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"The Impact of Ulceration of Motility Reflex Circuits in Guinea Pig TNBS Colitis"

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ABSTRACT

The overall goal of this dissertation project was to characterize the impact of ulceration on propulsive motility in guinea pig tri-nitrobenzene sulfonic acid (TNBS) colitis. The study was comprised of three aims: to determine how ulceration affects motility; to examine changes in neural control of muscle contractility; and to test whether there is a relationship between previously identified sensory neuron hyperexcitability and alterations in neuromuscular inputs in colitis.

Analysis of propulsive motor activity in isolated segments of guinea pig distal colon revealed that peristalsis and spontaneous motility patterns are impeded specifically at sites of ulceration. Peristalsis is, however, enhanced in regions adjacent to ulcers, possibly due to sensitization of motility reflex circuits as an adaptive response to obstruction at an ulcer. Fibrosis in the submucosa and loss of mucosal paracrine inputs to AH sensory neurons may contribute to impeded motility at an ulcer. Furthermore, the amplitude of inhibitory junction potentials in circular muscle is decreased in the ulcerated region. Pharmacological analysis revealed that the purinergic component of inhibitory junction potentials is decreased while the nitrergic component of these events is not altered. Neuromuscular transmission in the intestines is mediated by interstitial cells of Cajal, which form a network that also serves a pacemaker function in the gut; therefore, the integrity of this network was evaluated. The density of intramuscular interstitial cells of Cajal was decreased in the ulcerated region of the TNBS-inflamed colon. This disruption may contribute to the decrease in neuromuscular transmission, but it is not clear how purinergic transmission is affected without a change in the nitrergic component of these synaptic events.

Previous studies involving a number of models of intestinal inflammation have demonstrated that AH neurons, which serve as intrinsic sensory neurons, are hyperexcitable in response to inflammation. This has led to the theory that increased AH neuron activity may lead to decreased propulsive motor activity in the inflamed bowel through a form of attention deficit disorder in the enteric nervous system. This model was tested by pharmacologically increasing AH neuron excitability in normal colon preparations and decreasing excitability in TNBS-inflamed preparations in order to mimic and reverse the effects of inflammation, respectively. Addition of TRAM34, which inhibits the channel that mediates the AH neuron hyperpolarization, did not affect propulsive motility in normal preparations. Furthermore, decreasing AH neuron excitability by extending their afterhyperpolarization in inflamed colon did not restore motility or inhibitory junction potentials in the ulcerated region of inflamed preparations. These findings indicate that AH sensory neuron hyperexcitability alone is not responsible for altered motility in guinea pig TNBS colitis.