ROLE OF NEUTROPHILS IN ACETIC ACID-INDUCED COLITIS IN RATS

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Abstract—Intrarectal administration of 4% acetic acid produces diffuse inflammation that ultimately results in erosions and ulcerations of the rat colon. Although this model of colitis has been used extensively over the past several years, there are no quantitative data available regarding the relationship between neutrophil infiltration and mucosal injury during times of active inflammation. Therefore, the objective of this study was to define the role of extravasated neutrophils as mediators of mucosal injury and inflammation in acetic acid-induced colitis. We found the intrarectal administration of 4% acetic acid produced a 11-fold increase in colonic mucosal permeability, a 9-fold increase in colonic MPO activity, and a 1.6-fold increase in colon weight at 48 h following administration of acetic acid. In addition, we found significant correlations between colonic MPO activity and mucosal permeability and between colonic MPO activity and colon weight (P < 0.01 for both). These data suggested that inflammatory neutrophils may mediate mucosal injury and inflammation in this model of colitis. To assess the role of circulating neutrophils, rats were rendered neutropenic for 48 h by the intraperitoneal administration of antiserum directed toward rat neutrophils (ANS). Although ANS treatment reduced both the number of circulating neutrophils and colonic MPO activity to less than 10% of control values, it did not attenuate the increases in colonic mucosal permeability nor did it attenuate the increases in colon weight produced by acetic acid. Histological inspection confirmed that ANS treatment was not effective in attenuating the injury to the epithelial barrier. These data demonstrate that infiltrating neutrophils do not mediate the mucosal injury and inflammation observed in acetic acid-induced colitis.

INTRODUCTION

Ulcerative colitis (UC) is a diffuse, recurrent inflammation of the colon and rectum of unknown etiology that affects predominantly the colonic mucosa.

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Active episodes of UC are characterized by the infiltration of large numbers of neutrophils into the mucosal interstitium (lamina propria). This enhanced inflammatory infiltrate is accompanied by extensive mucosal injury, including disruption of the extracellular matrix, edema, epithelial cell necrosis, and ultimately erosions and ulcerations (1). The apparent association between neutrophil infiltration and mucosal damage suggests that neutrophils may play an important role in the pathogenesis of UC (2–4). Normally, neutrophils are protective by virtue of their ability to extravasate from the circulation, engulf, and destroy invading microorganisms. However, these phagocytes may become inadvertently activated by the interaction of certain ligands (e.g., immune complex, bacterial products, complement components) with specific receptors on the neutrophil plasma membrane. This metabolic activation results in the production and release of large quantities of potentially cytotoxic reactive oxygen metabolites, such as superoxide, hydrogen peroxide, hypochlorous acid, and N-chlorinated derivatives (5). In addition, activated neutrophils secrete a variety of proteases (e.g., elastase, collagenase, gelatinase) and hydrolytic enzymes (e.g., hyaluronidase) capable of degrading the interstitial matrix and epithelial cell membrane (6).

There are several different experimental models of colitis produced in rats, rabbits, and guinea pigs (7, 8). Virtually all of these models require the intraluminal administration of caustic agents (e.g., organic acids, ethanol, formalin) to initiate the inflammatory response. One model that has received substantial attention over the past few years is acetic acid-induced colitis (2, 9–14). This model, originally developed by MacPherson and Pfeiffer (10), uses the intrarectal administration of dilute solutions of acetic acid to produce a diffuse colitis in rats. Although the inflammation produced in this model of colitis is not identical to human ulcerative colitis, it does have some histological similarities to human UC, including epithelial cell necrosis, decreased mucin production, crypt abscesses, and infiltration of large numbers of neutrophils into the mucosal interstitium (10). Furthermore, it has been shown that the pattern of mucosal arachidonate metabolism produced by acetic acid is very similar to that found in biopsies obtained from human UC (12, 15). It has been suggested that inflammatory neutrophils may be responsible for generation of the arachidonate metabolites, leukotriene B_4, and 5-hydroxycicosatetraenoic acid in this model of colitis (12, 15). Although recent studies suggest an association between neutrophils and mucosal injury, there has been no systematic study to define the role of these phagocytes as mediators of mucosal injury and inflammation in this model of inflammation (2, 9). Therefore, the objective of this study was to define, using quantitative measures of mucosal injury and inflammation, the role of extravasated neutrophils in acetic acid-induced colitis in rats.