Life Sciences 93 (2013) 773–777

Contents lists available at ScienceDirect

Life Sciences

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

Variable alteration of regional tissue oxygen pressure in rat hippocampus by acute swimming exercise

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ARTICLE INFO

Article history:
Received 31 May 2013
Accepted 20 September 2013

Keywords:
Exercise
Exercise intensity
Hippocampus
Oxygen pressure (pO_2)

ABSTRACT

One of the events in the brain is an increasing cerebral blood flow during exercise. The tissue oxygen level may be increased because blood flow correlates with tissue oxygen level. However, it is little known whether the tissue oxygen pressure in hippocampal region (Hip-pO_2) will be affected by exercise.
Aims: The aim of this study is to examine Hip-pO_2 levels in the hippocampus and its changes during exercise.
Main methods: We applied improved Clark-type electrodes to measure Hip-pO_2 level in the hippocampus of rats that were subjected to three groups, 2 h swimming without weights (low intensity, n = 6), 2 h swimming with a 5 g weight (moderate intensity, n = 6), and 2 h swimming with a 10 g weight (high intensity, n = 6).
Key findings: Exercise affected the Hip-pO_2 level, the responses varied with the exercise intensity and duration. Interestingly during and after the Low intensity swimming the Hip-pO_2 level showed long lasting enhancement (10–20% above resting level). But the moderate and high intensity swimming increased Hip-pO_2 level at the start of the swimming (50%, $P < 0.05$ and slightly above resting level, respectively, at 10 min of 2 h swimming) and then began to decrease (at 120 min and 10 min of 2 h swimming, respectively), and suppressed the Hip-pO_2 levels during post exercise resting period (2 h) (85–95% of resting level, NS and 60–70% of resting level $P < 0.05$, respectively).
Significance: We propose that exercise-induced hippocampal hyper/hypo oxygen condition may participate in beneficial exercise effects on brain function.

Introduction

The functional benefits of exercise have been well studied in adult animals including humans (Kitamura et al., 2003; van praag et al., 2005; Erickson et al., 2011). Exercise training improves spatial learning in rodents, and increases some neurotrophic factors (BDNF, NGF) in the hippocampus (Van Praag et al., 1999; Cotman and Berchtold, 2002) and hippocampal neurogenesis (Van Praag et al., 1999). In addition, exercise training enhances the size of the hippocampus (Erickson et al., 2011). Although the hippocampal region does not have a critical role in motor control, hippocampal neurons would activate during running exercise (Oladehin and Waters, 2001; Nishijima and Soya, 2006). The physiological role of hippocampal neuronal activation during exercise is still unclear, but as a result it would show the exercise effects on this region (neurogenesis, spatial learning etc.).

Active neurons in the brain require an increased oxygen supply and it is well known that the brain demands an abundant supply of oxygen. Neurons are very sensitive to lack of oxygen and are known to take damage by ischemia. Cerebral blood flow (CBF) can investigate the situation indirectly. CBF is a main homeostatic regulator for oxygen supply that should be matched to tissue needs. Many studies have reported that the whole cerebral blood flow is increased by exercise in an intensity dependent manner (Herholz et al., 1987; Thomas et al., 1989). On the other hand, it is reported that CBF was decreased by extreme intensity exercise (Jorgensen et al., 1992; Moraine et al., 1993). In this case, it can be predicted that the tissue oxygen level may also be decreased in the brain.

Based on the current theory that neuronal activity is tightly coupled to regional cerebral blood flow (rCBF), it is hypothesized that an increase in rCBF in response to neuronal activation would occur in the rat hippocampus during exercise (Girouard and Iadecola, 2006; Sokoloff, 1981). Indeed, animal studies have shown increases in hippocampal cerebral blood flow (hip-CBF) in rats while grooming, walking, and running (Osborne, 1997; Nakajima et al., 2003; Nishijima and Soya, 2006; Nishijima et al., 2012). Although the increased rCBF during exercise is well known, the changes of Hip-pO_2 are still poorly understood.

A recent study reported that mild running exercise increased the regional cerebral blood flow (rCBF) and neuronal activity in the hippocampus (Nishijima and Soya, 2006). Increasing tissue O_2 consumption and blood flow, however, is not always tightly coupled (Raichle et al., 1976), therefore it is uncertain whether regional hippocampal oxygen conditions are increased or decreased during exercise. To address this

Abbreviations: Hip-pO_2, the tissue oxygen pressure in hippocampal region; h, hour; pO_2, the tissue oxygen pressure; VO_2max, maximal oxygen uptake.

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0024-3205/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.lfs.2013.09.022

issue, we have developed a Clark-type electrode for monitoring Hip-pO_2 in rats during swimming. A Clark-type electrode that measures oxygen on a catalytic platinum surface using the net reaction (Clark, 1956) has the advantage of monitoring changes in Hip-pO_2 in real-time, with high sensitivity and stability, while the rat continues to exercise. The aim of this study was to examine the regional hippocampal tissue oxygen pressure (Hip-pO_2) during the three different swimming intensities in rats.

Materials & methods

Animals and training

All animal procedures were approved by the Nagoya Institute of Technology's Laboratory Animal Care and Use Committee. Adult male Wistar rats (10 weeks of age) were purchased from SLC (Shizuoka, Japan) and were housed individually under a constant temperature of 22 °C and a 12 h light/12 h dark cycle (light on at 07:00 h) for at least 1 week before experiments. Food and water were available ad libitum.

All rats were habituated to swimming in the pool (a circular tank, 80 cm in diameter and 90 cm in height, filled to the 60 cm mark with 32–35 °C water) for 2 h, once a day, three times in a week. Rats were subjected to three groups 2 h swimming without a weight (low intensity, n = 6), 2 h swimming with a 5 g weight attached around the neck (moderate intensity, n = 6), and 2 h swimming with a 10 g weight attached around the neck (high intensity, n = 6).

Surgery

After learning to swim three times, rats were anesthetized with sodium pentobarbital (50 mg/kg, ip), and a stainless steel guide cannula (O.D. 0.8 mm, Unique Medical Co., Tokyo, Japan) was stereotaxically implanted into the left dorsal hippocampal region (co-ordinates: anteroposterior + 1.5 mm, mediolateral 4.0 mm from the Bregma, and dorsoventral −2.0 mm from the dura). The guide cannula was fixed to the skull with an anchor screw using dental cement (Shofu Co., Tokyom, Japan). After surgery, the rats were housed individually and allowed to recover for one day at least.

Measurement of tissue oxygen level in hippocampus (Hip-pO_2)

Hip-pO_2 was measured by using improved Clark-Type electrodes (U0E-04TS, Unique Medical Co., Tokyo, Japan) composed with a sensor at the tip (diameter 0.4 mm, length 10 mm of Teflon tube coating) and followed by a 35 mm stainless steel coating. Each electrode was connected to a digital pO_2 monitor (POG-203, Unique Medical Co., Tokyo, Japan) (Clark, 1956). Each electrode sensor was calibrated in water that was saturated with standard gas series (0, 1.03, 2.02, 5, 16.7, 20.9%O_2-N_2 balance) in glass chambers immediately prior to insertion into the brain (Fig. 1). The value of pO_2 at 150 mm Hg was corrected to the current value of 20.9%O_2-N_2 balance, air. The regression coefficient was calculated to gain the standard line.

After calibration, the electrode sensor tip was heparinized, then inserted into the hippocampal region through the guide cannula and fixed with rocking nut. The tip of the sensor protruded 1.0 mm from the end of the guide cannula. After insertion of the sensor, rats were stabilized in a plastic cage for 2 h, and then gently transferred to the water pool. Rats swam for 2 h with or without a sinker weight (5 g or 10 g, approximately 1.5% or 3.0% body weight, respectively). After swimming the rats were gently wiped with a soft towel, then transferred again to the same plastic cage, and had rest for 2 h.

Exercise intensity

Prior to the main experiments, we measured oxygen uptake by using Scholander gas analyzing equipment to decide the exercise intensity during the acute swimming (Scholander, 1947; Baker and Horvath, 1964; McArdle, 1967; Armstrong et al., 1974; Yoshimura et al., 1992). The VO_2max was provided at the initial exercise which was burdened with a sinker of 10% of the rat body weight and the value was $135.8 \pm 6.9\ ml^{-kg-min}$. The VO_2 in each exercise measured at 2 h that was the end of exercise (Table 1). Swimming without a sinker weight is regarded as low intensity exercise, and in this present study corresponds to approximately 52% VO_2max. Swimming intensity with a 5 or 10 g sinker weight corresponded to above 65% (moderate intensity) and 75% VO_2max (high intensity), respectively.

Statistic analysis

The data were analyzed by one- or two-way ANOVA, followed by a post-hoc test (Fisher's PLSD) for comparison among means. All data were expressed as means ± SE.

Results

The Hip-pO_2 levels during the resting period (pre-swimming)

Fig. 2 shows the absolute Hip-pO_2 levels during the whole time-course of the swimming test in three groups. During the resting period (2 h) the range of changes of the hippocampal pO_2 values in the low, moderate, and high intensity exercise groups were 15–17 mm Hg, 14–16 mm Hg, and 14–15 mm Hg, respectively. At 0 time (after the 2 h rest point), these values were 16.4 ± 4.2 mm Hg, 15.9 ± 1.9 mm Hg, and 15.0 ± 4.3 mm Hg, respectively. No statistically significant differences were observed at any point during the resting period.

The Hip-pO_2 levels during the three different intensity swimming exercises

In the low intensity swimming exercise, Hip-pO_2 levels began to be slightly increased (10–20% above resting level) after the onset of swimming, and this level was maintained till the end of the exercise (Fig. 2A). No statistically significant differences were observed. On the other hand, the moderate intensity swimming exercise increased Hip-pO_2 levels significantly to 30–50%, a peak value appeared at the 10–30 min time point, and then began to decrease slowly, keeping an elevated level when compared to the resting level (Fig. 2B). However, during the high intensity swimming exercise the Hip-pO_2 levels were slightly increased at the 10 min time point, but not significantly so (Fig. 2C),

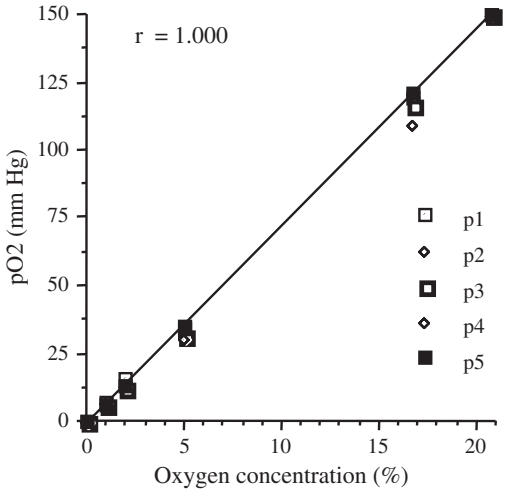

Fig. 1. The standard line of oxygen pressure (pO_2) measurement of standard gas series (0, 1.03, 2.02, 5, 16.7, 20.9%O_2-N_2 balance). Each electrode sensor was calibrated in water that was saturated with standard gas series before measurement. Symbols indicate each five electrode sensor; p1 to p5. The linear regression lines and correlation coefficient (r) are shown.