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Glucocorticoids in the dorsomedial striatum modulate the consolidation of spatial but not procedural memory

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ABSTRACT

Glucocorticoid hormones are known to influence widely interconnected brain networks, thereby enhancing the consolidation of memory of several types of training experiences. In this network, the dorsal striatum plays an important role in transforming goal-directed behavior into habitual behavior. Many studies have shown that the dorsolateral striatum (DLS) enables the formation of stimulus–response associations that are needed for procedural learning. In contrast, the dorsomedial striatum (DMS) is predominantly involved in influencing goal-directed behaviors via interactions with the dorsal hippocampus and medial prefrontal cortex. To date, most studies that have supported a functional dissociation of the dorsal striatum in memory have focused on the behavioral deficits produced by lesions or temporary inactivation of different striatal regions. Few studies have investigated the effect of pharmacological activation of the DMS in modulating memory of distinct kinds of spatial navigation. Therefore, in the present study corticosterone (CORT) was administered into the DMS immediately after training on either a place or cue water-maze task to investigate possible effects on the consolidation of spatial and procedural memory. Our findings indicate that CORT (5, 10 and 20 ng) enhanced 24-h retention of place training, without affecting retention of cue training. However, CORT administration after place and cue training did not shift the selection from a procedural to a spatial navigation strategy in a place-cue competition test. These findings support the functional heterogeneity of the dorsal striatum and suggest that the DMS can modulate the consolidation of allocentric spatial information via glucocorticoid action.

1. Introduction

Stress is known to have profound effects on a variety of memory functions (McGaugh, 2004; Roozendaal, McEwen, & Chattarji, 2009; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012). Glucocorticoid hormones, released from the adrenal cortex during stressful episodes, not only increase the organism's ability to cope with the stress by influencing target systems in the periphery, but also by inducing a myriad of effects on the brain (Findling, Aron, & Tyrrell, 1997). Extensive evidence indicates that glucocorticoids enhance the consolidation of memory of emotionally arousing training experiences by activating glucocorticoid receptors (GRs) across networks of interconnected brain regions (Akirav et al., 2004; Barsegyan, Mackenzie, Kurose, McGaugh, & Roozendaal, 2010; Joëls & Baram, 2009; McEwen, 1998; Okuda, Roozendaal, & McGaugh, 2004; Roozendaal & McGaugh, 2011; White & McDonald, 2002). Corticosterone (CORT), the main glucocorticoid in the rat, or a selective GR agonist infused into the basolateral amygdala (BLA) is known to enhance the consolidation of memory of many different kinds of training experiences via its projections to efferent brain structures such as the hippocampus, prefrontal cortex and striatum (Roozendaal, 2002; Roozendaal & McGaugh, 2011). On the other hand, glucocorticoid administration into the dorsal hippocampus has been shown to selectively facilitate memory consolidation of spatial–contextual training (Oitzl, Fluttert, Sutanto, & de Kloet, 1998; Roozendaal & McGaugh, 1997). We recently reported that glucocorticoid administration into the dorsal striatum enhances the consolidation of procedural memory in rats trained on a cue water-maze task (Quirarte et al., 2009), consistent with the evidence that this brain region contributes to the formation of stimulus–response associations (White & McDonald, 2002).

The dorsal striatum, however, is a heterogeneous brain structure and differences in topographically organized afferents between its lateral and medial subdivisions lead to functional differences that affect interacting memory systems (Graybiel & Mink, 2009; Packard

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& Knowlton, 2002; Parent & Hazrati, 1995; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004; Yin & Knowlton, 2006). In rodents, somatosensory and motor cortical areas innervate the dorsolateral striatum (DLS), and lesions of this region impair the acquisition of stimulus–response associations that rapidly become habitual (Featherstone & McDonald, 2005; McDonald & White, 1993, 1994; Packard & McGaugh, 1992). In contrast, the dorsomedial striatum (DMS) receives both direct and indirect inputs from the BLA, dorsal hippocampus and medial prefrontal cortex, and lesions or inactivation of the DMS produce selective deficits in allocentric spatial navigation and impair performance on place–response shifting tasks (Devan, McDonald, & White, 1999; Devan & White, 1999; Featherstone & McDonald, 2005; Holahan et al., 2005; Ragozzino, Ragozzino, Mizumori, & Kesner, 2002; Voorn et al., 2004; Whishaw, Mittleman, Bunch, & Dunnett, 1987). It has not been investigated whether glucocorticoids induce differential memory effects within these two striatal regions.

As spatial and procedural learning rely upon hippocampal–striatal networks, their respective representations interact in the acquisition and selection of navigation strategies (Chang & Gold, 2003; Devan & White, 1999; Mizumori, Yeshenko, Gill, & Davis, 2004; Packard & McGaugh, 1992, 1996). Furthermore, within the dorsal striatum, lateral and medial loops make different contributions to spatial and procedural memory, depending upon training intensity and other task demands (Mizumori et al., 2004). Behaviorally, this dynamic interaction between striatal–hippocampal and lateral–medial dorsal striatal regions can be observed in tasks where rats must choose between one of two previously learned navigation strategies when these are presented concurrently. Prior findings indicate that lesions of the DMS inhibit the selection of a spatial navigation strategy, significantly increasing the selection of a procedural navigation strategy in a place-cue water-maze competition or T-maze task (Devan et al., 1999; Whishaw et al., 1987; Yin & Knowlton, 2006). Emerging evidence from animal and human studies indicates that stress exposure increases the relative use of a procedural strategy above that of a spatial strategy (Schwabe, Schächinger, de Kloet, & Oitzl, 2010; Schwabe & Wolf, 2012), suggesting that glucocorticoid hormones might not have an equal impact on these two memory systems (Schwabe et al., 2012).

The current study investigated whether posttraining administration of CORT into the DMS enhances the consolidation of spatial memory and thereby influences the selection of competing navigation strategies. In the first phase of the study we examined whether CORT administration into the DMS would enhance memory consolidation of place or cue water-maze training. In the final phase of these experiments, we investigated whether the enhanced memory consolidation of place training would bias the selection of an allocentric spatial navigation strategy when it is presented concurrently with a competing procedural navigation strategy.

2. Materials and methods

2.1. Subjects

Adult male Wistar rats ($n = 48$; 250–350 g at the time of training) from the breeding colony at the Instituto de Neurobiología, Universidad Nacional Autónoma de Mexico were housed individually in transparent acrylic cages (24 cm × 21 cm × 45 cm) in a temperature-controlled (22 °C) vivarium and maintained on a 12 h/12 h light/dark cycle (lights on: 7:00 AM to 7:00 PM) with food and water available *ad libitum*. Training and testing were performed during the light phase of the cycle between 10:00 AM and 3:00 PM, at the rat's nadir of endogenous glucocorticoid levels. All experimental procedures were in compliance with the National Institutes of Health guidelines and approved by the Bioethics Committee of the Instituto de Neurobiología, Universidad Nacional Autónoma de México.

2.2. Cannula implantation

Rats, adapted to the vivarium for 1 week, were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and subsequently injected with atropine sulfate (0.4 mg/kg, i.p.) and 3 ml of saline. The skull was positioned in a stereotaxic frame (Stoelting Co.; Illinois) and two 15 mm long stainless-steel guide cannulae (23 gauge) were implanted bilaterally into the DMS (coordinates: anteroposterior, +0.7 mm relative to Bregma; mediolateral, ±2.6 mm from midline: dorsoventral, 4.4 mm below skull surface), based on the coordinates taken from Paxinos and Watson (2005). The cannulae were affixed to the skull with four anchoring screws and dental cement. Stylets (15 mm long) were inserted into each cannula to maintain patency and were removed only for the infusion of drugs. After surgery, the rats were kept in an incubator until fully recovered from anesthesia and were then returned to their home cages. Following surgery, rats were allowed to recover for 10 days before initiation of training.

2.3. Water-maze apparatus and procedures

A black circular plastic tank (60 cm height × 154 cm diameter), elevated 60 cm above the floor, was used for both the place and cue tasks. The tank was functionally divided into four equal virtual quadrants, with an escape platform positioned in one of the quadrants. The room was dimly illuminated with four 60 W light bulbs located in each of the corners of the room. A video camera was mounted above the pool to record swimming trials, and video tracking software (Smart 3.0, San Diego Instruments) calculated swimming paths, escape latencies and the number of crossings into the different target regions of the four quadrants. All rats were trained and tested at a water temperature of 25 ± 1 °C and were handled for 3 days prior to the first training day.

Training and testing on the place and cue tasks were conducted for four consecutive days with a competition test on the fifth day. The experiments were counterbalanced with respect to training order, such that half of the rats ($n = 24$) were trained and tested first on the cue task (Day 1 and 2), followed by training and testing on the place task (Day 3 and 4). The other half was trained and tested in the reverse order (i.e., place-cue task) (Fig. 1). Training was done in a massed schedule such that each rat was run on all eight trials followed by another rat.

2.3.1. Place task

A training session on the place task consisted of eight consecutive trials. On each trial, the rat was placed inside the tank, facing the wall, at one of four designated starting points. An escape platform (12 × 12 cm) was submerged 1.5 cm below the water surface in the center of the northeast quadrant during the entire training session. Extra-maze visual cues located on the walls of the experimental room served as orientation landmarks. The latency to find the escape platform was recorded on all trials. If a rat failed to escape on the first trial within 60 s, it was manually guided toward the platform. After mounting the platform, the rat was allowed to remain there for 30 s and was then placed into an acrylic box with a red heating bulb inside for 30 s until the start of the next trial. Twenty-four hours later, retention of the place training was assessed by means of a 60 s test trial without an escape platform. The rat was released at a point in the tank from where it had not been previously trained. The latency to reach the target zone (virtual zone where the platform was formerly located) and the number of entries into the target zone compared to an oppositely located zone were selected as an index of spatial memory because