Pharmacology Biochemistry and Behavior, Vol. 64, No. 3, pp. 461–466, 1999

0091-3057/99/$–see front matter

PII S0091-3057(99)00214-2

Tolerance to Anxiolytic- and Antidepressant-Like Effects of a Partial Agonist of Glycine$_B$ Receptors

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Received 25 June 1998; Revised 27 October 1998; Accepted 27 October 1998

PRZEGALIŃSKI, E., E. TATARCZYŃSKA, A. KŁODZIŃSKA AND E. CHOJNACKA-WÓJCIK. *Tolerance to anxiolytic- and antidepressant-like effects of a partial agonist of glycine$_B$ receptors.* PHARMACOL BIOCHEM BEHAV **64**(3) 461–466, 1999.—The present study examined effects of acute and repeated administration of 1-aminocyclopropanecarboxylic acid (ACPC), a partial agonist of glycine$_B$ receptors, in the conflict drinking test and the forced swim test in rats. Diazepam and imipramine were used, respectively, as reference drugs in those tests. In the conflict drinking test, acute administration of ACPC (200 mg/kg) increased fivefold the number of punished licks. A three- and fivefold increase in the number of punished licks was observed in rats treated repeatedly with ACPC (200 mg/kg daily; 14 days) and challenged with the same dose of the drug 24 h or 4 days later, respectively. A single injection of ACPC (400 mg/kg) reduced by 40% the immobility time in the forced swim test. In rats treated repeatedly with ACPC (400 mg/kg daily; 14 days) and challenged with the same dose 24 h or 4 days later, the drug either produced no singnificant effect or reduced the immobility time by 50%, respectively. On the other hand, no changes in anxiolytic- and antidepressant-like effects of chronically administered diazepam (10 mg/kg daily; 14 days) and imipramine (30 mg/kg daily; 14 days), respectively, were observed. The above results indicate that tolerance develops to the anxiolytic- and, particularly, to the antidepressant-like activity of ACPC. © 1999 Elsevier Science Inc.

ACPC (1-aminocyclopropanecarboxylic acid) Tolerance Conflict drinking test Forced swim test Rat

THE *N*-methyl-D-aspartate (NMDA) receptor complex is a highly regulated ligand-gated ion channel. This receptor complex is comprised of subunits with interdependent recognition sites for glutamate and NMDA, glycine, polyamines, and cation channel blockers (45). It appears that activation of the cation channel crucially depends on the binding of agonists at both NMDA and glycine sites (38). Moreover, due to its action at the strychnine-insensitive glycine receptor (glycine$_B$ receptor), glycine is essential for in vivo activation of the NMDA receptor (15). Substances with a partial agonistic or antagonistic activity at glycine sites can function as NMDA receptor antagonists. In line with their action at the receptor level, antagonists at NMDA and glycine sites share similar pharmacology in vivo. For example, NMDA receptor antagonists, as well as glycine receptor partial agonists and antagonists show psychotropic properties, including an antidepressant- and an anxiolytic-like activity in different animal models (1,7,9,21,22,27,40). However, potential utility of competetive and noncompetetive NMDA antagonists is strictly limited by their undesirable side effects such as muscle relaxation, ataxia, amnesia, and psychotomimetic effects (8), while glycine partial agonists and antagonists are devoid of such properties (10,18,31).

The results of our earlier study with 1-aminocyclopropanecarboxylic acid (ACPC), a partial agonist at glycine$_B$ receptors (23,35), showed an antidepressant-like activity in the forced swim test (34) and an anxiolytic-like effect in the conflict drinking test in rats (33), thus confirming the findings of other authors (28,39,41,44); however, negative results revealing an anxiolytic-like activity of the drug were also reported (16).

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Depending on the experimental model used, the pharmacological activity of chronically administered ACPC is either maintained (4,28,30,36,43) or desensitizated (19,36). Notably, the anxiolytic-like activity of ACPC was maintained during chronic treatment in the elevated plus-maze in mice (36), and positive neuroprotective effects of chronic ACPC persisted in animal models of neurodegeneration (4,43). However, chronic treatment with ACPC produced a loss of behavioral activity in the Porsolt swim test in mice (36) and rats (19), although downregulation of cortical β-adrenoceptors and reversal of chronic mild stress-induced reductions in sucrose consumption, i.e., effects characteristic of chronic treatment with a number of effective antidepressants (12,29), were observed after repeated administration of ACPC (28,30).

The aim of the present study was to determine whether the lack of tolerance to an anxiolytic-like activity of ACPC is a general phenomenon. To this end we examined in rats the effect of chronic treatment with the drug in the conflict drinking test using the forced swim test as a reference. The traditional anxiolytic diazepam and the antidepressant imipramine were also examined in both those tests, respectively.

METHOD

Animals and Housing

Male Wistar rats (purchased from a licensed dealer Górzkowscy, Warsaw, Poland), weighing 250 ± 20 g, were used in the study. The animals were kept in groups of eight to a cage (60 × 38 × 20 cm) on a natural day–night cycle (from September to December), at a room temperature of 19–21°C, with free access to food (standard laboratory pellets, LSM) and tap water before the experiment.

During the week preceding drug administration, the rats were handled briefly and injected with saline each day to reduce stress associated with injection. The animals were used only once throughout the study. All the experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

Treatment Schedules and Drugs

The rats received daily intraperitoneal (IP) injections of ACPC, diazepam, imipramine, or saline in a volume of 4 ml/kg for 14 days. Injections were administered between 0900 and 1000 h. Twenty-four hours or 4 days after the last injection, a challenge dose of those drugs or saline was administered. The tests started 60 min after administration of the challenge dose. All the experiments were performed between 1000 and 1400 h.

The following drugs were used: 1-aminocyclopropanecarboxylic acid (ACPC) (Symphony Pharmaceutical Inc., Malvern, PA), diazepam (Relanium, amp., Polfa, Poznań), and imipramine (hydrochloride, Polfa, Starogard Gdański). ACPC and imipramine were dissolved in sterile saline. Diazepam from original ampoules was diluted in sterile saline.

Conflict Drinking Test (Vogel Test)

A modification of a method of Vogel et al. (42) was used. On day 13 of treatment with saline, ACPC or diazepam (60 min before administration), or on day 2 of the washout period, the rats were adapted for 10 min to the test chamber. It was a Plexiglas box (27 × 27 × 50 cm), equipped with a grid floor of stainless steel bars, and a drinking bottle with tap water. After an initial 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 placed again 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 were released every 2 s (timed from the moment when a preceding shock was delivered) in 1-s periods, between the grid floor and the spout of the drinking bottle.The number of shocks accepted throuhgout a 5-min experimental session was counted by an experimenter who observed a behavioral reaction (e.g., body jerks) of rats to the electric shock. The experimenter did not know which treatment had been applied to the rats.

Shock Threshold and Free-Drinking Tests

To control the possibility of drug-induced changes in the perception of the stimulus or in the thirst drive, which might have contributed to the activity in the conflict drinking test, a stimulus threshold measurements and a free-drinking experiment were also carried out. In the shock threshold and free-drinking tests, the rats were treated in the same manner (before the experiment) as it was described in the conflict drinking test (twofold adaptation in experimental boxes and 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 by manually increasing the current (0.1, 0.2, 0.3, 0.4, 0.5, 0.6 mA; the shocks lasted 1 s) delivered through the grid-floor until a rat showed an avoiding reaction (jump, jerk, or alike) to an electric stimulus.There was a 15-s shock-free interval between the steps.

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 during 5 min, was recorded for each rat.

Behavioral responses were recorded by one experimenter who did know which treatment the rats had received.

Forced Swim Test (Porsolt Test)

The studies were carried out on rats according to the method of Porsolt et al. (32). Briefly, on day 14 of treatment with saline, ACPC or imipramine (60 min before administration), or on day 3 of the washout period, the animals were individually placed in Plexiglas cylinders (40 cm high; 18 cm in diameter) containing 15 cm of water, maintained at 25°C. After 15 min they were removed to a drying room (30°C) for 30 min. They were replaced in the cylinder 24 h later, and the total duration of immobility was measured during a 5-min test. The time during which the animals were immobile was measured by two experimenters who did not know which treatment the rats had received.

Statistical Analysis

All the data are expressed as the mean ± SEM. A statistical analysis of each block of results (obtained on the same day) was made by a separate one-way ANOVA. Specific comparisons were carried out with the Newman–Keuls test.

TABLE 1

EFFECTS OF CHRONIC TREATMENT WITH ACPC AND DIAZEPAM IN THE CONFLICT DRINKING TEST IN RATS

Chronic Dose (14 days)	Challenge Dose	*n*	Number of Accepted Shocks/ 5 Min	
			Mean ± SEM	%
Saline	Saline	8	7.6 ± 0.6	100
Saline	ACPC (200)	8	37.3 ± 7.1†	490.8
ACPC (200)	ACPC (200)	9	21.4 ± 3.4†§	281.6
ACPC (200)	ACPC (200)*	8	37.4 ± 7.2‡	492.1
Saline	Diazepam (10)	8	53.5 ± 7.8‡	703.9
Diazepam (10)	Diazepam (10)	9	46.9 ± 5.4‡	617.1
			$F(5, 44) = 9.796$	
			$p < 0.0001$	

Rats were injected (IP) with saline, ACPC or diazepam for 14 days and challenged with saline, ACPC or diazepam 24 h later.

*A challenge dose of ACPC was administered 96 h (4-day washout) later.

n—number of rats per group.

†$p < 0.05$, ‡$p < 0.01$ vs. chronic saline + saline; §$p < 0.01$ vs. chronic saline + ACPC, Newman–Keuls test.

RESULTS

The general behavior of rats chronically treated with ACPC, diazepam, and imipramine did not differ from that of animals treated repeatedly with saline. No significant difference was observed, either, in the body weight. In fact, increases in the body weight of animals treated with saline, ACPC (200 mg/kg), ACPC (400 mg/kg), diazepam (10 mg/kg), and imipramine (30 mg/kg) were 56.4 7.9 g, 42.9 ± 2.4 g, 45.6 ± 3.8 g, 44.3 ± 4.4 g, and 48.2 ± 4.1 g, respectively.

Anxiolytic-Like Activity

ACPC administered in a single dose (200 mg/kg) to rats chronically pretreated with saline showed an axiolytic-like activity in the conflict drinking test in rats: the drug increased fivefold the number of shocks accepted. Chronic treatment with ACPC (200 mg/kg) attenuated the effect of a challenge dose of ACPC (200 mg/kg; 24 h after the last dose) and increased only about threefold the punished responding. In another group of rats, a 4-day washout after chronic ACPC treatment was sufficient to induce such an increase in the number of shocks accepted after ACPC (200 mg/kg) challenge as that observed after single injection of the drug (Table 1).

In rats chronically pretreated with saline or diazepam (10 mg/kg), a challenge dose of the drug (10 mg/kg; 24 h after the last treatment) increased ca. seven- and sixfold the number of shocks accepted, respectively (Table 1).

Shock Threshold and Free-Drinking Tests

As shown in Table 2, a challenge dose of ACPC (200 mg/kg) injected to rats chronically pretreated with saline or ACPC (200 mg/kg), as well as a challenge dose of diazepam (10 mg/kg) injected to rats chronically pretreated with saline or diazepam (10 mg/kg) increased neither the threshold current nor the water intake.

Antidepressant-Like Activity

A single dose of ACPC (400 mg/kg) injected to rats chronically pretreated with saline significantly reduced the immobility by ca. 40%. In the animals pretreated with ACPC (400 mg/kg) and challenged 24 h or 4 days later with the same dose (400 mg/kg) of the drug, a 15% (nonsignificant) or 50% reduction, respectively, in the immobility was observed (Table 3).

In rats chronically pretreated with vehicle or imipramine (30 mg/kg), a challenge dose of the drug (30 mg/kg; 24 h after the last treatment) shortened the immobility time by ca. 37 and 62%, respectively.

DISCUSSION

The results of the present study show that tolerance to anxiolytic- and antidepressant-like effects of ACPC develops in rats after chronic (14 days) treatment with this partial agonist of glycine$_B$ receptors (23) and functional antagonist of NMDA receptors (41), the drug being administered in doses selected on the basis of our previous results (33,34).

Actually, a single dose of ACPC (200 mg/kg) produced an antianxiety effect, having increased almost five times the number of punished licks in control animals treated chronically (14 days) with saline in the conflict drinking test. On the other hand, the same challenge dose of ACPC induced a significantly weaker effect (an only threefold increase in the number of punished licks) in rats chronically pretreated with ACPC (200 mg/kg daily). However, the tolerance to the anti-

TABLE 2

EFFECTS OF CHRONIC TREATMENT WITH ACPC AND DIAZEPAM ON THE SHOCK THRESHOLD AND THE AMOUNT OF WATER CONSUMED BY WATER-DEPRIVED RATS

Chronic Dose (14 days)	Challenge Dose	*n*	Shock Threshold (mA)	Water Consumption (ml)
Saline	Saline	6	0.43 ± 0.03	11.5 ± 0.4
Saline	ACPC (200)	7	0.48 ± 0.03	12.4 ± 0.5
ACPC (200)	ACPC (200)	7	0.44 ± 0.02	11.0 ± 0.6
Saline	Diazepam (10)	7	0.46 ± 0.02	11.6 ± 0.6
Diazepam (10)	Diazepam (10)	7	0.40 ± 0.03	11.6 ± 0.4
			$F(4, 29) = 1.471$	$F(4, 29) = 0.9833$
			NS	NS

Rats were injected (IP) with saline, ACPC, or diazepam for 14 days and challenged with saline, ACPC, or diazepam 24 h later.

n—Number of rats per group.

TABLE 3
EFFECTS OF CHRONIC TREATMENT WITH ACPC AND IMIPRAMINE IN THE FORCED SWIMMING TEST IN RATS

Chronic Dose (14 days)	Challenge Dose	*n*	Mean ± SEM	%
Saline	Saline	10	216.6 ± 7.7	100
Saline	ACPC (400)	10	128.9 ± 14.4†	59.5
ACPC (400)	ACPC (400)	10	184.3 ± 9.0‡	85.1
ACPC (400)	ACPC (400)*	10	109.3 ± 10.5†	50.5
Saline	Imipramine (30)	10	136.5 ± 10.6†	63.0
Imipramine (30)	Imipramine (30)	10	82.3 ± 8.7*§	38.0
			$F(5, 54) = 21.943$	
			$p < 0.0001$	

Rats were injected (IP) with saline, ACPC or imipramine for 14 days and challenged with saline, ACPC or imipramine 24 h later.

*A challenge dose of ACPC was administered 96 h (4-day washout) later.

n—number of rats per group.

†$p < 0.01$ vs. chronic saline + saline; ‡$p < 0.01$ vs. chronic saline + ACPC.

§$p < 0.01$ vs. chronic saline + imipramine, Newman–Keuls test.

conflict effect of ACPC was found to be reversible, as it was fully restored within 4 days after cessation of treatment with the drug.

The above observations differ from the results reported by Skolnick et al. (36), who have found that ACPC administered chronically retains its anxiolytic-like activity in the elevated plus-maze test in mice. Similarly, no tolerance to the antianxiety effect in the conflict drinking test, but even enhancement of the antineophobic action in the open-field test in rats have recently been described following repeated treatment with the competitive NMDA receptor antagonist CGP 37849 (14). The cause of these discrepancies is obscure; nevertheless, they seem to indicate that the development of tolerance to anxiolytic-like effects of ACPC is species and test dependent. Moreover, it is noteworthy that in the above-mentioned studies (14,36) ACPC and CGP 37849 were administered only for a period of 7 and 5 days, respectively, while in our experiment the animals were treated with ACPC for14 days. At the same time, the duration of treatment seems to be important to the development of tolerance to anxiolytic-like effects. For example, it has been reported that such a phenomenon requieres, as a rule, at least 3 weeks of treatment with benzodiazepines (5,11); therefore, this may be the reason why we observed no tolerance to an anticonflict effect of diazepam administered—like ACPC—for 14 days. Nonetheless, it should be noted that the issue of whether tolerance develops to an anxiolytic-like activity of benzodiazepines is controversial (17).

Importantly, the anticonflict effect of ACPC and diazepam, as well as the tolerance or its lack to such an effect of the former or the latter drug, respectively, seem to be independent of changes in the baseline drinking, the pain threshold, or the locomotor activity. In fact, neither acute nor chronic treatment with either drug affected the nonpunished water intake or the shock threshold, this observation being supported—at least regarding the single dose effect of ACPC—by our earlier results (33). Moreover, it was also reported that ACPC administered acutely in doses up to 400 mg/kg IP, or chronically in a dose of 200 mg/kg intravenously did not affect the locomotor activity (19,34). At the same time, rapid development of tolerance to the depressant effect of high doses of diazepam (15 mg/kg IP or 20 mg/kg perorally) on the locomotor activity was described in mice and rats, respectively (24,37).

The antidepressant-like activity of ACPC was measured in a forced swim test (32), which is commonly accepted as a preclinical behavioral screening test for detecting an antidepressant drug action (2). We found that in control saline-treated rats a single dose (400 mg/kg) of the drug reduced the immobility time by about 40%. On the other hand, in animals chronically treated with ACPC (400 mg/kg, daily) and later challenged with the same dose of the drug, it lost its activity, producing only a nonsignificant, 15% reduction in immobility. Again, that effect was apparently reversible, as the antiimmobility action of ACPC was fully restored after a 4-day washout period. In contrast to ACPC, the antiimmobility effect of chronic imipramine, a prototype of antidepressant drugs, was sustained or even potentiated, this observation being supported by the results by Skolnick et al. (36) obtained in mice, and by other authors in rats (2).

The lack of changes in the locomotor activity after acute and chronic treatment with ACPC (see above) indicates that both the antiimmobility effect and the tolerance to this effect of the drug are apparently specific phenomena. Similarly, the antiimmobility effect of imipramine, as well as potentiation of the effect observed after its repeated administration, seem to be unrelated to alterations in the locomotor behavior, because the antidepressant drug, administered acutely (34) or chronically (Maj, Rogóż, Skuza, personal information) in a dose (30 mg/kg IP) effective in the forced swim test, did not influence the locomotor activity.

The development of tolerance to the antidepressant-like activity of ACPC in the forced swim test was also reported by other authors. For example, Skolnick et al. (36) and Lopes et al. (19) found such an effect after 7- or 5-day administration of a dose of 200 mg/kg of the drug to mice and rats, respectively. Moreover, Lopes et al. (19) observed tolerance to the antiimmobility effect of D-cycloserine, another partial agonist at glycine$_B$ receptors (13), and crosstolerance beetwen ACPC and the latter drug. However—in contrast to our and the above-cited results—it has been reported that chronic, but not acute, treatment with ACPC reduced the density of cortical β-adrenoceptors (30) and reversed the chronic mild stress-induced reduction in sucrose consumption in rats (28), these effects being characteristic of many clinically effective antidepressants and of other antidepressant therapies (12,29). The above discrepancies may indicate that—like in the case of anxiolytic activity—also tolerance to the antidepressant-like effect of ACPC is a test-dependent phenomenon that originates in different mechanisms of the antidepressant drug action in these experimental models (3,20,26).

Of the two possible mechanisms that may be responsible for the development of tolerance to the anxiolytic- and antidepressant-like activity of ACPC, i.e., a pharmacokinetic alteration or a pharmacodynamic mechanism, the former would rather be excluded, because the plasma and brain levels of ACPC are comparable after acute or chronic administration of the same doses of the drug to mice (36); however, such findings have not been reported for rats. On the other hand, several lines of evidence indicate that the loss of anticonflict or antiimmobility effect of chronic ACPC may be related to adaptive changes within the NMDA receptor complex, which were originally regarded by Skolnick et al. (36) as "uncoupling" between glycine$_B$ and NMDA receptors: 1) ACPC is a partial agonist at glycine$_B$ receptors that belong to the family of allosteric sites that control the physiological functioning of the NMDA receptor complex whose activation is potentiated

by glycine (15); 2) in the acute experiment, glycine antagonizes the antidepressant- and anxiolytic-like activity of ACPC (41,44), though in the latter case such antagonism was found in a rat pup ultrasonic vocalization test (44) and not in the conflict drinking test (6); 3) chronic treatment with ACPC reduces the ability of glycine to inhibit the binding of [^{3}H]5,7-dichlorokynurenic acid (an antagonist at glycine$_B$ receptors) to the NMDA receptor complex in the cerebral cortex (25), and alters mRNA levels encoding NMDA receptor subunits in different brain structures including the hippocampus (4), which was found to be involved in the anticonflict and antiimmobility effects of ACPC (33,34).

In conclusion, although our results indicate that tolerance develops to the anxiolytic- and, especially, to the antidepressant-like activity of ACPC, in the light of other results reported in this respect only clinical observations can decide whether such tolerance is of any significance to a potential therapeutic application of the drug.

ACKNOWLEDGEMENTS

The authors would like to thank Symphony Pharmaceutical Inc. (Malvern, PA) for the generous gift of ACPC.

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