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Effects of genistein on cognitive dysfunction and hippocampal synaptic plasticity impairment in an ovariectomized rat kainic acid model of seizure

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ABSTRACT

The major objective of this study was to investigate the probable effects of genistein (one of the most important soy phytoestrogens-SPEs) on seizure-induced cognitive dysfunction, hippocampal early long-term potentiation (E-LTP) impairment and morphological damage to CA1 neurons in ovariectomized (OVX) rats.

Three weeks after ovariectomy, cannulae were implanted over the left lateral ventricle. After a 7-day recovery period, animals were injected by genistein (0.5 or 5 mg/kg) or vehicle during four consecutive days, each 24 h. One h after the last treatment, kainic acid (KA) or vehicle was perfused into the left lateral ventricle to induce generalized tonic-clonic seizures. Finally, 7 days later, spatial learning and memory of animals were examined using the Morris water maze (MWM) task, hippocampal E-LTP was assessed using in-vivo field potential recordings and the morphology of hippocampal CA1 area was examined using Fluoro-Jade C staining.

KA-induced generalized seizures resulted in spatial learning and memory impairment, E-LTP deficit and CA1 cell injury. Seizure-induced abnormalities improved partially only by the lower dose of genistein (0.5 mg/kg). However, genistein at the higher dose (5 mg/kg) did not have any beneficial effects. Also, genistein did not affect seizure activity.

It is concluded that genistein may have partially preventive effects against seizure-induced cognitive impairment in OVX rats. Also, it seems that such effects of genistein are correlated with its beneficial effects on hippocampal synaptic plasticity and morphology.

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1. Introduction

Seizure can induce consciousness impairment, cognitive dysfunction, synaptic reorganization and hippocampal neurodegeneration (Arthuis et al., 2009; Artinian et al., 2015; Ben-Ari, 2001; Chan et al., 2004; Nadler et al., 1978). Hippocampal synaptic plasticity is involved in memory formation (Neves et al., 2008) and seizure-induced hippocampal damage, especially in the CA1 area, impairs memory (Kotloski et al., 2002; Ramírez-Munguía et al., 2003). Intracerebroventricular (i.c.v.) administration of kainic acid (KA, an analog of glutamate) is a standard experimental model which results in severe limbic seizures and hippocampal neuronal damage (Nadler et al., 1978).

There are various antiepileptic drugs to control seizure; however, some types of seizures are drug-resistant and some antiepileptic drugs have adverse effects (Perucca and Gilliam, 2012; Regesta and Tanganelli, 1999). It seems that further investigations are needed on alternative therapies, like herbal compounds. Soy phytoestrogens (SPEs), like genistein, are herbal compounds that bind to estrogen receptors and therefore mimic the actions of estrogen (Molteni et al., 1995). It is stated that SPEs can be used as an alternative therapy in postmenopausal women (Molteni et al., 1995; Soni et al., 2014) instead of estrogen replacement therapy which has more adverse effects (Beral, 2003; Grady et al., 1995). It is worth pointing out that ovariectomized (OX) rat is an experimental model of postmenopausal women which can be used to study the effects of the herbal medicine or other experimental designs in the absence of ovarian hormones (Gallo et al., 2005; Kalu, 1991).

Various studies have investigated the effects of estrogen on seizure (Nicoletti et al., 1985; Velísková et al., 2000; Woolley, 2000). It has been reported that estrogen has neuroprotective

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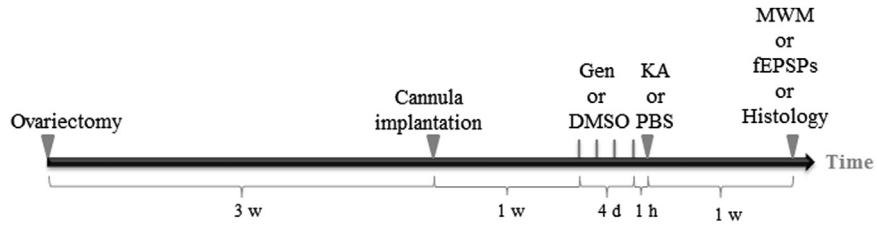

Fig. 1. The Overview and timeline of the experimental protocol used in this study. Three weeks after ovariectomy, cannulae were implanted over the left lateral ventricle. After a 7-day post-operative recovery period, animals were injected by genistein (0.5 or 5 mg/kg) or vehicle (DMSO) during four consecutive days, each 24 h. One h after the last treatment, KA or vehicle (PBS) was injected into the left lateral ventricle. Finally, the Morris water maze test, hippocampal field excitatory post-synaptic potential recordings or morphological experiments were conducted 7 days later. Gen: genistein, KA: kainic acid, MWM: Morris water maze, fEPSPEs: field excitatory post-synaptic potentials, w: week, d: day, h: hour.

effects against seizure (Velísková et al., 2000); however, many studies have shown the proconvulsant effects of estrogen (Nicoletti et al., 1985; Woolley, 2000). But, a few studies have focused on the effects of genistein on seizure. This study therefore set out to assess the effect of genistein on cognitive impairment, hippocampal synaptic plasticity deficit and CA1 neurodegeneration following KA-induced seizure in OVX rats.

2. Materials and methods

2.1. Animals

Female Wistar rats (200–250 g in weight) were used in this study. Animals were maintained under controlled conditions including temperature of 23 ± 1 °C, 12-h light-dark cycle (lights on: 07:00–19:00 h) and free access to food and water. The present study was approved by the Regional Ethics Committee of Kerman Neuroscience Research Center, Kerman, Iran (Ethics Code: EC/KNRC/91-36) and the experimental procedures had been conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

2.2. Ovariectomy

Ovariectomy was done according to a previous study (Saadati et al., 2015). Rats were anesthetized with ketamine (60 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) and the ovaries were removed under a laparotomy surgery.

2.3. Cannula implantation

After a 3-week recovery period, ovariectomized rats were again anesthetized with ketamine and xylazine and placed in a stereotaxic frame. The scalp was cut, a hole was drilled in the skull and a unilateral stainless steel (21-gauge) guide cannula was inserted into the brain so that its tip was placed 1 mm over the left lateral ventricle (AP = 0.9 mm; ML = 1.3 mm; DV = 3.5 mm) (Paxinos and Watson, 1998). Skull screws and dental cement were used for securing of the guide cannulae so that the skull over the right hippocampus remained uncovered.

2.4. Treatment and seizure induction

After a 7-day post-operative recovery period, animals were randomized into five main groups. Before KA administration, animals were intraperitoneally (i.p.) injected for four consecutive days, each 24 h, by genistein (G-6649; Sigma, St. Louis MO, USA) at two doses; 0.5 mg/kg for lower dose genistein (LDG-KA) groups and 5 mg/kg for higher dose genistein (HDG-KA) groups (Qian et al., 2012; Rodríguez-Landa et al., 2009). The DMSO-KA groups received i.p. injection of dimethyl sulfoxide (DMSO) as vehicle of genistein. The animals of the KA and PBS groups just received i.c.v. injection of KA or PBS, respectively. Each of the five main groups was divided into 3 subgroups for behavioral (n = 7–8), electrophysiological (n = 7–8) or histological (n = 4–5) studies.

One h after the last injection of genistein or DMSO, kainic acid (KA) (K-0250; Sigma, St. Louis Mom USA) (0.5 μg/1 μl) (Li et al., 2010; Nadler et al., 1978) was dissolved in 0.1 M phosphate buffered saline (PBS) and perfused slowly into the left lateral ventricle during 1 min Injection was conducted through pre-implanted guide cannulae and using a microinjection cannula which was connected to a 10-μl Hamilton syringe. Microinjection cannula protruded a further 1 mm longer than to the tip of the guide cannula to perfuse KA into the ventricle.

Seizure stages were scored as follows: 1- mouth and facial movements, 2- head nodding, 3- forelimb clonus, 4- rearing, 5- rearing and falling (Racine, 1972). The seizure activity of animals were recorded for 3–4 h and only those rats which showed the fifth stage of the scale were selected for behavioral, electrophysiological or histological studies which were conducted 7 days later (Fig. 1). It has been shown that neuronal damage happens at this time following i.c.v. administration of KA (Li et al., 2010). It should be noted that we also conducted a separate study for the same groups (n = 7 in each group) to examine the effects of KA and genistein administration on seizure activity (seizure stages and latency to onset of seizures).

2.5. Morris water maze (MWM)

2.5.1. Spatial learning

The MWM included a metallic circular tank, 160 cm in diameter, 80 cm height, and filled with water to a depth of 40 cm. The tank was divided into 4 quadrants, and a platform (10 cm in diameter) was placed in the center of the training quadrant at ~1.5 cm beneath the surface of water. Various posters were placed on the wall around the tank as spatial navigation cues and a smart video tracing system (Noldus Ethovision® system, version 5, USA) was used to record the performance of animals. Learning acquisition consisted of three blocks which were separated by 30-min resting periods and each block included four consecutive trials with 60 s duration and 60 s inter-trial intervals. In each trial, rats were randomly released into water from the center of one of the quadrants of the maze and allowed to swim for 60 s If the animals found the platform during 60 s, the trial would finish; otherwise, rats were helped by the experimenter to find the platform. Rats were allowed to rest on the platform for 30 s and then to rest at their cages for 20–30 s The time and path length to find the hidden platform were recorded to measure spatial learning (Hajali et al., 2012; Saadati et al., 2015).

2.5.2. Spatial short-term memory retention

To examine spatial short-term memory, a single probe trial was conducted 2 h after the last training trial. During the probe test,

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