the mean number of nose-pokes done by each group in 5 min ± SEM. $^{***}p < 0.001$, ns: not significant, in both cases compared with the number of nose-pokes done during the training session.

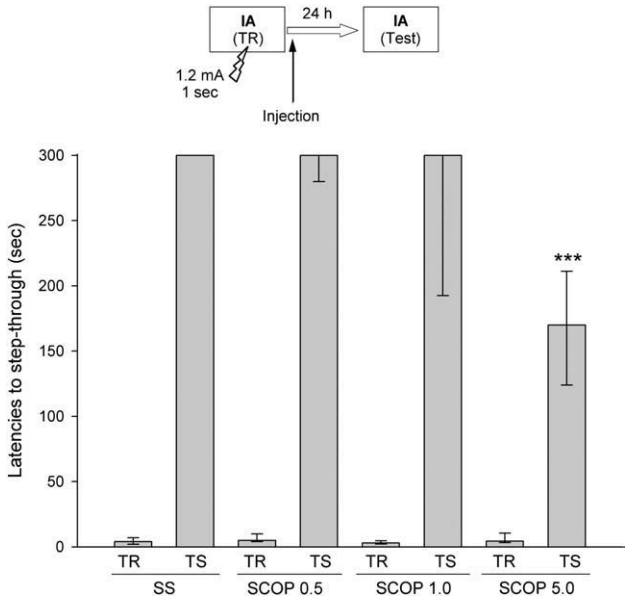

Fig. 3. Effects of SCOP (0.5–5.0 mg/kg) administered immediately after training in the IA task. Each bar represents the median and interquartile range ($n=10$ mice/group). IA: inhibitory avoidance; TR: training session. ***$p<0.001$, compared with group injected with SS.

on memory reconsolidation (Fig. 4). During the reactivation session, all the mice showed retention performance at the ceiling (300 s). SCOP exerted a dose-dependent post-reactivation impairing effect on retention performance, evident for doses higher than 0.5 mg/kg ($p<0.01$ and $p<0.001$), but the dose of 0.1 mg/kg was not effective ($p>0.05$, compared with SS control group).

3.5. Effects of acquisition of the NPH task on memory consolidation of the IA task

In this experiment, mice were exposed to both tasks, that is, to the NPH 20 min after training in the IA task, and an injection of SCOP (0.5 mg/kg) was given during the time elapsing between both learning sessions. Mice that were not exposed to the NPH after training showed a high retention performance in the IA task not only during the 1st but also at the 2nd retention test, despite receiving SS or SCOP. On the contrary, when mice were exposed to the NPH apparatus, subjects receiving SS exhibited a poor retention performance ($p<0.001$), but those mice which received SCOP showed high retention scores in the IA task (Fig. 5), indicating that SCOP prevented the impairment caused by the exposure to the NPH.

The results of the retention performance in the NPH task are shown in Table 2, and are quite similar to those obtained in the experiment 2 (see Section 3.2).

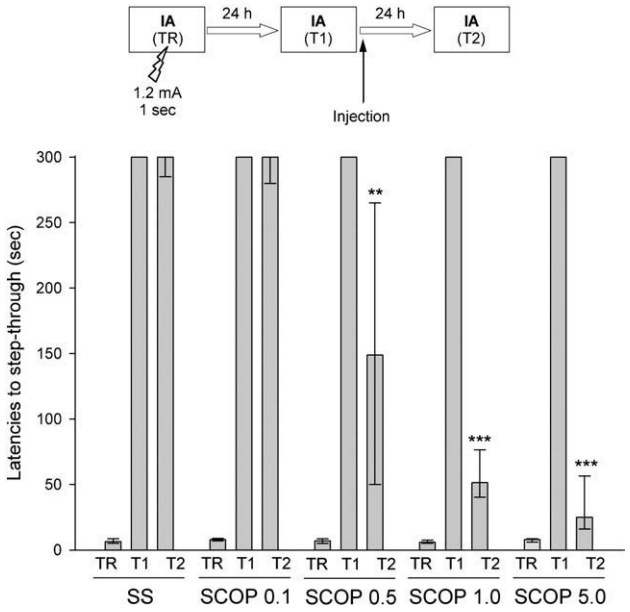

Fig. 4. Effects of SCOP (0.1–5.0 mg/kg) administered immediately after memory reactivation in the IA task. Each bar represents the median and interquartile range ($n=10$ mice/group). IA: inhibitory avoidance; TR: training session; T1 and T2: retention tests. **$p<0.01$; ***$p<0.001$, compared with the SS-injected mice.

3.6. Effects of acquisition of the NPH task on memory reconsolidation of the IA task

In the last experiment, mice were exposed to the NPH task 20 min after the memory reactivation of the IA task; SCOP (0.1 mg/kg) was administered between presentations of both tasks. Mice that were not exposed to the NPH after memory reactivation showed a high retention performance in the IA task not only during T1 but also at T2, despite receiving SS or SCOP. On the contrary, when animals were exposed to the NPH immediately after reactivation of the IA memory (T1), mice receiving SS exhibited a poor retention performance ($p<0.001$), but those mice which received SCOP performed well (Fig. 6), again indicating that SCOP prevented the impairment caused by the exposure to the NPH.

The results of NPH behavior are shown in Table 2, and are quite similar to those obtained in the experiment 2 (see Section 3.2).

4. Discussion

When subjects are exposed to different learning situations, some of them can cause interference with learning processing of others [32].

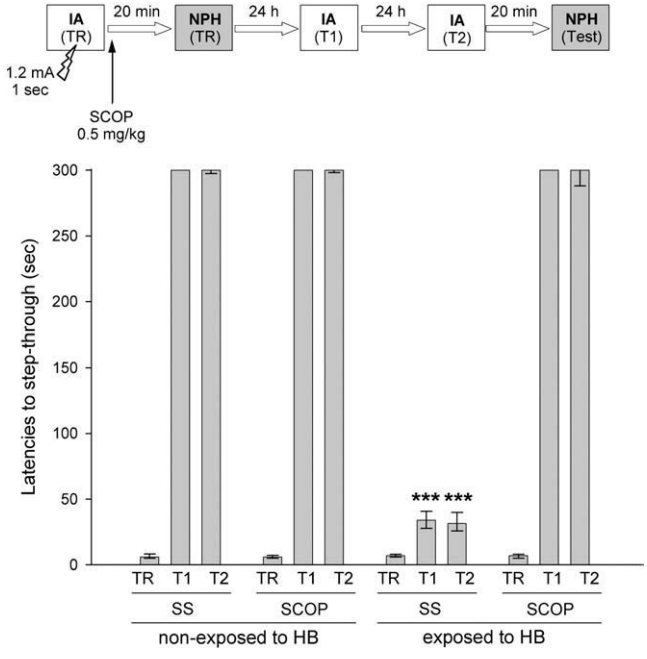

Fig. 5. Effects of acquisition of the NPH task and its blockade, on memory consolidation of the IA task. SCOP (0.5 mg/kg) was administered immediately after training in the IA task, 20 min before training in the NPH task. Each bar represents the median and interquartile range ($n=15$ mice/group). IA: inhibitory avoidance; NPH: nose-poke habituation task; TR: training session; T1 and T2: retention tests. ***$p<0.001$, compared with the group not exposed to the NPH.

Table 2
Effects of SCOP on the NPH task.

Exposure to HB	Group	Exploratory activity during training (nose-pokes/5 min)	Exploratory activity during the test (nose-pokes/5 min)
Post-training of the IA task (experiment 6)	SS	66.4 ± 3.9	31.5 ± 2.6 (***)
	SCOP (0.5 mg/kg)	73.5 ± 4.1	67.2 ± 2.9 (ns)
Post-reactivation of the IA task (experiment 7)	SS	61.7 ± 2.8	29.4 ± 3.0 (***)
	SCOP (0.1 mg/kg)	70.1 ± 3.3	51.5 ± 2.8 (**)

SCOP (0.1 or 0.5 mg/kg) was administered immediately after training or immediately after memory reactivation of the IA task, that is, 20 min prior to the first exposure to the NPH apparatus. Data show the mean number of nose-pokes done by each group in 5 min ± SEM. $^{**}p<0.01$, $^{***}p<0.001$, compared with the number of nose-pokes during the training session.

Although up to now the ultimate reasons for this interference remain elusive, the main finding of the present work indicates that the sole exposure to the novel situation and the mere perception of the novelty are not sufficient conditions to cause the interference between the two behavioral tasks.

Animals exposed for the first time to the hole-board (the NPH apparatus) perceived this environment as new and began to move through the apparatus within the first 2 s, consistent with previous findings [4], but performed the first nose-poke between the 5th and the 10th seconds. So, mice exposed to the NPH for only 3 s had enough time to perceive the environment as a new one, but could not effectively begin to explore the context because they did not have enough time to perform the first nose-poke. On the contrary, subjects exposed to this novel context for 10 s could effectively begin to explore it. These times of exploration involve different levels of information processing, implicating various systems [33,34]. Brief exposures activate the temporary sensory registers (short-term stores) [33,34].

When mice are exposed to the NPH apparatus after being trained in the IA task, an interfering effect was observed between these two learnings [3]. If the presentation of the new environment occurred immediately after each mouse was left from de IA apparatus, that is, between 10 and 15 s after receiving the footshock, the information of the IA task is still within working memory (WM) [33,34]. In these conditions, mice exposed to the NPH for 3 or 10 s performed in the IA similar to control mice, and those exposed for 30 s exhibited a slight decrease (although not statistically significant). There were necessary at least 60 s of exploration of the new environment to effectively cause interference between both learning situations, indicating that the presentation of the novelty and the perception of the situation as novel are not sufficient conditions for producing the interference between tasks. It could also be indicating that disrupting WM of the IA task is not sufficient either. It seems to be possible that another type of information processing, triggered by the novel context, was needed for interfering memory consolidation of the first learning task. If this hypothesis were true, when animals are sequentially exposed to two learning situations, blockade of processing of the second task (i.e., blocking its acquisition or its consolidation) should allow consolidate memory of the first one.

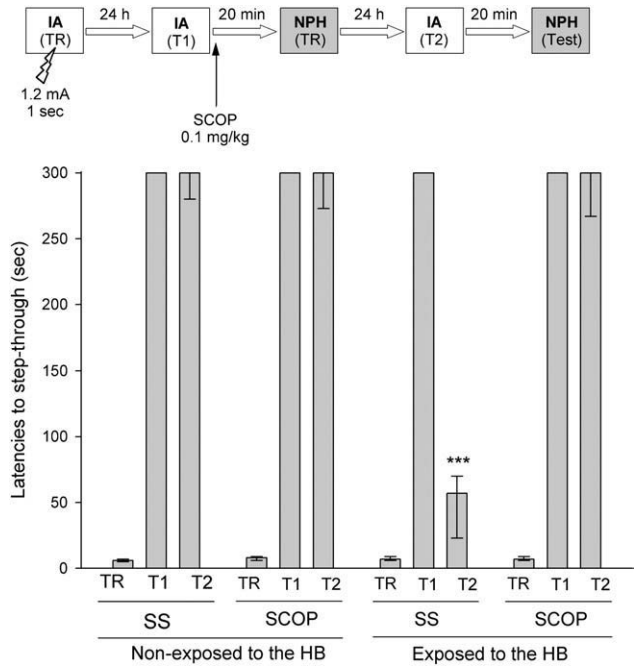

Fig. 6. Effects of acquisition of the NPH task and its blockade, on memory reconsolidation of the IA task. SCOP (0.1 mg/kg) was administered immediately after memory reactivation (T1) in the IA task, 20 min before training in the NPH task. Each bar represents the median and interquartile range ($n = 10$ mice/group). IA: inhibitory avoidance; NPH: nose-poke habituation task; TR: training session; T1 and T2: retention tests. $^{***}p<0.001$, compared with the group not exposed to the NPH.

It was found that the administration of low doses of SCOP can impair retention of the IA task if given before a learning trial [25,26], but higher doses are necessary to impair memory if the drug is given after training [24]. These findings were confirmed here using the IA and NPH tasks, and extended to memory reconsolidation of the IA response. The lack of difference in the exploratory activity between the training session and the test indicates that acquisition of the NPH task was blocked by SCOP. In addition, short-term memory was impaired in mice receiving SCOP, again indicating blockade of acquisition. Memory reconsolidation of the IA task was found to be more sensitive than memory consolidation to disruption by the drug, since the dose range of the drug impairing memory reconsolidation was lower than the range affecting consolidation.

The mentioned properties allowed us to use low doses of SCOP as a pharmacological tool to selectively impair the acquisition of the novel learning situation, without affecting either memory consolidation or reconsolidation of the previously acquired one.

In this context, when animals were trained in the IA task and put in the NPH apparatus after it, interference was observed [3]. However, when SCOP was administered following a protocol blocking acquisition of the NPH task, though not impairing memory consolidation of the IA, the interference was not produced and memory of the IA was conserved. In addition, blocking acquisition of the NPH task with SCOP, but without affecting reconsolidation of the avoidance memory, also allowed the maintenance of the IA memory. In the case of reconsolidation, it is necessary to consider that the dose of SCOP employed was 0.1 mg/kg. Although this dose was less effective to impair acquisition of the NPH task than 0.5 mg/kg, this degree of NPH task acquisition impairment was enough to spare the avoidance memory. This observation could be a consequence of the ceiling time employed in the IA task during the retention test: if the mouse does not enter the dark compartment within 300 s, the test is finished and the animal is removed from the platform and returned to its home cage [27]. Hence, impairing effects needing more than the ceiling time are not observable.

Although the first and the fifth experiments used different delays between exposures to both learning tasks (that is, in the first experiment IA training was immediately followed by NPH exposure, but in the fifth experiment there was employed a necessary 20-minute-gap between tasks to ensure that SCOP acceded to the central nervous system to exert its effects), it was possible to use the 20-minute-gap because the post-training time window susceptibility of the IA learning is longer than 30 min [35].

The results obtained here using the muscarinic cholinergic antagonist SCOP, confirm that the cholinergic system is critically involved in information processing. Other groups reported that acetylcholine enhances the cortical response to sensory input, that

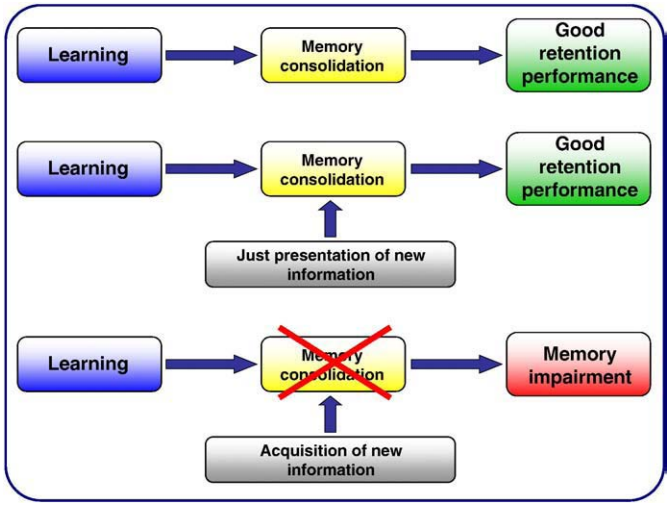

Fig. 7. When information processing coming from two different learning situations interact, the retrograde interference is observed only if the novel information is effectively learned. If the novel information is not learned, previously acquired memories are spared.

is, it enhances attention to sensory stimuli in the environment by optimizing input processing in sensory regions [36], and increases memory encoding for these stimuli [22]. At the same time, this neurotransmitter prevents influences on this new encoding caused by previously encoded memories, by suppressing synapses strengthened by prior learning [37–39]. Blockade of muscarinic receptors using SCOP prevents the physiological effects of ACh. Other groups proposed that this blockade results in the following actions: cortical response to novel sensory stimuli is reduced, encoding of novel information is impaired, and previously learned information is not suppressed [37–39]. As a consequence, the acquisition of the NPH task was impaired and memory of the IA task was spared.

It is worth pointing out that animals injected with SS and exposed to the NPH while consolidation or reconsolidation of the avoidance memory is taking place, stay on the platform for about 50 s during the following retention test. This retention performance is larger than the 10 s expected for unshocked animals [3,27], meaning that the avoidance memory is actually present at the retention test, but finally fails to entirely take control of behavior. Hence, more studies are necessary to elucidate whether the interference results in a weak storage process, or in some degree of retrieval disability of the avoidance task.

The main findings of the present work are summarized in Fig. 7. Taken together, results indicate that cholinergic system blockade by SCOP impairs acquisition but is less able to affect memory consolidation. The characteristics of the drug were used to show that the exposure and perception of a novel situation are not sufficient conditions to cause impairment of retention performance about previously learned information, but effective processing leading to acquisition of the NPH task information is necessary to cause the interference between both learning situations. If the novel information is not learned, previously acquired memories are spared.

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