

# The sympathetic mesenteric nerve regulates experimental colitis

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## Background & Aim

The autonomous nervous system plays a regulatory role in the immune response.

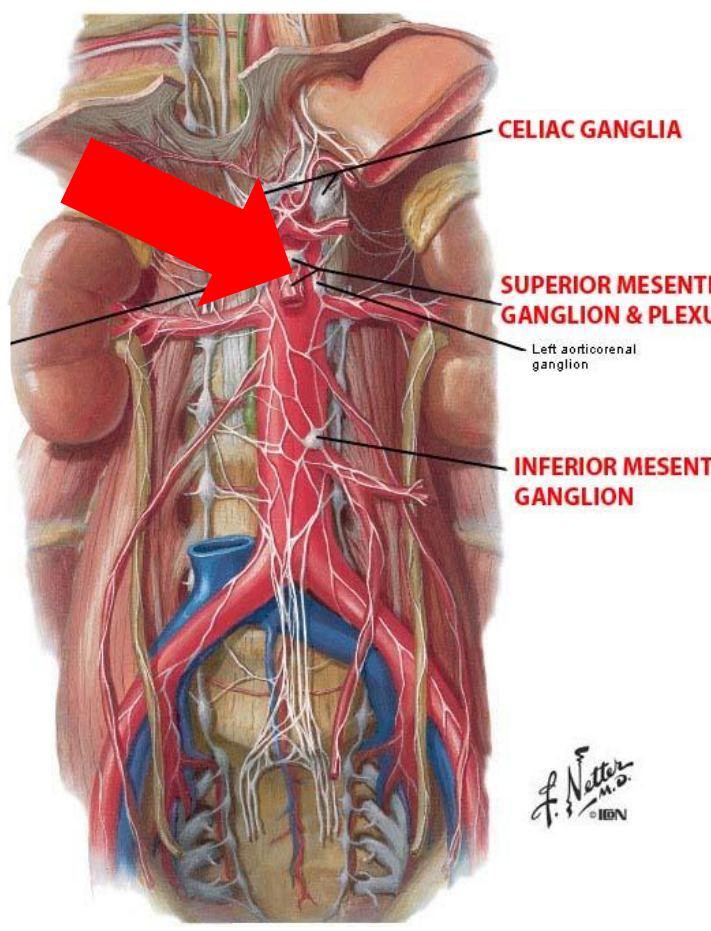
The sympathetic neurotransmitter norepinephrine has anti-inflammatory effects on dendritic cell activation.<sup>1</sup> This is a critical event in colitis.

**Our aim was to investigate the effect of norepinephrine depletion via surgical or chemical sympathectomy on the course of experimental colitis.**

1. Nijhuis, L.E. et al. Adrenergic beta2 receptor activation stimulates anti-inflammatory properties of dendritic cells in vitro. *PLoS one* 9, 2014.

## Methods

- 1) CD45RB<sup>high</sup> T-cell transfer colitis was induced in Rag1<sup>-/-</sup> mice to investigate the effect of chemical sympathectomy, using 6-hydroxydopamine (6-OHDA), or surgical sympathectomy, cutting the supra mesenteric nerve (Sx).
- 2) In a dextran sodium sulphate (DSS)-induced colitis model, Sx or Sx combined with gastrointestinal-selective vagotomy (Cx) was performed.



## Results

In CD45RB<sup>high</sup> T-cell transfer colitis, 6-OHDA caused a significant decrease of norepinephrine (Fig. 1), but had no effect on colitis parameters (not shown). Surprisingly however, in control Rag1<sup>-/-</sup> mice, 6-OHDA aggravated colitis pathology score, however not significantly (Fig. 2).

When Sx was performed, a significant decrease of norepinephrine was observed (Fig. 3). Furthermore, Sx caused clinical signs of spontaneous colitis starting at day 8 (Fig. 4) and a significant increase of pro-inflammatory cytokines IL-1 $\beta$  and IL-6 (Fig. 5). No spontaneous colitis was seen after Sx in WT mice (not shown).

In DSS-induced colitis, Sx did not significantly affect colonic IL-1 $\beta$  and IL-6 expression, although Cx did augment clinical signs and biomarkers compared to sham-operated mice in DSS-induced colitis in the distal colon (Fig. 6 and 7).

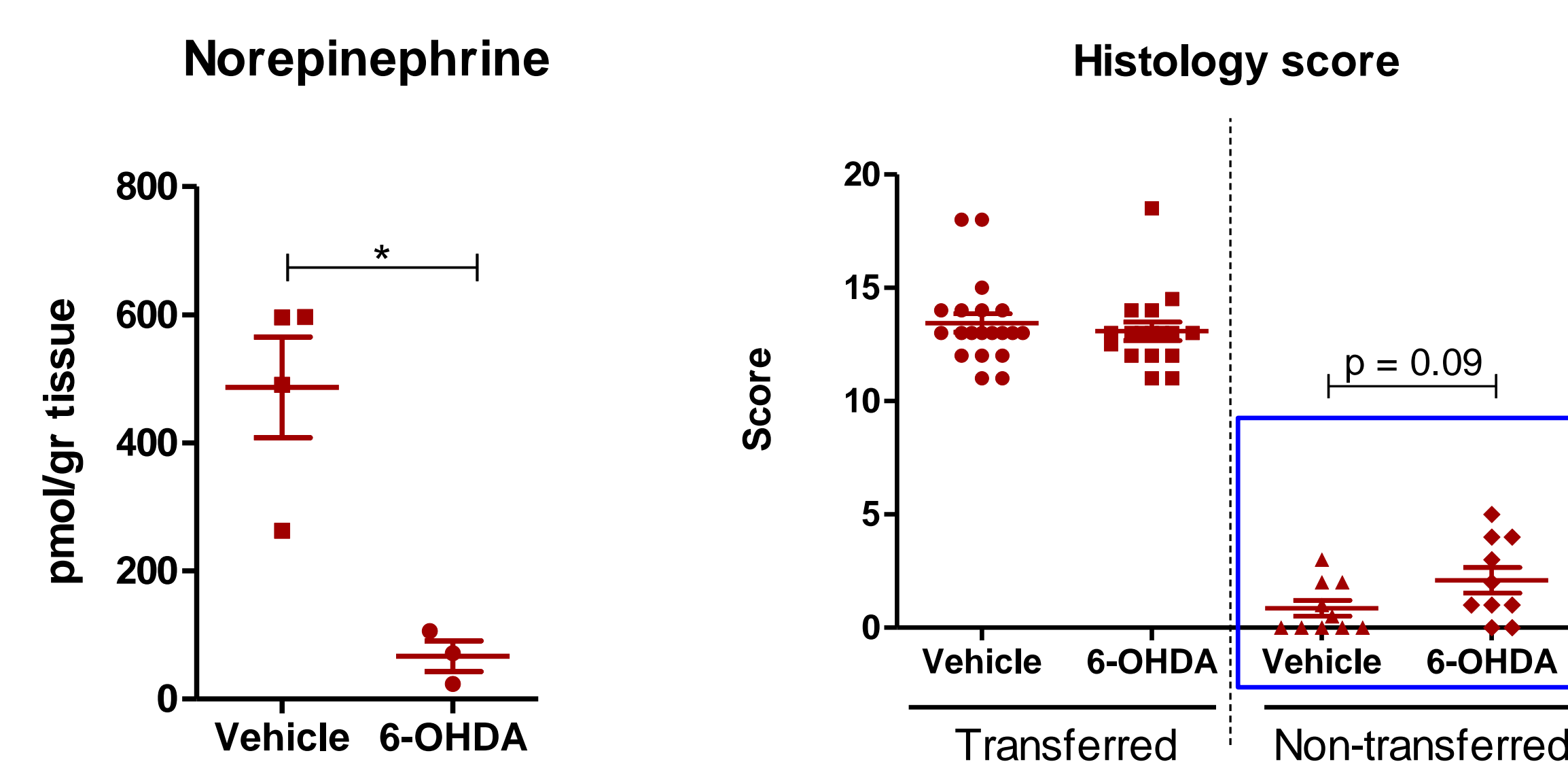


Fig. 1 Ileal norepinephrine levels

Fig. 2 Histology score after CD45RB<sup>high</sup> T-cell transfer and 6-OHDA treatment

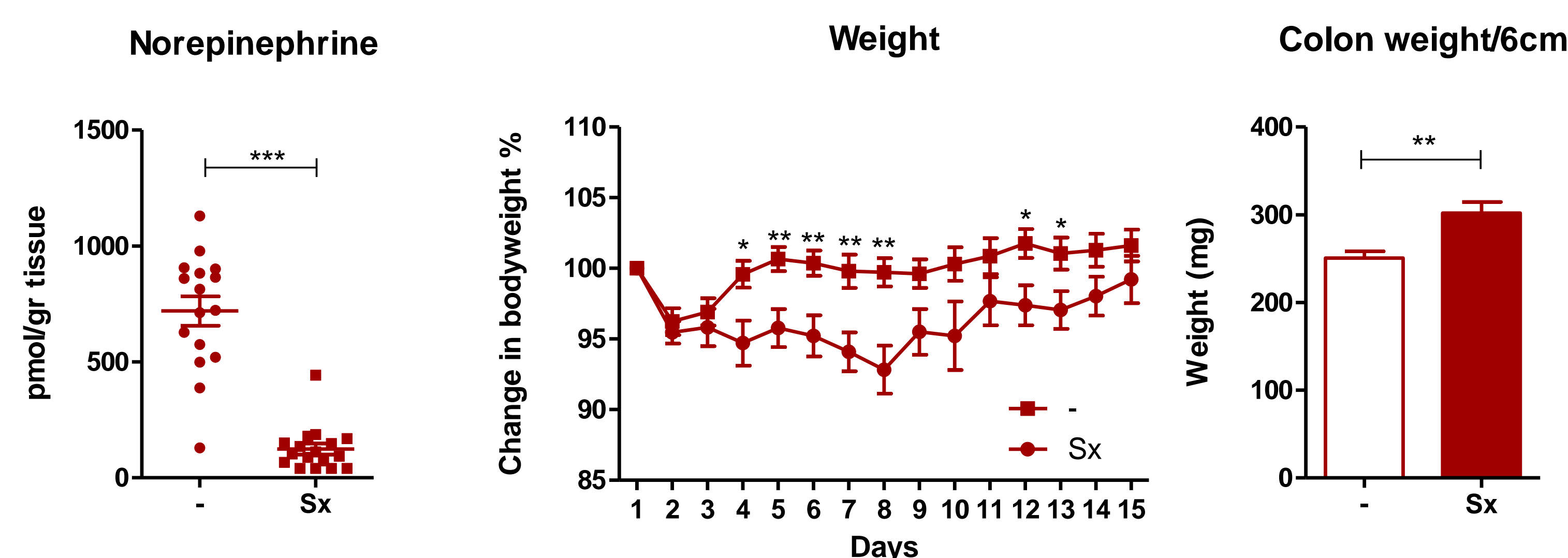


Fig. 3 Ileal norepinephrine levels

Fig. 4 Clinical signs of colitis (weight loss and colon weight) Statistical analysis was performed with Mann-Whitney U test \* P < 0.05, \*\* P < 0.01

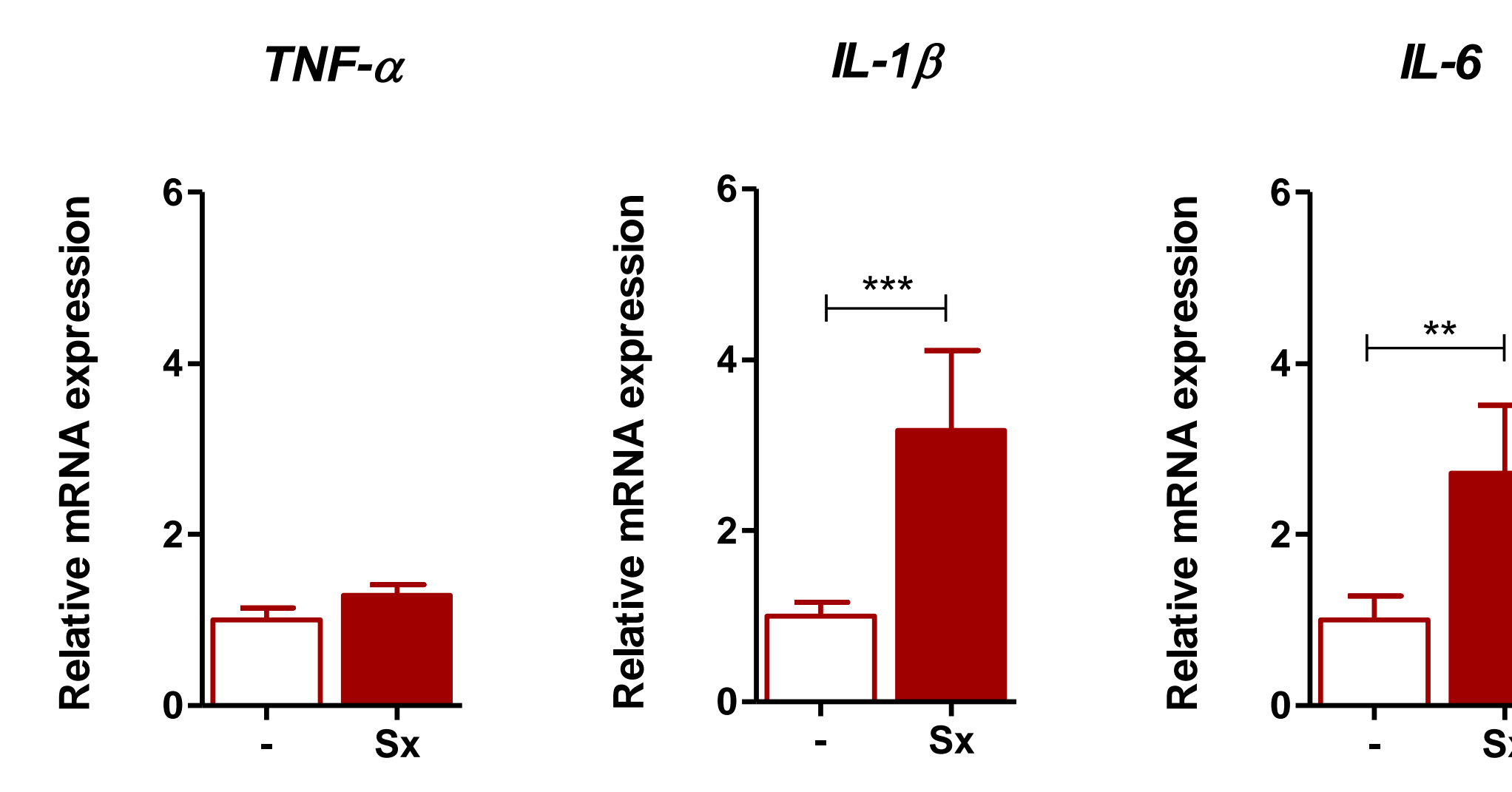


Fig. 5. mRNA expression of different inflammatory cytokines in the colon, relative to the sham-operated mice, normalized for housekeeping genes. Statistical analysis was performed with Mann-Whitney U test. \* P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001

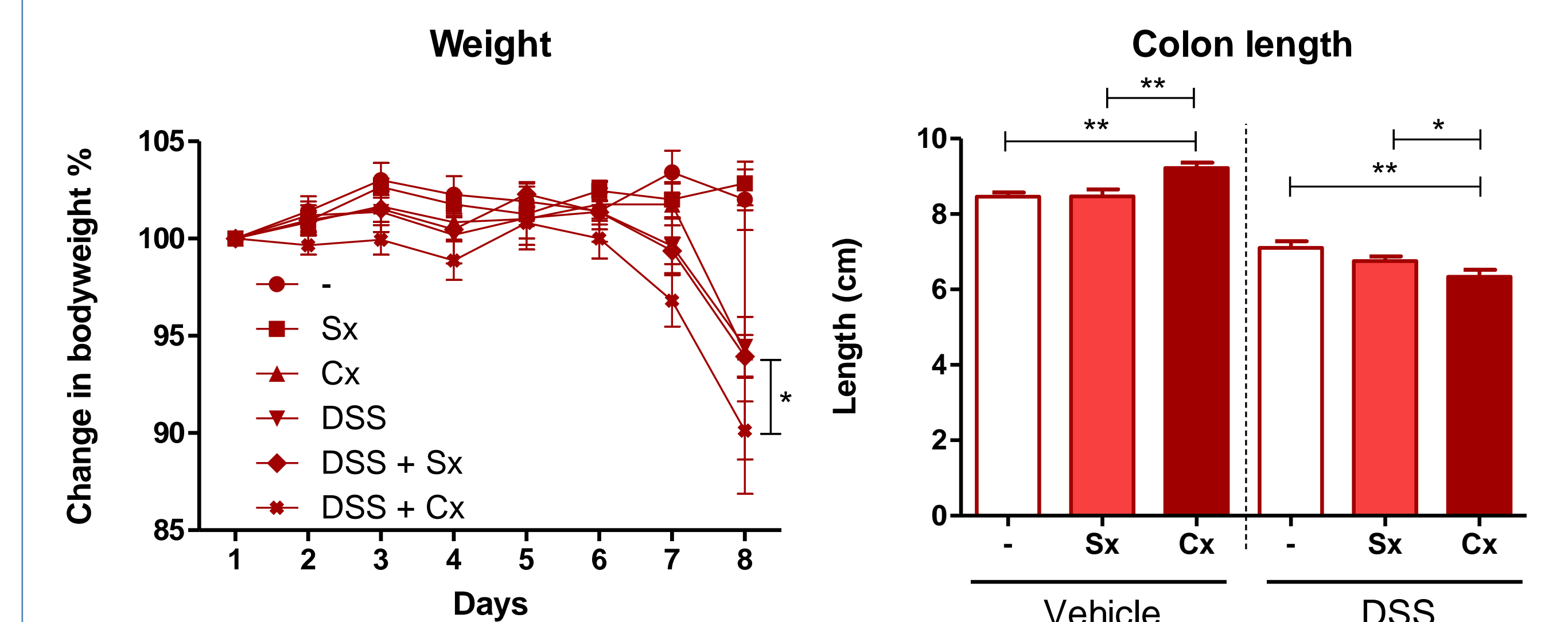


Fig. 6 Clinical parameters for colitis (weight loss and colon length). Statistical analysis was performed with Mann-Whitney U test \* P < 0.05, \*\* P < 0.01

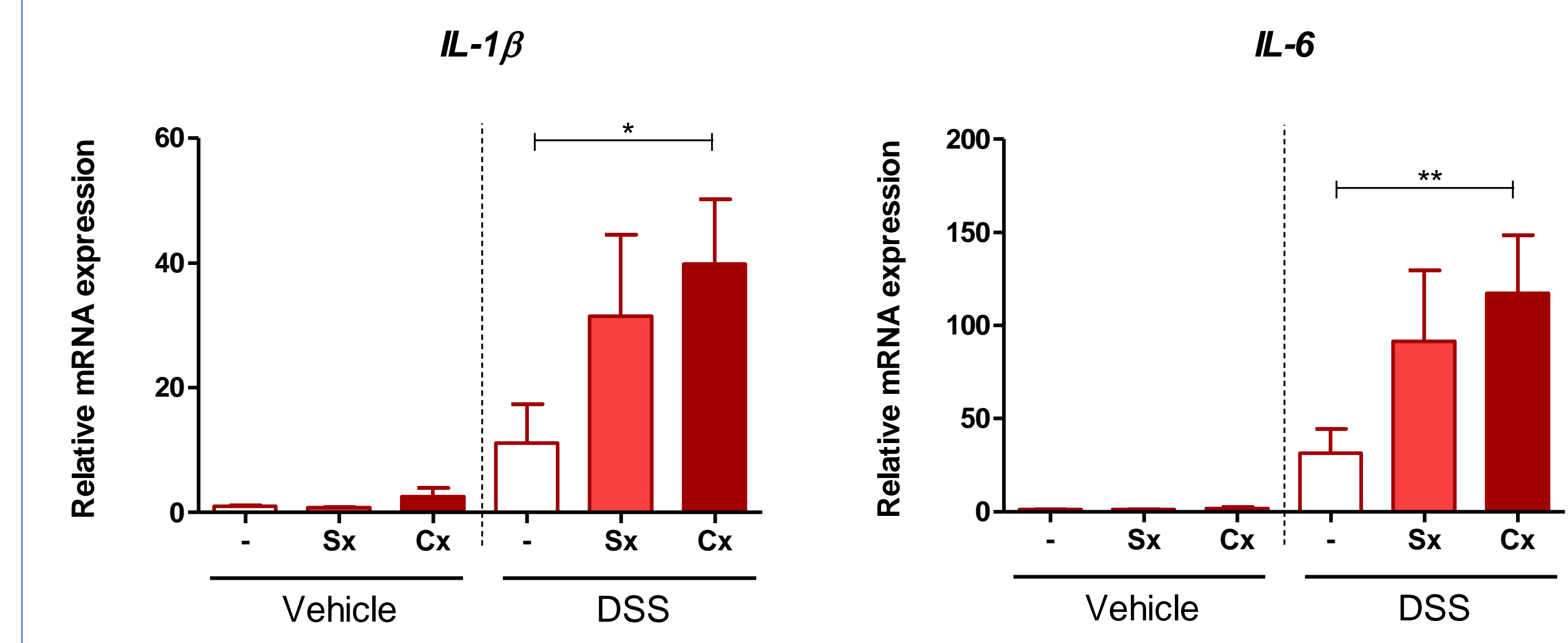


Fig. 7 mRNA expression of different inflammatory cytokines in the distal colon, relative to the vehicle-treated, sham-operated mice, normalized for housekeeping genes. Statistical analysis with Mann-Whitney U test. \* P < 0.05, \*\* P < 0.01

## Conclusion

Sympathetic innervation maintains homeostasis in the gut.

Norepinephrine is critical in maintaining mucosal tolerance towards luminal microbiota. This may explain how neuronal damage and plasticity contributes to pathology in IBD.

