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Alterations of taurine in the brain of chronic kainic acid epilepsy model

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Summary. The aim of the study was to investigate the changes of taurine in the kainic acid (KA, 10 mg/kg, s.c.) chronic model of epilepsy, six months after KA application. The KA-rats used were divided into a group of animals showing weak behavioural response to KA (WDS, rare focal convulsion; rating scale <2 up to 3 h after KA injection) and a group of strong response to KA (WDS, seizures; rating >3 up to 3 h after KA injection). The brain regions investigated were caudate nucleus, substantia nigra, septum, hippocampus, amygdala/piriform cortex, and frontal, parietal, temporal and occipital cortices. KA-rats with rating <2 developed spontaneous WDS which occurred chronically and six months after KA injection increased taurine levels were found in the hippocampus (125.4% of control). KA-rats with rating >3 developed spontaneous recurrent seizures and six months after injection increased taurine levels were found in the caudate nucleus (162.5% of control) and hippocampus (126.6% of control), while reduced taurine levels were seen in the septum (78.2% of control). In summary, increased taurine levels in the hippocampus may involve processes for membrane stabilisation, thus favouring recovery after neuronal hyperactivity. The increased taurine levels in the caudate nucleus could be involved in the modulation of spontaneous recurrent seizure activity.

Keywords: Taurine – Epilepsy – Kainic acid

Abbreviations: KA, kainic acid; WDS, wet dog shakes; GABA, γ-amino-butyric acid; NMDA, *N*-methyl-D-aspartate; AMPA, alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; *n*, number of animals

Introduction

Changes in the concentrations of taurine have been found in the brains of epileptic humans and animals, as demonstrated by van Gelder and Courtois (1972), van Gelder et al. (1972), Koyama (1978), Lehmann et al. (1983), Wade et al. (1987), and Wilson et al. (1996). Barbeau and Donaldson (1974) and Mutani et al. (1977) demonstrated that taurine deficits cause the prolongation of seizure activities and the persistence of a state of hyperexcitability in the brain, on the other side anticonvulsive effects of taurine have been demonstrated by pharmacological studies in various models of epilepsy, e.g. by van Gelder (1972), Barbeau and Donaldson (1974), van Gelder et al. (1977), French et al. (1986), Huxtable (1989), and El-Idrissi et al. (2003). The therapeutic activity of taurine involvement in human epilepsy has been demonstrated by Barbeau and Donaldson (1974), Durelli and Mutani (1983), Anyanwu and Harding (1993), Birdsall (1998), and El-Idrissi et al. (2003). Also taurine analogues like homotaurine, taltrimide, acamprosate and tauromustine acting as anticonvulsant are used in treating human epilepsy, as demonstrated by Fariello et al. (1982) and Gupta et al. (2005). Taurine exerts its protective function against the glutamate-induced neuronal excitotoxicity by counter acting the glutamate-induced increase of free intracellular calcium and by preventing the glutamate-induced membrane depolarisation as described by Wu et al. (2005). Furthermore, cell osmoregulation is the most pervasive physiological role of taurine and significantly contributes to the neuroprotective activities of taurine, as described by Lehmann et al. (1984), Huxtable (1989), and Huxtable (1992). As demonstrated by Baran et al. (1987) washing out brain oedema by mannitol significantly reduces the seizures and brain damage in the KA-rats.

Excitatory amino acids act on several glutamatergic receptor types, the best characterised of which are three classes of ionotropic receptors, e.g. NMDA, KA, and AMPA, and at least eight metabotropic receptors, as described by Conn and Pin (1997) and Dingledine et al. (1999). KA has been used in several studies to investigate the correlation between neurotransmitter changes and seizure severity or seizure related neurodegeneration, as demonstrated by Sperk et al. (1983), Ben-Ari (1985), Baran et al. (1988), Sperk (1994), and Baran et al. (2004).

The effect of peripheral KA administration on the amino acid levels in the brain during induced seizures has been demonstrated by Chapman et al. (1984) and Nicoletti et al. (1984). Both groups demonstrated independently decreases of glutamate, aspartate and taurine in the hippocampus and no changes of the GABA content during acute induced seizures. Spontaneous recurrent seizures and changes of neurotransmitter markers of the GABA-ergic, cholin-ergic and somatostatin-ergic neurons in the chronic KA epileptic model have been recently described by Baran et al. (2004). In the present study the changes of taurine levels in frontal, cingulate, occipital, parietal and temporal cortices, in amygdala/piriform cortex, hippocampus, septum, caudate nucleus and substantia nigra in KA-rats with different seizure severity six months after KA injection have been investigated.

Materials and methods

Animals and materials

Male Sprague-Dawley rats (Forschungsinstitut für Versuchstierzucht, Himberg, Austria) of 280–320 g body weight were used.

KA (Sigma, USA) dissolved in saline at 10 mg/ml and adjusted to pH 7.0 was administered subcutaneously (s.c.) in the neck area at a dose of 10 mg/kg. The control animals were treated with the corresponding amount of saline. The injections were given in the morning, between 9–10 a.m.

Evaluation of the behavioural changes after KA treatment

According to a rating scale, previously described by Sperk et al. (1983), the behaviour of each animal was continuously evaluated during 3 h after KA or vehicle injection. The following scores were used for rating the severity of KA-induced seizures: 0 – normal, rare wet dog shakes (WDS), no convulsions; 1 – intermediate number of WDS, staring, rare focal convulsions affecting head and extremities; 2 – frequent WDS, frequent focal convulsions, eye closure, sniffing, facial clonus, staring; 3 – frequent WDS, frequent convulsions, head nodding associated with more severe facial clonus, unilateral or bilateral forelimb clonus with rearing and salivation (but without falling); 4 – continuous generalised seizures, rearing with loss of balance and falling accompanied by generalised clonic seizures; 5 – sustained generalised clonic convulsions, frequently death within 3 h.

For the six months experiment KA-treated rats with rating 3 and 4 ($n = 15$) and KA-treated rats with rating 1 and 2 ($n = 6$) and control animals ($n = 10$) were observed every Monday and Wednesday from 9 to 10 a.m. and their behaviour was evaluated by counting the occurrences of the WDS, focal epileptic activities and spontaneous seizures. Focal seizures are characterised by myoclonal ipsilateral movements of extremities and/or head, lasting from 5 to 10 sec. During the six months period four KA-animals of rating 4 died due to status epilepticus.

Brain dissection and homogenate preparation

The animals were sampled by decapitation six months after injection of KA or saline, the brains were removed and the regions of frontal, cingulate, temporal and occipital cortices, and caudate nucleus, substantia nigra, hippocampus and amygdala/piriform cortex were dissected using as references the atlas by König and Klippel (1970) and dissection guide by Skinner (1971). The brain areas frozen at −70 °C over a period of maximal 7 days were homogenised by sonicating in 20 voles of H_2O/N_2 (0 °C), and an aliquot of the homogenate was added to the same volume of 0.2 M perchloric acid, containing 0.8 mM $NaHSO_3$, and centrifuged at 28,000 × *g* at 4 °C for 10 min. The supernatant was used for the measurement of taurine.

Determination of taurine

The levels of taurine were measured by HPLC after post-column derivatization with the fluorogenic reagent o-phthalaldehyde according to the method described by Schmid et al. (1980). The following minor modifications were introduced: the column was packed with Aminex A-9 (sodium form) and maintained at 76 °C; the two-step gradient of buffers consisted of 0.2 M sodium formate/H_3PO_4 (pH 3.3 to 3.4) and 0.2 M sodium acetate/H_3PO_4, pH 5.6; the buffers as well as the o-phthalaldehyde reagent were pumped at a flow rate of 0.8 ml per min.

Data analyses

All data are given as means ± S.E.M. For statistical analyses the one-way ANOVA-test was applied. A Student's t-test was used, where appropriate. Asterisks indicate a significant difference: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ compared to control.

Results

Behaviour

Rats with KA-induced symptoms, such as WDS and only rare focal convulsions, i.e. WDS 78.3 ± 19.8 ($n = 6$); rating scale 1.33 ± 0.21 ($n = 6$) developed spontaneous WDS during the entire period of the experiment (Table 1). There could be observed rare focal convulsions during the second and third months, and a fluctuating enhancement of WDS over the entire period of the experiment (Table 1). Rats with KA-induced symptoms, such as WDS and generalised seizures, i.e. WDS 68.6 ± 17.8 ($n = 11$); rating scale 3.36 ± 0.15 ($n = 11$) developed spontaneous seizures and only moderate number of WDS during the entire period

Table 1. Occurrence of WDS in KA-rats during six months after injection (KA, 10 mg/kg, s.c.) (see Materials and methods)

Time period after KA injection	No. of WDS in KA-rats with rating >3 ($n = 11$)	No. of WDS in KA-rats with rating <2 ($n = 6$)
1st month	6.2 ± 1.3	26.2 ± 3.9*
2nd month	6.8 ± 0.9	56.8 ± 3.9*
3rd month	7.0 ± 0.9	50.0 ± 7.2*
4th month	5.8 ± 0.7	30.5 ± 3.9*
5th month	5.9 ± 0.7	42.8 ± 7.5*
6th month	6.7 ± 1.3	25.5 ± 5.5*

The data represent means ± S.E.M. Significance versus KA-rats with rating >3; unpaired Student's t-test. * $p < 0.001$

Table 2. Taurine levels in different rat brain regions of control animals. Changes of taurine levels in the brain six months after KA (10 mg/kg, s.c.) injection

Region	Taurine (ng/mg wet tissue weight) Control	Taurine (% of control)	
		KA-rats with rating >3	KA-rats with rating <2
Frontal cortex	836.0 ± 42.9	107.8 ± 4.3	97.8 ± 2.5
Cingulate cortex	898.0 ± 53.7	115.5 ± 5.5	102.5 ± 3.8
Occipital cortex	909.5 ± 49.2	105.0 ± 9.5	92.3 ± 3.9
Parietal cortex	748.9 ± 23.2	107.3 ± 4.1	91.1 ± 7.9
Temporal cortex	814.5 ± 23.3	100.2 ± 5.8	100.8 ± 6.3
Amygdala/ piriform ctx	922.0 ± 15.3	82.6 ± 3.8	111.2 ± 4.5
Hippocampus	755.5 ± 26.1	126.6 ± 3.6**	125.4 ± 3.4*
Septum	570.5 ± 29.5	78.2 ± 2.2*	81.0 ± 7.1
Nucleus caudate	964.0 ± 46.7	162.5 ± 6.2***	117.4 ± 2.3
Substantia nigra	485.5 ± 13.8	114.6 ± 10.9	97.2 ± 6.4

Data represent mean ± S.E.M. Number of animals (n): Control group, $n = 10$; KA-rats with rating >3, $n = 11$; KA-rats with rating <2, $n = 6$. Significance vs. control group; unpaired Students t-test: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

of the experiment (Table 1). In the first fifth months of the experiment 1 to 2 and during the sixth month 3 to 5 spontaneous seizures per month and rat could be observed. The spontaneous seizures lasted from 5 to 15 sec. The control animals did not show WDS or any epileptic symptoms.

Taurine in control rat brain

Data on normal levels of taurine in different rat brain regions are shown in Table 2. Our data correlate with and extend the information found in the literature, as presented by Nicklas et al. (1979), Schmid et al. (1980), Chapman et al. (1984), and Palkovits et al. (1986).

Taurine in the brain of KA-rats six months after injection

In the brain of KA-rats with spontaneous recurrent seizures six months after injection the taurine levels were significantly increased in the caudate nucleus and moderately increased in the hippocampus, while in the septum and the amygdala/piriform cortex taurine was moderately reduced (Table 2). In the brain of KA-rats with spontaneous WDS six months after KA injection a moderate increase of taurine levels was seen in the hippocampus and no significant alterations of taurine levels were measured in other brain regions (Table 2).

Discussion

The neurotransmitter alterations in the brains of KA-rats with developed spontaneous seizures six months after KA injection indicate complex properties of abnormal circuit in the epileptic tissue, as demonstrated by Baran et al. (2004). There has been found a dissociation and association between various behavioural and neurochemical changes. In the present study, in KA-rats with spontaneous recurrent seizures six months after KA administration we found a marked increase of taurine levels in the caudate nucleus and in the hippocampus and a lowered taurine content in the septum. In KA-rats with developed WDS six months after KA administration a significant increase of taurine levels was measured only in the hippocampus. The data revealed would suggest a relationship between changes of taurine levels in different brain regions and seizure severities. Increased levels of taurine in the caudate nucleus would indicate an increased taurine metabolism and probably increased inhibitory neurotransmission. The hyperactivity of the inhibitory GABA-ergic system in the nigrostriatal pathway of the chronic KA-induced epilepsy model has been recently described by Baran et al. (2004). Speculatively, the enhancement of both inhibitory taurine and GABA activities may augment the inhibitory mechanism(s) of the caudate nucleus. The pharmacological manipulation of the nigrostrial route results in the modulation of seizure activities, as demonstrated by Iadarola and Gale (1982), Turski et al. (1986), and Depanulis et al. (1994). Interestingly, the co-existence of taurine, GABA and aspartate as transmitters in the striatonigral pathway has been suggested by Korf and Venema (1983), however their way of action and interaction is not yet clear. Six months after KA-injection there was found a significant increase in the inhibitory GABA-ergic activity in the cortical brain regions as demonstrated by Baran et al. (2004), whereas the taurine levels remained unchanged in these regions.

Increased taurine levels in the hippocampus have been seen in KA-rats with developed spontaneous seizures as well as in KA-rats showing high incidence of WDS. The data revealed would suggest a lack of correlation between severity of symptoms and changes of taurine levels in the hippocampus in KA-rats with chronic epilepsy. The low incidence of WDS in KA-rats with spontaneous seizures could be masked by the seizures. An interesting observation has been made by Vezzani et al. (1985) stating that there is no correlation between the increase in extracellular taurine levels in the hippocampus and seizures following intrahippocampal neurotoxic convulsant quinolinic acid injection. In the contralateral hippocampus where

seizures activity was equally high no increase of taurine has been observed. Vezzani et al. (1985) suggested the increase of taurine levels in the hippocampus to be a selective tissue response to the neurotoxic effects of quinolinic acid rather than a consequence of the induced seizures. After ipsilateral quinolinic acid injection, a functional connection was found between seizure events and decrease of noradrenaline in the hippocampus, as demonstrated by Vezzani and Schwarcz (1985). Sperk et al. (1983) also demonstrated that there exist a functional connection between WDS and lowered noradrenaline in the hippocampus, but not in the amygdala/piriform cortex. These data would suggest an increased inhibitory noradrenergic activity in the hippocampus. Moreover, after systemic KA administration there have been found different patterns of changes in the biosynthesis of quinolinic acid in the hippocampus and in the piriform cortex of epileptic rats, as shown by Speciale and Schwarcz (1988), suggesting higher quinolinic acid levels in the amygdala/piriform cortex than in the hippocampus. The permanent nerve cell damage in the amygdala/piriform cortex six months after KA injection, as demonstrated by Baran et al. (2004), reflect a process of neurodegeneration and would explain the brain's inability to provide sufficient taurine to counteract the endogenous neurotoxin action of quinolinic acid. In fact, no increase of taurine has been observed in the amygdala/piriform cortex of KA-rats six months after injection. The possible role of quinolinic acid as an endogenous neurotoxin/excitotoxic in human epilepsy has been described by Foldable et al. (1988), Morselli et al. (1989), and Lloyd et al. (1990). The above mentioned findings would suggest the involvement of endogenous quinolinic acid in the increase of taurine levels in the hippocampus or other regions of chronic KA-induced epileptic rats. In summary, increased taurine in the brain of epileptic KA-rats may modulate and compensate the progression of neurodegeneration. The effect of the low taurine levels found in the septum in chronic KA-epileptic rats still needs to be clarified. Studies on the efficiency of co-administration of taurine or taurine analogues and GABA-mimetic drugs, shown by Löscher et al. (1983) and Anyanwu and Harding (1993), might provide potential value for effectiveness in the treatment of chronic epilepsy.

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