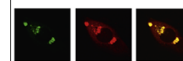


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Research Report

Effect of sparteine on status epilepticus induced in rats by pentylenetetrazole, pilocarpine and kainic acid [☆]

Fridha Villalpando-Vargas¹, Laura Medina-Ceja^{*,1}

Laboratory of Neurophysiology and Neurochemistry, Department of Cellular and Molecular Biology, CUCBA, University of Guadalajara, Jalisco, Mexico

ARTICLE INFO

Article history:

Accepted 15 July 2015

Available online 21 July 2015

Keywords:

Kainic acid

Pentylenetetrazole

Pilocarpine

Seizures

Sparteine

Status epilepticus

ABSTRACT

The long-term effects of status epilepticus (SE) include severe clinical conditions that result in disorders of various organs and systems as well as neurological damage that could lead to death. Sparteine is a quinolizidine alkaloid synthesized from most *Lupine* species, and its anticonvulsive effect was evaluated in the pentylenetetrazole model of SE. However, efforts to clearly determine the anticonvulsive effect of sparteine have not been made previously. For this reason, we consider it important to study the anticonvulsant effects of sparteine at the level of behavior and EEG activity in three different SE models. The animals of the control groups, which received intraperitoneal pentylenetetrazole (90 mg/kg), kainic acid (9 mg/kg) or pilocarpine (370 mg/kg), exhibited convulsive behavior and epileptiform activity. After sparteine pretreatment (13 mg/kg, administered 30 min before the convulsive drug), the animals administered pentylenetetrazole and pilocarpine exhibited reduced mortality rates compared with the corresponding control groups, while the animals administered kainic acid exhibited a delayed onset of convulsive behavior and decreased seizure duration compared with the corresponding control group. In the three models of SE, a significant reduction in the amplitude and frequency of discharge trains was observed. These results support the anticonvulsant effect of low doses of sparteine and allow us to direct our efforts to other new anticonvulsant strategies for seizure treatment. However, it is necessary to perform more experiments to determine the precise mechanism through which sparteine produces an anticonvulsant effect at this concentration.

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[☆] Grant sponsor: CONACYT. Grant number: 106179.

^{*} Correspondence to: Laboratorio de Neurofisiología y Neuroquímica, Departamento de Biología Celular y Molecular, Centro Universitario de Ciencias Biológicas y Agropecuarias, Universidad de Guadalajara, Camino Ing. R. Padilla Sánchez 2100, Las Agujas, Nextipac, Zapopan, Jalisco CP 45110, Mexico. Fax: +52 33 37771191.

E-mail addresses: lmolina@cucba.udg.mx, lauramedcej@gmail.com (L. Medina-Ceja).

¹ FVV and LMC contributed equally to this work.

1. Introduction

Epilepsy is a neurological disorder that affects 50 million people worldwide. Antiepileptic drugs (AEDs) are effective in 70% of patients, although in developing countries, this percentage drops drastically (Newton and Garcia, 2012). Status epilepticus (SE) (Sanchez-Fernandez et al., 2014) is defined as a prolonged seizure or recurrent seizures without full recovery between them, and in the literature, a seizure lasting longer than 30 min is classified as SE (McCandless, 2012). The long-lasting effects of SE include severe clinical conditions that result from disorders of various organs and systems as well as neurological damage that can lead to death (Jenssen et al., 2006).

Models of SE provide good tools to study the cellular and molecular mechanisms of this pathological condition. Pilocarpine (Pilo, a non-selective muscarinic receptor agonist) and kainic acid (KA; an agonist of kainate-type glutamate receptors) models induce electroencephalographic (EEG) discharges in limbic structures with secondary generalization (Turski et al., 1983, 1984; Miller et al., 1990; Sampieri et al., 2011), while the pentylenetetrazole (PTZ) model induces primary generalized discharges (Erdogan et al., 2014). PTZ acts as a noncompetitive agonist of GABA_A receptors by binding at the t-butylbicyclophosphorothionate site (Olsen, 1981; Ramanjaneyulu and Ticku, 1984; Hansen et al., 2004).

Sparteine (Sp) is a quinolizidine alkaloid (QA) synthesized from most *Lupine* species (Wink, 1992, 1993a). In the nervous system, Sp inhibits ganglionic transmission (Schmitt, 1980; Yovo et al., 1984), activates acetylcholine receptors (nicotinic and muscarinic (mAChRs)) and inhibits Na⁺ and K⁺ channels (Kingham and Balandrin, 1984; Piéri and Kirkiacharian, 1986; Wink, 1987, 1992, 1993a, 1993b; Schmeller et al., 1994; Körper et al., 1998). Subcutaneous administration of Sp (25 mg/kg) in neonatal rats decreases the mRNA of the m1–m3 subtypes of mAChRs and increases m7 mRNA between 7 and 14 days post-administration (Flores-Soto et al., 2006). The anticonvulsive effect of Sp was evaluated in the PTZ model of SE, and intraperitoneal (i.p.) administration of Sp (13 mg/kg) 30 min before PTZ (125 mg/kg, i.p.) delayed the onset of convulsive behavior and increased the survival period (Pothier et al., 1998).

However, there have not been previous efforts to clearly determine the anticonvulsive effects of Sp. For this reason, we consider important to study the anticonvulsant effects of Sp on acute seizures at the level of behavior and EEG activity in three different SE models. To accomplish this objective, convulsive behavior and the survival period as well as the amplitude, frequency, duration and latency of discharge trains were analyzed after Sp administration. Furthermore, the protocol applied allowed us to evaluate behavior and EEG activity before and after drugs administration.

2. Results

2.1. Behavior analysis

During basal analysis (30 min), normal behavior was observed in every group, and motor impairment secondary to the

surgical procedure was discarded. Normal behavior was characterized as chewing and search and grooming movements, with short and intermittent periods of sleep. After saline solution (SS) or Sp administration, normal behavior was observed for 3 h and compared with basal behavior.

After PTZ administration, the animals showed progressive convulsive behavior according to Velisek's scale, while in the experimental group (pre-treated with Sp), the convulsive behavior was not progressive, and the animals came back to "minor" phases (from phase V to III or from phase III to I). In some Sp pre-treated animals, behavior was even normal during long periods or throughout almost the entire experiment (3 h) (Fig. 1A). The time to reach phase V from phase II in Sp pretreated animals increased, as did the time to reach loss of posture ($p < 0.05$) (Fig. 1A). Seizure duration with Sp pretreatment was prolonged, but not significantly different from the control group, and a tendency toward a higher survival rate was observed in animals pretreated with Sp in comparison with the PTZ control group (68.64 ± 26.16 vs. 18.37 ± 2.6 min, respectively). In addition, pretreatment with Sp reduced the mortality rate compared with the PTZ control group (75% vs. 100%, respectively; $p < 0.05$) (Fig. 1A).

Animals administered Pilo had progressive convulsive behavior according to the Racine (1972), but in Sp pretreated animals, a non-significant delay in the onset of each phase (1–4) was observed, and the convulsive behavior was prolonged (Fig. 1B). However, Sp pretreatment reduced the mortality rate in comparison with the control group (17% vs. 80%), and there was also an increase in survival time (164.9 ± 15.08 vs. 115.7 ± 22.18 min, respectively; $p < 0.05$) (Fig. 1B).

The convulsive behavior was progressive in the group treated with KA. Sp pretreatment in the animals significantly delayed the onset of convulsive behavior in scales 1–3 ($p < 0.05$) (Fig. 1C). In addition, Sp pretreatment decreased seizure duration in the experimental animals compared with the control group (142.7 ± 6.65 vs. 169.5 ± 3.14 min, respectively; $p < 0.05$). The mortality was 0% in both groups.

2.2. EEG analysis

During basal recording (30 min) in all of the studied groups, the EEG activity showed slow activity characterized by low amplitude and frequency, without evidence of pathological activity (Table 1). Similar EEG activity was found after SS and Sp administration. No significant differences between basal EEG activity and EEG activity after SS and Sp administration were observed (Table 1).

The epileptiform activity of the PTZ group was characterized by rhythmic spike waves with discharge trains of high amplitude and frequency. In the animals pretreated with Sp, this pattern was preserved but there was a significant reduction in the amplitude and frequency of the discharge trains during status compared with controls (Fig. 2). In both groups, the epileptiform activity was initiated in the fronto-parietal region (Fig. 2). Regarding the number and duration of discharge trains during status, no significant differences were found in the first segments, but at the end of the experiment, there were not discharge trains in 28% of the experimental animals. The onset of partial and widespread epileptiform

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