

Abdominal pain is a major cause of morbidity for patients who suffer from inflammatory bowel disease (IBD) and can severely limit their quality of life. Current treatment of pain is largely limited to the use of narcotics such as morphine, which have non-specific actions throughout the body, including cognition, drowsiness, decreased energy levels, and nausea and vomiting. The long term goal of my research program is to identify new mechanisms involved in the generation of inflammatory pain in IBD which might provide selective targets for new pharmacological treatments.

We have focused on several ion channels which are uniquely involved in transmitting pain signals in the gut. The Nav1.8 sodium channel is only found on pain sensing neurons (and hence provides a uniquely selective target) and its activity is markedly increased during inflammation, thereby exaggerating pain signals. We have used a sophisticated technique to isolate the neurons containing these channels called laser capture microdissection. We then applied quantitative molecular techniques to determine whether the increased activity is due to the availability of more channels and if so, whether this is the result of increased transcription (i.e. more message RNA to drive the translation of more proteins). We found that increased channel protein is expressed during inflammation but not as a result of increased message. These important findings help us to understand how increased pain results and what targets in the pathway would be most rewarding.

We also examined the role a TRP channels which are also known to be a major mechanism underlying the expression of inflammatory pain. We found, with our collaborators, that mast cell proteases can sensitize these channels and thereby play a critical role in the expression of mechanosensitive pain.

Most recently we have examined the supernatant from human biopsies from patients with active ulcerative colitis. This contains the representative inflammatory mediators which are sensitizing the nerves and we chose to examine whether TNF α may be a major player talking directly to the pain sensing nerves. We found convincing evidence for this and hence have novel data that anti-TNF treatments may not only help pain by decreasing inflammation but also by directly interfering with the ability of TNF to sensitize nerves.

Publications:

Manuscripts-

Sipe et al. Am J Physiol 294:G1288-G1298, 2008.

King et al. Neurogastroenterol Motility (under review).

Abstracts-

Ibeakanma et al. Can J Gastroenterol 2008.

Cruz et al. Gastroenterology 2008.