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GR 127935 Blocks the Locomotor and Antidepressant-Like Effects of RU 24969 and the Action of Antidepressants in the Mouse Tail Suspension Test

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O'NEILL, M. F., A. G. FERNÁNDEZ AND J. M. PALACIOS. *GR 127935 blocks the locomotor and antidepressant-like effects of RU 24969 and the action of antidepressants in the mouse tail suspension test.* PHARMACOL BIOCHEM BEHAV 53(3) 535–539, 1996. – The 5-$HT_{1A/B}$ agonist RU 24969 induces hyperactivity in rodents and also shows antidepressant-like effects in some animal models of depression. We have examined the effects of selective antagonists at 5-HT_{1A} and 5-$HT_{1B/D}$ receptors (WAY 100135 and GR 127935, respectively) on both the hyperlocomotor and anti-immobility effects of RU 24969. While a high dose of WAY 100135 (10 mg/kg) had no effect in either paradigm, GR 127935 attenuated the behavioural effects of RU 24969 in both. WAY 100135 was also without effect on the antidepressant effect of paroxetine, while GR 127935 blocked the effects of paroxetine (1 mg/kg) and imipramine (10 mg/kg). Furthermore, while coadministration of paroxetine or imipramine enhanced the effects of RU 24969 in the mouse tail suspension test, imipramine had no effect on the locomotor activating effects of the 5-HT_{1B} agonist, suggesting different neural substrates may underly the effects in the different tests. These studies indicate a role for the 5-$HT_{1B/D}$ receptor in the mediation of the effects of antidepressant treatment.

5-$HT_{1B/D}$ RU 24969 GR 127935 Depression Locomotor activity

THERE is a considerable body of evidence implicating serotonergic mechanisms in the amelioration of depressive symptoms in humans. Drugs that are effective as antidepressants increase the availability of serotonin (5-HT) either by preventing its enzymatic breakdown, as in the case of monoamine oxidase inhibitors (MAOIs), or by preventing its reuptake as in the case of the selective inhibitors of 5-HT reuptake (SSRI) (e.g., Ref. 2). It remains to be determined via which, of the many 5-HT receptor subtypes thus far identified (see Ref. 15 for review), the elevated levels of 5-HT exert their clinically beneficial effects. This study set out to examine the role of one subtype, the 5-$HT_{1B/D}$ receptor, in the mediation of antidepressant-like effects in an animal model of depression, the mouse tail suspension test.

The 5-HT_{1B} and 5-HT_{1D} receptors are closely related at the molecular, pharmacological, and signal transduction mechanism levels. The two receptors are believed to represent species variants of the same receptor subfamily. Thus, the 5-HT_{1B} receptor is believed to be the analog in rats and mice of the 5-HT_{1D} human receptor (13). It is primarily located on presynaptic terminals (3,29) and is believed to function as a terminal autoreceptor modulating 5-HT release (7,19,20) or as a heteroreceptor on nonserotonergic terminals modulating release of other transmitters such as dopamine (10). It differs in its cellular distribution from the 5-HT_{1A} receptor, which is primarily located on the cell bodies of the serotonergic neuron (28).

In every species examined to date, 5-$HT_{1B/D}$ binding sites have been shown to be most abundant in the basal ganglia (caudate nucleus, globus pallidus, and the substantia nigra pars reticulata) (3,29). These sites are thought to be primarily involved in the control of motor activity (17).

The 5-HT_{1B} agonist RU 24969 reduces immobility in the forced swim test in rats (5) and has shown antidepressant-like activity in a learned helplessness paradigm in rats (18). Anpir-

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toline, another 5-HT_{1B} agonist, reduces isolation-induced social deficit (24), believed to reflect antidepressant activity (9). However, it has also been shown that 5-HT_{1B} agonists increase locomotor activity. RU 24969 induces a characteristic hyperactivity in rats (11). The locomotor-stimulant effect in mice was reduced by the nonspecific 5-HT_1 antagonist propranolol (6).

Psychostimulant or locomotor-activating compounds can show positive effects in antidepressant tests such as the tail suspension test by virtue of a direct effect on activity (22,30). Thus, it is of considerable interest to establish whether it is possible to dissociate the effects of RU 24969 in the different paradigms. It has been suggested by Green et al. (12) and later corroborated by Rempel et al. (23) that the locomotor stimulant actions of RU 24969 are not significantly altered by coadministration with antidepressants. To our knowledge this possible synergism, or lack of it, has not been investigated in depression models in animals.

As RU 24969 has almost equal affinity at 5-HT_{1A} and 5-HT_{1B} receptors (14), and has shown behavioural effects consistent with activation of both 5-HT_{1A} and 5-HT_{1B} receptors (27), any antidepressant-like effects of RU 24969 could also implicate receptors of the 5-HT_{1A} subtype. This is especially important as 5-HT_{1A} agonists have shown antidepressant activity in a number of tests (see Ref. 16 for review). To investigate the possible role of 5-HT_{1A} receptors in the mediation of antidepressant-like actions of RU 24969 in the mouse tail suspension test, we examined the effects of pretreatment with WAY 100135. WAY 100135 has been described as a "silent" antagonist at the 5-HT_{1A} receptor; while it is devoid of any intrinsic activity, it decreases cell firing in the raphe and 5-HT release as measured by in vivo dialysis (8). It has previously been used to demonstrate the lack of involvement of 5-HT_{1A} receptors in the mediation of RU 24969-induced hyperactivity (6).

GR 127935 is a potent antagonist of 5-HT_{1D} receptor (25) with almost equal affinity for 5-HT_{1B} receptors (26). It presents an opportunity, therefore, to directly examine the role of these receptors in the mediation of the behavioural effects of RU 24969. In addition to the aims already described, these studies also set out to examine whether the recently described 5-HT_{1A} or 5-HT_{1D} antagonists revealed antidepressant-like effects in an animal model of depression, the mouse tail suspension test (22), and to examine the effects of these compounds on the previously described effects of clinically effective antidepressive agents.

METHODS

Animals

Male Swiss mice, 20–25 g, (Interfauna, Spain) were housed in groups of 25 under standard conditions with normal light cycle (light 7:00 a.m. to 7:00 p.m.) prior to use in the tail suspension test.

In the experiments involving locomotor activity, male BKTO mice, 20–25 g, (Bantin and Kingman, UK) housed in the same conditions as outlined above, were used. All experiments were of an independent design and each mouse was used once only.

The different strains were selected on the basis of their differing baseline levels of activity in preliminary studies. The BKTO mice are more active and show a more consistent response to stimulant compounds, while the less active Swiss mice showed more consistent responses in the TST.

Drugs

Imipramine, CGS 120066 (both RBI), and RU 24969 (kindly donated by Roussel Uclaf, France) were dissolved in physiological saline. WAY 100135, paroxetine, and GR 127935 (synthesized in the medicinal chemistry department of Laboratorios Almirall) were suspended in a vehicle composed of 0.5% methylcellulose and 0.1% Tween-80 in distilled water. All drugs were administered subcutaneously in the scruff of the neck in a volume of 10 ml/kg.

Equipment

Activity of mice in 1 m diameter open field (OF), illuminated by a single 10 W fluorescent bulb, was monitored via video linked to a SMART image analysis system (Letica, Spain), which recorded distance covered and number of entries into the central area of the arena. The tail suspension test (TST) was performed using the Itematic tail suspension test meter (Itemlabo, France).

Experimental Procedures

Open field. The mice received an SC injection of RU 24969 and were returned to their home cages for 45 min. When the pretreatment time had elapsed the animals were placed in the centre of the open field and their activity was monitored for 5 min.

In antagonism studies the animals first received the pretreatment followed 30 min later by RU 24969. Following a further 45 min interval the animals were placed in the open field and their activity was recorded for 5 min.

Tail suspension test. Where the effect of a single drug was examined the animals were first injected SC and returned to the home cage for 30 min before being suspended by the tail in the tail suspension apparatus (TST). Where a pretreatment

TABLE 1

EFFECTS OF GR 127935, CGS 12066 AND IMIPRAMINE ON RU 24969 INDUCED HYPERACTIVITY OF MICE IN THE OPEN FIELD

Treatment	Dose (mg/kg)	*n*	Distance (cm)	
Saline		6	5936 ± 571	
RU 24969	0.3	6	6748 ± 321	NS
	1	6	8091 ± 374	*
	3	6	9948 ± 545	***
Veh + Saline		10	4731 ± 406	
Veh + RU (1 mg/kg)		10	6632 ± 331	*
GR127935 + RU	0.03	10	5756 ± 324	NS
	0.3	10	5047 ± 530	NS
	3	10	4141 ± 383	NS
Veh + Saline		13	4003 ± 339	
Veh + RU (1 mg/kg)		13	6748 ± 408	***
CGS 12066 + RU	1	8	6001 ± 470	*
	3	8	5649 ± 464	NS
	10	8	5984 ± 412	*
Sal + Sal		9	4958 ± 368	
Sal + RU (1 mg/kg)		9	6963 ± 475	*
Imipramine + RU	1	10	6650 ± 477	*
	3	10	6888 ± 412	*
	10	9	6234 ± 350	NS

Data are mean distances travelled (cms) ± SEM. Differences vs. appropriate control *$p < 0.05$, ***$p < 0.001$, vs. vehicle/RU 24969 + $p < 0.05$, + +$p < 0.01$, NS not significant vs. vehicle control, calculated by Bonferroni test following significant one-way ANOVA.

TABLE 2

EFFECTS OF RU 24969, GR 127935, WAY 100135 AND CGS 12066 ON THE TAIL SUSPENSION TEST IN MICE

Treatment	Dose (mg/kg)	n	Immobility (s)	
Saline		8	148.6 ± 16.4	
RU 24969	0.30	7	132.6 ± 21.6	NS
	1.00	8	109.6 ± 15.6	NS
	3.00	7	65.6 ± 17.5	*
Saline		8	113.9 ± 20.1	
WAY 100135	0.003	8	115.5 ± 17.6	NS
	0.03	8	145.5 ± 16.5	NS
	0.30	8	114.4 ± 33.7	NS
	3.00	8	119.3 ± 16.0	NS
Saline		8	122.5 ± 10.7	
GR 127935	0.10	8	168.6 ± 24.1	NS
	1.00	8	145.8 ± 17.5	NS
	10.00	8	177.4 ± 14.9	NS
Vehicle		8	112.9 ± 17.1	
CGS 12066	0.30	8	134.5 ± 20.8	NS
	1.00	8	129.5 ± 17.2	NS
	3.00	8	143.1 ± 20.6	NS
	10.00	8	123.5 ± 14.9	NS

Data are mean times spent immobile in seconds (s) ± SEM. Difference vs. appropriate control *$p < 0.05$, NS not significant, calculated by Bonferroni test following significant ANOVA.

was used the animals were injected with the appropriate drug or vehicle and returned to the home cage for 30 min before receiving the second treatment. Thirty minutes later, the mice were suspended by the tail for 6 min in the TST. The TST monitored time spent immobile, energy, and power of movements made.

Data analysis. The locomotor activity counts and the tail suspension data were analysed by a one-way ANOVA and subsequently submitted to post hoc analysis by a *t*-test with Bonferroni adjustment for multiple comparisons.

RESULTS

Effects of GR 127935, WAY 100135, CGS 12066, and Imipramine Pretreatment on RU 24969-Induced Hyperactivity

RU 24969 dose-dependently increased the distance travelled in the OF. The minimum effective dose was (1 mg/kg) and therefore this dose was selected for use in subsequent antagonism studies. The stimulant effect of RU 24969 was significantly reduced by 0.3 mg/kg of GR 127935 but not by the lower dose of 0.03 mg/kg, indicating a dose-dependent reversal (Table 1). Although in some studies the number of entries to the centre of the OF was altered by RU 24969, this did not occur in a consistent manner and only the distance covered by the animals was considered for analysis. CGS 12066 reduced, although not dose-dependently, the effect of RU 24969 (Table 1). GR 127935 alone had no effect on locomotor activity at any of the doses tested (data not shown).

Imipramine (1,3 mg/kg) failed to alter the pattern of behaviour induced by a submaximal dose of RU 24969 (1 mg/kg) in the mouse in the OF (Table 1). The highest dose of 10 mg/kg appeared to slightly but significantly reduce the locomotor stimulant effect of RU 24969.

Effects of Selective 5-HT$_{1B}$ and 5-HT$_{1A}$ Ligands on Antidepressant Activity in the Mouse Tail Suspension Test

RU 24969 (minimum effective dose: 3 mg/kg) decreased time spent immobile in the TST in a dose-dependent manner (Table 2). GR 127935 alone slightly raised the time spent immobile but failed to significantly alter the behaviour of mice in this test (Table 2). WAY 100135 and CGS 12066 were likewise without effect when given alone (Table 2).

The anti-immobility effect of RU 24969 is completely reversed by GR 127935 at 10 mg/kg (Table 3). The 5-HT$_{1A}$ antagonist WAY 100135, up to a dose of 10 mg/kg, did not significantly alter the effect of RU 24969 (Table 3). The 5-HT$_{1B}$ partial agonist CGS 12066 (10 mg/kg) reduced the effect of RU 24969 in this test (Table 3) but did not cause a significant reversal.

The decrease in immobility caused by imipramine (10 mg/kg) was blocked by GR 127935 at all doses tested, but a higher dose of imipramine (30 mg/kg), was not significantly altered by treatment with GR 127935, showing that the blockade was overcome with higher doses of the antidepressant. The reduction in immobility induced by the selective serotonin reuptake inhibitor (SSRI), paroxetine (1 mg/kg), was reversed by a dose of 10 mg/kg of GR 127935, but not by WAY 100135 over the same dose range (Table 4).

A subthreshold dose of imipramine (3 mg/kg), which when administered alone had no effect, induced a significant decrease in immobility in the mouse tail suspension test when the subjects were pretreated with 1 mg/kg of RU 24969 (Table 5). Furthermore, pretreatment with subthreshold doses of RU 24969 also had an additive effect with an submaximal doses of imipramine (10 mg/kg).

TABLE 3

EFFECTS OF GR 127935, WAY 100135, AND CGS 12066 ON RU 24969 (3 MG/KG) EFFECT ON THE TAIL SUSPENSION TEST IN MICE

Treatment	Dose (mg/kg)	n	Immobility (s)	
Saline + Saline		8	139.2 ± 16.7	
Saline + RU 24969		8	51.6 ± 6.6	*
GR 127935 + RU	0.1	8	52.0 ± 15.7	**
	1.0	8	59.7 ± 15.0	*
	10.0	8	125.3 ± 19.6	
Vehicle + Saline		16	132.6 ± 14.2	
Vehicle + RU		13	37.3 ± 14.2	***
WAY 100135 + RU	0.1	13	54.5 ± 4.8	***
	1.0	15	75.5 ± 13.3	**
	10.0	14	56.9 ± 12.5	***
Vehicle + Saline		8	166.6 ± 20.0	
Vehicle + RU		8	53.9 ± 9.7	**
CGS 12066 + RU	0.1	8	37.1 ± 11.3	***
	1.0	8	67.0 ± 22.5	**
	10.0	8	97.5 ± 18.7	NS

Data shown are mean times spent immobile in seconds (s) ± SEM. Difference vs. appropriate control *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; vs. vehicle/RU group +$p < 0.05$, NS not significant, calculated by Bonferroni test following significant one-way ANOVA.

TABLE 4

EFFECTS OF GR 127935 ON THE ACTION OF IMIPRAMINE AND PAROXETINE, AND THE WAY 100135 ON PAROXETINE IN THE MOUSE TAIL SUSPENSION TEST

Treatment	Dose (mg/kg)	n	Immobility (s)	
Saline + Saline		15	155.1 ± 9.5	
Saline + Imipramine (10)		6	86.5 ± 10.7	*
GR 127935	0.10	7	155.7 ± 11.6	NS
+	1.00	8	133.2 ± 16.9	NS
Imipramine (10)	10.00	8	140.3 ± 27.0	NS
Saline + Imipramine (30)		16	76.2 ± 9.0	***
GR 127935	0.10	16	90.0 ± 10.7	**
+	1.00	16	87.9 ± 12.2	**
Imipramine (30)	10.00	16	68.3 ± 7.9	***
Saline + Saline		8	133.0 ± 10.3	
Saline + Paroxetine (1)		8	67.4 ± 15.6	*
GR127935	0.10	8	67.6 ± 10.4	*
+	1.00	8	66.9 ± 12.0	*
Paroxetine (1)	10.00	8	146.8 ± 14.9	
Saline + Saline		8	179.8 ± 15.9	
Saline + Paroxetine (1)		8	104.3 ± 19.0	*
WAY 100135	0.10	8	101 ± 11.8	*
+	1.00	8	102.9 ± 23.0	*
Paroxetine (1)	10.00	8	73.8 ± 12.4	**

Data shown are mean times spent immobile in seconds (s) ± SEM. Difference vs. saline/saline group *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ NS not significant; vs. saline/paroxetine group + +$p < 0.01$, calculated by Bonferroni test following significant one-way ANOVA.

DISCUSSION

RU 24969 (1 mg/kg) increased the distance travelled in the OF apparatus. The stimulant effect of RU 24969 was blocked by GR 127935 at a dose of 0.3 mg/kg. These results indicate that GR 127935 is a functional antagonist for the 5-HT_{1B} receptor, without intrinsic activity, as it has no effect on locomotor activity alone. In contrast to previous findings (6), another 5-HT_{1B} agonist, CGS 12066 (21), did not have a significant effect on RU 24969-induced hyperactivity as measured in the OF. This may simply have been due to the fact that lower doses were used than in the previous study.

RU 24969 showed antidepressant-like activity in reducing immobility in the mouse TST. It is possible that the effects of RU 24969 in antidepressant tests are simply due to its powerful locomotor stimulant effects. The dose of RU 24969 required to reduce immobility was higher than that required to increase activity in the open field (3 mg/kg and 1 mg/kg, respectively). This would seem to implicate the locomotor-activating effects of RU 24969 in the mediation of the anti-immobility effects in the TST. However, evidence for a dissociation of the locomotor and antidepressant effects of RU 24969 comes from the finding that RU 24969 has an additive effect with antidepressive treatments in the TST, while no such interaction has been shown for pretreatment with antidepressants with the motor effects of RU 24969 (12,23; and present data). This suggests that activity in the two tests may be differentially mediated.

The antidepressant-like action of RU 24969 was also significantly attenuated by CGS 12066 (10.0 mg/kg). It has previously been shown that CGS 12066 reduced the ability of serotonin reuptake inhibitors to reverse escape deficits in a learned helplessness model of depression (18). The authors suggested that the partial agonist antagonized the action at 5-HT_{1B} receptors of the serotonin, whose synaptic levels had been increased by the reuptake inhibitors. This would also explain why the antidepressant-like effects of RU 24969 were blocked by pretreatment with CGS 12066.

The present results suggest that 5-$HT_{1B/D}$ receptors play a role in the mediation of the antidepressant effects of not only RU 24969 but also in the effects of antidepressants such as imipramine and paroxetine. The decrease in immobility induced by all three treatments was reversed by pretreatment with GR 127935. The dose required to reverse the antidepressant effect of RU 24969 and paroxetine was high (10 mg/kg), higher than that which reversed the locomotor activating effects of RU 24969 (0.3 mg/kg). However, this range of doses of GR 127935 (up to 10 mg/kg) has been shown not to affect head twitches induced by 5-HT agonists in the guinea pig (25), suggesting some degree of selectivity for 5-$HT_{1B/D}$ receptor even at relatively high doses. Further studies are required to characterize this compound as a 5-HT_{1B} antagonist in vivo before any definitive conclusion can be made.

RU 24969 also has appreciable affinity for the 5-HT_{1A} receptor (pEC50 = 8.2; Ref. 14) In the experiments presented here we have shown that WAY 100135 has no effect on antidepressant effects of RU 24969, indicating that the antidepressant-like actions of RU 24969 are unlikely to be related to its activity at 5-HT_{1A} receptors. Cheetham and Heal (6) have previously shown that the locomotor effects of RU 24969 were similarly unaffected by pretreatment with WAY 100135.

Moreover, in contrast to the effects of GR 127935, the 5-HT_{1A} antagonist WAY 100135 had no effect on the behavioural effect of paroxetine in the mouse TST even at doses as high as 10 mg/kg. This indicates that the 5-HT_{1A} receptor may not be involved in the mediation of the behavioural effects of acute administration of paroxetine.

It has been suggested that compounds that presynaptically modulate 5-HT release acting via 5-HT_{1A} or 5-HT_{1D} receptors could have antidepressant properties (1,4). These studies have shown that blockade of the 5-HT_{1B} receptor reduces the antidepressant-like effects of compounds from various classes, whereas 5-HT_{1A} receptor blockade has no such effect. This

TABLE 5

COMBINED EFFECTS OF RU 24969 AND IMIPRAMINE IN THE MOUSE TAIL SUSPENSION TEST

Treatment	Dose (mg/kg)	n	Immobility (s)	
Saline + Saline		8	130.4 ± 20.1	
Saline + Imipramine (3)		8	124.8 ± 15.2	NS
RU 24969	0.10	8	91.0 ± 19.1	NS
+	0.30	8	76.8 ± 11.6	NS
Imipramine (3)	1.00	8	58.6 ± 11.6	*+
Saline + Saline		8	153.8 ± 19.3	
Saline + Imipramine (10)		8	98.5 ± 15.6	NS
RU 24969	0.30	8	78.5 ± 19.2	*
+	1.00	7	38.7 ± 9.4	***
Imipramine (10)	3.00	7	49.1 ± 8.3	***

Data shown are mean times spent immobile in seconds (s) ± SEM. Difference vs. saline/saline group *$p < 0.05$, ***$p < 0.001$; vs. vehicle/RU group +$p < 0.05$, NS not significant, calculated by Bonferroni test following significant one-way ANOVA.

may suggest a role for 5-$HT_{1B/D}$ receptor agonism in the action of antidepressants.

In summary, RU 24969 shows antidepressant-like activity in the tail suspension test and induces hyperactivity in mice. Both effects are blocked by GR 127935, indicating that this compound can serve as a functional 5-HT_{1B} antagonist. The fact that the antidepressant-like and locomotor activating effects were not blocked by WAY 100135 means it is unlikely that the 5-HT_{1A} receptor is involved in the mediation of these effects. It still remains to be determined to what extent to antidepressant-like action of RU 24969 is due to its locomotor stimulant properties. Further testing in a model of depression not so dependent on locomotor behaviours would provide a more definitive answer. Finally, the finding that GR 127935 attenuated the antidepressant effects of imipramine and paroxetine suggests that the 5-$HT_{1B/D}$ receptor may be involved in the mediation of their effects in the TST, although further studies are required to establish the specificity of this effect.

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