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The $GABA_B$ receptor antagonist CGP36742 improves learned helplessness in rats

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Abstract

Effects of 3-aminopropyl-*n*-butyl-phosphinic acid (CGP36742), a $GABA_B$ receptor antagonist, in the learned helplessness paradigm were examined in rats in comparison with those of imipramine and endo-8-methyl-8-azabicyclo[3,2,1]oct-3-ol indol-3-yl-carboxylate hydrochloride (ICS205-930). Rats were treated with CGP36742, imipramine or ICS205-930 for 14 days. On day 14, the rats were subjected to 90 inescapable shocks. On day 15, the rats received the 40-trial escape test. The inescapable shocks increased escape failures in the escape test. CGP36742, imipramine and ICS205-930 dose-dependently improved the escape failures induced by the inescapable shocks. Baclofen attenuated the escape failures-improving effect of CGP36742, imipramine and ICS205-930. Although the action of imipramine and ICS205-930 was attenuated by 1-(*m*-chlorophenyl)-biguanide (mCPBG), mCPBG failed to influence the CGP36742 action. Therefore, it is suggested that CGP36742 may have an antidepressant profile and that the mechanisms of CGP36742 in antidepressant action may be different from those of imipramine and ICS205-930. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: CGP36742; $GABA_B$ receptor antagonist; Imipramine; ICS205-930; Learned helplessness; Baclofen; mCPBG (1-(*m*-chlorophenyl)-biguanide)

1. Introduction

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain. GABA interacts with three receptor subtypes designated $GABA_A$, $GABA_B$ and $GABA_C$ (Matsumoto, 1989; Bowery, 1993; Johnston, 1997). There are two GABA receptor hypotheses of the antidepressant action: an increase in $GABA_A$ receptor-mediated neurotransmission or a decrease in $GABA_B$ receptor-mediated neurotransmission may contribute to action of antidepressants. Pilc and Lloyd (1984) and Lloyd (1990) found that chronic treatment with antidepressants up-regulated $GABA_B$ receptor binding in the rat frontal cortex. These results raise the possibility that chronic antidepressants treatment may decrease $GABA_B$ receptor-mediated neurotransmission resulting in an increase in postsynaptic $GABA_B$ receptor binding. On the other hand, Suzdak and Gianutsos (1985) reported that chronic treatment with antidepressants decreased $GABA_A$ receptor binding in the mouse cortex and hippocampus, suggesting that chronic treatment with antidepressants may increase $GABA_A$ receptor-mediated neurotransmission, thereby decreasing postsynaptic $GABA_A$ receptor binding.

We previously examined the involvement of GABAergic systems in antidepressant action in the forced swim test and the learned helplessness paradigm in rats (Nakagawa et al., 1996a,b). We found that baclofen ($GABA_B$ receptor agonist) attenuated the action of antidepressants, suggesting that the increased $GABA_B$ receptor-mediated neurotransmission may attenuate antidepressant action (Nakagawa et al., 1996a,b). On the other hand, bicuculline ($GABA_A$ receptor antagonist) failed to antagonize the effect of antidepressants (Nakagawa et al., 1996a). Muscimol ($GABA_A$ receptor agonist) did not improve learned helplessness (Nakagawa et al., 1996b). Therefore, our previous findings support the above-mentioned $GABA_B$ receptor hypothesis of depression rather than $GABA_A$ receptor hypothesis of depression and have an implication

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that $GABA_B$ receptor antagonists may have an antidepressant action.

CGP36742 (3-aminopropyl-*n*-butyl-phosphinic acid) has an affinity for the $GABA_B$ receptor with an IC_{50} of 32 μM (Bittiger et al., 1996) and antagonizes the baclofen action in vitro and in vivo (Carletti et al., 1993; Olpe et al., 1993; Bittiger et al., 1996; Knight and Bowery, 1996; Nakagawa and Takashima, 1997). Pratt and Bowery (1993) found that chronic CGP36742 treatment decreased β-adrenoceptor binding in rat brain, which manifest in the desipramine-treated rats. It has been widely accepted that chronic antidepressants treatment decreases β-adrenoceptors in the brain (Banerjee and Kung, 1977). Bittiger et al. (1996) reported that CGP36742 decreased the duration of immobility in the rat forced swim test.

It has become increasingly clear that 5-hydroxytryptamine (5-HT)$_3$ receptors may be involved in antidepressant action (Greenshaw, 1993). It was reported that responses mediated by 5-HT_3 receptor activation were inhibited by antidepressants in vitro (Fan, 1994; Lucchelli et al., 1995). 5-HT_3 receptor antagonists were effective in the forced swim test and the learned helplessness paradigm in rats (Martin et al., 1992; Nakagawa et al., 1998). In our previous study (Nakagawa et al., 1998), we showed that 1-(*m*-chlorophenyl)-biguanide (mCPBG), a 5-HT_3 receptor agonist attenuated antidepressant action in the rat forced swim test. These observations suggest that the suppression of 5-HT_3 receptor activity may contribute to antidepressant action. Since presynaptic 5-HT_3 receptors regulate Ca^{2+}-dependent neurotransmitter release (Barnes et al., 1989; Blandina et al., 1989), it would be expected that antidepressants may decrease neurotransmitter release via 5-HT_3 receptors.

In this study, therefore, effects of CGP36742 in the learned helplessness paradigm were examined in comparison with those of imipramine and endo-8-methyl-8-azabicyclo[3,2,1]oct-3-ol indol-3-yl-carboxylate hydrochloride, 5-HT_3 receptor antagonist (ICS205-930). We also assessed whether mCPBG as well as baclofen attenuated the effects of CGP36742, imipramine and ICS205-930 to characterize the sites of action for these drugs.

Table 1
Effects of CGP36742, imipramine and ICS205-930 on the intertrial crossings in the escape test
CGP36742, imipramine, ICS205-930 and saline were injected i.p. once daily for 14 days. On day 14, rats received 90 inescapable shocks. On day 15, they underwent the 40-trial escape test. Ten rats were used in each group. Data are expressed as mean with S.E.M.

Doses (mg/kg, i.p.)	Number of intertrial crossings		
	CGP36742	Imipramine	ICS205-930
Saline (no shocks)	2.1±0.7	2.5±0.7	2.1±0.7
Saline (90 shocks)	1.3±0.6	1.7±0.8	1.1±0.7
0.03			0.9±0.5
0.1			1.0±0.7
0.3			1.5±0.5*
1		1.2±0.4	
3		1.6±0.8	
10	1.4±0.6	1.1±0.8	
30	0.9±0.3		
100	1.1±0.5		

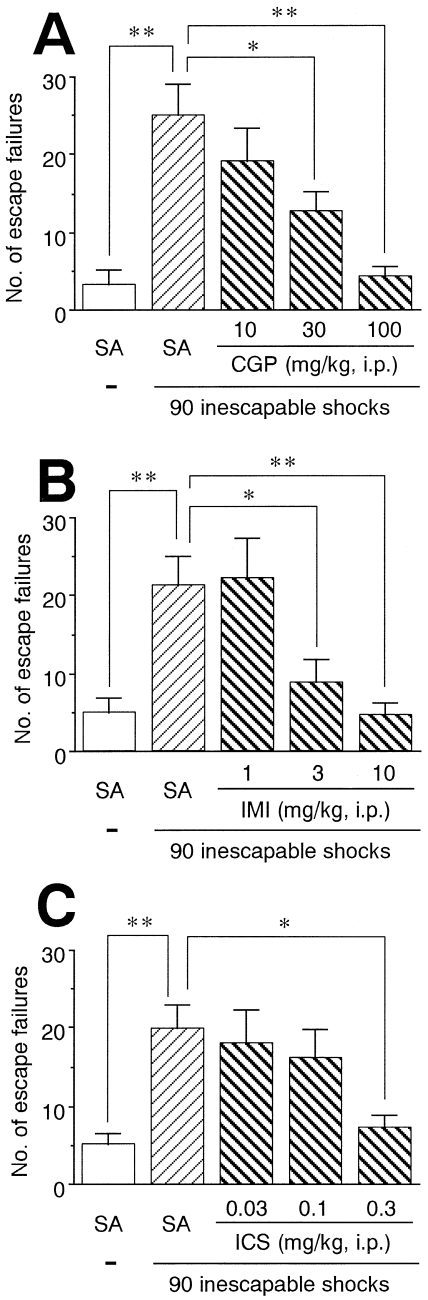

Fig. 1. Effects of CGP36742 (A), imipramine (B) and ICS205-930 (C) on the escape failures in the learned helplessness paradigm in rats. CGP36742 (CGP), imipramine (IMI), ICS205-930 (ICS) and saline (SA) were injected i.p. once daily for 14 days. On day 14, rats received 90 inescapable shocks. On day 15, they underwent the 40-trial escape test. Ten rats were used in each group. $^*P < 0.05$; $^{**}P < 0.01$ vs. shocked control. Data are expressed as mean with S.E.M.

2. Materials and methods

2.1. Animals

Male Wistar rats (Charles River, Japan) weighing 130–180 g, at the beginning of the experiment, were used. They were housed in groups of five in an air- and light-controlled room (temperature; 24 ± 2°C, light phase; 0800–2000 h). Food and water were given ad libitum. Experiments were all carried out in accordance with the Guide for the Care and Use of Laboratory Animals of Japanese Pharmacological Society.

2.2. Apparatus

A shock pre-treatment chamber (28 × 21 × 25 cm^3) and a two-way shuttle box (56 × 21 × 25 cm^3; Toyo Sangyo, Toyama) were used. The shuttle box was divided into equal-size chambers by a stainless steel divider. The floors of the shock pre-treatment chamber and the shuttle box consisted of stainless steel rods. Scrambled shocks were delivered by a shock generator (MSG-001, Toyo Sangyo).

2.3. Procedure

The learned helplessness paradigm was performed according to our previous studies (Nakagawa et al., 1996b,c).

Rats were injected i.p. with drugs or vehicle once daily for 14 days. On day 14, the rats were individually placed in the shock pre-treatment chamber and given 90 inescapable shocks (1 mA) of 10-s duration with a 2-s inter-shock interval. No shocks were delivered to control rats. Immediately after the shock pre-treatment session, the rats were injected i.p. with drugs or vehicle. On day 15 (24 h after the final injection of drugs or vehicle), the rats received the 40-trial escape test. The rats were individually placed in the shuttle box and given a 5-min adaptation period. A tone signal was presented during the first 5 s of each trial. If there was no avoidance response within this period, the tone signal remained on and a 1-mA shock (10-s duration) was delivered through the grid floor. In the case of no escape response within this period, both the tone signal and shock were automatically terminated. The intertrial interval was 10 s. The number of escape failures and the number of intertrial crossings were recorded. Es-

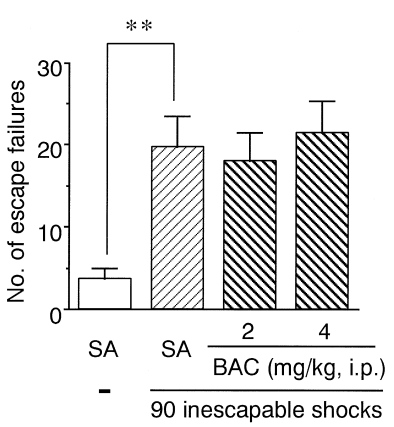

Fig. 2. Effects of baclofen on the escape failures in the learned helplessness paradigm in rats. Baclofen (BAC) and saline (SA) were injected i.p. once daily for 14 days. Ten rats were used in each group. $^{**}P < 0.01$ vs. shocked control. See Fig. 1 for further information.

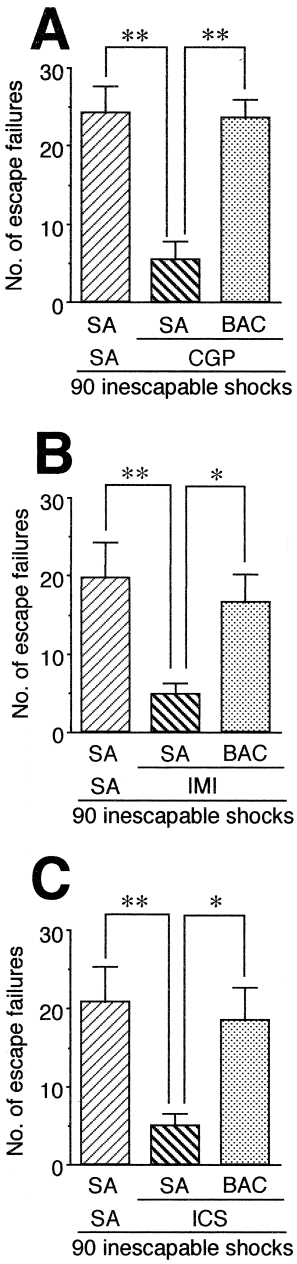

Fig. 3. Effects of baclofen on the escape failures-improving effect of CGP36742 (A), imipramine (B) and ICS205-930 (C) in the learned helplessness paradigm in rats. Rats were injected i.p. with baclofen (BAC, 4 mg/kg) or saline (SA) in combination with either CGP36742 (CGP, 100 mg/kg), imipramine (IMI, 10 mg/kg), ICS205-930 (ICS, 0.3 mg/kg) or saline once daily for 14 days. Ten rats were used in each group. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. respective controls. See Fig. 1 for further information.

cape failure is referred to a non-crossing response during the shock delivery. Ten rats were used in each group.

2.4. Drugs

CGP36742 (Novartis), imipramine hydrochloride (Sigma), ICS205-930 (RBI), (±)-baclofen (RBI) and 1-(*m*-chlorophenyl)-biguanide hydrochloride (mCPBG) (RBI) were used. All drugs except ICS205-930 were dissolved in saline. ICS205-930 was dissolved in 10% polyethylene glycol solution. Baclofen was injected in a volume of 4 ml/kg. Other drugs were injected in a volume of 1 ml/kg. The dosages of drugs were expressed as the salt.

2.5. Statistics

Between-group comparisons were assessed by Dunnett's test following one-way analysis of variance (ANOVA).

3. Results

3.1. Antidepressant effect of CGP36742, imipramine and ICS205-930 in the learned helplessness paradigm

The escape test was carried out 24 h after the final drug treatment in order to avoid a false-positive effect induced by increased motor activity. CGP36742, imipramine and ICS205-930 had no significant effects on the intertrial crossings in the escape test (Table 1). ANOVA indicated no significant group differences [for CGP36742: $F(4, 45) = 0.65$, $P > 0.05$; for imipramine: $F(4, 45) = 0.57$, $P > 0.05$; for ICS205-930: $F(4, 45) = 0.61$, $P > 0.05$].

As shown in Fig. 1, the exposure to inescapable shocks induced the subsequent increase in escape failures. CGP36742, imipramine and ICS205-930 dose-dependently improved the increased escape failures induced by the inescapable shocks [for CGP36742: $F(4, 45) = 10.02$, $P < 0.01$; for imipramine: $F(4, 45) = 7.19$, $P < 0.01$; for ICS205-930: $F(4, 45) = 5.13$, $P < 0.01$]. Post-hoc analysis showed that CGP36742 at doses of 30 and 100 mg/kg, imipramine at doses of 3 and 10 mg/kg and ICS205-930 at a dose of 0.3 mg/kg significantly improved the increased escape failures induced by the inescapable shocks.

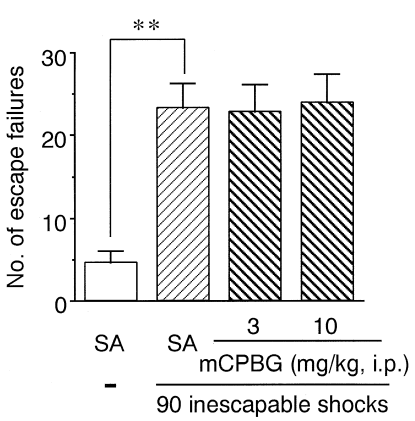

Fig. 4. Effects of 1-(*m*-chlorophenyl)-biguanide (mCPBG) on the escape failures in the learned helplessness paradigm in rats. mCPBG and saline (SA) were injected i.p. once daily for 14 days. Ten rats were used in each group. $^{**}P < 0.01$ vs. shocked control. See Fig. 1 for further information.

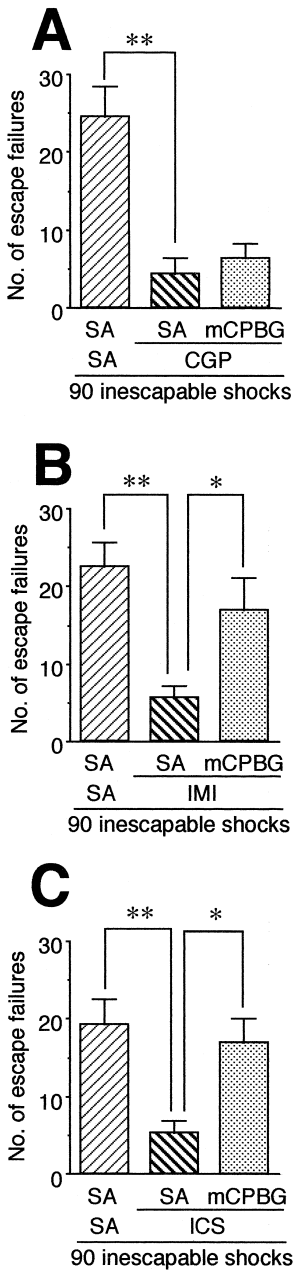

Fig. 5. Effects of 1-(*m*-chlorophenyl)-biguanide (mCPBG) on the escape failures-improving effect of CGP36742 (A), imipramine (B) and ICS205-930 (C) in the learned helplessness paradigm in rats. Rats were injected i.p. with mCPBG (10 mg/kg) or saline (SA) in combination with either CGP36742 (CGP, 100 mg/kg), imipramine (IMI, 10 mg/kg), ICS205-930 (ICS, 0.3 mg/kg) or saline once daily for 14 days. Ten rats were used in each group. $^{*}P < 0.05$; $^{**}P < 0.01$ vs. respective controls. See Fig. 1 for further information.

There were few avoidance responses in the escape test. CGP36742, imipramine and ICS205-930 failed to influence the avoidance responses (data not shown).

3.2. Involvement of $GABA_B$ receptors in antidepressant action of CGP36742, imipramine and ICS205-930

Baclofen had no effects on the increased escape failures when it was given alone (Fig. 2). Although ANOVA indicated significant group differences [$F(3, 36) = 6.60$, $P < 0.01$], post-hoc analysis showed there was no significant effect of baclofen on the increased escape failures.

However, baclofen (4 mg/kg) attenuated the improving effect of CGP36742 (100 mg/kg), imipramine (10 mg/kg) and ICS205-930 (0.3 mg/kg) on the increased escape failures (Fig. 3). ANOVA indicated significant group differences [for CGP36742: $F(2, 27) = 15.28$, $P < 0.01$; for imipramine: $F(2, 27) = 5.29$, $P < 0.05$; for ICS205-930: $F(2, 27) = 5.44$, $P < 0.05$]. Post-hoc analysis of these data showed that in the baclofen-treated groups there was significant attenuation of the escape failures-improving effect of CGP36742, imipramine and ICS205-930.

3.3. Involvement of 5-HT_3 receptors in antidepressant action of CGP36742, imipramine and ICS205-930

mCPBG failed to influence the increased escape failures when it was given alone (Fig. 4). Although ANOVA indicated significant group differences [$F(3, 36) = 10.63$, $P < 0.01$], post-hoc analysis showed no significant effect of mCPBG on the increased escape failures.

mCPBG (10 mg/kg) failed to influence the improving effect of CGP36742 (100 mg/kg) on the increased escape failures, whereas the escape failures-improving effect of imipramine (10 mg/kg) and ICS205-930 (0.3 mg/kg) was attenuated by mCPBG (Fig. 5). ANOVA indicated significant group differences [for CGP36742: $F(2, 27) = 15.86$, $P < 0.01$; for imipramine: $F(2, 27) = 7.67$, $P < 0.01$; for ICS205-930: $F(2, 27) = 7.38$, $P < 0.01$]. Post-hoc analysis showed that there was no significant effect of mCPBG on the escape failures-improving action of CGP36742, whereas mCPBG significantly attenuated the effect of imipramine and ICS205-930.

4. Discussion

CGP36742 has an affinity for the $GABA_B$ receptor with an IC_{50} of 32 μM (Bittiger et al., 1996) and antagonizes the baclofen action in vitro and in vivo (Carletti et al., 1993; Olpe et al., 1993; Bittiger et al., 1996; Knight and Bowery, 1996; Nakagawa and Takashima, 1997). In the present study, we showed that a 14-day treatment with CGP36742 dose-dependently improved the increased escape failures induced by the inescapable shocks as imipramine did (Fig. 1). As shown in Fig. 3, the escape failures-improving effect of CGP36742 was attenuated by baclofen, confirming that the CGP36742 action is mediated by $GABA_B$ receptors. Our present observations support the previous findings. Bittiger et al. (1996) reported that CGP36742 decreased the duration of immobility in the rat forced swim test. Pratt and Bowery (1993) found that CGP36742 as well as desipramine decreased β-adrenoceptor binding in rat brain following a chronic treatment. It has been widely accepted that chronic antidepressants treatment decreases β-adrenoceptor binding in the brain (Banerjee and Kung, 1977). Therefore, it is concluded that $GABA_B$ receptor antagonists may have an antidepressant profile.

There is much evidence that the decreased $GABA_B$ receptor-mediated neurotransmission may be associated with antidepressant action. Chronic treatment with antidepressants has been reported to increase $GABA_B$ receptor binding in rodent frontal cortex (Pilc and Lloyd, 1984; Suzdak and Gianutsos, 1986; Szekely et al., 1987; Lloyd, 1990; Lloyd et al., 1985; Pratt and Bowery, 1990, 1993). There was a decrease in cortex $GABA_B$ receptor binding in the animal models of depression such as the helpless rats and the olfactory bulbectomized ones, and chronic treatment with antidepressants improved the behavioral changes as well as decreased $GABA_B$ receptor binding in the models (Lloyd and Pichat, 1986; Joly et al., 1987; Martin et al., 1989). Baclofen-induced decrease in 5-HT release from brain slices and hypothermia were enhanced by repeated administration of antidepressants in mice (Gray and Green, 1987; Gray et al., 1987). We found here that baclofen attenuated the escape failures-improving effect of imipramine (Fig. 3) in agreement with our previous studies (Nakagawa et al., 1996a,b). Baclofen exacerbated helplessness in the rats exposed to 15 inescapable shocks although baclofen had no effects in the rats exposed to 90 shocks (Nakagawa et al., 1996b,c). In addition to these animal studies, it was clinically reported that baclofen exacerbated depression (Post et al., 1991). These results suggest that antidepressants may decrease $GABA_B$ receptor-mediated neurotransmission, thereby increasing postsynaptic $GABA_B$ receptor binding following a chronic treatment.

We previously found that chronic desipramine treatment improved the increased escape failures induced by the inescapable shocks in the rat learned helplessness paradigm (Nakagawa et al., 1996b). The escape failures-improving effect of desipramine at a dose of 10 mg/kg in that study was equivalent to that of CGP36742 at a dose of 100 mg/kg in the present study. Pratt and Bowery (1993) studied the changes in $GABA_B$ receptor binding in rat brain following chronic treatment with desipramine (10 mg/kg) and CGP36742 (100 mg/kg), and found that CGP36742 was equivalent to desipramine in increasing $GABA_B$ receptor binding. Therefore, our behavioral data are in agreement with those in neurochemical studies, and suggest that an increase in $GABA_B$ receptor binding in brain may be common to $GABA_B$ receptor antagonists and

conventional antidepressants following a chronic treatment.

Recent evidence suggests that 5-HT_3 receptors may regulate GABA release and may be involved in antidepressant action. *p*-Chloroamphetamine-induced increase in GABA release was attenuated by ICS205-930 from slices of rat caudate–putamen (Meyer et al., 1991). ICS205-930 antagonized the 5-HT-induced facilitation of unitary inhibitory postsynaptic potentials (IPSPs) in rat hippocampal slices (Ropert and Guy, 1991). 5-HT_3 receptor antagonists facilitated the induction of long-term potentiation in rat hippocampus, resulting from attenuation of $GABA_B$ receptors-mediated IPSPs (Freund et al., 1990; Staubli and Otaky, 1994; Staubli and Xu, 1995). Lucchelli et al. (1995) reported that antidepressants such as clomipramine, paroxetine and fluoxetine inhibited responses to 2-methyl-5-HT in guinea-pig ileum. Fluoxetine and imipramine were found to inhibit the inward current mediated by 5-HT_3 receptor activation in rat nodose ganglion neurons (Fan 1994). We found here that ICS205-930 dose-dependently improved the increased escape failures (Fig. 1), suggesting antidepressant action in agreement with the previous studies (Martin et al., 1992; Redrobe and Bourin, 1997; Nakagawa et al., 1998). As shown in Fig. 5, mCPBG attenuated the escape failures-improving action of imipramine and ICS205-930. Moreover, the escape failures-improving effect of ICS205-930 was attenuated by baclofen (Fig. 3), suggesting that the decreased $GABA_B$ receptor-mediated neurotransmission may be related to the antidepressant action induced by 5-HT_3 receptor antagonism. Therefore, it is expected that antidepressants may suppress the presynaptic 5-HT_3 receptor activity, decreasing $GABA_B$ receptor-mediated neurotransmission.

However, mCPBG failed to influence the escape failures-improving effect of CGP36742 (Fig. 5). Our present results support those reported by Froestl et al. (1995) who observed CGP36742 at 1 mM failed to inhibit the binding of [^{3}H]BRL43694 to 5-HT_3 receptors. On the other hand, conventional antidepressants are reported to affect 5-HT_3 receptor activity (Fan, 1994; Lucchelli et al., 1995). Therefore, altogether above data suggest that the mechanisms of CGP36742 in antidepressant action may be different from those of conventional antidepressants as well as ICS205-930: CGP36742 may directly block $GABA_B$ receptor-mediated neurotransmission by acting on postsynaptic $GABA_B$ receptors, whereas imipramine and ICS205-930 may interact with presynaptic 5-HT_3 receptors, thereby decreasing GABA release. Our findings support the $GABA_B$ receptor hypothesis of depression and suggest that the decreased $GABA_B$ receptor-mediated neurotransmission may be involved in antidepressant action.

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