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DEFICIT OF ENDOGENOUS KYNURENIC ACID IN THE FRONTAL CORTEX OF RATS WITH A GENETIC FORM OF ABSENCE EPILEPSY

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The present studies sought to determine the concentrations of endogenous kynurenic acid (KYNA) and to measure the activity of kynurenine aminotransferases (KAT) I and II in the discrete brain regions of 3- and 6-month old WAG/Rij rats, a genetic model of absence epilepsy. Analogues experiments were performed using age-matched ACI rats, which served as a non-epileptic control.

The age-dependent increase in KYNA concentration in the frontal cortex of WAG/Rij rats was considerably reduced in comparison to what was found in ACI rats. Consequently, the concentration of KYNA in the frontal cortex of epileptic rats was significantly lower than in non-epileptic controls. There were no such strain differences in other brain regions. The activities of KAT I and II also showed age-dependent increase with an exception for KAT II in the frontal cortex.

Our data suggest that selective deficits of endogenous KYNA may account for increased excitability in the frontal cortex, which in turn may lead to the development of spontaneous spike-wave discharges in WAG/Rij rats.

Key words: *kynurenic acid, aminotransferase, WAG/Rij rats, ACI rats, absence epilepsy, genetic models*

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INTRODUCTION

Kynurenic acid (KYNA) is endogenously synthesized from tryptophan *via* the kynurenine pathway by kynurenine aminotransferases (KAT) I and II. KYNA is a broad spectrum antagonist of glutamate receptors and it may bind to the glycine site of the N-methyl-D-aspartate (NMDA) receptor with relatively high affinity. It also binds with similar affinity to the nicotinic receptors containing the α7 subunit (for reviews see [30, 34–36]).

Glutamatergic neurotransmission plays a pivotal role in the pathogenesis of epilepsy and antagonists of glutamate receptors are powerful anticonvulsants [3, 37]. In line with this, KYNA and its synthetic analogues are generally efficacious anticonvulsants in a variety of models of experimental epilepsy [9, 17, 39, 41]. Moreover, reduction of KYNA levels increases vulnerability to excitotoxic insults, whereas elevation of KYNA content has an opposite effect [29, 45, 46].

A significant role of glutamate receptors has also been postulated for non-convulsive epilepsy [4, 5, 16, 25, 26]. In WAG/Rij rats, serving as a well-validated, genetic model of absence epilepsy [42, 43], spontaneous spike-wave discharges (SWD) can be inhibited by KYNA administration. Moreover, KYNA blocks NMDA-induced potentiation of SWD in these rats [25, 26]. The above-mentioned findings prompted us to examine the concentrations of endogenous KYNA and the activity of KAT in the discrete brain regions of WAG/Rij rats.

MATERIALS and METHODS

Animals

The analyses were performed in the parts of the brain where SWD are either evoked [23] or modulated [6]. The measurements were carried out at the age when WAG/Rij rats (i) begin to develop SWD (3 months) and (ii) display hundreds of SWD per day (6 months) [2]. Analogous experiments were performed in age-matched ACI rats, which are virtually devoid of SWD [15]. Such experimental design allows studying not only the age- and strain-dependent changes but also their interaction. Since only the 6 months old WAG/Rij rats show SWD, while the other groups do not, the interaction can be tentatively interpreted as that the biochemical changes are related to the presence of SWD. This paradigm has been previously employed in other studies [19, 20]. The number of animals in each strain/age-matched group ranged from 3 to 6. Experimental procedures were in agreement with European Communities Council Directive (86/609/EEC) and were approved by the local Ethics Committee.

Determination of KYNA concentration

Animals were sacrificed by decapitation and their brains were rapidly removed from the scull. The frontal cortex, striatum and thalamus were dissected and immediately frozen for further studies. KYNA levels were estimated according to the modified method of Turski et al. [40]. Tissue material was homogenized with 1 ml of water by ultrasonication and centrifuged (20000 rpm, 10 min). Subsequently, 10 µl of 50% trichloroacatic acid and 100 µl of 1 M HCl were added to each sample of the obtained supernatant. Denatured protein was removed by centrifugation and the resulting supernatant was applied to the columns containing cation-exchange resin (Dowex 50 W+: 200–400 mesh) prewashed with 0.1 M HCl. Then, the columns were washed with 1ml of 0.1 M HCl and 1ml of water, and the fraction containing KYNA was eluted with 2 ml of water. Eluate was subjected to HPLC and KYNA was detected fluorometrically (Hewlett Packard 1050 HPLC system: ESA catecholamine HR-80, 3 µm, C18 reversed-phase column, flow rate of 1.0 ml/min, excitation 344 nm, emission 398 nm) according to the method of Shibata [32].

Determination of KAT I and KAT II activities

KAT I and KAT II activities were assayed according to the method of Guidetti et al. [12] with modification. Tissue was homogenized (1:10 w/v) in 5 mM Tris-acetate buffer, pH 8.0, containing 50 µM pyridoxal-phosphate and 10 mM 2-mercaptoethanol. The resulting homogenate was dialyzed overnight at 8°C, using cellulose membrane dialysis tubing, against 4 l of the same buffer. Active samples contained the enzyme preparation with reaction mixture containing 2 µM L-kynurenine, 1 mM pyruvate, 70 µM pyridoxal-5'-phosphate, 150 mM Tris-acetate buffer pH of 7.0 (KAT II) or 150 mM Tris-acetate buffer pH 9.5 (KAT I) in a total volume of 0.2 ml. In KAT II assay a KAT I inhibitor, glutamine (final concentration: 2 mM), was added to each sample. Blank samples containing heat-deactivated enzyme (100°C for 10 min) and active samples were incubated at 37°C for 24 h. Transfer of the samples to an ice-bath and the addition of 10 µl of 50% trichloroacetic acid and 100 µl of 1 M HCl terminated the reaction. The denatured proteins were removed by

centrifugation and the supernatant was applied to a Dowex 50 W+ column and quantified by HPLC.

Protein content was determined spectrophotometrically in small aliquots of the respective enzyme preparations according to the method of Lowry et al. [21]. The final results were expressed as the amount of KYNA (pmol) synthesized by 1 mg of protein during 1 h of incubation (pmol/h/mg).

Statistics

The results obtained from the assays were compared separately for each brain region with the use of two-way analysis of variance (ANOVA), where age and strain of rats were used as independent factors. The two-way ANOVA was followed by the Bonferroni *t*-test for group comparisons.

RESULTS

The content of KYNA in the frontal cortex ($F_{1,16}$ = 20.3, $p < 0.001$), striatum ($F_{1,17}$ = 15.4, $p < 0.01$) and thalamus ($F_{1,16}$ = 33.3, $p < 0.001$) increased in an age-dependent manner (Fig. 1A, B, C). Only in the frontal cortex a significant strain difference ($F_{1,16}$ = 9.5, $p < 0.01$) and strain times age interaction ($F_{1,16}$ = 7.4, $p < 0.05$) were observed (Fig. 1A). Outcomes of the *post hoc* tests showed that there was only a significant increase in the content of KYNA in the frontal cortex from 3 to 6 months in ACI rats, not in WAG/Rij rats (Fig. 1A, B, C). Moreover, the 6-month-old ACI rats had higher levels of KYNA ($p < 0.01$) than all other groups, including the age-matched WAG/Rij rats (Fig. 1A).

The activities of KAT I and KAT II are presented in Table 1. The two-way ANOVA revealed significant age-dependent increases of KAT I activity in the frontal cortex ($F_{1,13}$ = 5.2, $p < 0.05$) and thalamus ($F_{1,13}$ = 10.1, $p < 0.01$); no strain effects were found. Likewise, the *in vitro* activity of KAT II measured in samples from frontal cortex and thalamus did not differ between the WAG/Rij and ACI rats. There was, however, an age-dependent increase in KAT II activity in the thalamus ($F_{1,14}$ = 12.5, $p < 0.01$), but not in the frontal cortex.

DISCUSSION

The present study demonstrates an age-dependent increase in the content of KYNA in the discrete brain regions of epileptic WAG/Rij and non-epileptic ACI rats. These results are consistent with pre-

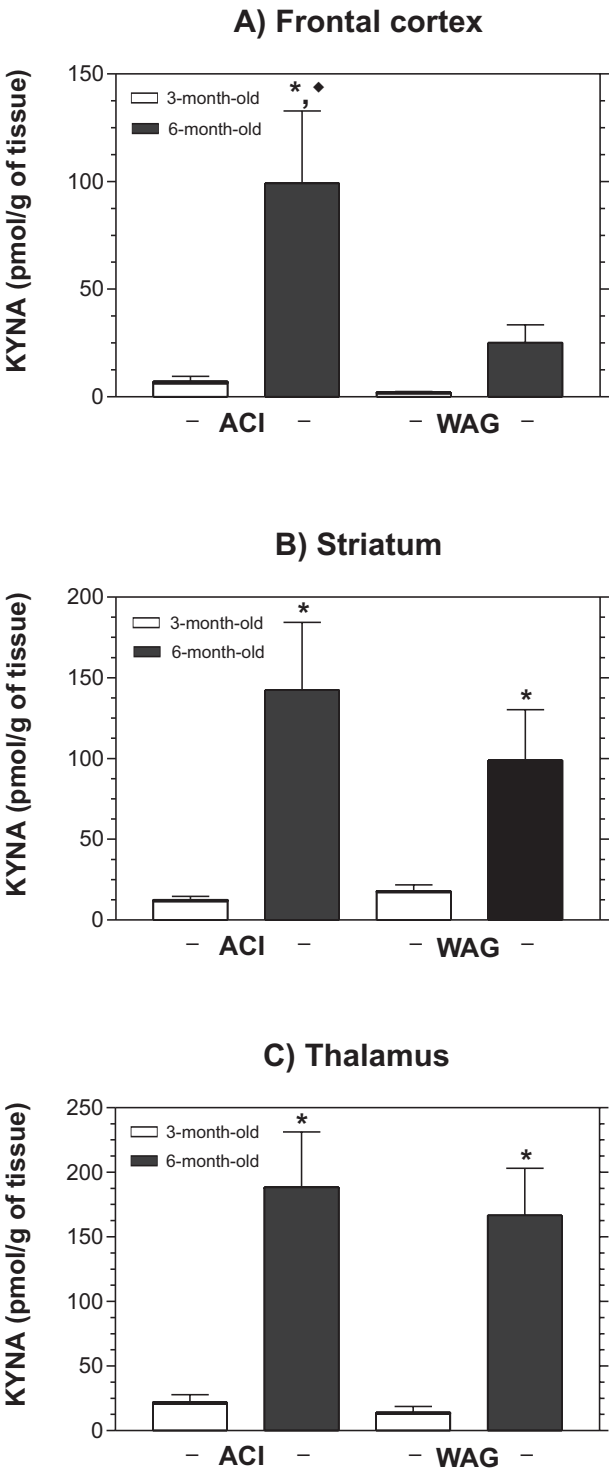

Fig. 1. The levels of endogenous kynurenic acid (KYNA) in the frontal cortex (A), striatum (B) and thalamus (C) of WAG/Rij and ACI rats. Each bar represents the mean ± SEM (pmol/g of wet weight). Number of animals used in these experiments was as follows: 3- and 6-month-old ACI rats (n = 3 per group), 3- and 6-month-old WAG/Rij rats (n = 6 per group). * $p < 0.05$ vs. 3-month-old same strain rats, ◆ $p < 0.05$ vs. vs. 6-month-old WAG/Rij rats (Bonferroni *t*-test)

Table 1. In vitro activity of kynurenine aminotransferase (KAT) I and II obtained from the frontal cortex and thalamus of WAG/Rij and ACI rats. The results are expressed as means ± SEM and represent the amount of KYNA (pmol) synthesized by 1 mg of protein during 1 h of incubation (pmol/h/mg). The increase in KAT I activity in the frontal cortex ($F_{1,13} = 5.2$, $p < 0.05$) and thalamus ($F_{1,13} = 10.1$, $p < 0.01$) was age-dependent (two-way ANOVA). KAT II showed an age-dependent increase, but it reached statistical significance only in the thalamus ($F_{1,14} = 12.5$, $p < 0.01$). * $p < 0.05$ *vs.* 3-month-old the same strain rats (Bonferroni *t*-test)

Age and strain	KAT I (pmol/h/mg)		KAT II (pmol/h/mg)	
	Frontal cortex	Thalamus	Frontal cortex	Thalamus
3-month-old ACI (n = 3)	7.9 ± 0.7	15.8 ± 2.1	12.4 ± 1.1	31.6 ± 2.4
6-month-old ACI (n = 3)	17.2 ± 2.7	20.7 ± 4.3	21.2 ± 3.0	62.7 ± 11.6*
3-month-old WAG/Rij (n = 4)	13.5 ± 0.9	12.1 ± 1.6	17.2 ± 0.5	37.5 ± 4.9
6-month-old WAG/Rij (n = 5)	21.2 ± 5.9	23.5 ± 2.3*	27.6 ± 9.1	55.9 ± 7.0

viously reported data from other rat strains [11, 24], thus, such age-depended increase in KYNA concentration could be considered as a more general feature. Interestingly, selectively in the frontal cortex of 6 months old WAG/Rij rats, this increase was absent. Therefore, it seems that genetically epileptic rats have lower levels of KYNA in the frontal cortex than age-matched ACI rats, whereas no difference was found in 3-month-old rats of both strains. It is important to underline that only 6 months old WAG/Rij rats display several hundreds of spontaneous SWD per day, while age-matched ACI rats and 3 months old WAG/Rij rats have no or much less SWD [2, 15].

Ample data show that neuronal excitability and seizure activity can be dampened by increased concentration of KYNA, resulting from either exogenous application or enhanced endogenous production [9, 27, 39, 41, 45, 46]. KYNA (50–500 nmol) injected *icv* inhibits spontaneous [26] and NMDA-enhanced SWD [25] in WAG/Rij rats. Local administration of KYNA (5 mM) to a slice preparation with intact thalamocortical circuitry also completely abolishes spindle-like oscillations, resembling those seen in electroencephalogram (EEG) during absence seizures [38]. More recent studies performed on similar preparations obtained from WAG/Rij rats also confirm the importance of NMDA-mediated events in the generation of rhythmic thalamocortical oscillations [5]. It should be noted, however, that the effective concentrations of KYNA in the above-mentioned experiments were much higher than those established in the present study. As such, the possible role of endogenous KYNA in controlling epileptic phenomena should be further scrutinized. Nevertheless, these findings suggest that KYNA could be an important factor involved in suppression of cortical excitability.

The frontal cortex, striatum and thalamus are key structures for the development and maintenance of SWD hallmarking absence epilepsy [1, 4, 23, 33]. The present study shows selective reduction of KYNA concentration in the frontal cortex of WAG/Rij rats at an age when they display large number of spontaneous SWD [2]. In contrast, there was no such difference in the striatum and thalamus of either epileptic or non-epileptic rats. Several pieces of evidence suggest that neuronal hyperexcitability in the frontal cortex seems to have critical importance for the initiation of SWD [4, 5, 22, 33]. Indeed, using non-linear association analysis of the EEG signals recorded *in vivo* from multiple cortical and thalamic sites, it has recently been demonstrated that spontaneous SWD developing in WAG/Rij rats originate from the frontal cortex [23]. Moreover, stimulation of the sensorimotor cortex by NMDA application produces responses that spread much more widely in rats with a genetic form of absence epilepsy (GAERS) than those seen in control rats [28]. These observations correspond well with the theory developed by Steriade and Contreras [31], suggesting a dominant role of the neocortex in generation of SWD. Moreover, a hyperexcitable cortex is a prerequisite for the transformation from sleep spindles to SWD [18]. Therefore, it could be hypothesized that selective reduction of KYNA content in the frontal cortex may account, at least in part, for the development of SWD in WAG/Rij rats.

Both strains of rats displayed age-dependent increase in KAT I activity in samples obtained from the frontal cortex and thalamus. Similar changes in KAT II were also found in the samples obtained from the thalamus. Finally, KAT II activity in the frontal cortex also showed an age-dependent in-

crease, however, this effect did not reach statistical significance.

The results obtained in the KAT activity assays should be interpreted with caution, even though they showed some degree of correlation with the endogenous KYNA levels. *In vitro* assays of KAT reflect only the maximal capability of these enzymes to synthesize KYNA under artificial conditions. It should be underlined that *in vivo* activity of KAT enzymes is regulated by a number of factors [10, 12, 44] and that *in vitro* KAT activity does not necessarily correlate with *in vivo* KYNA levels [11]. Nevertheless, the lack of significant, age-dependent increase in KAT II activity in the frontal cortex is intriguing. It has been previously established that KAT II is primarily responsible for the synthesis of endogenous KYNA [12]. Therefore, we may suggest that the observed deficit of KYNA might be, at least partially, related to enzymatic dysfunction of KAT II in the frontal cortex.

Additionally, compromised cellular energy metabolism has been shown to have a negative impact on both *in vitro* and *in vivo* KYNA production [13, 14, 31]. Metabolic dysregulation and increased energy metabolism have also been shown in GAERS. Thus, it was proposed that metabolic deficits may underlie the occurrence of SWD in this genetic model of absence epilepsy [7, 8]. Perhaps disturbed neuronal metabolism could also be a factor responsible for the observed deficit of endogenous KYNA production in epileptic WAG/Rij rats.

The present results suggest a possible contribution of kynurenine pathway dysfunction to the generation of SWD in WAG/Rij rats. Even though the interpretation of these results might be hampered by a limited number of experiments, they may initiate further research focused on unveiling the role of KYNA in absence epilepsy.

REFERENCES

1. Coenen A.M., Drinkenburg W.H., Inoue M., van Luijtelaar E.L.: Genetic models of absence epilepsy, with emphasis on the WAG/Rij strain of rats. Epilepsy Res., 1992, 12, 75–86.
2. Coenen A.M., van Luijtelaar E.L.: The WAG/Rij rat model for absence epilepsy: age and sex factors. Epilepsy Res., 1987, 1, 297–301.
3. Czuczwar S.J. Perspectives for the use of excitatory amino acid ionotropic receptor antagonists as antiepileptic drugs. Pol. J. Pharmacol., 2000, 52, 67–70.
4. Danober L., Deransart C., Depaulis A., Vergnes M., Marescaux C.: Pathophysiological mechanisms of genetic absence epilepsy in the rat. Prog. Neurobiol., 1998, 55, 27–57.
5. D'Arcangelo G., D'Antuono M., Biagini G., Warren R., Tancredi V., Avoli M.: Thalamocortical oscillations in a genetic model of absence seizures. Eur. J. Neurosci., 2002, 16, 2383–2393.
6. de Bruin N.M., van Luijtelaar E.L., Cools A.R., Ellenbroek B.A.: Dopamine characteristics in rat genotypes with distinct susceptibility to epileptic activity: apomorphine-induced stereotyped gnawing and novelty/amphetamine-induced locomotor stimulation. Behav. Pharmacol., 2001, 12, 517–525.
7. Dufour F., Nalecz K.A., Nalecz M.J., Nehlig A.: Metabolic approach of absence seizures in a genetic model of absence epilepsy, the GAERS: study of the leucine-glutamate cycle. J. Neurosci. Res., 2001, 66, 923–930.
8. Dutuit M., Didier-Bazes M., Vergnes M., Mutin M., Conjard A., Akaoka H., Belin M.F., Touret M.: Specific alteration in the expression of glial fibrillary acidic protein, glutamate dehydrogenase, and glutamine synthetase in rats with genetic absence epilepsy. Glia, 2000, 32, 15–24.
9. Foster A.C., Vezzani A., French E.D., Schwarcz R.: Kynurenic acid blocks neurotoxicity and seizures induced in rats by the related brain metabolite quinolinic acid. Neurosci. Lett., 1984, 48, 273–278.
10. Gramsbergen J.B., Hodgkins P.S., Rassoulpour A., Turski W.A., Guidetti P., Schwarcz R.: Brain-specific modulation of kynurenic acid synthesis in the rat. J. Neurochem., 1997, 69, 290–298.
11. Gramsbergen J.B., Schmidt W., Turski W.A., Schwarcz R.: Age-related changes in kynurenic acid production in rat brain. Brain Res., 1992, 588, 1–5.
12. Guidetti P., Okuno E., Schwarcz R.: Characterization of rat brain kynurenine aminotransferases I and II. J. Neurosci. Res., 1997, 50, 457–465.
13. Hodgkins P.S., Schwarcz R.: Metabolic control of kynurenic acid formation in the rat brain. Develop. Neurosci., 1998, 20, 408–416.
14. Hodgkins P.S., Wu H.Q., Zielke H.R., Schwarcz R.: 2-Oxoacids regulate kynurenic acid production in the rat brain: studies in vitro and in vivo. J. Neurochem., 1999, 72, 643–651.
15. Inoue M., Peeters B.W., van Luijtelaar E.L., Vossen J.M., Coenen A.M.: Spontaneous occurrence of spike-wave discharges in five inbred strains of rats. Physiol. Behav., 1990, 48, 199–201.
16. Kamiński R.M., van Rijn C.M., Turski W.A., Czuczwar S.J., van Luijtelaar G.: AMPA and GABA(B) receptor antagonists and their interaction in rats with a genetic form of absence epilepsy. Eur. J. Pharmacol., 2001, 430, 251–259.
17. Kiś J., Czuczwar M., Zielińska E., Bojar I., Czuczwar S.J., Turski W.A.: Kynurenic acid does not protect against nicotine-induced seizures in mice. Pol. J. Pharmacol., 2000, 52, 477–480.
18. Kostopoulos G.K. Spike-and-wave discharges of absence seizures as a transformation of sleep spindles:

the continuing development of a hypothesis. Clin. Neurophysiol., 2000, 111, Suppl. 2, S27–S38.
19. Lasoń W., Przewłocka B., van Luijtelaar G., Coenen A.: Proenkephalin and prodynorphin mRNA level in brain of rats with absence epilepsy. Neuropeptides, 1994, 27, 343–347.
20. Lasoń W., Przewłocka B., van Luijtelaar E.L., Coenen A.M., Przewłocki R.: Endogenous opioid peptides in brain and pituitary of rats with absence epilepsy. Neuropeptides, 1992, 21, 147–152.
21. Lowry O.H., Rosebrough N.J., Farr A.L., Randall R.J.: Protein measurement with the Folin phenol reagent. J. Biol. Chem., 1951, 193, 265–275.
22. Luhmann H.J., Mittmann T., van Luijtelaar G., Heinemann U.: Impairment of intracortical GABAergic inhibition in a rat model of absence epilepsy. Epilepsy Res., 1995, 22, 43–51.
23. Meeren H.K., Pijn J.P., van Luijtelaar E.L., Coenen A.M., Lopes da Silva F.H.: Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats. J. Neurosci., 2002, 22, 1480–1495.
24. Moroni F., Russi P., Carla V., Lombardi G.: Kynurenic acid is present in the rat brain and its content increases during development and aging processes. Neurosci. Lett., 1988, 94, 145–150.
25. Peeters B.W., Ramakers G.M., Ellenbroek B.A., Vossen J.M., Coenen A.M.: Interactions between NMDA and nonNMDA receptors in nonconvulsive epilepsy in the WAG/Rij inbred strain. Brain Res. Bull., 1994, 33, 715–718.
26. Peeters B.W., Ramakers G.M., Vossen J.M., Coenen A.M.: The WAG/Rij rat model for nonconvulsive absence epilepsy: involvement of nonNMDA receptors. Brain Res. Bull., 1994, 33, 709–713.
27. Poeggeler B., Rassoulpour A., Guidetti P., Wu H.Q., Schwarcz R.: Dopaminergic control of kynurenate levels and N-methyl-D-aspartate toxicity in the developing rat striatum. Develop. Neurosci., 1998, 20, 146–153.
28. Pumain R., Louvel J., Gastard M., Kurcewicz I., Vergnes M.: Responses to N-methyl-D-aspartate are enhanced in rats with petit mal-like seizures. J. Neural Transm. Suppl., 1992, 35, 97–108.
29. Scharfman H.E., Ofer A.: Pretreatment with L-kynurenine, the precursor to the excitatory amino acid antagonist kynurenic acid, suppresses epileptiform activity in combined entorhinal/hippocampal slices. Neurosci. Lett., 1997, 224, 115–118.
30. Schwarcz R., Pellicciari R.: Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. J. Pharmacol. Exp. Ther., 2002, 303, 1–10.
31. Schwarcz R., Poeggeler B., Rassoulpour A., Ceresoli-Borroni G., Hodgkins P.S.: Regulation of kynurenic acid levels in the developing rat brain. Amino Acids, 1998, 14, 243–249.
32. Shibata K.: Fluorimetric micro-determination of kynurenic acid, an endogenous blocker of neurotoxicity, by high-performance liquid chromatography. J. Chromatogr., 1988, 430, 376–380.
33. Steriade M., Contreras D.: Spike-wave complexes and fast components of cortically generated seizures. I. Role of neocortex and thalamus. J. Neurophysiol., 1998, 80, 1439–1455.
34. Stone T.W.: Kynurenic acid antagonists and kynurenine pathway inhibitors. Expert. Opin. Investig. Drugs, 2001, 10, 633–645.
35. Stone T.W.: Kynurenines in the CNS: from endogenous obscurity to therapeutic importance. Prog. Neurobiol., 2001, 64, 185–218.
36. Stone T.W., Darlington L.G.: Endogenous kynurenines as targets for drug discovery and development. Nat. Rev. Drug Discov., 2002, 1, 609–620.
37. Świąder M., Kuźniar H., Kleinrok Z., Czuczwar S.J.: Influence of LY 300164, an AMPA/kainate receptor antagonist upon the anticonvulsant action of antiepileptic drugs against aminophylline-induced seizures in mice. Pol. J. Pharmacol., 2003, 55, 103–107.
38. Tancredi V., Biagini G., D'Antuono M., Louvel J., Pumain R., Avoli M.: Spindle-like thalamocortical synchronization in a rat brain slice preparation. J. Neurophysiol., 2000, 84, 1093–1097.
39. Turski W.A., Dziki M., Urbańska E., Calderazzo-Filho L.S., Cavalheiro E.A.: Seizures induced by aminooxyacetic acid in mice: pharmacological characteristics. Synapse, 1991, 7, 173–180.
40. Turski W.A., Gramsbergen J.B., Traitler H., Schwarcz R.: Rat brain slices produce and liberate kynurenic acid upon exposure to L-kynurenine. J. Neurochem., 1989, 52, 1629–1636.
41. Turski W.A., Urbańska E., Dziki M., Parada-Turska J., Ikonomidou C.: Excitatory amino acid antagonists protect mice against seizures induced by bicuculline. Brain Res., 1990, 514, 131–134.
42. van Luijtelaar E.L., Coenen A.M.: Two types of electrocortical paroxysms in an inbred strain of rats. Neurosci. Lett., 1986, 70, 393–397.
43. van Luijtelaar E.L.J.M., Drinkenburg W.H.I.M., Smirnova G.P., van Rijn C.M., Coenen A.M.L.: Rat models of genetic absence epilepsy: what do EEG spike-wave discharges tell us about drug effects. Meth. Find. Exp. Clin. Pharmacol., 2002, 24(D), 65–70.
44. Wu H.Q., Baran H., Ungerstedt U., Schwarcz R.: Kynurenic acid in the quinolinate-lesioned rat hippocampus: studies in vitro and in vivo. Eur. J. Neurosci., 1992, 4, 1264–1270.
45. Wu H.Q., Guidetti P., Goodman J.H., Varasi M., Ceresoli-Borroni G., Speciale C., Scharfman H.E., Schwarcz R.: Kynurenergic manipulations influence excitatory synaptic function and excitotoxic vulnerability in the rat hippocampus in vivo. Neuroscience, 2000, 97, 243–251.
46. Wu H.Q., Lee S.C., Scharfman H.E., Schwarcz R.: L-4-chlorokynurenine attenuates kainate-induced seizures and lesions in the rat. Exp. Neurol., 2002, 177, 222–232.

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