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Impact of genetic strain on body fat loss, food consumption, metabolism, ventilation, and motor activity in free running female rats☆

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HIGHLIGHTS

- Rodent model of wheel running is used to study mechanisms of obesity.
- Little is known on impact of genetic strain on metabolic response to exercise.
- Genetic strain affects efficacy of running on fat loss, food intake, ventilatory function, and motor activity.
- Long–Evans strain loses most fat during chronic wheel running.

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ABSTRACT

Chronic exercise is considered as one of the most effective means of countering symptoms of the metabolic syndrome (MS) such as obesity and hyperglycemia. Rodent models of forced or voluntary exercise are often used to study the mechanisms of MS and type 2 diabetes. However, there is little known on the impact of genetic strain on the metabolic response to exercise. We studied the effects of housing rats with running wheels (RW) for 65 days compared to sedentary (SED) housing in five female rat strains: Sprague–Dawley (SD), Long–Evans (LE), Wistar (WIS), spontaneously hypertensive (SHR), and Wistar-Kyoto (WKY). Key parameters measured were total distance run, body composition, food consumption, motor activity, ventilatory responses by plethysmography, and resting metabolic rate (MR). WKY and SHR ran significantly more than the WIS, LE, and SD strains. Running-induced reduction in body fat was affected by strain but not by distance run. LE's lost 6% fat after 21 d of running whereas WKY's lost 2% fat but ran 40% more than LE's. LE and WIS lost body weight while the SHR and WKY strains gained weight during running. Food intake with RW was markedly increased in SHR, WIS, and WKY while LE and SD showed modest increases. Exploratory motor activity was reduced sharply by RW in all but the SD strain. Ventilatory parameters were primarily altered by RW in the SHR, WKY, and WIS strains. MR was unaffected by RW. In an overall ranking of physiological and behavioral responses to RW, the SD strain was considered the least responsive whereas the WIS was scored as most responsive. In terms of RW-induced fat loss, the LE strain appears to be the most ideal. These results should be useful in the future selection of rat models to study benefits of volitional exercise.

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1. Introduction

Female rats housed in cages with running wheels will consistently run several kilometers per day, predominantly at night, leading to marked physiological adaptations compared to sedentary animals without access to wheels. This level of intense running activity leads to a variety of physiological, biochemical, and behavioral changes including marked loss in total body fat and body weight [1,21], improved cardiovascular response to stress [17], attenuation or reversal of symptoms of type 2 diabetes and metabolic syndrome [10,14].

Genetic strain is, of course, a crucial variable in essentially all biomedical research but relatively little is known on how strain affects the physiological response to running wheel training in rats. There have been some studies on effects of strain on overall running wheel performance and nightly patterns of activity [24]. Otherwise, there is apparently little work in this area.

Other than changes in diet, chronic exercise is considered to be the most effective means of countering the symptoms of metabolic syndrome [22]. There has been a marked increase in research that delves into the beneficial impacts of voluntary and forced exercise as

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compared to a sedentary life style using rodent models [2,14,19]. Hence, a better understanding of how genetic strain influences the physiological and behavioral responses to running wheel training would be of benefit. To this end, we performed a systematic assessment of the physiological and behavioral responses to voluntary running wheel training in five commonly used strains of female laboratory rats. Using non-invasive techniques to perform repeated longitudinal measurements of body composition as well as assessments of exploratory motor activity and ventilatory parameters, we summarize and rate responses as influenced by genetic strain.

2. Materials and methods

2.1. Animals

Female rats were acquired from Charles River Laboratory (LE, SD, and WIS) or from Harlan Laboratory (SHR and WKY) at 60 days of age and were maintained in AAALAC approved facilities, housed individually in polycarbonate cages (25 cm × 15 cm × 50 cm) containing laboratory-grade hardwood beta chips (Granville Mills, Creedmoor, NC). Food (Purina 5001) and water were provided ad lib food and water at an ambient temperature of 22 °C, 50% relative humidity, under a 12:12 light:dark cycle (lights on at 6:00 h). The rats had to be purchased from two different sources due to availability. These five strains were selected due to their widespread use in biomedical research.

2.2. Running wheels

The running wheel system consists of 40 separate wheels (Starr Life Sciences, Oakmont, PA). The wheels were made of stainless wire steel (33 cm diameter; 1.02 m circumference) that were positioned in a standard acrylic cage. Wheel revolutions were detected with a magnetic switch positioned near the wheel. The activity of the wheels was monitored and analyzed simultaneously for 40 wheels using Vitaview software (Starr Life Sciences). Rats had continuous access to the running wheel. Wheel activity occurred primarily during the dark cycle. Food pellets and water through a sipper tube were supplied through the top of the cage.

2.3. Body composition

Body composition for each rat was measured non-invasively using a Bruker LF90 II "minispec" body composition analyzer (Bruker Optics, Inc., Billerica, MA) nuclear magnetic resonance (NMR) system. All tests were run between 9:00 and 12:00 h. On each day of testing, a system quality control check was performed using a standard made of canola seeds with a fixed composition of fat, lean, and fluid components. Individual animals were then placed in a clear, plastic ventilated cylinder (8 cm diameter), closed at each end. The cylinder was placed into the bore of the instrument for approximately 1 min while the scan was completed. Measurements of fat, lean, and fluid mass (absolute and relative) were recorded for each animal (see Ref. [9]). Note that the lean parameter represents a measure of skeletal muscle and fluid mass is a measure of the water in liquid form (i.e., mostly blood volume) and does not include bound water. Body composition was measured in sedentary and active rats prior to the start of wheel training and retested following 3 and 6 weeks of wheel training.

2.4. Ventilatory parameters

A four chamber whole-body plethysmograph system using Buxco BioSystem XA software (Buxco Electronics, Wilmington, NC) measured minute volume, tidal volume, breathing frequency, and the enhanced pause (Penh), an index of airflow limitation and a surrogate for bronchoconstriction. All testing occurred between 7:30–9:30 h. Rats were placed in a plethysmograph and allowed 6 min to adapt prior to assessing the respiratory parameters. Sedentary and active rats were tested prior to the start of wheel training and then retested following 8 weeks of wheel training.

2.5. Horizontal and vertical activity

These parameters were evaluated in six rats simultaneously using a commercially made photocell device (Motron Electronic Motility Meter, Stockholm). All testing occurred between 07:30–1200 h. This is essentially a measure of exploratory motor activity of a rat placed in a novel environment. All animals were tested for 30 min per session. Sedentary and active rats were evaluated prior to the start of wheel training and following 6 weeks of training. Each system had a platform that housed a 5 × 8 matrix of 40 photodetectors that was illuminated by a single overhead incandescent (30 W) lamp. Any movement that occluded a photodetector was recorded as a horizontal activity count. A bank of six infrared LEDs and detectors was oriented in a horizontal plane approximately 16.5 cm above the platform. Interruption of one of these detectors was recorded as a vertical activity count. A Plexiglas chamber (33 × 21 × 26 cm) was placed over the platform to contain the rat and had a removable Plexiglas lid with holes for ventilation. Each device was housed in a larger light- and sound-attenuating ventilated chamber maintained at room temperature, and placed in a room dedicated to testing. Data were recorded using a Window PC programmed with MED-PC software and hardware (Med Associates, St. Albans VT).

2.6. Metabolism

Metabolic rate and respiratory quotient were measured in all rats prior to placement in the running wheels and after 7 to 10 weeks of training. Individual calorimeters (Oxymax, Columbus Inst., Columbus, OH) measured oxygen consumption, carbon dioxide production, and respiratory quotient. Respiratory quotient calculated from gas exchange on indirect calorimetery is used to study the relative contribution of different substrates to energy metabolism. The calorimeter chambers were made of clear plastic (length 30.4 cm, width 19 cm, height 19 cm) and had perforated plastic floors to allow feces and urine to drop through.

Fresh, dry air was pumped into each calorimeter at a controlled rate 2.0 L/min. The calorimeters were housed in the animal vivarium maintained at 22 °C. Food and water were withheld during testing. On the day of testing, each rat was placed in an individual calorimeter at 8:30 AM and remained undisturbed for 4 h. At the end of the session, the rats were returned to their home cages. Oxymax software provided a measure of heat production in kcal/h and respiratory quotient (termed respiratory exchange ratio by manufacturer of the calorimeter). Heat production was converted to basal metabolic rate in units of W/kg. The calorimeter was calibrated prior to the start of each experiment using a certified gas mixture standard of oxygen, carbon dioxide, and nitrogen.

2.7. Food consumption/water intake

Food consumption and water intake were determined in sedentary and active rats after 5 and 10 weeks of training in running wheels. The change in weights of the food bins and water bottles was determined before and after a 3 day period for each rat. Food consumption was expressed in terms of grams of food/kg body weight/day. Water intake was expressed in dimensions of ml/kg body weight/day.

2.8. Statistical analysis

The data were analyzed using one- or two-way analysis of variance (ANOVA) (Sigma Plot, ver. 13; Systat Software, San Jose, CA). Total running activity was assessed using one-way ANOVA with a post-hoc