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Carbamazepine enhances brain production of kynurenic acid in vitro

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Abstract

Disturbed formation of kynurenic acid, an endogenous antagonist of glutamate ionotropic receptors, might contribute to the pathogenesis of seizures. Here, the effect of anticonvulsant drug, carbamazepine on the production of kynurenic acid was studied. Carbamazepine (0.5–3 mM) enhanced kynurenic acid synthesis in rat cortical slices and also increased the activity of kynurenine aminotransferase (KAT) I at 0.1–3.0 mM concentration. Thus, anticonvulsant drugs, such as carbamazepine, might act partially via stimulation of kynurenic acid production.

Keywords: Kynurenic acid; Carbamazepine

Kynurenic acid is an endogenous tryptophan metabolite blocking, with particularly high affinity, the coagonist site of *N*-methyl-D-aspartate (NMDA) receptor complex (Stone, 2001). Formation of kynurenic acid in the central nervous system is catalyzed by kynurenine aminotrasferases (KATs) I and II. Altered levels of kynurenic acid may influence the glutamate-mediated neurotransmission, and thus contribute to the pathogenesis of neurological disorders including epilepsy or neurodegeneration (Stone, 2001). Indeed, the experimental reduction of brain kynurenic acid synthesis may cause seizures (Turski et al., 1991). The compounds known to evoke neurodegeneration and seizures such as mitochondrial toxins, e.g., 1-methyl-4-phenylpyridinium ion (MPP+) or 3-nitropropionic acid, and some of the endogenous glutamate receptor agonists diminish kynurenic acid production (Urbanska et al., 1997; Kocki et al., 2003; Luchowska et al., 2003). Conversely, the exogenously applied kynurenic acid acts as an anticonvulsant and neuroprotectant (Stone, 2001). Moreover, hippocampal kynurenic acid level increases early after acute seizure induction, possibly as a result of regulatory defense mechanism (Wu and Schwarcz, 1996).

CBZ is a commonly used anticonvulsant drug effective in partial and generalized tonic–clonic seizures acting via the blockade of sodium channels in the neuronal membrane (Löscher, 1998). Here, we assessed the effect of carbamazepine on the brain production of kynurenic acid and KATs activities under in vitro conditions.

The experiments were carried out on adult male Wistar rats, weighing 200–240 g. Experimental procedures have been approved by the Local Ethical Committee in Lublin and are in agreement with European Communities Council Directive on the use of animals in experimental studies. Kynurenic acid production in vitro and the activities of KAT I and KAT II were investigated as previously described using high-performance liquid chromatography (HPLC) method (Urbanska et al., 1997).

Carbamazepine at 0.5, 1.0 and 3.0 mM concentration increased kyunaric acid production in cortical slices to 130.0±11.2% ($P<0.01$), 141.6±7.3% ($P<0.001$) and 151.3±8.9% ($P<0.001$) of control, respectively (Fig. 1A). Carbamazepine at 0.1, 0.5, 1.0 and 3.0 mM enhanced the activity of KAT I to 120.2±5.3% ($P<0.01$),

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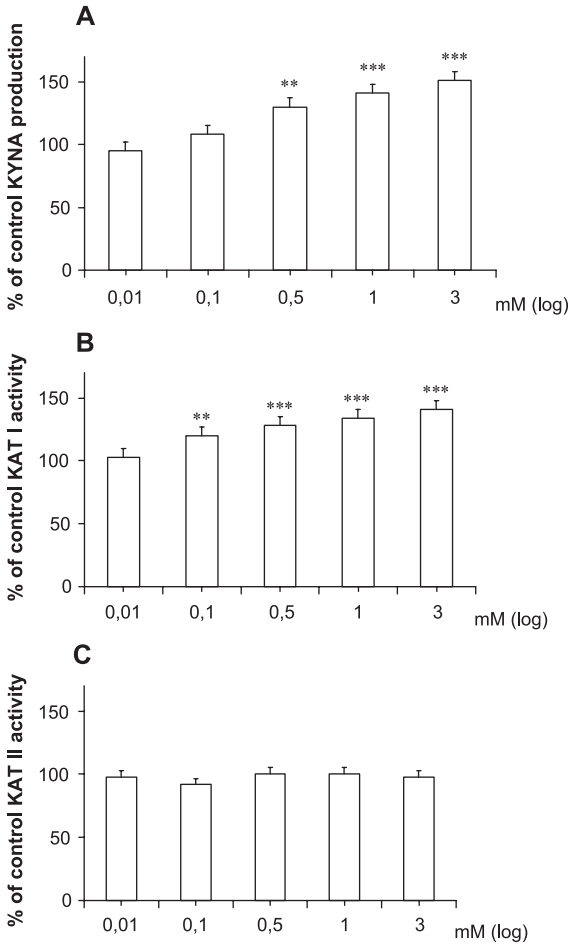

Fig. 1. (A) Effect of carbamazepine on the production of kynurenic acid in cerebral cortical slices. Data are mean values±S.D. of six determinations. The mean control production of kynurenic acid in the presence of 10 μM L-kynurenine was 6.0±0.5 pmol/h/well. (B and C) Influence of carbamazepine on the brain activity of KAT I and KAT II. Data are mean±S.D. values of six determinations. The mean control activity of KAT I and KAT II in the presence of 2 μM L-kynurenine was 4.22±0.34 and 1.35±0.13 pmol/mg tissue/h, respectively. $^{**}P<0.01$; $^{***}P<0.001$ vs. control (100%) (ANOVA with post hoc comparisons according to Bonferroni method).

128.5±9.6% ($P<0.01$), 134.5±6.8% ($P<0.001$) and 141.7±5.8% ($P<0.001$) of control, respectively (Fig. 1B). In contrast, carbamazepine (up to 3 mM) did not influence the activity of KAT II (Fig. 1C).

Previous studies have shown that carbamazepine blocks the NMDA-induced currents in cultured neurons (Lampe and Bigalke, 1990), and that its anticonvulsant action is enhanced by the competitive antagonists of NMDA receptors (Zarnowski et al., 1994). In the view of data presented here, the actions of carbamazepine could partially result from the enhanced synthesis of kynurenic acid, an endogenous NMDA receptor antagonist.

The regulation of kynurenic acid production might involve various mechanisms. The attempts to modify kynurenic acid synthesis intracellularly, via interference with KAT activity have lead to diminished kynurenic acid formation in majority of cases (Turski et al., 1991; Urbanska et al., 1997). Until now, only one clinically used drug is known to possess the ability to increase kynurenic acid synthesis. Tacrolimus (FK506), neuroimmunophilin ligand interacting intracellularly with calcineurin, and used as immunosuppressant, enhanced kynurenic acid formation in vitro (Luchowska et al., 2003). Presented finding suggests a possible novel mechanism, which might be involved in the activity of anticonvulsant drug(s). Our current research is aimed on evaluating the influence of a broad range of anticonvulsants on the formation of kynurenic acid.

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