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Resistance to Adenovirally Induced Hyperleptinemia in Rats
Comparison of Ventromedial Hypothalamic Lesions and Mutated Leptin Receptors

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Abstract

Leptin regulates appetite and body weight via hypothalamic targets, but it can act directly on cultured pancreatic islets to regulate their fat metabolism. To obtain in vivo evidence that leptin may act peripherally as well as centrally, we compared the effect of adenovirally induced hyperleptinemia on food intake, body weight, and islet fat content in ventromedial hypothalamic-lesioned (VMHL) rats, sham-lesioned (SL) controls, and Zucker Diabetic Fatty (ZDF) rats in which the leptin receptor is mutated. Infusion with recombinant adenovirus containing the rat leptin cDNA increased plasma leptin by ∼ 20 ng/ml in VMHL and ZDF rats but had no effect on their food intake, body weight, or fat tissue weight. Caloric matching of hyperphagic VMHL rats to SL controls did not reduce their resistance to hyperleptinemia. Whereas prediabetic ZDF rats had a fourfold elevation in islet fat, in VMHL rats islet fat was normal and none of them became diabetic. Isolated islets from ZDF rats were completely resistant to the lipogenic action of leptin, while VMHL islets exhibited 50% of the normal response; caloric matching of VMHL rats to SL controls increased leptin responsiveness of their islets to 92% of controls. We conclude that leptin regulation of adipocyte fat requires an intact VMH but that islet fat content is regulated independently of the VMH. (J. Clin. Invest. 1998. 102:728–733.) Key words: leptin resistance • Zucker Diabetic Fatty (ZDF) rats (fa/fa) • adenoviral gene transfer • islets • triglycerides

Introduction

The hypothalamus plays a crucial role in the control of food intake, thermogenesis, and body composition (1–8). The discovery of leptin (3) and neuropeptide Y (NP-Y) (4) have expanded our understanding of the mechanisms involved in hypothalamic obesity. It has been established that the full-length leptin receptor isoform, OB-Rb,1 is preferentially expressed in the ventromedial hypothalamic (VMH) nucleus (5) and that it downregulates the expression of the NP-Y gene, which encodes an appetite-stimulating neuropeptide (6–8). When leptin is deficient, as in ob/ob mice (3), when OB-Rb is defective, as in db/db mice (9, 10), when all OB-R isoforms are defective, as in the homozygous (fa/fa) Zucker Diabetic Fatty (ZDF) rats (11, 12), or when the VMH nucleus is ablated (13), hyperphagia and obesity ensue. However, the latter syndrome differs from the three genetically determined syndromes in that the loss of leptin action is presumably confined to the ablated area and, unlike the genetic syndromes, should not involve extrahypothalamic tissues that express the normal OB-R. Furthermore, diabetes, which complicates all three of the genetic forms of obesity, is reported not to occur in VMH-lesioned (VMHL) animals (14).

Although an abundance of evidence points to leptin as the principal signal to the hypothalamus for regulation of body composition, leptin also has striking direct extraneuronal effects on both adipocytes (15) and nonadipocytes (16, 17). For example, it lowers the fat content of isolated islets by directly upregulating the mRNA of enzymes of fatty acid oxidation, carnitine palmitoyl transferase-1 (CPT-1) and acyl-CoA oxidase (ACO), and downregulating mRNA of enzymes of lipogenesis, fatty acid synthetase, fatty acyl-CoA synthetase, and glycerol-phosphate acyl transferase (18). There are also in vivo observations consistent with direct leptin action. For example, when ectopic hyperleptinemia is induced by adenoviral transfer of the leptin cDNA into normal lean rats, all visible fat tissue disappears within 1 wk (19) and fat content falls dramatically in nonadipocytes as well (20); the disappearance of fat is accompanied by the same increase in expression of genes encoding enzymes of fatty acid oxidation, CPT-1 and ACO (19), as was observed in vitro.

In an attempt to determine if the rapid generalized fat depletion caused by ectopic hyperleptinemia is entirely mediated by the VMH nucleus, we induced hyperleptinemia by adenoviral leptin gene transfer in a group of VMHL rats. We had expected that hyperphagia, which is clearly the result of the hypothalamic lesion, would be resistant to the ectopic hyperleptinemia; however, given the presumed qualitative and quantitative integrity of the extrahypothalamic leptin receptors, we expected that all

1. Abbreviations used in this paper: AdCMV-leptin, recombinant adenovirus containing the rat leptin cDNA under control of the CMV promoter; AdCMV-β-gal, recombinant adenovirus containing the bacterial β-galactosidase gene under control of the CMV promoter; OB-R, leptin receptor; OB-Rβ, leptin receptor b isoform; SL, SL-lesioned; TG, triglyceride; VMH, ventromedial hypothalamus; VMHL, VMH-lesioned; ZDF, Zucker Diabetic Fatty.
OB-R–expressing peripheral tissues, including adipocytes, would respond to the hyperleptinemia. This study was designed to test this prediction.

Methods

VMHL and sham-lesioned controls. This VMHL was performed at the Department of Neuroscience, University of Florida (Gainesville, FL) as approved by the University of Florida Institutional Animal Care and Use Committee, which follows the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Adult Sprague Dawley (HSD-HD: Harlan Sprague-Dawley, Indianapolis, IN) male rats weighing 250–300 g were housed in air-conditioned rooms (22–25°C) with lights on from 0500–1900 h. Food and water were available ad libitum. Rats were weighed and anesthetized with sodium pentobarbital (50 mg/kg i.p.; Abbott Laboratories, North Chicago, IL). The VMH was destroyed bilaterally by the previously described electrolytic lesion procedure (21). Briefly, rats were placed in the stereotaxic instrument and positioned with the nose bar set 3.3 mm below the interaural line. The electrode, consisting of an insulated stainless steel insect pin with exposed tip, was positioned 2.6 mm behind the bregma, 0.6 mm lateral to the midline, and then lowered to the base of the brain and then raised 0.5 mm. A direct anodal current of 2.5 mA for 15 s was passed through the electrode aimed at the VMH with a rectal electrode serving as a cathode. For sham-lesioning (SL), the same surgical procedures were performed except that no current was passed. Rats were allowed to recover for approximately 1 wk before any further procedures were undertaken. They were then flown to Dallas.

Animals. Homozygous (fa/ fa) ZDF–drt rats were bred in our laboratory from [ZDF/Drt–fa(F10)] rats purchased from R. Peterson (University of Indiana School of Medicine, Indianapolis, IN). 6- to 7-wk-old male ZDF (fa/ fa) rats were used in this study. All Sprague Dawley and ZDF (fa/ fa) rats were studied in individual metabolic cages (Nalgene, Rochester, NY), and body weight and food intake were measured daily. Free-feeding rats were on standard chow (50 mg/kg i.p.; Abbott Laboratories, North Chicago, IL). The VMH was destroyed bilaterally by the previously described electrolytic lesion procedure (21). Briefly, rats were placed in the stereotaxic instrument and positioned with the nose bar set 3.3 mm below the interaural line. The electrode, consisting of an insulated stainless steel insect pin with exposed tip, was positioned 2.6 mm behind the bregma, 0.6 mm lateral to the midline, and then lowered to the base of the brain and then raised 0.5 mm. A direct anodal current of 2.5 mA for 15 s was passed through the electrode aimed at the VMH with a rectal electrode serving as a cathode. For sham-lesioning (SL), the same surgical procedures were performed except that no current was passed. Rats were allowed to recover for approximately 1 wk before any further procedures were undertaken. They were then flown to Dallas.

Leptin gene transfer. To induce hyperleptinemia in SL and VMHL rats, recombinant adenovirus containing the rat leptin cDNA (AdCMV-leptin) was prepared as previously described (19). Briefly, a Bam HI– and Xba I–restricted leptin cDNA fragment that includes 60 bp of 5′ untranslated region and 76 bp of 3′ untranslated region was ligated to similarly treated pACCMVpLpA. The resulting plasmid was cotransfected with pJM17 into 293 cells by calcium phosphate precipitation (22). Stocks of AdCMV-leptin were amplified and purified as described (22), and then stored at −70°C in phosphate buffer solution with 0.2% bovine serum albumin and 10% glycerol at 37°C. After sonication, 10 pfu was infused into the right cervical vein of uncon- Theme of the year. Women’s issues. Tertiar descript regions.

Statistical analyses. All values shown are expressed as mean±SEM. Statistical analysis was performed by two-tailed unpaired Student’s t test by one-way analysis of variance.

Results

Leptin levels. AdCMV-leptin was infused into lean SL rats, obese VMHL rats, and obese ZDF (fa/ fa) rats. As shown in Fig. 1 A, baseline plasma leptin levels were elevated in VMHL

Figure 1. Plasma leptin levels in SL and VMHL Sprague Dawley rats (A), and ZDF (fa/ fa) rats (B) before and 14 days after AdCMV-leptin or AdCMV-βgal infusion. Values represent the mean±SEM of five experiments.
and ZDF (fa/fa) animals, averaging 7.8±0.7 ng/ml and 7.6±0.2 ng/ml, respectively, on the day of viral infusion compared with 0.98±0.1 ng/ml in SL rats (Fig. 1). In AdCMV-leptin–infused VMHL rats, plasma leptin rose to 21.5±3.2 ng/ml on day 3 and declined to 12.0±2.2 mg/ml on day 14 (Fig. 1 A). In ZDF (fa/fa) rats infused with AdCMV-leptin, plasma leptin reached a peak of 20.3±2.1 ng/ml on day 3 and averaged 14.8±1.9 ng/ml on day 14 (Fig. 1 B).

Food intake, body weight, and plasma insulin levels. As expected, the food intake and body weight of VMHL rats increased significantly above that of SL rats (Fig. 2, A and B). While both food intake and body weight were dramatically reduced in SL rats infused with AdCMV-leptin, in the AdCMV-leptin–treated VMHL rats, neither food intake nor body weight differed from untreated VMHL controls despite a threefold rise in their previously elevated plasma leptin levels. The weight of epididymal and retroperitoneal fat in VMHL rats was significantly greater than that of SL controls and was not reduced by the increase in hyperleptinemia. Plasma glucose of SL rats infused with AdCMV-leptin declined to 40.3±2.9 mg/dl on day 14, but there was no change in glucose in VMHL rats (Fig. 2 C). As shown in Fig. 2, D–F, food intake, body weight, and plasma glucose levels of ZDF (fa/fa) rats were similarly resistant to the effects of the ectopic hyperleptinemia. The lack of a change in either food intake or body weight in the hyperleptinemic VMHL rats indicated that both the anorectic and adipocyte-wasting effects of hyperleptinemia require an intact hypothalamus.

Fasting insulin levels averaged 23±11.3 μU/ml in VMHL rats infused with AdCMV-βgal compared with 11.6±1.9 μU/ml in SL rats infused with AdCMV-βgal. Hyperleptinemia did not significantly change insulin levels in either group; insulin averaged 17.7±4.9 μU/ml in AdCMV-leptin–infused VMHL rats and 10.2±2.8 μU/ml in SL rats.

**Islet fat content and diabetes.** Because the islets of ZDF (fa/fa) rats are resistant to the lipopenic action of leptin, the fat content of their pancreatic islets ranges from 10 to 100 times normal (25). Islet fat exceeds 25–50 ng/islet at the time that diabetes begins, generally between 8–12 wk of age. If the islets of VMHL rats are also resistant to the lipopenic action of leptin, an increase in fat content and the appearance of diabetic abnormalities should have been evident. However, the islet TG content of VMHL rats averaged only 19 ng/islet, not significantly different from that of SL controls, whereas islets of prediabetic ZDF (fa/fa) rats of similar age and weight contained over twice as much fat (Fig. 3). This indicates that the islets of VMHL rats must have been far more responsive to leptin in vivo than the islets of ZDF (fa/fa) rats and almost as responsive as normal islets. However, whereas the genetic leptin resistance of ZDF (fa/fa) rats had existed throughout the 7 wk of their life, the VMHL rats had been leptin-resistant for only 3 wk after their surgery. To determine if more prolonged leptin resistance would cause accumulation of islet fat and diabetes, a second group of five VMHL rats was sacrificed 12 wk after VMH lesioning. The fat content of their islets averaged 21 ng/islet, which is still not significantly above the SL controls.

Consistent with the lack of increased islet fat content in the VMHL rats was the absence of overt diabetes during careful observation up to the age of 20 wk. Although none of the rats developed fasting hyperglycemia, their intraperitoneal glucose tolerance test was slightly impaired (Table I). Thus, it appeared that the islets of VMHL rats escape the diabetogenic consequences of leptin resistance, confirming earlier observations by others (14).

**Skeletal muscle fat.** We had previously reported that in leptin-resistant ZDF (fa/fa) rats, the TG content in islets is paralleled by an increase in the TG content of other tissues. In skeletal muscle for example, it rose to 13.8 ng/g/wet weight, which is almost three times the normal content of 4.1±1.2 ng/g/wet weight (20). This may have been a key factor in their insulin resistance. For this reason, we measured skeletal muscle TG content in VMHL rats. It averaged only 1.1±0.1 ng/g/wet weight.

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**Figure 2.** Food intake (A), body weight (B), plasma glucose in SL and VMHL male Sprague Dawley rats (C), and food intake (D), body weight (E), and plasma glucose (F) in ZDF (fa/fa) rats before and 14 d after AdCMV-leptin or AdCMV-βgal infusion. Values represent the mean±SEM of five experiments.

**Figure 3.** Pancreatic islet triglyceride content of SL and VMHL Sprague Dawley rats and ZDF (fa/fa) rats 14 d after AdCMV-leptin or AdCMV-βgal infusion and 14 wk after VMHL of Sprague Dawley rats. Values represent the mean±SEM of five rats. *P < 0.05 vs. SL AdCMV-leptin–infused rats.
weight, about the same as in normal rats made lipopenic by adeno- viral leptin gene transfer (20). This low skeletal muscle fat may have provided additional protection against diabetes by increasing insulin sensitivity.

Effect of caloric restriction on in vivo leptin resistance of VMHL rats. Since leptin resistance can be induced in normal rodents by increasing their caloric intake (26), we wished to eliminate any diet-induced impairment of leptin action in VMHL rats. We therefore placed five hyperphagic VMHL rats on a diet calorically matched to that of five SL controls and infused them with AdCMV-leptin. This diet matching had reduced their caloric intake by 28% prior to the infusion. Their body weight averaged 326 ± 4.2 g 14 d after the infusion, compared with 421 ± 3.9 g in hyperleptinemic rats without dietary restrictions (P < 0.01); however, this was not less than the body weight of calorically matched uninfused VMHL rats (without ectopic hyperleptinemia) and was significantly above the hyperleptinemic SL rats (260 ± 13 g; P < 0.01) (Table II). Thus, caloric restriction in VMHL rats failed to reverse or reduce their resistance to the fat-depleting action of ectopic hyperleptinemia. In addition, the weight of their epididymal and retroperitoneal fat depots was no less than that of uninfused VMHL rats (Fig. 4).

Effects of VMHL on leptin action on islets in vitro. Earlier studies had shown that leptin directly lowers TG content in pancreatic islets from normal rats but has no effect in ZDF (fa/ fa) rats with defective leptin receptors. We therefore deter-
mined the in vitro effects of leptin on the TG content of cultured islets from VMHL rats, expecting it to be normal. However, the lipopenic activity of leptin in VMHL rats was only 50% of SL controls (Fig. 5). To determine if this leptin resistance was due to the ablative procedure itself, or if it was secondary to the increased food intake that follows VMHL, we matched the caloric intake of a group of VMHL rats to that of the SL rats for 2 wk beginning 4 d after the VMH ablation. This reduced their caloric intake by 28%. This caloric matching resulted in a twofold increase in sensitivity to the lipopenic action of leptin; the islets were now only 8% less sensitive than SL controls in terms of lipopenic activity, and this difference was not significant (NS).

Discussion

This study was designed to determine if obesity produced by ablation of the VMH causes leptin resistance comparable to that observed in ZDF (fa/ fa) rats, in which a Glu 269 → Pro mutation in the leptin receptor renders tissues completely resistant to the direct lipopenic effects of recombinant leptin (16). Whereas the pancreatic islets of wild-type ZDF (+/+) rats exhibit a > 70% reduction in fat intake when cultured in the presence of 20 ng/ml of leptin, in islets from ZDF (fa/ fa) rats the elevated TG content is unresponsive to leptin at any

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**Table I. Postprandial Plasma Glucose (PG), Triglyceride (TG), Free Fatty Acids (FFA) Levels, and Glucose Tolerance 64 d after SL and VMHL of Male Sprague Dawley Rats**

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<tr>
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<th>SL</th>
<th>VMHL</th>
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<tr>
<td>Plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PG (mg/dl)</td>
<td>119.5±4.2</td>
<td>93.8±3.5*</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>90.0±6.1</td>
<td>175.7±9.5†</td>
</tr>
<tr>
<td>FFA (mmol/l)</td>
<td>0.77±0.09</td>
<td>2.47±0.49‡</td>
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<tr>
<td>Time (h)</td>
<td></td>
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<tr>
<td>0</td>
<td>103.3±3.9</td>
<td>92.2±2.4*</td>
</tr>
<tr>
<td>1</td>
<td>238.3±26.5</td>
<td>344.6±14.0‡</td>
</tr>
<tr>
<td>2</td>
<td>161.0±14.7</td>
<td>287.8±14.2‡</td>
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</tbody>
</table>

Data represent the mean±SEM of five experiments. Glucose was injected intraperitoneally in a dose of 2 g/kg/body weight. *P < 0.05 vs. SL; †P < 0.05 vs. VMHL ad libitum; ‡P < 0.05 vs. VMHL ad libitum controls; §P < 0.01 vs. SL controls; #p < 0.01 vs. sham without AdCMV-leptin

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**Table II. Plasma Leptin Levels and Body Weight 14 d after AdCMV-Infusion in SL, VMHL Sprague Dawley Rats Fed Ad Libitum and VMHL Rats Calorically Matched to SL Control Rats**

<table>
<thead>
<tr>
<th></th>
<th>SL</th>
<th>VMHL ad libitum</th>
<th>VMHL calorically matched to SL control</th>
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<tr>
<td></td>
<td>Control</td>
<td>AdCMV-leptin</td>
<td>Control</td>
</tr>
<tr>
<td>Plasma leptin (ng/ml)</td>
<td>0.98±0.06</td>
<td>14.5±1.5*</td>
<td>7.8±0.7*</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>337±11.5</td>
<td>260±12.6*</td>
<td>395±29.0</td>
</tr>
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</table>

Data represent the mean±SEM of five experiments. *P < 0.01 vs. SL controls; †P < 0.05 vs. VMHL ad libitum controls; ‡P < 0.01 vs. VMHL calorically matched controls.
Pancreatic islet triglyceride content of islets of SL, VMHL rats fed ad libitum, VMHL calorically matched to SL male Sprague Dawley rats, and ZDF (fa/fa) rats. Islets were cultured for 2 d with or without 20 ng/ml leptin. Values represent the mean ± SEM of five experiments. *P < 0.05 vs. SL rats with leptin. †P < 0.05 vs. VMHL rats fed ad libitum.

Figure 5. Pancreatic islet triglyceride content of islets of SL, VMHL rats fed ad libitum, VMHL calorically matched to SL male Sprague Dawley rats, and ZDF (fa/fa) rats. Islets were cultured for 2 d with or without 20 ng/ml leptin. Values represent the mean ± SEM of five experiments. *P < 0.05 vs. SL rats with leptin. †P < 0.05 vs. VMHL rats fed ad libitum.

concentration (16). These findings led us to postulate that leptin acts not only via the hypothalamus but also via direct extra-hypothalamic effects on tissues that express normal OB-R. Since it seemed unlikely that a VMH lesion in otherwise normal rats would reduce either the level of expression or functional activity of OB-R in such target tissues, we expected that the hyperphagia of VMHL rats would be resistant to the hyperleptinemia, but that adipocytes would be rapidly depleted of fat, as in normal rats. This was not the case. Despite plasma leptin values threefold above the control VMHL rats, neither body weight nor the weight of epididymal and retroperitoneal fat depots were reduced. Finally, although the normal fat content of their islets suggested that they had been sensitive to leptin in vivo, the direct in vitro lipopenic action of leptin on islets from VMHL rats was only minimally that of SL controls, indicating a modest level of resistance.

Since increased caloric intake causes leptin resistance (26), we reasoned that the increased caloric intake of the hyperphagic VMHL animals might be inducing peripheral resistance unrelated to the ablation of the hypothalamic nuclei. To test this hypothesis, the caloric intake of the hyperphagic VMHL rats was matched to that of SL controls. This did not reduce either body weight or the weight of epididymal or retroperitoneal fat, but it did improve the lipopenic action of leptin on isolated islets, bringing it to 92% of SL controls.

In contrast to the complete leptin resistance of ZDF (fa/fa) rats, in which islet TG content ranges from 10 to 100 times normal, the TG content in islets of VMHL rats was only minimally increased, about 10% above normal. In addition, skeletal muscle TG content, which is approximately three times normal in ZDF (fa/fa) rats, was subnormal in VMHL rats. This could be construed as evidence of sensitivity to leptin’s lipopenic action in vivo. Since the islet cell dysfunction, insulin resistance, and diabetes of ZDF (fa/fa) rats has been attributed to the accumulation of tissue fat (25), it was of interest to examine VMHL rats for evidence of diabetes. In VMHL rats, there was no elevation in fasting glucose levels at any time during 90 d of observation, and their postprandial blood glucose levels, though normal, were lower than in the SL controls (Fig. 2 C). However, the intraperitoneal glucose tolerance test carried out 64 d after lesioning revealed high levels at 1 and 2 h (Table I), which may reflect modest insulin resistance and account for the higher insulin levels of the VMHL rats.

The leptin resistance of VMHL rats is manifested by intense hyperphagia and substantial weight gain despite hyperleptinemia. A further increase in hyperleptinemia caused by ectopic leptin expression does not reduce food intake, body weight gain, or weight of fat depots. When the food intake of AdCMV-leptin–infused VMHL rats is calorically matched to SL controls to eliminate leptin resistance secondary to high caloric intake, there is still no apparent sensitivity to the ectopic hyperleptinemia in the form of a reduction in body weight or weight of fat depots. Thus, the fat-depleting effect of hyperleptinemia is either mediated by the VMH through direct neuronal signaling pathways or via a hypothalamic factor that directly or indirectly renders adipocytes sensitive to direct action of leptin.

Islets isolated from VMHL rats on an unrestricted diet were somewhat resistant to the lipopenic action of recombinant leptin; however, when the caloric intake of the VMHL rats was reduced to that of SL controls, there was marked improvement in their sensitivity to the lipopenic action of leptin. This suggests that the peripheral resistance of islets to leptin may in part be the result of the high caloric intake rather than to the loss of central regulatory factors originating from the VMH (27).

Clearly, the VMHL model of obesity differs strikingly from the fa/fa ZDF model. Although the hyperphagia is similar in the two, plasma and tissue lipids are considerably higher in the ZDF rats. Since food intake averages about 30 g/d in both groups of rats, it is likely that these differences reflect altered metabolism of the ingested nutrients in the ZDF rats. We have already established that lipogenesis is markedly increased in their tissues (25), and more recently, we have found that expression of the enzymes of lipogenesis such as acetyl CoA carboxylase and fatty acid synthetase (Zhou, Y.-T., Y. Lee, K. Koyama, T. Ferguson, and R.H. Unger, unpublished data) is greatly increased. Since the increased lipogenesis can be reversed by expressing the wild-type leptin receptor in their tissues (28), we speculate that in VMHL rats, overexpression of lipogenic enzymes and thus their lipogenic capacity is constrained by a direct action of the hyperleptinemia on OB-R–expressing tissues. In ZDF rats, by contrast, these tissues are completely unresponsive to the hyperleptinemia, and the lack of any direct leptin action results in a much greater lipogenic capacity.

Acknowledgments

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