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Effect of levetiracetam on extracellular amino acid levels in the dorsal hippocampus of rats with temporal lobe epilepsy

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ABSTRACT

Levetiracetam (LEV) is an anticonvulsant drug with a unique mechanism of action that is not completely understood. However, its activity profile may involve effects on excitatory and/or inhibitory neurotransmission since the primary target of LEV, synaptic vesicle protein 2A, is ubiquitously expressed in all types of synaptic vesicles. Therefore, the objective of the present study was to explore the effect of LEV (300 mg/kg/day for one week, administered *via* osmotic mini-pumps) on neurotransmitter release and its probable selective effect on extracellular gamma-amino butyric acid (GABA), glutamate (Glu), aspartate (Asp), glutamine (Gln), taurine (Tau) and glycine (Gly) concentrations (using *in vivo* microdialysis under basal and high-K^+ conditions) in the dorsal hippocampus (DH), a region that undergoes major synaptic changes during epilepsy. Epileptic rats developed clear signs of hyperexcitability, *i.e.*, an elevated Glu/GABA ratio in the DH. The LEV concentration in blood after 7 days of treatment was within the therapeutic range. In contrast, LEV was not detected four days after mini-pump removal (washout period). Furthermore, LEV restored the Glu/GABA ratio to approximately the control level and significantly increased the GABA concentration after the initiation of high-K^+ conditions. Based on these data, LEV treatment restored the lost balance between the excitatory and inhibitory systems under basal conditions. Moreover, LEV showed a selective effect by preferentially increasing vesicular release of GABA, a mechanism by which LEV could reduce epileptic seizures.

1. Introduction

Under physiological conditions, brain activity is maintained in a stable and dynamic state that is controlled by the balance of inhibitory and excitatory systems (López-Meraz et al., 2009). In the central nervous system, the main neurotransmitters responsible for preserving this balance are glutamate (Glu) and gamma-amino butyric acid (GABA), the primary excitatory and inhibitory molecules, respectively (Timmerman and Westerink, 1997), although other systems of neurotransmitters and neuromodulators also contribute to the maintenance of this equilibrium (Cavalheiro et al., 1994).

Temporal lobe epilepsy (TLE) is a chronic neurological disorder associated with a wide range of biochemical changes. Microdialysis studies of patients and animals suggest that this disorder affects various systems of neurotransmitters (monoamines, amino acids, and peptides) and second messengers, leading to the pathophysiological processes underlying the imbalance between inhibition and excitation, in favor of the latter (Al-Shorbagy et al., 2013; Cavalheiro et al., 1994; Klitgaard et al., 2003; Soukupová et al., 2014, 2015).

In particular, animal models of pilocarpine-induced TLE have shown that the imbalance between neuronal excitation and inhibition results from mossy fiber sprouting and the loss of hilar GABA neurons in the dentate gyrus (DG), which generates a hyperexcitable and hypersynchronous circuit responsible for the occurrence of spontaneous

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recurrent seizures (SRS; Harvey and Sloviter, 2005; Peng and Houser, 2005; Soukupová et al., 2014; Stafstrom, 2010).

Levetiracetam (LEV; [(*S*)-α-ethyl-2-oxo-1-pyrrolidineacetamide]) is a second-generation anticonvulsant drug with a unique profile of activity that decreases SRS (Surges et al., 2008). Unfortunately, the exact mechanism of action remains unknown, but it may involve effects on excitatory and inhibitory neurotransmitter release (Meehan et al., 2011, 2012), since the primary target of LEV, synaptic vesicle protein 2A (SV2A; Lynch et al., 2004), is involved in the vesicular cycle and is expressed ubiquitously in all types of nerve terminals (Bajjalieh et al., 1994). Furthermore, intrinsic differences in the machinery governing the release of GABAergic and glutamatergic neurotransmitters (Moulder and Mennerick, 2005; Moulder et al., 2007), neuronal activity (Levesque et al., 2015; Meehan et al., 2011, 2012) and SV2A expression (De Groot et al., 2011) may also be important regulatory points modulating the selective effects of LEV.

Finally, it is unclear whether LEV-SV2A binding increases or decreases presynaptic neurotransmitter release (Klitgaard et al., 2003; Margineanu et al., 2008). Thus, to clarify the effect of LEV on neurotransmitter release, we evaluated the extracellular concentrations of various amino acid neurotransmitters and neuromodulators in the DH of rats with pilocarpine-induced TLE that were treated with LEV or left untreated.

2. Materials and methods

2.1. Animals

Male Wistar rats (250–350 g; Envigo, Mexico) were used for all experiments. Rats were housed under standard conditions: regulated temperature (22 ± 2 °C), light/dark cycle (12:12 h) and food and water available *ad libitum*. Rats were randomly allocated into four groups: control group (n = 6), epileptic group (n = 8), control + LEV group (n = 6) and epileptic + LEV group (n = 6). All experimental procedures described in this study were conducted in accordance with the Mexican law SAGARPA NOM-062-Z00-1999 and were approved by the local ethics committee for animal experimentation (CICUAL INP-064/2015). The following experimental procedure was utilized (Fig. 1): In epileptic groups (epileptic and epileptic + LEV groups), status epilepticus (SE, see below) was induced at week 0. Beginning five weeks later, animals were video monitored for three weeks to record the frequency and duration of the SRS; the control groups (control and control + LEV groups) were kept in housing and video monitoring conditions similar to those of epileptic rats. At seven weeks, animals from the control + LEV and epileptic + LEV groups received LEV treatment *via* osmotic mini-pumps subcutaneously implanted. At week 8, the osmotic mini-pumps were removed, and blood samples were taken to measure LEV blood levels; 5 days after removing the mini-pumps, blood samples were again taken from these rats to confirm proper LEV washout. Finally, guide cannulas were implanted into the DH in all experimental groups, and four days later, the microdialysis assays were performed.

2.2. Induction of status epilepticus

Animals were pretreated with lithium chloride (127 mg/kg, i.p.) nineteen hours before pilocarpine administration. On the day of SE induction, rats were injected with scopolamine methyl-bromide (1 mg/kg, i.p.), and 30 min later, they received a single dose of pilocarpine hydrochloride (30 mg/kg, i.p; Glien et al., 2001); control rats received saline solution (NaCl 0.9%) at the same times and by a similar administration route. Convulsive behavior was scored according to the Racine scale (Racine, 1972); SE was defined as continuous convulsive activity (stage 4 or 5 on the Racine scale) for more than 30 min (Levesque et al., 2015).

Ninety minutes after SE induction, rats received an intramuscular (i.m.) injection of 5 mg/kg diazepam (Glien et al., 2001) and were then placed on an ice bed for one hour to decrease hyperthermia generated during SE. A second dose of diazepam was administered eight hours later, and then rats received an injection of saline solution (5 mL, 0.9%, s.c.) to rehydrate them on the first night. Finally, rats were housed overnight in a room at 17 ± 2 °C. From the second day after SE, the room temperature was reset at 22 ± 2 °C, and rats were fed with a commercial dietary supplement twice a day for 3 days and monitored constantly until their recovery (Glien et al., 2001; See Fig. 1).

2.3. Monitoring of spontaneous recurrent seizures

According to previous studies (Cavalheiro et al., 1991; Leite et al., 1990), SRS are established between 5 and 45 days after SE induction. In the present study, video monitoring of SRS began five weeks after SE induction (35 days after SE). Animals were housed in individual acrylic cages and were video monitored to record the frequency and duration of SRS. Video monitoring was performed with four cameras (Steren Model CCTV-970), and the recordings were collected during the light period (8:00 a.m.–6:00 p.m.; Arida et al., 1999) for 3 weeks (2 weeks before LEV treatment and 1 week during treatment; see Fig. 1). The videos were analyzed by trained observers who were blinded to the treatments to detect seizures using the fast-forward speed (eight times normal speed) of the video recorder. Once a seizure-like activity was observed, the videotape was rewound to the beginning of the behavior and examined at real-time speed (Glien et al., 2001). An animal was considered to have SRS when they presented some of the following behaviors: clonus of the anterior extremities, chewing and “wet dog shakes”, and clonic seizures with a loss of posture and uncontrolled jumps (Karlócai et al., 2011). The corresponding Racine scores were greater than or equal to 3 (Racine, 1972).

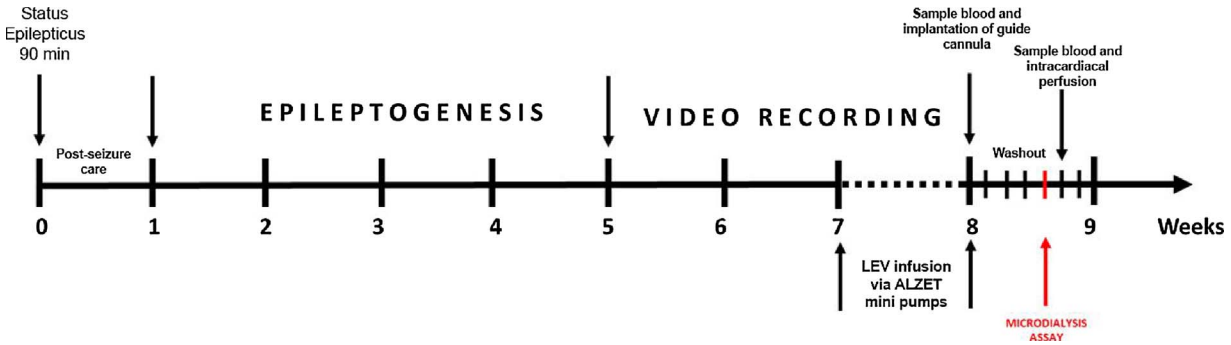

Fig. 1. Experimental design. At time 0, status epilepticus (SE) was induced in male Wistar rats *via* the administration of lithium-pilocarpine. Five weeks after SE induction, animals were video monitored to record the frequency and duration of the spontaneous recurrent seizures. Seven weeks after SE induction, ALZET® osmotic mini-pumps were subcutaneously implanted for one week to provide sub-chronic treatment with levetiracetam (LEV; 300 mg/kg/day dotted line). At the end of LEV treatment, a guide cannula was implanted into dorsal hippoampus, and four days later, microdialysis assays were performed.

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