Transgenic Restoration of Long-Chain n-3 Fatty Acids in Insulin Target Tissues Improves Resolution Capacity and Alleviates Obesity-Linked Inflammation and Insulin Resistance in High-Fat-Fed Mice

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OBJECTIVE—The catabasis of inflammation is an active process directed by n-3 derived pro-resolving lipid mediators. We aimed to determine whether high-fat (HF) diet-induced n-3 deficiency compromises the resolution capacity of obese mice and thereby contributes to obesity-linked inflammation and insulin resistance.

RESEARCH DESIGN AND METHODS—We used transgenic expression of the fat-1 n-3 fatty acid desaturase from C. elegans to endogenously restore n-3 fatty acids in HF-fed mice. After 8 weeks on HF or chow diets, wild-type and fat-1 transgenic mice were subjected to insulin and glucose tolerance tests and a resolution assay was performed. Metabolic tissues were then harvested for biochemical analyses.

RESULTS—We report that the n-3 docosanoid resolution mediator protectin D1 is lacking in muscle and adipose tissue of HF-fed wild-type mice. Accordingly, HF-fed wild-type mice have an impaired capacity to resolve an acute inflammatory response and display elevated adipose macrophage accrual and chemokine/cytokine expression. This is associated with insulin resistance and higher activation of iNOS and JNK in muscle and liver. These defects are reversed in HF-fed fat-1 mice, in which the biosynthesis of this important n-3 docosanoid resolution mediator is improved. Importantly, transgenic restoration of n-3 fatty acids prevented obesity-linked inflammation and insulin resistance in HF-fed mice without altering food intake, weight gain, or adiposity.

CONCLUSIONS—We conclude that inefficient biosynthesis of n-3 resolution mediators in muscle and adipose tissue contributes to the maintenance of chronic inflammation in obesity and that these novel lipids offer exciting potential for the treatment of insulin resistance and diabetes. Diabetes 59:3066–3073, 2010

Obesity is linked to chronic inflammation that plays a key role in the pathogenesis of insulin resistance, leading the way to type 2 diabetes and cardiovascular disease (1,2). Efforts to understand this process have focused on identifying the many factors that may initiate and promote inflammation. We took an alternate approach with the view that pathological inflammation in obesity likely represents an impaired endogenous capacity to “switch off” or more precisely counterregulate the natural immune response to adipose tissue expansion and lipid excess.

The newly identified genus of n-3 derived lipid mediators termed resolvins and protectins have been shown to play an important role in the endogenous regulation of inflammation (3,4). Interestingly, dietary long-chain n-3 polyunsaturated fatty acid (PUFA) insufficiency has been linked to the incidence of chronic metabolic disorders, including type 2 diabetes and cardiovascular disease (5–7). It is thus conceivable that inefficient biosynthesis of n-3 resolution mediators due to low substrate availability might inherently contribute to the development of obesity-linked inflammation.

González-Pérez et al. recently showed that acute administration of n-3 derived Resolvin E1 (RvE1) prevents hepatic steatosis in genetically obese mice (8). However, the other main resolution mediator Protectin D1 (PD1) remains to be investigated, and it is unknown whether high-fat (HF) feeding per se actually restricts resolution mediator biosynthesis and whether this might alter the endogenous resolution capacity of obese mice. Furthermore, it is critical to determine whether n-3 lipid mediators regulate key obesity-related inflammatory reactions such as macrophage accrual in adipose tissue or activation of inflammatory signaling molecules such as JNK and iNOS that play a role in the etiology of insulin resistance (1,2).

Unfortunately, studying the effects of dietary n-3 content in the context of HF feeding has proven to be rather complicated because incorporation of n-3 fatty acids in rodent diets often prevents weight gain (9). As a result, it is not clear whether it is the lack of weight gain or the n-3 fatty acids themselves that offer the protection from obesity-related inflammation and type 2 diabetes and what mechanism underlies this protection. Therefore, innovative models that overcome the requirement for dietary manipulation are needed to help clarify whether or not n-3 fatty acids act directly to prevent obesity-linked insulin resistance and which mechanisms are involved.

The fat-1 transgenic mouse has been genetically engi-
neered to ubiquitously express the fat-1 n-3 fatty acid desaturase from C. elegans (10). This enzyme, not found in mammals, efficiently converts endogenous n-6 to n-3 fatty acids such that, in fat-1 mice fed a diet extremely rich in n-6 and deficient in n-3, the tissue n-6:n-3 ratio is ~1:1 compared with ~50:1 in wild-type animals. The fat-1 transgenic mouse therefore represents the ideal model to study the effects of n-3 fatty acids in an environment that is not confronted by dietary issues.

Herein we show that HF feeding wild-type mice results in diminished n-3 docosanoid resolution mediator synthesis in muscle and adipose tissue and impaired resolution. Transgenic restoration of n-3 fatty acids in HF-fed fat-1 mice improved resolution capacity and prevented the development of obesity-linked inflammation and insulin resistance. These data uncover a new role for pro-resolving lipid mediators in the counter-regulation of obesity-linked inflammation and its associated metabolic complications.

**RESULTS**

**HF feeding reduces n-3 availability for resolution mediator synthesis.** We first examined the effect of HF feeding on n-3 bioavailability in metabolic tissues. The HF diet mimicked Western diets in terms of n-3 content with an n-6:n-3 ratio of ~18–1. After 8 weeks, HF-fed wild-type mice displayed an elevated long-chain n-6:n-3 ratio in skeletal muscle, liver, and adipose tissue membranes compared with their chow-fed counterparts (Fig. 1A). Importantly, transgenic expression of the fat-1 n-3 fatty acid desaturase that converts endogenous n-6 to n-3 fatty acids restored the membrane long-chain n-6:n-3 ratio of HF-fed fat-1 mice to levels comparable to chow-fed mice (Fig. 1A).

Using LC-MS/MS to detect n-3 lipid oxygenation products, we found evidence of both docosanoid and eicosanoid biosynthetic activity in metabolic tissues of HF-fed mice. 17-HDoHE and 18-HEPE, hydroxy-metabolites of docosahexaenoic and eicosapentaenoic acids and biosynthetic markers of PD1 and RV-E1, respectively, were readily detected in muscle, liver, and adipose tissue (Fig. 1B and C). Interestingly, the docosanoid biosynthetic route appeared to have greater flux in these tissues, because 17-HDoHE was present in significantly higher concentrations than 18-HEPE and PD1 was readily detected in all tissues whereas RV-E1 was under the detection limit. Compared with HF-fed wild-type mice, HF-fed fat-1 mice displayed increased flux through the docosanoid biosynthetic route in muscle and adipose tissues but not in liver (Fig. 1D). Indeed, 17-HDoHE was increased by ~215% in muscle and 138% in adipose tissue whereas PD1 was increased by ~170% in muscle and 201% in adipose tissue of fat-1 mice compared with wild-type mice (P < 0.05). These data suggest that fat-1 mice display increased n-3 bioavailability for pro-resolution mediator synthesis in these two key metabolic tissues.

**HF feeding impairs resolution.** We hypothesized that the HF diet-induced deficit in n-3 resolution mediator synthesis would impact endogenous counterregulation of inflammation in wild-type mice. To test this, we subjected mice to a dorsal air-pouch TNFα challenge, an established model of self-resolving inflammation (13). The injection of 10 ng of TNFα into the air pouch stimulated an influx of PMNs that peaked at 4 h and resolved completely 6.5 h postchallenge. In contrast to their chow-fed counterparts,
HF-fed wild-type mice only resolved ~65% of infiltrating PMN by this time (Fig. 2A and B). Restoration of n-3 in HF-fed fat-1 mice was sufficient to completely recover the deficit in resolution capacity (P < 0.001). This is the first evidence that HF-diet-induced n-3 deficiency can impede the normal resolution of inflammation.
Transgenic restoration of n-3 prevents adipose inflammation.

To determine what role the HF diet-induced deficit in n-3 docosanoid mediators plays in obesity-linked inflammation, we examined macrophage accrual in adipose tissue. Because PD1 directs tissue phagocyte flux in inflammatory exudates (16), we hypothesized that transgene restoration of n-3 prevents adipose inflammation in HF-fed mice. A: Clearance of inflammatory PMN infiltrates in dorsal air pouches of HF-fed mice is impaired during the resolution phase of the in vivo resolution assay (n = 5–6). B: Percent infiltrate clearance 6.5 h after TNFα injection was reduced by ~35% in obese HF-fed wild-type mice; HF-fed F1 transgenic mice displayed normal infiltrate clearance (n = 5–6). C: Representative image of F4/80 immunohistochemistry in epididymal adipose tissue shows mass accumulation of macrophage in HF-fed wild-type mice that is prevented in HF-fed transgenic mice. MØ, macrophage. D: Percent F4/80+ cells in epididymal adipose tissue (n = 4–6). E: Macrophages present in adipose HF-fed wild-type mice formed multiple CLS; the formation of these inflammatory macrophage aggregates was greatly reduced in HF-fed F1 mice (number of CLS per 100 adipocytes). F–J: Chemokine and cytokine expression in epididymal adipose tissue was elevated by HF compared with chow feeding in wild-type mice, but these factors were not significantly raised by HF feeding in F1 mice (n = 5–10). All data are mean ± SEM, *P < 0.05, **P < 0.01, ***P < 0.001 versus WTC; †P < 0.05, ††P < 0.01, †††P < 0.001 versus WTHF.
genetic restoration of this n-3 resolution pathway would be sufficient to limit adipose macrophage accumulation in HF-fed mice. Immunohistochemical staining for F4/80+ cells revealed that HF-fed wild-type mice have abundant accumulation of macrophages in adipose tissue compared with their chow-fed counterparts (Fig. 2C and D). Furthermore, many of the F4/80+ cells in HF-fed wild-type fat clearly formed inflammatory crown-like structures (CLSs) around adipocytes (Fig. 2C–E), a hallmark of obesity-linked inflammation (14). In line with the improved resolution capacity, macrophage accrual and CLS formation were entirely prevented in adipose tissue of HF-fed transgenic mice.

To further characterize the impact of n-3 resolution mediators on obesity-linked inflammation, we also examined adipose chemokine and cytokine expression. We detected elevated concentrations of the proinflammatory chemokines CCL2/MCP-1 and CCL5/RANTES alongside the cytokines, IL-1β, IL-2, and IL-6, in HF-fed wild-type mice (Fig. 2F–I). Importantly, these key inflammatory factors were not significantly raised by HF feeding in adipose of fat-1 mice.

**Transgenic restoration of n-3 protects against obesity-linked insulin resistance and glucose intolerance.**

We next characterized whole-body insulin sensitivity to determine whether transgenic restoration of n-3 also prevents the development of obesity-linked insulin resistance. Insulin sensitivity was markedly reduced in HF-fed wild-type mice, as illustrated by elevated fasting insulin levels and diminished glucose excursion during the ITT (Fig. 3A–D). Conversely, fat-1 mice were protected from HF-diet-induced insulin resistance because both fasting insulin values and ITT curves were similar to those observed for chow-fed mice.

**Fat-1 mice were also partially protected from HF-diet-induced glucose intolerance (Fig. 3E and F).** The area under the glucose tolerance curves of HF-fed wild-type mice was increased compared with their chow-fed counterparts (Fig. 3F); however, this parameter was not significantly different between HF-fed fat-1 mice and their...
chow-fed controls. Importantly, the improved metabolic phenotype of HF-fed fat-1 mice was not related to changes in food intake (data not shown), body weight gain (Fig. 3G), or adiposity (Fig. 3F). We also found no changes in hepatic lipid accretion as determined by liver weight (Fig. 3I) and histological examination of liver sections, which showed similar accumulation of fat vesicles in both HF-fed wild-type and fat-1 mice (Fig. 3J). Fasting plasma free fatty acids were not significantly influenced by 8 weeks of HF feeding or transgenic restoration of n-3 in our study (data not shown). Although not statistically significant, circulating adiponectin tended to be reduced by ~30% in HF-fed wild-type mice compared with their chow-fed counterparts (2,150 ± 638 ng/ml vs. 3,345 ± 768 ng/ml, respectively); this was not the case in HF-fed fat-1 mice, which displayed circulating levels of adiponectin that were comparable to chow-fed mice (3,420 ± 565 ng/ml).

To understand the mechanism underlying the improved metabolic phenotype of HF-fed fat-1 mice, we examined insulin signaling to Akt in muscle and liver. As expected, insulin stimulation induced robust phosphorylation of Akt on ser473 in muscle and liver of chow-fed wild-type mice, but this response was impaired in their HF-fed counterparts (Fig. 4A–B). Remarkably, this defect was normalized in both muscle and liver of HF-fed fat-1 mice, despite clear accumulation of ectopic lipid in the latter tissue.

We next examined whether the improved insulin action in metabolic tissues of HF-fed fat-1 mice resulted from decreased inflammatory signaling. As expected, HF feeding wild-type mice led to robust phosphorylation of JNK on thr183/tyr185 in both muscle and liver; however, this was not the case for HF-fed fat-1 mice in either tissue (Fig. 4C and D). HF feeding also resulted in significant iNOS induction in muscle of wild-type mice but not in HF-fed fat-1 mice (Fig. 4E). These data suggest that prevention of HF-diet-induced n-3 deficiency and the maintenance of resolution capacity protects from the development of obesity-linked insulin resistance not only by limiting inflammation in the expanding adipose tissue but also by inhibiting two key inflammatory mediators of insulin resistance, JNK (17) and iNOS (11), in muscle and liver.

**DISCUSSION**

In the present study, we took advantage of fat-1 mice to investigate the role of endogenous n-3 derived resolution mediators in key metabolic tissues in obesity. We found that the biosynthetic flux of the n-3 docosanoid resolution pathway in muscle and adipose tissue is dependent on long-chain n-3 PUFA bioavailability and that the pro-resolving lipid mediator, PD1, is lacking in normal mice chronically fed a typical Western diet (n-6:n-3 ratio ~18–1). HF-fed obese mice exhibited an impaired capacity to resolve an acute inflammatory response to TNFα and showed abundant macrophage infiltration in adipose tissue that was linked to heightened chemokine and cytokine expression, a hallmark of obesity-linked inflammation (18,19). Remarkably, restoration of PD1 via fat-1 transgenesis improved global resolution capacity and prevented adipose macrophage accrual in HF-fed fat-1 mice. Accordingly, the expression levels of five key proinflammatory chemokines/cytokines were not found to be significantly elevated in adipose tissue of HF-fed fat-1 mice compared with their chow-fed controls. To the best of our knowledge, this is the first demonstration that endogenous biosynthetic flux of n-3 derived resolution mediators is associated with obesity-linked inflammation in metabolic tissues.

This is also the first report on the regulation of inflammation and insulin sensitivity in an animal model of obesity in which n-3 status has been enhanced without confounding effects of dietary manipulation. Indeed, previous studies have documented that the anti-inflammatory and metabolic effects of dietary n-3 supplementation were associated with concomitant reductions in either food intake, body weight gain, adiposity, or liver fat accretion (9,20,21). However, we report herein that transgenic-based elevation of long-chain n-3 PUFAs protects from obesity-linked insulin resistance without altering food intake, weight gain, or lipid deposition in adipose tissue or liver. We propose instead that endogenous long-chain n-3 PUFAs exert their protective effect through the actions of their lipid oxygenation products, which resolve inflammation and limit macrophage accrual in the expanding adipose tissue of obese mice.

The lack of effect of fat-1 expression on hepatic lipid accretion seems at odds with the recent report that dietary supplementation of long-chain n-3 PUFAs reversed hepatic steatosis in genetically obese ob/ob mice possibly through the action of the EPA-derived eicosanoid RvE1 (8). However, this may be due in part to the different animal models used (i.e., diet-induced versus genetic-based obesity) and the fact that we readily detected the docosanoid PD1 but not the eicosanoid RvE1 in the liver of our HF-fed fat-1 mice. Although we saw no effect of fat-1 transgenesis on resolution mediator synthesis in liver, our data suggests that transgenic restoration of n-3 fatty acids dissociates insulin resistance from hepatic lipid deposition, and this is likely due to inhibition of inflammatory signaling, as revealed by prevention of JNK activation in liver of HF-fed fat-1 mice. This anti-inflammatory effect in liver may be the result of reduced inflammatory crosstalk from adipose tissue with fewer recruited macrophages or may represent the local actions of another class of bioactive n-3 metabolite such as the newly discovered maresins (22) or EFOX (23), which should be the focus of future investigations.

Our data showing protection from obesity-linked insulin resistance in HF-fed fat-1 mice in which the levels of long-chain n-3 PUFAs have been restored are in line with epidemiological studies in humans, which showed that native populations traditionally consuming high levels of long-chain n-3 PUFAs display a lower prevalence of type 2 diabetes (24,25). Interestingly, data from another clinical study suggests that the positive influence of long-chain n-3 PUFA supplementation on insulin sensitivity is greater in obese populations that display an inflammatory phenotype (26). These data lend support to our findings, which indicate that the anti-inflammatory actions of n-3 derived resolution mediators in metabolic tissues are key to the positive impact of long-chain n-3 PUFAs on insulin sensitivity. It will be interesting in future studies to examine whether direct administration of purified n-3 derived resolution mediators is sufficient to prevent the development of insulin resistance in obese animals and which mediators carry the greatest antidiabetic potential.

Although our work represents the first study into the effect of endogenously enhancing tissue n-3 content on insulin sensitivity in the context of obesity, it is noteworthy that another group has recently developed an adipose-specific fat-1 transgenic line (AP-3 mice) to expressly study the influence of adipose n-3 content on weight gain, insulin sensitivity, and glucose tolerance in lean mice (27).
It was found that 3-month-old male, but not female, AP-3 transgenic mice fed a high carbohydrate diet weigh slightly less than their wild-type littermates, although this could not be explained by changes in adiposity. Interestingly, whereas male AP-3 mice were more glucose tolerant than wild-type controls, female AP-3 mice exhibited glucose intolerance as compared with their wild-type littermates. Insulin sensitivity was not affected in either sex. These findings differ from those of our study in which we found that fat-1 transgenesis had no impact on weight gain or glucose tolerance in lean chow-fed animals. It is of interest that homozygous expression of the fat-1 transgene in our mice does not influence viability (10), whereas homozygous expression in the AP-3 mice was found to be lethal (27).

In conclusion, we propose that endogenous long-chain

**FIG. 4.** n-3 resolution mediators improve insulin signaling by blunting JNK and iNOS in muscle and liver. Transgenic restoration of n-3 resolution mediators improves insulin signaling to Akt in muscle and liver and blunts activation of JNK and iNOS in these tissues. A–E: Immunoblots for pAKTser473, total AKT, pJNKthr183/tyr185, and total JNK in gastrocnemius muscle and liver, and iNOS in muscle (n = 5–9). Quantification of densitometry analyses are shown below the representative gels. Lanes were run on the same gel but were noncontiguous. All data are mean ± SEM, ND not detected, *P < 0.05, **P < 0.01, ***P < 0.001 versus respective chow-fed control; †tP < 0.05 versus WTHF.
n-3 PUFAs exert their protective effects through their lipid oxygenation products, which reduce macrophage accrual and inflammation in the expanding adipose tissue of obese mice. Our data further suggest that restoring long-chain n-3 PUFAs also prevents obesity-linked insulin resistance by blunting lipid-induced JNK and iNOS activation in muscle and liver. Collectively, our findings unravel a novel mechanism by which endogenous n-3 fatty acids prevent the development of obesity-linked inflammation and insulin resistance. This work supports the use of long-chain n-3 PUFAs for the prevention of insulin resistance and glucose intolerance in obese individuals.

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P.J.W. planned experiments, researched data, and wrote the manuscript. M.A. researched data and reviewed/editied the manuscript. R.T. researched data. J.X.K. helped plan experiments, contributed to discussion, and reviewed/editied the manuscript. A.M. planned and supervised experiments and wrote and edited the manuscript.

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