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Partial role of 5-HT_2 and 5-HT_3 receptors in the activity of antidepressants in the mouse forced swimming test

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Abstract

The present study was designed to evaluate the roles of 5-HT_2 and 5-HT_3 receptors in the mouse forced swimming test, by using selective agonists and antagonists of 5-$HT_{2A/C}$ and 5-HT_3 receptor sites. Agonists/antagonists and antidepressants were administered 45 min and 30 min, respectively, prior to testing. Pretreatment with (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) (4 mg/kg, i.p.) or 2-methyl-5-HT (4 mg/kg, i.p.) had no effect on the anti-immobility effects of any antidepressant tested. Prior administration of ritanserin (4 mg/kg, i.p.) or ketanserin (8 mg/kg, i.p.), on the other hand, potentiated the effects of sub-active doses of imipramine (8 mg/kg, i.p.) and desipramine (16 mg/kg, i.p.) but not of maprotiline (8 mg/kg, i.p.), fluoxetine (16 mg/kg, i.p.), citalopram (16 mg/kg, i.p.) or fluvoxamine (8 mg/kg, i.p.). Pretreatment with ondansetron (1×10^{-5} mg/kg, i.p.) enhanced the antidepressant-like effects of sub-active doses of the selective serotonin reuptake inhibitors. The results of the present study suggested that, in the forced swimming test, the selective serotonin reuptake inhibitors act partially through 5-HT_3 receptor sites, whereas the tricyclic antidepressants exert effects at 5-$HT_{2A/C}$ receptor sites. Anti-immobility effects of the selective noradrenaline reuptake inhibitor, maprotiline, do not seem to be mediated by 5-$HT_{2A/C}$ or 5-HT_3 receptor function. © 1997 Elsevier Science B.V.

Keywords: Forced swimming test; 5-HT_2 receptor; 5-HT_3 receptor; Antidepressant

1. Introduction

The forced swimming test is a behavioural model developed to predict the efficacy of antidepressant drugs in humans. Previously, it has been shown that the anti-immobility effects of the selective serotonin reuptake inhibitors in the forced swimming test seem to be mediated by presynaptic 5-HT_{1A} receptors, as well as by postsynaptic 5-HT_{1B} receptors (Redrobe et al., 1996a). Antidepressant-like effects of the tricyclic antidepressants and noradrenaline reuptake inhibitors, e.g. maprotiline, in the forced swimming test seem, on the other hand, to be mediated by postsynaptic 5-HT_{1A} receptors (Redrobe et al., 1996a). Considering the variety of 5-HT receptors, it is possible that other subtypes may participate in the anti-immobility effects of antidepressants in the forced swimming test. The present study was designed to evaluate the roles of 5-HT_2 and 5-HT_3 receptors in the mouse forced swimming test, by using selective agonists and antagonists of 5-$HT_{2A/C}$ and 5-HT_3 receptor sites.

It has been shown that sub-active doses of several types of antidepressants produce significant anti-immobility effects in mice when combined with clonidine (Malinge et al., 1988; Bourin et al., 1991), and this effect was recently attributed to an action at 5-HT_2 receptors (Bourin et al., 1996). It has also been demonstrated that pretreatment with the potassium channel blockers, quinine and glyburide, potentiates the effects of antidepressant drugs in the forced swimming test (Guo et al., 1995a,b). This effect is thought to involve blockade of potassium ion channel-linked (Yakel et al., 1990) 5-HT_3 receptors (Bourin et al., 1996). It was subsequently found that the potassium channel activator, cromakalim, antagonised the anti-immobility effects of antidepressant drugs in the forced swimming test (Redrobe et al., 1996b).

Results of studies with antidepressant drugs in the forced swimming test that involve agonists/antagonists of 5-HT_2 and 5-HT_3 receptors are difficult to compare (for review, see Borsini, 1995), as different serotonergic compounds have been used under different experimental conditions. In general, serotonergic compounds tested in combination with antidepressant drugs have been found to have

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no effect in the mouse forced swimming test; the exceptions are the 5-HT_{2C} receptor antagonists mesulergine and metitepine, which were found to antagonize the anti-immobility effects of fluoxetine and imipramine (Borsini et al., 1991; Cesana et al., 1993). This suggested that the 5-HT_{2C} receptor may play a role in the ability of such antidepressants to reduce immobility in the forced swimming test. Several antidepressants (e.g., amitriptyline, clomipramine) are effective 5-HT_2 receptor antagonists and many established antidepressants share the ability to decrease 5-HT_2 receptor binding after repeated administration. If 5-HT_2 receptor down-regulation is relevant to the efficacy of antidepressant drugs, then it is possible that selective 5-HT_2 receptor antagonists should have antidepressant-like effects. Evidence from placebo-controlled trials does suggest that ritanserin has antidepressant actions in non-psychotic patients (Deakin, 1988).

There is a recent report (Luchelli et al., 1995) that the antidepressants, clomipramine, fluoxetine, paroxetine and litoxetin, possess low to moderate potency/affinity at both central and peripheral (enteric) 5-HT_3 receptors. The administration of 5-HT_3 receptor antagonists has been reported to attenuate the nausea often seen in patients being treated with selective serotonin reuptake inhibitors (Bailey et al., 1995), further suggesting a link between the activity of antidepressant drugs and 5-HT_3 receptor function.

With the above information in mind, we decided to investigate the effects of agonists/antagonists of 5-$HT_{2A/C}$ and 5-HT_3 receptor sites to evaluate the role played by such receptors in the action of antidepressants in the mouse forced swimming test. Drugs used in the present study included: the tricyclic antidepressant, imipramine (an inhibitor of reuptake of serotonin and noradrenaline), the noradrenaline reuptake inhibitors, desipramine and maprotiline (a tricyclic and a tetracyclic, respectively), the selective serotonin reuptake inhibitors, fluoxetine, fluvoxamine and citalopram, the potent and selective 5-HT_{2A}/5-HT_{2C} receptor agonist, (±)-2,5-dimethoxy-4-iodoamphetamine (DOI), the potent 5-HT_{2A}/5-HT_{2C} receptor antagonist, ritanserin, the potent 5-HT_{2A} receptor antagonist, ketanserin, the 5-HT_3 receptor agonist, 2-methyl-5-hydroxytryptamine (2-methyl-5-HT), and the 5-HT_3 receptor antagonist, ondansetron. Doses used refer to the salt form of the drug.

2. Materials and methods

2.1. Animals

Naive male Swiss mice (Centre d'élevage Janvier, France), weighing 20–24 g, were housed at constant room temperature (21 ± 1°C) under standard conditions, with free access to food and water. Each experimental group consisted of 10 randomly chosen mice. The mice were only used once. All experiments were performed within the guidelines of the French Ministry of Agriculture for experiments with laboratory animals (law No. 87 848).

2.2. Drugs and treatment

The following drugs were used in the study: imipramine HCl (Ciba-Geigy), desipramine HCl (Merck), maprotiline HCl (Ciba-Geigy), fluoxetine HCl (Lilly), fluvoxamine maleate (Duphar), citalopram HBr (Lundbeck), (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) hydrochloride (RBI), ritanserin (Janssen), ketanserin tartrate (Janssen), ondansetron (Glaxo), 2-methyl-5-hydroxytryptamine (2-methyl-5-HT) maleate (RBI).

All drugs were dissolved in distilled water, with the exception of ritanserin which was dissolved in a 1% aqueous solution of Tween 80 (Merck). Agonists/antagonists and antidepressants were injected intraperitoneally (i.p.) in a constant volume of 0.5 ml/20 g body weight, 45 and 30 min, respectively, prior to testing. Control animals received vehicle only.

2.3. Dose-response experiments

Dose-response experiments were performed with the forced swimming test and the locomotor activity apparatus to determine the appropriate sub-active doses of agonists/antagonists. The agonist or antagonist was administered to mice 45 min prior to placement in a photocell activity meter (OSYS) for 10 min or to testing in the forced swimming test. Sub-active/active doses of antidepressants were based on previous results from our laboratory.

2.4. Measurement of immobility in mice

The forced swimming test was essentially similar to that described earlier (Porsolt et al., 1977). Briefly, mice were dropped individually into glass cylinders (height: 25 cm, diameter: 10 cm) containing 10 cm of water, maintained at 23–25°C, and left there for 6 min. A mouse was judged to be immobile when it floated in an upright position, and made only small movements to keep its head above water. The duration of immobility was recorded during the last 4 min of the 6 min testing period.

2.5. Statistical analysis

Data were analysed by the non-parametric Kruskal-Wallis *H*-test for independent groups. Additional Steel's a posteriori tests (Armitage and Berry, 1987) were performed, when appropriate, to detect significant differences between groups. All analyses were conducted using the P.C.S.M. program (Deltasoft) for an IBM-compatible microcomputer.

The effects of each antidepressant or agonist/antagonist alone are expressed as median immobility time (s), with minimum and maximum values in parentheses. For antide-

pressant interactions with agonists/antagonists, the median time of immobility (s) of the combined treatment group is also expressed with minimum and maximum values in parentheses ($n = 10$).

3. Results

3.1. DOI: dose response (Fig. 1)

A range of doses of DOI (0, 0.25, 0.5, 1, 2 and 4 mg/kg) was tested in the forced swimming test and in the locomotor activity apparatus. The results showed that DOI did not induce any significant effects at the doses employed. The dose of 4 mg/kg was therefore chosen for use in interaction studies.

3.2. Ketanserin: dose response (Fig. 2)

Ketanserin (0, 0.5, 1, 2, 4 and 8 mg/kg) was tested in the forced swimming test and in the locomotor activity apparatus. Prior administration of ketanserin did not induce any significant effects at the doses employed in the forced swimming test. However, it had sedative effects at doses of 1, 2, 4 and 8 mg/kg. As these doses were not active alone in the forced swimming test, the dose of 8 mg/kg was chosen for use in interaction studies.

3.3. Ritanserin: dose response (Fig. 3)

Ritanserin (0, 0.25, 0.5, 1, 2 and 4 mg/kg) was tested in the forced swimming test and in the locomotor activity apparatus. Administration of ritanserin did not induce any significant effects in the forced swimming test. However, it displayed sedative effects at doses of 0.5, 1, 2 and 4 mg/kg. As these doses were not active alone in the forced swimming test, the dose of 4 mg/kg was chosen for use in interaction studies.

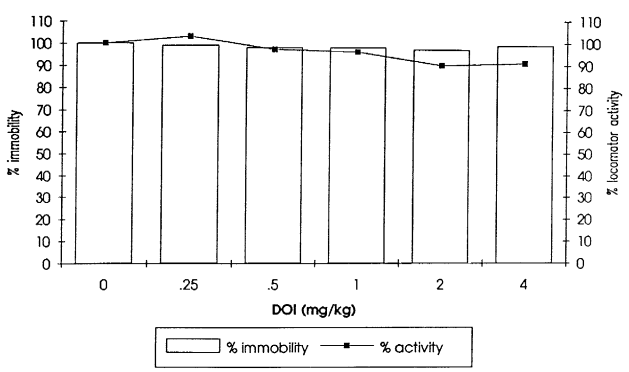

Fig. 1. The effect of DOI on immobility time in the forced swimming test and on locomotor activity. Results are expressed as percentage changes in immobility time or locomotor activity from the control group (CON) (mean immobility time (s): CON = 215 (205–238), $n = 10$; mean locomotor activity score: CON = 145 (138–162), $n = 12$).

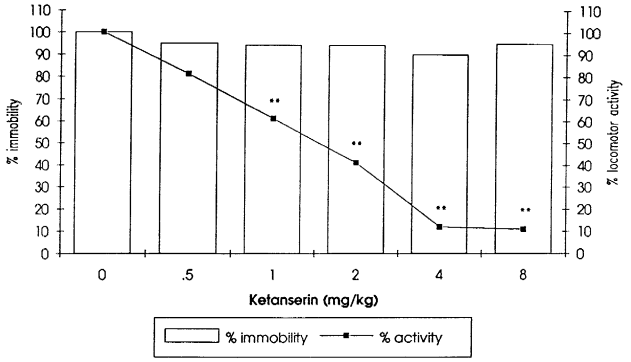

Fig. 2. The effect of ketanserin on immobility time in the forced swimming test and on locomotor activity. Results are expressed as percentage changes in immobility time or locomotor activity from the control group (CON) (mean immobility time (s): CON = 225 (210–232), $n = 10$; mean locomotor activity score: CON = 149 (131–159)). ** $P < 0.01$ versus CON locomotor activity ($n = 12$).

3.4. 2-Methyl-5-HT: dose response

The dose of 4 mg/kg 2-methyl-5-HT was chosen for use in interaction studies on the basis of previous results from our laboratory (results not shown).

3.5. Ondansetron: dose response

The dose of 1×10^{-5} mg/kg ondansetron was chosen for use in interaction studies on the basis of previous results from our laboratory (Bourin et al., 1996).

3.6. Interactions of antidepressants with DOI

DOI (4 mg/kg, i.p.) did not induce any significant effects with any of the antidepressants tested (active doses) in the mouse forced swimming test (results not shown).

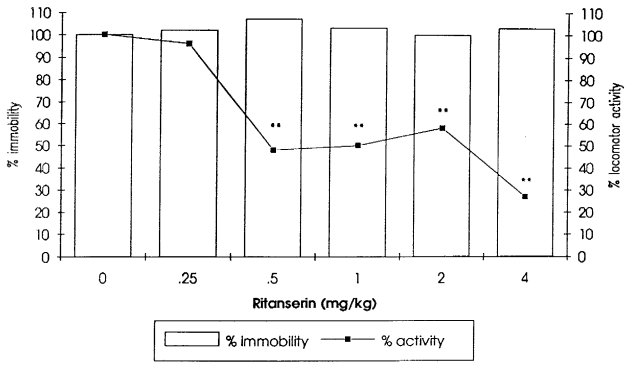

Fig. 3. The effect of ritanserin on immobility time in the forced swimming test and on locomotor activity. Results are expressed as percentage changes in immobility time or locomotor activity from the control group (CON) (mean immobility time (s): CON = 217 (202–225), $n = 10$; mean locomotor activity score: CON = 154 (140–161)). ** $P < 0.01$ versus CON locomotor activity ($n = 12$).

3.7. Interactions of antidepressants with ketanserin (Table 1)

Ketanserin (8 mg/kg, i.p.) significantly potentiated the anti-immobility effects of sub-active doses of imipramine (8 mg/kg; $P < 0.01$) and of the noradrenaline reuptake inhibitor, desipramine (16 mg/kg; $P < 0.05$), but did not induce any changes in immobility time with the selective serotonin reuptake inhibitors, fluoxetine (16 mg/kg), citalopram (16 mg/kg) or fluvoxamine (8 mg/kg).

3.8. Interactions of antidepressants with ritanserin (Table 2)

Ritanserin (4 mg/kg, i.p.) significantly enhanced the antidepressant-like effects of sub-active doses of imipramine (8 mg/kg; $P < 0.05$) and desipramine (16 mg/kg; $P < 0.05$). Ritanserin treatment did not induce any anti-immobility effects with fluoxetine (16 mg/kg), citalopram (16 mg/kg) or fluvoxamine (8 mg/kg).

3.9. Interactions of antidepressants with 2-methyl-5-HT

Administration of 2-methyl-5-HT (4 mg/kg, i.p.) did not induce any significant effects with any of the antidepressants tested (active doses) in the mouse forced swimming test (results not shown).

3.10. Interactions of antidepressants with ondansetron (Table 3)

Pretreatment with ondansetron (1×10^{-5} mg/kg, i.p.) slightly, but significantly, enhanced the antidepressant-like

Table 1
Interaction of antidepressant drugs with ketanserin (8 mg/kg) in the forced swimming test

Drug	Dose (mg/kg) (sub-active)	Ketanserin alone	Drug alone	Ketanserin + drug
Imipramine	8	236 (193–240)	210 (188–234)	146 (2–215) [b]
Maprotiline	8	232 (190–239)	220 (194–230)	224 (189–234)
Desipramine	16	226 (189–238)	218 (176–238)	172 (138–221) [a]
Fluoxetine	16	226 (189–238)	226 (185–236)	231 (166–239)
Citalopram	16	226 (189–238)	234 (215–240)	238 (231–240)
Fluvoxamine	8	226 (189–238)	225 (190–238)	230 (161–240)

Results expressed as median immobility time (s) with minimum and maximum values in parentheses. [a] $P < 0.05$, [b] $P < 0.01$ versus antidepressant alone (Steel's test for non-parametric data, $n = 10$). Median immobility time (s) of saline controls: 233 (209–239) (imipramine), 233 (209–239) (maprotiline), 234 (209–236) (desipramine), 234 (209–236) (fluoxetine), 234 (209–236) (citalopram), 234 (209–236) (fluvoxamine).

Table 2
Interaction of antidepressant drugs with ritanserin (4 mg/kg) in the forced swimming test

Drug	Dose (mg/kg) (sub-active)	Ritanserin alone	Drug alone	Ritanserin + drug
Imipramine	8	227 (171–235)	225 (194–238)	172 (139–217) [a]
Maprotiline	8	229 (162–237)	224 (170–237)	228 (185–239)
Desipramine	16	233 (214–238)	214 (159–237)	164 (78–222) [a]
Fluoxetine	16	233 (214–238)	202 (168–237)	223 (187–238)
Citalopram	16	227 (220–237)	214 (176–237)	202 (90–237)
Fluvoxamine	8	227 (220–237)	235 (194–238)	202 (138–236)

Results expressed as median immobility time (s) with minimum and maximum values in parentheses. [a] $P < 0.05$ versus antidepressant alone (Steel's test for non-parametric data, $n = 10$). Median immobility time (s) of saline controls: 231 (188–236) (imipramine), 230 (196–236) (maprotiline), 229 (209–238) (desipramine), 229 (209–238) (fluoxetine), 231 (216–238) (citalopram), 231 (216–238) (fluvoxamine).

Table 3
Interaction of antidepressant drugs with ondansetron (0.00001 mg/kg) in the forced swimming test

Drug	Dose (mg/kg) (sub-active)	Ondansetron alone	Drug alone	Ondansetron + drug
Imipramine	8	233 (201–239)	220 (202–231)	224 (180–239)
Maprotiline	8	215 (185–231)	224 (170–237)	217 (182–233)
Desipramine	16	229 (203–236)	200 (181–239)	193 (132–228)
Fluoxetine	16	233 (204–238)	234 (216–239)	200 (183–240) [a]
Citalopram	16	233 (204–238)	233 (159–238)	191 (90–213) [a]
Fluvoxamine	8	229 (203–236)	227 (180–238)	180 (135–212) [a]

Results expressed as median immobility time (s) with minimum and maximum values in parentheses. [a] $P < 0.05$ versus antidepressant alone (Steel's test for non-parametric data, $n = 10$). Median immobility time (s) of saline controls: 229 (223–236) (imipramine), 230 (196–236) (maprotiline), 234 (217–237) (desipramine), 232 (205–238) (fluoxetine), 232 (205–238) (citalopram), 234 (217–237) (fluvoxamine).

effects of sub-active doses of fluoxetine (16 mg/kg; $P < 0.05$), citalopram (16 mg/kg; $P < 0.05$) and fluvoxamine (8 mg/kg; $P < 0.05$). Ondansetron treatment did not induce any anti-immobility effects with imipramine (8 mg/kg) or desipramine (16 mg/kg).

4. Discussion

The results of the present study suggest a partial role for 5-$HT_{2A/C}$ and 5-HT_3 receptors in the action of antidepressants in the mouse forced swimming test (Table 4). We have found that while the antagonism of 5-$HT_{2A/C}$ receptors is important in the action of tricyclic antidepressants in the forced swimming test, the antagonism of 5-HT_3 receptors may play a partial role in the anti-immobility effects of the selective serotonin reuptake inhibitors.

In general, 5-HT_2 receptors are located at the cortical level as heteroreceptors. In the present study, activation of 5-HT_{2A} receptors by DOI did not induce any significant changes in immobility time in the presence of antidepressant drugs in the mouse forced swimming test, suggesting that agonism at such receptors is not important in the anti-immobility effects of antidepressants. On the other hand, antagonism at 5-HT_{2A} receptor sites by ketanserin and 5-$HT_{2A/C}$ receptors by ritanserin potentiated the effects of the tricyclic antidepressants, imipramine and desipramine. The effects observed with ketanserin, a selective 5-HT_{2A} receptor antagonist, were stronger than those seen with the selective 5-HT_{2A}/5-HT_{2C} receptor antagonist, ritanserin. This finding suggests that the antidepressant-like effects of imipramine and desipramine in the forced swimming test can be partly attributed to antagonism of 5-HT_{2A} rather than 5-HT_{2C} receptors. Interestingly, the 5-$HT_{2A/C}$ receptor antagonists did not potentiate the anti-immobility effects of the noradrenaline-uptake inhibitor, maprotiline. This may simply have been because maprotiline is a much weaker inhibitor of serotonin reuptake (Hyttel, 1982), and hence shows no activity when combined with a 5-HT_2 receptor antagonist. It has been shown that, when combined with clonidine, sub-active doses of several types of antidepressants produce a significant anti-immobility effect in mice (Malinge et al., 1988; Bourin et al., 1991), an effect recently attributed to an action at 5-HT_2 receptors (Bourin et al., 1996). However, in the present study, the selective 5-HT_{2A} receptor antagonist, ketanserin, and the 5-$HT_{2A/C}$ receptor antagonist, ritanserin, were found to potentiate the effects of imipramine and desipramine only. These results suggest that clonidine, an α_2-adrenoceptor agonist (Andén et al., 1970), may be acting at other classes of receptor, in addition to 5-HT_2 receptors, to potentiate the anti-immobility effects of several types of antidepressant in the mouse forced swimming test.

Previously it has been shown that, in the mouse forced swimming test, compounds such as imipramine and desipramine reduce immobility via postsynaptic 5-HT_{1A} receptor activation (Redrobe et al., 1996a). Several authors have suggested a functional link between 5-HT_2 receptors and 5-HT_{1A} receptors in relation to depression (Deakin, 1988; Berendsen, 1995; Borsini, 1994). It has been reported that blockade of 5-HT_2 receptors induces effects similar to those seen after 5-HT_{1A} receptor activation (Berendsen, 1995). Furthermore, ritanserin has been reported to exert antidepressant-like effects (Bersani et al., 1991). Together, these results might explain the potentiating effects of ketanserin and ritanserin in the present study, and emphasise the importance of the functional balance between 5-HT_2 and 5-HT_{1A} receptors in the action of antidepressant drugs in the forced swimming test. It has been suggested that a compound, BIMT 17, which activates 5-HT_{1A} receptors and concurrently antagonizes 5-HT_2 receptors, produces acutely effects similar to those seen only after chronic antidepressant treatment (Borsini, 1994, 1996). However, clinical trials are necessary to confirm this hypothesis as such effects have only been observed in animal studies.

Receptors of the 5-HT_3 subtype are located postsynaptically in the area postrema and the cortex (Leonard, 1994), and there has been some interest in the antidepressant-like effects of 5-HT_3 receptor antagonists (Greenshaw, 1993). In the present study, activation of 5-HT_3 receptors by 2-methyl-5-HT did not induce any significant changes in immobility time after antidepressant drugs. This would suggest that agonism at such receptors does not play a role in the action of antidepressant drugs in the mouse forced swimming test. On the other hand, pretreatment with the 5-HT_3 antagonist, ondansetron, at a very low dose, slightly

Table 4
Summary of the effects of agonists/antagonists with antidepressant drugs in the mouse forced swimming test

Drug	DOI	Ketanserin	Ritanserin	2-Methyl-5-HT	Ondansetron
Imipramine	−	+	+	−	−
Maprotiline	−	−	−	−	−
Desipramine	−	+	+	−	−
Fluoxetine	−	−	−	−	+
Citalopram	−	−	−	−	+
Fluvoxamine	−	−	−	−	+

(+) additive effect, (−) no effect (Steel's test for non-parametric data, $n = 10$).

enhanced the anti-immobility effects of the selective serotonin reuptake inhibitors, and was devoid of activity with imipramine or desipramine. These results suggest that antagonism at 5-HT_3 receptors may also play a partial role in the ability of the selective serotonin reuptake inhibitors to reduce immobility. Such observations agree with our previous findings in that quinine, a potassium channel blocker, was shown to selectively enhance the anti-immobility effects of the selective serotonin reuptake inhibitors, together with ondansetron; this effect was attributed to blockade of the potassium ion channel-linked 5-HT_3 receptor. Channel blockade results in prolongation of the nerve action potential and enhanced calcium ion influx that triggers neurotransmitter release (Bourin et al., 1996; Guo et al., 1995b). Conversely, the potassium channel activator, cromakalim, was found to antagonise the anti-immobility effects of antidepressant drugs in the forced swimming test. This effect was suggested to be a result of potassium ion channel-linked 5-HT_3 receptor activation (Redrobe et al., 1996b). However, in the present study, agonism at 5-HT_3 receptors by 2-methyl-5-HT did not induce any significant changes in immobility time with antidepressant drugs. These results indicate that activation of the potassium ion channel-linked 5-HT_3 receptor with a potassium channel opener does not necessarily have the same effect as direct activation of the 5-HT_3 receptor with an agonist.

The potentiation induced by ondansetron in the present study was not as strong as that obtained with the presynaptic 5-HT_{1A} receptor antagonist, pindolol, and the postsynaptic 5-HT_{1B} receptor agonist, RU 24969, in a previous study (Redrobe et al., 1996a). This finding suggests that the 5-HT_3 receptor may only play a partial role in the activity of selective serotonin reuptake inhibitors in the mouse forced swimming test. Other authors have previously suggested that 5-HT_3 antagonists reverse escape deficits in the learned helplessness test, an animal model of depression highly sensitive to antidepressant drugs (Martin et al., 1992).

One explanation for how the combination of an antagonist and a monoamine reuptake inhibitor at a receptor leads to a potentiation of the behavioural effects seen in the forced swimming test involves the affinity of 5-HT for different 5-HT receptor subtypes. It has been suggested that the single administration of a selective serotonin reuptake inhibitor increases 5-HT release in some brain regions (Borsini, 1994). It is now known that the affinity of 5-HT for 5-HT_2 receptors is about 100-fold less than that for 5-HT_{1A} receptors (Borsini, 1994), and that 5-HT_{1A} receptors play a major role in the activity of antidepressants in the mouse forced swimming test (Redrobe et al., 1996a). Thus, blockade of 5-$HT_{2A/C}$ and/or 5-HT_3 receptors enables 'free' 5-HT, following antidepressant administration, to act at 5-HT_{1A} receptors and therefore potentiate the effects of antidepressants in the mouse forced swimming test. These effects cannot be attributed to physiological potentiation of the different drug actions. Our interpretation of the results of the present study is supported by a recent report which demonstrated that treatment with the tricyclic antidepressants, imipramine and clomipramine, altered 5-HT_{2A} and 5-HT_{2C} receptor-mediated function in a genetic animal model of depression (Aulakh et al., 1995). Such changes suggest that these effects may be responsible for correcting the abnormalities of 5-HT function involved in the pathogenesis of depression. Further evidence suggesting that tricyclic antidepressants are acting at 5-HT_2 receptor sites is provided by results of a study in which the selective 5-HT_{2A} receptor antagonist, pipamperone (Lucki et al., 1984), enhanced the clinical therapeutic action of tricyclic antidepressants (Ansoms et al., 1977). These results agree with those of the present study in that the 5-HT_{2A} and 5-$HT_{2A/2C}$ receptor antagonists, ketanserin and ritanserin respectively, enhanced the anti-immobility effects of tricyclic antidepressants, but not the effects of selective serotonin reuptake inhibitors, in the mouse forced swimming test. It has been shown that when they are administered in combination with the potassium ion channel blocker, quinine, or the potassium ion channel activator, cromakalim, the selective serotonin reuptake inhibitors have their anti-immobility effects potentiated (Bourin et al., 1996) or attenuated (Redrobe et al., 1996b) respectively. These effects were not observed when antidepressants were administered in combination with the peripheral potassium channel activator, minoxidil, indicating a central effect (Redrobe et al., 1996b). As the 5-HT_3 receptor is the only serotonergic receptor linked to a potassium ion channel, these results suggest that the anti-immobility effects of the selective serotonin reuptake inhibitors are mediated by 5-HT_3 receptor function. Thus, the results obtained in the present study with ondansetron, together with other evidence presented herein, support this hypothesis.

In conclusion, the results now obtained indicate a partial role for 5-$HT_{2A/C}$ and 5-HT_3 receptors in the action of antidepressant drugs in the mouse forced swimming test. The selective serotonin reuptake inhibitors seem to induce anti-immobility effects via an action at 5-HT_3 receptors, whereas the effects of tricyclic antidepressants seem to be partly mediated by 5-$HT_{2A/C}$ receptors.

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