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Effect of endurance training on seizure susceptibility, behavioral changes and neuronal damage after kainate-induced status epilepticus in spontaneously hypertensive rats

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ABSTRACT

The therapeutic efficacy of regular physical exercises in an animal model of epilepsy and depression comorbidity has been confirmed previously. In the present study, we examined the effects of endurance training on susceptibility to kainate (KA)-induced status epilepticus (SE), behavioral changes and neuronal damage in spontaneously hypertensive rats (SHRs). Male SHRs were randomly divided into two groups. One group was exercised on a treadmill with submaximal loading for four weeks and the other group was sedentary. Immediately after the training period, SE was evoked in half of the sedentary and trained rats by KA, while the other half of the two groups received saline. Basal systolic (SP), diastolic (DP) and mean arterial pressure (MAP) of all rats were measured at the beginning and at the end of the training period. Anxiety, memory and depression-like behaviour were evaluated a month after SE. The release of 5-HT in the hippocampus was measured using a liquid scintillation method and neuronal damage was analyzed by hematoxylin and eosin staining. SP and MAP of exercised SHRs decreased in comparison with the initial values. The increased resistance of SHRs to KA-induced SE was accompanied by an elongated latent seizure-free period, improved object recognition memory and antidepressant effect after the training program. While the anticonvulsant and positive behavioral effects of endurance training were accompanied by an increase of 5-HT release in the hippocampus, it did not exert neuroprotective activity. Our results indicate that prior exercise is an effective means to attenuate KA-induced seizures and comorbid behavioral changes in a

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model of hypertension and epilepsy suggesting a potential influence of hippocampal 5-HT on a comorbid depression. However, this beneficial impact does not prevent the development of epilepsy and concomitant brain damage.

1. Introduction

In recent years, accumulated alternative neuroprotective and antiepileptogenic approaches have been applied for the prevention and treatment of epilepsy (Acharya et al., 2008). The beneficial role of aerobic exercise on epilepsy has been proved in both animal and human studies. Most of the preclinical and clinical research aimed at evaluating the effects of physical training programs on spontaneous seizures during the chronic epileptic state reported reduced ictal activity, decreased susceptibility to subsequently evoked seizures after exercise as well as positive plastic neurochemical changes in hippocampal formation (Arida et al., 2004, 2007, 2010; Camilo et al., 2009; Vancini et al., 2010). A few animal studies on the effects of exercise programs on seizure threshold and epileptogenesis reported that physical training delayed the development of amygdala kindling (Arida et al., 1998), increased the latency and decreased the duration of pilocarpine-induced status epilepticus (SE) (Setkowicz and Mazur, 2006) and attenuated pentylenetetrazole (PTZ)-induced seizures in rats (Souza et al., 2009).

It is know that hypertension should be a risk factor for seizures and epilepsy in the elderly (Delanty and Vaughan, 2002). Moreover, in addition to the positive influence of exercise on epilepsy, published data support the notion that physical activity constitutes an important alternative strategy in cardiovascular diseases and might be considered a therapeutic alternative in addition to conventional pharmacotherapy for treatment and prevention of hypertension (Dubow and Kelly, 2003). The long-term effects of physical exercise in hypertensive subjects are associated with decrease in blood pressure (BP) (Somers et al., 1991) and increase in baroreflex sensitivity in both hypertensive animals and humans (Graham and Rush, 2004; Moriguchi et al., 2005; Somers et al., 1991; Véras-Silva et al., 1997). Thus, the aerobic training program caused reduction in arterial BP and a significant decrease in cardiac output in hypertensive patients (Hagberg et al., 2000; Whelton et al., 2002) as well as in spontaneously hypertensive rats (SHRs) serving as model of essential hypertension (Barbosa et al., 2013; Gu et al., 2013). The predisposition to seizure and development of epilepsy might result from chronic hypertension (Delanty and Vaughan, 2002). There have been only a few studies to demonstrate that that SHRs are characterized by a lower seizure threshold than Wistar Kyoto rats in amygdala and piriform kindling models of epilepsy (Goldberg et al., 1975; Greenwood et al., 1989), destructive changes in the hippocampus, neurochemistry and behaviour (Hernandez et al., 2003; Pietranera et al., 2006; Scorza et al., 2005), suggesting that SHRs may also be studied as a relevant model of comorbidity between hypertension and epilepsy. Recently, we reported that SHRs demonstrated higher incidence of spontaneous seizure activity and more severe behavioral changes than normotensive Wistar rats in the kainate (KA) model of temporal lobe epilepsy (Tchekalarova et al., 2010, 2011).

A close relationship was suggested of epilepsy and associated psychiatric comorbidities with disturbance in brain monoamine (MA) systems such as serotonin (5-HT), noradrenaline and dopamine based on numerous preclinical and clinical studies (Arida et al., 2013). Alternatively, physical exercise can positively modulate MA levels in different brain structures (Blomstrand et al., 1989; Chaouloff, 1989) thereby supporting the idea that their restoration might contribute to the beneficial influence of exercise.

Taken together, the published data suggest that physical exercise may attenuate both hypertension and epilepsy. However, little is known whether regular exercise can affect the development of epileptogenesis and its deleterious consequences in hypertensive state. Therefore, in the present study, we examined the long-term effect of an aerobic exercise program on KA-induced status epilepticus (SE) and epileptogenesis, concomitant behavioral changes and hippocampal 5-HT release in a rodent model of hypertension and epilepsy comorbidity.

2. Results

2.1. *Arterial blood pressure of spontaneously hypertensive rats before and after treadmill training*

We found no significant differences between sedentary and trained rats in their systolic, diastolic and mean ABP at the end of the training period (Fig. 2A–C), but in the treadmill-trained rats there was a decrease of the systolic ABP by 7% ($t=2.557$, $p<0.05$) (Fig. 2A) and a tendency of decreased mean ABP ($t=1.862$, $p=0.07$) (Fig. 2C) compared with values measured before the training. No significant effect of training on diastolic ABP was found in comparison with the initial values ($t=0.613$, $p>0.05$) (Fig. 2B).

2.2. *KA-induced SE*

After 3–4 repetitive KA injections the sedentary control rats (Sed-KA) underwent a sustained SE with intensive motor seizures, class IV/V, i.e. more than 10 motor seizures per hour for at least three hours. The median dose of KA required to induce SE was 15 mg/kg, range: 10–25 (S.D. ± 3.82 mg/kg). Significantly more injections of KA were required in the Ex-KA group to reach SE (median ± S.D. 27 ± 4.37 mg/kg; range 20–32 mg/kg) ($p=0.001$) (Fig. 3A). The behaviour observed during the course of KA administration consisted of initial wet dog shakes, facial automatisms and head nodding, partial