THE NK_1 RECEPTOR ANTAGONIST SSR140333 AMELIORATES EXPERIMENTAL COLITIS IN RATS

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Introduction: Inflammatory bowel disease is characterized by increased visceral perception and nociception. Several lines of evidence showed that inflammation is associated with changes in the expression of tachykinins both in human and animal models. Tachykinins, including substance P (SP), are small peptides expressed in the extrinsic primary afferent nerve fibres and enteric neurons of the gut: they exert their action through three distinct receptors, termed NK_1, NK_2 and NK_3. SP modulates intestinal motility and enteric secretion, acting preferentially through the NK_1 receptor. SP neural network and NK_1 receptor expression are increased in patients with inflammatory bowel disease, and similar changes were observed in experimental models of inflammation. **Aim:** To investigate the possible protective effect of the NK_1 receptor antagonist SSR140333 on experimental colitis. **Methods:** Colitis was induced in male SD rats by intrarectal administration of 2,4 Dinitrobenzene Sulphonic Acid (DNBS). SSR140333 (10 mg/kg) was administered orally starting from the day before the induction of colitis for 7 days. Colonic damage was assessed by means of macroscopic and microscopic scores and myeloperoxidase activity (MPO) on day 6 after induction of colitis. Statistical analysis was performed using analysis of variance (one-way or two-way, as appropriate) with the Bonferroni's correction for multiple comparisons. **Results:** DNBS administration impaired body weight gain and markedly increased all inflammatory parameters ($p<0.01$ vs non-inflamed group). SSR140333 10 mg/kg significantly counteracted the impairment in body weight gain, decreased macroscopic and histological scores and reduced colonic myeloperoxidase activity (Table 1). Similar results were obtained administering the NK_1 receptor antagonist SSR140333 (3 and 10 mg/kg) for 5 days, starting the day after the induction of colitis.

Treatment	Weight gain (%)	Macr. score	Micr. score	MPO (U/mg)
Intrarectal DNBS (n=8)	9.0 ± 3.5	6.4 ± 0.8	4.5 ± 0.6	29.4 ± 7.2
DNBS+SSR 10 mg/kg (n=8)	18.4 ± 1.6*	2.0 ± 0.4*	1.8 ± 0.5*	5.1 ± 1.9*

* $p < 0.01$ vs DNBS

Conclusions: Treatment with SSR140333 showed a protective effect in DNBS-induced colitis. These results support the hypothesis of SP involvement in intestinal inflammation and indicate that NK_1 receptor antagonist may have a therapeutic potential in inflammatory bowel disease.