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The effect of thalidomide on ethanol-induced gastric mucosal damage in mice: Involvement of inflammatory cytokines and nitric oxide

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ABSTRACT

Excessive ethanol ingestion causes gastric mucosal damage through the inflammatory and oxidative processes. The present study was aimed to evaluate the protective effect of thalidomide on ethanol-induced gastric mucosal damage in mice. The animals were pretreated with vehicle or thalidomide (30 or 60 mg/kg, orally), and one hour later, the gastric mucosal injury was induced by oral administration of acidified ethanol. The animals were euthanized one hour after ethanol ingestion, and gastric tissues were collected to biochemical analyzes. The gastric mucosal lesions were assessed by macroscopic and histopathological examinations. The results showed that treatment of mice with thalidomide prior to the administration of ethanol dose-dependently reduced the gastric ulcer index. Thalidomide pretreatment significantly reduced the levels of pro-inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6], malondialdehyde (MDA) and myeloperoxidase (MPO) activity. In addition, thalidomide significantly inhibited ethanol-induced nitric oxide (NO) overproduction in gastric tissue. Histological observations showed that ethanol-induced gastric mucosal damage was attenuated by thalidomide pretreatment. It seems that thalidomide as an anti-inflammatory agent may have a protective effect against alcohol-induced mucosal damage by inhibition of neutrophil infiltration and reducing the production of nitric oxide and inflammatory cytokines in gastric tissue.

1. Introduction

Peptic ulcer disease is a common gastrointestinal disorder and is an important health problem in worldwide. The pathophysiology of gastric mucosal injury results from an imbalance between protective factors and aggressive factors. Various damaging agents are involved in the pathogenesis of gastric mucosal injury, including alcohol intake, gastric hydrochloric acid, free oxygen radicals, non-steroidal anti-inflammatory drugs (NSAIDs), stress, and Helicobacter pylori infection [1,2]. It is well known that ethanol causes acute gastric mucosal injuries through different mechanisms, including gastric microcirculatory disturbances, disruption of the gastric mucosal barrier and gastric epithelial cell damage [3,4]. Alcohol can trigger some of the acute inflammatory pathways leading to gastric mucosal injury [5]. It has been shown that neutrophil infiltration into the gastric mucosa has a critical role in the development of gastric mucosal inflammation and damage. Infiltration of neutrophils and mononuclear cells into the gastric mucosa during inflammation stimulates the synthesis and release of several pro-inflammatory mediators. It has been shown that some pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-8 and IL-10 are involved in the pathogenesis of alcohol mediated mucosal injury [6–9]. NO plays an important role in regulating physiological functions of gastrointestinal tract, however, NO has been implicated as a contributor to tissue injury in the gastrointestinal tract during inflammatory responses. Thus, NO appears to have a dual role in the inflammatory processes [10,11].

A number of compounds with anti-inflammatory activity have been studied to prevent the gastric mucosal injury induced by ethanol in animal models [7–9]. Thalidomide (α-N-phthalimido glutarimide) as an anti-inflammatory agent is effective in the treatment of inflammatory disorders. Thalidomide is a glutamic acid derivative that was first introduced in 1956 as a sedative drug but was withdrawn from clinical use in 1962 due to its teratogenic effects. Thalidomide is now used as a treatment for cutaneous lesions associated with erythema nodosum leprosum (ENL) and multiple myeloma. Thalidomide causes some adverse effects, particularly teratogenicity and peripheral neuropathy. New structural analogues of thalidomide have been developed in order to improve therapeutic efficacy and reducing side effects [12]. Several studies

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