Available online at www.sciencedirect.com

SCIENCE DIRECT®

Life Sciences 77 (2005) 2246–2261

Life Sciences

www.elsevier.com/locate/lifescie

Access to exercise and its relation to cardiovascular health and gene expression in laboratory animals

Natalie B. Schweitzer [a], Helaine M. Alessio [b,*], Ann E. Hagerman [c], Sashwati Roy [d], Chandan K. Sen [d], Szilvia Nagy [c], Robyn N. Byrnes [a], Ben N. Philip [a], Jane L. Woodward [b], Ronald L. Wiley [a]

[a] *Department of Zoology, Miami University, Oxford, OH 45056, USA*
[b] *Department of Physical Education, Health, and Sport Studies, Miami University, Oxford, OH 45056, USA*
[c] *Department of Chemistry and Biochemistry, Miami University, Oxford, OH 45056, USA*
[d] *Laboratory of Molecular Medicine, Department of Surgery, Davis Heart & Lung Research Institute, The Ohio State University Medical Center, Columbus, OH 43210, USA*

Received 16 November 2004; accepted 28 January 2005

Abstract

The interaction between genes and environment can influence cardiovascular disease (CVD). This 16 month study investigated if genes associated with cardiovascular (CV) regulation were expressed differently in animals having: 1) no access to physical activity or exercise (SED), 2) access to hour-long, twice weekly activity (PA), and 3) access every-other-day to a running wheel (EX). Out of 31,000 genes, a CV subset comprising 44 genes was investigated. Ten genes from this subset were expressed differently in EX compared with SED, and 34 genes were expressed differently in PA compared with SED ($p<0.05$). Total cholesterol (70 ± 8 vs. 101 ± 9 mg dl^{-1}), triglycerides (104 ± 8 vs. 127 ± 4 mg dl^{-1}), resting systolic blood pressure (130 ± 3 vs. 141 ± 3 mmHg), mean arterial pressure (110 ± 2 vs. 120 ± 2 mmHg) and heart rate (380 ± 6 vs. 405 ± 9 beats min^{-1}) were lower in EX compared with SED ($p<0.05$), but intracellular adhesion molecule levels did not differ among groups. Mean gene expressions for *Gja1, Fdft1, Edn1, Cd36,* and *Hmgb2* differed in animals according to access to physical activity. These genes play roles in heart rate, cholesterol biosynthesis, blood pressure, cell adhesion, and transcription and neurogenesis regulation, respectively. In

* Corresponding author. Tel.: +1 513 529 2707; fax: +1 513 529 5006.
E-mail address: alessih@muohio.edu (H.M. Alessio).

doi:10.1016/j.lfs.2005.01.036

conclusion, a total of 44 CV genes were expressed differently in SED compared to PA and EX; and SED showed more physiological evidence of CVD.

Keywords: Oxidative stress; Physical activity; Hypokinesis; Cardiovascular; DNA microarray; *Edn1*; *Hmgb2*; *Cd36*; *Gja1*; *Fdft1*

Introduction

Given the important interaction between genetics and environment, animal models pose an interesting paradox. Most animal studies use animals from the same genetic line, so genetics is controlled for in a way that most human studies usually are not. The environment in which most laboratory animals reside is also controlled in terms of type and amount of food and access to physical activity. A controlled environment may actually have some drawbacks, especially related to physical activity. That is because in natural settings, animals usually engage in physical activity such as exploration, foraging for food, or play (Sallis, 2000; McCarter et al., 1997; Ingram, 2000). In laboratory settings, animals are often sedentary and are fed ad libitum (AL). The combination of sedentary behavior and AL food places laboratory animals at risk for an early onset of adverse physiological events related to cardiovascular disease (CVD) (Keenan et al., 1999; O'Connor and Eikelboom, 2000; Bortz, 1982).

CVD is not a major cause of death in most rodent models. Nevertheless, laboratory rats do show signs and symptoms of CVD such as high blood pressure, hyperlipidemia, and diabetes (Bolego et al., 1999). It is well known that regular exercise improves CV function (Brown, 2003), in part by activating genes that encode components of contractile elements, metabolic pathways, and protein synthesis (Chen, 2001). Clusters of genes associated with CV energy metabolism and ischemia-reperfusion have been shown to change in an intensity-dependent manner (Boluyt et al., 2003; Iemitsu et al., 2003). Highly trained animals demonstrate healthier CV systems compared to less-trained animals. Nevertheless, even low-intensity running wheel exercise, if performed regularly, has been reported to have significant beneficial effects on blood lipid profile and resting blood pressure (Suzuki and Machida, 1995). Both acute and chronic exercise can modify gene expression of key components of cardiac function, including endothelin-1 (*Edn1*) (Iemitsu et al., 2003), atrial natriuretic peptide (*ANP*), and atrial myosin light chain (*aMLC*) (Diffee et al., 2003) which are associated with contractile function of the heart and vascular tone. Similarly, running wheel exercise increased levels of heat shock proteins (HSP) in cardiac tissue (Noble et al., 1999).

The benefits of both low and moderate intensity exercise on CV health and longevity have been reported in several large-scale human studies (Lee and Paffenbarger, 2000; Hakim et al., 1998; Paffenbarger et al., 1993; Blair et al., 1989). We used laboratory rats to investigate whether access to physical activity in a large box for 1 h, twice weekly would be adequate to elevate a sedentary status to a moderately active one, and thereby affect gene expression and/or physiological markers associated with CVD risk. We chose twice weekly activity in a large box to determine whether a minimal level of physical activity, similar to weekend activity among a human population, would mitigate the deleterious effects of a sedentary environment. We investigated the gene-environment interaction in rodents to learn whether some genes associated with CV regulation may be expressed differently in animals that resided