Mice with experimental colitis show an altered metabolism with decreased metabolic rate

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MATERIAL AND METHODS

Induction of colitis. Specific pathogen-free female C57BL/6JolaHsd mice (Harlan) were used. Mice were housed individually and acclimatized for 2 wk before being entered into the study at the age of 9 wk (weight: 18–21 g). Animals were kept in the animal house facilities at AstraZeneca R&D (Mölndal, Sweden) with 50% humidity and 12:12-h light-dark cycles and fed with standard pellet chow (R3 pellets, Lactamin) and tap water ad libitum. This study was approved by the Local Animal Research Board Committee in Göteborg, Sweden.

Induction of colitis. Mice received 3% (wt/vol) DSS (45,000 Da; TDB Consultancy, Uppsala, Sweden) as previously described (23).

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Briefly, DSS was given for 7 days to induce acute inflammation in one group of mice. A second group of mice received DSS for 5 days followed by 3 wk of water to induce chronic inflammation. A third group of mice consisted of healthy controls receiving regular tap water. DSS solutions were prepared daily, and mice were monitored for their clinical symptoms as previously described (23). The numbers of animals per group were 14, 16, and 13 in the healthy control, acute inflamed, and chronic inflamed groups, respectively.

Treatment with methyl-prednisolone was performed in mice with chronic inflammation (n = 4) compared with a healthy group of mice (n = 6) and a vehicle-treated group of inflamed mice (n = 6). Methyl-prednisolone (1 mg/kg, Sigma Aldrich, St. Louis, MO) was administered orally on three occasions (days 15, 18, and 21 post-DSS). Plasma was collected 14 days after the last methyl-prednisolone treatment.

Indirect calorimetry. Oxygen consumption (VO₂), carbon dioxide production (VCO₂), food intake, water intake, and locomotor activity were measured using an open-circuit calorimetry system (Oxymax, Columbus Instruments, Columbus, OH) (3). Metabolic parameters were assessed during a 24-h period following days 7 and 26 for the acute and chronic inflammation groups, respectively. Animals were placed in calorimeter chambers with ad libitum access to normal lab chow and water. An air sample was withdrawn for 75 s every 20 min, and O₂ and CO₂ content were measured by a paramagnetic O₂ sensor and a spectrophotometric CO₂ sensor. These values were used to calculate VO₂ and VCO₂. Data from the first 2 h were not used in the analysis of the results to allow mice to acclimatize to the novel environment. Data from corresponding hours were used in 2-h bins. The metabolic rate (in kcal/h) was calculated from the following equation: (3.815 + 1.232RER) × VO₂, where RER is the respiratory exchange ratio [volume of CO₂ produced per volume of O₂ consumed (both in ml·kg⁻¹·min⁻¹)] and VO₂ is the volume of O₂ consumed per hour and kilogram mass of the animal. RER reflects the balance of substrate oxidation with a theoretical limit between 1.0 and 0.7. A RER of 1.0 reflects carbohydrate oxidation, whereas a RER of 0.7 reflects fat oxidation. The value of the metabolic rate was correlated to individual body weights. The RER and metabolic rate were analyzed for resting metabolism, taken at the lowest value of VO₂ during the light period. The cumulative water intake was assessed by an automatic counter that recorded every droplet that the mouse licked from the drinking sipper. The size of the droplets was calibrated separately for each cage (~20 µl/droplet). The measurements of food and water intake were performed on days 1 and 21 after DSS removal.

Body composition. The body composition was determined by DEXA using a PIXIus imager (GE Lunar, Madison, WI) (31). Mice were anesthetized with an initial dose of 4% isoflurane (Abbot /H11011 20) and a vehicle-treated group of inflamed mice (n = 6). Methyl-prednisolone (1 mg/kg, Sigma Aldrich, St. Louis, MO) was administrated orally on three occasions (days 15, 18, and 21 post-DSS). Plasma was collected 14 days after the last methyl-prednisolone treatment.

Assessment of inflammation and sampling of tissue and plasma. After DEXA, mice were anesthetized with isoflurane, and blood was collected in EDTA-containing tubes by a retroorbital puncture followed by cervical dislocation. Plasma was frozen and kept at −80°C until analysis. The whole colon was excised and carefully rinsed with NaCl (GIBCO-BRL, Invitrogen). The inflammatory score, reflecting the degree of inflammation in the colon, was based on edema (0–3), thickness of the tissue (0–4), stiffness of the tissue (0–2), and presence of ulcerations (0–1), resulting in a maximal total score of 10 (21). Three centimeters of the distal colon were removed and divided longitudinally in two pieces. One piece was frozen directly in liquid nitrogen and used to measure IL-1β levels, whereas the other piece was fixed in zinc-formalin solution (pH 7.4, Histolab Products, Göteborg, Sweden), embedded in paraffin, and used for histological analysis using hematoxylin–eosin staining or Masson trichrome staining as previously described (23).

Plasma analysis. The plasma was performed by using the following commercial kits: triglycerides (TG) and total cholesterol from Roche Diagnostics [nos. 12146029216 (TG) and 2016630 (cholesterol), Mannheim, Germany]; alanine aminotransferase (ALT), total protein, and albumin from Randox Laboratories [AL 7904 (ALT), TP245 (total protein), and AB 362 (albumin)]; nonesterified fatty acids (NEFA) from Wako Chemicals (NEFA C-999-75406); and glucose from ABX Diagnostics-Parch Euromedecine (HK 125, Montpellier, France). Insulin, leptin, triiodothyronine (T₃), thyroxine (T₄), and corticosterone were determined with radioimmunoassays purchased from Linco Research [RI-13 K (insulin) and ML-82 K (leptin)], Diagnostic [Coat-A-Count, TKT 31 (T₃) and TKT 41 (T₄), Los Angeles, CA], and Amersham Biosciences [RPA 548 (corticosterone), Biotrak Assay System, Uppsala, Sweden]. The ACTH assay was from Nichols Institute Diagnostics (36T-2194). Osteocalcin was determined using an immunoradiometric assay from Immunotopics.

Feces analysis. Feces from individual mice were collected, dried overnight at 55°C, and stored air tight at −18°C until being assayed. The gross energy content was determined in a bomb calorimeter (C 5000, IKA, Werke, Germany). A tablet of benzoic acid (IKA, Werke, Germany) was used as a combustion aid when the material was not sufficient (1).

Statistics. One- or two-way ANOVA was used to analyze the indirect calorimetry data. Values are presented as means ± SE. P < 0.05 was considered as significant.

RESULTS

Assessment of inflammation and clinical symptoms. Mice exposed to 7 days of DSS developed acute inflammation characterized by decreased body weight (Fig. 1A), loose feces/diarrhea (Fig. 1B), and visible fecal blood. Mice with chronic inflammation started to decrease their body weights during DSS treatment and continued 1 wk after DSS removal. Thereafter, they slowly recovered the weight, reaching their initial weights after 3 wk of water (Fig. 1A). The only clinical sign of disease in these mice was loose feces (Fig. 1B). In addition, the inflammatory score was higher in mice with chronic inflammation compared with mice with acute inflammation or healthy
controls (Fig. 1C). The thickness of the colonic tissue was increased, as reflected by the significantly increased colonic weight in both groups of inflamed mice compared with healthy controls (114.4 ± 6.3, 259.6 ± 16.8, and 63.0 ± 3.5 mg in acute inflamed, chronic inflamed, and healthy control mice, respectively). The increased thickness was due to the infiltration of inflammatory cells, edema, and fibrosis (Fig. 1, e, f, h, and I). Furthermore, plasma haptoglobin was elevated in mice...
with acute (4.05 ± 0.36 g/l) and chronic inflammation (3.06 ± 0.43 g/l) compared with healthy controls (0.13 ± 0.03 g/l). Similarly, the colonic levels of IL-1β were increased in acute inflamed mice and were even higher in chronic inflamed mice (6,045 ± 1,360, 13,815 ± 2,350, and 70 ± 14 pg/100 mg colonic tissue in acute inflamed, chronic inflamed, and healthy control mice, respectively). Thus, mice in the acute phase have an acute inflammatory response characterized by clinical symptoms and elevated systemic and local inflammatory markers. Mice in the chronic phase show mild clinical symptoms with severe colonic inflammation characterized by high levels of proinflammatory cytokines and enlarged colonic tissue.

**Mice with chronic inflammation have decreased metabolic rates.** VO₂ and VCO₂ were measured by indirect calorimetry to determine the effect of colonic inflammation on energy metabolism. Mice with acute inflammation had a tendency toward reduced resting metabolic rates compared with healthy controls (P = 0.07), whereas mice with chronic inflammation had significantly decreased resting metabolic rates (Fig. 2A). Resting RER was significantly decreased in mice with acute inflammation compared with healthy controls and mice with chronic inflammation (Fig. 2B; RER of 0.7 in mice with acute inflammation vs. 0.9 in healthy mice and mice with chronic inflammation). Although mice with chronic inflammation had significantly decreased VO₂ and VCO₂ compared with healthy controls, no differences were measured in RER (Fig. 2B). Thus, the data suggest that mice with acute inflammation use fat as an energy substrate, whereas mice with chronic inflammation use carbohydrates as an energy substrate, similarly to healthy controls.

**Food and water intake are reduced in mice with acute but not chronic inflammation.** Food and water intake and activity were measured in a calorimetry system to investigate their impact on metabolic changes. Mice with acute inflammation showed a significantly decreased food and water intake and a tendency toward decreased locomotor activity compared with healthy controls (P = 0.12; Fig. 3A–C). In contrast, a tendency toward increased food and water intake was observed in mice with chronic inflammation compared with healthy mice (Fig. 3A and B). Significantly decreased locomotor activity was observed in mice with chronic and acute inflammation during the dark period compared with healthy controls (Fig. 3C). Furthermore, the amount of energy lost in feces was determined to investigate whether the changes in metabolism were related to an altered intestinal uptake of nutrients. A significantly increased energy loss was found during the acute as well as chronic inflammatory phase, suggesting an impaired nutrient uptake in these animals compared with controls (Fig. 3D). No significant differences in feces energy content were observed between mice with acute and chronic inflammation (Fig. 3D). Thus, a reduction in food/water intake is associated with mice with acute inflammation.

**Body fat content is reduced in mice with acute or chronic inflammation.** The body composition in mice with colitis and healthy controls was determined by DEXA. Mice with acute inflammation contained less body fat and had a reduced body lean mass compared with healthy controls (Fig. 4, A and B). Furthermore, mice with acute inflammation had significantly less lean mass than mice with chronic inflammation (Fig. 4B). The loss of fat content persisted in mice with chronic inflammation, whereas the lean mass recovered to values similar to those in healthy controls (Fig. 4, A and B). No significant changes in BMC levels were found in mice with either acute or chronic inflammation (data not shown). However, a significant reduction in BMD was measured during chronic inflammation (39.6 ± 0.7 mg/cm²) compared with either healthy controls (44.4 ± 0.5 mg/cm²) or mice with acute inflammation (44.7 ± 0.8 mg/cm²). Furthermore, the plasma levels of osteocalcin were increased by 50% in mice with chronic inflammation compared with healthy controls (202 ± 26 and 134 ± 12 ng/ml in chronic inflamed and healthy mice, respectively, P < 0.05). Osteocalcin levels were reduced by 18% upon treatment with methyl-prednisolone in mice with chronic inflammation; however, this reduction was not statistically significant (158 ± 6 ng/ml for the methyl-prednisolone-treated mice). No differences in BMD were found between controls and mice with acute inflammation. Thus, the body fat content is reduced in mice during acute inflammation and remains reduced during chronic inflammation, despite the normalized food intake and body weight.

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**Figure 2.** Decreased resting metabolic rates in mice with chronic inflammation. A: resting metabolic rates (in kcal/h) were calculated according to the following equation: (3.815 + 1.232RER) × VO₂, where RER is the respiratory exchange ratio and VO₂ is the volume of O₂ consumed per hour per kilogram mass of the animal. These values were correlated with individual body weights. B: the RER (y-axis) was measured by indirect calorimetry and calculated as the volume of CO₂ produced per volume of O₂ consumed (both in ml·kg⁻¹·min⁻¹). *P < 0.05, mice with acute inflammation compared with healthy controls; §P < 0.05, mice with chronic inflammation compared with mice with acute inflammation.
Metabolic plasma markers are differentially regulated during acute and chronic inflammation. The levels of TG, cholesterol, NEFA, insulin, glucose, leptin, corticosterone, ACTH, ALT, thyroid hormones (T3 and T4), and albumin were determined in plasma from mice with acute and chronic inflammation and in healthy controls. The results are summarized in Table 1. The levels of glucose, leptin, T4, and albumin were significantly decreased in mice with acute and chronic inflammation compared with healthy controls. Markers related to lipid metabolism (TG and cholesterol) were differentially regulated during acute and chronic inflammation. In mice with acute inflammation, the levels of TG were reduced, whereas cholesterol levels were increased, compared with controls. In contrast, mice with chronic inflammation had increased levels of TG and decreased cholesterol levels compared with mice with acute inflammation (Table 1). NEFA, insulin, ALT, T3, and ACTH were not significantly affected by inflammation.

**DISCUSSION**

Patients with IBD (UC and CD) have an affected quality of life with altered metabolic status (12). To investigate the metabolic changes in mice that have developed acute or chronic inflammation, we used indirect calorimetry and DEXA and measured the energy content in feces and levels of different metabolic plasma markers. It was observed that mice with acute inflammation had decreased body weights, fat and lean mass, RER, and food and water intake and a tendency to lower locomotor activity and metabolic rates compared with healthy controls. In contrast, mice with chronic inflammation were recovered and had comparable RER, food intake, body weight, and lean mass to healthy control mice. However, their metabolic rates and body fat content were significantly reduced compared with healthy controls. Mice with acute and chronic inflammation had decreased intestinal nutrient uptake compared with healthy mice. The recovery or metabolic adaptation during the chronic inflammatory phase is shown by the significantly higher RER, food/water intake, and increased lean mass compared with mice with acute inflammation. Thus, mice having acute or chronic inflammation alter their metabolism as a response or adaptation to severe colonic inflammation, although there are some differences in the adaptive mechanisms between the two inflammatory phases.

Lipid metabolism is altered during an acute inflammatory response. LPS-induced inflammation causes acutely increased serum TG levels (2–24 h after administration) by mechanisms involving increased lipolysis and suppression of fatty acid oxidation (11, 19). LPS administration also causes increased total serum cholesterol levels in rodents (10, 19). Previously, it
Table 1. Plasma markers delineating metabolic changes during acute and chronic inflammation

<table>
<thead>
<tr>
<th>Plasma Marker</th>
<th>Healthy</th>
<th>Acute Inflammation</th>
<th>Chronic Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides, mM</td>
<td>0.9±0.1</td>
<td>0.6±0.1*</td>
<td>1.2±0.1‡</td>
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<tr>
<td>Cholesterol, mM</td>
<td>2.1±0.1</td>
<td>2.7±0.1*</td>
<td>1.9±0.1‡</td>
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<tr>
<td>Nonesterified fatty acids, mM</td>
<td>0.3±0.0</td>
<td>0.3±0.1</td>
<td>0.2±0.0</td>
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<tr>
<td>Glucose, mM</td>
<td>10.8±0.5</td>
<td>8.4±0.5*</td>
<td>8.5±0.5†</td>
</tr>
<tr>
<td>Insulin, nM</td>
<td>0.1±0.0</td>
<td>0.1±0.0</td>
<td>0.1±0.0</td>
</tr>
<tr>
<td>Leptin, ng/ml</td>
<td>2.5±0.6</td>
<td>0.8±0.2*</td>
<td>0.8±0.2†</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>30.3±0.4</td>
<td>23.0±0.9*</td>
<td>21.9±0.3†</td>
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<tr>
<td>Alanine aminotransferase, μkat/l</td>
<td>0.5±0.0</td>
<td>0.4±0.0</td>
<td>0.4±0.0</td>
</tr>
<tr>
<td>Thyroxine, nmol/l</td>
<td>42.8±2.4</td>
<td>18.4±3.2*</td>
<td>26.5±2.8†</td>
</tr>
<tr>
<td>Triiodothyronine, nmol/l</td>
<td>1.7±0.2</td>
<td>0.9±0.1</td>
<td>1.5±0.4</td>
</tr>
<tr>
<td>Corticosterone, ng/ml</td>
<td>102.0±12.1</td>
<td>151.3±28.7</td>
<td>58.2±4.8‡</td>
</tr>
<tr>
<td>ACTH, pg/ml</td>
<td>1,022.0±195.0</td>
<td>1,288.0±138.2</td>
<td>1,206.0±229.9</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6–12 mice/marker. Plasma was collected from healthy mice and mice with acute or chronic inflammation and analyzed for 12 metabolic markers as described in MATERIAL AND METHODS. *P < 0.05, mice with acute inflammation compared with healthy controls; †P < 0.05, mice with chronic inflammation compared with healthy controls; ‡P < 0.05, mice with chronic inflammation compared with mice with acute inflammation.
Mice with chronic inflammation had recovered food intake, water intake, and body weight comparable with healthy controls, resulting in a relatively increased lean mass, whereas fat mass and leptin levels were still reduced. It could be speculated that a contribution to the normalized lean mass in mice with chronic inflammation might be due to the enlargement of the splanchic organs, as previously reported in rats and mice (23, 24).

A similarly increased fecal energy content in the acute and chronic phases of inflammation and a reduced metabolic rate in mice with chronic inflammation, despite normalized RER and food intake, were observed. Furthermore, the reduced metabolic rate was reflected by decreased motor activity (mainly during the dark phase) and also by a downregulation of the thyroid axis with a reduction in plasma levels of T₄. However, the T₃ levels were unchanged. Thyroid hormones promote cellular metabolisms and have a calorigenic effect. The reduced levels of T₄ might, therefore, directly correlate to a state of reduced metabolic rate during a wasting (acute inflammation) or a postwasting recovery phase (chronic inflammation). Interestingly, decreased levels of T₄ have been reported in CD patients (25). Previous studies in rats have reported a dissociation between fever and colitis, suggesting that the observed changes in T₃ levels during acute and chronic inflammation are linked to the metabolic rather than to thermogenic actions of this hormone. The reduction in fat in mice with chronic inflammation is similar to the reduction in fat in CD patients with active disease (29), but underweight CD patients have a higher RER/body mass due to greater loss of fat mass and sparing of lean mass (8). The normalization/recovery of the body weight in mice with chronic inflammation might be related to an adaptation of the metabolism in response to the presence of an ongoing inflammatory pathology rather than to a normalized nutrient uptake.

Patients with IBD are at risk of developing metabolic-related bone diseases, e.g., osteoporosis (20). In the present study, we observed that only mice with chronic inflammation had decreased BMD and increased levels of osteocalcin, a marker of bone formation, which may indicate a higher bone turnover osteoporosis. A reduction in BMD has been reported in newly diagnosed and long-standing CD patients but not in UC patients (15, 16). These abnormalities in IBD patients may be due to the worsened nutritional status (malnutrition), the inflammatory process itself, or a combination of both (20). Osteopenia has been reported in other IBD models, e.g., the CD4⁺CD45RBhigh T cell transfer model (5), IL-10-deficient mice (9), and rats treated with trinitrobenzene sulfonic acid (22). We favor the idea that decreased BMD may not immediately be related to malabsorption but instead to inflammatory factors. Steroid treatment has also been shown to reduce BMD in the majority of IBD studies, although conflicting data exist (13). In the present study, methyl-prednisolone treatment of mice with chronic inflammation tended to reduce osteocalcin levels.

Overall, mice with colitis, irrespective of the state of the inflammatory condition (acute or chronic), had decreased metabolic rates, which appeared to be associated with different metabolic changes. The lower RER in mice with acute inflammation suggests that they used fat, whereas mice with chronic inflammation, to a higher extent, used carbohydrates as an energy source. Interestingly, it has been reported that CD patients use lipids as an energy source, whereas UC patients use carbohydrates (7). Taken together, these data indicate that mice in the acute phase share some metabolic similarities to CD patients, whereas mice in the chronic phase display changes toward a UC patient-type metabolism.

In conclusion, we have shown that acute and chronic colonic inflammation in mice is associated with distinct metabolic changes comparable with those observed in IBD patients. Therefore, the present colitis model not only reproduces the inflammatory response correspondent to IBD but also other metabolic alterations associated with the course of the disease. To cope with the chronic inflammatory condition, mice develop profound metabolic compensatory changes resulting in an “apparently healthy” state despite gross colon pathology.

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