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Differential Effects of CGS 12066B and CP-94,253 on Murine Social and Agonistic Behaviour

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BELL, R., C. DONALDSON AND D. GRACEY. *Differential effects of CGS 12066B and CP-94,253 on murine social and agonistic behaviour.* PHARMACOL BIOCHEM BEHAV 52(1) 7-16, 1995.—Although it has been previously proposed that 5-HT_{1B} agonism specifically attenuates rodent agonistic behaviour, more recent investigations have indicated that such influences may be ancillary to an anxiogenic effect. The present study examined the influences of two 5-HT_{1B} agonists, CGS 12066B and CP-94,253, on murine agonistic behaviour. In a resident-intruder paradigm, CGS 12066B (0.5-5.0 mg/kg) decreased resident offensive aggression, social interest, and exploration while dose-dependently enhancing defensive behaviours across the dose range tested. CP-94,253 (2.5-10.0 mg/kg) also reduced elements of resident offensive behaviour whereas defensive behaviours were largely unchanged. Some elements of resident nonsocial and social behaviour were enhanced at 2.5 and 5.0 mg/kg but decreased at 10.0 mg/kg. The behavioural profile of CP-94,253, but not CGS 12066B, supports the proposal that 5-HT_{1B} receptors inhibit agonistic behaviour without concomitant sedative or anxiogenic effects. Findings are discussed in relation to 5-$HT_{1A/1B/2C}$ receptors involved in agonistic behaviour and anxiety.

CGS12066B CP-94,253 5-HT_{1B} agonists Social behaviour Agonistic behaviour Anxiety Ethological analysis

THE INFLUENCES of 5-HT_{1A} and 5-HT_{1B} receptors on rodent agonistic behaviour have been the subject of considerable research [for reviews see (3,24,27)]. Although there is general accord (3,4,15,23,24) that 5-HT_{1A} agonists act to reduce offensive behaviour, there are divergent opinions (3,23,24) concerning the behavioural specificity of such attenuation. It is suggested that this discrepancy arises for two reasons: firstly, the degree of selectivity demonstrated by such ligands employed for 5-HT_{1A} or 5-HT_{1B} receptors (17); secondly, a need to clarify what is meant by the specificity of action of such compounds on agonistic behaviour. Although some investigators [e.g., (23)] regard such behavioural specificity as implying inhibition of agonistic behaviour without concomitant sedation, we have argued that it is necessary to consider alterations in social behaviour in addition to any evidence of motoric impairment (3).

Previous investigations [for review see (3,27)] have indicated that 5-HT_{1B} receptors exert an inhibitory influence on parental defence (19,20,23) and predatory attack (18,23). In an earlier study (22) it was reported that a dose of 10 mg/kg IM eltoprazine [a 5-$HT_{1A/1B}$ agonist (31)] significantly attenuated porcine offensive aggression without any evidence of concomitant sedation. Furthermore, pigs demonstrated high levels of social interactions during the 4-h observation periods. However, because there is no evidence for the presence of 5-HT_{1B} receptors in pig, calf, monkey, and human brain (8), the influences of eltoprazine on porcine aggression must have been mediated via other serotonergic subreceptors. It may be the case that eltoprazine influenced 5-HT_{1A} and 5-HT_{1D} receptors to reduce porcine aggression because 5-HT_{1D} and 5-HT_{1B} receptors, although pharmacologically different, may serve the same type of function in the mammalian brain (8). More recently, on the basis of data obtained from studies employing 5-$HT_{1A/1B}$ agonists, it has been suggested that the 5-HT_{1B} site plays a specific inhibitory role in rodent offensive aggression (23,24). The 5-HT_{1A} site does not appear to play a specific role because 8-OH-DPAT, buspirone, ipsapirone, and flesinoxan either have no antiaggression activity or show a nonspecific effect (23,24). Such a conclusion is at variance with previous (4,15) and more recent (1-3) investigations concerned with the

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role of 5-HT_{1A} receptors in offensive behaviour. In addition, with respect to 5-HT_{1B} receptors, this deduction is based on the actions of relatively nonselective 5-$HT_{1A/1B}$ compounds (17). Although it had been previously claimed that RU 24969 [5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole], mCPP, and TFMPP are selective ligands for the 5-HT_{1B} binding site (32), several more recent studies (17,21,30) have demonstrated that these compounds are relatively nonselective. It is therefore suggested that because these ligands lack selectivity for the 5-HT_{1B} binding site, their ability to aid in the definition of any specific behavioural responses associated with this receptor is limited.

In contrast to previous findings (23,24), other studies have reported that attenuation of offensive behaviour by the 5-HT_{1A} agonists 8-OH-DPAT, (3,29), ipsapirone, and MDL73005EF (3) and, interestingly, the 5-HT_{1A} antagonists pindobind 5-HT_{1A} (1), (−)-pindolol, and SDZ 216-525 (2) is not accompanied by evidence of motoric impairment. However, significant changes were detected in the category of social behaviour and some other elements of nonsocial behaviour. If behavioural specificity is interpreted solely in terms of concomitant sedation, such 5-HT_{1A} ligands might be regarded as having a "specific" influence on agonistic behaviour. Therefore, it is of paramount importance to consider changes in social behaviour, in addition to evidence of motoric impairment, in order that a comprehensive view of behavioural specificity may be obtained (2,3).

In view of the equivocal conclusion concerning the behavioural specificity of 5-HT_{1B} receptor attenuation of murine offensive behaviour, the present study examined the influences of two selective 5-HT_{1B} agonists, CGS 12066B [7-trifluoremethyl-4(4-methyl-1-piperazinyl)-pyrolol(1,2-*a*)quinoxaline 1 : 2 maleate] (21) and CP-94,253 (3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-*b*]pyridine} (12) on resident-intruder agonistic behaviour in mice. Data from radioligand binding and biochemical studies have shown that CGS 12066B (21) and CP-94,253 (12,33) exhibit greater binding affinity at 5-HT_{1B} receptors than at 5-HT_{1A}, 5-HT_{2C}, and 5-HT_3 receptors.

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 (6). Because the full behavioural repertoire is available, this model can also be used to test the behavioural specificity of a compound (13). Hence, the basic aim of this investigation was to employ two selective 5-HT_{1B} agonists to determine whether 5-HT_{1B} receptors influence offensive behaviour in a specific manner. Although specificity of action would imply inhibition of agonistic behaviour without concomitant sedation, it should be appreciated that in limited duration encounters, if agonistic behaviour decreases, then other behaviours may be enhanced (3).

METHOD

Subjects and Procedure

One hundred and sixty adult male albino mice of the BKW strain, weighing between 25–35g, 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).

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 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.

CGS 12066B (RBI, USA) was dissolved in 3% (w/v) colloidal cornstarch vehicle containing 5% (w/v) PEG 400 (21). CP-94,253 (Pfizer, USA) was dissolved in dimethyl sulfoxide, emulphor, and physiological saline in the ratio 5 : 5 : 90 (12). Corresponding vehicles served as control injections. All injections were performed subcutaneously in a volume of 10 ml/kg 30 min prior to testing. Doses were selected on the basis of previous investigations for CGS 12066B (21) and CP-94,253 (12). 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. Singly housed (resident) animals were weighed, marked for recognition, and randomly assigned to dose treatment groups. Only resident mice received drug treatments. Thirty minutes after treatment of residents, intruder mice were introduced into the home cages of the residents and the ensuing 10-min encounters recorded on video tape for later analysis. Eight experimental groups were used (*n* pairs in each condition = 10): control vehicle for CGS 12066B, 0.5, 2.5, and 5.0 mg/kg CGS12066B, control vehicle for CP-94,253, 2.5 , 5.0, and 10 mg/kg CP-94,253.

Measures

Behavioural analysis was similar to previously detailed procedures (25). 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 behavioural elements (7). The following behavioural elements and categories were analysed:

Nonsocial: cage exploration, rearing, maintenance (animal grooms face/fur), digging.

Social: nasogenital, nasonasal, nonspecific partner investigation (investigation other than nasogenital or nasonasal), follow, attend/approach, stretched/attend.

Offensive: aggressive groom, tail rattle, offensive sideways, offensive upright, chase, bite/attack.

Defensive: evade, defensive sideways, defensive upright, submissive upright, frozen crouch.

Statistical Analysis

Results for each behavioural element were analysed using Kruskal–Wallis one-way analyses of variance (ANOVAs). Where statistical differences were detected, further comparisons (with control group) were performed by Mann–Whitney *U*-tests.

RESULTS

CGS 12066B

Resident nonsocial behaviour. Medians and *H* values are presented in Table 1. Kruskal–Wallis analysis revealed signifi-

TABLE 1

EFFECTS OF CGS 12066B (0.5–5 mg/kg) ON BEHAVIOURS DISPLAYED BY RESIDENT MICE

Behaviours	Vehicle	0.5 mg/kg	2.5 mg/kg	5.0 mg/kg	*H* Values
Nonsocial					
Cage exploration					
Frequency	37.5 (29–40.5)	33.0 (29–34.5)	19.0 (15–22)‡	25.0 (16–34)	13.4*
Duration	189.4 (150–223.9)	239.2 (217.7–261)†	157.9 (119–200)	118.8 (82–144.2)‡	20.3*
Rearing					
Frequency	9.0 (5–11)	6.0 (3.5–8.5)	3.0 (1–5)‡	6.5 (3–12)	9.9*
Duration	26.6 (10.5–42.1)	23.3 (7.5–39.9)	10.5 (1.7–16.6)	21.1 (7.3–57.6)	4.2
Maintenance					
Frequency	4.5 (3–6.5)	3.0 (2–4)	1.0 (0–2)‡	1.0 (0.5–2)‡	19.8*
Duration	21.8 (14.5–27.5)	21.5 (15.5–35)	3.8 (0–11.6)†	3.4 (0.6–11.6)†	14.3*
Digging					
Frequency	4.0 (2–5)	1.0 (0–1.5)‡	0 (0–1.5)‡	0 (0–1)‡	20.6*
Duration	16.6 (7.6–19.6)	1.5 (0–11.5)†	0 (0–0.7)‡	0 (0–9.6)†	19.3*
Social					
Nasogenital					
Frequency	4.5 (3.5–5)	2.0 (0.5–3.5)	1.0 (0–2)‡	1.0 (0.5–1.5)‡	16.7*
Duration	13.5 (12.1–17.1)	6.0 (0.63–15.6)	1.7 (0–3.5)‡	2.9 (0.7–5)‡	13.0*
Nasonasal					
Frequency	7.5 (4.5–9.5)	8.5 (5.5–10)	2.5 (1–4)†	2.5 (0.5–3.5)‡	17.7*
Duration	30.8 (17.8–34.5)	21.5 (15.4–29.1)	9.7 (1.8–18.9)†	8.6 (1.2–11.2)‡	17.5*
Nonspecific investigation					
Frequency	10.5 (6–12.5)	10.5 (8–12)	4.0 (2.5–4.5)†	2.5 (1–3.5)‡	20.0*
Duration	39.1 (29.4–41.1)	65.7 (20.9–82.6)	18.8 (4.8–33.1)	8.3 (4.8–14.9)‡	16.5*
Follow					
Frequency	1.5 (0.5–2)	1.5 (0–3)	0 (0–0.5)†	0 (0–0.5)	8.1*
Duration	2.4 (0.4–4)	6.5 (0–13.2)	0 (0–0.3)†	0 (0–1.1)	9.1*
Attend/approach					
Frequency	6.0 (4–7)	3.5 (3–4.5)†	0 (0–1)‡	1.0 (0.5–2.5)†	23.0*
Duration	22.6 (18–26.2)	9.8 (5.2–19.9)	0 (0–1.8)‡	1.7 (0–4.8)‡	27.4*
Stretch/attend					
Frequency	2.0 (1–3)	2.5 (1–3)	0.5 (0–1)*	1.0 (0–1.5)	10.2*
Duration	7.1 (3.7–9.6)	5.7 (1.6–8.8)	0.5 (0–1.9)†	1.9 (0–3.2)†	11.5*
Offensive					
Aggressive groom					
Frequency	4.5 (2.5–7.5)	1.0 (0–1.5)†	0.5 (0–0.5)‡	0 (0–0.5)‡	22.6*
Duration	17.8 (7.7–25.0)	2.1 (0–7.2)†	0.9 (0–2.4)‡	0 (0–1.9)‡	23.8*
Tail rattle					
Frequency	1.5 (0.5–2)	0 (0–0)‡	0 (0–0)‡	0 (0–0)‡	28.8*
Duration	4.6 (1.2–9.3)	0 (0–0)‡	0 (0–0)‡	0 (0–0)‡	28.8*
Offensive sideways					
Frequency	10.0 (7–11.5)	0 (0–1.5)‡	0 (0–0)‡	0 (0–0)‡	29.3*
Duration	46.9 (23.5–52.6)	0 (0–5.5)‡	0 (0–0)‡	0 (0–0)‡	29.0*
Offensive upright					
Frequency	7.0 (5–10)	0 (0–0.5)‡	0 (0–0)‡	0 (0–0)‡	30.0*
Duration	26.7 (19.9–54.6)	0 (0–1.9)‡	0 (0–0)‡	0 (0–0)‡	30.1*
Chase					
Frequency	9.5 (4–11)	1.5 (0–2.5)‡	1.0 (0–2)‡	0 (0–0.5)‡	26.7*
Duration	19.2 (8.6–30.1)	6.5 (0–14.3)‡	1.9 (0–3.8)‡	0 (0–1.9)‡	29.0*
Bite attack					
Frequency	9.5 (6–12)	0 (0–0)‡	0 (0–0)‡	0 (0–0)‡	35.6*
Duration	34.0 (20.7–39.5)	0 (0–0)‡	0 (0–0)‡	0 (0–0)‡	35.6*
Defensive					
Evade					
Frequency	0 (0–1)	7.5 (0–8)*	8.5 (1.5–14)‡	12.5 (7.5–16)‡	19.2*
Duration	0 (0–1.3)	26.0 (0–30.3)*	82.5 (8.1–112)‡	49.2 (25.8–91)‡	20.0*
Defensive sideways					
Frequency	1.0 (0–1.5)	6.0 (1–7)†	4.0 (2.5–5.5)†	4.5 (2.7–6.2)	9.2*
Duration	2.3 (0–5.6)	15.9 (2.6–22.5)	12.8 (5.2–17.3)*	7.8 (0–17)	5.4
Defensive upright					
Frequency	1.0 (0–2.5)	1.5 (0–3.5)	2.0 (0–4.5)	1.0 (0–1.5)	1.1
Duration	3.7 (0–13.8)	5.0 (0–25.5)	13.8 (0–22.5)	2.7 (0–6.3)	2.1
Submissive upright					
Frequency	0 (0–0)	0 (0–0)	0.5 (0–1.5)	0 (0–0.5)	7.4
Duration	0 (0–0)	0 (0–0)	0 (0–2.0)	0 (0–3.1)	6.8
Frozen crouch					
Frquency	0 (0–0)	0 (0–0.5)	0.5 (0–1.5)	0 (0–0.5)	7.1
Duration	0 (0–0)	0 (0–2.0)	2.0 (0–8.6)	0 (0–1.1)	7.0

Data expressed as medians (upper to lower quartiles) for frequency and duration. Significant values refer to Mann–Whitney comparisons with vehicle. *$p < 0.05$, †$p < 0.02$, ‡$p < 0.002$.

cant changes in the frequency of and duration of cage exploration ($p < 0.05$), maintenance ($p < 0.05$), and digging behaviour ($p < 0.05$). A significant effect was also detected for the frequency of rearing behaviour ($p < 0.05$). Mann–Whitney analysis indicated a significant decrease in the frequency of cage exploration at 2.5 mg/kg ($p < 0.002$). The duration of cage exploration increased at 0.5 mg/kg ($p < 0.02$) and decreased at 5 mg/kg ($p < 0.002$). The frequency of rearing behaviour was reduced at 2.5 mg/kg ($p < 0.002$). The frequency and duration of maintenance grooming was significantly reduced at 2.5 mg/kg ($p < 0.002$ and $p < 0.02$, respectively) and 5.0 mg/kg ($p < 0.002$ and $p < 0.02$, respectively). Significant decreases in the frequency and duration of digging behaviour were detected at 0.5 mg/kg ($p < 0.002$ and $p < 0.02$), 2.5 mg/kg ($p < 0.002$), and 5.0 mg/kg ($p < 0.002$ and $p < 0.02$, respectively).

Resident social behaviour. Significant changes were found for the frequencies and durations of all social elements ($p < 0.05$). Comparisons with vehicle control revealed that there were significant decreases in the frequency and duration of nasogenital behaviour at 2.5 mg/kg ($p < 0.002$) and 5.0 mg/kg ($p < 0.002$). There were significant reductions in the frequency and duration of nasonasal behaviour at 2.5 mg/kg ($p < 0.02$) and 5.0 mg/kg ($p < 0.002$). Nonspecific investigation decreased in frequency at 2.5 mg/kg ($p < 0.02$) and in frequency and duration at 5.0 mg/kg ($p < 0.002$). Displays of follow behaviour were significantly reduced in frequency and duration at 2.5 mg/kg ($p < 0.02$). Attend/approach behaviour decreased in frequency at 0.5 mg/kg ($p < 0.02$), and in frequency and duration at both 2.5 mg/kg ($p < 0.02$) and 5.0 mg/kg ($p < 0.02$ and $p < 0.002$, respectively). Stretched attend behaviour showed decreases at 2.5 mg/kg in frequency and duration ($p < 0.05$ and $p < 0.02$, respectively), and in duration at 5.0 mg/kg ($p < 0.02$).

Resident offensive behaviour. Kruskal–Wallis analysis demonstrated significant changes in the frequency and duration of all the offensive elements ($p < 0.05$). Comparisons with vehicle control indicated significant decreases in the frequency and duration of aggressive grooming at 0.5 mg/kg ($p < 0.02$), 2.5 mg/kg ($p < 0.02$), and 5.0 mg/kg ($p < 0.002$). Tail rattling did not occur at any dose ($p < 0.002$). Offensive sideways posturing significantly decreased in frequency and duration at 0.5 mg/kg ($p < 0.002$). Offensive sideways posturing was not observed at 2.5 and 5.0 mg/kg ($p < 0.002$). Offensive upright posturing significantly decreased in frequency and duration at 0.5 mg/kg ($p < 0.002$) and did not occur at 2.5 or 5.0 mg/kg ($p < 0.002$). Significant decreases were found in the frequency and duration of chase behaviour at 0.5 mg/kg ($p < 0.002$), 2.5 mg/kg ($p < 0.002$), and 5.0 mg/kg ($p < 0.002$). Bite/attacks were not noted at any dose ($p < 0.002$).

Resident defensive behaviour. Analysis detected significant changes in the frequency and duration of evade behaviour ($p < 0.05$) and in the frequency of defensive sideways behaviour ($p < 0.05$). Significant increases in the frequency and duration of evade behaviour were found at 0.5 mg/kg ($p < 0.05$), 2.5 mg/kg ($p < 0.002$), and 5.0 mg/kg ($p < 0.002$). The frequency of defensive sideways posturing was significantly increased at 0.5 mg/kg ($p < 0.02$) and both frequency and duration at 2.5 mg/kg ($p < 0.02$ and $p < 0.05$, respectively).

Intruder nonsocial behaviour. Medians and H values are presented in Table 2. Significant changes occurred in the frequency of cage exploration ($p < 0.05$), the frequency and duration of rearing ($p < 0.05$), the duration of maintenance ($p < 0.05$), and the frequency and duration of digging ($p < 0.05$). Further comparisons yielded significant increases in the frequency of cage exploration at 0.5 mg/kg ($p < 0.05$), 2.5 mg/kg ($p < 0.002$), and 5.0 mg/kg ($p < 0.002$). A significant increase in the frequency and duration of rearing occurred at 2.5 mg/kg ($p < 0.002$) and 5.0 mg/kg ($p < 0.02$). Digging showed significant increases in frequency and duration at 0.5 mg/kg ($p < 0.02$), 2.5 mg/kg ($p < 0.002$), and 5.0 mg/kg ($p < 0.002$).

Intruder social behaviour. Analysis revealed changes in the frequency of nonspecific investigation ($p < 0.05$), the frequency and duration of follow ($p < 0.05$), and the frequency of both attend/approach ($p < 0.05$) and stretch/attend ($p < 0.05$). Comparisons with vehicle control revealed significant decreases in the frequency of nasonasal exploration at 2.5 mg/kg ($p < 0.05$) and in frequency and duration at 5 mg/kg ($p < 0.02$). The frequency of nonspecific investigation increased at 0.5 mg/kg ($p < 0.02$) and 5.0 mg/kg ($p < 0.002$). Following behaviour was significantly reduced in frequency and duration at 2.5 mg/kg ($p < 0.02$) and in duration at 5.0 mg/kg ($p < 0.02$). The frequency of attend/approach was significantly increased at 2.5 mg/kg ($p < 0.02$) and 5.0 mg/kg ($p < 0.02$). Significant increases in the frequency and duration of stretched/attend movements were found at 0.5 mg/kg ($p < 0.02$ and $p < 0.05$, respectively), in frequency at 2.5 mg/kg ($p < 0.02$), and in frequency and duration at 5.0 mg/kg ($p < 0.02$ and $p < 0.05$, respectively).

Intruder offensive behaviour. Kruskal–Wallis analysis detected a significant change in the frequency of aggressive grooming ($p < 0.05$). Further comparisons revealed that the frequency of aggressive grooming was enhanced at 0.5 mg/kg ($p < 0.02$) and 5.0 mg/kg ($p < 0.02$). There was a significant increase in both the frequency and duration of this behaviour at 2.5 mg/kg ($p < 0.002$ and $p < 0.02$, respectively).

Intruder defensive behaviour. Significant changes were found in the frequency and duration of all the defensive elements ($p < 0.05$). A significant decrease was found in the frequency and duration of evade behaviour at 0.5 mg/kg ($p < 0.002$). At the 2.5- and 5.0-mg/kg treatment conditions evade behaviour was not observed ($p < 0.002$). Defensive upright posturing was significantly decreased in frequency and duration at all doses ($p < 0.002$). Defensive sideways behaviour was significantly reduced in frequency and duration at 0.5 mg/kg ($p < 0.002$), 2.5 mg/kg ($p < 0.002$), and 5.0 mg/kg ($p < 0.002$). Intruders did not display submissive upright ($p < 0.05$) or frozen crouch ($p < 0.05$) behaviour under any of the drug treatment conditions.

CP-94,253

Resident nonsocial behaviour. Medians and H values are presented in Table 3. Kruskal–Wallis analysis indicated significant changes in the duration of cage exploration ($p < 0.05$) and in the frequency and duration of digging behaviour ($p < 0.05$). Further comparisons revealed significant increases in the duration of cage exploration at 10.0 mg/kg ($p < 0.02$). Maintenance behaviour was significantly increased in frequency at 2.5 mg/kg ($p < 0.05$). The frequency and duration of digging was increased at 2.5 mg/kg ($p < 0.05$ and $p < 0.02$, respectively).

Resident social behaviour. Analysis detected significant changes across groups in the frequency and duration of nasogenital ($p < 0.05$), nasonasal ($p < 0.05$), and attend/approach behaviour ($p < 0.05$). Comparisons with vehicle control showed that there was a significant reduction in the

TABLE 2

BEHAVIOUR OF UNTREATED INTRUDERS AS A FUNCTION OF DRUG STATE OF RESIDENTS (0.5-5 mg/kg CGS 12066B)

Behaviours	Vehicle	0.5 mg/kg	2.5 mg/kg	5.0 mg/kg	*H* Values
Nonsocial					
Cage exploration					
Frequency	38.0 (35-40)	44.0 (37.5-50.5)*	47.5 (43-48.5)‡	51.0 (44.5-62)‡	16.6*
Duration	180.6 (170-234.2)	219.0 (182.6-250)	140.7 (105-193)	182.5 (142-212.6)	8.2
Rearing					
Frequency	16.0 (12-19)	25.5 (11.5-28.5)	32.5 (23-35)‡	34.0 (29-40.5)‡	21.4*
Duration	78.5 (53.9-90.6)	133.2 (69.3-148.8)	227.6 (175-257)‡	191.9 (160.7-214)‡	21.6*
Maintenance					
Frequency	3.5 (1-6)	3.5 (1.5-5)	3.0 (1.5-3)	4.0 (2-6)	1.7
Duration	11.9 (3.9-33.2)	32.8 (20.7-55.8)	8.6 (3.6-9.7)	12.0 (4.1-23.3)	11.3*
Digging					
Frequency	1.0 (0-2)	5.5 (1-10.5)†	7.0 (4-11)‡	10.0 (2-20.5)†	13.3*
Duration	2.8 (0-5.6)	33.3 (5.5-61)†	37.2 (22-61)‡	36.7 (7.9-85.9)†	12.8*
Social					
Nasogenital					
Frequency	2.0 (0.5-3)	3.0 (1-3)	4.0 (1.5-5)	2.0 (1-4)	2.3
Duration	7.5 (1.3-9.6)	7.7 (2.9-16.1)	8.9 (3.2-11.3)	8.7 (2.2-14.5)	0.5
Nasonasal					
Frequency	6.5 (5.4-7.6)	6.0 (5.1-6.9)	4.0 (2-6)*	4.5 (2-5)†	8.7
Duration	24.5 (16-34.6)	19.2 (12.8-24.4)	11.7 (5.5-27.7)	7.9 (3.7-10.7)†	7.8
Nonspecific investigation					
Frequency	8.0 (6-9.5)	11.5 (10.5-12)†	14.0 (6.5-17)	11.5 (10.5-13.5)‡	9.6*
Duration	29.1 (20.7-40.9)	52.6 (30.3-62.5)	41.8 (17.4-51.2)	42.8 (20.5-67.5)	3.6
Follow					
Frequency	2.0 (0.5-3)	1.0 (0-1)	0 (0-0.5)†	0 (0-1.5)	9.0*
Duration	4.5 (0.3-9.4)	2.0 (0-3.7)	0 (0-0.3)†	0 (0-2.3)†	10.6*
Attend/approach					
Frequency	3.0 (2-5)	5.0 (4.5-7)	6.5 (4.5-8.5)†	9.0 (6-14)†	13.3*
Duration	14.9 (5.4-17)	20.6 (10.9-25.7)	17.0 (8.1-18.3)	18.2 (14.6-21.9)	4.0
Stretch/attend					
Frequency	0 (0-0.5)	2.0 (0.5-2)†	1.0 (0.5-2.5)†	2.0 (0.5-3)†	10.9*
Duration	0 (0-1.4)	4.0 (1.2-6.6)*	2.6 (0.8-5.1)	4.1 (0.8-6)*	7.7
Offensive					
Aggressive groom					
Frequency	1.0 (0-1.5)	4.5 (1.5-9)†	5.5 (3-11)‡	5.5 (2-9.5)†	12.6*
Duration	3.2 (0-4.2)	9.6 (2.6-16.9)	14.8 (9.0-23.8)†	15.8 (2.3-18.4)	9.2
Tail rattle					
Frequency	0 (0-0.5)	0 (0-0)	0 (0-2)	0 (0-0)	3.0
Duration	0 (0-1.6)	0 (0-0)	0 (0-6.1)	0 (0-0)	3.3
Offensive sideways					
Frequency	2.0 (1-3)	2.0 (0-2.5)	4.0 (0-5.5)	2.5 (0-6.5)	1.8
Duration	10.0 (4.6-13)	6.0 (0-12.1)	12.0 (0-15.9)	5.5 (0-19.4)	1.3
Offensive upright					
Frequency	0.5 (0-1)	0 (0-1.5)	1.0 (0-2.5)	0 (0-0)	4.8
Duration	2.0 (0-5.3)	0 (0-3.5)	3.7 (0-6.3)	0 (0-0)	6.4
Chase					
Frequency	1.5 (0-2)	2.5 (0.5-5)	2.5 (0-10)	3.0 (0-5.5)	2.9
Duration	2.8 (0-4.5)	7.0 (1.2-11)	6.8 (0-13.2)	2.8 (0-8.4)	2.9
Bite attack					
Frequency	0 (0-1)	0.5 (0-2)	2.5 (0-7.5)	3.0 (0-5.5)	4.7
Duration	0 (0-2.1)	0.6 (0-6.5)	12.5 (0-29.8)	7.3 (0-11.9)	4.9
Defensive					
Evade					
Frequency	10.0 (7.5-13)	0.5 (0-2)‡	0 (0-0.5)‡	0 (0-0)‡	27.6*
Duration	51.6 (32.8-60.5)	2.8 (0-8.1)‡	0 (0-2.1)‡	0 (0-0)‡	27.6*
Defensive sideways					
Frequency	10.0 (5-12.5)	0 (0-0.5)‡	0 (0-0.5)‡	0 (0-0)‡	31.3*
Duration	40.3 (22.4-68.8)	0 (0-0.5)‡	0 (0-1.3)‡	0 (0-0)‡	31.3*
Defensive upright					
Frequency	8.5 (4-12.5)	0 (0-0.5)‡	0 (0-0)‡	0 (0-0)‡	32.7*
Duration	29.2 (9.7-32.6)	0 (0-0.5)‡	0 (0-0)‡	0 (0-0)‡	32.7*
Submissive upright					
Frequency	1.0 (0-1)	0 (0-0)*	0 (0-0)*	0 (0-0)*	16.9*
Duration	3.0 (0-4.2)	0 (0-0)*	0 (0-0)*	0 (0-0)*	17.5*
Frozen crouch					
Frequency	1.0 (0-2)	0 (0-0)*	0 (0-0)*	0 (0-0)*	20.5*
Duration	7.5 (0-12)	0 (0-0)*	0 (0-0)*	0 (0-0) *	20.5*

Data expressed as medians (upper to lower quartiles) for frequency and duration. Significant values refer to Mann-Whitney comparisons with vehicle. *$p < 0.05$, †$p < 0.02$, ‡$p < 0.002$.

TABLE 3

EFFECTS OF CP-94,253 (2.5–10 mg/kg) ON BEHAVIOURS DISPLAYED BY RESIDENT MICE

Behaviours	Vehicle	2.5 mg/kg	5.0 mg/kg	10.0 mg/kg	*H* Values
Nonsocial					
Cage exploration					
Frequency	35.5 (26–44.5)	38.5 (32.5–42)	40.5 (35.5–44)	35 (32–36.5)	2.6
Duration	300.2 (210–365.7)	317.3 (285.2–343.4)	299.3 (243.3–350.2)	420.5 (386–474.4)†	11.7*
Rearing					
Frequency	9.5 (2–23.5)	15 (4.5–17.5)	20.5 (7.5–29.5)	12 (8–14)	2.1
Duration	56.3 (5.1–100.2)	46 (11.2–61.2)	82.7 (22.7–108.4)	32.5 (20.9–47.7)	1.7
Maintenance					
Frequency	0.5 (0–1)	2.5 (1–3)*	1 (0.5–2)	0 (0–2)	6.5
Duration	1.8 (0–8.4)	9.5 (3.6–14.4)	2.7 (1–5.9)	0 (0–5)	7.4
Digging					
Frequency	0 (0–0)	1.5 (0–5.5)*	0 (0–0.5)	0.5 (0–5.5)	8.0*
Duration	0 (0–0)	4.3 (0–24.3)†	0 (0–1.2)	0.7 (0–10)	8.1*
Social					
Nasogenital					
Frequency	5.5 (3–7.5)	7.5 (3.5–8.5)	8 (5–13.5)	1 (0–3)†	11.5*
Duration	19.5 (9.1–30.5)	23.1 (16.7–33.9)	26 (17–41.9)	2.9 (0–7.5)†	11.4*
Nasonasal					
Frequency	13.5 (6.5–18.5)	19.5 (16–20)	19 (13.5–27.5)	8.5 (5–10)	13.5*
Duration	50.3 (19.8–66.9)	55.5 (43.3–61.6)	64.6 (39.5–82.9)	25.8 (13.2–29.9)	10.6*
Nonspecific investigation					
Frequency	5.5 (1–6.5)	7.5 (4–13.5)	8.5 (5–10.5)	3.5 (1–5)	6.9
Duration	21 (3.8–28.7)	34.3 (14.4–50.9)	30.8 (14–33.9)	10.5 (2.5–15.6)	6.5
Follow					
Frequency	0.5 (0–1.5)	2 (0–2)	2 (0.5–3)	0 (0–0.5)	6.5
Duration	1 (0–3.9)	5.5 (0–7.9)	4 (0.9–7.5)	0 (0–0.9)	6.9
Attend/approach					
Frequency	14 (11.5–16.5)	5.5 (2.5–8.5)‡	8.5 (6–11.5)†	8.5 (6.5–11.5)†	12.7*
Duration	37.8 (31.5–39.5)	16.3 (7.9–20.8)‡	22.3 (14.6–28.7)†	18.4 (12.9–25.9)†	13.7*
Stretch/attend					
Frequency	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	2.0
Duration	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	2.0
Offensive					
Aggressive groom					
Frequency	1 (0–1.5)	0 (0–0)*	0 (0–0)*	0 (0–0)†	12.9*
Duration	3 (0–7.8)	0 (0–0)*	0 (0–0)*	0 (0–0)†	12.7*
Tail rattle					
Frequency	1.5 (0–3.5)	0 (0–0)*	0 (0–2.2)	0 (0–0)*	9.8*
Duration	5.2 (0–12.8)	0 (0–0)*	0 (0–0)	0 (0–0)*	10.0*
Offensive sideways					
Frequency	0 (0–1.5)	0 (0–0)	0 (0–0)	0 (0–0)	6.6
Duration	0 (0–5.9)	0 (0–0)	0 (0–0)	0 (0–0)	6.8
Offensive upright					
Frequency	0.5 (0–2)	0 (0–0)	0 (0–0)	0 (0–0)	8.4*
Duration	1.3 (0–8)	0 (0–0)	0 (0–0)	0 (0–0)	8.3*
Chase					
Frequency	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.9
Duration	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.7
Bite attack					
Frequency	2.5 (0–9.5)	0 (0–2)	0 (0–1.5)	0 (0–0)*	8.8*
Duration	7.4 (0–20.3)	0 (0–9)	0 (0–7)	0 (0–0)*	8.7*
Defensive					
Evade					
Frequency	0 (0–0)	0 (0–0.5)	0 (0–0)	0 (0–0)	0.7
Duration	0 (0–0)	0 (0–2.1)	0 (0–0)	0 (0–0)	0.9
Defensive sideways					
Frequency	0 (0–0)	0 (0–0.5)	0 (0–1)	2 (0–6)	4.1
Duration	0 (0–0)	0 (0–3)	0 (0–0.8)	5.5 (0–25.1)	3.3
Defensive upright					
Frequency	0 (0–0.5)	0 (0–1.5)	0 (0–0)	0 (0–0.5)	1.9
Duration	0 (0–4.6)	0 (0–6.8)	0 (0–0)	0 (0–1.4)	2.1
Submissive upright					
Frequency	0 (0–0)	0 (0–0)	0 (0–0.5)	0 (0–1)	3.4
Duration	0 (0–0)	0 (0–0)	0 (0–0.9)	0 (0–4)	3.5
Frozen crouch					
Frequency	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	–
Duration	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	–

Data expressed as medians (upper to lower quartiles) for frequency and duration. Significant values refer to Mann–Whitney comparisons with vehicle. *$p < 0.05$, †$p < 0.02$, ‡$p < 0.002$.

frequency and duration of nasogenital behaviour at 10.0 mg/kg ($p < 0.02$). Significant decreases in the frequency and duration of attend/approach behaviour were found at 2.5 mg/kg ($p < 0.002$), 5.0 mg/kg ($p < 0.02$), and 10.0 mg/kg ($p < 0.02$).

Resident offensive behaviour. Analysis revealed that there were significant changes across groups in the frequency and duration of aggressive groom ($p < 0.05$), tail rattle ($p < 0.05$), offensive upright ($p < 0.05$), and bite/attack behaviour ($p < 0.05$). Further analysis found that aggressive grooming decreased in frequency and duration at 2.5 mg/kg ($p < 0.05$), 5.0 mg/kg ($p < 0.05$), and 10.0 mg/kg ($p < 0.02$). Tail rattling was reduced in frequency and duration at 2.5 mg/kg ($p < 0.05$) and 10.0 mg/kg ($p < 0.05$). Bite/attack was significantly decreased in frequency and duration at 10.0 mg/kg ($p < 0.05$).

Resident defensive behaviour. Analysis failed to reveal any significant changes in the frequency or duration across treatment groups for any of the defensive behaviours.

Intruder nonsocial behaviour. Medians and H values are presented in Table 4. Analysis revealed a significant change in the frequency of rearing behaviour ($p < 0.05$). Mann–Whitney analysis indicated a significant increase in the duration of rearing at 10.0 mg/kg ($p < 0.05$). Digging behaviour was found to increase significantly in frequency and duration at 2.5 mg/kg ($p < 0.02$ and $p < 0.002$, respectively).

Intruder social behaviour. Significant changes were detected in the frequency and duration of attend/approach behaviour ($p < 0.05$). Mann–Whitney analysis showed a significant increase in the duration of nonspecific partner investigation at 2.5 mg/kg ($p < 0.05$). Significant decreases in the frequency and duration of attend/approach behaviour were located at 2.5 mg/kg ($p < 0.002$), 5.0 mg/kg ($p < 0.002$), and 10.0 mg/kg ($p < 0.02$).

Intruder offensive behaviour. Kruskal–Wallis analysis failed to reveal any significant changes in frequency or duration across treatment groups for any of the offensive behaviours.

Intruder defensive behaviour. Significant changes were revealed for the frequency and duration of defensive sideways ($p < 0.05$), defensive upright ($p < 0.05$), and submissive upright behaviour ($p < 0.05$). Comparisons with vehicle control detected a significant reduction in the frequency and duration of defensive sideways posturing at 5.0 mg/kg ($p < 0.05$) and 10 mg/kg ($p < 0.02$). Defensive upright posturing decreased in duration at 5.0 mg/kg ($p < 0.05$) and in frequency and duration at 10 mg/kg ($p < 0.02$). Submissive upright behaviour decreased in frequency and duration at 2.5 mg/kg ($p < 0.05$) and 10 mg/kg ($p < 0.05$). Frozen crouch posturing did not occur at all.

DISCUSSION

There is now evidence that eltoprazine, fluprazine, TFMPP, and mCPP, which have been reported to attenuate agonistic behaviour via influences at 5-HT$_{1A/1B}$ receptors (23,24, 29), also produce anxiogenic-like effects in rodents (9,11,28). More specifically, fluprazine and eltoprazine have been demonstrated to induce dose-dependent anxiogenic effects in male mice examined in the elevated plus maze test (28). Previous studies have reported that whereas CGS12066B, a 5-HT$_{1A/1B/2C}$ receptor agonist, did not influence activity (34) or nonopioid defeat analgesia in mice (26), the compound did induce a weak anxiolytic effect in social interaction test when infused into the DRN (34). However, in the elevated plus maze test, CGS 12066B stimulated closed arm entries (28). Such evidence for anxiogenic-like responses casts doubt upon the behavioural specificity of 5-HT$_{1A/1B/2C}$ agonists on agonistic behaviour: attenuation of aggression may be ancillary to anxiogenic-like effects (16,28).

The ethological analysis of data from the present study supports the above conclusion because, as previously argued (1–3), drug influences on resident agonistic behaviour are parallelled by changes across nonsocial, social, and defensive categories of behaviour. Acute administration of CP-94,253 decreased offensive behaviour and enhanced some elements of nonsocial behaviour. In the case of CGS 12066B, although resident offensive behaviour was also significantly reduced across the dose range tested, the attenuation of agonistic behaviour by this compound was associated with decreases in social investigation, dose-dependent increases in evade behaviour, and enhancement of defensive sideways postures. However, the significant reductions in cage exploration, rearing, maintenance, and digging also produced by CGS 12066B, which may be considered as in-built checks for motoric effects (1–3), may not be indicative of sedative influences in this study. An alternative interpretation of the data is to consider that the significantly enhanced defensive behaviours indicate that CGS 12066B produced anxiogenic-like effects that, in turn, influenced the frequency and duration of motor activity and social behaviours. For this reason, the attenuation of activity produced by CGS 12066B in this study is not at variance with evidence for enhancement of activity by this compound as observed in rat pups (35). Furthermore, the conclusion that residents displayed heightened fear reactions towards intruders, at the expense of elements of nonsocial and social behaviour, agrees with evidence that CGS 12066B increases escape behaviour in isolated mice (5). Such anxiogenic-like resident behaviour is further reflected by the fact that untreated intruder animals demonstrated significant increases in nonsocial, social, and offensive behaviours and decreases in defensive postures across the dose range tested.

Rodgers et al. (28) reported that although CGS 12066B did enhance closed arm entries, the compound produced a behavioural profile that was not otherwise comparable to eltoprazine, fluprazine, mCPP, and TFMPP in terms of anxiogenic-like effects. These authors suggested that CGS 12066B may demonstrate less potent in vivo effects and that further anxiogenic-like effects produced by this compound may have been observed at higher doses. However, this conclusion assumes selectivity on the part of CGS 12066B for 5-HT$_{1B}$ receptors, and it is suggested that the degree of such selectivity requires closer scrutiny. Although the preliminary characterization of CGS 12066B (21) indicated that this compound should be selective for the 5-HT$_{1B}$ receptor, subsequent studies have reported that CGS 12066B possesses either equal selectivity for 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors (30) or greater selectivity for the 5-HT$_{1A}$ receptor compared to 5-HT$_{1B}$ receptors (14).

It is therefore suggested that the anxiogenic-like effects produced by CGS 12066B may be the result of stimulation of other serotonergic subreceptors, rather than attributable solely to 5-HT$_{1B}$ agonism. This point is discussed in more detail below. The question of behavioural specificity with respect to CGS 12066B may be a function of the selectivity of this compound for 5-HT$_{1B}$ receptors, that is, the compound is not as selective a 5-HT$_{1B}$ agonist as previous studies have suggested (21). However, before comparisons of behavioural profiles can be drawn between CGS 12066B and CP-94,253, it must be pointed out that the lower frequency of occurrence of baseline offensive elements observed for the latter compound means that such comparisons are tentative. Bearing this caveat

TABLE 4

BEHAVIOUR OF UNTREATED INTRUDERS AS A FUNCTION OF DRUG STATE OF RESIDENTS (2.5-10 mg/kg CP-94,253)

Behaviours	Vehicle	2.5 mg/kg	5.0 mg/kg	10.0 mg/kg	*H* Values
Nonsocial					
Cage exploration					
Frequency	34.5 (30-41.5)	34.5 (331-37)	39 (33.5-42.5)	41.5 (37.5-42.5)	5.1
Duration	212.2 (160.3-228.4)	228.5 (217.7-240.1)	224.7 (185.2-241.9)	215.5 (195.5-228.9)	1.4
Rearing					
Frequency	26 (15.5-40.5)	30 (23.5-34.5)	37 (33.5-38)	38.5 (37-40.5)	9.0*
Duration	118.2 (58.2-189.6)	186.55 (102.6-215.3)	188.1 (133.7-234)	221.9 (156.9-243.9)*	7.4
Maintenance	2.5 (1-4)	4 (2.5-4.5)	2.5 (1-3)	1.5 (1-2.5)	4.5
Duration	14.6 (5-23.2)	17.3 (9.9-29.5)	21 (3.6-24.1)	8.9 (6.2-13.7)	1.9
Digging					
Frequency	3.5 (0.5-5)	9.5 (6-14)†	3.5 (1-6.5)	3.5 (0-12.5)	7.8
Duration	6.3 (0.9-11.5)	42.3 (19.5-51.8)‡	8.9 (2.8-17.6)	10.6 (0-52.7)	8.0
Social					
Nasogenital					
Frequency	3.5 (2.1-4.9)	5 (3.9-6.1)	4.5 (2.5-11.5)	6.5 (2.5-8)	1.4
Duration	13 (2.5-29)	16.5 (5.9-24.7)	12.4 (7.9-36.7)	24.1 (8.4-30.2)	0.8
Nasonasal					
Frequency	12.5 (7-19.5)	15 (10-18)	22 (9-26)	10 (7.5-13)	4.5
Duration	40.8 (16.5-60.4)	43.2 (26.5-52.4)	54.3 (25.6-70.7)	34.5 (21.9-43.9)	3.0
Nonspecific investigation					
Frequency	2.5 (1-4)	6 (4.6-7.4)	8 (0-11.5)	4 (1.5-8)	2.8
Duration	7.6 (4.2-12.9)	24 (9.6-35.4)*	25.8 (4.3-32.7)	14.6 (3.9-31.3)	3.7
Follow					
Frequency	0 (0-0)	0.5 (0-2)	0.5 (0-2.5)	1 (0-2.5)	4.0
Duration	0 (0-0)	1.6 (0-5)	1 (0-4.7)	1.9 (0-5.5)	4.0
Attend/approach					
Frequency	13.5 (7.5-16.5)	2.5 (0.5-3)‡	4 (2.5-5.5)‡	6.5 (1.5-9.5)†	17.4*
Duration	34.9 (20-38.5)	6.1 (0.7-8)‡	9.1 (5.9-11.8)‡	15.7 (3.5-22.2)†	18.8*
Stretch/attend					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	–
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	–
Offensive					
Aggressive groom					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	8.1
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.4
Tail rattle					
Frequency	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	1.8
Duration	0 (0-0)	0 (0-2.9)	0 (0-0)	0 (0-0)	1.8
Offensive sideways					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	2.3
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	2.2
Offensive upright					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	2.3
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	2.3
Chase					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.7
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.7
Bite attack					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.7
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.7
Defensive					
Evade					
Frequency	0.5 (0-1.5)	0 (0-1)	0 (0-0.5)	0 (0-0)	5.6
Duration	1.1 (0-4.2)	0 (0-3.8)	0 (0-0.9)	0 (0-0)	5.6
Defensive sideways					
Frequency	2 (0-4)	0 (0-0)	0 (0-0)*	0 (0-0)†	13.0*
Duration	11.3 (0-15.2)	0 (0-0)	0 (0-0)*	0 (0-0)†	13.4*
Defensive upright					
Frequency	2 (0-4)	0 (0-1)	0 (0-0)	0 (0-0)†	11.5*
Duration	10 (0-21.2)	0 (0-5.2)	0 (0-1.5)*	0 (0-0)†	11.5*
Submissive upright					
Frequency	5.5 (0-8)	0 (0-0)*	0 (0-0.5)	0 (0-0)*	14.4*
Duration	22.8 (0-53)	0 (0-0)*	0 (0-5.7)	0 (0-0)*	14.4*
Frozen crouch					
Frequency	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	–
Duration	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	–

Data expressed as medians (upper to lower quartiles) for frequency and duration. Significant values refer to Mann-Whitney comparisons with vehicle. *$p < 0.05$, †$p < 0.02$, ‡$p < 0.002$.

in mind, the current study indicates that the behavioural profile of CGS 12066B does differ, with respect to nonsocial, social, and defensive behaviours, from that obtained for the more selective 5-HT_{1B} agonist CP-94,253.

Maintenance and digging activities were significantly enhanced by CP-94,253 at 2.5 mg/kg whereas the duration of cage exploration was increased at 10.0 mg/kg. Nonsignificant increases in nasogenital and nasonasal behaviour were observed at 2.5 and 5.0 mg/kg whereas attend/approach behaviour was reduced by CP-94,253 at all dose levels. Most of the offensive behaviour elements were significantly attenuated across the dose range whereas resident defensive behaviours were unchanged except for nonsignificant increases in defensive sideways and defensive upright postures at 10 mg/kg. At the low and medium doses tested, therefore, CP-94,253 decreased aggression with a concomitant increase in nonsocial activities and an enhancement of social interest. Analogous to the effects of CGS 12066B were the decreases in activity and, in this case, a modest enhancement of defensive behaviours observed at the highest dose tested. This finding may indicate the onset of anxiogenic effects, again at the cost of motor activity.

The behaviour of untreated intruder mice revealed some significant increases in elements of the nonsocial and social categories. Virtually no offensive behaviour was recorded whereas defensive behaviour was significantly reduced across all doses tested. These results may reflect an undertaking by the intruders to increase exploration, with reduced defensive postures, when encountering less aggressive resident mice (3). Furthermore, this behavioural profile for intruders contrasts sharply with the intruder behaviour recorded in the CGS 12066B conditions. In this case, the previously mentioned enhanced nonsocial and offensive behaviours of untreated intruders may reflect a facility to attack residents that displayed not only diminished offensive postures but also increased defensive behaviour as a consequence of CGS 12066B treatment. Considered collectively, data for the two intruder conditions indicate that the responses of intruders to decreased resident attack behaviour depend upon whether residents demonstrate concomitant enhanced defensive, and hence anxiogenic-like, behaviour.

In previous behavioural studies, oral administration of CP-94,253 (3.2–32 mg/kg) inhibited food intake and body weight gain in the rat while increasing locomotor activity at the highest dose tested (12). Such behavioural influences appear to result from CP-94,253 selective activation of central 5-HT_{1B} receptors (12,33). The results from this study, which indicate that attenuation of agonistic behaviour by CP-94, 253 is not accompanied by evidence of motoric impairment, therefore corroborate the suggestion that 5-HT_{1B} receptors play a specific role in agonistic behaviour (23,24). However, the interpretation of "specific" attenuation of agonistic behaviour by CP-94,253 must take into account the observed changes in social behaviour in addition to the lack of motoric impairment (1–3). Pharmacologically, the inference that 5-HT_{1B} receptors specifically inhibit offensive behaviour must be considered in conjunction with the evidence (1–3,29) that 5-HT_{1A} receptors play a similar role in this behaviour. Therefore, it would appear that acute agonism of either 5-HT_{1A} somatodendritic or 5-HT_{1B} terminal autoreceptors (34), which would result in depleted 5-HT function (3), attenuates agonistic behaviour without concomitant motoric impairment. Such a conclusion delineates a role for two serotonergic subreceptors in offensive and related behaviours and may indicate a possible target for therapeutic intervention in the control of human agonistic behaviour (16).

The comparison between 5-HT_{1A} and 5-HT_{1B} receptors may be extended to their respective roles in anxiety. Given that selective 5-HT_{1A} agonists (3,28) and the selective 5-HT_{1B} agonist CP-94,253 do not appear to induce anxiety, it is posited that the anxiogenic effects of CGS 12066B may be due to activation of serotonergic subreceptors other than 5-HT_{1A} and 5-HT_{1B} receptors (28). Although CGS 12066B displays a comparatively weak affinity for 5-HT_{2C} receptors (14,21), it should be borne in mind that in vitro binding affinity does not necessarily predict in vivo effects (22,23). Thus, it may be the case that CGS 12066B activates 5-HT_{2C} receptors to produce anxiogenic effects. Experimental support for this proposal comes from the work of Kennett and colleagues, who reported that the anxiogenic effects of mCPP and TFMPP are blocked by 5-HT_{2C} antagonists (9). Furthermore, 5-HT_{2C} antagonists display anxiolytic properties when tested in the rat social interaction test (10) and the rat Geller-Seifter model of anxiety (11).

In conclusion, 5-HT_{1B} receptors, in addition to 5-HT_{1A} receptors, act to attenuate offensive behaviour without concomitant motoric impairment. Such studies further illustrate the utility of an ethological analysis of agonistic behaviour that permits the detection of parallel drug influences across nonsocial, social, offensive, and defensive behaviours. It is thus possible to determine if these effects on agonistic behaviour are specific, in terms of concurrent changes in activity, or whether such influences are subsidiary to other behaviours such as anxiety.

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