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ORIGINAL INVESTIGATION

Roles of D1-like dopamine receptors in the nucleus accumbens and dorsolateral striatum in conditioned avoidance responses

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Abstract
Rationale Aversively motivated learning is more poorly understood than appetitively motivated learning in many aspects, including the role of dopamine receptors in different regions of the striatum.
Objectives The present study investigated the roles of the D1-like DA receptors in the nucleus accumbens (NAc) and dorsolateral striatum (DLS) on learning and performance of conditioned avoidance responses (CARs).
Methods Adult male Wistar rats received intraperitoneal (i.p.), intra-NAc, or intra-DLS injections of the D1 dopamine receptor agonist SKF 81297 or the D1 receptor antagonist SCH 23390 20 min before or immediately after a training session in the CAR task two-way active avoidance, carried out 24 h before a test session.
Results Pre-training administration of SCH 23390, but not SKF 81297, caused a significant decrease in the number of CARs in the test, but not in the training session, when injected into the DLS, or in either session when injected into the NAc. It also caused a significant increase in the number of escape failures in the training session when injected into the NAc. Systemic administration caused a combination of these effects. Post-training administrations of these drugs caused no significant effect.
Conclusions The results suggest that the D1-like receptors in the NAc and DLS play important, though different, roles in learning and performance of CAR.

Keywords Dorsolateral striatum · Nucleus accumbens · D1 dopamine receptor · Two-way active avoidance · Conditioned avoidance learning · Memory · Decision-making

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Introduction

There is strong evidence that appetitively motivated Pavlovian and instrumental learning depend on the nucleus accumbens (NAc) and dorsolateral striatum (DLS) (Balleine and O'Doherty 2010; Yin and Knowlton 2006). However, few studies have addressed the question of whether dopaminergic neurotransmission in these two regions of the striatum plays a role in aversively motivated learning, such

as in learning of conditioned avoidance responses (CARs). Computational models and empirical data suggest that learning actively to respond to a warning cue in order to avoid an aversive outcome depends on learning from positive prediction errors that occur when animals successfully avoid the aversive stimulus (Maia 2010; Moutoussis et al. 2008). As predicted by these models, active avoidance requires dopaminergic transmission (Beninger et al. 1980) and termination of an aversive stimulus is associated with phasic firing of dopamine (DA) neurons (Brischoux et al. 2009). Moreover, other models and data suggest that phasic DA signals reinforce responses via their actions on D1 receptors in the striatonigral "Go" (direct) pathway (Frank et al. 2004; Hikida et al. 2010). However, the role of D1 transmission per se, and of its specificity in ventral and dorsal striatum, in CAR has not been investigated.

The aim of this study is to address this question. CAR learning and performance were tested in two sessions of the two-way active avoidance task, a standard model of CAR in which rats learn that, when a warning stimulus (such as a light) appears, they can avoid a footshock by crossing to the opposite side of a two-chamber shuttle box. The role of D1 receptors in the NAc and DLS on CAR learning, memory consolidation, and performance was tested by evaluating the effects of pre- or post-training infusion of the D1 receptor agonist SKF 81297 or the D1 receptor antagonist SCH 23390 into these structures. The effects of systemic treatment with these drugs were also evaluated.

Materials and methods

Subjects

Adult male Wistar rats from our own breeding stock weighing 280–310 g at the beginning of the experiments were used. They were maintained in a temperature controlled room (22± 2°C) on a 12/12-h dark/light cycle (lights on, 7:00 a.m.) with food and water available ad libitum. All experimental procedures were approved by the UFPR Animal Care Committee (protocol 353) and were consistent with international legislation (EC Council Directive, 24 November 1986; 86/609/EEC).

Surgery

Seven days before the start of behavioral experiments rats received atropine sulfate (0.4 mg/kg, i.p.) and penicillin G-procaine (20,000 U in 0.1 ml, i.m.) and were anesthetized with 3 ml/kg equithesin (1% sodium thiopental, 4.25% chloral hydrate, 2.13% magnesium sulfate, 42.8% propylene glycol, and 3.7% ethanol in water). Next, stainless-steel guide cannulae (1 cm long, 23 ga.) were implanted bilaterally, aimed 2 mm above the DLS or NAc, according to the following coordinates adapted from the atlas of Paxinos and Watson (2005): DLS: AP 0.0 mm from bregma; ML ±3.8 mm from midline; DV −2.8 mm from skull surface; NAc: AP +1.7 mm from bregma; ML ±1.6 mm from midline; DV −5.2 mm from skull surface. The cannulae were fixed with polyacrylic cement anchored to the skull with stainless-steel screws. After surgery, rats were allowed to recover from anesthesia in a temperature controlled chamber and then placed back in their cages.

Drugs

SKF 81297 (2,3,4,5-tetrahydro-6-chloro-7,8-dihydroxy-phenyl-1*H*-3-benzazepine; Sigma Chemical, St. Louis, MO, USA) and SCH 23390 (*R*(+)-7-chloro-8-hydroxy-3-methyl-i-phenyl-2,3,4,5-tetrahy-dro-1*H*-3-benzazepine hydrochloride; Tocris Bioscience, USA) were dissolved in 1 ml/kg body weight saline (0.9% NaCl) for intraperitoneal (i.p.) injections; and in 0.4 μl/side artificial cerebrospinal fluid (aCSF: 8.66 g NaCl, 0.205 mg KCl, 0.176 g $CaCl_2{\cdot}2H_2O$, and 0.173 g $MgCl_2{\cdot}6H_2O$ in 1 l water, pH 7.4) for intra-NAc and intra-DLS injections.

Two-way active avoidance

The test apparatus was an automated 23×50×23 cm shuttle box (Insight Instruments, Ribeirao Preto, Brazil) with a Plexiglas front panel and floor made of parallel 5-mm caliber stainless-steel bars, 15 mm apart. The box was divided into two equal-sized compartments by a wall with a door that remained open during the tests. The animals were given training and test sessions, carried out 24 h apart. In the training session, after 10 min of habituation, 40 light cues (maximum duration of 20 s) were paired with a subsequent 0.4 mA footshock (maximum duration of 10 s, starting 10 s after the CS onset) until the animal crossed to the other compartment. The light cue consisted of illumination of two 30-W light bulbs that were centered on each side of the rear of the chambers. The rat could turn off the light and avoid footshock by crossing to the other chamber during presentation of the CS. If the rat did not avoid the shock by moving in advance of onset, it could still escape by crossing to the other chamber. The time between each trial varied randomly, ranging from 10 to 50 s. The numbers of active avoidances, escape failures, and inter-trial crossings (ITC) between the two compartments were recorded automatically. The test session was carried out

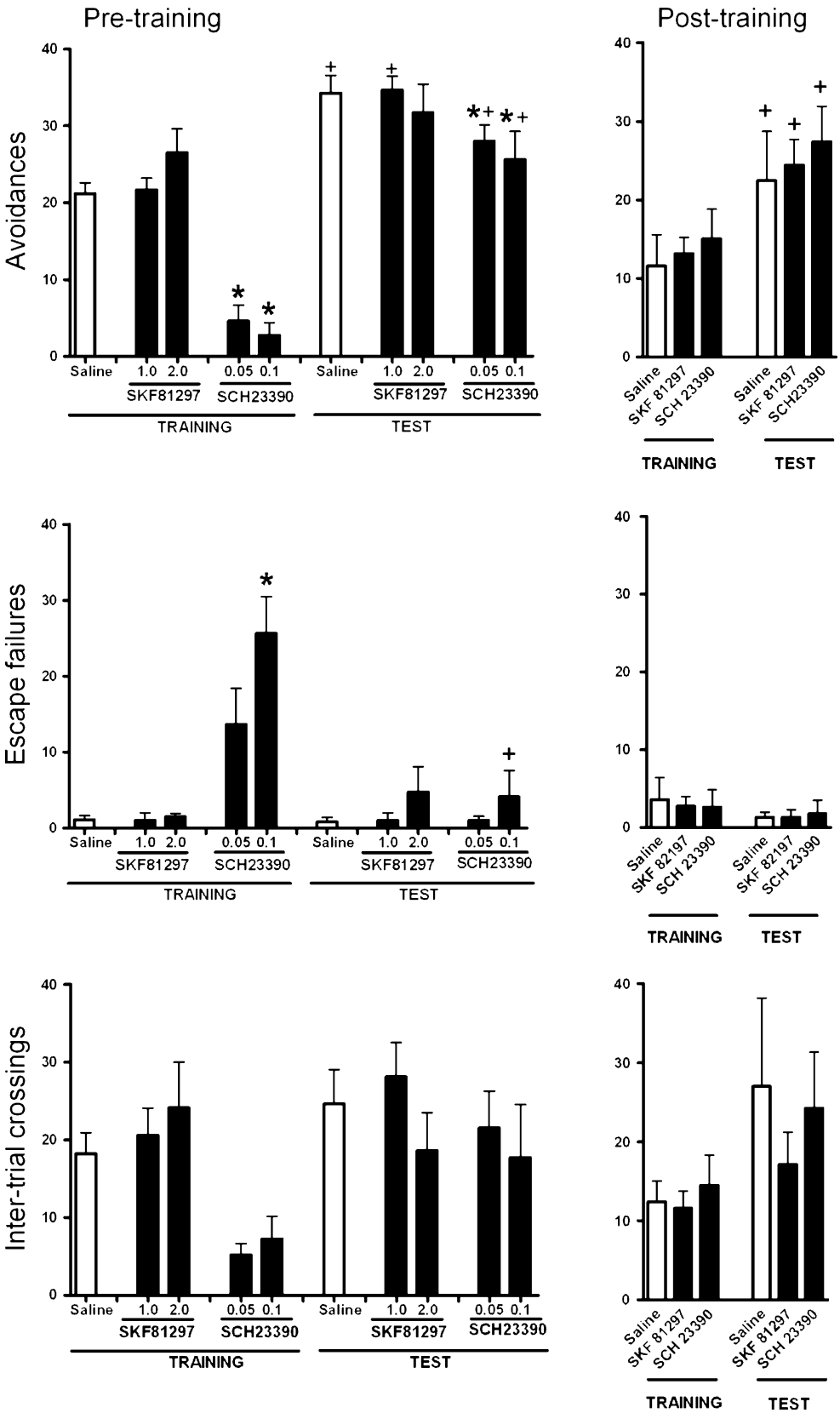


Fig. 1 Effect of i.p. injection of saline, the D1 dopamine receptor agonist SKF 81297, or the D1 receptor antagonist SCH 23390, 20 min before or immediately after the training session on two-way active avoidance scores. The doses are expressed in mg/kg and the data are expressed as mean± SEM. The post-training doses of SKF 81297 and SCH 23390 were 2 and 0.05 mg/kg, respectively. *$p<0.05$ compared to saline; $^{+}p<0.05$ compared to the same group on training session ($n=7–10$)

24 h later and was equal to the training sequence in all aspects, except that the habituation period was of 5 min.

Experiment 1: effect of systemic injection of SKF 81297 or SCH 23390 on two-way active avoidance

Drugs were administered by i.p. injection given 20 min before or immediately after the training session. Pre-training administrations were given to the following groups: saline (n=10), 1 mg/kg SKF 81297 (n=9), 2 mg SKF 81297 (n=8), 0.05 mg SCH 23390 (n=9), and 0.1 mg SCH 23390 (n=8). Drug doses and time schedules were chosen based on previous studies showing that, at the chosen doses, they produce reliable behavioral effects (Beninger and Rolfe 1995; Lapointe and Guertin 2008). Later, we selected the most effective dose for the post-training treatment. Post-training administrations were given to the following groups of different rats: saline (n=7), 2 mg SKF 81297 (n=7), and 0.05 mg SCH 23390 (n=8).

Experiment 2: effect of intra-NAc injection of SKF 81297 or SCH 23390 on two-way active avoidance

Drugs were infused into the NAc immediately before or immediately after the training session. We chose to administer the drugs immediately before training because the session started only 10 min after the rats were placed in the shuttle box. Infusions were made bilaterally through a pair of 30-ga. needles extending 2 mm beyond the tips of the implanted guide cannulae. They were gently inserted into each cannula while the rats were held. The injector was connected by polyethylene tubing to a 10-μl Hamilton syringe and the drug solution was injected over 1 min. The needles remained in place for an additional minute. Control animals received aCSF instead of drug solution.

Pre-training administrations were given to the following groups: aCSF (n=11), 0.4 μg/side SKF 81297 (n=9), and 0.4 μg/side SCH 23390 (n=9). Drug doses were chosen based on previous studies (Floresco and Phillips 1999; Schmidt and Pierce 2006). Post-training administrations were given to the following groups of different rats: aCSF (n=11), 0.4 μg/side SKF 81297 (n=6), and 0.4 μg/side SCH 23390 (n=14).

Experiment 3: effect of intra-DLS injection of SKF 81297 or SCH 23390 on two-way active avoidance

Drugs were infused into the DLS by using the protocol described in Experiment 2. The same doses and time schedules were maintained in order to compare the effects of the drugs in the two structures. Pre-training administrations were given to the following groups: aCSF (n=9), 0.4 μg/side SKF 81297 (n=8), and 0.4 μg/side SCH 23390 (n=7).

Post-training administrations were given to the following groups of different rats: aCSF (n=9), 0.4 μg/side SKF 81297 (n=8), and 0.4 μg/side SCH 23390 (n=13).

Histology

At the end of the experimental procedures, all rats were sacrificed with an overdose of pentobarbital. To check for cannulae placement, rats were transcardially perfused with a saline solution, followed by 4% paraformaldehyde; the brains were immediately post-fixed in the same fixative containing 20% sucrose for 48 h before sectioning. The brains were then cut in the frontal plane in 40-μm-thick sections with a vibrating blade microtome (Leica, VT1000 S, Bensheim, Germany). The sections were mounted on gelatin-coated slides and stained with thionin. Only the rats with appropriate placements in the DLS and the NAc were included in the statistical analysis of behavioral data.

Statistical analysis

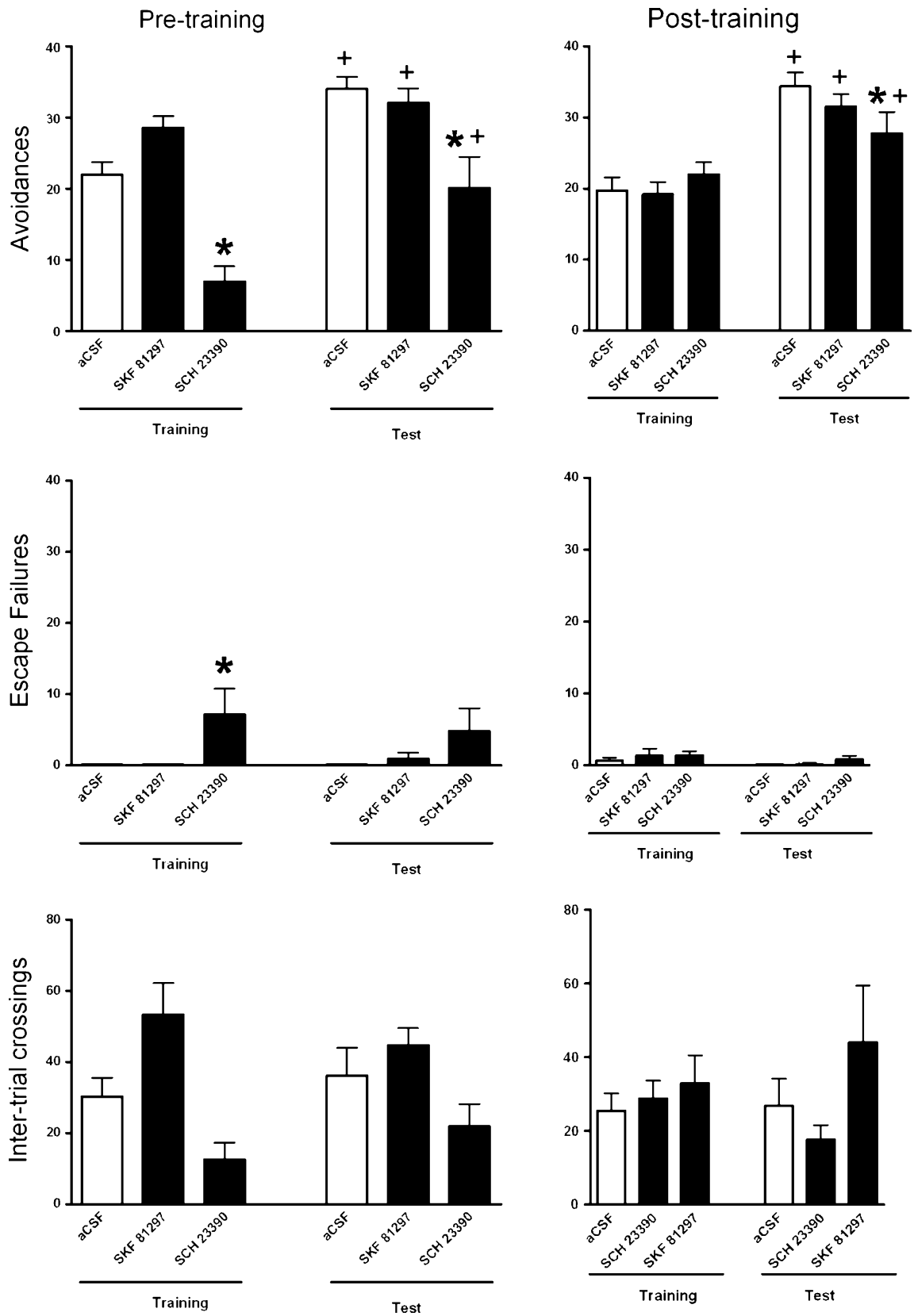
Data were analyzed by two-way ANOVA with repeated measures (session) followed by post-hoc Newman–Keuls tests. Differences were considered to be statistically significant when $p<0.05$.

Results

Experiment 1: effect of i.p. administration of SKF 81297 and SCH 23390 on two-way active avoidance

Avoidance data are shown in Fig. 1. Learning is evidenced by the significant increase in the number of CARs in the test compared to training session for the control (saline) group (session effect $F_{1,24}=34.43$; $p<0.001$, two-way ANOVA; $p<0.05$, Newman-Keuls post-hoc test). Pre-training administration of 0.05 or 0.1 mg/kg SCH 23390 caused a significant reduction in the number of CARs in the training and test sessions (group effect $F_{2,24}=16.80$, $p<0.001$; session effect $F_{1,24}=168.97$, $p<0.001$; interaction $F_{2,24}=5.15$, $p<0.01$, two-way ANOVA; $p<0.05$, Newman-Keuls post-hoc test). In the training, but not test session, escape failures were present after both doses (group effect $F_{2,24}=9.37$, $p<0.001$, two-way ANOVA), but this only achieved statistical significance with 0.1 mg/kg SCH 23390

Fig. 2 Effect of intra-NAc infusion of cerebrospinal fluid (aCSF), the D1 dopamine receptor agonist SKF 81297 (0.4 μg/side), or the D1 receptor antagonist SCH 23390 (0.4 μg/side) immediately before or immediately after the training session on two-way active avoidance scores. Data are expressed as mean (±SEM). *$p<0.05$ compared to saline; $^{+}p<0.05$ compared to the same group on training session (n=9–14). *aCSF* artificial cerebrospinal fluid


Pre-training
Post-training
Avoidances
Escape Failures
Inter-trial crossings
aCSF
SKF 81297
SCH 23390
Training
Test

($p<0.05$, Newman–Keuls post-hoc test). No significant effect was observed in the groups that received pre-training injections of SKF 81297 or post-training injections of any of these drugs.

Experiment 2: effect of administration of SKF 81297 and SCH 23390 into the NAc on two-way active avoidance

Avoidance data are shown in Fig. 2. Pre-training administration of 0.4 μg/side SCH 23390 caused a significant reduction in the number of CARs in the training and test sessions (group effect $F_{1,18}=22.30$, $p<0.001$; session effect $F_{1,18}=40.47$, $p<0.001$, two-way ANOVA; $p<0.05$ Newman–Keuls post-hoc test); a modest, but significant, increase in the number of escape failures in the training session ($F_{1,18}=6.51$, $p<0.05$; $p<0.05$ Newman-Keuls post-hoc test). SKF 81297 (0.4 μg/side) caused an increase and SCH23390 (0.4 μg/side) caused a decrease in the number of ITC in the training session, but this effect was not significant. No significant effect was observed in the groups that received post-training injections of any of these drugs.

Experiment 3: effect of administration of SKF 81297 and SCH 23390 into the DLS on two-way active avoidance

Avoidance data are shown in Fig. 3. The only significant effects were a reduction in the number of CARs in the test session caused by the pre-training administration of 0.4 μg/side SCH 23390 [group effect ($F_{1,14}=7.07$; $p<0.01$) and session effect ($F_{1,14}=7.27$; $p<0.01$), two-way ANOVA; $p<0.05$, Newman-Keuls post-hoc test] and a reduction in the number of ITC in the test session caused by the post-training administration of 0.4 μg/side SKF 81297 [non-significant group ($F_{1,15}=0.42$, $p=0.53$), and session ($F_{1,15}=2.93$, $p=0.11$) effects, but significant interaction ($F_{1,15}=6.18$; $p<0.05$), two-way ANOVA; $p<0.05$, Newman–Keuls post-hoc test].

Histology

The locations of the tip of the injection needles are shown in Figs. 4 and 5. All DLS cannulae were appropriately located. The majority of the NAc cannulae terminated in the core, with six found in the shell. The range of scores for all rats with NAc injections was similar. It is probable that the volume in which the drugs were injected spread through the core and shell regions.

Discussion

The results of the present study suggest that the activation of D1 receptors in the NAc and DLS play different roles in CAR learning and performance.

We found that the D1-like receptor antagonist SCH 23390 decreased CAR in the training sessions of two-way active avoidance when infused into the NAc, but not when infused into the DLS. On the other hand, intra-DLS administration of SCH 23390 caused a delayed reduction of CARs that appeared only in the test session carried out 24 h later. Pre-training administration of SKF into the NAc or i.p. caused a trend to increase CAR in the training session but this was not statistically significant. This suggests that activation of D1 receptors in the NAc and DLS is necessary for CAR learning and performance, but that they are optimally activated by endogenous DA. This adds to an important debate: striatal DA has been associated with reward processes for several decades but its role in aversively motivated learning remains uncertain and controversial (Berridge 2007; Horvitz 2000; Morris et al. 2010; Redgrave et al. 2008; Schultz 2010; Wise 2008).

CAR demands a mechanism by which an action can be triggered by a warning stimulus, and the striatum can provide such a mechanism (Da Cunha et al. 2009). Its projection neurons receive inputs from almost all areas of the cortex where warning stimuli are encoded (McGeorge and Faull 1989; Voorn et al. 2004). A subpopulation of neurons — "Go Neurons" (Frank et al. 2004) — trigger specific actions through direct projections to basal ganglia output stations that hold actions under tonic inhibition. These projections form the direct pathway (Alexander et al. 1990). D1 receptors expressed on Go Neurons play a dual role in cortico-basal ganglia neurotransmission: (i) they show long-term potentiation (LTP) (Lovinger 2010) when D1 receptors are activated by a large amount of DA released in response to unexpected aversive or appetitive events (Matsumoto and Hikosaka 2009; Shen et al. 2008); and (ii) they enhance signal-to-noise ratio — this facilitates Go Neurons to trigger learned responses (Hernandez-Lopez et al. 1987; Nicola et al. 2000; Wickens et al. 2007). Indeed, reversible blockade of neurotransmission in the direct pathway causes deficits in learning to approach in a rewarding context (Hikida et al. 2010).

These properties of striatal D1 receptors may explain why their blockade impairs both learning and performance of CAR. The same properties may also explain why SCH 23390 caused a significant increase of escape failures and a reduction (though not significant) of inter-trial crossings. In earlier times this would have been interpreted as an indication of motor impairment rather than a learning or action-selection deficit. However, the evidence that both learning and performance in Go Neurons are modulated by D1 receptors is now so solid (Matamales et al. 2009; Surmeier et al. 2007) that cognitive and motor aspects of action can be bound in a single function, making it difficult to consider response-reinforcement separately from motor performance (Di Chiara 2002). Indeed, computational

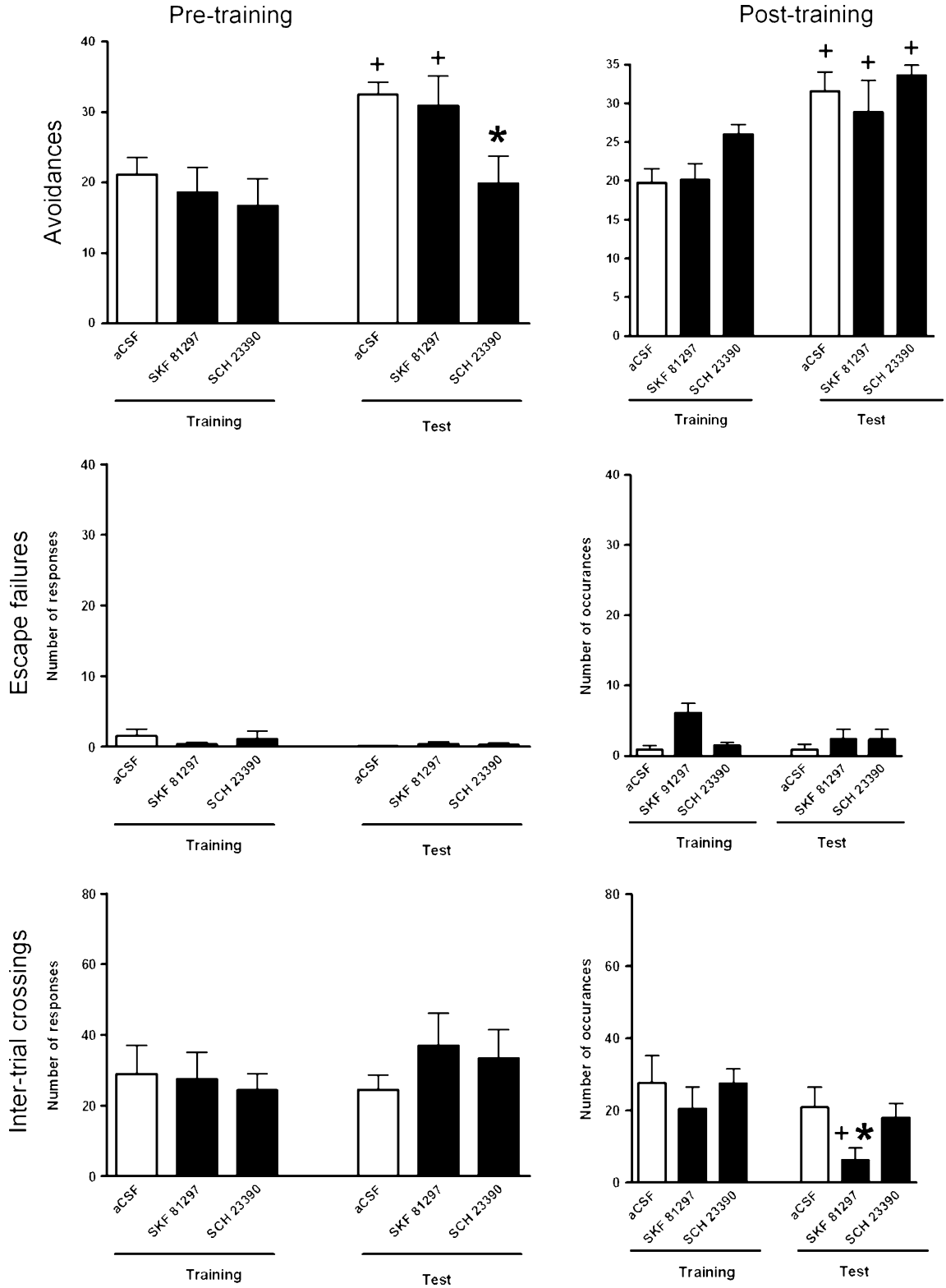


Fig. 3 Effect of intra-DLS infusion of artificial cerebrospinal fluid (*aCSF*), the D1 dopamine receptor agonist SKF 81297 (0.4 μg/side), or the D1 receptor antagonist SCH 23390 (0.4 μg/side) immediately before or immediately after the training session on two-way active avoidance scores. Data are expressed as mean (±SEM). *$p<0.05$ compared to saline; $^{+}p<0.05$ compared to the same group on training session (n=9–13)

models of basal ganglia suggest that even the motor deficits in Parkinson's disease (classically thought of as a performance effect) may be partially learned (Wiecki and Frank 2010).

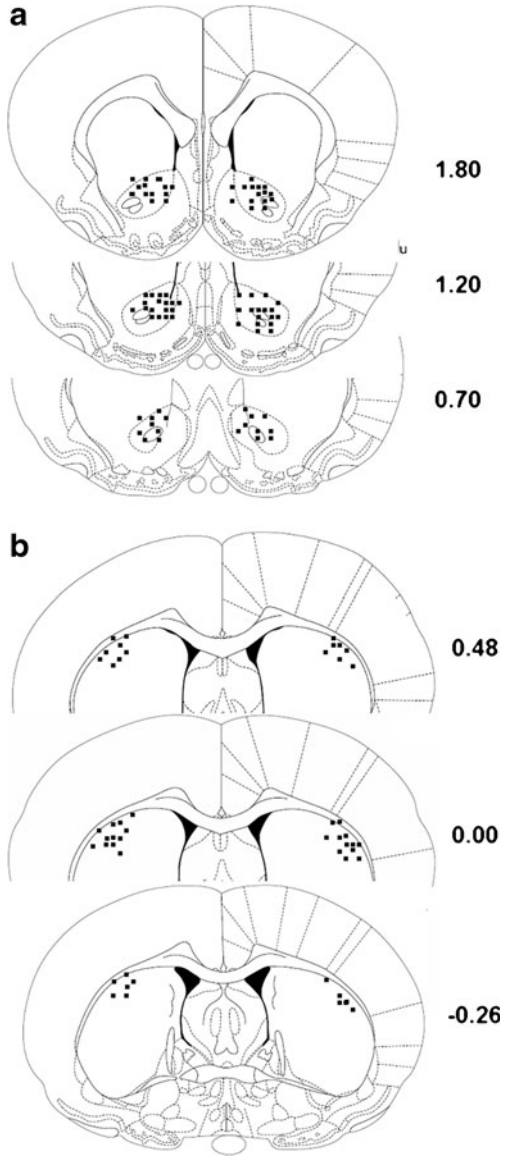


Fig. 4 Schematic coronal sections showing the locations of the tip of the cannulae used to infuse drugs into the nucleus accumbens (**a**) or dorsolateral striatum (**b**). On the right of each section, the approximate distance (mm) from bregma is indicated, according to the atlas of Paxinos and Watson (2005)

The finding that blockade of D1 receptors in the NAc impaired CAR learning and performance is apparently in contradiction to previous reports that lesions in the NAc not only failed to impair but also caused some improvement in learning two-way active avoidance (Gal et al. 2005; Lorens et al. 1970). However, in these studies, the lesions were electrolytic and may well have interrupted traffic of information though the anterior commissure and medial forebrain bundle. Another curious finding in the Gal et al. study was that while lesions in the NAc core-plus-shell improved learning, lesions restricted to the NAc shell impaired it. The authors suggested that this may be caused by an indirect inhibition of the NAc core by the shell — the shell inhibits VTA dopaminergic neurons that project to the core, a claim supported by the spiralling projections between the midbrain and the striatum (Ferreira et al. 2008; Nauta et al. 1978). By this explanation, the impairment caused by lesion of the shell depends on decreased release of DA in the core. However, this does not explain why lesion of the NAc core-plus-shell improved learning. A possible explanation for this finding is that the effect of the lesion resulted from disruption of the influence of the ventral subiculum (vSub) on striatal action-selection (the vSub projects to the NAc) and increased release of DA in the dorsal striatum due to loss of GABAergic neurons in the Nac core that project to the midbrain neurons that, in turn, project to the dorsal striatum (Ferreira et al. 2008; Nauta et al. 1978). In this situation, striatal action-selection is supposed to be more based on discrete stimuli (the sensorimotor cortex projects to the DLS; Voorn et al. 2004) and less based on the affective value of spatial locations (provided to the NAc by the vSub (Sesack and Grace 2010). Because during two-way active avoidance training rats receive shocks in two different locations, learning the locations in which it occurs may inhibit the action of returning to that location. This hypothesis is supported by reports of improved learning of two-way active avoidance in rats with a lesion in the hippocampus or related structures (Torras-Garcia et al. 2003; Woodruff et al. 1977). At the same time, the increased release of DA in the dorsomedial striatum (DMS) adds flexibility to the action-selection due to projections from the prefrontal cortex (PFC) to the DMS (Ragozzino et al. 2002; Yin et al. 2006). Such flexibility may be critical for rats to run back to the location in which shock was received. On the other hand, in the present experiment the infusion of a D2 antagonist may have affected more the PFC than the vSub drive of NAc: inhibition of the PFC drive of NAc depends on activation of presynaptic D2 by tonic DA but it is not affected by the blockade of D1 receptors (Sesack and Grace 2010; West and Grace 2002). This may favour the ratio vSub/PFC load to the NAc, thus allowing action-selection based on the affective valence of locations over flexible action-selection. This imbalance may explain the deficits caused by the infusion of SCH 23390 into the NAc on two-way avoidance learning. It may also explain the increased number of escape failures — when rats were reluctant to run back to locations in which they received a shock, even though they were receiving a shock in the current location.

Our findings suggest a differential role for D1 receptors expressed in the DLS and NAc. Different effects of manipulations in the NAc and dorsal striatum on learning and performance of different tasks were also observed in other studies, as reviewed by Nicola (2007). He proposed that "the dorsal striatum controls action-selection in

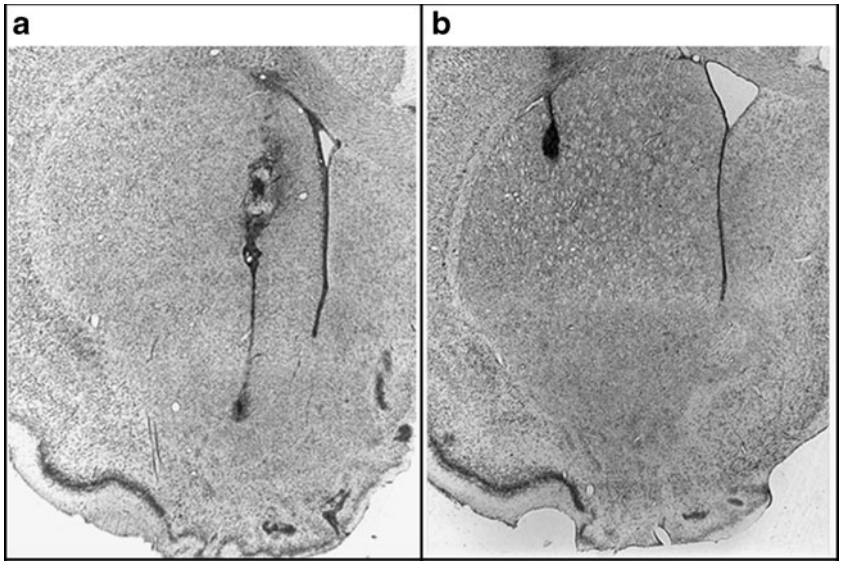


Fig. 5 Thionin stained tissue showing the locations of the tip of the cannulae used to infuse the drugs into the nucleus accumbens (**a**) or dorsolateral striatum (**b**)

response to temporarily predictable stimuli whereas the NAc controls action-selection in response to temporarily unpredictable stimuli." Such differences may also reflect the pattern of connections of these striatal subregions (McGeorge and Faull 1989; Voorn et al. 2004). The NAc receives projections from the amygdala, vSub and limbic regions of the prefrontal cortex, including orbitofrontal and anterior cingulate cortex (Goto and Grace 2008) and can affect actions by aiding in the translation of motivational signals into action (Carlezon and Thomas 2009).

Infusion of SKF 81297 or SCH 23390 into the DLS did not affect the number of avoidances in the training session, carried out immediately after drug infusions. However, infusion of SCH 23390 into the DLS probably impaired strengthening of synapses between cortical neurons representing the warning stimulus and the DLS neurons triggering the avoidance response, thus decreasing CAR only in the next session. In addition, contrary to intra-NAc infusions, intra-DLS infusions of SCH 23390 decreased the number of avoidance responses without causing failures to escape from the footshock. This suggests that CAR learning, but not its expression, is dependent on DLS D1 receptors.

In the present study, we also found that post-training administrations of SKF 81297 or SCH 23390 did not affect CAR learning. This suggests that, in order to affect memory consolidation, activation of D1 receptors in the striatum must be concomitant with the release of glutamate by the neurons that encode the warning stimulus, the footshock, and the activation of the Go Neurons that encode the avoidance action. Such a mechanism is in agreement with the finding that D1 and NMDA receptors must be activated at the same time to induce LTP in the striatum (Lovinger 2010). It is also possible that this window extends for a short period of time after training and did not affect CAR learning because the training sessions in the two-way active avoidance task were so long. Note that the tasks most used to study memory consolidation are learned in only one trial (McGaugh and Roozendaal 2009) while training sessions in the present study finished only after 40 trials, which took more than 25 min. This finding is in agreement with a recent report in which D2, but not D1, receptor antagonists were able to decrease the expression of conditioned fear in rats (Oliveira et al. 2009). On the other hand, the post-training administration of SKF 82297 into the DLS caused a significant reduction in the number of CARs in the test session, a finding that may be related to improved memory consolidation for habituation to the shuttle box.

The systemic administration of SCH 23390 caused the same effects as were observed after intra-NAc or intra-DLS infusions. In addition, systemic administration of the D1-like DA receptor agonist SKF 81289 caused a small, but significant increase in the number of CARs. These effects are consistent with previous studies showing that systemic administration of D1 DA receptor antagonists (Aguilar et al. 2000; Iorio et al. 1991; Ogren and Archer 1994; Reis et al. 2004; Stuchlik and Vales 2006; Wadenberg 1992) and treatment with neurotoxins that lesion DA neurons (Da Cunha et al. 2001; Gevaerd et al. 2001a, b) impair, and dopaminergic agonists improve (Stuchlik and Vales 2006) CAR learning. The action of these drugs in other brain structures may also have contributed to these effects (Izquierdo et al. 2007; LaLumiere et al. 2004; Rossato et al. 2009; Williams and Castner 2006).

These findings suggest that treatment with drugs that affect D1 receptors activation in the NAc and DLS (such as apomorphine, clozapine, levodopa, methylphenidate) may affect CAR, causing a beneficial impact on cognition in some cases (e.g., Parkinson's disease and ADHD) and worsening cognitive deficits in other cases (e.g., schizophrenia and other psychiatric diseases treated with antipsychotics).

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