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Intestinal, adipose, and liver inflammation in diet-induced obese mice

Hong Li[a,1], Christopher Lelliott[a], Pernilla Håkansson[a], Karolina Ploj[a], Anna Tuneld[b], Martina Verolin-Johansson[b], Lambertus Benthem[a], Björn Carlsson[c], Leonard Storlien[d,*], Erik Michaëlsson[a]

[a]*Department of Integrative Pharmacology, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden*
[b]*Department of Molecular Pharmacology, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden*
[c]*Department of Discovery Medicine, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden*
[d]*Institute of Obesity, Nutrition and Exercise, University of Sydney, NSW 2006, Australia*

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Abstract

Chronic inflammation and increased visceral adipose tissue (VAT) are key elements of the metabolic syndrome. Both are considered to play a pathogenic role in the development of liver steatosis and insulin resistance. The aim of the present study was to investigate the hypothesis that an inflamed intestine, induced both by diet and chemical irritation, could induce persistent inflammation in VAT. Female C57BL/6JOlaHsd mice were used. In study I, groups of mice (n = 6 per group) were given an obesity-inducing cafeteria diet (diet-induced obesity) or regular chow only (control) for 14 weeks. In study II, colitis in mice (n = 8) was induced by 3% dextran sulfate sodium in tap water for 5 days followed by 21 days of tap water alone. Healthy control mice (n = 8) had tap water only. At the end of the studies, all mice were killed; and blood and tissues were sampled and processed for analysis. Body weight of diet-induced obese mice was greatly increased, with evidence of systemic inflammation, insulin resistance, and liver steatosis. Tissue inflammation indexed by proinflammatory cytokine expression was recorded in liver, mesenteric fat, and proximal colon/distal ileum, but not in subcutaneous or perigonadal fat. In dextran sulfate sodium–induced colitis mice, mesenteric fat was even more inflamed than the colon, whereas a much milder inflammation was seen in liver and subcutaneous fat. The studies showed both diet- and colitis-initiated inflammation in mesenteric fat. Fat depots contiguous with intestine and their capacity for exaggerated inflammatory responses to conditions of impaired gut barrier function may account for the particularly pathogenic role of VAT in obesity-induced metabolic disorders.

1. Introduction

Chronic low-grade systemic inflammation is a feature of established obesity and is now considered by many as a key feature of the metabolic syndrome, at least when indexed by circulating cytokines and inflammatory markers [1-4]. Biomarkers of inflammation, such as circulating C-reactive protein, are now widely accepted as an indicator of cardiovascular risk in the context of the metabolic syndrome [5-7]. The source of these circulating factors is becoming clearer. White adipose tissue (WAT) is no longer recognized as a passive storehouse of excess energy, but also an active endocrine and secretory organ and a major contributor to the elevated levels of a number of inflammatory proteins. The role of adipose in inflammation has been extensively reviewed recently [8-10].

Different depots of WAT play diverging roles in the obesity-related inflammation and in energy metabolism [11]. Visceral, but not subcutaneous (SC), fat is strongly associated with the metabolic syndrome [11]. Indeed, abdominal obesity is a required criterion in the most recent consensus definition of metabolic syndrome [12]. Visceral adipose tissue (VAT) is generally found to be more inflamed than SC, producing more monocyte chemotactic protein–1, tumor necrosis factor (TNF)–α, and interleukin (IL)-6, and less adiponectin than SC and thus has been presumed as the key regulator of systemic inflammation in obesity [11,13-15]. Visceral adipose tissue is also strongly associated with nonalcoholic fatty liver disease including simple steatosis and nonalchoholic steatohepatitis, which may progress to fibrosis, cirrhosis, and carcinoma. In addition, VAT is thought to provide an

* Corresponding author. Tel.: +61 2 9036 3024; fax: +61 2 9036 3176.
E-mail address: lstorlien@usyd.edu.au (L. Storlien).
[1] Current address: BioDuro (Beijing) Ltd, Life Science Park Rd No. 29, Beijing 102206, P.R. China.

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immediate source of free fatty acid and proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, to the liver via the portal vein, which may initiate hepatic inflammation [16,17].

It is unclear why and how enlarged VAT depots become especially pathogenic. It has been suggested that WAT-secreted cytokines are closely associated with a number of gastrointestinal diseases, such as Crohn disease, functional bowel disorders, and gastrointestinal cancers [18,19]. The hypertrophied mesenteric adipose tissue in inflammatory bowel diseases was presumed to be a major contributor of the increased circulating proinflammatory cytokines and steatosis seen in these patients [20]. This link between VAT and intestinal inflammation was also observed by Schäffler and his colleagues [21,22]. They found a pronounced infiltration of macrophages along with up-regulated cytokines in the creeping fat of patients with Crohn disease and proposed that hypertrophic mesenteric fat could be a cause of or a consequence of intestinal inflammation.

The present studies were aimed to study the cross impact between metabolic disorders and intestinal inflammation. We hypothesized that diet-induced obesity is an inflammatory condition in intestine, adipose, and liver, which shares metabolic features with induced gastrointestinal inflammation. To test this hypothesis, we studied the expression of inflammatory markers in different tissues in diet-induced obese (DIO) mice, especially to see if inflammation occurred in the intestinal tissues of the obese animal. To get perspective on the degree and nature of the inflammation in DIO mice, we compared it with the most commonly used gastrointestinal inflammatory model, that is, dextran sulfate sodium (DSS) colitis [23]. In the mouse strain used herein (C57BL/6JOlaHsd), DSS causes an acute disease that progresses into severe chronic colitis characterized by highly elevated plasma levels of acute phase proteins and elevated levels of cytokines in colon [24]. In addition to inflammatory end points measured in colon and plasma, we also studied how adipose and liver reacted to the DSS-induced inflammation in the intestinal mucosa and compared the pattern of inflammation markers with that observed in the DIO model.

2. Materials and methods

2.1. Animal experiments

Female C57BL/6JOlaHsd mice (Harlan, Horst, the Netherlands), 8 to 10 weeks old and weighing around 18 g, were used in the studies. The animals were kept in Macrolon 2L cages (Scanbur A/S, Karslunde, Denmark; 6-8 mice per cage) in rooms with regulated temperature (18°C-22°C), humidity (about 50%), and 12-hour/12-hour light-dark cycle. The mice had free access to regular chow pellets (R3; containing 5% fat, 52% carbohydrate, and 21% protein; Lactamin, Vadstena, Sweden) and tap water. They were allowed at least 1 week of acclimatization before study initiation. The local Animal Research Ethics Board Committee (Göteborg) approved these studies.

2.1.1. Study 1

One group of 6 mice was given cafeteria diet, including cheese (containing 38% fat, 1% carbohydrate, and 20% protein; Arla Ost, Västervik, Sweden), chocolate (containing 32% fat, 58% carbohydrate, and 6% protein; Marabou, Kraft Foods, Upplands Väsby, Sweden), nougat (containing 39% fat, 47% carbohydrate, and 6% protein; Odense Marcipan, Odense, Denmark), and chocolate/cocoa pastry (containing 31% fat, 52% carbohydrate, and 5% protein; Delicatoboll, Delicato, Huddinge, Sweden), together with regular chow for 14 weeks and was named as *DIO*. Regular chow–fed mice (n = 6) served as age-matched lean controls.

2.1.2. Study 2

Mice were given regular chow pellets. One group of mice (n = 8) was given tap water with 3% (wt/vol) DSS (45 kd; TdB Consultancy, Uppsala, Sweden) for 5 days, followed by tap water only for further 21 days. The 5-day DSS exposure is sufficient to induce a chronic phenotype of colitis 3 weeks later, as previously described [23,24]. The control group (n = 8) was given tap water throughout the study.

Body weights (BWs) were recorded weekly in both studies. At the end of the studies, the plasma glucose level of mice, in an awake and fed state, was measured by ACCU-CHEK Compact Plus Blood Glucose Meter (Roche Diagnostics, Mannheim, Germany) between 12:00 PM and 3:00 PM (6-9 hours after light on). The mice were then killed under deep isoflurane anesthesia. During anesthesia, retroorbital blood was sampled using an EDTA-containing capillary tube. The plasma was separated and stored at −20°C until analysis. The whole liver, total mesenteric fat, perigonadal fat, and abdominal SC fat, as well as the proximal colon, were removed, weighed, frozen in liquid nitrogen, and stored in −80°C until analysis.

2.2. Analysis of triglyceride, haptoglobin, insulin, leptin, and alanine aminotransferase

Liver tissues (50 mg/mL isopropanol in Lysing Matrix D tubes) were homogenized in a FastPrep FP120 (Qbiogene, Illkirch Cedex, France). The samples were centrifuged at 1300*g* (4°C) for 5 minutes, and the supernatants were used to determine liver triglyceride (TG) levels. The TG concentrations in the plasma and liver were measured (catalog no. A11A01640; ABX Diagnostics, Montepellier, France) and expressed as millimoles per liter and grams per 100 g, respectively (assay coefficient of variation [CV], 3%). The plasma levels of haptoglobin (Phase Range, catalog no. TP801; Tridelta Development, Maynooth, Ireland; assay CV, 8%), leptin (catalog no. 90030; Christal Chemical, Downers Grove, IL; assay CV, 10%), and insulin (catalog no. R1-13K; Linco Research, St Charles, MO; assay CV, 7%) were measured; and results were expressed as grams per liter, nanograms per milliliter, and nanomoles per liter, respectively. Alanine aminotransferase (ALAT) activities were determined with an enzymatic colorimetric assay (REF AL7904; Randox Laboratories, Crumlin, United Kingdom; assay CV, 8%) and expressed as microkatals per liter. The

assays were performed by using a Cobas Mira analyzer (Roche Diagnostica, Basle, Switzerland).

2.3. Analysis of cytokines in the tissues

Dissected tissue pieces were put in Lysing Matrix D tubes and homogenized in phosphate-buffered saline supplemented with protease inhibitor (Complete Mini, Roche Diagnostics), at 250 mg tissue per milliliter, on a FastPrep FP120 (Qbiogene). The homogenates were then centrifuged at 5000*g* (4°C) for 5 minutes. The supernatants were transferred to new tubes and centrifuged once more at 10 000*g* (4°C) for 10 minutes. The final supernatants were stored at −80°C until analysis.

The cytokines including IL-1β, IL-6, IL-12p40, and TNF-α (assay CVs, 10%-15%) in liver, proximal colon, and mesenteric and SC adipose depots were determined by using bead-based multiplex suspension array kits (Bio-Rad, Hercules, CA) with the Luminex technology and BioPlex Manager 4.0 software (Bio-Rad) on a BioPlex following the manufacturer's instructions. The results are expressed as picograms per milligram protein.

2.4. Statistics

Results are expressed as mean ± SEM and were statistically evaluated using Student *t* test for the median because of the skewed data sets. Differences were considered to be significant at a *P* value less than .05.

3. Results

3.1. Study 1: DIO mice

3.1.1. Body and tissue weights

The DIO mice gained more weight than controls during the feeding protocol (Fig. 1A, B). They were significantly heavier by week 2; and by the end of 14 weeks, BW in DIO mice was double that of the control (46 ± 0.8 g vs 23.2 ± 0.3 g, $P < .001$). The weights of whole liver, total mesenteric fat, and a depot of abdominal SC fat in DIO mice were 2- to 5-fold higher than corresponding tissues in lean mice, all at *P* less than .001 (Fig. 1B).

3.1.2. Plasma and liver biochemistry

In DIO mice, plasma haptoglobin was 7-fold and leptin was 5-fold higher than those in lean mice (both $P < .001$). Plasma insulin was significantly elevated in DIO compared with lean mice (Fig. 1C, $P < .01$), as was plasma glucose (Fig. 1D, $P < .001$). In DIO mice, liver TG concentration was 8-fold higher than that in lean mice (Fig. 1D, $P < .01$); and the plasma ALAT was also significantly elevated (Fig. 1C, $P < .001$). However, the plasma TG in DIO mice was only slightly elevated (Fig. 1C, not significant).

3.1.3. Cytokines in tissues

Concentrations of IL-6 and TNF-α in both liver and mesenteric adipose of DIO mice were significantly increased in comparison with those of lean mice (Fig. 2; IL-6 elevated 193% in liver [$P < .05$] and 609% in mesenteric fat [$P < .05$], TNF-α increased 222% in liver [$P < .01$] and 426% in mesenteric fat [$P < .05$]). Interleukin-12p40 levels did not differ between groups in either tissue. Interleukin-1β levels were increased 233% in DIO mice in mesenteric fat (Fig. 2B, $P < .05$), but not liver. In contrast, in the proximal colon of DIO mice, IL-1β levels were significantly higher than those of lean mice (Fig. 2C; 259% increased, $P < .01$), as was IL-12p40 (Fig. 2C; 162% increased, $P < .05$), whereas IL-6 and TNF-α did not differ. The cytokine levels in SC fat were not significantly different between DIO and lean mice (Fig. 2D), and the same was true for perigonadal fat (Fig. 2E).

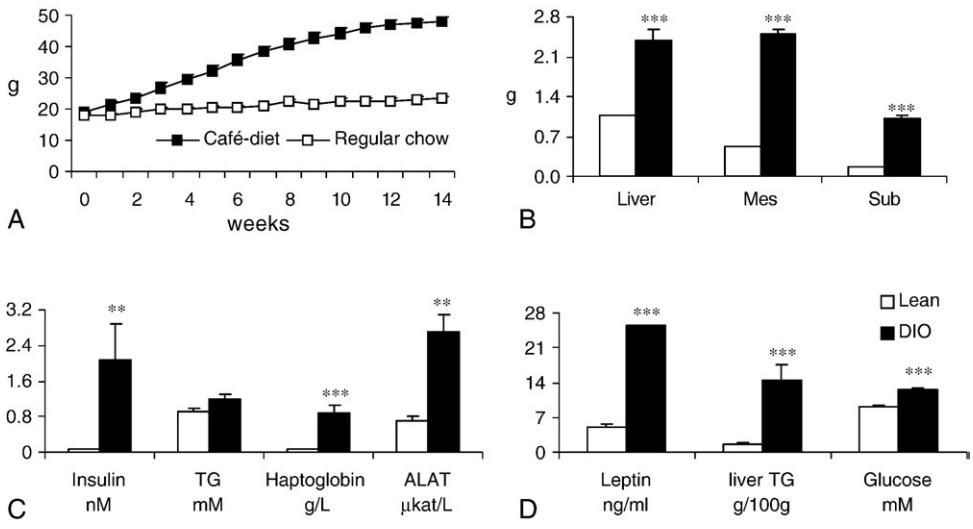

Fig. 1. Body and tissue weights, and plasma biochemistry in DIO and lean mice. (A) The BW in the mice given cafeteria diet was significantly higher than that in mice given regular chow by 14-week measurements after diet treatment ($P < .05$ to $P < .001$). (B) Weights of whole liver, whole mesenteric fat, and a depot of SC fat in DIO and lean mice. (C and D) Plasma chemical analysis in DIO and lean mice at the end point of experiment (mean ± SEM, n = 6 per group; *$P < .05$, **$P < .01$, ***$P < .001$). Note that, for the BW, the error bars are very small and obscured by the symbols. Groups differed significantly in BW from the second week of diet.

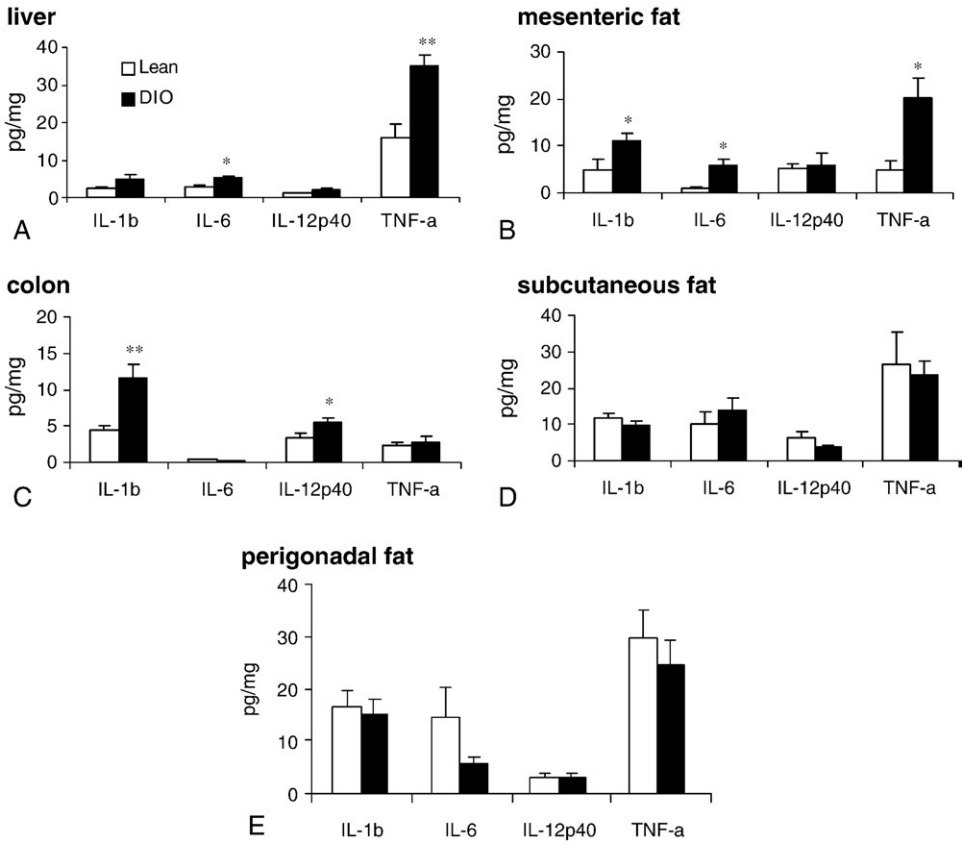

Fig. 2. Inflammation indexed by cytokine concentrations in liver, proximal colon, and mesenteric and SC adiposes of DIO and lean mice (mean ± SEM, n = 6 per group except for the mesenteric fat, n = 4; *$P < .05$, **$P < .01$, ***$P < .001$).

3.2. Study 2: DSS-treated mice

3.2.1. Body and tissue weights

The BW of the mice with DSS-induced colitis began to decrease at 4 days after the initiation of DSS treatment, with the lowest BW being approximately 1 week after the cessation of DSS (16.1 ± 0.9 g at day 11, loss of 3.5 g) (Fig. 3A, B). The BW of the DSS group then gradually increased to 19.6 ± 0.7 g at the end of the experiment, close to that of healthy control (HC) mice (20.9 ± 1.0 g). In comparison with HC mice, the weight of SC fat in DSS-treated mice was significantly reduced, whereas mesenteric fat remained unchanged. In contrast, the liver weight of the DSS-treated mice was significantly elevated (Fig. 3B).

3.2.2. Plasma and liver biochemistry

Plasma haptoglobin in DSS-treated mice was significantly elevated in comparison with that in HC mice (2.0 ± 0.3 vs 0.05 ± 0.01g/L) (Fig. 3C, D). Plasma glucose and insulin levels were not different between HC and DSS-treated mice. Plasma levels of leptin, TG, and ALAT were also slightly lower in DSS-treated mice than in HC mice, but liver TG concentration in DSS-treated mice was significantly reduced compared with that in HC mice.

3.2.3. Cytokines in tissues

In DSS-treated mice, the concentrations of cytokines in the proximal colon, including IL-1β, IL-6, IL-12p40, and TNF-α, were all significantly elevated (by 4858%, 1471%, 209%, and 321%, respectively; all $P < .01$) in comparison with those in HC mice (Fig. 4A-D). In liver, mesenteric fat, and SC fat, only IL-1β and IL-12p40 were significantly higher in DSS-treated mice compared with HC mice (IL-1β increased by 3437% in mesenteric and 415% in SC fat, both $P < .01$; IL-12p40 increased by 661% in mesenteric and 254% in SC fat, both $P < .05$).

4. Discussion

The connection between high-fat diet (HFD)–induced obesity, insulin resistance, and circulating markers of inflammation in rodents has been reported in a number of studies [25-27]. Increased expression of cytokines in white adipose occurs even within 2 days of initiation of HFD feeding in mice [26]. After a longer period of HFD feeding (6-20 weeks), inflammation has been observed not only in adipose [26-28]; but it is present also in liver, muscle [25], and hypothalamus [29]. This widespread tissue inflammation suggests the development of a chronic low-grade, but

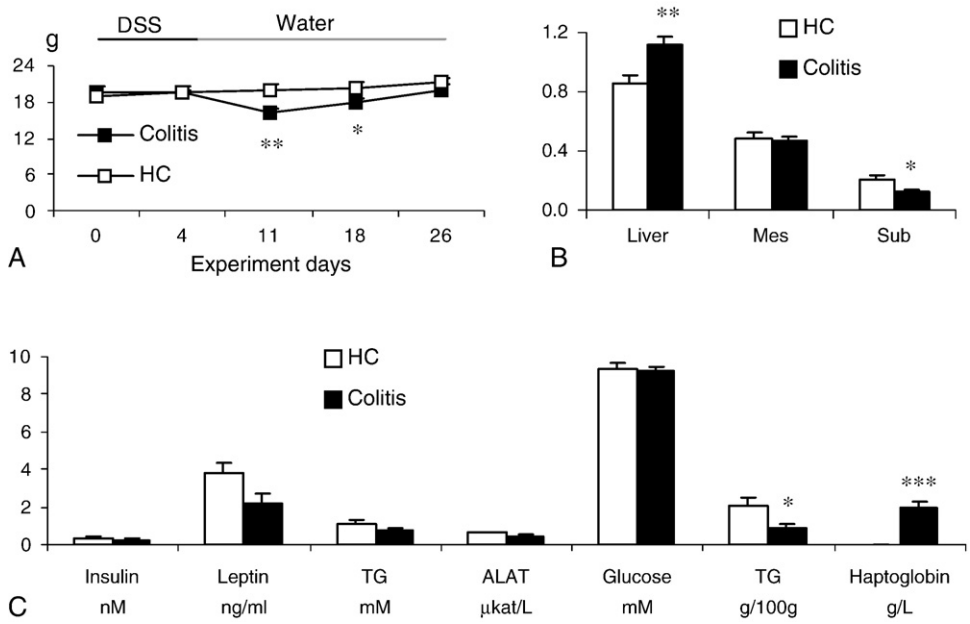

Fig. 3. Body and tissue weights, and plasma biochemistry in DSS-induced colitic and HC mice. (A) Development of BW in DSS-induced colitic and HC mice during entire experimental period. (B) Weights of whole liver, whole mesenteric fat, and a depot of SC fat in colitis and HC mice. (C and D) Plasma chemical analysis in colitic and HC mice at the end point of experiment (mean ± SEM, n = 8 per group; $*P < .05$, $**P < .01$, $***P < .001$).

systemic inflammation with higher dietary fat intake. Although the initial increased level of cytokines might presumably come directly from adipocytes or vascular endothelial cells residing in adipose [26], more recent evidence has demonstrated that the chronic inflammation in HFD or genetically obese animals is associated with the infiltration of monocytes and macrophages [30-33].

The DIO mice in the present study showed a greatly increased adiposity, liver steatosis, and evidence of insulin resistance. Together with these typical metabolic disorders, the mice manifested widespread inflammation shown by a high level of circulating haptoglobin and elevated cytokine markers in liver and mesenteric fat. Furthermore, a significant inflammation as indexed by the specific markers for gut inflammation, IL-1β and IL-12p40, was found in the proximal colon in the DIO mice. This finding is in line with a human study showing a low-grade asymptomatic bowel inflammation in obese subjects as measured by calprotectin in feces [34]. Interestingly, in contrast, there was no evidence of increased inflammation in SC adipose tissue.

Next, to find if mesenteric fat, which is contiguous to the intestine, reacts to intestinal inflammation, we used a mouse

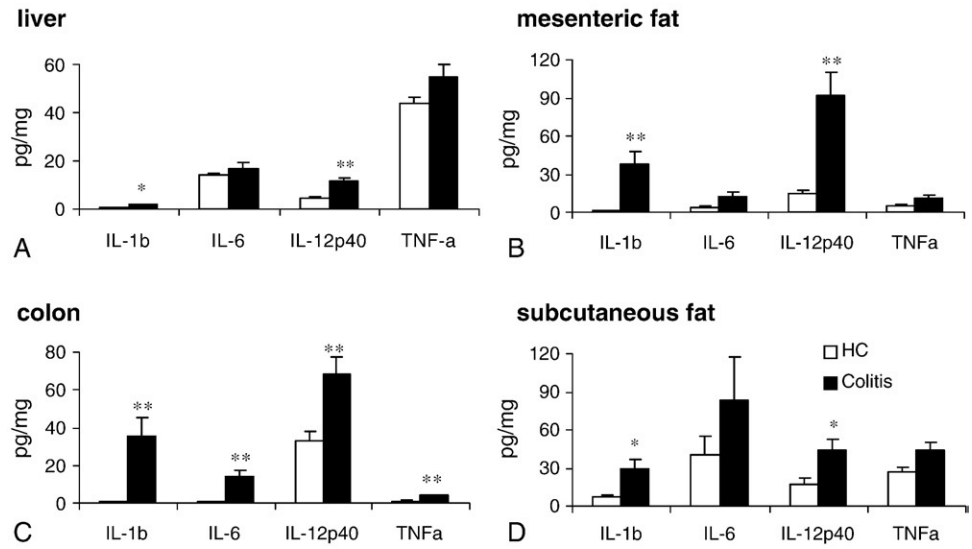

Fig. 4. Inflammation indexed by cytokine concentrations in liver, proximal colon, and mesenteric and SC adiposes of colitic and HC mice (mean ± SEM, n = 8 per group; $*P < .05$, $**P < .01$, $***P < .001$).

model of inflammatory bowel disease, the DSS-induced colitis. As described previously [24,35], 3 weeks after DSS treatment, a severe colitis, indexed by elevated IL-1β and IL-12p40, was seen in the mice. Importantly, a more profound inflammation was seen in the mesenteric fat than in colon and also relative to the milder inflammation seen in liver and SC fat. The chemical-induced inflammation produced by DSS is somewhat different in pattern to that seen in DIO obese mice. However, both models lead to inflammation in the intestine-contiguous mesenteric fat of the DIO mice.

A key question is how the intestinal inflammation is transferred from the gut to the mesenteric adipose tissue. A salient possibility is an impaired gut barrier function and increased bacterial translocation to the mesentery as shown in experimental colitis [36]. Intraabdominal adipose tissue plays an important role in immune defense by clearance of bacteria from the peritoneal cavity [37], and a decreased intestinal barrier function may lead to increased bacterial load provoking an inflammatory defense response in intraabdominal adipose tissue. Most likely, immune cells including macrophages, plasma cells, and T cells present in omental fat play important roles in the process [38-40]. A recent study has demonstrated that intestinal permeability and antigenic uptake in genetically induced obese mice (*ob/ob* and *db/db*) are increased, which leads to increased portal endotoxemia and inflammatory damage in the liver [41]. Extending these data, our studies indicate that the intestinal mucosa itself is in an inflammatory state in HFD-derived obesity and that inflammation in mesenteric fat can result from the induced intestinal inflammation. We suggest that the interaction of inflammation between mesenteric fat and the intestinal mucosa could trigger and worsen to a persistent inflammation in VAT. This would place VAT as a key pathogenic tissue in obesity-induced metabolic disorders, as is consistently observed, and suggest that it is the VAT contiguous with the intestine that is most critical.

It must be emphasized that the DSS model is used here in 2 ways. The first is to demonstrate that the intestinal inflammation induced by the HFD is really quite comparable with that seen after a chemical insult used as an industry standard mouse model of colitis. The second is to show that this intestinal chemical insult results in inflammation not only of the intestine, but also of the fat contiguous with it. There is no intention to claim more than this in mechanistic terms. Certainly, the data are consistent with, but in no way prove, the fact that the mesenteric fat inflammation of diet-induced obesity has its genesis in the intestinal tract.

The nature of the macronutrients in an obesogenic diet is also likely to be important in the genesis and severity of the inflammatory response. The harmful effect of HFD on symptomatic bowel inflammation has been shown in patients with Crohn disease [42]. The specific composition of fat is also of critical importance as demonstrated previously where the long-chain fatty acid oleate (18:1 n-9) increased lymphocyte flux and enhanced its proliferative response in intestinal lymph, an effect not seen with the medium-chain fatty acid octanoate (8:0) [43]. Long-chain unsaturated fatty acids are potent gene regulators [44], and the balance between fatty acid subtypes in the intestinal inflammatory response to obesogenic diets is an important area of investigation.

In conclusion, our studies showed diet-induced inflammation both in intestine and in mesenteric fat. Fat depots contiguous with intestine and their capacity for exaggerated inflammatory responses to conditions of impaired gut barrier function may help account for the particularly pathogenic role of VAT in obesity-induced metabolic disorders.

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References

[1] Lee H, Pratley RE. The evolving role of inflammation in obesity and the metabolic syndrome. Current Diabetes Reports 2005;5:70-5.
[2] Trayhurn P. Adipose tissue in obesity—an inflammatory issue [comment]. Endocrinology 2005;146:1003-5.
[3] Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? Nutr Metab Cardiovasc Dis 2004;14:228-32.
[4] Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. Eur Cytokine Netw 2006;17:4-12.
[5] Pickup JC. Inflammatory markers and type 2 diabetes. Diabetes Technol Ther 2006;8:1-6.
[6] Florez H, Castillo-Florez S, Mendez A, et al. C-reactive protein is elevated in obese patients with the metabolic syndrome. Diabetes Res Clin Pract 2006;71:100.
[7] Szmitko PE, Wang CH, Weisel RD, et al. New markers of inflammation and endothelial cell activation: part I. Circulation 2003;108:1917-23.
[8] Murdolo G, Smith U. The dysregulated adipose tissue: a connecting link between insulin resistance, type 2 diabetes mellitus and atherosclerosis. Nutr Metab Cardiovasc Dis 2006;16(Suppl 1): S35-8.
[9] Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83:461S-5S.
[10] Nawrocki AR, Scherer PE. Keynote review: the adipocyte as a drug discovery target. Drug Discov Today 2005;10:1219-30.
[11] Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med 2006;38:52-63.
[12] Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. Lancet 2005;366:1059-62.
[13] Lihn AS, Bruun JM, He G, et al. Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. Mol Cell Endocrinol 2004;219:15.
[14] Malavazos AE, Cereda E, Morricone L, et al. Monocyte chemoattractant protein 1: a possible link between visceral adipose tissue–associated inflammation and subclinical echocardiographic abnormalities in uncomplicated obesity. Eur J Endocrinol 2005;153:871-7.
[15] Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte chemoattractant protein–1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. J Clin Endocrinol Metab 2005;90:2282-9.
[16] Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.

[17] Cancello R, Henegar C, Viguerie N, et al. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes 2005;54:2277-86.
[18] Karmiris K, Koutroubakis IE, Kouroumalis EA. The emerging role of adipocytokines as inflammatory mediators in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:847-55.
[19] John BJ, Irukulla S, Abulafi AM, Kumar D, Mendall MA. Systematic review: adipose tissue, obesity and gastrointestinal diseases. Aliment Pharmacol Ther 2006;23:1511-23.
[20] Bargiggia S, Maconi G, Elli M, et al. Sonographic prevalence of liver steatosis and biliary tract stones in patients with inflammatory bowel disease: study of 511 subjects at a single center. J Clin Gastroenterol 2003;36:417-20.
[21] Paul G, Schäffler A, Neumeier M, et al. Profiling adipocytokine secretion from creeping fat in Crohn's disease. Inflamm Bowel Dis 2006;12:471-7.
[22] Schäffler A, Herfarth H. Creeping fat in Crohn's disease: travelling in a creeper lane of research? Gut 2005;54:742-4.
[23] Okayasu IHS, Yamada M, Ohkusa T, Inagaki Y, Nakaya R. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. Gastroenterology 1990;98:694-702.
[24] Melgar S, Karlsson A, Michaelsson E. Acute colitis induced by dextran sulfate sodium progresses to chronicity in C57BL/6 but not in BALB/c mice: correlation between symptoms and inflammation. Am J Physiol Gastrointest Liver Physiol 2005;288:G1328-38.
[25] Borst SE, Conover CF. High-fat diet induces increased tissue expression of TNF-[alpha]. Life Sci 2005;77:2165.
[26] Chen A, Mumick S, Zhang C, et al. Diet induction of monocyte chemoattractant protein–1 and its impact on obesity. Obes Res 2005; 13:1311-20.
[27] Yu R, Kim CS, Kwon BS, Kawada T. Mesenteric adipose tissue–derived monocyte chemoattractant protein–1 plays a crucial role in adipose tissue macrophage migration and activation in obese mice. Obesity 2006;14:1353-62.
[28] Brake DK, Smith EOB, Mersmann H, Smith CW, Robker RL. ICAM-1 expression in adipose tissue: effects of diet-induced obesity in mice. Am J Physiol Cell Physiol 2006;291:C1232-9.
[29] De Souza CT, Araujo EP, Bordin S, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 2005;146:4192-9.
[30] Permana PA, Menge C, Reaven PD. Macrophage-secreted factors induce adipocyte inflammation and insulin resistance. Biochem Biophys Res Commun 2006;341:514.
[31] Cinti S, Mitchell G, Barbatelli G, et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 2005;46:2347-55.
[32] Bouloumie A, Curat CA, Sengenes C, et al. Role of macrophage tissue infiltration in metabolic diseases. Curr Opin Clin Nutr Metab Care 2005;8:347-54.
[33] Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112: 1796-808.
[34] Poullis A, Foster R, Shetty A, Fagerhol MK, Mendall MA. Bowel inflammation as measured by fecal calprotectin: a link between lifestyle factors and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2004;13:279-84.
[35] Melgar S, Bjursell M, Gerdin AK, et al. Mice with experimental colitis show an altered metabolism with decreased metabolic rate. Am J Physiol Gastrointest Liver Physiol 2007:165-72.
[36] Asfaha S, MacNaughton WK, Appleyard CB, Chadee K, Wallace JL. Persistent epithelial dysfunction and bacterial translocation after resolution of intestinal inflammation. Am J Physiol Gastrointest Liver Physiol 2001;281:G635-44.
[37] Platell C, Cooper D, Papadimitriou JM, Hall JC. The omentum. World J Gastroenterol 2000;6:169-76.
[38] Gabrielsson BG, Johansson JM, Lonn M, et al. High expression of complement components in omental adipose tissue in obese men. Obes Res 2003;11:699-708.
[39] Palming J, Gabrielsson BG, Jennische E, et al. Plasma cells and Fc receptors in human adipose tissue–lipogenic and anti-inflammatory effects of immunoglobulins on adipocytes. Biochem Biophys Res Commun 2006;343:43-8.
[40] Wu H, Ghosh S, Perrard XD, et al. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. Circulation 2007;115:1029-38.
[41] Brun P, Castagliuolo I, Di Leo V, et al. Increased intestinal permeability in obese mice: new evidences in the pathogenesis of nonalcoholic steatohepatitis. Am J Physiol Gastrointest Liver Physiol 2007;292: G518-25.
[42] Bamba T, Shimoyama T, Sasaki M, et al. Dietary fat attenuates the benefits of an elemental diet in active Crohn's disease: a randomized, controlled trial. Eur J Gastroenterol Hepatol 2003;15:151-7.
[43] Miura S, Imaeda H, Shiozaki H, et al. Increased proliferative response of lymphocytes from intestinal lymph during long chain fatty acid absorption. Immunology 1993;78:142-6.
[44] Jump DB. Fatty acid regulation of gene transcription. Crit Rev Clin Lab Sci 2004;41:41-78.