Early dietary intervention: long-term effects on blood pressure, brain neuropeptide Y, and adiposity markers

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Submitted 22 October 2004; accepted in final form 1 January 2005

THE INCREASING INCIDENCE in Western societies of childhood obesity is of particular concern (29) and is associated with subsequent hyperlipidemia, glucose intolerance, and hypertension (5, 6). Several factors can contribute to the development of obesity including genetic makeup, dietary intake, or level of physical activity.

Many circulating peptides, several of which are derived from adipose tissue, are involved in the central regulation of food intake, body weight, and metabolism. One of the most studied is leptin, produced by adipose tissue and whose plasma concentration is directly proportional to fat mass in animals (18) and humans (10). The actions of leptin are mediated by the leptin receptors found predominantly in the hypothalamus (18) and humans (10). The actions of leptin are mediated by the leptin receptors found predominantly in the hypothalamus (18) and humans (10).

postnatal overnutrition; high-fat diet; leptin; obesity

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Velkoska, Elena, Timothy J. Cole, and Margaret J. Morris. Early dietary intervention: long-term effects on blood pressure, brain neuropeptide Y, and adiposity markers. Am J Physiol Endocrinol Metab 288:E1236–E1243, 2005. First published January 11, 2005; doi:10.1152/ajpendo.00505.2004.—Early life nutrition impacts on subsequent risk of obesity and hypertension. Several brain chemicals responsible for both feeding and cardiovascular regulation are altered in obesity. We examined effects of early postnatal overnutrition on blood pressure, brain neuropeptide Y (NPY), and adiposity markers. Rat pup litters were adjusted to either 3 or 12 male animals (overnutrition and control, respectively) on day 1 of life. After weaning, rats were either given a palatable high-fat diet or standard chow. Smaller litter pups were significantly heavier by 17 days of age. By 16 wk, the effect of litter size was masked by that of diet. Postweaning, small and normal litter animals fed a high-fat diet had similar increases in body weight, plasma insulin, leptin, and adiponectin concentrations, leptin mRNA, and fat masses relative to chow-fed animals. An increase in 11β-hydroxysteroid dehydrogenase-1 mRNA in white adipose tissue, and a decrease in uncoupling protein-1 mRNA in brown adipose tissue in both small litter groups at 16 wk of age, may represent a programming effect of the altered litter size. NPY concentration in the paraventricular nucleus of the hypothalamus was reduced in high fat-fed groups. Blood pressure was significantly elevated at 13 wk in high-fat-fed animals. This study demonstrates that overnourishment during early postnatal development leads to profound changes in body weight at weaning, which tended to abate with maturation. Thus, the effects of long-term dietary intervention postweaning can override those of litter size-induced obesity.

The influence of postnatal overnutrition has recently generated great interest (12, 46). Many of the cardiovascular consequences that characterize obesity during adulthood are preceded by abnormalities that begin in childhood. In rodents, reducing litter size increases food availability and has been shown to be an appropriate experimental model to study the immediate and long-term consequences of overnutrition during the early postnatal period. Reducing the number of pups per mother to 3–4 led to an early increase in body weight and fat mass compared with a normal litter of 10–12 pups (4, 16). Recent studies in rats indicate that overnutrition in the early postnatal period results in persisting hyperphagia, obesity, hyperleptinaemia, hyperinsulinaemia, impaired glucose tolerance, elevated triglycerides, and increased systolic pressure (45). Although limited evidence showed that feeding patterns during adulthood may be of greater importance (25), long-term

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consequences of continuous overnutrition beginning at an early age have not been examined. To contrast the long-term consequences of early overnourishment vs. later-onset overnourishment, we compared the impact of continuous overnutrition from birth with a short period of overnutrition and introduced overnutrition postweaning. As our focus was on metabolic and cardiovascular consequences of these models, in this study we measured the body weight, blood pressure, and brain NPY of the animals, as well as changes in plasma leptin, insulin, adiponectin, and TNF-α, which are known to be important mediators in obesity and the development of cardiovascular disturbances. We also investigated the expression of leptin in adipose tissue, in addition to other adipocyte-derived mediators such as 11β-HSD1 and uncoupling protein-1 (UCP1), which is important in thermoregulation (1).

MATERIALS AND METHODS

Animals

Experiments were performed on Sprague-Dawley rats maintained under controlled light (0600–1800) and temperature (20 ± 1°C) conditions.

Female rats were mated and allowed free access to standard laboratory chow (GR2, Barastock, Australia) and water. On day 1 after birth, the rat pup litters were adjusted to litter sizes of 3 [small litter (SL)] and 12 [normal litter (NL)] male animals of similar body weights to induce early postnatal overnutrition or normal nutrition in SL and NL animals, respectively. Body weight of pups was monitored twice a week. After weaning (day 24), pups of each litter size were divided into two diet groups such that their body weights within the litter size group were similar before the onset of the different diets. The control group comprised of pups from the NL fed standard chow only [12% calories as fat (NC), n = 11], whereas the remaining pups from the NL were presented with a highly palatable cafeteria-style diet [consisting of supplemented chow, meat pies, pasta, and cakes, 30% calories as fat (NF), n = 11]. The SL rats were divided in the same manner, with some of the pups receiving standard chow (SC; n = 12) and the rest a high-fat diet (SF; n = 10). The percentage of fat in the diet is calculated from the nutritional information available for each product and the amount in grams consumed by the animals. The 30% fat content of this diet has previously been shown to be sufficient in causing changes related to obesity (24). All animals were housed three per cage postweaning, and body weight and food intake were monitored weekly. All procedures were approved by the Animal Experimentation Ethics Committee of the University of Melbourne.

Experimental Protocol

Blood pressure measurement. Blood pressure measurements were taken at 7, 10, and 13 wk of age in conscious animals with tail-cuff pulse plethysmography using a pneumatic pulse transducer (SDR Clinical Technology) and MacLab data acquisition program. Rats were prewarmed by placing them in a cage under a heat lamp set at 37°C for 5 to 8 min to facilitate tail blood flow before blood pressure was measured. The average of three to five readings of systolic blood pressure was used for each rat. Plasma and tissue collection. During the course of this study, blood samples (0.3 ml) were obtained at 5, 8, 11, and 14 wk of age from the tail vein of previously warmed and gently restrained rats. Animals became accustomed to the procedure and did not show any outward signs of stress. At 16 wk of age, cardiac blood was obtained from deeply anesthetized rats (100 mg/kg ip pentobarbitone sodium). The blood was centrifuged (12,000 rpm, 25°C, 10 min) and the separated plasma stored at −20°C for subsequent determination of plasma insulin, leptin, adiponectin, and TNF-α.

Following blood collection, the animals were decapitated to allow the rapid removal of the brain. Serial coronal sections of the hypothalamus were made on ice, starting at the rostral border, and were then dissected into areas containing the paraventricular nucleus (PVN), anterior and posterior hypothalamus (AH and PH, respectively), arcuate nucleus (ARC), and preoptic area (PO), as previously described (23). The brain regions were weighed and stored at −80°C for subsequent determination of NPY content. Left retroperitoneal white adipose tissue (RpWAT), visceral WAT, gonadal WAT, and interscapular brown adipose tissue (iBAT) were removed, weighed, and frozen in liquid nitrogen for subsequent preparation of mRNA. Heart, liver, kidney, and thymus were also dissected and weighed for comparison. The length of the right tibia was measured as an additional growth marker.

Plasma and Brain Measurements

Plasma leptin, insulin, and adiponectin concentrations were measured with commercially available radioimmunoassay kits (Linco, St. Charles, MO). The plasma concentrations of TNF-α were determined using an ELISA kit (Pharmingen, San Diego, CA), using standard concentrations ranging from 15 to 2,000 pg/ml.

NPY was extracted from PVN, ARC, AH, PH, and PO regions by boiling the brain tissue in 0.5 M acetic acid for 10 min, followed by homogenization and centrifugation at 7,500 rpm for 35 min at 4°C (Beckman J2MI). The supernatant was decanted and weighed, and 50 μl were lyophilized and then reconstituted with assay buffer (0.04 M sodium phosphate buffer containing 0.01 M NaCl, 0.02% NaN3, 0.25% BSA, pH 7.3). NPY-like immunoreactivity (NPY-LI) was measured using synthetic NPY as a standard (10–1,280 pg/tube, Auspep) and Bolton Hunter labeled 125I-NPY (2,000 Ci/mmol, Amersham Pharmacia Biotech UK, Buckinghamshire, UK) (41).

Northern Blot Analysis

Total RNA was extracted from RpWAT and iBAT by homogenization in TRIZol reagent (Life Technologies, Grand Island, NY). Homogenates were extracted with chloroform, and total RNA was precipitated from the aqueous phase with isopropanol. RNA pellets were washed in 70% ethanol, dried, and finally redissolved in sterile nuclease-free water. For Northern blot analysis, total RNA (3–5 μg) was separated in 1% agarose gel containing formaldehyde and transferred to GeneScreen Plus membranes (New England Nuclear Life Science Products, Boston, MA) by capillary blotting. The filters were then prehybridized for 1 h in ULTRAhyb buffer (Ambion, RNA) at 68°C before the addition of various antisense [32P]UTP RNA probes and left to hybridize overnight at 68°C. The filters were then washed as previously described (8). All filters were rehybridized with a riboprobe to a cDNA for mouse GAPDH to control for loading of the RNA. All washed filters were exposed for 1–3 h on a phosphorimager screen (Fuji Photo Film, Tokyo, Japan) and scanned for analysis of mRNA levels (Typhoon 8600 Scanner, Molecular Dynamics).

Statistics

Results are expressed as means and SD. Body weight and blood pressure were analyzed by two-way ANOVA with repeated measures, followed by post hoc least significant difference tests (GraphPad Prism 3.0, Statview). Organ weights, fat mass, plasma leptin, insulin, adiponectin, TNF-α mRNA levels, and brain NPY concentrations were analyzed using two-way ANOVA, followed by post hoc Bonferroni tests. Correlation coefficients were determined for leptin and insulin vs. body weight, RpWAT, NPY, and blood pressure.
Effect of Litter Size

On day 1 of life, litter groups were adjusted to similar starting body weights. By 17 days of age, the SL animals were already significantly heavier [43.4 g (SD6.7) vs. 37.5 g (SD2.9); P < 0.05; Fig. 1]. At 24 days of age, the pups raised in small litters were 20% heavier than the NL pups [70.3 g (SD11.2) vs. 58.0 g (SD5.7); P < 0.05; Fig. 1]. In parallel studies, using the same protocol, we demonstrated a 20–30% increase of milk consumption in SL animals. After weaning, the increase in body weight as a result of the reduced litter size persisted up to 10 wk of age, such that the SL animals were significantly heavier than the NL animals (SC vs. NC and SF vs. NF; Fig. 2). However, from 11 wk of age there was no significant difference in body weight between the two litter groups on the same diet. Caloric intake postweaning was similar between both SL and NL sizes within dietary groups as shown in Table 1 at 16 wk of age. This was a consistent finding from 5 to 16 wk of age (data not shown). Although at 16 wk of age the SL animals tended to be slightly heavier than those from normal litters, there were no significant litter size-related changes in organ weights or fat mass at death (Table 1).

In line with the body weight difference at 8 wk of age, plasma leptin was elevated in both SL groups compared with NL groups irrespective of their diet (Fig. 3A). No litter size effect was observed on plasma insulin (Fig. 3B) and adiponectin concentrations (Table 1).

To further investigate the changes in adipocyte-derived mediators, Northern blot analysis was used to determine mRNA levels of leptin, UCP1, and 11β-HSD1 in adipose tissue. Measuring leptin mRNA levels in both RpWAT and iBAT revealed no significant differences between SL and NL groups (Fig. 4, A and B, respectively). An increase in the mRNA level of 11β-HSD1 in RpWAT was observed in both the SL groups regardless of their diet, compared with the respective NL animals (Fig. 4C). Although there appeared to be a reduction in the expression of UCP1 mRNA levels in iBAT in both SL groups, this did not reach significance (Fig. 4D).

ANOVA revealed no overall effect of litter size on blood pressure at 13 wk; however, when comparing only SC and NC, the modest elevation in blood pressure (9 mmHg) in the SL group reached significance on unpaired t-test (t = 2.13, P < 0.05; Fig. 5).

When examining hypothalamic NPY at 16 wk of age, no effect of litter size was evident. Within each diet group, rats from SL and NL showed similar NPY concentrations in all hypothalamic regions (Fig. 6).

Effect of High-Fat Diet Postweaning

As a result of the high-fat diet, body weight of both fat-fed groups significantly increased (i.e., NF vs. NC; SF vs. SC) after only 2 wk postweaning. After 10 wk of age (6 wk of diet), the litter effect was no longer significant and there was a greater effect of the high-fat diet on body weight (Fig. 2). Throughout the study, the SF group remained the heaviest, whereas the control group (NC) was the lightest. At 16 wk of age, both fat-fed groups were significantly heavier compared with chow-fed animals, and their fat mass was doubled (Table 1). The effect of high-fat diet on fat mass was still evident after correcting for body weight (Table 2).

Food intake increased, in both amount and kilojoules, as rats matured (data not shown), and in addition the high-fat-fed animals ate more than double the kilojoules eaten by chow-fed animals over the duration of the study (Table 1).

At 7 wk of age, systolic blood pressure was similar in the four treatment groups (Fig. 5). At 13 wk of age, increases in blood pressure were evident in both high-fat-fed groups relative to their chow-fed controls [NF 152.6 mmHg (SD8.3) vs. NC 132.1 mmHg (SD9.2); SF 152.9 mmHg (SD6.5) vs. SC 141.2 mmHg (SD7.4); P < 0.01]. When both diet groups were combined, there was a significant positive correlation between blood pressure and both plasma leptin (SL r = 0.61, P < 0.003; NL r = 0.66, P < 0.003) and insulin (SL r = 0.61, P < 0.003; NL r = 0.58, P < 0.005) at 13 wk of age in both litter size groups.

A diet-related increase in plasma leptin was evident as early as 8 wk and was particularly obvious at 16 wk of age with a
tripling of leptin concentration (Fig. 3A). Insulin was almost doubled at both 11 and 16 wk of age (Fig. 3B). In both litter size groups, plasma leptin was positively correlated with body weight (SL $r = 0.79$, $P < 0.0001$; NL $r = 0.77$, $P < 0.001$) and RpWAT (SL $r = 0.86$, $P < 0.0001$; NL $r = 0.76$, $P < 0.0001$).

Plasma adiponectin was elevated in the high fat-fed animals reaching significance when comparing NC with NF (Table 1). Plasma TNF-α concentrations in these animals demonstrated no change under these conditions (data not shown).

Northern blot analysis showed significant increases of leptin mRNA in RpWAT (Fig. 4A) and iBAT (Fig. 4B) in rats consuming the high-fat diet (overall diet effect, $P < 0.05$, 2-way ANOVA). The high-fat diet did not significantly change the mRNA levels of either 11β-HSD1 mRNA in RpWAT (Fig. 4C) or UCP1 mRNA in iBAT (Fig. 4D) when compared within each litter group.

A significant decrease in NPY concentration was observed in the PVN and AH regions in both high fat-fed groups compared with chow-fed animals. NPY concentration in the ARC of high fat-fed animals approached significance ($P < 0.058$; Fig. 6). In addition, a significant negative correlation was apparent between leptin and total hypothalamic NPY in both litter size groups (SL $r = -0.45$, $P < 0.05$; NL $r = -0.57$, $P < 0.01$).

### DISCUSSION

Recently, the “early origins” hypothesis of adult disease was put forward, proposing that not only fetal but also postnatal nutrition is able to trigger programming of adiposity (37). Although many studies have focused on prenatal effects that normally cannot be readily controlled, little is known about the positive and negative effects of various postnatal variations to the environment, such as early nutritional differences.

In the current study, postnatal overnutrition induced by small litter size led to early changes in body weight, in part related to increased milk consumption as previously shown (3). The litter effect on body weight was maintained for a period into adulthood (10 wk) in accord with previous studies (4, 16, 45), which have also shown increased fat mass and fat cell number as a result of early overnutrition. Our observations also show the development of hyperleptinemia but not hyperinsulinemia in the SL animals along with the greater body weight gain.

In contrast to many studies, this work also examined the effect of prolonging the early-onset overnourishment by subjecting animals to a high-fat diet postweaning. Regardless of litter size, the high-fat diet resulted in a significant increase in body weight compared with chow diet after only 2 wk. At the

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**Table 1. Caloric intake, body and organ weights, and fat mass at 16 wk of age**

<table>
<thead>
<tr>
<th></th>
<th>Normal Litter</th>
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<tbody>
<tr>
<td></td>
<td>Chow ($n = 11$)</td>
<td>High fat ($n = 11$)</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>503.3 (SD 55.2)</td>
<td>602.9 (SD 80.2)$^&lt;$</td>
</tr>
<tr>
<td>Food intake, kJ/rat</td>
<td>23.1 (SD 3.6)</td>
<td>51.4 (SD 3.2)$^&lt;$</td>
</tr>
<tr>
<td>Adiponectin, μg/ml</td>
<td>3.8 (SD 0.6)</td>
<td>5.6 (SD 0.6)$^*$</td>
</tr>
<tr>
<td>Atria, g</td>
<td>0.08 (SD 0.01)</td>
<td>0.08 (SD 0.02)</td>
</tr>
<tr>
<td>Ventricle, g</td>
<td>1.34 (SD 0.12)</td>
<td>1.48 (SD 0.18)$^*$</td>
</tr>
<tr>
<td>Thymus, g</td>
<td>0.70 (SD 0.19)</td>
<td>0.80 (SD 0.23)</td>
</tr>
<tr>
<td>Liver, g</td>
<td>19.00 (SD 3.07)</td>
<td>20.87 (SD 3.04)</td>
</tr>
<tr>
<td>Kidney, g</td>
<td>1.44 (SD 0.10)</td>
<td>1.78 (SD 0.49)</td>
</tr>
<tr>
<td>BAT, g</td>
<td>0.37 (SD 0.12)</td>
<td>0.54 (SD 0.13)$^*$</td>
</tr>
<tr>
<td>RpWAT, g</td>
<td>5.64 (SD 1.30)</td>
<td>11.89 (SD 2.05)$^*$</td>
</tr>
<tr>
<td>Gonadal WAT, g</td>
<td>7.57 (SD 2.61)</td>
<td>19.69 (SD 6.91)$^*$</td>
</tr>
<tr>
<td>Visceral WAT, g</td>
<td>8.10 (SD 2.69)</td>
<td>14.18 (SD 4.26)$^*$</td>
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Values expressed as means with SD. BAT, brown adipose tissue; RpWAT, retroperitoneal white adipose tissue. *$P < 0.05$, †$P < 0.01$ (high fat-fed groups vs. chow-fed groups). No significant litter size effect was observed [normal litter chow fed (NC) vs. small litter chow fed (SC), normal litter high fat fed (NF) vs. small litter high fat fed (SF)].
end of the study, we observed diet-induced hyperleptinaemia and hyperinsulinaemia, as well as significant increases in fat mass in both litter size groups. These findings demonstrate that long-term dietary intervention can override the litter size-induced effects, thus showing that overnutrition in later life may have a greater impact. However, in both the chow-fed and high fat-fed groups, the animals raised in the small litters remained moderately heavier than NL animals throughout adulthood, although this failed to reach significance. This may suggest that early nutrition may still play a small but important role. This suggestion is supported by another study with similar results in female rats subjected to a later onset of high-fat diet (25), as opposed to the continuous overnutrition to which the rats in this study were subjected.

NPY concentration was reduced in the PVN, a region of the hypothalamus important in the regulation of feeding, in both high fat-fed groups compared with animals on a standard diet. We (24) previously observed this pattern in chronic dietary obesity induced in the adult rat only after a long period of high-fat feeding, possibly due to decreased production of hypothalamic NPY. As high fat-fed animals manifest hyperleptinemia and hyperinsulinemia, this may contribute to the reduced NPY, suggesting that the negative feedback loop involved in satiety is still functioning and attempting to reduce the hyperphagia in the high fat-fed animals. However, the persistent hyperphagia in the high fat-fed animals may suggest the involvement of other hypothalamic mechanisms in the development and progression of obesity, highlighting the complexity of the feeding system.

Adjustment of litter size or, more to the point, adjustment of early feeding patterns can influence adult blood pressure (42, 45), as can the type of diet (13). In the current study, we also observed an increase in blood pressure as animals fed the high-fat diet gained weight. The effect of short-term overnu-
The mechanisms of the development of obesity and the relationship to cardiovascular disturbances remain unclear. Early work showed that high caloric intake can increase sympathetic activity, thus increasing norepinephrine turnover in peripheral tissues and raising resting plasma norepinephrine, resulting in elevated blood pressure (30). Obesity-related increases in blood pressure can also be associated with hyperleptinemia (17, 36), possibly due to the increased sympathetic activity to the iBAT, kidney, and adrenal (27). Recent studies have shown that microinjection of leptin into the ventromedial hypothalamus led to an increase in circulating catecholamines (50), suggesting that sympathetic activation due to leptin is mediated primarily via the central nervous system. Other observations also support this suggestion, as lesion of the ARC abolished the sympathetic response to leptin infusion (26). In contrast, injections of NPY into the third ventricle or the PVN result in decreased sympathetic activity to iBAT (15). Therefore, it is not surprising that, in this study, plasma leptin was positively correlated with blood pressure, and in turn, negatively correlated with NPY, which could all be associated with an overall increase in sympathetic activity.

There are a number of mediators that can regulate the production of leptin, including insulin, glucocorticoids, and catecholamines (19). Our leptin mRNA data suggest that the high fat-fed animals may be producing more leptin from adipose tissue compared with Chow-fed rats. An increased level of leptin mRNA has previously been demonstrated in dietary obesity (9, 52). In humans, it has been speculated that increased gene expression enhances leptin production, thereby increasing leptin secretion and circulating plasma leptin (33). Under the conditions of overnourishment used in this study, leptin mRNA data, together with increased plasma leptin concentrations, also suggest increased leptin production.

Adiponectin was recently reported to have anti-atherogenic properties, as it inhibits monocyte adhesion to endothelial cells (44). In the current study, we observed modest increases of plasma adiponectin in the high fat-fed groups. This finding is supported by a recent study (43), which reported an increase in plasma adiponectin with a long-term high-fat diet despite decreased mRNA as reported by most studies (2, 56). Higher plasma adiponectin was reported in hypertensive men, thought to be due to a counterregulatory response aimed at lessening the endothelial damage and associated cardiovascular risk (35). This may relate to our findings, although it remains to be investigated further.

We examined the effects of different types of overnutrition on the mRNA levels of 11β-HSD1 in WAT, as well as the UCP-1 mRNA levels in BAT. It has been speculated that increased glucocorticoid production as a result of increased 11β-HSD1 mRNA in fat tissue from obese rodents and humans may influence fat accumulation (32, 48). In our hands, the high-fat diet was not associated with elevation of 11β-HSD1 mRNA expression; however, overall there was a significant increase in SL group animals, suggesting that there may be some long-term modest effects of early-onset overnutrition on 11β-HSD1 and possibly glucocorticoid levels. Glucocorticoids can directly inhibit the transcription of the UCP1 gene in iBAT cells (54). Although iBAT UCP1 expression may be a useful marker of thermogenesis and a reduction in UCP1 may make animals more susceptible to gaining weight, no significant effects of diet or litter were observed in this study. However, as UCP1 expression was measured only at 16 wk of age, we cannot assess whether changes may have occurred during the onset of obesity. Further studies need to be done to establish the clear role of UCP1 in obesity, especially as UCP1-deficient mice that are expected to be more prone to obesity were found to be resistant to diet-induced obesity (31). There also seem to be variable data on UCP1 gene expression in lean and obese humans (11).

Studies have shown that children who have higher body mass are more likely to become obese adults and are at higher risk of developing cardiovascular disturbances (21, 28). Childhood obesity is already at epidemic proportions in some countries and on the rise in others (53). The causes of this epidemic need to be established to help in the development of strategies that will reduce the disease burden. According to the literature, the greatest risk is seen in overweight children who become overweight adults, as has been demonstrated in the current study involving rats.

In summary, these findings indicate that rats overfed from an early age develop subsequent increases in body weight, along with profound changes of central and peripheral mediators involved in the regulation of feeding and body weight. Although the effects of early postnatal overnourishment are important, these results demonstrate that it is possible for long-term overnutrition postweaning to override these effects
long-term effects in overfed neonatal rats

in adulthood. It is not yet clear whether the timing of the onset of the high-fat diet might influence the outcome. Further research is required to increase our understanding of the mechanisms underlying the development of increased blood pressure in obesity.

GRANTS

This work was supported by a Postgraduate Scholarship from the National Heart Foundation of Australia and a Project Grant from National Health and Medical Research Council of Australia.

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