Psychopharmacology (2003) 168:397–409
DOI 10.1007/s00213-003-1389-y

ORIGINAL INVESTIGATION

Mark J. Millan · Sylvie Veiga · Sylvie Girardon · Mauricette Brocco

Blockade of serotonin 5-HT_{1B} and 5-HT_{2A} receptors suppresses the induction of locomotor activity by 5-HT reuptake inhibitors, citalopram and fluvoxamine, in NMRI mice exposed to a novel environment: a comparison to other 5-HT receptor subtypes

Received: 6 August 2002 / Accepted: 14 December 2002 / Published online: 30 April 2003

Abstract *Rationale:* Though 5-HT plays an important role in the modulation of motor function, which is perturbed in depressive states, little is known concerning the influence of serotonin reuptake inhibitors (SSRIs) on locomotor activity (LA). Recently, we demonstrated that SSRIs, such as citalopram, enhance LA in mice exposed to a novel environment. *Objectives:* This study examined the role of multiple classes of 5-HT receptor in citalopram-induced LA. *Methods:* The most selective antagonists currently available were used. *Results:* Citalopram-induced LA was dose-dependently attenuated by the 5-$HT_{1B/1D}$ receptor antagonists, S18127, GR125,743 and GR127,935, and by the selective 5-HT_{1B} antagonist, SB224,289, but unaffected by the selective 5-HT_{1A} antagonist, WAY100,635. The selective antagonists at 5-HT_{2A} receptors, MDL100,907 and SR46,349 also dose-dependently attenuated induction of locomotion by citalopram, whereas the 5-HT_{2B} antagonist, SB204,741, and the 5-$HT_{2B/2C}$ antagonist, SB206,553 were ineffective. Further, the selective 5-HT_{2C} antagonist, SB242,084, potentiated the response to citalopram. Selective antagonists at 5-HT_3 (ondansetron), 5-HT_4 (GR125,487), 5-HT_6 (SB271,046) and 5-HT_7 (SB269,970) receptors did not significantly modify the action of citalopram. Underpinning these findings, SB224,289, GR125,743, MDL100,907 and SR46,349 likewise attenuated induction of locomotion by a further SSRI, fluvoxamine. *Conclusions:* The locomotor response to SSRIs of mice exposed to a novel environment is mediated via 5-HT_{1B} and 5-HT_{2A} receptors. In view of the importance of motor function to the etiology and treatment of depression, the significance of these observations to the clinical actions of SSRIs will be of interest to elucidate.

Keywords Serotonin (5-HT) · SSRI · Citalopram · Antidepressant · Locomotion · 5-HT_{1B} · 5-HT_{2A} · SB224,289 · MDL100,907

M. J. Millan (✉) · S. Veiga · S. Girardon · M. Brocco
Psychopharmacology Department,
Institut de Recherches Servier, Centre de Recherches de Croissy,
125 Chemin de Ronde, 78290 Croissy/Seine, France
e-mail: mark.millan@fr.netgrs.com
Tel.: +33-1-55722425
Fax: +33-1-55722470

Introduction

By actions at diverse loci, including the spinal cord, the basal ganglia, the limbic system and the frontal cortex (FCX), 5-HT plays an important role in the control of motor behaviour (Millan 2002). This action reflects the direct modulation of motor systems by serotonergic mechanisms per se, as well as their influence on mood, nociception and cognition, all of which impact on motor behaviour (Maes and Meltzer 1995; Geyer 1996; Barnes and Sharp 1999; Menard and Treit 1999; Meneses 1999; Millan 2002). Accordingly, a dysfunction of serotonergic transmission is involved in the motor symptoms of neurological and psychiatric states such as Parkinson's disease, schizophrenia and depression: further, serotonergic actions of psychotropic agents contribute to their influence on motor (as well as affective and cognitive) symptoms of these disorders (Maes and Meltzer 1995; Millan 2000; Millan et al. 2000).

Inasmuch as psychomotor retardation constitutes a core symptom of depressive disorders (Sachdev and Aniss 1994; Caligiuri and Ellwanger 2000), the role of serotonergic mechanisms in the influence of antidepressant agents on motor behaviour is of considerable interest. The pronounced sedative effects of tricyclic drugs such as amitryptiline, and atypical agents such as mirtazapine, which reflect their potent antagonist properties at α_1-adrenoceptors and histaminergic receptors, virtually precludes evaluation of this issue (Tatsumi et al. 1997). However, it can be addressed employing two classes of antidepressant essentially devoid of actions at these sites:

SSRIs, such as citalopram and fluvoxamine (Sanchez and Meier 1997; Tatsumi et al. 1997; Goodnick and Goldstein 1998; Popik 1999; Millan et al. 2001a), and mixed 5-HT/NA reuptake inhibitors (SNRIs), such as venlafaxine and S33005 (Barker and Blakely 1995; Millan et al. 2001a, 2001b). Though little information is available concerning their influence on locomotor behaviour, we recently demonstrated that, in contrast to selective inhibitors of noradrenaline reuptake, tricyclics, mirtazapine and other classes of antidepressant agent, SSRIs and SNRIs elicit a dose-dependent and specific enhancement in the LA of naive NMRI mice exposed to a novel environment (Brocco et al. 2002) at doses similar to those active in models of potential antidepressant activity (Reneric and Lucki 1998; Popik 1999; Millan et al. 2001a, 2001b). This response bears comparison to the increase in LA elicited by the 5-HT releasers, methylenedioxymethamphetamine (MDMA) and para-chloroamphetamine (Callaway et al. 1992; Rempel et al. 1993, Fletcher et al. 2002). However, in contrast to the latter agents, SSRIs increase LA only in subjects unfamiliar with the test environment (Brocco et al. 2002). Thus, in addition to motor function, a role of "arousal", "exploratory drive" and, possibly, decreased fear, in the facilitation of LA by SSRIs and SNRIs should not be neglected (Paulus and Geyer 1992; Brocco et al. 2002). Irrespective of its precise functional, and potential therapeutic significance, LA provides a simple, robust and instructive parameter for examination of receptorial mechanisms involved in the influence of SSRIs on motor behaviour.

Correspondingly, the purpose of the present investigation was to examine the role of specific classes of 5-HT receptor in the induction of LA by SSRIs in naive mice. On the basis of their contrasting structures and coupling to transduction mechanisms, seven classes of 5-HT receptor are recognized (Barnes and Sharp 1999). Of these, several subtypes have been implicated in the control of motor function, both directly and indirectly via their influence on mood and cognitive-attentional function: notably, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C} and 5-HT_4 receptors (see Barnes and Sharp 1999 and Discussion). We thus examined the influence of the most selective antagonists currently available (Table 1) at individual subtypes of 5-HT receptor on the induction of LA by citalopram and a further SSRI, fluvoxamine. The drugs utilized were as follows: 5-HT_{1A} receptors, WAY100,635 (Fletcher et al. 1996); 5-HT_{1B} receptors, SB224,289 (Gaster et al. 1998; Millan et al. 1999c, 2000, 2002; Newman-Tancredi et al. 2000; Audinot et al. 2001); 5-HT_{1B}/5-HT_{1D} receptors, GR125,743 and GR127,935 (Skingle et al. 1996; Doménech et al. 1997; Gobert et al. 1998; Millan et al. 2002) and S18127 (Millan et al. 1999c, 2002; Newman-Tancredi et al. 2000; Audinot et al. 2001); 5-HT_{2A} receptors, MDL100,907 and SR46,349 (Rinaldi-Carmona et al. 1992; Millan et al. 1999a, 2000); 5-HT_{2B} receptors, SB204,741 (Duxon et al. 1997; Gobert et al. 2000b; Cussac et al. 2002); 5-HT_{2B}/5-HT_{2C} receptors, SB206,553 (Kennett et al. 1996; Millan et al. 1997); 5-HT_{2C} receptors, SB242,084 (Kennett et al. 1997; Dekeyne et al. 1999, 2000; Gobert et al. 2000b); 5-HT_3 receptors, ondansetron (Jones et al. 1988; Olivier et al. 2000); 5-HT_4 receptors, GR125,487 (Barnes and Sharp 1999; Lucas et al. 2001); 5-HT_6 receptors, SB271,046 (Routledge et al. 2000; Dawson et al. 2001) and 5-HT_7 receptors, SB269,970 (Hagan et al. 2000; Roberts et al. 2001). All drug doses were selected on the basis of those defined as active at their respective central targets in previous studies in this and other laboratories (see above citations).

Table 1 5-HT antagonists employed in the present study

Drug	Class	References
WAY100,635	5-HT_{1A}	Fletcher et al. (1996)
GR125,743	5-HT_{1B}/5-HT_{1D}	Millan et al. (2002)
GR127,935		Harrison et al. (1999)
S18127		Millan et al. (1999c)
SB224,289	5-HT_{1B}	Gaster et al. (1998)
MDL100,907	5-HT_{2A}	Millan et al. (1999a)
SR46,349		Rinaldi-Carmona et al. (1992)
SB204,741	5-HT_{2B}	Duxon et al. (1997)
SB206,553	5-HT_{2B}/5-HT_{2C}	Kennett et al (1996)
SB242,084	5-HT_{2C}	Kennett et al (1997)
Ondansetron	5-HT_3	Olivier et al. (2000)
GR125,487	5-HT_4	Barnes and Sharp (1999)
SB271,046	5-HT_6	Dawson et al. (2001)
SB269,970	5-HT_7	Hagan et al. (2000)

As concerns the SSRIs employed in the present study, citalopram was chosen since it is the most selective SSRI to date described, while fluvoxamine was also used inasmuch as this "prototypical" agent has been very extensively employed both experimentally and clinically (Popik 1999; Goodnick and Goldstein 1998). They were employed at doses which we have previously demonstrated, employing dose-response studies, to elicit robust and reproducible increases in LA in NMRI mice (Brocco et al. 2002).

Although partial agonist actions of GR127,935 and GR125,743 have been seen at cloned, human (h)5-HT_{1B} receptors, they behave as "pure" antagonists at central 5-HT_{1B} sites in vivo: further, S18127 and SB224,289 display negligible efficacy at h5-HT_{1B} and native, 5-HT_{1B} receptors (Watson et al. 1996; Gaster et al. 1998; Millan et al. 1999c; Newman-Tancredi et al. 2000; Audinot et al. 2001).

Materials and methods

Animals

LA was determined in male NMRI mice weighing 22–28 g and of 6 weeks of age (Iffa-Credo, L'Arbresle, France). They were maintained in sawdust-lined cages with unrestricted access to food and water and allowed 1 week of acclimation prior to testing. They were used once only. Laboratory temperature was 21±1°C and humidity, 60±5%. There was a 12-h light/dark cycle, with lights "on" at 7:30 a.m. All animal use procedures conformed with international European ethics standards (86/609-CEE) and the French National Committee (décret 87/848) for the care and use of laboratory animals.

Evaluation of locomotor activity in mice

As previously (Brocco et al. 2002), 24 h before testing, the mice were isolated into transparent polycarbonate cages (23×13×13 cm) with sawdust floor covering and free access to chow and water. Testing was performed in the morning between 0900 h and 1200 h with each session lasting 10 min. The test cage was made of white plexiglass (27×27×30 cm) and was illuminated with a 6 W light. Photocells (four on each of two walls facing each other) were located 6 cm apart, 2 cm above the floor and connected via an interface (Osys-Orga System, Changé, France) to a computer. Software was written by Hesperid, Loiron, France. The interruption of two adjacent beams corresponded to a locomotion count. Citalopram or fluvoxamine (10.0 mg/kg, SC) was administered 30 min prior to evaluation. Antagonists were administered 30 min prior to citalopram or fluvoxamine. For drugs for which complete dose-response curves were performed, data were analyzed employing ANOVA followed by Dunnett's test. Inhibitory Doses (ID_{50}s) plus 95% confidence limits (CL) for blockade of the actions of citalopram were computed from the percentage inhibition elicited by each drug dose, which was calculated as follows: 1−(drug+citalopram)−(vehicle+vehicle)/vehicle+citalopram)−(vehicle+vehicle)]×100. For drugs evaluated at single doses, Student's two-tailed *t*-test was employed.

Drugs

All drug doses are in terms of the base. Drugs were dissolved in distilled water. For fluvoxamine, a few drops of lactic acid were added and the pH adjusted to as close to neutrality as possible (>5.0). With the exception of SB242,084, all drugs were administered subcutaneously in a volume of 10 ml/kg. SB242,084 was administered intraperitoneally (IP) as a suspension in distilled water with a few drops of Tween 80. Drug structures, sources and salts were as follows. Ondansetron (Sigma Chimie, St Quentin-Fallavier, France); fluvoxamine maleate (Tocris, Bristol, UK) and SR46,349 ({[1(Z)-2 (dimethylamino)ethoxyiminol]-1–2-(2-fluorophenyl)-3-(4-hydroxyphenyl)-2(E)propene} hemi-fumarate) (Sanofi, Montpellier, France). Citalopram HBr, GR127,935 (N-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2-methyl-4′-(5-methyl-1,2,4-oxadiozol-3-yl) biphenyl-4-carboxamide), SB242,084 (6-chloro-5-methyl-1-[6-(2-methylpyridin-3-yloxy)pyridin-3-yl carbamoyl]indoline), GR125,487 (1-2(methylsulphonylamino)ethyl]-4-piperidinyl]-methyl-5-fluoro-2-methoxy-1H-indole-3-carboxylate hydrochloride), GR125,743 (N-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiozol-3-yl) biphenyl-4-carboxamide), SB271,046 (5-chloro-3-methyl-benzo[b]thiophene-2-sulfonic acid (4-methoxy-3-piperazin-1-yl-phenyl)-amide)HCl, SB206,553 (N-3pyridinyl-3,5-dihydro-5-methyl-benzo[1,2-b:4,5-b′]dipyrrole-1(2H)-carboxamide HCl), SB204,741 (N-(1-methyl-5-indolyl-5-isothazolyl)urée) and MDL100,907 (2,3-dimethoxy-phenyl)-{1-[2-(4-fluoro-phenyl)-ethyl]-piperidin-4-yl}methalol) were synthesised by G. Lavielle (Servier), S18127 (N-[3-(1,4-benzodioxan-5-yl) piperidin-4-yl]N-(indan-2yl)amine), WAY100,635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinyl-cyclohexane-carboxamide maleate), SB224,289 (1′-methyl-5-[2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)-biphenyl-4-ylcarbonyl]-2,3,6,7-tetrahydro-5H-spiro[furo[2,3-f]indole-3,4′-piperidine]) and SB269,970 ((R)-1-{2-[1-(3-hydroxy benzenesulfonyl)pyrrolidin-2-yl]ethyl}-4-methylpiperidine)HCl were synthesised by J.L.Péglion (Servier).

Results

Influence of SSRIs on LA in mice exposed to a novel activity chamber

In corroboration of our previous study (Brocco et al. 2002), the SSRIs, citalopram and fluvoxamine, elicited a pronounced, significant and comparable increase in the LA of mice exposed to a novel environment (Figs. 1, 2, 3, 4, 5 and 6).

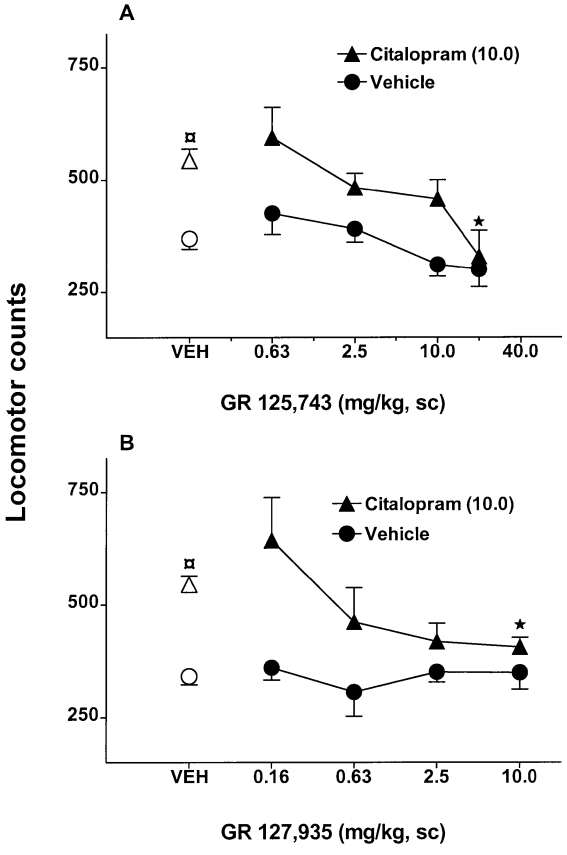

Fig. 1 Influence of the 5-HT_{1B}/5-HT_{1D} receptor antagonists, GR125,743 (**A**) and GR127,935 (**B**) on the increase in locomotor activity elicited by the SSRI, citalopram (10.0 mg/kg), in mice exposed to a novel environment. Data are means±SEM. *n*=5–11 per value. Symbols indicate significance of vehicle plus citalopram versus vehicle plus vehicle (¤), and of GR125,743 and GR127935 plus citalopram versus vehicle plus citalopram (*) values in Dunnett's test. $P<0.05$

Influence of the 5-HT_{1B}/5-HT_{1D} receptor antagonists, GR125,743 and GR127,935, on induction of LA by citalopram

The chemically related, mixed 5-HT_{1B}/5-HT_{1D} receptor antagonists, GR125,743 and GR127,935, both dose-dependently and significantly reduced the elevation of LA elicited by citalopram [ANOVAs as follows: GR125,743, $F(4,43)=4.66$, $P<0.005$ and GR129,735, $F(4,38)=4.06$, $P<0.005$] (Table 1, Fig. 1). Their ID_{50}s (95% CLs) were 4.8 (2.5–9.1) and 2.4 (0.9–6.6) mg/kg, respectively. On administration alone, neither GR125,743 nor GR127, 935 significantly modifed LA [GR125,743: $F(4,39)=2.34$, $P>0.05$ and GR127,935: $F(4,35)=0.33$, $P>0.05$].

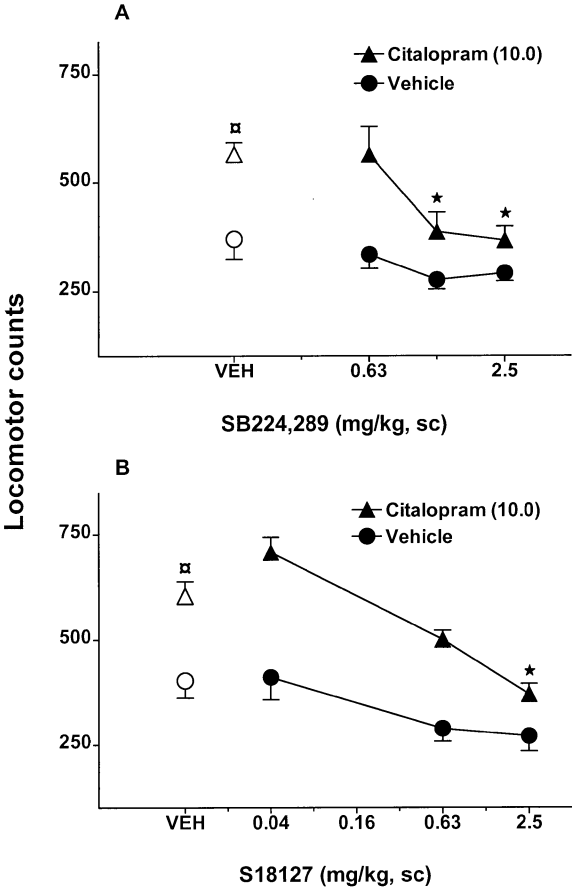

Fig. 2 Influence of the selective antagonist at 5-HT_{1B} receptors, SB224,289 (**A**), as compared to the 5-HT_{1B}/5-HT_{1D} receptor antagonist, S18127 (**B**), on the increase in locomotor activity elicited by the SSRI citalopram (10.0 mg/kg), in mice exposed to a novel environment. Data are means±SEMs. n=5–7 per value. Symbols indicate significance of vehicle plus citalopram versus vehicle plus vehicle (¤),and of S18127 plus citalopram versus vehicle plus citalopram (*) values in Dunnett's test. P<0.05

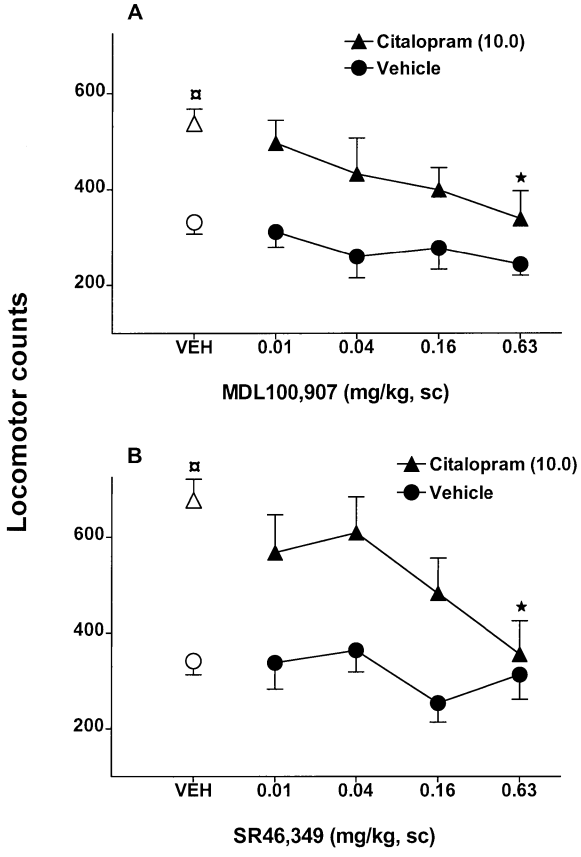

Fig. 3 Influence of the 5-HT_{2A} receptor antagonists, MDL100,907 (**A**) and SR46,349 (**B**), on the increase in locomotor activity elicited by the SSRI, citalopram (10.0 mg/kg), in mice exposed to a novel environment. Data are means±SEM. n=4–9 per value. Symbols indicate significance of vehicle plus citalopram versus vehicle plus vehicle (¤) and of MDL100,907 and SR46,349 plus citalopram versus vehicle plus citalopram (*) values in Dunnett's test. P<0.05

Influence of the 5-HT_{1B}/5-HT_{1D} antagonist, S18127, and of the selective 5-HT_{1B} receptor antagonist, SB224,289, on induction of LA by citalopram

The 5-$HT_{1B/1D}$ receptor antagonist, S18127, dose-dependently and markedly suppressed the action of citalopram with an ID_{50} (95% CL) of 0.39 (0.19–0.81) mg/kg [F(3,28)=17.9, P<0.0001] (Table 2, Fig. 2). Administered alone, S18127 did not significantly modify LA [F(3,23)=2.44, P>0.05]. By analogy to S18127, the selective 5-HT_{1B} antagonist, SB224,289, which shows only weak affinity for 5-HT_{1D} receptors, dose-dependently abolished the induction of LA by citalopram [F(3,20)=7.15, P<0.005]. It expressed this action with an ID_{50} (95% CL) of 1.05 (0.77–1.44) mg/kg. SB224,289 did not itself affect LA at doses which attenuated the action of citalopram [F(3,20)=1.49, P>0.05].

Influence of selective 5-HT_{2A} receptor antagonists as compared to antagonists at 5-HT_{2B} and/or 5-HT_{2C} receptors on induction of LA by citalopram

The highly selective antagonist at 5-HT_{2A} receptors, MDL100,907, dose-dependently and markedly reduced the elevation in LA evoked by citalopram [F(4,33)=2.98, P<0.05] with an ID_{50} (95% CL) of 0.04 (0.02–0.12) mg/kg (Table 2, Figs. 3 and 4). Similarly, a further selective 5-HT_{2A} antagonist, SR46,349, dose-dependently and significantly interfered with the induction of LA by citalopram [F(4,32)=3.46, P<0.05] with an ID_{50} (95% CL) of 0.11 (0.05–0.23) mg/kg. Neither MDL100,907 nor SR46,349 significantly modified LA alone [MDL100,907: F(4,26)=1.25, P>0.05 and SR46349: F(4,27)=1.14, P>0.05]. In contrast to MDL100,907 and SR46,349, the 5-$HT_{2B/2C}$ antagonist, SB206,553, and the selective 5-HT_{2C} antagonist, SB242,084, failed to reduce the action of citalopram [SB206,553: F(4,36)=2.47, P>0.05]. Indeed, the latter significantly enhanced its induction of LA at doses of 0.63 and 2.5 mg/kg [F(4,37)=3.44, P<0.05]. SB206,553 tended to decrease LA itself and this action was significant

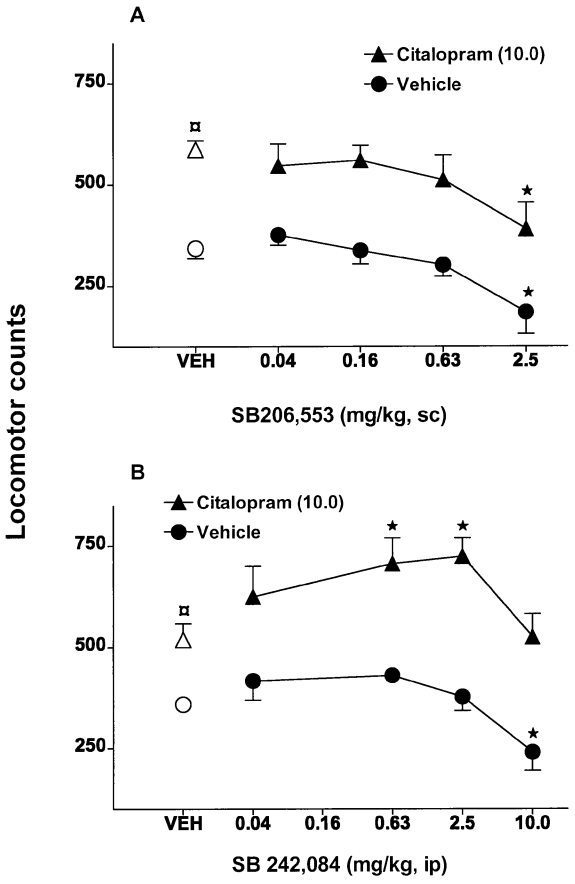

Fig. 4 Influence of the 5-HT_{2B}/5-HT_{2C} receptor antagonist, SB206,553 (**A**) and of the 5-HT_{2C} antagonist, SB242,084 (**B**), on the increase in locomotor activity elicited by the SSRI, citalopram (10.0 mg/kg), in mice exposed to a novel environment. Data are means±SEM. *n*=5–10 per value. Symbols indicate significance of vehicle plus citalopram versus vehicle plus vehicle (¤) and of SB206,553 and SB242,084 plus citalopram versus vehicle plus citalopram (*) values in Dunnett's test. $P<0.05$

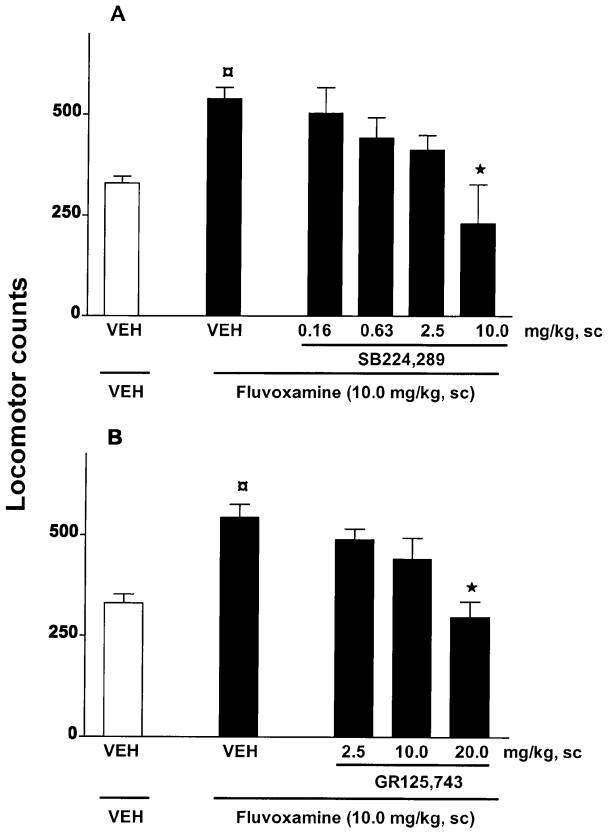

Fig. 5 Influence of the 5-HT_{1B} receptor antagonist, SB224,289 (**A**) and of the 5-HT_{1B}/5-HT_{1D} antagonist, GR125,743 (**B**), on the increase in locomotor activity elicited by the SSRI, fluvoxamine (10.0 mg/kg), in mice exposed to a novel environment. Data are means±SEM. *n*=5–12 per value. Asterisks indicate significance of vehicle plus fluvoxamine versus vehicle plus vehicle (¤) and of SB224,289 and GR125,743 plus fluvoxamine versus vehicle plus fluvoxamine (*) values in Dunnett's test. $P<0.05$

at the highest dose evaluated [$F(4,31)=4.49$, $P<0.01$]. The selective 5-HT_{2B} antagonist, SB204,741 did not modify the influence of citalopram. Vehicle×citalopram=502.5±36.0 versus SB204,741 (10.0 IP)×citalopram=539.8±28.4: $P>0.05$. SB204,741 did not affect LA alone (not shown).

Influence of antagonists at 5-HT_{1A}, 5-HT_3, 5-HT_4, 5-HT_6 and 5-HT_7 receptors on induction of LA by citalopram

The selective antagonists at 5-HT_{1A}, 5-HT_3, 5-HT_4, 5-HT_6 and 5-HT_7 receptors, WAY100,635, ondansetron, GR125,487, SB271,046 and SB269,970, respectively, all failed to significantly modify the action of citalopram. They also did not affect LA on application alone (Table 3).

Table 2 Effects of various 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} antagonists on induction of locomotor activity by citalopram. ID_{50} inhibitory $dose_{50}$ (mg/kg, SC, unless otherwise indicated), MED Minimal Effective Dose (mg/kg, SC)

Class	Drug	ID_{50}, blockade of citalopram-induced hyperlocomotion	*n*
5-HT_{1B}/5-HT_{1D} ANT	GR125,743	4.8	5–11
	GR127,935	2.4	5–8
	S18127	0.39	5–7
5-HT_{1B} ANT	SB224,289	1.05	5–6
5-HT_{2A} ANT	MDL100,907	0.04	4–7
	SR46,349	0.11	5–9
5-HT_{2B} ANT	SB204,741	>10.0 (IP)	6–10
5-HT_{2B}/5-HT_{2C} ANT	SB206,553	MED=2.5*	5–10
5-HT_{2C} ANT	SB242,084	>10.0§	4–10

*At a dose of 2.5 mg/kg, SC, SB206,553 decreased LA itself ($P<0.05$)
§At doses of 0.63 and 2.5 mg/kg, SC, SB242,084 increased citalopram-induced hyperlocomotion ($P<0.05$)

Table 3 Lack of influence of antagonists at 5-HT_{1A} (WAY100,635), 5-HT_3 (ondansetron), 5-HT_4 (GR125,487), 5-HT_6 (SB 271,046) and 5-HT_7 (SB269,970) receptors on induction of locomotor activity by citalopram. Data are means±SEM. In ANOVA, *F* values were significant in each case for the influence of citalopram, but in no case for the influence of the antagonist (not shown)

Drug	Dose	Drug	Dose	Locomotor activity	*n*
Vehicle	–	Vehicle	–	337.1±34.7	7
Vehicle	–	Citalopram	10	555.3±36.8*	8
WAY100,635	0.63	Vehicle	–	276.2±27.7	5
WAY100,635	0.63	Citalopram	10	513.5±62.8	6
Vehicle	–	Vehicle	–	348.0±45.8	5
Vehicle	–	Citalopram	10	595.8±30.5*	6
Ondansetron	0.16	Vehicle	–	337.8±27.6	5
Ondansetron	0.16	Citalopram	10	517.0±43.5	5
Vehicle	–	Vehicle	–	357.2±50.1	5
Vehicle	–	Citalopram	10	522.6±36.7*	5
GR125,487	0.63	Vehicle	–	421.0±17.4	5
GR125,487	0.63	Citalopram	10	597.7±66.0	6
Vehicle	–	Vehicle	–	366.0±52.0	5
Vehicle	–	Citalopram	10	545.0±55.5*	6
SB271,046	10	Vehicle	–	280.2±66.4	5
SB271,046	10	Citalopram	10	486.8±64.7	5
Vehicle	–	Vehicle	–	325.0±30.4	7
Vehicle	–	Citalopram	10	663.0±54.2*	7
SB269,970	10	Vehicle	–	266.7±8.8	7
SB269,970	10	Citalopram	10	528.4±50.9	7

Vehicle+citalopram versus vehicle+vehicle values, *$P<0.05$ in Dunnett's test

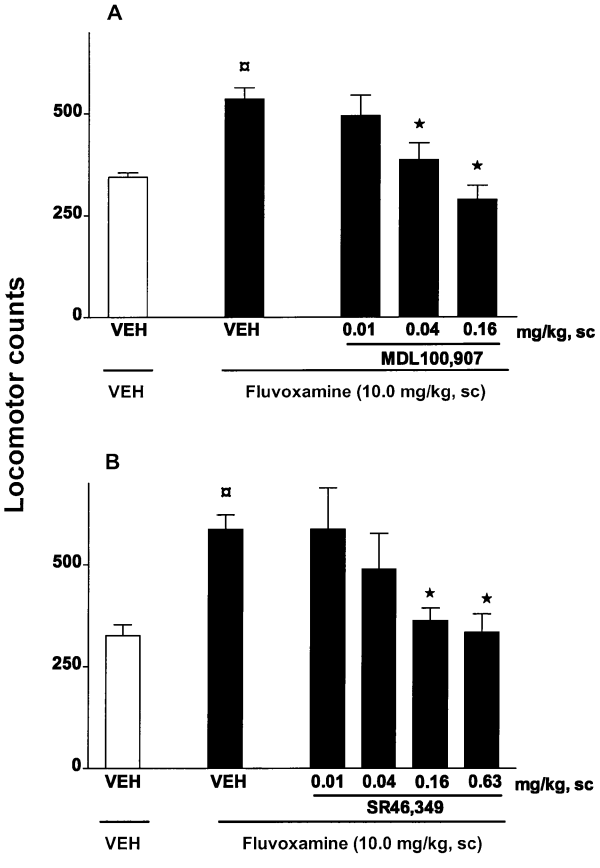

Fig. 6 Influence of the 5-HT_{2A} receptor antagonists, MDL100,907 (**A**) and SR46,349 (**B**), on the increase in locomotor activity elicited by the SSRI, fluvoxamine (10.0 mg/kg), in mice exposed to a novel environment. Data are means±SEM. *n*=4–9 per value. ANOVA as follows. Symbols indicate significance of vehicle plus fluvoxamine versus vehicle plus vehicle (¤) and of MDL100,907 and SR46,349 plus fluvoxamine versus vehicle plus fluvoxamine (*) values in Dunnett's test. $P<0.05$

Influence of SB224,289, GR125,743, MDL100,907 and SR46,349 on the induction of LA by fluvoxamine

By analogy to citalopram, the induction of LA by a further SSRI, fluvoxamine, was blocked by SB224,289 [$F(4,39)=5.83$, $P<0.001$] with a similar ID_{50} (95% CL) of 0.7 (0.13–1.6) (Figs 5 and 6). GR125,743 also antagonised the induction of LA by fluvoxamine [$F(3,30)=6.9$, $P<0.005$] with an ID_{50} (95% CL) of 3.7 (2.1–6.4). MDL100,907 and SR46,349 blocked the induction of LA by fluvoxamine [MDL100,907: $F(3,33)=7.51$, $P<0.001$ and SR46,349: $F(4,25)=4.26$, $P<0.01$]. Their ID_{50}s (95% CL)s were 0.02 (0.01–0.03) and 0.06 (0.03–0.14), respectively. Thus, the potencies of SB224,289, GR125,743, MDL100,907 and SR46,349 for blockade of fluvoxamine-induced LA were similar to their potencies for blocking the actions of citalopram (see above).

Discussion

Induction of LA by citalopram and fluvoxamine

The present observations with citalopram and fluvoxamine corroborate the results of our previous study with these and other SSRIs in which they were shown to dose-dependently elicit LA in NMRI mice (Brocco et al. 2002). As discussed therein, this response is distinctive to NMRI mice inasmuch as a CD strain of mice as well as Sprague-Dawley and Wistar rats do not display such an elevation in LA (see Brocco et al. 2002). In this article, it was pointed out that the facilitatory influence of SSRIs on LA in NMRI mice should be borne in mind in the interpretation of their actions in models of potential antidepressant activity. Despite the fact that psychomotor impairment is a cardinal symptom of depression (Caligiuri and Ellwanger 2000) it would be naive to directly

relate the present data to clinical depression and its treatment. Further, it is still unclear whether the implication of 5-HT receptors in the management of depressive states reflects their "acute" activation (analogous to the present model) or gradual down-regulation on long-term exposure (Caldecott-Hazard et al 1991). Nevertheless, as discussed below, the present parameter of LA provides a robust and efficient parameter for characterization of the roles of individual classes of 5-HT in the actions of SSRIs. In light of the important role of DA in the control of motor function, the ensuing discussion extensively evokes the significance of interactions between serotonergic and dopaminergic mechanisms in the induction of LA by SSRIs (see also Millan et al. 2000; Sasaki-Adams and Kelley 2001). However, the precise significance of dopaminergic receptors under the present conditions remains to be characterized.

5-HT_{1A} receptors

The influence of 5-HT_{1A} receptors on motor function is complex, reflecting the precise conditions and species of study, actions at presynaptic versus postsynaptic sites and their modification of arousal, anxious states and cognitive-attentional function: indeed, activation of 5-HT_{1A} receptors can either enhance, depress or not affect LA (Mittman and Geyer 1989; Hillegaart 1990; Kalkman and Soar 1990; De la Garza and Cunningham 2000; Millan 2000). Though they participate in the facilitatory influence of SSRIs on cocaine-induced LA in rat (Herges and Taylor 1998), herein, citalopram-induced LA was resistant to the selective antagonist, WAY100,635. This observation is analogous to the lack of influence of WAY100,635 on MDMA-induced LA (McCreary et al. 1999; Bankson and Cunningham 2002a, 2002b). Further, the reduction in LA elicited by fluoxetine in rats is abrogated by WAY100,635 (Bagdy et al. 2001). Interestingly, despite the lack of a role for 5-HT_{1A} sites in the mediation of citalopram-induced LA, blockade of 5-HT_{1A} receptors attenuated actions of SSRIs in experimental models of antidepressant properties in certain, but not all, studies (Redrobe et al. 1996; Moser and Sanger 1999; Mayorga et al. 2001; O'Neill and Conway 2001). Further, the anxiogenic effects of SSRIs are enhanced by 5-HT_{1A} receptor antagonists (Bristow et al. 2000; Dekeyne et al. 2000), reflecting blockade of inhibitory 5-HT_{1A} autoreceptors and a potentiation of extracellular levels of 5-HT (Gobert et al. 2000a; Millan et al. 2000; Mayorga et al. 2001).

5-HT_{1B} receptors

Though certain studies suggest that 5-HT_{1B} and 5-HT_{1A} receptors synergistically enhance LA (O'Neill and Parameswaran 1997), the 5-HT_{1B} antagonists, SB224,289, GR125,743, GR127,935 and S18127, in contrast to WAY100,635, abolished induction of LA by citalopram. A role for postsynaptic 5-HT_{1B} receptors is underpinned by several arguments. First, these antagonists show marked selectivity for 5-HT_{1B} receptors. Second, they blocked induction of citalopram-induced LA at doses little influencing basal LA and corresponding to those active in other models of 5-HT_{1B} receptor-mediated activity (Skingle et al. 1996; Harrison et al. 1999; Millan et al. 1999c, 2000; O'Neill et al. 2000). Notably, comparable doses attenuate the induction of hyperactivity by the 5-HT_{1B} agonist, RU24969 (Cheetham and Neal 1993; O'Neill et al. 1996, 2000; O'Neill and Parameswaran 1997; Chaouloff et al. 1999). Third, 5-HT_{1B} receptors likewise mediate the induction of LA by MDMA (McCreary et al. 1999; Bankson and Cunningham 2002a, 2002b; Fletcher et al. 2002) which elicits a pattern of locomotion behaviourally similar, and showing cross-tolerance, to 5-HT_{1B} agonists (Callaway and Geyer 1992; Callaway et al. 1992; Rempel et al. 1993). Further, 5-HT_{1B} sites are implicated in the induction of sensitization to the hyperlocomotion provoked by amphetamine (Przegalinski et al. 2001). Interestingly, it has been suggested that 5-HT_{1B} receptors contribute to antidepressant properties of SSRIs and tricyclic agents (O'Neill et al. 1996; Redrobe et al. 1996; Mayorga et al. 2001; O'Neill and Conway 2001).

5-HT_{1B} receptors are concentrated in many structures controlling motor function, including the nucleus accumbens, striatum and FCX (Bruinvels et al. 1993; Sari et al. 1999; Varnäs et al. 2001). Moreover, they interact with mesolimbic dopaminergic pathways in the facilitation of locomotor behaviour (Parsons et al. 1999; Yan and Yan 2001) and there is evidence for a role of dopaminergic mechanisms in the induction of LA by 5-HT_{1B} agonists (Oberlander et al. 1987; Cheetham and Neal 1993; O'Neill et al. 2000). However, the interrelationship between 5-HT_{1B} receptors and mesolimbic DA release is complex (Harrison et al. 1999; Parsons et al. 1999; Bronsert et al. 2001). Indeed, an interaction of postsynaptic 5-HT_{1B} sites with GABAergic, cholinergic and glutamatergic pathways provides alternative substrates for modulation of motor function (Johnson et al. 1992; Consolo et al. 1996; Morikawa et al. 2000). The role of 5-HT_{1B} receptors in the control of anxious states (Moret and Briley 2000; Dirks et al. 2001), arousal (Fletcher and Korth 1999; Belzung et al. 2000) and cognitive-attentional function (Malleret et al. 1999; Meneses 1999) might also be relevant to the present observations.

Inhibitory 5-HT_{1B} autoreceptors are localized on the terminals of serotonergic pathways (Gobert et al. 2000a; Trillat et al. 1998; Millan et al. 2000). Though they may interact with co-localized 5-HT transporters (Daws et al. 2000), the significance of such actions in vivo remains unclear. Such interactions are unlikely to be relevant to the present findings inasmuch as, in analogy to 5-HT_{1B} knock-out mice, blockade of 5-HT_{1B} autoreceptors by SB224,289 transiently enhances the increase in extracellular levels of 5-HT elicited by citalopram, fluvoxamine and other SSRIs (Evrard et al. 1999; Knobelman et al. 2001; Millan et al. 2000, unpublished observation).

5-HT_{1D} receptors

Since SB224,289 mimics the influence of S18127, GR127,935 and GR125,743 on citalopram-induced LA, their common blockade of 5-HT_{1B} receptors is clearly involved. Unfortunately, the only drug which preferentially blocks 5-HT_{1D} (pK_i 7.5) versus 5-HT_{1B} (6.1) sites, BRL15,772 ({1′-methyl-5-[[2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]carbonyl]-2,3,6,7-tetrahydro-spiro[furo[2,3-f]indole-3′,4′-piperidine]}), is poorly selective versus other receptors such as 5-HT_{2A} (6.8) receptors and 5-HT reuptake sites themselves (6.9) (Price et al. 1997; Gobert et al. 2000a; Millan et al., unpublished observation). Further, BRL15,772 markedly decreases basal LA. Nevertheless, the highest dose of BRL15,772 which did not affect LA alone (0.63 mg/kg) failed to modify induction of LA by citalopram (not shown). Though postsynaptic 5-HT_{1D} receptors are well represented in the basal ganglia, a region involved in motor control, their functional role remains obscure. Further, blockade of inhibitory, dendritic 5-HT_{1D} receptors by S18127, GR127,935 and GR125,743 (Davidson and Stanford 1995) would, in principle, enhance the influence of citalopram on extracellular levels of 5-HT and, accordingly, LA.

5-HT_{2A} receptors

Although citalopram displays weak antagonist activity at 5-HT_{2A} and 5-HT_{2C} receptors (Jenck et al. 1993; Pälvimäki et al. 1996), direct actions at these sites are unlikely to intervene in its hyperlocomotor properties, since selective 5-HT_{2A} and 5-HT_{2C} antagonists do not mimic its induction of LA. Further, fluvoxamine, venlafaxine and S33005, which likewise increase LA, have negligible affinity for 5-HT_{2A} and 5-HT_{2C} receptors (Tatsumi et al. 1997; Millan et al. 2001b; Brocco et al. 2002).

Blockade by MDL100,907 and SR49,369 of the actions of citalopram is supported by other studies indicating a broad role of 5-HT_{2A} receptors in the mediation of LA. First, MDL100,907 and other 5-HT_{2A} antagonists suppressed induction of LA by the 5-HT releaser, MDMA, in rats (Bankson and Cunningham 2002a, 2002b; Fletcher et al. 2002). Second, MDL100,907 attenuated the facilitatory influence of fluoxetine on the LA elicited by the DA uptake inhibitor, mazindole, (McMahon and Cunningham 2001b). Further, an additional 5-HT_{2A} antagonist, ketanserin, inhibited the ability of fluoxetine to potentiate induction of LA by the monoamine releaser, cocaine (Herges and Taylor 1998). Third, MDL100,907 and ketanserin attenuated the locomotor actions of cocaine in rats though data are conflicting as concerns their interference with stimulation of LA by a further psychostimulant, amphetamine (Millan et al. 1999a; McMahon and Cunningham 2001a; Munzar et al. 2002). Fourth, 5-HT_{2A} receptors are involved in the induction of LA by the "dopaminergic" agonist, pergolide, which displays agonist properties at 5-HT_{2A} receptors (Hagen et al. 1994; Moore et al. 1999). Finally, MDL100,907 attenuated the LA elicited in rats by the open channel blocker at NMDA receptors, PCP (Millan et al. 1999a), without modifying its influence on extracellular 5-HT: comparable observations were made here with citalopram.

5-HT_{2A} sites mediating PCP-induced LA in rats are localized in the nucleus accumbens: they are activated by local pools of 5-HT (Millan et al. 1999a). On the other hand, 5-HT_{2A} receptors on dopaminergic cell bodies in the VTA are involved in the induction of LA by cocaine (Doherty and Pickel 2000; McMahon and Cunningham 2001a). Indeed, 5-HT_{2A} receptors augment the activity of mesolimbic, as well as nigrostriatal and frontocortical, dopaminergic projections (Ng et al. 1999; Bowers et al. 2000; Millan et al. 2000; Yan et al. 2000; De Deurwaerdère and Spampinato 2001). Thus, 5-HT_{2A} receptors facilitatory to mesolimbic dopaminergic mechanisms may well be implicated in the present observations, although this remains to be directly examined. Further, the possible significance of 5-HT_{2A} receptors modulating anxious states should not be neglected (Griebel et al. 1997; Dekeyne et al. 2000).

It should be noted that 5-HT_{2A} receptor antagonists do not modify the influence of SSRIs on dialysis levels of 5-HT in rats, so the inhibitory influence of MDL100,907 and SR46,349 on the induction of LA by citalopram and fluvoxamine is unlikely to reflect modulation of extracellular levels of 5-HT (Millan et al. 2000; A. Gobert and M.J. Millan, unpublished observations).

5-HT_{2B} receptors

5-HT_{2B} receptors are poorly represented in the CNS, wherein their functional significance remains obscure (Duxon et al. 1997; Barnes and Sharp 1999). Though their activation may be associated with anxiolytic properties, a role in the enhancement of LA by citalopram may be discounted in view of its lack of sensitivity to 5-HT_{2B} receptor antagonists.

5-HT_{2C} receptors

5-HT_{2C} receptor agonists exert a suppressive influence on locomotor behaviour (Lucki et al. 1989; Kennett et al. 1996, 1997; Martin et al. 1998), reflecting their inhibition of central dopaminergic pathways (Millan et al. 2000; De Deurwaerdère and Spampinato 2001; Di Matteo et al. 2001). Correspondingly, SB206,553 and SB242,084 did not inhibit the induction of LA by citalopram. Indeed, SB242,084 facilitated its action, indicating that concurrent activation of 5-HT_{2C} receptors may oppose the induction of LA via 5-HT_{2A} sites. Similarly, in contrast to 5-HT_{2A} antagonists, 5-HT_{2C} antagonists potentiated the induction of LA by MDMA (Bankson and Cunningham 2002b; Fletcher et al. 2002), a combination of fluoxetine

and mazindole (McMahon and Cunningham 2001b), dizocilpine (Wood et al. 2001) and (at high doses) cocaine (Herges and Taylor 1998; McMahon and Cunningham 1999). Moreover the decrease in LA elicited by fluoxetine is attenuated by SB242,084 (Bagdy et al. 2001). Thus, the contrasting roles of 5-HT_{2C} versus 5-HT_{2A} receptors (vide supra) in the influence of citalopram on LA parallel their opposite inhibitory and facilitatory influence on motor function and dopaminergic transmission, respectively (Millan et al. 2000; De Deurwaerdère and Spampinato 2001; Di Matteo et al. 2001). Indeed, 5-HT_{2C} receptors may intervene in the modest inhibition of mesolimbic dopaminergic transmission by SSRIs (Prisco and Esposito 1995).

5-HT_{2C} antagonists block the anxiogenic actions of citalopram and other SSRIs (Bristow et al. 2000; Dekeyne et al. 2000; Bagdy et al. 2001). Thus, the facilitatory influence of SB242,084 on citalopram-induced LA in this novel environment might also involve relief of its anxiogenic properties. Indeed, 5-HT_{2C} receptors are of special interest in light of their broad implication in the actions of SSRIs (Millan et al. 1999b). In analogy to LA, antidepressant actions of SSRIs were enhanced by 5-HT_{2C} antagonists in certain studies (Yamada and Sugimoto 2001), though other authors reported their attenuation (Clemett et al. 2001). Correspondingly, most evidence suggests that blockade of 5-HT_{2C} receptors, or their long-term down-regulation (with SSRIs), improves depressed mood (Martin et al. 1998; Millan et al. 2000).

5-HT_3 and 5-HT_4 receptors

The potential influence of 5-HT_3 receptors on striatal DA release remains controversial while the facilitatory influence of 5-HT_3 receptors on mesolimbic dopaminergic transmission and locomotor behaviour is variable (De Deurwaerdère et al. 1998; Kankaanpää et al. 2002). Indeed, ondansetron failed to modify the induction of LA by citalopram, suggesting that 5-HT_3 receptors are not involved in this effect. 5-HT_4 receptors are concentrated in mesolimbic and striatal tissue, in the latter of which their engagement enhances DA release (De Deurwaerdère et al. 1997; Lucas et al. 2001) and may be involved in cocaine-induced LA (McMahon and Cunningham 1999). However, Reavill et al. (1998) reported that 5-HT_4 sites do not play an important role in the modulation of motor behaviour in rats, and 5-HT_4 antagonists such as GR125,847 (Barnes and Sharp 1999) do not modify LA in rodents (Fontana et al. 1997). Thus, the lack of influence of GR125,487 on citalopram-induced LA is unsurprising. Moreover, like 5-HT_3 sites, activation of 5-HT_4 receptors enhances anxious states (Jones et al. 1988; Menard and Treit 1999; Olivier et al. 2000), actions inconsistent with an elevation of LA by citalopram.

5-HT_6 and 5-HT_7 receptors

The inhibitory influence of the 5-HT_6 antagonist, Ro-04-6790, on ipsilateral rotation induced in unilateral substantia nigra pars compacta-lesioned rats by muscarinic antagonists indicates a facilitatory influence of 5-HT_6 sites on LA, in line with their occurrence in the basal ganglia and nucleus accumbens (Gerald et al. 1997; Bourson et al. 1998; Neumaier et al. 2001). However, 5-HT_6 antagonists do not modify central dopaminergic transmission (Dawson et al. 2001), pronounced alterations in motor function are not apparent in mice lacking 5-HT_6 sites (Tecott et al. 1998) and antisense probes neutralizing 5-HT_6 receptors did not modify LA in rats (Otano et al. 1999). These observations, together with indications that the activation of 5-HT_6 receptors is anxiogenic (Otano et al. 1999), are consistent with the present findings that the selective 5-HT_6 antagonist, SB271,046 did not attenuate the increase of LA by citalopram in mice. As regards 5-HT_7 sites, they are not enriched in structures controlling motor function (Hagan et al. 2000; Neumaier et al. 2001) and intracerebral administration of antisense probes against 5-HT_7 sites did not modify LA (Clemett et al. 1998). These findings are in line with the lack of influence of the selective 5-HT_7 antagonist, SB269,970, on induction of LA by citalopram.

Combined role of 5-HT_{1B} and 5-HT_{2A} receptors in mediating induction of LA

It is of particular interest that blockade of either 5-HT_{1B} or 5-HT_{2A} receptors suppressed induction of LA by SSRIs. Isobolographic analyses of interactions between 5-HT_{1B} and 5-HT_{2A} antagonists would be necessary to clarify whether they exert actions additively, synergistically or otherwise. In any case, these data imply that activation of 5-HT_{1B} or 5-HT_{2A} receptors is necessary but not sufficient for induction of LA by SSRIs. 5-HT_{1B} and 5-HT_{2A} receptors may be localized "in series": for example, 5-HT_{2A} sites in the ventrotegmental area and 5-HT_{1B} counterparts downstream in the nucleus accumbens (vide supra). Alternatively, both 5-HT_{1B} and 5-HT_{2A} receptors may be co-localized in limbic structures controlling motor function. Their precise localization and their "functional" interrelationship remain, thus, to be elucidated. Interestingly, this implication of both 5-HT_{1B} and 5-HT_{2A} sites in the increase of LA by citalopram mimics their cojoint role in mediating the increase of LA elicited by MDMA (McCreary et al. 1999; Bankson and Cunningham 2002a, 2002b; Fletcher et al. 2002). Further, more generally, the present data draw attention to the notion that simultaneous actions at multiple subtypes of 5-HT (and other) receptor may be required for full expression of antidepressant (and other) properties of SSRIs and SNRIs.

Conclusions

5-HT_{1B} and 5-HT_{2A} receptors fulfill complementary roles in the induction of LA by SSRIs in NMRI mice exposed to a novel environment. Additional study will be necessary to clarify the neuronal substrates underlying their involvement, as well as the role of modulation of motor function per se as compared to other parameters such as anxiety and vigilance. The pertinence of the present data to the antidepressant properties of SSRIs will also be of interest to evaluate. In the elucidation of such issues, it would likely be instructive to examine more complex measures of motor function, in addition to the parameter of horizontal displacement exploited herein. Finally, the present model should prove of use in further exploration of receptor and neuronal mechanisms involved in the actions of SSRIs.

Acknowledgements We thank Marianne Soubeyran for secretarial assistance.

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