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Discriminative Stimulus Effects of Tizanidine Hydrochloride: Studies With Rats Trained to Discriminate Either Tizanidine, Clonidine, Diazepam, Fentanyl, or Cocaine

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ABSTRACT

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Male Sprague Dawley rats were trained in a two-lever food-reinforced procedure to discriminate between the effects of saline and either tizanidine hydrochloride, clonidine hydrochloride, diazepam, fentanyl, or cocaine hydrochloride. Tizanidine-trained rats dose-dependently generalized the effects of tizanidine and clonidine but not pentobarbital, diazepam, morphine, or cocaine. Clonidine-trained rats dose-dependently generalized the effects of clonidine and tizanidine but not pentobarbital, diazepam, or morphine. Diazepam-trained rats dose-dependently generalized the effects of diazepam but did not generalize tizanidine. Fentanyl-trained rats dose-dependently generalized the effects of fentanyl but did not generalize tizanidine. Cocaine-trained rats did not generalize the effects of tizanidine to the cocaine discriminative stimulus. Yohimbine hydrochloride but not naloxone hydrochloride dose-dependently antagonized the discriminative stimuli produced by both tizanidine and clonidine. These data demonstrate that tizanidine shares discriminative stimulus properties with clonidine but not with pentobarbital, diazepam, fentanyl, morphine, or cocaine. The discriminative stimuli produced by tizanidine and clonidine are mediated via an agonistic interaction with alpha$_2$-adrenergic receptors and not via an agonistic interaction with opioid receptors.

Key words: pentobarbital, morphine, drug discrimination, discriminative stimulus

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INTRODUCTION

Tizanidine hydrochloride (5-chloro-4-(2-imidazoline-2-yl-amino)-2,1,3 benzothiadiazole, Fig. 1) is currently used for the treatment of spasticity associated with various CNS disorders [Rinne, 1980; Smolenski et al., 1981; Newman et al., 1982] and for painful muscle spasm in muscoskeletal conditions [Bragstad and Blirka, 1979; Roosen, 1981]. Tizanidine is a centrally acting agent with a pharmacodynamic profile different from that of myotonolytic drugs currently in use such as diazepam, baclofen, and dantrolene (Sayers et al., 1980].

As an imidazoline derivative, tizanidine has structural similarities with clonidine. Clonidine is known to produce a variety of central nervous system and psychopharmacological actions [for review, see Shearman and Lal, 1982]. Recently, Bennett and Lal [1982] and D'Mello [1982] reported on the discriminative stimulus properties of clonidine in rats. It was the purpose of this work to evaluate the discriminative stimulus effects of tizanidine in this species and to compare these effects with those of clonidine, pentobarbital, diazepam, fentanyl, morphine, and cocaine.

METHODS

Subjects

Sixty male Sprague Dawley rats (Sandoz AG, Basel) weighing between 300 and 400 g were used. The animals were housed in single cages in a colony room maintained at 24 ± 1°C. The room lights were turned on from 7.00 a.m. to 7.00 p.m. Water was continuously available in the home cages, but food was restricted to 20 g a day made available approximately 4 h following each operant session.

Apparatus

The behavioural apparatus consisted of six identical conventional Skinner boxes housed in lightproof, sound-attenuated, and fan-ventilated chambers. Each Skinner box contained a houselight, which was located above a food receptable. The latter was installed in the center of one wall equidistant from two response levers. Scheduling of behavioural contingencies and recording of data was made with solid-state programming modules (Coulbourn Instruments Inc., Lehigh Valley, PA).

Discrimination Training

The rats were trained to discriminate between the effect of saline (1 ml/kg) and either tizanidine hydrochloride (0.32 mg/kg, t = 60 min), clonidine hydrochloride (0.04 mg/kg, t = 60 min), fentanyl (0.04 mg/kg, t = 30 min), diazepam (2.5 mg/kg, t = 30 min), or cocaine

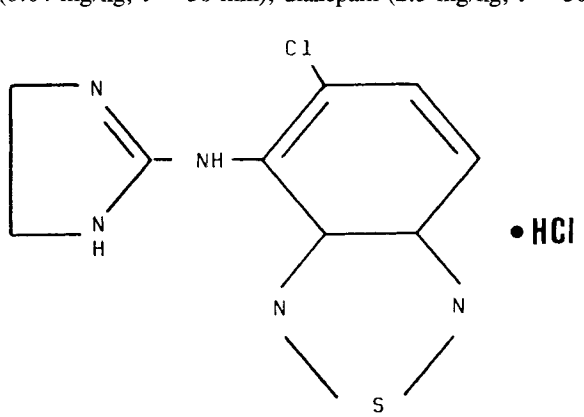

Fig. 1. Chemical structure of tizanidine hydrochloride (DS 103–282).

hydrochloride (10 mg/kg, t = 20 min). The animals were first magazine trained and shaped to lever press for food reinforcement (45 mg Noyes food pellets) according to the procedure of Colpaert et al. [1976]. The animals were then trained to respond with one of the levers at a specified time after training-drug injection and with the other lever after a saline (1 ml/kg) injection. Every tenth response (FR 10) with the correct lever resulted in the delivery of a food pellet. Responses with the incorrect lever (i.e., drug lever after saline injection or saline lever after drug injection) were recorded but were not reinforced by delivery of food.

The drug lever was on the right side of the food receptacle for half of the rats and on the left side for the remaining animals. For each rat, the position of the drug and saline levers remained constant on each subsequent session. To avoid the possibility that olfactory cues associated with the correct lever for rats previously tested in the boxes would serve as a discriminative stimulus [Extance and Goudie, 1981], the sequence of drug-saline injections was varied separately for each group of rats trained successively on the same day. Initially, the drug-saline injection alternated. This training continued until five such alterations were achieved, and responding was stabilized with the appropriate lever. Following this, the rats entered the final phase of training in which drug saline sessions were carried out 5 days a week according to an irregularly alternating sequence of drug-saline injections. In this and all subsequent phases of the experiment, the session length was fixed at 15 min. The rats were trained to a criterion of emitting four or less responses with the incorrect lever prior to the first reinforcement (ten responses with the correct lever) on nine out of ten consecutive sessions.

Discrimination Testing

After the rats reached the criterion level of performance, they were repeatedly used in generalization and antagonism tests. These tests consisted of 15-min sessions that were separated by at least two practice sessions in which the number of responses with the incorrect lever before selection of the correct lever did not exceed four. If the rat's performance on these practice sessions failed to meet the criterion, further training sessions were given before testing was reinstated. For half of the rats, test sessions were preceded by a saline practice session, whereas for the remaining rats, test sessions were preceeded by a drug practice session. For generalization tests, following injection of the test drug (for pretreatment times, see Tables), each rat was placed in its assigned Skinner box and allowed to respond with the levers. The lever with which the animal emitted ten responses first was considered the selected lever and responses with this lever were reinforced (FR 10) for the remainder of the test session. The other lever was considered the nonselected lever and responses emitted with this lever were recorded but not reinforced. For antagonism tests, animals were injected with the test drug and training drug (for pretreatment times see Tables) and placed in the assigned Skinner boxes and tested for lever selection as described above. Test drugs and the doses of each test drug were administered in an irregular order. All drugs were injected i.p. except fentanyl, which was injected s.c.

Data Analysis

Data were expressed as the number of rats selecting the training drug lever following each drug treatment divided by the number of rats tested. ED_{50}^{S} were calculated with slope (m) and Y-intercept (b_O) of log-linear regression lines using the equation $y = m\log x + b_O$.

Drugs

Tizanidine hydrochloride, clonidine hydrochloride, morphine hydrochloride, cocaine hydrochloride, fentanyl citrate, yohimbine hydrochloride, and naloxone hydrochloride were dissolved in 0.9% saline. Diazepam was suspended in 13% propylen glycol, 1% Tween 80, and saline. Pentobarbital (solution) was obtained from Abbott AG, Zug, Switzerland.

Doses of all drugs refer to the forms listed above except for fentanyl in which doses refer to the base form.

RESULTS

Tizandine Discrimination

All of the rats acquired the tizanidine hydrochloride-saline discrimination. The number of sessions needed to reach this criterion ranged from 33 to 53 with a mean (± S.E.) of 42 ± 2. An initial training dose of 0.08 mg/kg was increased to 0.32 mg/kg after 18 training sessions because of relatively poor discrimination performance with the 0.08 mg/kg dose. Following this training-dose increase the rats reliably discriminated tizanidine from saline. On the 23rd training session 83% of the rats injected with tizanidine (0.32 mg/kg) selected the tizanidine lever, whereas on the 23rd saline session only 17% of the rats injected with saline selected the tizanidine lever.

Data summarized in Table 1 show that the tizanidine-trained rats dose-dependently selected the tizanidine lever after injections of tizanidine (0.02–0.32 mg/kg) or clonidine (0.01–0.04 mg/kg). The ED_{50} values were 0.12 and 0.015 mg/kg, respectively. Both tizanidine and clonidine dose-relatedly suppressed the rate of lever pressing for food reinforcement. The ED_{50}s for this effect were approximately 0.32 and 0.02 mg/kg, respectively. As shown in Table 1 the tizanidine-trained rats did not significantly (Fisher exact probability tests, $P < 0.05$) generalize the effects of either pentobarbital (2.5 and 10 mg/kg), diazepam (0.64 and 2.5 mg/kg), morphine (5 and 10 mg/kg), or cocaine (2.5 and 5 mg/kg).

Data summarized in Table 2 indicate that yohimbine hydrochloride (0.64 and 2.5 mg/kg) dose-dependently antagonized the tizanidine (0.32 mg/kg) discriminative stimulus. The ED_{50} for yohimbine antagonism was approximately 1.1 mg/kg. As shown in Table 2 neither

TABLE 1. Generalization Tests With Rats Trained to Discriminate Between the Effects of Tizanidine Hydrochloride (0.32 mg/kg) and Saline

Test drug[a]	Doses mg/kg	Pretreatment time (min)	N[b]	N–DL[c]/ NT	Percent saline level[d] (mean ± SE)
Tizanidine HCl	0.02	60	6	1/6	99 ± 3
	0.08		6	2/6	78 ± 4*
	0.32		6	6/6	46 ± 5*
Saline	—	60	10	0/10	99 ± 3
Clonidine HCl	0.01	60	6	1/6	77 ± 3*
	0.02		6	5/6	47 ± 4*
	0.04		6	5/6	33 ± 5*
Pentobarbital	2.5	30	6	2/6	99 ± 14
	10		6	1/6	61 ± 13*
Diazepam	0.64	30	6	0/6	103 ± 2
	2.5		6	1/6	110 ± 5
Morphine HCl	5.0	30	6	2/6	77 ± 18
	10.0		4	1/4	
			2	No selection	56 ± 18*
Cocaine HCl	2.5	20	6	1/6	88 ± 8
	5.0		6	0/6	102 ± 4

[a]Following the injection of the test drug, each rat was placed in its assigned Skinner box and allowed to respond with the levers. The lever with which ten responses were completed first was considered the selected lever.

[b]No. of rats tested.

[c]No. of rats selecting the training drug lever divided by the total No. of rats tested. No selection indicates that ten responses were not emitted on either lever during the entire 15-min test session.

[d]Response rate expressed as a percentage (mean ± SE) of the response rate during the saline session preceding each test.

*$P \leq .05$ (Wilcoxon Test; Siegel [1956]) vs. preceeding saline session.

TABLE 2. Antagonism Tests With Rats Trained to Discriminate the Effects of Tizanidine Hydrochloride (0.32 mg/kg) From Saline

Test drug[a]	Dose mg/kg	Pretreatment time (min)	N[b]	N−DL[c] NT	Percent saline level[d] (mean ± SE)
Tizanidine HCl + Saline	0.32 —	60 15	8	8/8	59 ± 8*
Tizanidine HCl + Yohimbine HCl	0.32 0.64	60 75	6	5/6	80 ± 7
	1.25		6	3/6	91 ± 6
	2.5		6	0/6	70 ± 7*
Tizanidine HCl + Naloxone HCl	0.32 1.0	60 15	6	5/6	51 ± 14*

[a,b,c,d,*]All footnotes as in Table 1.

TABLE 3. Generalization Tests With Rats Trained to Discriminate Between the Effects of Clonidine Hydrochloride (0.04 mg/kg) and Saline

Test drug[a]	Dose mg/kg	Pretreatment Time (min)	N[b]	N-DL[c]/ NT	Percent saline level[d] (mean ± SE)
Clonidine HCl	0.01	60	6	0/6	67 ± 3*
	0.02		6	3/6	58 ± 4*
	0.04		6	6/6	41 ± 3*
Saline	—	60	10	0/10	99 ± 3
Tizanidine HCl	0.02	60	6	0/6	89 ± 2*
	0.08		6	3/6	80 ± 4*
	0.32		6	6/6	54 ± 10*
Pentobarbital	10.0	30	6	1/6	99 ± 13
	20.0		4	No selection	0 ± 0
Diazepam	2.5	30	6	0/6	81 ± 15
	5.0		4	1/4	
			2	No selection	37 ± 22
Morphine HCl	5.0	30	6	1/6	111 ± 39
	10.0		5	1/5	
			1	No selection	41 ± 18*

[a,b,c,d,*]All footnotes as in Table 1.

saline (1 ml/kg) nor naloxone (1 mg/kg) significantly (Fisher exact probability tests, $P > 0.05$) antagonized the tizanidine discriminative stimulus.

Clonidine Discrimination

All of the rats acquired the clonidine hydrochloride-saline discrimination. The number of sessions needed to reach the criterion for discrimination ranged from 18 to 36 with a mean (± S.E.) of 26 ± 2.

Data summarized in Table 3 show that the rats dose-dependently selected the clonidine lever after injection of clonidine (0.01–0.04 mg/kg) and tizanidine (0.02–0.32 mg/kg). The ED_{50} values were 0.02 and 0.08 mg/kg, respectively. Both clonidine and tizanidine dose-dependently suppressed the rate of lever pressing for food reinforcement. The ED_{50}s for this effect were approximately 0.03 and 0.32 mg/kg. The rats did not significantly (Fisher exact

probability test, $P < .05$) generalize the effects of either pentobarbital (10 mg/kg), diazepam (2.5 and 5 mg/kg), or morphine (5 and 10 mg/kg).

Data summarized in Table 4 indicate that yohimbine hydrochloride (0.04–2.5 mg/kg) dose-dependently antagonized the discriminative stimulus produced by clonidine (0.04 mg/kg). The ED_{50} for yohimbine antagonism was approximately 0.16 mg/kg. Neither saline (1 ml/kg) nor naloxone (1 mg/kg) antagonized the clonidine discriminative stimulus in any rats.

Diazepam Discrimination

Data summarized in Table 5 show that the diazepam-saline-trained rats dose-dependently generalized the effects of diazepam. The ED_{50} was approximately 0.64 mg/kg. The rats did not significantly (Fisher probability tests, $P < .05$) generalize the effects of either saline, solvent, or tizanidine (0.02 - 0.32 mg/kg). Response rate during the solvent test session was significantly lower than the rate of responding during the saline session preceding this test (Wilcoxon test, $P < .05$). Tizanidine dose-dependently reduced the rate of lever pressing for food reinforcement, and this effect was significant (Wilcoxon test, $P = .05$) after the 0.08 and 0.32 mg/kg doses.

TABLE 4. Antagonism Tests With Rats Trained to Discriminate the Effects of Clonidine Hydrochloride (0.04 mg/kg) From Saline

Test drug[a]	Dose mg/kg	Pretreatment time (min)	N[b]	N-DL[c]/ NT	Percent saline level[d] (mean ± SE)
Clonidine HCl	0.04	60			
+					
Saline	—	15	6	6/6	29 ± 3*
Clonidine HCl	0.04	60			
+					
Yohimbine HCl	0.04	75	6	6/6	52 ± 15
	0.16		6	3/6	58 ± 9*
	0.64		6	2/6	67 ± 6*
	2.5		6	1/6	76 ± 7*
Clonidine HCl	0.04	60			
+					
Naloxone HCl	1.0	15	6	6/6	38 ± 2*

[a,b,c,d,*]All footnotes as in Table 1.

TABLE 5. Generalization Tests With Tizanidine Hydrochloride in Rats Trained to Discriminate Between Diazepam (2.5 mg/kg) and Saline

Test drug[a]	Dose mg/kg	Pretreatment time (min)	N[b]	N−DL[c] NT	Percent saline level[d] (mean ± SE)
Diazepam	0.04	30	6	0/6	90 ± 4
	0.16		6	2/6	110 ± 10
	0.64		6	3/6	116 ± 3*
	2.5		6	6/6	111 ± 11
Saline	—	30	6	0/6	105 ± 7
Solvent	—	30	10	0/10	87 ± 4*
Tizanidine HCl	0.02	60	6	1/6	85 ± 5
	0.08		6	1/6	78 ± 3*
	0.32		6	0/6	41 ± 4*

[a,b,c,d,*]All footnotes as in Table I.

Fentanyl Discrimination

Data summarized in Table 6 show that the fentanyl-saline-trained rats dose-dependently generalized the effects of fentanyl. The ED_{50} was 0.016 mg/kg. The rats did not significantly (Fisher exact probability tests $P < .05$) generalize the effects of either saline or tizanidine (0.02–1.25 mg/kg) to the fentanyl discriminative stimulus.

Response rate for food reinforcement was significantly different (Wilcoxon test, $P < .05$) during fentanyl (0.04 mg/kg) test sessions compared to the rates of responding on the saline sessions preceding these tests. Tizanidine (0.02–1.25 mg/kg) dose-dependently reduced the rate of lever pressing for food reinforcement. The ED_{50} for this effect was 0.12 mg/kg.

Cocaine Discrimination

Data summarized in Table 7 show that all of ten rats selected the cocaine lever after injection of cocaine hydrochloride (10 mg/kg), whereas none of the ten rats selected the cocaine lever after saline (1 ml/kg) injection. Response rate during the cocaine hydrochloride test session was significantly different from that during the saline session preceeding the test (Wilcoxon test, $P = .05$).

None of the six rats injected with tizanidine hydrochloride (0.32 or 0.64 mg/kg) selected the cocaine lever. All of these rats selected the saline lever. Tizanidine hydrochloride dose-dependently suppressed the rate of lever pressing for food reinforcement in comparison to the saline sessions preceding these tests, and this effect was significant (Wilcoxon test, $P = .05$) after the 0.64 mg/kg dose.

DISCUSSION

The present data show that tizanidine hydrochloride shared discriminative stimulus properties with the imidazoline derivative and prototype alpha$_2$-receptor agonist clonidine but

TABLE 6. Generalization Tests With Tizanidine Hydrochloride in Rats Trained to Discriminate Between Fentanyl (0.04 mg/kg) and Saline

Test drug[a]	Dose mg/kg	Pretreatment time (min)	N[b]	N−DL[c]/ NT	Percent saline level[d] (mean ± SE)
Fentanyl	0.005		10	1/10	100 ± 4
	0.01		8	2/8	115 ± 12
	0.02		8	3/8	85 ± 10
	0.04		12	12/12	53 ± 6*
Saline	—		12	0/12	102 ± 3
Tizanidine HCl	0.02		6	0/6	86 ± 3*
	0.08		6	0/6	63 ± 4*
	0.32		6	0/6	25 ± 4*
	1.25		5	No selection	0

[a,b,c,d,*]All footnotes as in Table 1.

TABLE 7. Generalization Tests With Tizanidine Hydrochloride in Rats Trained to Discriminate Between Cocaine Hydrochloride (10 mg/kg) and Saline

Test drug[a]	Dose mg/kg	Pretreatment time (min)	N[b]	N-DL[c]/ NT	Percent saline level[d] (mean ± SE)
Cocaine HCl	10.0	20	10	10/10	50 ± 6*
Saline	—	20	10	0/10	100 ± 6
Tizanidine HCl	0.32	60	6	0/6	84 ± 12
	0.64		6	0/6	64 ± 9*

[a,b,c,d,*]All footnotes as in Table 1.

did not share discriminative stimulus properties with either pentobarbital, diazepam, fentanyl, morphine, or cocaine. It was recently reported that the discriminative stimulus effects of clonidine in rats were mediated via its agonistic action at $alpha_2$-adrenergic receptors [Bennett and Lal, 1982]. The data reported here confirm this suggestion and also suggest that, like clonidine, the discriminative stimulus effects of tizanidine are mediated via $alpha_2$-receptors since the selective $alpha_2$-adrenergic antagonist yohimbine antagonized the tizanidine discriminative stimulus. Recently, Davies et al. [1984] reported that tizanidine-induced depression of excitation of feline dorsal horn neurones to noxious peripheral stimuli was mediated via $alpha_2$-receptors.

The opioid receptor antagonist naloxone has been reported to antagonize the discriminative stimulus effects of opioids [Shannon and Holtzman, 1976; Sherman and Herz, 1982]. In the present study, naloxone did not antagonize the discriminative stimulus induced by tizanidine. This finding suggests that the tizanidine discriminative stimulus is not mediated via an agonistic interaction with opioid receptors. This suggestion is supported by recent data that show that the antinociceptive effect of tizanidine in mice and rats was not affected by naloxone [Kameyama et al., 1985]. Previously, Bennett and Lal [1982] reported that a discriminative stimulus induced by clonidine was not antagonized by naloxone. The lack of cross-generalization between tizanidine and morphine or fentanyl observed in the present study also supports the suggestion that the tizanidine discriminative stimulus is not mediated by opioid receptors. Miksic et al. [1978] reported that clonidine was not generalized to a discriminative stimulus induced by morphine in rats, and D'Mello [1982] found that morphine was not generalized to clonidine.

In the present study it was observed that rats trained to discriminate tizanidine did not generalize diazepam or pentobarbital. Furthermore, it was found that diazepam-trained rats did not generalize tizanidine. We also found that rats trained to discriminate clonidine did not generalize pentobarbital or diazepam. However, D'Mello [1982] reported that clonidine-trained rats generalized chlordiazepoxide and amylobarbitone and suggested that a major component of the clonidine discriminative stimulus may be general sedation. The lack of generalization between tizanidine and diazepam or pentobarbital suggests that sedation may not be a major component of the tizanidine discriminative stimulus. This suggestion is supported by the present data showing that at equieffective doses in acting as discriminative stimuli, tizanidine appears to be less sedating than clonidine as may be measured by the ratio of the ED^{50} to decrease the rate of operant responding for food reinforcement and the ED_{50} for drug discrimination (Tables 1, 3). Thus, an important difference between tizanidine and clonidine may be that tizanidine is less sedating than clonidine. Sayers et al. [1980] showed that tizanidine had a pharmacological profile different from diazepam and did not cause sedation at muscle-relaxing doses.

In the present investigation it was found that tizanidine-trained rats did not generalize cocaine and that cocaine-trained rats did not generalize tizanidine. Thus, tizanidine does not share discriminative stimulus properties with cocaine. This finding is particularly interesting since a one-way generalization of clonidine to a discriminative stimulus produced by cocaine was recently reported [Weed et al., 1985]. Therefore, it appears that only clonidine but not tizanidine shares discriminative stimulus properties with cocaine.

In conclusion, the present data show that tizanidine shares some discriminative stimulus properties with clonidine. However, there also appears to be important differences in the discriminative stimulus properties of these two drugs. The discriminative effects of both tizanidine and clonidine appear to be mediated by $alpha_2$ but not opioid receptors. At equieffective doses in producing discriminative stimulus effects, tizanidine was three to four times less sedating than clonidine. Furthermore, clonidine generalized to a discriminative stimulus produced by cocaine [Wood et al., 1985], tizanidine did not.

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