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Effects of Pindobind 5-Hydroxytryptamine$_{1A}$ (5-HT$_{1A}$), a Novel and Potent 5-HT$_{1A}$ Antagonist, on Social and Agonistic Behaviour in Male Albino Mice

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BELL, R. AND H. HOBSON. *Effects of pindobind 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$), a novel and potent 5-HT$_{1A}$ antagonist, on social and agonistic behaviour in male albino mice.* PHARMACOL BIOCHEM BEHAV **46**(1) 67–72, 1993. – In view of inconsistent results reported for 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor involvement in murine social conflict, this study examined the effects of N^1-(bromoacetyl)-N^8-[3-(4-indolyloxy)-2-hydroxypropyl]-(Z)-1,8-diamino-*p*-menthane (pindobind) 5-HT$_{1A}$, a novel 5-HT$_{1A}$ antagonist, on agonistic and social behaviour in mice. Employing a resident-intruder paradigm, administration of pindobind 5-HT$_{1A}$ (0.5–10 mg/kg) to resident animals produced a reduction in offensive sideways and chasing behaviour. Defensive postures were unchanged except for evasion, which was reduced. Within social behaviour, nonspecific social behaviour and following behaviour were reduced while stretch/attend behaviour was enhanced. Nonsocial behavioural changes included an increase in resident cage exploration and rearing. Intruder data indicated no significant change in offensive behaviours, an attenuation of defensive sideways posturing and evasion, decreases in attend behaviour, and increases in cage exploration, rearing, and digging. Results are discussed in relation to the effects of 5-HT$_{1A}$ receptor (ant)agonism on murine offensive behaviour.

Pindobind 5-HT$_{1A}$ Agonistic behaviour Social behaviour 5-HT$_{1A}$ antagonist Ethological analysis

STUDIES examining the role of 5-HT receptor mechanisms in rodent social conflict reported inconsistent results [for review, see (16)]. Recent ethologically orientated studies indicated that nonselective 5-hydroxytryptamine$_2$ (5-HT$_2$) antagonists specifically inhibit attack behaviour (9), nonspecifically inhibit attack behaviour (4), or show no effect (15).

Inhibitory effects on agonistic behaviour have been demonstrated using the 5-HT$_1$ agonists 5-methoxytryptamine and quipazine and the 5-HT$_2$ antagonist mianserin (9). From these findings, it was predicted (9) that a mixed 5-HT$_1$ agonist/5-HT$_2$ antagonist would potently inhibit offensive aggression. However, the lack of specificity of the drugs employed by these investigators and the finding that the 5-HT$_2$ agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-amino-propane (DOI) appears to be nonspecific in reducing isolation-induced aggression (18) cast doubt on this prediction.

With respect to 5-HT$_{1A}$ receptors, a number of research groups (2,10,18,19) employing ethological techniques have shown that the 5-HT$_{1A}$ agonists 8-OH-DPAT, buspirone, gepirone, and ipsapirone selectively inhibit isolation-induced aggression in mice. Studies demonstrated that, with the exception of the mixed 5-HT$_{1A/1B}$ agonist fluprazine, the affinity of these compounds for 5-HT$_{1A}$ (postsynaptic) binding sites in the hippocampus is related to their ability to inhibit isolation-induced aggression in mice (10).

However, other investigators (14) found that the mixed 5-HT$_{1A/1B}$ agonists eltoprazine, fluprazine, and TFMPP dose dependently decreased isolation-induced aggression accompanied by an enhancement of social and nonsocial activity. Further, no sedation was evident even at high doses (14). While fluprazine has been demonstrated to reliably inhibit aggressive behaviour in mice without any sedation (6), this compound also decreased defensive escape behaviour and increased locomotion and social investigation. A similar pattern of influence has been reported for befiperide (21), a mixed 5-HT$_{1A/2}$ agonist. By contrast, the specific 5-HT$_{1A}$ agonists 8-OH-DPAT, ipsapirone, buspirone (15), and flesinoxan (13) reduce aggression but also cause a decrease in activity and avoidance behaviour.

Such results led to the conclusion (14) that although drugs with specific 5-HT properties (e.g., 5-HT$_{1A}$ antagonists) are still lacking the available data suggests that the 5-HT$_{1B}$ site

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plays a specific inhibitory role in offensive aggression. The 5-HT_{1A} site appears not to play a specific role because 8-OH-DPAT, buspirone, ipsapirone, and flesinoxan have either no antiaggression activity or show a nonspecific effect (14).

Given the lack of consistent findings discussed, the present study employed a recently developed selective 5-HT_{1A} antagonist, N^1-(bromoacetyl)-N^8-[3-(4-indolyloxy)-2-hydroxypropyl]-(Z)-1,8-diamino-*p*-menthane (pindobind) 5-HT_{1A}, to examine the role of 5-HT_{1A} receptors in murine social conflict, as observed in the resident–intruder paradigm (17).

Pindobind 5-HT_{1A} is extremely potent at 5-HT_{1A} sites labeled by [^{3}H]8-OH-DPAT and interacts moderately with β-adrenergic receptors labeled with [^{3}H]DHA (8). While having no effect on baseline forskolin-stimulated adenylate cyclase activity in the rat hippocampus, pindobind 5-HT_{1A} significantly reversed 8-OH-DPAT-induced inhibition of forskolin-stimulated activity. In behavioural studies, pindobind 5-HT_{1A} significantly attenuated the reciprocal forepaw treading induced by 8-OH-DPAT (8). Such data suggest that pindobind 5-HT_{1A} is a potent and selective antagonist of 5-HT_{1A} receptors in the CNS (8). However, there is no indication (8) as to whether pindobind 5-HT_{1A} influences presynaptic receptors, postsynaptic receptors, or both.

The resident–intruder paradigm mainly represents offensive aspects of agonistic behaviour in the resident mouse, but where the intruder is also studied defensive aspects of agonistic behaviour are represented as well. Because the full behavioural repertoire is available, this model can also be used to test the behavioural specificity of a compound (6). 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 behaviour in a specific manner. Specificity of action would imply inhibition of agonistic behaviour without concomitant sedation or alterations in social behaviour.

METHOD

Subjects and Procedure

Eighty 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, mice were randomly allocated to resident or intruder status. Residents were individually caged (cage size 30 × 15 × 13 cm) and intruders 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 12 D : 12 L reversed cycle was operative (light on 2400 h).

Behavioural testing took place in the residents "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 videocamera (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 videorecorder, a VDU, an IBM portable computer (Model 5155 640K), and a tractor printer.

Pindobind 5-HT_{1A} (Research Biochemicals, Inc., Natick, MA), being water soluble, was dissolved in physiological saline, which also served as vehicle control. All injections were performed SC in a volume of 10 ml/kg 30 min prior to testing. Doses were selected on the basis of previous investigations (8). 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 during the dark phase under red light. 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 recorded on videotape for later analysis. Four experimental conditions were used (n pairs in each condition = 10): control vehicle, 0.5, 2.5, and 10.0 mg/kg pindobind 5-HT_{1A}.

Measures

Behavioural analysis was similar to previously detailed procedures (17). Briefly, videotapes were analysed using direct keyboard inputs to the microcomputer, which had been programmed to produce data output in the form of frequency and real-time duration of behavioural elements (5).

The following behavioural elements and categories were analysed:

Category	Elements
Nonsocial	Cage exploration, rearing, maintenance, digging
Social	Nasogenital, nasonasal, nonspecific partner investigation, follow, attend/approach, stretched/attend
Offensive	Aggressive groom, tail rattle, offensive sideways, ofensive 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 behavioural element were analysed using Kruskal–Wallis one-way analyses of variance. Where statistical differences were detected, further comparisons (with control group) were performed by Mann–Whitney U-tests.

RESULTS

Resident (Table 1) Nonsocial Behaviour

Nonsignificant effects were found for maintenance (H = 3.18[F]0.55[D]), digging (H = 0.4[F]4[D]), rearing duration (H = 2.53), and cage exploration frequency (H = 5.72). Mann–Whitney procedures showed that cage exploration significantly increased in duration at 10 mg/kg (median = 335.52 vs. control median 209.37, U = 10, $p < 0.002$), 2.5 mg/kg (median = 293.57 vs. control median 209.37, U = 12, $p < 0.02$), and 0.5 mg/kg (median = 329.27 vs. control median, 209.37 U = 15, $p < 0.02$). Rearing significantly increased in frequency at 2.5 mg/kg (median = 11 vs. control median 7, U = 22 ,$p < 0.05$) and 0.5 mg/kg (median = 9 vs. control median 7, U = 21.5, $p < 0.05$).

Resident Social Behaviour

Kruskal–Wallis analysis failed to reveal significant effects for nasogenital (H = 4.04[F]1.09[D]), nasonasal investigation (H = 2.10[F]0.65[D]), attend/approach behaviour (H

TABLE 1

EFFECTS OF PINDOBIND 5-HT$_{1A}$ (0.5-10.0 mg/kg) ON BEHAVIOURS DISPLAYED BY RESIDENT MICE

Behaviours		Vehicle	Pindobind 5-HT$_{1A}$ (mg/kg) 0.5	2.5	10.0
Cage exploration	F	28(23-32)	34.5(30.5-38)	36.5(28.5-38.5)	34(29-35)
	D	209.4(174.5-221.7)	329.3(292.1-363.6)*	293.6(240-379.9)*	335.5(265-423.7)†
Rearing	F	7(4.5-7)	9(6.5-12.5)‡	11(4.5-11.5)‡	4.5(4-9)
	D	21.1(8.5-28.5)	22(14.5-31.2)	23.9(9.3-31.9)	13.7(6.9-20.6)
Maintenance	F	3.5(2-4)	6(2-7)	4(2-4.5)	4.5(3.5-5.5)
	D	16.1(10.4-29.7)	20.4(10.3-33.5)	16.3(9.6-25)	15.5(9.1-23.7)
Digging		–	–	–	–
Nasogenital	F	6(3.5-9)	9(6-12.5)	9.5(8-11.5)	8(5.5-9)
	D	28(10.8-48.5)	34.5(22.1-53.8)	32(20.3-36.3)	31.7(19.9-45.5)
Nasonasal	F	3(1-4)	3(1.5-3.5)	4(2.5-5)	2.5(2-5.5)
	D	9.6(3.6-15.7)	8.7(4-12.9)	12.9(5.7-14.8)	10.7(5.3-15.3)
Nonspecific investigation	F	23.5(16.5-25)	15(10.5-19)*	23.5(9.5-24.5)	16(12-23)
	D	163.1(85.1-207.1)	86.9(68.7-105)‡	139(54.9-161.1)	97.2(50.1-119.9)‡
Follow	F	6(2.5-7.5)	2(1-2.5)*	5.5(2-7.5)	2(.5-4)
	D	11(5.8-14.4)	5.4(2-6.7)‡	8.4(4.7-12.7)	5.6(.6-7.5)
Attend/approach	F	7.5(5.5-12)	11(5.5-12)	7.5(4-12.5)	6.5(5-9)
	D	24.4(14.7-32.7)	26(17.6-30.9)	17.4(9.9-25.6)	20.9(17.3-23.1)
Stretch/attend	F	2(1-2)	3.5(1.5-4.5)	3.5(2-6)	3(2-5.5)
	D	5.1(2.6-6.3)	8.4(3.9-13.5)	8.8(5-17.2)‡	8.8(4.5-11.7)
Aggressive groom	F	1.5(1-4)	0(0-3)	1.5(0-2)	0(0-1)
	D	8.6(2.3-15.1)	0(0-7.8)	9.7(0-15.3)	0(0-6.8)
Tail rattle	F	1(0-3)	0(0-3)	0(0-0)	0(0-1)
	D	3(0-6)	0(0-6.3)	0(0-0)	0(0-1.4)
Offensive sideways	F	4(0-8)	0.5(0-3.5)	0(0-.5)	0(0-1)
	D	11.7(0-37.7)	1.4(0-12.4)	0(0-2.8)‡	0(0-5.7)
Offensive upright	F	0.5(0-4)	0(0-0)	0(0-0)	0(0-0)
	D	0.6(0-13.8)	0(0-0)	0(0-0)	0(0-0)
Chase	F	3(0-5)	0.5(0-1.5)	0(0-0)†	0(0-.5)
	D	8.0 (0-15.2)	2(0-4.6)	0(0-0)*	0(0-.8)
Bite/attack	F	1(0-2)	0(0-2)	0(0-0)	0(0-0)
	D	4.6(0-11.6)	0(0-7.9)	0(0-0)	0(0-0)
Evade	F	3(1-7.5)	1(.5-2.5)	0(0-1)*	1.5(.5-3.5)
	D	5.1(2.9-19.3)	3.3(1-6.5)	0(0-2.5)*	2.8(.8-8)
Defensive upright	F	0(0-1.5)	0(0-0)	0(0-0)	0(0-0)
	D	0(0-6.1)	0(0-0)	0(0-0)	0(0-0)
Defensive sideways	F	0(0-2)	0(0-0)	0(0-0)	0(0-0)
	D	0(0-6.8)	0(0-0)	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 ‡$p < 0.05$, *$p < 0.02$, †$p < 0.002$.

= 0.88[F]1.89[D]), and stretched attend frequency only (H = 6.09). Mann-Whitney analysis revealed that nonspecific partner investigation decreased significantly in frequency at 0.5 mg/kg (median = 15 vs. control median 23.5, U = 16, $p < 0.02$) and in duration at 10 mg/kg (median = 97.15 vs. control median 163.06, U = 21, $p < 0.05$) and 0.5 mg/kg (median = 86.88 vs. control median 163.06, U = 23, $p < 0.05$). Following behaviour decreased significantly in frequency at 0.5 mg/kg (median = 2 vs. control median 6, U = 17.5, $p < 0.02$) and in duration at the same dose (median = 5.37 vs. control median 10.96, U = 19.5, $p < 0.05$). Stretched attend behaviour significantly increased in duration only at 2.5 mg/kg (median 8.81 vs. control median 5.1, U = 22.5, $p < 0.05$).

Resident Offensive Behaviour

Kruskal-Wallis analysis produced nonsignificance for aggressive grooming (H = 3.59[F]3.49[D]), offensive upright posturing (H = 5.84[F]5.48[D]), bite attack (H = 7.03[F] 6.96[D]), tail rattling (H = 3.17[F]3.21[D]), and offensive sideways frequency only (H = 6.17). Mann-Whitney procedures revealed that offensive sideways posturing significantly decreased in duration only at 2.5 mg/kg (median = 0 vs. control median 11.71, U = 22.5, $p < 0.05$). Chase behaviour significantly decreased at 2.5 mg/kg for frequency and duration (medians = 0 vs. control medians, 3[F]8.02[D], U = 19, $p < 0.02$, and 20, $p < 0.05$, respectively).

Resident Defensive Behaviour

No significant effects were found for defensive sideways (H = 2.55[F]2.49[D]) and frozen crouch posturing (H = 2.05[F]2.05[D]). Defensive upright posturing produced overall significance for frequency and duration (H = 9.94[F]9.79[D], $p < 0.05$). Submissive upright posturing did not occur at all. Mann-Whitney indicated that evade behaviour significantly decreased in frequency and duration at 2.5 mg/kg (medians = 0 vs. control medians, 3[F]5.14[D], U = 17.5 and 15, respectively, $p < 0.02$).

Intruder (Table 2) Nonsocial Behaviour

Kruskal-Wallis analysis indicated nonsignificant changes for maintenance (H = 0.48[F]0.65[D]), cage exploration duration (H = 3.36), rearing duration (H = 3.47), and digging duration (H = 1.15). Mann-Whitney procedures showed that cage exploration significantly increased in frequency at 10.0 mg/kg (median = 37 vs. control median 29.5, U = 6, $p < 0.002$), 2.5 mg/kg (median = 42.5 vs. control median 29.5, U = 0, $p < 0.002$), and 0.5 mg/kg (median = 38.5 vs. control median 29.5, U = 19.5, $p < 0.05$). Rearing significantly increased in frequency at 2.5 mg/kg (median = 17.5 vs. control median 10, U = 8.5, $p < 0.002$) and digging increased in frequency also at 2.5 mg/kg (median = 10 vs. control median 5.5, U = 14, $p < 0.02$).

Intruder Social Behaviour

No significant effects were found for nasogenital investigation (H = 1.65[F]4.23[D]), nasonasal investigation (H = 2.56[F]0.57[D]), nonspecific partner investigation (H = 2.14[F] 5.93[D]), following (H = 2.10[F]2.38[D]), and stretched attend (H = 4.02[F]1.15[D]). Mann-Whitney analysis found attend/approach behaviour significantly increased in frequency at 10.0 mg/kg (median = 10 vs. control median 5.5, U = 17.5, $p < 0.02$) and 0.5 mg/kg (median = 11.5 vs. control median 5.5, U = 15.5, $p < 0.02$) and in duration at 0.5 mg/kg (median = 24.31 vs. control median 13.23, U = 16, $p < 0.02$).

Intruder Offensive Behaviour

Analysis failed to reveal significant effects for any of the behaviours in this category. Respective H-values were: aggressive grooming (H = 2.58[F]2.63[D]), tail rattling (H = 4.40[F]4.62[D]), offensive sideways (H = 2.32[F]2.23[D]), offensive upright (H = 4.49[F]4.62[D]), chase (H = 2.09[F] 2.57[D]), and bite attacks (H = 4.29[F]4.03[D]).

Intruder Defensive Behaviour

Kruskal-Wallis analysis failed to reveal significant effects for defensive upright posturing (H = 5.93[F]5.43[D]), submissive upright posturing (H = 6.16[F]6.16[D]), and frozen crouch behaviour (H = 1.05[F]1.05[D]). Mann-Whitney procedures revealed that defensive sideways posturing produced significant decreases in frequency at 10.0 mg/kg (median = 0 vs. control median 6.5, U = 19, $p < 0.02$) at 2.5 mg/kg (median = 0 vs. control median 6.6, U = 17, $p < 0.02$) and 0.5 mg/kg (median = 0 vs. control median 6.5, U = 23, $p < 0.05$). For duration, significant decreases were found at 10.0 mg/kg (median = 0 vs. control median 21.86, U = 23, $p < 0.05$) and 2.5 mg/kg (median 0 vs. control median 21.86, U = 18, $p < 0.02$). Evade behaviour significantly decreased in frequency at 10.0 mg/kg (median 0 vs. control median 5, U = 19, $p < 0.02$) and in duration at the same dose (median = 0 vs. control median 11.97, U = 20, $p < 0.05$).

DISCUSSION

While 8-OH-DPAT potentiation of 5-HT_{1A} receptor mechanisms has been reported to attenuate social conflict in mice (14), antagonism of 5-HT_{1A} receptors by pindobind 5-HT_{1A} produced nonsignificant reductions in offensive behaviour.

Inspection of the data for offensive behaviour in resident mice indicates that pindobind 5-HT_{1A} produced, at all doses tested, a nonsignificant reduction in bite-attack, aggressive grooming, offensive upright, tail rattle, and the frequency of offensive sideways behaviour. A significant reduction in the duration (2.5 mg/kg) of offensive sideways and in the frequency (2.5 mg/kg) and duration (2.5 mg/kg) of chase behaviour was noted. For defensive behaviour, the only significant change recorded was a reduction in both the frequency (2.5 mg/kg) and duration (2.5 mg/kg) of evade behaviour. Nonsocial behaviour showed similar nonsignificant changes, with the exception of an enhancement of the duration (all doses) of cage exploration and frequency (0.5 and 2.5 mg/kg) of rearing. With respect to social behaviour, the frequency (0.5 mg/kg) and duration (0.5 and 10 mg/kg) of nonspecific partner investigation and the frequency (0.5 mg/kg) and duration (0.5 mg/kg) of follow behaviour were significantly reduced. In addition, the duration (2.5 mg/kg) of stretch/attend behaviour was significantly increased.

The untreated intruder partners of these animals also demonstrated significant behavioural changes, with increases in the frequencies (all doses) of cage exploration, rearing (2.5 mg/kg), and digging (2.5 mg/kg). The frequency (0.5 and 10 mg/kg) and duration (0.5 mg/kg) of attend behaviour were increased. Finally, the frequency (all doses) and duration (2.5 and 10 mg/kg) of defensive sideways and the frequency (10 mg/kg) and duration (10 mg/kg) of evade behaviour showed a reduction.

The interpretation of the present data depends critically upon the site of pindobind 5-HT_{1A} action, that is, presynaptic vs. postsynaptic receptors. While behavioural 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} presynaptic somatodendritic autoreceptors (1) by 8-OH-DPAT might effect a behavioural profile comparable to 5-HT_{1A} postsynaptic receptor antagonism produced by pindobind 5-HT_{1A}. To a certain extent, the present data support this proposal.

Pindobind 5-HT_{1A} did inhibit offensive behaviour to some degree but also significantly enhanced resident locomotor/exploratory behaviour, as indicated by rearing and cage exploration. Therefore, in terms of behavioural specificity while

TABLE 2

BEHAVIOUR OF UNTREATED INTRUDERS AS A FUNCTION OF DRUG STATE OF RESIDENTS (0.5–10.0 mg/kg PINDOBIND 5-HT$_{1A}$)

Behaviours		Vehicle	Pindobind 5-HT$_{1A}$ (mg/kg) 0 5	2.5	10.0
Cage exploration	F	29.5(26.5–33.5)	38.5(30–40)*	42.5(40.5–46)†	37(34.5–38)†
	D	321.7(264.1–398.1)	386.2(365.3–404.2)	403.9(357–438.8)	389.6(336.4–401)
Rearing	F	10(6–12)	12(8–14)	17.5(14–19.5)†	12.5(8.5–15.5)
	D	25.1(13.3–44.6)	20.2(14.6–29.4)	34.4(26.8–42.6)	22.8(14.2–34.7)
Maintenance	F	3(2–4)	3.5(1–4)	4(2–6)	3(2–3)
	D	16.2(5.3–22.9)	21.9(3.5–35.1)	23.6(8.7–28.5)	18.2(12.9–18.9)
Digging	F	5.5(4–7.5)	8(1–9.5)	10(7.5–11.5)‡	7.5(6–9)
	D	26.8(14.4–35)	23.2(4.3–35.4)	33.8(14.8–34.9)	29.5(21.5–45.1)
Nasogential	F	4(2–5.5)	6(3–7.5)	5.5(4–7)	4.5(3–7.5)
	D	11.5(7.1–16.9)	23.2(10.9–30.7)	15.9(10.5–19.3)	18.2(13.9–23.5)
Nasonasal	F	3.5(1.5–5)	4(2–4.5)	4.5(2.5–5.5)	2.5(1.5–3.5)
	D	8.9(2.4–13.5)	9.6(4.3–12.2)	10.4(5.7–12.5)	7.3(3.5–13.1)
Nonspecific investigation	F	6.5(5.5–8)	6(3–10.5)	7(4.5–9.5)	9.5(5 5–11.5)
	D	26.3(19.5–42.5)	22.6(10.4–30)	34.9(13.2–45.1)	50.6(23.8–61)
Follow	F	1(.5–2)	1.5(0–2)	0.5(0–1.5)	2(.5–2.5)
	D	2.4(.8–3.8)	2(0–3.2)	0.5(0–3.8)	3.3(.0–4.7)
Attend/approach	F	5.5(4–6.5)	11.5(8.5–13)‡	10(5–13.5)	10(6–16.5)‡
	D	13.2(9.3–14.7)	24.3(16.7–27.8)‡	19.2(9.1–27.5)	19.7(11.7–32.8)
Stretch/attend	F	0.5(0–1)	1(1–1.5)	0.5(0–1.5)	1(0–1)
	D	1.5(0–3.4)	2.5(1.3–3.5)	1.3(0–5)	1.6(0–2.8)
Aggressive groom		–	–	–	–
Tail rattle	F	0(0–1.5)	0(0–1)	0(0–0)	0(0–0)
	D	0(0–3)	0(0–2)	0(0–0)	0(0–0)
Offensive sideways	F	1(0–2)	0(0–1)	0(0–0)	0(0–1)
	D	1.8(0–7.6)	0(0–2.5)	0(0–0)	0(0–4.2)
Offensive upright	F	0(0–2.5)	0(0–0)	0(0–0)	0(0–0)
	D	0(0–7.1)	0(0–0)	0(0–0)	0(0–0)
Chase	F	0(0–2.5)	1.5(0–2.5)	0(0–1)	0(0–1)
	D	0(0–7.2)	3.9(0–6.9)	0(0–1.5)	0(0–2.3)
Bite/attack	F	0(0–3)	0(0–.5)	0(0–0)	0(0–0)
	D	0(0–13.4)	0(0–1.3)	0(0–0)	0(0–0)
Evade	F	5(2–8.5)	1.5(0–5)	1(.5–3.5)	0(0–2.5)‡
	D	12(6.7–20.2)	2.9(0–14.3)	2.9(.7–9.5)	0(0–7.7)*
Defensive upright	F	2.5(0–5)	0(0–1)	0(0–1)	0(0–0)
	D	8(0–16.6)	0(0–3.2)	0(0–3.9)	0(0–0)
Defensive sideways	F	6.5(.5–10.5)	0(0–2)*	0(0–.5)‡	0(0–1.5)‡
	D	21.9(1.3–42.9)	0(0–6.9)	0(0–1.6)‡	0(0–5)*
Submissive upright	F	0(0–1.5)	0(0–0)	0(0–0)	0(0–0)
	D	0(0–9)	0(0–0)	0(0–0)	0(0–0)
Frozen crouch		–	–	–	–

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

pindobind 5-HT$_{1A}$ did not produce any sedation the influence of this compound on offensive behaviour may be the result of behavioural competition. In other words, the influence of pindobind 5-HT$_{1A}$ on agonistic behaviour may be considered secondary to activation of 5-HT$_{1A}$ receptor mechanisms involved in locomotor behaviour (20). This effect would be consistent with the nonspecific attenuation of offensive behaviour reported in studies using 8 OH-DPAT (15) except that 5-HT$_{1A}$ agonism reduced locomotor activity whereas 5-HT$_{1A}$ antagonism enhanced activity.

Although this discussion focused on pindobind 5-HT$_{1A}$ influences at 5-HT$_{1A}$ receptors, an alternative site of action

could explain the effects of this compound on offensive behaviour. Given that pindobind 5-HT_{1A} also interacts with β-adrenergic receptors (8), it may be the case that blockade of β-adrenoreceptors may produce a reduction in attack behaviour. However, lack of support for this suggestion comes from evidence that attenuation of offensive behaviour in mice is not correlated with β-blockade (3).

In conclusion, the present results support data obtained from studies employing 5-HT_{1A} agonists (12): 5-HT_{1A} receptors act to attenuate murine offensive behaviour in a nonspecific manner. Bearing in mind the problems of drug specificity for serotonergic subreceptors (11), there is evidence that the influences of 5-$HT_{1A/1B}$ and 5-HT_{1B} agonists produce a more specific inhibition of agonistic behaviour (12).

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