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Role of 5-HT_{1A} and 5-HT_{1B} Receptors in the Mediation of Behavior in the Forced Swim Test in Mice

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The purpose of this study was to further examine the effect of activation of 5-HT_{1A} and 5-HT_{1B} receptors in the forced swim test in mice and to determine if activation of these receptors played a role in the mediation of the effects of the tricyclic antidepressant imipramine. The 5-HT_{1A} agonist 8-OH-DPAT decreased immobility in the forced swim test in mice as previously described. Both the selective 5-HT_{1B} agonist anpirtoline (1.25–5 mg/kg) and mixed 5-$HT_{1A/B}$ agonist RU24969 (0.6–2.5 mg/kg) significantly increased time spent swimming in the FST.

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KEY WORDS: *5-HT_{1A} receptors; 5-HT_{1B} receptors; Anpirtoline; Isamoltane; Forced swim test; Mouse*

WAY100635 (0.1–0.5 mg/kg) reversed the effect of 8-OH-DPAT over a dose range that did not alter swimming when given alone. The effect of anpirtoline (1.25 mg/kg) was reversed by GR127935 (1.25 mg/kg) and isamoltane (2.5–5 mg/kg) but not by WAY100635 (0.1–0.5 mg/kg). The effect of the mixed agonist RU24969 (0.6 mg/kg) was also reversed by GR127935 (1.25–2.5 mg/kg) and isamoltane (1–5 mg/kg), but not by WAY100635 (0.1–0.5 mg/kg).

The effect of imipramine (5 mg/kg) was significantly reversed by GR127935 (1.25 mg/kg) and isamoltane (5 mg/kg) while WAY100635 (0.1–0.5 mg/kg) was without effect.

These results confirm previous findings that direct stimulation of either 5-HT_{1A} or 5-HT_{1B} receptors induces antidepressant-like effects in the FST. This study further suggests that the effects of RU24969 and imipramine in the forced swim test are mediated by 5-HT_{1B} rather than 5-HT_{1A} receptors. These findings confirm previous findings that blockade of 5-HT_{1B} receptors attenuates the anti-immobility effects of imipramine in "behavioral despair"–type tests suggesting that activity at these receptors may be an important mediator of its behavioral effects in this test.

INTRODUCTION

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine have been shown to be of major benefit in the treatment of depression. The mechanism by which the elevation of synaptic concentrations of 5-HT alleviates the symptoms of depression is not known, but activation of postsynaptic 5-HT receptors would appear to be an obvious factor. 5-HT-$_{1A}$ receptors are located pre- and post-synaptically and there is evidence to suggest that they are also involved in the mediation of antidepressant-like responding in behavioural tests (Wieland and Lucki 1990; Detke et al. 1995). Singh and Lucki (1993) also showed that agonist efficacy at 5-HT_{1A} receptors correlated with the ability of compounds to reduced immobility in the FST in rats. 8-OH-DPAT also showed an-

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tidepressant-like effects in the mouse version of this test (Luscombe et al. 1993). Furthermore, destruction of 5-HT terminal with 5,7,-DHT did not alter the response to 8-OHDPAT in the FST, suggesting that post-synaptic 5-HT_{1A} receptors not affected by the neurotoxin mediate this response (Luscombe et al. 1993).

Like 5-HT_{1A} receptors, 5-HT_{1B} receptors are located both pre- and post-synaptically (Maroteaux et al. 1992) and may also have a role in the mediation of antidepressant-like effects in behavioral tests in animals. The non-selective 5-$HT_{1A/B}$ agonist RU24969 decreased immobility in the forced swim test in mice (Cheetham and Heal 1993) and in the tail suspension test, also in mice (O'Neill et al. 1996), a test similar to the FST (Porsolt et al. 1978). The effects of RU24969 were blocked by pretreatment with GR127935 but not by WAY100135 suggesting that the effects induced by this compound are mediated via 5-HT_{1B} rather than by 5-HT_{1A} receptors (O'Neill et al. 1996). O'Neill et al. (1996) found that GR127935 reversed the antidepressant-like action of imipramine and paroxetine in the tail suspension test. This suggested that 5-HT_{1B} receptors were also involved in the mediation of the behavioral effects of the antidepressant compounds in this test.

To help to clarify the effect of 5-HT_{1B} receptor stimulation in the FST we set out to examine the effects of a more selective 5-HT_{1B} agonist anpirtoline (Schlicker et al. 1992). We also tested the effects of the 5-HT_{1B} selective antagonist isamoltane (Waldmeier et al. 1988) against both RU24969 and anpirtoline to evaluate its in vivo profile as a 5-HT_{1B} antagonist. To determine the potential role of 5-HT_{1B} receptors in the mediation of the effects of clinically efficacious antidepressants we also examined the effect GR127935 (Skingle et al. 1995) and isamoltane on the response to imipramine in the FST.

METHODS

Subjects

Female BKTO (Bantin and Kingman, Hull, UK) were housed in groups of 15. Animals were kept in the holding facility for three weeks after arrival before experimental use. Animals were 25–35 g at time of use.

Apparatus

Immobility was measured in 11 beakers with 600 ml of water (23°C), that is, 10 cm deep. Time spent immobile was measured with a stopwatch.

Drugs

GR127935 (synthesised at Eli Lilly) was dissolved in a few drops of acid (lactic) and then filled to the correct volume in distilled water. 8-OH-DPAT (RBI), WAY 100635, RU24969 (both synthesised at Eli Lilly), and anpirtoline (Tocris Cookson) were dissolved in distilled water. Isamoltane (Tocris Cookson) was made up in β-cyclodextrin. All compounds were injected subcutaneously (sc) in a volume of 10ml/kg. Drug treatment bottles were coded so that the observer was unaware of the treatment the animals had received. A positive control of imipramine (10 mg/kg) was included in all dose response studies.

Procedure

Animals were removed from their home cages and placed in individual holding cages (10 × 15 × 13 cm) for at least 60 min prior to the beginning of the experiment.

Mice were dosed with the test compound and then returned to the holding cages for 30 min. When the 30 min pretreatment time had elapsed, the animals were placed in the beakers and the time spent immobile was recorded.

Where drug interactions were being examined, the animals received their first treatment and were then returned to the holding cages for 30 min. When this time had elapsed the animals received the second treatment and were then returned to the holding cages for a further 30 min before being tested.

The animals were placed in the beakers and activity recorded for 5 min. Immobility was measured only for the last 4 min as all animals swam for the first minute irrespective of treatment. Each group was made up of a minimum of 6 subjects.

Data Analysis

Data were analyzed by ANOVA and significant differences were determined by the Least Square Means test for post hoc analysis using SAS programs using the GLM procedure.

RESULTS

The 5-HT_{1A} receptor agonist 8-OH-DPAT significantly attenuates immobility in the FST [$F(4,35) = 16.3$, $p < .001$]. The effect is not significant at the highest dose tested as the compound begins to affect motor co-ordination at this dose (Table 1). The highest efficacious dose 0.5 mg/kg was used in the subsequent antagonism studies. The 5-HT_{1A} receptor selective antagonist WAY100635 (0.1–0.5 mg/kg) had no effect on swimming when given alone (Table 1).

The selective 5-HT_{1B} receptor agonist anpirtoline (0.25–2.5 mg/kg), and the mixed 5-HT1A/B receptor agonist RU24969 (0.25–2.5 mg/kg) both significantly reduced immobility in the FST (Table 2). Neither of the

Table 1. Effect of 5-HT$_{1A}$ Ligands and Imipramine on Swimming in the FST in Mice

Compound (mg/kg)	Mean
Imipramine	
0	169 ± 15
1	159 ± 12
2.5	119 ± 18**
5	69 ± 17***
10	49 ± 18***
8-OHDPAT	
0	174 ± 9
0.25	127 ± 15*
0.5	126 ± 18*
1	148 ± 10
WAY100635	
0	175 ± 11
0.1	166 ± 15
0.25	167 ± 14
0.5	192 ± 6

Data are means of time spent swimming for each group ± SEM. Significant differences calculated by Least square means test following significant ANOVA. *$p < .05$; **$p < .01$; ***$p < .001$ vs. Veh.

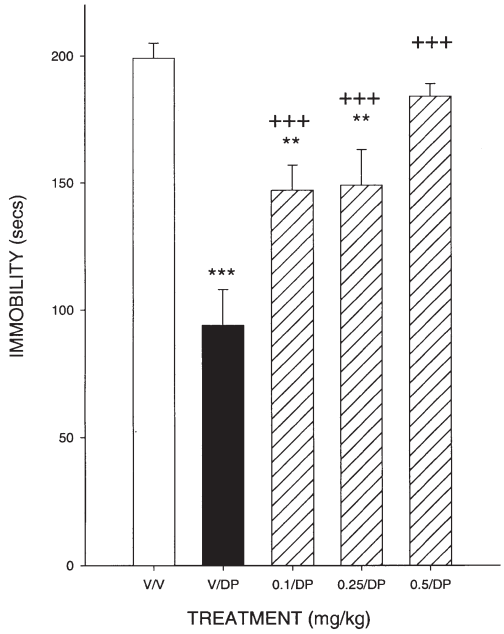

Figure 1. Effect of WAY100635 (0.1–0.5 mg/kg) on reduction in immobility induced by 8-OH-DPAT (0.5 mg/kg) in the FST in mice. Data are mean time spent immobile for each group (N ⩾ 6). Significant differences determined by Least Square Means test following significant ANOVA. V, Vehicle, DP, 8-OH-DPAT. ***$p < .001$ vs. V/V; **p, .01 vs. V/V; +++$p < .001$ vs. V/DP.

5-HT$_{1B}$ antagonists GR127935 (0.5–2.5 mg/kg) nor isamoltane (2.5–10 mg/kg) given alone had any effect on swimming in the FST (Table 2).

The significant effect of 0.5 mg/kg of 8-OH-DPAT [$F(4,35) = 14.9$, $p < .0001$] was dose-dependently prevented by pretreatment with the 5-HT$_{1A}$ antagonist WAY 100635 (0.1–0.5 mg/kg). Post hoc tests showed that even the lowest dose tested (0.1 mg/kg) significantly attenuated the response to 8-OH-DPAT while the highest dose (0.5 mg/kg) completely blocked the effects of 8-OH-DPAT (Figure 1).

Table 2. Effect of 5-HT$_{1B}$ Ligands on Swimming in the FST in Mice

Compound (mg/kg)	Mean
RU24969	
0	136 ± 21
0.25	55 ± 14***
0.5	53 ± 22***
1.25	1 ± 0.9***
2.5	2 ± 1.2***
Anpirtoline	
0	135 ± 22
0.25	86 ± 25
0.5	67 ± 23*
1.25	35 ± 14***
2.5	18 ± 8***
GR127935	
0	172 ± 14
0.5	185 ± 10
1	165 ± 22
2.5	155 ± 12
Isamoltane	
0	180 ± 6
2.5	179 ± 11
5	187 ± 8
10	151 ± 15

Data are means of time spent swimming for each group ± SEM. Significant differences calculated by Least square means test following significant ANOVA. *$p < .05$; ***$p < .001$ vs. Veh.

Anpirtoline (1.25 mg/kg) induced a significant increase in swimming [$F(4,35) = 6.6$, $p < .001$] which was significantly reversed by both GR127935 (1.25 mg/kg) and isamoltane (1–5 mg/kg) (Figure 2a and 2b, respectively) while WAY100635 had no effect (Fig 2c).

RU24969 (0.62 mg/kg) induced a significant increase in swimming [$F(7,55) = 7.25$, $p < .001$] that was also dose-dependently reduced by GR127935 (0.5–2.5 mg/kg) (Figure 3a). Isamoltane (2.5–5 mg/kg) like GR127925, significantly reversed the effect of RU24969 (0.62 mg/kg) [$F(4,35) = 5.5$, $p < .001$] (Figure 3b) while again the 5HT1A antagonist WAY100635 had no effect (Figure 3c).

In the same experiment, GR127935 reversed the antiimmobility effect of imipramine (5 mg/kg) (Figure 4a). Post hoc tests showed that the minimum effective dose of GR127935 for significant reversal was 2.5 mg/kg. Isamoltane also dose-dependently reversed the effects of imipramine (5 mg/kg) in the FST [$F(4,35) = 6.98$, $p <$

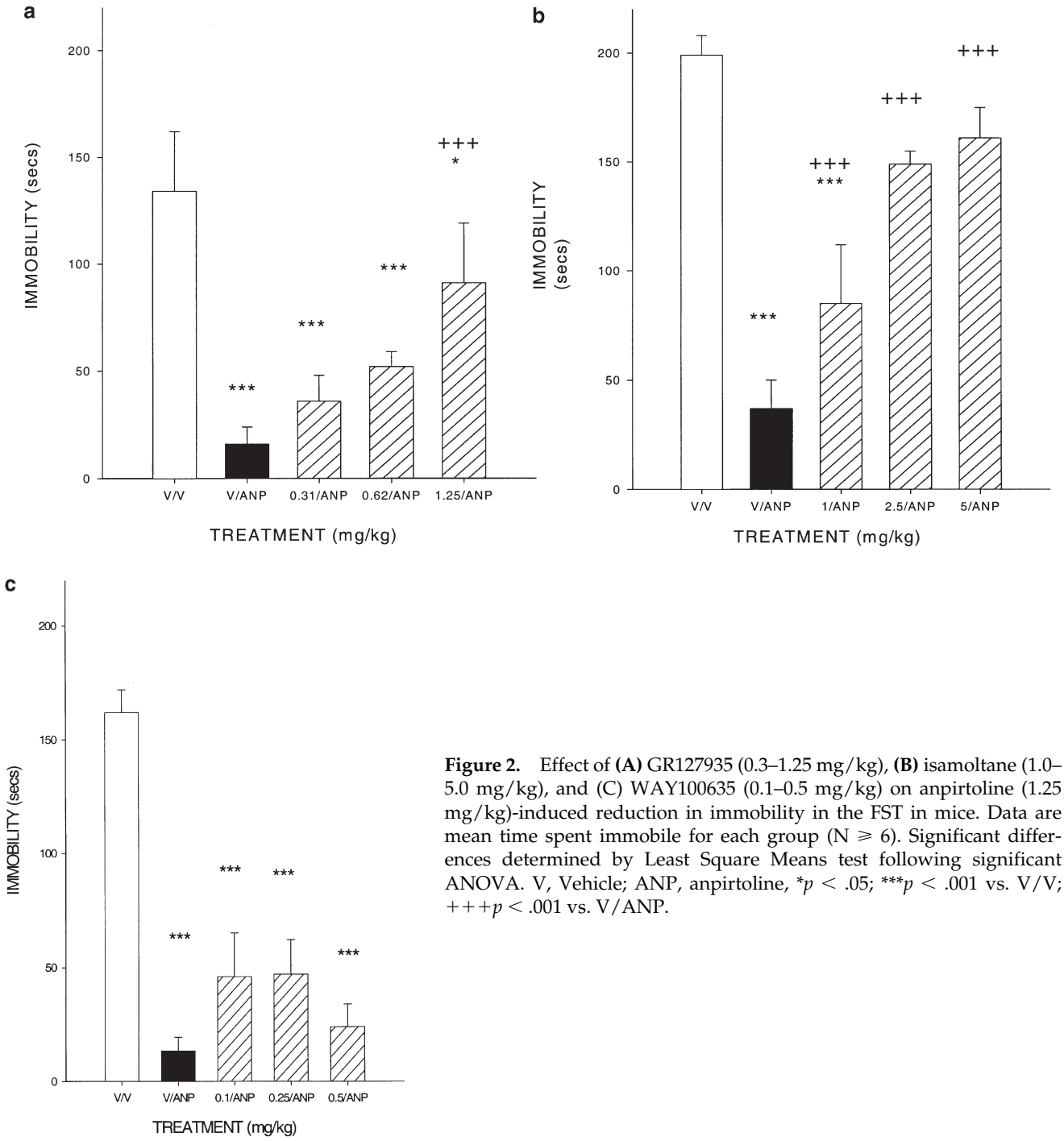

Figure 2. Effect of **(A)** GR127935 (0.3–1.25 mg/kg), **(B)** isamoltane (1.0–5.0 mg/kg), and (C) WAY100635 (0.1–0.5 mg/kg) on anpirtoline (1.25 mg/kg)-induced reduction in immobility in the FST in mice. Data are mean time spent immobile for each group (N ⩾ 6). Significant differences determined by Least Square Means test following significant ANOVA. V, Vehicle; ANP, anpirtoline, $*p < .05$; $***p < .001$ vs. V/V; $+++p < .001$ vs. V/ANP.

.001] with the post hoc tests showing that the min ED was 2.5 mg/kg with a complete reversal evident at 10 mg/kg (Figure 4b). Imipramine (5 mg/kg) significantly decreased immobility [$F(7,48) = 5.2$, $p < .001$]. The 5-HT_{1A} antagonist, WAY100635, had no effect on imipramine-induced decrease in immobility at doses that significantly reversed the effects of 8-OH-DPAT (0.1–0.5 mg/kg) (Figure 4c).

DISCUSSION

The 5-HT_{1A} agonist 8-OH-DPAT induced a modest but significant decrease in immobility in the FST in mice as has previously been demonstrated in rats and mice (Cervo and Samanin 1987; Singh and Lucki 1993). The dose response curve was bell-shaped. Maximal increases in swimming were seen with a dose of 0.5 mg/kg while

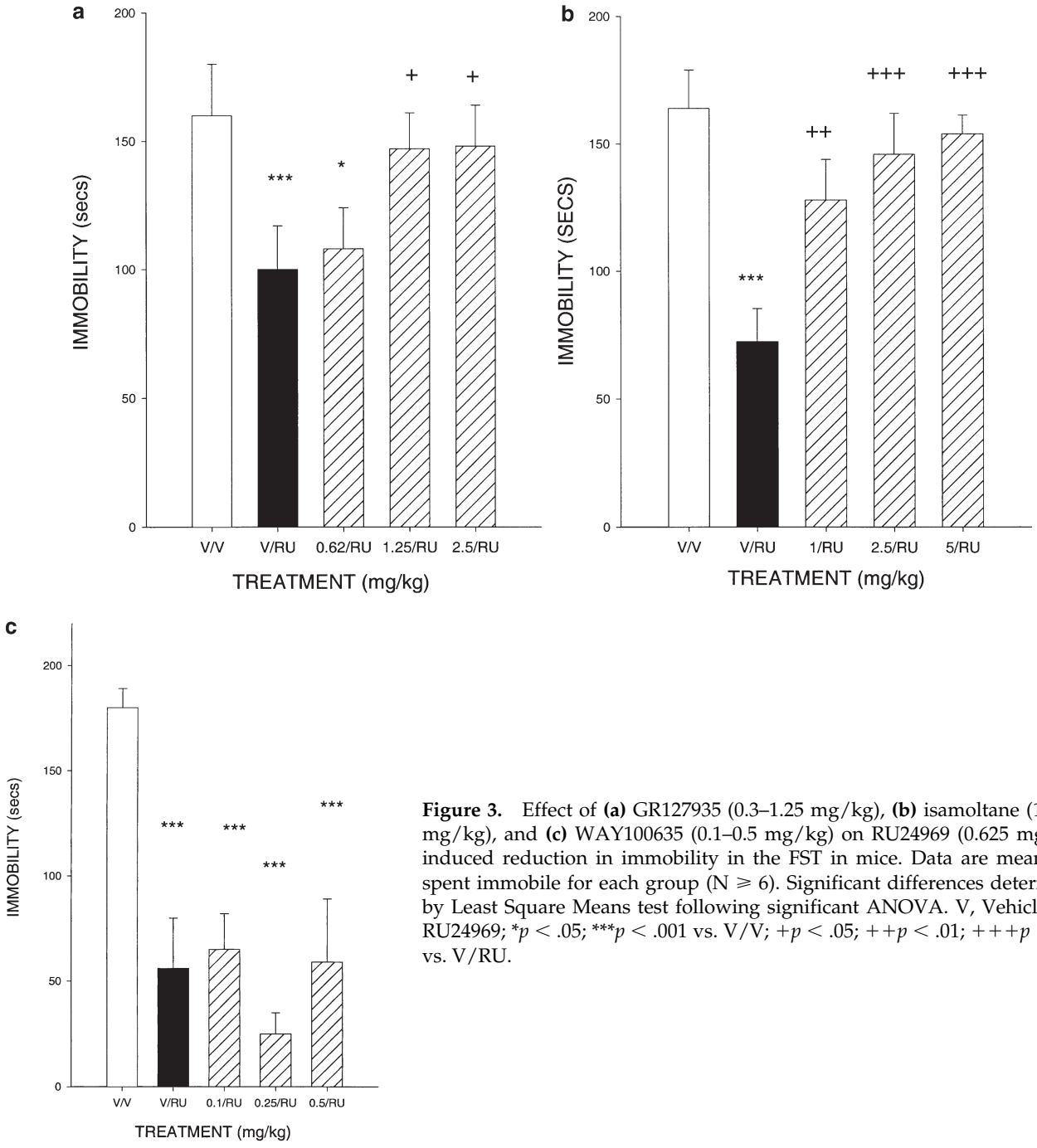

Figure 3. Effect of **(a)** GR127935 (0.3–1.25 mg/kg), **(b)** isamoltane (1.0–5.0 mg/kg), and **(c)** WAY100635 (0.1–0.5 mg/kg) on RU24969 (0.625 mg/kg)-induced reduction in immobility in the FST in mice. Data are mean time spent immobile for each group (N $\geqslant$ 6). Significant differences determined by Least Square Means test following significant ANOVA. V, Vehicle; RU, RU24969; *$p < .05$; ***$p < .001$ vs. V/V; +$p < .05$; ++$p < .01$; +++$p < .001$ vs. V/RU.

the highest dose tested (1.0 mg/kg) did not significantly alter swimming time. This may have been due to the fact that this dose can cause some motor disruption, which may have interfered with the animals' capacity to swim. The anti-immobility effect of 8-OH-DPAT was dose-dependently reversed by WAY100635, an antagonist selective for 5-HT$_{1A}$ receptors confirming that the effect was mediated by these receptors (Khawaja et al. 1995).

RU24969, an agonist with equal affinity for 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors (Hoyer 1991) significantly increased time spent swimming in the FST. The more selective 5-HT$_{1B}$ agonist, anpirtoline, also significantly increased swimming.

The effects of anpirtoline and RU24969 were reversed by GR127935 and isamoltane, but not WAY100635. This suggests that the effects of the agonists were selectively mediated by 5-HT$_{1B}$ receptors in this test. The lack of effect of WAY100635 in antagonizing the increase in swimming induced by RU24969 corroborates the finding that another 5-HT$_{1A}$ antagonist, WAY100135, failed to reverse the decrease in immobility observed in the tail suspension test (O'Neill et al.

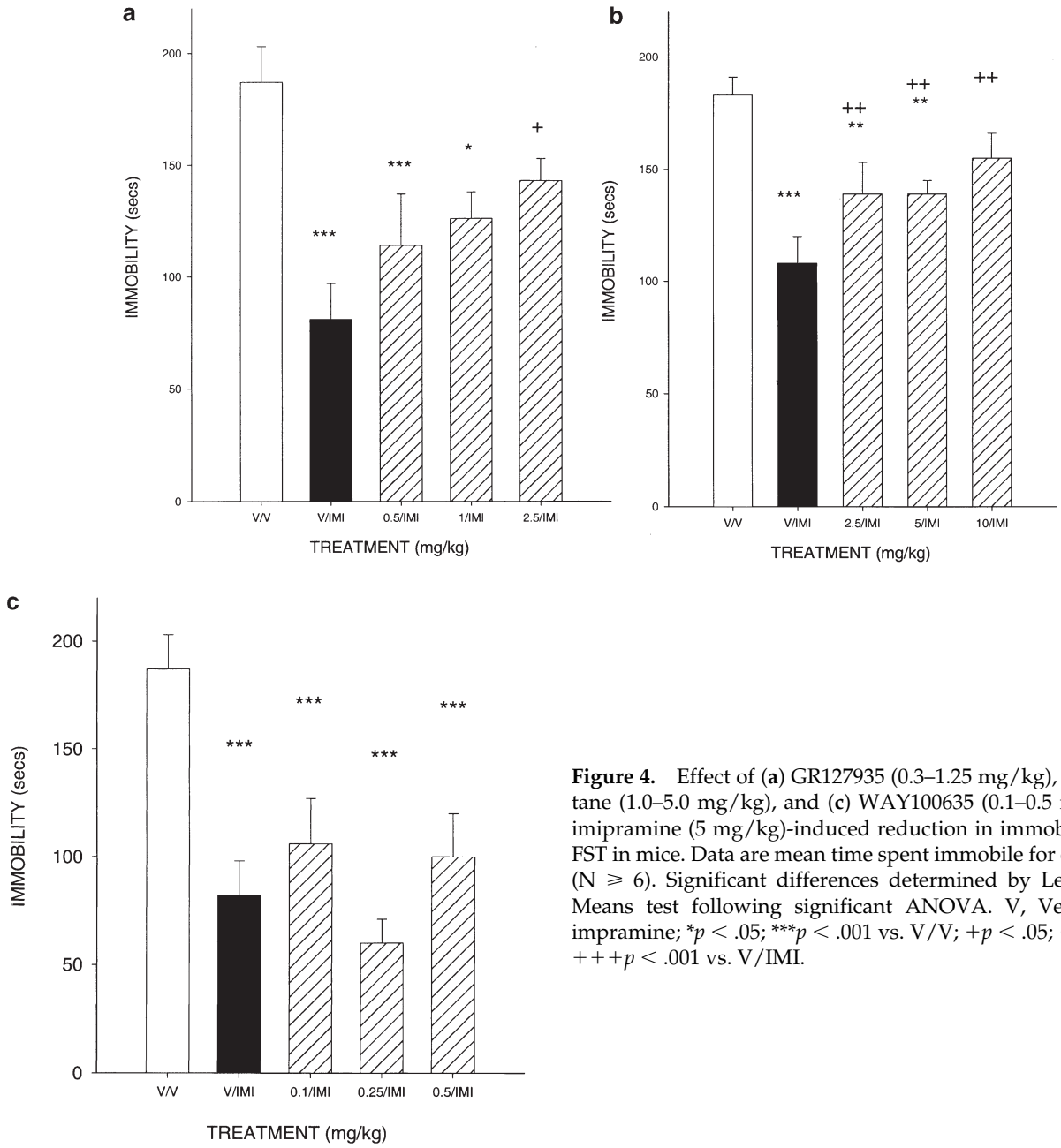

Figure 4. Effect of (**a**) GR127935 (0.3–1.25 mg/kg), (**b**) isamoltane (1.0–5.0 mg/kg), and (**c**) WAY100635 (0.1–0.5 mg/kg) on imipramine (5 mg/kg)-induced reduction in immobility in the FST in mice. Data are mean time spent immobile for each group ($N \geqslant 6$). Significant differences determined by Least Square Means test following significant ANOVA. V, Vehicle; IMI, impramine; $^{*}p < .05$; $^{***}p < .001$ vs. V/V; $+p < .05$; $++p < .01$; $+++p < .001$ vs. V/IMI.

1996). This further supports the contention that the activity of RU24969 in the FST is due to its stimulation of 5-HT_{1B} receptors. This contrasts with its effect on locomotor activity, where both 5-HT_{1A} (WAY100635) and 5-$HT_{1B/D}$ (GR127935) antagonists have been shown to attenuate its locomotor stimulant effects (Kalkman 1995).

The studies with selective agonists suggested that either 5-HT_{1A} and 5-HT_{1B} receptor activation could increase swimming time in the FST, although it is clear that effects of the agonists on motor behavior may contribute to the effects observed in this test. To examine the further possibility that these receptors were involved in the mediation of the behavioral effects of an antidepressant compound it was necessary to examine the effects of pretreatment with the selective 5-HT_{1A} and 5-HT_{1B} antagonist WAY100635, GR127935, and isamoltane on the response to imipramine in the FST.

Both isamoltane and GR127935 reversed the effects of imipramine (5 mg/kg) in the FST, while doses of WAY100635 that had previously been shown to block the effects of 8-OH-DPAT, had no effect. The doses of both isamoltane and GR127935 used in these studies also selectively blocked the effects of RU24969 and anpirtoline suggesting that these compounds were acting as antagonists at 5-HT_{1B} receptors. It has been shown

previously that GR127935 reversed the effect of imipramine in the tail suspension test in mice (O'Neill et al. 1996). The findings in the current study indicate that 5-HT_{1B} but not 5-HT_{1A} receptors are involved in the mediation of the anti-immobility effects of imipramine in the FST.

The 5-HT_{1B} agonists RU24969 and anpirtoline have been shown to increase locomotor activity in mice at doses that decrease immobility (Cheetham and Heal 1993; O'Neill et al. 1997). This poses difficulties for interpreting the effects of these compounds in the FST as other locomotor stimulants such as amphetamine show up as false positives in this test. However, the effect of both GR127935 and isamoltane in reversing the effects of imipramine suggests that 5-HT_{1B} receptors may be involved in the mediation of the behavioural effects of a clinically effective antidepressant in this test, independently of their effects on locomotor activity.

In contrast to the results of experiments with the 5-HT_{1A} antagonist, the effect of both GR127935 and isamoltane in reversing the effects of imipramine suggests that 5-HT_{1B} receptors may be involved in the mediation of the behavioural effects of imipramine in this test. Methiothepin a non-selective antagonist at 5HT1 receptors has also been shown to block the effects of paroxetine, fluvoxamine and citalopram in the FST (Bourin et al. 1998).

Blockade of 5-HT_{1A} presynaptic autoreceptors increases synaptic concentrations of 5-HT and potentiates the effects of reuptake inhibitors as measured by in vivo microdialysis (e.g., Arborelius et al. 1996; Romero et al. 1996). Similarly blockade of presynaptic 5-HT_{1B} autoreceptors synergistically enhances the effects of SSRIs in elevating synaptic levels of 5-HT (Davidson and Stamford 1997; Rollema et al. 1996) in a manner analogous to the effects of 5-HT_{1A} antagonists described above. The increased synaptic concentrations of 5-HT should consequently enhance the effects of an antidepressant compound. No such potentiation was evident in the current study. Unfortunately, SSRIs produce only weak or inconsistent effects in the FST in our laboratory and thus a directly analogous experiment using the selective antagonists in combination with SSRIs was not possible.

The lack of enhancement of the effect of imipramine by either GR127935 or WAY100635 may be due to several factors. First, it may be argued that the effect of imipramine was large and there may have been a ceiling effect where no increase was possible over the response achieved. This is unlikely to be the case in this experiment as the 10 mg/kg dose of imipramine produced a larger increase in swim-time that did the 5 mg/kg used in the antagonist challenge studies, indicating than the dose used was submaximal. Secondly it is possible that the effect of the antagonists on presynaptic receptors disinhibiting 5-HT release is counteracted by the effects of the antagonists acting at postsynaptic receptors implying again that activation of postsynaptic 5-HT_{1B} receptors is required for the expression of the behavioural effect of imipramine in the FST.

While it would appear clear that elevation of synaptic concentrations of 5-HT is involved in the relief of depressive symptoms it is not known which mechanism(s) mediate these beneficial effects at the postsynaptic level. Activation of postsynaptic 5-HT_{1B} receptors increases the release of dopamine in rats and guinea pigs as measured by in vivo microdialysis (Benloucif and Galloway 1991; Galloway et al. 1993; Hallbus et al. 1997). This may also contribute to the locomotor activating effects of 5HT_{1B} agonists. SCH23390, the selective dopamine D1 antagonist reduced the locomotor stimulant effects of RU24969 in mice (Cheetham and Heal 1993) and 5-$HT_{1B/D}$ agonists induce contralateral rotations in guinea pigs via dopaminergic mechanisms (Higgins et al. 1991). While it is unlikely that a single transmitter or even a single receptor system for that neurotransmitter could mediate the diverse symptoms seen in depression, dysregulation of dopamine may also underlie a subset of the symptoms in depressed patients (Brown and Gershon 1993). The dopaminergic system is known to be involved in the mediation of hedonic processes (Trujillo et al. 1993) and anhedonia, a diminished capacity for enjoyment or pleasure is a pronounced feature of depression (Fibiger 1995). The increase in dopaminergic activity following stimulation of 5-$HT_{1B/D}$ receptors may mediate part of the beneficial effect of antidepressant treatments that increase synaptic availability of serotonin.

In conclusion, although it is difficult to dissociate the effects of 5-HT_{1B} agonist on locomotor activity from their effects in the FST, the blockade of the effects of impramine by GR127935 and isamoltane strongly implicates 5-HT_{1B} receptors in the mediation of the effects of imipramine in this test. The lack of effect of WAY100635 suggests that 5-HT_{1A} receptors play a less crucial role.

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