Inflammatory bowel diseases (IBD) are a scourge of humanity, but well adapted mouse models exist. IBD is induced by transrectal enemas of haptenizing agents like TNBS or oxazolone which leads to development of an ulcerative autoimmune colitis driven by TH1 (IL-17&21) or by TH2 (IL-13) and natural killer cells, respectively. DSS in the drinking water induces a primary chronic colitis by activation of the innate immune system. Like the human diseases, the animal models have been understood and treated as genuine immunologically defined pathologies, although an involvement of the peripheral nervous system was not excluded. Our recent studies now suggest that sensory neurons in the colonic wall and their release of substance P (SP) form a decisive link in a vicious cycle that generates and maintains the aberrant immune response and chronic inflammation. At first, this was obvious for the acute TNBS colitis, because the chemical TNBS turned out to act as a full agonist at TRPA1, a chemosensory neuronal ion channel that depolarizes and conducts calcium ions inside, governing SP release, and – upon strong activation – induces action potential discharge eventually leading to pain sensation. TRPA1 and SP knockouts were protected from TNBS colitis, despite the haptenizing action. However, even severely sick wildtype mice were almost cured by TRPA1 or SP (NK1) receptor blocking drugs, suggesting that neurogenic inflammation remains essential in the chronic stage of colitis. This hypothesis was confirmed in both oxazolone and DSS colitis, because both chemicals did not activate TRPA1 nor release SP but still were disarmed by blocking the channel or receptor. This could mean that colitis as such upholds the TRPA1-SP pathomechanism, e.g. by sensitizing TRPA1. Indeed, in colitis TRPA1 and the sensory nerve endings were found in a sensitized state, releasing excessive amounts of SP. Many sensitizing mediators can be considered, but a particularly suspicious compound, 4-HNE, was found massively increased in the inflamed colon. Like other products of lipid peroxidation such as 4-ONE and acrolein, 4-HNE had been known to sensitize TRPA1, and all three were found to release SP from the colon. Thus, the vicious cycle of chronified inflammation appears to be closed for now. However, much remains to be elucidated, in particular the neuro-immune interaction of SP with immune and epithelial cells, yet well ignored by immunology.

Engel MA et al., 2011, Gastroenterology. Engel MA et al., 2011, J. Gastroenterol. Engel MA et al., 2012, Dig. Liver Dis.