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Effects of (−)-Pindolol and SDZ 216-525 on Social and Agonistic Behavior in Mice

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BELL, R. AND H. HOBSON. *Effects of (−)-pindolol and SDZ 216-525 on social and agonistic behavior in mice.* PHARMACOL BIOCHEM BEHAV 46(4) 873–880, 1993. — In view of conflicting results reported for 5-HT_{1A} receptor involvement in murine social conflict, this study examined the effect of two compounds, SDZ 216-525 and (−)-pindolol, on agonistic and social behavior in male mice. In a resident-intruder paradigm, (−)-pindolol (1.0–20.0 mg/kg), a β-adrenergic 5-$HT_{1A/1B}$ antagonist, significantly attenuated all agonistic behaviors across the dose range employed. Social behaviors showed significant decreases, while nonsocial cage exploration showed significant increases at all doses. Defensive evade was significantly attenuated at 20.0 mg/kg. SDZ 216-525 (0.025–1.0 mg/kg), a selective 5-HT_{1A} antagonist, significantly attenuated offensive posturing and bite-attacks at 1.0 mg/kg, and all offensive behaviors nonsignificantly at the smaller doses tested. Rearing was significantly attenuated at 1.0 mg/kg, while cage exploration increased at this dose. Defensive and social behaviors remained largely unchanged. These results show that both compounds tested produced significant reductions in offensive behavior, with concomitant changes in defensive, social, and nonsocial behaviors. Results are discussed in relation to SDZ 216-525 and (−)-pindolol potential for the control of anxiety and agonistic behavior.

SDZ 216-525 (−)-Pindolol Agonistic behavior Social behavior 5-HT_{1A} antagonists Ethological analysis

STUDIES employing 5-HT_{1A} agonists to examine the role of 5-HT_{1A} receptor mechanisms in rodent social conflict have reported inconsistent results [for review see (21)]. The use of 5-HT_{1A} antagonists, such as (−)-pindolol, has also produced mixed results. The possibility that some β-adrenoreceptor blocking agents, such as (−)-propranolol, (−)-alprenolol, and (−)-pindolol, possess the additional property of interacting with central 5-HT receptor sites has been suggested by radioligand binding studies [e.g., (12,17)]. However, the (+)-enantiomers of these compounds and some selective β_1 and β_2 agents are devoid of such activity. (−)-Pindolol has been reported (8) to cause a dose-related reduction in brain 5-HT synthesis similar in magnitude to 8-OH-DPAT and buspirone; the steady-state 5-HIAA level and the 5-HIAA/5-HT ratio are also stereospecifically decreased by (−)-pindolol. This apparent inhibition of 5-HT activity may be due to direct stimulation of 5-HT presynaptic autoreceptors controlling synthesis and/or release in the CNS (8). (−)-Pindolol displays mixed agonist/antagonist properties at central 5-HT receptors (14,15) and has high affinity for 5-HT_{1A} and 5-HT_{1B} sites, but competes only weakly for 5-HT_2 radioligand sites (4). Whether the biochemical actions of (−)-pindolol correspond to 5-HT_{1A} or 5-HT_{1B} sites remains to be verified. (−)-Pindolol has previously been found to attenuate aggressive behavior in male mice (3) or to have little effect in this paradigm (23). Since (−)-pindolol has high affinity for 5-HT_{1A} and 5-HT_{1B} receptor sites (4), the question arises whether the effects of this compound are the result of 5-HT_{1A} activity, 5-HT_{1B} activity, β-adrenergic properties, or a combination of activity at these receptor sites.

Given the lack of consistent findings discussed, the present study employed a recently developed selective 5-HT_{1A} antagonist, SDZ 216-525, to examine the role of 5-HT_{1A} receptors in murine social conflict, as observed in the resident-intruder paradigm. The influences of SDZ 216-525 were compared with those of (−)-pindolol, a β-adrenergic 5-$HT_{1A/1B}$ antagonist (16). In radioligand binding studies, SDZ 216-525 {methyl 4-[4-[4-(1,1,3-trioxo-2*H*-1,2-benziosothiazol-2-yl)-butyl]-*i*-piperazinyl]1*H*-indole-2-carboxylate} showed high affinity and selectivity for 5-HT_{1A} sites, while affinity for α_1-, α_2-, β_1-, and β_2-adrenoreceptors and dopamine D_2 receptors was at least 50–100 times lower than for the 5-HT_{1A} sites (9). In autoradiographic studies (9), SDZ 216-525 displaced, in a concentration-dependent manner, the binding to all specific 5-HT_{1A} sites labelled with 8-OH-DPAT, and labelled high-affinity sites in the pig cortex with a profile typical of that of 5-HT_{1A}. Quantitative autoradiography in rat brain revealed that the distribution of sites labelled by SDZ 216-525 and 8-OH-DPAT was identical. In vivo, SDZ 216-525 did not induce forepaw treading or flat body posture in reserpinised rats (9) at doses up to

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1 mg/kg SC, whereas the response to a submaximal dose of 8-OH-DPAT (0.25 mg/kg, SC was inhibited dose dependently by SDZ 216-525 over the range 0.03–1.0 mg/kg, SC. These results show that SDZ 216-525 acts as a potent, selective 5-HT_{1A} antagonist both in vitro and in vivo (9).

The resident–intruder paradigm mainly represents offensive aspects of agonistic behavior in the resident mouse, but where the intruder is also studied, defensive aspects of agonistic behavior are represented as well (6). Since the full behavioral repertoire is available, this model can also be used to test the behavioral specificity of a compound (10). Hence, the basic aim of this investigation was to employ a selective 5-HT_{1A} antagonist to determine whether 5-HT_{1A} receptors influence offensive behavior in a specific manner. Specificity of action would imply inhibition of agonistic behavior without concomitant sedation or alterations in social behavior.

METHOD

Subjects and Procedure

One hundred and sixty adult male albino mice of the BSVS strain, weighing between 25–35 g from Queens University Belfast Medical Biology Centre Breeding stock were used. Four weeks prior to testing the mice were randomly allocated to resident or intruder status. Residents were individually caged (cage size 30 × 15 × 13 cm) and intruders were housed with siblings in groups of approximately 10 (cage size 44 × 28 × 13 cm). Throughout the 4 weeks prior to testing, all animals were given fresh bedding weekly, with food and water available ad lib . All subjects were maintained in a temperature-controlled room (24 ± 1°C), in which a 12L : 12D reversed cycle was operative (lights on 2400 h).

Behavioral testing took place in the resident's home cage. Food and water were removed from test cages for the duration of encounters. Resident/intruder encounters were recorded on tape by a Panasonic Saticon colour video camera (model WVP200E) with low light facility. The test cages were illuminated by two 60-W "angle-poise" lamps during social encounters. Tape analysis was carried out using a Panasonic video recorder, a VDU, an IBM portable computer (model 5155 640K), and a tractor printer.

SDZ 216-525 (Sandoz) was dissolved in a weak solution of maleic acid, and (−)-pindolol (Sandoz) was ultrasonically dissolved in 0.9% physiological saline to which two drops of Tween 80 had been added. Doses were selected on the basis of previous investigations for SDZ 216-525 (9) and (−)-pindolol (8). All injections were performed subcutaneously (SC) in a volume of 10 ml/kg 30 min prior to testing. Animals used were both drug and experimentally naive. The experimenter remained blind to the conditions until data analysis was complete.

All testing was carried out under red light during the mid-portion of the dark phase. Isolates were weighed, marked for recognition, and randomly assigned to dose treatment groups. Only isolate (resident) mice received drug treatments. Thirty minutes after treatment (residents), intruder mice were introduced into the home cages of the residents and the ensuing 10-min encounters were recorded on video tape for later analysis. Eight experimental groups were used (n = 10 pairs in each group): control vehicle for pindolol, 1.0, 10.0, and 20.0 mg/kg pindolol; control vehicle for SDZ 216-525, 0.025, 0.25, and 1.0 mg/kg SDZ 216-525.

Measures

Behavioral analysis was similar to that previously described (22). Briefly, videotapes were analysed using direct keyboard inputs to the microcomputer that had been programmed to produce data output in the form of frequency and real-time duration of behavioral elements [for review see (7)]. The following behavioral elements and categories were analysed: Nonsocial cage exploration—rearing, maintenance, digging; social—naso-genital, naso-nasal, nonspecific partner investigation, follow, attend/approach, stretch/attend; offensive—aggressive groom, tail rattle, offensive sideways, offensive upright, chase, bite-attack; defensive—evade, defensive upright, defensive sideways, submissive upright, frozen crouch.

Statistical Analysis

Given the nonparametric nature of the data, results for each behavioral element were analysed using Kruskal–Wallis one-way analyses of variance (ANOVA). Where statistical differences were detected, further comparisons (with control group) were performed by Mann–Whitney U-tests.

RESULTS

(−)-Pindolol

Resident nonsocial behavior. Analysis failed to reveal significant effects for rearing, maintainance, and digging (Table 1). However, Mann–Whitney procedures showed that cage exploration produced significant increases in frequency at 20.0 mg/kg (median 35 vs. control median 30, $U = 12.5$, $p < 0.02$) and 10.0 mg/kg (median 36 vs. control median 30, $U = 23$ $p < 0.05$) and in duration at 20.0 mg/kg (median 357.13 vs. control median 216.28, $U = 22$, $p < 0.05$) and 1.0 mg/kg (median 353.26 vs. control median 216.28, $U = 23$ $p < 0.05$).

Resident social behavior. Attend/approach behavior changed significantly in both frequency (f) and duration (d) [$H = 8.07$(f), 9.17(d), $p < 0.05$]. Following frequency and duration, stretched/attend frequency and duration, naso-genital frequency , naso-nasal frequency, and nonspecific investigation duration produced no significant changes. Significant decreases were detected in naso-genital investigation duration at 10.0 mg/kg (median 18.62 vs. control median 27.10, $U = 22$, $p < 0.05$), naso-nasal investigation duration at 1 mg/kg (median 5.29 vs. control median 12.71, $U = 19$, $p < 0.02$), and nonspecific investigation frequency at 1.0 mg/kg (median 12 vs. control median 19.5, $U = 20.5$, $p < 0.05$).

Resident offensive behavior. Aggressive grooming decreased significantly in frequency and duration at 20.0 mg/kg [medians 0 vs. control medians 1(f), 2.95(d), $U = 15$, $p < 0.02$]. Tail rattling decreased in frequency at 20.0 mg/kg (median 0 vs. control median 1, $U = 15$, $p < 0.02$) and 1.0 mg/kg (median 0 vs. control median 1, $U = 22.5$, $p < 0.02$) and 10.0 mg/kg ($p < 0.05$). In duration, tail rattling decreased significantly at 20.0 mg/kg only (median 0 vs. control median 3.05, $U = 15$, $p < 0.02$). Offensive sideways posturing decreased significantly at 20.0 mg/kg for frequency and duration [medians 0 vs. control medians 4(f), 16.19(d), $U = 15$. $p < 0.02$], at 10.0 mg/kg for frequency (median 0 vs. control median 4, $U = 18$, $p < 0.02$), and duration (median 0 vs. control median 16.19, $U = 20$, $p < 0.05$), and at 1.0 mg/kg frequency and duration [medians 0 vs. control medians 4(f), 16.19(d), $U = 21.5$ and 22, respectively, $p < 0.05$]. Offensive upright posturing decreased significantly in frequency and duration at 20.0 mg/kg [medians 0 vs. control medians 1(f), 2.53(d), $U = 20$, $p < 0.05$]. Frequency and duration of bite-attacks decreased at 20.0 mg/kg [medians 0 vs. control medians 1(f), 4.88(d), $U = 15$, $p < 0.02$] and 10.0 mg/kg [medi-

TABLE 1

EFFECTS OF (−)-PINDOLOL ON BEHAVIORS DISPLAYED BY RESIDENT MICE

Behaviors		Vehicle	1.0 mg/kg	10.0 mg/kg	20.0 mg/kg
Cage exploration	f	30 (24.5-31)	28 (22.5-33)	36 (30.5-38.5)*	35 (33.5-38.5)†
	d	216.3 (156.8-272.9)	353.3 (262.7-387.1)*	335.5 (269.2-408)	357.1 (305.3-387.5)*
Rearing	f	9 (2.5-13)	7 (1.5-10.5)	12.5 (7.5-13.5)	9.5 (6-10)
	d	29.7 (4.2-42.9)	13.9 (3-21)	23.4 (14.9-28.4)	24.6 (14.9-34)
Maintainance	f	7.5 (3.5-10.5)	4 (3-5.5)	6 (3-8.5)	6 (4-12)
	d	37.1 (18.4-72.9)	31.3 (17.1-55.9)	35.4 (8.9-45.4)	30.5 (13.9-47.9)
Digging	f	0	0	0 (0-0.5)	0 (0-1)
	d	0	0	0 (0-0.9)	0 (0-3)
Naso genital	f	6.5 (4.5-11)	6 (4-8)	6.5 (2-7)	7.5 (3.5-10)
	d	27.1 (18.9-43.2)	28.9 (14.6-33.6)	18.6 (8-21.2)*	24.2 (13.3-46.1)
Naso nasal	f	3 (2-4.5)	2 (0.5-2.5)	2.5 (2-3.5)	3.5 (2.5-4.5)
	d	12.7 (7-16.1)	5.3 (0.8-7.5)†	9.9 (7.1-18.7)	10.1 (5.7-17.4)
Nonspecific investigation	f	19.5 (13-23)	12 (8.5-12.5)*	14.5 (9.5-21)	18.5 (12.5-19.5)
	d	134.5 (59.1-148.4)	66.3 (36.3-137)	93.6 (59.1-127.2)	96 (76.3-117.3)
Follow	f	3.5 (2-6)	2.5 (0.5-4)	3 (0-3.5)	2 (1-2.5)
	d	9.7 (4.8-12)	6 (1.6-7)	5.8 (0-7)	4.2 (2.3-6.1)
Attend/approach	f	7 (5-8)	5 (3.5-6)	11 (5.5-12.5)	8.5 (5.5-11.5)
	d	19.1 (14.7-23.1)	16.2 (11.3-18.6)	26.9 (15.4-31.8)	23.2 (18.1-30.4)
Stretch/attend	f	1 (1-2)	3 (1-6)	3 (1.5-4)	1 (1-2)
	d	3.1 (2-5.5)	7.4 (3.2-15.5)	7.9 (2.6-11.9)	3.3 (1.6-6.7)
Tail rattle	f	1 (0-6.5)	0†	0*	0†
	d	3.1 (0-14.8)	0	0	0†
Aggressive groom	f	1 (0-1.5)	0.5 (0-1)	0.5 (0-1)	0†
	d	3 (0-9.5)	0.9 (0-4.1)	1.1 (0-2.2)	0†
Offensive sideways	f	4 (0-7.5)	0*	0†	0†
	d	16.2 (0-22.9)	0*	0*	0†
Offensive upright	f	1 (0-2.5)	0	0	0*
	d	2.5 (0-8)	0	0	0*
Chase	f	1.5 (0-2.5)	0	0	0†
	d	2.1 (0-4.6)	0	0	0†
Bite-attack	f	1 (0-2)	0*	0*	0†
	d	4.9 (0-8.5)	0	0*	0†
Evade	f	1 (0-2)	0	2 (1-2.5)	0*
	d	3.3 (0-6.2)	0	5.4 (2.3-8)	0*
Defensive sideways	f	0 (0-2.5)	0	0	0
	d	0 (0-5.7)	0	0	0
Defensive upright		–	–	–	–
Submissive upright		–	–	–	–
Frozen crouch		–	–	–	–

Data expressed as median (upper to lower quartiles) for frequency (f) and duration (d).
*†Significance at *$p < 0.05$ and †$p < 0.02$.

ans 0 vs. control medians 1(f), 4.88(d), $U = 20.5$, $p < 0.05$] and for frequency only at 1.0 mg/kg (median 0 vs. control median 1, $U = 21.5$, $p < 0.05$). Chase behavior decreased significantly at 20.0 mg/kg for frequency and duration [medians 0 vs. control medians 1.5(f), 2.05(d), $U = 15$, $p < 0.02$].

Resident defensive behavior. No significant changes were detected for defensive upright, defensive sideways, submissive upright, and frozen crouch behavior. However, evade behavior decreased significantly in frequency and duration at 20.0 mg/kg [medians 0 vs. control medians 1(f), 3.26(d), $U = 20.5$, $p < 0.05$].

Intruder nonsocial behavior. Kruskal-Wallis failed to reveal significant effects for digging maintainance duration and rearing frequency (summarized in Table 3). Cage exploration significantly increased at 20.0 mg/kg for duration (median 394.46 vs. control median 305.61, $U = 18$, $p < 0.02$), at 10.0mg/kg for frequency (median 35.5 vs. control median 29.5, $U = 20$, $p < 0.05$) and duration (median 386.74 vs. control median 305.17, $U = 17$, $p < 0.02$), and at 1.0 mg/kg for frequency and duration [medians 34.5(f), 416(d) vs. control medians 29.5(f), 305.61(d), $U = 20$, $p < 0.05$]. Rearing significantly decreased in duration at 10 mg/kg (median 24.24 vs. control median 42.86, $U = 9$, $p < 0.002$) and 1.0 mg/kg (median 23.27 vs. control median 42.86, $U = 17$, $p < 0.02$).

Maintainance increased significantly in frequency at 20.0 mg/kg (median 4 vs. control median 2, $U = 18, p < 0.02$).

Intruder social behavior. Statistical analysis revealed an overall significant effect for naso-genital investigation duration ($H = 8.38$, $p < 0.05$). Naso-genital frequency, naso-nasal, nonspecific investigation, stretched/attend, attend/approach, and following frequency failed to produce significant results. Mann–Whitney procedures showed that following decreased significantly in duration at 1.0 mg/kg (median 0.85 vs. control median 2.71, $U = 22.5, p < 0.05$).

Intruder offensive behavior. Analysis revealed an overall effect for chase behavior [$H = 8.67$(f), 8.92(d), $p < 0.05$]. No significant effects were detected for the remaining behaviors in this category.

Intruder defensive behavior. No significant changes were revealed for defensive upright, submissive upright, and frozen crouch posturing. Evade behavior was significantly attenuated in frequency and duration at 20.0 mg/kg [medians 0 vs. control medians 5(f), 10.65(d), $U = 10, p < 0.002$] and in frequency at 10.0 mg/kg (median 0.5 vs. control median 5, $U = 21, p < 0.05$). Defensive sideways posturing decreased significantly in frequency and duration at 20.0 mg/kg [medians 0 vs. control medians 2.5(f), 17.32(d), $U = 15, p < 0.02$], at 10.0 mg/kg [medians 0 vs. control medians 2.5(f), 17.32(d), $U = 20.5$ and 19.5, respectively, $p < 0.05$], and at 1.0 mg/kg for duration only [median 0 vs. control median 17.32, $U = 20, p < 0.05$].

SDZ 216-525

Resident nonsocial behavior. Analysis did not reveal significant effects for maintainance behavior, digging and cage exploration frequency (Table 2). Cage exploration duration increased at 1.0 mg/kg (median 386.92 vs. control median 294.52, $U = 6, p < 0.002$). Significant increases were detected at 1.0 mg/kg for rearing frequency and duration [medians 5.5(f), 13.35(d) vs. control medians 8.5(f), 26.65(d), $U = 23$ and 20, respectively, $p < 0.05$].

Resident social behavior. In this category, the one significant change found was for stretch/attend behavior, which increased in duration at 0.025 mg/kg (median 10.25 vs. control median 3.49, $U = 21, p < 0.05$).

Resident offensive behavior. No significant changes were detected for aggressive grooming, tail rattling, or chase behavior. However, offensive sideways posturing decreased significantly in frequency and duration at 1.0 mg/kg [medians 0 vs. control medians 5(f), 10.36(d), $U = 16.5, p < 0.05$], as did offensive upright posturing [medians 0 vs. control medians 1(f), 3.67(d), $U = 18.5$ and 17.5, respectively, $p < 0.02$]. Bite-attacks also decreased significantly at 1.0 mg/kg [medians 0 vs. control medians 1.5(f), 5.57(d), $U = 20, p < 0.05$].

Resident defensive behavior. Analysis failed to reveal significant effects for evade behavior, defensive upright posturing, and frozen crouch behavior. Submissive upright posturing did not occur. Kruskal–Wallis analysis revealed an overall significant effect for defensive sideways posturing ($H = 8.57$, $p < 0.05$), which decreased in frequency at 1.0 mg/kg (median 0 vs. control median 1.5, $U = 22.5, p < 0.05$).

Intruder nonsocial behavior. Rearing, maintainance, and cage exploration duration did not demonstrate significant changes (summarized in Table 3). Cage exploration frequency increased significantly at 0.025 mg/kg (median 35 vs. control median 31, $U = 21.5$, $p < 0.05$) and digging increased at 0.025 mg/kg for frequency (median 14 vs. control median 4.5, $U = 18$, $p < 0.02$) and duration (median 67.8 vs. control median 20.09, $U = 21, p < 0.05$).

Intruder social behavior. Following, attend/approach, naso-nasal duration, and nonspecific investigation frequency did not show significant changes. An overall significant change was found for naso-genital frequency ($H = 8.44, p < 0.05$). Naso-nasal frequency increased at 0.025 mg/kg (median 5.5 vs. control median 2.5, $U = 12.5, p < 0.02$), nonspecific investigation duration increased significantly at 1.0 mg/kg (median 54.57 vs. control median 31.16, $U = 16, p < 0.02$), and naso-genital duration decreased significantly at 0.25 mg/kg (median 5.53 vs. control median 19.9, $U = 20, p < 0.05$). Stretch/attend decreased in frequency and duration at 1.0 mg/kg [medians 0 vs. control medians 2.5(f), 6.56(d), $U = 17$ and 14, respectively, $p < 0.02$].

Intruder offensive behavior. One significant change was detected in this category: offensive upright posturing decreased significantly at 1.0 mg/kg for frequency and duration [medians 0 vs. control medians 1(f), 4.79(d), $U = 20, p < 0.05$].

Intruder defensive behavior. Submissive upright posturing and frozen crouch posturing did not alter significantly. Evade behavior significantly decreased in frequency at 1.0 mg/kg (median 0 vs. control median 3.5, $U = 19, p < 0.02$) and in duration at the same dose (median 0 vs. control median 11.9, $U = 21, p < 0.05$). Defensive upright posturing was significantly decreased at 1.0 mg/kg for frequency and duration [medians 0 vs. control medians 1.5(f), 4.85(d), $U = 20, p < 0.05$] and at 0.25 mg/kg [medians 0 vs. control medians 1.5(f), 4.85(d), $U = 22.5$ and 22, respectively, $p < 0.05$]. Defensive sideways posturing significantly decreased in frequency at 1.0 mg/kg (median 0 vs. control median 3, $U = 21, p < 0.05$) and in duration at the same dose (median 0 vs. control median 10.4, $U = 19, p < 0.02$).

DISCUSSION

Results from this study indicate that both (−)-pindolol (1.0–20.0 mg/kg, SC) and SDZ 216-525 (0.025–1.0 mg/kg, SC) produced apparently nonspecific attenuation of resident offensive behavior, with defensive behaviors showing widespread reductions and social and nonsocial behaviors producing significant increases and decreases. A similar behavioral profile has been reported for the 5-HT_{1A} antagonist pindobind 5-HT_{1A} (1).

The paradoxical finding (8) that (−)-pindolol caused a selective dose-related reduction in brain 5-HT synthesis rate similar in magnitude to the selective 5-HT agonist 8-OH-DPAT may indicate that this compound displays mixed agonist/antagonist properties at central 5-HT receptors. The reduction in 5-HT synthesis may therefore relate to stimulation of agonist-sensitive autoreceptors (8). Since β-adrenergic mechanisms are known to influence plasma and blood levels of tryptophan (5), so it could be argued that the action of (−)-pindolol upon 5-HT activity is indirectly mediated via its action at β-adrenoreceptor. However, investigations using other selective β blockers (13,20) cast doubt upon this proposal. Whether the central receptors involved in the biochemical actions of (−)-pindolol correspond to 5-HT_{1A} and/or 5-HT_{1B} sites remains to be verified, and would be aided by the development of a truely selective antagonist (8).

The mixed 5-HT_{1A}1B agonists TFMPP and eltoprazine have been found to decrease maternal aggression, resident-intruder aggression, and aggression induced by electrical stimulation and muricide, in a specific manner (11,18). Having found that the 5-HT_{1A} agonists 8-OH-DPAT, buspirone, and ipsapirone have either no antiaggressive effects or produce

TABLE 2

EFFECTS OF SDZ 216-525 ON BEHAVIORS DISPLAYED BY RESIDENT MICE

Behaviors		Vehicle	0.025 mg/kg	0.25 mg/kg	1.0 mg/kg
Cage exploration	f	28 (24.5-33)	29 (27-31)	27.5 (25-31)	28.5 (26-30.5)
	d	294.5 (252.9-313.9)	330 (235.7-353.8)	340.4 (282-365.2)	386.9 (359.4-404.7)*
Rearing	f	8.5 (6.5-10)	7 (3-11.5)	10 (4-11)	5.5 (2.5-7)†
	d	26.7 (17-29.2)	25.3 (13.6-30.3)	21.8 (6.9-32.5)	13.4 (6.5-20.2)†
Maintainance	f	4 (0.5-6)	1.5 (0.5-3)	3.5 (1.5-6)	3.5 (1-5)
	d	24.8 (0.9-31.7)	13.4 (1.1-18.8)	36.3 (13.1-37.52)	19.2 (2.2-30.5)
Digging	f	0 (0-0)	0 (0-0)	0 (0-0.5)	0 (0-0)
	d	0 (0-0)	0 (0-0)	0 (0-5.5)	0 (0-0)
Naso genital	f	8 (6-9.5)	7.5 (5.5-9)	7.5 (3.5-8)	6.5 (4-8)
	d	36.5 (21.1-46.1)	27.9 (20.4-36.1)	36.7 (14.3-40.2)*	24.2 (13.8-34.2)
Naso nasal	f	3 (2-4)	3.5 (3-4.5)	4 (1.5-4)	2 (0.5-4)
	d	9.9 (5-13)	11.9 (6.4-20.5)	10.8 (2.7-12.7)	4.7 (0.4-9.1)
Nonspecific investigation	f	13 (9.5-20)	12 (9.5-16)	11 (6.5-12)	12 (11-15)
	d	83.2 (55.1-122.2)	61.8 (49-102.4)	90.2 (48.4-97.1)	73.7 (53.6-80.7)
Follow	f	3.5 (2-5)	3 (1.5-5)	2 (2-2)	2.5 (0.5-3.5)
	d	7.5 (3.1-12.8)	7.6 (3.1-11.5)	8.2 (3.9-9.1)	6.3 (0.5-8.5)
Attend/approach	f	10 (7-11.5)	7 (5-9)	6.5 (4-9)	7 (4.5-8.5)
	d	25.9 (17.8-29.9)	17.5 (10.3-27.3)	13.9 (9.5-24.8)	19.7 (12-23)
Stretch/attend	f	2 (1-3.5)	4 (2-7)	4 (1-5)	3.5 (2-5)
	d	3.5 (1.6-7.4)	10.3 (3.3-14.4)†	7.6 (2-12)	9.9 (4.5-14.6)
Aggressive groom	f	1.5 (0-3)	0 (0-1)	1 (0-3)	0.5 (0-1)
	d	10.6 (0-20.6)	0 (0-4.9)	5.2 (0-11.6)	1.3 (0-7.9)
Tail rattle	f	1.5 (0-4)	0 (0-2)	0 (0-0.5)	0 (0-1.5)
	d	2.8 (0-8.4)	0 (0-3.9)	0 (0-1)	0 (0-3.7)
Offensive sideways	f	5 (0-7)	1 (0-5)	0 (0-0.5)	0 (0-0)†
	d	10.4 (0-23.4)	2.4 (0-14.6)	0 (0-1.5)	0 (0-0)†
Offensive upright	f	1 (0-2.5)	0 (0-1.5)	0 (0-0)	0 (0-0)†
	d	3.7 (0-7.9)	0 (0-5.6)	0 (0-0)	0 (0-0)†
Chase	f	2 (0-4.5)	0.5 (0-3)	0 (0-3)	0 (0-0.5)
	d	5.6 (0-10)	1.2 (0-5.1)	0 (0-7)	0 (0-0.5)
Bite-attack	f	1.5 (0-2.5)	0 (0-1.5)	0 (0-0)	0 (0-0)†
	d	5.6 (0-8.4)	0 (0-5.3)	0 (0-0)	0 (0-0)†
Evade	f	5 (0-7.5)	1.5 (0-4.5)	1 (0-2.5)	1 (0-1)
	d	12.7 (0-21.4)	4.5 (0-11.1)	5.3 (0-7.6)	2.4 (0-3.6)
Defensive upright	f	0 (0-1)	0 (0-0.5)	0 (0-0)	0 (0-0)
	d	0 (0-3)	0 (0-1.7)	0 (0-0)	0 (0-0)
Defensive sideways	f	1.5 (0-2)	1 (0-2.1)	0 (0-0)	0 (0.0)†
	d	3.9 (0-6.9)	5.3 (0-14.8)	0 (0-0)	0 (0-0)
Submissive upright		–	–	–	–
Frozen crouch		–	–	–	–

Data expressed as median (upper to lower quartiles) for frequency (f) and duration (d).
*†‡Significance at *$p < 0.002$, †$p < 0.05$, and ‡$p < 0.02$.

behaviorally nonspecific attenuation of behavior in these paradigms, it has been proposed that the 5-HT_{1B} receptor site may play a specific role in the control of rodent agonistic behavior (18).

Therefore, the effects of (−)-pindolol on agonistic behavior, as reported in this study, may be the result of 5-HT_{1A} and/or 5-HT_{1B} activity. Given that (−)-pindolol also interacts with β-adrenergic receptors (12), it may also be the case that blockade of β-adrenoreceptors may produce a reduction in attack behavior. However, lack of support for this suggestion comes from evidence that attenuation of offensive behavior in mice is not correlated with β blockade (3).

Consistent with previous findings (18) would be the suggestion that while 5-HT_{1B} receptor site antagonism by (−)-pindolol was responsible for its extensive attenuation of agonistic behavior, activity at the 5-HT_{1A} sites may have resulted in this attenuation being behaviorally nonspecific. Furthermore, if 5-HT_{1A} and 5-HT_{1B} receptors are operating as antagonistic sites, then a 5-HT_{1B} antagonist might be expected to produce a profile similar to a 5-HT_{1A} agonist.

TABLE 3

SUMMARY EFFECTS OF (−)-PINDOLOL AND SDZ 216-525 ON BEHAVIORS DISPLAYED BY RESIDENT AND INTRUDER MICE

Behavior		Residents		Intruders	
		(−)-Pindolol	SDZ 216-525	(−)-Pindolol	SDZ 216-525
Cage exploration	f	+	nsc	+	+
	d	+	+	+	nsc
Rearing	f	nsc	−	nsc	nsc
	d	nsc	−	−	nsc
Digging	f	nsc	nsc	nsc	+
	d	nsc	nsc	nsc	+
Maintain	f	nsc	nsc	+	nsc
	d	nsc	nsc	nsc	nsc
Nasogenital	f	nsc	nsc	nsc	nsc
	d	−	nsc	nsc	−
Nasonasal	f	nsc	nsc	nsc	−
	d	−	nsc	nsc	nsc
Nonspecific	f	−	nsc	nsc	nsc
	d	nsc	nsc	nsc	+
Follow	f	nsc	nsc	nsc	nsc
	d	nsc	nsc	−	nsc
Attend/approach	f	nsc	nsc	nsc	nsc
	d	nsc	nsc	nsc	nsc
Stretch/attend	f	nsc	nsc	nsc	−
	d	nsc	+	nsc	−
Tail rattle	f	−	−	nsc	nsc
	d	−	−	nsc	nsc
Aggressive groom	f	−	nsc	nsc	nsc
	d	−	nsc	nsc	nsc
Offensive sideways	f	−	−	nsc	nsc
	d	−	−	nsc	nsc
Offensive upright	f	−	−	nsc	−
	d	−	−	nsc	−
Chase	f	−	nsc	nsc	nsc
	d	−	nsc	nsc	nsc
Bite attack	f	−	−	nsc	nsc
	d	−	−	nsc	nsc
Defensive upright	f	nsc	nsc	nsc	−
	d	nsc	nsc	nsc	−
Defensive sideways	f	nsc	−	−	−
	d	nsc	nsc	−	−
Submissive upright	f	nsc	nsc	nsc	nsc
	d	nsc	nsc	nsc	nsc
Frozen crouch	f	nsc	nsc	nsc	nsc
	d	nsc	nsc	nsc	nsc
Evade	f	−	nsc	−	−
	d	−	nsc	−	−

Results expressed in terms of statistical significance: nsc, no significant change within groups; −, significant decrease(s) found within groups; +, significant increase(s) found within groups.

The behavioral profile for SDZ 216-525 is also one of nonspecific attenuation of resident agonistic behavior, with defensive behaviors showing widespread reductions and social and nonsocial behaviors producing significant increases and decreases.

The interpretation of present data for SDZ 216-525 depends critically upon the site of action (i.e., pre- vs. postsynaptic receptors). While behavioral results alone do not permit identification of sites of action, it is suggested that agonism at presynaptic and antagonism at postsynaptic receptors would

produce similar functional consequences as a result of depleted 5-HT function. Thus, agonism of 5-HT$_{1A}$ somatodendritic autoreceptors by 8-OH-DPAT (2) might induce a behavioral profile comparable to 5-HT$_{1A}$ postsynaptic receptor antagonism produced by SDZ 216-525. To a certain extent, present data support this proposal.

SDZ 216-525 did significantly inhibit offensive behavior but also significantly enhanced resident exploratory behavior and attenuated the frequency and duration of rearing. Therefore, in terms of behavioral specificity, while SDZ 216-525 did not produce any sedation, the influence of this compound on offensive behavior may be the result of behavioral competition. In other words, the effect of SDZ 216-525 on agonistic behavior may be considered secondary to the actions of this compound at 5-HT$_{1A}$ receptor mechanisms involved in locomotor behavior (24). This effect would be consistent with the nonspecific attenuation of offensive behavior reported in studies using 8 OH-DPAT (18,19), except that 5-HT$_{1A}$ agonism reduced locomotor activity, whereas 5-HT$_{1A}$ antagonism enhanced activity.

It is suggested that, while a preliminary examination of the influences of SDZ 216-525 and (−)-pindolol indicates both compounds exert a nonspecific attenuation of offensive behavior in mice, closer inspection of the data reveals some other important trends.

The concept of specificty of action, by these compounds, requires further consideration. Although both SDZ 216-525 and (−)-pindolol altered activity, the direction of effect was enhancement of either exploration or activity in resident animals. Interestingly, untreated intruders also demonstrated increased cage exploration. Assuming that cage exploration and rearing are inbuilt controls for sedation, then clearly the effects of these compounds are not due to general motoric impairment. Indeed, as discussed earlier, the influences of SDZ 216-525 and (−)-pindolol on offense may be subordinate to locomotor stimulation. Such changes in activity would be expected, since a significant reduction in agonistic behavior must result in alterations elsewhere in the behavioral repertoire. These "compensatory" changes could appear across a number of other behavioral elements or be focussed on a subset.

Defensive behavior demonstrates interesting changes for residents as well as intruders in both drug conditions. SDZ 216-525 produced a significant reduction in resident defensive sideways behavior while untreated intruders demonstrated attenuation of both defensive upright and sideways behavior. Untreated intruders in the (−)-pindolol conditions showed a reduction in defensive sideways behavior. Taken together, these influences on defensive behavior may reflect possible antianxiety effects of these compounds. It may also be argued that the reductions in offensive and defensive behavior, coupled with the lack of evidence for sedation, may indicate possible "antiaggressive" effects for both SDZ 216-525 and (−)-pindolol.

In conclusion, the present results support data obtained from studies employing 5-HT$_{1A}$ agonists (18,19): 5-HT$_{1A}$ receptors act to attenuate murine offensive behavior in a nonspecific manner. Nonetheless, this nonspecific influence on agonistic behavior may indicate important potential for the control of anxiety and agonistic behavior.

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