# Increased myenteric neuronal activity contributes to dysmotility in the inflamed guinea pig distal colon

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Previous studies have shown intestinal inflammation causes alterations in myenteric neural function, including enhanced excitability of afterhyperpolarization (AH) neurons and facilitated synaptic transmission in AH and synaptic (S) neurons in animal models of colitis. These changes are associated with disrupted colonic motility, and persist for weeks beyond recovery of inflammation. The aim of this investigation was to test the hypothesis that altered neural function contributes to dysmotility. We tested whether pharmacological manipulations that mimic the effects of inflammation disrupt motility, and whether suppression of AH neuron excitability restores propulsive motility in inflamed preparations. Motility assays were performed in control and trinitrobenzenesulfonic acid (TNBS)-inflamed guinea pig colons. In controls, the intermediate conductance $Ca^{2+}$-activated K+ channel (IK) inhibitor TRAM-34 and 5-$HT_4$ receptor agonist tegaserod were used to mimic the effects of inflammation-induced AH neuronal hyperexcitability and synaptic facilitation. Bath application of TRAM-34 decreased the rate of motility, and TRAM-34 plus tegaserod led to a further decrease. Propulsive motility was also reduced when the voltage-activated Na+ channel opener veratridine was added, thus activating repetitive action potentials in myenteric neurons. Colitis-induced AH neuron hyperexcitability involves an increase in hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel activity. Therefore, the HCN channel inhibitor ZD7288 was used to suppress neuronal activity in TNBS-treated preparations. When inflamed preparations were bathed in Krebs solution, motility was halted or obstructed. However, when ZD7288 was added, normal motility was restored in the region of previously disrupted motility. In control studies, ZD7288 did not alter the electrical properties of colonic smooth muscle or the rate of propulsive motility. Collectively, these data indicate that altered neuronal function contributes to disrupted motility in the inflamed colon and dampening the hyperexcitability of AH neurons can restore motor function. These findings support the concept that increases in sensory neuron activity can have a deleterious effect on motor function.