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

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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 between IL-6−/− and IL-6+/+ mice. 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 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 increases 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 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 (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.

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**METHODS**

**Animals.** IL-6<sup>−/−</sup> mice breeder pairs (C57BL/6J-Il6<sup>−/−</sup>(Kopf)) were purchased from Jackson Labs (Bar Harbor, ME), and a colony of IL-6<sup>−/−</sup> mice was established. This is the same strain of IL-6<sup>−/−</sup> mice reported previously (32). A breeder pair of normal C57BL/6J 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 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<sup>−/−</sup> mice.** Polymerase chain reaction was used to identify mice containing an insertion of the neo<sup>+</sup> cassette in exon 2 on either side of the IL-6 gene. Primers were designed to lie within exon 2 on either side of the neo<sup>+</sup> 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’-TTCATCCAGGTGCTCCTTGG-3’, and the sequence for the reverse primer was 5’-TTCTCA- TTTCACGATTCCAG-3’. The presence of the neo<sup>+</sup> cassette was confirmed in IL-6<sup>−/−</sup> mice.

Measurement of serum IL-6 was used in combination with genotyping results and verification of IL-6<sup>−/−</sup> 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO 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 ± 0.7 pg/ml in wild-type mice and a 1314-bp product was generated for KO mice.

**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 for 5 min, 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>21.2±2.1*</td>
</tr>
<tr>
<td></td>
<td>High fat</td>
<td>0.38±0.02</td>
<td>43.3±2.2*</td>
</tr>
<tr>
<td>14</td>
<td>Low fat</td>
<td>NA</td>
<td>29.2±7.2</td>
</tr>
<tr>
<td></td>
<td>High fat</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data represent means ± SE. DEXA, dual-energy X-ray absorptiometry; BMI, body mass index; NA, not applicable. *Significant difference (P < 0.001) from the low-fat diet group with similar genotype.
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%
α-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-orbital
ly 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 libitum 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 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></td>
<td>Low fat</td>
<td>High fat</td>
<td>Low fat</td>
<td>High 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>168.2±25.3</td>
<td>471.7±40.4</td>
<td>1090±158.3</td>
</tr>
</tbody>
</table>

Data represent means ± SE. 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 = not significant (NS)). In a similar fashion, there were no significant gender-related differences in triglyceride in older mice or in high-fat-fed mice.

Effects of genotype and diet on adipokines. Diet and genotype did not affect serum TNF-α levels or secretion of TNF-α by adipose tissue in any of the treatment groups (data not shown). In contrast, serum adiponectin levels were increased nearly twofold in high-fat-fed IL-6^{-/-} mice compared with other treatment groups (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).

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 groups mean.

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</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</td>
</tr>
</tbody>
</table>

Fig. 3. Effect of diet on insulin tolerance in IL-6^{-/-} mice. Blood glucose levels during an insulin tolerance test (ITT) in 14-mo-old male and female mice fed either an LF- or HF diet. Data are expressed as %control. Control is the mean glucose values for each treatment group at time 0 of the ITT and is designated 100%. Glucose levels, which were similar for each treatment group at time 0, were +/+LF: 194.1 ± 10.7 mg/dl; +/+HF: 217.4 ± 10 mg/dl; −/−LF: 181.7 ± 10.1 mg/dl; and −/−HF: 223 ± 13 mg/dl. *Significant difference from contemporary genotype-matched LF-fed mice. Values represent means ± SE.

Table 4. Effects of genotype and high-fat diet on total LPL activity and serum triglycerides in young and old mice

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Young Mice</th>
<th>Old Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adipose</td>
<td>Muscle</td>
</tr>
<tr>
<td>IL-6^{+/+}</td>
<td>Low fat</td>
<td>326±38</td>
</tr>
<tr>
<td></td>
<td>High fat</td>
<td>437±83</td>
</tr>
<tr>
<td>IL-6^{-/-}</td>
<td>Low fat</td>
<td>282±49</td>
</tr>
<tr>
<td></td>
<td>High fat</td>
<td>287±47</td>
</tr>
</tbody>
</table>

Data represent means ± SE. Tissue lipoprotein lipase (LPL) activity is expressed as nmol h^{-1} mg protein^{-1}. Postheparin plasma (PHP) LPL activity is expressed as nmol h^{-1} ml^{-1}. Old mice were 14 mo old and had been on a high-fat diet for 12 wk. Young mice were 5 mo old and had been fed a high-fat diet for 8 wk. †P < 0.05, significant difference from low-fat-fed IL-6^{+/+} mice.
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 difference 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.

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