



Time course of scopolamine effect on memory consolidation and forgetting in rats



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ABSTRACT

The effect of scopolamine on the consolidation and forgetting of emotional memory has not been completely elucidated yet. The aim of the present study was to investigate the time course of scopolamine effect on consolidation and forgetting of passive avoidance response. In a first experiment of the present study, we tested the effect of scopolamine (1 mg/kg, i.p., immediately after acquisition), on 24 h and 48 h retention performance of the step-through passive avoidance task, in adult male Wistar rats. On the 24 h retested trial, the latency of the passive avoidance response was significantly lower, while on the 48 h retested trial it was significantly higher in scopolamine-than in the saline-treated group. In a second experiment, we assessed the 24 h time course of scopolamine (1 mg/kg) effect on memory consolidation in passive avoidance task. We found that scopolamine administration only within the first six and half hours after acquisition improved memory consolidation in 48 h retention performance. Finally, a third experiment was performed on the saline- and scopolamine-treated rats (given immediately after acquisition) that on the 48 h retention test did not step through into the dark compartment during the cut-off time. These animals were retested weekly for up to first three months, and after that, every three months until the end of experiment (i.e., 15 months after acquisition). The passive avoidance response in the saline treated group lasted up to 6 weeks after acquisition, while in the scopolamine treated group 50% of animals conserved the initial level of passive avoidance response until the experiment end point. In conclusion, the present data suggest that (1) improving or impairment effect of scopolamine given in post-training periods depends on delay of retention trial, (2) memory consolidation process could be modify by scopolamine within first six and half hours after training and (3) scopolamine could delay forgetting of emotional memory.

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1. Introduction

Scopolamine, a nonselective muscarinic receptor antagonist, consistently has produced impairment of emotional based learning in rodents (for a review see [Klinkenberg & Blokland, 2010](#)). In contrast, the effect of scopolamine on memory consolidation, extinction and forgetting of emotional memory is still inconclusive and depends on several factors (i.e. site of administration, time of administration and testing, dose, cognitive task, experimental protocol, species, strain, etc.).

Systemic post-training scopolamine administration in relatively low doses (range from 0.6 to 1.2 mg/kg) did not change olfactory

fear conditioned response ([Kroon & Carobrez, 2009](#)), disturbed both tone and context fear conditioning ([Rudy, 1996](#)) or improved tone but did not change context fear conditioning ([Young, Bohenek, & Fanselow, 1995](#)), in rats. However, there are also reports showing that scopolamine post-training treatment in higher doses (dose range from 1 to 50 mg/kg) changed neither tone nor context fear conditioning, in rats ([Anagnostaras, Maren, & Fanselow, 1995](#); [Anagnostaras, Maren, Sage, Goodrich, & Fanselow, 1999](#)).

Memory consolidation in the passive avoidance task, tested in mice, was impaired ([Bernaerts, Lamberty, & Tirelli, 2004](#); [Tobe, Yamaguchi, Nagai, & Egawa, 1985](#)) or not affected ([Agrawal, Tyagi, Saxena, & Nath, 2009](#); [Blake, Boccia, Krawczyk, & Baratti, 2011](#); [Bohdanecký & Jarvik, 1967](#); [Da Silva Costa-Aze, Quiedeville, Boulouard, & Dauphin, 2012](#); [Dilts & Berry, 1967](#); [Glick & Zimmerman, 1971](#); [Nomura, Nishiyama, Saito, & Matsuki, 1994](#); [Rush, 1988](#)) after systemic post-training scopolamine administration in doses ≤ 1 mg/kg. Although some authors reported that

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scopolamine in dose ranged from 1.5 to 5 mg/kg could impair memory consolidation in mice tested in passive avoidance (Agrawal et al., 2009; Blake et al., 2011; Botton et al., 2010; da Silva, da Silva Martins, de Moura Linck, & Herrmann, 2009; Molinengo, Di Carlo, & Ghi, 1999), it was not demonstrated by others (Glick & Zimmerberg, 1971; Nomura et al., 1994; Rush, 1988). Namely, to induce impairment of memory consolidation in the passive avoidance task, a relatively high dose of scopolamine (between 10 and 30 mg/kg) should be used (Glick & Zimmerberg, 1971, 1972; Rush, 1988). Similarly in rats, some studies showed that 0.7–1.5 mg/kg of scopolamine impaired memory consolidation of the passive avoidance task (Doyle & Regan, 1993; Foley et al., 2004; Gutierrez et al., 2012; Hefco et al., 2003; Murphy et al., 2001; Sigala, Missale, & Spano, 1997) while other studies indicated that doses lower than 8 mg/kg did not disturb memory consolidation (Cruz-Morales, Duran-Arevalo, Diaz Del Guante, Quirarte, & Prado-Alcala, 1992; Elrod & Buccafusco, 1988; Mishima et al., 2001; Roldán, Bolaños-Badillo, González-Sánchez, Quirarte, & Prado-Alcalá, 1997).

One factor that was frequently considered that contributes in diversity of scopolamine effects on passive avoidance task is the shock intensity applied during the learning procedure. Namely, to induce the amnesic effect in rats trained under more severe conditions (shock intensity ≥ 2.5 mA) of the step-thorough passive avoidance task, higher doses of scopolamine should be used. Thus, 3 mg/kg of scopolamine, administered immediately after the acquisition, under 3 mA shock protocol, did not affect the step-through passive avoidance response on the 24 h retention period (Mishima et al., 2001). Similarly, at the same shock intensity, only 6, 8 and 12 mg/kg of scopolamine but not 2 and 4 mg/kg, administered i.p., 5 min after the acquisition, impaired the passive avoidance response on the 24 h retention trial (Durán-Arévalo, Cruz-Morales, & Prado-Alcalá, 1990). These authors did not find any effect of 8 and 12 mg/kg (i.p.) on consolidation memory, if 6 or 9 mA shock intensity was applied. Moreover, Cruz-Morales et al. (1992) demonstrated that only 8 mg/kg but not 4 and 12 mg/kg of scopolamine, given 5 min after the training, impaired memory consolidation when the shock intensity was in range of 2.5–2.8 mA, while Roldán et al. (1997) showed that scopolamine in the doses of 8 and 16 mg/kg but not at the dose of 4 mg/kg, impaired memory consolidation of passive avoidance when a shock of 2.5 mA was used during the training.

Another factor that is implicated in fluctuation in passive avoidance response is time delay between training and retest trial (Holloway & Wansley, 1973). Thus, the percentage of rats that successfully completed the task was high at 24, 48 and 72 h, moderate at 12, 36, 60 and 66 h and low at 6, 18, 30, 42 and 54 h after training. In the active avoidance test, it has been demonstrated that post-training scopolamine administration in the dose of 1 mg/kg, produced strong amnesia of active avoidance in mice tested on the 1st, 3rd, 14th and 28th post-training day, but normal retention was found in animals tested on 7th and 10th post-training day (Quartermain & Leo, 1988). However, the effect of scopolamine post-training administration on memory consolidation in function of time delay between training and retest trial has not been considered yet.

In contrast to extensive studies on the effect of scopolamine on memory consolidation, there are few data concerning its effect on memory extinction and forgetting. It was demonstrated that scopolamine treatment in dose of 2, 4 and 8 mg/kg could recover the extinguished passive avoidance response long after a single training session (Prado-Alcalá, Haiek, Rivas, Roldan-Roldan, & Quirarte, 1994; Roldán, Cobos-Zapíaín, Quirarte, & Prado-Alcalá, 2001). Lately, it was found that pre-extinction systemic scopolamine administration in low dose (0.1 mg/kg), but not in slightly higher doses (0.5, 1.35 and 2.7 mg/kg), significantly attenuated

the renewal of fear, in both novel and original conditioning context, suggesting that it interferes with the contextualization of extinction learning (Zelikowsky et al., 2013). Conversely, in the same study, animals injected with scopolamine subsequently to extinction sessions, showed significant renewal. Further, it has been shown that long-term memory traces were retained without forgetting and were resistant to the scopolamine treatment (2 mg/kg) in rats tested on one-trial learning of motor skills (jumping out of the water) (Podolski IYa, 1998).

It has been proposed that high levels of hippocampal acetylcholine are crucial for attention and encoding new information, while low levels of acetylcholine facilitate memory consolidation (Hasselmo, 1999; Hasselmo & McGaughy, 2004; Micheau & Marighetto, 2011; Pepeu & Giovannini, 2010). In humans, attenuating cholinergic neurotransmission after learning improves consolidation of declarative memory without affecting consolidation of procedural memory, which is not depending on hippocampal functioning (Rasch, Born, & Gais, 2006). Having in mind that passive avoidance learning is partly hippocampal dependent (for review see Robinson, Platt, & Riedel, 2011), we hypothesized that scopolamine post-training treatment could facilitate memory consolidation and delay forgetting in this particular task. With this purpose, the present study was designed to investigate, for the first time to our knowledge, the detailed time course of scopolamine effect on consolidation and forgetting of passive avoidance response.

2. Material and methods

2.1. Experimental animals

Experiments were carried out on male Wistar rats, weighing 200–250 g. The animals were housed in standard Macrolon cages on sawdust bedding. They were kept in an air-conditioned room (20 ± 1 °C), at 30% humidity and under a 12 h light/12 h dark cycle (lights on from 08:00 to 20:00 h). Food and tap water were available *ad libitum*. One week before the experimental procedure, the rats were handled, daily, for 5 min each. The behavioral tests were performed during the light period (16:00–20:00 h).

All procedures related to the animal maintenance and experimentation were in accordance with the European Communities Council Directive of November 24, 1986 (86/609/EEC) and the guidelines issued by the Spanish Ministry of Agriculture, Fishing and Feeding (Royal Decree 1201/2005 of October 21, 2005) and were approved by the Institutional Animal Ethics Committee. Efforts were made to minimize the number of animals used, as well as their suffering.

2.2. Drugs

Saline solution of scopolamine hydrobromide (Sigma, St. Louis, MO) was, administered intraperitoneally, at the dose of 1 mg/kg. Control animals were treated with physiological saline in the dose of 1 ml/kg body weight. Dose and delay of administration of scopolamine were chosen on the basis of the literature (for a review, see Klinkenberg & Blokland, 2010), as well as on unpublished results from our laboratory.

2.3. Experiment 1

The first experiment was performed to test whether scopolamine differently affect memory consolidation in depends on the delay of the retention trial from the acquisition trial. Eight animals were assigned in each tested group.

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