PROTECTIVE ROLE OF 15-deoxy-$D^{12,14}$ PROSTAGLANDIN J_2 IN AN EXPERIMENTAL MODEL OF COLITIS IN THE RAT

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Inflammatory bowel disease (IBD) is characterised by oxidative and nitrosative stress, leukocyte infiltration, and increased expression of the adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and P-selectin in the colon (1-3). Recent evidence also suggests that the cyclopentenone prostaglandin (PG) 15-deoxy-Ä^{12,14} PGJ_2 (15d-PGJ_2), which is a metabolite of the prostaglandin D_2, functions as an early anti-inflammatory signal (4,5). In the present study we have investigated the effects of 15d-PGJ_2 in rats subjected to experimental colitis. Colitis was induced in rats by intra-colonic instillation of dinitrobenzene sulfonic acid (DNBS). Rats experienced hemorrhagic diarrhoea and weight loss. At 4 days after administration of DNBS, the mucosa of the colon exhibited large areas of necrosis. Neutrophil infiltration [determined by histology as well as an increase in myeloperoxidase (MPO) activity in the mucosa] was associated with increased expression of ICAM-1 as well as high tissue levels of malondialdehyde. Immunohistochemistry for nitrotyrosine and poly (ADP-ribose) polymerase (PARP) showed an intense staining in the inflamed colon. Furthermore, expression of inducible nitric oxide synthase (iNOS) was found mainly in macrophages located within the inflamed colon of DNBS-treated rats. 15d-PGJ_2 (given at 20 or 40 mg/kg i.p. daily) significantly reduced the degree of hemorrhagic diarrhoea and weight loss caused by administration of DNBS. 15d-PGJ_2 also caused a substantial reduction of (i) the activation of NF-kB, (ii) the degree of colonic injury, (iii) the rise in MPO activity, (iv) the increase in the tissue levels of malondialdehyde, (v) the increase in staining for iNOS, nitrotyrosine and PARP, as well as (vi) the increased expression of ICAM-1 caused by DNBS in the colon. Furthermore, 15d-PGJ_2 stimulates the activation of heat shock protein 72 in the inflamed colon. Thus, 15d-PGJ_2 reduces the development of experimental colitis. Therefore, the cyclopentenone prostaglandin 15d-PGJ_2 may be useful in the therapy of IBD.

References

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