

MINIREVIEW

Determinants Affecting Physical Activity Levels In Animal Models¹

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Weight control is dependent on energy balance. Reduced energy expenditure (EE) associated with decreased physical activity is suggested to be a major underlying cause in the increasing prevalence of weight gain and obesity. Therefore, a better understanding of the biological determinants involved in the regulation of physical activity is essential. To facilitate interpretation in humans, it is helpful to consider the evidence from animal studies. This review focuses on animal studies examining the biological determinants influencing activity and potential implications to human. It appears that physical activity is influenced by a number of parameters. However, regardless of the parameter involved, body weight appears to play an underlying role in the regulation of activity. Furthermore, the regulation of activity associated with body weight appears to occur only after the animal achieves a critical weight. This suggests that activity levels are a consequence rather than a contributor to weight control. However, the existence of an inverse weight-activity relationship remains inconclusive. Confounding the results are the multifactorial nature of physical activity and the lack of appropriate measuring devices. Furthermore, many determinants of body weight are closely interlocked, making it difficult to determine whether a single, combination, or interaction of factors is important for the regulation of activity. For example, diet-induced obesity, aging, lesions to the ventral medial hypothalamus, and genetics all produce hypoactivity. Providing a better understanding of the biological determinants involved in the regulation of activity has important implications for the development of strategies for the prevention of weight

gain leading to obesity and subsequent morbidity and mortality in the human population. [Exp Biol Med Vol. 227(8):587–600, 2002]

Key words: activity; body weight; obesity; energy expenditure; rodents

The study of weight control is essentially a study of energy balance. The components of energy balance consists of energy input and energy output. When energy input equals energy output, body weight remains constant. However, imbalances resulting in a cumulative positive energy balance leads to weight gain and possibly obesity. The growing prevalence of obesity and its association with diabetes, hypertension, hyperlipidemia, and cardiovascular disease has made obesity a major public health concern (1). The prevention and/or treatment of obesity will require a reduction in food intake and/or increases in energy expenditure (EE).

Total EE is comprised of basal metabolic rate (BMR), thermic effect of food (TEF), and physical activity. Physical activity is the most variable and easily altered component of total EE. Therefore, increasing physical activity is often prescribed to individuals seeking to lose weight. However, it is difficult to distinguish whether weight control is influenced by exercise alone or if other factors such as: genetics, gene-environmental interactions, biological, psychological, and sociological factors are involved (2). The tighter controls permitted by animal studies reduces some of the confounding factors complicating the interpretation of human studies. This paper will review the animal literature on biological determinants (i.e., diet, age, strain, surgical, and pharmacological) influencing physical activity in a variety of animal models. The relevance of the animal studies to humans will also be briefly discussed.

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Definition of Physical Activity and Its Components

Physical activity is the energy used above that which is needed for BMR and TEF. Physical activity is usually measured as volitional exercise (i.e., conscious sports, fitness-related activities, and active lifestyle). Another component of physical activity is nonexercise activity thermogenesis (NEAT) (3). NEAT encompasses the unconscious activities of daily living and the energy cost of all nonvolitional activity such as fidgeting, muscle tone, and maintenance of posture when not lying down. Various terms used to describe nonvolitional exercise are voluntary movement, spontaneous activity, nonresting EE, and fidgeting. This review uses the term NEAT when referring to nonvolitional activity.

In rodent studies, volitional activity is measured as either locomotor or exploratory activity. Locomotor activity is measured by the "home cage" method. Testing takes place in a cage where the animal has become habituated and its activity is monitored for at least 24 hr. Different technologies are used to measure locomotor activity. Commonly used apparatus are running wheels, runways, or learning situations (i.e., mazes, shuttleboxes, etc.). On the other hand, exploratory activity is measured by the "open field" method. In the open field method, animals are placed in a new environment devoid of any apparatus. In the new environment, rats and mice typically display exploratory activity and measurements last 5–30 min (4). By this method, activity is influenced by both motivational and behavioral components, leading to suggestions that locomotion and exploration are non-interchangeable activities that cannot be directly compared (5–7). For example, Simmel *et al.* (8), investigating the role of age, strain, and gender on the activity of young mice, found a significant age effect. However, when exploratory activity was separated from locomotor activity, strain rather than age was found to significantly affect activity levels. Apparently, results can differ depending on the measurement used (9–10). Thus, care must be taken when selecting a method to measure physical activity.

In the animal studies, the various devices used to measure NEAT are infrared sensors, motion detectors, and seismographic recorders (11). In our laboratory, telemetry was used to measure NEAT in rats and mice. The telemeter was implanted in the abdomen of the animal to monitor both body temperature and movement. Any distance the animal moved generated a digital pulse that was counted by a data acquisition system. This method enabled continuous monitoring of NEAT throughout the duration of the study (12). It is important to account for NEAT because NEAT represents approximately 30%–60% of total EE as well as the majority of the energy dissipated by physical activity (13–14).

Physical Activity as a Function of Weight

The regulation of physical activity is incompletely understood, in large part because it is affected by numerous

regulatory components. It is generally reported and accepted that reduced physical activity associated with a sedentary lifestyle contributes to weight gain and obesity (15). However, we propose that activity is a response rather than a contributor to weight gain. Increasing weight gain is accompanied by decreasing activity; whereas, decreasing weight is accompanied by increasing activity. A number of studies support an inverse weight-activity relationship. In mature hamsters, the doubling of body weight was accompanied by a 50% reduction in activity levels (16). Similarly, Zucker obese rats weighing 340–400g, twice as much as their lean counterparts (175–200 g), were observed to run half as fast (17). In Figure 1A, locomotor activity and body weight for different mice strains of the *ob/ob*, *db/db*, viable yellow, lethal yellow, and New Zealand obese (NZO) are

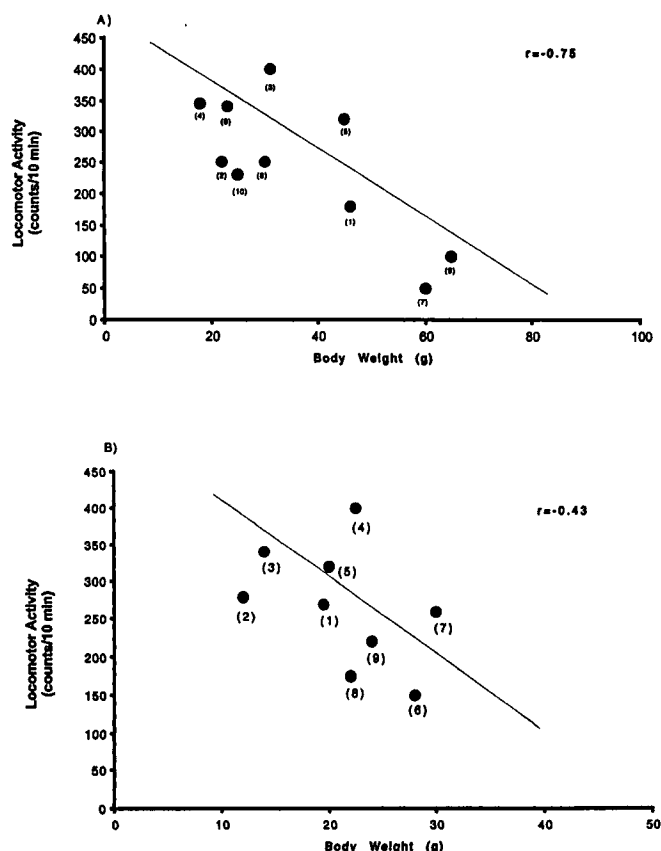


Figure 1. (A) Scatter plot depicting the relationship between body weight and locomotor activity for different strains of genetically obese mice. The mice strains used in this study are: (1) New Zealand obese (NZO) prior to obesity; (2) obese NZO; (3) VY/Wf-A^y/a (viable yellow) prior to obesity; (4) obese VY/Wf-A^y/a (viable yellow); (5) VS/ChWf-A^y/a (lethal yellow) prior to obesity; (6) obese VS/ChWf-A^y/a (lethal yellow); (7) C57BL/6J-*db/db* (diabetic) prior to obesity; (8) obese C57BL/6J-*db/db* (diabetic); (9) C57BL/6J-*ob/ob* (obese) prior to obesity; and (10) obese C57BL/6J-*ob/ob* (obese). Values represent the mean of $n = 4$ –6/group. Adapted from Yen and Acton, 1972 (Ref. 123). (B) Different strains of genetically obese mice and weight-matched normal mice. The mice strains used in this study are: (1) New Zealand obese (NZO); (2) YS/ChWf-a/a (normal); (3) VS/ChWf-A^y/a (lethal yellow); (4) VY/Wf-a/a (normal); (5) VY/Wf-A^y/a (viable yellow); (6) C57BL/6J *db⁺/db⁺* (normal); (7) C57BL/6J *db/db* (diabetic); (8) C57BL/6J *ob⁺/ob⁺*; and (9) C57BL/6J *ob/ob*. Values represent the mean of $n = 5$ –6/group. Adapted from Yen and Acton, 1972 (Ref. 18).

presented (18). Results show a significant negative correlation ($r = -0.75$) between body weight and activity.

The establishment of an inverse weight-activity relationship is challenging. One problem is the difficulty of accounting for the contribution of NEAT to total EE. According to Levine *et al.* (3), NEAT is a strong predictor of weight gain in humans. Yet, few studies have investigated the role of NEAT on weight gain and obesity. We investigated the effect of body weight of rats on NEAT using centrifugation. Centrifugation was used to investigate the weight-activity relationship based on the knowledge that body weight is the product of the animal's body mass and the gravity field to which it is exposed. In the normal environment, animals are exposed to a 1.0g gravity load and body mass equals body weight. Therefore, increasing the gravity field to 2.0g doubles the body weight of the animal. Telemetry (described earlier) was used to measure NEAT in the centrifuged rats. The results showed energy balance was maintained by a reduction in NEAT proportional to the increase in body weight so that the energy cost of activity was not altered (our unpublished observations). Thus, further complicating the establishment of an inverse weight-activity relationship is the changes in EE resulting from NEAT not always being reflected in the energy balance equation. Failure to account for NEAT may be a reason why suggestions of an inverse weight-activity relationship remain inconclusive.

Dewsbury (19) showed no significant correlation ($r = -0.21$) between body size and voluntary wheel running activity across 12 species of muroid rodents. Clark and Gay (20), using weight-matched animals, found obese (*ob/ob*) mice to be less active than normal mice of similar weights. Figure 1B compares the locomotor activity of genetically obese mice before they became obese with weight-matched normal mice. The data indicates the absence of a significant correlation ($r = -0.43$) between body weight and locomotor activity (18). It appears that decreased locomotor activity in genetically obese *ob/ob* and *db/db* mice occurs only after they develop their characteristic obesity (Fig. 1A). In support, Pullar and Webster (21) observed that the activity of genetically obese rats was not noticeably less than their lean controls until they became very obese. Based on these findings, it appears that a critical body weight, in this case obesity, must be attained before activity is significantly affected. In support, Zucker lean rats expend approximately 2.3% of their metabolizable energy on running wheel activity, whereas Zucker obese rats expend only 0.3% of their metabolizable energy on running wheel activity (22). However, Keesey *et al.* (23) reported the percentage of total EE attributed to activity was nearly identical in Zucker obese (19.3%) versus lean rats (19.7%). In this study, values became identical after the contribution of activity to total EE was adjusted for total daily heat production.

Decreased locomotor activity has been observed to precede the onset of obesity, suggesting that the weight-activity relationship is more complicated than simply the restriction

of movement due to a state of obesity. We propose that weight regulation of activity is dependent on weight gain preceding obesity. The reduction of activity in response to weight gain leads to further weight gain that may eventually result in obesity. To our knowledge, no systematic studies have measured changes in activity levels during gradual weight gain. Currently, the evidence in support of an inverse weight-activity relationship independent of obesity comes from reports of increases in activity during weight loss under conditions such as food restriction. Figure 2 shows various determinants directly regulating activity. These determinants also act indirectly by affecting body weight that in turn regulates activity. In the following sections, we will examine several determinants influencing physical activity levels.

Diet as a Determinant of Body Weight

If diet is key to regulating body weight, then investigating the importance of physical activity may not be essential. We begin by examining the role of diet as a determinant of body weight. Chronic excess energy intake over EE results in obesity. The growing prevalence of obesity is attributed not only to an increasingly sedentary lifestyle, but to higher food consumption. Hill *et al.* (24) investigated the effect of food intake on body weight by feeding a >20% fat diet (the 20% fat used in the animal studies is considered low fat based on a human diet) and restricting physical activity by maintaining the animals in small cages. Results showed obesity rarely developed, suggesting food intake had little effect on body weight. However, providing sedentary animals with diets containing 30% or more energy from fat reliably produces obesity in rats and mice (25–27). Studies show higher total caloric intake on a high-fat diet resulted from the higher energy density of fat (28–30) and increased voluntary food intake due to the palatability of fat (31). Another explanation for obesity in response to a high-fat diet may be attributed to the oxidation of macronutrients. Excessive carbohydrate and protein intakes are disposed of by increasing oxidation, but excessive fat intakes are not. Instead, fat is efficiently stored in the body (32). Although there is extensive literature supporting a role of high-fat diets and weight gain in rodents (27, 33–34), the importance

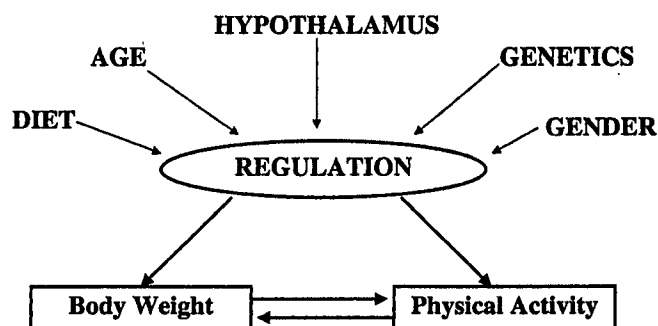


Figure 2. Schematic of the weight-activity relationship and the various determinants, i.e., age, strain, gender, diet, and hypothalamus, affecting body weight and activity.

of dietary fat in the development of obesity continues to be debated.

Several arguments exist against the role of dietary fat as a regulator of body weight. Studies show that feeding high-fat diets to different rodent strains produces variable weight gains ranging from 12% to 56% (35). The observation of this marked variability in susceptibility to diet-induced obesity (DIO) among rodent strains suggests genetics rather than dietary fat is the major determinant of body weight gain. In support, studies report some rodent strains resist becoming obese when fed a high-fat diet (35–36). Thus, it appears that a high-fat diet can only produce obesity in those genetically predisposed to obesity. In humans, a recent diet survey of adult males in the United Kingdom reported most individuals consuming a high fat diet to be of normal weight and only a minor portion of the subjects consuming a high-fat diet to be obese (37). Others argue against the importance of dietary fat on weight because only modest weight loss occurs when dietary fat is reduced (38). Perhaps most significant is that the prevalence of obesity in the population has increased while the percentage of energy intake from dietary fat has declined (39). The inconclusive results of the role of dietary fats in obesity has lead to suggestions that consuming a “cafeteria diet” is responsible for DIO. The so-called cafeteria diet regimens are typically high in fat, sucrose, and energy, and provide a mixture of commercially available supermarket foods consumed by humans. In support, West and York (27) reported that rats become more obese when fed a cafeteria diet compared with high-fat diets. Whether referring to a high-fat or cafeteria diet, food intake as the major contributor to obesity is questioned. This is based on reports that DIO rats consume an equivalent amount or only slightly more calories than obesity resistant rats (27, 36). If an animal is depositing more energy as fat but is consuming the same amount of energy, then some alteration of EE must be occurring. Studies of overfeeding show EE is altered to compensate and oppose changes in energy balance (40–41), therefore, increasing energy intake without a concurrent reduction in EE may result in failure to gain weight.

Diet as a Determinant of Activity

Studies of EE components during overfeeding show that 8% of the excess calories is dissipated in resting metabolic rate (RMR) and 14% in TEF. The slight changes in RMR and TEF are too minimal to explain the differences reported for weight gain (14). Similarly, the slight changes in total EE produced by the lack of adjustment of fat oxidation to high fat intake fails to account for interindividual variability in body weight gain. Of the EE components, physical activity is the most labile EE and thus able to account for the large variations in body weight gains. Thus, physical activity appears to be the major mechanism regulating body weight.

Food-deprived rats lose weight and exhibit hyperactivity as measured by increased locomotor activity on the running wheel and stabilimeter cages (42). Imposing negative

energy balance on rats (43–45), hamsters (46–47), gerbils (48), and kangaroo rats (49) for 1–10 days results in activity increasing in inverse proportion to decreasing body weight. However, Peck (50) reported no difference in the running activity of DIO versus lean and normal weight rats during a 2-day fast. In this study, the time period of fasting may not have been long enough to observe any changes in activity levels. Furthermore, female rats were used in this study. Running activity in female rats fluctuates depending on the phase of the estrous cycle. Gender as a determinant of activity will be discussed later. Hyperactivity in food-deprived rodents appears to occur upon attaining a critical weight loss, as illustrated in Figure 3. Although rats increase their wheel running during weight loss, control rats appear most active when their weight fell to 75%–85% of their predeprived baseline, dietary lean rat when their weights fell to 85%–95% of their predeprived baseline, and DIO rats when their weight fell to 65%–75% of their predeprived baseline (51). However, others failed to show an influence of diet on activity levels.

Feeding high-fat/high-sucrose, high-fat/low-sucrose, low-fat/high-sucrose, or low-fat/low-sucrose diets produces no differences in the activity levels of DIO mice compared with obesity-resistant mice (52). Thus, hypoactivity does not appear to be regulated by the diet, but by some other determinant. Age is suggested to be a determinant of activity based on studies showing the earlier the high-fat feeding regimen is begun and the longer the duration, the greater the effect on body weight gain (53). Age as a determinant of activity will be discussed in another section of the review paper. Another determinant of activity is body weight. Levin (54) found that following 3 months on a cafeteria diet, the DIO rats gained 71% more weight and had 28% fewer movements than the DIO-resistant rats, suggesting activity levels are modulated by body weight. The DIO rats being 71% heavier may have been hypoactive as a result of their obese state.

In reviewing the literature, energy intake did not appear to be the major determinant influencing body weight based on inconclusive evidence linking dietary fat to obesity and similar caloric intake by DIO and lean rats. Therefore, EE, the other side of the energy balance, was investigated. Of the EE components, only physical activity accounts for the large variability in weight gain. Diet as a determinant of physical activity is suggested by hyperactivity in food-deprived animals. However, diet failed to explain reduced activity in DIO rodents. The only factor consistently associated with activity was body weight. Both the DIO and food-deprived animals exhibit an inverse weight-activity relationship.

Physical Activity as a Function of Hypothalamic Injury

The hypothalamus regulates energy intake and EE. The ventromedial hypothalamus (VMH) is regarded as the region of the satiety center. Lesions produced by electrolytic

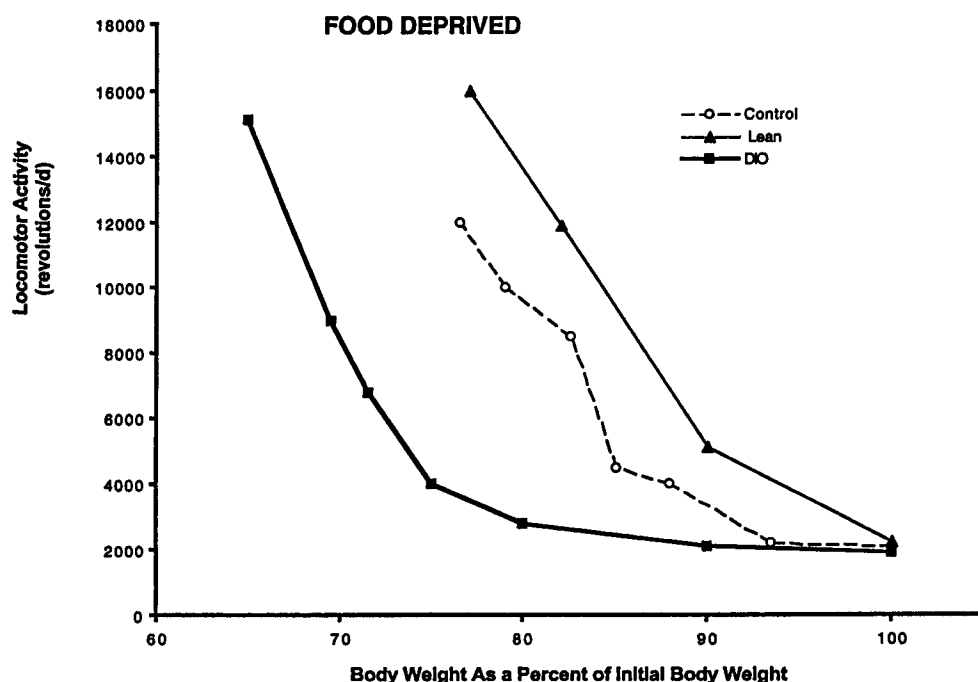


Figure 3. Mean locomotor activity of DIO, lean, and control rats as a function of percentage of body weight during food deprivation. The rats in the DIO group are *ad libitum* fed commercially available foods in addition to their standard rodent chow. The rats in the lean group are *ad libitum* fed standard rodent meal adulterated with quinine hydrochloride (0.8%, w/w), and the control rats are *ad libitum* fed unadulterated standard rodent meal. The rats weighed 310–400 g upon receipt. At the start of the food deprivation, the obese group weighed 41 g (10%) more than control and lean group weighed 58 g (16%) less than controls. Thus, body weight is expressed as a percentage of the actual predeprivation weight of each rat. Adapted from Sclafani and Rendel, 1978 (Ref. 51).

injury, radio frequency lesions, or knife cuts to the VMH (55) result in increased food intake, gradual accumulation of body weight, and obesity (55). Rodents with obesity due to hypothalamic lesions are another model of obesity. Humans sustaining similar lesions to the hypothalamus also increase their food intake and typically develop obesity (56). However, not all cases of obesity associated with VMH lesions are produced by higher food intakes. Benardis (57) reported both VMH-lesioned weanling and adult rats show increases in their percentages of body fat without accompanying increases in food intake. VMH-lesioned animals are also more finicky eaters, consuming an excess of calories when given palatable foods, but depressing their consumption more readily than nonlesioned animals when given unpalatable foods (58). These findings suggest that high energy intake is not essential to the development of obesity in VMH-lesioned animals. Similar to the DIO animal model, the other side of the energy balance equation, EE, appears to be key to weight gain and development of obesity in VMH-lesioned animals.

Early studies report that VMH-lesioned rats display reduced motivation to seek food and decreased responsiveness when the workload to obtain food is increased compared with nonlesioned control rats (59). Measuring activity using running wheels and stabilimeters confirmed that locomotor activity was reduced in VMH-lesioned rodents (60). These results suggest that the major contributor to weight gain in hypothalamic-lesioned animals is reduced activity. This in turn leads to questions about parameters influencing physical activity. The importance of body weight in the modulation of activity is shown by hypoactivity in VMH-lesioned rats that became obese and absence of hypoactivity in VMH-lesioned animals kept at 80%–100% of their postoperative weight (61). The results clearly

demonstrate that activity is dependent on body weight and that a critical body mass must be obtained before VMH-lesioned rodents are able to exhibit hypoactivity.

Not all studies using the hypothalamic-induced obese rodents support the suggestion that body weight regulates activity. Beatty *et al.* (62) found that rats trained to exercise prior to the induction of VMH lesions were able to increase their workload, suggesting that the activity deficit seen in VMH-lesioned rats is a separate phenomenon from body weight. It should be noted that the use of the surgical hypothalamic-lesioned animal as a model of obesity requires caution. Different syndromes can be produced depending on the size, type, or location of the lesion in the hypothalamus. For example, VMH-lesioned rats exhibit hypoactivity, but not paraventricular nucleus (PVN)-lesioned rats despite similar body weights between the two groups (63). VMH-lesioned rodents become obese even when pair-fed with sham-lesioned controls, whereas the PVN-lesioned rats develop obesity only through overfeeding (64). Thus, certain lesions to the hypothalamus may override the regulation of activity by body weight.

Another method of producing hypothalamic lesions is by chemical means using systemic injections of gold thioglucose (GTG) or monosodium glutamate (MSG) (65). Similar to the surgical hypothalamic-lesioned animals, the chemical hypothalamic-lesioned animals accumulate fat even when food intake is reduced, indicating that altering food intake is not the principle underlying cause of obesity. If food intake is not responsible, then reduced EE must be the contributing factor leading to positive energy balance in chemically induced obese animals. In the early studies, MSG-induced obese mice were described as lethargic (66). In agreement, Poon *et al.* (67), measuring both vertical and horizontal locomotor movements of MSG-treated male

mice in a radio field using a digital counter, reported diminished locomotor activity starting 2 weeks after weaning and persisting throughout the study (up to 20 weeks). The hypoactivity in this study is explained by an inverse weight-activity relationship. Postweaning, the increasing body weight associated with growth produces the observed reduction in activity levels. Pizzi *et al.* (68) injected neonatal mice (1 and 5 days of age) and older mice (25 days of age) with increasing doses of MSG over a 10-day period reported hypoactivity in the young mice, whereas older mice took much longer to show effects or failed to show any effects. In this study, the young rats experienced weight gain, but not the older mice who were weight stable. Taken together, these studies provide further evidence that body weight is the underlying factor responsible for hypoactivity in the chemical hypothalamic lesioned rodents. However, not all studies report hypoactivity in chemically induced obese rodents. Nikolettseas (69) observed that despite MSG-treated rats having greater body weights, their activity levels were not significantly different from nontreated controls. This suggested that the regulation of activity was due to the hypothalamic lesions rather than a weight-activity relationship. Furthermore, Araujo and Mayer (70) reported hyperactivity in MSG-treated male mice despite their increasing body weight. A methodological consideration of this study is the type of activity testing used. The use of a tilt-type cage raises the question as to whether the mice in this study would be hyperactive if devices that permit vigorous activity (i.e., a running wheel) had been used.

Finally, the validity of the hypothalamic-lesioned animal as a model of obesity is questioned because only in rare incidences are gross abnormalities of the hypothalamus reported as an underlying cause in human obesity. The use of genetically obese animal models is replacing the hypothalamic-lesioned obese animal model in obesity research. The hypothalamic-lesioned obese and the genetically obese rodent model differ in many respects (71). For example, vagotomy reverses obesity in VMH-lesioned obese rats but not in genetically obese rats. Also, the hypothalamic-induced (surgical and chemical) VMH-lesioned obese animals display different activity responses upon fasting and refeeding than other animal models of obesity. In the genetically obese and DIO animals models, food deprivation produces hyperactivity, whereas in VMH-lesioned animals, the hyperactivity associated with food deprivation is attenuated or absent (72, 73). Similarly, GTG-treated mice fail to show increase spontaneous activity upon starvation. Nor did GTG-treated mice decrease their activity upon refeeding (74). Given these differences, the results obtained from the hypothalamic obese versus other animal models of obesity are not directly comparable.

Activity as a Function of Strain

Another potential determinant of activity is genetics. In the animal studies, activity measured using either open field, running wheels, runways, or learning situations re-

ported activity levels differed depending on the rodent strain (75–78). Festing (79), measuring wheel activity in 26 different strains of mice, observed that closely related mouse strains have similar activity levels. Inbred rodent strains rather than outbred rodent strains are used to study genetics. This is because inbred animals show little genetic variation from one individual to the next, whereas the results obtained from outbred animals are confounded by large interindividual variations. Studies using inbred rodent strains show a clear genetic component influencing activity levels. Lassalle and Pape (80), comparing male mice of two inbred strains, i.e., BALB/c and C57BL/6, reported higher locomotor activity in the BALB/c mice. Figure 4, comparing the locomotor activity of male mice (age 6–10 weeks) of several different inbred mice strains, shows locomotor activity differs depending on the strain. Unfortunately, these studies did not provide body weight measurements. Thus, it could not be determined whether differences in body weight among mice strains may have contributed to the differences in locomotor activity observed in these studies.

Genetically obese rodents are increasingly being used as animal models of weight gain and obesity because recently, all single autosomal recessive gene defects (i.e. *ob*, *db*, and *fa*) that produce obesity in rodents have been cloned (81). The *ob/ob* mouse, regarded as the classic animal model of obesity, develops obesity from a single gene defect. Due to a mutation in the *ob* gene, the secretion of leptin from adipose tissue is absent. This has important implications because leptin is responsible for increasing EE. In the early studies, *ob/ob* obese mice were found to exhibit lethargic behavior and reduced activity (82). Therefore, the mechanism responsible for hypoactivity in genetically obese rodents may be reduced leptin levels. Leptin will be discussed in more detail later.

Another possible determinant of hypoactivity is the increasing body weight of genetically obese rats (see Fig. 1). Dauncey and Brown (83) observed that *ob/ob* mice exhibit 51%–70% less motor activity compared with lean mice, suggesting body weight restricts activity. However, regulation of activity by weight is more complicated than the simple restriction of movement due to extreme body weight. This is indicated by findings that young *ob/ob* mice begin to display low levels of activity before the development of their characteristic obesity (83). Similarly, running wheel activity was consistently lower in Zucker obese (*fa/fa*) rats compared with their lean littermates from the time of weaning to 6 months of age (84, 85). These findings suggest that even gradual increases in body weight affect activity levels in those predisposed to obesity. Swallow *et al.* (86) estimated the genetic correlation between body mass and running wheel to be -0.50 .

On the other hand, the failure of genetically obese mice such as the agouti and obese NZO to become less active than their lean littermates (87) argues against the suggestion of body weight as a determinant of activity. In reviewing the data, NZO mice were 58% heavier than lean mice and had

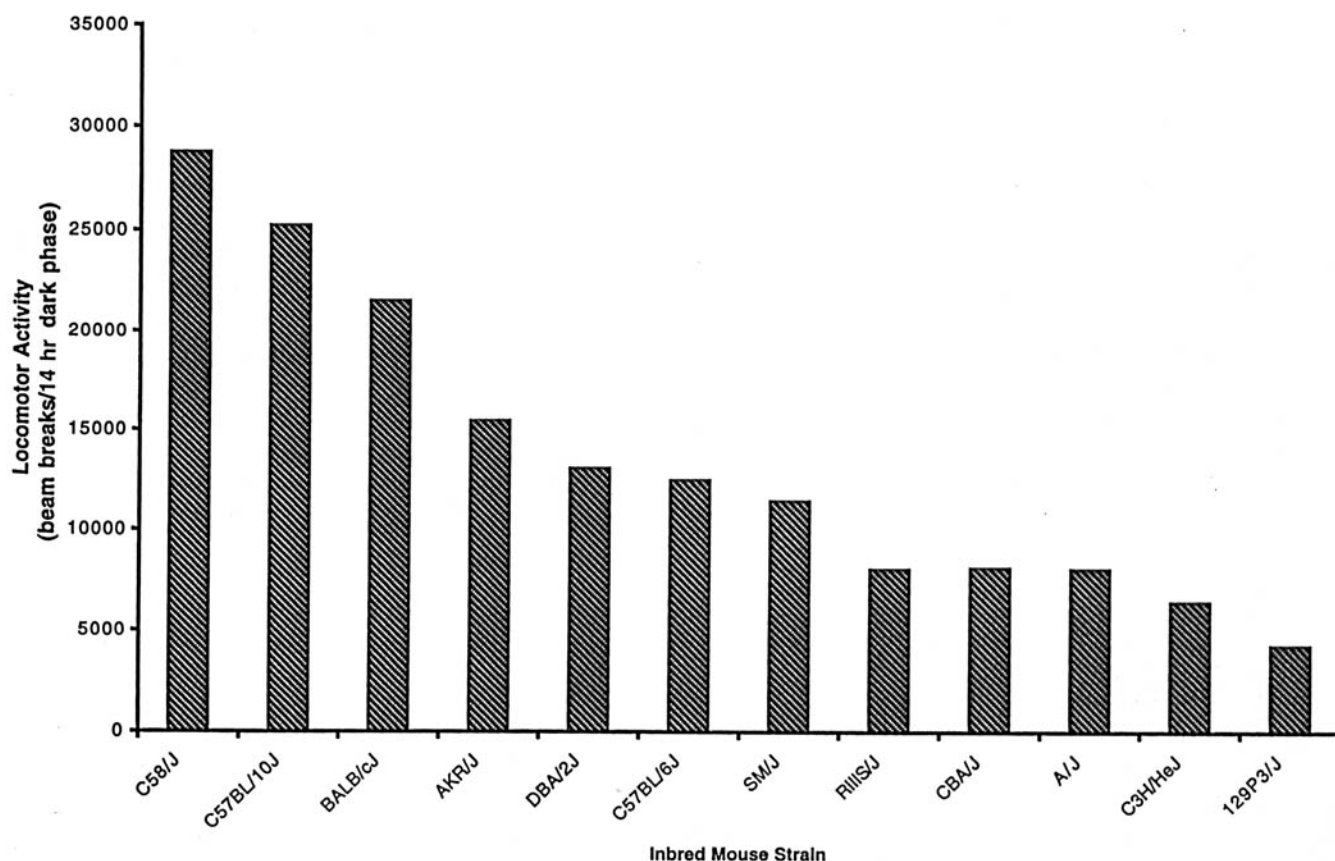


Figure 4. Locomotor activity measured as the mean horizontal + vertical (rearing) beam breaks in 4 hr during the dark cycle for different inbred strains of male mice aged 6–10 weeks. Values are the means of $n = 8$. Adapted from data from the Jackson Laboratory Mouse Phenome database: <http://aretha.jax.org/pub/cgi/phenome/>.

wheel running activity levels of 180 ± 65 counts/10 min compared with wheel-running activity levels of 250 ± 120 counts/10 min in lean mice. Thus, activity levels in the obese NZO mice were, in fact, numerically, although not statistically, lower than the lean controls. Therefore, differences were more likely due to random sampling. It should also be pointed out that devices used to measure activity levels often lack sensitivity. For example, Haberey *et al.* (11), using a seismograph, found no difference in activity despite the obese Zucker rats being 46% heavier than their respective lean counterparts. According to Yen and Acton (18), obese agouti mice were 50% heavier and exhibited higher activity (400 ± 60 counts/10 min) than their lean littermates (345 ± 20 counts/10 min), thus refuting an inverse weight-activity relationship. On closer examination, both lean and obese agouti displayed higher activity levels in comparison with other mice strains. Even when weight-matched with normal mice, agouti obese mice exhibit higher activity, suggesting this strain may be genetically prone to hyperactivity. The agouti obese mouse demonstrates that genetics can confound the weight-activity relationship. However, even with a genetic predisposition to obesity, the phenotype expressed depends on environmental factors (88).

Homozygosity for *ob* or *db* genes on a C57BL/6J background results in massive obesity, but the severity of the

accompanying diabetes is greatly diminished compared with the mutant phenotype on a C57BL/K background (89). Artificial selection is one method that may be applied to separate genetic from environmental influences on particular phenotypic traits. Swallow *et al.* (90) used selective breeding to create four replicate lines of mice with high activity levels. Mice from lines selected for high activity for 10 generations ran significantly more than did mice from unselected mice lines throughout the 8 week study (91). At maturity, the selected mice lines weighed 13.6% less than unselected mice lines, suggesting hypoactivity may be partly due to weight differences. Although a portion of individual differences in body weight can be explained by genetic differences, it seems unlikely that the increasing global prevalence of obesity has been driven by a dramatic change in the gene pool (92). It is more likely that certain changes in environmental factors, i.e., body weight, may override genetics. Thus, body weight may be a more important determinant of activity than genetics.

Activity as a Function of Age

In his review, Ingram (4) reported the existence of an age-related decline in exploratory activity across various strains of rats and mice. Mice from maturity (6 months) to senescence (32 months) experienced a greater than 50%

decline in exploratory activity. Similarly, an age-related decline in locomotor activity was also reported. Matching the findings for exploratory activity, mice over the adult range decreased their overall locomotor activity by approximately 50%. Age-related decline in physical activity is a well-established phenomenon in laboratory rodents and provides a useful tool for investigating the effect of age on physical activity in humans. However, the biological basis for an age-related decline in physical activity remains unclear. Several hypotheses have been put forth. Inoue *et al.* (93) observed that dopamine receptors decline in all brain regions as part of the normal process of aging. Furthermore, interventions that stimulated dopamine receptors or dopamine release resulted in increased locomotor activity, suggesting that an alteration in the dopamine neurotransmitter system is the underlying mechanism in age-related activity

decline. However, more studies are needed to confirm the role of dopamine on age-related activity decline.

Another hypothesis suggests that age-related decline in activity may be related to leptin, based on the observation that the F344 $\times$ BN rat, a rodent model for late-onset obesity, exhibits impaired leptin responsiveness (94). Leptin stimulates EE; thus, the reduction of leptin levels associated with aging may be responsible for declining activity levels with age. Another mechanism whereby leptin may exert its effects is through the regulation of body weight. Studies found that genetically obese *ob/ob* mice and *db/db* mice lose weight in response to administration of leptin (95). Figure 5 shows that *ob/ob* mice treated with weekly injections of leptin have reduced body weight gain and increased activity levels compared with untreated *ob/ob* mice. Taken together, the data indicate that body weight regulation by leptin func-

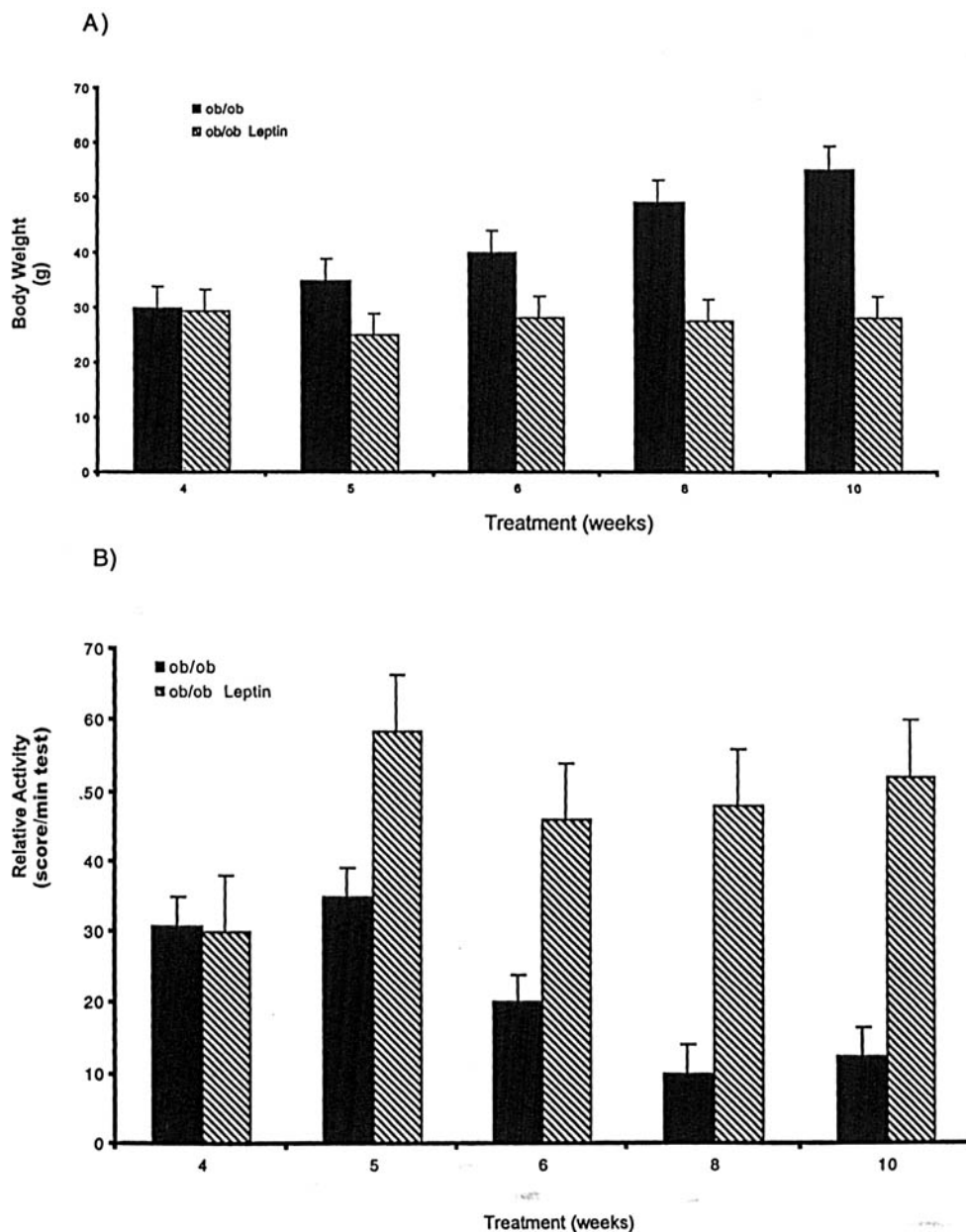


Figure 5. The effect of daily injection (ip) of leptin (1 μ g/g body wt) or saline on female C57BL/6J *ob/ob* mice (age 4 weeks) on body weight (A) and activity in an open field test (B). Relative activity was determined by assigning scores for walking (number of floor grid lines crossed), climbing, rearing, and grooming during a 1-min test period. Data are the mean $\pm$ SEM of $n = 5$ /group. Adapted from Ahima *et al.* 1999 (Ref. 95).

tions as the determinant of activity. However, Surwit (96) showed only a moderate effect of leptin treatment on body weight and no effect on the locomotor activity in C57BL/6J obese prone and A/J obesity-resistant mice (96).

Finally, body weight is hypothesized to regulate activity. Aging rodents and humans have been observed to gain weight (97–99). The close association of weight gain to aging leads to the suggestion that body weight is the determinant of activity. This close association also makes it difficult to examine their effects separately. Genetically obese and lean rodents provide a useful model for investigating a potential age-weight-activity relationship because of their vast weight differences at similar ages. Ahima *et al.* (95) reported that at 4–5 weeks of age, *ob/ob* mice, despite increasing body weight by 25%, showed no significant effect on locomotor activity. At 10 weeks, body weight increased by 80% and locomotion decreased by 50%. In this study, it could not be distinguished whether critical weight, age, or an age-weight interaction was the underlying mechanism for reduced activity levels. In another study, Mowrey and Hershberger (100) found decreased activity in obese male Zucker rats starting at age 44 days compared with their lean littermates. Reduced activity at a young age suggests that decreased activity is not due to senescence, but to the weight differences between the obese and lean animals. However, the activity differences between the obese and lean rats in this study did not reach statistical significance until age 205-days. This may have been due to the study's small sample size ($n = 4/\text{group}$) and high standard deviations.

A problem with establishing an inverse weight-activity relationship in young animals is the absence of large weight differences in growing animals. Prior to weaning, the activity of lean and genetically obese rats are similar (101). Except for one study reporting Zucker obese rats to be significantly heavier than Zucker lean rats at 15 days of age (100), no other study has been able to establish significant differences in body weight between obese and lean Zucker rats before weaning age. According to Bray and York (87) Zucker (*fa/fa*) rats cannot be distinguished by body weight from their lean littermates before 4–5 weeks of age. Following weaning, genetically obese rats become progressively less active than their lean littermates (85). Figure 6 shows that during postweaning days 16–22, body weights are higher in Zucker (*fa/fa*) obese male rat pups compared with the lean controls, but the pups do not differ in activity. Only after postweaning day 22 was motor activity decreased in Zucker obese rat pups (85). Based on these findings, an inverse activity-weight relationship appears invalid in young growing animals. Unfortunately, the animal data do not permit firm conclusions about activity patterns during youth because most activity studies have been conducted using adult male animals.

In mature animals, there does appear to be a consistent inverse relationship between body weight and activity. Still, it should be cautioned that the genetically obese animal models, the DIO and hypothalamic lesion obese

animals have limitations. The genetically obese animal may not be the best model for investigating an age-weight-activity relationship because, in addition to obesity, other metabolic abnormalities are expressed. At 4 weeks of age, obese rodent display an almost 3-fold increase in carcass fat accompanied by elevated plasma glucose, insulin, and triglycerides (82). Hyperglycemia, a prominent feature of *ob/ob* mice, appears at the onset of obesity and hyperinsulinemia appears by 12 months of age (102). In aging genetically obese animals, results may be confounded by depressed activity associated with health problems. It appears that age is another factor that confounds the weight-activity relationship.

Activity as a Function of Gender

Most of the research investigating physical activity has been conducted using adult male animals. Studies using female rats report more exploration in an open maze field (103), higher activity in an open field box (104), and a greater number of entries into the open arms of an elevated maze compared with male rats (105). These findings suggest gender differences in activity levels. Based on the rodent studies, females appear to be more active than males. Tropp and Markus (104) found female and male rats differ in their initial interaction with the environment, but these gender differences diminish upon repeated exposures. It is proposed that the gender difference in activity is the result of sex differences in overall cognitive performance, behavior, or anxiety. Thus, it is important to consider these factors when designing experiments that measure activity. For example, using learning situations (i.e., mazes) to measure activity can lead to the results being confounded by cognitive differences between males and females. Measurement of exploratory versus locomotor activity also produces variable results. Simmel *et al.* (8) reported higher locomotor activity in male rats compared with female rats, whereas in exploratory tests, activity was higher in female than in male rats (103, 104). This is because in exploratory tests, volitional activity is influenced by behavior. Furthermore, West and Michael (106) found that handling animals prior to testing significantly increases activity levels, with effects being more pronounced in female than in male rats.

Another hypothesis for the gender differences in activity is attributed to the higher estrogen levels in females. The role of estrogen in the regulation of activity is apparent from the hormonal changes accompanying estrous cycling in female rats. During the proestrus phase when blood estrogen levels are high, activity levels increase. On the other hand, during the diestrus phase when blood estrogen levels are low, activity levels decline (107, 108). The importance of estrogen in the regulation of activity is further indicated by studies showing that removal of estrogen by ovariectomy (OVX) results in a sharp decline in running wheel activity of rats. On the other hand, OVX rats treated with physiological doses of estrogen results in the restoration of their activity to the pre-OVX level (108, 109). Several mecha-

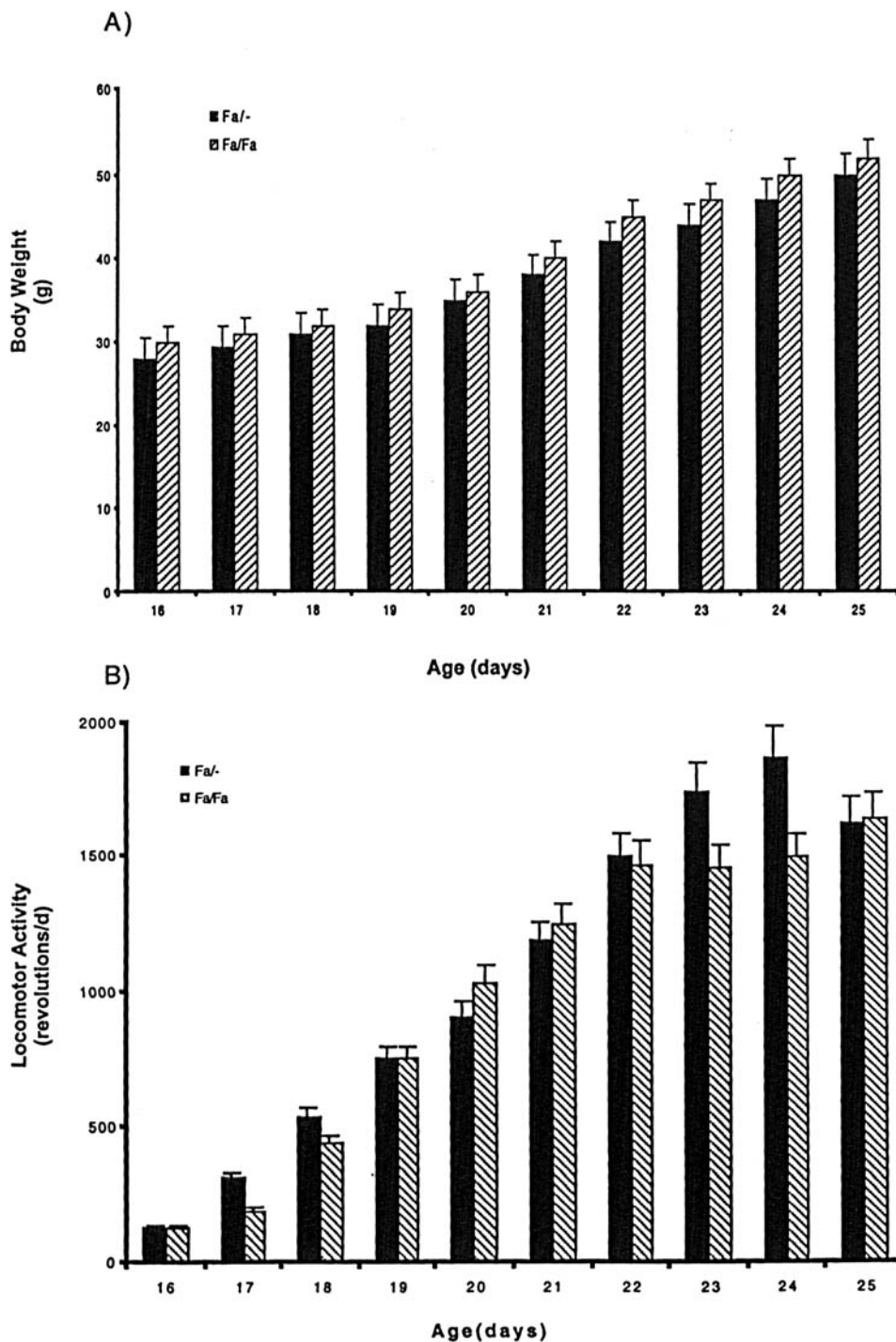


Figure 6. Comparison of lean (*Fa/-*) versus genetically obese (*Fa/Fa*) male rat pups during the preweaning stage (age 16–25 days) body weight gain (A) and locomotor activity indicated by wheel turns during 3 hr during the dark cycle. (B) Values are the mean $\pm$ SEM for $n = 34$ lean (*Fa/-*) and $n = 16$ obese (*Fa/Fa*) rats. Adapted from Stern and Johnson, 1977 (Ref. 85).

nisms for the regulation of activity levels by estrogen are proposed. One suggestion is regulation of activity by the differential effects of estrogen levels on memory (103). However, this only explains activity differences in exploratory, maze, and other learning tests.

Another suggestion is based on estrogen's regulation of food intake and body weight. During proestrus, blood estrogen levels are high and food intake decreases, resulting in weight loss (107, 108). As previously discussed, acute weight loss is associated with hyperactivity. Thus, reduc-

tions in body weight may be the mechanism responsible for rising activity levels during proestrus. In support, studies show that body weight increases in OVX rats (110). An inverse weight-activity relationship explains the sharp decline in activity observed following the OVX of rats. Furthermore, body weight appears to regulate activity independent of food intake. Shimomura *et al.* (111) found no differences in food intake between OVX and control rats. Instead, weight gain was attributed to reduced EE by gradual decreases in ambulatory activity in OVX rats. Fi-

nally, body weight as a determinant of activity explains the difference in activity between male and female rats. Male rats become heavier than female rats after Day 33 of age due to increasing testosterone (112). Figure 7 shows that female rats have lower body weights and higher locomotor activity than male rats (113). In accordance with our proposed inverse weight-activity relationship, the higher activity expressed by female compared with male rats is attributed to their lower body mass. To our knowledge, no direct comparisons of activity levels in male and female rats have been made due in large part to the difficulties of controlling the variability in activity associated with estrous cycling in females.

Arguments against body weight as the determinant of gender differences are based on the absence of significant changes in body weight during the different phases of the estrous cycle in obese and OVX obese Zucker rats (114, 115). However, the lack of change in body weight was accompanied by a lack of change in activity. Thus, the weight-activity relationship remains valid. In the case of obese animals, estrogen levels are often elevated. Therefore, abnormal endogenous estrogen levels may have confounded the results of studies using obese animals. In reviewing the literature, it appears possible that gender differences in physical activity exist. It appears that gender is another factor that confounds the weight-activity relationship. More

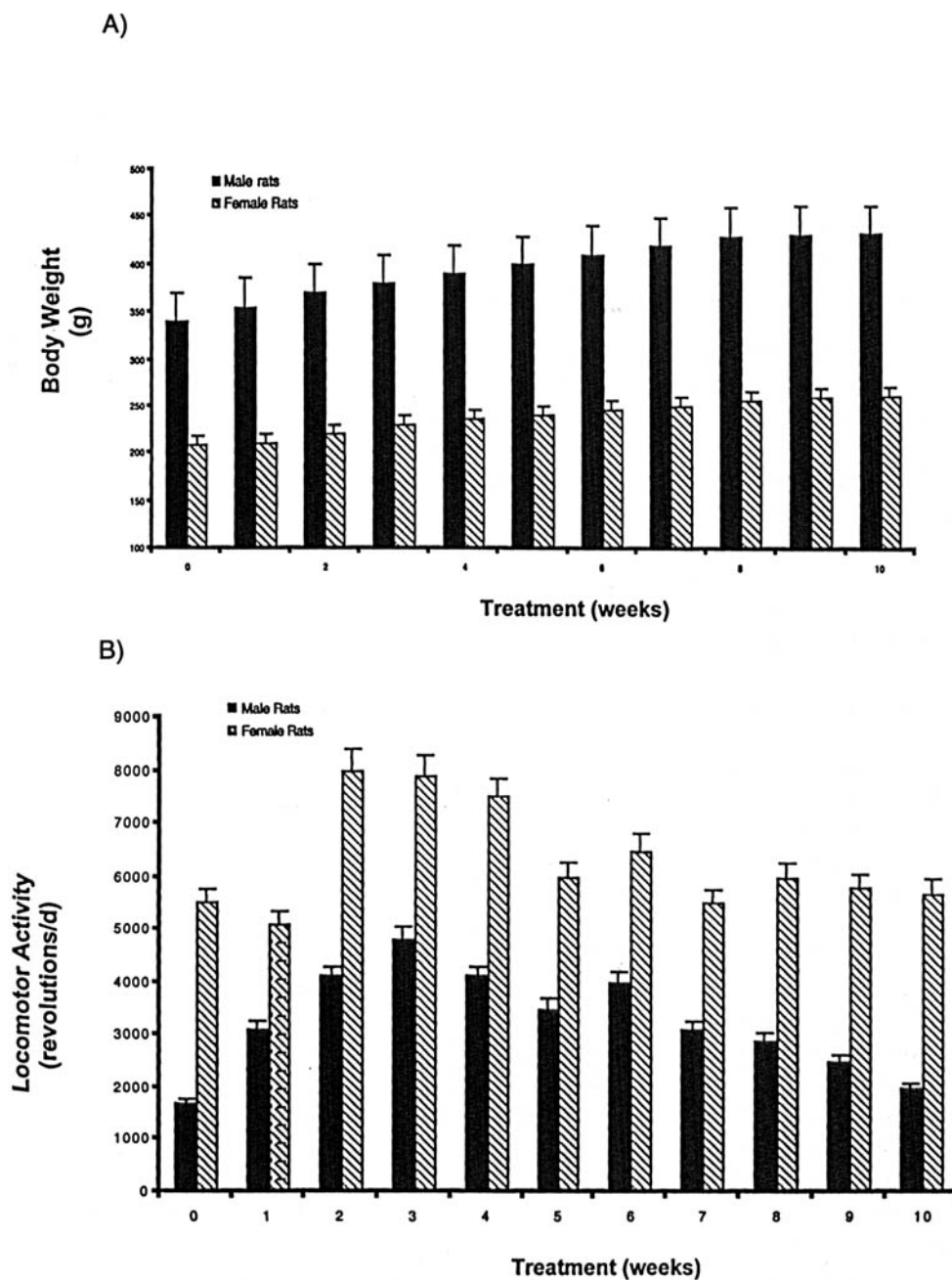


Figure 7. The effect of gender differences in Lister rats age 9–12 weeks fed commercial rodent chow on body weight (A) and locomotor activity by running wheels (B). Adapted from Rolls and Rowe, 1979 (Ref. 113).

studies are needed to determine the existence of gender differences in weight gain and its implications in the management of weight loss in humans.

Relevance to Humans

Many factors are capable of influencing weight and physical activity, making it difficult to establish an inverse weight-activity relationship. The advantage of using animal models is the ability to control for these factors. Few question the importance of genetics in body weight regulation. Studies have consistently shown that approximately 40%–70% of obesity-related phenotypes in humans such as body mass index, skinfold thickness, fat mass, and leptin levels are heritable (116–118). However, due to the lack of homogeneity in the human population, studies on the effect of genetics on EE have been confined to parent-child, and monozygous and dizygous twin studies (119). On the other hand, the genetics of animals can be manipulated to minimize such intervariability. Whenever animals are used, the relevance of findings to humans is questioned. In genetically obese animals, obesity is due to a single mutation. This may be too simplistic because obesity in humans is the result of polymorphism. However, environment often overrides genetics. In both animals and humans, expression of a certain phenotype is dependent on the environment to which the individual is exposed. Again, animal models have the advantage of permitting greater control of environmental factors. In humans, failure to control for the numerous factors that affect body weight and activity makes it difficult to tease out a weight-activity relationship. For example, in free-living humans, the contribution of NEAT to EE is difficult to measure. This has important implications because NEAT is a large contributor of EE. Animal studies are useful in providing information about NEAT until improvements can be made in the methodology for measuring both conscious and unconscious activity in free-living humans. Animal findings also suggest gender differences in activity. Women have lower BMR than males, suggesting that similar gender differences in activity may also exist in humans. Not all findings in animals are applicable to humans. The role of leptin in the regulation of body weight is well-defined in animals, but the importance of leptin in the regulation of body weight in humans is not definitive. Hypothalamic lesions leading to obesity have been studied extensively in animals, but rarely occur in humans. The manifestations of hypothalamic lesion-induced obesity differ from other models of obesity, suggesting the lack of relevance of this model to humans. In both animals and humans, aging leads to body weight gain and reduced activity. However, humans differ from animals in that they are conscious of the benefits of physical activity. Human awareness can alter factors such as aging that may otherwise contribute to the weight-activity relationship. The animal studies provide several advantages that can yield useful insight into the role of body weight and other determinants on activity in humans. However, caution should be used when

extrapolating these results to humans. The suggestion of an inverse weight-activity relationship in humans remains to be determined.

Conclusions

In our increasingly sedentary environment, it is important to determine the parameters affecting activity levels. This is especially relevant because the growing prevalence of obesity has been attributed to declining activity levels. Increasing EE through physical activity is commonly prescribed as a regimen in weight loss programs. Based on the review of the animal studies, physical activity appears to be influenced by a number of biological parameters. Factors such as diet, hypothalamic lesions, genetics, age, and gender all affect activity as well as weight gain. Body weight consistently appears to be an underlying mechanism regulating activity levels. However, suggestions that activity decline is a manifestation of increased body weight are inconclusive and difficult to prove. This is because many of the factors influencing activity levels are closely interlocked, allowing a combination or an interaction of factors to influence activity levels. The conflicting results of the role of weight on activity levels are also partially related to the difficulty of accurately assessing physical activity using existing methodology. A greater knowledge of the factors influencing activity levels will likely follow with the development of better methods for quantifying physical activity as well as development of methods that permit the measurement of NEAT. A better understanding of the biological determinants affecting physical activity is important for the development of strategies to prevent and/or treat the growing prevalence of weight gain and obesity in the human population.

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1. James W. Epidemiology of obesity. *Int J Obes Relat Metab Disord* **2S**:23S–26S, 1992.
2. Sallis J, Hovell M. Determinants of exercise behavior. *Exerc Sport Sci Rev* **18**:307–330, 1990.
3. Levine J, Eberhardt N, Jensen M. Role of non-exercise activity thermogenesis in resistance to fat gain in humans. *Science* **283**:212–214, 1999.
4. Ingram D. Age-related decline in physical activity: generalization to non-humans. *Med Sci Sports Exerc* **32**:1623–1629, 2000.
5. Elias P, Elias M, Eleftheriou B. Emotionality, exploratory behavior, and locomotion in aging inbred strains of mice. *Genontologia* **21**:46–55, 1975.
6. Goodrick C. Activity and exploration as a function of age and deprivation. *J Genetic Psychol* **108**:239–252, 1966.
7. Simmel E. Social facilitation of exploratory behavior in rats. *J Comp Physiol Psychol* **55**:831–833, 1962.
8. Simmel E, Haber S, Harshfield G. Age, sex and genotype effects on stimulus exploration and locomotor activity in young mice. *Exp Aging Res* **2**:253–269, 1976.
9. Mather J. Wheel-running activity: a new interpretation. *Mammal Rev* **11**:41–51, 1981.
10. Sherwin C. Voluntary wheel running: a review and novel interpretation. *Animal Behav* **56**:11–27, 1998.
11. Haberey P, Bach A, Schaefer A, Piquard F. Spontaneous activity and

- food requirements for maintenance and for growth in the genetically obese Zucker rat. *Nutr Metab* 23:218–227, 1980.
12. Moran M, Roy R, Wade C, Corbin B, Grindeland R. Size constraints of telemeters in rats. *J Appl Physiol* 85:1564–1571, 1998.
 13. Ravussin E, Lillioja S, Anderson T, Christin L, Bogardus C. Determinants of 24-hr energy expenditure in man: methods and results using a respiratory chamber. *J Clin Invest* 78:1568–1578, 1986.
 14. Ravussin E, Tataranni P. Dietary fat and human obesity. *J Am Diet Assoc* 97:42S–46S, 1997.
 15. U.S. Department of Health and Human Services. Physical Activity and Health: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion, 1996.
 16. Borer K, Kaplan L. Exercise-induced growth in golden hamsters: effects of age, weight and activity levels. *Physiol Behav* 18:23–34, 1977.
 17. Ardevol A, Adan C, Remesar X, Fernandez-Lopez J, Alemany M. Hindleg heat balance in obese Zucker rats during exercise. *Pflügers Arch* 435:454–464, 1998.
 18. Yen T, Acton J. Locomotor activity of various types of genetically obese mice. *Proc Soc Exp Biol Med* 140:647–650, 1972.
 19. Dewsbury D. Wheel running behavior in 12 species of murid rodents. *Behav Process* 6:271–280, 1980.
 20. Clark L, Gay P. Activity and body relationships in genetically obese animals. *Biol Psychol* 4:247–250, 1972.
 21. Pullar J, Webster A. Energy metabolism during growth in normal and congenitally obese rats. *Proc Nutr Soc* 32:19A, 1973.
 22. Jenkins T, Hershberger T. Effect of diet, body, type and sex on voluntary intake, energy balance and body composition of Zucker rats. *J Nutr* 108:124–136, 1978.
 23. Keeseey R, Swiergiel AH, Corbett SW. Contribution of spontaneous activity to daily energy expenditure of adult obese and lean Zucker rats. *Physiol Behav* 48:327–331, 1990.
 24. Hill J, Melanson E, Wyatt H. Dietary fat intake and regulation of energy balance: implications for obesity. *J Nutr* 130:284S–288S, 2000.
 25. Hill J, Dorton J, Sykes M, Digirolamo M. Reversal of dietary obesity is influenced by its duration and severity. *Int J Obesity* 13:711–722, 1989.
 26. West D, Boozer C, Moody D, Atkinson R. Obesity induced by a high-fat diet in strains of inbred mice. *Am J Physiol Regulatory Integrative Comp Physiol* 262:1025–1032, 1992.
 27. West D, York B. Dietary fat, genetic predisposition, and obesity: lessons from animal models. *Am J Clin Nutr* 67:505S–512S, 1998.
 28. Lissner L, Heitmann B. Dietary fat and obesity: evidence from epidemiology. *Eur J Clin Nutr* 49:79–90, 1995.
 29. Lissner L, Levitsky D, Strupp B, Kalkwarf H, Roe D. Dietary fat and the regulation of energy intake in human subjects. *Am J Clin Nutr* 46:886–892, 1997.
 30. Stubbs R, Harbron C, Murgatroyd P, Prentice A. Covert manipulation of dietary fat and energy density: effect on substrate flux and food intake in men eating ad libitum. *Am J Clin Nutr* 62:316–329, 1995.
 31. Schiffman S, Graham B, Sattely-Miller E, Warwick Z. Orosensory perception of dietary fat. *Curr Dir Psychol Sci* 7:137–143, 1998.
 32. Flatt J, Ravussin E. Effects of dietary fat on postprandial substrate oxidation and on carbohydrate and fat balances. *J Clin Invest* 76:1019–1024, 1985.
 33. Sclafani A. Diet-induced obesity in rodents. In: Oomura Y, Tarui S, Inoue S, Eds. *Progress in Obesity Research*. London: John Libbey and Company, pp441–444, 1991.
 34. Sclafani A. Dietary obesity. In: Stunkard AJ, Wadden TA, Eds. *Obesity: Theory and Therapy*. New York: Raven Press, pp123–135, 1993.
 35. Schemmel R, Mickelsen O, Gill J. Dietary obesity in rats: body weight and body fat accretion in seven strains of rats. *J Nutr* 100:1041–1048, 1970.
 36. Pagliassotti M, Gayles E, Hill J. Fat and energy balance. *Ann NY Acad Sci* 20:431–448, 1997.
 37. Blundell J, Lawton C, Cotton J, MacDiarmid JJ. Control of human appetite: implications for the intake of dietary fat. *Rev Nutr* 79:451–480, 1996.
 38. Willet W. Dietary fat and obesity: an unconvincing relation. *Am J Clin Nutr* 68:1149–1150, 1998.
 39. Jequier E, Tappy L. Regulation of body weight in humans. *Physiol Rev* 79:451–480, 1999.
 40. Horton T, Drougas H. Fat and carbohydrate overfeeding in humans: different effects on energy storage. *Am J Nutr* 62:19–29, 1995.
 41. Roberts S, Fuss P. Effects of age on energy expenditure and substrate oxidation during experimental overfeeding in healthy men. *J Gerontol* 51:148–157, 1996.
 42. Baumeister A, Hawkins W, Cromwell R. Need state and activity level. *Psychol Bull* 61:438–458, 1964.
 43. Collier G, Hirsch E. Reinforcing properties of spontaneous activity in the rat. *J Comp Physiol Psychol* 77:155–160, 1971.
 44. Collier G, Hirsch E, Levitsky D, Leshner A. Effort as a dimension of spontaneous activity in rats. *J Comp Physiol Psychol* 88:89–96, 1975.
 45. Moskowitz M. Running wheel activity in the white rats as a function of combined food and water deprivation. *J Comp Physiol Psychol* 52:621–625, 1959.
 46. Borer K. The nonhomeostatic motivation to run. In: Morrison AR, Strick PL, Eds. *Changing Concepts of the Nervous System*. New York: Academic Press, pp539–567, 1982.
 47. Borer K. The reciprocal relation between endurance physical activity and body fatness. In: Hansen BC, Ed. *Controversies in Obesity*. New York: Praeger Scientific, pp255–273, 1983.
 48. Collier G. Work: a weak reinforcer. *Trans NY Acad Sci* 32:557–576, 1970.
 49. Dill D, Soholt L, Morris JJ. Wheel running of kangaroo rats, *Dipodomys merriami*, as related to food deprivation and body composition. *J Appl Physiol* 44:17–20, 1978.
 50. Peck J. Rats defend different body weights depending on the palatability and accessibility of their food. *J Comp Physiol Psychol* 92:555–570, 1978.
 51. Sclafani A, Rendel A. Food deprived-induced activity in dietary obese, dietary lean and normal weight rats. *Behav Biol* 24:220–228, 1978.
 52. Brownlow B, Petro A, Feinglos M, Surwit R. The role of motor activity in diet-induced obesity in C57BL/mice. *Physiol Behav* 60:37–41, 1996.
 53. Peckham S, Entenman C, Carrol H. The influence of hypercaloric diet on gross body and adipose tissue composition in the rat. *J Nutr* 77:187–197, 1962.
 54. Levin B. Spontaneous motor activity during the development and maintenance of diet-induced obesity in the rat. *Physiol Behav* 5:573–581, 1991.
 55. Bray G, York D. Hypothalamic and genetic obesity in experimental animals: an autonomic and endocrine hypothesis. *Phys Rev* 59:719–784, 1979.
 56. Bray G, Gallagher T. Manifestation of hypothalamic obesity in man: a comprehensive investigation of 8 patients and a review of the literature. *Medicine* 54:301–330, 1975.
 57. Bernardis L. Disruption of diurnal feeding and weight gain cycles in weanling rats by ventromedial and dorsomedial hypothalamic lesions. *Physiol Behav* 10:855–861, 1973.
 58. Kennedy G. The role of dietary fat in the hypothalamic control of food intake in the rat. *Proc R Soc Lon Ser B* 140:578–592, 1953.
 59. Miller N, Bailey C, Stevenson J. Decreased “hunger” but increased food intake resulting from hypothalamic lesions. *Science* 112:256–259, 1950.
 60. Teitelbaum P. Random and food-directed activity in hyperphagic and normal rats. *J Comp Physiol* 50:486–490, 1957.
 61. Marks H, Remley N. The effects of type of lesions and percentage body weight loss on measures of motivational behavior in rats with hypothalamic lesions. *Behav Biol* 7:95–111, 1972.
 62. Beatty W, Vilberg T, Shirk T, Siders W. Pretraining effects on operant responding for food, frustration and reactivity to food-related cues in rats with VMH lesions. *Physiol Behav* 15:577–584, 1975.
 63. Tonkunaga K, Matsuzawa Y, Fujioka S, Kobatake T, Keno Y, Odaka H, Matsua T, Tarui S. PVN-lesioned obese rats maintain ambulatory activity and its circadian rhythm. *Brain Res Bull* 26:393–396, 1991.
 64. Cox J, Powley T. Intragastric pair feeding fails to prevent VMH obesity or hyperinsulinemia. *Am J Physiol Endocrinol Metab* 240:566–572, 1981.
 65. Djazayery A, Miller D. The use of gold-thioglucose and monosodium glutamate to induce obesity in mice. *Proc Nutr Soc* 32:30A–31A, 1973.
 66. Olney J. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 164:719–721, 1969.
 67. Poon T, Cameron D. Measurement of oxygen consumption and lo-

- comotor activity in monosodium glutamate-induced obesity. *Am J Physiol Endocrinol Metab* 234:532–534, 1978.
68. Pizzi W, Barnhart J. Effects of monosodium glutamate on somatic development, obesity and activity in the mouse. *Pharmacol Biochem Behav* 5:551–557, 1976.
 69. Nikolettseas M. Obesity in exercising, hypophagic rats treated with monosodium glutamate. *Physiol Behav* 19:767–773, 1977.
 70. Araujo P, Mayer J. Activity increase associated with obesity induced by monosodium glutamate in mice. *Am J Physiol* 225:764–765, 1973.
 71. Eng R, Gold R, Sawchenko P. Hypothalamic hypoactivity prevented but not reversed by subdiaphragmatic vagotomy. *Physiol Behav* 20:637–641, 1977.
 72. Greenwood M, Quartermain D, Johnson P, Cruce J, Hirsch J. Food motivated behavior in genetically obese and hypothalamic-hyperphagic rats and mice. *Physiol Behav* 13:687–692, 1974.
 73. Challet E, Le Maho Y, Malan A. Locomotor activity and utilization of energy reserves during fasting after ventromedial hypothalamic lesions. *Physiol Behav* 58:257–264, 1995.
 74. Hollifield G. Studies of food drive and satiety in mice with gold thioglucose-induced obesity and the hereditary obesity-diabetes syndrome. *Metabolism* 4:537–541, 1955.
 75. Parsons P. The behavior phenotype in mice. *Am Nat* 108:377–385, 1974.
 76. Peeler D. Activity as a function of genetic variables and opportunity for exploration. *Psychol Sci* 27:176–178, 1972.
 77. Symons J. Wheel-running activity during ad lib and food deprivation conditions in four inbred mouse strains. *Bull Psychol Soc* 1:78–80, 1972.
 78. Thompson W. The inheritance of behavior activity differences in five inbred mouse strains. *J Heredity* 47:147–148, 1956.
 79. Festing M. Wheel activity in 26 strains of mouse. *Lab Animals* 11:257–258, 1977.
 80. Lassalle J, Pape G. Locomotor activity of two inbred strains of mice in a seminatural and a breeding cage environment. *Behav Genet* 8:371–376, 1978.
 81. Bray G. Progress in understanding the genetics of obesity. *J Nutr* 127:940S–942S, 1997.
 82. Mayer J. Decreased activity and energy balance in the hereditary obesity-diabetes syndrome of mice. *Science* 117:504–505, 1953.
 83. Dauncey M, Brown D. Role of activity-induced thermogenesis in twenty-four hour energy expenditure of lean and genetically obese (*ob/ob*) mice. *Exp Physiol* 72:549–559, 1987.
 84. Ennis M, Wecker J, Grinker J. Interrelationships among activity, food intake and weight gain in genetically obese and lean Zucker rats. *Physiol Behav* 28:1059–1064, 1982.
 85. Stern J, Johnson P. Spontaneous activity and adipose cellularity in the genetically obese Zucker (*fa/fa*) rat. *Metabolism* 26:371–380, 1977.
 86. Swallow J, Koteja P, Carter P, Garland T. Artificial selection for increased wheel-running activity in house mice results in decreased body mass at maturity. *J Exp Biol* 202:2513–2520, 1999.
 87. Bray G, York D. Genetically transmitted obesity in rodents. *Phys Rev* 51:598–646, 1971.
 88. Hirsch J. Pathophysiology of obesity. *J Nutr* 127:1874S, 1997.
 89. Leibel R, Bahary N, Friedman J. Genetic variation and nutrition in obesity: approaches to the molecular genetics of obesity. In: Simopoulos AP, Childs B, Eds. *World Review of Nutrition and Diet: Genetic Variation and Nutrition*. New York: Basel and Karger, pp90–101, 1990.
 90. Swallow J, Carter P, Garland TJ. Artificial selection for voluntary activity levels in random-bred house mice. *Am Zool* 35:39, 1995.
 91. Swallow J, Garland TJ, Carter P, Zhan W, Sieck G. Effects of voluntary activity and genetic selection on aerobic capacity in house mice (*Mus domesticus*). *J Appl Physiol* 84:69–76, 1998.
 92. Goran M, Treuth M. Energy expenditure, physical activity and obesity in children. *Pediatr Clin North Am* 48:931–953, 2001.
 93. Inoue M, Suhara T, Sudo Y, Okubo Y, Yasuno F, Kishimoto T, Yoshikawa K, Tanada S. Age-related reduction of extrastriatal dopamine D2 receptor. *Life Sci* 69:1079–1084, 2001.
 94. Scarpace P, Matheny M, Shek E. Impaired leptin signal transduction with age-related obesity. *Neuropharmacology* 39:1872–1879, 2000.
 95. Ahima R, Bjorbaek C, Osei S, Flier J. Regulation of neuronal and glial proteins by leptin: implications for brain development. *Endocrinology* 140:2755–2762, 1999.
 96. Surwit R. Transient effects of long-term leptin supplementation in the prevention of diet-induced obesity in mice. *Diabetes* 49:1203–1208, 2000.
 97. Brazilai N, Rossetti L. Relationship between changes in body composition and insulin responsiveness in models of the aging rat. *Am J Physiol Endocrinol Metab* 269:591–597, 1995.
 98. Masoro J. Rats as models for the study of obesity. *Exp Aging Res* 6:261–270, 1980.
 99. Newby F, Digirolam M, Cotsonis G, Kuner M. Model of spontaneous obesity in aging male Wistar rats. *Am J Physiol Regulatory Integrative Comp Physiol* 259:1117–R1125, 1990.
 100. Mowrey R, Hershberger T. Effect of age and body weight on the maintenance requirement of lean and obese Zucker rats. *J Nutr* 112:2116–2121, 1982.
 101. Bell G, Stern J. Development of obesity and hyperinsulinemia in the Zucker obese rat (*fa/fa*). *Fed Proc* 35:657–661, 1979.
 102. Storlien L. Animal models of obesity. In: Bond NW, Ed. *Animal Models of Psychopathology*. New York: Academic Press, pp147–176, 1984.
 103. Joseph R, Hess S, Birecree E. Effects of hormone manipulations and exploration on sex differences in maze learning. *Behav Biol* 24:364–377, 1978.
 104. Tropp J, Markus E. Sex differences in the dynamics of cue utilization and exploratory behavior. *Behav Brain Res* 119:143–154, 2001.
 105. Leret M, Molina-Holgado F, Gonzalez M. The effect of perinatal exposure to estrogens on the sexually dimorphic response to novelty. *Physiol Behav* 55:371–373, 1994.
 106. West C, Michael R. Mild stress influences sex differences in exploratory and amphetamine-enhanced activity in rats. *Behav Brain Res* 30:95–98, 1988.
 107. Brobeck J, Wheatland M, Stronminger J. Variations in regulation of energy exchange associated with estrus, diestrus and pseudopregnancy in rats. *Endocrinology* 40:65–72, 1947.
 108. Colvin G, Sawyer C. Induction of running activity by intracerebral implants of estrogen in ovariectomized rats. *Neuroendocrinology* 4:309–320, 1969.
 109. Rodier W. Progesterone-estrogen interactions in the control of activity-wheel running in the female rat. *J Comp Physiol Psychol* 74:365–373, 1971.
 110. Hervey E, Hervey G. The influence of sex hormones on energy balance. In: Cioffi LA, James WPT, Vanlallie TB, Eds. *The Body Weight Regulation System*. New York: Raven Press, pp345–352, 1981.
 111. Shimomura Y, Shimizu H, Takahashi M, Sato N, Uehara Y, Fukatsu A, Negishi M, Kobayashi I, Kobayashi S. The significance of decreased ambulatory activity during the generation by long-term observation of obesity in ovariectomized rats. *Physiol Behav* 47:155–159, 1990.
 112. Gabriel S, Roncancio J, Ruiz N. Growth hormone pulsatility and endocrine milieu during sexual maturation in male and female rats. *Neuroendocrinology* 56:619–625, 1992.
 113. Rolls B, Rowe E. Exercise and the development and persistence of dietary obesity in male and female rats. *Physiol Behav* 23:241–247, 1979.
 114. Bray G. Endocrine factors in the modulation of food intake. *Proc Nutr Soc* 37:301–309, 1978.
 115. Shaw ME, Whitaker E, Hervey E, Hervey G. The effects of ovarian hormones on the regulation of energy balance in Zucker rats. *J Endocrinol* 98:165–171, 1983.
 116. Allison D, Kaprio J, Korkeila M, Koskenvuo M, Neale M, Hayakawa K. The heritability of body mass index among an international sample of monozygotic twins reared apart. *Int J Obes Relat Metab Disord* 6:501–506, 1996.
 117. Comuzzie A, Blangero J, Mahaney M, Haffner S, Mitchell B, Stern M, MacCluer MJ. Genetic and environmental correlations among hormone levels and measures of body fat accumulation and topography. *J Clin Endocrinol Metab* 81:597–600, 1996.
 118. Comuzzie A, Blangero J, Mahaney M, Mitchell B, Stern M, MacCluer J. Genetic and environmental correlations among skinfold measures. *Int J Obes Relat Metab Disord* 18:413–418, 1994.
 119. Bouchard C, Perusse L. Genetics of obesity. *Annu Rev Nutr* 13:337–354, 1993.