

## **The sympathetic mesenteric nerve regulates experimental colitis.**

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**Background.** The autonomic nervous system plays a regulatory role in the immune response. It has been established that norepinephrine (NE) has anti-inflammatory effects on dendritic cell activation,<sup>1</sup> which is a critical event in colitis pathophysiology.

Our aim was to investigate the effect of sympathetic nerve activity on experimental colitis.

**Methods.** 1) In a T-cell transfer colitis model, using Rag1<sup>-/-</sup> mice, sympathectomy was achieved chemically using 6-hydroxydopamine (6-OHDA) or surgically by cutting the supra mesenteric nerve (Sx). 2) In a dextran sodium sulfate (DSS) induced colitis model, mice underwent Sx or Sx combined with gastrointestinal-selective vagotomy (Cx) to assess the additive effect of the vagus nerve. Colitis was evaluated by histology and mRNA levels of inflammatory cytokines, along with clinical parameters such as weight loss and diarrhea. Ileal NE was measured by mass spectrometry.

**Results.** 6-OHDA as well as Sx caused a significant decrease in ileal NE levels. In Rag1<sup>-/-</sup>, but not in wild type mice, Sx caused clinical signs of spontaneous colitis from day 8 and a significant increase of pro-inflammatory cytokines IL-1 $\beta$  and IL-6. 6-OHDA similarly elicited signs of colitis, but inflammatory cytokines were not significantly elevated. In DSS induced colitis, Cx aggravated colitis and increased IL-1 $\beta$  and IL-6 expression in the distal colon. Sx alone did not significantly affect IL-1 $\beta$  and IL-6 expression.

**Conclusion.** Sympathetic innervation maintains homeostasis in the gut. Mucosal NE levels are critical determinants in maintaining mucosal tolerance towards luminal microbiota. Our data may explain how neuronal damage and plasticity contributes to pathology in IBD.

1 Nijhuis, L. E. *et al.* Adrenergic beta2 receptor activation stimulates anti-inflammatory properties of dendritic cells in vitro. *PLoS one* **9**, e85086, doi:10.1371/journal.pone.0085086 (2014).