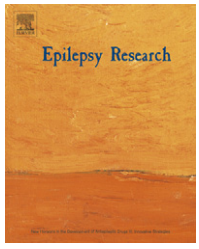
Epilepsy Research (2007) **73**, 65—74

journal homepage: www.elsevier.com/locate/epilepsyres



Effect of levetiracetam on visual-spatial memory following status epilepticus

Jun-Li Zhou, Qian Zhao, Gregory L. Holmes*

Neuroscience Center at Dartmouth, Section of Neurology, Dartmouth Medical School, Lebanon, NH, United States

Received 21 March 2006; received in revised form 5 August 2006; accepted 22 August 2006
Available online 6 October 2006

KEYWORDS
Levetiracetam;
Memory;
Learning;
Place cells;
Status epilepticus;
Water—maze

Summary Status epilepticus (SE) is often followed by severe cognitive impairment, including memory impairment. Previous studies have shown that SE is associated with impairment of single cells in the hippocampus that fire action potentials when the animal is in a specific location in space, the so-called place cells, and that place cell function correlates well with performance in tasks of visual-spatial memory. Place cell patterns therefore appear to be an excellent measure of spatial memory and may serve as a tool to assess seizure-induced impairment in memory. In this study we determined the relationship between visual-spatial memory and place cell function following SE. In addition, we determined if levetiracetam (LEV), an antiepileptic drug with a novel mechanism of action, can improve cognitive function and place cell firing patterns when administered following SE. SE was induced in adult male rats which were then randomized to post-SE treatment with LEV or normal saline (NS) treatment for 14 days. Non-SE control rats also were randomized to LEV or NS. Following discontinuation of LEV rats were tested for visual-spatial memory in the Morris water—maze and then underwent unit recording in the CA1 region of the hippocampus. Brains were then evaluated for cell loss and mossy fiber sprouting. SE was associated with severely impaired performance in the water—maze with SE rats demonstrating no learning over four days of testing. Paralleling this memory deficit was a marked disturbance in firing patterns of pyramidal neurons in CA1. Non-SE rats learned quickly over four days of water—maze testing and had normal pyramidal cell firing patterns. LEV had no major effects on water—maze performance or place cell function. Histopathological examination of the brains showed severe cell loss in CA1 in all of the SE rats with lesser degrees of injury in CA3 and the hilus. LEV treatment resulted in less histological damage in the hippocampus but had no effect on visual-spatial function or place cell physiology in either control or SE rats.
© 2006 Published by Elsevier B.V.

Introduction

Status epilepticus (SE), defined as 30 min or more of continuous epileptic seizure activity, is a common neurological emergency associated with a high morbidity and mortality (Aicardi and Chevrie, 1970, 1983; DeLorenzo et al., 1992;

* Corresponding author at: Center for Neuroscience at Dartmouth, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, United States. Tel.: +1 603 650 7910; fax: +1 603 650 7617.
E-mail address: Gregory.L.Holmes@Dartmouth.edu (G.L. Holmes).

0920-1211/$ — see front matter © 2006 Published by Elsevier B.V.
doi:10.1016/j.eplepsyres.2006.08.007

Working Group on Status Epilepticus, 1993; van Esch et al., 1996; Sahin et al., 2001). Although SE with or without recurrent seizures is associated with a wide variety of neuropsychological problems, memory deficits including impairment of episodic memory are particularly prominent (Jambaque et al., 1993; Krumholz et al., 1995; van Esch et al., 1996).

SE is preferentially associated with histologically detectable damage of the hippocampus and related areas (''mesial temporal sclerosis''). This form of damage is characterized by cell loss in CA1, CA3, the hilus and dentate gyrus and synaptic reorganization as evidence by sprouting of mossy fibers (Liu et al., 1995). Since normal episodic memory, the ability to learn and recall specific information about people, places and events, depends on a properly functioning hippocampus (Squire, 1992) it is not surprising that impaired memory in patients following SE occurs.

There is a need to develop neuroprotective therapies that will prevent or reduce cognitive impairment occurring following SE. There has been a growing interest in the use of antiepileptic drugs (AEDs) for neuroprotection, and in the possible role of AEDs in disease modification (Sankar and Holmes, 2004; Willmore, 2005). One such compound, levetiracetam (LEV), has generated considerable interest since it has been demonstrated to slow the rate of kindling (Loscher et al., 1998; Klitgaard et al., 1998; Stratton et al., 2003), a model of epileptogenesis (McNamara et al., 1985).

LEV is structurally related to a class of drugs called nootropic agents, which have produced cognitive enhancement in certain models of learning and memory (Sankar and Holmes, 2004). The structural analogs piracetam (Bryant et al., 1973) and etiracetam (Sara, 1980; Wolthuis, 1981) have been shown to have a positive effect on learning and memory. LEV has been reported to have beneficial cognitive effects, antagonizing the amnestic effects of scopolamine (Verloes et al., 1988) and reducing infarction size when administered prior to and after middle cerebral artery occlusion (Hanon and Klitgaard, 2001).

In this study we determined whether LEV, administered after SE had any long-term benefits. Our behavioral outcome measure was performance in the Morris water—maze, a test measuring visual-spatial memory. Our morphological outcome measure was hippocampus cell loss and mossy fiber sprouting. To directly address the cellular concomitants of spatial memory impairments, we recorded the activity of single hippocampal neurons in freely moving rats subjected to SE and compared this activity to that in control rats. Among the pyramidal cells recorded, a substantial number discharge rapidly only when the rat's head is in a cell-specific part of the environment, the so-called ''firing field.'' These firing fields are stable over long times (weeks or months) in a constant environment, indicating that the representation is remembered and not created *de novo* each time the rat enters the environment (Muller and Kubie, 1987; Muller et al., 1987; Thompson and Best, 1989, 1990).

We report here that adult rats who experienced SE have severe cell loss in CA1 of the hippocampus. These animals showed severe deficits in a complex visual-spatial task and in parallel had aberrant firing patterns of pyramidal neurons. LEV had no effect on visual-spatial function and place cell physiology in either control or SE rats.

Materials and methods

Overview of the experiments

The study was designed to (i) assess to relationship between learning and memory as measured in the Morris water—maze with place cell firing patterns and histopathology in rats with and without a prior history of SE and (ii) determine whether LEV administered after SE alters subsequent outcome as measured by performance in the water—maze, place cell function, and histopathology. Adult male rats were subjected to lithium-pilocarpine (Li-Pilo) SE at postnatal (P) day 70 and then treated with LEV or normal saline (NS) for 14 days. LEV was started 24 h after the onset of SE to assure that animals were no longer having seizures at the time the drug was administered. Following discontinuation of the drug animals were studied in the water—maze and then had electrodes placed and single units recorded starting at P120. Following the physiological testing, rats were sacrificed and their brains examined for cell loss using Thionin and mossy fiber sprouting using the Timm stain. Fig. 1 illustrates the study design in cartoon form.

Li-Pilo induced seizures

The experimental procedures were approved by the Animal Care and Use Committee of Dartmouth Medical School and were performed in accordance with NIH guidelines for the humane treatment of animals.

Male Sprague—Dawley rats at P70 were divided into a control group ($n = 14$) and a Li-Pilo seizure group ($n = 26$). They were maintained on a 12/12 light/dark cycle and had free access to food and water except during place cell recording. For the seizure group, lithium chloride (127 mg/kg) was given intraperitoneally (IP) 18 h before a IP injection of pilocarpine (34 mg/kg) to induce SE as previously described. The dosage of lithium and pilocarpine is similar to what has been used in other studies in our laboratory (Rutten et al., 2002; Liu et al., 2003; Zhao et al., 2006) and others (Noyan and Gulec, 2000; Ekdahl et al., 2002; Chu et al., 2004). For the control group, NS was given IP in the same manner.

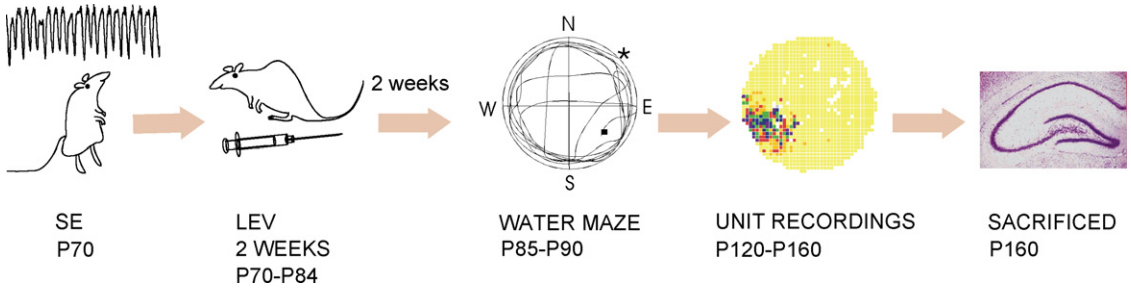


Figure 1 Cartoon of study design.

Download English Version:

https://daneshyari.com/en/article/3053140

Download Persian Version:

https://daneshyari.com/article/3053140

Daneshyari.com