Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice

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Bullen JW Jr, Bluher S, Kelesidis T, Mantzoros CS. Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice. Am J Physiol Endocrinol Metab 292: E1079–E1086, 2007. First published December 12, 2006; doi:10.1152/ajpendo.00245.2006.—Adiponectin and its receptors play an important role in energy homeostasis and insulin resistance, but their regulation remains to be fully elucidated. We hypothesized that high-fat diet would decrease adiponectin but increase adiponectin receptor (AdipoR1 and AdipoR2) expression in diet-induced obesity (DIO)-prone C57BL/6J and DIO-resistant A/J mice. We found that circulating adiponectin and adiponectin expression in white adipose tissue are higher at baseline in C57BL/6J mice compared with A/J mice. Circulating adiponectin increases at 10 wk but decreases at 18 wk in response to advancing age and high-fat feeding. However, adiponectin levels corrected for visceral fat mass and adiponectin mRNA expression in WAT are affected by high-fat feeding only, with both being decreased after 10 wk in C57BL/6J mice. Muscle AdipoR1 expression in both C57BL/6J and A/J mice and liver adiponectin expression in C57BL/6J mice increase at 18 wk of age. High-fat feeding increases both AdipoR1 and AdipoR2 expression in liver in both strains of mice and increases muscle AdipoR1 expression in C57BL/6J mice after 18 wk. Thus advanced age and high-fat feeding, both of which are factors that predispose humans to obesity and insulin resistance, are associated with decreasing adiponectin and increasing AdipoR1 and/or AdipoR2 levels.

In vivo experiments

We performed in vivo experiments in DIO-prone and DIO-resistant mice (experiments 1 and 2).

In Vivo Experiments

Animals. Three- to five-week-old C57BL/6J and A/J mice were obtained from Jackson Laboratories (Bar Harbor, ME). All mice were given a 7-day acclimation period with access to normal chow (Purina Rodent Chow no. 5008) and water ad libitum. Mice were maintained at 25°C with a 12:12-h light-dark cycle for the duration of the study (8, 31). After acclimation, DIO was achieved by putting C57BL/6J mice on a high-fat diet, as described below (Harlan-Teklad no. TD88137) (8, 31). All animals were handled, and the protocol was approved by the BIDMC Committee, in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, as previously described (7).

Experimental procedures. Animals were divided into two cohorts. The first cohort was used to explore, over a 10-wk period, longitudinal changes in circulating hormone levels (insulin, leptin, and adiponectin) in DIO-prone C57BL/6J and DIO-resistant A/J mice fed a high-fat diet. These mice were also used to assess baseline and 10-wk mRNA expression levels of adiponectin in white adipose tissue (WAT) and AdipoR1/R2 in muscle and/or liver (experiment 1). The second cohort was used to study, over an 18-wk period, baseline and 18-wk mRNA expression levels of adiponectin in WAT and AdipoR1/R2 in muscle and/or liver in DIO-prone C57BL/6J mice fed a high-fat diet and to compare these with levels in C57BL/6J mice fed a Chow diet for the same time period (experiment 2).

Experiment 1: effect of high-fat feeding for 10 wk on circulating adiponectin levels and mRNA expression of adiponectin and AdipoR1/R2 in C57BL/6J and A/J mice. Mice were either placed on a high-fat diet or maintained on a normal chow diet for 0, 4, 6, 8, or 10 wk for each respective strain (n = 5/mouse strain/time point, as outlined in Table 1). Body weights and food intake were measured weekly between 2:30 and 4:30 PM, and in vivo body composition was measured by dual-energy X-ray absorptiometry on anesthetized mice (7, 26). Each group of mice was killed between 8:30 and 11:30 AM.

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and sera, WAT (perigonadal), liver, and muscle were collected and stored at −80°C (7, 24, 31).

Experiment 2: effect of high-fat feeding for 18 wk on mRNA expression of adiponectin and AdipoR1/R2 in C57BL/6J mice. In this cohort, C57BL/6J mice were divided into two groups (n = 8/group). One group was fed a normal chow diet for 18 wk, and the other group was fed a high-fat diet for 18 wk, as outlined in Table 1. Body weights, food intake, and in vivo body composition were measured, mice were killed, and tissues were collected as mentioned above.

Quantitative PCR Analysis of Adiponectin and AdipoR1/R2 mRNA Expression

Total RNA isolation and cDNA synthesis from muscle, liver, and WAT was performed as previously described (24). Adiponectin mRNA expression in WAT, as well as AdipoR1/R2 mRNA expression in muscle and/or liver, was assayed and quantified using real-time quantitative PCR (qPCR) with mouse-specific “gene expression assays” (Applied Biosystems, La Jolla, CA) (47). qPCR reactions were performed in triplicate, in an automated Stratagene Mx3000 PCR System (Stratagene, La Jolla, CA) using Taqman Universal PCR Master Mix (Applied Biosystems). The reaction conditions for all templates were 10 min at 95°C, followed by 40 cycles at 95°C for 15 s and 60°C for 1 min. Amplification was performed using a FAM/TAMRA-labeled gene-specific probe in a 20-μl reaction mixture. Relative quantities of adiponectin and AdipoR1/R2 mRNA were normalized to respective mouse cyclophilin levels.

Serum Hormone and Statistical Analyses

Sera were collected and assayed in duplicate for adiponectin, insulin, and leptin by RIA (Linco Research Institute, St. Louis, MO) (47). Blood glucose was determined using a commercially available glucometer (Yellow Springs Instruments). Descriptive characteristics are expressed as means ± SE. Data for mRNA expression are presented as percent change from respective control groups. Statistical analysis was performed using Statview (Abacus Concepts, Berkeley, CA). Statistical significance was assessed by standard Student t-tests or paired two-tailed t-test and ANOVA with post hoc tests (least significant difference) as appropriate. Values were considered to be significant at the two-tailed P ≤ 0.012 value due to internal comparisons (Bonferroni correction) of four groups of mice (2 different genetic backgrounds × 2 different diets) over time.

RESULTS

Experiments 1 and 2

Effect of high-fat feeding on body weight and body composition in DIO-prone C57BL/6J mice over a 10- and 18-wk period and in DIO-resistant A/J mice over a 10-wk period.

BODY WEIGHT: High-fat-fed C57BL/6J mice exhibited a significant and progressive increase in body weight (94.9% after 10 wk and 110.66% after 18 wk, P < 0.0001) compared with an increase of 42.2% after 10 wk and of 46.1% after 18 wk in chow-fed mice (P < 0.0001; Table 1 and Fig. 1A). A/J mice fed either normal chow or high-fat diet exhibited increases of 29.0 and 39.6%, respectively (Table 1 and Fig. 1A).

BODY FAT COMPOSITION: High-fat-fed C57BL/6J mice exhibited a significant and progressive increase in percent body fat (145.1% from baseline after 8 wk, P < 0.0001) compared with an increase of only 3.9% in mice fed a normal chow diet for 8 wk (P < 0.0001; Fig. 1B). There was an even more pronounced progressive increase in total fat mass (g) in high-fat-fed C57BL/6J mice (467.8% from baseline after 8 wk, P < 0.0001) compared with an increase of only 34.6% in mice fed a normal chow diet for 8 wk (P < 0.0001; Fig. 1C). Visceral fat mass (g) was also significantly and progressively increased in C57BL/6J mice compared with both baseline levels (665.1% after 8 wk, P < 0.0001) and levels of respective chow-fed controls at the same time point (P < 0.0001; Fig. 1D).
Although A/J mice exhibited an increase in percent body fat after 8 wk of high-fat feeding (29.1% from baseline, $P < 0.05$; Fig. 1B), this increase was far less substantial than that observed in high-fat-fed C57BL/6J mice. Similarly, although total body fat mass (g) was significantly increased in A/J mice fed a high-fat diet for 8 wk ($P < 0.05$; Fig. 1C), this increase was far less substantial than that observed in C57BL/6J mice fed a high-fat diet for 8 wk. Chow-fed C57BL/6J mice exhibited minimal increases in total and visceral fat mass after 8 wk compared with baseline values ($P < 0.05$ for both). As expected, A/J mice did not exhibit any significant increases in percent body fat, total fat mass, or visceral fat mass after 8 wk of chow feeding (Fig. 1).

**Effect of high-fat feeding on blood glucose and serum insulin and leptin levels in DIO-prone C57BL/6J mice over the course of 18 wk and in DIO-resistant A/J mice over the course of 10 wk.**

**GLUCOSE.** Baseline blood glucose levels were significantly higher in C57BL/6J mice compared with A/J mice (15.74 ± 0.69 vs. 11.84 ± 0.88 mmol/l, respectively, $P = 0.0028$). There was no consistent and statistically significant effect of aging, high-fat feeding, or strain on glucose levels in C57BL/6J and A/J mice at later time points studied herein (Table 1).

**INSULIN.** There were no significant differences in baseline serum insulin levels between A/J and C57BL/6J mice. A/J mice fed either normal chow or high-fat diet had lower circulating insulin levels over the course of 10 wk ($P < 0.05$ for both diets; Fig. 2A). Serum insulin levels progressively increased to approximately twofold and threefold in C57BL/6J mice fed a high-fat diet for 10 wk ($P < 0.0001$) and were significantly higher than chow-fed C57BL/6J mice at the same time point ($P < 0.0001$; Fig. 2B). Although A/J mice exhibited significantly elevated insulin levels after 10 wk of high-fat feeding compared with chow-fed A/J mice ($P < 0.001$; Fig. 2B), this increase was not statistically significant compared with respective baseline levels at the 0-wk time point.

**LEPTIN.** There were no significant differences in baseline leptin levels between A/J and C57BL/6J mice. In addition, neither C57BL/6J nor A/J mice exhibited significant differences in circulating leptin levels after 10 wk of normal chow feeding (Fig. 2B). Serum leptin levels progressively increased to approximately twofold in C57BL/6J mice fed a high-fat diet for 10 wk ($P < 0.0001$) and were significantly higher than chow-fed C57BL/6J mice at the same time point ($P < 0.0001$; Fig. 2B). Although A/J mice exhibited significantly elevated leptin levels after 10 wk of high-fat feeding compared with chow-fed A/J mice ($P < 0.001$; Fig. 2B), this increase was not statistically significant compared with respective baseline levels at the 0-wk time point.

**Effect of high-fat feeding on serum adiponectin levels in DIO-prone C57BL/6J mice over the course of 10 and 18 wk and in DIO-resistant A/J mice over the course of 10 wk.**

**ADIPONECTIN.** Baseline adiponectin levels in A/J mice were significantly lower than those observed in C57BL/6J mice (6.2 ± 0.9 vs. 11.5 ± 1.1 µg/ml, respectively, $P = 0.0016$). Serum adiponectin levels in C57BL/6J mice fed either normal chow or high-fat diet for 10 wk progressively increased to approximately two- and threefold, respectively ($P < 0.0001$; Fig. 2C). There was a greater increase in serum adiponectin levels in high-fat-fed C57BL/6J mice compared with chow-fed mice after 10 wk ($P < 0.01$; Fig. 2C). As expected, there was a decrease back toward baseline serum adiponectin levels in both high-fat-fed and chow-fed C57BL/6J mice after 18 wk (Table 2). Serum adiponectin levels in A/J mice fed a normal chow diet essentially remained at baseline for the entire study (Fig. 2C). There was an approximate twofold increase...
in serum adiponectin levels in A/J mice fed a high-fat diet for 10 wk (P < 0.01), but this remained relatively similar to levels observed in chow-fed A/J mice at the same time points (Fig. 2C).

**SERUM ADIPONECTIN IN RELATION TO VISCERAL FAT MASS, PERCENT BODY FAT MASS, AND SERUM INSULIN AND LEPTIN LEVELS.** Similar to serum adiponectin levels, baseline adiponectin per gram visceral fat levels in A/J mice were significantly lower than those observed in C57BL/6J mice (7.3 ± 1.1 vs. 14.4 ± 1.1 μg·ml⁻¹·g visceral fat⁻¹, P = 0.0002). In addition, adiponectin per gram visceral fat levels in A/J mice on both feeding regimens were significantly lower than levels in chow-fed C57BL/6J mice over the course of 10 wk (P < 0.01 for all groups). When adiponectin levels were normalized to both total and visceral fat, we noticed that both baseline adiponectin per gram total fat and baseline adiponectin per gram visceral fat levels were significantly higher in C57BL/6J mice compared with A/J mice (P < 0.01; data not shown). Both adiponectin per gram total fat and adiponectin levels per gram visceral fat in A/J mice on both feeding regimens were significantly lower than levels in chow-fed C57BL/6J mice over the course of 10 wk (P < 0.01 for all groups; data not shown). Although high-fat-fed C57BL/6J mice exhibited a progressive threefold decrease in serum adiponectin levels per gram visceral fat over the course of 10 wk (P < 0.0001) and there were no changes in adiponectin per gram visceral fat levels in chow-fed C57BL/6J mice or chow- or high-fat-fed A/J mice (Fig. 2D), no statistically significant pattern existed for adiponectin levels per gram total fat. Moreover, adiponectin levels per gram visceral fat were also significantly and negatively correlated with percent body fat mass (P < 0.0001), as well as with circulating insulin (P < 0.05) and leptin (P < 0.01) levels, but no statistically significant pattern existed for adiponectin levels per gram total fat, although circulating adiponectin were significantly and positively correlated with percent body fat mass in all mice (P < 0.0001; Fig. 3). Therefore, although there was a strong positive association between adiposity and circulating adiponectin levels during the first 10 wk in all mice, there was only a progressive relative deficiency in adiponectin secretion per gram of visceral adipose tissue in high-fat-fed C57BL/6J mice, suggesting that there is minimal, if any, effect of aging on adiponectin secretion from visceral fat during the first 10 wk. These results, in part, may explain the observed decrease in adiponectin levels back to baseline in C57BL/6J mice fed a high-fat diet for 18 wk.

**Effect of high-fat feeding on adiponectin, AdipoR1, and AdipoR2 mRNA expression in DIO-prone C57BL/6J and DIO-resistant A/J mice.** **ADIPONECTIN EXPRESSION IN WAT.** Baseline adiponectin mRNA expression in A/J mice was ~38% lower in C57BL/6J mice (P < 0.0001; Table 2). In addition, there was a significant decrease in adiponectin mRNA expression in WAT of C57BL/6J mice fed a high-fat diet for 10 wk (P < 0.0001; Table 2), but there were no significant differences in C57BL/6J mice on chow diet or A/J mice on both diets for 10 wk (Table 2). Of note, there were no significant differences in adiponectin mRNA expression in WAT of C57BL/6J mice fed a high-fat or chow diet for 18 wk (Table 2).

**ADIPOR1 EXPRESSION IN MUSCLE.** After 10 wk, there was a significant increase in muscle AdipoR1 expression in chow-fed C57BL/6J mice (P < 0.01), as well as in chow- and high-fat-fed A/J mice (P < 0.01 and P < 0.05, respectively; Table 2), but there was no significant increase in muscle AdipoR1 expression in high-fat-fed C57BL/6J mice (Table 2). After 18 wk, however, there was a significant increase in muscle AdipoR1 expression in both chow- and high-fat-fed C57BL/6J mice (P < 0.01 and P < 0.001, respectively; Table 2), with a more significant increase observed in the high-fat-fed
mice (P < 0.01 vs. chow-fed C57BL/6J mice at the same time point; Table 2).

**DISCUSSION**

Adiponectin has been shown to have insulin-sensitizing effects that are mediated through at least two receptors, AdipoR1 and AdipoR2 (17, 22, 44, 46). We present herein the first studies investigating longitudinal in vivo regulation of adiponectin and its receptors in response to advancing age and high-fat feeding in mice. Similar to most previous studies (6, 10–12, 15, 21, 35, 41), we measured circulating protein levels and assessed expression of adiponectin receptors by measurement of mRNA expression levels. Inukai et al. (20) have recently shown that physiological variations in adiponectin receptor mRNA and protein levels are directly related.

Our study confirms that A/J mice effectively resist DIO and insulin resistance in response to prolonged high-fat feeding (37) and reports that baseline adiponectin levels are significantly lower in A/J mice compared with C57BL/6J mice at baseline, remaining lower for the duration of the 10-wk study, irrespective of diet. Because adiponectin increases energy expenditure and fatty acid oxidation in liver and skeletal muscle (30, 43, 45), one could postulate either that adiponectin levels are elevated in A/J mice, conferring resistance to development of DIO-induced insulin resistance, or that adiponectin levels are decreased in C57Bl6J mice, contributing to their prone-ness to DIO-induced insulin resistance. Our data exclude both of these possibilities, however, raising the hypothesis that another molecule downstream of adiponectin may be responsible for proneness and resistance of DIO and A/J mice, respectively, to develop obesity-induced insulin resistance. In this regard, the changes in adiponectin observed herein could be part of a compensatory mechanism. Future studies aimed at further elucidation of the mechanisms underlying these results could provide valuable insights into the regulation of adiponectin in a hypercaloric metabolic environment.

We also report that circulating adiponectin levels initially increase before eventually decreasing in high-fat-fed DIO-prone C57BL/6J mice. We observed a similar, but smaller in magnitude, increase in chow-fed C57BL/6J and high-fat-fed A/J mice over the same initial study period. Plasma levels of adiponectin have been reported to be significantly reduced in mice and humans with established obesity/diabetes (2, 19, 46).

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**Table 2. Effect of 10 and 18 wk of high-fat feeding on serum adiponectin and adiponectin mRNA expression levels in WAT, AdipoR1 mRNA expression in muscle and liver, and AdipoR2 mRNA expression in liver in male C57BL/6J and A/J mice**

<table>
<thead>
<tr>
<th>Time, wk</th>
<th>C57BL/6J (Chow)</th>
<th>C57BL/6J-DIO (high fat)</th>
<th>A/J (Chow)</th>
<th>A/J (High fat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum adiponectin, µg/ml</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>9.11 ± 0.91</td>
<td>13.80 ± 1.41</td>
<td>5.83 ± 1.30</td>
<td>6.47 ± 1.39</td>
</tr>
<tr>
<td>10</td>
<td>23.32 ± 1.04</td>
<td>29.44 ± 1.90</td>
<td>7.32 ± 0.96</td>
<td>11.87 ± 1.02</td>
</tr>
<tr>
<td>18</td>
<td>8.81 ± 0.59</td>
<td>9.73 ± 1.06</td>
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<td>ND</td>
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<tr>
<td>Adiponectin mRNA expression in WAT</td>
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<tr>
<td>0</td>
<td>100.0 ± 3.4</td>
<td>85.2 ± 6.7</td>
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<td>10</td>
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<td>0</td>
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<td>144.2 ± 13.2</td>
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<td>AdipoR1 mRNA expression in liver</td>
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Data are expressed as means ± SE by ANOVA with post hoc tests. WAT, white adipose tissue; AdipoR1, adiponectin receptor 1; AdipoR2, adiponectin receptor 2. *P < 0.05; †P < 0.01; ‡P < 0.001 vs. the “0-wk” time point for each group; ‡P < 0.005; †P < 0.01; ‡P < 0.001 vs. the chow-fed group at each time point of the respective mouse strain; †P < 0.05; ‡P < 0.01; †P < 0.001 vs. chow-fed C57BL/6J mice at each time point.
We found that, although serum adiponectin levels were elevated during the first 10 wk of high-fat diet, once adiponectin levels were corrected for visceral fat mass, a clear progressive decrease of adiponectin expression and production per gram of adipose tissue was observed in high-fat-fed C57BL/6J mice only; the final adiponectin/visceral fat mass ratio was threefold lower at 10 wk than that at baseline. Additionally, although adiponectin at 10 wk was positively correlated with percent body fat, adiponectin levels corrected for visceral fat mass were negatively correlated with percent body fat. From the above observations, it is evident that a decrease in adiponectin derived from visceral fat is the main reason for reduced adiponectin levels in response to high-fat feeding and the development of the metabolic syndrome, including increasing leptin and insulin levels. When adiponectin levels were normalized to total fat, no significant differences were noticed in the parameters cited above, raising the question of whether increasing adiponectin levels, paralleling progressively increasing adiposity, may be a compensatory mechanism by which C57BL/6J mice attempt to prevent the “development” of insulin resistance in early stages of exposure to high-fat diet. This remains to be conclusively studied in future interventional studies. Whether differences in circulating levels of adiponectin during different time periods also reflect differences in the different forms (high molecular weight or low molecular weight) of circulating adiponectin also remains to be studied in the future.

Interestingly, our studies demonstrate a reciprocal relationship between the regulation of circulating adiponectin and expression of AdipoR1 in muscle in response to high-fat feeding in DIO-prone mice. In contrast to adiponectin secretion per gram of visceral fat, we found that muscle AdipoR1 expression is increased after 10 wk in chow-fed C57BL/6J mice, as well as in chow- and high-fat-fed A/J mice, but relatively decreased after 10 wk of high-fat feeding in C57BL/6J mice. Consistent with these data, AdipoR1 levels are increased in muscle after 18 wk of high-fat feeding in C57BL/6J mice, when serum adiponectin levels are low. Finally, we report that AdipoR1 and AdipoR2 expression is...
increased in liver after 10 wk of high-fat feeding in both C57BL/6J and A/J mice and after 18 wk of high-fat feeding in C57BL/6J mice. The specific mechanisms mediating the effects of aging and/or high-fat feeding as well as whether changes in muscle AdipoR1 expression are directly and specifically due to alterations in circulating adiponectin levels and/or hyperinsulinemia or other metabolic factors remains to be fully elucidated. Moreover, aging did not alter levels of AdipoR2 in liver significantly, whereas levels of AdipoR1 were regulated in the same way in liver (13, 29) and in other tissues (10, 32, 39).

Our observational findings in mice are in accordance with a recent study in humans (35) demonstrating a strong correlation between AdipoR1 expression in muscle and first-phase insulin secretion. We (5) have also recently demonstrated an association of both AdipoR1 and AdipoR2 with insulin resistance in humans, although only the association with AdipoR1 remained significant after multivariate adjustment. Discordant results regarding expression of adiponectin receptors in liver have been reported in 15-wk-old high-fat-fed leptin deficient ob/ob mice and 18-wk-old obese (fa/fa) Zucker rats despite higher plasma adiponectin in obese (fa/fa) Zucker rats (decreased AdipoR1 and AdipoR2 mRNA concentrations in liver) (28, 41) vs. in 13-wk-old leptin resistant db/db or insulin-deficient streptozotocin mice (unchanged expression of AdipoR2 in liver) (20). Both AdipoR1 and AdipoR2 expression were increased in the liver of 16-wk-old Zucker rats (4) placed on high-fat or high-cholesterol diet for 6 wk. The above suggests that, in addition to advancing age or high-fat diet, other factors, including leptin or leptin resistance, may play a role in regulation of adiponectin receptors in liver, but this remains to be studied in the future.

Differences between species and/or differences in the timing of tissue sampling (20, 41) may introduce bias in the assessment of adiponectin and/or adiponectin receptor levels. The regulation of adiponectin receptor expression may differ depending on the site and/or oxidative status of the muscle tissue being sampled (3, 14). There are sex differences in plasma levels of adiponectin in rodents and in humans, with higher values in females than in males (9, 18, 27). Since both AdipoR1 and AdipoR2 may follow a parallel circadian gene expression pattern with decreased synthesis during the night in tissues such as white and brown adipose tissue (6), precise timing of sampling is important, as previously suggested (4). Although relevant data are not provided in all previous studies (20, 41), we have carefully controlled for this potential confounding factor in our studies. To standardize for the site of muscle tissue, we sampled only quadriceps muscle in all experiments. In addition, we and others (6, 20, 41), have studied only male rodents. Whether there are also differences in the regulation of the expression of adiponectin receptors between males and females remains to be determined, but Debard et al. (12) and Civitarese et al. (11) have reported no difference in the expression level of adiponectin receptors between men and women. Finally, although C57BL/6J mice can live as long as 2 yr, the age of mice (5–6 mo) used in this study is an acceptable time period to study early metabolic changes and regulation of adiponectin and its receptors in terms of development of DIO and insulin resistance, which start occurring at 4–5 and 14–15 wk of age, respectively.

In conclusion, these studies demonstrate that 1) DIO-prone C57BL/6J mice have higher baseline adiponectin levels than DIO-resistant A/J mice, 2) circulating adiponectin increases at 10 wk in response to advancing age and high-fat feeding but decreases at 18 wk in response to aging and high-fat feeding, 3) advancing age increases AdipoR1 expression in muscle in both DIO-prone C57BL/6J and DIO-resistant A/J mice and AdipoR1 expression in liver in DIO-prone C57BL/6J mice after 18 wk, and 4) high-fat feeding increases both AdipoR1 and AdipoR2 expression in liver in both strains of mice and increases AdipoR1 in muscle in DIO-prone C57BL/6J after 18 wk. Although observational studies cannot prove causality, the studies presented herein are the first longitudinal studies in this field and suggest that not only strain differences but advancing age and high-fat feeding also significantly regulate adiponectin and its receptors and thus may be of importance in the pathophysiology of DIO and insulin resistance.

GRANTS

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