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The Act of Voluntary Wheel Running Reverses Dietary Hyperphagia and Increases Leptin Signaling in Ventral Tegmental Area of Aged Obese Rats

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Key Words
Wheel running · Leptin · Aged obese rats

Abstract
To test the hypothesis that exercise increases central leptin signaling, and thus reduces dietary weight gain in an aged obese model, we assessed the effects of voluntary wheel running (WR) in 23-month-old F344×BN rats fed a 60% high-fat (HF) diet for 3 months. After 2 months on the HF diet, half of the rats were provided access to running wheels for 2 weeks while the other half remained sedentary. Following the removal of the wheels, physical performance was evaluated, and 4 weeks later leptin signaling was assessed in hypothalamus and VTA after an acute bout of WR. Introduction of a HF diet led to prolonged hyperphagia (63.9 ± 7.8 kcal/day on chow diet vs. 88.1 ± 8.2 kcal/day on high-fat diet (when food intake stabilized), $p < 0.001$). As little as 9 (ranging to 135) wheel revolutions per day significantly reduced caloric consumption of HF food (46.8 ± 11.2 kcal/day) to a level below that on chow diet (63.9 ± 7.8 kcal/day, $p < 0.001$). After 2 weeks of WR, body weight was significantly reduced (7.9 ± 2.1% compared with prerunning weight, $p < 0.001$), and physical performance (latency to fall from an incline plane) was significantly improved ($p = 0.04$). WR significantly increased both basal ($p = 0.04$) and leptin-stimulated ($p = 0.001$) STAT3 phosphorylation in the ventral tegmental area (VTA), but not in the hypothalamus. Thus, in aged dietary obese rats, the act but not the extent of voluntary WR is highly effective in reversing HF consumption, decreasing body weight, and improving physical performance. It appears to trigger a response that substitutes for the reward of highly palatable food that may be mediated by increased leptin signaling in the VTA.

Introduction

The prevalence of obesity among older adults has risen dramatically over the last two decades and is projected to continue to increase [1]. Obesity significantly increases risk for a number of conditions including insulin resistance, diabetes, increased cardiac risk, atherosclerosis, and stroke, which ultimately lead to impaired physical performance, sarcopenia, disability and premature death [2]. Thus, obesity presents a major health threat to the aging population. Weight loss therapy may be particularly

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important in obese elderly persons to improve physical function and independence, in addition to improving the medical complications associated with obesity.

Dietary obesity in adolescence and adults has been the subject of intense research, but diet-induced obesity has been largely ignored in the elderly. This is concerning because the appeal of palatable high-fat (HF) food may present as much or greater of a threat to the aging population as it does to the young. In fact, aged rats exposed to a HF diet exhibit a greater weight gain and disproportionally higher fat deposition compared to young counterparts. Whereas young rats respond to the HF diet with similar increases in both lean and fat mass, the aged rats accumulate 3 times as much fat as lean mass, and thus, may be more susceptible to obesity and obesity-induced disabilities [3].

Leptin is a critical hormone linking adiposity and food stores in the periphery to the energy homeostatic regulatory center in the brain by reducing food intake and increasing energy expenditure [4]. It is produced mostly in the adipose tissue and is secreted into the bloodstream in proportion to fat depots and in response to food intake. Leptin receptors are found in many areas of the brain, including the hypothalamus, a center of homeostatic regulation, and in the reward center (VTA of the mesolimbic system).

Leptin is a potent fat- and weight-reducing protein in young lean rodents. However, a state of leptin resistance within the brain develops with either diet-induced [5] or age-related obesity [6, 7]. Despite high serum levels, leptin fails to activate its receptors, reduce food intake, and increase energy expenditure. Restoring leptin responsiveness would be an effective approach to treat obesity; however, a strategy to overcome central leptin resistance is lacking.

Exercise is known to enhance leptin signaling in the hypothalamus of young animals [8–10]. Thus, it provides a rationale to examine the effectiveness of voluntary physical activity on central leptin signaling in an animal model of age- and diet-induced leptin resistance.

Research Design and Methods

Experimental Animals

Thirty-nine 23-month-old male F344 × Norway Brown rats, obtained from National Institute on Aging, were cared for in accordance with the principles of the Guide to the Care and Use of Experimental Animals. Rats were housed individually with a 12:12-hour light/dark cycle (07:00 to 19:00 h).

Experimental Design

Upon arrival, rats were fed a standard chow diet (Harlan Teklad 7912, 17% kcal from fat, 25% from protein, 58% from carbohydrates, 3.1 kcal/g) for 1 week. Rats were then switched to a HF diet (60% kcal from fat, 20% from protein, 20% from carbohydrate, 5.24 kcal/g, diet D12492, Research Diets, New Brunswick, N.J., USA), ad libitum. After 2 months on the HF diet, half of the rats were provided access to running wheels (n = 20) for 2 weeks while the other half remained sedentary (n = 19). Following the removal of the wheels, physical performance assessment and locked running wheels test were performed. Four weeks later, running wheels were provided to the previously sedentary rats for an overnight (18 h) period, followed immediately by assessment of leptin signaling. Rats from the other group, those previously WR and now sedentary, served as controls. An overnight period was chosen because this corresponded to earliest assessment of food consumption.

Wheel Running and Physical Performance

Voluntary WR and incline plane evaluation was assessed as previously described [9, 11].

Locked Running Wheels Test

On day 68, 6 rats in the previously sedentary group were introduced to running wheels while 6 other rats were introduced to the running wheels that were taped to prevent movement (locked wheels) for 24 h. Food intake and body weights were measured before and after the test (at 10 a.m., the usual time these measurements were taken throughout the experiment).

Acute Leptin Signaling

Rats were administered 4 μl of artificial cerebrospinal fluid (ACSF) or 2 μg of murine leptin (in 4 μl of ACSF) as previously described [12]. Rats were killed 45 min later and leptin signaling in the ventral tegmental area (VTA) and hypothalamus was assessed by STAT3 phosphorylation levels. This time point was chosen based the observation that PSTAT3 reaches its maximum between 30 and 60 min after leptin administration (data not shown).

Western Analysis

Hypothalamus and VTA were excised, processed and examined for total and phosphorylated STAT3 as previously described [13, 14].

Statistical Analysis

Data were analyzed by the two-way ANOVA. When the main effect was significant ($p < 0.05$), a Bonferroni post-hoc test was applied to determine individual differences between means.

Results

Response to HF Diet: Body Weight and Food Consumption

During the pre-experimental period, rats consumed 63.9 ± 7.8 kcal/day on the chow diet. Following the introduction of the HF diet, rats demonstrated the expected increase in caloric intake (158.2 ± 28.1 kcal/day) that

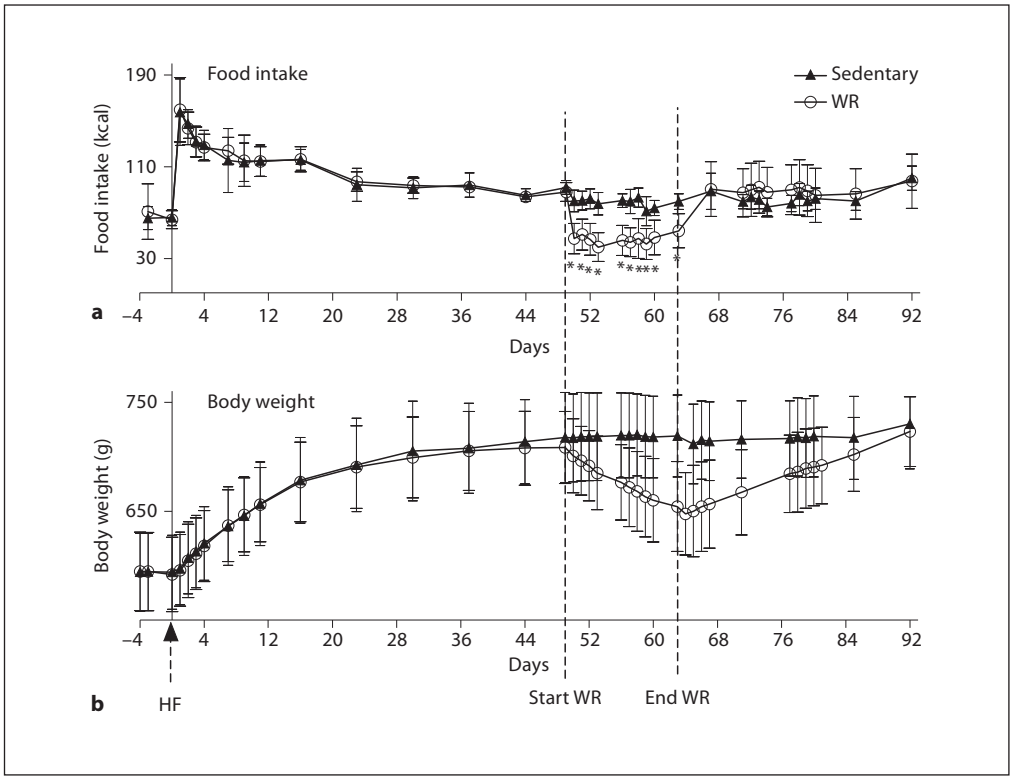

Fig. 1. Changes in HF food intake (**a**) and body weight (**b**) over 92 days in sedentary rats (closed triangles) and WR rats (open circles) over 2 weeks. Values represent the mean ± SE of 19 sedentary and 20 wheel-running rats. * $p < 0.001$ with t test starting on the first day of WR.

gradually normalized over a period of 3 weeks to a stable, but significantly elevated caloric intake (88.1 ± 8.2 kcal/day; $p < 0.001$) compared to that on chow (fig. 1a). Immediately before HF feeding, the average body weight of the rats was 594 ± 35.6 g. Upon the introduction of the HF diet, the rats steadily gained weight over the next 4 weeks reaching 710 ± 41.2 g. Body weight of sedentary animals was stable over the next 9 weeks until the termination of the experiment (fig. 1b, sedentary group).

Voluntary Wheel Running. The 26-month-old rats had nearly negligible levels of WR activity, ranging from 9 to 135 and averaging 62 ± 27 revolutions/day. Daily WR activity was stable over the 13-day period, except for the first day when the WR was higher (data not shown).

Response to Voluntary Wheel Running

Food Consumption and Body Weight. Introduction of running wheels caused an immediate 47.2 ± 12.7% reduction in food intake from 88.1 ± 8.2 to 47.5 ± 13.2 kcal/day. This reduced level of food consumption continued during the 2 weeks of WR (fig. 1a). Removal of the wheels restored food intake to the pre-running level. Following the introduction of the running wheels, the rats steadily lost weight and by the end of the 2-week WR period, body weight was reduced by 7.9 ± 2.1% compared with pre-running weight ($p < 0.001$, paired t test). Removal of the wheels resulted in a steady weight gain and by the end of 4 weeks, body weight merged with that of the sedentary counterparts (fig. 1b). There was no correlation between the amount of WR and the reduction in food intake ($p = 0.3$, $r^2 = 0.05$) or the amount of WR and the decrease in body weight ($p = 0.3$, $r^2 = 0.04$). Remarkably, even the rats that ran as little as 9 or 34 revolutions per day reduced their food intake by 46.7 and 51.7% and lost 8 and 8.5% of the initial body weight.

Physical Performance Assessment. After 2 weeks of WR, physical performance was examined by an incline plane test. Those rats with access to the running wheels ($n = 20$) demonstrated a significantly ($p = 0.04$) longer latency to fall from an inclined plane than their sedentary

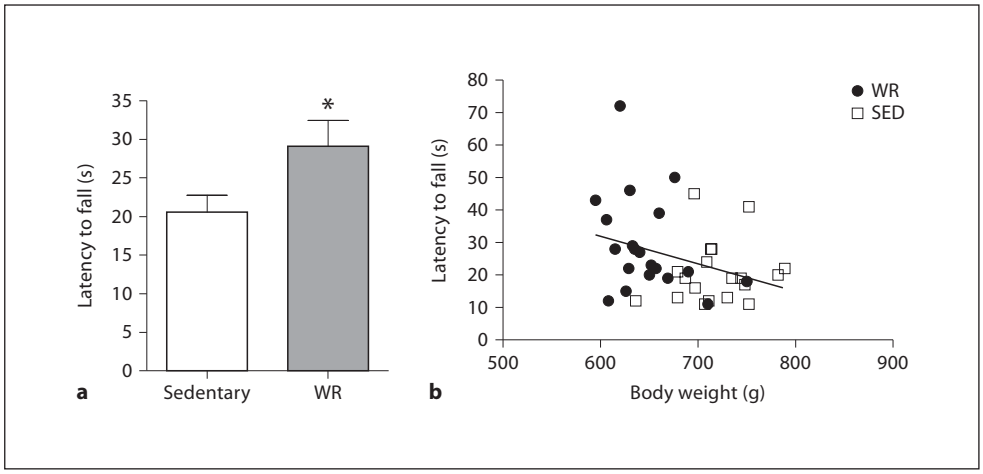

Fig. 2. Latency to fall (**a**) from an incline plane in rats that were wheel running for 2 weeks (n = 20) or were sedentary (n = 19). * p = 0.04 for difference from a wheel-running group by t test. **b** Correlation between latency to fall from an incline plane and body weight, p = 0.037, $r^2 = 0.112$.

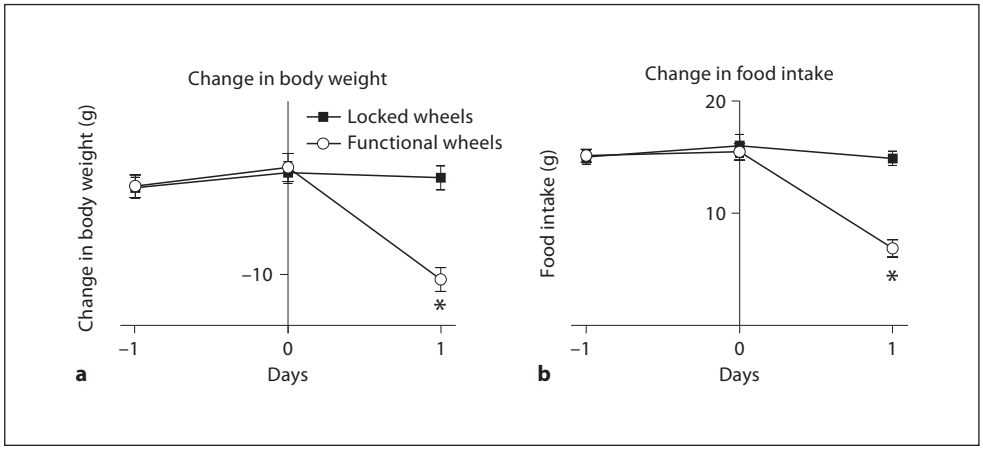

Fig. 3. Body weight (**a**) and food intake (**b**) changes in rats that were sedentary (days –1 and 0), then (day 1) provided functional running wheels, n = 6 (open circle symbols) or locked wheels, n = 6 (closed square symbols), * $p < 0.001$ with t test for both food intake and body weight changes.

counterparts (n = 19) (fig. 2a). Because body weight was less in the WR compared with the sedentary rats, we examined the relationship between latency to fall and body weight, and found a significant inverse correlation (p = 0.037, $r^2 = 0.112$, fig. 2b). In addition, comparison of the rats with similar body weights from WR and sedentary groups (n = 6 in each group) showed no difference in their physical performance (data not shown).

Locked Wheels Test. To address whether the introduction of the running wheels to the cages alone (as a novelty or a stress factor), as opposed to the act of running, affected either food consumption or body weight, we performed a locked wheels test in the previously sedentary rats. Only in the presence of functional running wheels was food consumption reduced and body weight diminished; the presence of locked wheels did not decrease food intake or body weight (fig. 3).

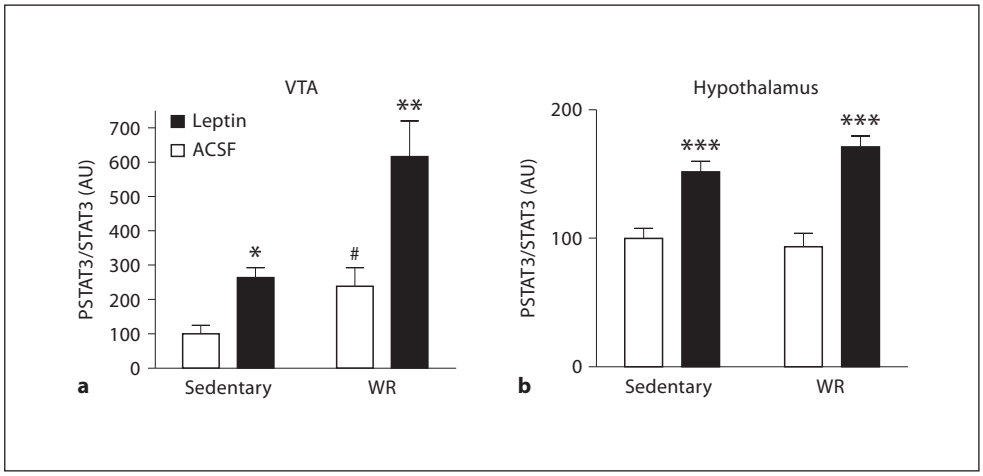

Fig. 4. Basal and leptin-stimulated protein levels of phosphorylated STAT3 in VTA (**a**) and hypothalamus (**b**) in sedentary rats and rats that were exposed overnight (18 h) to running wheels. Values represent the mean ± SE (n = 6). **a** $p = 0.0004$ for leptin stimulated compared to vehicle (ACSF) by two-way ANOVA. $p = 0.001$ for WR compared to sedentary by two-way ANOVA. * $p < 0.05$ for leptin stimulated compared to vehicle in sedentary rats by post-hoc analysis. ** $p < 0.05$ for leptin stimulated compared to vehicle in WR rats by post-hoc analysis. # $p < 0.05$ for WR compared to sedentary rats among ACSF treated rats by post-hoc analysis. **b** $p < 0.0001$ for difference with leptin by two-way ANOVA, *** $p < 0.001$ for leptin stimulated compared to vehicle by post-hoc analysis.

Acute Leptin Signaling

At day 93 of the HF feeding, acute leptin signaling was examined after an acute bout of WR. Running wheels were provided overnight to previously sedentary rats. The extent (102.0 ± 57.6 revolutions) of this acute overnight WR was similar to the level of WR observed on first day of previous wheel introduction on day 50 (146.2 ± 57.6). Status of phosphorylated-STAT3 (PSTAT3/total STAT3) signaling was assessed in the VTA and hypothalamus 45 min after an i.c.v. leptin administration. The average of total STAT3 was not different across groups (data not shown). In the VTA of sedentary animals, leptin produced a 2.6-fold increase in PSTAT3 compared with vehicle (ACSF), whereas with acute WR, the leptin-stimulated increase was greater than 6-fold over vehicle sedentary control (fig. 4a). In addition, acute WR increased basal levels of PSTAT3 (fig. 4a). This was in contrast to the results in the hypothalamus. Leptin administration resulted in a 1.5-fold increase of PSTAT3 in the hypothalamus compared with ACSF administration (fig. 4b). WR, however, did not have any additional effect on the PSTAT3 levels in the hypothalamus: it did not affect basal (nonstimulated), nor leptin-stimulated PSTAT3 levels (fig. 4b).

Discussion

The development of obesity is, by definition, characterized by energy intake exceeding energy expenditure. Therefore, it seems logical that increasing energy expenditure through physical activity should retard the development of obesity [15]. Exercise is an often recommended treatment for overweight and obesity. However, the consensus opinion concerning studies of the effectiveness of exercise in weight loss programs is that exercise alone (without caloric restriction) is largely ineffective for weight loss [16]. In humans, moderate intensity exercise is necessary for the prevention of weight gain [17], whereas only intensive exercise, sufficient to produce high levels of energy expenditure, is associated with a reduction in body weight [18–20]. Similarly, in rats , mild voluntary exercise alone is not sufficient to reduce or prevent dietary weight gain in young obese animals; WR did not affect weight gain in 5-month-old HF-fed obese Sprague-Dawley rats [9].

The American College of Sports Medicine recommends that adults participate in at least 150 min/week of moderate-intensity physical activity to prevent significant weight gain and reduce associated chronic disease risk factors [21]. However, adoption and maintenance of the high and even moderate levels of exercise, especially

for older obese adults may be challenging and not feasible. Moreover, obesity contributes to disability further preventing participation in exercise activities. Strategies to reduce body weight may be particularly important in obese elderly persons to improve physical function and independence.

The results presented in this study demonstrate that very small amounts of voluntary WR, as little as 9 revolutions per day, were effective in significantly reducing body weight by approximately 8.5% in HF-fed aged obese rats. Of the two potential contributors to the weight loss (i.e. energy intake and energy expenditure), the latter was unlikely to play an important role since such a small amount of physical activity would not be sufficient to produce a negative energy balance. Food intake, however, was substantially affected by WR in aged obese rats by nearly 50%. This dramatic reduction in food intake was considerably more than in a previous study with WR in young lean rats [9]. In those chow-fed young lean rats, WR decreased food intake to a smaller extent, 20–21% and for a much shorter time. In addition, the decrease in food consumption in young rats [9] peaked on the first day and quickly returned to the pre-WR levels within one week [9]. In contrast to the food consumption, the WR-induced decrease in body weight was similar in the aged obese animals in the current experiment and the young lean animals in the previous study [9]. However, the WR activity of the young animals was much higher, 4,167 ± 1,091 revolutions/day, and, more importantly, the body weight reduction was directly correlated with the extent of WR [9]. In contrast, there was no correlation between body weight change and WR activity in old rats. This suggests in young rats the extent of WR was causative in the reduction in body weight, whereas in aged rats, the mere act of wheel running, independent of the extent, was sufficient to induce a similar amount of body weight loss.

A more direct comparison to the present study were the results from the HF-fed young rats in our previous study [9]. Those diet-induced, obese young rats ran 5-times less than their lean counterparts, and accordingly, WR had no effect on food intake or body weight [9]. Moreover, their level of WR (865 ± 265 revolutions/day) was still much more than WR in the aged diet-obese rats in the present study (62 ± 27 revolutions/day). Thus, a small amount of WR in HF-fed *aged* rats counteracts HF food consumption and reduces body weight, whereas greater amounts of physical activity in HF-fed young rats are without these beneficial effects.

The dramatic decrease in HF food intake in aged obese rats in this study immediately followed the introduction of the running wheels. This lower level of caloric intake was sustained during the period of WR and returned to the pre-WR level of caloric intake of HF diet when the wheels were removed. Importantly, there was no correlation between the amount of WR and reduced food intake. The locked wheels test indicated that the decrease in food intake was not due to the presence of wheels in the cages, it occurred only when the rats could run in the wheels. These data indicate that it is the act of WR rather than the amount of WR that triggered the decrease in food consumption. Moreover, the rather large decrease in food intake coupled with the very low levels of WR suggests that it is the reduction in food intake that underlies the weight loss and not the extent of WR. Although the degree of WR seems unimportant to the outcome, the act of WR is necessary to trigger the sequence of events that leads to diminished food consumption.

The idea that the act of WR rather than the extent of WR is more important is also supported by the physical performance data. The extent of exercise would be expected to increase physical performance and physical performance was increased in the WR group; however, this increase was more related to body weight than WR. Thus, the increase in physical performance is likely secondary to the WR-initiated decrease in body weight rather than the exercise-mediated increase in muscle performance.

HF diet is a highly palatable and rewarding food. Positive reinforcement of HF feeding can lead to caloric intake beyond caloric needs. In addition to the hyperphagia that follows the introduction of HF food, a new baseline of caloric consumption is maintained that is significantly greater than the calories consumed on a chow diet. WR is known to represent a natural reward [22–24] and displays features in common with other rewarding behaviors, such as eating [25] or drug abuse [26]. We suggest that in aged rats, the act of WR substitutes for the reward properties of highly palatable HF food. When the running wheels are removed, caloric intake resumes at the elevated level typical of high fat feeding.

The VTA, a group of neurons located close to the midline on the floor of the midbrain, is the origin of dopaminergic cell bodies that comprise the mesocorticolimbic dopamine system, and is widely implicated in the reward circuitry of the brain. Although energy homeostasis research has concentrated primarily on the role of the hypothalamus, the central nervous system circuitry of reward is another area that plays an important role in food selection and consumption [27].

Leptin receptors are expressed in the VTA [28] and leptin action on VTA dopamine neurons is suggested to modulate food intake by altering the motivation to consume or the incentive value of certain foods [29]. Recent evidence identified leptin action in the VTA to curb both HF food consumption and decrease sensitivity to sucrose consumption [30]. However, central leptin responsiveness declines with age, and this has been associated with diminished leptin receptor signaling in the hypothalamus [6]. Although the present report did not directly examine leptin signaling with age in the VTA, arguably leptin signaling may decline in the VTA with age in parallel to the hypothalamus. Thus, one mechanism by which exercise may curb HF food consumption in aged rats is through enhancing leptin function in the VTA. Several reports [8, 10] suggested that exercise is associated with increased leptin signaling, and we reported that long-term WR is associated with increased hypothalamic STAT3 phosphorylation in diet-induced obese young rats [9]. In the present study, acute WR increased both basal and leptin-stimulated STAT3 phosphorylation specifically in the VTA.

Whether this increase in signaling is causative for the observed physiology is uncertain. The increased PSTAT3 signaling in the VTA was assessed some 18 h after the initiation of WR, thus could either be the cause or the consequence (or neither) of the diminished food consumption. Resolution of this issue requires further investigations.

Since there was both an increase in basal STAT3 and leptin-mediated STAT3 phosphorylation, factors other than leptin may mediate the increased STAT3 signaling. STAT3, a member of the STAT family, is activated in response to various cytokines and growth factors in addition to leptin. Thus, the WR-associated increase in basal PSTAT3 in this study could be due to any one of the neuropeptides that signal through STAT3, especially those that modify food intake. Cytokines associated with regulation of food intake and energy homeostasis that can activate STAT3 include the ciliary neurotrophic factor, tumor necrosis factor-α and leptin. Additional experimentation is necessary to distinguish between these possibilities.

Our study demonstrates that in aged diet-obese rats, low-intensity exercise is very effective in reducing consumption of highly palatable HF food, resultant body weight loss and increasing physical performance. An almost negligible amount of voluntary physical activity resulted in significant physiological changes that were not observed in similarly fed young obese rats (from previous study [9]). The act of WR resulted in reversal of HF-induced hyperphagia in aged rats, while low-intensity WR in young animals [9], though higher than in old, did not alter food consumption. This suggests that the threshold level for the beneficial effect of WR may be lower in aged versus young animals. Other studies support this finding; there is a greater sensitivity to low-intensity exercise for preservation of bone mass [31], for the reversal of age-associated decline in muscle mass and contractile function [32], and for the reversal of age-related decrement in oxygen debt and exercise efficiency [33].

In conclusion, in an aged dietary obese rodent model, merely the act of WR, unrelated to the amount of WR, increases leptin signaling in the VTA, and is very effective and, in fact, more effective than in young obese rats in reducing HF diet intake and body weight. The act of WR appears to be a more favored activity substituting for the consumption of a palatable HF food, and the mechanism may involve increased leptin signaling in the VTA.

Acknowledgements

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