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Abstract

This study evaluated the effects of chronic treadmill training on body mass gain and visceral fat accumulation in overfed rats. Overfeeding was induced by reducing the litter size to 3 male pups per mother during the suckling period. The litter size of control rats was adjusted to 10 male pups per mother. Seven weeks after birth overfed and normally fed rats were selected and assigned to a sedentary protocol or to a low-intensity treadmill training protocol (60 min, 5 times/week, for 9 weeks). Four groups (overfed sedentary, N = 23; normally fed sedentary, N = 32; overfed exercised, N = 18, and normally fed exercised, N = 18) were evaluated at 18 weeks. Data are reported as means ± SEM. Initial body weight was similar in control and overfed rats [8.0 ± 0.2 g (N = 42) *vs* 8.0 ± 0.1 g (N = 50); P > 0.05] and body weight gain during the suckling period was higher in the overfed rats (30.6 ± 0.9 *vs* 23.1 ± 0.3 g; P < 0.05). Exercise attenuated the body weight gain of overfed compared to sedentary rats (505 ± 14 *vs* 537 ± 12 g; P < 0.05). The sedentary overfed rats showed higher visceral fat weight compared to normally fed animals (31.22 ± 2.08 *vs* 21.94 ± 1.76 g; P < 0.05). Exercise reduced visceral fat by 36.5% in normally fed rats and by 35.7% in overfed rats. Exercise attenuated obesity in overfed rats and induced an important reduction of visceral fat.

Key words: Obesity; Exercise; Abdominal fat; Overfeeding

Introduction

The prevalence of obesity is increasing worldwide, representing a serious public health problem (1). Body fat distribution is particularly important because intra-abdominal fat accumulation, usually denoted visceral fat, is closely related to the development of several cardiovascular and metabolic diseases, including hypertension and type 2-diabetes mellitus (2-4).

Obesity is a complex disease and several animal models have been developed in order to elucidate the complex interplay between genetic and environmental factors contributing to body weight gain along life (5-7). Overnutrition in childhood favors obesity development later on in adulthood (8). Therefore, there is an increasing necessity to obtain a better understanding of the physiological processes related to fat accumulation during the earliest periods of life, which may influence body weight along the life span. An experimental model for the study of this relationship can be obtained easily by adjusting the litter size (9,10). In this model, rats raised in small litters (3-4 pups per mother) ingest larger amounts of milk (11) and gain more body weight than rats raised in normal or large litters (8 or more rats/mother). Interestingly, the increased body weight of the rats growing in small litters continues even after weaning (9,10,12-17). Hypothalamic and neuroendocrine axis changes and a permanent reprogramming of thermogenesis in the brown adipose tissue may contribute to a persistent increase of the visceral fat deposits and to body weight gain in animals submitted to overfeeding in the early phases of postnatal life (9,10,18,19).

Several studies on humans and animals have shown that long-term aerobic exercise may reduce or prevent obesity (20-28). However, the long-term effects of exercise on the body weight gain in this experimental model of obesity have not been investigated. Moreover, the exact time when differentiation in body weight gain occurs between rats growing in normal or in small litters has not been clearly defined in previous studies. Thus, the objective in the present study was to compare body weight gain and visceral fat accumulation in sedentary and exercised rats submitted or not to overfeeding during the suckling period.

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Material and Methods

Female Wistar rats (N = 16) from the colony of our Department (Federal University of Espírito Santo, Brazil) were mated at 3 months of age with males of the same strain. On the 1st day after birth the pups were mixed and equally distributed at random among the mothers to reduce the influence of genetic factors on body weight gain. On the third day the litter size was adjusted to 3 male pups to induce early postnatal overnutrition (overfed group, OF, N = 42), or to 10 male pups (normally fed control group, NF, N = 50). Ten pups is the usual litter size in this rat strain (9). All animals were maintained in a room with controlled temperature (23-25°C) and light-dark cycle (lights on from 6:00 am to 6:00 pm). Water and standard pellet diet (Purina®, Brazil) were provided *ad libitum.* The cages were always cleaned in the morning (6:00 to 12:00 am) and all animals received similar handling during the growing period. During the suckling period, mothers were maintained in individual cages with their pups (3 or 10) until weaning at the age of 30 days. The animals were then transferred to collective cages (4 animals/cage). The initial body weight of each animal was determined on the third day after birth when pups were randomly allocated to mothers. Body weight was measured weekly throughout the study period. The project was approved by our institutional Ethics Committee on animal research (Ethics Committee for the Use of Animals, UFES, protocol #025/2007) and all experiments were conducted in accordance with the Guide for Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication #85-23, revised 1996).

Treadmill training

In the seventh week of life the animals were divided into four groups: overfed-sedentary (OF-S, N = 23), overfed-exercised (OF-E, N = 18), normal fed-sedentary (NF-S, N = 32), and normal fed-exercised (NF-E, N = 18). Only rats that accepted to run in a single treadmill test session before the training protocol were included in the exercise group. Rats that did not run were maintained in their respective sedentary group. The treadmill (Insight EP 131, Brazil) provided an aversive electric stimulus (150 V of alternating current and 3 mA) in the back region of each lane to force the rats to run. The rats were allowed to adapt to treadmill running for 1 week (running for 10 min at 5-10 m/min). Training sessions were always held in the morning (6-12 am). During the running sessions sedentary rats remained in the same room as exercising rats. Animals trained 5 times a week for 9 weeks (from the 8th to the 17th week of age). In the first 3 weeks, exercise intensity was maintained at 16 m/min and duration was increased from 30 to 60 min (15 min increase every week). Exercise sessions were held for 60 min thereafter and the treadmill speed was increased at 1 m/min for each 2 sessions until it reached 20 m/min. Treadmill inclination was maintained at 5° throughout the training period. Although we did not measure exercise intensity, according to a previous study (29) this long-duration training protocol maintains exercise intensity from 55 to 60% of VO_2 max. No animal was excluded from the experiment. Only two animals (1 OF-E and 1 NF-E) were removed from two training sessions to recover from small traumatic lesions in the tail and paw.

Morphologic and hemodynamic parameters

After the last exercise session, the rats were anesthetized with ketamine and xylazine (50 + 10 mg/kg, *ip*) in the afternoon (about 4:00-5:00 pm) to obtain the final body length (distance between the mental protuberance and the anus), abdominal circumference (measured in the midpoint between the costal arch and the anus) and body weight. A polyethylene catheter (PE-50 attached to PE-10 tubing) was inserted into the femoral artery and tunneled to the dorsal neck region. The animals remained fasting until 7:00-8:00 am next day to obtain direct values of blood pressure in awake and unrestrained animals (TRA021 BP transducer, coupled to an ML 110 Amplifier, ADInstruments, Australia) and to collect a blood sample for biochemical analysis. Blood pressure and heart rate values computed for each animal were averaged from 30 min of continuous recording (Chart 5.5.1 - ADInstruments).

Biochemical parameters

Arterial blood samples (1.5 mL) were obtained after blood pressure recording and biochemical determinations were performed on the same day. Glucose was measured by the glucose oxidase colorimetric method (Glucox 500, Doles Reagentes, Brazil). Plasma concentrations of triglycerides were determined by enzymatic assay (Triglycerides 120, Doles Reagentes) and total serum cholesterol was measured by an enzymatic method (Cholesterol 250, Doles Reagentes).

Visceral weights

After blood collection, the rats were euthanized in a chamber saturated with halothane. The heart, lungs, liver, spleen, and adrenal glands were rapidly removed, rinsed in cold saline, and dried on filter paper to obtain wet weights. The right and left ventricles were dissected and weighed separately. The abdominal fat was also dissected and separated into four components: retroperitoneal, perirenal, mesenteric, and epididymal. Weights were corrected for body weight.

Statistical analysis

Data are reported as means ± SEM. Body weight gain in the 1st week of postnatal life was compared by the one-tailed *t*-test. Growth curves for the four groups were compared by two-way ANOVA for repeated measures. Differences between groups at each week were tested by the Tukey *post hoc* test. ANOVA was used to compare linear regres-

sion analysis of OF and NF groups. The hemodynamic and biochemical parameters, visceral weights, and visceral fat weight were compared with two-way ANOVA following the Tukey *post hoc* test when significant differences were found. The power of the study was set at 90% and the minimum number of animals per group was calculated to detect a difference of one standard deviation in abdominal fat between the four groups. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using the SPSS 13.0 software.

Results

Body weight gain

Figure 1 shows the body weight gain of the animals during the first 7 days of life and Figure 2A shows the body weight of the OF and NF groups during the first 5 postnatal weeks. An exponential body weight increase was observed in the two groups during this period. The initial weights after separation of the animals into normal and small litters were equal in the two groups (OF = 8.0 ± 0.1 *vs* NF = 8.0 ± 0.2 g; $P > 0.05$). Seven days later, OF rats were about 3 g heavier than NF rats (Figure 1A). Body weight gain was 104 in NF rats and 144% ($P < 0.001$) in the OF group (Figure 1B). By the end of the 2nd week, the body weight of the OF group was significantly higher than that of the NF group (OF = 30.6 ± 0.9 *vs* NF = 23.1 ± 0.3 g; $P < 0.001$) and the relative difference remained similar throughout the pre-exercising period. Figure 2B shows regression analysis of body weight (after logarithm transformations) during the first 5 weeks of the postnatal period and a significant linear correlation can be observed from the 2nd to the 5th week of life. Regressions showed similar angular coefficients (0.98 for NF rats and 0.96 for OF rats) in the two groups suggesting similar growth rates during this period. Therefore, from the 2nd week of postnatal life the absolute difference between groups remained essentially constant during the suckling period.

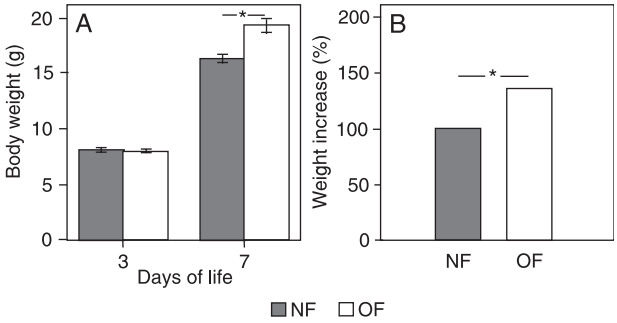

Figure 1. *A*, Body weight gain from the 3rd to the 7th day of postnatal life of normally fed (NF) and overfed (OF) rats. *B*, Percent of increase in the weight between the 3rd and 7th day of life for each group. Data are reported as means ± SEM. *$P < 0.001$ (*t*-test for paired data in A, and for independent samples in B).

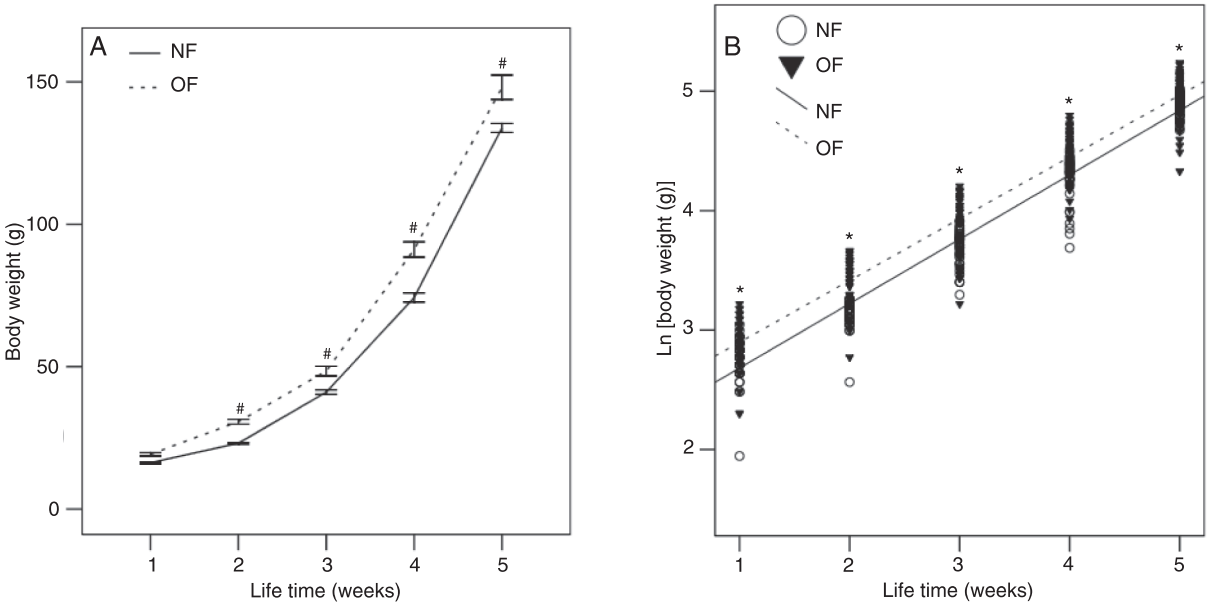

Figure 2. Growth curves during the suckling period (week 0 to 4) and during the first week after weaning. *A*, Body weights presented on a linear scale. *B*, Regression curve of natural logarithm (Ln) of body weight. Data are reported as means ± SEM in Panel A. NF = normally fed; OF = overfed. #$P < 0.001$ [two-way ANOVA for repeated measures (Panel A) and ANOVA for regression (Panel B) followed by the Tukey *post hoc* test]. *$P < 0.01$ OF *vs* NF.

Figure 3 shows the increase in body weight during the intervention period (week 7 to week 17). At the 7th week, the OF-E and NF-E groups started treadmill training. The initial body weights of the OF-S and OF-E groups (210.6 ± 6.7 *vs* 201.5 ± 7.8; P > 0.05) and of the NF-S and NF-E groups (188.3 ± 2.3 *vs* 186.3 ± 3.3 g; P > 0.05) were similar. The growth curve of the OF-S group progressively deviated from that for the OF-E group, and the difference became significant from the 10th week (3 weeks after the beginning of the exercise sessions). The body weight of OF-S group was greater than the body weight of the NF-S group throughout this period. Chronic aerobic exercising reduced the body weight gain in the OF-E group by 24 g (7.6%) and by 12 g (4.3%) in the NF-E group compared to their respective sedentary controls (OF-S and NF-S groups).

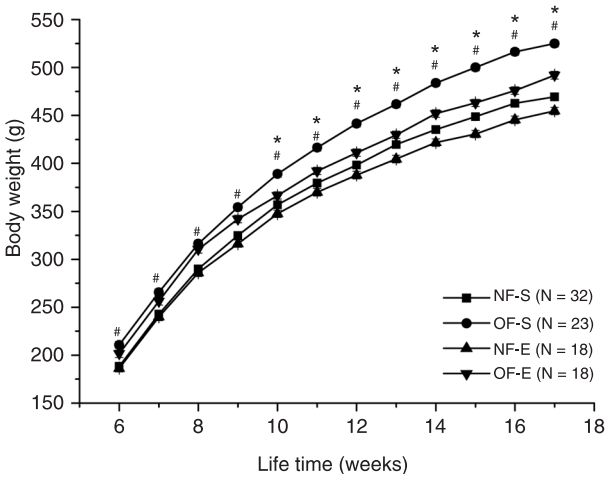

Figure 3. Effect of aerobic exercise on the body weight gain curve. Data are reported as means ± SEM. NF-S = normally fed sedentary; OF-S = overfed sedentary; NF-E = normally fed exercised; OF-E = overfed exercised. *P < 0.05 OF-S *vs* OF-E; #P < 0.05, NF-S *vs* OF-S (two-way ANOVA for repeated measures followed by the Tukey *post hoc* test).

Table 1. Body weight and wet visceral weight of the four groups of rats.

	NF-S (N = 31)	OF-S (N = 24)	NF-E (N = 17)	OF-E (N = 18)
Body weight (g)	479 ± 11	537 ± 12+	470 ± 12	505 ± 14*
RV (mg)	314 ± 12.7	337 ± 14.0	339 ± 17.2	326 ± 11.5
RV/BW (mg/g)	0.66 ± 0.02	0.63 ± 0.02	0.72 ± 0.03	0.65 ± 0.02
LV (mg)	865 ± 15.7	943 ± 18.2+	890 ± 32.0	961 ± 30.4
LV/BW (mg/g)	1.82 ± 0.03	1.76 ± 0.03	1.89 ± 0.04	1.90 ± 0.04*
Lungs (g)	2.1 ± 0.0	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.1
Lungs/BW (mg/g)	4.39 ± 0.14	3.99 ± 0.10	4.49 ± 0.24	4.03 ± 0.30
Liver (g)	15.4 ± 0.5	17.0 ± 0.6	15.6 ± 0.7	17.2 ± 0.7
Liver/BW (mg/g)	31.80 ± 0.57	31.85 ± 0.82	33.05 ± 0.99	33.83 ± 1.11
Spleen (mg)	824.2 ± 28.5	929.0 ± 65.8	891.6 ± 41.6	939.7 ± 65.9
Spleen/BW (mg/g)	1.73 ± 0.06	1.72 ± 0.11	1.89 ± 0.14	1.90 ± 0.10
Adr (mg)	87.2 ± 3.2	91.1 ± 6.7	81.6 ± 3.7	82.7 ± 9.0
Adr/BW (mg/g)	0.18 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.16 ± 0.02

Data are reported as means ± SEM. NF-S = normally fed sedentary; OF-S = overfed sedentary; NF-E = normally fed exercised; OF-E = overfed exercised; RV = right ventricle; LV = left ventricle; Adr = adrenal gland; BW = body weight. The symbols indicate significant differences (P < 0.05) between OF-S and OF-E (*), NF-S and OF-S (+; two-way ANOVA and Tukey *post hoc* test).

Hemodynamic and biochemical evaluation

Blood pressure and heart rate measured in awake and unrestrained animals were similar in the four groups, as also were the biochemical data measured in plasma. Values of the NF-S group were: mean blood pressure = 101 ± 1 mmHg; heart rate = 323 ± 7 bpm; glycemia = 86 ± 4 mg/dL; cholesterol = 45 ± 2 mg/dL; triglycerides = 64 ± 6 mg/dL.

Visceral and abdominal fat weights

Visceral weights are shown in Table 1. Overfeeding produced an increase of absolute heart weight (NF-S = 1298 ± 20 mg *vs* OF-S = 1281 ± 23 mg; P < 0.05), a difference due to the increase of left ventricular weight in the OF-S group (942 ± 18 *vs* 865 ± 16 mg; P < 0.05). The OF-E group showed greater cardiac weight compared to the OF-S group. However, no difference between the exercised groups was found regarding cardiac weight or right and left ventricular weight. Differences between exercised and sedentary groups tended to increase when relative cardiac weight was considered because of the lower body weight of the exercised groups. The weights of the other viscera were unaffected by overfeeding or exercise (Table 1).

Table 2 shows the weight of several abdominal fat deposits. Both litter size and chronic aerobic exercise significantly affected total abdominal fat accumulation. Overfeeding increased visceral fat (NF-S *vs* OF-S) by 42% (21.9 ± 1.8 to 31.2 ± 2.1 g; P < 0.01) and the relative increase was similar in exercised animals. Exercise, however, prevented (about 36%) abdominal fat accumulation in both NF-E and OF-E rats. Epididymal and retroperitoneal fat deposits showed the greatest increase due to the overfeeding procedure (about 50%). Accordingly, these fat components showed the highest reduction with exercise. Therefore, the exercise protocol tested in this study was able to normalize the abdominal fat content produced by the overfeeding procedure (NF-S = 21.94 ± 1.76 *vs* OF-E = 20.08 ± 2.35 g; P > 0.05).

Table 2. Weight of the visceral fat components.

Fat	NF-S (N = 31)	OF-S (N = 24)	NF-E (N = 17)	OF-E (N = 18)
Epididymal (g)	4.60 ± 0.42	6.83 ± 0.49#	2.88 ± 0.58*	4.53 ± 0.56§+
Retroperitoneal (g)	9.67 ± 0.87	14.32 ± 1.02#	5.66 ± 1.19*	8.56 ± 1.15§
Perirenal (g)	1.41 ± 0.19	1.67 ± 0.22	0.89 ± 0.26	1.46 ± 0.25
Mesenteric (g)	6.25 ± 0.60	8.40 ± 0.71#	4.48 ± 0.83	5.54 ± 0.80§
Total fat (g)	21.94 ± 1.76	31.22 ± 2.08#	13.92 ± 2.42*	20.08 ± 2.35§
Relative total fat (mg/g)	44 ± 2	57 ± 3#	29 ± 3*	39 ± 3§

Data are reported as means ± SEM. NF-S = normally fed sedentary; OF-S = overfed sedentary; NF-E = normally fed exercised; OF-E = overfed exercised. The symbols indicate significant differences ($P < 0.05$) between NF-S and NF-E (*), OF-S and OF-E (§), NF-S and OF-S (#), NF-E and OF-E (+) (two-way ANOVA and Tukey *post hoc* test).

There was a positive and significant correlation between abdominal circumference and total visceral fat ($r = 0.75$; $P < 0.01$; data not shown).

Discussion

Obesity is a complex disease of multifactorial etiology and several experimental models of this disease have been used to reach a better understanding of its pathogenic mechanisms, thus providing better conditions to prevent and to treat the disease. In rodents, obesity can be induced by lesion in the ventromedial hypothalamic nucleus, oophorectomy, hypercaloric diets, and early overfeeding during the perinatal period. Genetic models of obesity have also been developed in rodents, such as the Zucker rat and the ob/ob mouse. Our study confirms previous observations that rats overfed during the suckling period gain more body weight and that this difference in relation to normally fed animals persists throughout postnatal life (9,10). Other studies, however, have reported that body weight tends to present similar values in NF and OF rats after the suckling period (30,31).

Disagreement among the results of these studies may be related to different numbers of pups in litters in different investigations. Some studies (12-16), for instance, compared the body weight gain of overfed rats raised in small litters (2-4 pups/litter) to that of malnourished rats raised in very large litters (16-24 pups/litter). Other studies (9,10,17,30-35) compared rats of small litters (3-4 pups/litter) to rats of normal litters (8-12 pups/litter). Some differences may also be due to sex, since males show more body weight gain during the overfeeding period (15,17). To avoid this confounding variable, only males were used in our experiments. Moreover, pups that grew up in both small and normal litters were randomly divided among mothers, so that different genetic influences on body weight gain were equally distributed between the overfed and normally fed groups.

Our results showed that animals growing up in small litters attain a greater body weight than normal litters and that this difference is partially due to increased accumulation of central fat. Our finding suggests that the experimental procedure used here seems to be an experimental model of overweight and not of obesity as considered by others (10), because the final body weight of the overfed rats was about 11% higher than that of the normally fed animals.

The exact mechanisms by which early overfeeding determines a permanent change in body weight regulation were not still fully elucidated. However, it is postulated that changes in neurohormonal regulation may play a main role in changes in body weight control of overfed rats (9,10,19).

Studies have shown that regular physical activity determines a modest increase of energy expenditure and thus has been recommended as an additional strategy to prevent obesity and to reduce excessive fat accumulation (20-28). Visceral obesity represents a risk factor for several cardiometabolic diseases. In spite of the large number of studies on early overfeeding models, our study is the first to show that the difference in body weight between overfed and normally fed animals becomes evident by the end of the 1st week of postnatal life and that this difference tends to remain constant until adulthood. These data suggest that excessive body weight gain in the earlier periods of postnatal life may change the body weight history for life. Moreover, our study showed that chronic aerobic exercise can significantly attenuate visceral fat accumulation in overfed animals. All the components of abdominal fat were reduced in chronically exercised animals. Since reduction of body weight gain was about 3 times greater than the reduction of abdominal fat, it is likely that some decrease of fat accumulation also occurred in other body compartments such as subcutaneous fat. Since we have shown that a difference in body weight is already observed 1 week after birth, our data suggest that overfeeding during this period seems to imprint these animals to maintain a higher body weight throughout their life span. However, since we did not evaluate food intake, we cannot determine whether the origin of this difference was secondary to a permanent modification of food intake behavior or to energy expenditure.

There is no study comparing the effects of physical exercise in different obesity models. Since obesity can be induced by different strategies to modify energy intake and expenditure, it is conceivable to speculate that a single intervention to increase energy expenditure (exercise) may produce different results in different obese individuals or experimental models. Obesity induced by hypothalamic

lesion (36) can promote body weight gain of nearly 100% compared to intact controls. Early overfeeding increased the body weight by only 11%. Physical exercise was less efficient in reducing fat content in animals with hypothalamic lesion (37) compared to controls. In our study, exercise was more efficient in reducing the body weight of overfed rats (7.64%) compared to control (4.27%).

Some studies have shown that exercise reduces visceral fat to a greater extent than subcutaneous fat (38). Our data agree with this view because exercise reduced body weight by about 30 g in overfed animals and two thirds of this difference (nearly 20 g) was due to a reduction of abdominal visceral fat. Therefore, our data confirm that low-intensity aerobic exercise seems to be more efficient to reduce visceral fat compared to subcutaneous fat. This is an important finding since visceral fat accumulation is related to several metabolic disorders predisposing to glucose intolerance, hypertension, type 2 diabetes, and coronary heart disease (2,3,38-40). Interventions that reduce abdominal fat, therefore, are extremely important to reduce the incidence of these highly prevalent conditions in the human population.

Unlike other studies (9), we did not observe changes in plasma biochemical variables. However, similar findings for basal parameters were also shown in a previous study (10) in which biochemical changes in overfed rats were only observed in the fed state and not during fasting. In our study, blood samples were collected after a long fasting period (about 16 h) because our main purpose was to record blood pressure directly in awake and unrestrained animals. This long fasting period may interfere with the values of biochemical variables. Thus, it seems that the overfed animals included in our study developed a central-like obesity without evident signs of insulin resistance or hypertension during the study period.

Finally, we have to address to some study limitations. The first refers to the distribution of the animals since only rats prone to run on the treadmill were allocated to the exercised groups while the sedentary groups had rats prone and not prone to run. However, it is unlikely that this trait may interfere with other variables, such as appetite, thus influencing the lower body weight gain and fat accumulation in exercised rats. The food intake control during the training period could confirm this explanation. Moreover, we did not obtain a direct evaluation of exercise intensity based on oxygen consumption. Based on other studies (29), we estimated that rats ran at low intensity facilitating adhesion to the training protocol. Finally, unlike others (9,10), we did not detect hemodynamic or metabolic changes suggestive of insulin resistance. Perhaps if the animals had been studied later in life such changes could have been detected. For example, this obesity model (9) demonstrated changes in blood pressure in rats at the age of 53 weeks, while our measurements were obtained much earlier (18 weeks). We also did not measure insulin levels or sensitivity after a glucose test. Thus, the basal glucose level may be normal even in the presence of insulin intolerance.

Our data show that overfeeding a small rat litter during the initial suckling period can determine long-term changes in body weight regulation leading to an increased fat deposition in the abdomen later on. For the first time, it was demonstrated that the differentiation in body weight gain between rats of normal and of small litters occurs in the 1st week of life, and that long-term aerobic exercise, even of low intensity, can determine an important reduction of visceral fat.

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