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Effect of neurokinin 1 (NK1) receptor antagonism and the differential role of NK1 receptors in dextran-sulfate (DSS) induced colitis in mice

I Szitter[1], E Pintér[1], A Perkecz[1], Á Kemény[1], C Pietra[2], J Quinn[3], A Zimmer[4], A Berger[5], Zs Helyes[1].
[1]University of Pécs, Department of Pharmacology and Pharmacotherapy, 7624, Hungary, [2]Helsinn Healthcare SA, Preclinical R&D, Pambio-Noranco, Lugano, Switzerland, [3]Liverpool University, School of Biomedical Sciences, UK, [4]Institute of Molecular Psychiatry, University of Bonn, Germany, [5]University Health Network, Ontario Cancer Institute, Canada

Background: Previous data have shown that the tachykinin system is involved in the regulation of inflammatory processes of the gastrointestinal tract, but the mechanisms have not yet been clarified. Data on the role of the neurokinin 1 (NK1) receptor, which is the primary target of substance P, are contradictory. Therefore, the aim of the present study was to investigate the functions of NK1 receptors in the DSS induced mouse colitis model using genetic deletion of the receptor, as well as selective pharmacological antagonism.

Methods: Dextran-sulfate (2%) solution was administered orally for 7 days to C57Bl/6 and NK1 receptor KO animals (n=5-7 per group, female animals, age 6-8 weeks) to induce colitis. During the induction, one half of the C57Bl/6 group received netupitant (potent NK1 receptor antagonist) in 3mg/kg or 6mg/kg, daily i.p. doses, respectively. NK1 receptor deficient mice were used to evaluate the neurokinin 1 receptor blockade of netupitant. Overall disease activity status was monitored on a daily basis (body weight, fecal blood, stool consistency) and scored, Disease activity index (DAI) was expressed as a means of these scores. After 7 days, mice were sacrificed under ketamine-xylazine anaesthesia, and tissue samples were collected. Histological evaluation (semiquantitative scoring), myeloperoxidase activity, cytokine measurement and receptor expression analysis were performed.

Results: Netupitant treatment decreased the disease activity index in general and the 6 mg/kg dosage was most efficient (saline: 1,933 ± 0,386 vs. 6 mg/kg netupitant: 0,524 ± 0,190, two-way ANOVA, Bonferroni post test). The histological scoring correlated with this finding (P value: 0,0141, sum of rank: C57Bl/6 DSS: 54,50, netupitant 6 mg/kg: 23,50, Mann-Whitney U value: 2,5, Mann-Whitney U-test). On the other hand, the myeloperoxidase activity was decreased significantly in the 3 mg/kg netupitant-treated group (C57Bl/6 DSS: 407,8 ± 43,16 unit/g tissue; netupitant 3 mg/kg: 128,4 ± 28,68 unit/g tissue) but the higher dose did not alter the MPO levels significantly, compared to the saline treated group (unpaired t-test with Welch correction). Surprisingly, the IL-1beta and MPO levels were higher in the NK1 receptor KO DSS-treated group compared to the C57Bl/6 DSS- treated controls (IL1beta: C57Bl/6 DSS: 269,2 ± 41,79 pg/mg tissue; NK1KO DSS: 726,6 ± 206,5 pg/mg tissue; MPO: C57Bl/6: 407,8 ± 43,16 unit/g tissue, NK1KO: 511,0 ± 61,09 unit/g tissue) but 3 mg/kg netupitant reduced the IL-1beta level. Receptor expression study of C57Bl/6 DSS-treated animals showed that not only NK1 but NK2 and NK3 receptors are also up-regulated in DSS-induced colitis.

Conclusions: The increased expression of NK2 and NK3 receptors may explain the contradictory results at MPO and IL-1beta levels in NK1 receptor KO animals. It seems that NK1 receptor antagonism could be beneficial in colitis but NK2 and NK3 receptors might also play role in inflammatory processes.