

Project Title: Neural regulation of the GI microvasculature during colitis (2006-2009)
Recipient: Alan Lomax

Year 2 progress. This was my second as an independent investigator and the second year of this CCFC grant. My laboratory is established now and we are making rapid progress in several areas. My first graduate student, Mohamed Motagally, will graduate with an MSc this summer.

Neural regulation of the vasculature during colitis

My laboratory has found a defect in neural regulation of blood flow during colitis as a consequence of an important neurotransmitter being broken down during colitis. This substance, ATP, plays many other roles in the gut in addition to being a neurotransmitter so the discovery of its selective breakdown in colitis could have broad ramifications beyond altering the viability and barrier function of the GI mucosa. These findings were recently published in the Journal of Physiology and have been followed up by using molecular biological and physiological techniques to identify the enzyme responsible for ATP breakdown during colitis. This work is under review for publication in GUT. We have also developed an in vivo technique to optically measure neural regulation of colonic blood flow during colitis.

Effects of inflammation on sympathetic neurons

Sympathetic neurons regulate a variety of gut functions, including blood flow and motility. They also can regulate immune activation. We have developed techniques to record the behavior of these neurons during health and during colitis. We also examine the effects of inflammatory mediators. We have discovered how colitis reduces the ability of the sympathetic neurons to release their neurotransmitters. During inflammation, circulating levels of many immune substances called cytokines are increased. We have found that cytokines and a model of IBD reduce the activity of a membrane ion channel that translates the electrical activity of neurons into the release of neurotransmitters. This work has been submitted as two papers to the Journal of Physiology.

Serotonin signaling during colitis

Serotonin is an important molecule used by cells to communicate with one another that regulates gut motility and pain sensation. Signaling by this molecule is disordered in IBD patients and in animal models of IBD. My laboratory has established a collaboration with an Australian investigator who has pioneered the use of electrochemical techniques to measure serotonin release from enterochromaffin cells in real time. We have closely examined the changes in serotonin release and reuptake that occur in a model of IBD and identified potential mechanisms of these changes. This work is the first real time recording of serotonin dynamics in the inflamed gut and is under preparation for submission to the journal Gastroenterology.

Publications funded by CCFC:

Lomax AE, O'Reilly MT, Neshat S and Vanner S. Sympathetic vasoconstrictor regulation of colonic submucosal arterioles is altered in experimental colitis. *Journal of Physiology* 583: 719-730.

Neshat S, Barajas-Espinosa AR, deVries M, Skeith L, Chisholm SP, **Lomax AE**. Loss of purinergic vascular regulation in the colon during colitis is associated with upregulation of CD39. Under review at GUT.

Motagally M, Neshat S, **Lomax AE**. Tumor necrosis factor α activates nuclear factor κ B to inhibit N-type voltage-gated Ca^{2+} current in postganglionic sympathetic neurons. Under review at *Journal of Physiology*.

Motagally M, Neshat S, **Lomax AE**. Inhibition of sympathetic noradrenaline release and N-type Ca^{2+} channels during experimental colitis. In preparation for submission to *Journal of Physiology*.

Bertrand PP, Barajas-Espinosa AR, Bertrand RL, **Lomax AE**. Real time electrochemical detection of mucosal serotonin release during experimental colitis. In preparation for submission to *Gastroenterology*.

Lomax AE. The burgeoning field of neurogastroimmunology: anti-inflammatory effects of β_3 adrenoceptors. Editorial in press at *Neurogastroenterology and Motility*.

Presentations resulting from CCFC-funded research

Bertrand PP, Barajas-Espinosa AR, Bertrand RL, **Lomax AE** (2008). Inflammation-induced increases in the release and uptake of serotonin in mouse colon. EPHAR meeting, 2008.

Motagally M, Neshat S, **Lomax AE** (2008). Tumour necrosis factor α activates NF κ B to inhibit N-type voltage-gated Ca^{2+} current in postganglionic sympathetic neurons. *Gastroenterology* 134, 4. 48. Selected for oral presentation.

Motagally M, Neshat S, **Lomax AE** (2008). Colitis reduces N-type Ca^{2+} current in neurons from superior mesenteric ganglia. *Gastroenterology* 134, 4 W1372.

Neshat S, deVries M, Barajas-Espinosa AR, Chisholm SP, **Lomax AE** (2008). Loss of purinergic vasoregulation in the colon during colitis is associated with increased expression and activity of CD39. *Gastroenterology* 134, 4. M1664.

Motagally M, **Lomax AE** (2008). Effect of TNF α on calcium channels in superior mesenteric ganglia. *Canadian Journal of Gastroenterology* 22, pp179A.

Motagally M, Neshat S, **Lomax AE** (2008). DSS-induced colitis reduces Ca^{2+} current in sympathetic neurons of superior mesenteric ganglia. *Canadian Journal of Gastroenterology* 22, pp77A. Selected for oral presentation.