Potential anti-anxiety, anti-addictive effects of LY 354740, a selective group II glutamate metabotropic receptors agonist in animal models

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Abstract

Despite there being a lot of biochemical data about metabotropic glutamate (mGlu) receptors, our knowledge of the behavioural effects of mGlu receptor agonists/antagonists is still inadequate. LY 354740 is a systemically active agonist of group II mGlu receptors. After peripheral administration, LY 354740 produced anxiolytic-like effects in the conflict drinking test in rats and a four-plate test in mice. It was also found that LY 354740 decreased spontaneous locomotor activity in mice, but did not disturb motor coordination. In behavioural models of depression including the despair test and a tail suspension test, LY 354740 did not produce antidepressant-like effects. LY 354740 inhibited the naloxone-induced symptoms of morphine withdrawal in morphine-dependent mice. The above results indicate that agonists of group II mGlu receptors may play a role in the therapy of anxiety and/or drug-dependence states. The brain sites of action of LY 354740 need to be identified and the mechanism of both the above described effects remains to be elucidated. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: mGlu II receptors; LY 354740; Behavioural despair test; Tail suspension; Conflict drinking test; Four-plate test; Morphine withdrawal; Anxiety; Dependence; Depression

1. Introduction

Excitatory amino acids (EAA) are in abundance in the brain: it is estimated that ca. 50% of neurons in the brain may utilize glutamate as a neurotransmitter (McGeer et al., 1987). Glutamate acts by stimulating ionotropic and metabotropic glutamate receptors (Monaghan et al., 1989; Conn and Pin, 1997), and seems to play a major role in both the physiology and pathophysiology of the central nervous system. Some data show that changes in ionotropic glutamate neurotransmission may be involved in a variety of neuropsychiatric disorders (Wroblewski and Danysz, 1989; Danysz et al., 1996). Converging lines of evidence indicate a crucial involvement of glutamate receptors in the phenomena related to drug-seeking behaviour (Stephens, 1995; Trujillo and Akil, 1995), as well as in the mechanism of action of anxiolytic (for review see Wiley and Balster, 1993) and antidepressant drugs (Skolnick et al., 1996; Layer et al., 1998). With regard to the physical dependence on opioids, antagonists of the NMDA receptor complex have been shown to attenuate development (Marek et al., 1991), expression (Cappendijk et al., 1993) and maintenance (Popik and Skolnick, 1996; Popik et al., 1998) of the ongoing morphine dependence. Regarding the role of this receptor complex in anxiety and depression, it has been shown that antagonists of NMDA receptors, as well as glycine partial agonists exhibit an anxiolytic (Jessa et al., 1996; Przegaliński et al., 1996) and an antidepressant-like activity in animals (Trullas and Skolnick, 1990; Trullas et al., 1991; Przegaliński et al., 1997).

Great hopes that ionotropic receptor antagonists, mainly NMDA receptor antagonists, could be applied in the therapy of CNS disorders, were hampered by the fact that several of the antagonists (mainly NMDA...
receptors) produce pronounced, undesirable side-effects such as psychotomimetic effects, memory impairment and ataxia in preclinical studies (Danyasz et al., 1996). One of the possible solutions to this problem is to use substances which modulate the function of NMDA receptors, antagonists or partial agonists of the glycine site (Skolnick et al., 1996). Another approach is connected with the discovery of a new major subtype of glutamate receptors–metabotropic receptors, which also modulate the function of the glutamatergic system.

Metabotropic glutamate (mGlu) receptors are members of a relatively new receptor family. Eight different subtypes of mGlu receptors have been cloned so far (mGlu 1-8). On the basis of their sequence homology, effector coupling and pharmacology, mGlu receptors have been subdivided into three groups: group I mGlu receptors (mGlu1 and mGlu5), positively coupled to phospholipase C; group II mGlu receptors (mGlu2 and mGlu3) and group III mGlu receptors (mGlu4, mGlu6, mGlu7 and mGlu8), negatively coupled to adenylate cyclase (Pin and Duvoisin, 1995; Conn and Pin, 1997).

Group II mGlu receptors have both a post- and presynaptic localization (Petralia et al., 1996) and may serve as autoreceptors at brain structures (Ugolini and Bordi, 1995). It has been proposed that activation of presynaptic mGlu receptors located on glutamatergic nerve terminals causes a decrease in glutamate release, therefore inhibiting glutamatergic excitatory transmission (for review, see Glaum and Miller, 1994). Hence agents stimulating presynaptic autoreceptors (including group II mGluR receptors) can act as functional antagonists of the glutamatergic system (Lovingier and McGool, 1995; Manzoni et al., 1995). Stimulation of postsynaptic group II mGlu receptors also leads to inhibition of cAMP accumulation in the brain (Schoepp et al., 1992). Therefore, irrespective of their synaptic localization, stimulation of group II mGlu receptors produces inhibitory responses in the brain.

A number of reports on the molecular biology/biochemistry of mGlu receptors have been published recently. However, data concerning pharmacological effects of mGlu receptor agonists/antagonists are still limited, mainly due to the lack of selective pharmacological tools which would penetrate into the brain.

Despite the lack of mGlu receptor agonists/antagonists which penetrate to the brain, Fundytus and Coderre (1994, 1997) and Fundytus et al. (1997) demonstrated that chronic inhibition of PI-coupled mGluRs by intracerebroventricular administration of (S)-4-carboxyphenylglycine resulted in the diminished severity of naloxone-precipitated withdrawal symptoms in morphine-dependent rats. Similar effects were exerted by chronic administration of the group II mGlu receptor antagonist 2s,1s,2’s-2-methyl (2’carboxy-cyclopropanol) glycine or the group III mGlu receptor antagonist 2-ethyl-1-amino-4-carboxyphenylglycine. Pile and Legutko (1995a,b) reported that mGlu receptors were influenced by antidepressant drugs. Some data on the anxiolytic effects of mGlu receptor antagonists after intrahippocampal injections have also been published (Chojnacka-Wojcik et al., 1997a,b).

The discovery of the potent subtype-selective mGlu receptor agonist (+)-2-aminobicyclo[3,1,0]hexane-2,6-dicarboxylic acid (LY 354740) (Monn et al., 1997; Bond et al., 1997), which is a selective agonist at human recombinant and native rat II mGlu receptors and is the first agonist of this class of receptors that penetrates into the brain, has offered a valuable tool to study its central effects following systemic (i.p. or p.o.) administration to animals. LY 354740 has nanomolar agonist activity at group II mGlu receptors and possesses no activity at other ionotropic or metabotropic glutamate receptors (Monn et al., 1997). LY 354740 prevented ACPD-induced limbic seizures in mice, produced a potent anxiolytic-like activity in an elevated plus maze test in mice and fear-potentiated startle models in rats (Helton et al., 1998), and ameliorated symptoms of nicotine withdrawal in rats (Helton et al., 1997); therefore we decided to study its effects in different models of anxiety, depression and drug withdrawal.

2. Materials and methods

2.1. Animals and housing

The experiments were performed on male Wistar rats (200–250 g), male Albino Swiss mice or male C57BL/6J (20–25 g) mice. The animals were kept on a natural day-night cycle at a room temperature of 19–21°C, with free access to food and tap water before the experiment. Each experimental group consisted of six to 10 animals/dose, and the animals were used only once in each test. In rats, all injections were given in a volume of 4 ml/kg, and in mice in a volume of 10 ml/kg. The experiments were performed by an observer blind to the treatment. All experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences in Krakow.

2.2. Conflict drinking test (Vogel test)

A modification of the method of Vogel et al. (1971) was used. On the first day of the experiment, the rats were adapted to the test chamber for 10 min. It was a plexiglass box (27 × 27 × 50 cm), equipped with a grid floor of stainless steel bars and a drinking bottle containing tap water. After the adaptation period, the animals were deprived of water for 24 h, and were then placed in the test chamber for another 10-min adaptation period during which they had free access to the
drinking bottle. Afterwards, they were allowed a 30-min free-drinking session in their home cage. After another 24-h water deprivation period, the rats were again placed in the test chamber and were allowed to drink for 30 s. Immediately afterwards, drinking attempts were punished with an electric shock (0.5 mA). The impulses, delivered as a square wave pulses between the grid floor and the spout of the drinking bottle lasted for 1 s and were released every 2 s. The number of shocks accepted throughout a 5-min experimental session was recorded.

2.3. Shock threshold and free-drinking tests

To control for the possibility of drug-induced changes in the perception of a stimulus or in the thirst drive, which might have contributed to the activity in the conflict drinking test, stimulus threshold measurements and a free-drinking experiment were also carried out. In both cases, the rats were treated before the experiment in the same manner as described in the conflict drinking test, including two 24-h water deprivation periods separated by 30 min of water availability. In the shock threshold test, the rats were placed individually in the box, and electric shocks were delivered through the grid floor. The shock threshold was determined stepwise at 15 s shock free intervals by increasing manually the current (0.1, 0.2, 0.3, 0.4, 0.5 mA), the shock lasted for 1 s and was delivered through the grid-floor until a rat showed an avoidance reaction (jump or jerk) to an electric stimulus Table 1.

In the free-drinking test, each animal was allowed to drink from the water spout. Licking was not punished. The total amount of water (ml), consumed in 5 min, was recorded for each rat.

2.4. Water intake test

The rats were housed and tested in individual cages (40 × 27 × 15 cm), with free access to food and tap water at all times. On the day of the test, water bottles were weighted at the time of drug administration. Tap water was presented immediately after drug injection. Water intake (ml) was recorded 1, 2, 4, 6, and 24 h later. 5-Hydroxy-L-tryptophan (L-5-HTP) was used as a reference drug (Rowland et al., 1987).

2.5. Four-plate test

Single mice were dropped gently onto the plate, and each animal was allowed to explore for 15 s. Afterwards, each time a mouse passed from one plate to another, the experimenter electrified the whole floor for 0.5 s, which evoked a visible flight reaction of the animal. If the animal continued running, it received no new shock for the following 3 s. The number of punished crossings was counted for 60 s (Aron et al., 1971).

2.6. Locomotor activity

The spontaneous locomotor activity of mice was measured with photoresistor actometers (circular cages, diameter 25 cm, two light sources, two photoresistors). The mice were placed individually in an actometer for a period of 30 min.

2.7. Rota-rod test

Mice were preselected 1 h before the test on the rotating rod (3 cm in diameter, 6 r.p.m.). The animals that maintained their balance for 2 min were placed on the same rod after drug administration and were observed for 2 min. The number of animals falling from the rota-rod within 2 min was recorded.

2.8. Behavioural despair test

The studies were carried out on mice according to the method of Porsolt et al. (1977).

Briefly, mice were dropped individually into a 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 the water. The duration of immobility was recorded during the last 4 of the 6 min testing period.

2.9. Tail suspension test

Immobility was induced by tail suspension according to the procedure of Steru et al. (1985). C57BL/6J mice were hung individually on a plastic string 75 cm above the table top with an adhesive tape placed ca. 1 cm from the tip of the tail. Immobility duration was recorded for 8 min. Mice were considered immobile only when they hung passively and completely motionless.

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>Shock threshold (mA)</th>
<th>Water consumption (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>—</td>
<td>0.4 ± 0.03</td>
<td>8.0 ± 0.5</td>
</tr>
<tr>
<td>LY354740</td>
<td>0.5</td>
<td>0.4 ± 0.03</td>
<td>8.0 ± 0.7</td>
</tr>
<tr>
<td>LY354740</td>
<td>1.0</td>
<td>0.4 ± 0.03</td>
<td>8.1 ± 0.4</td>
</tr>
</tbody>
</table>

*LY 354740 was administered 30 min before the test. The values represent the mean ± SEM (n = 6–7 rats per group).*
2.10. Morphine dependence and withdrawal

Mice were treated with morphine (30 mg/kg, twice daily, at 09:30 h and 17:30 h) for 3 days, and an additional dose was administered on the morning of the 4th test day. One hour and 30 min after the last dose of morphine, the mice were injected with LY 354740. The animals were challenged with naloxone (4 mg/kg) 30 min. after administration of LY 354740 and placed immediately in transparent glass beakers (vol. of 10 l). The number of jumps was recorded during a 10-min test period (Popik and Skolnick, 1996).

2.11. Analysis of the data

The obtained data were presented as means ± SEM, and evaluated by a one-way analysis of variance, followed by Dunnett’s multiple comparison test, where P < 0.05 was considered significant.

2.12. Drugs

(+) -2- Aminobicyclo-[3,1]hexane -2,6 -dicarboxylic acid (LY 354740, donated by Dr D.D. Schoepp (Eli-Lilly, Indianapolis IN), and diazepam (Polfa-Poznań, Poland) were suspended in a 1% aqueous solution of Tween 80. Morphine hydrochloride and imipramine hydrochloride (Polfa-Krakow, Poland), naloxone (RBI, Nantick, MA) and L-5-Hydroxytryptophan (Sigma, St. Louis, MO) were dissolved in saline. All the compounds were administered intraperitoneally (i.p.). LY 354740 was given at 30 min before the tests; diazepam and imipramine, at 60 min.

3. Results

3.1. Conflict drinking test in rats

LY 354740 at doses of 0.5 and 1.0 mg/kg i.p. significantly (by 330% and 270%, respectively) increased the number of shocks accepted during the experimental session in the Vogel test. The dose response curve to LY 354740 was bell shaped. The effect of LY 374540 at a dose of 0.5 mg/kg was comparable to that caused by diazepam at a dose of 8 mg/kg. LY 354740 at doses of 0.25, 2 and 4 mg/kg was inactive in this test (Fig. 1). The possibility that the efficacy of effective doses of LY 354740 was related to reduced perception of the stimulus or to an increased thirst drive, was excluded since LY354740, tested at the effective doses in the conflict drinking test, did not change the threshold current (0.4 ± 0.03 mA) nor water intake (8.0 ± 0.5 ml) compared to vehicle treatment. Since 8 ml of water is a high level of consumption, although similar to that reported by others (Stefanski et al., 1992), it might be argued that rats would find it difficult to drink at a faster rate. Therefore we performed experiments with the water intake in water non-deprived rats. LY 354740 tested at doses effective in the conflict drinking test (1 mg/kg) had no significant effect on the water consumption (Table 2), while 5-HTP (20 mg/kg) used as a standard drug (Rowland et al., 1987) significantly increased the water intake. The results further excluded the possibility that the action of LY 354740 was due to that increased thirst drive.

3.2. Four-plate test in mice

LY 354740 given at doses of 1.0, 2.0, 4.0 and 8.0 mg/kg increased the number of punished crossings in a four-plate test. The increase observed after doses of 4 and 8 mg/kg i.p. was statistically significant, the maximum effect appearing after a dose of 8 mg/kg (a 50% increase above the control level). The effect of LY 354740 at a dose of 8 mg/kg was comparable to that of diazepam, 2 mg/kg (Fig. 2).

3.3. Locomotor activity and rota-rod test in mice

Administration of LY 354740 at doses of 2.0, 4.0 and 8.0 mg/kg produced a dose-dependent and statistically significant reduction in spontaneous locomotor activity, by about 32, 40 and 55%, respectively (Fig. 3). LY 354740 at doses of 2.0, 4.0 and 8.0 mg/kg did not disturb locomotor coordination on the rota-rod (data not shown).

3.4. Behavioural despair test and tail suspension test in mice

LY 354740 at doses of 0.5, 1.0, 4.0 and 16.0 mg/kg did not change the behaviour of mice in the be-

Table 2

Effect of LY 354740 on the amount of water intake in water non-deprived rats a

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Water consumption (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>Vehicle</td>
<td>—</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>LY354740</td>
<td>1.0</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>5-HTP</td>
<td>20.0</td>
<td>1.4 ± 0.3*</td>
</tr>
</tbody>
</table>

* LY 354740 and L-5-HTP were administered immediately before the test. The values represent the mean ± SEM (n = 6 rats per group).

havioural despair test. Imipramine, 30 mg/kg, used as the standard drug, significantly decreased the immobility time in Porsolt’s test (Fig. 4). LY 354740 used in doses of 0.5 and 8.0 mg/kg did not change the behaviour of mice in the tail suspension test; in contrast imipramine, 10 mg/kg, significantly decreased immobility time (Fig. 5).

3.5. Naloxone-induced morphine withdrawal symptoms

The morphine-dependent mice pretreated with naloxone (4 mg/kg i.p.) demonstrated a pronounced withdrawal syndrome which was manifested by vertical jumping. Jumping was not observed in vehicle-treated mice challenged with naloxone or in morphine-dependent mice challenged with vehicle (data not shown). LY 354740 at doses of 0.15, 0.3 and 5 mg/kg, significantly reduced the naloxone-induced jumping, the 5 mg/kg dose of LY 354740 decreased jumping by 67% (Fig. 6).

4. Discussion

Metabotropic glutamate receptors are widely spread across the central nervous system (e.g. Conn and Pin, 1997). In spite of a great number of biochemical and/or molecular pharmacology reports behaviour data on the effects of mGlu receptor agonists/antagonists are still sparse. The main reason is the absence of brain-penetrating substances. LY 354740 is the first agonist of the group II mGlu receptors which penetrates into the brain and is potent at a nanomolar range (Monn et al., 1997).

4.1. Anxiolytic-like effects of LY 354740

An anxiolytic-like effect of LY 354740 was evaluated in two behavioural tests. The rat Vogel test (Vogel et al., 1971) is a procedure widely employed as a screening method for anxiolytics, and is considered to be one of the most specific screening methods for these drugs (Pollard and Howard, 1990). The four-plate test in mice is a simple, efficient, high-speed procedure (Aron et al., 1971) for anti-anxiety drugs. In both these tests LY 354740 produced anxiolytic-like effects. The present results corroborate and extend the data of Helton et al., 1998 and Bond et al., 1997, who reported that LY 354740 produced anxiolytic responses in a fear-potentiated startle and in an elevated plus-maze model of anxiety in rats. Sedation produced by LY 354740 in mice is not responsible for the anti-anxiety effects, as in such a case a reduced number of punished-crossings episodes in mice is expected, while an opposite effect was found in our experiment. The bell shaped dose response observed in our experiment in the Vogel test is characteristic for various drugs with anxiolytic properties, for example for pentobarbital (Vogel et al., 1971), or for buspirone (Przegaliński et al., 1989). Sedation was observed after higher doses of LY354740 in our experiments, that might explain the bell shaped dose response.

LY 354740 exerts an anxiolytic-like effect, its efficacy being similar to that of the glycine partial agonist-ACPC (e.g. Przegaliński et al., 1996). ACPC acts as a functional antagonist at glycine receptors in vivo (Marvizon et al., 1989), leading to a decrease in NMDA-mediated neurotransmission. Since glutamatergic

![Fig. 2. The effect of LY 354740 on the punished behaviour in mice (a four-plate test). LY 354740 was administered at 30 min, and diazepam at 60 min before the test. Values represent the mean ± SEM (n = 8–10 mice per group) of the number of punished crossing episodes. ANOVA as follows F(6,49) = 7.693, P < 0.001. * P < 0.05; ** P < 0.01 versus control group.](image-url)
transmission via mGlu receptors may result in potentiation of the ionotropic glutamate response in various preparations (see Glaum and Miller, 1994), a functional blockade of mGlu receptors (via simulation of presynaptic receptors) may also lead to a decrease in the NMDA-receptor mediated neurotransmission.

Benzodiazepines, which are the most popular anxiolytic drugs, act via facilitation of inhibitory GABA-ergic transmission. Benzodiazepines are effective agents, but disadvantageous side effects as sedation, ataxia and abuse liability are associated with their administration. Decreased glutamatergic transmission, which leads to overall inhibitory effects in the central nervous system may have consequences similar to the effect of increased GABA-ergic transmission and may thus be an important outcome of stimulation of group II mGlu receptors in brain.

4.2. Effects of LY 354740 in models of depression

LY 354740 did not shorten the immobility time in two different models of depression in mice, a tail suspension test and a behavioural despair test, whereas the classical antidepressant drug imipramine did remarkably. Our earlier data indicate that the group I mGlu receptor system is influenced by antidepressant drugs, as the action of (R,S)-3,5-dihydroxyphenylglycine, an agonist of group I glutamate receptors, was attenuated by chronic imipramine and electroconvulsive shock treatments (Palucha et al., 1998; Pilc et al., 1998). The receptors negatively coupled to adenylate cyclase (group II and III mGlu receptors) were not affected by either treatment (Pilc and Legutko, 1995a,b). Therefore the negative results obtained with LY 354740 indicate...
that stimulation of group II mGlu receptors is not effective in models of depression, which further supports the notion that group II mGlu receptors are not involved in the mechanism of action of antidepressant drugs.

However both tests detect a drug interaction with noradrenergic and/or serotonergic transmission (Lucki, 1997). Experiments applying different models of depression (e.g. chronic mild stress (Willner and Papp, 1997)), which are based upon chronic drug administration, and are able to detect antidepressant-like properties of ACP (Przegalinski et al., 1997), a substance which similarly to LY 354740 decreases glutamatergic transmission, should be performed in order to fully address the issue.

4.3. Effects of LY 354740 in morphine dependence

Our results extend the data which show that LY 354740 ameliorated symptoms of nicotine withdrawal in rats, while its racemate compound LY 314582 was effective in attenuation of diazepam withdrawal symptoms (Helton et al., 1997, 1998). Sedative effects of higher doses of LY 354740 may contribute to its inhibition of the naloxone-precipitated symptoms of morphine withdrawal; however, its effectiveness at a lower dose (0.3 mg/kg), which was without effect on the locomotor activity, point to the specificity of action of LY 354740. Attenuation of the naloxone-precipitated morphine abstinence syndrome by LY 354740 in mice is in line with some earlier data of Fundytus and Coderre (1994, 1997) and Fundytus et al. (1997), who reported that intraventricular infusions of (S)-4-carboxyphenylglycine attenuated the development of morphine dependence. (S)-4-carboxyphenylglycine is an antagonist of group I mGlu receptors and an agonist of group II mGlu receptors. Since α-methyl-2-(carboxycyclopropyl)glycine (MCCG), an antagonist of group II mGlu receptors, significantly lengthened the time during which the animals were in a withdrawal state (Fundytus et al., 1997), it may be speculated that stimulation of group II mGlu receptors is responsible for attenuation of morphine withdrawal, while the blockade of II group mGlu receptors may enhance the symptoms of drug withdrawal. The mechanism by which LY 354740 blocks the effects of naloxone in morphine-dependent rats cannot be determined at present; nevertheless inhibition of glutamate release via stimulation of presynaptic mGlu II receptors and, in consequence blockade of glutamate-induced hyperexcitability may be involved.

In conclusion, LY 354740 is a systemically active agonist of group II mGlu receptors. LY 354740 produced anxiolytic-like effects in the Vogel test in rats and in the four-plate test in mice. It was also found that LY 354740 decreased spontaneous locomotor activity in mice, but did not disturb motor coordination. In behavioural models of depression, LY 354740 did not produce any antidepressant-like effects. LY 354740 inhibited the symptoms of morphine withdrawal in morphine-dependent mice. The above results indicate that agonists of II group mGlu receptors may play a role in the therapy of anxiety and/or drug-dependence states. Identification of the brain sites of action of LY 354740 and of the mechanism of these effects still requires further studies.

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