

Determinants Affecting Physical Activity Levels  
In Animal Models

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## **Abstract**

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 multi-factorial 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.

## **Introduction**

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 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 factor 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.

## **Definition of Physical Activity and Its Components**

Physical activity is the energy used above that 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 non-exercise activity

thermogenesis (NEAT) (3). NEAT encompasses the unconscious activities of daily living and the energy cost of all non-volitional activity such as: fidgeting, muscle tone and maintenance of posture when not lying down. Various terms used to describe non-volitional exercise are voluntary movement, spontaneous activity, non-resting EE and fidgeting. This review uses the term NEAT when referring to non-volitional 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 their activity monitored for at least 24 h. 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, 6, 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 (i.e. non-volitional exercise) 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 (175-200g), 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 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 1.0 G gravity load and body mass equals body weight. Therefore, increasing the gravity field to 2.0 G 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 (unpublished). 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 remains inconclusive.

Dewsbury (19) showed no significant correlation ( $r=-0.21$ ) between body size and voluntary wheel running activity across 13 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 to weight-matched normal mice. The data indicates the absence of 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 (Figure 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, Keeseey 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 proceed 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 exam 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. By definition obesity is when energy intake exceeds EE. 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, in reference to humans, a low (>20%) fat 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, 26, 27). Studies show higher total caloric intake on a high fat diet resulted from the higher energy density of fat (28, 29, 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 (33, 34, 27), the importance 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 feeding high fat diets to different rodent strains produces variable weight gains ranging from 12-56% (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, Pagliasotti et al. (36) reported some rodent strains resist becoming obese when fed a high fat diet. 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 provides 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 to 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 (36, 27). If an animal is depositing more energy as fat but 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 8% of the excess calories is dissipated in 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 inter-individual 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, 44, 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 pre-deprived baseline, dietary lean rat when their weights fell to 85-95% of their pre-deprived baseline and DIO rats when their weight fell to 65-75% of their pre-deprived baseline. 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 diet produces no differences in the activity levels of DIO mice compared to obesity resistant mice (51). 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 (52). Age as a determinant of activity will be discussed in another sections of the review paper. Another determinant of activity is body weight. Levin (53) found 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. Therefore, the hypothalamic-induced obese rodent is another animal model of obesity. The ventromedial hypothalamus (VMH) is regarded as the region of the satiety center. Lesions produced by electrolytic injury, radio frequency lesions or knife cuts to the VMH (54) results in increased food intake, gradual accumulation of body weight and obesity (54). Humans sustaining similar lesions to the hypothalamus also increase their food intake and typically develop obesity (55). However, not all cases of obesity associated with VMH lesions are produced by higher food intakes. Benardis (56) 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 non-lesioned animals when given unpalatable foods (57). 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 VMH lesioned rats display reduced motivation to seek food and decreased responsiveness when the workload to obtain food is increased compared to non-lesioned control rats (58). Measuring activity using running wheels and stabilimeters confirmed that locomotor activity was reduced in VMH lesioned rodents (59). 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 post-operative weight (60). 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. (61) found 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 models 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 (62). VMH lesioned rodents become obese even when pair-fed with sham-lesioned controls, whereas, the PVN lesioned rats develop obesity only through overfeeding (63). 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) (64). 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 (65). In agreement, Poon et al. (66), 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 persisted throughout the study (up to 20 weeks). The hypoactivity in this study is explained by an inverse weight-activity relationship. Post-weaning, the increasing body weight associated with growth produces the observed reduction in activity levels. Pizzi et al. (67) injected neonatal mice (1 and 5 days of age) and older mice (25 days of age) with increasing doses of MSG over a ten 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. 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. Nicoletseas (68) observed despite MSG-treated rats having greater body weights, their activity levels were not significantly different from non-treated controls. This suggested that the regulation of activity was due to the hypothalamic lesions rather than a weight-activity relationship. Furthermore, Araujo and Mayer (69) 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. 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 (70). For example, vagotomy reverses obesity in VMH lesioned obese rats but not in genetically obese rats. Also, the hypothalamic (surgical and chemical) induced 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 VHM lesioned animals the hyperactivity associated with food deprivation is attenuated or absent (71, 72). Similarly, GTG treated mice fail to show increase spontaneous activity upon starvation. Nor did GTG treated mice decrease their activity upon refeeding (73). 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 reported activity levels differed depending on the rodent strain (74, 75, 76, 77). Festing (78) 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 inter-individual variations. Studies using inbred rodent strains show a clear genetic component influencing activity levels. Lassalle and Pape (79) 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*, *fa*) that produce obesity in rodents have been cloned (80). 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 (81). Therefore, the mechanism responsible for hypoactivity in genetically obese rodent 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 Figure 1). Dauncey and Brown (82) observed *ob/ob* mice exhibit 51-70% less motor activity compared to 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 (82). Similarly, running wheel activity was consistently lower in Zucker obese (fa/fa) rats compared to their lean littermates from the time of weaning to six months of age (83, 84). These findings suggest that even gradual increases in body weight affects activity levels in those predisposed to obesity. Swallow et al. (85) 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 New Zealand obese (NZO) to become less active than their lean littermates (86) 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 wheel running activity levels of  $180 \pm 65$  counts/10 min compared to wheel running activity levels of  $250 \pm 120$  counts/10 min in lean mice. Therefore, activity levels in the obese NZO mice were in fact lower than the lean controls, although not statistically. 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 ( $400 \pm 60$  counts/10 min) than their lean littermates ( $345 \pm 20$  counts/10 min), thus refuting an inverse weight-activity relationship. On closer examination both lean and obese agouti displayed higher activity levels in comparison to 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 (87).

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 to the mutant phenotype on a C57BL/K background (88). Artificial selection is one method that may be applied to separate genetic from environmental influences on particular phenotypic traits. Swallow et al. (89) 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 eight weeks study (90). 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 (91). 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 (92) observed 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 alterations 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 age-related decline in activity may be related to leptin, based on the observation that the F344xBN rat, a rodent model for late-onset obesity, exhibit impaired leptin responsiveness (93). 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 genetically obese ob/ob mice and db/db mice lose weight in response to administrations of leptin (94). Figure 5 shows ob/ob rats treated with weekly injections of leptin have reduced body weight gain and increased activity levels compared to untreated ob/ob rats. Together the data indicate that body weight regulation by leptin functions as the determinant of activity. However, Surwit (95) 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 (95).

Finally, body weight is hypothesized to regulate activity. Aging rodents and humans have been observed to gain weight (96, 97, 98). 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. (94) reported 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 (99) found decreased activity in obese male Zucker rats starting at age 44 days compared to their lean littermates. Reduced activity at a young age suggests 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 d. This may have been due to the study's small sample size (n=4/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 (100). Except for one study reporting Zucker obese rats to be significantly heavier than Zucker lean rats at 15 d of age (99), 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 (86) 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 (84). Figure 6 shows during post-weaning days 16-22, body weights are higher in Zucker (fa/fa) obese male rat pups

compared to the lean controls but do not differ in activity. Only after post-weaning day 22 was motor activity decreased in Zucker obese rat pups. 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 like the DIO and hypothalamic lesions 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 (88). Hyperglycemia, a prominent feature of ob/ob mice, appears at the onset of obesity and hyperinsulinemia by 12 months of age (101). 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 (102), higher activity in an “open field” box (103) and a greater number of entries into the open arms of an elevated maze compared to male rats (104). These findings suggest gender differences in activity levels. Based on the rodent studies, females appear to be more active than males. Tropp and Markus (103) 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 to female rats; whereas, in exploratory tests, activity was higher in female than male rats (102, 103). This is because in exploratory tests volitional activity is influenced by behavior. Furthermore, West and Michael (105) 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 (106, 107). The importance of estrogen in the regulation of activity is further indicated by studies showing that removal of estrogen by the 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-ovariectomized level (107, 108). Several mechanisms 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 (102). 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 (106, 107). As previously discussed, acute weight loss is associated with hyperactivity. Thus, reductions 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 (109). 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. (110) 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. Finally, 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 (111). Figure 7 shows female rats have lower body weights and higher locomotor activity than male rats. In accordance with our proposed inverse weight-activity relationship, the higher activity expressed by female compared to 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 (112, 113). 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 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 (114, 115, 116). 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, monozygous and dizygous twin studies (117). On the other hand, the genetic of animals can be manipulated to minimize such inter-variability. 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 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 difference in activity may also exist in humans. Not all finding in animals are applicable to humans. Leptin is well-defined in animals but its role in human obesity is not definitive (39). Hypothalamic lesions leading to obesity has been studied extensively in animals but rarely occur in humans. The manifestations of hypothalamic lesion induced obesity differs from other models of obesity suggests that lack of relevance of 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 conscience 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. Thus, 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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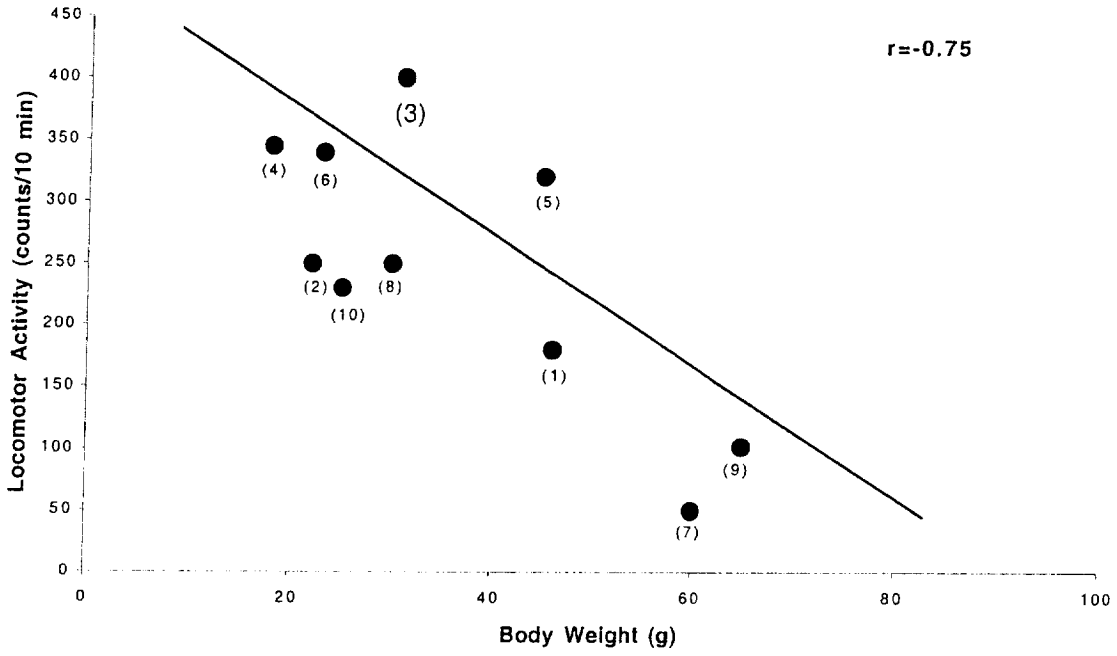
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Figure 1A. Scatter plot depicting the relationship between body weight and locomotor activity for A) different strains of genetically obese mice. The mice strains used in this study are: 1) New Zealand obese (NZO) prior to obesity, 2) obese NZO, 3) VY/Wf-A<sup>vy</sup>/a (viable yellow) prior to obesity, 4) obese VY/Wf-A<sup>vy</sup>/a (viable yellow), 5) VS/ChWf-A<sup>y</sup>/a (lethal yellow) prior to obesity, 6) obese VS/ChWf-A<sup>y</sup>/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, 10) obese C57BL/6J-ob/ob (obese). Values represent the mean of n=4-6/group. Adapted from Yen and Acton, 1972 (123).

Figure 1B. 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<sup>y</sup>/a (lethal yellow), (4) VY/Wf-a/a (normal), (5) VY/Wf-A<sup>vy</sup>/a (viable yellow) (6) C57BL/6J db<sup>+</sup>/db<sup>+</sup> (normal) (7) C57BL/6J db/db (diabetic), (8) C57BL/6J ob<sup>+</sup>/ob<sup>+</sup> and (9) C57BL/6J ob/ob (10). Values represent the mean of n=5-6/group. Adapted from Yen and Acton, 1972 (123).

Figure 1  
A)



B)

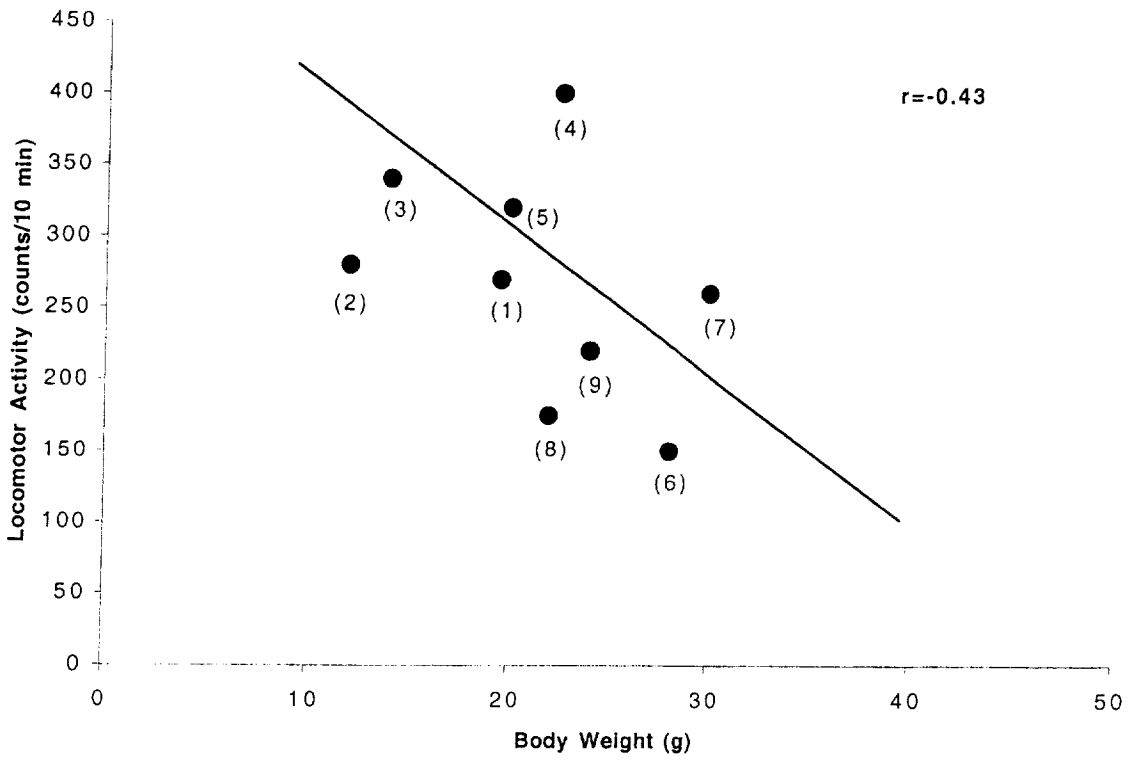




Figure 2. Schematic of the weight-activity relationship and the various determinants i.e. age, strain, gender, diet and hypothalamus, affecting body weight and activity.

Figure 2

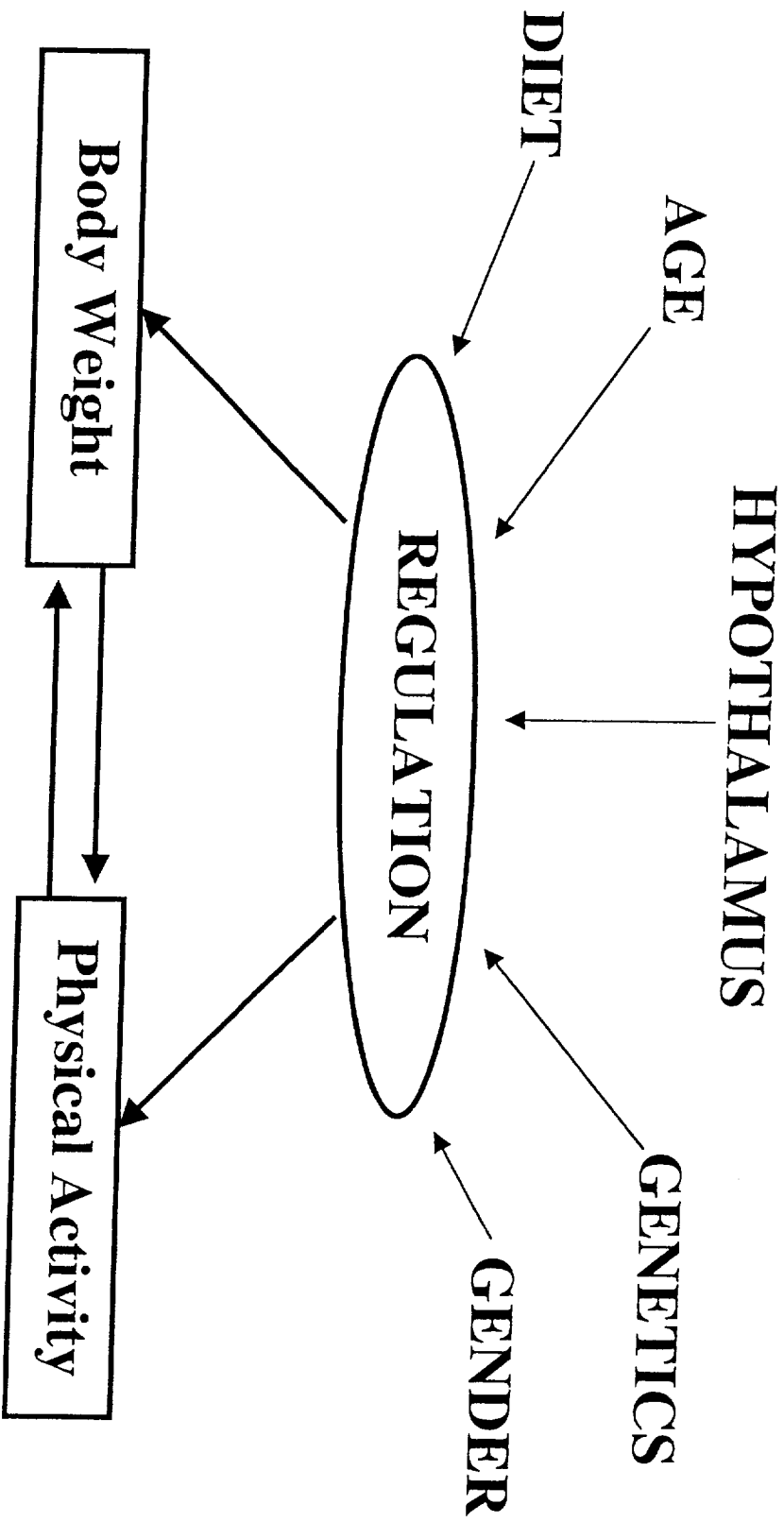


Figure 3. Mean locomotor activity of dietary induced obese (DIO), lean and control rats as a function of percentage body weight during food-deprivation. The rats in the DIO group are *ad lib* fed commercially available foods in addition to their standard rodent chow. The rats in the lean group are *ab lib* fed standard rodent meal adulterated with quinine hydrochloride (0.8% w/w) and the control rats are *ab lib* 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 pre-deprivation weight of each rat. Adapted from Sclafani and Rendel, 1978 (100).

Figure 3

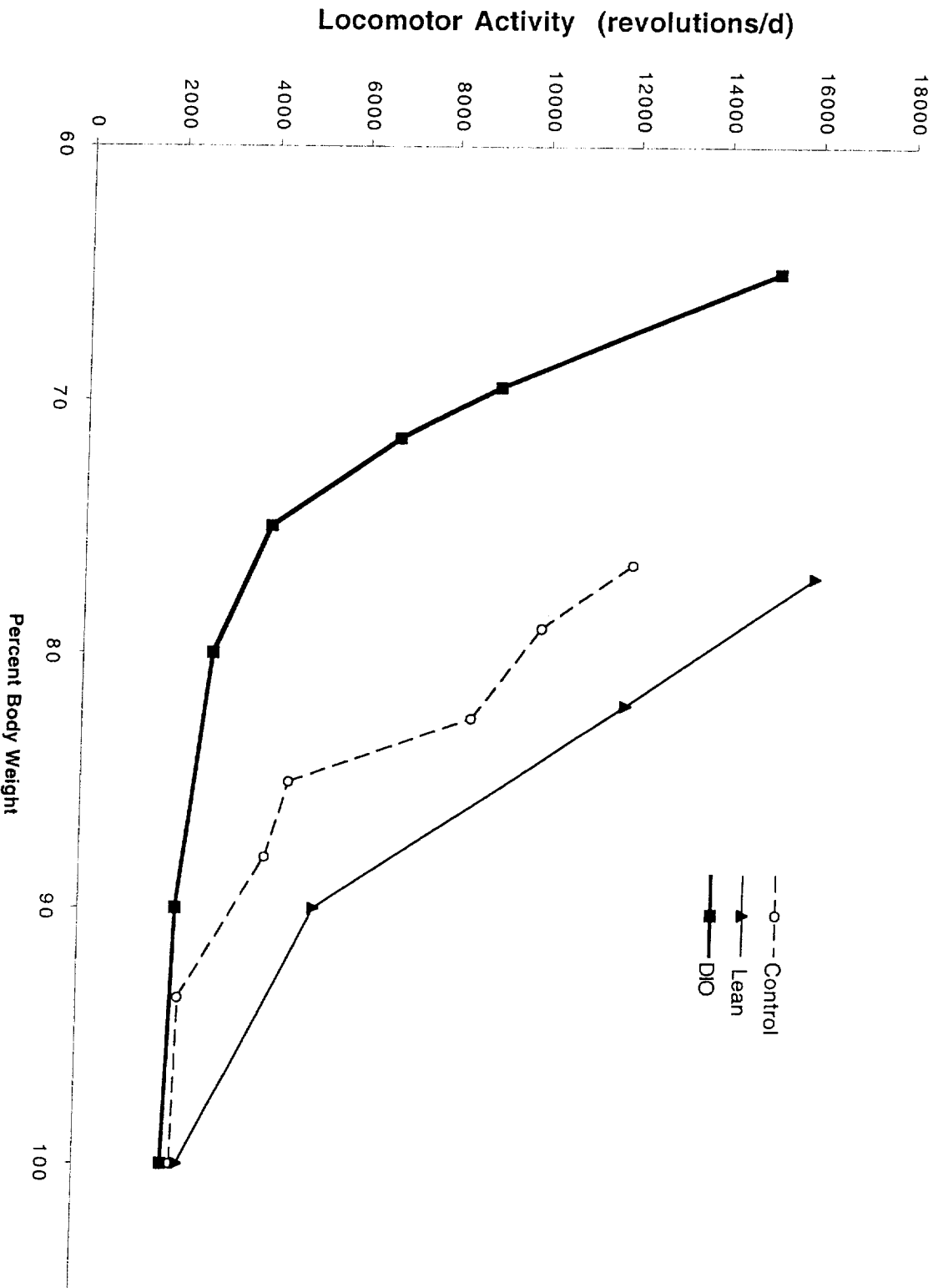


Figure 4. Locomotor activity measured as the mean horizontal+vertical (rearing) beam breaks in 4 h during the dark cycle for different inbred strains of male mice aged 6-10 weeks. Values are the means of n=8. Adapted from data from the Jackson Laboratory Mouse Phenome data base <http://aretha.jax.org/pub-cgi/phenome/>.

Figure 4

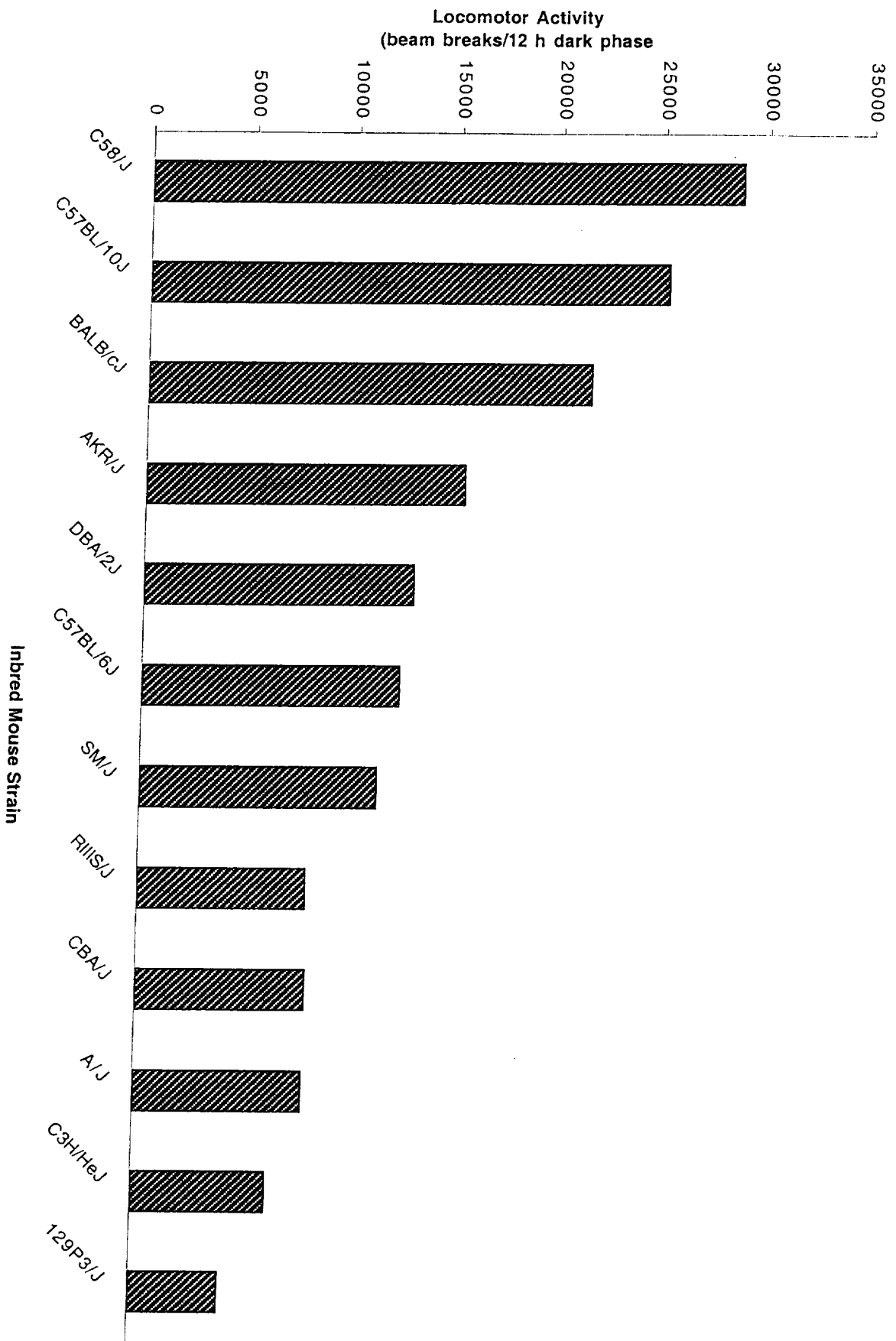


Figure 5. The effect of daily injection (i.p.) of leptin (1 $\mu$ g/g bwt) or saline on female C57BL/6J ob/ob mice (age 4 weeks) on A) body weight and B) activity in an open field test. Relative activity was determined by assigning scores for walking (number of floor grid lines crossed) climbing, rearing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

Figure 5

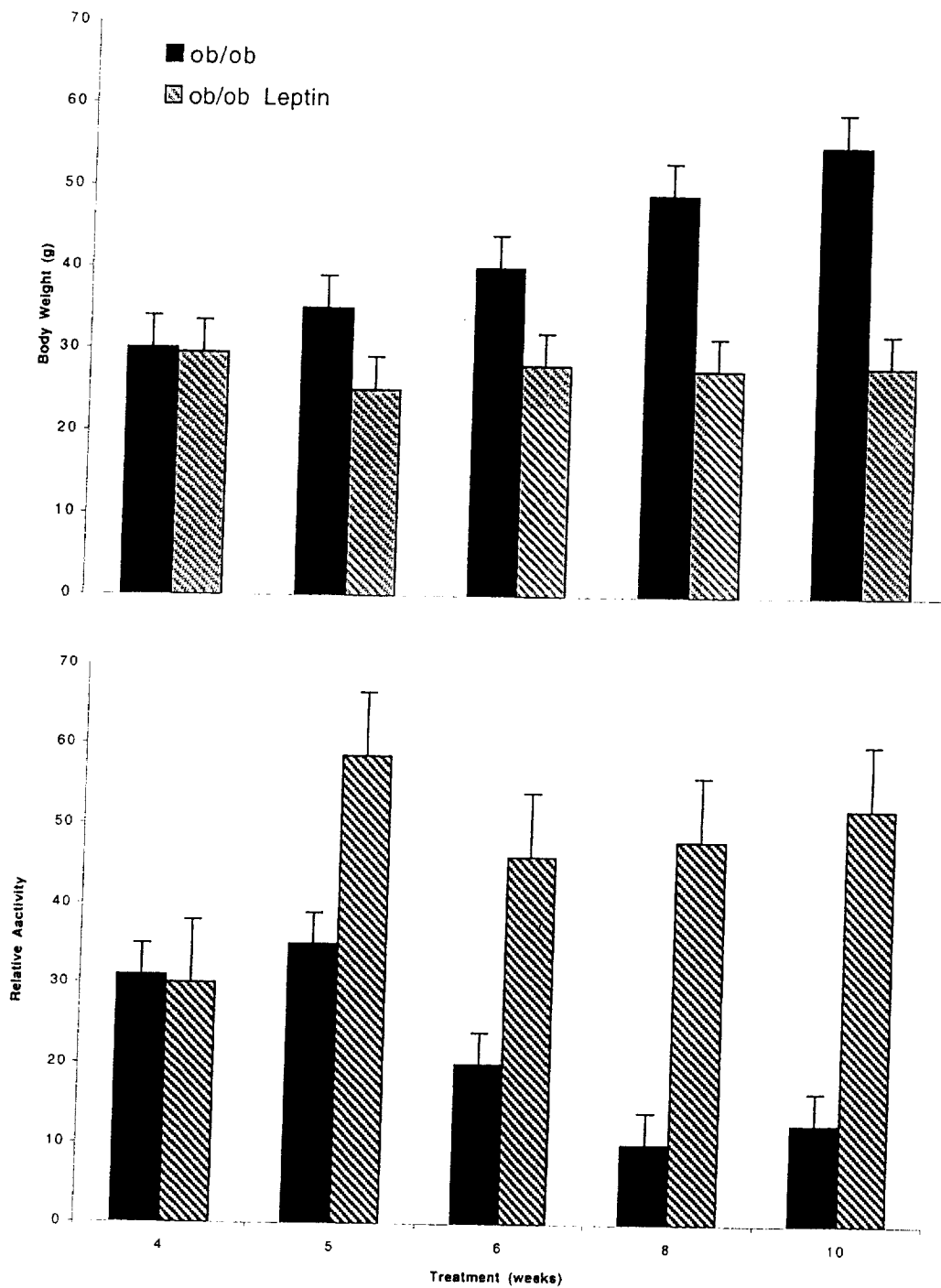




Figure 6. Comparison of lean (Fa/-) versus genetically obese (Fa/Fa) male rat pups during the preweaning stage (age 16-25 days) A) body weight gain and B) locomotor activity indicated by wheel turns during 3 h during the dark cycle. Values are the mean  $\pm$ SEM for n=34 lean (Fa/-) and n=16 obese (Fa/Fa) rats. Adapted from Sterns and Johnson, 1977 (107).

Figure 6

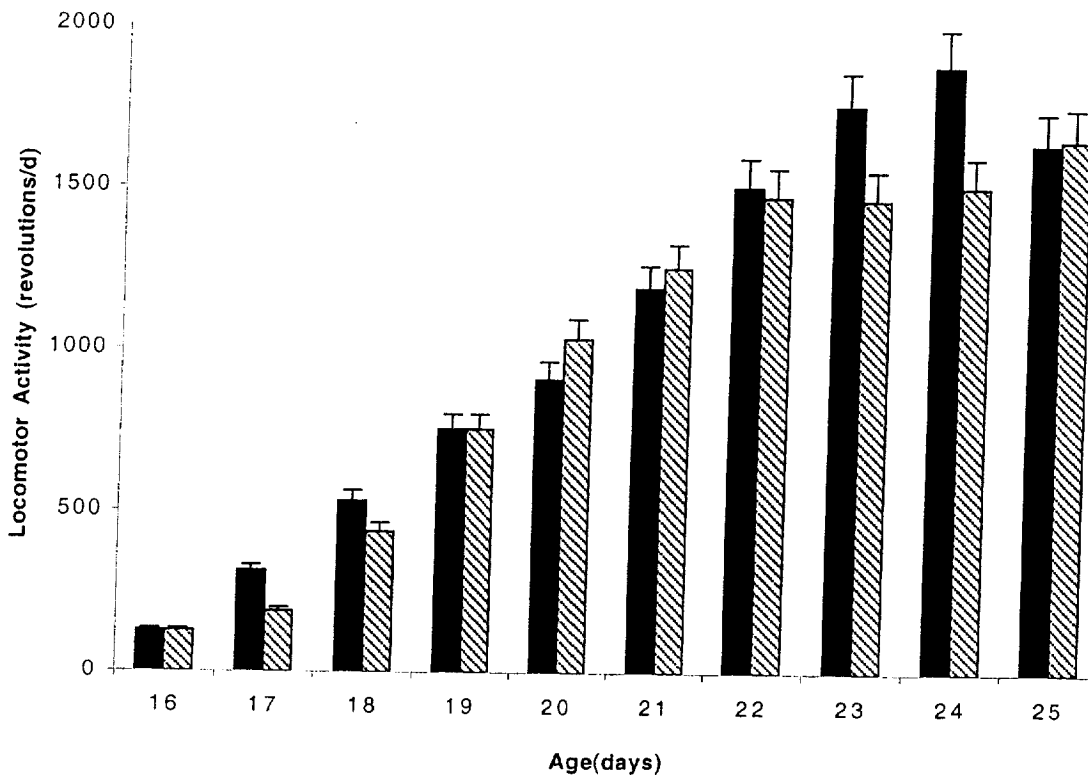
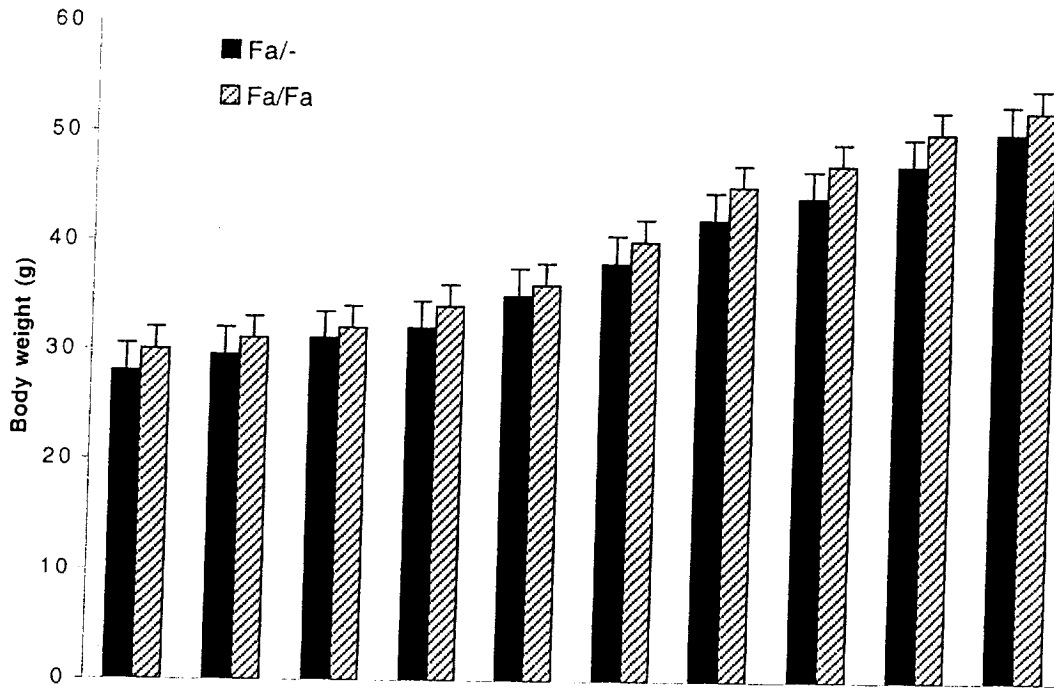


Figure 7. The effect of gender differences in Lister rats age 9-12 weeks fed commercial rodent chow on A) body weight and B) locomotor activity by running wheels. Adapted from Rolls and Rowe, 1979 (94).

Figure 7

