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Effects of leptin treatment and Western diet on wheel running in selectively bred high runner mice

Thomas H. Meek *,[1], Elizabeth M. Dlugosz, Kim T. Vu, Theodore Garland Jr.

Department of Biology, University of California, Riverside, Riverside, CA 92521, USA

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ABSTRACT

The role of leptin in regulating physical activity is varied. The behavioral effects of leptin signaling depend on the type of activity and the animal's physiological state. We used mice from lines selectively bred for high voluntary wheel running to further study how leptin regulates volitional exercise. Mice from four replicate high runner (HR) lines typically run ~3-fold more revolutions per day than those from four non-selected control (C) lines. HR mice have altered dopamine function and differences from C in brain regions known to be important in leptin-mediated behavior. Furthermore, male HR mice have been found to dramatically increase running when administered Western diet, an effect possibly mediated through leptin signaling. Male mice from generation 61 (representing three HR lines and one C line) were allowed wheel access at 24 days of age and given either Western diet (high in fat and with added sucrose) or standard chow. After four weeks, Western diet significantly increased circulating leptin, insulin, C-peptide, gastric inhibitory polypeptide, and inflammatory hormone resistin concentrations in HR mice (C mice not measured). Western diet increased running in HR mice, but did not significantly affect running in C mice. During the fifth week, all mice received two days of intra-peritoneal sham injections (physiological saline) followed by three days of murine recombinant leptin injections, and then another six days of sham injections. Leptin treatment significantly decreased caloric intake (adjusted for body mass) and body mass in all groups. Wheel running significantly increased with leptin injections in HR mice (fed Western or standard diet), but was unaffected in C mice. Whether Western diet and leptin treatment stimulate wheel running in HR mice through the same physiological pathways awaits future study. These results have implications for understanding the neural and endocrine systems that control locomotor activity, food consumption, and body weight, and how they may vary with genetic background.

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1. Introduction

Behaviors such as eating and engaging in volitional activity are regulated by a myriad of physiological and neurobiological interactions [1]. Eating and voluntary exercise also interact through their effects on homeostasis and by various direct mechanisms. In rodents, wheel access has been shown many times to increase food consumption, e.g. [2–5] although the effect does not always occur [6,7]. Severe underfeeding or food deprivation can result in substantial increases in locomotor activity, postulated to represent an increase in motivation for foraging behavior in mice and rats [8,9].

Different diets can have diverse effects on locomotor activity in rodents. However, determining to what extent variable effects are caused by different macronutrient compositions, the amount of energy ingested, differences among strains of rodents, changes in body mass or composition, or the type of locomotor activity measured has been challenging [3,10–13].

The role of leptin as an endocrine signaling molecule in both the periphery and central nervous system has become well-appreciated [14–16]. Many studies have focused on leptin's role in food consumption, thermoregulation, metabolic rate, and corresponding changes in body mass. Fewer studies have examined leptin's effect on physical activity, particularly voluntary exercise [17,18]. Both spontaneous physical activity (also known as non-exercise activity thermogenesis [NEAT]) and voluntary exercise can have large impacts on energy expenditure and consequently energy balance and body fat [19–21]. As both of these forms of activity can function as electively modifiable components of total energy expenditure, they may serve as major options for the treatment of obesity and many metabolic diseases.

To shed light on the role leptin may play in regulating levels of voluntary exercise, we studied mice from lines that have been selectively bred for high voluntary wheel running. Mice from the four replicate high runner (HR) lines typically run ~3-fold more revolutions per day than those from four non-selected control lines, and have evolved lower body size and lower body fat [22,23]. Circulating leptin

* Corresponding author. Tel.: +1 206 897 5286.
E-mail address: thmeek@uw.edu (T.H. Meek).
[1] *Present address*: 815 Mercer St., Department of Medicine, University of Washington Seattle, Seattle, WA 98109, USA.

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concentrations are also lower in some studies of HR mice [24] (see also [25,26]) and, interestingly, leptin is lower than predicted based on fat mass, at least in young adult females [24]. As a corollary, HR mice also have elevated food consumption [5], but still remain leaner than controls [27]. It is unknown whether depressed leptin concentrations play a part in the motivation for increased wheel running, are a result of high activity, or are a correlated response to selection that is unrelated to activity levels per se.

The heightened wheel running of HR mice involves neurochemical changes affecting motivation and reward. Dopamine transporter blockers (Ritalin, cocaine, GBR 12909), which increase function of dopamine, reverse hyperactivity on wheels in HR mice, with an increase or no change in C lines. This suggests reduced functionality of the dopamine receptors in HR mice. Specifically, HR mice are more sensitive to blocking D1-like receptors rather than blocking D2-like receptors [28–30]. When wheel access is denied, the caudate–putamen complex, prefrontal cortex, nucleus accumbens, and lateral hypothalamus have differential activity in HR as compared with control mice (measured immunohistochemically using c-Fos) [31]. Not only are these brain regions involved in voluntary locomotion and/or motivation, but the latter two, along with the mesolimbic dopaminergic system, are known to be important in leptin-mediated behavior [14,32].

None of a number of previously-tested pharmacological agents increased running in HR mice [30,33], but administration of a Western diet increased daily wheel running in HR mice up to 75%, with no change in control mice [27]. In that study, both control and HR mice gained substantial fat mass when fed Western diet, and presumably circulating leptin concentrations rose as well. Given that HR mice have changes in brain regions involved in leptin signaling, differences in baseline circulating leptin concentrations, and respond uniquely to Western diet, we investigated leptin's role in modulating wheel running, and determined if leptin's effects were consistent between different diets.

2. Materials and methods

2.1. Experimental animals

Mice from generation 61 of an ongoing selection experiment for high voluntary wheel running were used. The original progenitors of the colony were outbred, genetically variable Harlan Sprague Dawley mice: Institute for Cancer Research strain (Indianapolis, Indiana, USA). Eight closed lines were formed, four selected for high voluntary wheel running (based on days 5 and 6 of a 6-day test) and four bred without regard to running [34].

58 male mice from generation 61 were weaned at 21 days of age and housed with access to Harlan Teklad Laboratory Rodent Diet [W]-8604 until they reached 24 days of age. One control line and three of the four selected HR lines were represented in this study as our focus was on elucidating the HR phenotype. The excluded HR line (lab designation #6) was polymorphic for the mini-muscle phenotype (see below). Room temperature was maintained at ~73 °F and photoperiod was 12:12, with lights on at 0700 Pacific Time.

2.2. Experimental groups

At 24 days of age, all mice were singly housed with Wahman-type wheels (1.12 m circumference, 35.7 cm diameter, 10 cm-wide running surface) attached to standard cages (27×17×12.5 cm) (Fig. 1). Wheel running was recorded for 23 h each day with the final hour (1200–1300) used to reset the computers, check for any wheel malfunctions, and check the health of the animals. Half the mice received standard diet (SD) (Harlan Teklad Rodent Diet [W] 8604, 14% kJ from fat) and the other half received Western diet (WD) with similar concentrations of vitamin D (Harlan Teklad TD.88137 Western Diet, 42% kJ from fat with added sucrose; see [27] for details of diet composition). Every six days mice were weighed, body length (tip of snout to base of tail) was taken, while the mouse was held behind the neck, and apparent food consumption measured. Food consumption was determined as the difference in hopper mass between two time points, after accounting for any obvious wastage. Our standard chow food consumption values are in agreement with a previous study using these lines that, in the absence of bedding, sorted, dried, and weighed all uneaten food to account for wastage [35]. Because the diets differ in mass-specific energy content, we converted food consumption from grams to caloric intake, using total kJ of metabolizable energy of 12.98 and 19.01 per gram of wet mass for SD and WD, respectively [27].

In some cases, a pair-fed group would provide clearer evidence as to the effects of caloric intake on the phenotype of interest. However, with regard to wheel running, we chose not to have a pair-fed group because limiting food intake in rodents can have profound effects to increase wheel running a response that is believed to represent foraging behavior [8,9]. If so, then the effect would be distinctly different from that of Western diet, and could have a more confounding than clarifying effect.

2.3. Blood sample

A 130 μl blood sample was taken after mice had been in experimental groups for two weeks (42 days of age). Blood was acquired through the orbital sinus under isoflurane anesthesia. Blood was collected in non-heparinized microcapillary tubes. 1.1 μl of dipeptidyl peptidase IV inhibitor (EC 3.4.14.5, Millipore MO, USA), 2.5 μl of 0.05 M phenylmethanesulfonylfluoride dissolved in methanol, and 10 μl of Roche mini Complete serine protease inhibitor cocktail (Roche Diagnostics Mannheim, Germany) were added to whole blood and mixed thoroughly. Serum was collected after blood was centrifuged (Sorvall Legend Micro 17R) at 13,000 rpm for 10 min at 4 °C.

Hormones were assayed using a Milliplex Mouse Metabolic Magnetic Bead Panel MMHMAG-44K-14 (Millipore MO, USA) in a Luminex 200. Standards were plotted and concentrations determined using Milliplex Analyst software version 3.5.5. Due to the limited number of wells, and to ensure adequate sample sizes in HR lines, only the three HR lines had blood assayed (blood samples from control mice were not assayed).

2.4. Injections

Starting at 24 days of age, mice were given 3 weeks of uninterrupted wheel access to allow daily wheel running to plateau before injections began. Recombinant mouse leptin (R&D Systems, Inc.) was prepared by dissolving in physiological saline immediately prior to use. Mice were given 2 μg/g body mass 2 h before lights off via intraperitoneal (i.p.) injections. Each mouse received two consecutive days of sham (physiological saline) followed by three consecutive days of leptin treatment and six more days of sham injections (Fig. 1). The mass used to adjust injection volume was measured during the initial two days of sham injection. Accordingly, even though leptin treatment changed body mass, injection volumes of leptin did not change over the course of the experiment. Injection volumes ranged from 0.12 ml to 0.17 ml.

2.5. Dissections

Mice were dissected one day after the final sham injection (26 days after the blood sample). Body mass, body length, and food consumption were recorded. The mouse was skinned and its pelt weighed. The ventricles, liver, and triceps surae were then dissected and weighed. Different fat pad masses were also dissected and weighed, including the subscapular brown fat with the sub-scapular adipose tissue, epididymal fat, and retroperitoneal fat [36]. For analyses, “total fat” refers to the sum of all fat pad masses.

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