Lipid and carbohydrate metabolism in mice with a targeted mutation in the IL-6 gene: absence of development of age-related obesity

Gina B. Di Gregorio,1 Lori Hensley,1 Tong Lu,1 Gouri Ranganathan,1 and Philip A. Kern2
1Division of Endocrinology, Department of Medicine, University of Arkansas for Medical Sciences;
2The Central Arkansas Veterans HealthCare System, Little Rock, Arkansas 72205

Submitted 25 April 2003; accepted in final form 6 February 2004

Di Gregorio, Gina B., Lori Hensley, Tong Lu, Gouri Ranganathan, and Philip A. Kern. Lipid and carbohydrate metabolism in mice with a targeted mutation in the IL-6 gene: absence of development of age-related obesity. Am J Physiol Endocrinol Metab 287: E182–E187, 2004; 10.1152/ajpendo.00189.2003.—Obesity-related insulin resistance may be caused by adipokines such as IL-6, which is known to be elevated with the insulin resistance syndrome. A previous study reported that IL-6 knockout mice (IL-6−/−) developed maturity onset obesity, with disturbed carbohydrate and lipid metabolism, and increased leptin levels. Because IL-6 is associated with insulin resistance, one might have expected IL-6−/− mice to be more insulin sensitive. We examined body weights of growing and older IL-6−/− mice and found them to be similar to wild-type (IL-6+/+) mice. Dual-energy X-ray absorptiometry analysis at 3 and 14 mo revealed no differences in body composition. There were no differences in fasting blood insulin and glucose or in triglycerides. To further characterize these mice, we fed 11-mo-old IL-6−/− and IL-6+/+ mice a high-(HF)- or low-fat diet for 14 wk, followed by insulin (ITT) and glucose tolerance tests (GTT). An ITT showed insulin resistance in the HF animals but no difference due to genotype. In the GTT, IL-6−/− mice demonstrated elevated postinjection glucose levels by 60% compared with IL-6+/+ but only in the HF group. Although IL-6−/− mice gained weight and white adipose tissue (WAT) with the HF diet, they gained less weight than the IL-6+/+ mice. Total lipoprotein lipase activity in WAT, muscle, and postheparin plasma was unchanged in the IL-6−/− mice compared with IL-6+/+ mice. There were no differences in plasma leptin or TNF-α due to genotype. Plasma adiponectin was ∼53% higher (71.7 ± 14.1 µg/ml) in IL-6−/− mice than in IL-6+/+ mice but only in the HF group. Thus these data show that IL-6−/− mice do not demonstrate obesity, fasting hyperglycemia, or abnormal lipid metabolism, although HF IL-6−/− mice demonstrate elevated glucose after a GTT.

interleukin-6; adipose tissue

INSULIN RESISTANCE IS AN EARLY FEATURE in the development of type 2 diabetes and is closely associated with obesity (7). Most whole body glucose uptake occurs in skeletal muscle (8), and obesity is associated with increased lipid accumulation in both adipose tissue and muscle, possibly resulting in lipotoxicity and decreased insulin action (29). The link between insulin resistance and adipose tissue has been tightened considerably with the description of cytokine expression by adipocytes (14). Leptin-deficient mice become obese, insulin resistant, and diabetic, and recent studies suggest that leptin may sensitize skeletal muscle to catecholamine-mediated increased in lipid oxidation (21), resulting in a decrease in muscle lipid accumulation. Another important cytokine in the obesity-insulin resistance syndrome is tumor necrosis factor-α (TNF-α). Obese rodents express higher levels of TNF-α in adipose tissue, and the infusion of such animals with anti-TNF-α-binding proteins reverses the insulin resistance (12). Although the mechanism of TNF-α-mediated insulin resistance is not clear, TNF-α or TNF-α receptor knockout (KO) mice demonstrate less insulin resistance with high-fat feeding (30).

IL-6 is another important component of obesity-related insulin resistance. IL-6 is expressed by many cells and tissues, including adipose tissue, and circulates at fairly high levels in plasma. IL-6 is expressed at higher levels by omental adipose tissue (10) and is released following a meal (24). IL-6, TNF-α, and perhaps other adipokines may interact with each other. In both 3T3-L1 adipocytes and mice, TNF-α caused an increase in IL-6 expression, suggesting a possible role of IL-6 in TNF-α-mediated alterations in carbohydrate and lipid metabolism (4, 11). Plasma IL-6 is higher in subjects with hyperinsulinemia and obesity (3) and was significantly associated with insulin resistance independently of obesity (16). Together, the association between IL-6 and insulin resistance in humans is compelling and leads to the hypothesis that the suppression of IL-6 might have favorable effects on insulin sensitivity.

IL-6 KO (IL-6−/−) mice have been available for some time. These mice are viable, and earlier studies did not evaluate these mice for a phenotype involving carbohydrate metabolism (2, 25, 27). In a recent study, IL-6−/− mice developed maturity onset obesity, with disturbed carbohydrate and lipid metabolism, and increased leptin levels (32). These results were surprising, because high IL-6 is associated with insulin resistance in humans, and therefore one would have expected IL-6−/− mice to be more insulin sensitive than wild-type mice.

In this study, we examined IL-6−/− mice, paying particular attention to phenotypes associated with obesity and insulin resistance. We did not observe an increase in obesity or in total body fat with aging, even when the mice were fed a high-fat diet. Although there were some subtle differences in carbohydrate and lipid metabolism between IL-6−/− and IL-6+/+ mice when they were fed a high-fat diet, there were no consistent changes suggestive of insulin resistance. In addition, adipose tissue secretions of leptin and TNF-α were similar. Therefore, our results show that IL-6−/− mice do not develop any obvious phenotype related to maturity onset obesity and diabetes.
METHODS

Animals. IL-6−/− mice breeder pairs (C57BL/6J-Il6tm1Kopf) were purchased from Jackson Labs (Bar Harbor, ME), and a colony of IL-6−/− mice was established. This is the same strain of IL-6−/− mice reported previously (32). A breeder pair of normal C57BL/6 mice was also purchased from Jackson Labs, and their littermate mice were used as wild-type controls for the experiment. All experiments were conducted from this colony, and no backcrosses to other strains were made. The breeding strategy used by Jackson Labs to maintain the IL-6 KO mouse strain was similar to that used by others (32). Animals were maintained on mouse chow and water ad libitum according to guidelines provided by the Animal Care and Use Committee, in accordance with accepted standards of humane animal care as outlined in The Endocrine Society’s Ethical Guidelines for Research. For the high-fat feeding experiment, 3-mo and 11-mo-old mice were randomly assigned to receive either mouse chow (6% fat; Harlan Teklad, Madison, WI, www.harlan.com) or a high-fat diet (59% fat; BioServ, Frenchtown, NJ, www.bio-serv.com). The precise composition of these diets can be found on the company websites. In brief, the low-fat diet contained 16% protein, 59% fat, and 0.1% fiber. The high-fat diet contained 20% protein, 6% fat, and 4% fiber, and the high-fat diet contained 16% protein, 59% fat, and 0.1% fiber.

Verification of IL-6−/− mice. Polymerase chain reaction was used to identify mice containing an insertion of the neo’ cassette in an exon of the IL-6 gene. Primers were designed to lie within exons 2 on either side of the neo’ cassette such that a 174-bp product was generated for wild-type mice and a 1314-bp product was generated for KO mice. The primer sequence for the forward primer was 5’-TTCCATCAGTTGCTCTTTG-3’, and the sequence for the reverse primer was 5’-TTCTCA-TTTCACGATTTCCAG-3’. The presence of the neo’ cassette was confirmed in IL-6−/− mice.

Measurement of serum IL-6 was used in combination with genotyping to distinguish IL-6−/− mice from IL-6+/+ mice. IL-6 was measured with a sensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) that has a sensitivity of 3.1 pg/ml. Mean (±SE) serum levels of IL-6 were 23.7 ± 7.6 pg/ml in IL-6+/+ mice and were undetectable in IL-6−/− mice. All samples were measured in duplicate in one assay. The blood levels of IL-6 confirmed the genotyping results and verified that the mice did not express IL-6.

Medium secretion. White adipose tissue (WAT) was collected from mice at the time of death, and 100 mg of WAT from each animal were incubated with 500 µl of DMEM containing 20 mM HEPES for 4 h. The samples were centrifuged at 1,500 g, and the medium was collected and frozen at −20°C for assay at a later date.

Table 1. Percent body fat in young (5-mo-old) and old (14-mo-old) mice as determined by DEXA and BMI

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>Diet</th>
<th>BMI, g/cm²</th>
<th>Percent Body Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Low fat</td>
<td>0.31±0.01</td>
<td>42.1±2.1</td>
</tr>
<tr>
<td>14</td>
<td>Low fat</td>
<td>NA</td>
<td>27.9±6.9</td>
</tr>
</tbody>
</table>

Data represent means ± SE. DEXA, dual-energy X-ray absorptiometry; BMI, body mass index; NA, not applicable. *Significance (P < 0.001) from the low-fat diet group with similar genotype.

Fig. 1. Effect of age and IL-6 deficiency on body weights of wild-type (IL-6+/+) and IL-6 knockout (IL-6−/−) mice at 3 and 8 mo of age. Bar graph shows the average weight in grams of male mice at both ages (n = 7 mice per group). A similar trend in body weight was seen for female mice at 9 and 11 mo of age (IL-6−/−: 27.6 ± 1.6 g; IL-6−/−: 24.4 ± 2.0 g). Values represent means ± SE.

Fig. 2. Effect of diet on body weight of IL-6−/− mice. IL-6−/− and IL-6+/+ mice were fed a Chow diet until 11 mo of age (week 0). At that time, mice were randomized to receive either the low-fat (LF) or high-fat (HF) diet (see METHODS). Body weights were recorded at 0, 4, 8, and 14 wk. Data are expressed as % baseline, and both male and female mice were included. Baseline is the mean body weight for each group at week 0 and is designated 100%. Body weights, which were similar among the groups at week 0, were 28.5 ± 2.7 g for IL-6+/+ mice and 27.9 ± 4.6 g for IL-6−/− mice. HF feeding significantly increased the body weights of mice (P < 0.001), and mean body weights of HF-fed IL-6−/− (+/+) mice were significantly greater than those of HF-fed IL-6−/− (−/−) mice (P < 0.001). Values represent means ± SE.
with substrate for 1 h at 37°C, liberated 3H-labeled free fatty acids (3H-FFA) were separated and quantitated by liquid scintillation. Adipose LPL activity was expressed as nanomoles of FFA released per milligram of protein per hour, and postheparin plasma (PHP) LPL activity was expressed as nanomoles of FFA released per milliliter per hour.

**Glucose and insulin tolerance tests.** Mice were fasted for 4 h before the glucose tolerance test (GTT). GTT and insulin tolerance tests (ITT) were performed ~1 wk apart. Animals were given 2 g of 50% d-glucose/kg body wt intraperitoneally for GTT and human regular insulin (0.75 U/kg; Eli Lilly, Indianapolis, IN) intraperitoneally for ITT, as described previously (1). Mice were not anesthetized during this procedure, and a 75-μl aliquot of blood was taken retro-orbitally from mice after they received an eye drop of proparacaine (Bausch and Lomb Pharmaceuticals, Tampa, FL) at 0, 15, 30, 60, and 120 min. Blood samples were assayed for glucose.

**Statistics.** Data were tested for normality and homogeneity of variance. Differences among treatment groups for GTT and ITT tests were determined using one-way analysis of variance, and comparisons were made using Tukey’s test. A two-tailed t-test was used to identify differences among groups for body weights and WAT weights, total LPL activity, and quantities of cytokines in the blood and secreted by adipose tissue. 

**RESULTS**

**Effects of genotype and diet on body weight and composition.** IL-6−/− and wild-type mice grew and developed normally, and no evidence of obesity was observed. Figure 1 shows body weight at 3 and 8 mo of age. IL-6−/− mice weighed 10% less than IL-6+/+ males at 3 mo of age (P = 0.002), and body weights of the two groups were similar at 8 mo (Fig. 1). To examine both weight and body composition, the body mass index (BMI) was calculated as weight (g)/length (cm)², as described previously (20), and percent body fat was assessed using dual-energy X-ray absorptiometry. As shown in Table 1, a high-fat diet resulted in a predictable increase in BMI and percent body fat; however, there were no differences between IL-6−/− and IL-6+/+ mice. Older mice (14 mo) had a higher body fat than the younger mice (5 mo), but there was no difference due to genotype. In a previous study, the obesity/diabetes phenotype of IL-6−/− mice was more pronounced with aging (32). To further characterize body weight with aging and diet in these mice, mice were fed a chow diet until 11 mo of age and were then randomized to either a low-fat or high-fat diet for 14 wk. Both male and female IL-6−/− and IL-6+/+ mice gained weight on the high-fat diet, but IL-6+/+ mice gained slightly less weight compared with IL-6+/+ mice (P < 0.001; Fig. 2).

**Effects of genotype and diet on carbohydrate and lipid metabolism.** IL-6−/− and IL-6+/+ mice had similar fasting glucose levels at 3 and 8 mo of age (Table 2). At 8 mo of age, after ad libidum consumption of normal chow (low-fat diet), carbohydrate metabolism was assessed with a GTT and ITT, as described in METHODS. When the IL-6−/− mice were compared with wild-type mice, peak glucose levels during a GTT at 8 mo of age were not significantly different, nor were nadir glucose levels during an ITT (Table 2). Hence, these studies provided no evidence for insulin resistance at this age. Additional studies were performed in older mice after high-fat feeding. In response to high-fat feeding, both IL-6−/− and IL-6+/+ mice demonstrated evidence of insulin resistance, with higher blood glucose values in response to a GTT, and elevated fasting serum insulin and a higher value for homeostasis model assessment of insulin resistance (HOMA-IR; Table 3). During the GTT, IL-6−/− mice fed a high fat diet had 1.6-fold higher glucose levels compared with IL-6+/+ mice (Table 3). Such an effect would imply that the IL-6−/− mice were more insulin resistant than the IL-6+/+ mice. However, these findings were not confirmed by the ITT. During the ITT, both genotypes of mice demonstrated less insulin-mediated glucose suppression in response to high-fat feeding (P < 0.001; Fig. 3), and overall glucose levels were twofold higher compared with low-fat-fed mice. However, there were no significant differences between the IL-6−/− and IL-6+/+ mice in the ITT. Therefore, there were no consistent changes in the IL-6−/− mice to suggest genotype-mediated insulin resistance in these mice.

**Effects of genotype and diet on LPL activity.** We measured total LPL activity in WAT, muscle, and postheparin plasma (PHP) of male and female mice and found that LPL activity was similar in IL-6−/− mice and IL-6+/+ mice (Table 4). This absence of effect of genotype was noted in both young (5 mo) and older (14 mo) mice. In addition, no effect of gender was observed. After young mice consumed a high-fat diet, there was an approximately twofold increase in PHP LPL activity. Although the increase in PHP activity was slightly greater in the IL-6+/+ mice, the difference between the IL-6+/+ and

### Table 2. Effects of age and genotype on blood glucose levels

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Fasting Glucose</th>
<th>Nadir Glucose During ITT</th>
<th>Peak Glucose During GTT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IL-6−/−</td>
<td>IL-6+/+</td>
<td>IL-6−/−</td>
</tr>
<tr>
<td>3</td>
<td>208.3±13.4</td>
<td>218.6±10.7</td>
<td>68±5.4</td>
</tr>
<tr>
<td>8</td>
<td>192.9±12.5</td>
<td>193.3±8.5</td>
<td>72.0±5.9</td>
</tr>
</tbody>
</table>

Data represent means ± SEM in mg/dl. ITT and GTT, insulin and glucose tolerance tests.

### Table 3. Effects of genotype and high-fat diet on fasting blood glucose and insulin levels in 14-mo-old mice

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Fasting Glucose, mg/dl</th>
<th>Peak Glucose During GTT, mg/dl</th>
<th>Fasting Serum Insulin, ng/ml</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low fat</td>
<td>High fat</td>
<td>Low fat</td>
<td>High fat</td>
<td>Low fat</td>
</tr>
<tr>
<td>IL-6−/−</td>
<td>195.0±11.7</td>
<td>213.0±20.6</td>
<td>611.7±51.7</td>
<td>678.3±20.9</td>
</tr>
<tr>
<td>IL-6+/+</td>
<td>209.7±8.4</td>
<td>168.7±25.3</td>
<td>471.7±40.4</td>
<td>1090±158.3</td>
</tr>
</tbody>
</table>

Data represent means ± SEM. HOMA-IR, homeostasis model assessment of insulin resistance. *P < 0.05, significant difference from low-fat-fed mice; †P < 0.05 from high-fat-fed IL-6−/− mice.
IL-6−/− mice was not statistically significant (Table 4). Northern blots were performed on adipose tissue, and no differences in mRNA levels were observed between IL-6−/− and IL-6−/+ mice (data not shown). We also examined the effects of diet and genotype on serum triglyceride levels. There were no significant differences in triglyceride levels between IL-6−/+ and IL-6−/− mice. In young mice, fasting triglyceride levels were 93 ± 18.9 and 78.6 ± 4.8 mg/dl, respectively, in IL-6−/+ and IL-6−/− mice (P = 0.006; Table 5). Secretion of adiponectin by adipose tissue was also higher in IL-6−/− mice, but only in the low-fat-fed group. As expected, serum leptin levels were markedly higher in high-fat-fed mice (P = 0.002), and there were no differences due to genotype (Table 5). A similar trend was observed for secretion of leptin by adipose tissue, which was markedly elevated in response to high-fat feeding and was not influenced by genotype (P < 0.001).

**DISCUSSION**

IL-6 is expressed by many tissues and has been extensively studied with regard to numerous physiological processes and disease states. IL-6 is expressed and secreted by adipose tissue and therefore may represent one of a number of obesity-related inflammatory cytokines that cause insulin resistance. In a number of human studies, there was a significant correlation between plasma IL-6 and insulin sensitivity. IL-6 was associated with insulin resistance in obese and lean humans (3, 16), and this relationship between plasma IL-6 and insulin sensitivity was independent of obesity. The injection of IL-6 into healthy human volunteers increased blood glucagon and increased fasting glucose (28). Finally, several studies in humans have suggested that common polymorphisms in the IL-6 gene, which may alter expression, result in altered insulin sensitivity (9, 18).

As with any knockout mouse, one would not necessarily expect a phenotype that mimics a human disease entity. In addition to the species difference, the IL-6−/− mouse lacked IL-6 during embryogenesis and development, and other systems likely substituted for the functions of this rather ubiquitous cytokine. Nonetheless, we hypothesized that the absence of IL-6 would result in a more insulin-sensitive animal. To test our hypothesis, we studied IL-6−/− mice and have summarized our findings on the growth and metabolic characteristics for IL-6−/− mice from these studies in Table 6. IL-6−/− mice had

---

**Table 5. Effects of genotype and high-fat diet in 14-mo-old mice on blood cytokines and their secretion by WAT**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Diet</th>
<th>Leptin, ng/ml</th>
<th>Adiponectin, μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Adipose</td>
<td>Serum</td>
</tr>
<tr>
<td>IL-6+/+</td>
<td>Low fat</td>
<td>12.3±2.6</td>
<td>9.0±1.7</td>
</tr>
<tr>
<td></td>
<td>High fat</td>
<td>52.6±6.2†</td>
<td>25.9±1.6†</td>
</tr>
<tr>
<td>IL-6−/−</td>
<td>Low fat</td>
<td>9.1±1.1</td>
<td>7.2±0.7</td>
</tr>
<tr>
<td></td>
<td>High fat</td>
<td>52.9±14.3†</td>
<td>17.3±3.6†</td>
</tr>
</tbody>
</table>

Data represent means ± SE. White adipose tissue (WAT, 100 mg) was incubated for 4 h in 500 μl of serum-free medium. Serum and medium leptin and adiponectin were measured as described in METHODS. †P < 0.05, significant difference from low-fat-fed mice; ‡P < 0.001 and *P = 0.012, significant difference from all other treatment group means.

---

**Table 6. Phenotype of IL-6−/− mice**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IL-6−/− vs. IL-6+/+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>Low-fat diet: less at 3 mo; High-fat diet: less weight gain</td>
</tr>
<tr>
<td>Body composition</td>
<td>No difference</td>
</tr>
<tr>
<td>LPL activity</td>
<td>No difference</td>
</tr>
<tr>
<td>Adipose TNF</td>
<td>No difference</td>
</tr>
<tr>
<td>Adipose leptin</td>
<td>No difference</td>
</tr>
<tr>
<td>Adipose adiponectin</td>
<td>High-fat diet: increased</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>No difference</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>GTT: elevated glucose, high-fat diet only; ITT: no difference</td>
</tr>
</tbody>
</table>
a slightly slower weight gain at 3 mo of age compared with normal mice, but there was no difference in body weight and composition thereafter, even when mice were fed a high-fat diet for 3 mo. In fact, it appeared that IL-6−/− mice were somewhat resistant to gaining weight on a high-fat diet, since they did not gain as much as did normal mice. There were no differences in any of the parameters associated with lipid metabolism and adipose tissue secretion in IL-6−/− mice except for an increase in adiponectin. Previous reports have shown that IL-6 inhibits the expression and activity of LPL (4, 11). Therefore, one would expect that, upon removal of endogenous IL-6, adipose tissue LPL activity would be increased. However, we observed no changes in LPL activity, suggesting that the IL-6 deficiency was compensated by other regulatory influences. In addition, we observed no consistent differences in carbohydrate metabolism. Although blood glucose was more elevated following the GTT in the IL-6−/− mice, this was observed only after high-fat feeding, and there were no differences in fasting glucose or insulin and no differences during the ITT. Thus there was no consistent evidence that the IL-6−/− mice were either more insulin sensitive or insulin resistant than the IL-6+/+ mice. It is possible that the IL-6−/− mice were defective in maximal insulin secretion, which may have resulted in the elevated glucose following the GTT.

Our data are in disagreement with a previous study (32), which showed that IL-6−/− mice developed maturity onset obesity and insulin resistance by 9 mo of age. In the study by Wallenius et al. (32), the IL-6−/− mice were generated by Kopf et al. (17) and appeared to be the same strain of mice used in our studies. A 50–60% increase in total body fat was noted, along with an impairment in glucose tolerance following a GTT (32). Also inconsistent with our data were the findings that their IL-6−/− mice had increased leptin levels and leptin insensitivity, and females had increased circulating triglycerides. In our studies, only after feeding on a high-fat diet did mice have decreased glucose tolerance and increased adipose secretion of leptin, and these effects were seen in both IL-6−/− and IL-6+/+ mice. Additional studies by the same group showed perturbations in metabolism that were only partly reversed with injections of IL-6, suggesting that another factor could also be responsible for this phenotype (31). Furthermore, they noted that daily injections of leptin, which decreased body weight and appetite in wild-type mice, had no effect on IL-6−/− mice.

The reason for the discrepancies between this and the aforementioned study is unclear. It is possible that there are subtle genetic differences introduced into the IL-6−/− line, and this could contribute to the differences between these studies. There are numerous examples where background strain has affected lipid and carbohydrate metabolism in mice. The Lep-ob and Lepr-db mutations both produce identical phenotypes on the same background strain and yet a pronounced tendency to diabetes on different backgrounds (5). Genetic background has a profound effect on many aspects of the A-ZIPF-1 lipoatrophic mouse phenotype, including opposite effects on muscle and liver insulin resistance and triglyceride clearance (6). It has also been shown that the specific strain on which the mutation is maintained determines the response of the endocrine pancreas to hyperglycemia and insulin resistance (5). For example, some strains, such as C57BL/6J and 129/J, have the ability to undergo compensatory hyperplasia of the pancreatic insulin-producing cells, with the resultant phenotype of near-euglycemia due to hyperinsulinemia (19). It is possible that β-cell hyperplasia and the resultant hyperinsulinemia are dependent on IL-6, since our IL-6−/− mice became hyperglycemic on a high-fat diet. As with this study, Wallenius et al. (32) studied IL-6−/− mice on a C57BL/6 background. Therefore, it is unclear why we obtained different results, unless there are subtle differences in strains related to either breeding strategy, or important differences in environment or diet.

Removal of endogenous IL-6 in mice did not influence adipose tissue secretion of TNF-α, adiponectin, or leptin. High-fat feeding resulted in an increase in adiponectin only in IL-6−/− mice and not in IL-6+/+ mice. Circulating levels of adiponectin are reduced in several mouse models of insulin resistance (26). Others found decreased levels of adiponectin in obese and diabetic subjects (13), and there is a strong positive association between plasma adiponectin and insulin sensitivity (15). These data suggest that the increase in adiponectin secretion in high-fat-fed IL-6−/− mice may be uniquely associated with the IL-6−/− genotype and perhaps is due to a regulatory interaction between IL-6 and adiponectin.

In summary, IL-6−/− mice did not manifest maturity onset obesity. Although several subtle phenotypes were observed, such as a higher glucose following a GTT in fat-fed mice, and some changes in adiponectin, these mice were generally characterized by a lack of overt diabetes and obesity compared with wild-type mice.

ACKNOWLEDGMENTS

We thank Dr. Charles O’Brien for providing the primer sequences for the PCR to genotype the IL-6−/− mice. We also thank Brian Wells, Dale Paulson, Ginger Brown, and Margaret McIntire for technical assistance.

GRANTS

This study was funded in part by a Career Development Award from the American Diabetes Association, Grant DK-39176 from the National Institute of Diabetes and Digestive and Kidney Diseases, and a Merit Review Grant from the Veterans Administration.

REFERENCES


