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Methylsulfonylmethane is effective against gastric mucosal injury

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ABSTRACT

Methylsulfonylmethane (MSM) is a natural organosulfur compound has been widely used as a dietary supplement. MSM has protective effects against various disorders through its anti-inflammatory and antioxidant properties however the effect of MSM on gastric mucosal injury remains unclear. The aim of the present study is to determine whether MSM has beneficial effects on ethanol/HCl-induced gastric ulcer in mice. Macroscopic and histopathological evaluation of gastric mucosa revealed that ethanol/HCl administration produced apparent mucosal injuries, while pretreatment with MSM (200 and 400 mg/kg, orally) could effectively protect gastric mucosa against the injuries caused by acidified ethanol. MSM significantly increased the levels of glutathione (GSH), catalase (CAT) and prostaglandin E_2 (PGE_2), and decreased the levels of malondialdehyde (MDA), myeloperoxidase (MPO), carbonyl protein, and nitric oxide (NO) in gastric tissues compared with those in the ethanol group. MSM suppressed gastric inflammation by reducing the levels of proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, monocyte chemoattractant protein (MCP)-1 and matrix metalloproteinase (MMP)-9. Moreover, pretreatment of mice with MSM decreased the expression of nuclear factor kappa B (NF-κB) as a key regulator of inflammation in gastric mucosa. Taken together, these data suggest that MSM is able to decrease the severity of ethanol/HCl-induced gastric mucosal injury through inhibition of oxidative stress and inflammation.

1. Introduction

Peptic ulcer is a chronic multifactorial disease of the gastrointestinal tract that affects the mucosal lining of the stomach. The pathophysiology of gastric mucosal injury results from an imbalance between defensive factors, such as gastric mucus, bicarbonate and prostaglandin E, and aggressive factors such as gastric acid, pepsin, non-steroidal anti-inflammatory drugs (NSAIDs), alcohol and Helicobacter pylori infection (Pérez et al., 2017). It has been demonstrated that alcohol consumption causes gastric mucosal injury through direct effects such as gastric epithelial cell damage and indirect effects such as the recruitment of leukocytes and induction of inflammation and oxidative stress (Kang et al., 2017). Ethanol metabolism results in the production of large amounts of reactive oxygen species (ROS) including the superoxide radicals, hydrogen peroxide and peroxynitrite. Ethanol also significantly diminishes the levels of antioxidant agents that can remove ROS. The imbalance between the formation and removal of free radicals plays an important role in the pathogenesis of gastric mucosal damage (Yu et al., 2014; Amirshahrokhi and Khalili, 2016a). It has also been shown that infiltration of neutrophils into the gastric mucosa and release of proinflammatory cytokines such as TNF-α, IL-1β, IL-6 and chemokine MCP-1 have a critical role in the development of gastric mucosal inflammation and injury (Amirshahrokhi and Khalili, 2015a; Watanabe et al., 2004). Nuclear factor-kappa B (NF-κB) is an important transcription factor that regulates inflammatory processes in gastric mucosal damage (Arab et al., 2015). Prostaglandin E (PGE) has been shown to protect gastric mucosa from gastric irritants and the decreased formation of PGE aggravates peptic ulcer disease (Hoshino et al., 2003). In the recent few years, many alternative medicines from natural resources are considered for treatment of gastric ulcer disease (Boeing et al., 2016; Sidahmed et al., 2013).

Methylsulfonylmethane (MSM) or dimethyl sulfone is a natural organosulfur compound (Fig. 1A) found in many green plants, fruits, vegetables and grains. MSM is widely used as a dietary supplement in worldwide and is believed to be nontoxic to humans. MSM is considered as an important source of sulfur for the production of the sulfur-containing amino acids methionine and cysteine. Clinical and experimental studies have shown potential preventive and therapeutic effects of this compound. MSM has not been approved by FDA however it has no toxicity in human studies and is generally recognized as safe by the FDA. MSM has been shown to possess strong antioxidant and anti-inflammatory activities in many studies (Amirshahrokhi and

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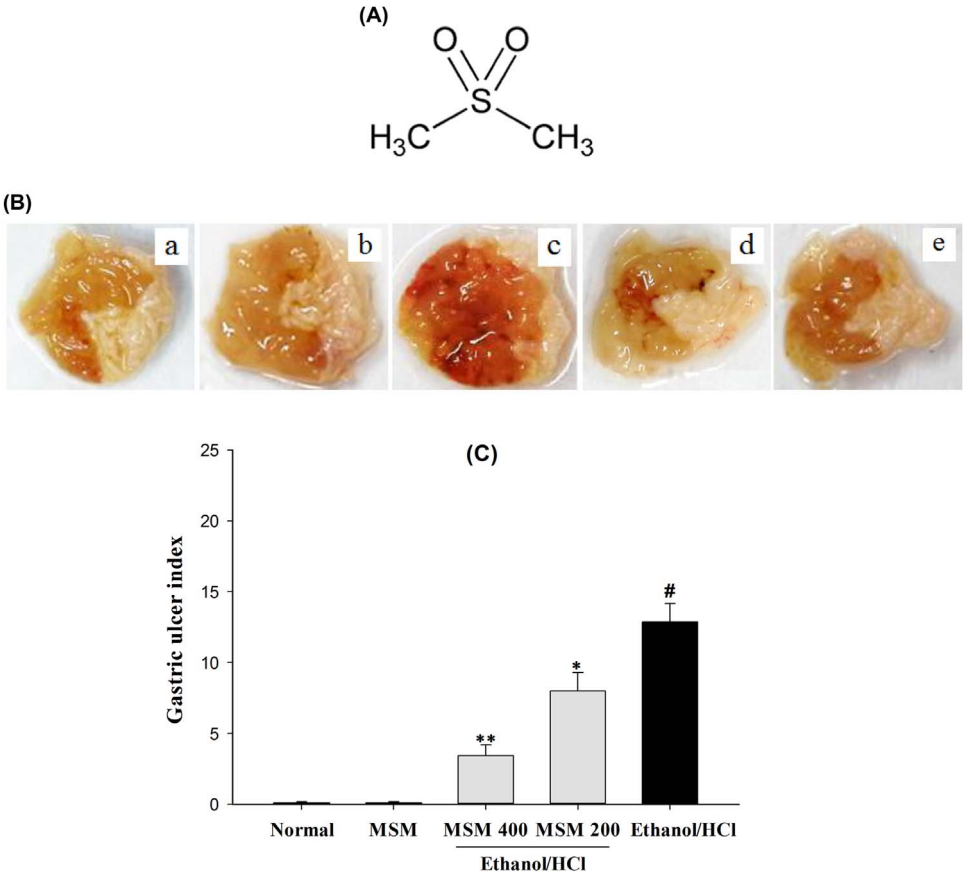

Fig. 1. (A) Chemical structure of MSM (B) Effect of MSM on the macroscopic appearance of the gastric mucosa in ethanol/HCl-induced gastric mucosal lesions in mice. (a) Normal, (b) MSM (400 mg/kg) only, (c) ethanol/HCl, (d) MSM (200 mg/kg) + ethanol/HCl and (e) MSM (400 mg/kg) + ethanol/HCl. (C) gastric ulcer index in each experimental group. The results are the mean ulcer score ± S.E.M. (n = 8). $^{\#}P < 0.001$ compared with normal group; $^{*}P < 0.05$, $^{**}P < 0.01$ compared with ethanol/HCl control group.

Bohlooli, 2013). It has been reported that MSM improves symptoms of pain and physical function in patients with knee osteoarthritis (Kim et al., 2006). MSM has been shown to protect against obesity-induced metabolic disorders, constipation, hyperacidity, mucous-membrane inflammation, intestinal cystitis, colitis and liver damages through its anti-inflammatory and antioxidant properties (Sousa-Lima et al., 2016; Parcell, 2002; Amirshahrokhi et al., 2011).

We hypothesized that, because of its antioxidant and anti-inflammatory effects, MSM may prevent gastric mucosal injury. In this study, we investigated the possible effectiveness and the mechanisms of action of MSM on ethanol/HCl-induced gastric ulcer in mice.

2. Material and methods

2.1. Animals

Experiments were performed on Swiss albino mice weighing 25–30 g. Animals were kept in our animal house under controlled conditions and allowed free access to water and a standard diet. Mice were fasted overnight with free access to water before the induction of gastric ulcers. Animal experiments were conducted in accordance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals (NIH publication 85-23, revised 1996). Study protocol (1395.129) was approved by the animal ethics committee.

2.2. Materials

2,4-dinitrophenylhydrazine, guanidine hydrochloride, trichloroacetic acid, potassium phosphate and Tris–HCl, 5,5′-Dithiobis-2-nitrobenzoic acid, tetramethylbenzidine, thiobarbituric acid, glutathione reduced, 1,1,3,3-tetraethoxypropane, hydrochloric acid, hydrogen peroxide and methylsulfonylmethane were purchased from Sigma-Aldrich. Protease inhibitors (Complete Mini tablets) were purchased from Roche (Germany).

2.3. Experimental design

Administration of ethanol/HCl has long been used as an experimental model to induce gastric mucosal lesions in mice. This model has many clinical and pathophysiologic similarities to human peptic ulcer disease (Lu et al., 2014; Oliveira et al., 2012). The animals were randomly divided into five groups (8 mice per group). The first group served as normal control group and received vehicle only (0.9% saline, orally). The second group of mice was given MSM (400 mg/kg, orally) alone. The third group of mice was given a single dose of acidified ethanol orally. The fourth group was given MSM (200 mg/kg, orally) and acidified ethanol. The fifth group was given MSM (400 mg/kg, orally) and acidified ethanol. MSM was dissolved in saline and administered by gavage 1 h before ulcer induction. After pretreatment with MSM the animals received acidified ethanol (60% ethanol/0.15 M HCl, 0.1 ml/10 g body weight, orally) to induce gastric mucosal damage. The dose of MSM used in this study was selected based on our preliminary experiments.

2.4. Sample collection

One hour after administration of ethanol/HCl all animals were anesthetized with ketamine and xylazine and their stomachs were immediately removed. The stomachs were opened along the greater curvature and rinsed with cold saline solution to remove the gastric