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Attenuation of kainic acid-induced status epilepticus by inhibition of endocannabinoid transport and degradation in guinea pigs

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Summary Status epilepticus (SE) is a medical emergency associated with a high rate of mortality if not treated promptly. Exogenous and endogenous cannabinoids have been shown to possess anticonvulsant properties both in vivo and in vitro. Here we study the influence of endocannabinoid metabolism on the development of kainic acid-induced SE in guinea pigs. For this purpose, the inhibitors of endocannabinoid transport, AM404, and enzymatic (fatty acid amide hydrolase) degradation, URB597, were applied. Cannabinoid CB1 receptor antagonist, AM251, was also tested. Animal behavior as well as local electric field potentials in four structures: medial septum, hippocampus, entorhinal cortex and amygdala were analyzed when AM404 (120 nmol), URB597 (4.8 nmol) or AM251 (20 nmol) were administrated alone or together with 0.4 μg of kainic acid. All substances were injected i.c.v. AM404, URB597 or AM251 administered alone

Abbreviations: 2-AG, 2-arachidonoylglycerol; AEA, N-arachidonoylethanolamide, anandamide; BA, basal nucleus of the amygdala; ECs, endocannabinoids; Ent, entorhinal cortex; FAAH, fatty acid amide hydrolase; Hip, hippocampus; KA, kainic acid; LFP, local field potential; MS, medial septum; SE, status epilepticus.

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did not alter markedly local field potentials of all four studied structures in the long-term compared with their basal activity. AM404 and URB597 significantly alleviated kainic acid-induced SE, decreasing behavioral manifestations, duration of seizure events and SE in general without changing the amplitude of local field potentials. AM251 did not produce distinct effects on SE in terms of our experimental paradigm. There was no apparent change of the seizure initiation pattern when kainic acid was coadministrated with AM404, URB597 or AM251. The present study provides electrophysiologic and behavioral evidences that inhibition of endocannabinoid metabolism plays a protective role against kainic acid-induced SE and may be employed for therapeutic purposes. Further investigations of the influences of cannabinoid-related compounds on SE genesis and especially epileptogenesis are required.

Introduction

Status epilepticus (SE), defined as continuous self-sustaining seizure activity lasting 30 min or longer, is one of the most serious manifestations of epilepsy. SE may lead to severe brain damage or even death if left untreated. Furthermore, a single episode of SE is thought to be enough to trigger epileptogenesis and cause development of epilepsy (Hesdorffer et al., 1998). Terminating SE is challenging, and up to one-third of SE patients show resistance to currently available treatments (Mayer et al., 2002; Mazarati et al., 1998; Treiman et al., 1998). This suggests that new more effective anticonvulsants and antiepileptic drugs are still required.

Interest in using cannabinoids as a treatment of choice in many disorders, including epilepsy, has increased over the last decade. It has been shown that natural and synthetic cannabinoids possess anticonvulsant properties in vivo (Bahremand et al., 2008; Citraro et al., 2013; Kozan et al., 2009; Mason and Cheer, 2009; Rizzo et al., 2009; Shafaroodi et al., 2004; Wallace et al., 2001, 2002, 2003) and in vitro (Ameri and Simmet, 2000; Ameri et al., 1999; Blair et al., 2006; Deshpande et al., 2007a,b) models of epilepsy. Thus, cannabinoid compounds can dampen acute epileptiform activity in an electroshock model of a secondarily generalized seizure (Wallace et al., 2001, 2002), in a model of partial seizures (Rizzo et al., 2009), in a model of penicillin-induced epilepsy (Kozan et al., 2009) and in a model of status epilepticus in neuronal cultures (Blair et al., 2006; Deshpande et al., 2007a,b). They also can increase the threshold for pentylenetetrazole seizures (Bahremand et al., 2008; Shafaroodi et al., 2004). Treatment with cannabinoids might be useful in the chronic models of epilepsy. Cannabinoid-induced suppression of spontaneous recurrent epileptiform discharges has been reported for the pilocarpine (Wallace et al., 2003) and neuronal culture (Blair et al., 2006) models of acquired epilepsy, as well as for the genetic absence epilepsy model (Citraro et al., 2013).

The existence of endogenous cannabinoids (ECs) was discovered at the end of last century (for review see Katona and Freund, 2008) and they have also been demonstrated to regulate seizure activity (Ameri et al., 1999; Ameri and Simmet, 2000; Citraro et al., 2013; Wallace et al., 2002; Deshpande et al., 2007b). Two major endocannabinoids in the central nervous system are 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamide (anandamide, or AEA). They are synthesized and released ''on demand'' from postsynaptic neurons in response to sustained excitation and bind to presynaptic $G_{i/o}$-coupled cannabinoid CB1 receptors, which in turn inhibit neurotransmitter release, modulating excitatory and inhibitory neuronal activity and long-term synaptic plasticity (for review see Katona and Freund, 2008). Thus, endogenous and exogenous cannabinoids can regulate neuronal excitability and prevent excitotoxicity and seizure activity (Katona and Freund, 2008; Khaspekov et al., 2004) through the CB1 receptors. In the experimental studies mentioned above, anticonvulsant action of cannabinoids was abolished by CB1 receptor antagonists. Genetical deletion of CB1 receptors in principal forebrain neurons increased seizure susceptibility and vulnerability of neurons during excitotoxicity (Marsicano et al., 2003; Monory et al., 2006). In the same way, pharmacological blockade of CB1 receptors was found to facilitate seizure activity in certain animal models of epilepsy (Deshpande et al., 2007c; van Rijn et al., 2011; Wallace et al., 2002). These findings indicate that the endocannabinoid system can be a key player in regulating synaptic transmission, and that CB1 signaling can promote neuronal survival during excitotoxicity (Katona and Freund, 2008). In this light, inhibition of ECs inactivation mechanisms can be a potential target for managing seizure activity. In our previous work we have shown that synthetic agonist of CB1 receptors WIN55,212-2 produces an ''antikindling'' effect during the electrical stimulation of the perforant path and decreased susceptibility to kainic acid (KA) (Shubina and Kichigina, 2012).

In the present study, enhanced cannabinoid signaling was achieved by blocking EC reuptake with AM404 and inhibiting AEA degradation enzyme fatty acid amide hydrolase (FAAH) with URB597. For preventing the CB1 receptor function, AM251 was applied. We employed local field potential (LFP) recordings to electrophysiologically verify the influences of investigated substances on activity of several brain structures during SE. We investigated whether treatment with inhibitors of EC metabolism would alter the KA-induced SE, a widely used model of acquired epilepsy with morphological and neurochemical disturbances quite similar to those seen in human temporal lobe epilepsy and neurodegeneration that occurs in limbic structures (for review see Ben-Ari and Cossart, 2000). The study was performed in guinea pigs, a species seldom used for in vivo neurophysiological investigations of seizure activity (Astasheva and Kitchigina, 2011; Carriero et al., 2012; Diehl et al., 1984; Popova et al., 2008; Shubina and Kichigina, 2012).