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Adrenergic enhancement of consolidation of object recognition memory

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Abstract

Extensive evidence indicates that epinephrine (EPI) modulates memory consolidation for emotionally arousing tasks in animals and human subjects. However, previous studies have not examined the effects of EPI on consolidation of recognition memory. Here we report that systemic administration of EPI enhances consolidation of memory for a novel object recognition (NOR) task under different training conditions. Control male rats given a systemic injection of saline (0.9% NaCl) immediately after NOR training showed significant memory retention when tested at 1.5 or 24, but not 96 h after training. In contrast, rats given a post-training injection of EPI showed significant retention of NOR at all delays. In a second experiment using a different training condition, rats treated with EPI, but not SAL-treated animals, showed significant NOR retention at both 1.5 and 24-h delays. We next showed that the EPI-induced enhancement of retention tested at 96 h after training was prevented by pretraining systemic administration of the β-adrenoceptor antagonist propranolol. The findings suggest that, as previously observed in experiments using aversively motivated tasks, epinephrine modulates consolidation of recognition memory and that the effects require activation of β-adrenoceptors.

Keywords: Epinephrine; Adrenoceptors; Recognition memory; Memory consolidation

1. Introduction

Extensive evidence indicates that adrenal stress hormones, namely epinephrine (EPI) and glucocorticoids, modulate consolidation of emotionally motivated memory in animals and human subjects (for reviews, see Cahill & McGaugh, 1998; McGaugh, 1983, 2004; McGaugh, Cahill, & Roozendaal, 1996; McGaugh & Roozendaal, 2002). In rodent models, the kind of stimulation typically used in learning experiments induces release of endogenous EPI (McCarty & Gold, 1981; McGaugh et al., 1996), and systemic administration of EPI shortly after training enhances consolidation of memory for arousing tasks (McGaugh, 1983; McGaugh et al., 1996; Nordby, Torras-Garcia, Portell-Cortes, & Costa-Miserachs, 2006). The memory-enhancing effects of peripheral administration of EPI require release of norepinephrine and activation of β-adrenoceptors in brain areas including the basolateral amygdala (BLA) (Liang, Juler, & McGaugh, 1986; McGaugh et al., 1996; McGaugh & Roozendaal, 2002). Together, these findings strongly indicate that endogenous EPI released during learning modulate the formation of long-lasting memories for arousing events (McGaugh, 1983, 2004; McGaugh et al., 1996; McGaugh & Roozendaal, 2002).

In contrast to the large body of evidence available from studies in emotionally motivated tasks, the role of the adrenergic system in modulating memory for tasks in which

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learning occurs under conditions of lower arousal remains poorly understood. In the present study we investigated the effects of EPI on consolidation of memory for a novel object recognition (NOR) task. NOR training relies on a rodent's spontaneous tendency to explore a novel object more than a familiar one. During training for this task, rats or mice are presented with two identical or different novel objects, which they explore for some time. When animals are presented at a retention test trial carried out after training with two different objects, one of which was presented previously during training ("familiar"), and the other of which is novel, animals that remember the familiar object will spend more time exploring the novel one (Ennaceur & Delacour, 1988; Steckler, Drinkenburg, Sahgal, & Aggleton, 1998). Since no explicit rewarding or aversive stimulation is used during training, NOR is considered to be a poorly motivated task involving low levels of arousal when compared to aversively motivated tasks. Two recent studies evaluating the role of adrenal stress hormones on consolidation of NOR have indicated that corticosterone influences memory for NOR only when an experimental condition in which the level of experimental arousal associated with training was higher (Okuda, Roozendaal, & McGaugh, 2004; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). However, previous studies have not evaluated whether consolidation of memory for NOR can be affected by peripheral EPI. To address this issue, EPI was administered systemically immediately after NOR training to rats that were exposed to two identical objects during training and given retention test trials at different post-training delays. A second experiment examined the effects of post-training administration of EPI on memory for NOR training in rats exposed to two different objects during training (an experimental condition in which control rats showed no significant retention 1 day after training). To examine whether the effects of EPI depend upon β-adrenoceptors, a third experiment evaluated the effect of pretraining administration of propranolol on EPI-induced enhancement of consolidation.

2. Materials and methods

2.1. Subjects

Adult male Wistar rats (age: 60 days at the time of arrival) were used as experimental subjects. Animals were housed five to a cage with food and water available *ad libitum*, and were maintained on a 12-h light/dark cycle (lights on at 7:00 h). All behavioral procedures were conducted between 9:00 and 16:00 h. All experimental procedures were performed in accordance with the NIH Guide for Care and Use of Laboratory Animals (NIH publication No. 80-23 revised 1996), and were approved by the Ethics Committee of the Pontifical Catholic University.

2.2. Drug administration

In Experiments I and II, animals received an intraperitoneal (i.p.) injection of either saline solution (SAL, NaCl 0,9%) or epinephrine (EPI, 2.5; 25 or 250 μg/kg) immediately after NOR training. In Experiment III, an i.p. injection of propranolol (2 mg/kg, PROP) was given 15 min prior NOR training, followed by an i.p. injection of SAL or EPI (25 μg/kg) immediately after training. Drugs were purchased from Sigma-Aldrich, São Paulo, Brazil, and were dissolved in SAL in a 1.0 ml/kg injection volume. Drug doses were chosen on the basis of previous studies (Nordby et al., 2006; Roozendaal, de Quervain, Schelling, & McGaugh, 2004; Sternberg, Isaacs, Gold, & McGaugh, 1985).

2.3. Behavioral apparatus and procedures

For NOR training, rats were left to explore two objects in a training box to which they had been previously familiarized. The apparatus and procedures for the object recognition task have been described elsewhere (de Lima, Luft, Roesler, & Schröder, 2006; de Lima et al., 2005; de Lima, Laranja, Bromberg, Roesler, & Schröder, 2005 Schröder, O'Dell, & Marshall, 2003). Briefly, the task took place in a 40 cm × 50 cm open field surrounded by 50 cm high walls, made of plywood with a frontal glass wall, with a floor covered with sawdust. All animals were given a habituation session where they were left to freely explore the open field for 2 min. No objects were placed in the box during the habituation trial. All objects used in training and testing trials presented similar textures, colors, and sizes, but distinctive shapes. Between trials the objects were washed with 10% ethanol solution. Exploration was defined as sniffing or touching the object with the nose and/or forepaws. NOR procedures were conducted in a dimly lit room in order to minimize the influence of contextual information.

2.3.1. Experiment I

Twenty-four hours after habituation, training was conducted by placing individual rats for 2 min into the field, in which two identical objects (objects A1 and A2; Duplo Lego toys) were positioned in two adjacent corners, 10 cm from the walls. In a short-term retention test given 1.5 h after training, the rats explored the open field for 2 min in the presence of one familiar (A) and one novel (B) object. In a long-term retention test given 24 h after training, rats explored the field for 2 min in the presence of familiar (A) and a novel (C) object. An additional retention test was performed 96 h after training, where rats again explored the field for 2 min in the presence of the familiar (A) and a novel (D) object. The same groups of animals were submitted to NOR testing trials at 1.5, 24, and 96 h after training.

2.3.2. Experiment II

In Experiment II, we assessed the effects of post-training administration of EPI in rats exposed to two different objects during training. In this and the following experiment, training duration was increased. Twenty-four hours after habituation, training was conducted by placing individual rats for 5 min into the field, in which two distinct objects (A and B) were positioned in two adjacent corners, 10 cm from the walls. In a short-term retention test given 1.5 h after training, the rats explored the open field for 5 min in the presence of one familiar (either A or B) and one novel object. In a long-term retention test given 24 h after training, the rats explored the open field for 5 min in the presence of one familiar (either A or B) and one novel object. Short- (1.5 h) and long- (24 h) retention tests were conducted in two separate groups of rats.

2.3.3. Experiment III

In Experiment III, training and testing trials were conducted as described for Experiment I except that trial duration was 5 min.

Data for all three experiments were analysed by calculating a recognition index for each animal, expressed as the ratio $T_B/(T_A + T_B)$ [T_A = time spent exploring the familiar object A; T_B = time spent exploring the novel object B] (de Lima et al., 2006, 2005, 2005; Schröder et al., 2003).

2.4. Statistical analysis

Data for recognition indexes were expressed as median (interquartile ranges). Comparisons among groups were performed using a Kruskal–Wallis analysis of variance followed by Mann–Whitney *U*-tests when necessary. Total exploration time during object recognition training is