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Selection for aerobic capacity affects corticosterone, monoamines and wheel-running activity

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Abstract

A positive genetic relationship between aerobic capacity and voluntary exercise has been suggested from earlier studies of mice selected for increased wheel-running activity. To further investigate the relationship between aerobic capacity and exercise behavior, wheel-running activity was studied in female rats bidirectionally selected for intrinsic aerobic capacity (high capacity runners — HCR; low capacity runners — LCR). Aerobic capacity was measured using a forced treadmill paradigm; the subpopulations of animals used in this experiment exhibited a 471% difference in endurance capacity. Rats were housed individually, with or without access to running wheels. Wheel-running activity was recorded and analyzed from weeks two through seven during an eight-week trial to determine voluntary activity levels. HCR animals exhibited 33% greater total wheel-running distance per day compared to LCR rats (16,838.7 + 1337.30 m versus 12,665.8 + 893.88 m), which was due to the HCR rats exhibiting increases in both running speed and duration over LCR rats. Differences in the intermittency of wheel running were also observed. HCR rats engaged in more bouts of running per day than LCR rats, and trended towards running faster, for more time, and for longer distances during bouts of running than LCR rats. Following the running trial, measurement of plasma corticosterone concentration and striatal dopaminergic activity showed differences between HCR and LCR rats, suggesting a divergence of physiological systems that could potentially influence locomotor behaviors in these lines. These results are consistent with earlier work, and suggest an evolutionarily conserved relationship between physiological capacity and behavioral activity of exercise.

Keywords: Artificial selection; Correlated response; Endurance capacity; Voluntary exercise; Corticosterone; Dopamine

1. Introduction

The physiological capacity and motivational behavior to exercise are considered multifactorial traits, implying influence by genetic and environmental factors. As a result of the polygenic and pleiotropic features of these complex traits, it is likely that the associated genes could simultaneously affect two seemingly disparate traits. A genetic correlation between key physiological characteristics and the expression of behavior suggests shared or common mechanisms [1]. Human twin studies demonstrate that a substantial genetic component exists for both the ability to perform aerobic exercise [2] as well as a propensity to engage in exercise [3]. Whether a genetic correlation between one's level of aerobic capacity and tendency to exercise exists is unclear.

Animal models generated from artificial selection are tools that can be used to gain a better understanding of the genetic suite that forms the variation for complex traits [4,5]. The usual goal of selective breeding is to change the mean value of a trait in a defined population, compared to a control population. In theory, divergent artificial selection for a complex trait produces somewhat ideal genetic models because contrasting allelic variation segregates at the extremes from one generation to the next. In addition, the selection process often carries the phenotypic means for each line beyond the range of the extremes

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within the founder population [6]. By maintaining a high level of heterozygosity at each generation during selection, the main complement of allelic variants causative of trait difference is concentrated within each line. If gene overlap or pleiotropy is present, artificial selection for one trait can result in a correlated response to selection for other traits [4,7].

Over the past decade, large-scale artificial selective breeding has been used to develop two different models of physical activity in rodents [8,9]. In the first model, Swallow et al. [9] used voluntary wheel-running activity as a selection criterion to establish replicate lines of outbred mice (Hsd:ICR strain) that differed in voluntary exercise activity levels. After 10 generations of selection, high activity lines exhibited a 70% increase in wheel-running behavior (total number of ~1 meter revolutions run per day) relative to controls; [9]. High activity lines also differed in a variety of physiological traits compared to controls [10–13], including a 7% increase in maximal aerobic capacity (VO_2max) [12,14] , intermediate differences in skeletal muscle metabolism (indicated by elevated glucose uptake levels; [15], and increased mitochondrial and glycolytic enzyme levels [16]. Taken together, these results support an association between aerobic capacity and increased voluntary activity.

The second model, generated by Koch and Britton [8], resulted in lines of rats that diverged in untrained aerobic running capacity by using bidirectional artificial selection for forced treadmill running capacity on a widely heterogeneous N-NIH stock base population. After 10 generations, rats bred as low capacity runners (LCR) and high capacity runners (HCR) differed by 317% in treadmill running capacity [8]. The selected lines also diverged for VO_2max, economy of running, left ventricular cell contractility, and skeletal muscle oxidative enzyme activity [17].

Physiological responses to physical activity include the release of glucocorticoids such as corticosterone [18], which helps to stimulate the release of energy stores in the body, such as glycogen and fat, allowing the animal to exercise [19]. These hormones also initiate a psychological response to environmental stressors via receptors in a variety of brain regions such as the amygdala and hippocampus [20]. Blood plasma levels of corticosterone can provide information regarding an animal's level of stress, and also the extent of physical exertion [21]. Both acute and long term voluntary wheel running affect plasma concentrations of corticosterone [22,23], however previous data are not always in agreement (see [22]). Selective breeding for endurance capacity could have dramatic effects on resting or exercise induced plasma corticosterone levels due to the role of this hormone in the mobilization of energy, and maintenance of physical activity [19], and these changes could influence other physiological or psychological systems.

Previous studies have shown that central dopaminergic activity affects levels of wheel-running behavior [24]. For example, depletion of dopamine (DA) in the nucleus accumbens can lead to a decrease in the performance of energetically expensive activity [24], and the age related decreases in physical activity seen in many rodent species are associated with decreases in dopamine release and receptor expression in the forebrain [25]. Reciprocally, voluntary exercise can affect central dopaminergic activity. Treadmill running increases DA release and dopamine type-2 (D_2) receptor levels in the nucleus accumbens [24]. Dopaminergic activity in the striatum is also affected by physical activity, with reduced levels of striatal DA and D_2 receptor expression observed with decreases in physical activity, and increased levels of striatal DA following forced treadmill running [24]. Exercise mediated changes in neurotransmitter function also affect a variety of traits such as anxiety, depression, and motivational drive (reviewed by [26,27]). The effect of the striatal dopaminergic system on motivational drive is thought to play a role in determining an individual's endurance capacity [28]. Supporting this idea, mice selected for increased voluntary wheel-running behavior [9] not only experience an increase in aerobic capacity [14], but also exhibit an increased expression of the immediate early gene *Fos* in the striatum, indicating increased activity in this brain area [13].

The purpose of this study was to test the hypothesis that selection for aerobic capacity results in a correlated response in voluntary exercise activity, changes in corticosterone response to exercise, and altered dopaminergic activity in the striatum. Rats derived from the LCR and HCR colony were housed with or without running wheels for an eight-week period, and activity levels were recorded from weeks two through seven. Following this period, tissue was collected to analyze levels of plasma corticosterone and central dopaminergic activity. The data show a difference in voluntary activity levels between groups of rats bred for low and high intrinsic aerobic capacity. However, within selected lines, there is no association between aerobic capacity and level of voluntary activity. Microanalysis of wheel-running activity revealed behavioral differences in running periodicity between LCR and HCR rats. These two populations exhibit different corticosterone responses to 8 weeks of wheel running, with HCR animals exhibiting decreased levels of plasma corticosterone compared to LCR only after this running period. Additionally, HCR animals exhibited higher levels of striatal dopaminergic activity than LCR animals, but diverged in their response to running wheel access.

2. Materials and methods

2.1. Animals

A previous report gives a detailed description on the development of the rat models for aerobic exercise capacity [8]. In summary, bidirectionally selected lines were generated from a founder population of 80 male and 88 female N-NIH stock rats based on intrinsic aerobic treadmill running capacity. Thirteen families for each line were set up for a within-family rotational breeding paradigm. This schedule permits $<1\%$ inbreeding per generation to maintain a heterogeneous substrate within each selected line.

At each generation young adult rats (11 weeks of age) were tested for their inherent ability to perform forced speed-ramped treadmill running until exhausted. This test was performed daily over five consecutive days. The greatest distance in meters (m) achieved out of the five trails was considered the best estimate of an individual's aerobic exercise capacity [8]. The highest scored female and male from each of the thirteen families were