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5-$HT_{1B/D}$ receptor agonist, SKF99101H, induces locomotor hyperactivity in the guinea pig

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Abstract

Previous studies in guinea pigs have shown that while a serotonin 5-$HT_{1B/D}$ receptor agonist, GR46611, does not induce locomotor activation when given alone, it markedly enhances the locomotor response to selective 5-HT_{1A} receptor agonists, 8-OH-DPAT and buspirone. In these studies, we found that another 5-$HT_{1B/D}$ agonist, 3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate (SKF99101H), significantly elevated locomotor activity in guinea pigs when given alone. We assessed the relative contribution of 5-$HT1_{1A}$ and 5-$HT_{1B/D}$ receptors in the mediation of this effect.

Activity was measured by photobeam interrupts in opaque Perspex cylinders linked to a computer. SKF99101H (20 mg/kg s.c.) significantly increased the locomotor activity in guinea pigs. The locomotor stimulant effect of SKF99101H (20 mg/kg s.c) was reversed by the selective 5-$HT_{1B/D}$ receptor antagonist *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1biphenyl]4-carboxamide (GR127935; 0.06–0.25 mg/kg s.c.). The 5-HT_{1A} receptor antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride (WAY100635; 0.05–0.25 mg/kg s.c.), slightly but significantly attenuated the hyperactivity induced by SKF99101H. These findings suggest that 5-$HT_{1B/D}$ receptor agonists may require concomitant activation of 5-HT_{1A} receptors to induce locomotor activity in guinea pigs. The 5-HT_{2A} receptor antagonist 6[2-[4-[bis(4-fluorophenyl)methylene]-1-piperidinyl]-ethyl]-7-methyl-5H-thiazol[3,2-a]pyrimidin-5-one (ritanserin) had no effect on SKF99101H-induced hyperactivity, suggesting that these receptors are not involved in the mediation of SKF99101H-induced hyperactivity. SKF99101H-induced hyperactivity was significantly attenuated by the D_1 dopamine receptor antagonist SCH 23390 (0.005–025 mg/kg), but not by the D_2 dopamine receptor antagonist raclopride (0.25–1.0 mg/kg), possibly suggesting the selective involvement of D_1 dopaminergic receptors in the mediation of the stimulant actions of the 5-$HT_{1B/D}$ agonist.

Keywords: 5-$HT_{1B/D}$ receptor; Locomotor activity; (Guinea pig); SKF99101H; GR127935; WAY100635

1. Introduction

5-$HT_{1B/D}$ receptor agonists, such as sumatriptan and rizatriptan, have been shown to have clinical efficacy in the treatment of migraine (Dooley and Faulds, 1999). This effect is believed to be mediated mainly by the effects of the agonists acting on 5-HT receptors in the cerebral vasculature (Hamel, 1999). The functional role of 5-$HT_{1B/D}$ receptors in the central nervous system has yet to be determined. These studies set out to examine the effects of a centrally acting 5-$HT_{1B/D}$ receptor agonist 3-(2-dimethylaminoethyl)-4-chloro-5-propoxyindole hemifumarate (SKF99101H) to determine if its behavioural effects could enhance our understanding of the function of these receptors.

5-$HT_{1B/D}$ receptors have been shown to be present in high concentrations in regions of the basal ganglia such as the caudate putamen, nucleus accumbens and in the subthalamic nucleus of mice (Maroteaux et al., 1994) rat and guinea pig brains (Bruinvels et al., 1993, 1994). This abundance of 5-$HT_{1B/D}$ receptors in these regions would imply that these receptors may play a role in the mediation of locomotor activity. Activation of central 5-HT_{1B} receptors with agonists, such as RU24969 and anpirtoline, increases locomotor activity in mice (Cheetham and Heal, 1993; O'Neill et al., 1996, 1997b) and in rats (O'Neill and Parameswaran, 1997). Furthermore, this increase in locomotion is reversed by pretreatment with the antagonist *N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3-yl)[1,1biphenyl]4-carboxa-

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mide (GR127935) (O'Neill et al., 1996; O'Neill and Parameswaran, 1997). This antagonist is selective for the 5-$HT_{1B/D}$ family of receptors over other 5-HT receptor subtypes (Starkey and Skingle, 1994), implicating further these receptors in the mediation of the locomotor response to the agonists. However, the 5-HT_{1B} receptor in the rat and mouse represents a pharmacologically distinct entity from that found in the other species, including guinea pigs, primates and humans (Hoyer and Martin, 1997). While there is some evidence to suggest that the rat and mouse receptor is a functional analog of the 5-$HT_{1B/D}$ receptors found in other species, this work has predominantly been confined to neurochemical studies relating to the autoreceptor function of these receptors (for review, see Pineyro and Blier (1999)). Given the abundance of 5-$HT_{1B/D}$ receptors in regions associated with locomotor activity, we sought to examine the effect of a 5-$HT_{1B/D}$ receptor agonist on locomotor activity in the guinea pig to further determine if stimulation of these receptors resulted in increased locomotion, analogous to the increase in locomotion observed in rats and mice following the administration of 5-HT_{1B} receptor agonists.

While it has been shown that 5-HT_{1A} receptor agonists can cause locomotor activation in guinea pigs (Evenden, 1994), the behavioural effects of 5-$HT_{1B/D}$ receptor selective agents have yet to be fully characterised in a species endowed with these receptors, such as the guinea pig. Studies examining the role of 5-$HT_{1B/D}$ receptors in the mediation of locomotor activity in guinea pigs have yielded conflicting results. Intrastriatal administration of sumatriptan, a 5-HT_{1D} receptor agonist, induced rotation in guinea pigs (Higgins et al., 1991). RU24969 has been reported to increase locomotor activity in guinea pigs (Sipes and Geyer, 1996), but this compound also has, as outlined above, significant levels of 5-HT_{1A} activity, which may also be responsible for an increase in locomotor activity in guinea pigs. GR46611 is an agonist with equal activity at 5-HT_{1B} and 5-HT_{1D} receptors (Starkey and Skingle, 1994). This compound reduces body temperature in guinea pigs when given systemically (Skingle et al., 1995). GR46611 does not increase locomotor activity when given systemically to guinea pigs (O'Neill and Sanger, 1999). It does, however, potentiate the locomotor activity induced by the selective 5-HT_{1A} receptor agonist 8-OH-DPAT.

Another agonist has been described, which also induces hypothermia in guinea pigs, SKF99101H (Hatcher et al., 1995). The hypothermia induced by both GR46611 and SKF99101H is reversed by GR127935 (Skingle et al., 1995; Hatcher et al., 1995), suggesting that its effects were mediated by 5-$HT_{1B/D}$ receptors.

We set out to profile the effects of SKF99101H on locomotor activity in order to determine the relative contribution of 5-HT_{1A} and of 5-$HT_{1B/D}$ receptors in the mediation of this response. The drugs used were GR127935 for antagonism of 5-$HT_{1B/D}$ receptors (Starkey and Skingle, 1994) and *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride (WAY100635) for antagonism of 5-HT_{1A} receptors (Fletcher et al., 1995). To examine the role of 5-HT_{2A}

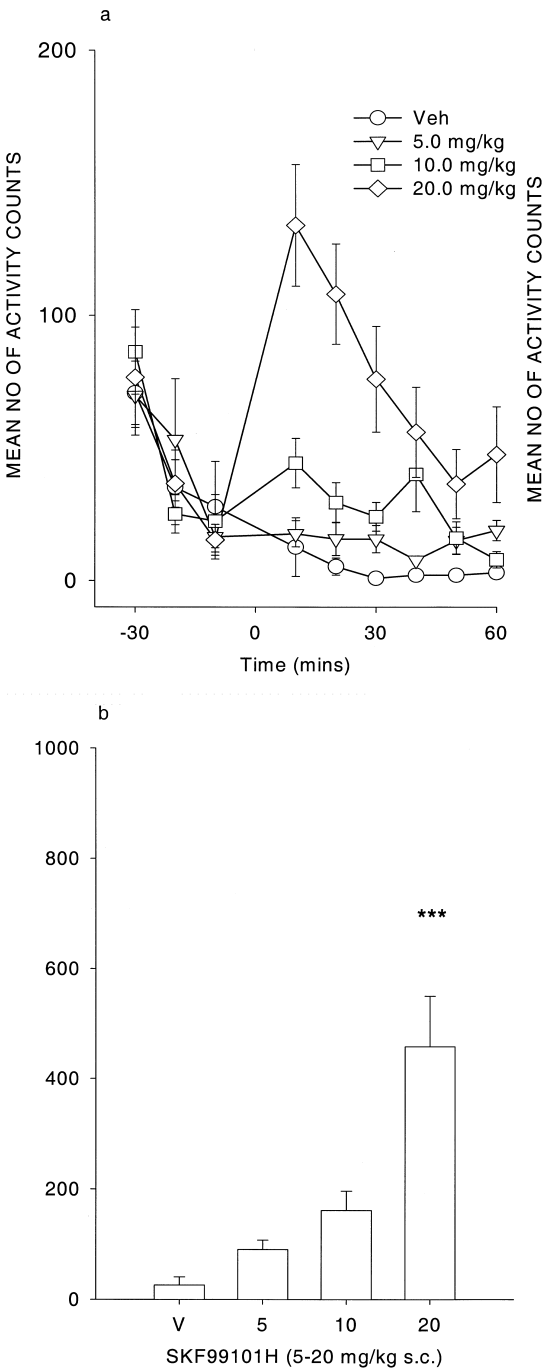

Fig. 1. (a) Effect of SKF99101H on locomotor activity in guinea pigs. *X*-axis shows the time after injection in minutes. *Y*-axis shows the mean number of photocell counts recorded. ○ — Vehicle, ▽ — 5 mg/kg, □ — 10 mg/kg, ◇ — 20 mg/kg. (b) Effect of SKF99101H on locomotor activity in guinea pigs. Data are means of total locomotor activity summed over the 60 min test for each group with SEM. *X*-axis indicates dose of SKF99101H received by each group, while *Y*-axis shows the mean of total activity for each group. Significant differences were calculated by an LSM test following a significant ANOVA. $^{***}p < 0.001$ vs. vehicle.

receptors, 6[2-[4-[bis(4-fluorophenyl)methylene]-1-piperidinyl]-ethyl]-7-methyl-5H-thiazol[3,2-a]pyrimidin-5-one (ritanserin) was used. While this compound has also an affinity in vitro for 5-HT_{2C} receptors, over the dose-range used in vivo, this compound appears to selectively antagonise 5-HT_{2A} receptors only (Kennett and Curzon, 1991). To determine if the locomotor response to SKF99101H was mediated by dopaminergic mechanisms, we also examined the effects of pretreatment with the selective D_1 dopamine receptor agonist SCH23390, and the selective D_2 receptor antagonist raclopride.

2. Methods

2.1. Animals

Female Dunkin Hartley guinea pigs (250–350 g) were housed in groups of five under standard conditions with

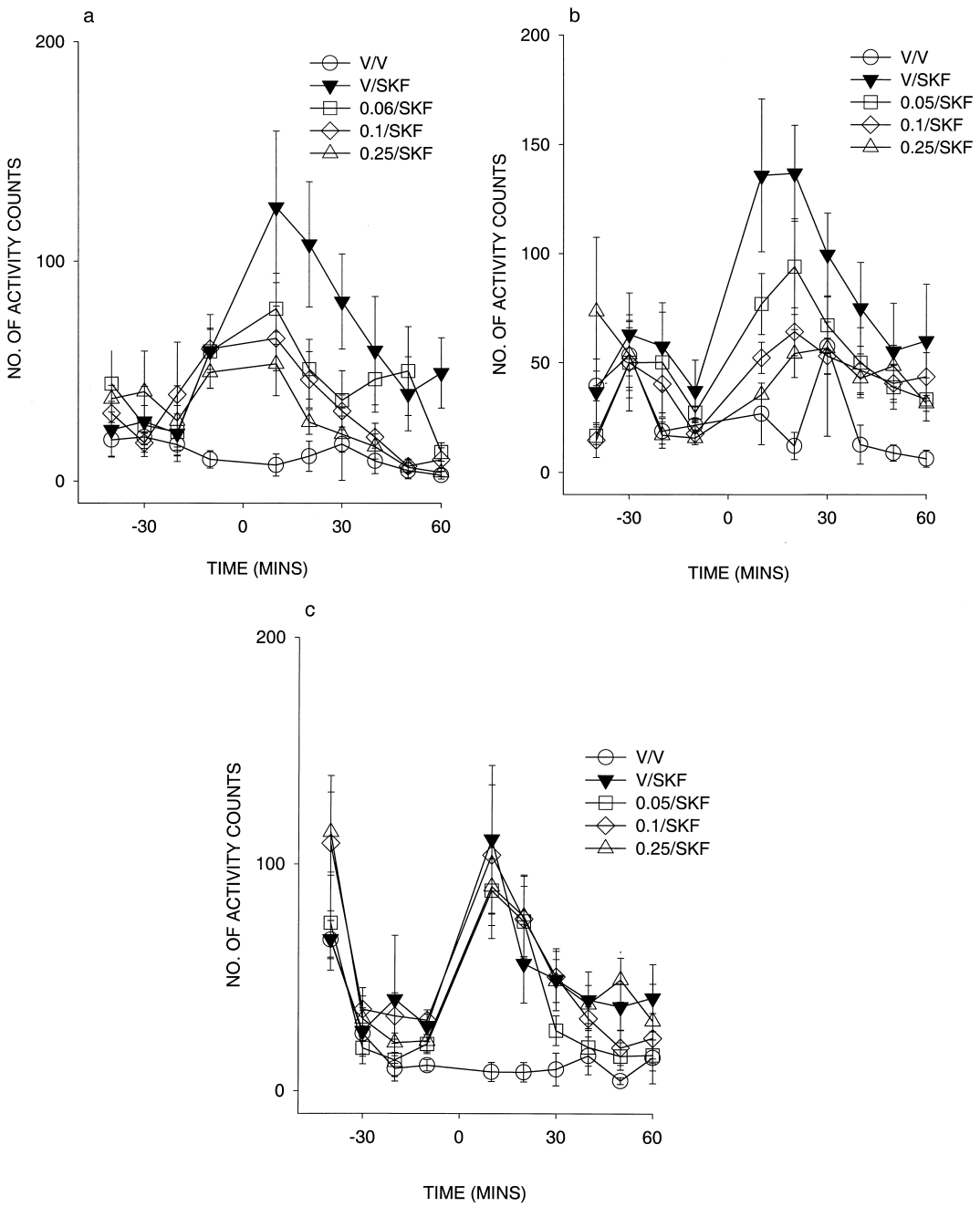

Fig. 2. Effect of serotonin antagonists on hyperactivity induced by SKF99101H in guinea pigs. *X*-axis shows the time after injection in minutes. *Y*-axis shows the mean number of photocell counts recorded. (a) Effect of GR127935 on SKF99101H-induced hyperactivity. ○ — Veh/Veh, ▼ — Veh/SKF (0.06 mg/kg/SKF), ◇ — 0.1/SKF, △ — 0.25 mg/kg. (b) Effect of WAY100635 on SKF99101H-induced hyperactivity. ○ — Veh/Veh, ▼ — Veh/SKF (0.05 mg/kg), ◇ — 0.01/SKF, △ — 0.025 mg/kg. (c) Effect of ritanserin vs. SKF99101H-induced hyperactivity. ○ — Veh/Veh, ▼ — Veh/SKF (0.05 mg/kg), ◇ — 0.1/SKF, △ — 0.25 mg/kg.

normal light cycle (from 0700 to 1900 h). Animals were allowed food and water ad libitum. Experiments were performed between 1000 and 1700 h. Each guinea pig was used once only. Animals were housed and all experiments were conducted in compliance with, and under, the guidance of UK Home Office Animals (Scientific Procedures) Act (1986).

2.2. Drugs

SCH23390 and raclopride (both RBI, Semat, UK) were dissolved in distilled water. Ritanserin (Janssen, Beerse, Belgium) was suspended in β-cyclodextrin (25%). SKF99101H, GR127935, and WAY100635 were all synthesized at Lilly Research Centre. GR127935 was dissolved in 20 μl of concentrated lactic acid and subsequently dissolved in distilled water. pH of solutions was readjusted to pH 4–5 using 1 M NaOH. The remaining compounds were dissolved in 25% β-cyclodextrin. All drugs were administered subcutaneously (s.c) in the scruff of the neck in a volume of 1 ml/kg.

2.3. Apparatus

Activity was measured in opaque Perspex cylinders 40 cm in diameter with three equally spaced photocells and a central light source. An activity count was measured when the animal moved between the light source and the detector photocell. The locomotor apparatus was connected to a BBC microcomputer, which simultaneously recorded activity.

2.4. Experimental procedures

Guinea pigs were individually placed into the apparatus for a 30-min habituation period. They were then removed from the apparatus and injected s.c. with the appropriate dose of test compound or vehicle ($n = 6$ per group). The animals were then immediately returned to the test apparatus, and their activity monitored for a further 60 min.

In the pretreatment studies, the guinea pigs were injected s.c. with pretreatment or vehicle control and were placed immediately in the photocell cages, where activity was measured for 30 min. When 30 min elapsed, they were then injected with the appropriate agonist or vehicle, and then returned to the activity cages and their activity was measured for 60 min.

2.5. Measurements and data analysis

The activity counts were accumulated into 10 min bins. Data from these bins were analysed by one-way ANOVA (SAS) for total activity over the test period and for each 10-min test bin. When the ANOVA was significant, the means were compared by a least square means (LSM) test to determine the significance of the differences observed.

3. Results

3.1. Effect of SKF99101H on locomotor activity

SKF99101H dose-dependently increased the number of photocell beam interrupts made by the guinea pigs [$F(3,25) = 33.34$, $p < 0.0001$]. For the 20 mg/kg treated animals, the peak in activity was seen at 10 min post injection (Fig. 1a). Post hoc LSM tests for significant ANOVAs for each individual time point showed that the highest dose tested (20 mg/kg) induced levels of activity significantly different from controls up to 30-min post injection. The minimum effective dose (min ED) for a significant elevation of activity, totalled over the entire 60-min test period, was 20 mg/kg (Fig. 1b). This dose was selected for use in all of the subsequent antagonist studies.

3.2. Effect of 5-HT receptor antagonist compounds on agonist-induced hyperactivity

The 5-$HT_{1B/D}$ receptor antagonist, GR127935 (0.06–0.25 mg/kg), dose-dependently reduced the increase in

Table 1
Effect of antagonist compounds on locomotor activation induced by SFF99010H. Data are means of total number of activity counts recorded over 60 min test period. Significant differences were calculated by LSM test following significant ANOVA
Veh — vehicle; SKF — SKF99101H.

GR127935	Activity	WAY100635	Activity	Ritanserin	Activity	SCH23390	Activity	Raclopride	Activity
Veh/Veh	52.3 ± 27	Veh/Veh	125 ± 56	Veh/Veh	61 ± 18	Veh/Veh	37 ± 12	Veh/Veh	31 ± 17
Veh/SKF	$462 \pm 130^{***}$	Veh/SKF	$462 \pm 130^{***}$	Veh/SKF	$334 \pm 83^{***}$	Veh/SKF	$332 \pm 125^{**}$	Veh/SKF	$252 \pm 92^{*}$
0.06/SKF	$276 \pm 66^{*}$	0.05/SKF	$361 \pm 49^{*,\dagger}$	0.05/SKF	$240 \pm 48^{***}$	0.005/SKF	$343 \pm 82^{**}$	0.25/SKF	$299 \pm 73^{**}$
0.1/SKF	$179 \pm 36^{\dagger\dagger}$	0.1/SKF	$301 \pm 45^{\dagger}$	0.1/SKF	$304 \pm 66^{**}$	0.01/SKF	154 ± 29	0.5/SKF	$305 \pm 90^{**}$
0.25/SKF	$127 \pm 23^{\dagger\dagger}$	0.25/SKF	$270 \pm 37^{\dagger\dagger}$	0.25/SKF	$333 \pm 56^{**}$	0.025/SKF	$93 \pm 23^{\dagger}$	1.0/SKF	$309 \pm 54^{**}$

Veh — vehicle; SKF — SKF99101H.
$^{*}P < 0.05$ vs. Veh/Veh groups.
$^{**}P < 0.01$ vs. Veh/Veh groups.
$^{***}P < 0.001$ vs. Veh/Veh groups.
$^{\dagger}P < 0.05$ vs. Veh/SKF groups.
$^{\dagger\dagger}P < 0.01$ vs. Veh/SKF groups.

activity induced by SKF99101H [$F(4,29) = 5.3$, $p < 0.005$]. Post hoc LSM test showed that the min ED was 0.1 mg/kg (Fig. 2a, Table 1).

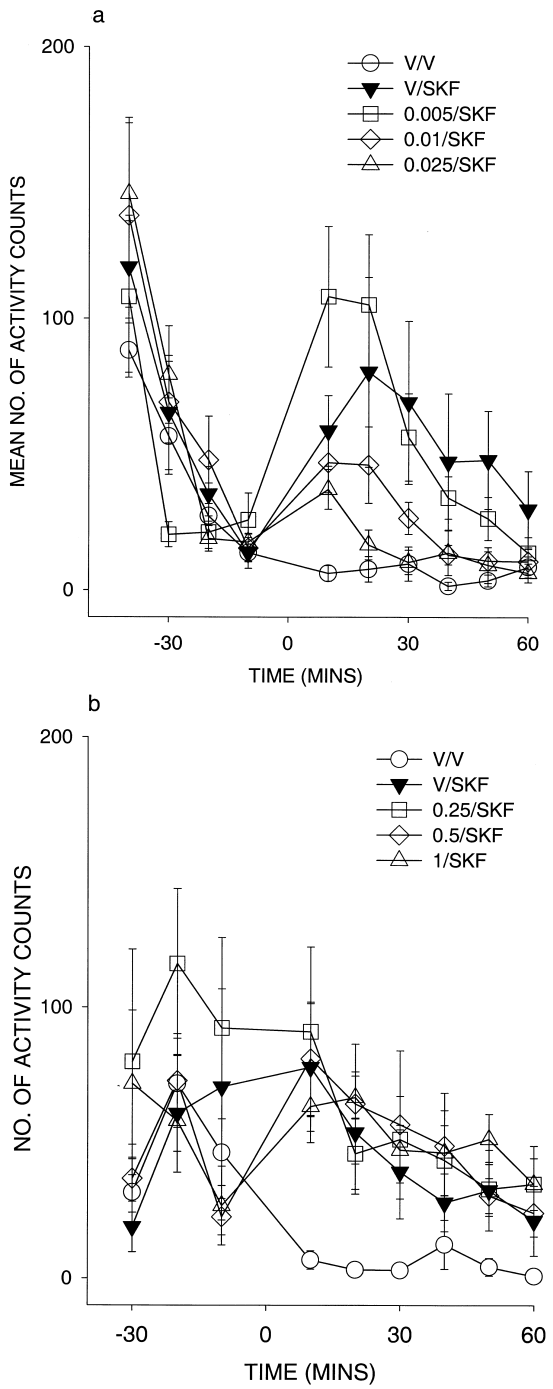

Fig. 3. Effect of dopamine receptor antagonists on hyperactivity induced by SKF99101H in guinea pigs. *X*-axis shows the time after injection in minutes. *Y*-axis shows the mean number of photocell counts recorded. (a) Effect of SCH23390 on SKF99101H-induced hyperactivity. ○ — Veh/Veh, ▼ — Veh/SKF (0.005 mg/kg), ◇ — 0.01/SKF, △ — 0.025 mg/kg. (b) Effect of raclopride on SKF99101H-induced hyperactivity. ○ — Veh/Veh, ▼ — Veh/SKF (0.25 mg/kg), ◇ — 0.5/SKF, △ — 1.0 mg/kg.

The 5-HT_{1A} receptor antagonist, WAY100635, dose-dependently reduced the hyperactivity induced by SKF99101H [$F(4,29) = 9.9$, $p < 0.0001$]. The min ED, as determined by the post hoc tests, was 0.1 mg/kg (Fig. 2b, Table 1).

The 5-HT_{2A} receptor antagonist ritanserin (0.05–0.25 mg/kg) had no effect on the hyperactivity induced by SKF99101H [$F(4,29) = 3.9$, $p < 0.05$] (Fig. 2c, Table 1).

3.3. Effect of dopamine receptor antagonist compounds on agonist-induced hyperactivity

The significant increase in locomotor activity induced by SKF99101H (20 mg/kg) [$F(4,29) = 4.08$, $p < 0.01$] was dose-dependently reduced by pretreatment with SCH23390 (0.005–0.025 mg/kg). The min ED was 0.01 mg/kg (Fig. 3a, Table 1). The selective D_2 dopamine receptor antagonist raclopride (0.25–1.0 mg/kg) had no significant effect on SKF99101H-induced hyperactivity [$F(4,29) = 2.8$, $p < 0.05$] (Fig. 3b, Table 1).

4. Discussion

The 5-$HT_{1B/D}$ receptor agonist, SKF99101H, induced a significant increase in locomotor activity in guinea pigs habituated to the test environment. The locomotor stimulant effect of a compound is most evident when baseline levels of activity are low. In this case, a 30-min habituation period was sufficient to reduce activity in untreated animals to minimal levels. The stimulatory effect of SKF99101H was significantly attenuated by GR127935 at doses in the same range that have previously been shown to reverse hypothermia induced by GR46611 (Skingle et al., 1995) and by SKF99101H (Hatcher et al., 1995), indicating that the locomotor activating effect of SKF99101H is also mediated by 5-$HT_{1B/D}$ receptors. GR46611 has previously been shown to have no effect on locomotor activity in guinea pigs when given alone (O'Neill and Sanger, 1999). One possible explanation of the discrepancy in the locomotor-inducing effects of SKF99101H and the lack of effect of GR46611 could be that the latter may not cross the blood-brain-barrier. However, it has been demonstrated that GR46611 (10 mg/kg s.c.) significantly reduced extracellular concentrations of 5-HT, as measured by in vivo microdialysis (Skingle et al., 1995; O'Neill et al., 1997a). This suggests that GR46611 clearly affect the central 5-HT function and that any difference in functional effects cannot be ascribed to differential penetration of the blood-brain-barrier.

SKF99101H shows no selectivity between 5-HT_{1B} and 5-HT_{1D} receptors (Hatcher et al., 1995). Neither does the antagonist compound, GR127935, distinguish between these subtypes. Thus, as yet, it is not possible to say which receptor subtype or subtypes may mediate the effects

described here. Further studies, with selective agents as they become available, will clarify this issue.

SKF99101H has some modest affinity for the 5-HT_{1A} receptor ($pK_i = 7.43$). This is approximately 10-fold less than its affinity for the various 5-$HT_{1B/D}$ receptors, where it had affinity ($pK_i = 8.7$) for human-type 5-HT_{1B} and 5-HT_{1D} receptors expressed in CHO cells (Hatcher et al., 1995). Although the doses of SKF99101H required to induce hyperactivity were large (20 mg/kg), this is also the range of doses required to lower the body temperature by a GR127935-sensitive mechanism (Hatcher et al., 1995).

The present study found that the hyperactivity induced by SKF99101H was also attenuated by the selective 5-HT_{1A} receptor antagonist, WAY100635. Although the min ED of the antagonist was greater than that previously required to block the effects of 1 mg/kg 8-OH-DPAT (0.1 vs. 0.006 mg/kg respectively), it is possible that part of the effect of SKF99101H may be due to activity at 5-HT_{1A} receptors (O'Neill and Sanger, 1999). The higher doses of WAY100635 that produced the significant attenuation of the SKF99101H-induced hyperlocomotion may also have reduced the tonic activation of 5-HT_{1A} receptors. Tonic activation of these receptors may be necessary for the full expression of the 5-$HT_{1B/D}$ receptor-mediated stimulation of locomotor activity. SKF99101H administration may also have reduced extracellular levels of 5-HT via its action on autoreceptors, further reducing tonic 5-HT_{1A} activity.

5-HT_{1A} and 5-HT_{1B} receptors interact synergistically to increase locomotor activity in rats. RU24969 is an agonist with equivalent activity at both 5HT_{1A} and 5-HT_{1B} receptors (Hoyer, 1991). RU24969-induced hyperactivity is attenuated by antagonists acting at both 5-HT_{1A} and 5-$HT_{1B/D}$ receptors (Kalkman, 1995; O'Neill and Parameswaran, 1997). Recently, studies in our laboratory have shown that GR46611 potentiates the effects on 8-OH-DPAT on locomotor activity, while having no effects on activity when given alone even at large doses (O'Neill and Sanger, 1999). It is therefore possible that the locomotor activation induced by SKF99101H requires joint stimulation of both 5-$HT_{1B/D}$ and 5-HT_{1A} receptors. The lack of an intrinsic locomotor effect of GR46611 may reflect a lack of functional activity at 5-HT_{1A} receptors in vivo, although it has been reported to have affinity for these receptors in vitro (Skingle et al., 1994).

The hyperactivity induced by SKF99101H is not altered by ritanserin, The 5-HT_{2A} receptor antagonist had no effect when given prior to SKF99101H treatment. The doses of ritanserin used in the current study have previously been shown to significantly attenuate hyperthermia caused by administration of the 5-HT_{2A} receptor agonist DOI in guinea pigs (Moore, personal communication). This suggests that the doses used were sufficient to achieve a significant blockade of 5-HT_{2A} receptors in vivo in guinea pigs. It is therefore unlikely that these receptors play any role in the mediation of the effects of SKF99101H observed in this study. Ritanserin and the more selective 5-HT_{2A} receptor antagonist, MDL100907, reduced the locomotor response to indirectly acting stimulants, such as amphetamine and cocaine in mice (Gleason and Shannon, 1997; O'Neill et al., 1999), but not the locomotor hyperactivity induced by a directly acting dopamine D_1 receptor agonist C-APB (O'Neill et al., 1999). This suggests that in the mouse, 5-HT_{2A} receptors can act presynaptically to modulate synaptic concentrations of dopamine, but do not modulate the sensitivity of post-synaptic dopamine receptors. In guinea pig, ritanserin had no effect on the locomotor response to SKF99101H in this study. This would suggest that 5-HT_{2A} receptors do not mediate SKF99101H-induced behavioural effects via any direct effect of the agonist on 5HT_{2A} receptors nor have they any indirect modulatory effect on systems downstream of the action on 5-$HT_{1B/D}$ receptors.

The high levels of 5-$HT_{1B/D}$ receptor, binding in the basal ganglia as stated in Section 1, suggest a role for these receptors in the control of movement (Bruinvels et al., 1993). 5-$HT_{1B/D}$ receptors are primarily located on axon terminals, as evidenced by the differential location of 5-$HT_{1B/D}$ binding sites and 5-$HT_{1B/D}$ mRNAs in these areas (Maroteaux et al., 1992). 5,7-DHT lesions did not attenuate RU24969-induced locomotor activity in the mouse (Cheetham and Heal, 1993) suggesting that the 5-HT_{1B} receptors mediating this response were not located on 5-HT axon terminals. This suggests that 5-$HT_{1B/D}$ receptor agonists may increase locomotor activity via modulating the release of transmitters other than 5-HT.

The blockade of the stimulant effect of SKF99101H by the selective dopamine D_1 receptor antagonist SCH23390, but not the D_2 receptor antagonist raclopride, implicates D_1 dopaminergic mechanisms in the mediation of this response. This parallels the finding that SCH23390 blocked the locomotor response to RU24969 in mice (Cheetham and Heal, 1993). 5-HT, locally applied to the nucleus accumbens, results in an increase in extracellular levels of dopamine in guinea pigs (Hallbus et al, 1997). This effect was markedly attenuated by GR127935, indicating that 5-$HT_{1B/D}$ receptors were involved in the mediation of this effect. Interestingly, the more 5-$HT_{1B/D}$ selective receptor agonist sumatriptan had no effect when given alone, suggesting that activation of these receptors was only insufficient to induce the increase in extracellular dopamine. It is possible, therefore, that the activation of other 5-HT receptor subtypes, such as 5-HT_{1A} receptors, was also necessary for the induction of increased extracellular dopamine and the consequent induction of locomotor activity in guinea pigs.

Further studies to elucidate the interaction with other neuronal systems will increase our understanding of this area and possibly indicate the therapeutic relevance of these findings to conditions involving an impairment of motor control, such as Parkinson's Disease or Huntingdon's Chorea.

In conclusion, SKF99101H increases locomotor activity in guinea pigs, an effect which is reversed by the selective 5-$HT_{1B/D}$ antagonist GR127935. The hyperactivity induced by SKF99101H is also partly attenuated by WAY100635, although at doses considerably higher than those previously required to block 8-OH-DPAT-induced hyperactivity. This may implicate receptors other than 5-HT_{1A} in the mediation of WAY100635, or may imply that these high doses reduce a tonic level of activation at 5-HT_{1A} receptors necessary for the full expression of the locomotor response to SKF99101H.

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