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The rate of training response to aerobic exercise affects brain function of rats

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ABSTRACT

There is an increasing volume of data connecting capacity to respond to exercise training with quality of life and aging. In this study, we used a rat model in which animals were selectively bred for low and high gain in running distance to test t whether genetic segregation for trainability is associated with brain function and signaling processes in the hippocampus. Rats selected for low response (LRT) and high response training (HRT) were randomly divided into control or exercise group that trained five times a week for 30 min per day for three months at 70% VO2max. All four groups had similar running distance before training. With training, HRT rats showed significantly greater increases in VO2max and running distance than LRT rats ($p < 0.05$). On the reverse Morris Maze test HRT-trained rats outperformed HRT control ones. Significant difference was noted between LRT and HRT groups in redox milieu as assessed by levels of reactive oxygen species (ROS), carbonylation of proteins, nNOS and S-nitroso-cysteine. Moreover the silent information regulator 1 (SIRT1), brain-derived neurotrophic factor (BDNF), ratio of phospho and total cAMP-response element binding protein (CREB), and apoptotic index, also showed significant differences between LRT and HRT groups. These findings suggest that aerobic training responses are not localized to skeletal muscle, but differently involve signaling processes in the brain of LRT and HRT rats.

1. Introduction

The level of cardiovascular fitness, as measured by VO_2max, has become an important biomarker for quality of life, since a high VO_2max is strongly associated with decreased incidence of life-style related diseases (Andersen, 1995; Carnethon et al., 2005; Lacza and Radak, 2013). It has been suggested that higher VO_2max was important to early humans, because it could increase the efficiency of hunting, in which early humans chased the prey animals (Bramble and Lieberman, 2004) and as a result greater aerobic capacity could have significant advantage for more and higher quality food. Therefore, it suggested that aerobic exercise, especially running, could be important for the evolution of homo sapiens (Lieberman and Bramble, 2007; Radak et al., 2013).

Based partly on this hypothesis, it has been suggested that a larger brain and enhanced brain function evolved to support endurance capacity-dependent hunting, and in turn, endurance running helped support more efficient development of the brain (Mattson, 2012). Indeed, current studies show that regular exercise has beneficial structural, metabolic, and functional effects on human and rodent brain (Radak et al., 2014; van Praag et al., 2014). Based on these observations, we suggest that not only an inherited high endurance capacity, but also the inherent ability to increase aerobic endurance capacity in response to aerobic activity also influences the brain. It is well established that adaptive response to exercise could be dependent on genetics, and probably on epigenetics (Denham et al., 2014).

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Recently a rat model has been developed via artificial selective breeding, which permits to study the inherited components of low and high trainability (Koch et al., 2013). Selection was based on the acquired change in maximal running distance evaluated by a treadmill-running test to exhaustion. In the untrained condition, LRT and HRT rats are similar for exercise capacity. In that study the animals were trained 3 days per week for 8 wk with the running intensity started at 10 m/min up to a maximum speed of 21 m/min. On average, 8 wk of this moderate endurance running training resulted in an 84 ± 20 m gain in running capacity. However, the inter-individual training response varied widely from +754 m gain to a −438 m decline (2.7-fold) in running distance (Koch et al., 2013).

HRT rats improve on average by 200 m for distance run whereas those bred as LRT fail to improve and, on average, decline for running capacity by 65 m (Koch et al., 2013) for the given moderate intensity training.

Recently we have shown that mitochondrial factors could be behind the different adaptive response to aerobic training (Marton et al., 2015). Significant differences were found in peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), mitochondrial transcription factor A (TFAM), nuclear respiratory factor 1 (NRF-1) and Lon protease in low and high responder group in gastrocnemius muscle. In addition, it has been shown that the training response of slow and fast twitch fiber dominated skeletal muscle is very different (Bishop et al., 2014). High intensity training does not cause greater increase in mitochondrial content in slow type of skeletal muscle than low intensity training, while the duration of the training dose is important to increase mitochondrial mass in soleus but not in white vastus lateralis muscle (Bishop et al., 2014). Therefore, despite of the fact that the effects of exercise is systemic (Radak et al., 2008), it is appears that not just muscle type specific but organ specific differences could be present in rats with different aerobic trainability. Recently, Nokia et al. provide evidence that neurogenesis in hippocampus is greater in high response to training rats compared to low response rats, and especially when the exercise is aerobic and of sustained duration (Nokia et al., 2016). Therefore, it was suggested that low and high training responders to aerobic training could have different adaptive response in cognitive brain function and molecular adaptation in hippocampus.

In this study, we used a rat model in which animals were selectively bred for low and high gain in running distance to test whether genetic segregation for trainability is associated with brain function and signaling processes in the hippocampus. We report here that training responses are not localized to skeletal muscle, but differently involve signaling processes in the hippocampus in low and high training responders.

2. Methods

2.1. Animals and exercise protocol

We have utilized a previously established experimental model of genetically heterogeneous N:NIH stock of rats. These rats were developed using “selective breeding” method based on their running capacity (Koch and Britton, 2001).

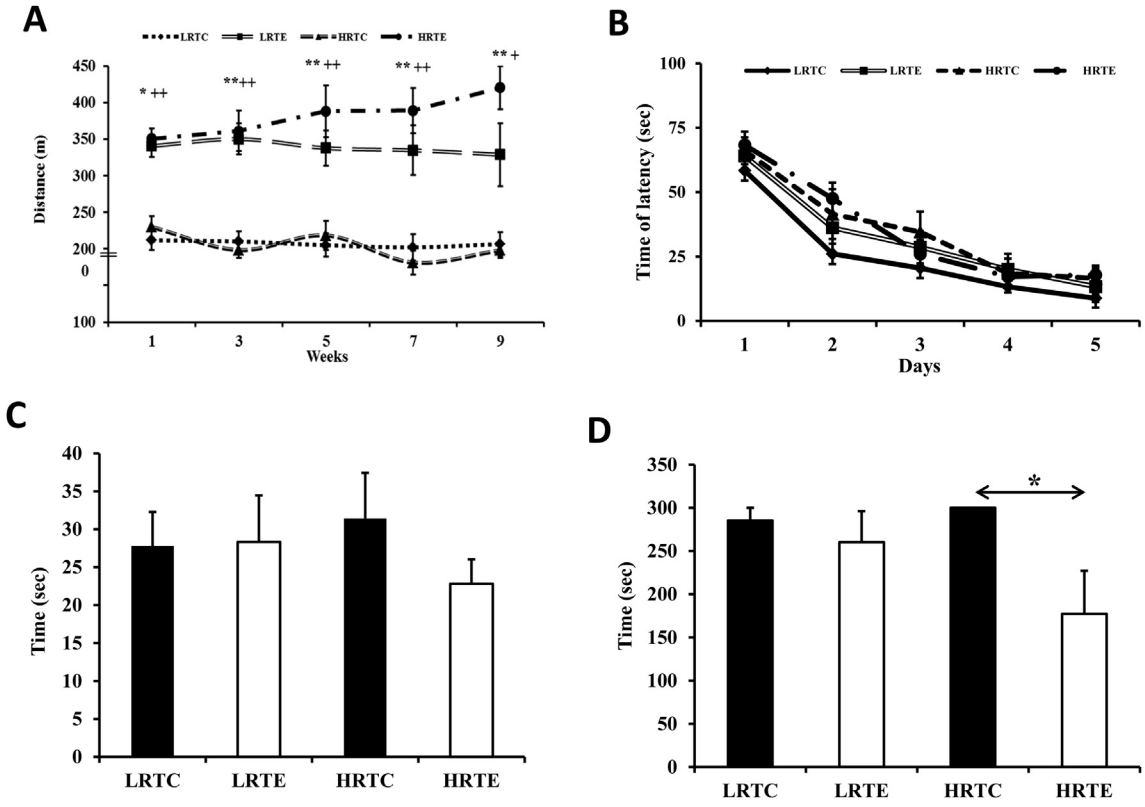

Fig. 1. Assessment of cognitive function prior and after training. Panel A shows the running distance of animals during the experimental period. Morris maze test (B), reverse Morris maze test (C) and passive avoidance test (D) were used to assess brain function. No significant difference in the time to find the hidden platform was found among the groups in Morris Maze test, while in the reverse test the HRTE rats found the platform in shorter time period than the HRTC rats ($p < 0.062$). In the fear-associated passive avoidance test, HRTC rats had a perfect performance, which was decreased after exercise training. The “y” access shows the time and the bars represents the mean ± SD time in which the animals entered the dark chamber. Low Response Trainers Control (LRTC) ($n = 6$), exercised LRT (LRTE) ($n = 7$), High Response Trainers control (HRTC) ($n = 6$) and exercised HRT (HRTE) ($n = 8$) groups. *$p < 0.05$ HRTC vs HRTE.