Pharmacology Biochemistry and Behavior, Vol. 64, No. 3, pp. 549–554, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00105-7

Lack of Effect of the 5-HT_{1A} Receptor Antagonist WAY-100635 on Murine Agonistic Behaviour

ROBERT BELL,* KARL LYNCH* AND PAUL MITCHELL†

*School of Psychology, The Queen's University of Belfast, Belfast, BT7 INN, Ireland
†School of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK

BELL, R., K. LYNCH AND P. J. MITCHELL. *Lack of effect of the 5HT_{1A} antagonist WAY-100635 on murine agonistic behavior.* PHARMACOL BIOCHEM BEHAV **64**(3) 549–554, 1999.—The present study examined the influences of the selective 5-HT_{1A} receptor antagonist, WAY-100635, on the social and agonistic behavior exhibited by male resident mice during encounters with unfamiliar intruder conspecifics. Acute administration of WAY-100635 (0.01–1.0 mg/kg sc) dose dependently enhanced the duration of resident maintenance behavior, reaching statistical significance at 1.0 mg/kg. The duration of resident attend/approach behavior was reduced at 0.01 mg/kg. Drug-free intruder animals showed a reduction in the frequency and duration of attend/approach behavior when the resident mice were treated with 0.01 mg/kg WAY-100635. No other significant effects on behavior were detected for WAY-100635. A previous investigation reported that WAY-100635 induced anxiolytic-like effects in the mouse light/dark box test. In the present study, however, the level of defensive behavior of the saline-treated resident mice was too low for any further anxiolytic-like attenuation of this behavior to be observed. Therefore, no conclusions regarding the potential anxiolytic activity of WAY-100635 may be drawn from the data presented here. Current results are consistent with data for the lack of effect of WAY-100635 on rat agonistic behavior but contrast with findings for the effects of the 5-HT_{1A} receptor antagonists (+)-WAY-100135 and SDZ 216-525 on mouse agonistic behavior.

WAY-100635 Social behavior Agonistic behavior 5-HT_{1A} antagonist Ethological analysis

THE development of selective 5-HT_{1A} receptor antagonists has been moderate, and a number of promising compounds have subsequently been demonstrated to lack potency and/or selectivity (9). Furthermore, many of the postulated antagonists have latterly been shown to possess partial agonist properties (3,9,15). However, one compound that appears to satisfy the requirements of selectivity and antagonist activity at both pre- and postsynaptic 5-HT_{1A} receptors is the phenylpiperazine WAY-100635 (N-{2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride)(9,15).

WAY-100635 is a novel, potent, and selective 5-HT_{1A} receptor antagonist that is >100-fold selective for 5-HT_{1A} sites relative to a range of other CNS receptors (9). In vitro electrophysiological studies indicated that although WAY-100635 did not possess any agonist properties, the compound dose dependently blocked the effects of agonists in the CA1 region of the hippocampus and somatodendritic 5-HT_{1A} receptors located on the dorsal raphe 5-HT neurons (9). In tests of behavior, although WAY-100635 did not influence cognition in the delayed matching-to-position model of short-term memory in the rat, the compound blocked the ability of 8-OH-DPAT to induce the "5-HT syndrome," hyperphagia, hypothermia, and elevate plasma ACTH levels (9).

Germane to the current study, in terms of the possible link between murine agonistic behavior and anxiety (2–6), are reports that WAY-100635 produced anxiolytic-like effects in the elevated plus maze (7) and the mouse light:dark test (9). By contrast, WAY-100635 did not influence conditioned emotional responding in the rat (16). Furthermore, central application of WAY-100635 into the dorsal region of the periaqueductal grey increased D,L-homocysteic acid induced aversive behavior in rats, whereas systemic application of WAY-100635 was without effect (1).

Given our previous findings for the effects of pindobind 5-HT_{1A} (2), (−)-pindolol, (3) SDZ 216-525, and (+)-WAY-100135 (6) on murine agonistic behavior, it was of interest to compare such data with results obtained for the more se-

Requests for reprints should be addressed to Robert Bell, The Queen's University of Belfast, School of Psychology, Belfast BT7 INN, UK.

lective 5-HT_{1A} antagonist WAY-100635, as observed in the resident–intruder paradigm. The resident–intruder (isolation-induced aggression) paradigm, allows offensive aspects of agonistic behavior in the resident mouse to be recorded. However, where the intruder conspecific is also examined, defensive aspects of agonistic behavior may also be measured (12).

METHOD

Subjects and Procedure

Eighty adult male albino mice of the BKW strain, weighing between 30–40 g from Queens University Belfast Medical Biology Centre Breeding stock were used. Four weeks prior to testing the mice were randomly allocated to resident (n = 40) or intruder (n = 40) status. Resident mice were isolated (cage size 30 × 15 × 13 cm), while intruder mice were housed with siblings in groups of approximately ten (cage size 44 × 28 × 13 cm). Throughout the 4 weeks prior to testing, all animals were housed under a 12:12-h reverse light/dark schedule (lights off at 1200 h) in a temperature-controlled room (24±1°C) and given fresh bedding weekly, with food and water available ad lib.

Behavioral testing took place during the dark phase under red light in the resident's "home cage." Food and water were removed from test cages for the duration of encounters. Isolated resident mice were weighed, marked for recognition, and randomly assigned to dose treatment groups. Only isolated resident mice received drug treatments, and four experimental conditions were used (n pairs in each condition = 10); saline, 0.01, 0.1, and 1.0 mg/gk WAY-100635. Intruder mice were then introduced into the home cages of the residents and the ensuing 10-min encounters recorded on video tape by a Panasonic Saticon color video camera (model WVP200E) with low-light facility for later analysis. 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, and an IBM computer equipped with "Hindsight" software.

WAY-100635 was dissolved in physiological saline, which also served as drug-vehicle control. All injections were performed subcutaneously (SC) in a volume of 10 ml/kg 30 min prior to behavioral testing (9). Doses were selected on the basis of previous investigations (9). Animals used were both drug and experimentally naive. The experimenter remained unaware of the conditions until data analysis was complete.

The experimental protocol was in compliance with the UK Animals Scientific Procedures Act 1986.

Measures

Behavioral analysis was similar to previously detailed procedures (2–6,10). Briefly, videotapes were analyzed 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 (Table 1).

Statistical Analysis

Data for each behavioral element were grouped according to treatment and analyzed using Kruskal–Wallis nonparametric one-way analysis of variance across treatment groups. Where significant, variations in the data were identified, post hoc comparisons (with control group) were performed by Mann–Whitney U-tests. Figures depict the frequency and duration measures for each behavioral element as medians for each treatment group.

RESULTS

Drug-Treated Resident Mice (Table 2)

Nonsocial behavior. Kruskal–Wallis analysis revealed no significant variation in the frequency of maintenance behavior or the frequency and duration of cage exploration, rearing, and digging behaviors across treatment groups (Hs $\leqslant$ 5.80, $p > 0.05$ in all cases). However, a significant H-value was identified for maintenance duration (H = 10.768, $p <$ 0.05). Post hoc Mann–Whitney procedure indicated a significant increase in maintenance duration at 1.0 mg/kg (U = 10.5, $p < 0.02$).

Social behavior. Kruskal–Wallis analysis detected a significant variation in the duration of attend/approach behavior (H = 8.248, $p < 0.05$) but failed to identify any significant variation in the frequency of this behavioral element or, indeed, in the frequency and duration measures for any of the other behavioral elements of social behavior ($H \leqslant 5.48$, $p < 0.05$ in all cases). Post hoc analysis revealed that the duration of attend/approach behavior was significantly decreased following treatment with WAY-100635 at 0.01 mg/kg (U = 16.5, $p < 0.02$).

Offensive/defensive behavior. Kruskal–Wallis analysis failed to reveal any significant variation in the frequency and duration measures for any of the behavioral elements of offensive behavior (Hs $\leqslant$ 4.14, $p > 0.05$ in all cases) or defensive behavior (Hs $\leqslant$ 4.40, $p > 0.05$ in all cases).

Intruder Mice (Table 3)

Nonsocial behavior. Kruskal–Wallis analysis did not reveal any significant variation in the frequency and duration mea-

TABLE 1

BEHAVIORAL ELEMENTS (GROUPED ACCORDING TO MOTIVATIONAL CATEGORY) USED TO EXAMINE THE EFFECTS OF WAY-100635 ON MURINE BEHAVIOR

Category	Elements
Nonsocial	Cage exploration, rearing, maintenance, digging.
Social	Naso-genital, naso-nasal, nonspecific partner investigation, 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

TABLE 2

EFFECTS OF WAY-100635 (0.01–1.0 MG/KG) ON BEHAVIORS DISPLAYED BY RESIDENT MICE

Behaviors		Vehicle	0.01 mg/kg	0.1 mg/kg	1.0 mg/kg	H values
Nonsocial						
Cage exploration	f	26 (23.5–28.5)	23 (21.38–24.63)	23.5 (20.38–26.63)	25.5 (22.63–28.38)	2.009
	d	253.14 (231.43–267.62)	290.67 (261.30–320.03)	342.85 (317.38–355.25)	332.11 (311.53–352.69)	4.851
Rearing	f	0.5 (0–1.13)	0 (0–0.13)	0 (0–0)	0 (0–0.13)	5.254
	d	2.99 (0.84–5.14)	0 (0–0.19)	0 (0–0)	0 (0–0.095)	5.804
Maintenance	f	2 (1.5–2.5)	3 (2.75–3)	3 (2.38–3.5)	4 (3–5)	5.105
	d	8.78 (5.81–11.75)	12.44 (8.81–16.07)	26.77 (19.97–33.56)	33.02 (25.6–40.43)‡	10.768*
Digging	f	0.5 (0.25–0.75)	0 (0–0)	0 (0–0.13)	0 (0–0)	3.544
	d	1.19 (0–2.88)	0 (0–0)	0 (0–0.40)	0 (0–0)	4.376
Social						
Naso-genital	f	6.5 (4.38–8.63)	2.5 (0–5.13)	3 (1.38–4.63)	4 (2.25–5.75)	1.774
	d	27.56 (16.77–38.34)	12.56 (2.97–22.15)	16.09 (9.55–22.62)	23.77 (15.17–32.36)	1.078
Naso-nasal	f	8.5 (6.88–10.13)	6.5 (5.5–7.5)	6 (4.5–7.5)	5.5 (4.38–6.63)	3.581
	d	26.87 (16.95–36.78)	28.98 (23.38–34.58)	16.13 (7.62–24.64)	18.48 (13.02–23.93)	4.043
Nonspecific investigation	f	7 (5.5–8.5)	10 (7.25–12.75)	8 (5.75–10)	9 (6.13–11.88)	1.084
	d	31.19 (19.78–42.6)	56.81 (35.53–78.09)	26.03 (15.08–36.97)	50.67 (34.05–67.01)	1.421
Follow	f	3.5 (2.13–4.88)	1 (0.25–1.75)	1.5 (.63–2.38)	2.5 (1.38–3.63)	1.731
	d	13.59 (9.15–18.03)	1.86 (0.08–3.64)	7.93 (3.86–1.99)	4.45 (0.38–8.52)	2.570
Attend/approach	f	4 (3–5)	2 (1.25–2.75)	4.5 (3.25–5.75)	5 (3.75–6.25)	5.482
	d	13.47 (9.65–17.30)	4.25 (2.87–5.53)†	10.12 (7.65–12.58)	7.04 (3.11–10.97)	8.249*
Stretch/attend	f	0 (0–0.25)	0 (0–0.13)	0 (0–0)	0 (0–0.13)	2.704
	d	0 (0–1.70)	0 (0–0.21)	0 (0–0)	0 (0–0.19)	3.250
Offensive						
Aggressive groom	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.724
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.724
Tail rattle	f	13 (8.5–17.5)	6 (3.13–8.86)	8.5 (5.25–11.75)	4.5 (2.25–6.75)	2.547
	d	40.97 (27.39–54.29)	15.95 (5.26–26.64)	26.24 (17.12–35.35)	8.725 (2.88–14.57)	2.052
Offensive sideways	f	15.5 (9.88–21.13)	8 (4.25–11.75)	12 (6.75–17.25)	9 (6.13–11.88)	1.491
	d	77.27 (48.99–105.54)	32.06 (14.33–49.79)	58.24 (37.17–79.30)	46.01 (31.48–60.53)	1.717
Offensive upright	f	0 (0–0.25)	0 (0–0)	0 (0–0.25)	1 (0.63–1.38)	3.325
	d	0 (0–1.10)	0 (0–0)	0 (0–0.93)	3.10 (1.19–5.00)	4.137
Chase	f	0 (0–0.75)	0 (0–0.13)	0 (0–0)	0 (0–0.13)	1.600
	d	0 (0–1.03)	0 (0–0.19)	0 (0–0)	0 (0–0.08)	1.482
Bite attack	f	11.5 (5.63–17.38)	23 (11.75–34.25)	14 (6.63–21.38)	16 (3.88–28.13)	0.452
	d	22.99 (6.97–39.02)	26.24 (12.25–40.23)	16.78 (8.95–24.60)	17.90 (5.81–29.98)	0.263
Defensive						
Evade	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.235
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.235
Defensive sideways	f	0 (0–0)	0 (0–0)	0 (0–0.13)	0 (0–0)	4.219
	d	0 (0–0)	0 (0–0)	0 (0–0.52)	0 (0–0)	4.401
Defensive upright	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.000
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.000
Submissive upright	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
Frozen crouch	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	

Data expressed as medians (upper to lower quartiles) for frequency (f) and duration (d). Significant values refer to Mann–Whitney comparisons with vehicle.

* $p < 0.05$, † $p < 0.02$, ‡ $p < 0.002$.

sures for any of the behavioral elements of nonsocial behavior (Hs ≤ 3.99, $p > 0.05$ in all cases) of the intruder mice following acute treatment of resident animals with WAY-100635.

Social behavior. Kruskal–Wallis analysis of variance yielded a significant variation in both the frequency ($H = 7.83$, $p < 0.05$) and duration ($H = 8.989$ at $p < 0.05$ of attend/approach behavior but failed to reveal any other significant variations in the frequency and duration measures for each of the other behavioral elements of social behavior (Hs ≤ 6.63, $p > 0.05$ in all cases). Post hoc analysis indicated that intruder mice exhibited a significant decrease in the frequency ($U = 18$, $p < 0.02$) and duration ($U = 16$, $p < 0.02$) of attend/approach behavior following treatment of the resident mice with WAY-100635, 0.01 mg/kg.

Offensive/defensive behavior. Kruskal–Wallis analysis did not detect any significant variation in the frequency and duration measures for any of the behavioral elements of offensive

TABLE 3

BEHAVIOR OF UNTREATED INTRUDERS AS A FUNCTION OF DRUG STATE OF RESIDENTS (0.01–1.0 mg/kg WAY-100635)

Behaviors		Vehicle	0.01 mg/kg	0.1 mg/kg	1.0 mg/kg	H values
Nonsocial						
Cage exploration	f	28.5 (25.38–31.63)	21 (19.25–22.75)	28 (25.88–29)	24.5 (22.13–26.88)	3.986
	d	337.89 (297.33–373.6)	353.28 (319.21–387.36)	339.4 (319.46–359.33)	374.69 (339.27–410.11)	0.915
Rearing	f	1 (0.5–1.5)	0 (0–0.25)	0 (0–0.25)	0 (0–0)	3.474
	d	1.45 (0.84–2.06)	0 (0–0.39)	0 (0–0.18)	0 (0–0)	2.712
Maintenance	f	5.5 (3–8)	2.5 (1.88–3.13)	3.5 (2.5–4.5)	2.5 (1.5–3.5)	0.731
	d	45.4 (32.19–57.55)	15.55 (12.09–19.01)	38.73 (27.89–49.57)	16.12 (3.40–28.84)	1.741
Digging	f	3 (1.63–4.38)	3.5 (2.25–4.75)	3.5 (0.63–6.38)	6 (3–9)	0.447
	d	9.97 (6.12–13.81)	7.29 (2.83–11.75)	15.98 (5.54–26.42)	16.75 (2.79–30.71)	1.840
Social						
Naso-genital	f	2.5 (1.5–3.5)	1.5 (0.88–2.13)	2 (1.38–2.63)	1 (0.5–1.5)	1.240
	d	5.89 (3.6–8.17)	3.86 (1.15–6.57)	6.35 (4.21–8.49)	5.71 (3.15–8.27)	0.202
Naso-nasal	f	8 (6.38–9.63)	4.5 (3.88–5.13)	3.5 (2.88–4.13)	4.5 (3.5–5.5)	6.630
	d	20.35 (15.48–25.22)	21.2 (16.63–25.77)	14.45 (11.22–17.68)	18.6 (14.52–22.68)	4.616
Nonspecific investigation	f	4 (2.88–5.13)	4.5 (3–6)	3.5 (2.88–4)	3.5 (2.25–4.75)	0.869
	d	16.32 (8.41–24.22)	20.25 (13.41–27.09)	13.65 (10.7–16.59)	15.95 (9.00–22.89)	1.204
Follow	f	0 (0–0.25)	0 (0–0.25)	0.5 (0.25–0.75)	0 (0–0)	2.458
	d	0 (0–0.89)	0 (0–0.36)	1.13 (0.15–2.1)	0 (0–0)	3.451
Attend/approach	f	2 (1–3)	0 (0–0)†	1.5 (1–2)	1 (0.5–1.5)	7.833*
	d	3.73 (1.51–5.94)	0 (0–0)†	3.05 (1.47–4.64)	1.98 (0.49–3.46)	8.989*
Stretch/attend	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0.13)	1.315
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0.16)	1.384
Offensive						
Aggressive groom	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.000
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.000
Tail rattle	f	0 (0–1.13)	0 (0–0.13)	0 (0–0.25)	0 (0–0.13)	0.464
	d	0 (0–3.22)	0 (0–0.25)	0 (0–0.51)	0 (0–0.29)	0.513
Offensive sideways	f	0 (0–0.13	0 (0–0)	0.5 (0.25–0.75)	0 (0–0)	4.703
	d	0 (0–0.58)	0 (0–0)	1.6 (0.04–3.14)	0 (0–0)	5.306
Offensive upright	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	
Chase	f	0 (0–0)	0 (0–0)	0 (0–0.63)	0 (0–0)	6.587
	d	0 (0–0)	0 (0–0)	0 (0–2.86)	0 (0–0)	6.814
Bite attack	f	0 (0–0.13)	0 (0–0)	0 (0–0.5)	0 (0–0)	4.789
	d	0 (0–0.16)	0 (0–0)	0 (0–0.65)	0 (0–0)	4.834
Defensive						
Evade	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.000
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	3.000
Defensive sideways	f	13.5 (8.38–18.63)	13 (8.63–17.38)	13.5 (9.25–17.75)	12.5 (8.75–16.25)	0.145
	d	52.71 (30.43–74.98)	95.04 (65.12–119.7)	85.33 (61.64–103.29)	103.02 (77.62–119.84)	1.769
Defensive upright	f	9 (6.63–9.5)	0 (0–0.63)	0 (0–0.38)	1 (0.38–1.63)	7.213
	d	38.84 (27.71–44.51)	0 (0–4.6)	0 (0–2.63)	5.56 (1.14–9.98)	6.214
Submissive upright	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	6.154
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	6.154
Frozen crouch	f	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	4.318
	d	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	4.318

Data expressed as medians (upper to lower quartiles) for frequency (f) and duration (d). Significant values refer to Mann–Whitney comparisons with vehicle.

* $p < 0.05$, † $p < 0.02$, ‡ $p < 0.002$.

behavior ($Hs \leqslant 6.81, p > 0.05$ in all cases) or defensive behavior ($Hs \leqslant 7.21, p > 0.05$ in all cases) of the intruder mice following acute treatment of resident animals with WAY-100635.

DISCUSSION

The exiguous change in murine behavior following acute sc treatment with the selective 5-HT_{1A} receptor antagonist WAY-100635, in the dose range 0.01–1.0 mg/kg, differs markedly from the reported effects on murine agonistic behavior of other 5-HT_{1A} antagonists (2,3,6) in the resident–intruder paradigm. Thus, in contrast to pindobind 5-HT_{1A} (2), (−)-pindolol, and SDZ 216-525 (3), WAY-100635 (0.01–1.0 mg/kg SC) did not significantly alter any elements of offensive and defensive behavior. This result also contrasts with the increases in tail rattle behavior and both offensive and defensive sideways behaviors induced by acute treatment with

(+)-WAY-100135 (2.5–10.0 mg/kg) (6). However, the lack of effect of WAY-100635 on murine agonistic behavior is in general agreement with the reported lack of effect of acute (8) and chronic (14) administration of WAY-100635 on the agonistic behavior exhibited by resident rats in a similar experimental paradigm.

We have previously reported (5) the effects of the 5-HT_{1B} agonists CGS 12066B and CP-94,253 on murine social and agonistic behavior. The behavioral profile of CP-94,253, but not CGS 12066B, supported the proposal that 5-HT_{1B} receptors, in addition to 5-HT_{1A} receptors, inhibit murine agonistic behavior without concomitant motoric effects (5).

The only significant behavioral changes induce by WAY-100635 in resident mice were a dose-dependent enhancement in the duration of maintenance behavior, reaching significance at 1.0 mg/kg, and a significant reduction in both the frequency and duration of attend/approach behavior at 0.01 mg/kg. By comparison, (+)-WAY-100135 significantly reduced attend/approach behavior at 1.0 mg/kg but enhanced this behavior at 5.0 mg/kg (6).

The drug-free intruder animals exhibited reduced frequency and duration of attend/approach behavior following the treatment of the resident mice with WAY-100635, 0.01 mg/kg. This change in the behavioral profile of intruder animals may reflect the reduction in this element of social behavior displayed by resident animals; in other words, the intruder mice adapt their behavior as a function of the change in behavior of the resident animals. Thus, in this study, the decreased attend/approach behavior exhibited by the resident animals following treatment with WAY-100635, 0.01 mg/kg, is reflected by a decrease in the same element of social behavior displayed by intruder conspecifics (3,6).

We have previously argued (2–6) that the elements of nonsocial behavior function as "in-built" checks for any drug influence on the activity of the resident animals. As discussed above, the only change in murine nonsocial behavior induced by WAY-100635 was an enhancement of resident maintenance behavior at the highest dose tested. The lack of effect of WAY-100635 on elements of nonsocial behavior is, therefore, in general agreement with previously published data for the lack of motoric impairment induced by compounds with 5-HT_{1A} receptor antagonist activity, for example, pindobind 5-HT_{1A}, (−)-pindolol, SDZ 216-525, and (+)-WAY-100135 (2,3,6).

Previous studies by our group have shown that acute treatment of resident mice with compounds that possess antagonist activity 5-HT_{1A} receptors induce changes in murine behavior that may be explained as typical indicators of reduced levels of anxiety (2–6). Although, as previously mentioned, WAY-100635 has been shown to induce anxiolytic-like changes in murine behavior in both the light/dark box (9) and elevated plus-maze (7) models of anxiety, the level of defensive behavior of the saline-treated resident mice observed here was too low for any further anxiolytic-like attenuation of this behavior to be observed. Therefore, no conclusions regarding the potential anxiolytic activity of WAY-100635 may be drawn from the data presented here.

A comparison of the possible mechanisms by which (+)-WAY-100135, SDZ 216-525, and WAY-100635 exert their respective behavioral influences may explain the different effects of these compounds on murine agonistic behavior. (+)-WAY-100135 has been reported to possess antagonistic properties at presynaptic somatodendritic 5-HT_{1A} autoreceptors (15), postsynaptic 5-HT_{1A} receptors (9), or α_1-adrenoceptors (13). In comparison, SDZ 216-525 has been reported to behave as a partial agonist at presynaptic somatodendritic 5-HT_{1A} autoreceptors (13) and as an antagonist at α_1-adrenoceptors (15). Thus, both of these 5-HT_{1A} ligands exert their behavioral effects via serotonergic/nonadrenergic mechanisms. By contrast, WAY-100635 probably increases serotonergic neuronal activity by blockade of somatodendritic 5-HT_{1A} autoreceptors (11,15), which may counteract the antagonist action of WAY-100635 at postsynaptic 5-HT_{1A} receptors (7). The consequences of this mechanism of action by WAY-100635, in the dose range employed in this study (9), are minimal effects on the behavioral profile of both resident and drug-free intruder animals.

In summary, WAY-100635 produced no significant changes in the offensive and defensive elements of murine behavior. In addition, data from this study do not provide any evidence for an anxiolytic-like effect of this compound.

REFERENCES

1. Beckett, S; Marsden, C. A.: The effect of central and systemic injections of the 5-HT_{1A} receptor agonist 8-OHDPAT and the 5-HT_{1A} receptor antagonist WAY-100635 on periaqueductal grey-induced defence behaviour. J. Psychopharmacol. 11:35–40; 1997.
2. Bell, R.; Hobson, H.: The effects of pindobind 5-HT_{1A}, a novel and potent 5-HT_{1A} antagonist, on social and agonistic behaviour in male albino mice. Pharmacol. Biochem. Behav. 46:67–72; 1993.
3. Bell, R.; Hobson, H.: The effects of (−)-pindolol and SDZ 216-525 on social and agonistic behaviour in mice. Pharmacol. Biochem. Behav. 46:873–880; 1993.
4. Bell, R.; Hobson, H.: 5-HT_{1A} receptor influences on rodent social and agonistic behaviour: A review and empirical study. Neurosci. Biobehav. Rev. 18:325–338; 1994.
5. Bell, R.; Donaldson, C.; Gracey, D.: Differential effects of CGS 12006B and CP-94,253 on murine social and agonistic behaviour. Pharmacol. Biochem. Behav. 52:7–16; 1995.
6. Bell, R; Mitchell, P.: Effects of the antagonists (+)-WAY 100135 on murine social and agonistic behaviour. Pharmacol. Biochem. Behav. 54:159–167; 1996.
7. Cao, B.-J.; Rodgers, R. J.: Influence of 5-HT_{1A} receptor antagonism on plus-maze behaviour in mice. II. Way-100635, SDZ 216-525 and NAN-190. Pharmacol. Biochem. Behav. 58:593–603; 1997.
8. Cobain, M. R.; Forester, E. A.; Mitchell, P. J.; Fletcher, A.: Effect of acute treatment with selective 5-HT_{1A} ligands on the agonistic behaviour of rats. J. Psychopharmacol. Abst. 24; 1994.
9. Fletcher, A.; Forster, E. A.; Bill, D. J.; Brown, G.; Cliffe, I. A.; Hartley, J. A.; Jones, D. E.; McLenachan, A.; Stanhope, K. J.; Critchley, D. J. P.; Childs, K. J.; Middlefell, V. C.; Lanfumey, L.; Corradetti, R.; Laporte, A.-M.; Gozlan, H.; Hamon, M.; Dourish C. T.: Electrophysiological, biochemical, neurohormonal and behavioural studies with WAY-100635, a potent, selective and silent 5-HT_{1A} receptor antagonist. Behav. Brain. Res. 73:337–353; 1996.
10. Hendrie, C. A.; Rodgers, R. J.: Microcomputer-based data logging and analysis in psychopharmacology. In: West, R.; Christie, M; Weinman, J., eds. Computers, psychology and medicine. Chichester: Wiley; 1990:187–201.
11. Jacobs, B. L.; Fornal, C. A.: Physiology and pharmacology of brain serotonegic neurons. In: Baumgarten, H. G.; Gothert, M., eds. Serotonergic neurons and 5-HT receptors in the CNS. Berlin: Springer; 1997:91–116.
12. Krsiak, M.: Effects of drugs on the behaviour of aggressive mice. Br. J. Pharmacol. 65:525–533; 1979.
13. Lanfumey, L.; Haj-Dahmane, S.; Hamon, H.: Further assessment of the antagonist properties of the novel and selective 5-HT_{1A}

receptor ligands (+)-WAY-100135 and SDZ 216-525. Eur. J. Pharmacol. 249:25–35; 1993.
14. Mitchell, P. J.; Redfern, P. H.: Potentiation of the time-dependent, antidepressant-induced changes in the agonistic behaviour of resident rats by the 5-HT_{1A} receptor antagonist, WAY-100635. Behav. Pharmacol. 8:585–606; 1997.
15. Routledge, C.: Development of 5-HT_{1A} receptor antagonists. Behav. Brain Res. 73:153–156; 1996.
16. Stanhope, K. J.; Dourish, C. T.: Effects of 5-HT_{1A} receptor agonists, partial agonist and a silent antagonist on the performance of the conditioned emotional response test in the rat. Psychopharmacology (Berlin) 128:293–303; 1996.