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Low doses of AMPA exert anticonvulsant effects on pentylenetetrazol-kindled seizures

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Abstract

Excitatory amino acids (EAAs) are critically involved in the initiation and propagation of seizures. *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors appear to be of special interest in this regard. Besides receptor binding by antagonists, the function of glutamatergic synapses can be altered via autoreceptor-mediated mechanisms or by receptor desensitisation. Therefore, the effect of AMPA (1, 10 or 100 pmol per animal, intracerebroventricular injection) was tested on acutely induced pentylenetetrazol (PTZ) seizures. The lowest dose exerted clear anticonvulsant effects. Furthermore, 1 and 10 pmol AMPA were tested for their efficacy to suppress PTZ kindling. The lower dose reduced seizure severity significantly but 10 pmol AMPA was ineffective. In reaction to a test dose of PTZ, the kindled groups pretreated with AMPA reached seizure scores similar to saline-pretreated kindled rats, suggesting that the kindled state was reached. In a further experiment, we tested the effect of cyclothiazide (CYC, which blocks AMPA receptor desensitisation) on the 1 pmol AMPA-mediated anticonvulsant effect. The AMPA response was not altered. These results suggest that autoreceptor-mediated mechanisms rather than desensitisation might contribute to the anticonvulsant effect found.

Keywords: AMPA; Epilepsy; Seizures; Pentylenetetrazol kindling; Rat

1. Introduction

Studies in recent years have provided evidence on the prominent role of central excitatory amino acids (EAAs) in neurodegenerative diseases, including ischemia and seizure-related brain damage. On the other hand, EAAs were found to be involved in processes of synaptic plasticity, such as LTP, learning and memory.

Considering the biological effects of EAAs the interest in the development of EAAs receptor antagonists as therapeutic agents is not surprising. Interestingly, *N*-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists differ in specific effects, e.g. in the protection against hypoxic damage (Choi, 1993). There is evidence that NMDA receptor antagonists retard the development of kindling, but these substances are less potent in suppressing fully kindled seizures (Gilbert, 1988; Holmes et al., 1990; Sato et al., 1998). Thus, it was suggested that these substances have therapeutic potential in the treatment of epileptogenesis and other neurological disorders (Dingledine et al., 1990; Rogawski, 1993, 1995; Lees, 1996; Bleakman and Lodge, 1998; Rogawski et al., 2001). Löscher et al. (1993) reported that both non-NMDA and NMDA receptors are critically involved in the kindled state and that combinations of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) and NMDA receptor antagonists provide a new strategy for treatment of epilepsy. Recent investigations provided evidence that AMPA receptors are involved in the initiation of seizures and their propagation (Löscher et al., 1993; Meldrum et al., 1992; Peeters et al., 1994a; Velisek et al., 1995). It was shown that non-NMDA receptor-mediated synaptic transmission plays a role in the genesis of tonic components of tonic–clonic seizures during individual development (Velisek et al., 1995). However, other studies (Dürmüller et al., 1994) do not support a specific involvement of enhanced AMPA receptor sensitivity as a major factor in the expression of kindled seizures.

EAA receptor activity can be modulated by different mechanisms of synaptic transmission. Beside action at

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presynaptic and postsynaptic receptor sides, AMPA was reported to act as antagonist or weak partial agonist at kainate receptors (Perouansky and Grantyn, 1989; Tang et al., 1989; Martin et al., 1991; Rainnie and Shinnick-Gallagher, 1992; Zhou et al., 1995). Additionally, AMPA receptor desensitisation might contribute to functional alterations (Mayer et al., 1991). A body of evidence suggests that AMPA responses can be modulated by presynaptic autoreceptors (Martin et al., 1991; Rannie and Shinnick-Gallagher, 1992; Zhou et al., 1995). In the experiments reported here, the receptor agonist AMPA was administered prior to convulsive doses of pentylenetetrazol (PTZ) and, moreover, in the course of PTZ kindling in rats to approach the mechanisms of kindling related to AMPA receptors.

2. Materials and methods

For all procedures used, ethical approval was sought prior to the experiments according to the requirements of the National Act on the Use of Experimental Animals (Germany).

2.1. Animals

Experiments were carried out with male Wistar rats [Shoe:Wist(Shoe), Tierzucht Schönwalde] aged 7 weeks at the beginning of the experiments. The animals were kept under controlled laboratory conditions (light regime of 12 h light/12 h dark, lights on at 06:00 a.m.), temperature 20±2 °C, air humidity 55–60%. They had free access to commercial rat pellets (Altromin 1326) and tap water. The rats were housed in groups of five per cage.

2.2. Surgery

AMPA was injected in the right lateral cerebral ventricle (intracerebroventricular) via a chronic microcannula. For implantation, each rat was anaesthetised with Nembutal (40 mg/kg ip) and a cannula was inserted according to stereotaxic coordinates AP 0.25 mm, lat. 1.6 mm, vent. 4.0 mm related to bregma and bregma 1.0 mm above lambda (Paxinos and Watson, 1997). The cannula was fixed on the skull with dental acrylic cement.

After completion of the experiments, the animals received an overdose of Nembutal. Histological verification of the cannula placement was made or by localisation of a dye (toluidine blue) which had been infused into the lateral ventricle.

2.3. Experimental protocol

After a recovery period of 1 week postsurgery, three different experiments were carried out.

(1) The first experiment was aimed at measuring the effectiveness of different doses of AMPA (1, 10 and 100 pmol/animal) compared to saline-injected control animals on acute PTZ-induced seizures. AMPA was dissolved in sterile isotonic saline (pH of the solution was 6.6) and injected intracerebroventricularly over a period of 60 s. Injection volume was 5 μl per animal. Ten minutes after injection, 45 mg/kg PTZ ip was given. Resultant seizures were scored as described below for a period of 20 min.

PTZ (Roth) and (*S*)-AMPA (Tocris Cookson) were freshly dissolved in saline. Per dose of AMPA, 15 rats were used.

(2) In the second experiment, the effect of two different doses of AMPA (as measured in Experiment 1) was tested on kindling development. The number of animals used is mentioned in Fig. 2. The period between the two tests was 2 months, and therefore, separate control groups were used.

For PTZ kindling, an initially subeffective dose of 40 mg/kg body weight PTZ (ED_{16} related to clonic seizures, tested in a separate group of rats) was injected intraperitoneally (1 ml/100 g body weight) once every 48 h. After each injection, the convulsive behaviour was observed for 20 min. The resultant seizures were classified as follows:

Stage 0: no response
Stage 1: ear and facial twitching
Stage 2: myoclonic jerks of the forelimbs without rearing
Stage 3: myoclonic jerks of the forelimbs, rearing
Stage 4: turn over into side position, clonic–tonic seizures
Stage 5: turn over into back position, generalised clonic–tonic seizures

In total, rats received 13 kindling stimulations. Control animals received the same number of saline injections; injection volume was 1 ml/100 g body weight. Ten minutes prior to intraperitoneal injection, saline or AMPA was given intracerebroventricularly in a volume of 5 μl per animal.

One characteristic feature of kindling is the lowered seizure threshold. To test the effect of AMPA on kindling success, the rats received a challenge dose of PTZ (35 mg/kg) which did not evoke clonic seizures in saline-injected control animals from the kindling experiment, 8 days after finishing the kindling procedure.

(3) Finally, the third experiment was directed towards finding out whether AMPA effects as measured in the first and the second experiments were caused by receptor desensitisation. For that purpose, cyclothiazide (CYC; Tocris Cookson) was used. This substance blocks desensitisation, allowing the ion channel to remain open (Yamamada and Tang, 1993; Zorumski et al., 1993; Williams and Glowinski, 1996; Atassi and Glavinovic, 1999). CYC was dissolved in equimolar NaOH and the pH was adjusted to between 9 and 10. This solution was injected intraperitoneally (injection volume 0.1 ml/100 g body weight) 50 min prior to intracerebroventricular AMPA, which was followed 10 min later by an acute dose of 45 mg/kg PTZ. Per group, from 9 to 10 rats were used. After CYC injection, we observed moderate abdominal constrictions for approximately 10 min.

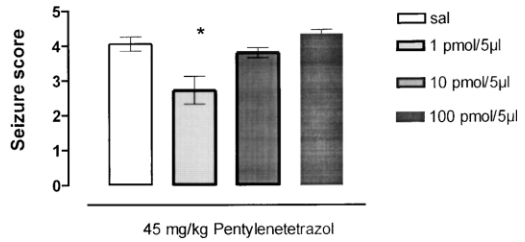

Fig. 1. Effect of different AMPA doses on acutely induced PTZ seizures in rats. Mean ± S.E.M. * $P < .05$ (saline-injected control rats vs. animals pretreated with 1 pmol AMPA). Per group, 15 animals were used.

For Experiments 1–3, separate groups of animals were used.

2.4. Statistics

To evaluate the development of seizures in the course of kindling, development seizure scores were analysed using ANOVA for repeated measures. The basis of statistical decision was a significance level of .05.

3. Results

After intracerebroventricular injection of AMPA, we did not observe alterations in animal's behaviour compared with saline-injected control rats. This is in line with observations by other authors (Peeters et al., 1994a; Patel et al., 2001).

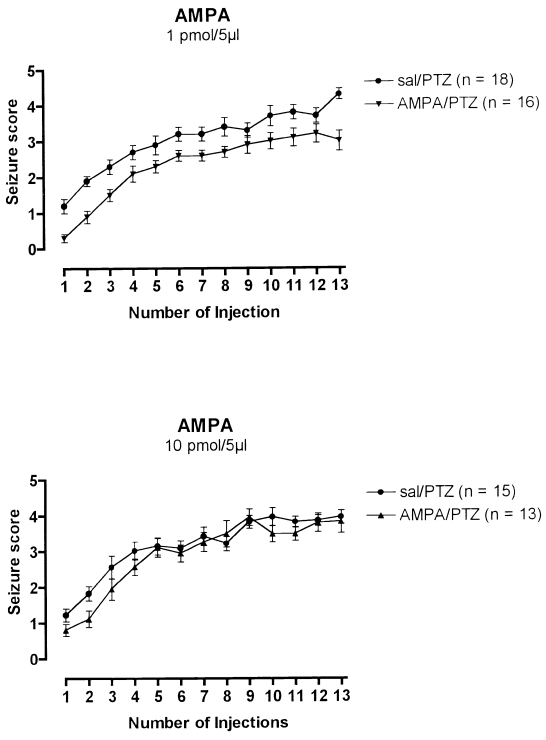

Fig. 2. Effect of AMPA on the development of PTZ kindling. Mean ± S.E.M.

3.1. Experiment 1 — acutely induced seizures

As illustrated in Fig. 1, the experimental groups differed in their response to acutely injected PTZ in dependence on pretreatment ($F_{3,57} = 11.6$, $P = .0001$, ANOVA). AMPA (1 pmol) exerted significant anticonvulsant activity ($P < .05$, Student–Newman–Keuls' test). Animals pretreated with 10 or 100 pmol of AMPA reached seizure scores similar to control rats.

Based on this result, doses of 1 or 10 pmol were chosen for Experiment 2.

3.2. Experiment 2 — kindling

3.2.1. Groups injected with 1 pmol/5 µl AMPA

Saline-pretreated rats repetitively injected with PTZ acquired the kindling syndrome as expressed by constantly increasing seizure scores (Fig. 2). Interestingly, the group dosed with 1 pmol AMPA demonstrated a significant suppressive effect of kindled seizures ($F_{1,32} = 5.51$, $P = .025$). In reaction to challenge (Fig. 3), striking differences between the four experimental groups occurred ($F_{3,61} = 89.8093$, $P < .0001$). This is due to higher scores in the sal/PTZ and the AMPA/PTZ group ($P < .05$, Stu-

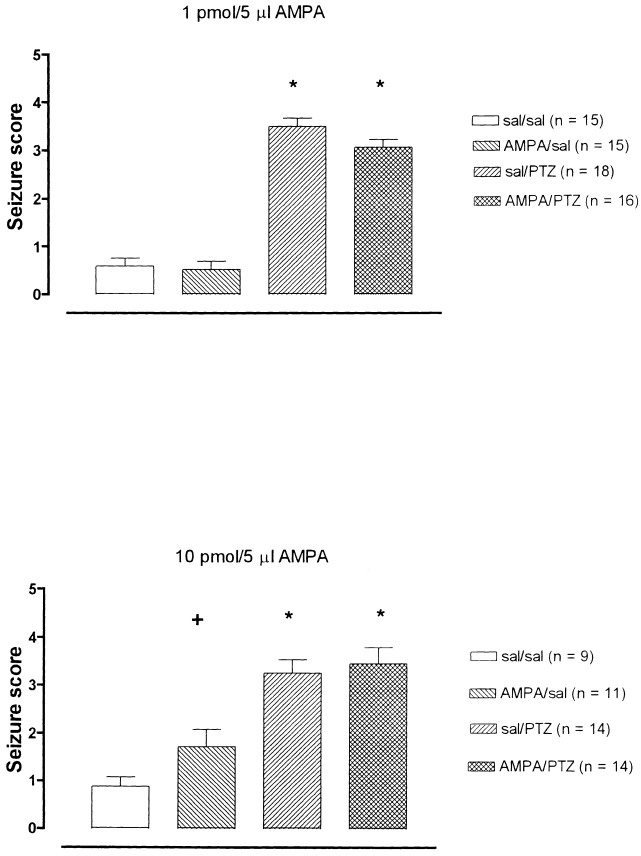

Fig. 3. Response of rats to a challenge dose of 35 mg/kg PTZ injected 8 days after kindling completion. Mean ± S.E.M. * $P < .05$ sal/sal vs. kindled animals pretreated with either saline or AMPA, $^{+}$ $P < .05$ sal/sal vs. saline-injected control groups pretreated with AMPA.

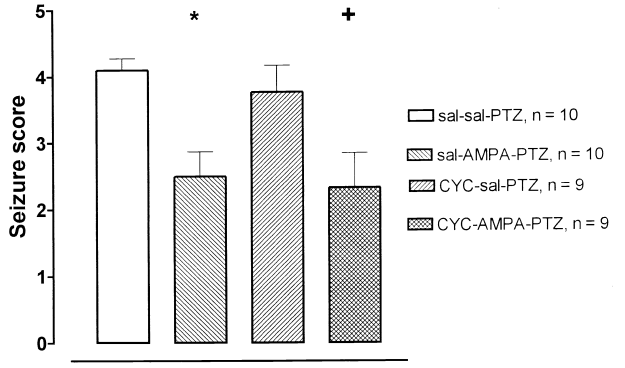

Fig. 4. Effect of 1 pmol AMPA per animal (intracerebroventricular application) on acutely induced PTZ seizures in rats after pretreatment with CYC. Mean ± S.E.M. * $P < .05$ sal-sal-PTZ vs. sal-AMPA-PTZ, $^{+}$ $P < .05$ CYC-sal-PTZ vs. CYC-AMPA-PTZ.

dent–Newman–Keuls' test). The difference between the sal/PTZ and the AMPA/PTZ group is not significant ($P > .05$, Student–Newman–Keuls' test).

3.2.2. Groups injected with 10 pmol/5μl AMPA

There was no effect of 10 pmol AMPA on kindling development and both groups (sal/PTZ and AMPA/PTZ) exhibited similar seizure scores ($F_{1,26} = 0.97$, $P = .334$) (Fig. 2). In reaction to challenge (Fig. 3), significant differences between the experimental groups were measured ($F_{3,45} = 14.52$, $P < .0001$). The kindled groups reached significantly higher scores compared with saline groups ($P < .05$, Student–Newman–Keuls' test). Interestingly, the saline group repetitively pretreated with 10 pmol AMPA had higher seizure scores than the sal/sal group ($P < .05$, Student–Newman–Keuls' test). The difference between the sal/PTZ group and the AMPA/PTZ group is insignificant ($P > .05$, Student–Newman–Keuls' test).

3.3. Experiment 3—effect of CYC

To find out whether the anticonvulsant effects as found in Experiments 1 and 2 are due to receptor desensitisation, CYC was used in an acute PTZ convulsion test. As shown in Fig. 4, significant differences between the experimental groups ($F_{3,35} = 5.4922$, $P = .0035$, ANOVA) exist. First, the anticonvulsive effect of 1 pmol AMPA was confirmed (sal/sal/PTZ vs. sal/AMPA/PTZ; $P < .05$, Student–Newman–Keuls' test). CYC pretreatment did not affect the strength of seizures induced by PTZ. Finally, the anticonvulsive effect of 1 pmol AMPA was not influenced by CYC pretreatment ($P > .05$, Student–Newman–Keuls' test) (Fig. 4).

4. Discussion

Our data clearly demonstrate anticonvulsant activity of 1 pmol AMPA. As shown in Fig. 1, 1 pmol AMPA significantly suppressed acutely induced PTZ seizures. Moreover, development of PTZ kindling was retarded (Fig. 2). However, in reaction to PTZ challenge (Fig. 3), there was no significant difference between sal/PTZ and AMPA/PTZ groups, suggesting that the kindled state was reached regardless of reduced seizure severity in the course of kindling development in the experimental group injected with 1 pmol AMPA. These findings support results (Namba et al., 1994; Kodama et al., 1999; Rogawski et al., 2001) indicating that AMPA receptors play an important role in seizure mechanisms and the development of kindling-induced epileptogenesis.

This anticonvulsant potency of low-dosed AMPA was unexpected. It is widely accepted that EAAs are involved in the initiation and propagation of seizures. NMDA receptors play a major role in these mechanisms, although more recent evidence indicates potential roles for AMPA receptors (Dingledine et al., 1990; Meldrum et al., 1992; Löscher et al., 1993).

Previously, it was found that 1 pmol AMPA increased the nonconvulsive absence epilepsy in rats (Peeters et al., 1994a). After intracerebroventricular injection, no clear behavioural alterations were observed (Peeters et al., 1994a). These results appear to be contradictory to the results obtained in our study. However, in their study, Peeters et al. (1994a) used WAG/Rij rats. This inbred strain is recognised as an animal model for human absence epilepsy (Coenen et al., 1992; Peeters et al., 1994b). Studies have emphasised the importance of the GABAergic and glutamatergic systems in this type of epilepsy. Thus, it might be assumed that an increased level of basic central excitability in these rats was increased by AMPA injection, whereas in normal rats, the opposite effect occurred. Further investigations of electroencephalographic events are needed because absence epilepsy and generalised clonic–tonic seizures differ in their neurophysiological base.

Studies have clearly demonstrated anticonvulsant potency of AMPA receptor antagonists (Löscher et al., 1993; Velisek et al., 1995). Our investigation revealed anticonvulsant effects of low-dosed AMPA, the receptor agonist. Thus, we have to ask for factors inhibiting AMPA receptor functioning. Beside application of antagonists, AMPA responses can be inhibited by presynaptic autoreceptors (Martin et al., 1991; Rainnie and Shinnick-Gallagher, 1992; Zhou et al., 1995) on glutamatergic synapses or by receptor desensitisation (Arai and Lynch, 1996; David et al., 1996; Fleck et al., 1996; Lodge et al., 1996). AMPA receptors characteristically undergo rapid desensitisation, and it has been suggested that this loss of receptor responsiveness may protect against excitotoxicity by preventing excessive glutamate neurotransmission (Zorumski et al., 1990). CYC appears to act at a distinct site on AMPA/kainate receptors to block AMPA receptor desensitisation, thereby increasing the frequency of ion channel openings and the duration of spontaneous miniature excitatory postsynaptic currents in the hippocampus (Yamada and Tang, 1993; Zorumski et al., 1993, David et al., 1996). Lodge (personal communication) found CYC effects within a few

minutes after intravenous injection and after oral administration maximal effects were found about 30–60 min after administration. Under the precondition that the anticonvulsant effect as found in Experiment 1 and 2 is due to receptor desensitisation, one would expect CYC pretreatment to reverse this effect. As shown in Fig. 4, CYC did not alter the AMPA effect on seizure severity. This suggests that in our experiments synaptic functions are altered by autoreceptor-mediated mechanisms rather than receptor desensitisation. In higher doses (10 and 100 pmol), postsynaptically mediated functions might abolish effects mediated by autoreceptors. The enhanced response to challenge in the saline group repetitively pretreated with 10 pmol AMPA (Fig. 3) might reflect increased dominance of postsynaptic effects expressed as proconvulsive effect.

However, it demonstrated the presence of presynaptic AMPA receptors of a novel CYC- and aniracetam-insensitive subtype on presynaptic nerve terminals in the rat striatum, acting to enhance glutamate and GABA release (Patel et al., 2001). The influence of AMPA on GABA efflux produced a bell-shaped dose–response curve and the maximum of enhancement of GABA efflux was 166.8% of basal. This enhancement of GABA efflux might contribute to the anticonvulsant effect as found in our experiments. On the other hand, Perouansky and Grantyn (1989) and Tang et al. (1989) proposed that AMPA act as antagonist or weak partial agonist at a kainate receptor. Possibly, this mode of action might contribute to anticonvulsant effects as found in our experiments. Further experiments are needed to clarify whether stimulation of presynaptic AMPA receptors is involved in AMPA-mediated anticonvulsant activity since presynaptic autoreceptors were also reported to enhance the synaptic release of EAAs in the mammalian forebrain (Patel and Croucher, 1997).

Finally, it was shown that AMPA receptors expressed in hippocampal neurones are assembled in a variety of subunit and splice variant combinations that might serve as a mechanism to fine-tune the kinetics of synaptic transmission (Fleck et al., 1996). Such heterogeneity might partly be responsible for different effects on specific functions.

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