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# A role for the mesolimbic dopamine system in the reinforcing properties of diazepam

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**Abstract.** The conditioned place preference paradigm was used to investigate the neurochemical and neuroanatomical substrates which mediate the rewarding properties of diazepam. The results confirmed that diazepam (1 and 2.5 mg/kg, IP) produced place preference for a distinctive environment that had previously been paired with injections of the drug. Pretreatment with haloperidol (0.1 mg/kg) antagonised the place preference induced by diazepam (1 mg/kg). Pretreatment with domperidone (2 mg/kg) failed to influence this effect of diazepam. Haloperidol (0.1 mg/kg) and domperidone (2 mg/kg) alone did not produce place aversion. In separate experiments the diazepam-induced place preference was examined in rats having 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens. These animals did not show preference for the compartment associated with diazepam. Depletion of central noradrenaline produced by systemic injections of DSP4 did not affect diazepam-induced place preference conditioning. These findings suggest that dopamine-containing neurons of the mesolimbic system are a component of the neural circuitry that mediates the reinforcing properties of diazepam.

**Key words:** Diazepam – Haloperidol – Domperidone – 6-Hydroxydopamine – DSP-4 – Place conditioning – Dopamine – Noradrenaline – Reward – Rat

Since the discovery that animals will work to self administer many drugs that are abused by humans (Schuster and Thompson 1969), pharmacological and neurobiological studies have attempted to delineate the neurochemical and/or neuroanatomical substrates which mediate drug-induced reward. Despite some contradictory findings (Ettenberg et al. 1982; Spyraki et al. 1983), the evidence gathered to date suggests that the mesolimbic dopaminergic system is a neural substrate for the rewarding properties of opiates and some psychostimulants (Roberts et al. 1980; Fibiger 1978; Wise 1978; Wise and Bozarth 1982, 1984; Bozarth 1983). In contrast to the sizeable literature concerning the rewarding actions of opiates and psychostimulants, there are relatively few reports dealing with the reinforcing properties of minor tranquilizers. To some extent this is due to the fact that self-administration of minor tranquilizers, especially of benzodiazepines, is difficult to demonstrate in lower animals (Griffiths and Ator 1982), despite the abuse potential of these drugs (Cox et al. 1983; Nutt 1986). It is not clear whether the lack of reliable benzodiazepine self-administration is due to weak reinforcing properties, long half-lives, or whether their sedative effects interfere with motor performance and thus mask the rewarding actions of these compounds.

Recently, the reinforcing properties of diazepam have been demonstrated using a place preference paradigm (Spyraki et al. 1985; File 1986). This procedure, which is based on classical conditioning between drug and environmental stimuli, can be used to measure the reinforcing properties of drugs without requiring motor responses from the animal. Thus, the potentially confounding effects of diazepam on motor activities are avoided. In the earlier study (Spyraki et al. 1985), it was demonstrated that a central benzodiazepine receptor system mediates diazepam-induced place preference. Attempts to define a role of GABAergic and endorphinergic transmission in the rewarding or the antiaversive properties of diazepam were unrevealing.

The present study sought to determine if dopamine-containing neurons of the mesolimbic system may participate in the rewarding actions of the benzodiazepine, diazepam. To that purpose, the effects of the dopamine receptor antagonist haloperidol and of 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens on diazepam-induced place preference were investigated. In addition, because noradrenergic neurons have been proposed as being involved in the antianxiety effects of benzodiazepines (Redmond 1979), diazepam-induced place preference was also tested in rats pretreated with a neurotoxin for noradrenergic neurons, DSP-4.

## Methods

*Animals.* Experimentally naive male Wistar rats, weighing 250–280 g, were housed in group cages ($N=8$) in a climatically controlled colony room. Except for periods of testing, food and water were continuously available and the colony was maintained under a 12 h light-dark cycle (lights on 8 a.m.).

*Behavioural testing.* The behavioural testing took place during the light phase of the diurnal cycle (9 a.m.–4 p.m.) in an isolated room. Each experiment was carried out over 12 consecutive days. The behavioural tests were conducted in rectangular Plexiglass shuttle boxes (80 × 36 cm) divided into three compartments. Each of the two large (34 × 36 cm) end compartments was distinctive in flooring and

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wall covering, one having a grid floor and black walls and the other having a mesh floor and white walls.

The procedure, as described previously (Spyraki et al. 1982a, b, c, 1983), consisted of three phases and briefly was as follows: during the first, preconditioning phase (3 days) the animals were allowed to investigate the entire shuttle box, for 15 min per day. On the 3rd day, the time spent by each animal in each of the compartments was recorded, thus providing a measure of the initial unconditioned preference for the two compartments. During the second (8-day) conditioning phase, animals were injected every 2nd day with drug(s) and after a standard interval that varied for the different drug treatments, they were confined for 30 min to one side of the shuttle box. This was the initially non-preferred side when the drug was tested for place preference, and the initially preferred side when the drug was tested for place aversion. On alternate days, rats received vehicle injections and were confined to the opposite side of the apparatus. During the third phase (1 day) the animals received no injection and had access to both compartments. The amount of time spent in each compartment during the 15-min test was recorded. The difference in the time spent in the drug paired compartment, between the final test trial, and the trial on the last day of the preconditioning phase, represented a measure of place conditioning.

*Experiments.* Three experiments were conducted. The first was designed to confirm diazepam-induced place preference and to assess the effect of central and peripheral dopamine (DA) receptor blockade on diazepam-induced place preference. Additionally, the DA receptor antagonists haloperidol (Janssen) and domperidone (Janssen) were tested for possible aversive effects. Animals were divided into seven groups, each containing ten rats. The first, second and third groups were injected with vehicle (1 ml/kg), 30 min prior to vehicle or diazepam (1 or 2.5 mg/kg, IP) administration. The fourth and sixth groups received haloperidol (0.1 mg/kg), 30 min prior to diazepam (1 mg/kg) or vehicle injections, respectively. The dose of haloperidol used in this experiment would be expected to have selective effects on DA receptors (Andèn et al. 1970). Previous experiments using a similar dose of haloperidol (0.15 or 0.2 mg/kg) have shown that the drug, administered 1 h prior to conditioning, was effective in blocking amphetamine (Spyraki et al. 1982a) or heroin (Spyraki et al. 1983) place preference. The fifth and seventh groups received domperidone (2 mg/kg, SC) 30 min prior to diazepam (1 mg/kg) or vehicle injections, respectively. Domperidone is a DA receptor antagonist (Laduron and Leysen 1979) that does not readily cross the blood-brain barrier and does not affect brain DA turnover, at least at the dose and time tested (Farah et al. 1983). It was used to determine if an effect of haloperidol could be attributed to peripheral DA receptor blockade. On drug days, 30 min following diazepam or vehicle injections animals in groups 1–5 were confined for 30 min to the initially non-preferred side, while animals of the sixth and seventh groups were confined to the initially preferred side.

In the second experiment, diazepam (2.5 mg/kg) – induced place preference was assessed in animals with 6-OHDA lesions of the nucleus accumbens.

In the third experiment the effect of DSP-4-induced noradrenaline (NA) depletion on diazepam (1 mg/kg) – induced place preference was determined. Previous experiments (Spyraki et al. 1985) and this study have shown that the two different doses of diazepam chosen for the second (2.5 mg/kg) and the third (1 mg/kg) experiment produce similar effects on place conditioning.

*Surgery.* Surgery was performed on 20 rats each weighing 280 g. Anaesthesia was induced with sodium pentobarbital (Nembutal, 40 mg/kg, IP) 20 min following desipramine HCl(25 mg/kg) and pargyline (50 mg/kg) administration. A group of ten animals received bilateral injections of 6-OHDA HBr (8 μg/2 μl; dosage expressed as the base, in 0.9% saline containing 0.2 mg/ml ascorbic acid) into the nucleus accumbens. Coordinates from stereotaxic zero were: A +8.8 mm; L ±1.3 mm; DV: 2.5 mm with the head held in the plane of König and Klippel (1970). The injection rate was 0.2 μl/min. The needle was left in place for 8 min following the infusion. A control group of ten animals received bilateral injections of the vehicle. The operated animals were housed singly and behavioural testing started on the 5th day after surgery.

*DSP-4 treatment.* Male Wistar rats ($N=10$) weighing 220 g received two injections of DSP-4 (50 mg/kg, IP). One week elapsed between the two injections. Controls ($N=10$) were treated with an equal volume of vehicle. The treatment with DSP-4 alters transiently sympathetic neurons in the periphery and produces an extensive and long-lasting depletion of the central NA (Jaim-Etcheverry and Zieher 1980). Behavioural testing was carried out 1 week after the second DSP-4 or vehicle injection.

*Assay for catecholamines.* At the completion of the behavioural testing, animals with bilateral injections of 6-OHDA or vehicle into the nucleus accumbens were killed by cervical fracture. The brain was removed and placed on a freezing microtome and sectioned. The nucleus accumbens + olfactory tubercle and striatum were dissected from 1 mm thick sections and assayed for dopamine.

In the DSP-4-treated group, animals were killed by guillotine and the cortex, hippocampus, hypothalamus and cerebellum were assayed for noradrenaline. Catecholamines were determined in triplicate by the spectrofluorimetric method of Anton and Sayre (1962).

*Statistical analysis.* The behavioural results were analyzed by a two-way ANOVA with drug side (pre- and post-conditioning) and treatment as grouping variables and time spent on the drug associated side as the dependent variable. Individual comparisons and analysis of the biochemical data were conducted using Student's *t*-test.

## Results

### *Attenuation of diazepam-induced place preference following DA receptor blockade*

The results of the first experiment are summarized in Fig. 1. The data confirm that diazepam (1 and 2.5 mg/kg) can be used to condition a significant preference ($P<0.01$) for environmental cues paired with the effects of systemic injections of this drug. In accordance with previous results (Spyraki et al. 1985) the diazepam-induced place preference does not appear to be dose related. The data also demonstrate that diazepam-induced place preference is blocked

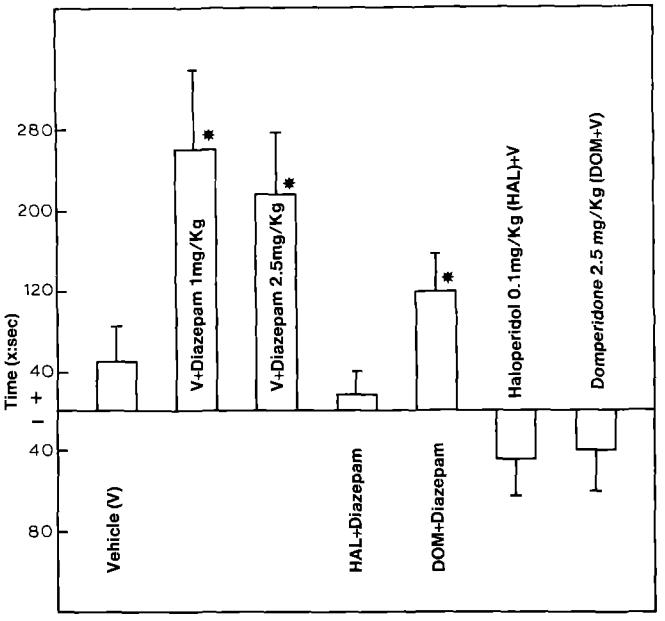


**Fig. 1.** The effect of haloperidol and domperidone pretreatment on diazepam-induced place preference. The effect of diazepam, haloperidol and domperidone alone on place conditioning is also illustrated. Data represent means (±SEM) of the difference in time spent in the drug-paired compartment between pre and post-conditioning test sessions ($N=10$/group).
*Significant shift to the side associated with the drug ($P<0.05$–0.01). See text for details

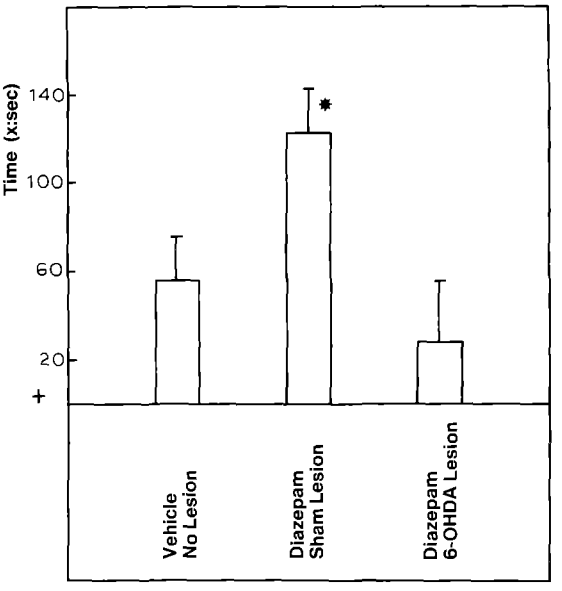


**Fig. 2.** Effect of 6-OHDA lesions of the nucleus accumbens on diazepam (2.5 mg/kg, IP)-induced place preference. Data represent means (±SEM) of the difference in time spent in the environment paired with diazepam between pre- and post-conditioning test sessions ($N=10$/group).
*Significant preference for the diazepam-associated side ($P<0.05$)

by haloperidol and is not significantly attenuated by domperidone pretreatment. Furthermore, haloperidol and domperidone alone do not affect place conditioning.

When the data from all seven groups (Fig. 1) were analyzed by a split-plot factorial ANOVA, there were significant main effects for the group [$F(6, 126)=7.6$, $P<0.01$] and trials [$F(1, 126)=20.20$, $P<0.01$] factors. There was also a significant group × trials interaction [$F(6, 126)=2.3$, $P<0.05$], indicating a difference between specific groups over the two test sessions. Although there was no significant difference between groups before conditioning ($F<1$), following conditioning significant differences between groups were detected [$F(6, 63)=15.09$, $P<0.01$]. Post hoc analyses revealed a significant difference between the vehicle-diazepam groups and the vehicle-vehicle group ($P<0.05$), but not between the two vehicle-diazepam groups. A significant difference was also detected between the vehicle-diazepam (1 mg/kg) group and the haloperidol-diazepam group ($P<$ 0.01). The domperidone-diazepam group did not differ significantly from either the vehicle-vehicle or vehicle-diazepam groups. However, the domperidone-diazepam group spent significantly ($P<0.05$) more time on the drug side after than before conditioning, thus showing that the diazepam-induced place preference could still be obtained following pretreatment with domperidone. There were no significant differences between vehicle-vehicle, haloperidol-vehicle and domperidone-vehicle groups.

*Effects on diazepam-induced place preference of bilateral 6-OHDA injections into the nucleus accumbens*

Figure 2 shows that diazepam-induced place preference can be significantly attenuated by destruction of the mesolimbic DA pathway at the level of the nucleus accumbens. The two way ANOVA yielded a significant effect for the trial [$F(1, 54)=5.01$, $P<0.05$]. Although the group effect failed to reach statistical significance [$F(2, 54)=2.8$], the group × trials interaction was significant [$F(2, 54)=21.6$, $P<0.01$]. Post hoc analyses revealed that the three groups did not differ in the time spent on drug side before conditioning. After conditioning the sham-lesion group treated with diazepam differed significantly ($P<0.05$) from both the 6-OHDA lesion group treated with diazepam and the unoperated contol treated with saline. Unexpectedly, the sham-lesion group exhibited weaker preference for the diazepam side (140 s increase, Fig. 2) than that manifested by rats (200 s. increase, Fig. 1) in previous experiments (Spyraki et al. 1985; Experiments 1 and 3 of this study). However, comparisons between studies cannot be made, as, unlike previous situations, the sham-lesion animals of this study underwent surgery and they were singly housed, both factors probably interfering with the establishment and/or manifestation of diazepam place conditioning. No differences were detected between saline-treated unoperated animals and the 6-OHDA-lesioned animals treated with diazepam.

The results of the biochemical analyses are summarized in Table 1. The 6-OHDA injections into the nucleus accumbens reduced DA in the accumbens to 13.4% of control values and resulted in a smaller but significant decrease in striatal DA.

*Diazepam-induced place preference in NA-depleted animals*

Figure 3 shows that the NA depletion produced by systemic administration of the neurotoxin DSP-4 failed to influence the diazepam-induced place preference. Two-way ANOVA of the data revealed significant main effects for the trial

**Table 1.** Dopamine concentrations in the nucleus accumbens + olfactory tubercle and striatum after bilateral 6-OHDA injections into the nucleus accumbens

| Region | Control ($N=6$) | Treated ($N=10$) | Per cent of Control |
|---|---|---|---|
| Striatum | 14500±1300 | 11080±1030* | 76.4 |
| N. Acc.+O.T. | 7130± 500 | 960±200** | 13.4 |

Values represent means (±SEM) in ng/g wet weight of tissue Significantly different from controls * $P<0.05$ ** $P<0.001$

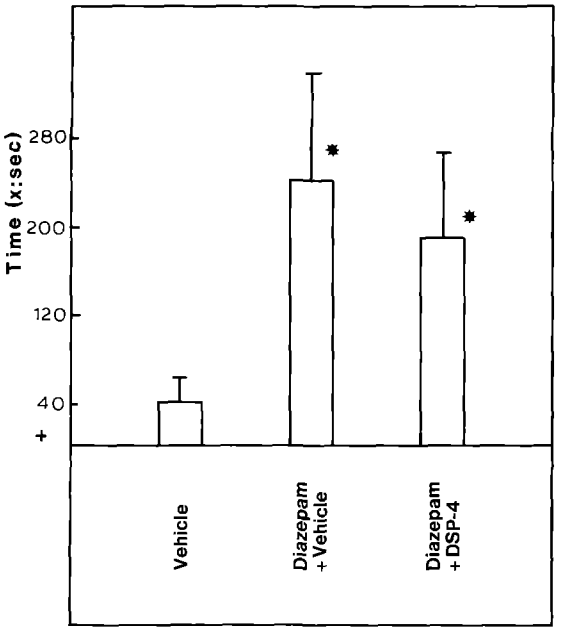


**Fig. 3.** Effect of NA depletion by DSP-4 on diazepam (1 mg/kg, IP)-induced place preference. Data represent means (±SEM) of the difference in time spent in the distinctive environment paired with diazepam between pre and post-conditioning test sessions ($N=10$/group).
*Significant preference for the diazepam-associated side ($P<0.05$)

[$F(1, 48)=8.1$, $P<0.01$] and for the group [$F(2, 48)=3.18$, $P<0.05$] factors. The group × trials interaction was also significant [$F(2, 48)=16.7$, $P<0.01$]. Post-hoc analyses showed that both diazepam injected groups (vehicle and DSP-4 treated) were significantly ($P<0.05$) different from vehicle-injected controls. No differences were detected between DSP-4-diazepam and vehicle-diazepam groups. The results of the NA assays are shown in Table 2. In accordance with our previous results (Spyraki and Fibiger 1982) animals treated with DSP-4 suffered severe depletion of NA in the cortex, hippocampus and cerebellum, while hypothalamic NA was not significantly reduced.

**Table 2.** Regional concentrations of noradrenaline after DSP-4 treatment

| Region | Control ($N=5$) | Treated ($N=8$) | Per cent of Control |
|---|---|---|---|
| Cortex | 488.0± 5.3 | 134.6± 29.0* | 27.5 |
| Hippocampus | 730.0± 64.2 | 119.6± 19.0* | 16.3 |
| Hypothalamus | 2980.0±257.0 | 2512.0±230.0 | 84.0 |
| Cerebellum | 403.0± 22.0 | 130.2± 2.1* | 32.0 |

Values represent means (±SEM) in ng/g wet weight of tissue. Significantly different from controls * $P<0.001$

## Discussion

The attenuation of diazepam-induced place preference by pretreatment with haloperidol or by prior destruction of the mesolimbic dopaminergic terminals with 6-OHDA suggests that this brain DA system plays an important role in mediating the rewarding effects of diazepam. Furthermore, the results with domperidone argue against the possibility that diazepam-induced place preference is mediated through peripheral DA receptors.

A number of studies have suggested that noradrenaline is important for the behavioural effects of benzodiazepines (Fuxe et al. 1975; Stein et al. 1977; Vachon et al. 1984). Although the 6-OHDA lesions of the nucleus accumbens may have caused a partial lesion of the noradrenergic projections to the cortex and hippocampus, these effects could be discounted in the present instance. Systemic injections of DSP-4 produced severe depletion of NA in cortex and hippocampus, but this treatment had no effect on diazepam-induced place preference.

In contrast to the situation with NA, the evidence for an involvement of DA in the actions of benzodiazepines is fragmentary. In diazepam-pretreated animals haloperidol-induced catalepsy is enhanced and the increase in DA turnover in striatal and mesolimbic areas following the neuroleptic is counteracted (Keller et al. 1976). More indirectly, there is one report which might argue for a GABA-DA interaction in positive reinforcement: the lowering by the GABA antagonist picrotoxin of self stimulation thresholds in the VTA (Nazzaro and Gardner 1980). However, several attempts to demonstrate an involvement of a GABA-DA interaction in the rewarding effects of benzodiazepines have failed (Porino and Coons 1980; Herberg and Williams 1983). Similarly, in a parallel study, we failed to provide unequivocal evidence for a role of GABA in diazepam-induced place preference (Spyraki et al. 1985).

The possibility that benzodiazepines influence mesolimbic dopaminergic function directly should not be neglected. Biochemical studies show that benzodiazepines reduce DA turnover in DA-innervated areas (Rastogi et al. 1977; Ishiko et al. 1983), a property shared with dopamine agonists. Fuxe and associates (1975) reported that diazepam (1 mg/kg, IP) reduces DA turnover in the mesolimbic but not in the nigrostriatal projection. Although the effects of benzodiazepines on DA turnover may be mediated by long loop GABAergic mechanisms (Speth et al. 1981), the facilitation of potassium-induced DA release by benzodiazepines observed in in vitro studies (Mitchell and Martin 1980) points to an additional action of benzodiazepines on dopamine presynaptic terminals. It is perhaps significant that the density of benzodiazepine receptors in nucleus accumbens is higher than in striatum or in substantia nigra and VTA (Möhler et al. 1978). It is also noteworthy that diazepam induces metenkephalin release in DA innervated areas (Duka et al. 1979). In addition to the fact that met-enkephalin injections into the VTA are rewarding (Phillips et al. 1983), the effect of diazepam on met-enkephalin release appears to be dopamine dependent (Harsing et al. 1982). It

is evident, therefore, that multiple brain neurotransmitter systems are affected by benzodiazepines. Clarification of the extent to which any of these mechanisms are responsible for enhancing mesolimbic DA activity and thereby contribute to the rewarding actions of diazepam is an interesting challenge for future research.

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