GRADUATE COLLEGE DEFENSE NOTICE

Neuroscience Graduate Program

The following dissertation is open to those in the University community.

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“Propulsive motility in the colon: neural mechanisms of disruption in colitis, and improvement with 5-HT4 receptor agonists.”

Friday, September 9, 2011
1:00 pm
HSRF 400
ABSTRACT

Chronic gastrointestinal (GI) disorders such as Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) share several key features including symptoms of disrupted colonic motility and visceral pain. To better understand and treat these conditions, it is necessary to elucidate the neural mechanisms responsible for altered gut functions and to develop targeted therapeutic strategies. The objectives of my dissertation studies were: (1) to test the hypothesis that intrinsic sensory neuron hyperexcitability leads to disrupted colonic propulsive motility, and (2) to test the hypotheses that 5-HT4 receptors are located in the colonic mucosa, and activation of mucosal 5-HT4 receptors promotes motility and attenuates visceral hypersensitivity.

Altered enteric neural functions are thought to contribute to the symptoms of chronic GI disorders, but a cause and effect relationship has not been resolved. A consistent feature of inflammation-induced neuroplasticity in the GI tract is enhanced excitability of myenteric intrinsic sensory neurons, and we have recently demonstrated that propulsive motility is obstructed or halted in ulcerated regions. In my studies, I found that increasing neuronal excitability of these neurons by pharmacologically inhibiting their afterhyperpolarization decreased the rate of propulsive motility. Furthermore, by reducing neuronal excitability in inflamed preparations, I was able to restore colonic motor patterns. These findings indicate that there is a direct relationship between the physiological properties of intrinsic sensory neurons and propulsive motility, and that inflammation-induced changes in these neurons contribute to altered motility in colitis.

5-HT4 receptors are an effective therapeutic target to promote colonic propulsive motility and attenuate visceral pain, yet reports of adverse side effects have limited their availability. Despite clinical effectiveness of compounds targeting these receptors, the distribution and functions of 5-HT4 receptors in the GI tract have not been well described. In my studies, I have demonstrated that 5-HT4 receptors are expressed on a variety of cell types in the colonic epithelium, including 5-HT-containing enterochromaffin (EC) cells, mucin secreting-goblet cells and enterocytes. Furthermore, activation of mucosal 5-HT4 receptors evokes mucosal 5-HT release, goblet cell degranulation and Cl− secretion. Results of functional studies indicate that activation of mucosal 5-HT4 receptors result in prokinetic and anti-nociceptive actions, as intraluminal administration of 5-HT4 agonists accelerates propulsive motility and attenuates visceral hypersensitivity. These findings suggest that 5-HT4 agonists could mediate their therapeutic actions when targeted to the colonic epithelium.

The studies described in this dissertation improve our knowledge of basic mechanisms underlying GI symptoms, and indicate that dampening neuronal excitability can restore colonic motor function. Furthermore, they suggest mucosal 5-HT4 receptors as a novel target to promote motility and alleviate visceral pain, while restricting systemic bioavailability and resulting adverse side effects.