ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 54, No. 1, pp. 73–77, 1996

0091-3057/96 $15.00 + .00

SSDI 0091-3057(95)02157-4

Anticonflict Effects of a Competitive NMDA Receptor Antagonist and a Partial Agonist at Strychnine-Insensitive Glycine Receptors

E. PRZEGALIŃSKI,[1] E. TATARCZYŃSKA, A. DEREŃ-WESOŁEK AND E. CHOJNACKA-WÓJCIK

Polish Academy of Sciences, Institute of Pharmacology, 12 Smętna Street, 31-343 Kraków, Poland

PRZEGALIŃSKI, E., E. TATARCZYŃSKA, A. DEREŃ-WESOŁEK, AND E. CHOJNACKA-WÓJCIK. *Anticonflict effects of a competitive NMDA receptor antagonist and a partial agonist at strychnine-insensitive glycine receptors.* PHARMACOL BIOCHEM BEHAV **54**(1) 73–77, 1996.—Using the conflict drinking Vogel test in rats as a model, in the present study we examined the anxiolytic-like activity of DL-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP 37849), a competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist and 1-aminocyclopropanecarboxylic acid (ACPC), a partial agonist at strychnine-insensitive glycine receptors associated with the NMDA receptor complex, after their intraperitoneal (IP) and intrahippocampal (IHP) administration. CGP 37849, administered in doses of 1.25–5 mg/kg IP, produced an anticonflict effect in a dose-dependent manner, but was inactive when injected in doses of 0.01–0.1 μg IHP. At the same time, when administered in higher doses (10 mg/kg IP or 0.3 μg IHP), that drug induced motor impairment. On the other hand, ACPC exhibited an anxiolytic-like activity after both IP (100–200 mg/kg) and IHP (3–30 μg) administration. These results, as well as the literature data on the lack of motor-impairing effects of ACPC, indicate that the latter drug seems to be more advantageous than CGP 37849 as a potential therapeutic agent in the treatment of anxiety disorders. Furthermore, they also show that the hippocampus may be one of the neuroanatomical sites of the anxiolytic-like effect of ACPC, but not of CGP 37849.

CGP 37849 1-Aminocyclopropanecarboxylic acid Drinking conflict test Peripheral administration Intrahippocampal injection Rats

OF THE receptor subtypes that mediate excitatory amino acid (e.g., glutamate or aspartate) synaptic neurotransmission, the *N*-methyl-D-aspartate (NMDA) receptor and its associated cation channel is the best described. This complex is constituted as a heterooligomer, possessing subunits with interdependent recognition sites for glutamate, glycine, cation channel blockers, and polyamines (46). Glycine, through its action at the glycine site, allosterically potentiates the NMDA receptor activation (15), this effect being insensitive to strychnine.

Ligands of the NMDA and strychnine-insensitive glycine receptors have been shown to evoke several pharmacological effects. For example, noncompetitive and competitive NMDA receptor antagonists, as well as strychnine-insensitive glycine receptor partial agonists and antagonists, have been reported to exert anxiolytic-like actions in animal models (3,6,8,17, 31,36,37,38,44,45). Showing similar pharmacological profiles in experimental paradigms, the NMDA and glycine receptor ligands differ, however, in terms of their potential clinical utility. In fact, although noncompetitive and competitive NMDA receptor antagonists induce a number of undesirable side effects, such as muscle relaxation, ataxia or amnesia, as well as some reinforcing and psychotomimetic effects (2,4, 13,14,18,19,26,28,39,43), glycine receptor partial agonists and antagonists are devoid of such properties (10,17,34).

As regards the neuroanatomical site of antianxiety actions of the NMDA and glycine receptor ligands, the dorsal periaqueductal gray (12,23) and hippocampus (30) have been suggested to be involved. The latter structure seems to be of particular interest in this respect, as it: 1. plays an important role in the control of anxiety (11); 2. is a site in which local injections of different antianxiety drugs, including benzodiazepines, 5-hydroxytryptamine$_{1A}$ receptor ligands and β-adrenoceptor antagonists evoke anxiolytic-like effects (5,16, 20,32,33,35); and 3. has a high density of NMDA receptors (24,25).

Using the conflict drinking Vogel test (40) as a model, in the present paper, we studied the anxiolytic-like activity of DL-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP 37849), a competitive NMDA receptor antagonist (9), and 1-aminocyclopropanecarboxylic acid (ACPC), a partial agonist

[1] To whom requests for reprints should be addressed.

at strychnine-insensitive glycine receptors associated with the NMDA receptor complex (22,42), after their intraperitoneal (IP) and intrahippocampal (IHP) administration. Unlike the case with other competitive NMDA receptor antagonists, there is only one report on the antianxiety effects of CGP 37849 in the literature (31). At the same time, ACPC has only been examined in nonconflict models of anxiety (1,37, 38,44). Furthermore, no data are available on the antianxiety effect of these drugs administered locally into the hippocampus.

METHOD

Animals and Housing

Male Wistar rats, weighing 250 ± 20 g, were used in the study. After operation, the animals were housed individually in a cage (40 × 27 × 15 cm), on a natural day-night cycle (winter-spring) and at a room temperature of 19–21 °C, with free access to food and tap water before the experiment.

Surgery

The rats were operated under equithesin anaesthesia. A socket with two stainless steel guide cannulae (0.4 mm OD, 0.3 mm ID, 8.0 mm long) was implanted stereotaxically 2 mm above the CA1 region of the dorsal hippocampus (A 5.2 mm, L 2.0 mm, H 7.3 mm from the interaural line) (29), and was fixed to the skull with stainless steel screws and dental acrylic cement. Seven days later, the rats were subjected to behavioural testing.

Treatment Schedules and Drugs

Intrahippocampal (IHP) injections of drugs were made using Hamilton microsyringes connected, *via* polyethylene tubing, with two stainless steel needles (0.3 mm OD). The injection needles were lowered 2 mm below the tip of the guide cannula (i.e., at a level of the CA1 region of the dorsal hippocampus). Solutions were administered bilaterally over 60 s. The injection needle remained in place for the additional 30–60 s before it was removed and replaced with a stylet.

The following drugs were used: 1-aminocyclopropanecarboxylic acid (ACPC) (Symphony Pharmaceuticals Inc., Malvern, PA), DL-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP 37849) (Ciba-Geigy, Basel). Both the drugs were dissolved in a sterile saline immediately before administration and injected intraperitoneally (IP) in a volume of 4 ml/kg, or IHP in a volume of 1 μl/site at 60 or 10 min before the test, respectively. Control rats received vehicle according to the same schedule.

All the experiments were always performed between 10 a.m. and 2 p.m.

Conflict Drinking Test (Vogel Test)

A modification of the method of Vogel (40) was used. On the first day of the experiment, the rats were adapted to the test chamber for 10 min. It was a Plexiglas box (27 × 27 × 50 cm), equipped with a grid floor of stainless steel bars and with a drinking bottle containing tap water. After the 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-second periods, between the grid floor and the spout of the drinking bottle. The number of shocks accepted throughout a 5-min experimental session was recorded. The animals were used only once in this test.

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 a manner similar to that 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 by increasing manually the current (0.1, 0.2, 0.3, 0.4, 0.5 mA) delivered through the grid-floor until a rat showed an avoiding reaction (jump, jerk, or the like) 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.

The animals were used only once in either test.

Histological Analysis

After IHP injections, all the animals were killed on the final testing day; their brains were removed and stored in a 10% formalin solution. The frozen tissue was dissected, and the injection sites were verified visually. In each experiment, only the data from rats in which the cannulae were located bilaterally in the intended structure were included in the results.

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 with separate one-way ANOVA. Specific comparisons were carried out with Dunnett's test.

RESULTS

A one-way analysis of variance showed that CGP 37849 and ACPC administered IP produced a dose-dependent increase in the number of shocks accepted during experimental sessions in the conflict drinking test: $F(3, 25) = 6.04$, $p < 0.01$ and $F(3, 23) = 6.74$, $p < 0.01$, respectively. The minimum effective dose of CGP 37849 was 1.25 mg/kg; however, a distinct effect (an increase by about 170%) was observed after a dose of 5 mg/kg of the drug. ACPC administered in a dose of 50 mg/kg was ineffective, but given in doses of 100 and 200 mg/kg, it significantly increased the punished responding by about 126% and 200%, respectively (Table 1).

After IHP injection, a significant increase in the punished drinking was observed after ACPC, $F(3, 41) = 5.19$, $p < 0.01$, but not after CGP 37849. The minimum effective dose of ACPC was 3 μg; however, when injected in doses of 10 and

TABLE 1

THE EFFECT OF CGP 37849 AND ACPC IN THE CONFLICT DRINKING VOGEL TEST IN RATS

Compounds	Route of Injection	Dose	N	Number of Accepted Shocks/ 5 min Mean ± SEM
Vehicle	IP	-	7	6.6 ± 1.0
CGP 37849	IP	1.25 mg/kg	8	10.7 ± 1.6*
		2.5 mg/kg	8	11.9 ± 2.0*
		5.0 mg/kg	8	17.9 ± 2.3**
Vehicle	IP	-	7	8.7 ± 1.6
ACPC	IP	50 mg/kg	8	10.7 ± 1.4
		100 mg/kg	8	19.7 ± 3.5*
		200 mg/kg	8	26.1 ± 4.0**
Vehicle	IHP	-	7	6.7 ± 0.8
CGP 37849	IHP	0.01 μg	8	8.0 ± 1.1
		0.03 μg	8	11.5 ± 3.9
		0.1 μg	8	6.5 ± 1.1
Vehicle	IHP	-	10	6.2 ± 0.6
ACPC	IHP	3 μg	11	13.4 ± 4.0*
		10 μg	12	24.9 ± 5.1**
		30 μg	12	19.1 ± 3.5*

CGP 37849 and ACPC were administered 60 min (IP) or 10 min (IHP) before the test.

N = number of rats per group.

*$p < 0.05$, **$p < 0.01$ *vs.* respective control (Dunnett's test).

30 μg, the drug increased the number of shocks accepted by about 300% and 210%, respectively. CGP 37849 administered in doses of 0.01–0.1 μg was ineffective (Table 1). In our experiment, the three cannula placements fell outside the CA1 hippocampus target area. In each case, the error was only unilateral, but the scores for those animals were discarded. In those three discarded rats, the obtained results were at a control level.

Higher doses of CGP 37849 (10 mg/kg IP or 0.3 μg IHP) were not examined in the conflict drinking test because they induced muscle hypotonia and ataxia, and—in some animals (after IHP administration)—even loss of the righting reflex.

As shown in Table 2, the possibility that the efficacy of CGP 37849 and ACPC is related to a reduced perception of the stimulus or to an increased thirst drive may be excluded, as these drugs—administered in their highest doses effective in the conflict drinking test—increase neither the threshold current nor water intake.

DISCUSSION

The results of the present paper indicate that CGP 37849, a competitive NMDA receptor antagonist, and ACPC, a partial agonist at strychnine-insensitive glycine receptors associated with the NMDA receptor complex (either drug being administered peripherally, IP) exert an anxiolytic-like activity in rats. In fact, the drugs tested dose-dependently increased the number of punished licks in the conflict drinking Vogel test, with this effect being seemingly specific because, when given in doses evoking an anticonflict activity, they affected neither the shock threshold nor the nonpunished water consumption.

Our results are consistent with other findings in this respect. Actually, Płaźnik et al. (31) reported that CGP 37849, administered to rats in doses similar to those used in our experiment, increased the exploratory activity in central sectors of the open field (anti-neophobic reaction) and produced anticonflict effect in the Vogel test. On the other hand, the antianxiety activity of ACPC was found in nonconflict models only. The drug has been reported to increase the exploration of the open arms of the elevated plus-maze by mice (37,38), to reduce the separation-induced ultrasonic vocalization in rat pups (44), and to block the fear-potentiated startle response in rats (1). Again, all those effects of ACPC were observed when the drug was administered at a dose range similar to that of the present study, its strongest effect being found (on the basis of the minimum effective dose) in the ultrasonic vocalization model (44).

The results of the present study are also in line with several observations indicating an anxiolytic-like activity of other NMDA antagonists and glycine receptor ligands. In fact, both noncompetitive (dizolcipine) and competitive [e.g., 2-amino-5-phosphonovaleric acid (AP-5), 2-amino-7-phosphonoheptanoic acid (AP-7), 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP)] NMDA receptor antagonists were found to be active in a number of models used to predict antianxiety activity, including a social interaction test, elevated plus-maze, separation-induced ultrasonic vocalization, and the Cook and Davidson conflict paradigm (3,6,7,17,43). In the same models, as well as in the fear-potentiated startle response, antianxiety effects were also reported for (+)-3-amino-1-hydroxy-2-pyrrolidinone (HA-966), 5,7-dichlorokynurenic acid (5,7-DCKA),

TABLE 2

THE EFFECT OF CGP 37849 AND ACPC ON THE SHOCK THRESHOLD AND THE AMOUNT OF WATER CONSUMED BY WATER-DEPRIVED RATS

Compounds	Route of Injection	Dose	N	Shock Threshold (mA)	Water Consumption (ml)
Vehicle	IP	-	6	0.38 ± 0.03	7.2 ± 0.7
CGP 37849	IP	5 mg/kg	8	0.49 ± 0.06	6.8 ± 1.0
Vehicle	IP	-	6	0.35 ± 0.02	7.3 ± 0.7
ACPC	IP	200 mg/kg	7	0.44 ± 0.04	7.0 ± 0.6
Vehicle	IHP	-	7	0.37 ± 0.03	6.9 ± 0.6
ACPC	IHP	30 μg	7	0.43 ± 0.03	6.0 ± 0.5

CGP 37849 was administered 60 min and ACPC – 60 min (IP) or 10 min (IHP) before the test.

N = number of rats per group.

and 7-chloro-kynurenate (7-Cl-KYN) (1,6,8,17,38,44), all of them being glycine receptor antagonists. In the light of the latter findings, despite the fact that some neurochemical evidence indicates that ACPC is a high-affinity, partial agonist ligand at strychnine-insensitive glycine receptors (22,27), the anticonflict effect of the drug observed in our study seems to be related to its antagonistic properties at these receptors. A similar conclusion has also been suggested by other authors, who found an anxiolytic-like activity of ACPC in other models of anxiety (1,38,44). Furthermore, some other data also indicate that ACPC may behave as a functional antagonist at glycine receptors in vivo. Actually, the drug has been found to exert a protective effect against NMDA-induced convulsions (34) and to have neuroprotective efficacy (41), such effects being expected in the case of an antagonist, rather than agonist, of glycine receptors.

In our experiment, we found that the minimum effective dose of CGP 37849 in the conflict drinking test was 1.25 mg/kg, whereas a distinct anticonflict effect was observed after a dose of 5 mg/kg of the drug. At the same time, only a dose twice as high of CGP 37849 (i.e., 10 mg/kg) induced muscle relaxation and marked ataxia. The latter observation, consistent with that reported by Löscher and Hönack (21), indicates that the drug studied is characterized by a very low ratio (2 : 1) between the dose inducing motor impairment and that producing an antianxiety effect. We also found that the anticonflict effect of ACPC, comparable with that produced by 5 mg/kg of CGP 37849, appeared after doses of 100–200 mg/kg of the former drug. Although we did not examine the effect of the higher doses of ACPC, some literature data clearly show that, at least in mice, it is devoid of any motor impairment activity in doses up to 2000 mg/kg (24). In other words, ACPC may be more advantageous than CGP 37849 as a potential drug in the treatment of anxiety disorders. In this context, it is also noteworthy that, in contrast to CGP 37849 (28), ACPC is inactive in conditioning a place preference paradigm in rats (M. Papp, personal communication), this observation indicating that the glycine receptor ligand is devoid of rewarding properties and, consequently, has no potential abuse liability.

Unlike the case of peripheral administration, CGP 37849 and ACPC differ in terms of the exerted effects in the conflict drinking test after their local IHP administration. Thus ACPC administered in doses of 3–30 μg evoked an anticonflict effect, with the maximum effect being observed after a dose of 10 μg, and CGP 37849 injected in doses of 0.01–0.1 μg was ineffective in that model. The reason for this inactivity of CGP 37849 is unclear, the more so as two other NMDA receptor antagonists (dizolcipine and AP-7), administered IHP, were found to produce anxiolytic-like effects in the open field test (antineophobic reaction) and in the Vogel test (30). Nevertheless, because a higher dose of CGP 37849 injected IHP (0.3 μg) produced marked motor impairment (ataxia, loss of the righting reflex), the hippocampus does not seem to be a neuroanatomical site of anticonflict activity of the drug. In this context, it is noteworthy that another brain structure (i.e., the dorsal periaqueductal gray) has been suggested as the site of the antianxiety effect of AP-7 in the elevated plus-maze model (12). At the same time, our results seem to indicate that the hippocampus may be one of the brain structures involved in the anticonflict effect of ACPC, and such a conclusion is consistent with several data pointing to the role of the above-mentioned brain structure in antianxiety effects of different anxiolytic drugs (5,16,20,32,33,35). However, it should also be kept in mind that an anxiolytic-like activity of glycine receptor antagonists (HA-966, 7-Cl-KYN) has been found after their local injection into the dorsal periaqueductal gray (23).

In conclusion, the results of the present study indicate that ACPC exhibits an anxiolytic-like activity in the conflict drinking test in rats that resembles the activity of CGP 37849 in this respect. In the light of some literature data that show that ACPC is devoid of undesirable side effects of CGP 37849, the strychnine-insensitive glycine receptor ligand seems to be more advantageous as a potential antianxiety drug than the NMDA receptor antagonist. Our results also seem to indicate that the hippocampus is one of the brain structures involved in the anticonflict effect of ACPC, but not CGP 37849.

ACKNOWLEDGEMENTS

The authors would like to thank Symphony Pharmaceuticals Inc. (Malvern, PA) for a generous gift of ACPC, and Ciba-Geigy (Basel) for CGP 37849.

REFERENCES

1. Anthony, E. W.; Nevins, M. E. Anxiolytic-like effects of *N*-methyl-D-aspartate-associated glycine receptor ligands in the rat potentiated startle test. Eur. J. Pharmacol. 250:317–324; 1993.
2. Beardsley, P. M.; Hayes, B. A.; Balster R. L. The self-administration of MK-801 can depend upon drug-reinforcement history, and its discriminative stimulus properties are phencyclidine-like in rhesus monkeys. J. Pharmacol. Exp. Ther. 252:953–996; 1990.
3. Bennett, D. A.; Amrick, C. L. 2-Amino-7-phosphonoheptanoic acid (AP7) produces discriminative stimuli and anticonflict effects similar to diazepam. Life Sci. 39:2455–2461; 1986.
4. Bennett, D. A.; Bernard, P.; Amrick, C. L.; Wilson, D.; Liebman, J.; Hutchison, A. Behavioral pharmacological profile of CGS 19755, a competitive antagonist at *N*-methyl-D-aspartate receptors. J. Pharmacol. Exp. Ther. 250:454–460; 1989.
5. Campbell, J. K.; Sherman, A. D.; Petty, F. Diazepam anxiolytic activity in hippocampus. Commun. Psychopharmacol. 4:387–392; 1980.
6. Corbett, R.; Dunn, R. W. Effects of 5,7-dichlorokynurenic acid on conflict, social interaction and plus-maze behaviors. Neuropharmacology 32:461–466; 1993.
7. Dunn, R. W.; Corbett, R.; Fielding, S. Effects of 5-HT_{1A} receptor agonists and NMDA receptor antagonists in the social interaction test and the elevated plus-maze. Eur. J. Pharmacol. 169:1–10; 1989.
8. Dunn, R. W.; Flanagan, D. M.; Martin, L. L.; Kerman, L. L.; Woods, A. T.; Camacho, F.; Wilmot, C. A.; Cornfeldt, M. L.; Effland, R. C.; Wood, P. L.; Corbett, R. Stereoselective R-(+)enantiomer of HA-966 displays anxiolytic effects in rodents. Eur. J. Pharmacol. 214:207–214; 1992.
9. Fagg, G. E.; Olpe, H.-R.; Pozza, M. F.; Baud, J.; Steinmann, M.; Schmutz, M.; Portet, C.; Baumann, P.; Thedinga, K.; Bittiger, H.; Allgeier, H.; Heckendorn, R.; Angst, C.; Brundish, D.; Dingwall, J. G. CGP 37849 and CGP 39551: Novel and potent competitive *N*-methyl-D-aspartate receptor antagonists with oral activity. Br. J. Pharmacol. 99:791–797; 1990.
10. Faiman, C. P.; Viu, E.; Skolnick, P.; Trullas, R. Differential effects of compounds that act at strychnine-insensitive glycine receptors in a punishment procedure. J. Pharmacol. Exp. Ther. 270:528–533; 1994.
11. Gray, J. A. Precis of the neuropsychology of anxiety: and enquiry into the functions of the septo-hippocampal system. Behav. Brain Sci. 5:469–534; 1982.
12. Guimarães, F. S.; Carobrez, A. P.; De Aguiar, J. C.; Graeff, F.

G. Anxiolytic effect in the elevated plus-maze of the NMDA receptor antagonist AP7 microinjected into the dorsal periaqueductal grey. Psychopharmacology 103:91-94; 1991.
13. Herberg, L. J.; Rose, I. C. The effect of MK-801 and other antagonists of NMDA-type glutamate receptors on brain-stimulation reward. Psychopharmacology 99:87-90; 1989.
14. Izquierdo, I. Role of NMDA receptors in memory. Trends Pharmacol. Sci. 12:128-129; 1991.
15. Johnson, J. W.; Ascher, P. Glycine potentiates the NMDA responses in cultured mouse brain neurons. Nature 325:529-531; 1987.
16. Kataoka, Y.; Shibata, K.; Miyazaki, A.; Inoue, Y.; Tominaga, K.; Koizumi, S.; Ueki, S.; Niwa, M. Involvement of the dorsal hippocampus in mediation of the antianxiety action of tandospirone, a 5-hydroxytryptamine$_{1A}$ agonistic anxiolytic. Neuropharmacology 30:475-480; 1991.
17. Kehne, J. H.; McCloskey, T. C.; Baron, B. M.; Chi, E. M.; Harrison, B. L.; Whitten, J. P.; Palfreyman, M. G. NMDA receptor complex antagonists have potential anxiolytic effects as measured with separation-induced ultrasonic vocalizations. Eur. J. Pharmacol. 193:283-292; 1991.
18. Koek, W.; Colpaert, F. C. Selective blockade of *N*-methyl-D-aspartate (NMDA)-induced convulsions by NMDA antagonists and putative glycine antagonists: relationship with phencyclidine-like behavioral effects. J. Pharmacol. Exp. Ther. 252:349-357; 1990.
19. Koek, W.; Woods, J. H.; Winger, G. D. MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. J. Pharmacol. Exp. Ther. 245: 969-974; 1988.
20. Kostowski, W.; Płaźnik, A.; Stefański, R. Intrahippocampal buspirone in animal models of anxiety. Eur. J. Pharmacol. 168: 393-396; 1989.
21. Löscher, W.; Hönack, D. The novel competitive *N*-methyl-D-aspartate (NMDA) antagonist CGP 37849 preferentially induces phencyclidine-like behavioral effects in kindled rats: attenuation by manipulation of dopamine, alpha$_1$ and serotonin$_{1A}$ receptors. J. Pharmacol. Exp. Ther. 257:1146-1153; 1991.
22. Marvizón, J. C. G.; Lewin, A. H.; Skolnick, P. 1-Aminocyclopropane carboxylic acid: a potent and selective ligand for the glycine modulatory site of the *N*-methyl-D-aspartate receptor complex. J. Neurochem. 52:992-994; 1989.
23. Matheus, M. G.; Nogueira, R. L.; Carobrez, A. P.; Graeff, F. G.; Guimarães, F. S. Anxiolytic effect of glycine antagonists microinjected into the dorsal periaqueductal grey. Psychopharmacology 113:565-569; 1994.
24. Monaghan, D.; Holets, W.; Toy, D.; Cotman, C. Anatomical distribution of four [^{3}H]glutamate binding sites. Nature 306:176-179; 1983.
25. Monaghan, D.; Yao, D.; Olverman, H.; Watkins, J.; Cotman, C. Autoradiography of D-2-[^{3}H]amino-5-phosphonopentanoate binding sites in rat brain. Neurosci. Lett. 52:253-258; 1984.
26. Morris, R. G.; Anderson, E.; Lynch, G. S.; Baudry, M. Selective impairment of learning and blockade of long-term potentiation by a *N*-methyl-D-aspartate antagonist AP5. Nature 319:774-776; 1986.
27. Nadler, V.; Kloog, Y.; Sokolovsky, M. 1-Aminocyclopropane-1-carboxylic acid (ACC) mimics the effects of glycine on the NMDA receptor ion channel. Eur. J. Pharmacol. 157:115-116; 1989.
28. Papp, M.; Moryl, E. Rewarding properties of noncompetitive and competitive NMDA antagonists as measured by place preference conditioning in rats. Pol. J. Pharmacol. 46:79-81; 1994.
29. Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. Sydney: Academic Press; 1982.
30. Płaźnik, A.; Nazar, M.; Jessa, M. The limbic location of some central effects of competitive and noncompetitive NMDA receptor antagonist: the role in emotional control. Eur. Neuropsychopharmacol. 4:335; 1994.
31. Płaźnik, A.; Pałejko, W.; Nazar, M.; Jessa, M. Effects of antagonists at the NMDA receptor complex in two models of anxiety. Eur. Neuropsychopharmacol. 4:503-512; 1994.
32. Przegaliński, E.; Tatarczyńska, E.; Chojnacka-Wójcik, E. The role of hippocampal 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptors in the anticonflict activity of β-adrenoceptor antagonists. Neuropharmacology 34:1211-1217; 1995.
33. Przegaliński, E.; Tatarczyńska, E.; Kłodzińska, A.; Chojnacka-Wójcik, E. The role of postsynaptic 5-HT$_{1A}$ receptors in the anticonflict effect of ipsapirone. Neuropharmacology 33:1109-1115; 1994.
34. Skolnick, P.; Marvizón, J. C. G.; Jackson, B. W.; Monn, J. A.; Rice, K. C.; Lewin, A. H. Blockade of *N*-methyl-D-aspartate induced convulsions by 1-aminocyclopropanecarboxylates. Life Sci. 45:1647-1655; 1989.
35. Stefański, R.; Pałejko, W.; Bidziński, A.; Kostowski, W.; Płaźnik, A. Serotonergic innervation of the hippocampus and nucleus accumbens septi and the anxiolytic-like action of midazolam and 5-HT$_{1A}$ receptor agonists. Neuropharmacology 32:977-985; 1993.
36. Stephens, D. D.; Meldrum, B. S.; Weidmann, R.; Schneider, C.; Grutzner, M. Does the excitatory amino-acid receptor antagonist 2-APH exhibit anxiolytic activity. Psychopharmacology 90:166-169; 1986.
37. Trullas, R.; Folio, T.; Young, A.; Miller, R.; Boje, K.; Skolnick, P. 1-Aminocyclopropanecarboxylates exhibit antidepressant and anxiolytic actions in animal models. Eur. J. Pharmacol. 203:379-385; 1991.
38. Trullas, R.; Jackson, B.; Skolnick, P. Anxiolytic properties of 1-aminocyclopropanecarboxylic acid, a ligand at strychnine-insensitive glycine receptors. Pharmacol. Biochem. Behav. 34:313-316; 1989.
39. Turski, L.; Klockgether, T.; Sontag, K. H.; Herrling, P. L.; Watkins, J. C. Muscle relaxant and anticonvulsant activity of 3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid, a novel *N*-methyl-D-aspartate antagonist in rodents. Neurosci. Lett. 73:143-148; 1987.
40. Vogel, J. R.; Beer, B.; Clody, D. E. A simple and reliable conflict procedure for testing antianxiety agents. Psychopharmacologia 21:1-7; 1971.
41. Von Lubitz, D. K. J. E.; Lin, R. C.-S.; McKenzie, R. J.; Davlin, T. M.; McCabe, R. T.; Skolnick, P. A novel treatment of global cerebral ischemia with glycine partial agonist. Eur. J. Pharmacol. 219:153; 1992.
42. Watson, G. B.; Lanthorn, T. H. Pharmacological characteristics of cyclic homologues of glycine at the *N*-methyl-D-aspartate receptor-associated glycine site. Neuropharmacology 29:727-730; 1990.
43. Willetts, J.; Balster, R. L.; Leander, J. D. The behavioural pharmacology of NMDA receptor antagonists. Trends Pharmacol. Sci. 11:423-428; 1990.
44. Winslow, J. T.; Insel, T. R.; Trullas, R.; Skolnick, P. Rat pup isolation calls are reduced by functional antagonists of the NMDA receptor complex. Eur. J. Pharmacol. 190:11-21; 1990.
45. Xie, Z.; Commissaris, R. L. Anxiolytic-like effects of the noncompetitive NMDA antagonist MK-801. Pharmacol. Biochem. Behav. 43:471-477; 1992.
46. Young, A. B.; Fagg, G. E. Excitatory amino acid receptors in the brain: membrane binding and receptor autoradiographic approaches. Trends Pharmacol. Sci. 11:126-132; 1990.