

Chronic superior mesenteric nerve stimulation in acute DSS induced colitis in rats.

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Background & Aim

Currently, vagal nerve stimulation is tested in IBD to reduce inflammation.

The vagal anti-inflammatory effect is known to rely on sympathetic activity, that plays a negative regulatory role in the immune response.

Our aim was to apply chronic stimulation of the sympathetic superior mesenteric nerve (SMN) and examine its effect on experimental colitis in rats.

Methods

- 1) Optimized the dextran sodium sulphate (DSS)-induced colitis model in rats based on clinical parameters. Resulting in 9 days 5% DSS in the drinking water ad libitum.
- 2) Optimized the cuff electrode, placement around the SMN and stimulation parameters. Resulting in stimulation of 5 minutes BID, 10 Hz, 200 μ A, 1 ms.
- 3) **Chronic stimulation of the SMN in DSS-induced colitis in rats.**



Cuff electrode around the SMN

Results

Optimal scheme for DSS-induced colitis in rats.

Considering clinical parameters, an optimal regimen of 9 days of 5% DSS in the drinking water was determined (data not shown). A targeted qPCR array showed marked upregulation in colonic tissue of several genes comparing rats treated with 5% DSS in the drinking water for 9 days to control (non-treated) rats (Table 1).

Gene symbol	Fold Upregulation
Cxcl5	23,1
Nos2	14,62
Ccl17	11,31
Ccl4	7,52
Cxcl3	7,52
Ccl3	7,16
Tnfsf14	5,54
Ccl12	5,39
Cxcr2	5,13
Ccl19	4,03

Table 1. Top 10 most upregulated genes in DSS-treated rats versus control rats according to targeted qPCR array.

Optimal stimulation parameters for the SMN.

At 160-180 μ A stimulation of the sciatic nerve, a leg twitch was seen in an anesthetized animal indicating current was transduced (data not shown). The optimal stimulation parameter was identified as the parameter that did not result in a decrease in mesenteric blood flow (Figure 1) and did not elicit behavioural response, i.e. 200 μ A.

Finally, the effect of chronic SMN stimulation in DSS-induced colitis was assessed according to the scheme in Figure 2.

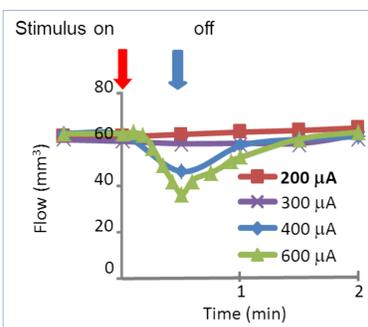


Figure 1. Mesenteric blood flow during and after stimulation of the SMN with current ranging from 200 to 600 μ A. Other parameters: 10 Hz, 1 ms

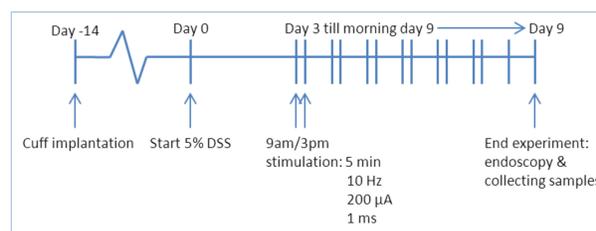


Figure 2. Final regimen investigating the effect of chronic SMN stimulation in DSS-induced colitis.

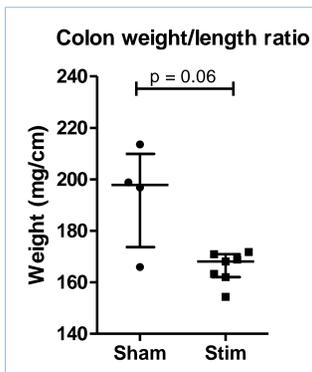


Figure 3. Colon weight/length ratio. Statistical analysis was performed with a Mann-Whitney U test. Median and IQR is depicted.

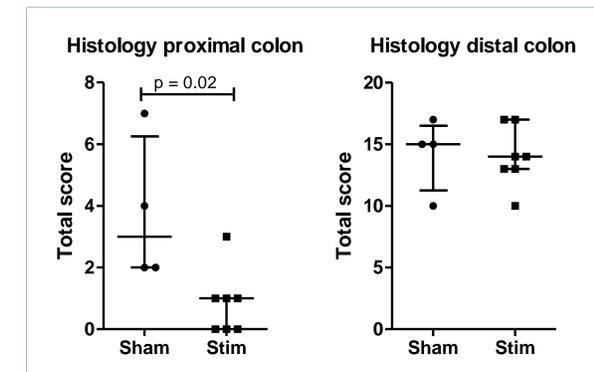


Figure 4. Histology proximal colon. Statistical analysis was performed with a Mann-Whitney U test. Median and IQR is depicted.

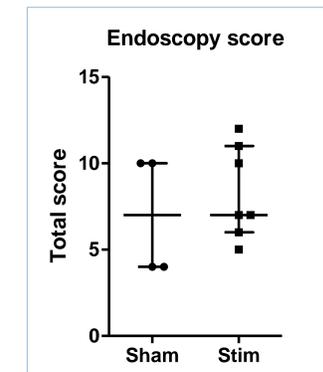


Figure 5. Histology and endoscopy distal colon. Statistical analysis was performed with a Mann-Whitney U test. Median and IQR is depicted.

Chronic SMN stimulation decreased colon weight/length ratio, an indicator of colitis (mean: 194 mg/cm (sham stimulated rats) vs. 166 mg/cm (stimulated rats); $p = 0.06$), however not significant (Figure 3). mRNA expression from chemokines (detected in the qPCR array) in the distal colon showed downregulation in the stimulated rats compared to the sham group, however not significantly (mean fold decrease CCL3 5.3; CCL12 1.5; CCL17 4.8). Chronic SMN stimulation significantly improved inflammation in the proximal colon (mean: 3.8 (sham group) vs. 0.9 (stimulated group); $p = 0.02$) (Figure 4). Endoscopy and histology of the distal colon did not show a difference in inflammation between groups (Figure 4 and 5).

Conclusion

We developed an animal model to investigate the effect of chronic nerve stimulation.

Our data show that chronic stimulation of the superior mesenteric nerve may ameliorate experimental colitis.

