Glucocorticoid-cholinergic interactions in the dorsal striatum in memory consolidation of inhibitory avoidance training

Oscar Sánchez-Resendis¹, Andrea C. Medina¹, Norma Serafin¹, Roberto A. Prado-Alcalá¹, Benno Roozendaal² and Gina L. Quirarte¹*

¹ Departamento de Neurobiología Conductual y Cognitiva, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Querétaro, México
² Departamento de Neurobiología Conductual y Cognitiva, Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus Juriquilla, Querétaro, México

INTRODUCTION

It is well established that glucocorticoid hormones (corticosterone in rodents, cortisol in humans), released from the adrenal cortex during stressful episodes, act in a neurocircuitry of interconnected brain regions to enhance the consolidation of memory of emotionally arousing training experiences (de Kloet et al., 1999; Roozendaal, 2002; McGaugh, 2004; Miranda et al., 2008; Roozendaal et al., 2009; Joëls et al., 2011; Schwabe et al., 2012). For example, corticosterone or a specific glucocorticoid receptor (GR) agonist administered into either the basolateral complex of the amygdala (BLA) or hippocampus is known to enhance memory consolidation of inhibitory avoidance training (Roozendaal and de Kloet, 1997a,b). Recently, we reported that the dorsal striatum is another target structure for glucocorticoids in modulating memory consolidation of inhibitory avoidance training (Medina et al., 2007), these findings suggest that corticosterone might act within the dorsal striatum to specifically enhance the consolidation of memory of procedural aspects of inhibitory avoidance training, consistent with the evidence that the dorsal striatum is crucially involved in memory formation of procedural or non-declarative training (Packard and White, 1991; McDonald and White, 1993; Packard et al., 1994; Packard and Knowlton, 2002; Prado-Alcalá et al., 2003; White, 2009).

One of the neurotransmitter systems of the dorsal striatum that has received most attention is its intrinsic cholinergic system. On the one hand, it has been shown that striatal cholinergic interneurons are involved in motor control, as seen in humans where dysfunction of this complex system leads to movement disorders such as Huntington’s and Parkinson’s disease (Sandberg et al., 1984; Galarraga et al., 1999; Pisani et al., 2001; Wilson, 2004; Graybiel, 2008). On the other hand, muscarinic receptor antagonists administered into the dorsal striatum are known to induce

Extensive evidence indicates that glucocorticoid hormones act in a variety of brain regions to enhance the consolidation of memory of emotionally motivated training experiences. We previously reported that corticosterone, the major glucocorticoid in the rat, administered into the dorsal striatum immediately after inhibitory avoidance training dose-dependently enhances memory consolidation of this training. There is also abundant evidence that the intrinsic cholinergic system of the dorsal striatum is importantly involved in memory consolidation of inhibitory avoidance training. However, it is presently unknown whether these two neuromodulatory systems interact within the dorsal striatum in the formation of long-term memory. To address this issue, we first investigated in male Wistar rats whether the muscarinic receptor agonist oxotremorine administered into the dorsal striatum immediately after inhibitory avoidance training enhances 48 h retention of the training. Subsequently, we examined whether an attenuation of glucocorticoid signaling by either a systemic administration of the corticosterone-synthesis inhibitor metyrapone or an intra-striatal infusion of the glucocorticoid receptor (GR) antagonist RU 38486 would block the memory enhancement induced by oxotremorine. Our findings indicate that oxotremorine dose-dependently enhanced 48 h retention latencies, but that the administration of either metyrapone or RU 38486 prevented the memory-enhancing effect of oxotremorine. In the last experiment, corticosterone was infused into the dorsal striatum together with the muscarinic receptor antagonist scopolamine immediately after inhibitory avoidance training. Scopolamine blocked the enhancing effect of corticosterone on 48 h retention performance. These findings indicate that there are mutual interactions between glucocorticoids and the striatal cholinergic system in enhancing the consolidation of memory of inhibitory avoidance training.

Keywords: glucocorticoid receptor, caudate nucleus, corticosterone, oxotremorine, scopolamine, stress hormone

Original Research Article

Published: 22 June 2012
doi: 10.3389/fnbeh.2012.00033

Frontiers in Behavioral Neuroscience www.frontiersin.org

June 2012 | Volume 6 | Article 33 | 1
retrograde amnesia of inhibitory avoidance training (Haycock et al., 1973; Prado-Alcalá et al., 1980) in a time- and dose-dependent fashion (Prado-Alcalá et al., 1984b, 1985; Giordano and Prado-Alcalá, 1986), whereas the intra-striatal administration of muscarinic receptor agonists improves retention of this training (Solana-Figueroa and Prado-Alcalá, 1990). Additional support for the view that the striatal cholinergic system modulates memory consolidation came from experiments indicating that local activation or blockade of the cholinergic system either enhances or impairs memory of active avoidance, lever pressing, and autoshaping (Neill and Grossman, 1970; Prado-Alcalá et al., 1984a; Bermúdez-Rattoni et al., 1986).

Several findings indicate that stress exposure influences activity of the cholinergic system in the brain (Mark et al., 1996; Ortega et al., 1996; Gold, 2003) as well as that the stress associated with certain training procedures can alter cholinergic activity (Tajima et al., 1996; Orsini et al., 2001; Helm et al., 2004). However, much less is known of whether such stress effects on cholinergic activity are mediated by glucocorticoid actions. Given that both glucocorticoids and the cholinergic system play an important role within the dorsal striatum in memory consolidation, the present study investigated whether glucocorticoids and the striatal cholinergic system interact in modulating memory consolidation of inhibitory avoidance training. To address this issue, we first investigated whether the muscarinic receptor agonist oxotremorine administered into the dorsal striatum immediately after inhibitory avoidance training enhances the consolidation of memory of the training experience. Subsequently, we examined whether either systemic administration of the corticosterone-synthesis inhibitor metyrapone, suppressing the endogenous corticosterone response, or an infusion of the GR antagonist RU 38486 directly into the dorsal striatum would block the enhancing effect of oxotremorine on inhibitory avoidance memory. In the last experiment, we used a complementary approach and investigated whether a blockade of muscarinic receptors in the dorsal striatum after inhibitory avoidance training would prevent the memory enhancement induced by corticosterone.

**MATERIALS AND METHODS**

**ANIMALS**

Adult male Wistar rats (250–350 g at the time of surgery), obtained from the breeding colony of the Instituto de Neurobiología, Universidad Nacional Autónoma de México, were housed individually in acrylic cages with food and tap water available ad libitum. They were maintained on a 12/12 h light-dark cycle (lights on at 7:00 h) and a constant room temperature of 21°C. The rats were randomly assigned to the different experimental groups, with initial sample sizes ranging from 10 to 12 rats per group. All experimental procedures were approved by the Animal Ethics Committee of the Instituto de Neurobiología, Universidad Nacional Autónoma de México, and were in compliance with the “Principles of Laboratory Animal Care” of the National Institutes of Health.

**SURGERY**

Animals, adapted to the colony room for at least one week, were anesthetized with sodium pentobarbital (50 mg/kg of body weight, ip) and given atropine sulfate (0.4 mg/kg, ip) to maintain respiration. The skull was positioned in a stereotaxic frame (Stoelting, Co. IL) and two stainless-steel guide cannulae (11 mm long, 23 gauge) were implanted into the anterior division of the dorsal striatum (coordinates: anteroposterior, 0.0 mm from Bregma; mediolateral, ±3.2 mm from midline; dorsoventral, 4.2 mm below skull surface, incisor bar –3.3 mm from interaural line) according to the atlas of Paxinos and Watson (2005). The cannulae were affixed to the skull with two anchoring screws and dental cement. Stylets (11 mm long 00-insect dissection pins) were inserted into each cannula to maintain patency and were removed only for the infusion of drugs. After surgery, the rats received a subcutaneous 1 ml injection of saline to prevent dehydration and were retained within an incubator until recovered from anesthesia and were then returned to their home cages. The rats were allowed to recover for a minimum of seven days before initiation of training and were handled three times for 3 min each during this period to accustom them to the infusion procedures.

**INHIBITORY AVOIDANCE APPARATUS AND PROCEDURES**

The rats were trained and tested in an inhibitory avoidance apparatus consisting of a trough-shaped alley (20 cm wide at the top and 8 cm wide at the bottom) with two distinct compartments of the same size (30 × 30 × 30 cm), separated by a sliding door. The starting compartment had walls and lid made of red-colored acrylic with a floor of stainless steel bars (6 mm in diameter, separated by 9 mm) and was illuminated by a 10-W light bulb. The shock compartment was made of two electrically stainless steel plates and was not illuminated with its end walls and lid constructed of red-colored acrylic. In the middle of the floor, a 1.5 cm slot separated the two stainless steel plates that made up the walls and floor. The apparatus was located inside a dark, sound-attenuated room provided with background masking noise (San Diego Instruments).

For training, the rat was placed into the starting compartment of the apparatus and 10 s later the sliding door was opened and the latency to enter the dark compartment was recorded. After the animal stepped into the shock compartment with all four paws, the door was closed and a single, inescapable footshock (0.60 mA, 1 s) was delivered using a precision-regulated animal shock generator (Coulbourn Instruments, USA). Automated equipment controlled the duration of the footshock and measured the rat’s latency to cross from one compartment to the other. The rat was removed from the shock compartment 10 s after termination of the footshock and, after drug treatment, returned to the home cage. On the 48 h retention test, as on the training session, the latency to re-enter the shock compartment with all four paws (maximum latency of 600 s) was recorded and used as a measure of retention. Longer latencies were interpreted as indicating better retention. Shock was not administered on the retention test trial.

**DRUG AND INFUSION PROCEDURES**

The muscarinic receptor agonist oxotremorine (0.15, 0.30, 0.45, 0.60, or 1.0 μg in 1 μl, Sigma-Aldrich) was dissolved in sodium phosphate buffer, pH 7.4, and infused into the dorsal striatum immediately after inhibitory avoidance training. Bilateral infusions of drug, or an equivalent volume of vehicle, were made using
30-gauge injection needles connected to 10 μl Hamilton microsyringes by polyethylene (PE-20) tubing, driven by an automated microinfusion pump (model 220i, WPI). The injection needles protruded 2 mm beyond the tip of the cannula and an injection volume of 1 μl per hemisphere was delivered over 1 min. The injection needles were retained within the cannulae for an additional minute following drug infusion to maximize diffusion and prevent backflow of drug into the cannulae.

For adrenocortical suppression, the 11-β-hydroxylase inhibitor metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone; 50 mg/kg; Sigma-Aldrich) was injected subcutaneously in a volume of 2 ml/kg 90 min before training. Metyrapone was first dissolved in 100% polyethylene glycol and subsequently diluted with 0.9% saline to reach the appropriate concentration. The final concentration of polyethylene glycol was 40%. The vehicle control contained the same polyethylene glycol concentration.

The dose of metyrapone was selected on the basis of previous findings indicating that it effectively blocks stress-induced increases in circulating levels of corticosterone without affecting basal levels (Roozendaal et al., 1996). In this study we did not measure corticosterone levels because there is evidence showing that the dose of metyrapone that we used (50 mg/kg) induced a significant reduction of peripheral corticosterone levels and produces memory impairment in different tasks such as passive avoidance in chicks (Loscertales et al., 1997), conditioned taste aversion (Miranda et al., 2008), spatial memory (Akirav et al., 2004), and blocks the memory enhancing effects of amphetamine or ephinephrine (Roozendaal et al., 1996) as well as the memory facilitation by stressful conditions during learning (Conboy and Sandi, 2010).

The GR antagonist RU 38486 (17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one; 10 ng in 1 μl; Sigma-Aldrich) was microinjected into the dorsal striatum 15 min before training. RU 38486 was first dissolved in 100% ethanol and subsequently diluted in saline. The final ethanol concentration was 2%. The dose of RU 38486 was selected on the basis of previous findings indicating that, when administered into the dorsal striatum, it blocks memory enhancement of inhibitory avoidance training induced by concurrently administered corticosterone (Medina et al., 2007).

For the last experiment, corticosterone (10 or 30 ng in 1 μl; Sigma-Aldrich) was administered into the dorsal striatum together with the muscarinic receptor antagonist scopolamine (30 μg; Sigma-Aldrich) immediately after inhibitory avoidance training. Corticosterone and scopolamine were dissolved in a vehicle containing 2% ethanol in phosphate buffer, pH 7.4. The dose of corticosterone was selected on the basis of prior experiments (Medina et al., 2007).

HISTOLOGY
After completion of behavioral testing, the rats were deeply anesthetized with sodium pentobarbital and perfused transcardially with isotonic saline followed by 4% formaldehyde. After decapitation, the brains were removed and immersed in a 4% formaldehyde solution for at least five days. Sections of 50 μm were cut on a cryostat and stained with cresyl-violet. The sections were examined under a light microscope, and the location of injection needle tips within the dorsal striatum was determined.

Histological analysis revealed that the injection needle tips of seven rats were not located within the boundaries of the targeted area. The data of these animals were not included in the statistical analyses. Figure 1 shows the location of the injection needle tips within the dorsal striatum of rats included in the statistical analyses.

STATISTICS
Data are presented as median + interquartile ranges. Inhibitory avoidance training and retention latencies were analyzed with independent Kruskal–Wallis analyses of variance. When appropriate, Mann–Whitney U-tests were used to make comparisons between any two groups. A probability level of <0.05 was accepted as statistical significance. The number of rats per group is indicated in the figure legends.

RESULTS
IMMEDIATE POST-TRAINING INFUSIONS OF OXOTREMORINE INTO THE DORSAL STRIATUM DOSE-DEPENDENTLY ENHANCE INHIBITORY AVOIDANCE MEMORY
The first experiment investigated whether bilateral infusions of the muscarinic receptor agonist oxotremorine (0.15, 0.3, 0.45, 0.6
or 1.0 μg in 1 μl) given immediately after inhibitory avoidance training enhance performance on a 48 h retention test. Entrance latencies during the training trial, before footshock or drug treatment, did not differ among groups \( [H_{(5)} = 5.15, P = 0.39; \text{data not shown}] \). As is shown in Figure 2, Kruskal–Wallis test for 48 h retention latencies revealed a significant group effect \( [H_{(5)} = 18.24, P < 0.005] \). Oxotremorine in a dose of 0.3 μg produced significantly longer retention latencies than those of rats treated with vehicle \( (P < 0.05) \). Lower or higher doses of oxotremorine did not alter retention performance.

**OXOTREMORINE-INDUCED MEMORY ENHANCEMENT DEPENDS ON CONCURRENT GLUCOCORTICOID ACTIVATION**

In this experiment we investigated whether an attenuation of glucocorticoid signaling alters the memory-enhancing effects of post-training muscarinic cholinergic activation within the dorsal striatum. In the first part, rats were injected subcutaneously with the corticosterone-synthesis inhibitor metyrapone (50 mg/kg) or vehicle 90 min before inhibitory avoidance training, followed by a bilateral intra-striatal infusion of oxotremorine (0.3 or 1.0 μg) immediately after the training trial. Entrance latencies during training did not differ among groups \( [H_{(5)} = 6.45 P = 0.26] \). However, there were significant group differences in 48 h retention latencies \( [H_{(5)} = 20.48, P = 0.001] \). Consistent with the findings of the first experiment, Mann–Whitney U-tests indicated that rats treated with the 0.3 μg dose of oxotremorine had longer retention latencies than rats administered vehicle or the higher dose of oxotremorine (\( P \)'s ranging from 0.05 to 0.005). Metyrapone treatment blocked the retention enhancement induced by intra-striatal oxotremorine administration and retention latencies of the metyrapone-oxotremorine (0.3 μg) group were significantly shorter than those of the vehicle-oxotremorine (0.3 μg) group \( (P < 0.002) \) (Figure 3A).

In the second part of the experiment, the GR antagonist RU 38486 (10 ng) was administered bilaterally into the dorsal striatum 15 min before training, followed by oxotremorine (0.3 or 1.0 μg) immediately after the training. Entrance latencies during the training trial did not differ among groups \( [H_{(5)} = 7.61 P = 0.17] \). During 48 h retention testing, significant group differences were found \( [H_{(5)} = 17.49, P < 0.005] \). Rats treated with
the lower dose of oxotremorine (0.3 μg) had significantly longer retention latencies than rats treated with either vehicle or the higher dose of oxotremorine (P’s < 0.002 and 0.05, respectively). In rats also administered RU 38486, the memory-enhancing effect of oxotremorine was abolished and retention latencies of the RU 38486-oxotremorine (0.3 μg) group were significantly shorter than those of the vehicle-oxotremorine (0.3 μg) group (P < 0.05) (Figure 3B).

CORTICOSTERONE-INDUCED MEMORY ENHANCEMENT DEPENDS ON CHOLINERGIC ACTIVITY WITHIN THE DORSAL STRIATUM

To explore further the nature of the interaction between glucocorticoids and the cholinergic system in memory consolidation, corticosterone (10 or 30 ng) was administered bilaterally into the dorsal striatum either alone or together with the muscarinic receptor antagonist scopolamine (30 μg) immediately after inhibitory avoidance training. Entrance latencies during the training trial, before footshock or drug treatment, did not differ among groups [H(3) = 5.15 P = 0.40]. As is shown in Figure 4, Kruskal–Wallis analysis revealed significant differences in 48 h retention latencies [H(3) = 11.28, P < 0.05]. The 10 ng dose of corticosterone, but not the 30 ng dose, enhanced retention latencies (P < 0.05). However, scopolamine treatment blocked the memory-enhancing effect of corticosterone. Retention latencies of rats given corticosterone (10 ng) together with scopolamine were significantly shorter than those of rats given that dose of corticosterone alone (P < 0.05).

DISCUSSION

The present findings indicate that glucocorticoids and the cholinergic system of the dorsal striatum interact in enhancing the consolidation of memory of inhibitory avoidance training. Microinfusion of the muscarinic receptor agonist oxotremorine into the dorsal striatum immediately after inhibitory avoidance training dose-dependently enhanced 48 h retention performance. However, and importantly, an attenuation of glucocorticoid signaling with either a systemic administration of the corticosterone-synthesis inhibitor metyrapone or an intra-striatal administration of the GR antagonist RU 38486 blocked the memory-enhancing effect of oxotremorine. Further, we found that corticosterone enhanced memory when infused into the dorsal striatum after inhibitory avoidance training and that this corticosterone effect was blocked in rats concurrently administered the muscarinic receptor antagonist scopolamine.

The current finding that oxotremorine administered into the dorsal striatum after inhibitory avoidance training enhanced 48 h retention performance is consistent with extensive evidence from other studies indicating that post-training activation of muscarinic receptors in this brain region enhances retention of inhibitory avoidance training (Solana-Figueroa and Prado-Alcalá, 1990; Ortega et al., 1996; Packard et al., 1996) or of training on several other learning tasks (Brimblecombe, 1964; Baratti et al., 1979), whereas a post-training blockade of muscarinic receptors impairs retention of inhibitory avoidance and other training (Prado-Alcalá et al., 1984b; Giordano and Prado-Alcalá, 1986). Similarly, our finding that post-training infusions of corticosterone into the dorsal striatum enhance retention of inhibitory avoidance training is consistent with other recent findings from our laboratory (Medina et al., 2007). As these memory-enhancing drugs were administered after the training trial, non-specific drug influences on the acquisition (i.e., footshock sensitivity, locomotion, attention, arousal, etc.) are excluded. Also, because these drugs are effective at enhancing long-term retention only when given within several hours after the training experience (Flood et al., 1978; Giordano and Prado-Alcalá, 1986; Sandi and Rose, 1994), the present findings strongly suggest that these drug effects on retention performance are due selectively to influences on the consolidation of long-term memory.

The aim of the present experiments was to investigate whether the glucocorticoid and cholinergic systems of the dorsal striatum interact in modulating memory consolidation of inhibitory avoidance training. The interest of this question stems from previous work indicating that stressful stimulation, either exogenously or induced by the training procedure, can alter cholinergic activity in the brain. Stressful stimuli are known to promote the release of acetylcholine in the hippocampus (Mark et al., 1996), which might directly contribute to the enhancing effects of stress on synaptic plasticity and memory (Shinoe et al., 2005). In addition to such immediate effects of stress-induced acetylcholine release on synaptic plasticity, stressful experiences might also regulate synaptic plasticity in a slower fashion by increasing, for example, the genetic expression of cholinergic nicotinic (Takita and Muramatsu, 1995) and muscarinic receptors (Takayama et al., 1987; Mizukawa et al., 1989; Gonzalez and Pazos, 1992; Kaufer et al., 1998; Brand et al., 2008). Our findings indicating that a blockade of glucocorticoid signaling prevented memory enhancement induced by oxotremorine and, conversely, that a blockade of muscarinic receptors prevented memory enhancement induced by corticosterone, suggest that glucocorticoids might be involved in mediating at least some of these stress effects on the cholinergic system.
There is some evidence in other brain regions indicating interactions between glucocorticoids and the cholinergic system. An in vivo microdialysis study reported that complete removal of glucocorticoids by adrenalectomy enhanced hippocampal levels of acetylcholine in response to potassium chloride stimulation (Mizoguchi et al., 2008). Another study investigated the interaction between glucocorticoids and the cholinergic system within the BLA in enhancing memory consolidation of inhibitory avoidance training (Power et al., 2000). Consistent with the current findings, blockade of muscarinic cholinergic activity within the BLA with atropine prevented the memory-enhancing effect of a concurrently administered GR agonist. In view of the evidence that glucocorticoids enhance memory consolidation by facilitating arousal-induced noradrenergic activation within the BLA (Quijarte et al., 1997; Roozendaal, 2002; Roozendaal et al., 2006), these findings were interpreted in support of the view that noradrenergic activation requires downstream cholinergic signaling within the BLA in enhancing memory consolidation (Introini-Collison and McGaugh, 1988; Decker et al., 1990). Although very little is known concerning a possible involvement of the noradrenergic system within the dorsal striatum in memory consolidation, findings from our laboratory indicate that noradrenergic activity within the dorsal striatum is essential for mediating glucocorticoid effects memory consolidation (Espinoza-González et al., 2007). Thus, such findings suggest that glucocorticoids might interact with the cholinergic system indirectly via an activation of the noradrenergic system. However, the other findings of the current study indicating that a blockade of glucocorticoid signaling with either metyrapone or GR antagonist also prevented the memory-enhancing effect of the muscarinic receptor agonist oxotremorine cannot be readily explained by such a mechanism: previous findings indicated that a blockade of β-adrenoceptor activity within the BLA does not block the memory-enhancing effect of a muscarinic receptor agonist (Introini-Collison et al., 1996). Thus, these findings indicating that cholinergic effects on memory consolidation require concurrent glucocorticoid signaling suggest that glucocorticoids might also act within the dorsal striatum at a level that is downstream of the cholinergic system.

As glucocorticoids and muscarinic receptor agonists are known to act in many different brain regions, including the BLA, hippocampus, and prefrontal cortex, in enhancing memory consolidation of inhibitory avoidance training (Roozendaal and McGaugh, 1997b; Roozendaal et al., 1999; Barsegian et al., 2010), what is so interesting about their effects in dorsal striatum? In inhibitory avoidance, rats learn that they receive footshock in a particular place. Previously, we developed a modified inhibitory avoidance procedure to investigate which components of the inhibitory avoidance training experience (i.e., memory of the context or the footshock were influenced by our drug manipulations). Whereas a GR agonist or oxotremorine infused into the BLA enhanced memory of both the contextual and footshock components of inhibitory avoidance training (Malin et al., 2007; Roozendaal et al., 2009), the same drugs infused into the hippocampus selectively enhanced memory of the contextual information of the task (Malin et al., 2007; Roozendaal et al., 2009). However, corticosterone administration into the dorsal striatum did not enhance memory of either the contextual or aversively motivational aspects of the task (Medina et al., 2007). In view of the evidence that the dorsal striatum is essentially involved in learning and memory of procedural or implicit forms of training (Jog et al., 1999; Decoteau and Kesner, 2000; Packard et al., 2001; Packard and Wingard, 2004; Reiss et al., 2005; Izquierdo et al., 2006; Packard, 2009), these findings led to the suggestion that glucocorticoids might act within the dorsal striatum to selectively enhance memory consolidation of procedural aspects of inhibitory avoidance training. This view was supported by the finding that corticosterone infused into the dorsal striatum after water maze training also selectively enhanced memory of cued training, without affecting memory of spatial training (Quijarte et al., 2009). Thus, these findings indicate that although glucocorticoids and cholinergic system act in many different brain regions to enhance memory consolidation of inhibitory avoidance training, each of the brain regions might contribute in a unique fashion to enhance the consolidation of memory of specific components of information acquired during the task.

In summary, the findings presented in this work indicate that memory consolidation of inhibitory avoidance learning is facilitated by the concurrent activity of the striatal cholinergic system and glucocorticoids. Based on our prior studies, they further suggest that it is the memory of the procedural attributes of this task that was influenced by these interactions. It would seem important to determine whether the striatal cholinergic system is actually involved in the procedural aspects of inhibitory avoidance memory, as in the case of glucocorticoids in this brain region.

ACKNOWLEDGMENTS

The authors thank Martín García, Ángel Méndez, Leopoldo González, and Leonor Casanova for excellent technical assistance. This research was supported by grants DGAPA-PAPIIT-UNAM (IN214111) and CONACYT 130524. This work was carried out in partial fulfillment of the requirements to obtain the Doctor’s Degree (Doctorado en Ciencias Biomédicas, UNAM) by O. Sánchez-Resendis, who was a recipient of a Graduate Scholarship from CONACYT (16317) and PDCB of CGEP-UNAM (90854363).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 25 February 2012; paper pending published: 20 March 2012; accepted: 08 June 2012; published online: 22 June 2012.

Citation: Sánchez-Resendis O, Medina AC, Serafín N, Prado-Alcalá RA, Roozendaal B and Quirarte GL (2012) Glucocorticoid–cholinergic interactions in the dorsal striatum in memory consolidation of inhibitory avoidance training. Front. Behav. Neurosci. 6:33. doi: 10.3389/fnbeh.2012.00033

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