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MEETING ABSTRACT

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Lack of galanin receptor 3 but not receptor 2 influences inflammation and fecal microbiota during DSS-induced colitis

Susanne M. BRUNNER[1], Florian REICHMANN[2], Soraya WÖLFL[3], Gernot REIFENBERGER[4], Aitak FARZI[2], Markus M. HEIMESAAT[4], Peter HOLZER[2] and Barbara KOFLER[1]

[1]*Research Program for Receptor Biochemistry and Tumor Metabolism, Paracelsus Medical University, Salzburg, Austria;* [2]*Research Unit of Translational Neurogastroenterology, Otto Loewi Research Center, Division of Pharmacology, Medical University of Graz, Austria;* [3]*Private Pathological Laboratory, Salzburg, Austria;* [4]*Institute of Microbiology, Infectious Diseases and Immunology, Charité – University Medicine Berlin, Germany*

Background: The interaction of neurogenic and inflammatory processes contributes to the pathogenesis of inflammatory bowel disease (IBD). The regulatory peptide galanin (GAL) is widely distributed and mediates its effects via three G protein-coupled receptors ($GAL_{1–3}$). GAL and $GAL_{1–3}$ receptors are expressed in different immune cells and GAL is able to modulate immune cell function *in vitro*. In acute trinitrobenzenesulfonic acid (TNBS)-induced colitis GAL treatment improved mucosal damage and in dextran sulfate sodium (DSS)-induced colitis GAL increased colonic fluid secretion. Here, we use GAL_2-KO and GAL_3-KO mice to evaluate the role of these receptors in IBD.

Methods: 8–12-weeks-old mice [GAL_3-KO, GAL_2-KO and corresponding wild types (WT); $n = 9–11$] were treated for 7 days with 2% DSS added to the drinking water. At day 7 of treatment a disease activity score (DAS), including loss of body weight, stool consistency and presence of blood in the perianal region, was calculated. Intestinal inflammation was evaluated by semiquantitative scoring of HE stainings. The fecal microbiota was determined in cecal feces by qPCR applying species-, genera- or group-specific 16S rRNA gene primers.

Results: The DAS was significantly elevated in all DSS-treated animals compared to controls, independent of the genotype. While GAL_2-KO and corresponding WT lost a similar amount of body weight over the course of 7 days, GAL_3-KO lost significantly more body weight on days 5–7 compared to WT. In the colon of GAL_3-KOs significantly higher MPO levels were found compared to WT. Semiquantitative scores evaluating the intestinal architecture and inflammatory cell infiltrate showed a significantly exacerbated inflammation in the colon of GAL_3-KOs compared to WT. Accordingly, the cytokines IL-1β, IL-6, IL-17A, IL-22, CXCL1, CCL2 and TNFα were significantly higher in the inflamed colon of GAL_3-KOs compared to DSS-WT. Additionally, colitic GAL_3-KO showed significantly higher protein levels of IL-6, CXCL1 and CCL2 in plasma compared to WT. DSS-treatment was accompanied by significantly higher gene numbers of enterobacteria, lactobacilli and bacteroides in all genotypes compared to healthy controls. However, DSS-GAL_3-KO exhibited significantly more enterobacteria and bifidobacteria compared to DSS-WT.

Discussion: The course of DSS-induced colitis in mice remains unaffected by lack of GAL_2 but is influenced by loss of GAL_3. Although the clinical severity of DSS-induced colitis develops independent of GAL_3 expression, increased loss of body weight, a more severe intestinal inflammation, increased MPO content, higher inflammatory cytokine mRNA and protein levels in colon and plasma and elevated microbiota gene numbers clearly show an aggravated course of DSS-induced colitis in GAL_3-KO mice. Consequently, we identified GAL_3 as a novel target in the treatment of IBD.

Keywords: galanin – colitis – inflammation – microbiota

*Corresponding author e-mail: *su.brunner@salk.at*