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BRIEF COMMUNICATION

Kainate/AMPA Receptor Antagonists Are Anticonvulsant Against the Tonic Hindlimb Component of Pentylenetetrazol-Induced Seizures in Developing Rats

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VELÍŠEK, L., H. KUBOVÁ, P. MAREŠ AND D. VACHOVÁ. *Kainate/AMPA receptor antagonists are anticonvulsant against the tonic hindlimb component of pentylenetetrazol-induced seizures in developing rats.* PHARMACOL BIOCHEM BEHAV 51(1) 153–158, 1995.—Non-NMDA receptor antagonists CNQX, DNQX, and NBQX (10–40 mg/kg IP) were tested against pentylenetetrazol-induced (100 mg/kg SC) seizures in 7 to 90-day-old rats. All three drugs significantly decreased the incidence of tonic hindlimb component of tonic–clonic pentylenetetrazol seizures, often in favor of increased incidence of forelimb tonus throughout development. In addition, in 7 to 25-day-old rats, DNQX and NBQX decreased the severity of seizures due to a decrease in total incidence of the tonic component of tonic–clonic seizures compared to age-matched controls. However, neither drug was able to consistently suppress the incidence or increase latency to onset of clonic and tonic–clonic pentylenetetrazol seizures. The data suggest that, during development, non-NMDA receptor transmission may play a role in the generation of the tonic component, but not in the generation of other components of pentylenetetrazol-induced seizures.

Development Seizures Pentylenetetrazol Quinoxalines Rat

EXCITATORY amino acid (EAA) neurotransmission plays an important role in seizures. All three prototypic EAA [kainic acid, *N*-methyl-D-aspartic acid (NMDA) and quisqualic acid] as well as glutamic acid, induce seizures in experimental animals (2,14,18,22). The seizures are EAA specific and they are also age specific (1,13,22,28). On the other hand, antagonists of EAA receptors, especially of NMDA subtype, have anticonvulsant properties in various seizure models (5,6, 26,29).

Recently, we have demonstrated that NMDA receptor antagonists 2-amino-7-phosphonoheptanoic acid (2-APH) and MK-801 suppress pentylenetetrazol-induced tonic–clonic seizures in developing rats. MK-801 was more effective against pentylenetetrazol-induced seizures in 7-day-old than in 90-day-old rats, whereas 2-APH was virtually equipotent throughout development. Another seizure type induced by pentylenetetrazol, i.e., face and forelimb clonus, was not affected by the two NMDA receptor antagonists (26,27). NMDA receptor antagonists were also introduced into clinical trials as add-on anticonvulsants. However, these trials were ceased due to serious adverse effects (20,23).

Anticonvulsant action of non-NMDA receptor antagonists

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has been already demonstrated in several seizure models in adult animals (4,10,19,21,30). Because non-NMDA receptor antagonists poorly cross the blood–brain barrier, first we hypothesized that they would be better anticonvulsants in young than in adult rats. Second, we hypothesized that non-NMDA receptor antagonists would suppress both clonic and tonic–clonic pentylenetetrazol-induced seizures. We expected that these drugs would generally suppress the seizure initiation and spread throughout the CNS due to the blockade of fast excitatory synaptic transmission even if they would not directly affect specific seizure generators hypothesized previously (3,8).

We used male Wistar albino rats (n = 542) in five age groups: 7, 12, 18, 25, and 90 day olds. These ages roughly correspond to human preterm newborns (7 days of age), infants (12 days), children (18 days), prepubescents (25 days), and adults (90 days) (9).

The rats in control groups were treated by pentylenetetrazol (100 mg/kg SC; 100 mg in 1 ml of saline). To control for the effects of solvent for non-NMDA receptor antagonists, other groups were pretreated with 1 ml/kg of dimethylsulfoxide (DMSO) IP. The same volume of DMSO was used to dissolve the drugs tested.

Three non-NMDA receptor antagonists were used: CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), DNQX (6,7-dinitroquinoxaline-2,3-dione), and NBQX [2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo(F)quinoxaline] (all gifts from the Research Institute for Pharmacy and Biochemistry, Prague, the Czech Republic). The antagonists were administered in doses 10, 20, or 40 mg/kg IP, dissolved in the volume of DMSO corresponding to the total dose of 1 ml/1 kg.

Thirty minutes following the pretreatment with either dimethylsulfoxide or non-NMDA antagonists (4,17,30), the rats received the same dose of pentylenetetrazol as control groups (100 mg/kg SC).

Immediately after the injection of pentylenetetrazol, the rats were placed into the separate chambers and observed for 30 min for clonic seizures (clonus of head muscles and forelimbs with preserved righting ability) that occur regularly in 18-day-old and older rats (25), and tonic–clonic seizures (loss of righting, tonus of the limbs followed by a long clonus), that can be observed throughout development (25). Rat pups (7–18 days old) were placed in cages with an electrically heated floor to 34°C.

We recorded the incidence and latency to onset of clonic and tonic–clonic seizures. Our pilot experiments suggested that after the pretreatment with non-NMDA antagonists, there may be differences, especially in the expression of fore- and hindlimb tonic component of seizures. Therefore, the incidence of tonic phase on fore- and hindlimbs was carefully and separately recorded (11). In addition, to evaluate the overall severity of seizures (i.e., clonic seizures, tonic–clonic seizures, and tonic phases together) score points were arbitrarily assigned to each rat according to the maximal pattern in the following scale (15): 0.5—abnormal behavior (e.g., reorientation of already habituated rat, sniffing, rearing); 1—myoclonic twitches; 2—unilateral, asymmetric or incomplete clonic seizures (usually in pups); 3—bilateral symmetric clonic seizures; 4—seizures beginning with the loss of righting reflex followed by a long clonus, but without pronounced tonic component; 5—complete tonic–clonic seizures (tonic component present). The incidence of seizures and tonic components was statistically evaluated in a contingency table using χ^2-test with post hoc cell contributions. The latency to onset of seizures was compared within each age group using ANOVA with post hoc Tukey test, if the main effect was detected. Seizure score data were evaluated by nonparametric Kruskal–Wallis test followed with nonparametric paired comparisons, if the main effect was detected. The level of significance was set to 5% ($p < 0.05$).

Clonic Seizures (Data Not Illustrated)

Clonic seizures were regularly elicited by pentylenetetrazol in 18-, 25-, and 90-day-old control rats [93%, 93%, and 100% respectively; (25)]. Latency to onset of clonic seizures increased with age of the rats.

In 7-day-old rats, pretreatments with DNQX (10 and 40 mg/kg) and NBQX (10 mg/kg) significantly increased the incidence of clonic seizures compared to 6.3% in controls [$\chi^2(10) = 28.84, p < 0.05$]. In 12-day-old rats, there was an increase in the incidence of clonic seizures from 21% in controls to 67.5% after DMSO pretreatment [$\chi^2(10) = 24.86, p < 0.05$]. In 18-day-old rats, several doses of non-NMDA antagonists (DNQX 10 and 40 mg/kg, and NBQX 40 mg/kg) significantly increased the latency to onset of clonic seizures compared to controls [ANOVA with post hoc Tukey test; $F(10, 68) = 5.611, p < 0.05$]. In 25-day-old rats, the lowest dose of DNQX and NBQX (10 mg/kg) identically suppressed the incidence of clonic seizures to 50% [$\chi^2(10) = 23.29, p < 0.05$]. In the same age group, CNQX (40 mg/kg) increased the latency to onset of clonic seizures compared to controls [ANOVA; $F(10, 87) = 2.371, p < 0.05$]. In 90-day-old rats, there were no significant effects of DMSO and nonNMDA antagonist pretreatment on the incidence and latency to onset of clonic seizures.

Tonic–Clonic Seizures (Data Not Illustrated)

Tonic–clonic seizures were induced in 100% of 7–18-day-old rat pups, in 93% of 25-day-old rats, and in 62.5% of adult rats. The latency to onset of tonic–clonic seizures was somewhat longer in 7 day than in 12- and 18-day-old rat pups, with an increase in 25-day-old and adult rats (25).

DMSO did not significantly change the incidence of tonic–clonic seizures. There was rather a decreasing, but insignificant, trend in the latency to onset of tonic–clonic seizures after DMSO pretreatment. The effects of non-NMDA antagonists on tonic–clonic seizures were inconsistent. In 7-day-old rats, DNQX (40 mg/kg) and NBQX (20 mg/kg) compared to controls significantly increased latency to onset of tonic–clonic seizures [ANOVA, $F(10, 82) = 3.291, p < 0.05$]. In 12-day-old rats, CNQX (10 mg/kg) and DNQX (40 mg/kg) increased the latency to onset of tonic–clonic seizures, while the dose of 20 mg/kg of DNQX decreased the latency compared to controls [ANOVA; $F(10, 96) = 3.935, p < 0.05$]. In 18-day-old rats, there was no effect of pretreatment on tonic–clonic seizures. In 25-day-old rats compared to controls, NBQX (10 and 20 mg/kg) and DNQX (10 mg/kg) significantly suppressed the incidence of tonic–clonic seizures [to 37.5%, 50%, and 25%, respectively; $\chi^2(10) = 38.97, p < 0.05$]. In the same age group, CNQX (40 mg/kg) decreased and NBQX (10 mg/kg) increased the latency to onset of tonic–clonic seizures [ANOVA; $F(10, 73) = 2.446, p < 0.05$]. In adult rats, we did not find any effects of DMSO and non-NMDA receptor antagonists on either incidence or latency to onset of tonic–clonic pentylenetetrazol seizures.

Seizure score (severity of seizures; Table 1). In all age groups of control rats, the mean score was 4.3–5.0 due to prevailing fully developed tonic–clonic seizures (i.e., score 5 seizures).

TABLE 1

SEVERITY OF SEIZURES (EXPRESSED AS A SEIZURE SCORE) INDUCED BY PENTYLENETETRAZOL AND THE EFFECTS OF NON-NMDA RECEPTOR ANTAGONISTS

			Treatment								
			CNQX			DNQX			NBQX		
Age	Controls	DMSO 1 ml/kg	10 mg/kg	20 mg/kg	40 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg
7 days	4.9	5.0	5.0	4.8	4.9	4.7	4.0*†	3.7*†	5.0	4.4	4.4
	(4–5)	(5–5)	(5–5)	(4–5)	(4–5)	(4–5)	(1–5)	(1–5)	(5–5)	(4–5)	(4–5)
	$n = 16$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 9$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$
12 days	4.7	5.0	4.8	4.5	4.6	5.0	4.6	3.5*†	5.0	4.8	4.4
	(4–5)	(5–5)	(4–5)	(2–5)	(4–5)	(5–5)	(4–5)	(1–5)	(5–5)	(4–5)	(4–5)
	$n = 29$	$n = 8$	$n = 8$	$n = 8$	$n = 9$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$
18 days	5.0	4.4	5.0	5.0	5.0	3.7*	4.3	4.7	4.4	5.0	3.7*
	(4–5)	(1–5)	(5–5)	(5–5)	(5–5)	(0.5–5)	(1–5)	(4–5)	(0.5–5)	(5–5)	(0.5–5)
	$n = 27$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$
25 days	4.9	5.0	4.5	4.3	5.0	2.3*†	5.0	4.8	2.6*†	4.0	4.3
	(3–5)	(5–5)	(1–5)	(1–5)	(5–5)	(0.5–5)	(5–5)	(3–5)	(0.5–5)	(1–5)	(3–5)
	$n = 30$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$
90 days	4.30	3.4	4.8	5.0	4.3	4.4	5.0	4.8	5.0	4.5	4.8
	(3–5)	(0.5–5)	(3–5)	(5–5)	(3–5)	(3–5)	(5–5)	(3–5)	(5–5)	(3–5)	(3–5)
	$n = 16$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 10$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$

The values in the table represent mean (minimal-maximal value—illustrating the uniformity) in the subgroup.
*Significant difference ($p < 0.05$) compared to the age-matched control group.
†Significant difference ($p < 0.05$) compared to the age-matched DMSO group.

DMSO pretreatment did not significantly change the score. The pretreatment with non-NMDA antagonists decreased the severity of seizures in 7–25-day-old rats. In 7- and 12-day-old rats, only DNQX significantly attenuated the seizures compared to age-matched controls (Kruskal-Wallis test; $H = 30.759$, $p < 0.05$, and $H = 24.373$, $p < 0.05$, respectively). In 18- and 25-day-old rats, both DNQX and NBQX significantly decreased seizure severity ($H = 20.101$, $p < 0.05$, and $H = 39.135$, $p < 0.05$, respectively).

Effects of Non-NMDA Antagonists on the Expression of Tonic Component of Tonic-Clonic Seizures (Fig. 1)

In control rats, the total incidence of tonic component [either only forelimbs (Fig. 1; open part of the bars) or forelimbs together with hindlimbs (Fig. 1; dashed part of the bars)] was 62.5–100% with major (> 80% of total) contribution of combined forelimb and hindlimb tonus (dashed bars). We never observed hindlimb tonus without an accompanying forelimb tonus both in control conditions and after pretreatment.

DMSO did not significantly change either the total incidence of the tonic component or the share of forelimb tonic component. In 7-day-old rats, all three non-NMDA antagonists significantly suppressed the incidence of tonic hindlimb component of seizures [$\chi^2(10) = 39.55$, $p < 0.05$]; however, only the largest dose of DNQX (40 mg/kg) and both 20 and 40 mg/kg of NBQX decreased the total incidence of tonic component of seizures compared to age-matched controls [$\chi^2(10) = 40.44$, $p < 0.05$]. In 12-day-old rats, all doses of non-NMDA receptor antagonists decreased significantly the incidence of tonic hindlimb component of seizures [$\chi^2(10) = 36.27$, $p < 0.05$]; however, only the largest doses of DNQX and NBQX significantly suppressed total incidence of tonic component [$\chi^2(10) = 23.02$, $p < 0.05$]. In 18-day-old rats, all tested non-NMDA receptor antagonists suppressed the tonic hindlimb component compared to controls, but without an apparent dose dependence [$\chi^2(10) = 65.23$, $p < 0.05$]. In this age group, there was no effect of the drugs on the total incidence of tonic phase. In 25-day-old rats, although without a dose dependence, all drugs used suppressed the incidence of tonic hindlimb component of seizures compared to controls [$\chi^2(10) = 54.37$, $p < 0.05$]. Moreover, the lowest dose of DNQX (10 mg/kg) and all doses of NBQX suppressed the total incidence of tonic phase [$\chi^2(10) = 36.02$, $p < 0.05$]. In adult 90-day-old rats, we found only a suppression of tonic hindlimb component, without a specific dose dependence [$\chi^2(10) = 35.71$, $p < 0.05$]. Thus, the preatreatment with non-NMDA antagonists had two major effects on pentylenetetrazol seizures if compared to age-matched controls: a) the pretreatment significantly decreased the participation of hindlimb tonic component of seizures often in favor of increased incidence of forelimb tonic phase throughout the development and rarely b) suppressed the total incidence of tonic component of pentylenetetrazol seizures in all age groups except for adult rats.

Our data demonstrate that non-NMDA receptor antagonists (CNQX, DNQX, and NBQX) attenuate the severity of pentylenetetrazol-induced seizures throughout development due to suppression of the tonic hindlimb component in the pattern of tonic-clonic seizures. Except for adult rats, non-NMDA receptor antagonists also decrease the total incidence of tonic component of tonic-clonic seizures. In contrast, non-NMDA receptor antagonists have inconsistent effects on the incidence and latency to onset of pentylenetetrazol-induced clonic and tonic-clonic seizures in developing rats.

Our present results correspond with previous studies on the action of quinoxalines. In audiogenic seizure-prone rats, NBQX was about three times more potent in suppression of the tonic component of seizures than against the clonic component (19). Systemic administration of NBQX abolished

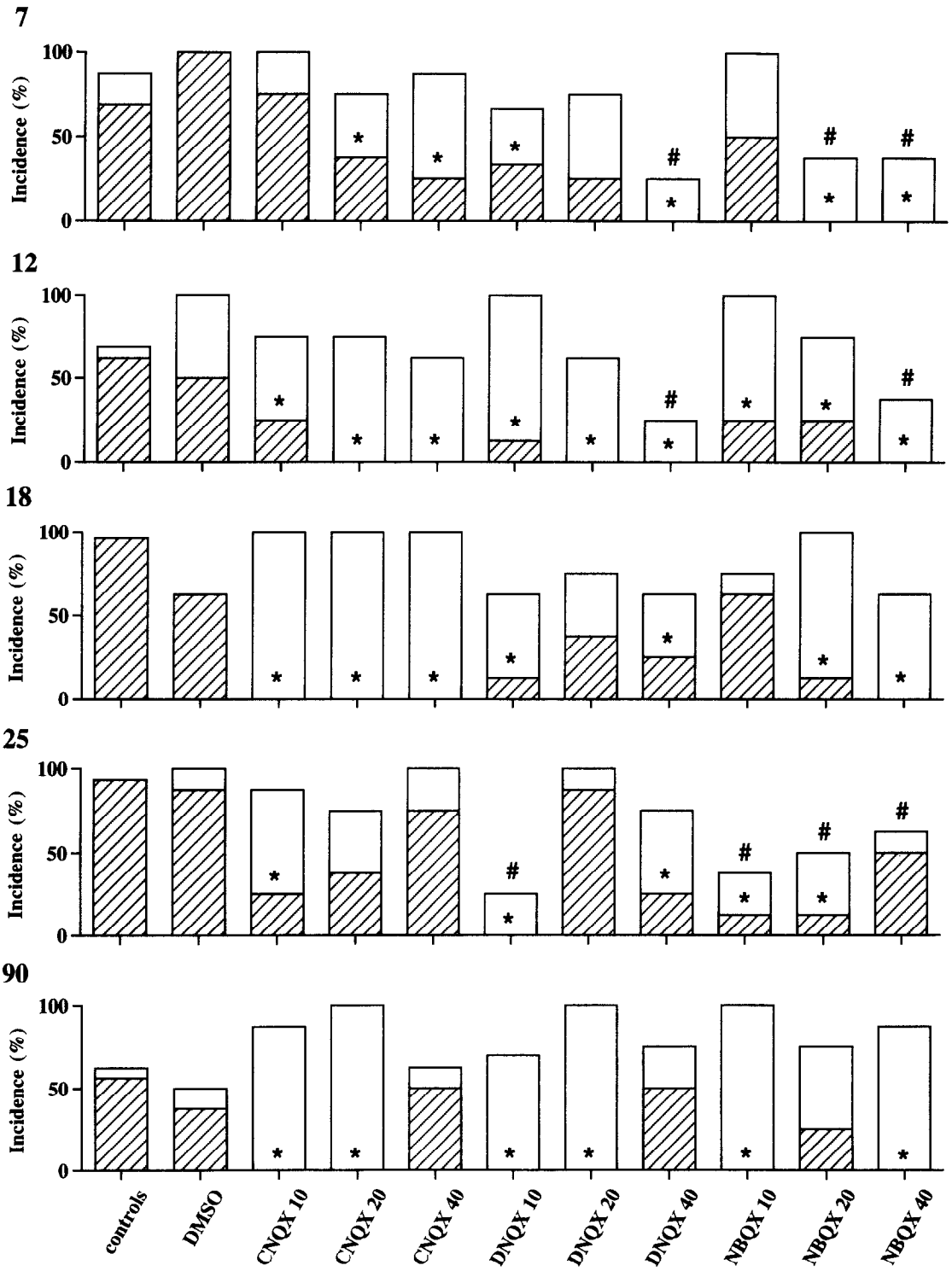

FIG. 1. The incidence of tonic components of pentylenetetrazol-induced seizures in developing rats. Age groups 7, 12, 18, 25, and 90 days are arranged from top to bottom. x axis—treatment, see the Method section for abbreviations; y axis—incidence in percent. Dashed bars represent the incidence of hindlimb tonus observed together with forelimb tonus. Open bars represent the incidence of forelimb tonus only. The entire bar shows the total incidence of any tonic component in the tonic-clonic seizures (i.e., forelimbs together with hindlimbs + forelimbs only). *Significant difference from controls in the incidence of the tonic component present on hindlimbs together with forelimbs (dashed bar); χ^2 test with post hoc cell contributions; $p < 0.05$. #Significant difference from controls in the incidence of all tonic components (dashed + open bar); χ^2 test with post hoc cell contributions; $p < 0.05$.

tonic hindlimb extension in maximal electroshock seizures in mice (21). The data suggest that non-NMDA receptor-mediated synaptic transmission may play a role in the genesis of tonic component of tonic-clonic seizures during development. The action of non-NMDA antagonists against the tonic component of seizures is similar to that seen in some classic antiepileptic drugs that suppress seizure spread (e.g., phenytoin and carbamazepine) (11,12). We can speculate that some of those antiepileptic drugs might also affect non-NMDA excitatory transmission as one of their mechanisms of action. It should be noted, however, that the antiextensor effects of some anticonvulsant and experimental drugs are sometimes difficult to interpret due to a possible interaction (coincidental or unrelated to anticonvulsant effects) with sustained muscle contraction and/or spinal reflexes at the muscle and spinal cord levels (16). It is not clear whether quinoxalines act also at a muscle or muscle spindle system. Nevertheless, the evaluation of the tonic component of the tonic-clonic seizure remains to be a part of routine screening for anticonvulsant potency of new drugs (11).

The induction of both clonic and tonic-clonic pentylenetetrazol-induced seizures was much less affected by non-NMDA receptor antagonists than the tonic component. In mice, NBQX ED_{50} against clonic pentylenetetrazol-induced seizures is approximately 85 mg/kg (30), which is a very high dose in comparison with our protocol.

The absence of significant anticonvulsant effects of non-NMDA antagonists in the adult rats suggests that there may be a substantial influence of blood-brain barrier on the permeability of quinoxalines into the brain of adult rats after systemic administration. Thus, anticonvulsant effects of quinoxalines were observed predominantly in young rats. Recent studies, however, have demonstrated anticonvulsant effects of non-NMDA antagonists in adult animals in various seizure models (audiogenic seizures in rats and mice, myoclonus in baboons, maximal electroshock, systemic pentylenetetrazol-, quisqualate-, kainate-, NMDA-, and AMPA-induced seizures, and ICV bicuculline-induced seizures) (4,7,10,19,21,24,30). CNQX also decreased the duration of spike-and-wave discharges in the WAG/Rij strain of nonconvulsive rat model of spontaneous absence epilepsy (17). The time factor of quinoxaline action could also play a role. Recent study demonstrated that NBQX had maximal anticonvulsant effects 20 min after IP administration, which is different from our 30 min pretreatment period. However, in the aforementioned study, the anticonvulsant effects were still significant after 60 min (4). In the more subtle model of spontaneous EEG absence seizures, the anticonvulsant effects of CNQX (ICV application) lasted for several hours (17).

EAA receptor antagonists, and especially NMDA receptor antagonists, are excellent experimental anticonvulsants effective against different patterns of experimental seizures. NMDA receptor antagonists suppress the occurrence of entire tonic-clonic seizure while non-NMDA receptor antagonists seem to be more specific against the tonic hindlimb component of tonic-clonic seizures. However, this class of experimental anticonvulsants did not fulfill the expectations in human epilepsy. Significant adverse effects (including a loss of anticonvulsant potency, memory deficits, and psychotic symptoms) of tested NMDA receptor antagonists MK-801 and D-CPP-ene interrupted ongoing clinical trials (20,23). This striking difference between experimental and clinical results suggests that it is necessary to adjust the battery of experimental tests available to depict more accurately the human condition. Furthermore, there should be a careful experimental and clinical search for predictable adverse effects in putative anticonvulsants.

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