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Research report

Short-term green tea supplementation prevents recognition memory deficits and ameliorates hippocampal oxidative stress induced by different stroke models in rats

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ABSTRACT

This study investigated the effect of green tea (GT) on short and long term declarative memory and oxidative damage induced by transient ischemia-reperfusion (IR) and intracerebral hemorrhage (ICH) in rats. Male Wistar rats were divided into 8 groups of 10 according the stroke type induced: Sham IR, Sham IR + GT, IR, IR + GT, Sham ICH, Sham ICH + GT, ICH, ICH + GT. Supplementation with GT was initiated 10 days before stroke surgery and continuous for 6 days after (GT dose 400 mg/kg). Short (STM) and long term memory (LTM) we evaluated with object recognition task (OR) and hippocampus were used to evaluate parameters related to oxidative stress (ROS, lipid peroxidation and total antioxidant capacity). The rats subjected to IR and ICH showed STM and LTM deficits and GT intervention prevented it in both stroke models. IR and ICH induced increase on ROS levels in hippocampus. ICH increased the lipid peroxidation in hippocampus and the GT supplementation avoided it. IR induced decrease on total antioxidant capacity and GT prevented it. These results reveal that GT supplementation presents a neuroprotective role, attenuates redox imbalance and might have a beneficial impact on cognitive function after stroke.

1. Introduction

According to the American Heart Association, cerebrovascular incidents are classified into two types – ischemic and hemorrhagic stroke. Together, these incidents are the leading cause of long-term disability and significant decrease in health and quality of life (Hinson et al., 2010). Ischemia-reperfusion (IR) accounts for 87 percent of all stroke cases (Association, 2012) and results from temporary or permanent reduction of cerebral blood flow (Choudhury and Ding, 2016; Rodriguez et al., 2014). Intracerebral hemorrhage (ICH) has lower incidence, but its consequences are more severe, causing high rates of mortality and morbidity (Hwang et al., 2013).

Stroke is a complex neurological syndrome defined as a sudden disturbance in the blood supply to the brain caused by IR or ICH, leading to functional and structural damage to the brain (Cheon, 2015; Jayaram et al., 2012). The two types of stroke have different pathophysiology but share some common mechanisms of secondary damage, such as increased oxidative stress and decreased antioxidant abilities, acute inflammatory response, excitotoxicity and apoptosis (Cai et al., 2015; Hadadha et al., 2015; Ritz et al., 2008; Zhang et al., 2015).

Ischemic stroke events result from suppression of blood flow to the brain, which decreases oxygen and glucose delivery to brain tissue (Zamani et al., 2013), causing metabolic and functional damage (Mestriner et al., 2013). During the ischemia, various pathogenic mechanisms could contribute to damage, including the energetic failure (glucose) (Abramov et al., 2007), the increase of intracellular calcium levels, the excitotoxity (Allen and Bayraktutan, 2009; Taniguchi et al., 2000), the generation of free radicals (Allen and Bayraktutan, 2009; Sosa et al., 2015), the disfunction of the blood-brain barrier, and the inflammation and the edema (Allen and Bayraktutan, 2009).

ICH results from ruptures of blood vessels within the brain and leakage of blood constituents into the brain parenchyma. Intraparenchymal blood deposited during ICH elicits a host of biologic responses, including increase on iron concentrations, overproduction of

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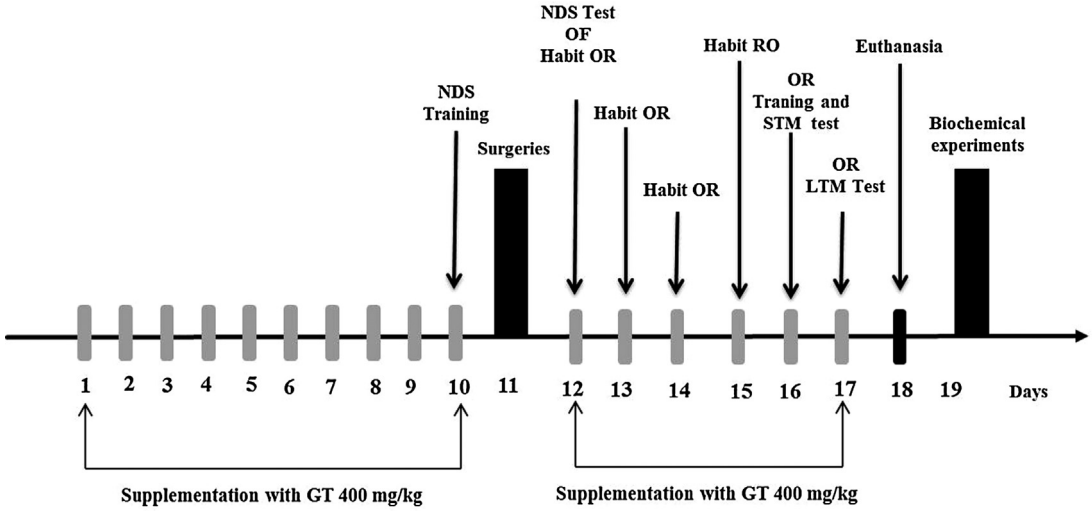

Fig. 1. Experimental design. The numbers represent the days of experiments. NDS: Neurologic Disability Scale; OF: Open Field; Habit: Habituation; OR: Object Recognition; STM: Short-Term Memory; LTM: Long-Term Memory.

oxidative stress, pro-inflammatory responses, cell death, and neurologic damage (Aronowski and Zhao, 2011; Zhou et al., 2014; Wang and Dore, 2007).

Previous studies have shown that both IR and ICH cause memory deficits in rats and humans (Pendlebury and Rothwell, 2009; Xiong et al., 2016). The hippocampus' role in cognitive functions, such as learning and memory, was very well demonstrated (Izquierdo and Medina, 1997), and this brain region is very sensitive to oxidative stress caused by several kinds of brain injury (Mergenthaler et al., 2013). Therefore, therapies that have a potential antioxidant effect and contribute to ameliorating brain function, including learning and memory performance, has been shown as a good approach for treating damage caused by IR and ICH.

Green tea (GT), derived from *Camellia sinensis*, has a high flavonoid content, especially of the catechin (−)-epigallocatechin-3-gallate (EGCG). Many studies have reported that EGCG is beneficial to health, considering its antioxidant (Assunção et al., 2010; Hsu et al., 2014), anti-inflammatory (Lee et al., 2013), anticancer (Singh et al., 2011), anti-diabetes (Tang et al., 2013) and anti-hypertensive activity (Bogdanski et al., 2012). Considering that EGCG is the catechin found in the highest concentration in green tea and that green tea can be easily purchased by the general population, some authors have studied the neuroprotective effects of the administration of a green tea mixture rather than of the isolated catechin. Many such studies have reported that the administration of green tea has a neuroprotective role in models of ischemic stroke, which is attributed to its antioxidant and free radical scavenging activities (Hong et al., 2000; Wu et al., 2012). Recently, our group demonstrated that long-term (8 weeks) administration of green tea can prevent various memory deficits induced by IR in rats (Schimidt et al., 2014).

Considering these previous results, the present study has been designed to verify whether (i) the neuroprotective effect of green tea in stroke could be observed with a shorter period of tea administration; (ii) the neuroprotective effect of green tea could ameliorate the short- and long-term recognition memory deficits induced by stroke; (iii) the neuroprotective effect of green tea could ameliorate the hippocampal oxidative stress induced by stroke; and (iv) the neuroprotective effect of green tea previously observed in ischemic stroke models could be observed in a hemorrhagic stroke model.

2. Materials and methods

2.1. Animals and experimental design

Eighty male Wistar rats (250–300 g, 3 months of age) obtained from the Reproduction Center of the Central Vivarium of Federal University of Santa Maria (RS, Brazil) were used. All animals were housed four per cage at a temperature of 22 ± 1 °C with a regular 12 h light-dark cycle and free access to water and food, according to the guidelines established by the university's Institutional Animal Care and Use Committee (Protocol approval #034/2014).

Since the aim of this study was to investigate the effects of green tea on memory deficits induced by two different types of stroke (ischemic and hemorrhagic) on memory, previously to memory evaluation the rats were divided into eight experimental groups according to the type of stroke induced and the treatment (n = 10/group):

(1) Sham Ischemic Stroke: Rats submitted to surgery without carotid artery occlusion;
(2) Green Tea + Sham Ischemic Stroke: Rats treated with green tea and submitted to surgery without carotid artery occlusion;
(3) Ischemic Stroke: Rats submitted to surgery with temporary occlusion of the carotid arteries (ischemia-reperfusion);
(4) Green tea + Ischemic Stroke: Rats treated with green tea and submitted to surgery with temporary occlusion of the carotid arteries (ischemia-reperfusion);
(5) Sham Hemorrhagic Stroke: Rats submitted to stereotaxic surgery without infusion of collagenase onto the hippocampus;
(6) Green Tea + Sham Hemorrhagic Stroke: Rats treated with green tea and submitted to stereotaxic surgery without infusion of collagenase onto the hippocampus;
(7) Hemorrhagic Stroke: Rats submitted to stereotaxic surgery with infusion of collagenase onto the hippocampus (to induce intracerebral hemorrhage);
(8) Green Tea + Hemorrhagic Stroke: Rats treated with green tea and submitted to stereotaxic surgery with infusion of collagenase onto the hippocampus (to induce intracerebral hemorrhage).

2.2. Green tea supplementation

Green tea was purchased from Madrugada Alimentos Ltda, Venâncio Aires, RS, Brazil. Green tea made from the leaves of the plant was prepared by infusion daily using distilled water (95–100 °C) and was administered at ambient temperature. The green tea or distilled