MECHANISMS OF ACUTE AND CHRONIC INTESTINAL INFLAMMATION INDUCED BY INDOMETHACIN

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Abstract—The objective of this study was to characterize the mechanisms of acute and chronic intestinal mucosal injury and inflammation induced by subcutaneously injected indomethacin (Indo). One injection of Indo (7.5 mg/kg) produced acute injury and inflammation in the distal jejunum and proximal ileum that were maximal at three days and completely resolved within one week. Two daily subcutaneous injections of Indo produced a more extensive and chronic inflammation that lasted in an active form in more than 75% of the rats for at least two weeks. Epithelial injury, as measured by enhanced mucosal permeability, was significantly elevated only at one day in the acute model (one injection) but was persistently elevated in the chronic model (two injections). Bile duct ligation completely attenuated increased mucosal permeability in the acute model, however, depletion of circulating neutrophils had no effect. Neither Indo (0-0.1 mg/ml) nor normal bile was cytotoxic to cultured rat intestinal epithelial cells; however, they synergistically promoted significant cytotoxicity. Bile collected from rats treated with Indo was cytotoxic towards the epithelial cells in a dose-dependent manner. Sulfasalazine and metronidazole (100 mg/kg/day, both) attenuated enhanced mucosal permeability in the chronic model. Massive bacterial translocation into the mesenteric lymph nodes, liver, and spleen following two injections of Indo was significantly attenuated by metronidazole. We conclude that:

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(1) a single injection of Indo produces acute intestinal mucosal injury and inflammation that resolve completely within three to seven days, whereas two daily injections of Indo produce both acute and chronic injury and inflammation, (2) enterohepatic circulation of Indo is important in promoting the acute phases of injury and inflammation, (3) circulating neutrophils do not play a role in the pathogenesis of this model, and (4) endogenous bacteria play an important role in exacerbating and/or perpetuating the chronic phases of injury and inflammation.

INTRODUCTION

Chronic administration of certain nonsteroidal antiinflammatory drugs (NSAIDs) such as indomethacin to humans or acute administration to experimental animals produces gastrointestinal inflammation. Approximately 70% of patients taking therapeutic doses of NSAIDs for more than six months exhibit increased small intestinal mucosal permeability and blood loss (1). Sublethal doses of Indo produce chronic inflammation of the distal jejunum and proximal ileum that persists for up to six weeks in outbred strains of rats (e.g., Sprague-Dawley) (2) or for more than 11 weeks in genetically susceptible (Lewis) rats (3). This Indo-induced enteritis is characterized by linear ulcerations, thickening of the small intestine and mesentery, adhesions, partial obstructions, acute and chronic transmural granulomatous inflammation, crypt abscesses, and fibrosis in susceptible rat strains (4). These lesions share clinical, histological, and pathophysiological characteristics with Crohn’s enteritis (2, 4–6).

Although the mechanisms by which Indo causes gastrointestinal inflammation have not been fully elucidated, several important pathogenetic factors have been suggested. Inhibition of protective prostaglandins (PGs) such as PGE₁, PGE₂, and prostacyclin (PGI₂) may be one mechanism by which Indo induces injury and inflammation (4, 7, 8). The enterohepatic circulation of bile and Indo may also be important in that bile duct ligation attenuates high-dose Indo-induced intestinal perforation and death (6, 9). In addition, bacteria, bacterial products, and food intake have been demonstrated to be important for the development of intestinal lesions (10–13) and genetically determined host susceptibility determines chronicity of inflammation (3). More recent studies have implied that neutrophils and neutrophil-derived oxidants are involved in the pathogenesis of Indo-induced acute gastropathy (14–16) as well as the microcirculatory disturbances associated with Indo administration (17, 18). However, the mechanisms responsible for the initiation and perpetuation of Indo-induced enteropathy appear to be quite different from Indo-mediated gastropathy since bile and bacteria are important determinants in the enteropathy but not gastropathy. We hypothesize that mechanisms responsible for acute injury vs. chronic inflammation induced by Indo are also very different. Furthermore, we submit that some of the controversy surrounding the pathogenesis of Indo-induced intestinal inflammation...