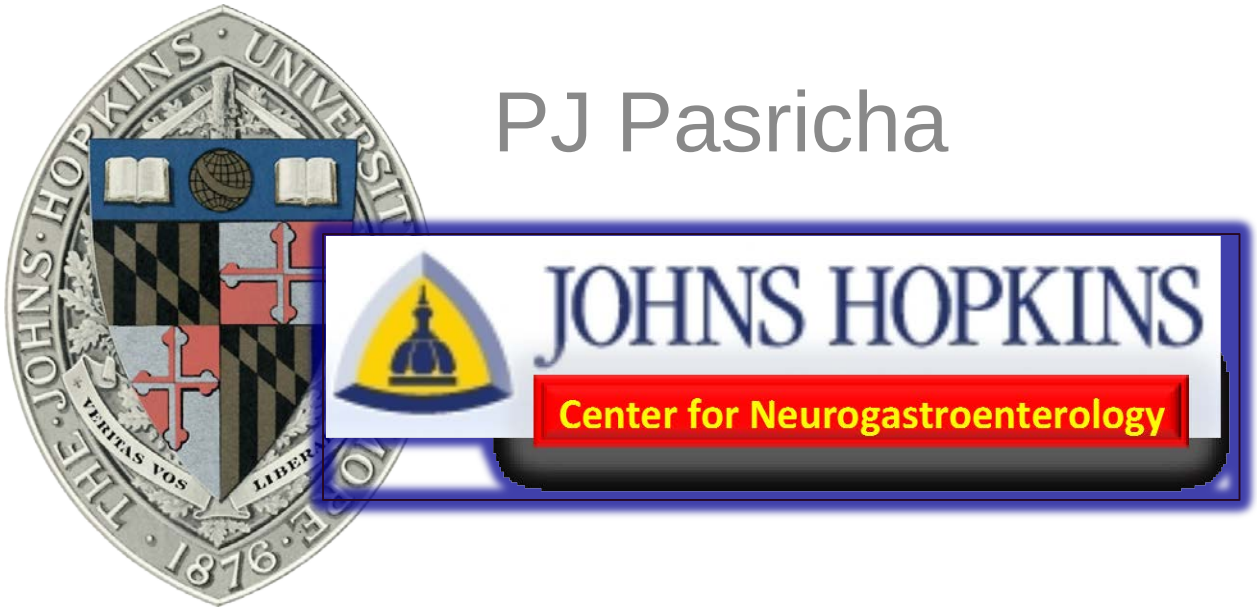
NIH Workshop on the SPARC Program

Duodeno-pancreatic Innervation: A Dichotomous Neural System with Implications for Inflammation and Metabolic Disease

PJ Pasricha



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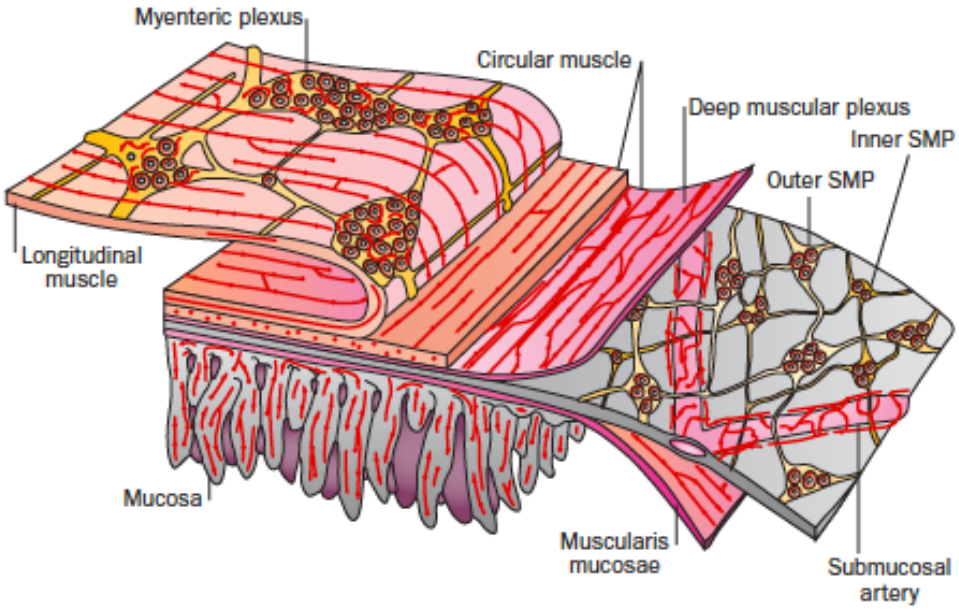
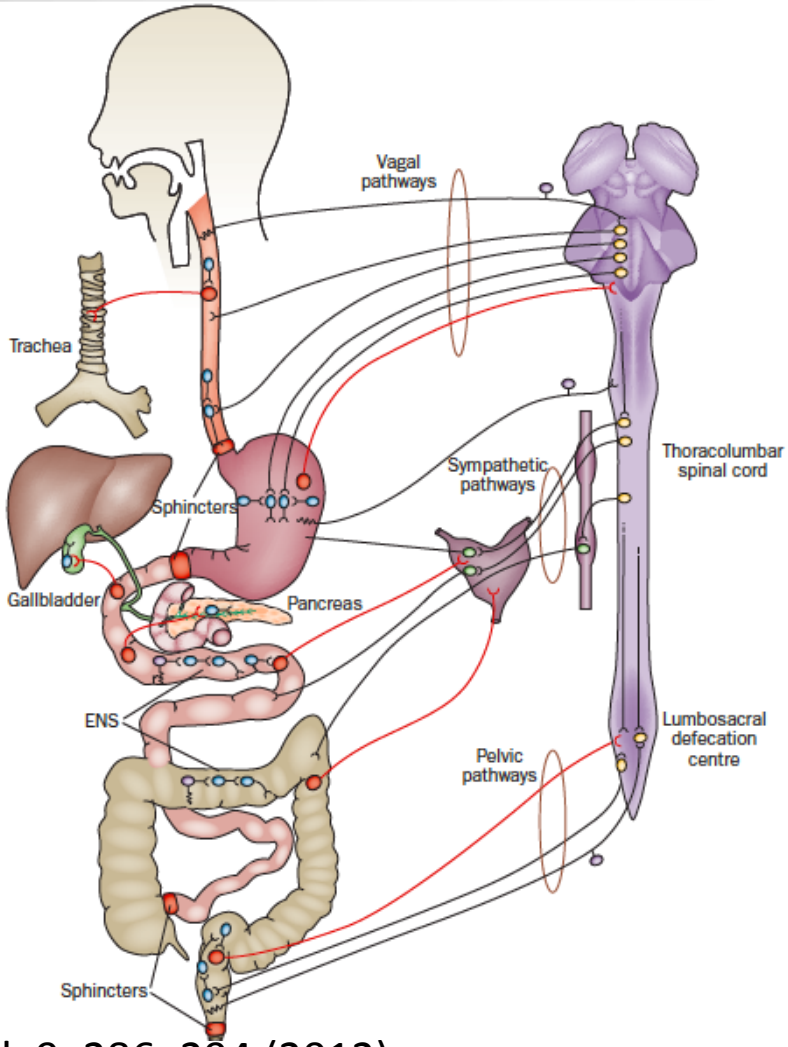
Outline

- Anatomical and functional description of dichotomous innervation
  - Implications for pain and inflammation
  - Implications for metabolic syndrome
  - How this may inform us about the mechanisms of bariatric surgeries and other approaches
- Needs
  - Mapping of neural networks from the duodenum across the body
  - Identification of “nodal point” for stimulation
  - Need for blocking protocols

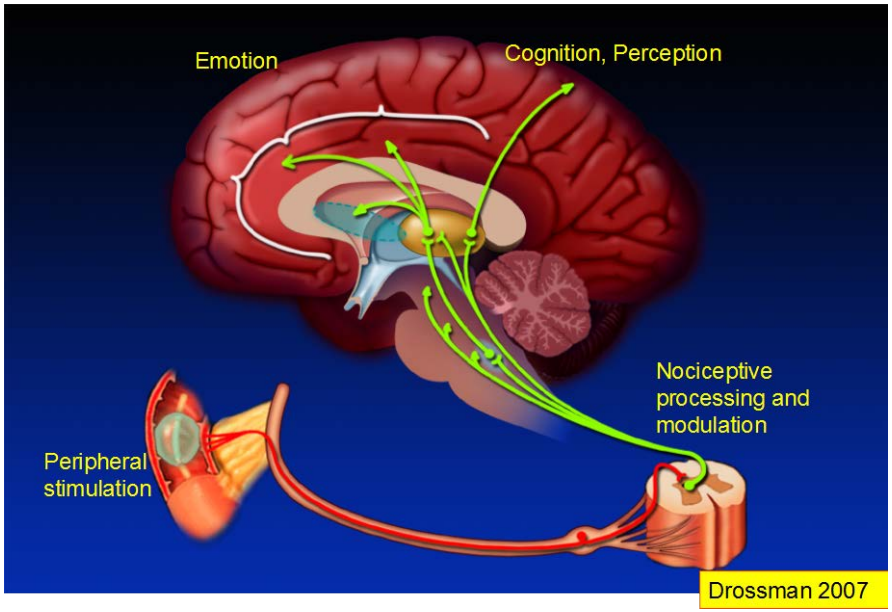
Visceral nerves

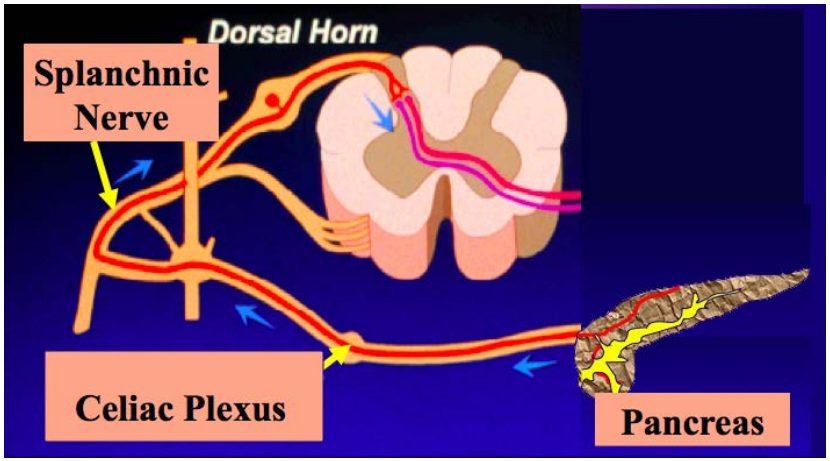




Furness, J. B. Nat. Rev. Gastroenterol. Hepatol. 9, 286–294 (2012)

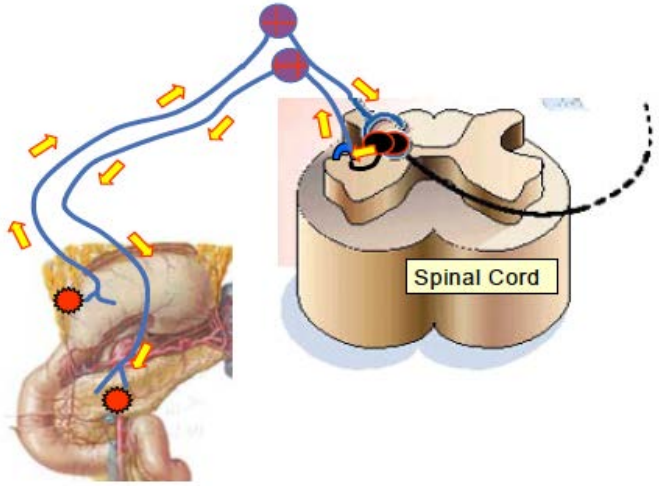
Another class of nerves: spinal nociceptive neurons



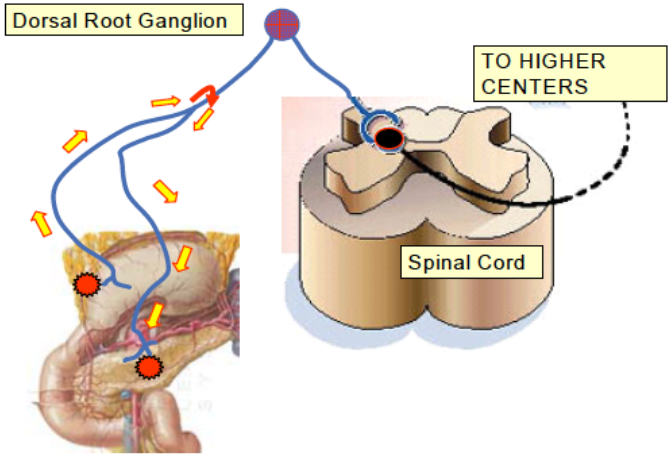


Visceral cross-talk

- Communication among abdominal/pelvic viscera is important for several physiological events that normally inhibit each other
  - Urination
  - Defecation
  - Coitus



- Convergence of information from two or more visceral organs can take place at several levels
  - Spinal cord
  - Peripheral central nervous system



Dichotomous Innervation of Viscera

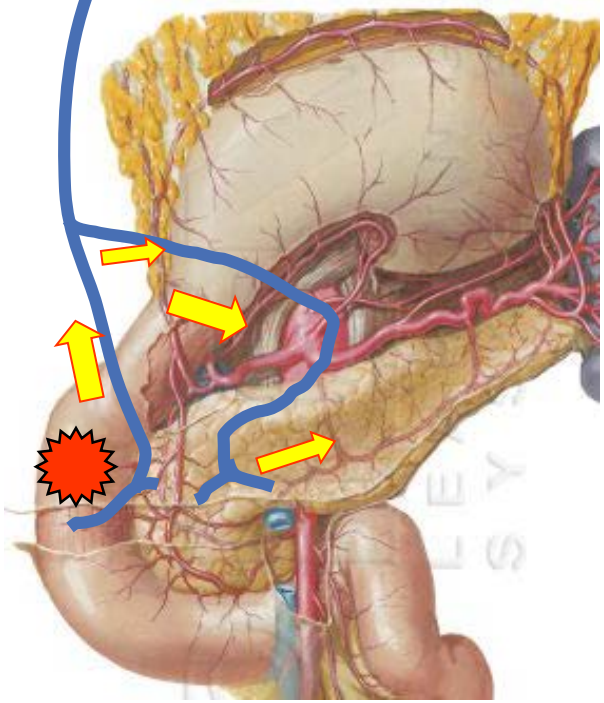
- Pathological events in one organ can induce disease in another via neurogenic mechanisms
  - Acute cystitis can be observed in response to colitis, prostatitis or endometriosis in rats
  - Acute colitis can lead to upregulation of sodium currents in primary sensory neurons emanating from the bladder
  - Increased vascular permeability in the bladder in response to colitis can be reduced by hypogastric nerve ablation implying the existence of hardwired neural pathways

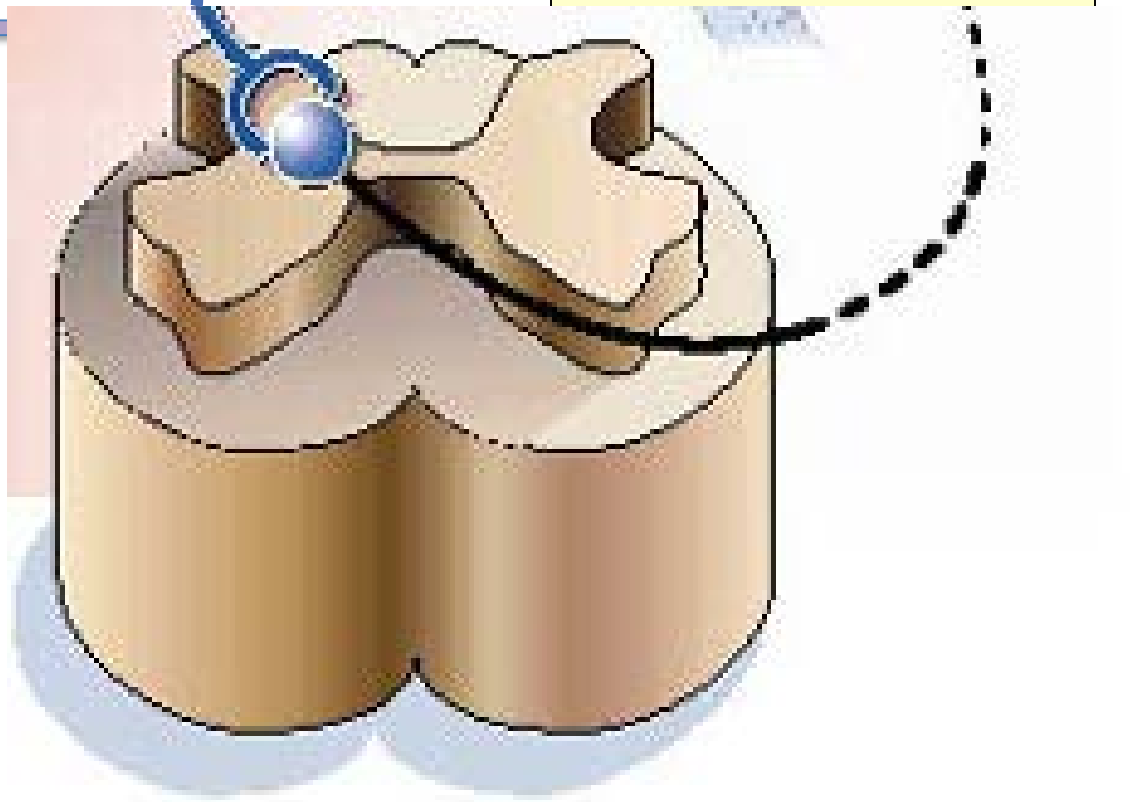
Winnard et al. Am J Physiol Regul Integr Comp Physiol 2006
Liang et al. Neurourol Urodyn 2007
Ustinova et al Am J Physiol Renal Physiol 2007

Ustinova et al Am J Physiol Renal Physiol 2006
Malykhina et al Neuroreport 2004
Keast JR. J Comp Neurol 1992
Christianson Pain 2007

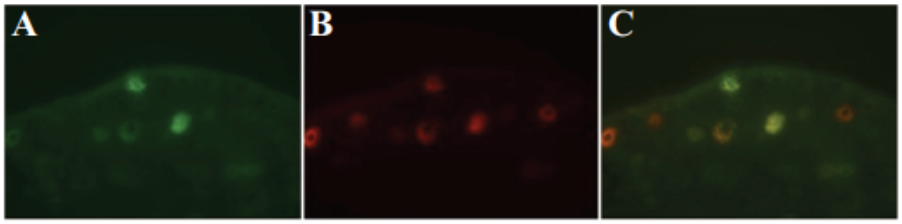
Dorsal Root Ganglion

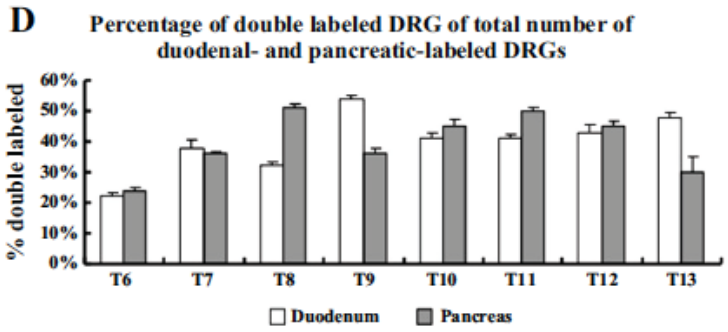
TO HIGHER CENTERS

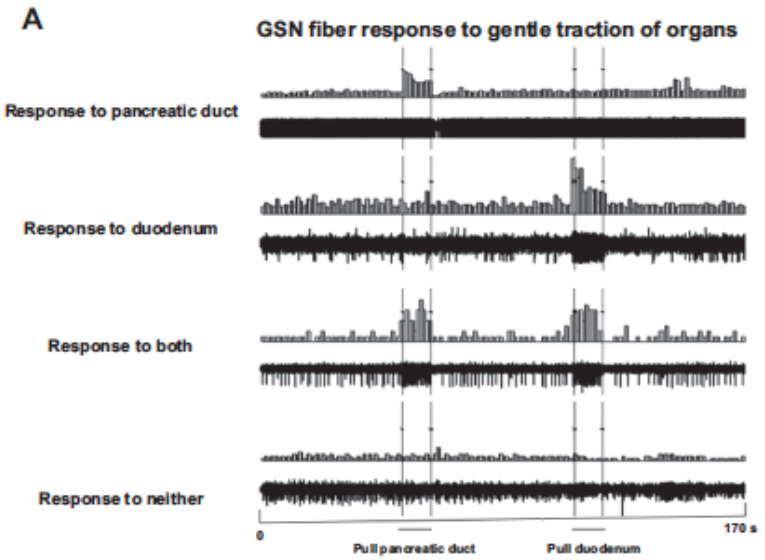


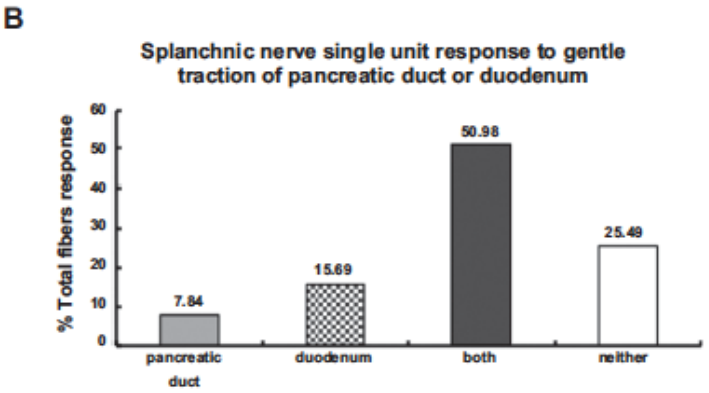


The duodenum and pancreas share many of the same spinal neurons



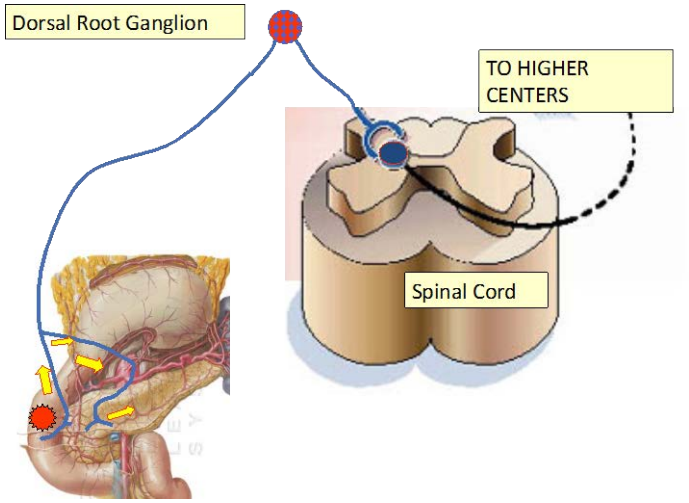


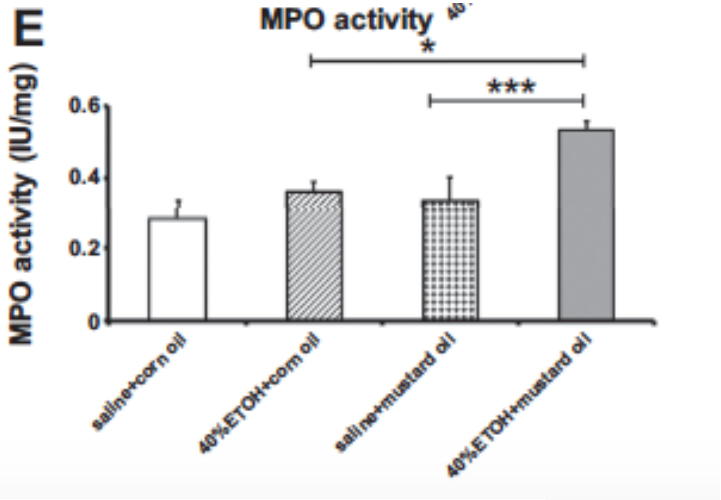


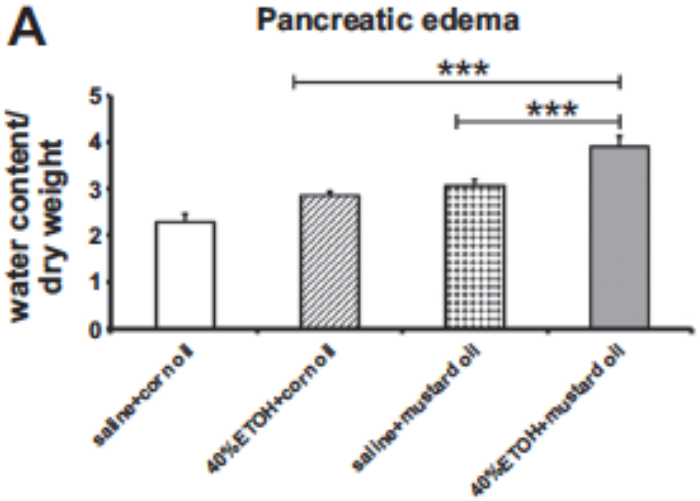


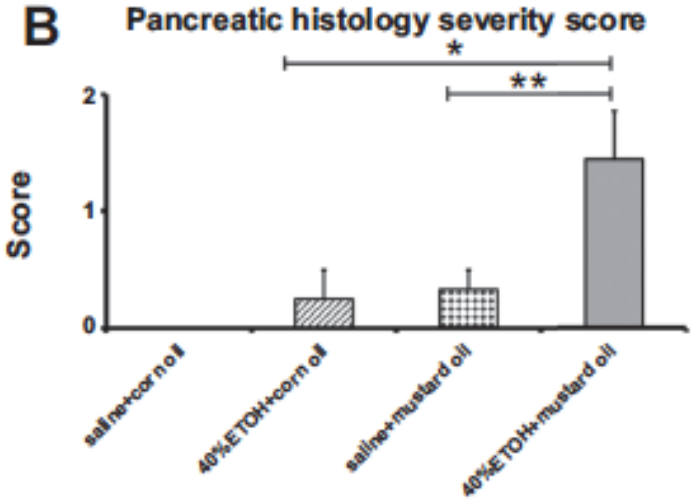
Li…Pasricha. Am J Physiol Gastrointest Liver Physiol; 2013 304:G490-500.

Noxious stimuli in the duodenum can result in pancreatitis



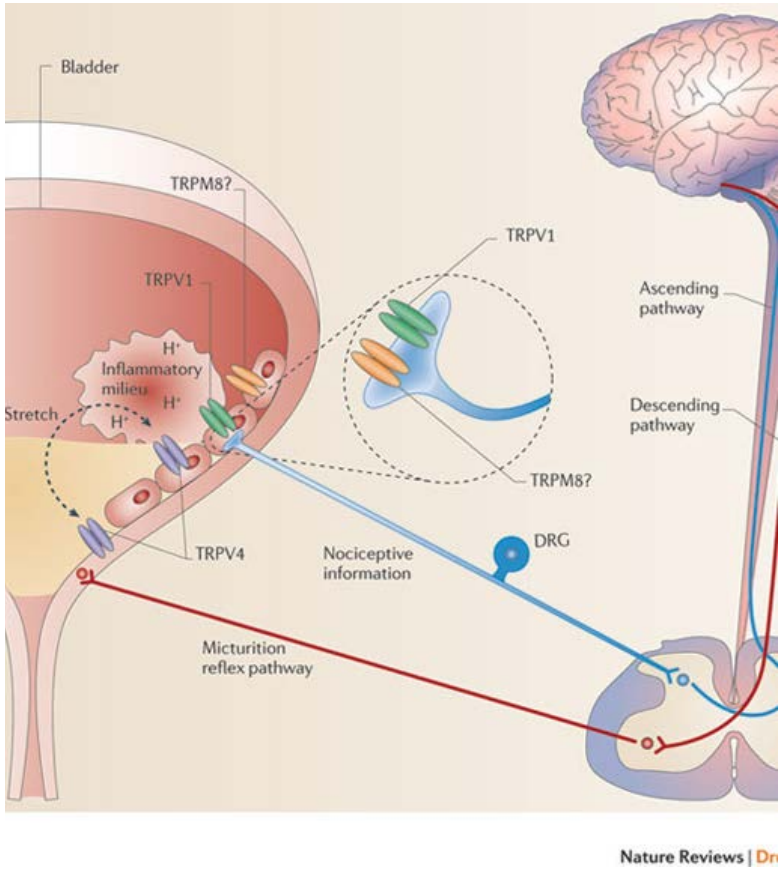






Li…Pasricha. Am J Physiol Gastrointest Liver Physiol; 2013 304:G490-500.

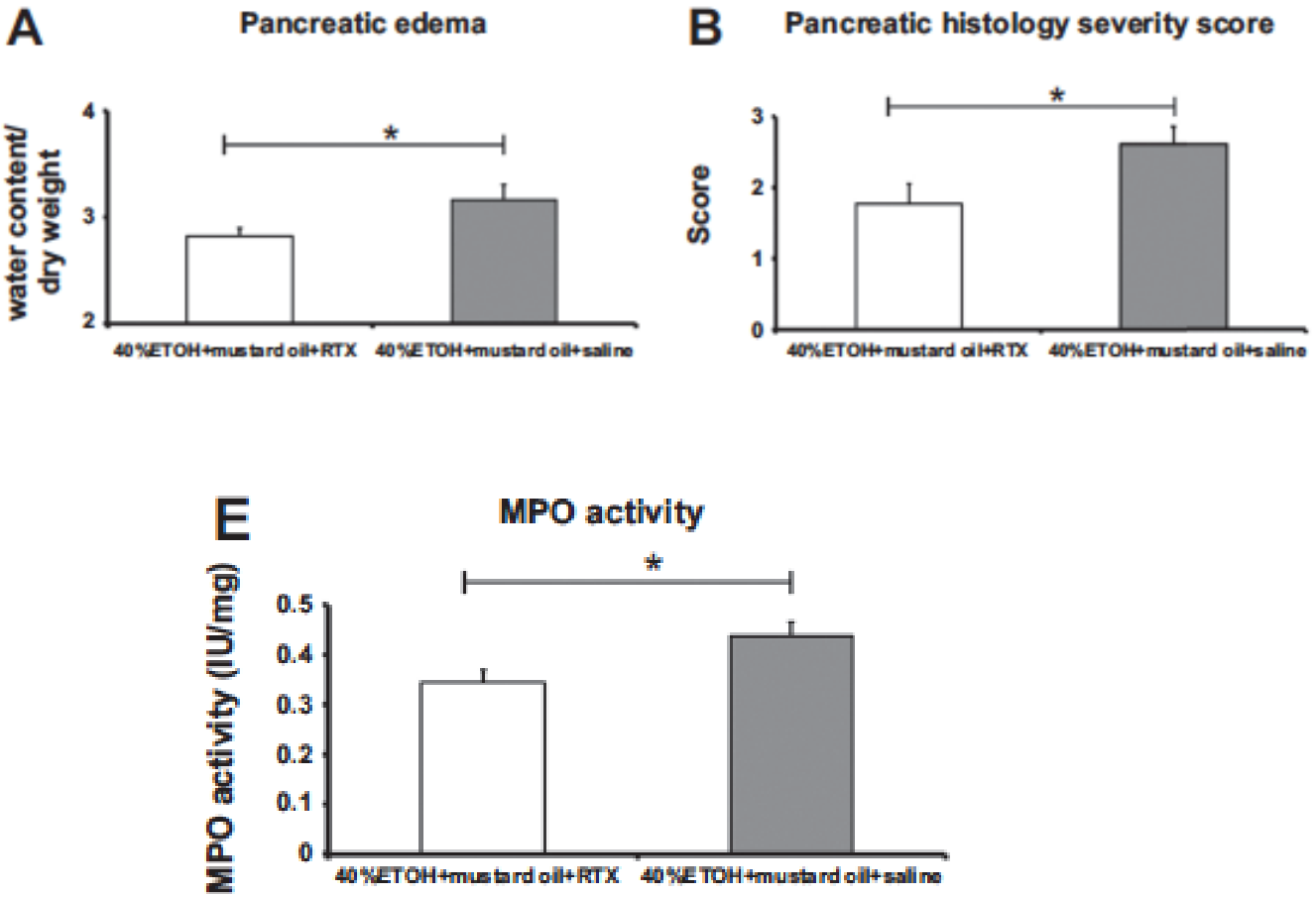
Ablating spinal nociceptive nerves with RTX



- TRPV1 is a master transducer of noxious stimuli and is expressed in a subpopulation of C- and A delta fibers
- Ablation of TRPV1-expressing nociceptive fibers with the potent capsaicin analog resiniferatoxin (RTX) results in long lasting pain relief
- RTX is particularly adaptable to focal application, and the induced chemical axonopathy leads to analgesia with a duration that is influenced by dose, route of administration, and the rate of fiber regeneration

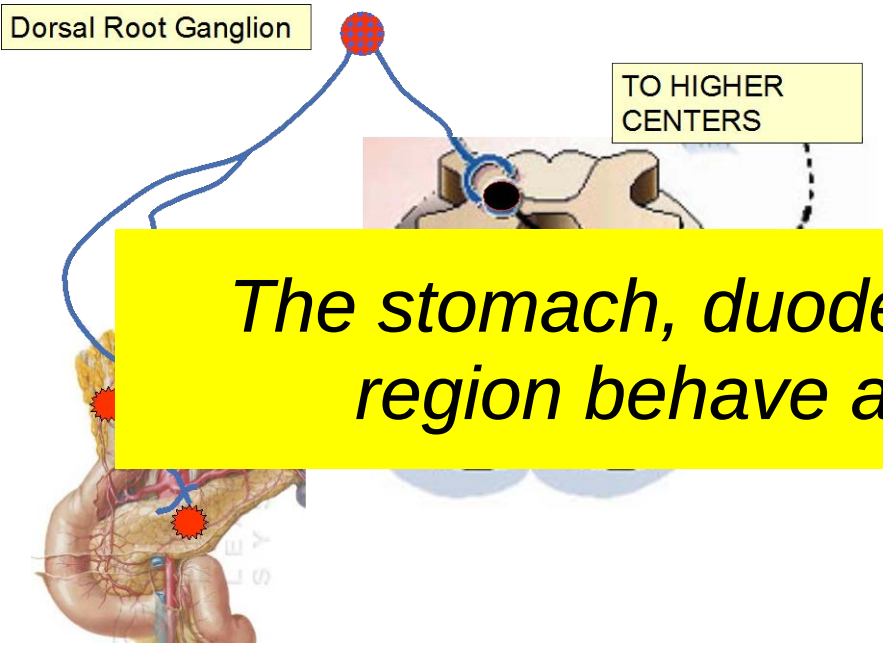
Mol Pain. 2010; 6: 94

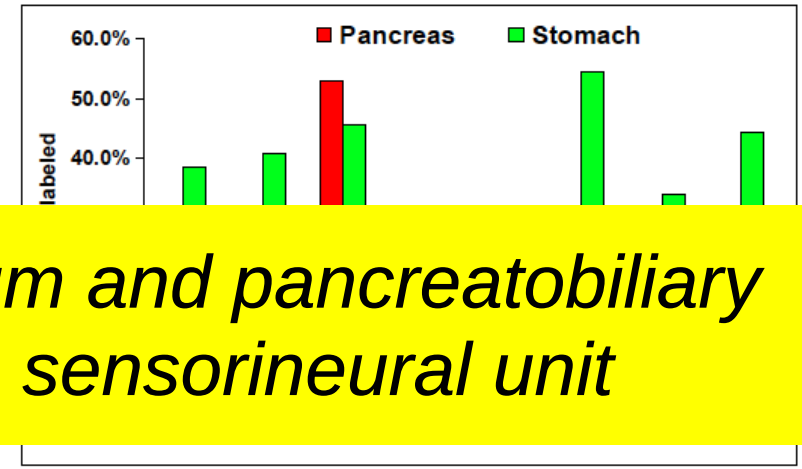
Neural basis for duodenal induced pancreatitis



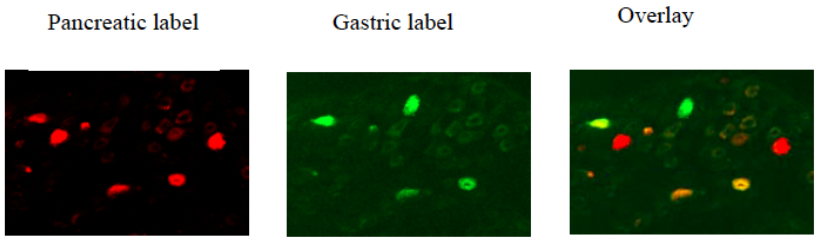
Li…Pasricha. Am J Physiol Gastrointest Liver Physiol; 2013 304:G490-500.

Its more than two organs…

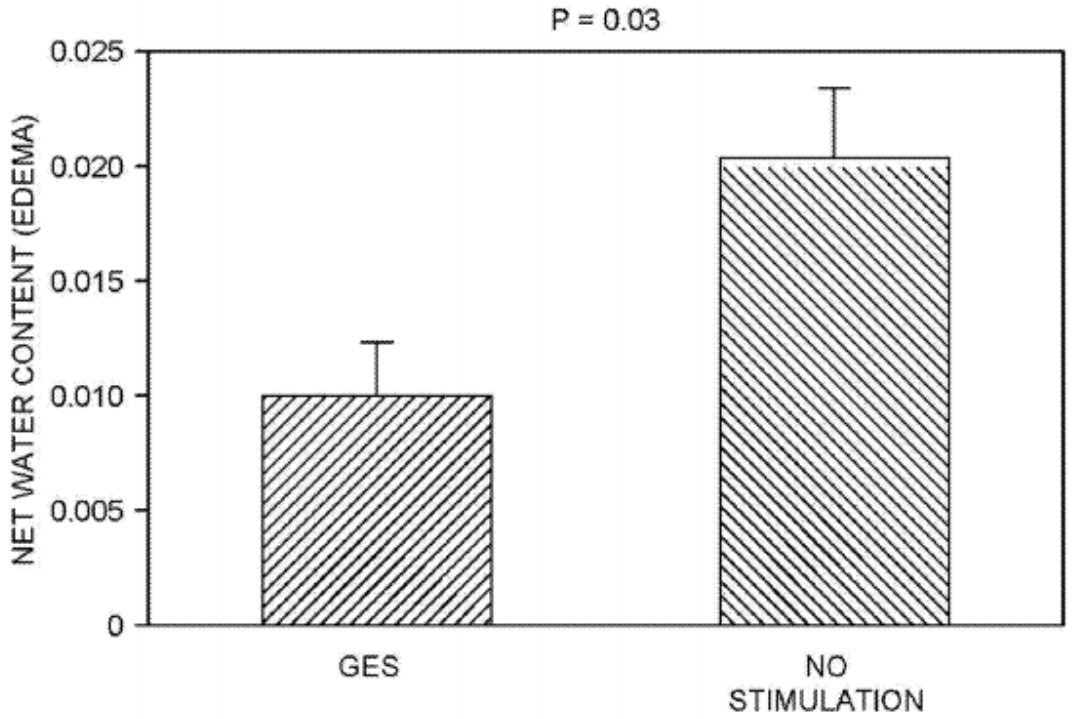




The stomach, duodenum and pancreatobiliary region behave as a sensorineural unit



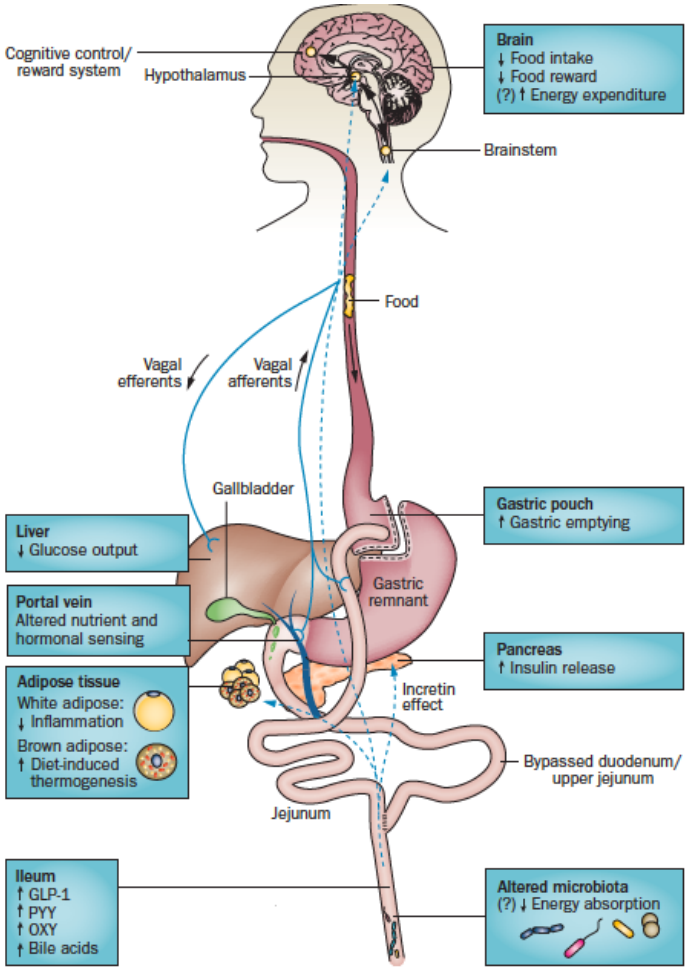
Effects of gastric electrical stimulation on cerulein-induced pancreatitis



(12) **United States Patent**
Pasricha et al.

(10) **Patent No.: US 8,326,427 B2**
(45) **Date of Patent: Dec. 4, 2012**

Metabolic effects



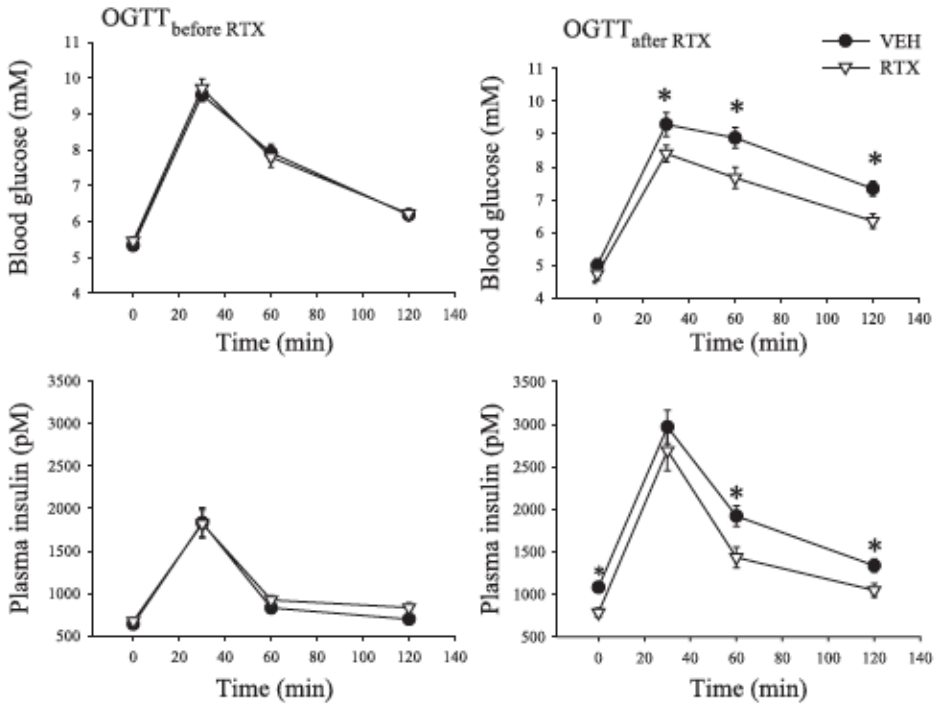
- Roux-en-y Gastric Bypass (RYGB) leads to remission of type 2 diabetes (T2DM) in vast majority of cases
- Duodenal-jejunal bypass sleeve (DJBS) can mimic effects of surgery by limiting GI tract wall contact with nutrients

Miras and Roux Nature Reviews GastroHep 2013

Effects of systemic RTX on Diabetes

Am J Physiol Endocrinol Metab 288: E1137–E1145, 2005;
doi:10.1152/ajpendo.00356.2004.

Sensory nerve inactivation by resiniferatoxin improves insulin sensitivity in male obese Zucker rats

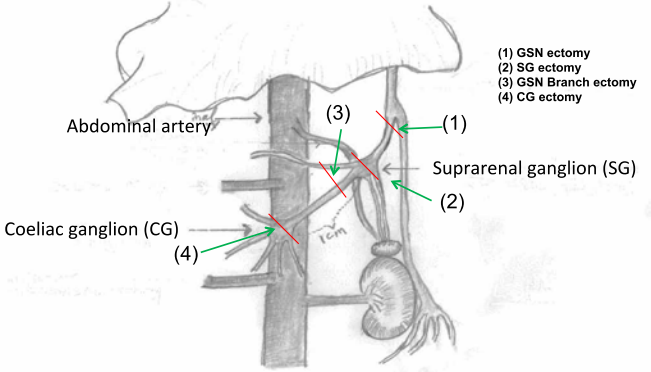


Conclusions

- Spinal sensory nerves to the viscera play an important role in health and disease
  - Inflammation
  - Pain
  - Metabolic state
- They may therefore be important targets for neuromodulation

Conclusions

- Multi-organ innervation is a characteristic feature of spinal sensory nerves
- This poses several challenges and opportunities for neuromodulation approaches
  - Finding the nodal point
  - Restricting the specificity of the effect
- Further research on the mechanisms underlying their effects is critically needed to fully realize their potential as therapeutic targets
  - Anatomical and functional mapping
  - Local, CNS and somatic connections



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