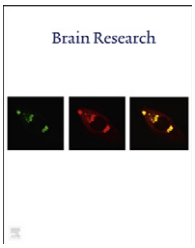
Available online at www.sciencedirect.com
SciVerse ScienceDirect
www.elsevier.com/locate/brainres



Research Report

Selection for increased voluntary wheel-running affects behavior and brain monoamines in mice

R.Parrish Waters[a,*], R.B. Pringle[b], G.L. Forster[c], K.J. Renner[b,c], J.L. Malisch[d], T. Garland Jr.[d], J.G. Swallow[e]

[a]Berlin Mouse Clinic, Charité University, Berlin, Germany
[b]University of South Dakota, Department of Biology, Vermillion, SD, USA
[c]Sanford School of Medicine, Vermillion, SD, USA
[d]University of California, Department of Biology, Riverside, CA, USA
[e]University of Colorado, Department of Integrative Biology, Denver, CO, USA

ARTICLE INFO

Article history:
Accepted 18 January 2013
Available online 23 January 2013

Keywords:
Artificial selection
Behavior
Dopamine
Motivation
Serotonin
Wheel-running

ABSTRACT

Selective-breeding of house mice for increased voluntary wheel-running has resulted in multiple physiological and behavioral changes. Characterizing these differences may lead to experimental models that can elucidate factors involved in human diseases and disorders associated with physical inactivity, or potentially treated by physical activity, such as diabetes, obesity, and depression. Herein, we present ethological data for adult males from a line of mice that has been selectively bred for high levels of voluntary wheel-running and from a non-selected control line, housed with or without wheels. Additionally, we present concentrations of central monoamines in limbic, striatal, and midbrain regions. We monitored wheel-running for 8 weeks, and observed home-cage behavior during the last 5 weeks of the study. Mice from the selected line accumulated more revolutions per day than controls due to increased speed and duration of running. Selected mice exhibited more active behaviors than controls, regardless of wheel access, and exhibited less inactivity and grooming than controls. Selective-breeding also influenced the longitudinal patterns of behavior. We found statistically significant differences in monoamine concentrations and associated metabolites in brain regions that influence exercise and motivational state. These results suggest underlying neurochemical differences between selected and control lines that may influence the observed differences in behavior. Our results bolster the argument that selected mice can provide a useful model of human psychological and physiological diseases and disorders.

Published by Elsevier B.V.

1. Introduction

Physical activity is central to the health and survival of an organism (Bouchard et al., 1994a, 1994b; Feder et al., 2010; Garland and Carter, 1994; Koch and Britton, 2001), and is influenced by an individual's propensity and ability to engage in exercise (Garland et al., 2011b). Selective-breeding experiments with laboratory mice (Swallow et al., 1998a) and rats (Koch and Britton, 2001) have demonstrated the heritability of both propensity and ability to exercise, and studies using each of

*Corresponding author. Fax: +49 30 450 539 937.
E-mail address: robert-parrish.waters@charite.de (R.Parris. Waters).

0006-8993/$ - see front matter Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.brainres.2013.01.033

these selective-breeding paradigms have provided evidence supporting a positive intrinsic (i.e., genetic) relationship between these traits (Swallow et al., 1998b; Waters et al., 2008b). Interestingly, several similar correlated responses have emerged in populations of mice selectively bred for increased voluntary wheel-running and rats selectively bred for treadmill endurance. These include parallel increases in voluntary wheel-running and treadmill endurance (Meek et al., 2009; Waters et al., 2008b), increased intermittency of wheel-running (Girard et al., 2001; Waters et al., 2008b), reduced body mass and body fat (Meek et al., 2009; Nehrenberg et al., 2009; Noland et al., 2007; Swallow et al., 1999, 2001), altered mitochondrial and glycolytic enzyme levels (Houle-Leroy et al., 2000; Walsh et al., 2006), altered muscle fiber phenotype (Guderley et al., 2006; Howlett et al., 2003), and changes in central monoamine activity (Mathes et al., 2010; Rhodes et al., 2005; Waters et al., 2008a). Some inconsistent correlated responses have also been reported, including increased baseline plasma corticosterone concentrations in selected mice of both sexes (Girard and Garland, 2002; Malisch et al., 2007, 2009), but not in selected female rats (Waters, 2007). Taken together, these selective-breeding programs demonstrate the intrinsic nature of exercise traits, and reveal some associations of exercise with other physiological and psychological traits.

The monoamine neurotransmitters dopamine (DA), norepinephrine (NE), and serotonin (5-hydroxytryptamine; 5-HT) play a role in mediating a wide range of behaviors, including adaptive and maladaptive responses to both appetitive (Koob, 1992, 2008) and noxious (Serafine et al., 2012) stimuli, aberrant behaviors associated with psychosis (Henn, 2011), and physical exercise (Dishman et al., 2006). A number of brain systems associated with physical activity utilize these neurotransmitters (Dishman, 2006, 2006; White-Welkley et al., 1996), and manipulating these neural systems can directly influence physical activity (Gainetdinov et al., 1999; Izenwasser et al., 1999; Uceyler et al., 2010, Rhodes et al., 2005). Reciprocally, physical exercise impacts central DA (Dishman et al., 2006), 5-HT (Greenwood et al., 2003, 2005) and NE (Dishman et al., 2006; Greenwood et al., 2005) systems. Given this close relationship, selective-breeding for traits that influence physical activity will likely impact these systems (Garland et al., 2011b).

The relationship between stress-related mental disorders, exercise, and central monoamines has major clinical importance. Animal studies demonstrate a strong ameliorative effect of voluntary exercise (such as wheel-running) on the long-term impact of intense and chronic stress exposure, and a wealth of evidence points toward monoamine systems being involved in this effect of exercise (reviewed in Novak et al. (2012)). As well, exercise is successfully utilized in clinical practice to treat stress-related mental disorders in humans (Blumenthal et al., 2007; Dunn et al., 2002, 2005). Thus, animals that differ in their intrinsic exercise abilities and habits will be important tools in advancing our understanding of the role that exercise can play in therapies for these mental disorders.

This utility is demonstrated in mice selectively bred for increased voluntary wheel-running activity. These animals exhibit heightened responses to both DA reuptake inhibitors (Rhodes et al., 2001), and DA type one (D_1) receptor antagonists (Rhodes and Garland, 2003); both these classes of drugs

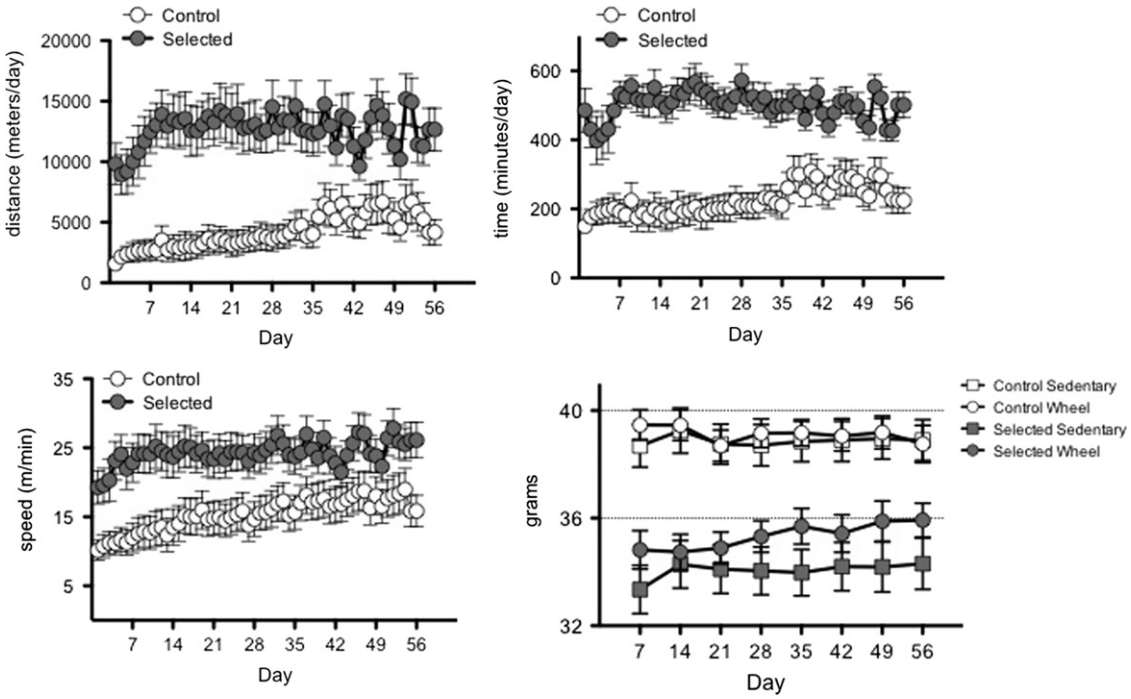


Fig. 1 – Wheel-running activity (distance, time, speed) and body mass of mice from selected and control lines over eight weeks, beginning at 96.5+1.4 days (mean+S.E.M.). Graphs illustrate daily means ± SEM (*n* = 12 selected and 12 control mice). Selected mice ran further than controls due to both increased duration and speed of wheel-running. Control mice consistently weighed more than selected mice throughout the study; presence of a running-wheel did not significantly affect body mass (means ± SEM).