Mitochondrial Electron Transport Chain Complex Dysfunction in the Colonic Mucosa in Ulcerative Colitis

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Background: Ulcerative colitis (UC) is characterized by an energy deficiency state of the colonic epithelium. This study evaluated mitochondrial electron transport chain (ETC) complex activity in normal and disease mucosa in patients with UC. Alterations in ETC complexes were also investigated in experimental colitis in mice.

Methods: Biopsies were obtained from macroscopically normal and diseased colonic mucosa of 43 patients with UC and 35 controls undergoing screening colonoscopy and ETC complex activity was assayed biochemically. ETC complex activities were also assayed in colonic epithelial cells isolated from Swiss albino mice with dextran sodium sulfate (DSS)-induced colitis at various stages of induction of colitis. Mucosal nitrite levels and protein carbonyl content were determined.

Results: The activity of Complex II was significantly decreased in colonic biopsies from UC patients compared with controls, while activities of other mitochondrial complex were normal. Complex II activity was equally decreased in diseased and normal mucosa in UC; the degree of reduction did not correlate with clinical, endoscopic, or histological grading of disease activity. In DSS-fed mice, a reduction in activity of Complex IV and Complex II was observed. Activity of other complex was not affected. Administration of aminoguanidine, an inducible nitric oxide synthase (iNOS) inhibitor, attenuated all parameters of colitis as well as the reductions in Complex IV and Complex II activity.

Conclusions: Reduction in Complex II activity appears to be a specific change in UC, present in quiescent and active disease. Mitochondrial complex dysfunction occurs in DSS colitis in mice and appears to be mediated by nitric oxide.

Key Words: ulcerative colitis, colonic mucosa, electron transport chain, mitochondrial dysfunction, nitric oxide

Abnormalities of the colonic epithelium are among the most prominent defects identified in ulcerative colitis (UC). The colonic mucosa in UC is in a state of energy deficiency characterized by low energy charge and low adenosine triphosphate (ATP) levels. ATP is produced from products of the Krebs cycle and fatty acid oxidation by the mitochondria. Mitochondrial abnormalities are observed in the colonic epithelial cells of patients with UC before other ultrastructural changes are evident in the epithelium, and well before the onset of mucosal inflammation or other light microscopic changes. The mitochondria contain the electron transport chain (ETC)—a series of four enzymes/complexes that function as electron donors and acceptors—which successively pass electrons from NADH and succinate to oxygen, which is reduced to water. Passage of electrons between these donors and acceptors releases energy. Complex I (NADH:ubiquinone oxidoreductase) accepts electrons from nicotinamide adenine dinucleotide generated in the Krebs cycle, while Complex II (succinate dehydrogenase) accepts electrons from succinate. The electrons from these two complexes pass via ubiquinone to Complex III (ubiquinol:cytochrome c oxidoreductase) and thereafter via cytochrome c to Complex IV (cytochrome c oxidase) which uses them to reduce oxygen to water. Complex V is ATP synthase, which uses the proton gradient to convert ADP to ATP. A recent study examined mitochondrial ETC complex activities in colonic mucosal biopsies from patients with UC and concluded that Complex I activity was normal, but that activity of Complex II, III, and IV were reduced in active UC. That study did not investigate relationships between disease activity and ETC complex dysfunction. Complex IV is the primary site of cellular oxygen consumption and is central to oxidative phosphorylation changes.

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and the generation of ATP. Nitric oxide (NO), an endogenously generated gas, modulates the activity of Complex IV.\textsuperscript{6} Depending on intracellular oxygen concentration, NO and Complex IV interact such that during cellular hypoxia, NO is not consumed and accumulates in the microenvironment of the cell.\textsuperscript{5} NO signaling is implicated in the pathogenesis of UC. Colonic mucosal nitric oxide synthase activity and luminal NO generation are elevated in UC.\textsuperscript{7–9} The genetic absence of inducible nitric oxide synthase (iNOS) or its pharmacological blockade significantly attenuates the severity of colonic inflammation in experimental colitis.\textsuperscript{10}

Alteration in mitochondrial complex activity could be secondary to epithelial cell damage and ulceration or it could be an early event that contributes to induction and progression of the disease. In this study we quantified mitochondrial ETC activity in colonic mucosal biopsies with the specific intent of correlating any changes with disease activity and extent. We also evaluated mitochondrial ETC activity in colonocytes isolated from mice with experimental colitis in order to study the temporal profile of change in ETC activity as well as its modulation by NO.

**MATERIALS AND METHODS**

**Human Study Participants**

The human study was approved by the institution’s Human Ethics Committee and all subjects provided informed written consent. Patients with UC who were scheduled to undergo colonoscopy were recruited from the outpatient department and the Gastrointestinal Endoscopy service as cases. Other patients who were scheduled to undergo screening colonoscopy for gastrointestinal blood loss or unexplained lower gastrointestinal symptoms were recruited as controls. Participants in the latter group were excluded from the study if they had any abnormality on colonoscopy or on colonic biopsy. The diagnosis and extent of UC was established on the basis of clinical, endoscopic, and histological criteria.\textsuperscript{11} Colonoscopy was performed after standard cleansing involving the administration of a PEG-electrolyte solution (PEGLEC, Tablets India) until the bowel return was clear. In all UC patients, three to four mucosal biopsies were taken from endoscopically abnormal areas in the rectosigmoid area 12–20 cm from the anal verge. In 14 patients with disease limited to the rectosigmoid, colonic biopsies were collected from endoscopically involved rectal mucosa as well as from endoscopically normal areas in the transverse or descending colon, remote from the margin of involvement. Latter biopsies were obtained in order to determine whether the defect in complex activity was present in both normal and ulcerated mucosa. Three to four biopsy bits were obtained from the rectosigmoid 12–20 cm from the anal verge in the control group. Mucosal biopsy specimens were snap-frozen in liquid nitrogen and stored at −80°C until use. Clinical disease severity of UC was graded by the Truelove–Witts criteria,\textsuperscript{12} and endoscopic severity of UC by the Mayo endoscopic subscore.\textsuperscript{13} Histological damage in UC was graded according to severity of crypt changes, while activity was graded according to the severity of neutrophil infiltration of the crypt mucosa (cryptitis, crypt abscess).

**Mitochondrial Complex Assays**

Mucosal biopsies were homogenized using a 0.5 mL Teflon pestle homogenizer (Kontes, Vineland, NJ) in 50 mM phosphate buffer (pH 7.0) containing 0.3 mM EDTA, and 200 μM PMSF. Assays for activities of the ETC complexes were performed spectrophotometrically using a Shimadzu UV-visible 160A spectrophotometer (Tokyo, Japan) using well-established protocols\textsuperscript{14,15} briefly described below.

**Complex I (NADH:Ubiquinone Oxidoreductase)**

Complex I activity was measured by monitoring the oxidation of NADH to NAD at 340 nm. To 20 μL of colonocyte lysate, 25 mM phosphate buffer (pH 7.2) containing 10 mM MgCl₂, 2.5 mg bovine serum albumin (BSA), 100 mM KCN, and 5 mM NADH was added. The reaction was initiated by the addition of 5 mM coenzyme Q₉, and the decrease in the optical density due to the oxidation of NADH was measured at 340 nm for 3 minutes. The NADH:ubiquinone c reductase activity was also measured in the presence of 1 mM rotenone. The enzymatic activity of Complex I was deduced from the difference between NADH oxidation activity with and without rotenone.

**Complex II (Succinate Dehydrogenase)**

The activity of succinate dehydrogenase (SDH) was measured at 600 nm by following the reduction of 2,6-dichlorophenol-indophenol (DCPIP). The reaction mixture containing 20 μL of colonocyte lysate, 100 mM KH₂PO₄, pH 7.4, 0.5 M succinate, 2.5 mM EDTA, 3 mM DCPIP, 100 mM KCN, and 1 mM rotenone was preincubated for 10 minutes at 37°C in a spectrophotometer to minimize the succinate dependent nonlinear rate. The reaction was started by the addition of 5 mM ubiquinone-2 and the optical density was recorded for 5 minutes at 600 nm. The SDH activity was also measured in the presence of 100 mM 2-thienyltrifluoroacetone (TTFA). The enzymatic activity of Complex II was deduced from the difference between DCPIP reduction with and without TTFA.

**Complex III (Ubiquinol:Cytochrome c Oxidoreductase)**

Complex III activity was measured by monitoring the reduction of ferricytochrome c at 550 nm. The reaction mixture (250 mM sucrose, 1 mM EDTA, 50 mM Tris-HCl, pH 7.4, 50 μM cytochrome C, 2 mM KCN, and 20 μg of colonocyte lysate) was incubated at 30°C for 10 minutes. Increase in absorbance was recorded after initiating the reaction by adding 50 μM decycloubiquinol. The experiment was repeated in the presence of 5 μg/mL antimycin A. The results were calculated using an initial quasilinear rate.

**Complex IV (Cytochrome c Oxidase)**

The cytochrome c oxidase activity was estimated by recording the oxidation of reduced cytochrome c at 550 nm. A 15
μM solution of reduced cytochrome c in 10 mM KH2PO4, pH 7, was preincubated for 5 minutes at 37°C. The reaction was initiated by the addition of 20 μL colonocyte lysate and the change in optical density was followed for 3 minutes at 550 nm.

**Complex V (ATP Synthase)**

Complex V activity was assayed by NADH oxidation using the coupled enzyme assay with pyruvate kinase and lactate dehydrogenase at 340 nm. The reaction mixture in a total volume of 1.0 mL contained 20 μL of colonocyte homogenate, 5 mM MgCl2, 10 mM KCl, 2 mM KCN, 0.2 mM NADH, 5 mg BSA, 2 mM phosphoenolpyruvate, 10 μM rotenone, 50 mM Tris-HCl, pH 8, 4 units lactate dehydrogenase, and 4 units pyruvate kinase. The reaction was started by the addition of 0.5 mM ATP and the absorbance was followed for 7 minutes. The reaction mixture with 3 μM oligomycin was used to determine the inhibitor-sensitive rate of mitochondrial ATPase. Complex V activity was deduced from the difference between NADH oxidation with and without oligomycin.

FIGURE 1. Mitochondrial ETC complex activities were measured spectrophotometrically in the colonic mucosa obtained from patients with UC and control subjects. Complex II (A), I (B), III (C), IV (D), and V (E). Values represented are mean ± SEM. ***P < 0.001 compared with the activity in colonic mucosa of control subjects.
Experimental Colitis in Mice

The animal study was approved by the institution’s Animal Ethics Committee. Colitis was induced in inbred Swiss albino mice (weighing 25–30 g) by the addition of 4% dextran sodium sulfate (DSS; Cat. No. 160110, MW 36000–50000, 17% sulfation, from MP Biomedicals, Mumbai, India) in the diet. The mice were fed with laboratory mouse chow and were divided into two groups, based on whether they only received DSS or DSS and aminoguanidine, as: Group I 4% DSS; Group II 4% DSS plus aminoguanidine (40 mg/kg). Aminoguanidine (AG) (a specific iNOS inhibitor) was mixed into the diet beginning 3 days before DSS administration and continuing during the period of DSS administration in order to elucidate the role of nitric oxide in modulation of ETC function. Mice in each group were sacrificed at various timepoints (0, 2, 4, and 8 days post-DSS administration). Animals were sacrificed on day 0 in both groups to serve as controls for the DSS or DSS+AG feeding. The colon was removed and colonocytes isolated by divalent cation chelation. Isolated colonocytes were homogenized on ice and centrifuged at 12,000g for 10 minutes and the supernatant was discarded. The remaining pellet was lysed in 0.75% lauryl maltoside and used for the analysis of mitochondrial electron transport chain enzyme activities as described above.

Studies with Colonocyte Mitochondria

Mitochondria were isolated from colonocytes as per the protocol of Masola and Evered with the following modifications. The colonocytes were homogenized in a buffer (pH 7.4) consisting of 250 mM sucrose / 5 mM Hepes / 1 mM EDTA.
The crude homogenate was centrifuged at 1000 g for 5 minutes at 4°C. The supernatant was centrifuged at 12,000 g for 15 minutes at 4°C to pellet the mitochondrial fraction. The pellet was washed thrice with wash buffer (pH 7.4) consisting of 250 mM sucrose / 5 mM HEPES and stored at −80°C until use. The purity of the mitochondrial fraction was assayed by comparing the activity of SDH in the nuclear and mitochondrial fractions. Mitochondrial fractions were used for study only when there was at least a 3-fold increase in SDH activity compared with the nuclear fraction.

Mitochondrial fractions from isolated colonocyte preparations were used for studying the mitochondrial complex proteins. Then 250 µg of mitochondrial protein was used for Blue Native-polyacrylamide gel electrophoresis (BN-PAGE) using a nondenaturing 5%–16.5% gradient gel to separate the individual mitochondrial complexes intact. After the run, the gels were stained using Coomassie Brilliant Blue G overnight in a cold room if a two-dimensional gel electrophoresis was not required. Two-dimensional electrophoresis was performed as mentioned earlier with some modifications. After BN-PAGE separation of mitochondrial proteins, bands corresponding to Complex II (4 days DSS-administered mice) and IV (2 and 4 days DSS-administered mice) were cut from the gel and subjected to denaturing 15%–20% Tris-Tricine SDS-PAGE to resolve their individual polypeptides based on molecular weight. Mitochondria isolated from control mice without DSS administration was used as controls. Following the denaturing SDS-PAGE, the gels were stained overnight using the Sypro Ruby fluorescent protein stain (Sigma Aldrich, St. Louis, MO) and visualized using a fluorescence gel documentation system (ChemiSmart, Vilber Lourmat, France). Densitometric analysis of the separated complex and their subunits was performed using Scion Image 4.0.2.

Measurement of NO Generation

Nitrite, the final by-product of NO, was measured in colonocyte homogenate spectrofluorometrically using diaminonaphthalene (DAN) as a substrate. Briefly, the sample was incubated with 10 µL of freshly prepared DAN (0.05 mg/mL of 0.62M HCl and incubated in dark at room temperature for 10 minutes). The reaction was stopped using 5 µL of 2.8N NaOH. Formation of 2,3-diaminonaphthotriazole was measured with excitation at 365 nm and emission at 450 nm.

Measurement of Protein Carbonyl Content

The protein carbonyl content formed was measured spectrophotometrically as described earlier using 2,4-dinitrophenyl hydrazine and calculated using an extinction coefficient of 22/mmol/cm.

Statistical Analysis

GraphPad Prism 3.02 (GraphPad Software, San Diego, CA) was used to perform statistical analysis and for graphing the data. The Mann–Whitney U-test for nonparametric data was used for determining the significance of differences between groups. A two-tailed P value <0.05 was considered significant.

RESULTS

Forty-three (32 male; mean age 42; range 18–67) UC patients were included in the study after obtaining informed consent. This included 21 patients with pancolitis, 14 patients with left-sided UC, and eight patients with proctitis. All patients were on therapy at the time of colonoscopy and biopsy and treatment included mesalazine or sulfasalazine in all, oral or rectal steroids in 25, and azathioprine in 14 patients. The disease duration in UC patients ranged from 5 weeks to 14 years. There were 35 patients (20 male; mean age 39; range 21–58) undergoing colonoscopy who were enrolled as controls. These patients were undergoing colonoscopy for investigation of bowel
symptoms or lower gastrointestinal bleeding. None of the control subjects had evidence of any endoscopic abnormality or evidence of mucosal inflammation on colonic biopsy.

ETC Activity in the Colonic Mucosa in UC

As there was a limited amount of biopsy homogenate available from each case and control, not all homogenates were used for all the complex activity assays that were done. Each figure shows the number of patients (cases:controls) from whom biopsy homogenate was used for assaying that particular activity. The activities of Complex I, III, IV, and V were similar in the diseased colonic mucosa of UC patients when compared with control biopsies (Fig. 1B–E). Interestingly, however, there was a statistically significant decrease in the activity of Complex II in the diseased UC mucosa compared with controls (Fig. 1A). This led to further investigations of the reasons for Complex II activity. In order to understand this phenomenon further, we examined Complex II activity in biopsies from the macroscopically and histologically normal mucosa of patients with limited forms of UC; we also evaluated biopsies from a large number of patients with UC for Complex II activity in order to allow subgroup analysis in patients with different degrees of disease activity, disease localization (limited versus pancolitis), and effect of concomitant medication. Complex II activity was found to be significantly decreased.

FIGURE 4. Spectrophotometric measurements of ETC complex activities in the isolated colonocytes of 4% DSS-administered mice with and without AG. Activities of mitochondrial Complex IV (A), II (B), Complex I (C), III (D), and V (E). Values represented are mean ± SEM, n = 5. *P < 0.01 compared with group I. #P < 0.01 compared with 0 day group I mice.
in the endoscopically and histologically normal colonic mucosa from patients with limited forms of colitis (Fig. 1A). Complex II activity was suppressed to similar degrees in UC regardless of clinical disease severity grade and endoscopic disease severity grade. Complex II activity was similar in patients with different grades of histological damage and with different grades of inflammatory activity histologically (Fig. 2A–D). In addition, the activity was not influenced by the nature of current treatment or the extent of the disease (Fig. 2E,F). These observations indicate that the reduced activity of Complex II was not a nonspecific phenomenon secondary to epithelial cell damage and mucosal ulceration, but very likely a feature highly specific to the disease process in UC.

ETC Complex Activities in Experimental Colitis in Mice

The feeding of DSS to mice induced significant decreases in body weight and colon length from day 4 of DSS administration onward (Fig. 3A,B). As seen in Figure 4, no significant change was evident in the activities of Complex I, III, or V (Fig. 4C–E) at any time up to 8 days after administration of DSS. However, a progressive decrease in activity of Complex IV was noted from day 2 of DSS administration (Fig. 4A) and continued till day 8. Complex II showed a significant decrease in activity from day 4 of DSS feeding and continued to progressively decrease up to day 8 (Fig. 4B). Administration of AG before and during DSS administration attenuated the decreases in body weight.
and colon length (Fig. 3A,B) as well as the changes in activity of Complex IV and Complex II (Fig. 4A,B).

One-dimensional BN-PAGE and two-dimensional SDS-PAGE of the colonic epithelial cell mitochondrial fraction did not show differences in protein expression of Complex IV (for 2 and 4 days DSS-administered mice) (Figs. 5A,B, 6A,B) and Complex II (4 days DSS-administered mice) (Fig. 6A,B) or their subunits (Figs. 5C,D, 6C–F) compared

FIGURE 6. Representative image of first-dimension BN-PAGE for mitochondria isolated from colonocytes of control and day 4 DSS-treated mice (A). The bands corresponding to Complex IV and II were cut from the first-dimension BN-PAGE gel and subjected to second dimensional analysis using SDS-PAGE (C,E). Densitometric analysis of the protein bands in the first and second dimension gels (B,D,F).
with control. This suggests that the altered complex activity was not due to decreased protein expression and likely due to posttranslational modifications in the early stage of the development of DSS colitis.

A significant increase in nitrite level was observed in colonocytes isolated from mice administered DSS for 2, 4, or 8 days and this was attenuated by coadministration of the iNOS inhibitor AG (Fig. 7A). AG administration also attenuated the decrease in Complex IV and Complex II activity induced by DSS feeding (Fig. 4A,B). Protein carbonyl content was measured as an index of oxidative stress and an increase was noted from day 4 of DSS administration. This too was prevented by coadministration of AG, suggesting that nitric oxide effects were upstream of induction of oxidative stress (Fig. 7B).

**DISCUSSION**

UC is characterized by an energy deficiency state in the colonic epithelium. The present study indicates that there is a specific reduction in mitochondrial ETC Complex II activity in the colonic mucosa of patients with UC, which is independent of disease severity or activity, and independent of disease distribution or medication.

Complex II activity was significantly reduced in UC, whereas the other complexes did not show any alteration in activity. An earlier study found that activity of Complex II, III, and IV were all reduced in mucosal biopsies from patients with UC when compared with healthy controls. The reason for the discrepant findings in these two studies is not clear. The previous study used similar substrates as this study for evaluating Complex II activity, but different substrates for the other complex activities. Furthermore, we used complex-specific inhibitors in our assays and determined the activity in the presence and absence of the inhibitors as specific demonstration of complex activity, whereas the earlier study does not mention the use of such specific respiratory complex inhibitors in their assays. Thus, we believe that the specific reduction in Complex II activity that we have documented in UC is indeed a real phenomenon, whereas the previous finding that activity of several complexes was reduced lacked specificity.

The defect in Complex II activity was independent of disease severity, clinical history, or medical treatment. The investigators in the earlier study did not evaluate their findings further by examining inflamed versus noninflamed mucosa in UC or by looking for correlations with disease activity and disease extent. Furthermore, in this study we have shown that the activity of mitochondrial Complex II is defective not only in the inflamed mucosa but also in the noninflamed or normal mucosa of patients with UC, indicating that this is likely a primary defect and is not secondary to mucosal damage. We have previously demonstrated that there is a specific decrease in the activity of mitochondrial acetoacetyl CoA thiolase (the enzyme catalyzing the final step in butyrate oxidation) in both the inflamed and noninflamed mucosa of patients with UC. We have also demonstrated increased production of H2O2 in both the inflamed and noninflamed mucosa of patients with UC compared with control mucosa. Ultrastructural examination of the colonic mucosa in UC has shown the presence of abnormal mitochondria in both inflamed and noninflamed areas. A proteomic study of the colonic mucosa in UC showed downregulation of several mitochondrial proteins including prohibitin (PHB), a major protein of the inner mitochondrial membrane that is required for normal functioning of the mitochondria. PHB was downregulated in both inflamed and noninflamed colonic mucosa. These observations are consistent with a specific mitochondrial defect in the colonic epithelium in UC, suggesting that...
mitochondrial abnormalities are important factors in the pathogenesis of UC.

The impaired activity of mitochondrial acetoacetyl CoA thiolase and mitochondrial Complex II are likely to lead to decreased energy levels in the colonic mucosa in patients with UC. In the energy deficiency hypothesis of UC, decreased cellular ATP is likely responsible for epithelial cell necrosis with resultant ulceration leading to mucosal inflammation. Although the cellular pathways for this in UC have not been investigated, studies in other tissues suggest that cellular energy deficiency can result in necrosis via multiple pathways including perturbation of membrane permeability, activation of the endoplasmic reticulum unfolded protein response, and activation of the autophagic lysosomal pathway.

DSS colitis is a model of UC, but could differ from human UC in many respects. The earliest detectable change upon DSS feeding is shortening of crypts without pronounced inflammation at day 2, followed by inflammatory changes and focal crypt loss on day 4, and extensive crypt loss and mucosal inflammation by day 8 (Fig. 8A–D). Reduced Complex IV activity was evident after 2 days of DSS feeding, and of Complex II after 4 days of DSS feeding. These data suggest that alteration in mitochondrial Complex IV activity could be involved in the initiation of colonic injury in DSS colitis. Since these changes were attenuated by AG, a specific inhibitor of iNOS, it is possible to speculate that the alteration in Complex IV activity was related to excess NO. Nitrite levels were elevated in the colonocyte fraction and AG reduced NO levels as well as parameters of oxidative stress, thus suggesting that both NO and oxidative stress may contribute to the genesis of altered activity of the mitochondrial complexes and to mucosal damage in this model. In DSS colitis, it appeared that altered mitochondrial respiratory complex activity was not due to changes in the level of protein expression, and therefore appear more likely to be due to posttranslational modifications. This was not specifically examined, but is consistent with the hypothesis that NO and oxygen free

FIGURE 8. Representative photomicrographs of mouse distal colon with and without 4% DSS administration. Day 0: control mice (A). Day 2: Absence of inflammation or crypt loss (B). Day 4: Infiltration and crypt loss (C). Day 8: Complete loss of crypt architecture (D).
radicals are involved. Inducible NOS is constitutively expressed in epithelial cells in the human colon. However, the present study did not examine its role in the pathophysiology of altered Complex II activity in human UC.

In conclusion, this study demonstrated a specific reduction in activity of mitochondrial Complex II in the colonic mucosa that is likely to contribute to the energy deficiency state of the colonic epithelium in UC. Mitochondrial dysfunction was an early event during the development of DSS colitis in mice, and NO appears to play a role in its genesis. Further investigation into the origin and significance of the mitochondrial dysfunction in UC appears to be warranted.

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