

Anti-inflammatory and antioxidant effects of dimethyl fumarate in an experimental model of inflammatory bowel disease

G.Casili¹, D.Impellizzeri¹, G.Bruschetta¹, I. Paterniti¹, S.Cuzzocrea^{1,2}, E.Esposito¹

¹Dept. of Biological and Environmental Science, University of Messina

²Dept. of Pharmacological and Physiological Science, Saint Louis University School of Medicine, 1402 South Grand Blvd, St Louis, MO 63104, USA

Inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis are poorly understood disorders affecting the intestinal tract. Oxidative stress and inflammatory response are thought to promote intestinal damage. Fumaric acid esters (FAEs) have proven their therapeutic efficacy in moderate to severe psoriasis. The efficacy of FAEs in psoriasis may therefore be mediated by immunomodulatory mechanisms, which might also play a role in the treatment of other inflammatory diseases. Several anti-inflammatory effects of FAEs have been suggested, including suppression of adhesion molecules and inhibition of cytokines production. The most pharmacologically effective molecule among the FAEs is dimethyl fumarate (DMF). DMF is a new orally available disease-modifying agent that was recently approved by the US FDA and the EMA for the management of relapsing forms of multiple sclerosis. The aim of this study was to examine the effects of DMF in mice subjected to experimental colitis. Colitis was induced in mice by intracolonic instillation of 2,4 dinitrobenzene sulfonic acid (DNBS), 4 mg/mouse. DMF was administered daily at 10, 30 and 100 mg/kg orally. On day 4, animals were sacrificed and descending and sigmoid colon tissues were taken for biochemical and histological analysis. Four days after DNBS administration, the increased production of colon tumor necrosis factor (TNF)- α and interleukin (IL)-1 β was associated with colon damage. Neutrophil infiltration, by myeloperoxidase (MPO) activity, in the mucosa was related to an up-regulation of adhesion molecules (ICAM-1 and P-selectin) in DNBS-injured mice. Immunohistochemistry for colon TNF- α expression also showed an intense staining in damaged tissues. Biochemical analysis was used to investigate matrix metalloproteinases (MMP)-9 and -2 in colon tissues from DNBS-injured mice. Treatment with DMF significantly reduced macroscopic damage score, the appearance of diarrhea, loss of body weight, MPO activity and lipid peroxidation. Moreover, the intensity of the positive staining for TNF- α and IL-1 β was reduced by DMF treatment. DMF significantly reduced the nuclear translocation of NF-kappaB p65 and degradation of I κ B- α . Activation of MMP-9 and MMP-2 pro-active form was lowered by DMF. DMF also modified up-regulation of ICAM-1 and the expression of P-selectin. In addition, treatment with DMF caused a decrease in superoxide dismutases Mn-SOD. Anti-inflammatory and antioxidant effects were more evident in animals treated with DMF at 100mg/kg. The results of this study suggest that administration of DMF, particularly at the dose of 100mg/kg, induces anti-inflammatory and antioxidant mechanisms, which potentially may be beneficial for the treatment of IBD in humans.