Epilepsy Research (2014) **108**, 223—231

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

BASIC RESEARCH

Ginseng extract attenuates early MRI changes after status epilepticus and decreases subsequent reduction of hippocampal volume in the rat brain

Elena Suleymanova[a,b,*], **Mikhail Gulyaev**[a], **Nina Chepurnova**[a]

[a] *Lomonosov Moscow State University, GSP-1, Leninskie Gory, Moscow 119991, Russia*
[b] *Institute of Higher Nervous Activity and Neurophysiology of RAS, 5A Butlerova St., Moscow 117485, Russia*

Received 13 May 2013; received in revised form 15 September 2013; accepted 21 November 2013
Available online 1 December 2013

KEYWORDS
Epilepsy;
Status epilepticus;
MRI;
Brain damage;
Panax ginseng

Summary Prolonged epileptic seizures during status epilepticus (SE) are known to cause neuronal death and lead to brain damage. Lesions in various brain regions can result in memory and cognitive impairment, thus searching of new neuroprotective drugs is important. We evaluated effects of single and chronic administration of ginseng extract on early and late changes in MRI measurements in the rat brain after lithium-pilocarpine SE. Butanol extract of ginseng root cell culture DAN-25 was administered after termination of SE. MRI study of the rat brain was performed 2, 7, and 30 days after SE. High-resolution T_2-weighed images and T_2-maps were obtained, and total damaged area, hippocampal volume, and T_2 relaxation time in several brain structures were calculated. Single administration of ginseng extract attenuated early changes in brain structures found on day 2 after SE. Both single and chronic treatment with ginseng extract decreased brain damage on day 7 after SE. An increase in T_2-relaxation time in the hippocampus on day 2 after SE was less prominent in ginseng-treated rats than in saline-treated rats. 30 days after SE, the reduction of hippocampal volume was found both in saline-treated and ginseng-treated rats; however, it was less pronounced in ginseng-treated rats. We conclude that administration of ginseng extract after SE termination reduced brain damage caused by prolonged seizures. Ginseng extract was effective during early period after SE and had a specific protective effect on the hippocampus.

Introduction

Status epilepticus (SE) is a dangerous neurological condition that is usually defined as seizures lasting for more than 30 min (Chen and Wasterlain, 2006). SE is considered an emergency and requires immediate therapy. SE can lead to

* Corresponding author at: Institute of Higher Nervous Activity and Neurophysiology of RAS, Butlerova St. 5A, Moscow 117485, Russia. Tel.: +7 495 3347000; +7 495 334 26 22; fax: +7 499 7430056.
E-mail address: e.m.suleymanova@gmail.com (E. Suleymanova).

0920-1211/$ — see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.eplepsyres.2013.11.018

the development of temporal lobe epilepsy (TLE) later in life (Fujiwara et al., 1979; Loscher and Brandt, 2010).

SE can be considered as an insult that induces a variety of pathologic changes including neurodegeneration, axonal sprouting, inflammation, and gliosis. These processes take place during the seizure-free latent period after SE that can last for several years and are believed to underlie epileptogenesis (Loscher and Brandt, 2010; Pitkanen and Lukasiuk, 2009). Pilocarpine and lithium-pilocarpine models are well-established experimental models of SE and subsequent TLE. Time course of pathologic processes in this model is similar to human acquired TLE and includes initial insult (SE), seizure-free latent period, and chronic period (Andre et al., 2007; Turski et al., 1989). Prolonged seizures during SE are known to induce neuron death in several subfields of the hippocampus, amygdala, thalamus, cerebellum, piriform, and entorhinal cortex both in humans (DeGiorgio et al., 1992; Fujikawa et al., 2000a) and experimental SE models (Honchar et al., 1983; Treiman, 1990). Neuroprotection is one of promising strategies in prevention or modification of pathologic consequences of SE. Though prevention of neurodegeneration in the hippocampus seems not to be sufficient for prevention of epileptogenesis (Brandt et al., 2006), neuroprotection may be important for attenuation of behavior impairment, learning, and memory deficits, associated with post-SE brain damage, and also reducing of resistance to antiepileptic drugs (AEDs) (Loscher and Brandt, 2010). Thus, searching for new neuroprotective drugs is important.

Ginseng is one of the most famous herbs that have been used in Asia for more than 2000 years. Many studies have shown numerous effects of ginseng and its components on brain including neuroprotective and anti-inflammatory effects Glycosides of ginseng called ginsenosides or ginseng saponins are responsible of most pharmacological effects of ginseng (Attele et al., 1999). Neuroprotective activity of whole ginseng extracts and single ginsenosides has been found in vivo and in vitro. Ginseng extract and its components prevented or attenuated neuron death induced by 3-nitropropionic acid (Lian et al., 2005a), kainic acid (KA) (Shin et al., 2009), and glutamate (Li et al., 2010). Ginsenosides Rb1, Re, Rb3, Rg3 decreased brain damage in cerebral ischemia in rodents (Chen et al., 2008; Tian et al., 2005; Ye et al., 2011; Zhu et al., 2012). Besides neuroprotective effect, ginsenosides were shown to have anticonvulsive properties: administration of ginsenosides attenuated seizures induced by KA and pentylenetetrazol (Lee et al., 2002; Lian et al., 2005b), and prevented pentylenetetrazol-induced kindling (Gupta et al., 2001). Pre-treatment with ginsenosides reduced neuron death in hippocampus of KA-treated rats (Lee et al., 2002; Shin et al., 2009). Thus components of ginseng have both anticonvulsant and neuroprotective effect. However, protective effects of ginseng against seizure-induced neuron damage were found either in vitro or in pre-treated animals. To our knowledge, an effect of administration of ginseng after an initial insult, such as SE, on subsequent pathologic changes in brain structures was not investigated. In this study we investigated effects of administration of *Panax ginseng* root cell culture extract after termination of seizures on brain damage induced by lithium-pilocarpine SE. We used structural and quantitative MRI for assessment of ginseng effects on changes in the rat brain after SE. MRI is a powerful non-invasive tool for assessment of brain damage that allows investigating the temporal evolution of pathological changes in the brain. There is strong evidence that MRI findings can be used for accurate quantifying brain lesions in vivo in brain ischemia, traumatic brain injury, and SE models (Allegrini and Sauer, 1992; Kharatishvili et al., 2009; Niessen et al., 2005; Roch et al., 2002). An increase in T_2-relaxation time is observed in damaged brain tissues after an insult such as ischemia or SE and can indicate irreversible neuron damage (Choy et al., 2010; Ebisu et al., 1996; Fabene et al., 2003; Hoehn-Berlage et al., 1995; Scott et al., 2002). For an objective and detailed analysis of changes in brain tissue after SE, we used quantitative MRI in addition to structural MRI.

Materials and methods

Animals

Adult male wistar rats ($n = 100$) weighting 300—350 g at the beginning of experiments were used in this study. All animal experiments were carried out according to EU Directive for animal experiments and approved by the local bioethical committee.

Lithium-pilocarpine model of SE

Seizures were induced by administration of 40 mg/kg pilocarpine hydrochloride (Acros Organics, USA). In order to potentiate SE, 127 mg/kg lithium chloride (Acros Organics, USA) was injected 24 h prior the administration of pilocarpine. Seizures were observed and scored using Racine scale (Racine, 1972) for 2 h after the onset of generalized seizures. After that SE was terminated by administration of 0.6 ml/kg paraldehyde (Acros Organics, USA). All drugs were freshly dissolved in 0.9% saline and administered intraperitoneally. Control rats received equivalent volume of saline instead of pilocarpine.

Experimental groups

Animals were divided into the following experimental groups:

1. 18 mg/kg ginseng extract treated rats ($n = 16$). Single injection was made 30 min after SE termination;
2. 180 mg/kg ginseng extract treated rats ($n = 8$). Single injection was made 30 min after SE termination;
3. VPA-treated rats ($n = 12$). Single injection was made 30 min after SE termination;
4. saline treated rats, single injection was made 30 min after SE termination ($n = 24$);
5. rats receiving chronic treatment with ginseng extract during 4 weeks after SE ($n = 11$);
6. rats receiving chronic treatment with saline during 4 weeks after SE ($n = 11$);
7. control rats (no SE) ($n = 18$).

Freeze-dried butanol extract of *Panax ginseng* C.A. Meyer root cell culture DAN-25 was used in the study. This strain