International Journal of Obesity (2006) 30, 722–727
 0307-0565/06 $30.00
www.nature.com/ijo

ORIGINAL ARTICLE

Differential effects of exercise on body weight gain and adiposity in obesity-prone and -resistant rats

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Objective: To determine the effect of exercise on weight gain and adiposity in obesity-prone and -resistant rats.
Design: Body weight gain, fat pad weights, food intake, plasma leptin and insulin levels were assessed in outbred male Sprague–Dawley rats, which remained sedentary or were given unrestricted access to running wheels either before or after they developed diet-induced obesity (DIO) or diet-resistance (DR) on a high energy (HE; 31% fat) diet.
Results: When fed a low fat (4.5%) chow diet, rats which would later develop DIO ($n=6$) after 3 weeks on HE diet ran the same amount as DR rats ($n=6$). Other rats were first made DIO ($n=12$) or DR ($n=12$) after 10 weeks on HE diet and then either kept sedentary or given running wheels for 4 weeks on HE diet. DIO and DR rats ran comparable amounts but only the DIO rats reduced their body weight gain, fat pad relative to body weights and plasma leptin levels significantly, compared to their sedentary controls. Exercise had no effect on food intake in either DIO or DR rats but reduced feed efficiency (weight gain/caloric intake) in both.
Conclusion: Although DIO and DR rats ran similar amounts, the greater reduction in body weight gain and adiposity of exercising DIO rats suggests that they are more sensitive to some metabolic or physiologic system that prevents them from increasing their intake sufficiently to compensate for their net reduction in energy stores.
International Journal of Obesity (2006) **30,** 722–727. doi:10.1038/sj.ijo.0803192; published online 10 January 2006

Keywords: diet-induced obesity; fat pads; insulin; leptin; food intake

Introduction

The recidivism rate in the long-term treatment of human obesity is high. Most weight-reduced obese subjects replace lost weight within a few months to years.[1,2] Similarly, weight-reduced obese rats quickly regain lost weight when allowed free access to food.[3–6] Weight regain in humans[7,8] and rats[9] may be partly attributable to the chronic reduction in resting metabolic rate associated with such weight loss. Some humans who successfully maintain their weight loss engage in high levels of exercise.[10] In rats, exercise is uniformly associated with a reduction in body weight gain and carcass adiposity.[11–16]

The model of diet-induced obesity (DIO) has many features in common with human obesity[17] and might potentially serve as a good model to study the effects of exercise on body weight regulation. In outbred Sprague–Dawley rats, approximately half become hyperphagic and develop DIO, whereas the rest are diet-resistant (DR) when fed a diet of moderate fat and energy content (high energy (HE) diet; 31% fat).[18,19] These two phenotypes are actually genetically separable substrains with regard to the development of obesity.[20,21] Here, we used outbred Sprague–Dawley rats to assess the effects of voluntary wheel running exercise on the regulation of energy homeostasis in DIO vs DR rats. Based on data from other rodent models of exercise-induced weight loss,[22,23] we postulated that voluntary exercise would reduce both body weight gain and adiposity selectively in DIO rats.

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Received 19 August 2004; revised 21 February 2005; accepted 24 February 2005; published online 10 January 2006

Methods (Experimental)

Animals and diet
Animal usage was in compliance with the animal care committee of the E Orange VA Medical Center. Outbred

male Sprague–Dawley rats (Charles River Labs) entered the vivarium at 8 weeks of age. They were singly housed and fed Purina rat chow (#5001) and water *ad libitum* on a 12:12 light–dark schedule with lights out at 1800 hours. Purina rat chow contains 3.30 kcal/g with 23.4% as protein, 4.5% as fat and 72.1% as carbohydrate, which is primarily in the form of complex polysaccharide.[24] At specific points in both the studies described below, rats were switched to HE diet. This is a defined diet (Research Diets #D12266B, New Brunswick, NJ, USA), which contains 4.47 kcal/g with 21% of the metabolizable energy content as protein, 31% as fat and 48% as carbohydrate, 50% of which is sucrose.[24]

Relationship between running and the development of DIO
We predicted that chow-fed DIO-prone rats might have lower levels of spontaneous running wheel activity than DR rats prior to the development of obesity. To test this hypothesis, 10 weeks old chow-fed Sprague–Dawley rats ($n=16$) were given continuous access to running wheels placed in their home cages (MiniMitter). Their running activity was monitored continuously and recorded as a cumulative number of revolutions at 5 min intervals. Rats were allowed access to the wheels for 1 week and gained a relatively stable baseline running rate after 3–5 days. During their last 24 h in the wheels, cumulative activity was recorded for statistical comparisons. The wheels were then removed and all rats were switched to HE diet for 3 weeks. At the end of this period, the six highest and six lowest weight gainers were retrospectively identified as DIO and DR, respectively. Food intake and body weight gain were monitored at 3–4 days intervals over the entire course of the experiment. After 3 weeks on HE diet, rats were decapitated and the fat pads (epididymal, retroperitoneal, perirenal and mesenteric) were removed and weighed.

Effect of exercise on body weight, fat mass, plasma leptin and insulin levels
A group of 30 male Sprague–Dawley rats were fed HE diet for 10 weeks beginning at 10 weeks of age. The 12 highest and 12 lowest weight gainers were retrospectively identified as DIO and DR, respectively. Rats of each weight gain phenotype were randomized by body weight, continued on HE diet and half of each group ($n=6$/phenotype) was given continuous access to running wheels placed in their home cages for 4 weeks. The remaining rats remained sedentary during this time ($n=6$/phenotype). Body weight was monitored at weekly intervals throughout. After 4 weeks, the running wheels were removed at dark onset and the rats were killed by decapitation between 0800 and 1100 hours, the next day. Trunk blood was collected for plasma leptin and insulin assays and fat pads were removed and weighed. Plasma leptin and insulin levels were assayed by radioimmunoassay (Linco) as indices of total carcass adiposity[25] and insulin sensitivity,[26] respectively.

Statistics
Body weight gain, food intake, plasma leptin and insulin measures were compared among various groups by one way analysis of variance (ANOVA) for Experiment 1 and by two way ANOVA for Experiment 2 with *post hoc* Bonferroni comparisons when significant differences were found. Feed efficiency (amount of weight gained relative to caloric intake) was calculated as the gain in body weight (g)/food intake (kcal) over a specified period of observation. Correlations between body weight gain, food intake and feed efficiency vs running over the last 3 days of running in chow-fed rats in Experiment 1 was carried out using Pearson's correlation coefficient.

Results

Wheel running as a predictor of DIO
When chow-fed rats were given access to running wheels for 1 week running rates stabilized by the last 3 days of the week such that there was a 4–7% variance across these days for the group as a whole. Nevertheless, the individual rates of running were highly variable such that during the last 24 h of the 1-week exposure ranged from 378 to 4623 revolutions per 24 h. We had predicted that DIO-prone rats might run less than DR rats. However, when the six highest and six lowest weight gainers were retrospectively identified as DIO and DR rats after 3 weeks on HE diet, respectively, there were no differences in the running rates over the last 3 days between the groups (Table 1). Also, there was no correlation between the amount of running over these 3 days, when rats were fed chow and subsequent weight gain on HE diet. Neither was there a correlation between food intake or feed efficiency (weight gain (g)/food intake (kcal) $\times$ 1000) on chow and the amount of running during the last 3 days of wheel exposure. As expected, on HE diet, sedentary DIO rats ate 14% more and gained 45% more body weight than DR rats. This was associated with a 26% greater feed efficiency and 32–79% heavier individual adipose depots. Total weights of the four depots were 50% heavier in DIO than DR rats (Table 1).

Effect of exercise on body weight, fat pad weight, plasma leptin and insulin levels
In this experiment, 30 rats were fed HE diet for 10 weeks beginning at 10 weeks of age. The 12 highest and 12 lowest weight gainers were retrospectively identified as DIO and DR, respectively (Figure 1, Table 2). When assigned in this way, DIO rats gained 25% more weight than DR rats over this period and were 10% heavier than DR rats at the end of this period. Half of each of the DIO and DR rats were then provided with continuous access to running wheels for 4 weeks, while the rest were left sedentary. During this period, DIO and DR rats had similar running rates although, again, there was enormous interanimal variability. Average

Table 1 Body weight gain, food intake, feed efficiency, fat pad weights and wheel running in outbred DR and DIO rats ($n=6$/group)

	DR	*DIO*
Weight gain – chow sedentary (g)	26.2±4.5	26.2±3.8
Weight gain – chow exercise (g)	23.8±6.4	14.8±6.0
Weight gain – HE sedentary (g)	102±3	148±9*
Final body weight (g)	599±5	639±12*
Food intake – chow sedentary (kcal/day)	91.8±4.2	97.5±1.6
Food intake – chow exercise (kcal/day)	89.2±2.9	82.7±3.9
Food intake – HE sedentary (kcal)	112±2.6	128±3*
Feed efficiency – chow sedentary (g/kcal) $\times 10^3$	40.2±7.7	38.8±5.6
Feed efficiency – chow exercise (g/kcal) $\times 10^3$	37.8±9.4	26.0±10.6
Feed efficiency – HE sedentary (g/kcal $\times 10^3$)	43.5±1.4	54.8±3.1*
Revolutions/24 h	1185±235	1173±198
Epi (g)	12.5±1.3	16.5±0.9*
RP (g)	12.2±0.8	17.9±2.2*
PR (g)	2.9±0.3	5.2±1.0*
Mes (g)	8.9±0.7	14.4±0.7*
Total fat pads (g)	36.0±2.5	54.0±4.0*

Sedentary outbred male Sprague–Dawley rats (400–425 g; $n=16$) were fed chow for 1 week (chow sedentary) and then given continuous access to running wheels in their home cages for 1 week (chow exercise). Running was calculated as the average number of revolutions per 24 h over the last 72 h of exposure to the wheels. The wheels were removed and then rats were fed HE diet for 3 weeks (HE Sedentary). DIO and DR rats were identified retrospectively as the six highest and six lowest weight gainers on HE diet, respectively. Feed efficiency is the amount of weight gain (g)/food intake (kcal) over the defined period $\times 1000$. Epi = epididymal fat pad; RP = retroperitoneal fat pad; PR = perirenal fat pad; Mes = mesenteric fat pad; total fat pad – weight of all four pads. Data are mean±s.e.m.; *$P=0.05$ or less when a given parameter in DIO rats was compared to DR rats.

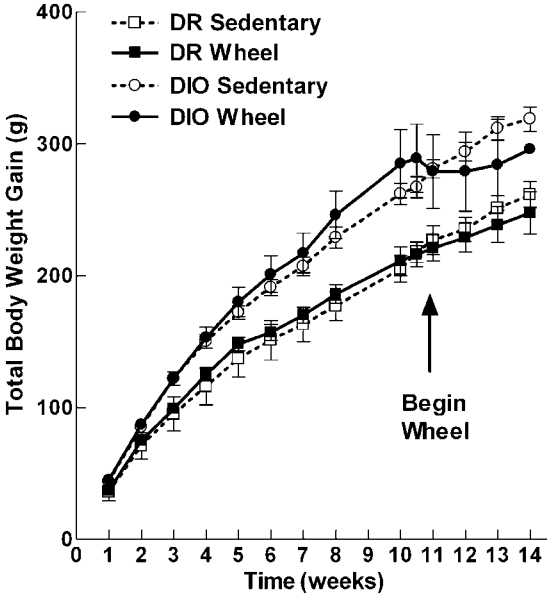

Figure 1 Outbred male Sprague–Dawley rats ($n=30$) were fed high-energy (HE) diet for 10 weeks beginning at 10 weeks of age. At that time, the 12 highest weight gainers were designated as diet-induced obese (DIO) and the 12 lowest weight gainers as diet-resistant (DR). Half of each phenotype was provided with running wheels in their home cages whereas the remaining rats remained sedentary for 4 weeks ('Wheel'). *$P=0.05$ when body weight gain between sedentary and exercising (wheel) DIO rats were compared by *post hoc t* test after repeated measures ANOVA showed a significant intergroup difference in weight gain over the last 4 weeks period. By definition, DIO and DR rats differed significantly in weight gain over the initial 10 weeks on HE diet.

Table 2 Body weight, fat pad weight, wheel running, plasma leptin and insulin levels in DR and DIO rats

	DR sedentary	*DR exercise*	*DIO sedentary*	*DIO exercise*
Initial body weight (g)	352±5	345±5	346±4	353±6
Body weight at 10 weeks sedentary (g)	578±15^a	566±11^a	628±10^b	632±32^b
Final body weight (g)	619±12^a	591±15^a	673±9^b	654±25^b
10 weeks weight gain Exercise/sedentary (g)	227±11^a	221±10^a	281±8^b	280±10^a
4 weeks weight gain Exercise/sedentary (g)	49.3±7.5^a	30.6±8.1^{ab}	59.9±4.4^a	22.1±4.3^b
4 weeks food intake Exercise/sedentary (kcal)	2374±90^a	2265±95^a	2554±78^b	2509±84^b
4 weeks feed efficiency exercise/sedentary (g/kcal $\times 10^3$)	20.8±3.3^a	13.8±2.1^b	23.7±3.1^a	8.8 ±1.4^c
Revolutions/24 h		673±159^a		887±443^a
Epi (g)	16.8±1.3^{ab}	14.2±1.2^a	21.6±1.5^b	17.3±1.2^{ab}
RP (g)	16.8±2.1^{ab}	14.1±1.2^a	21.0±1.9^b	14.1±1.2^a
PR (g)	4.1±0.5^a	4.2±0.4^a	5.5±0.4^b	3.8±0.3^a
Mes (g)	13.9±1.5^{ac}	8.8±0.7^b	17.4±1.6^c	11.1±1.1^{ab}
Total fat pads (g)	51.5±4.8^a	41.3±3.2^b	65.4±3.1^c	46.4±5.4^{ab}
Total fat pad weight/body weight (%)	7.6±0.4^a	6.5±0.3^a	10.3±0.2^b	6.5±0.3^a
Leptin (ng/ml)	19.1±1.5^a	16.8±2.2^a	26.2±1.2^b	21.3±1.4^a
Insulin (ng/ml)	1.71±0.37^a	1.35±0.12^a	2.95±0.35^b	2.53±0.31^b

Outbred male Sprague–Dawley rats ($n=30$) were fed HE diet for 10 weeks beginning at 10 weeks of age (Body weight 10 weeks Sedentary). DIO and DR rats were identified retrospectively as the 12 highest and 12 lowest weight gainers on HE diet, respectively. Half of each phenotype was given access to running wheels in their home cages and the other half remained sedentary for the next 4 weeks on HE diet. Data are mean±s.e.m. Data with differing superscripts differ from each other by $P\leqslant 0.05$ by *post hoc* Bonferroni test after ANOVA showed significant intergroup differences. Abbreviations are the same as in Table 1.

running over the last 24 h in the wheel varied from 301 to 2205 revolutions, irrespective of weight gain phenotype (Table 2). Overall, exercising rats gained less weight over the 4 weeks of wheel running than their sedentary counterparts ($F[1,20]=18.8$; $P=0.001$). While there was no phenotype-specific difference in weight gain over this 4 weeks period by ANOVA, the exercising DIO rats had a significant 63% reduction in weight gain, while DR rats had a nonsignificant

38% reduction in weight gain compared to their respective sedentary controls (Table 2). Importantly, there was no correlation between the total number of revolutions run over the 4 weeks period and the amount of body weight gained for either DIO or DR rats.

There was a great deal of variability in the effect of exercise on individual fat pads weights (Table 2). Overall, DIO rats had the heaviest total of four adipose depot weights ($F[1,20] = 7.03$; $P = 0.015$), but this was due entirely to the fact that sedentary DIO rats had 27–58% heavier pad weights than all other groups. Although exercise did not significantly affect weight gain in DR rats, it did lead to a significant 20% reduction in total fat pad weights compared to their sedentary controls. However, when expressed as a function of body weight, there was no significant reduction in their relative fat pad mass (Table 2). On the other hand, exercise caused a 29% reduction in total pad weights in DIO rats compared to their sedentary counterparts and this was even more marked when expressed as a function of body weight. Exercising DIO rats had 37% lower relative fat pad mass than their sedentary controls. The reduction in fat pad mass was particularly evident in the retroperitoneal and mesenteric depots. The exercise-induced reduction in adipose depot weights was paralleled by reductions in plasma leptin levels (Table 2). Exercise reduced leptin levels in both DIO and DR rats ($F[1,20] = 4.54$; $P = 0.04$), but DIO rats still had higher levels than DR rats overall ($F[1,20] = 9.10$; $P = 0.006$). This latter effect was solely due to the fact that sedentary DIO rats had 37–56% higher leptin levels than all other groups. The 19% lower leptin levels in exercising than sedentary DIO rats also accounted for the overall effect of exercise since leptin levels did not differ between exercising and sedentary DR rats. Thus, by several markers of adiposity, DIO rats were fatter and showed a selective exercise-induced reduction in adiposity.

Unlike the lack of correlation with running, there were significant correlations between the amount of food intake and the amount of weight gain during the 4 weeks period of running for both DR ($r = 0.81$; $P = 0.001$) and DIO ($r = 0.89$; $P = 0.001$) rats. There were similar correlations with total adipose pad weights (DR; $r = 0.92$; $P = 0.001$; DIO; $r = 0.90$; $P = 0.001$). Overall, DIO rats ate more than DR rats ($F[1,20] = 5.12$; $P = 0.04$; Table 2) over the final 4 weeks period. However, exercising rats ate the same amount as sedentary rats, regardless of their phenotype. Since they gained less weight overall, exercising rats had significantly lower feed efficiency over this period ($F[1,20] = 10.9$; $P = 0.005$). As they gained the least amount of weight over this period, exercising DIO rats had the lowest feed efficiency of all groups (Table 2). Their feed efficiency was only 46% of their sedentary controls. Thus, despite their reduced weight gain and adiposity, exercising rats never fully compensated by increasing their intake enough to correct for the increase in exercise-induced energy expenditure and net negative energy balance.

Discussion

Voluntary wheel running over a 4 weeks period reduced the body weight gain and adiposity of outbred DIO rats fed a 31% fat HE diet. Whereas there was a tendency for exercising DR rats to gain less weight and adiposity than that of their sedentary controls, this did not reach statistical significance. Importantly, 50 year ago Mayer *et al*.[27] showed a similar selective effect of exercise on lowering body weight in obese vs lean mice. Although there was wide interindividual variability in the amount of running, outbred DIO rats in the current study ran the same average distance as DR rats, both before and after HE diet exposure. Neither was there a correlation with the amount of running and the reduction in body weight gain nor adiposity. On the other hand, both of these parameters correlated highly with food intake in exercising rats. These findings are remarkably similar to our previous ones in rats selectively bred to develop DIO from the same outbred population of rats used here. In those rats, body weight gain and adiposity were also independent of the amount of running but correlated highly with the amount of food intake during exercise.[28] Thus, it appears that rats maintain their lower levels of weight gain and adiposity on HE diet by adjusting food intake but not the amount of exercise they perform. Since they reduced their weight gain but did not decrease their overall intake, exercising rats had significantly reduced feed efficiency compared to sedentary rats, and this was more marked in DIO rats. This lowering of feed efficiency is likely to be due to a combination of exercise-induced energy expenditure plus an increase in both the resting metabolic rate and the thermic effect of food.[12]

Regardless of the adjustments made, it is clear that exercising DIO rats did not increase their energy intake sufficiently to compensate for their net negative level of energy balance. On the other hand, although they had a nonsignificant tendency to gain less body weight and adiposity than sedentary controls, exercising DR rats made appropriate adjustments to allow them to remain in relatively better energy homeostasis than exercising DIO rats. This is similar to the differential adjustments in intake made by DIO and DR rats when they are first exposed to the HE diet.[29] Such a differential loss of adiposity in exercising obese rats has been reported in obese vs lean Zucker[22] and obesity-prone Osborne–Mendel vs obesity-resistant SB5/Pl rats.[23] On the other hand, neither corpulent (LA/N-cp) rats[30] nor rats with lesions of the ventromedial hypothalamus[31] show a differential exercise-induced loss of adiposity compared to their respective lean controls.

The amount of running rats do in a running wheel may be more a measure of the rewarding properties of running than of their inherent activity levels. In fact, this hardly matters to the way in which exercise influences the defended level of adiposity. Nevertheless, outbred DIO and DR rats not only have similar levels of running wheel activity but also have comparable levels of activity in a 40×40 cm open field before exposure to HE diet.[32] However, unlike running wheel

activity which was halved after 4 weeks on HE diet in both DIO and DR rats in the current study, DIO rats progressively reduced their open field activity as they became obese, while DR rats on HE diet maintained the same level of activity over the same period.[32] Importantly, running wheel activity is not an invariant characteristic of the DIO and DR weight gain phenotypes. While running rates were similar in outbred DIO and DR rats, rats selectively bred from this same outbred population to be DIO run only half as much as those bred to be DR both before HE diet exposure (unpublished observation). On the other hand, when selectively bred DIO rats were backcrossed against obesity-resistant Fischer F344 rats, the resultant substrain had the same level of running wheel activity as the parent F344 strain but still maintained the DIO phenotype.[21] Thus, while the amount of wheel running activity may reflect the genetic background of a rat, it appears to have little impact on the regulated level of adiposity.

In fact, the most important feature of exercise in rats is that, despite a consistent reduction in weight gain and adiposity, they do not increase their intake sufficiently to compensate for this negative energy balance. We previously showed this same lack of compensation for lost adiposity in selectively bred DIO rats provided with running wheels.[28] This failure to compensate occurs even when there is increased hypothalamic arcuate nucleus neuropeptide Y (NPY) expression,[33] a change which is usually associated with reduced energy expenditure, increased hunger, food intake and body weight.[34,35] Chronically food restricted sedentary rats have comparably elevated arcuate NPY expression and quickly regain lost weight and adiposity when allowed free access to food.[3,36] The effect of exercise on food intake is highly dependent upon several experimental factors including strain, dietary fat content[11,15] and palatability.[16] Depending upon these conditions, exercise is associated with increased,[14,23] decreased[15] or no change in intake.[11–13] However, regardless of the overall effect on intake, exercising rats fail to make the appropriate alterations in their overall energy homeostasis to maintain the rate of body weight gain or adiposity of sedentary rats.

This raises the question of whether there is some metabolic or physiologic signal produced by exercise, which lowers the defended level of body weight and adiposity. Clearly, a variety of metabolic and physiologic signals can have important effects on these parameters. Dehydrated rats become hypophagic and lose weight, even in the face of elevated arcuate nucleus NPY expression.[37] Similarly, tumor-bearing rats reduce intake and body weight, despite elevated arcuate NPY expression and reduced expression of the catabolic corticotrophin-releasing hormone.[38] Perhaps exercise-produces some metabolic or physiologic signal which is sensed differently than those related to pure restriction of energy intake. The cytokine interleukin-6 (IL-6) is one such potential signal. It is generated and released by exercising muscles at rates which are inversely proportional to the amount of muscle glycogen stores.[39–42] Importantly, IL-6 can enhance leptin signaling both peripherally[42] and centrally[43] and reduces body weight and adiposity when administered centrally.[43,44] Lactate is another potential candidate. Exercise increases plasma and brain lactate levels[45–49] and lactate can act as an alternate energy source and/or signaling molecule for metabolic sensing neurons involved in the regulation of energy homeostasis.[50] Such neurons might interpret the excess of lactate as an excess of peripheral energy stores leading to a reduction in the defended body weight and adiposity.

In conclusion, voluntary wheel running produced a selective lowering of body weight gain and adiposity in outbred DIO, as compared to DR rats. The greater effect in DIO rats was not a function of the amount of running since running both before and after exposure to the obesity-producing HE diet did not differ between the phenotypes. The most striking feature of the exercise-induced reduction in weight gain and adiposity in rats is the lack of a consistent compensatory alteration in energy homeostasis to offset the negative energy balance. It is possible that some metabolic or physiologic signals associated with exercise are responsible for this lowering of the defended body weight and adiposity. Whatever that additional signal might be, it appears that DIO rats are more sensitive to its negative feedback.

Acknowledgements

We thank Ghoufeng Zhou, Matthew Klein and Antoinette Moralishvilli for expert technical assistance. This work was supported by the Research Service of the Veterans Administration and NIDDK (RO1-30066).

References

1 Stunkard A, McLaren-Hume M. The results of treatment for obesity: a review of the literature and report of a series. *AMA Arch Intern Med* 1959; **103**: 79–85.
2 Kramer FM, Jeffery RW, Forster JL, Snell MK. Long-term follow-up of behavioral treatment for obesity: patterns of weight regain among men and women. *Int J Obes Relat Metab Disord* 1989; **13**: 123–136.
3 Levin BE, Keesey RE. Defense of differing body weight set-points in diet-induced obese and resistant rats. *Am J Physiol* 1998; **274**: R412–R419.
4 Levin BE, Dunn-Meynell AA. Defense of body weight against chronic caloric restriction in obesity-prone and -resistant rats. *Am J Physiol* 2000; **278**: R231–R237.
5 Levin BE, Dunn-Meynell AA. Sibutramine alters the central mechanisms regulating the defended body weight in diet-induced obese rats. *Am J Physiol* 2000; **279**: R2222–R2228.
6 Hill JO, Thacker S, Newby D, Sykes MN, Digirolamo M. Influence of food restriction coupled with weight cycling on carcass energy restoration during ad-libitum refeeding. *Int J Obes* 1987; **11**: 251–262.
7 Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Eng J Med* 1995; **332**: 621–628.

8 Leibel RL, Hirsch J. Diminished energy requirements in reduced-obese patients. *Metabolism* 1984; **33**: 164–170.
9 Corbett SW, Stern JS, Keesey RE. Energy expenditure in rats with diet-induced obesity. *Am J Clin Nutr* 1986; **44**: 173–180.
10 Wing RR, Hill JO. Successful weight loss maintenance. *Ann Rev Nutr* 2003; **21**: 323–341.
11 Applegate EA, Upton DE, Stern JS. Exercise and detraining: effect on food intake, adiposity and lipogenesis in Osborne–Mendel rats made obese by a high fat diet. *J Nutr* 1984; **114**: 447–459.
12 Hill JO, Davis JR, Tagliaferro AR. Effects of diet and exercise training on thermogenesis in adult female rats. *Physiol Behav* 1983; **31**: 133–135.
13 Hoffman-Goetz L, MacDonald MA. Effect of treadmill exercise on food intake and body weight in lean and obese rats. *Physiol Behav* 1983; **31**: 343–346.
14 Monda M, Amaro S, De Luca B. The influence of exercise on energy balance changes induced by ventromedial hypothalamic lesion in the rat. *Physiol Behav* 1993; **54**: 1057–1061.
15 Kibenge MT, Chan CB. The effects of high-fat diet on exercise-induced changes in metabolic parameters in Zucker fa/fa rats. *Metabolism* 2002; **51**: 708–715.
16 Rolls BA, Rowe EA. Exercise and the development and persistence of dietary obesity in male and female rats. *Physiol Behav* 1979; **23**: 241–247.
17 Levin BE, Routh VH. Role of the brain in energy balance and obesity. *Am J Physiol* 1996; **271**: R491–R500.
18 Levin BE, Finnegan MB, Marquet E, Triscari J, Comai K, Sullivan AC. Effects of diet and obesity on brown adipose metabolism. *Am J Physiol* 1984; **246**: E418–E425.
19 Levin BE, Triscari J, Hogan S, Sullivan AC. Resistance to diet-induced obesity: food intake, pancreatic sympathetic tone and insulin. *Am J Physiol* 1987; **252**: R471–R478.
20 Levin BE, Dunn-Meynell AA, Balkan B, Keesey RE. Selective breeding for diet-induced obesity and resistance in Sprague–Dawley rats. *Am J Physiol* 1997; **273**: R725–R730.
21 Levin BE, Dunn-Meynell AA, McMinn JE, Cunningham-Bussel A, Chua Jr SC. A new obesity-prone, glucose intolerant rat strain (F.DIO). *Am J Physiol* 2003; **285**: R1184–R1191.
22 Jen KL, Almario R, Ilagan J, Zhong S, Archer P, Lin PK. Long-term exercise training and retirement in genetically obese rats: effects on food intake, feeding efficiency and carcass composition. *Int J Obes Relat Metab Disord* 1992; **16**: 519–527.
23 Zachwieja JJ, Hendry SL, Smith SR, Harris RB. Voluntary wheel running decreases adipose tissue mass and expression of leptin mRNA in Osborne-Mendel rats. *Diabetes* 1997; **46**: 1159–1166.
24 Levin BE, Hogan S, Sullivan AC. Initiation and perpetuation of obesity and obesity resistance in rats. *Am J Physiol* 1989; **256**: R766–R771.
25 Ricci MR, Levin BE. Ontogeny of diet-Induced obesity in selectively-bred Sprague-Dawley rats. *Am J Physiol* 2003; **285**: R610–R618.
26 Chang S, Graham B, Yakubu F, Lin D, Peters JC, Hill JO. Metabolic differences between obesity-prone and obesity-resistant rats. *Am J Physiol Regul Integr Comp Physiol* 1990; **259**: R1103–R1110.
27 Mayer J, Marshall NB, Vitale JJ, Christensen JH, Mashayekhi MB, Stare FJ. Exercise, food intake and body weight in normal rats and genetically obese adult mice. *Am J Physiol* 1954; **177**: 544–548.
28 Levin BE, Dunn-Meynell AA. Chronic exercise lowers the defended body weight gain and adiposity in diet-induced obese rats. *Am J Physiol* 2004; **286**: R771–R778.
29 Levin BE, Dunn-Meynell AA, Ricci MR, Cummings DE. Abnormalities of leptin and ghrelin regulation in obesity-prone juvenile rats. *Am J Physiol* 2003; **285**: E949–E957.
30 Tulp OL, Jones CT. Effects of increased energy expenditure on weight gain and adiposity in the LA-corpulent rat. *Comp Biochem Physiol A* 1987; **86**: 67–72.
31 Jenkins RR, Lamb DR. Effects of physical training on hypothalamic obesity in rats. *Eur J Appl Physiol Occup Physiol* 1982; **48**: 355–359.
32 Levin BE. Spontaneous motor activity during the development and maintenance of diet-induced obesity in the rat. *Physiol Behav* 1991; **50**: 573–581.
33 Lewis DE, Shellard L, Koeslag DG, Boer DE, McCarthy HD, McKibbin PE *et al*. Intense exercise and food restriction cause similar hypothalamic neuropeptide Y increases in rats. *Am J Physiol* 1993; **264** (Part 1): E279–E284.
34 Schwartz MW, Woods SC, Porte Jr D, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature* 2000; **404**: 661–671.
35 Billington CJ, Briggs JE, Grace M, Levine AS. Effects of intracerebroventricular injection of neuropeptide Y on energy metabolism. *Am J Physiol* 1991; **260**: R321–R327.
36 Levin BE. Arcuate NPY neurons and energy homeostasis in diet-induced obese and resistant rats. *Am J Physiol* 1999; **276**: R382–R387.
37 Watts AG, Sanchez-Watts G, Kelly AB. Distinct patterns of neuropeptide gene expression in the lateral hypothalamic area and arcuate nucleus are associated with dehydration-induced anorexia. *J Neurosci* 1999; **19**: 6111–6121.
38 McCarthy HD, McKibbin PE, Perkins AV, Linton EA, Williams G. Alterations in hypothalamic NPY and CRF in anorexic tumor-bearing rats. *Am J Physiol* 1993; **264**: E638–E643.
39 Febbraio MA, Hiscock N, Sacchetti M, Fischer CP, Pedersen BK. Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes* 2004; **53**: 1643–1648.
40 MacDonald C, Wojtaszewski JF, Pedersen BK, Kiens B, Richter EA. Interleukin-6 release from human skeletal muscle during exercise: relation to AMPK activity. *J Appl Physiol* 2003; **95**: 2273–2277.
41 Pedersen BK, Steensberg A, Fischer C, Keller C, Keller P, Plomgaard P *et al*. Searching for the exercise factor: is IL-6 a candidate? *J Muscle Res Cell Motil* 2003; **24**: 113–119.
42 Tomas E, Kelly M, Xiang X, Tsao TS, Keller C, Keller P *et al*. Metabolic and hormonal interactions between muscle and adipose tissue. *Proc Nutr Soc* 2004; **63**: 381–385.
43 Li G, Klein RL, Matheny M, King MA, Meyer EM, Scarpace PJ. Induction of uncoupling protein 1 by central interleukin-6 gene delivery is dependent on sympathetic innervation of brown adipose tissue and underlies one mechanism of body weight reduction in rats. *Neuroscience* 2002; **115**: 879–889.
44 Wallenius K, Wallenius V, Sunter D, Dickson SL, Jansson JO. Intracerebroventricular interleukin-6 treatment decreases body fat in rats. *Biochem Biophys Res Commun* 2002; **293**: 560–565.
45 De Bruin LA, Schasfoort EM, Steffens AB, Korf J. Effects of stress and exercise on rat hippocampus and striatum extracellular lactate. *Am J Physiol* 1990; **259**: R773–R779.
46 Ide K, Horn A, Secher NH. Cerebral metabolic response to submaximal exercise. *J Appl Physiol* 1999; **87**: 1604–1608.
47 Vissing J, Wallace JL, Scheurink AJ, Galbo H, Steffens AB. Ventromedial hypothalamic regulation of hormonal and metabolic responses to exercise. *Am J Physiol* 1989; **256** (Part 2): R1019–R1026.
48 Korf J. Intracerebral trafficking of lactate *in vivo* during stress, exercise, electroconvulsive shock and ischemia as studied with microdialysis. *Dev Neurosci* 1996; **18**: 405–414.
49 Wang L, Dong Y, Yu X, Shangguan DH, Zhao R, Han HW *et al*. Analysis of glucose and lactate in dialysate from hypothalamus of rats after exhausting swimming using microdialysis. *Biomed Chromatogr* 2002; **16**: 427–431.
50 Levin BE, Dunn-Meynell AA, Routh VH. CNS sensing and regulation of peripheral glucose levels. *Internat Rev Neurobiol* 2002; **51**: 219–258.