Neurobiology of Learning and Memory 141 (2017) 124–133

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Glucocorticoid administration into the dorsolateral but not dorsomedial striatum accelerates the shift from a spatial toward procedural memory

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ARTICLE INFO

Article history:
Received 27 June 2016
Revised 27 March 2017
Accepted 29 March 2017
Available online 30 March 2017

Keywords:
Dorsal striatum
Habit learning
Glucocorticoids
Memory consolidation
Memory systems
Behavioral switch

ABSTRACT

Glucocorticoid stress hormones are known to enhance the consolidation of hippocampus-dependent spatial and contextual memory. Recent findings indicate that glucocorticoids also enhance the consolidation of procedural memory that relies on the dorsal striatum. The dorsal striatum can be functionally subdivided into the dorsolateral striatum (DLS), which is primarily implicated in shaping procedural memories, and the dorsomedial striatum (DMS), which is engaged in spatial memory. Here, we investigated the hypothesis that posttraining glucocorticoid administration into the DLS promotes the formation of a procedural memory that will normally take place only with extensive training. Male Wistar rats were trained to find a reward in a cross maze that can be solved through either place or response learning. Rats received four trials per day for 5 days, a probe trial on Day 6, further training on Days 7–13, and an additional probe trial on Day 14. On Days 2–4 of training, they received posttraining infusions of corticosterone (10 or 30 ng) or vehicle into either the DLS or DMS. Rats treated with vehicle into either the DLS or DMS displayed place learning on Day 6 and response learning on Day 14, indicating a shift in control of learned behavior toward a habit-like procedural strategy with extended training. Rats administered corticosterone (10 ng) into the DLS displayed response learning on both Days 6 and 14, indicating an accelerated shift to response learning. In contrast, corticosterone administered posttraining into the DMS did not significantly alter the shift from place to response learning. These findings indicate that glucocorticoid administration into the DLS enhances memory consolidation of procedural learning and thereby influences the timing of the switch from the use of spatial/contextual memory to habit-like procedural memory to guide behavior.

1. Introduction

Stressful and emotionally arousing experiences are typically well retained, and it seems certainly highly adaptive to remember both dangerous and favorable situations (Joëls & Baram, 2009; Roozendaal & McGaugh, 2011). In these conditions, it is important to create strong memories of space, location, context, and stimulus-stimulus associations that all depend on the hippocampus, as well as to build skills or procedures leading to habits and stimulus-response associations that are encoded by other memory systems (White & McDonald, 2002). Extensive evidence indicates that the glucocorticoid hormones cortisol (in humans) and corticosterone (in rats) are crucially involved in mediating the facilitating effects of stress and emotional arousal on the consolidation of memory processing (Gaikwad et al., 2011; Roozendaal, 2000; Roozendaal, McEwen, & Chattarji, 2009; Roozendaal et al., 2010; Sandi & Rose, 1994; Schwabe, Joëls, Roozendaal, Wolf, & Oitzl, 2012; Schwabe & Wolf, 2010). Although most studies investigating the effects of glucocorticoids on memory consolidation have focused on their influence on hippocampal function and memory (Chaouloff & Groc, 2011; Cordero & Sandi, 1998; Lupien & Lepage, 2001; Roozendaal & McGaugh, 1997; Sandi, Loscertales, & Guaza, 1997; Schwabe, Bohringer, & Wolf, 2009; Schwabe, Romer, et al., 2009; Schwabe & Wolf, 2009; Schwabe & Wolf, 2012; Smeets, Giesbrecht, Jelicic, & Merckelbach, 2007), there is now accumulating evidence indicating that stress and glucocorticoids also influence the processing of non-hippocampal information (Atsak et al., 2016; Schwabe & Wolf, 2009; Schwabe & Wolf,

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http://dx.doi.org/10.1016/j.nlm.2017.03.020
1074-7427/

2012). Recent findings indicate that during stressful conditions both rodents and humans show a tendency to bias or prompt from a hippocampus-dependent spatial strategy to a striatum-dependent procedural-like strategy (Guenzel, Wolf, & Schwabe, 2014; Schwabe, Schachinger, de Kloet, & Oitzl, 2010). We previously reported that posttraining infusions of corticosterone into the dorsal striatum of rats enhanced the consolidation of inhibitory avoidance memory (Medina et al., 2007). Similarly, intra-striatal administration of corticosterone enhanced memory consolidation of cued training in a water maze, whereas it did not affect memory of spatial training (Quirarte et al., 2009). In the cued task, rats are trained to use a procedural-like strategy based on stimulus-response associations to swim to a visible cue mounted on a platform, which is placed in a different spatial location on each trial. These findings thus provide evidence of direct actions of glucocorticoids within the dorsal striatum in enhancing memory consolidation of procedural learning.

Procedural memory refers to memory for knowing how to do something and is non-accessible to awareness knowledge, manifested only through performance of a task and is built up gradually and incrementally with practice (Knowlton & Greenberg, 2008). It is known that procedural memories rely heavily on the dorsal striatum (Devan & White, 1999; Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; McDonald & White, 1994; Mishkin, Malamut, & Bachevalier, 1984; Packard & Knowlton, 2002; Saint-Cyr, Taylor, & Lang, 1988). The dorsal striatum can be divided into several functionally distinct sub-regions (Yin & Knowlton, 2004). The dorsolateral striatum (DLS) is engaged in processing procedural memory, whereas the dorsomedial striatum (DMS) is primarily involved in spatial-contextual processing (Liljeholm & O'Doherty, 2012; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004; Yin et al., 2009). Lesion and inactivation studies of the DLS have shown impairments in habit formation and, in parallel, an enhancement in the ability to detect changes in action-outcome contingencies (Packard & McGaugh, 1996; Yin, Knowlton, & Balleine, 2004; Yin, Knowlton, & Balleine, 2006). Furthermore, interfering with glutamatergic activity of the DLS impairs the acquisition of procedural learning (Palencia & Ragozzino, 2005). On the other hand, lesions of the DMS delay the onset of spatial learning (Lee, André, & Pittenger, 2014), and temporary inactivation of the DMS impairs reversal learning on a spatial task without affecting the initial learning (Ragozzino & Choi, 2004). Consistent with these findings, we recently reported that corticosterone administered selectively into the DMS enhanced memory consolidation of spatial, but not cued, water-maze training (Lozano, Serafín, Prado-Alcalá, Roozendaal, & Quirarte, 2013).

In the present study, we investigated the effect of corticosterone administration into the DLS and DMS on memory consolidation in a dual-solution task in a cross maze that could be solved by either a procedural or spatial strategy. By training rats to find a reward at a fixed location in a cross maze, at earlier phases of acquisition a place strategy is shaped, which is encoded by the hippocampus and DMS (Pennartz et al., 2009; Ragozzino & Choi, 2004; Yin & Knowlton, 2004). After extensive training, a shift occurs to a complimentary mechanism based on a more habit-like response strategy operated by the DLS (Barnes, Kubota, Hu, Jin, & Graybiel, 2005; Packard & McGaugh, 1996). A previous study reported that glutamate administered posttraining into the hippocampus during an early stage of training promoted the persistent use of a place strategy, whereas similar infusions into the dorsal striatum, not explicitly differentiating between the DLS and DMS, facilitated the expression of a response strategy (Packard, 1999). Here, we examined the effect of posttraining corticosterone infusions administered into either the DLS or DMS during an early phase of training on the relative use of a place and response strategy. We predicted that corticosterone administered into the DLS would enhance the consolidation of procedural memory and thereby accelerate the switch toward a response strategy, whereas corticosterone infused into the DMS would facilitate spatial memory which might attenuate the shift to a response strategy seen with extended training.

2. Methods

2.1. Subjects

Male adult Wistar rats (n = 171, eight weeks old, weighing 250–350 g at the time of surgery) were obtained from the breeding colony at the Instituto de Neurobiología, Universidad Nacional Autónoma de México. They were housed individually in transparent acrylic cages at a room temperature of 22 °C and a 12-h:12-h light:dark cycle (lights on from 7:00 to 19:00 h). Food was available *ad libitum* until food restriction commenced, and water was available in the home cage throughout the experiment. All experimental procedures were in compliance with the NIH Guide for Care and Use of Laboratory Animals (National Research Council, 2011) and were approved by the Ethics Committee of the Instituto de Neurobiología.

2.2. Surgery

After an acclimatization period of at least 1 week, rats received surgical implantation of bilateral cannulae aimed at either the DLS or DMS. They were first injected with atropine (PiSa, 0.4 mg/kg, ip) to prevent respiratory tract obstruction and maintain breathing, followed by sodium pentobarbital (Pisabarbital 50 mg/kg, ip) to induce anesthesia. Subsequently, 2 ml of isotonic saline was injected subcutaneously to prevent dehydration and facilitate clearance of the drugs. The rats were positioned in a stereotaxic frame (Stoelting Co, Illinois) with an incisor bar, and stainless-steel guide cannulae (11 mm, 23 gauge) were implanted bilaterally with the cannula tips aimed at either the DLS [coordinates: anteroposterior (AP): +0.7 mm to Bregma, mediolateral (ML): ±3.6 mm to midline, dorsoventral (DV): 4.0 mm below skull surface] or the DMS [coordinates: AP: +0.7 mm, ML: ±2.6 mm, DV: −4.0 mm], according to the atlas of Paxinos and Watson (2007). The cannulae were anchored to the skull with two jeweler's screws and dental acrylic. Stylets (11 mm long) were inserted into each cannula to maintain patency and were removed only during the handling sessions ("dummy injections") and drug administrations. After surgery, the rats were allowed to recover from anesthesia in an incubator until they were fully awake and were then returned to their home cages. They were allowed 1 week to recover before initiation of behavioral procedures.

2.3. Behavioral procedures

2.3.1. Apparatus

The apparatus was a wooden cross maze painted flat gray. The four identical arms (north, south, east and west) measured 16.5 cm wide × 22 cm high × 80 cm long with a recessed food well present at the end of each arm. The maze was located in a dimly illuminated room and surrounded by black curtains hanging from the ceiling to the floor. There were several extramaze cues attached to the curtains such as a black-and-white circle pattern (35 cm diameter), a poster (90 × 120 cm), a green star figure (20 cm high) and a cyan triangle framed by a white rectangle (40 × 35 cm). The experimenter was also considered an extramaze cue, so she remained at the same location for all training and test trials.