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Neuroanatomical substrates mediating the aversive effects of D–1 dopamine receptor antagonists

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Abstract. An unbiased place preference conditioning procedure was used to examine the secondary reinforcing effects of selective D–1 dopamine (DA) receptor antagonists and the neuroanatomical substrates mediating these effects. Systemic administration of SCH–23390 or the non-benzazepine D–1 receptor antagonist A–69024 produced dose-related conditioned aversions for the drug-associated place. In contrast, the D–2 antagonists spiperone and (−)sulpiride were without effect. SCH–23390-induced place aversions were also observed after intracerebroventricular administration. The minimum dose producing this effect was significantly lower than that after systemic injection. Aversive effects were also observed after microinjection of SCH–23390 into the n. accumbens. In contrast, microinjections of this antagonist into the ventral tegmental area, caudate putamen or medial prefrontal cortex were without effect. These data confirm that the blockade of D–1 but not D–2 DA receptors induces aversive states. Furthermore, they suggest that D–1 receptors in the n. accumbens may play an important role in the regulation of non-drug induced affective states.

Key words: Place conditioning – SCH–23390 – A–69024 – D–1 receptor – N. accumbens – Mesolimbic system – Rat

Increasing evidence suggests an involvement of dopamine (DA) systems and, in particular, the D–1 receptor in mediating drug-induced alterations in mood and affect. Studies employing the conditioned place preference paradigm have shown that pretreatment with the putative D–1 receptor selective antagonist SCH–23390 (Iorio et al. 1983; Billiard et al. 1984) abolishes the secondary reinforcing effects of opioids and psychostimulants (Leone and DiChiara 1987; Shippenberg and Herz 1987) and similar results have been obtained with regard to the positive reinforcing effects of these agents (Koob et al. 1987; Nakajima and Wise 1987). Chronic administration of SCH–23390 also abolishes the aversive effects of κ-opioid receptor agonists and opioid antagonists (Shippenberg and Herz 1987, 1988), suggesting that intact D–1 receptor function may be critical for the expression of both the reinforcing and aversive effects of certain drugs.

There is also data, although more limited, suggesting an involvement of the D–1 receptor in the regulation of non-drug-induced affective states. Employing an unbiased place preference conditioning procedure, we have recently shown that the acute administration of SCH–233390 to drug-naive animals produces aversive effects (Shippenberg and Herz 1987). Such findings suggest the existence of a tonically active DA pathway, the blockade of which results in aversive states. Furthermore, the inability of D–2 antagonists to produce effects similar to SCH–23390 indicates a critical role for the D–1 but not the D–2 receptor in the regulation of affective states. Fundamental questions, however, exist regarding both the site and mechanism of action of SCH–23390. Thus, although this benzazepine is considered to be a potent and selective D–1 antagonist (Hyttel and Arnt 1983; Billiard et al. 1984) there is some evidence (Waddington 1986; Clark and White 1987; Bijak and Smialowski 1989) that SCH–23390 may produce certain of its effects via a non-DAergic mechanism. Therefore, additional data regarding the actions of more selective antagonists are needed to determine whether those functions ascribed to the D–1 receptor on the basis of studies using SCH–23390 are, in fact, valid. In addition, if the aversive effects of D–1 receptor blockade can be confirmed, questions remain as to the anatomical substrate(s) underlying this effect. Thus, although the mesolimbic DA system has been implicated in mediating the reinforcing effects of several classes of drugs (Spyraki et al. 1982; Wise and Bozarth 1982), its role in mediating the aversive effects of psychoactive drugs is unknown.

In the present study, we have employed SCH–23390 and the novel non-benzazepine D–1 receptor antagonist 1-(2-bromo-4,5,dimethoxybenzyl)-7-hydroxy-6-meth-

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oxy-2-methyl-1,2,3,4 tetrahydroisoquinoline hydrobromide (A–69024; Kerkman et al. 1989) to address these issues. Employing an unbiased place preference conditioning paradigm in rats, we now report that the systemic administration of either antagonist induces aversive states. Furthermore, the results of microinjection studies suggest an important role of the nucleus accumbens in the mediation of this effect.

Materials and methods

Subjects. Male Spraque-Dawley rats (Charles River Wiga, FRG) weighing 180–200 g were housed individually in a climatically controlled colony room (temp: 22° C) for 1 week prior to the commencement of experiments. They were maintained on a 12:12 h light/dark cycle (lights on: 06:00 hours) with food and water available ad libitum.

Place conditioning procedure. Place conditioning was conducted as previously described (Shippenberg et al. 1987) using an unbiased procedure. The apparatus consisted of shuttleboxes (30 × 60 × 30 cm: w × l × h) made of plexiglas and wood. Each was equipped with a loose fitting lid. For conditioning sessions, each box was divided, by means of a sliding partition, into two equal sized compartments. One compartment was white and had a textured floor. The other was black and had a smooth floor. For test sessions, the sliding partition was raised 12 cm above the floor and a 5 × 2 cm (w × l) steel mesh platform (neutral environment) was inserted along the seam separating the two compartments.

Conditioning sessions (three drugs: three vehicle) were conducted once per day and consisted of the alternate day injection of the conditioning drug or its vehicle. Rats were immmediately confined to one compartment following drug injections and to the other compartment following vehicle injections. Each session was 60 min in duration. Treatment compartment and the order of presentation of drug and vehicle were counterbalanced for each drug dose. Each rat was conditioned with only one dose of a given drug.

On day 7, preference for a particular place was assessed in the drug-free state by allowing non-injected rats free access to both compartments of the testbox for 15 min. The time spent in the white, black and neutral environments was then determined.

All conditioning and test sessions were conducted under dim illumination (14.5 lux) with masking white noise present. We have previously shown that, under these conditions, control animals do not exhibit a preference for either compartment of the apparatus (Shippenberg et al. 1987). An Olympus VX315E video camera was used for data recording.

Stereotaxic surgery. Animals were anesthetized with sodium hexobarbital (60 mg/kg; IP) and placed in a stereotaxic instrument (David Kopf) for implantation of a stainless steel guide cannula (Plastic Products, USA) into either the lateral ventricle (intracerebroventricular: ICV), ventral tegmental area (VTA), nucleus accumbens (NAC), caudate/putamen (CPU) or medial prefrontal cortex (MFC). The guide cannulae were positioned 1.0 mm above the designated site of injection and were anchored to the skull with two stainless steel screws and dental acrylic. The coordinates and dimensions of the guide cannulae (gauge) are listed below. For all areas, the DV coordinates represent the distance from the skull surface.

ICV = AP: −0.9 mm, L: 1.5 mm, DV: 3.5 mm relative to bregma (Paxinos and Watson 1982) 22 gauge,

VTA = AP: +3,5 mm, L: 1.0 mm, DV: 8.0 mm relative to interaural line (Paxinos and Watson 1982) 26 gauge,

NAC = AP: +9.5 mm, L: 1.3 mm, DV: 7.0 mm relative to interaural line (Paxinos and Watson 1982) 22 gauge,

CPU = AP: +1.7 mm, L: 2.5 mm, DV: 3.5 mm relative to bregma (Paxinos and Watson 1982) 22 gauge,

MFC = AP: +4.4 mm, L: +0.8 mm, DV: 4.0 mm relative to bregma (Pellegrino et al. 1981) 22 gauge.

Each animal was implanted unilaterally unless otherwise specified. Cannula placement (left/right) was counter balanced for each brain site and drug dose tested. Animals were allowed a 1-week recovery period prior to the commencement of place conditioning.

Microinjection procedure. ICV and microinjections into the NAC, CPU and MFC were made manually with a 28 gauge injection needle attached to a Hamilton microsyringe via polyethylene tubing (ID: 0.7 mm). The volume of ICV injections was 3.0 µl, whereas the volume of NAC, CPU and MFC injections was 1.0 µl. Solutions were administered over a 30-s period and the injection needle was left in place for an additional 60 s to ensure complete solution delivery. Microinjections into the VTA were made with a 33 gauge needle which was attached to a Hamilton microsyringe. Injections (0.3 µl) were made over a 15-s period via a Sage infusion pump. The cannula was then left in place for 60 s to ensure complete solution delivery.

Verification of cannula placement. Following the completion of experiments, rats were anesthetized and sacrificed by decapitation. The brains were removed and sectioned in a cryostat to verify the location of the cannulae. Only data from animals with histologically correct cannulae placements were used for subsequent data analysis.

Drugs. SCH–23390 was prepared in sterile water and was injected either subcutaneously (SC: 1.0 ml/kg) or intracranially. A–69024 was prepared in sterile water containing 10% DMSO and was injected SC (1.0 ml/kg). (−)Sulpiride (Sigma, FRG) and spiperone hydrochloride (Sigma, FRG) were dissolved in distilled water containing DMSO and 1 N HCl (ph of final solution 6.5). Both were injected sc in a volume of 1.0–2.0 ml/kg.

Statistical analysis. Conditioning scores represent the time spent in the drug-paired place minus that spent in the vehicle-paired place and are expressed as means ± SE. Dose-response curves were analyzed with a one-way random effects model factorial analysis of variance (ANOVA). The Wilcoxon test, in which time spent in the vehicle-paired place was compared to time spent in the drug-paired place, was used to determine whether an individual dose produced significant place conditioning. The accepted value of significance for all tests was $P < 0.05$.

Results

Control tests of preference

In control tests, rats injected SC with sterile water during each of the conditioning sessions exhibited no preference for either compartment of the testbox (Fig. 1a). The mean time spent in the white and black compartments was 374 ± 19 s and 329 ± 22 s ($n = 10$), respectively. Similarly, rats receiving alternate day injections of the vehicles for A–69024, or the D–2 antagonists, and water exhibited no significant place preferences (Fig. 1b, Fig. 2). Conditioning produced by ICV and intracranial microinjections of sterile water are shown in Table 1. Regardless of the site of injection, animals exhibited no significant preference for either of the place cues.

Place conditioning produced by SCH–23390 and A–69024

The SC administration of SCH–23390 resulted in marked aversions for the drug-paired place (Fig. 1a). The mag-

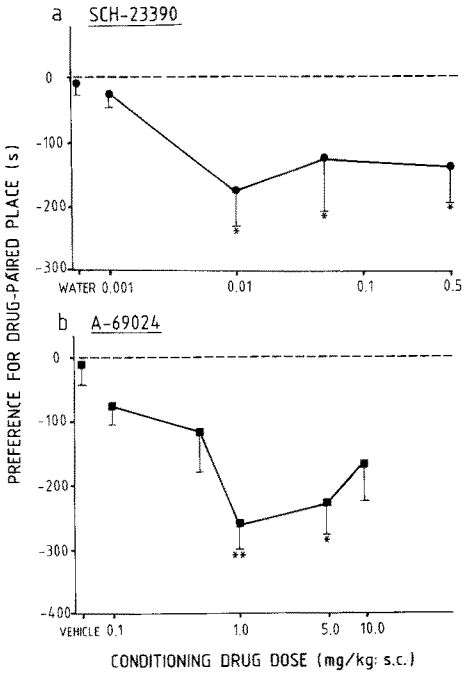

Fig. 1a, b Place conditioning produced by the SC administration of SCH–23390 (**a**) and A–69024 (**b**). *Ordinate:* mean difference (s) between time spent in the drug- and vehicle-paired sides of the testbox. The conditioning score for vehicle injections represents time spent in the black compartment minus that spent in the white compartment. *Abscissa:* drug dose. Each point represents the mean conditioning score ± SE of 8–10 rats. *Asterisks* denote significant place conditioning (Wilcoxon test: * $P<0.05$)

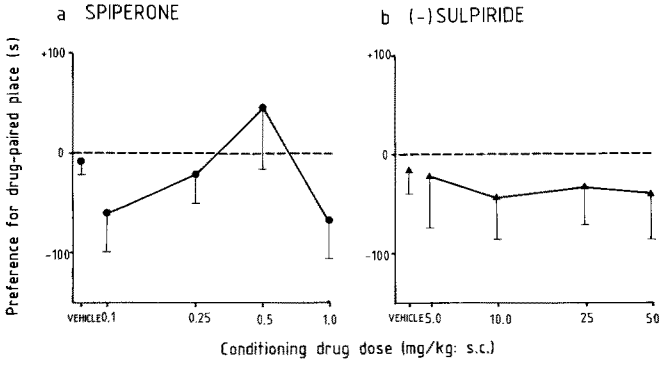

Fig. 2a, b. Place conditioning produced by the SC administration of the D–2 receptor antagonists spiperone (**a**) and (−)sulpiride (**b**). Each point represents the mean conditioning score ± SE of 6–10 rats

nitude of this effect was linearly related to dose [$F(1,40) = 12.75$; $P<0.009$] with significant conditioning observed in response to doses of 0.01 (-207 ± 52 s, $n=10$) and 0.05 (-181 ± 59 s, $n=10$) mg/kg (Wilcoxon test: $P<05$). As shown in Fig. 1b, the SC administration of the non-benzazepine D–1 antagonist A–69024 produced significant aversions for the drug-paired place at doses of 1.0 mg/kg (-264 ± 41 s, $n=10$) and 5.0 mg/kg (Wilcoxon test: $P<0.05$). This effect appeared to be linearly related to dose [$F(1,60) = 12.84$; $P<0.007$].

Table 1. Place conditioning produced by microinjections of sterile water

Site	Injection vol. (µl)	Time[a]		*N*
		Black place	White place	
ICV	3.0	380 ± 22	352 ± 24	10
VTA	0.3	377 ± 31	367 ± 32	8
NAC	1.0	359 ± 34	401 ± 36	10
CPU	1.0	392 ± 19	388 ± 17	9
MFC	1.0	361 ± 41	412 ± 34	9

[a] Values represent the mean time (s) ± SE spent in the black and white sides of the testbox. Rats received injections of sterile water during each of the conditioning sessions. Testing was then conducted as described in the text

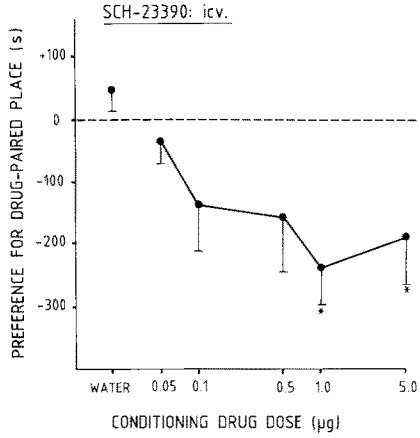

Fig. 3. Place conditioning produced by ICV adminstration of SCH–23390. Each value represents the mean conditioning score of 6–12 rats. *Asterisks* denote significant place conditioning (Wilcoxon test: * $P<0.05$)

Place conditioning produced by D–2 antagonists

In contrast to the D–1 DA receptor antagonists, administration of the preferential D–2 antagonist spiperone failed to produce significant place conditioning (Fig. 2a). Thus, there was no difference between time spent in the spiperone- and vehicle-paired sides of the testbox (Wilcoxon test: $P>0.1$). Similarly, the selective D–2 antagonist (−)sulpiride was ineffective as a conditioning stimulus (Fig. 2b; Wilcoxon test: $P>0.1$).

Place conditioning produced by ICV and intracerebral injections of SCH–23390

As shown in Fig. 3, ICV administration of SCH–23390 produced aversions for the drug-paired place and the magnitude of this effect were linearly related to dose [$F(1,52) = 4.63$; $P<0.04$]. Significant place conditioning was observed with doses of 1.0 (-237 ± 67 s, $n=10$) and 5.0 (-187 ± 80 s, $n=11$) µg.

Figure 4 illustrates the location of cannulae aimed at the VTA, CPU, NAC and MFC. Unilateral microinjections of SCH–23390 into either the VTA or CPU failed to produce a significant aversion for the drug-paired

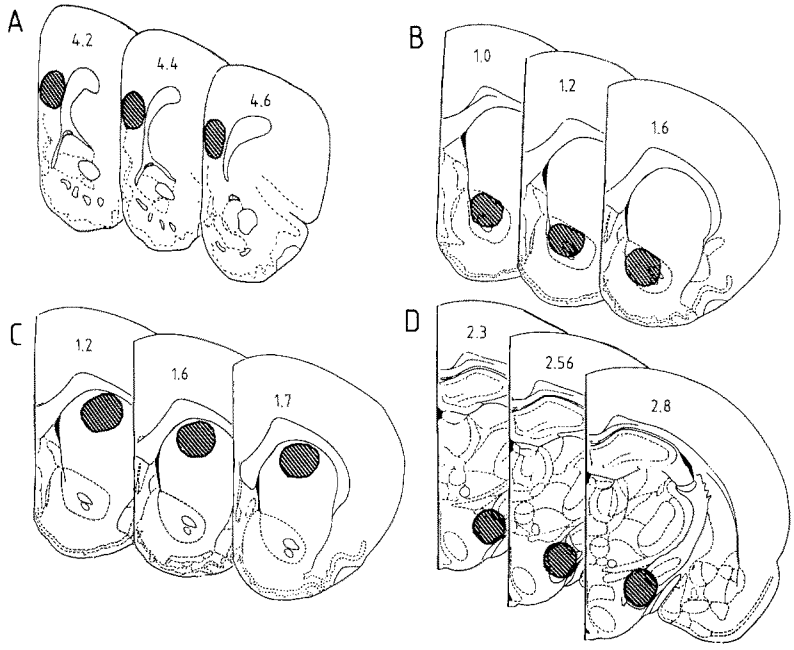

Fig. 4A-D. Location of intracerebral guide cannulae. The position of guide cannulae aimed at the MFC, NAC, CPU and VTA are shown in **A**, **B**, **C** and **D**, respectively. Sections represented in (**a**) are taken from the atlas of Pellegrino et al. (1979) and the anterior-posterior coordinates shown are relative to bregma. Sections shown in **B**, **C** and **D** are taken from the atlas of Paxinos and Watson (1986) and the anterior-posterior coordinates shown are relative to the interaural line

place (Fig. 5a). Thus, regardless of the dose administered, the place conditioning produced by SCH–23390 did not differ significantly from that observed in response to sterile water [VTA: $F(1,33) = 0.021$; $P > 0.88$, CPU: $F(1,28) = 0.168$; $P > 0.67$]. Similarly, MFC injections of SCH–23390 (0.5–5.0 μg) failed to produce significant place conditioning. In view of the conditioning score observed in response to the lowest dose, an additional group of animals was conditioned with a lower dose (0.1 μg) of SCH–23390. Again, however, no significant place aversion was seen (-48 ± 83 s, $n = 8$: data not represented).

In contrast to the other brain regions examined, unilateral microinjection of SCH–23390 into the NAC produced significant aversions for the drug-paired place (Fig. 5b). The magnitude of this effect was linearly related to dose [$F(1,36) = 5.22$; $P < 0.03$], with significant conditioning observed in response to doses of 0.5 μg (-218 ± 40 s, $n = 8$) and 1.0 μg. In view of the effectiveness of SCH–23390 injected into the NAC, additional conditioning studies were conducted to determine if D–2 receptor blockade would produce similar effects. As shown in Table 2, microinjection of (−)sulpiride, at doses previously shown to be effective in other behavioral tests (Kurumiya and Nakajima 1988; Nakajima and McKenzie 1986), failed to produce significant preferences or aversions for the drug-paired place (Wilcoxon test: $P > 0.1$).

Place conditioning produced by bilateral NAC injections of SCH–23390 was also examined in additional groups of animals. Injection of 0.25 μg SCH–23390 per NAC (total dose: 0.5 μg) produced catatonia and a disruption of behavior; effects which were not observed after unilateral injection of the same total dose. Bilateral injections of 0.15 μg SCH–23390 per NAC did not produce such effects and animals conditioned with this

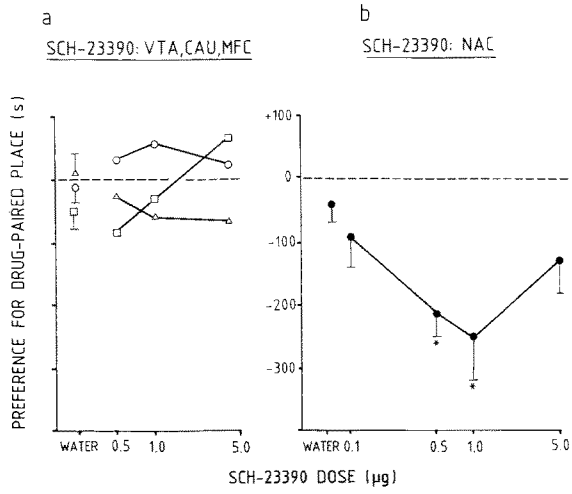

Fig. 5a, b. Place conditioning produced by intracerebral injections of SCH–23390. Sites which were ineffective in producing place aversions are shown in (**a**). Effective sites are shown in (**b**). Values represent the mean conditioning score of 6–10 rats. *Asterisks* denote significant place conditioning (Wilcoxon test: * $P < 0.05$). △ VTA; ○ CAU (CPU); □ MFC

Table 2. Place conditioning produced by microinjections of (−)sulpiride into the NAC

Dose (μg)	Time (s)		*N*
	Drug-paired place	Vehicle-paired place	
10	349 ± 70	419 ± 70	10
20	411 ± 50	389 ± 42	10

Values represent the mean time (s) ± SE spent in the drug- and vehicle-paired sides of the testbox. The volume of injections was 1.0 μl

dose of the antagonist exhibited a marked aversion for the drug-associated place (-413 ± 112 s, $n=5$).

Discussion

The conditioned place preference paradigm has been used to examine the affective states produced by a variety of psychoactive drugs and has proven to be an effective model for the detection of both rewarding and aversive states (Spyraki et al. 1982; Mucha and Herz 1985; Morency and Beninger 1986).

In the present study, animals exhibited a marked aversion for an environment previously associated with the SC administration of SCH–23390. Such findings are in agreement with those of a recent study (Shippenberg and Herz 1987), and suggest that the blockade of D–1 DA receptors induces aversive states. Indeed, the doses of SCH–23390 producing place aversions are those which have previously been shown to block a variety of D–1 but not D–2 receptor-mediated responses (Iorio et al. 1983; Arnt and Hyttel 1985). Furthermore, as shown here and in several previous conditioning studies (Bozarth and Wise 1981; Spyraki et al. 1982; Shippenberg and Herz 1987), in contrast to SCH–23390, D–2 antagonists lack aversive effects.

Although SCH–23390 may bind to serotonin 5HT–2 or 5HT–1 receptors (Waddington 1986; Clark and White 1987; Bijak and Smialowski 1989), it is unlikely that these actions underlie the aversive effects observed in the present study. Firstly, if such was the case, than antagonists at these receptor types should produce conditioning similar to that of SCH–23390. However, the 5HT–2 antagonist ritanserin is ineffective as a conditioning stimulus (Nomiko and Spyraki 1988; Shippenberg and Herz 1988). Similarly, the preferential 5HT–1 antagonist metergoline is inactive in the place conditioning paradigm (Leone and DiChiara 1987).

Data regarding the place conditioning produced by A–69024 provide further support for the hypothesis that the blockade of D–1 receptors produces aversive states. A recent study (Kerkman et al. 1989) has shown that this compound is a potent and highly selective antagonist of the D–1 receptor. Thus, in radioligand binding experiments, A–69024 exhibits nanomolar affinity for the D–1 receptor but only micromolar affinity for either D–2 or 5HT–1 receptors. The D–1 receptor selectivity of this antagonist has also been confirmed in vivo. In view of these data, the finding that A–69024 as well as SCH–23390 produces place aversions strongly suggests that a disruption in the functional activity of D–1 receptors leads to aversive states. In this regard, it is interesting to note that the potencies of these antagonists in producing aversive effects paralleled differences in their binding affinity to the D–1 receptor (Chipkin et al. 1988; Kerkman et al. 1989).

Evidence that a central site of action underlies the aversive effects of D–1 receptor blockade was obtained from studies in which SCH–23390 was administered ICV. Thus, injection of this antagonist into the lateral ventricle produced significant place aversions and the minimum dose producing this effect was ca. 3 times lower than that after SC administration. The finding of a shift to the left of the SCH–23390 dose-response curve strongly indicates that the aversive effects of this agent are mediated in the CNS, rather than peripherally.

Studies examining the place conditioning produced by intracerebral microinjections of SCH–23390 provide potential insights into the anatomical substrates mediating the aversive effects of D–1 receptor blockade. Thus, unilateral microinjections of SCH–23390 into the NAC produced significant conditioned place aversions at doses of 0.5 μg and greater. In contrast, doses of SCH–23390 equal to or 10 times greater than those effective in the NAC failed to produce conditioning following microinjection into the VTA, CPU or MFC. Such findings demonstrate that the blockade of D–1 receptors in the NAC is sufficient for the expression of SCH–23390's aversive effects.

SCH–23390 was ca. 2 times more potent following NAC as compared to ICV application. This rather modest difference in potency may indicate that the NAC is not the only site mediating the aversive effects of D–1 receptor blockade. However, the distribution of a drug following intracerebral injections is typically restricted to one hemisphere (Schubert et al. 1970; Routtenberg 1972). In contrast, ICV injections result in a bilateral pattern of distribution. Therefore, the injection procedure employed and the resulting area of penetration within the NAC may have contributed to the relatively weak effects observed. Indeed, data regarding the effects of bilateral administration of SCH–23390 provide apparent support for this conclusion. Thus, bilateral NAC injection of a total dose of 0.5 μg SCH–23390 produced marked behavioral disruption, an effect which precluded subsequent behavioral testing. This effect did not occur following unilateral injection of this dose. Furthermore, bilateral injections of 0.15 μg/NAC produced significant place aversions, whereas unilateral injections of the same total dose into either the lateral ventricle or NAC were without effect.

It is unlikely that the effectiveness of NAC injections resulted from the diffusion of SCH–23390 to areas bordering this structure. Thus, employing the same injection volume as that used for the NAC in the present study, several investigators (Schubert et al. 1970; Ott et al. 1974; Myers and Hoch 1978) have shown that various drugs are confined to within a 0.75 mm radius of the injection site. Therefore, diffusion in either the lateral or anterior/posterior plane would still result in the confinement of SCH–23390 to the NAC. Furthermore, a role of the CPU in mediating the aversive effects of NAC D–1 receptor blockade can be ruled out, since injections into this area were without effect.

In summary, the results of the present study demonstrate that the systemic administration of SCH–23390 or the non-benzazepine D–1 receptor antagonist A–69024 produce conditioned place aversions in rats, whereas D–2 receptor antagonists are without effect. Place aversions were also observed after microinjection of SCH–23390 into the NAC, but not other brain regions, suggesting a role of the NAC, and the D–1 receptors

located therein, in the mediation of this effect. Such findings provide evidence that D–1 receptors in the NAC are critically involved in the regulation of affective states. Furthermore, the ability of SCH–23390 to abolish the reinforcing as well as the aversive effects of several psychoactive drugs (Leone and DiChiara 1987; Shippenberg and Herz 1988) suggests that functional alterations of the D–1 receptor in the NAC may underlie these opposing motivational effects.

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