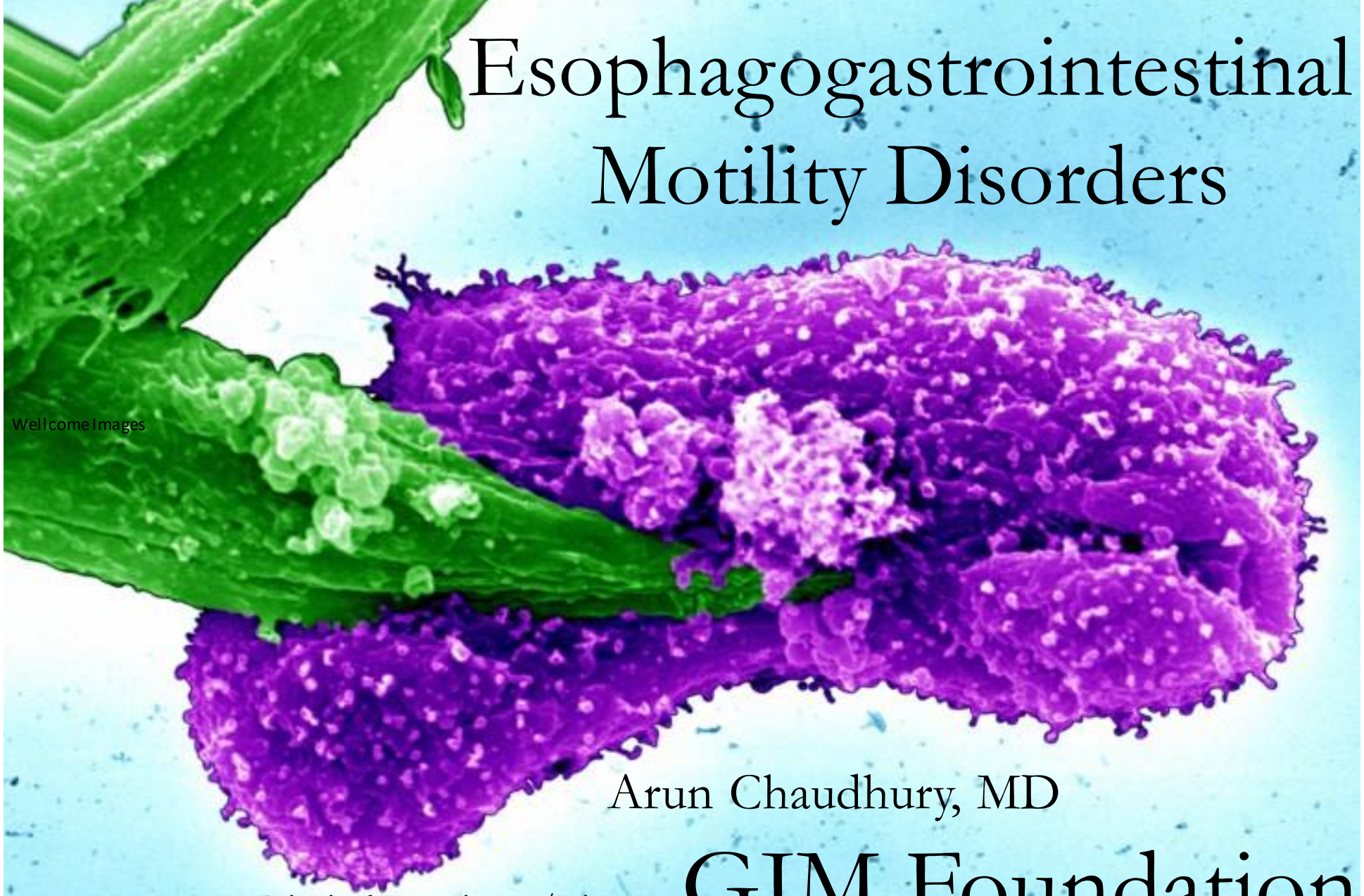
Esophagogastrointestinal Motility Disorders

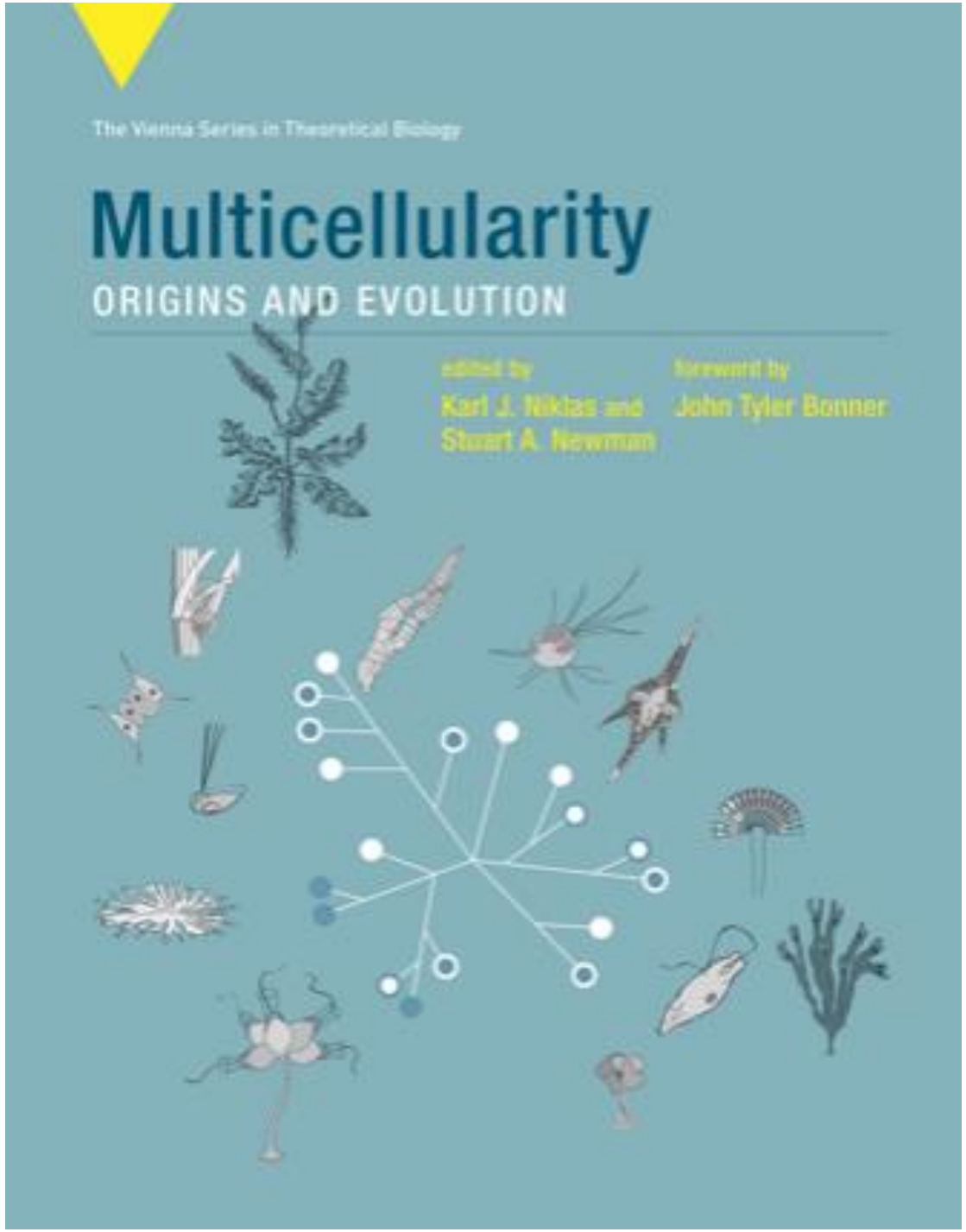


Wellcome Images

Arun Chaudhury, MD

Principal Investigator/Director, GIM Foundation

Little Rock, Arkansas, USA



Need for external acquisition of nutrition

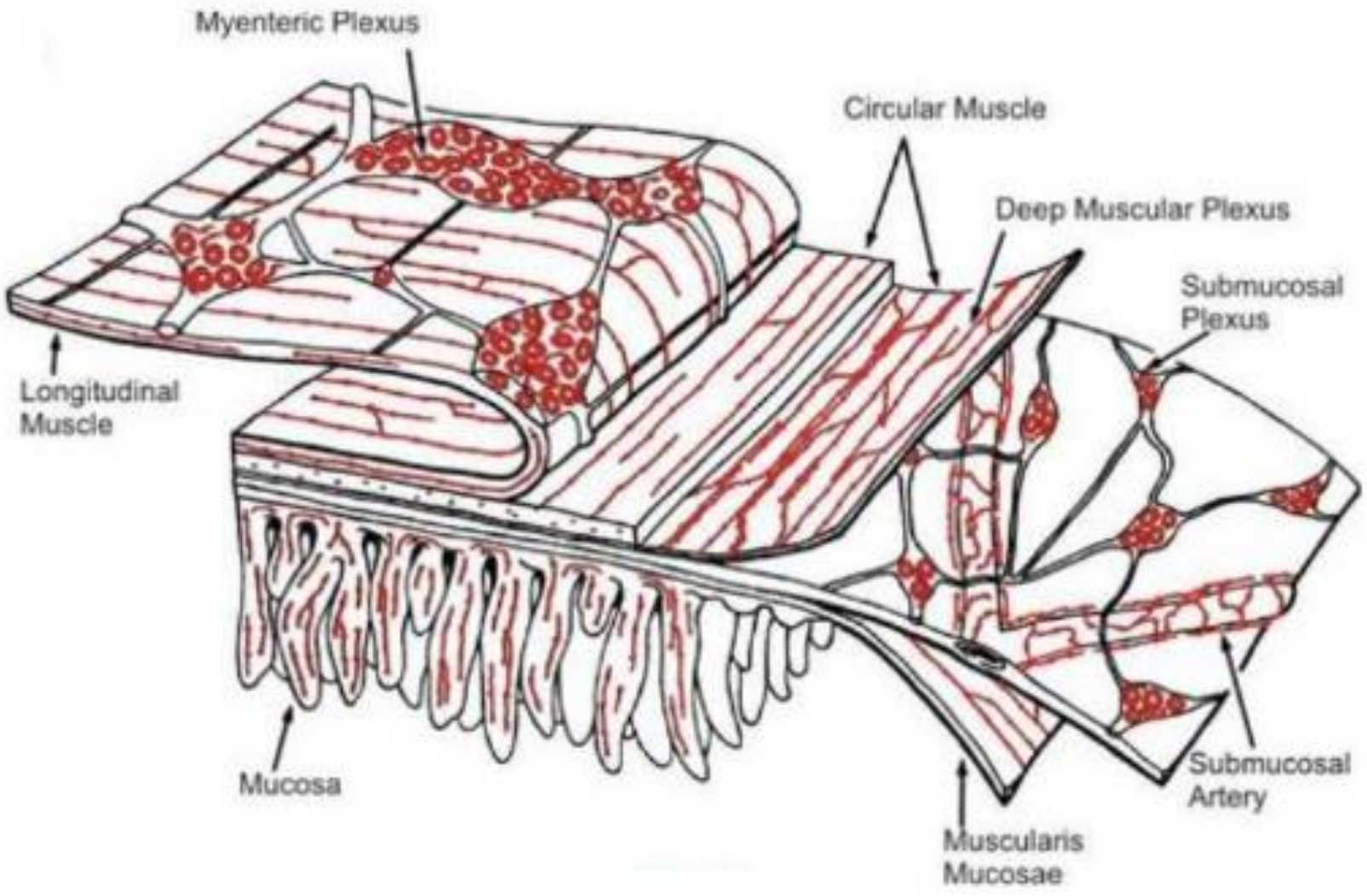
The gastrointestinal (GI) tract

- Anaerobic fermenter
- Long winding asymmetric tract with STOPCOCKS
- mostly silent except at the front and backend (belch/wind)…sometimes borborygmus
- Don’t forget to ask your patients whether they have “Passed Gas”..ask directly…*sine qua non* of patency of intestinal lumen in ICU/surgical ward

Layered organization

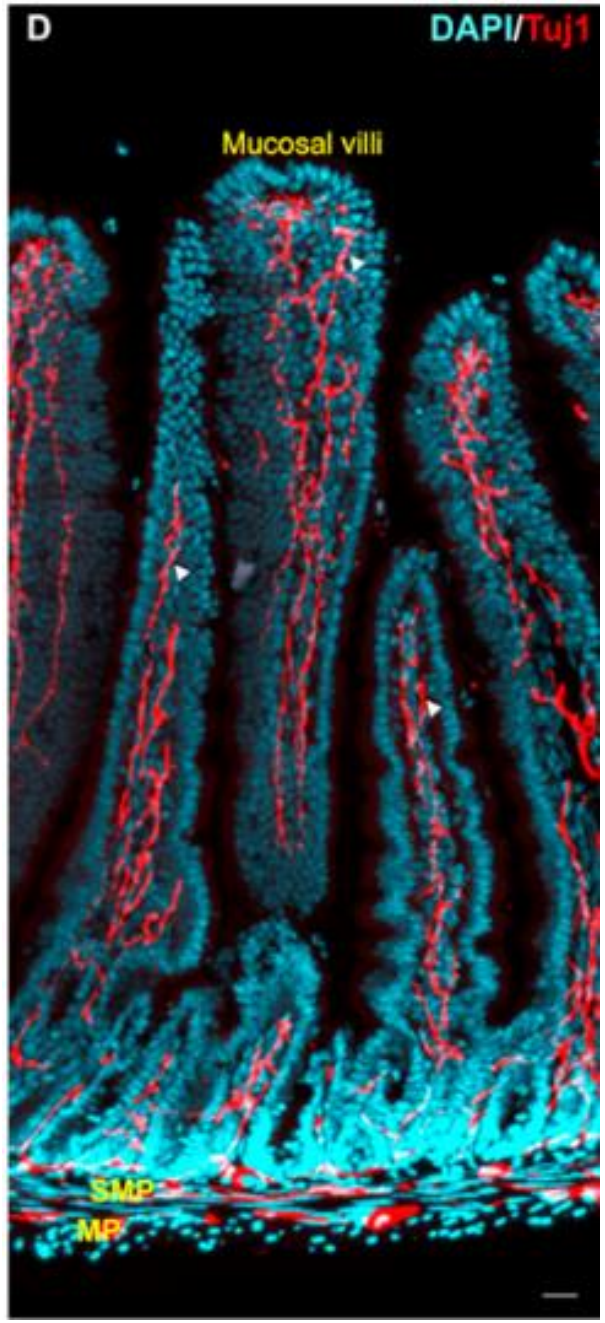
Enteric Nervous System

- Sensor
- Progressive motility
- Secretomotor
- Vasomotor
- Toxin detection
- Pain

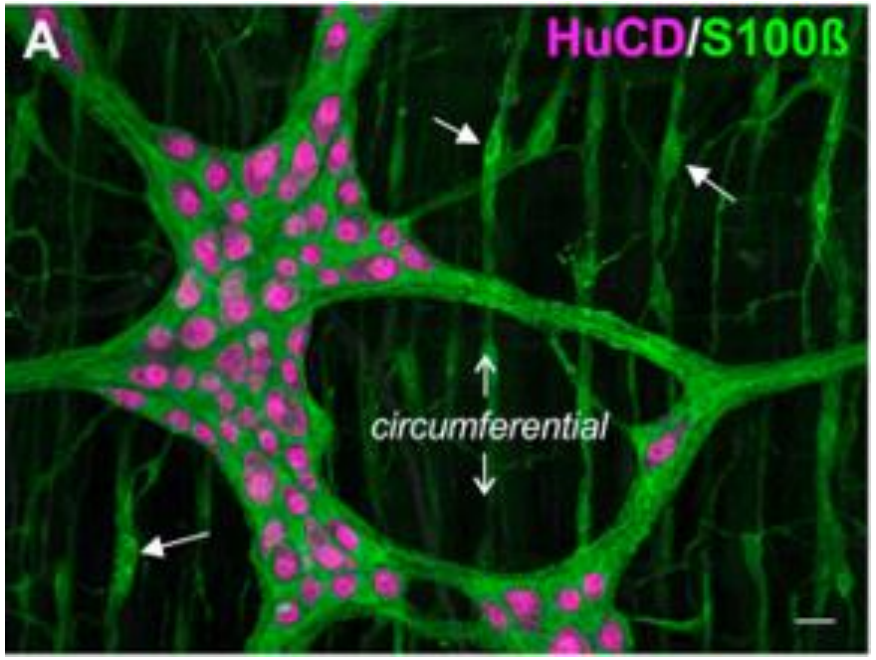


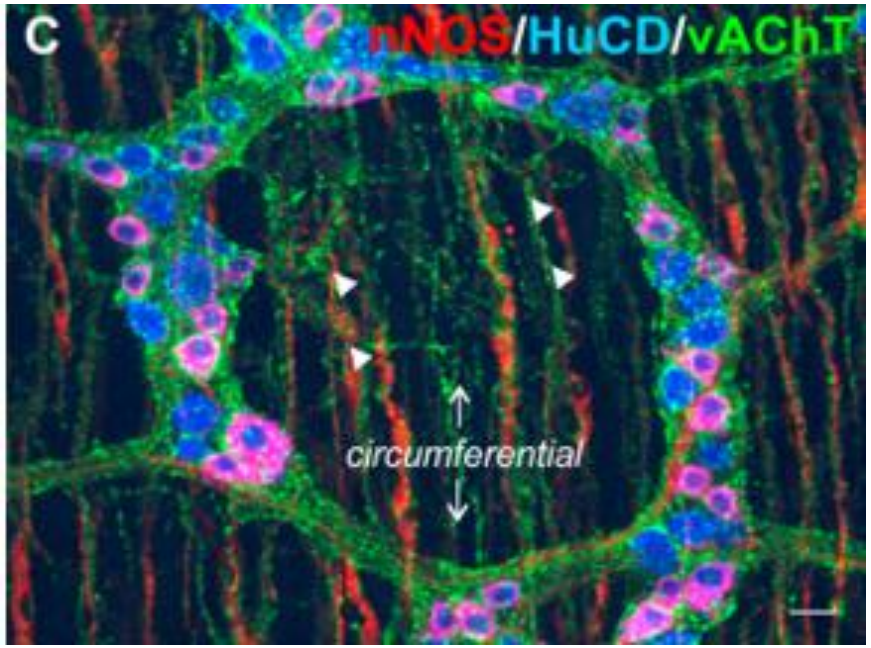
Hao et al, 2016, *Developmental Biology*

slice



laminar preparation

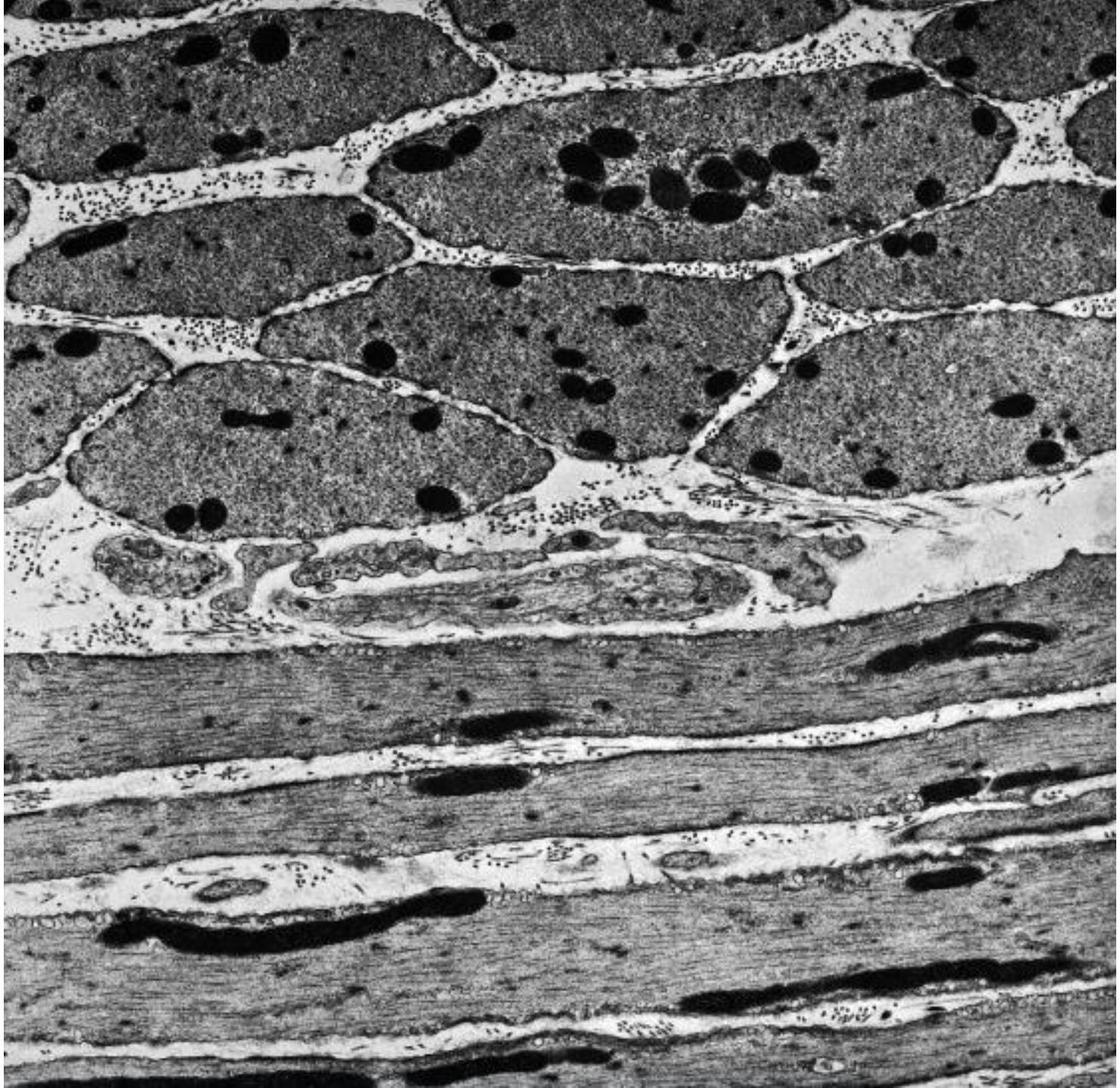




neurons
glia

Principal Neurotransmitters

Nitric oxide (NO)
Acetylcholine (ACh)

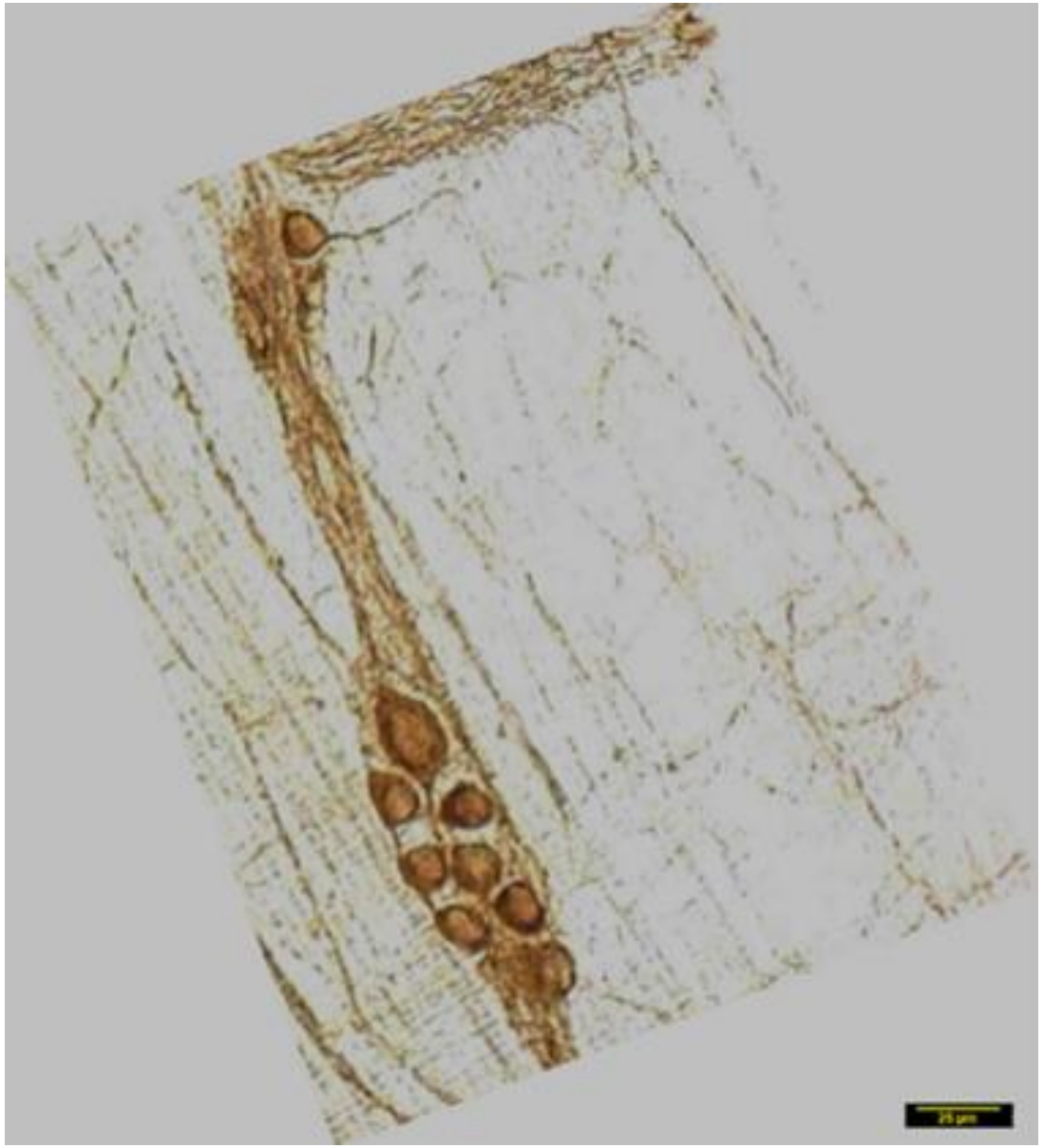


Wellcome Images

Sandwiched!

Myenteric Ganglia
(Auerbach's Plexi)

The **JUNCTION**



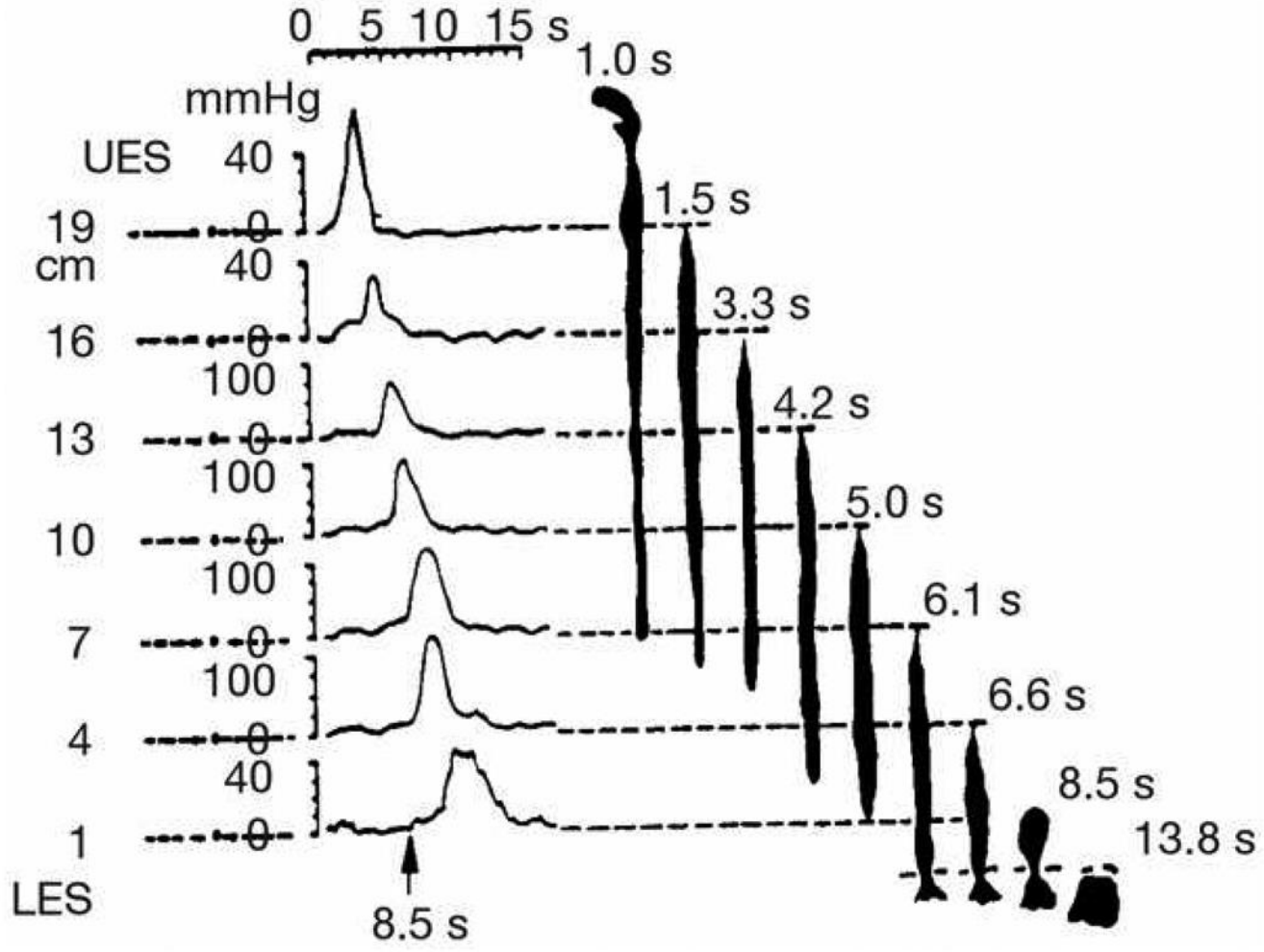
Dogiel neurons:
IPANs (intrinsic primary afferent neurons) & interneurons

Chaudhury et al, 2014, *Frontiers in Medicine (Gastroenterology)*

Can one drink during *sirshasan*?

Franz Ingelfinger

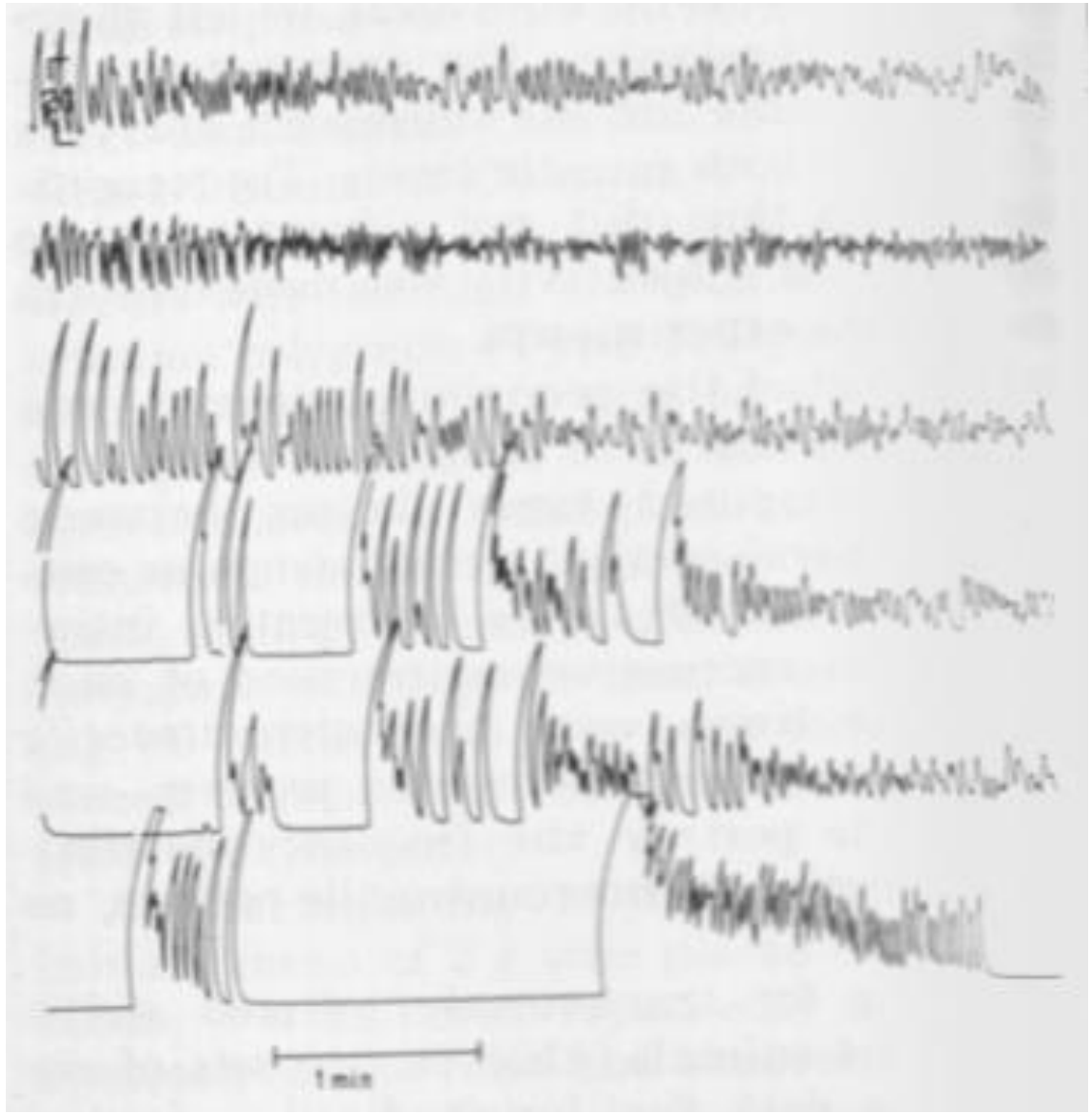
Simultaneous Fluoroscopy & Esophageal Manometry



Dodds WJ, Christensen J, Dent J, Arndorfer RC, Wood JD. Pharmacologic investigation of primary peristalsis in smooth muscle portion of opossum esophagus. Am J Physiol 1979;237(6):E561–E566

LES

Tonic



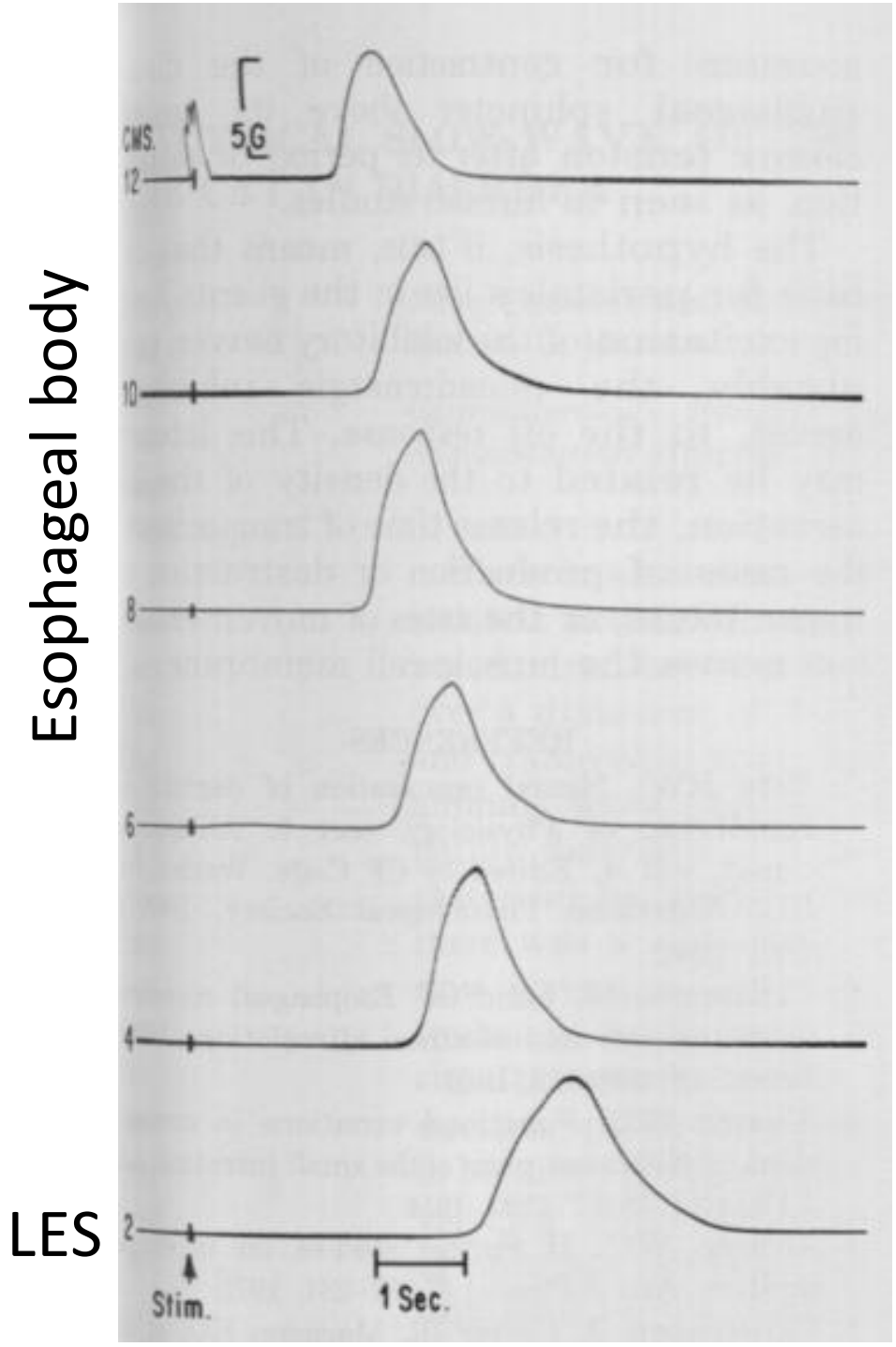
Esophageal body

Phasic

Gradients of Contractions in the Opossum Esophagus

Norman Weisbrodt & James Christensen,
Gastroenterology, 1972

Goyal and Chaudhury 2008, *Journal of Clinical Gastroenterology*

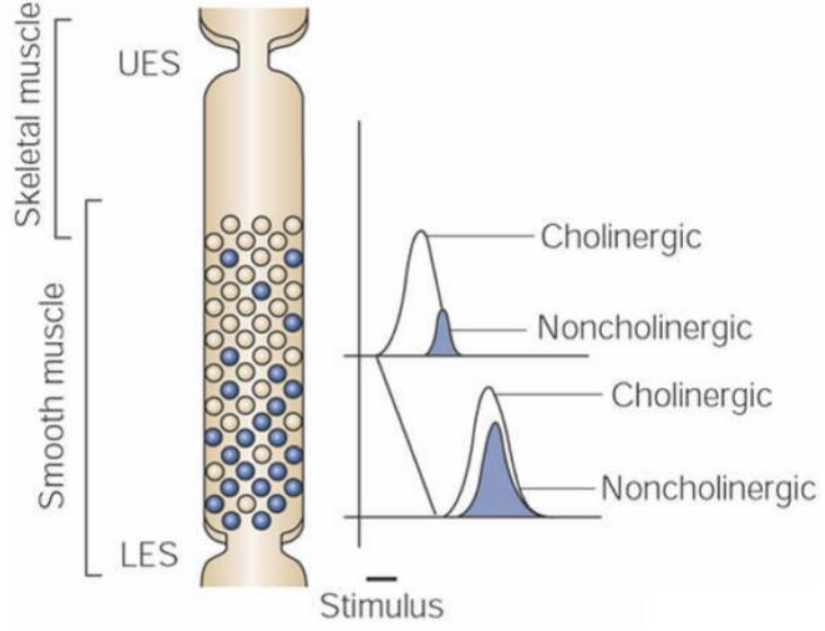


Relaxation as well!

Norman Weisbrodt & James Christensen, *Gastroenterology*, 1972

First rigorous evidence of

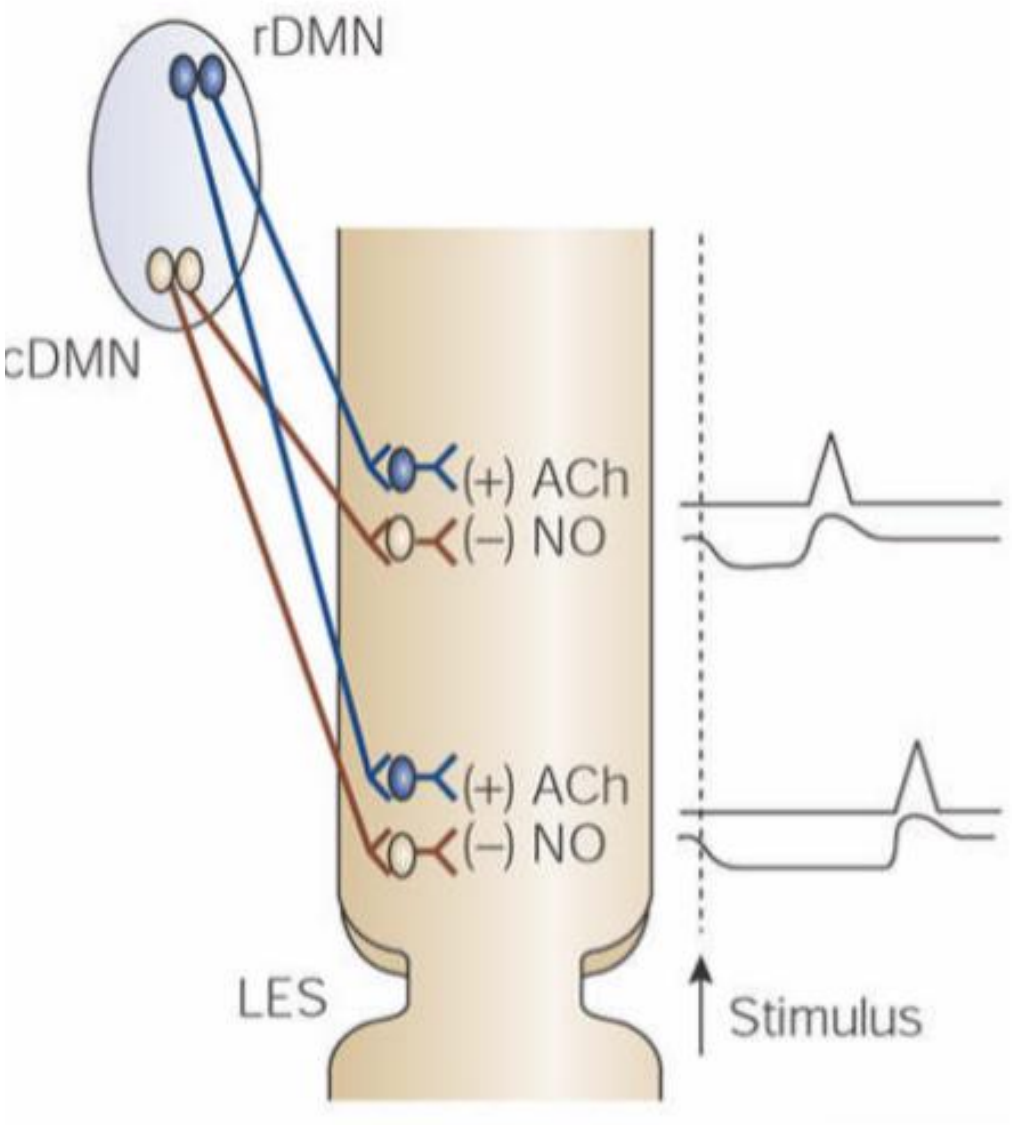
INHIBITORY NEURO-SMOOTH MUSCLE NEUROTRANSMISSION



Goyal and Chaudhury 2008, *Journal of Clinical Gastroenterology*

Ascending Excitation, Descending Inhibition

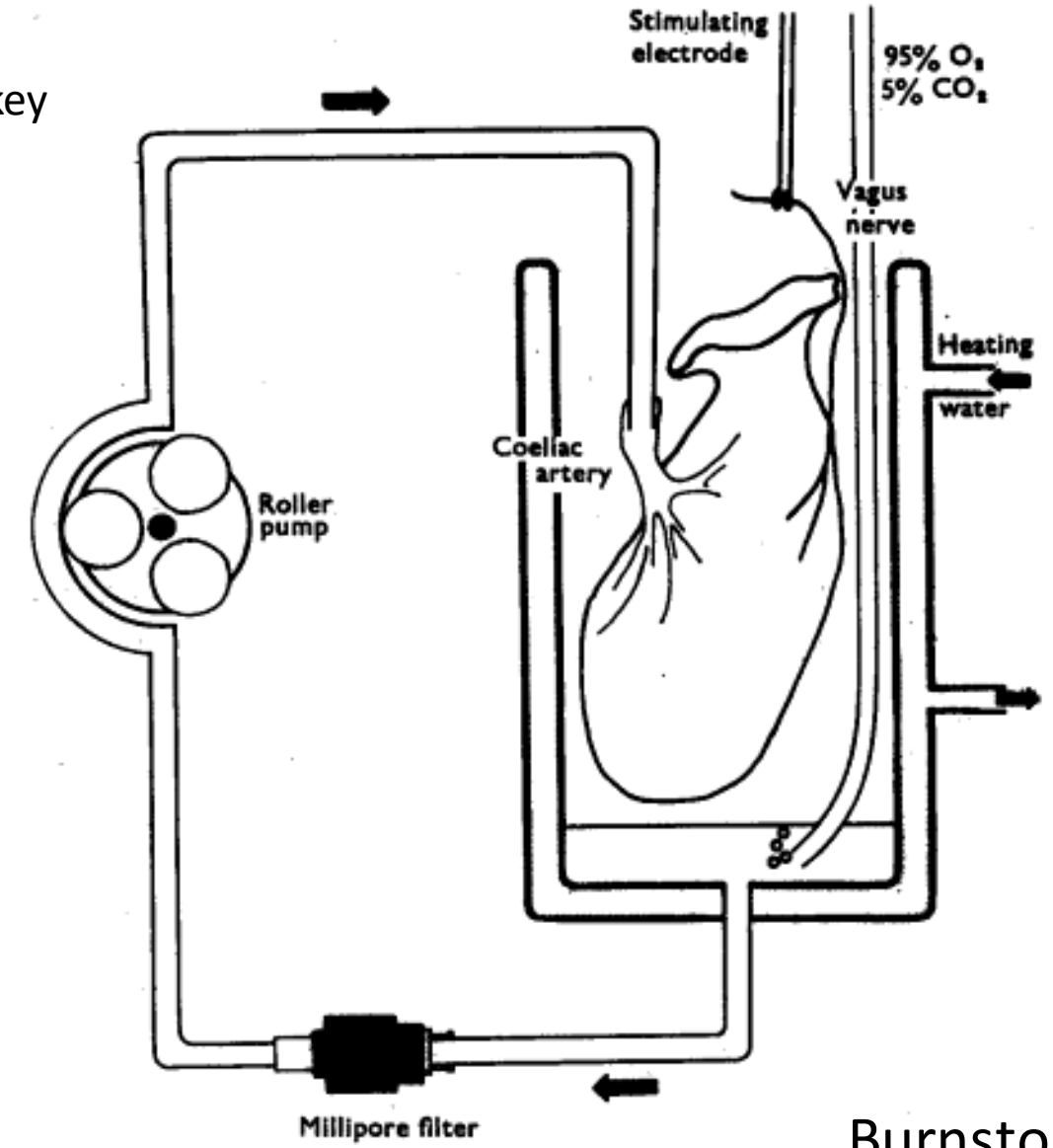
Accommodation of bolus



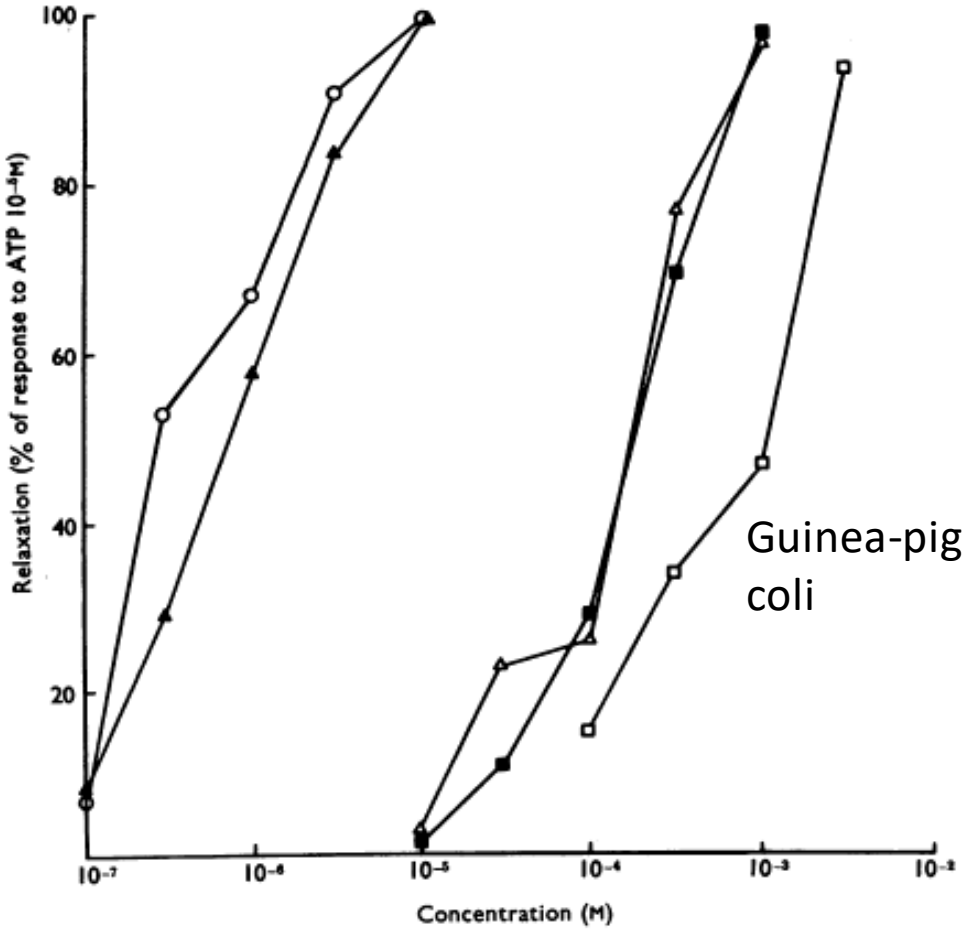
Goyal and Chaudhury, 2008

ATP as a NANC neurotransmitter

Turkey
Fish



Superfusion assay, Sir John Vane



Guinea-pig tenia coli

FIG. 5. Relative potencies of purine compounds in causing relaxation of the isolated guinea-pig taenia coli. Ordinate: amplitude of relaxation as a percentage of the response to ATP (10^{-5}M). Abscissa: molar concentration (log scale). Dose-response curves are shown for ATP (▲), ADP (○), AMP (△), adenosine (■) and GMP (□). The tissues were exposed to the agonists for 30 s. Each point is the mean of values obtained on three preparations.

Burnstock et al Br J Pharmacol 1970

Fiziol Zh. 1964 May-Jun;10:403-7.

[METHOD FOR THE INVESTIGATION OF THE ELECTRIC PROPERTIES OF NERVE AND MUSCLE FIBERS BY MEANS OF SURFACE EXTRACELLULAR ELECTRODES].

[Article in Russian]

ARTEMENKO DP, SHUBA MF.

KCl Amplify mV signals

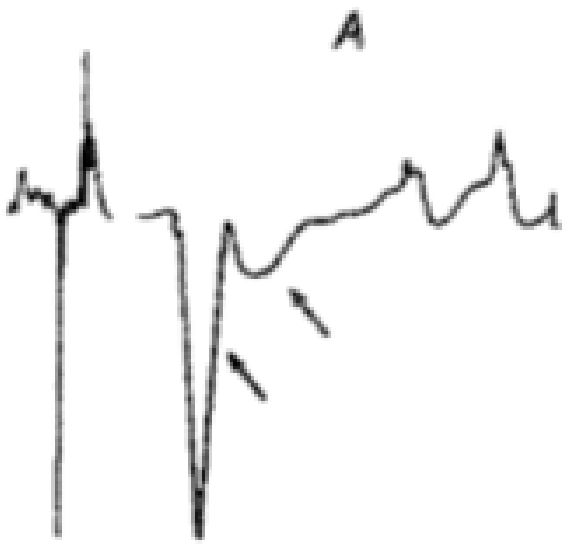
PMID: 14293445

[Indexed for MEDLINE]

impale

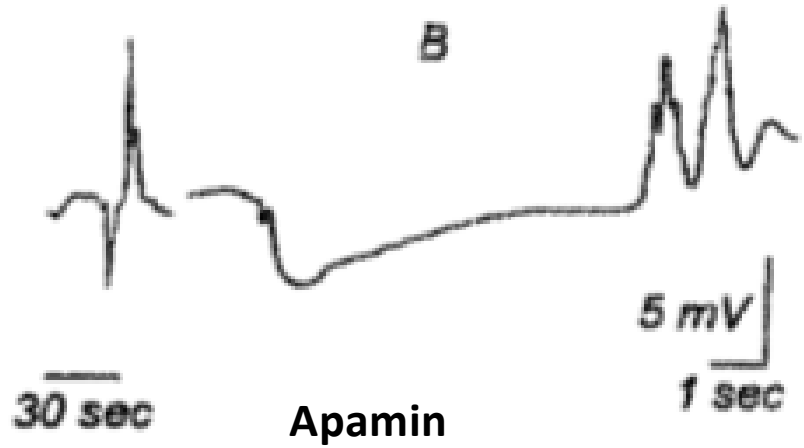
Inhibitory Junction Potential (IJP)

Compound IJP



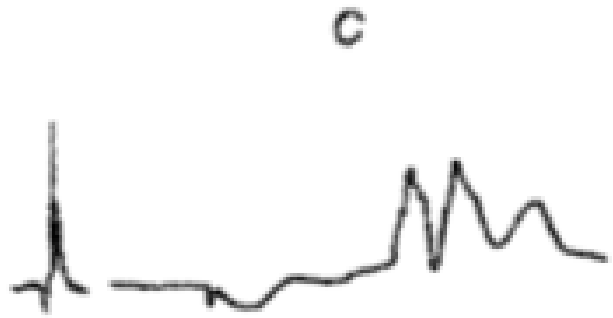
Atropine
Guanethidine

Fast IJP



Apamin

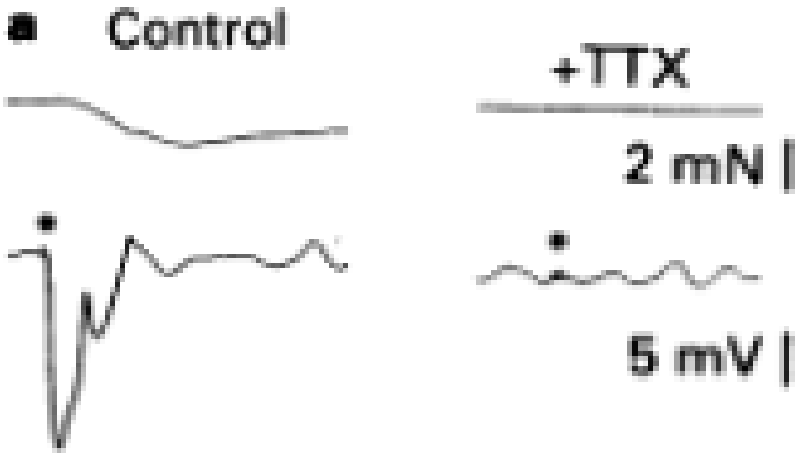
Slow IJP



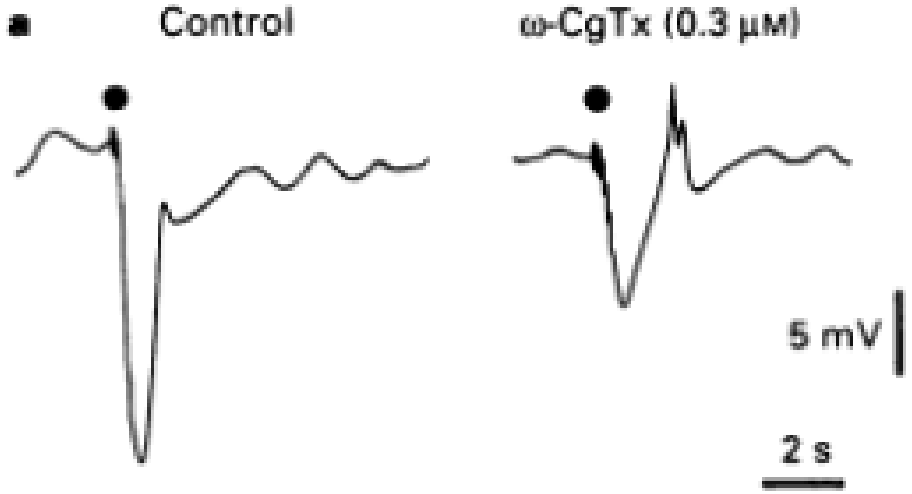
Apamin +
L-NAME

Shuba MF; Zagordynuk & Maggi; Goyal & He; Burnstock; Chaudhury; Furness; Jimenez M.

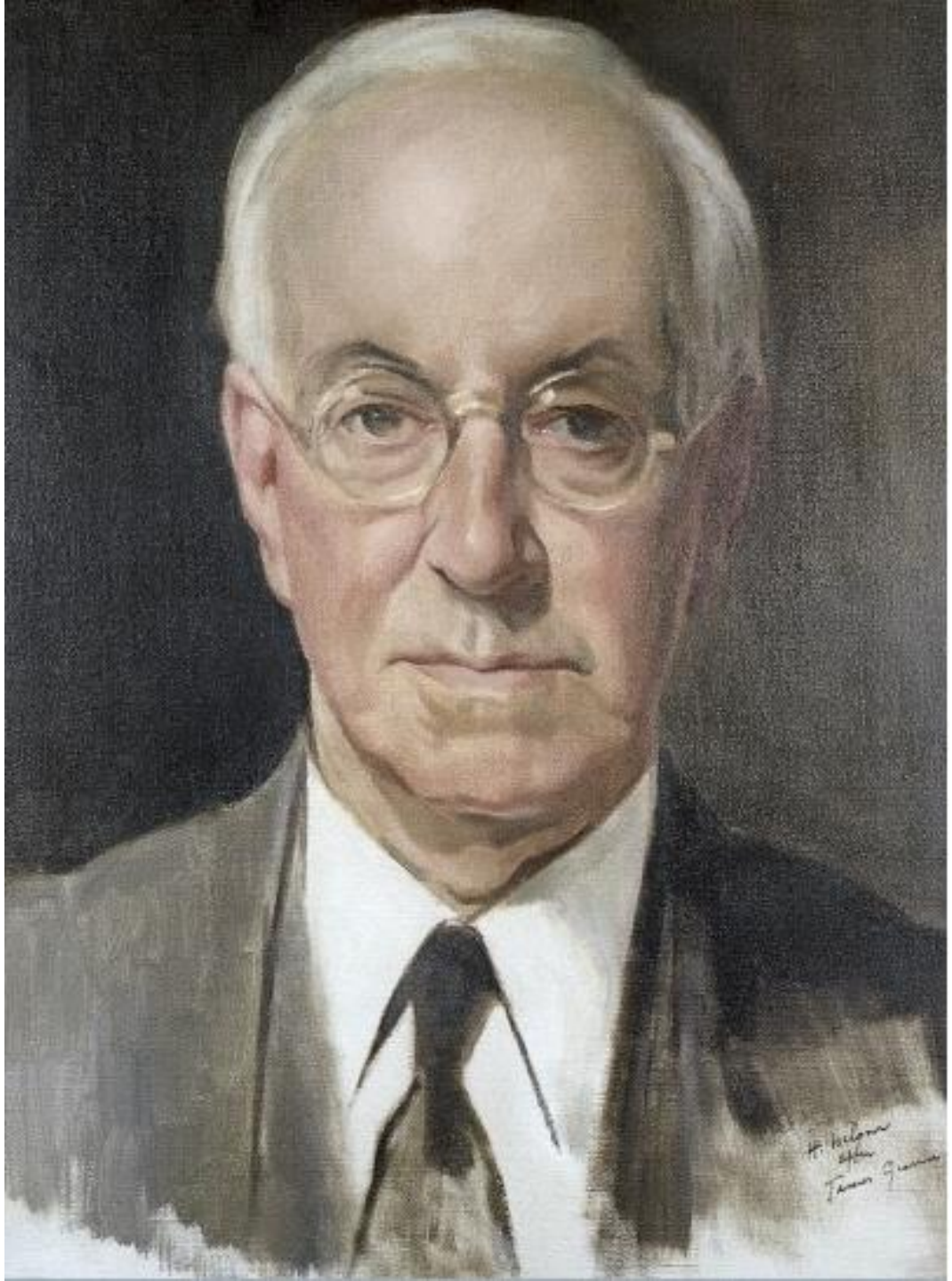
Characteristics of IJP



Neural prejunctional release



Calcium dependent



Sir Henry Dale

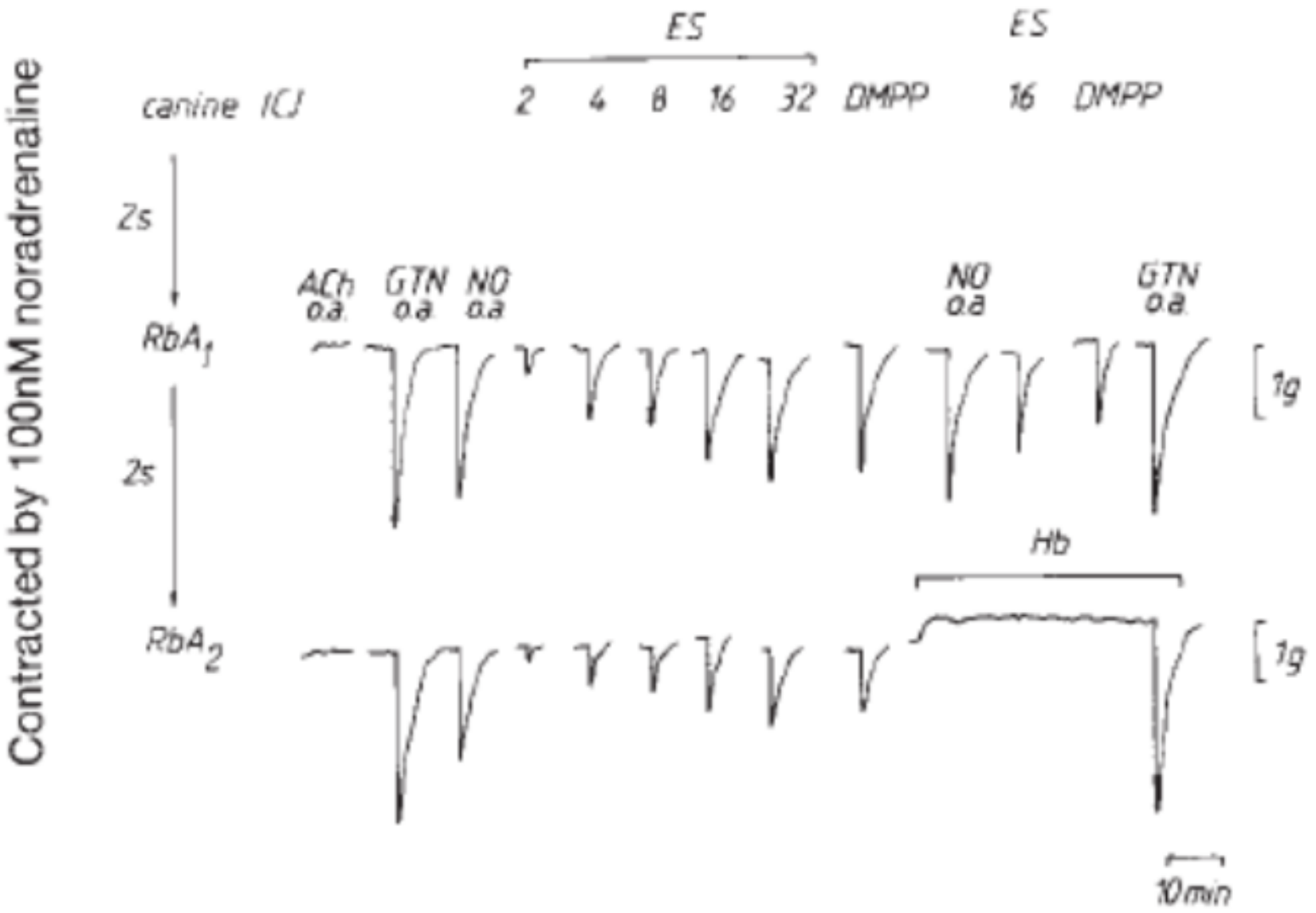
One neurone,
one neurotransmitter

Wellcome Images

?Multiplicity of neurotransmitters during enteric neuro-smooth muscle neurotransmission

Burnstock; Chaudhury

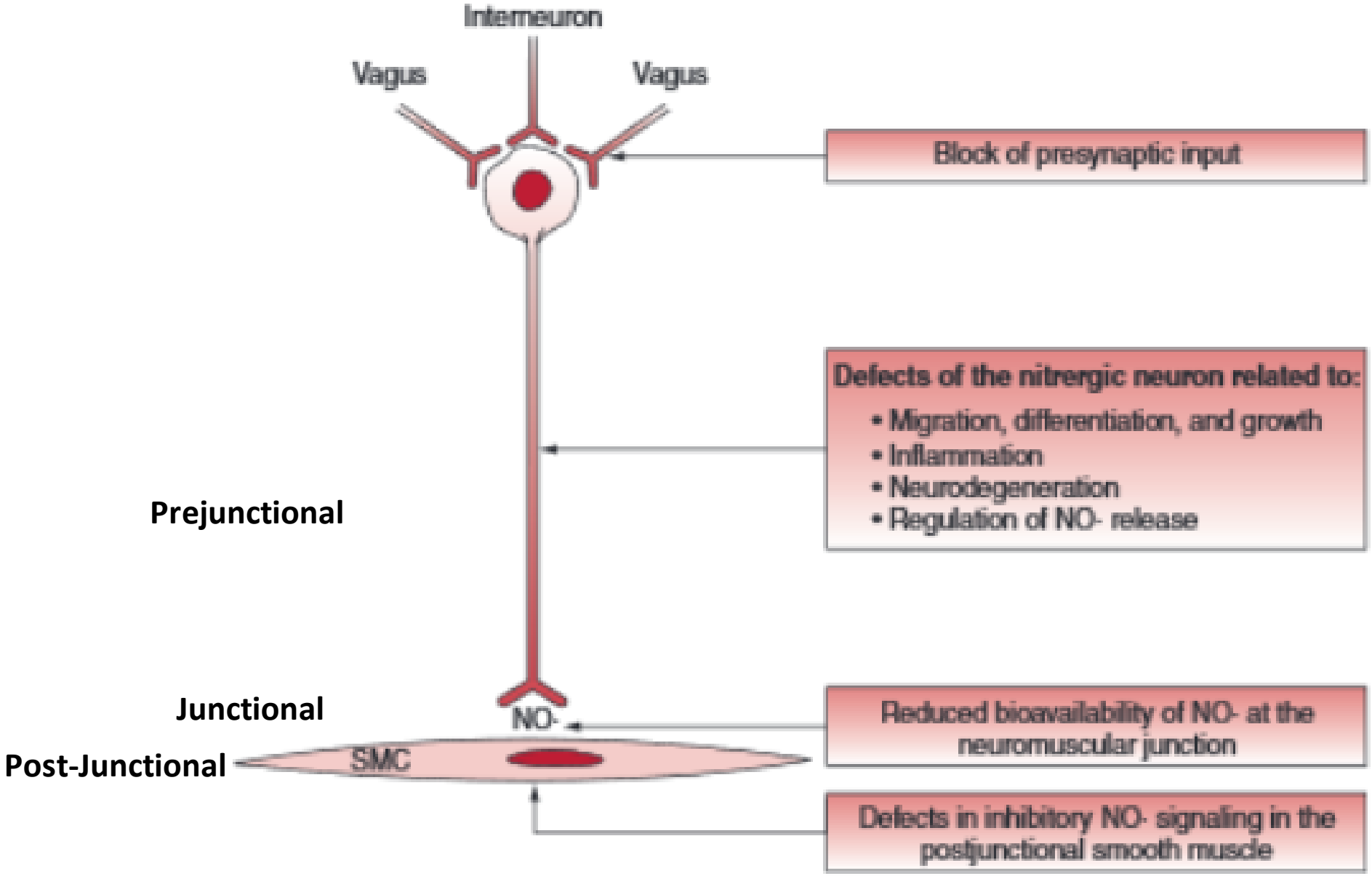
Gut nerve stimulation releases nitric oxide (NO)



Bult et al 1990

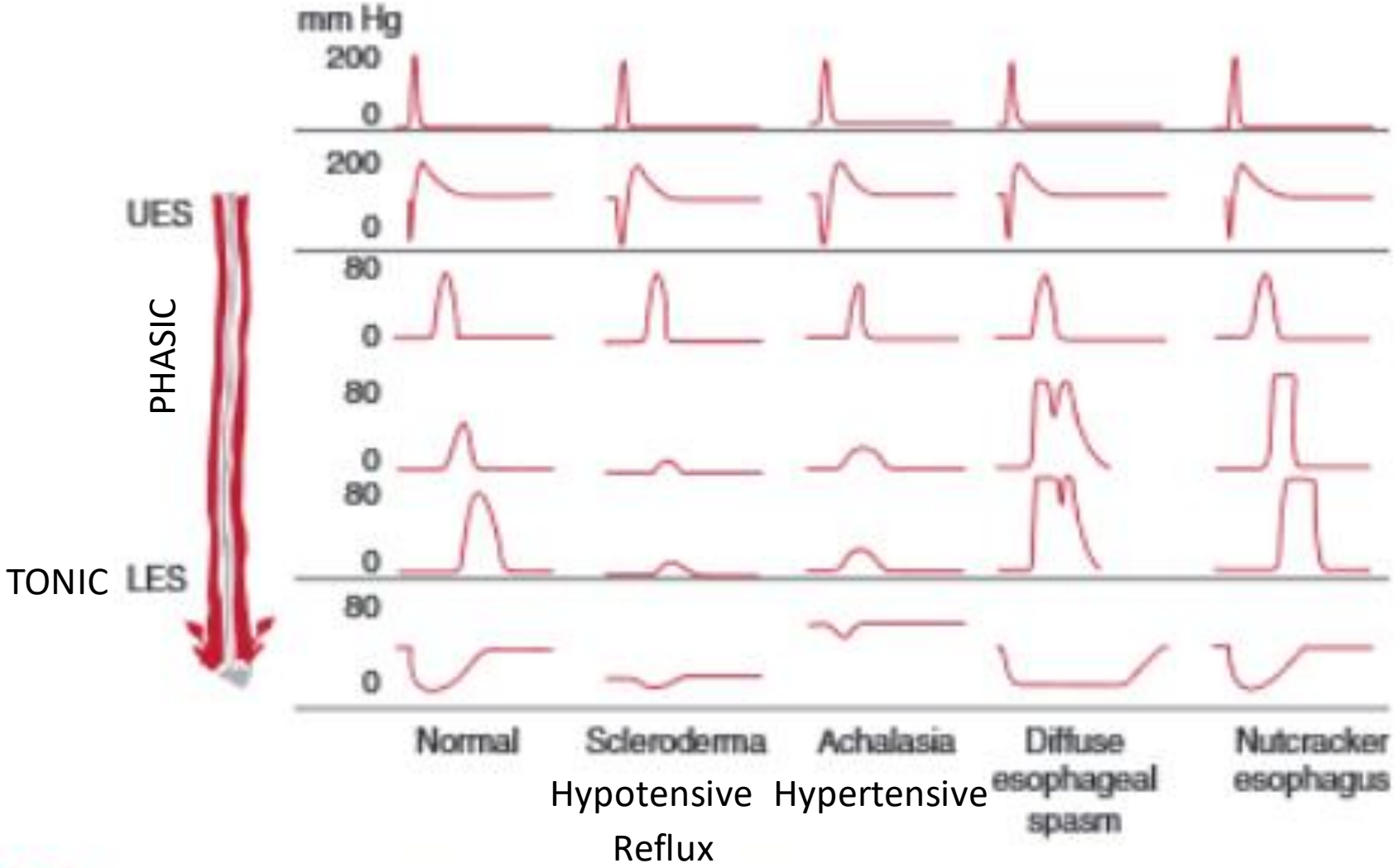
Defects in Nitrergic Function may explain gut motility disorders

Chaudhury & Mashimo, Ch 13, 3rd Edition, **Current Diagnosis and Treatment in Gastroenterology**



Manometry aids definitive diagnosis

Chaudhury & Mashimo, Ch 13, 3rd Edition, **Current Diagnosis and Treatment in Gastroenterology**

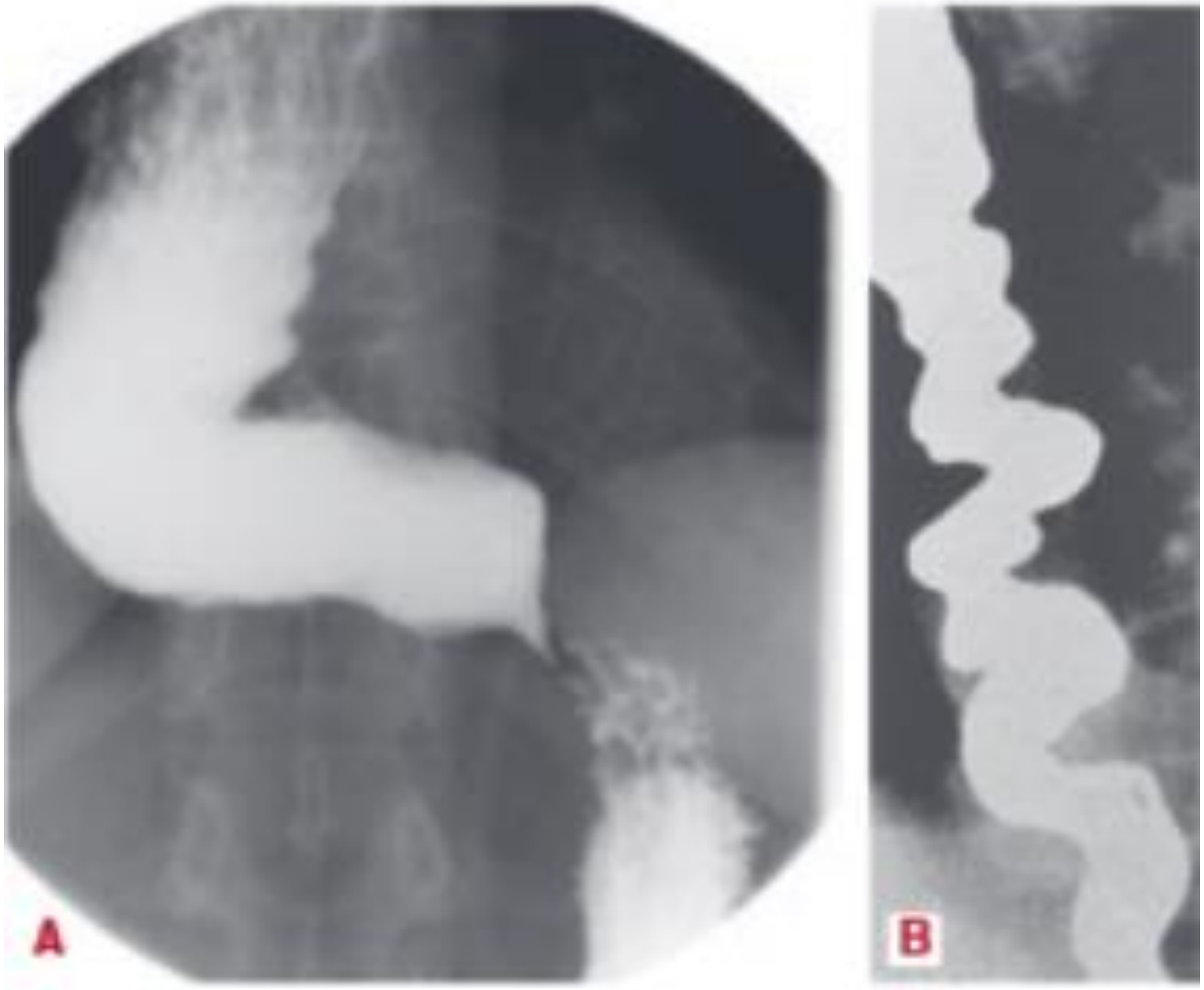


▲ **Figure 13–5.** Motility patterns in esophageal smooth muscle disorders. LES, lower esophageal sphincter; UES, upper esophageal sphincter. (Adapted, with permission, from Goyal RK: Diseases of the Esophagus. In: Fauci AS, Braunwald E, Kasper DL, et al (editors): *Harrison's Principles of Internal Medicine*, 17th ed. McGraw-Hill, 2008.)

Chaudhury & Mashimo, Ch 13, 3rd Edition, **Current Diagnosis and Treatment in Gastroenterology**

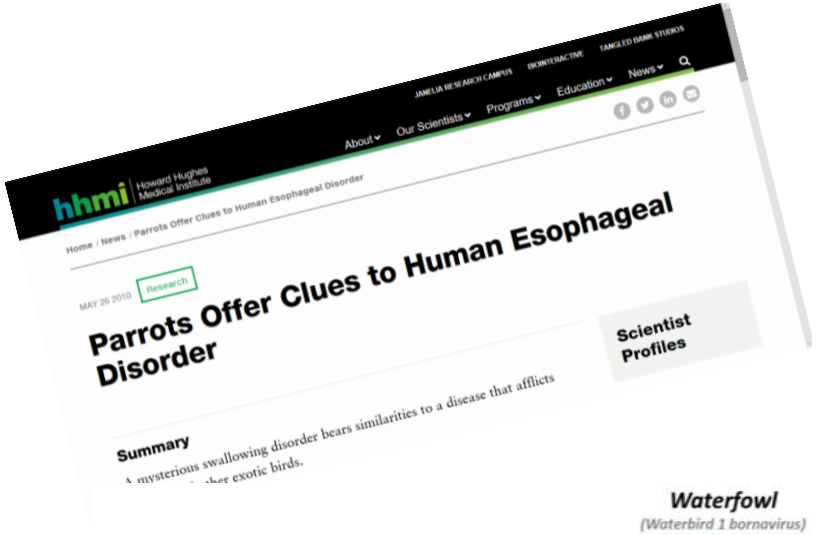
Achalasia

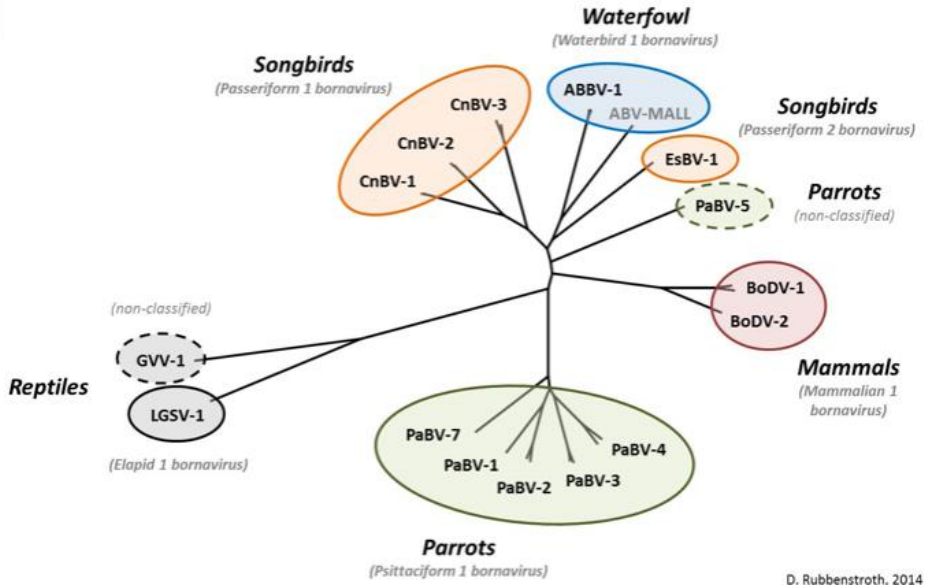
Diffuse Esophageal Spasm



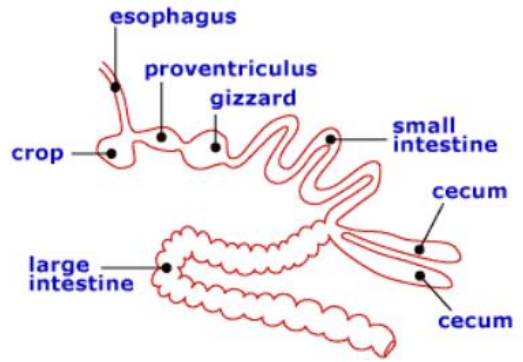
NCCP, Non-cardiac chest pain

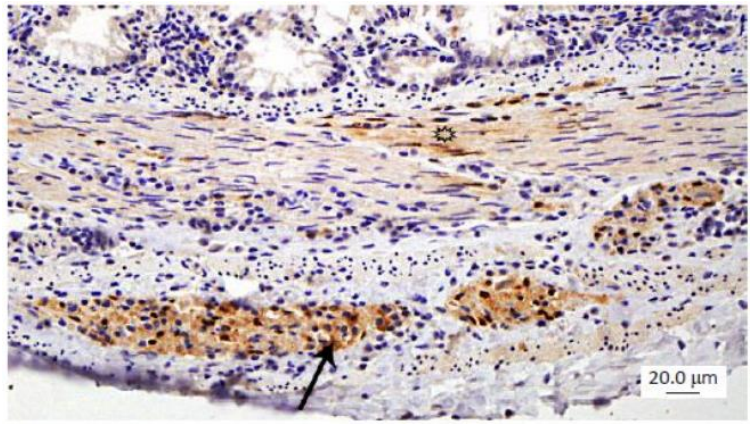
Proventricular dilation disease





Bornaviridae



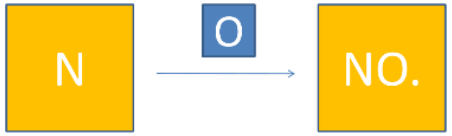


Last et al 2012, JSAVA

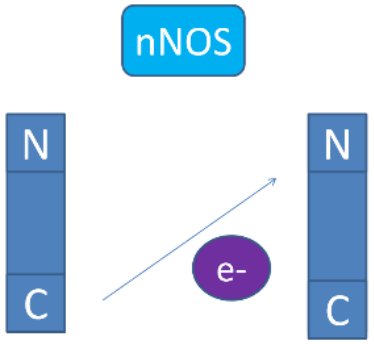
Goyal and Chaudhury, *Gastroenterology*, 2010;
Chaudhury, *Gastroenterology*, 2015

Bioelectronics of Nitric Oxide (NO) synthesis

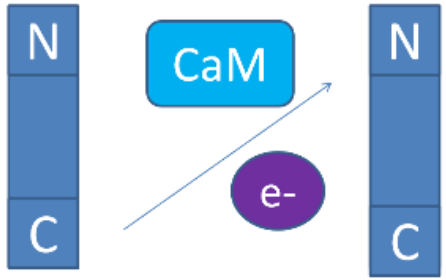
Synthesis of NO



Catalytic synthesis of NO



Facilitation of electron transfer



Active nNOS

Inhibition of electron transfer

Inactive nNOS

Non-vesicular transmitter follows Sherringtonian laws of neurotransmission

Chaudhury et al 2008, 2009

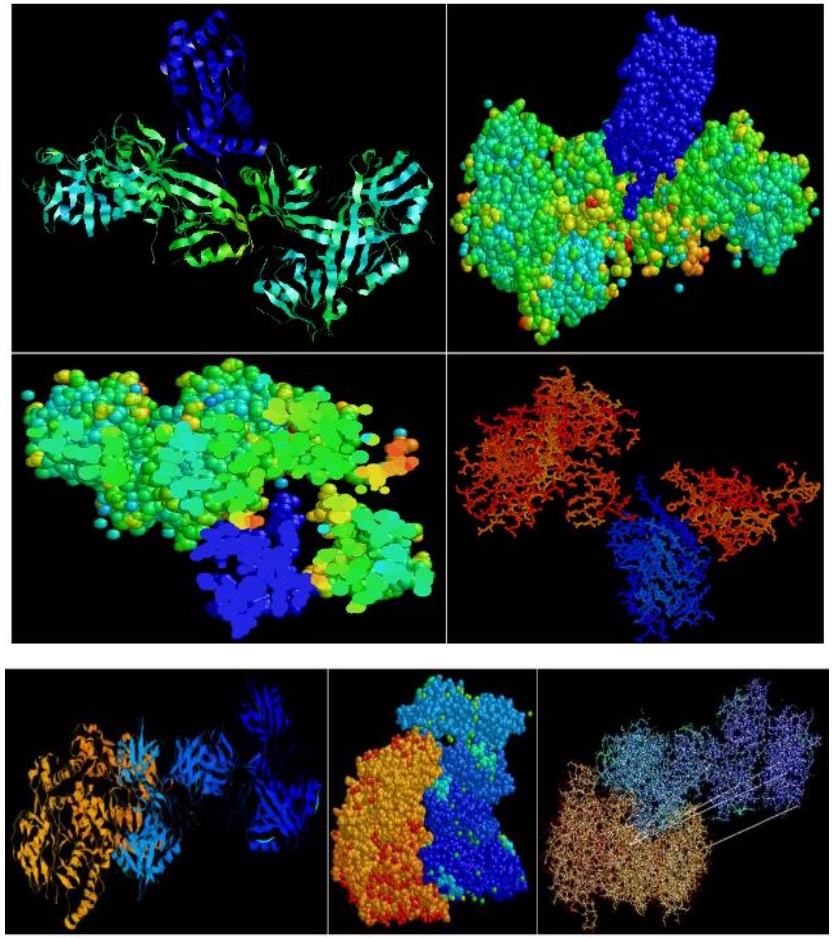
Molecular adaptors of nNOS

- LC8/DLC8/PIN
- PSD95
- BH4

Chaudhury
Gangula

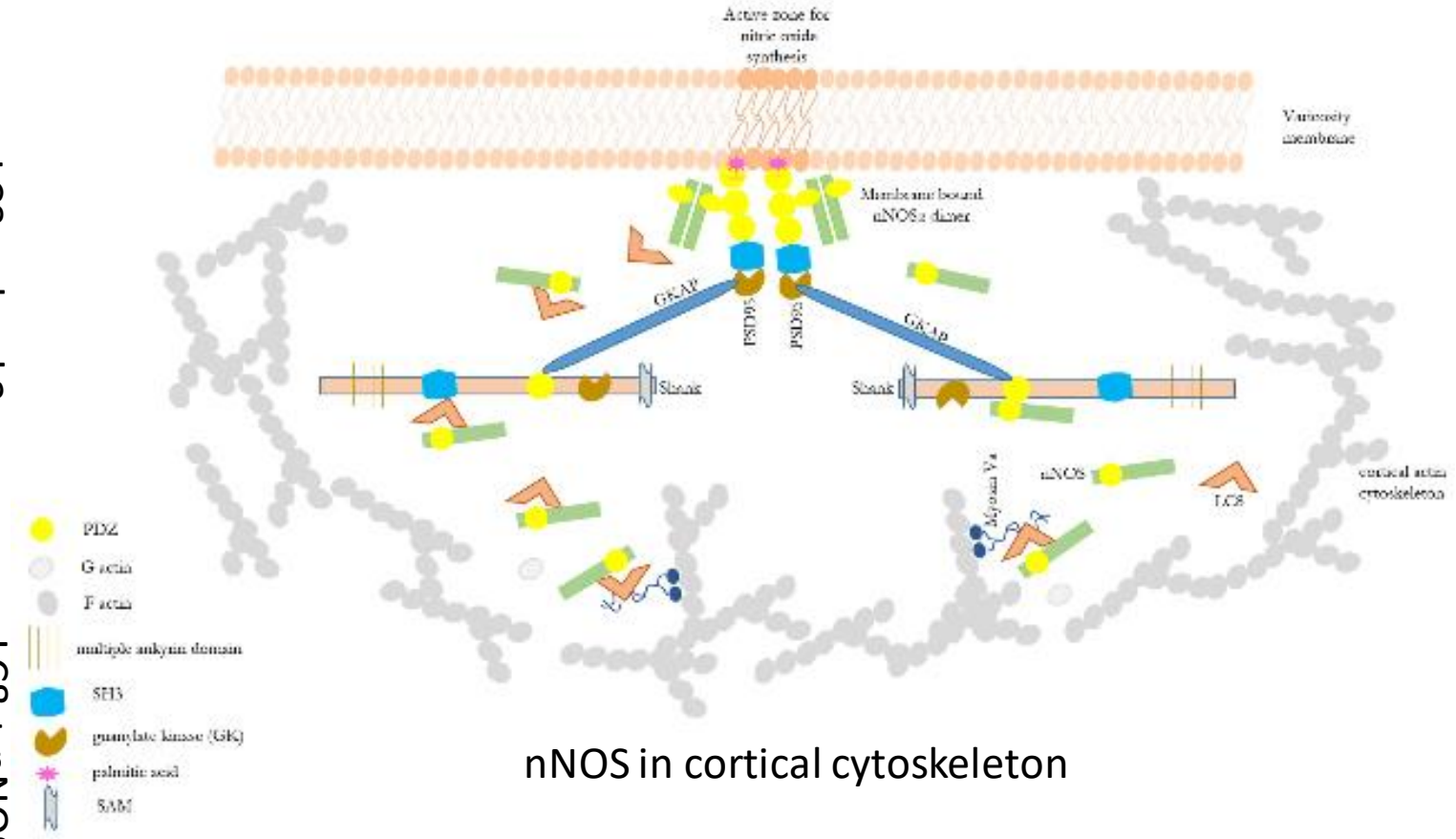
Molecular handoffs in nitrergic neurotransmission

- Phelan-McDermid syndrome & cyclical vomiting



LC8 + shank3

LC8 + nNOS

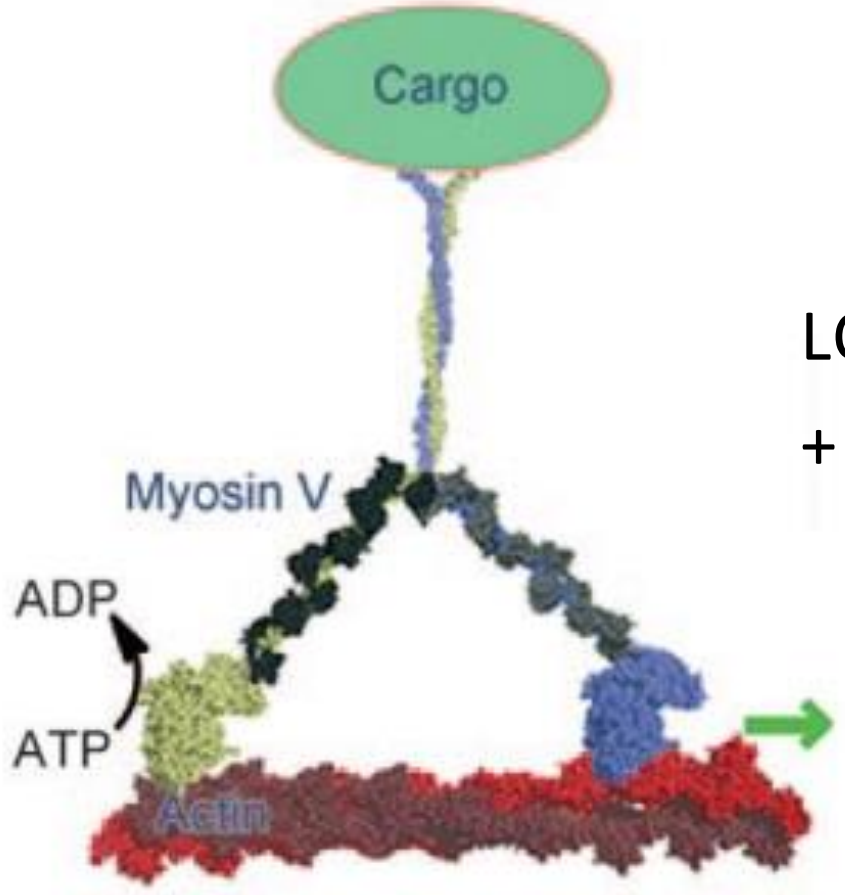


nNOS in cortical cytoskeleton

Chaudhury 2014

Myosin Va is a possible candidate for cargo transport in varicosity

LC8/DLC8/PIN



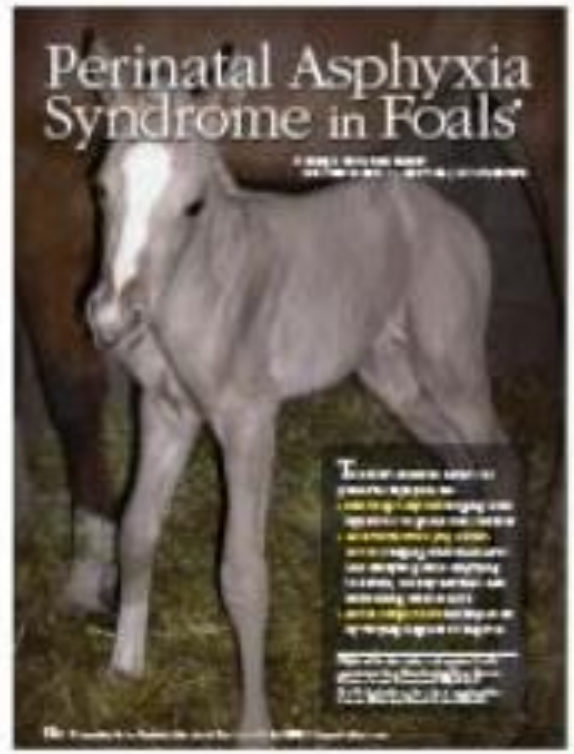
LC8 = BOTH anterograde + retrograde movement

Chaudhury et al 2008, 2011, 2012, 2014

‘Dilute’

DBA/2J

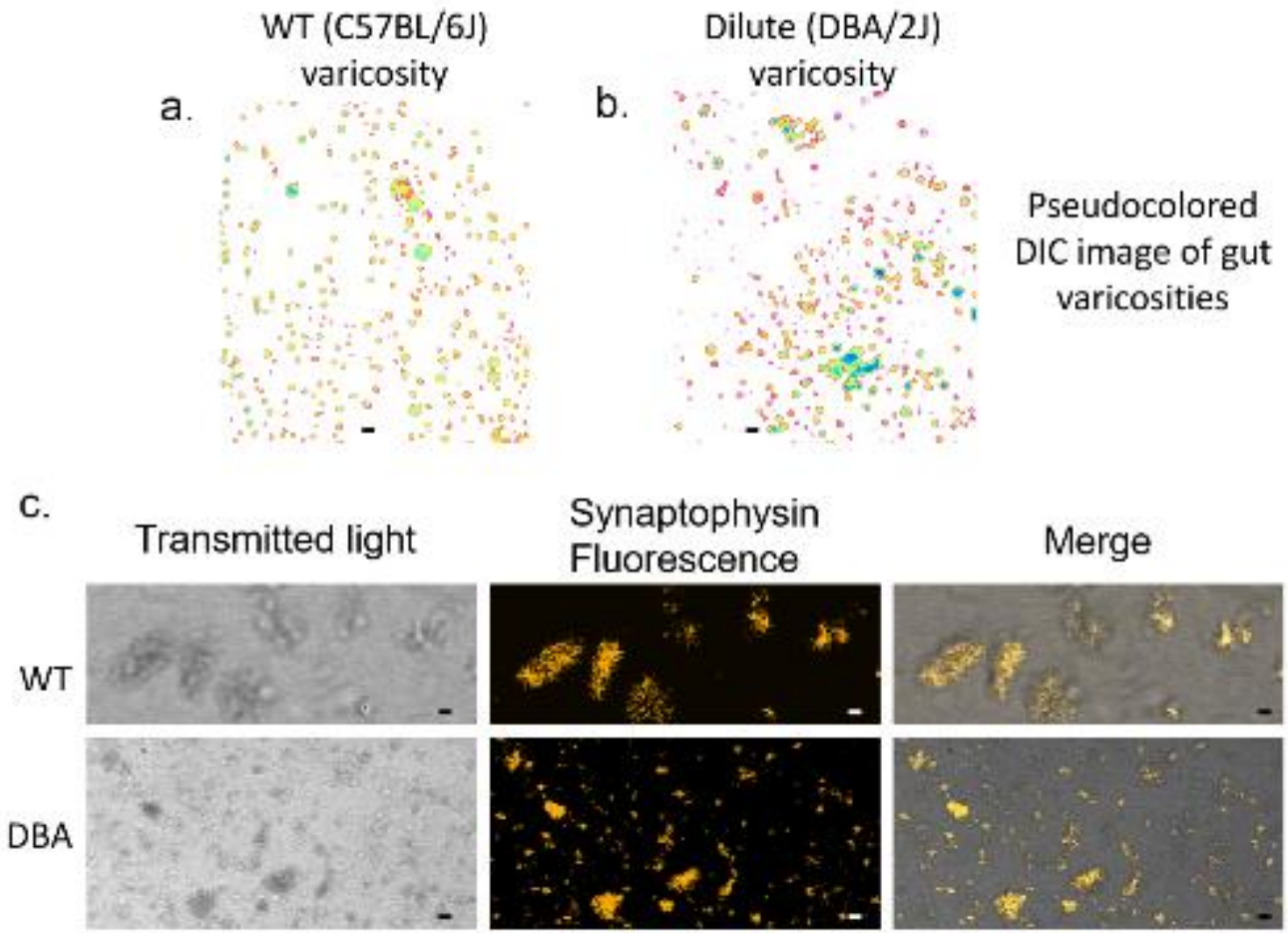
C57BL/6J



Lavender foal syndrome

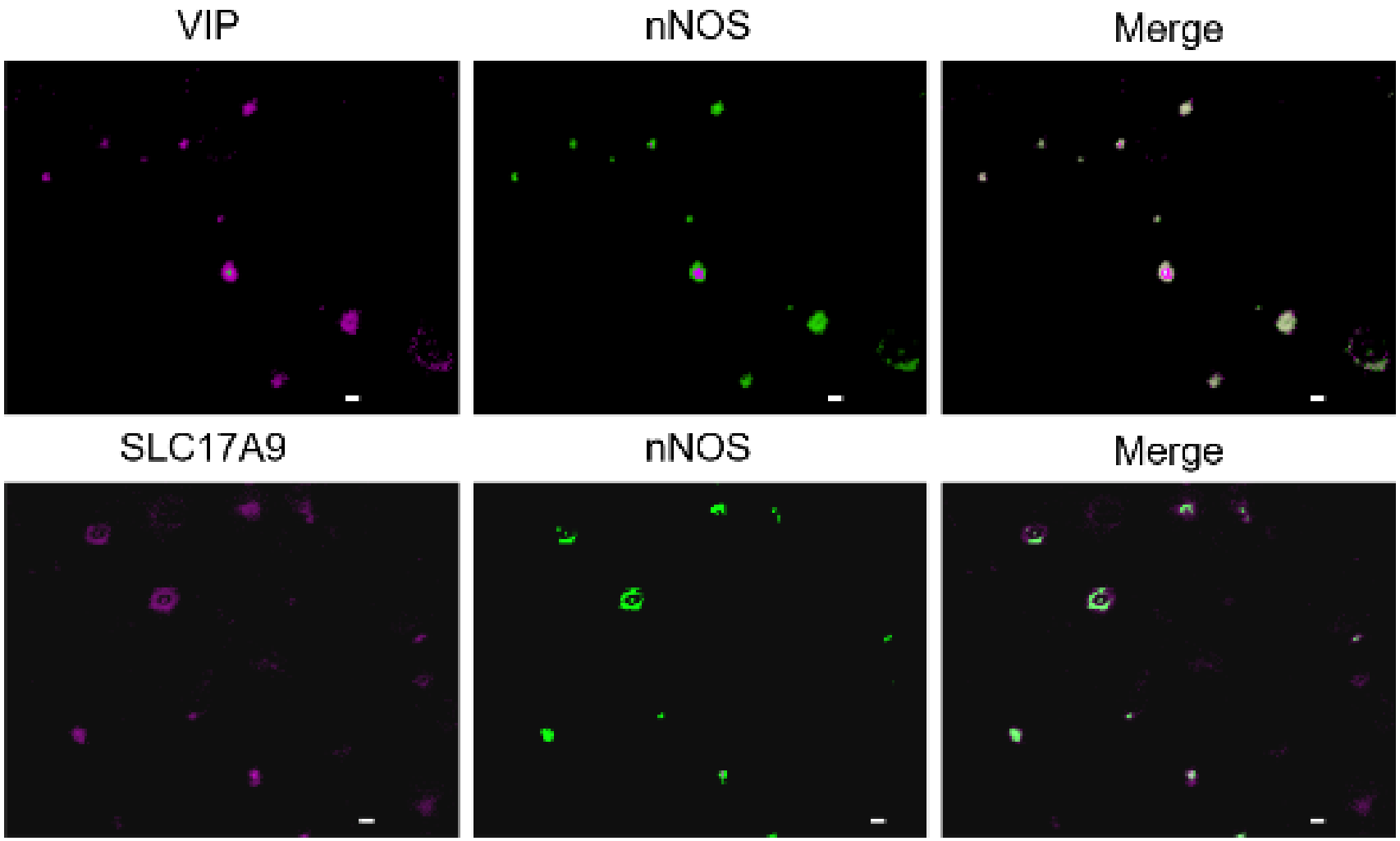
Griscelli syndrome

Myosin Va present in enteric varicosities



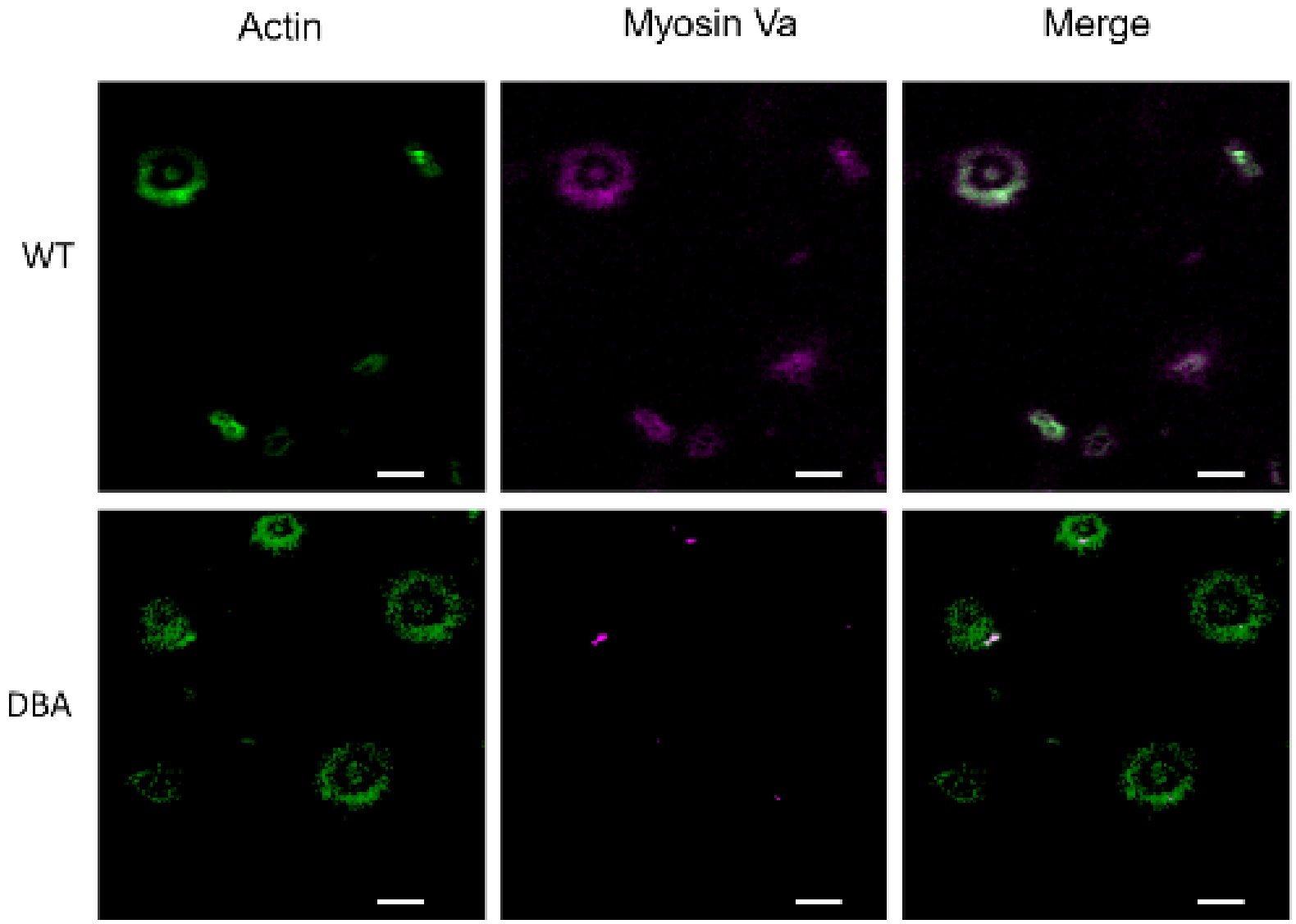
Chaudhury et al 2011, 2012

Inhibitory neurotransmitter systems present in enteric varicosities



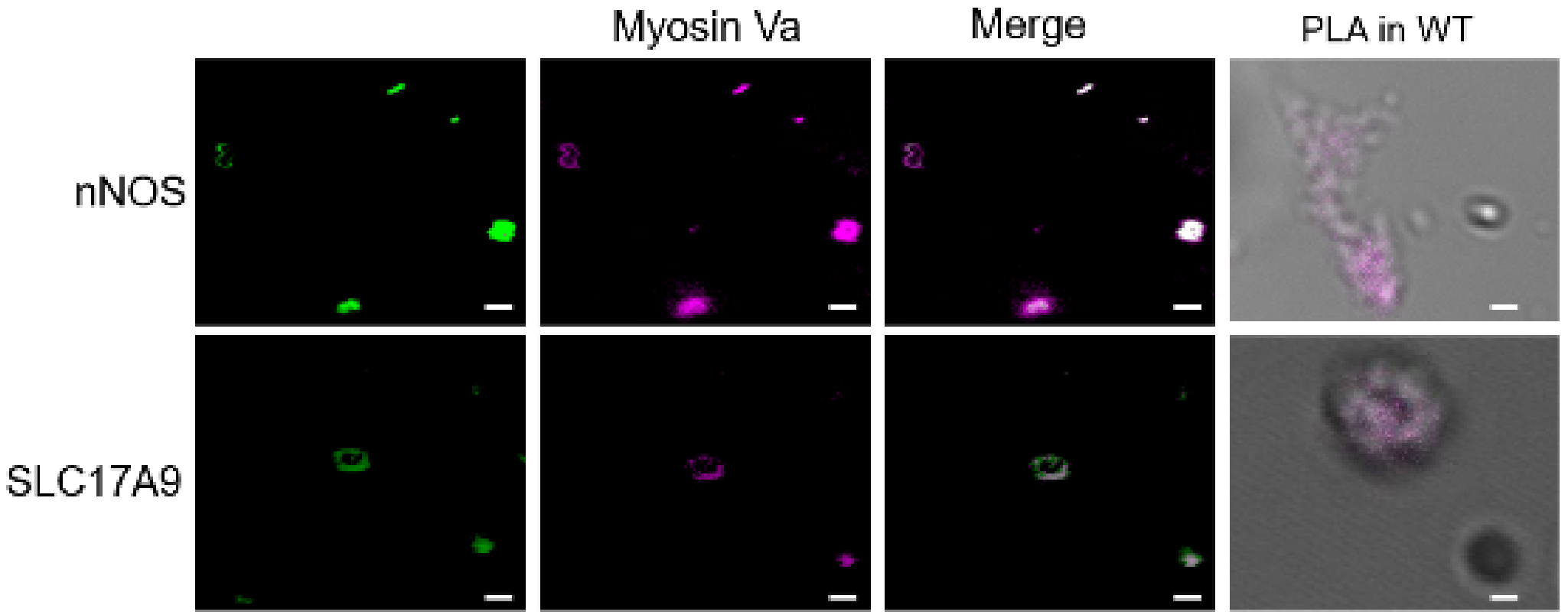
Chaudhury et al 2011, 2012

Myosin Va reduced in DBA/2J varicosities



Chaudhury et al 2011, 2012

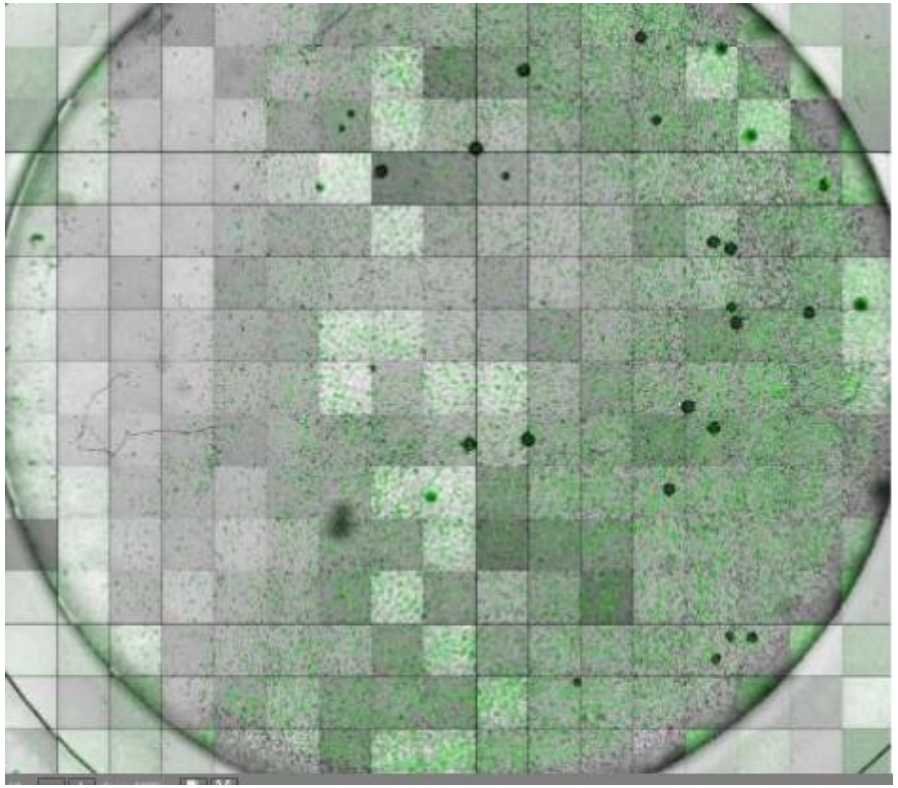
Myosin Va present in inhibitory varicosities



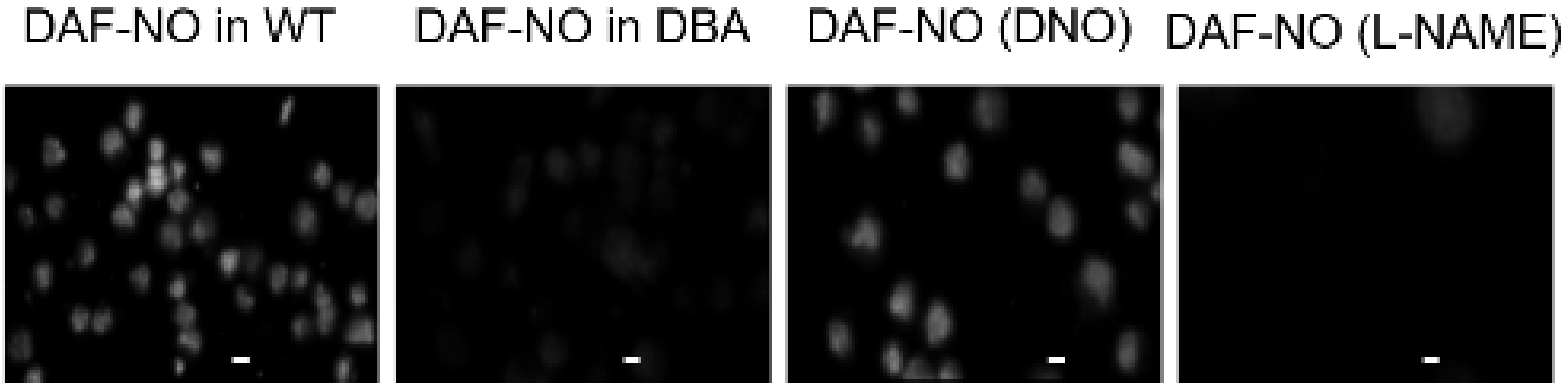
Chaudhury et al 2011, 2012

in vitro NO production reduced in DBA varicosities

DAF, diaminofluorescein

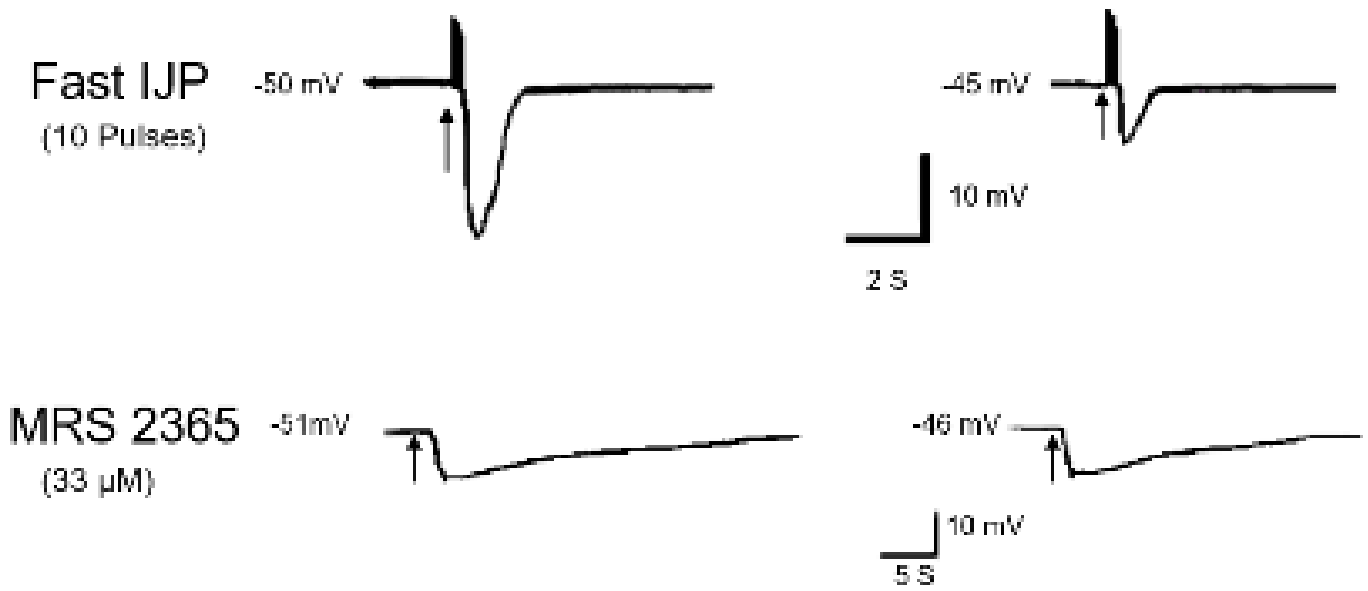


Nipkow spinning disc confocal

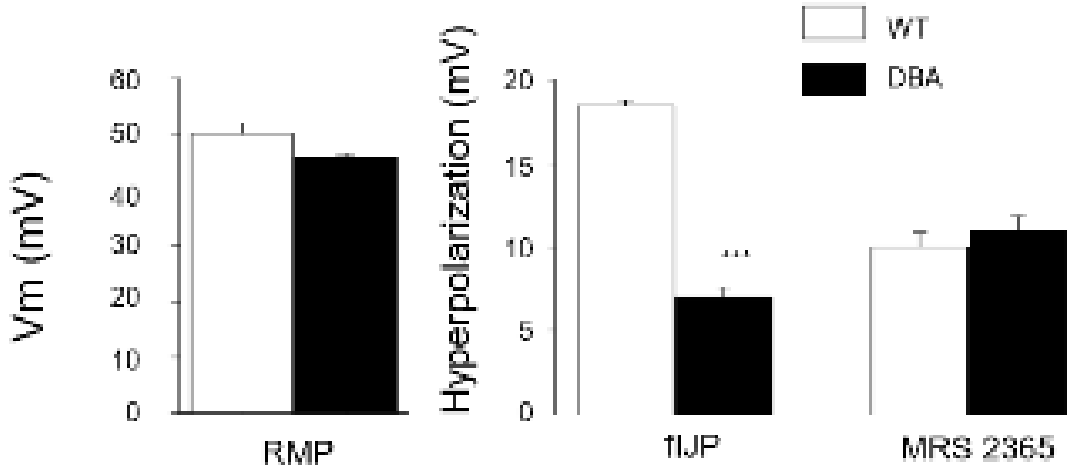


Chaudhury et al 2011

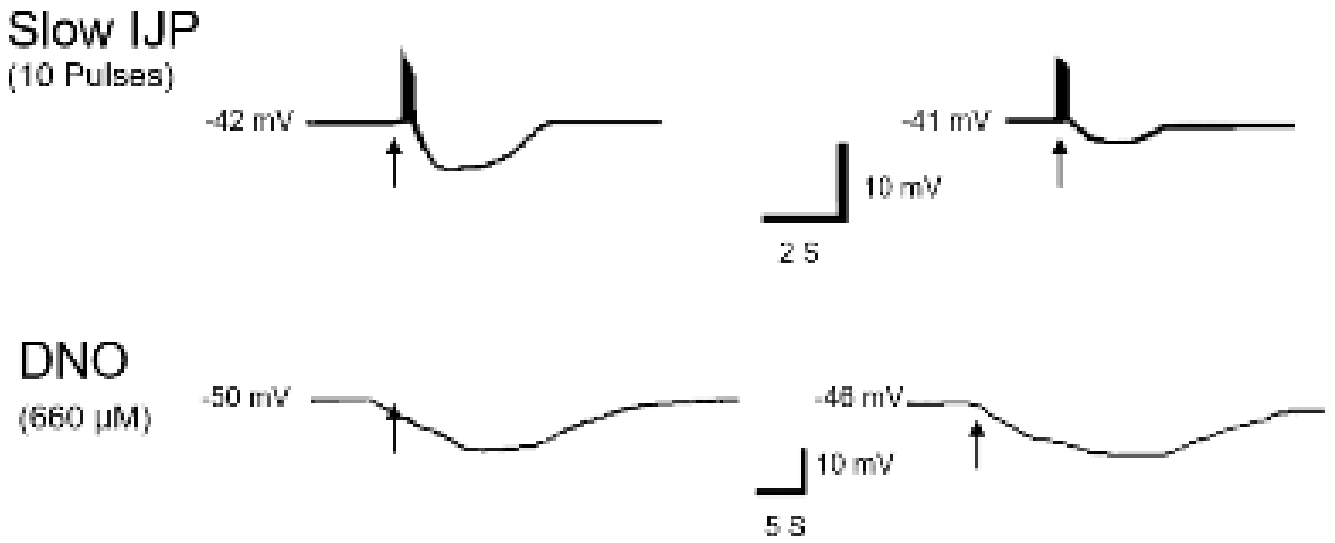
Fast IJP reduced in DBA/2J mice



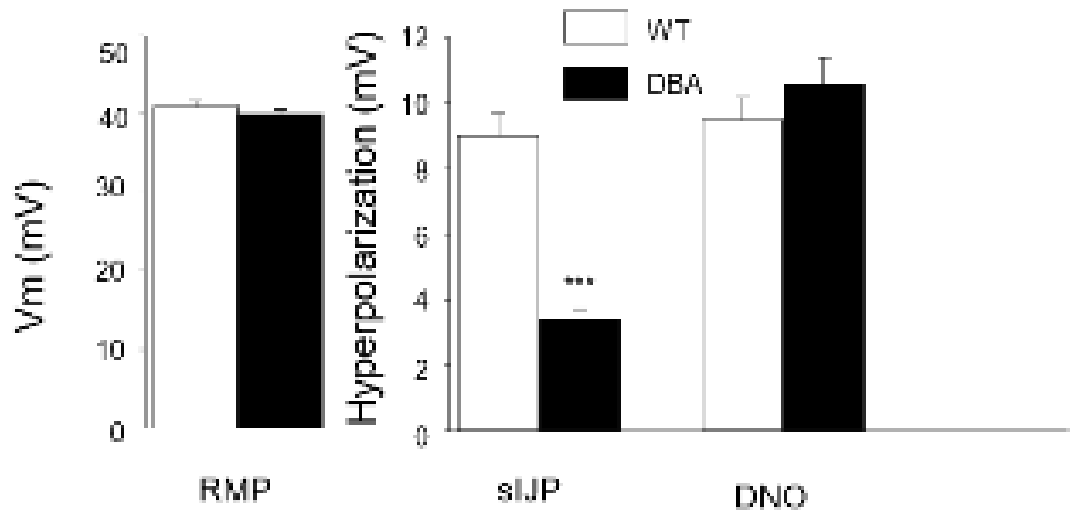
Chaudhury et al 2011



Slow IJP reduced in DBA/2J mice



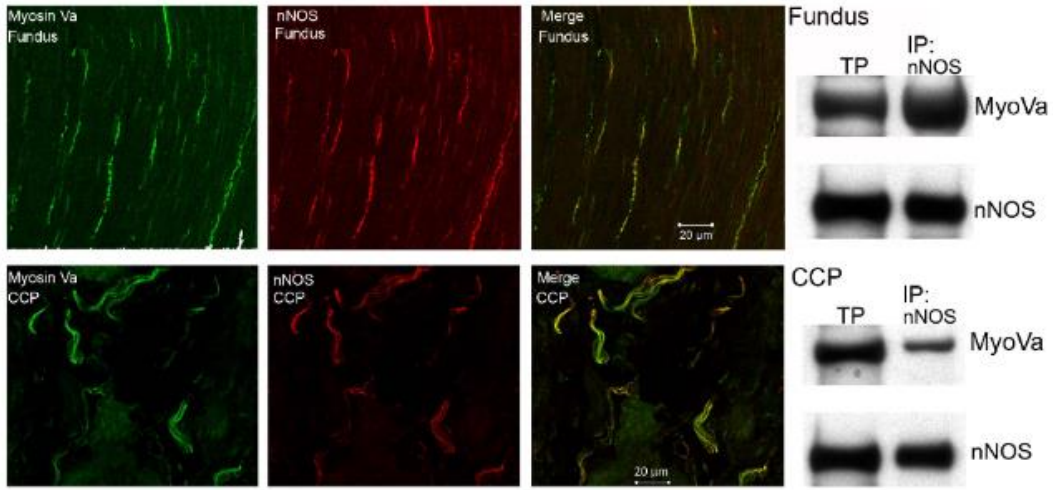
Chaudhury et al 2012



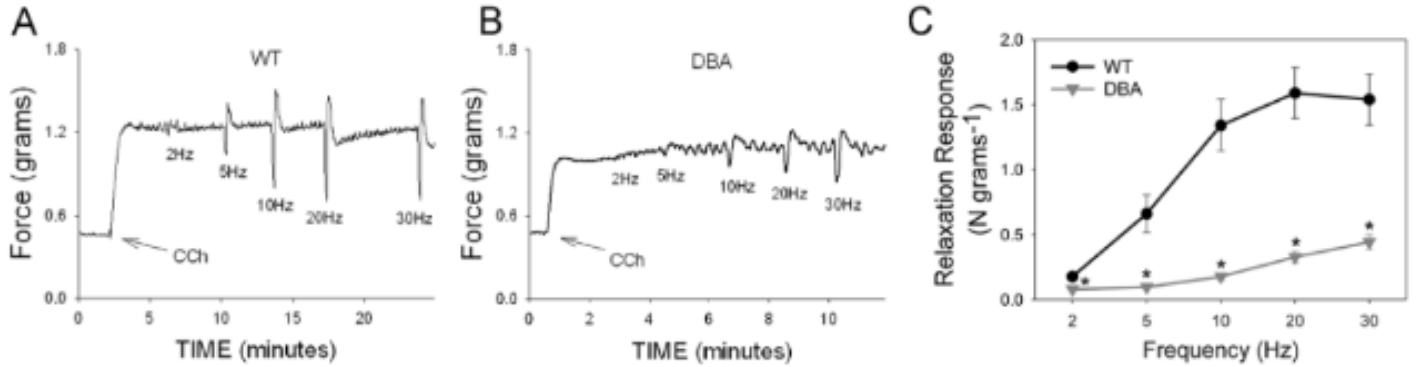
First demonstration of molecular basis of coordination for tandem release of neurotransmitters by molecular motors during a coordinated neurophysiological event

Chaudhury

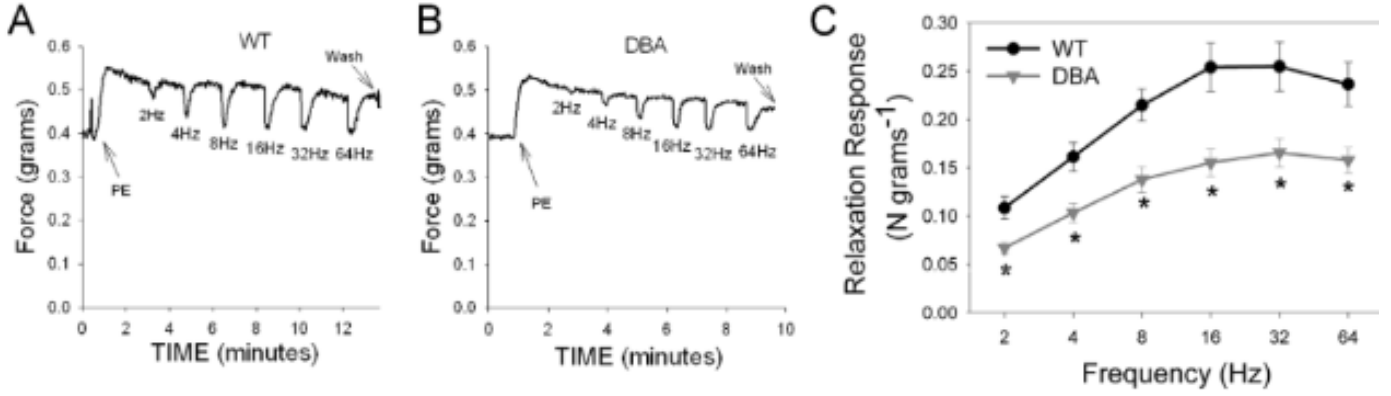
Loss of relaxation in penile cavernosa & gastric fundus of DBA/2J mice



Fundus

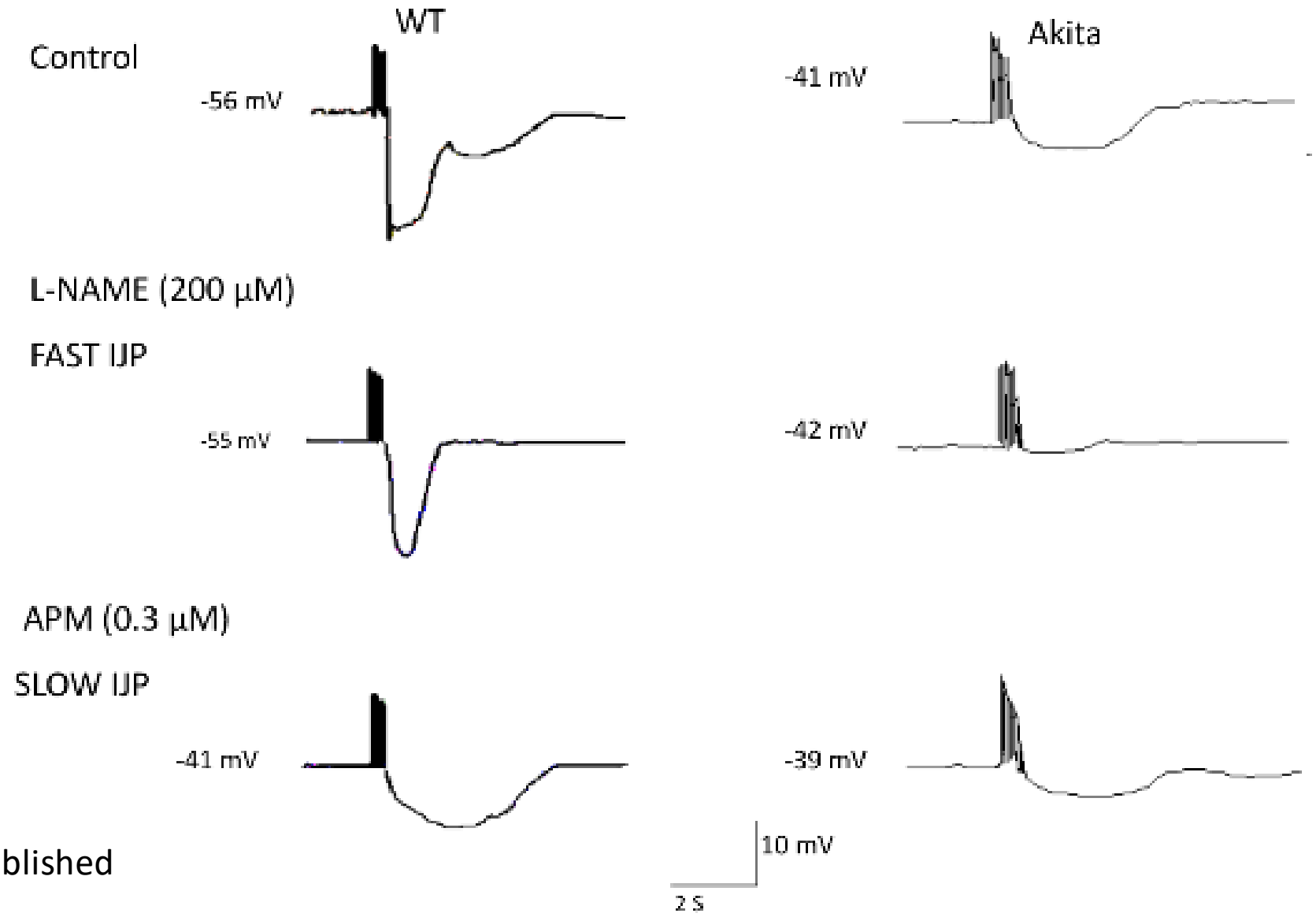


CCP



Chaudhury et al Plos One 2014

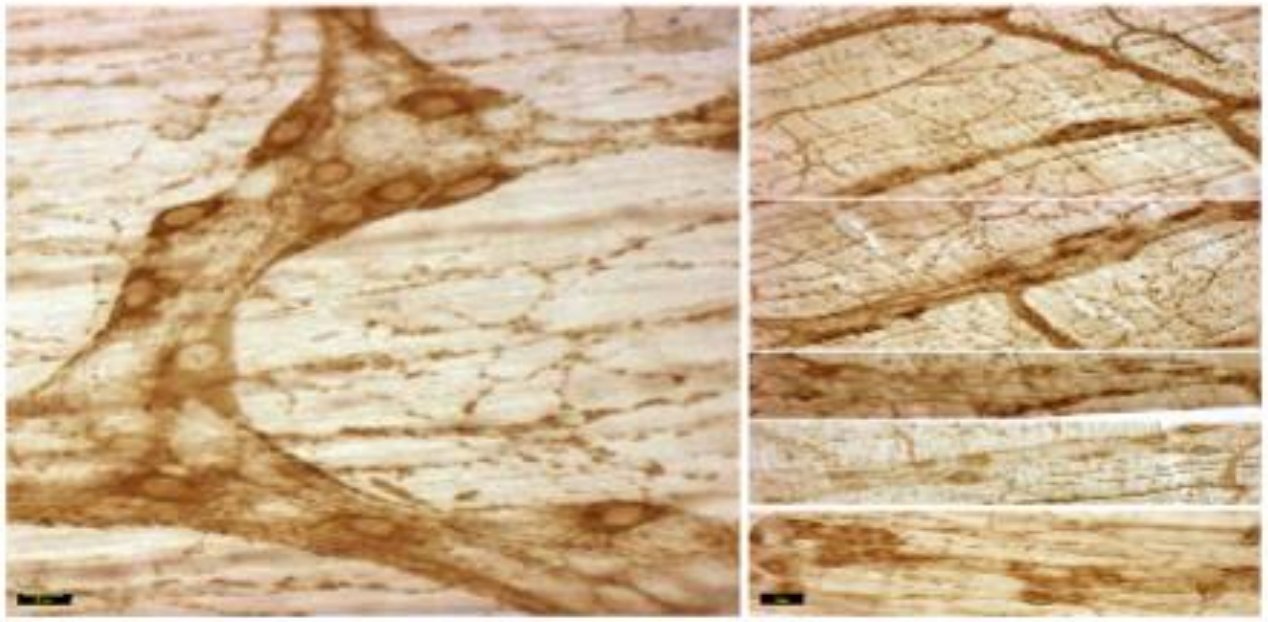
Fast and slow IJP reduced in *Ins2-Akita diabetic* mice



Chaudhury, He, unpublished

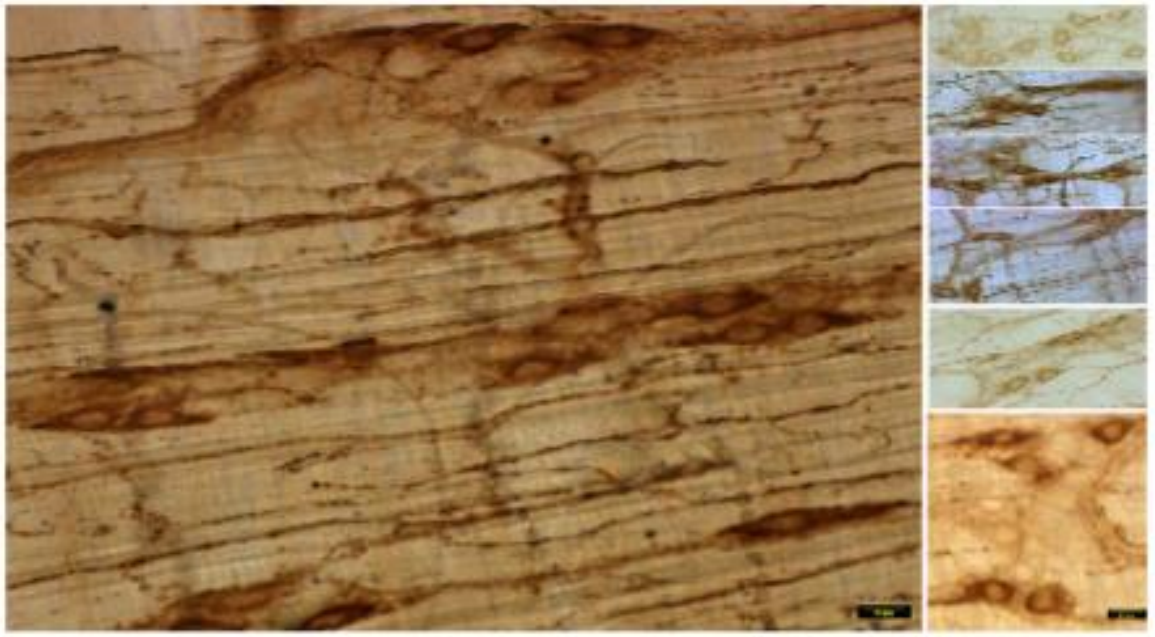
Nitrergic neurons look similar in wild-type & diabetic rat jejunum

Control



nNOS

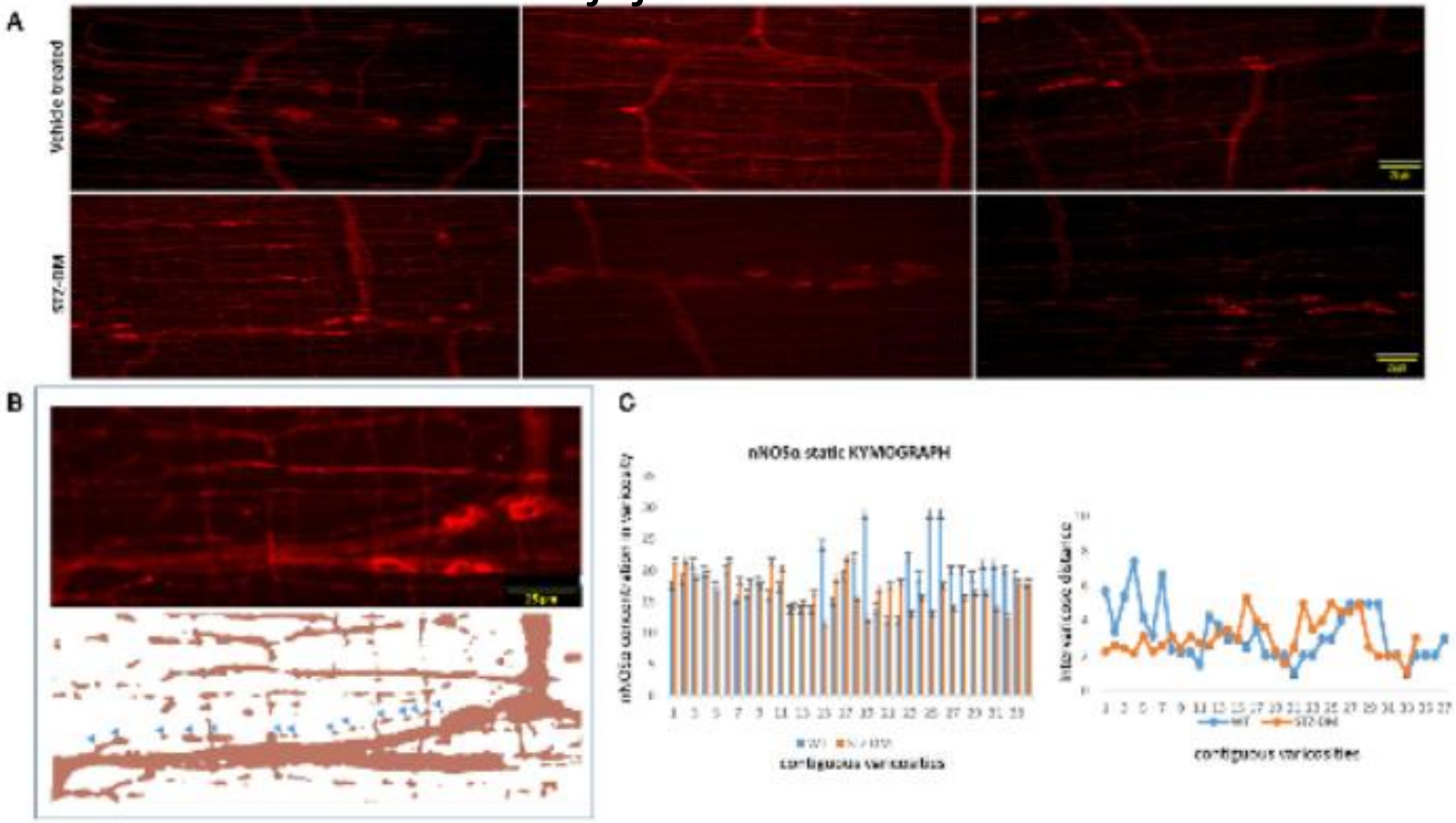
Streptozocin (STZ)



nNOS

Chaudhury et al 2014

nNOS uniformly distributed in wild-type & diabetic rat jejunal nerve terminals



Chaudhury et al 2014

Myosin Va reduced in diabetic rat jejunal nerve terminals

Control

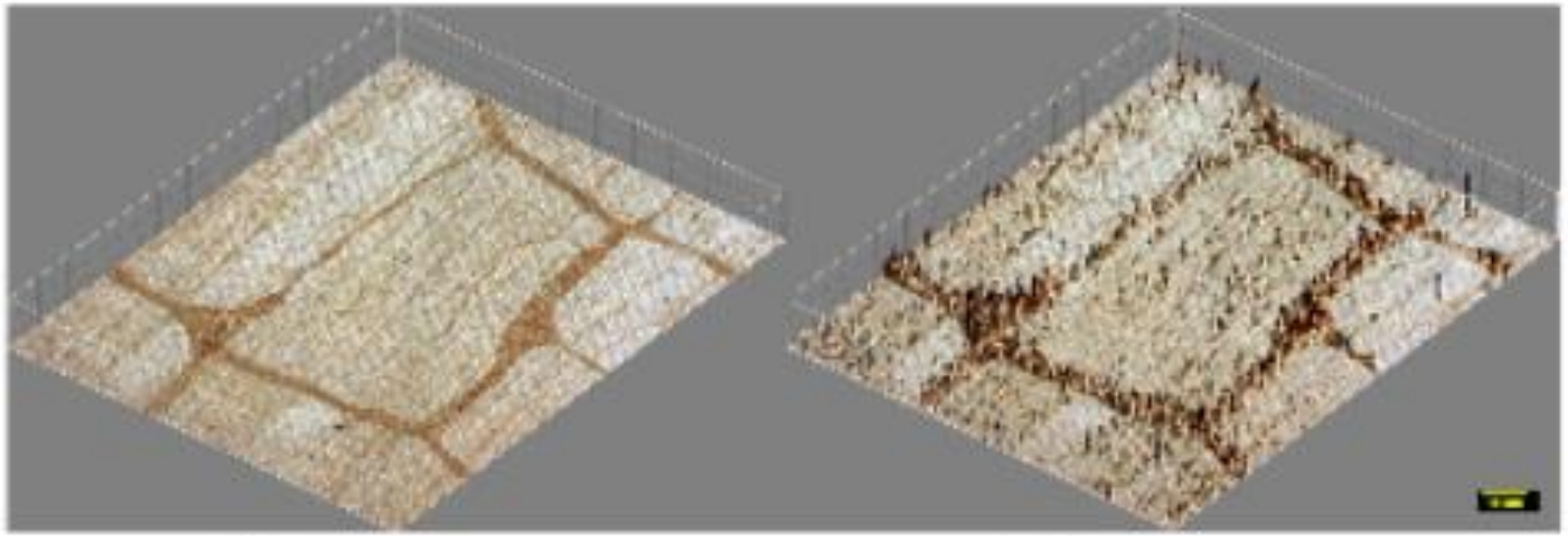
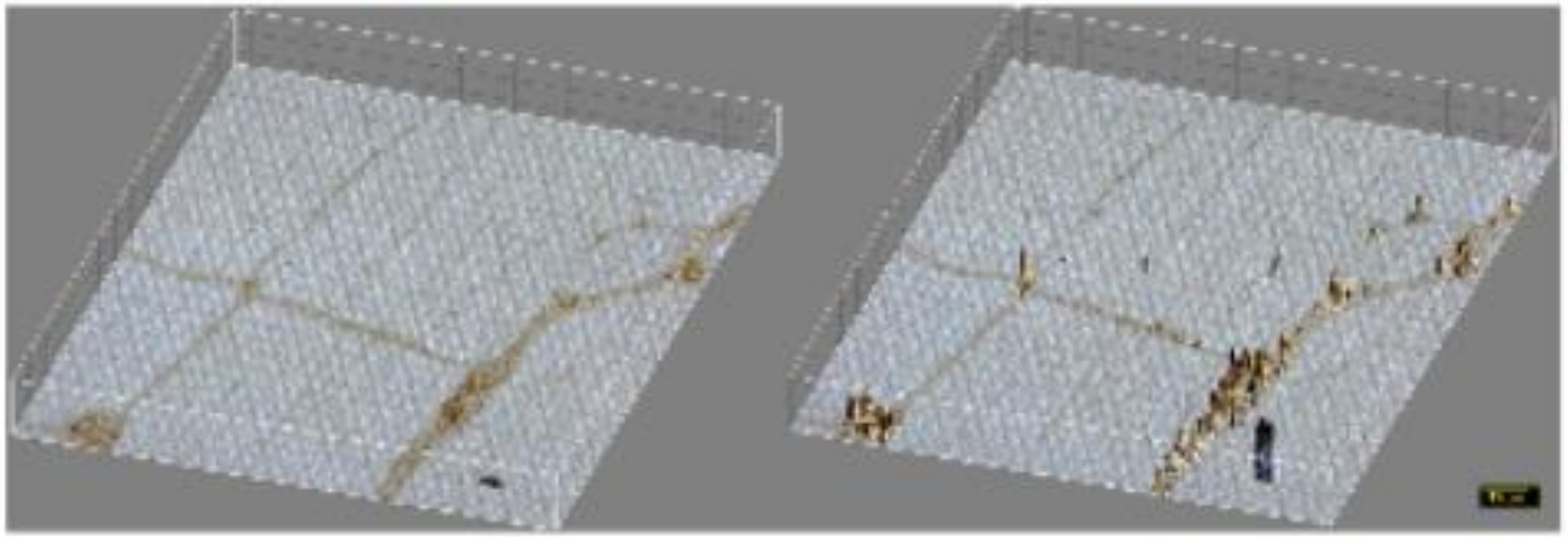


Image J, NIH

Diabetes



Chaudhury et al 2014

Project in Progression

Defective axonal transport of myosin Va or intra-varicosity transport of nNOS may underlie the pathophysiology of diabetic gastroparesis

Idiopathic Gastroparesis

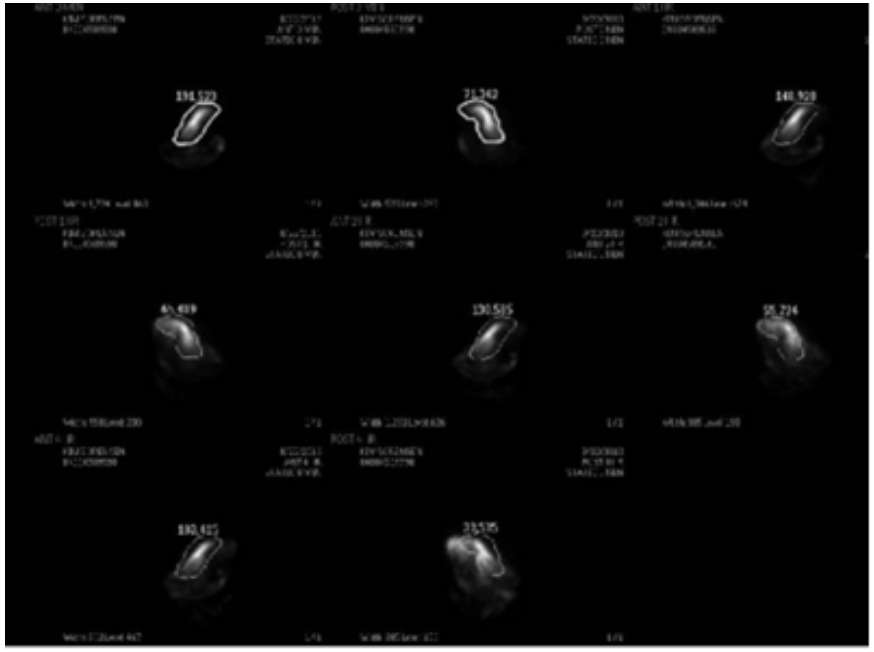


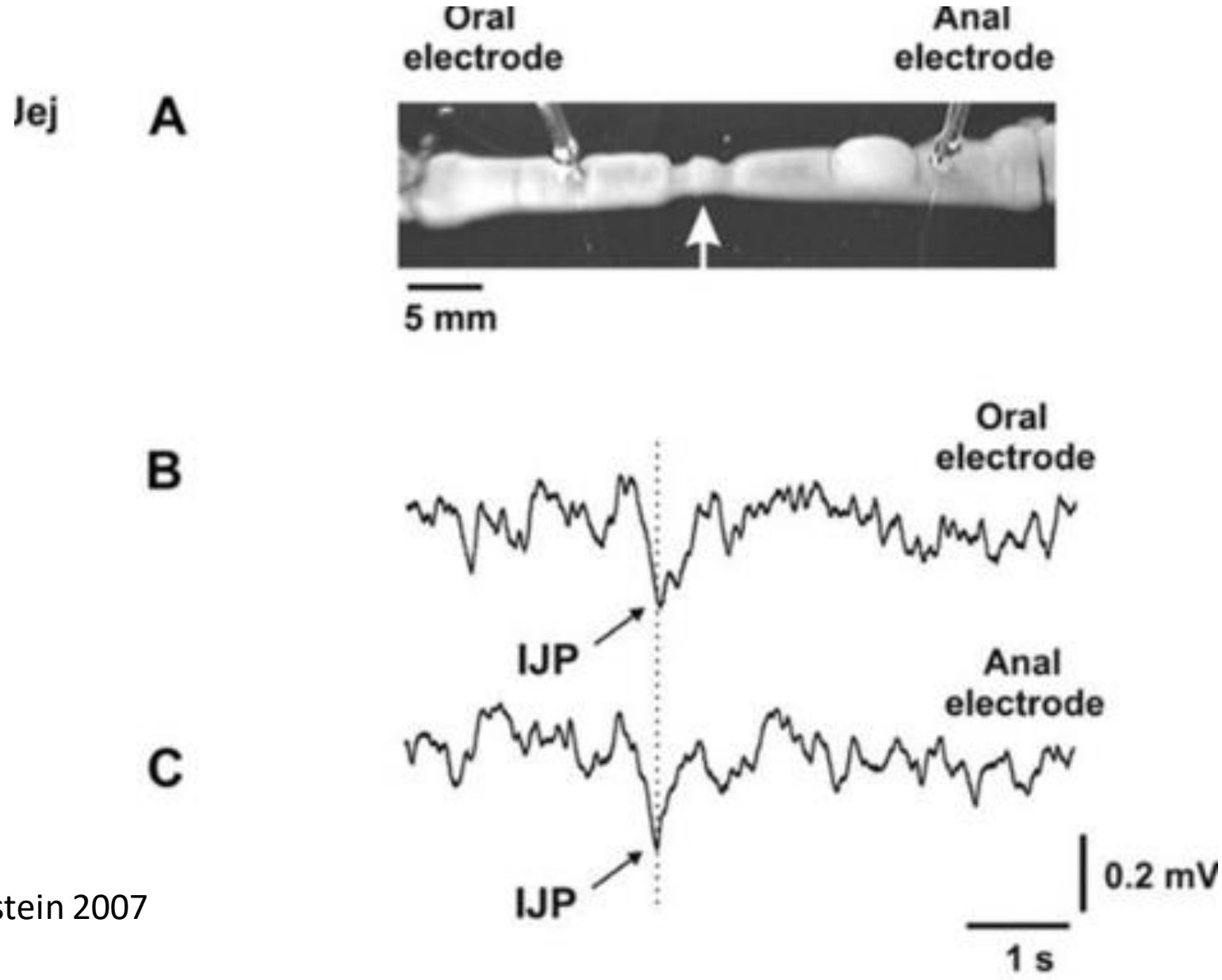
Figure 2. *Gastric emptying scintigraphy. There is 75% radiotracer remaining in the stomach at 1 h, 58% at 2 h and 32% at 4 h.*

Alvarez et al, 2015, 143-45, Acute Gastric Dysfunction after Catheter Ablation of Atrial Fibrillation, J Medical Cases

Food for thought

Are there similarity in mechanisms of diabetic gastroparesis and obesity?

IJPs recordable in small intestines



Gwynne and Bornstein 2007

GI motility pathophysiology in Celiac Disease and Down syndrome: Lessons from Snell's Waltzer

A model of myosin 6 deficiency

Snell's waltzer may provide pathophysiologic insights into multiorgan complications of Down syndrome including celiac disease, cardiomyopathy and hearing defects

Arun Chaudhury[1*], Vijaya S. Dendi[1], Chitharanjan Duvoor[1], Mousumi Chaudhury[1]

[1]GIM Foundation, USA

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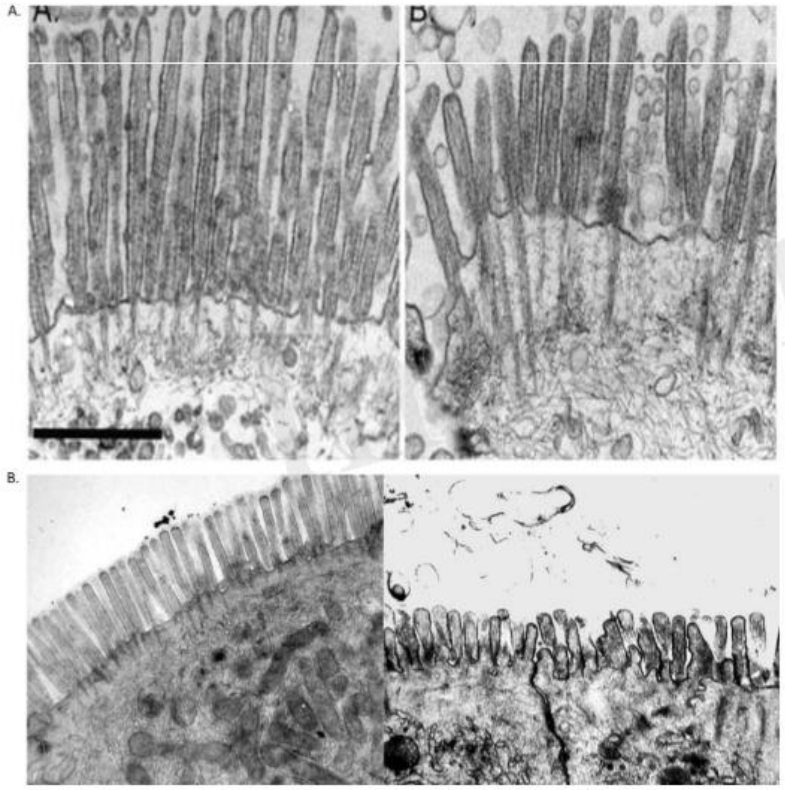
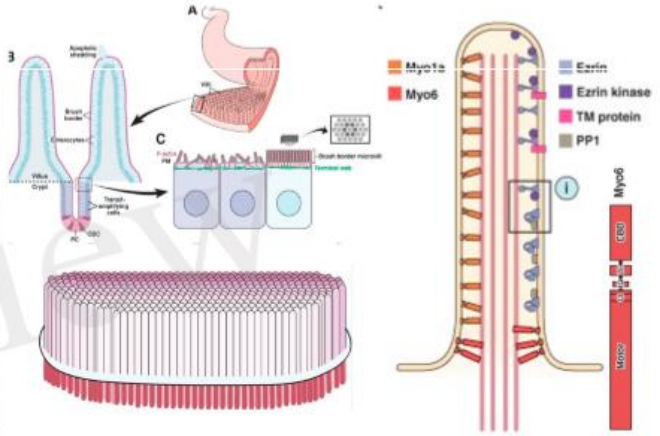
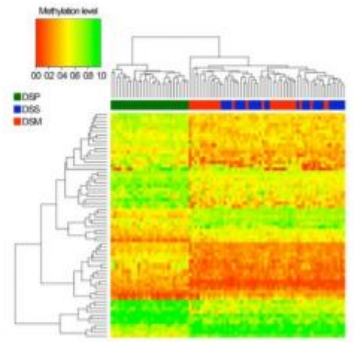


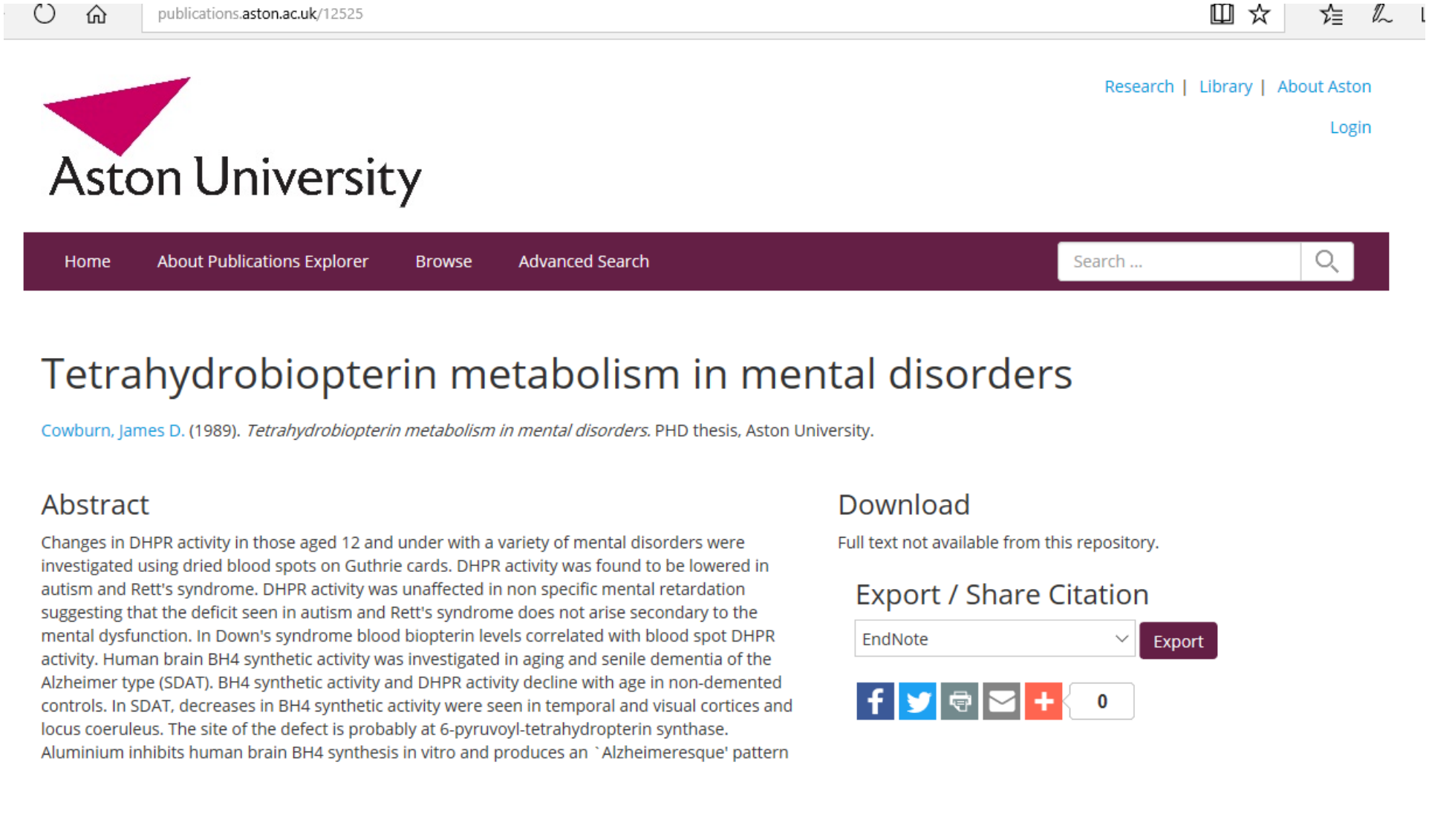




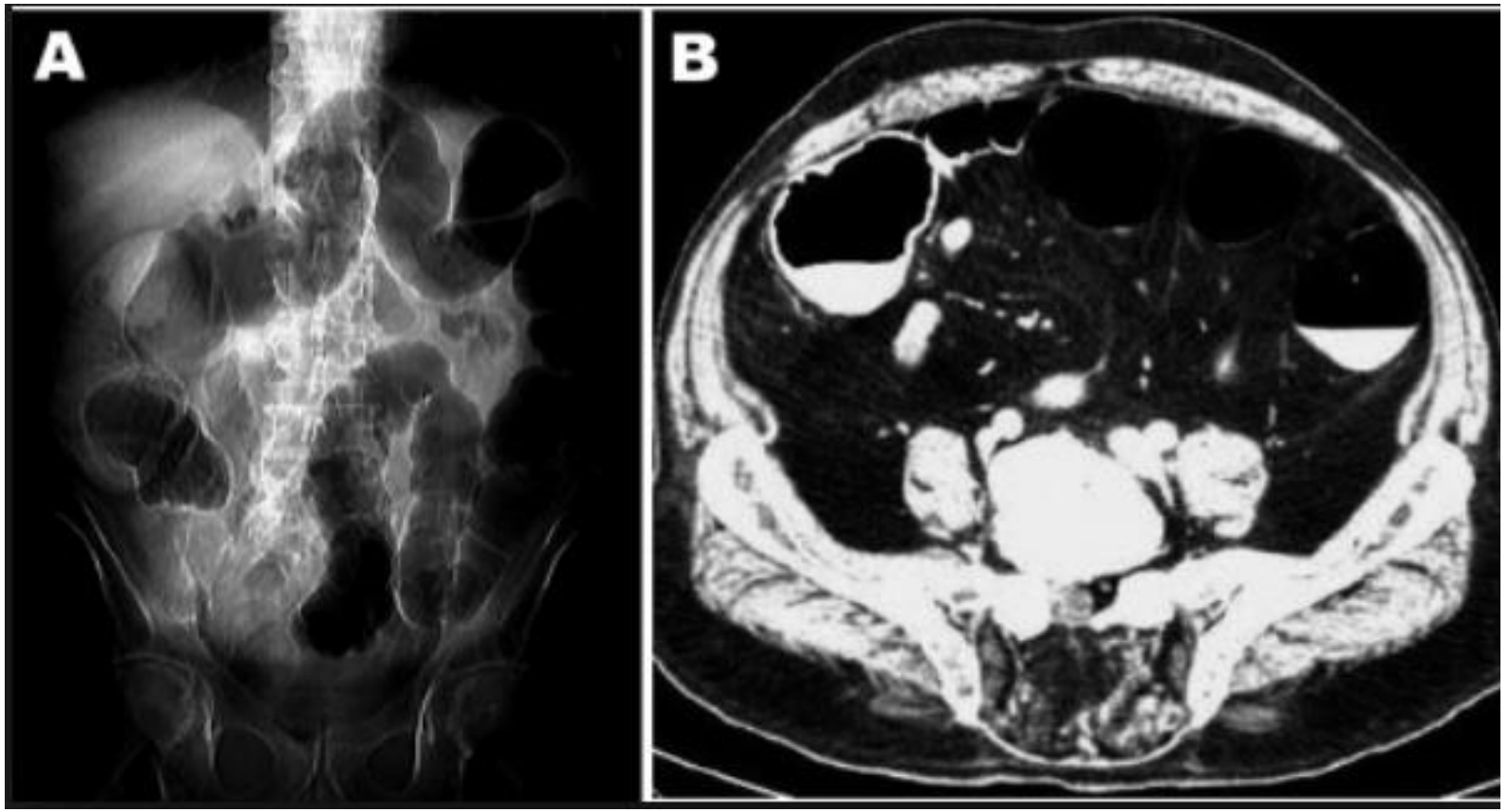
Enhanced methylation

Chaudhury et al 2017

May involve multiple mechanisms



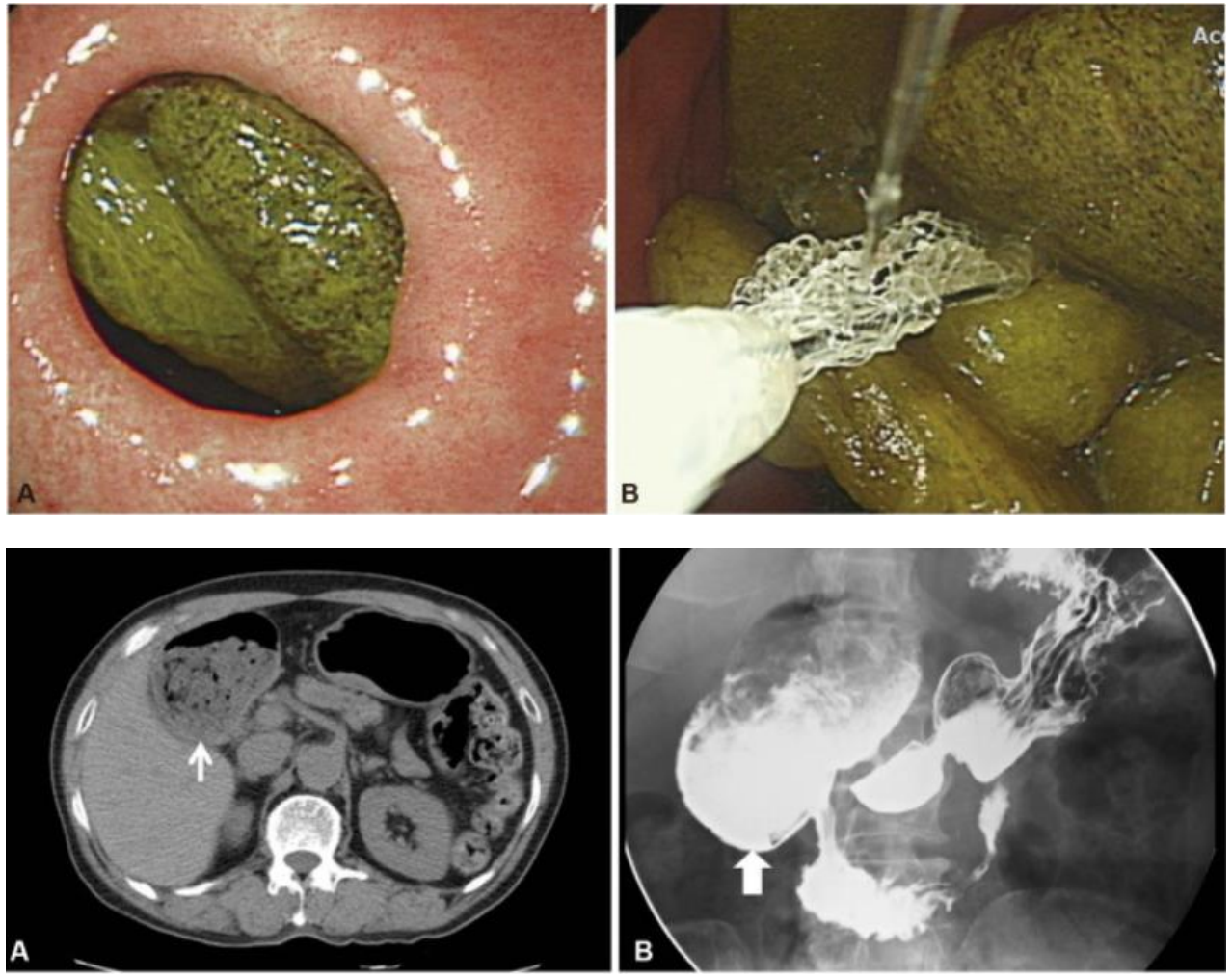
Ogilvie’s syndrome



Carrascosa et al, 2014, 2718-21, J Clin Microbiol

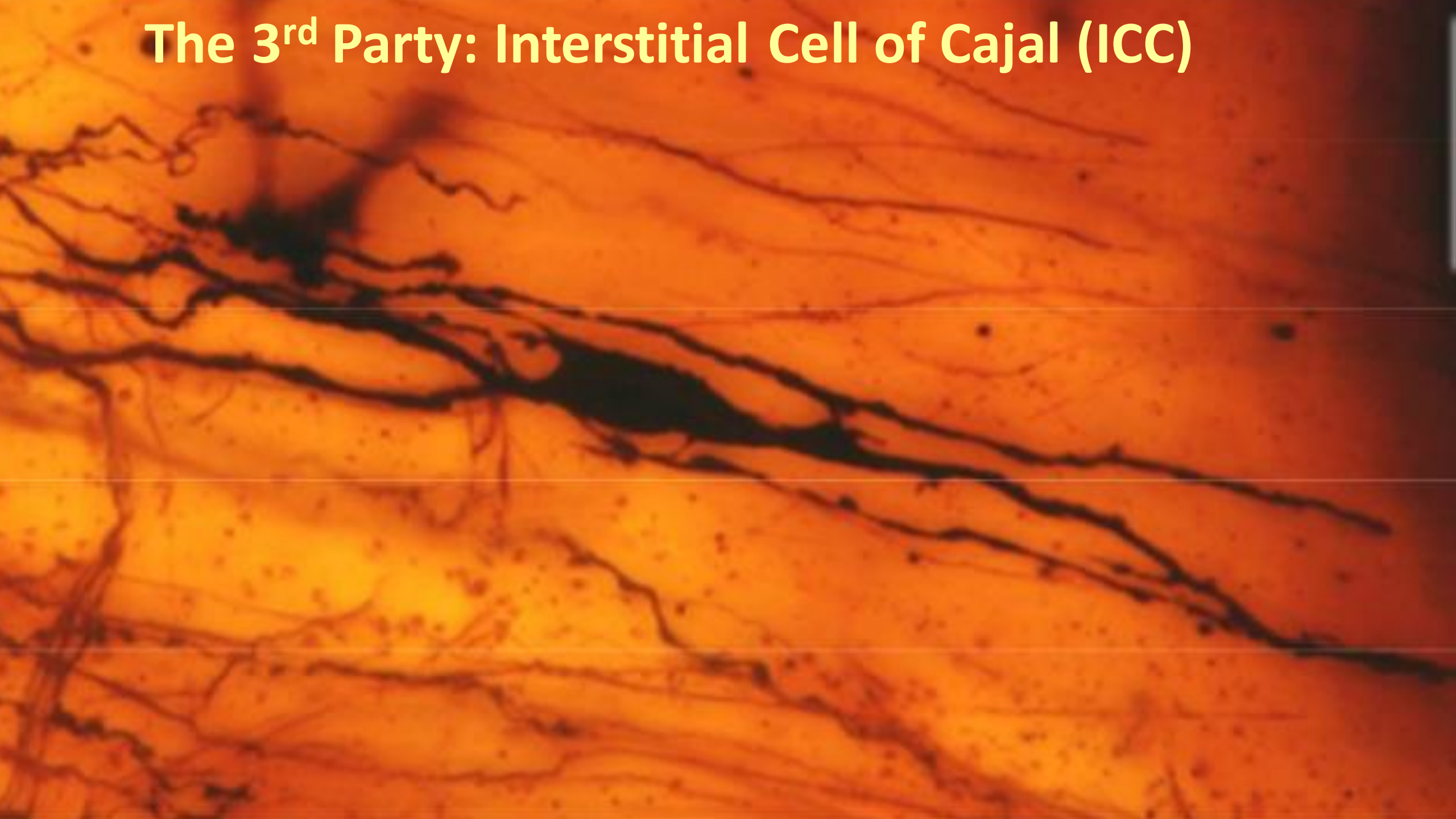
VIROCHIP

Phyto-Bezoar

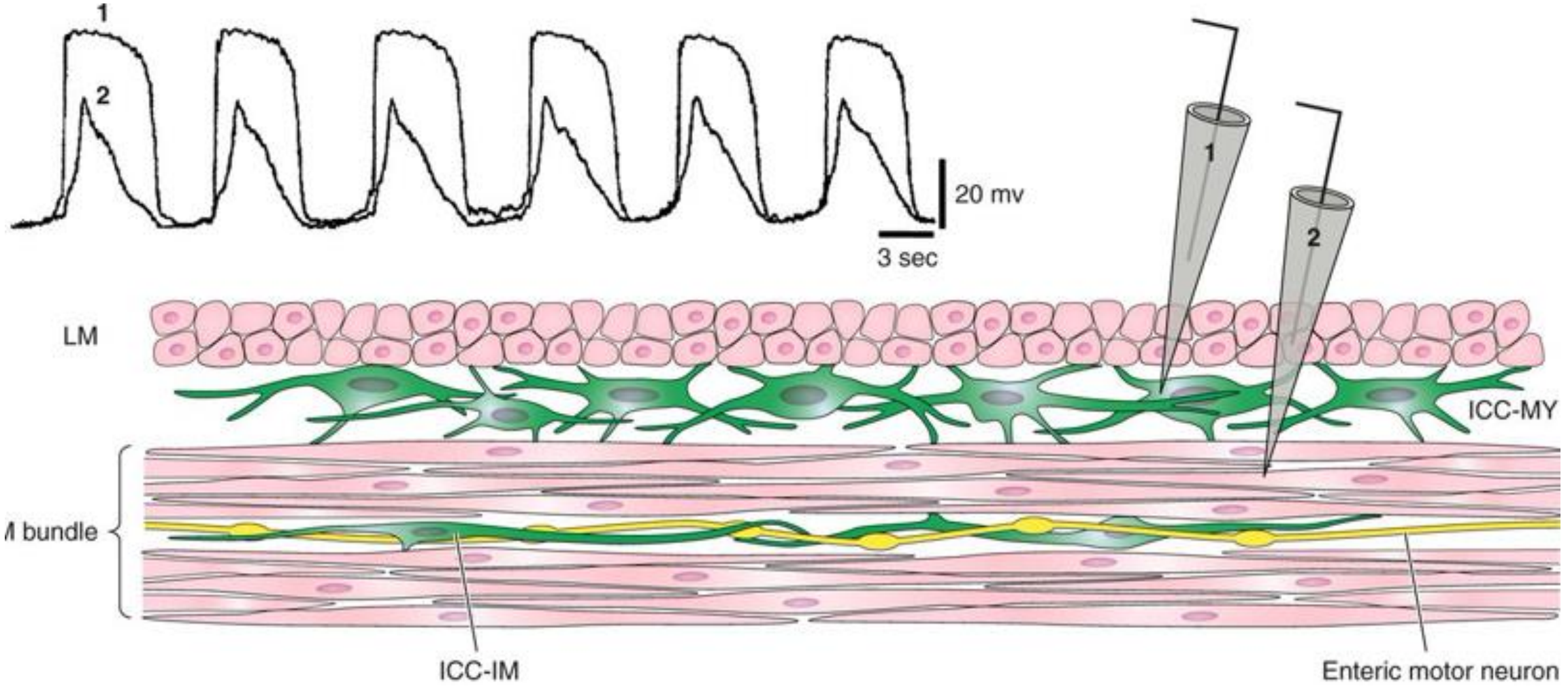


Park and Lee 2015, 436-439, Clinical Endoscopy

The 3rd Party: Interstitial Cell of Cajal (ICC)

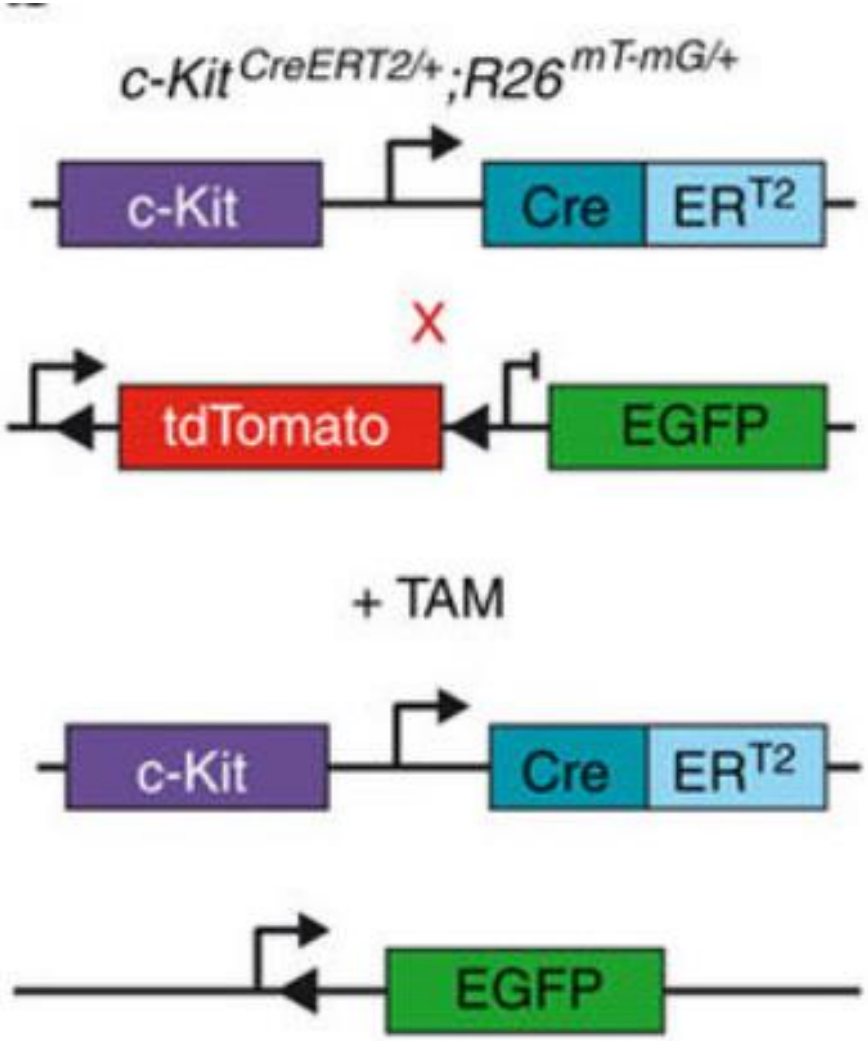


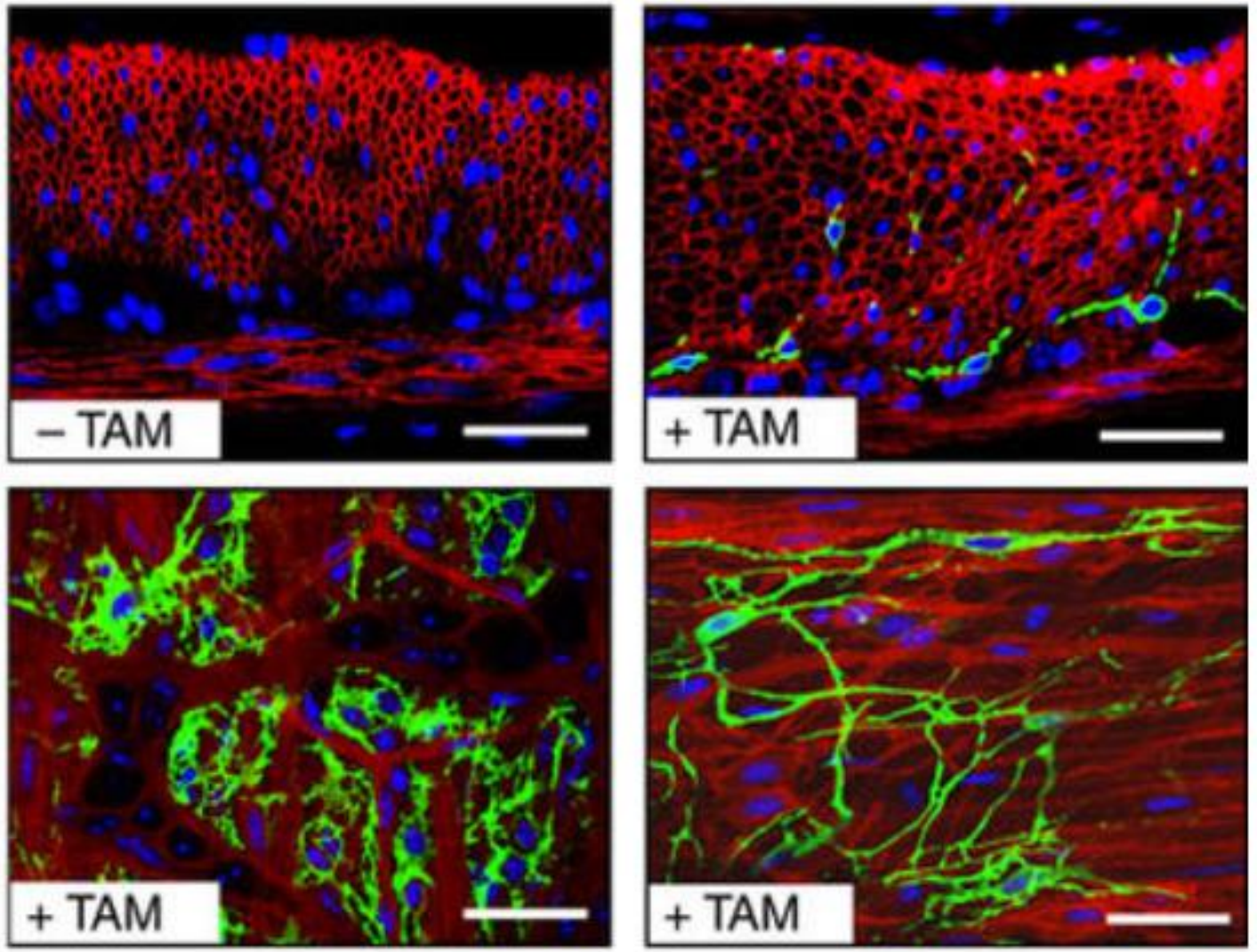
ICC: Intercalated or interspersed?



Sanders et al 2014

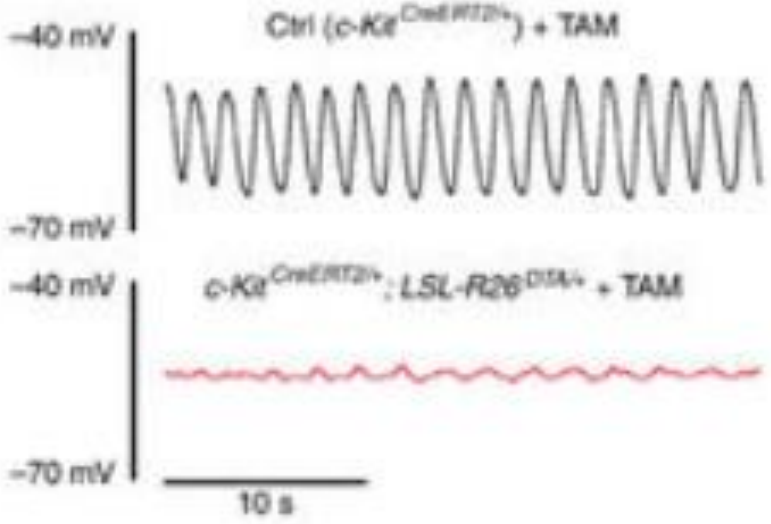
Genomic Knockout of ICC



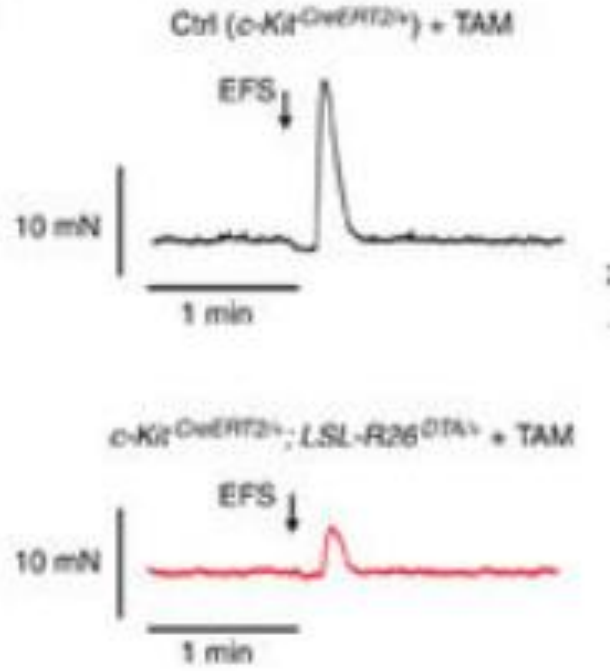


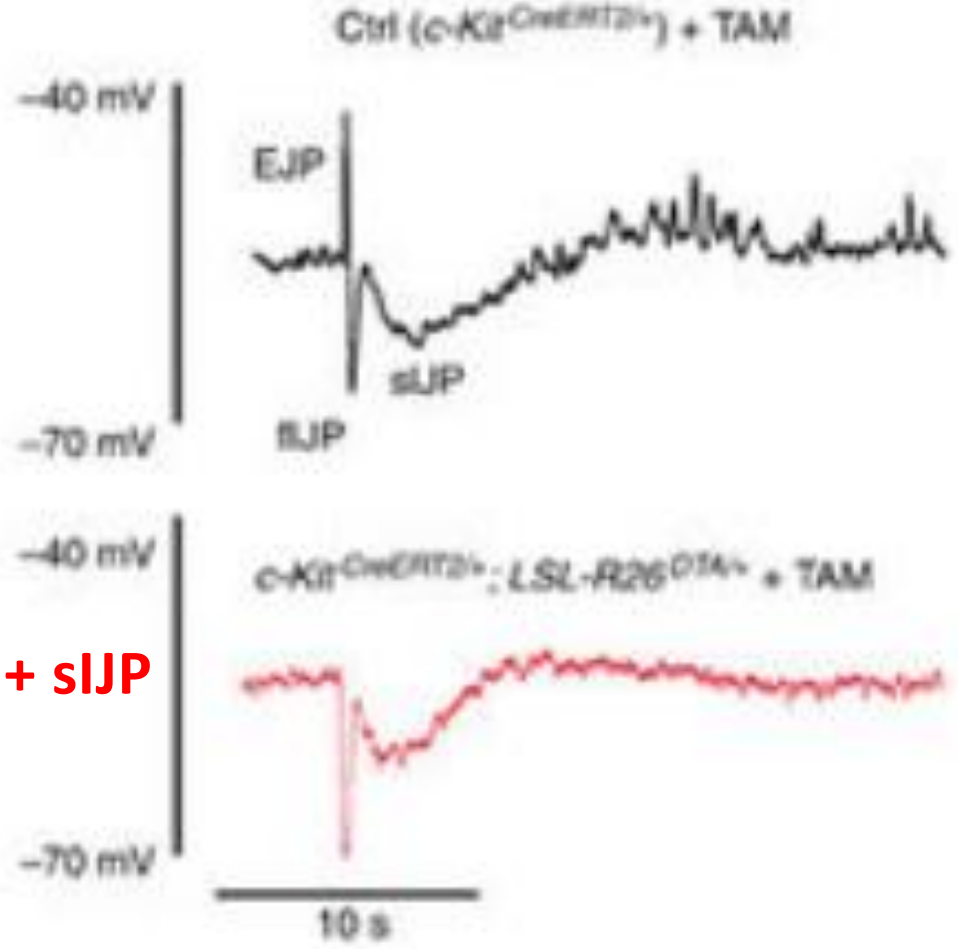
Klein et al 2013

Intact IJP in ICC genomic knockout mice



SLOW WAVE



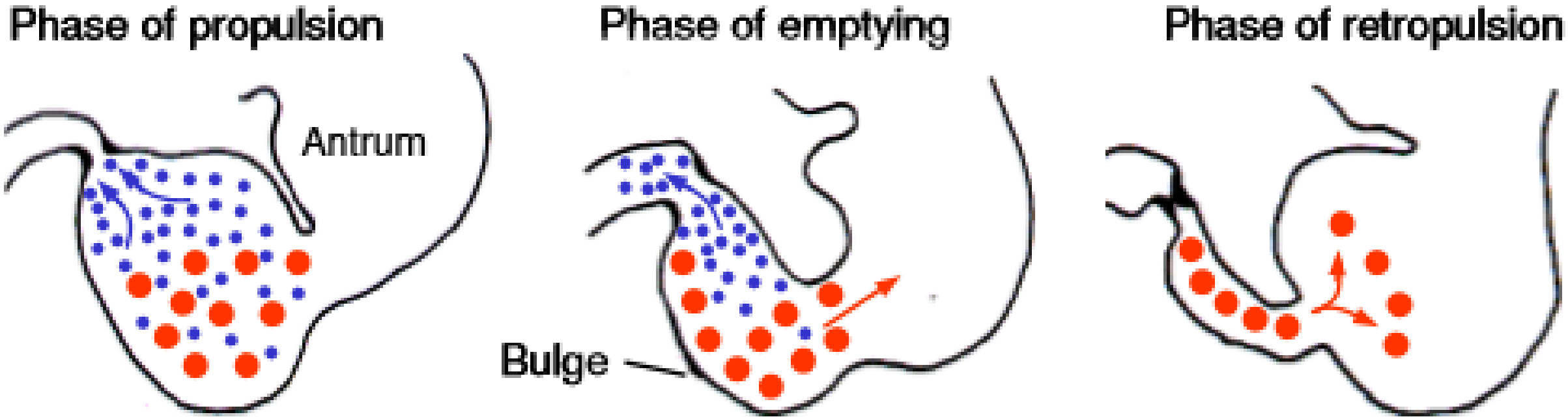


INTACT fIJP + sIJP

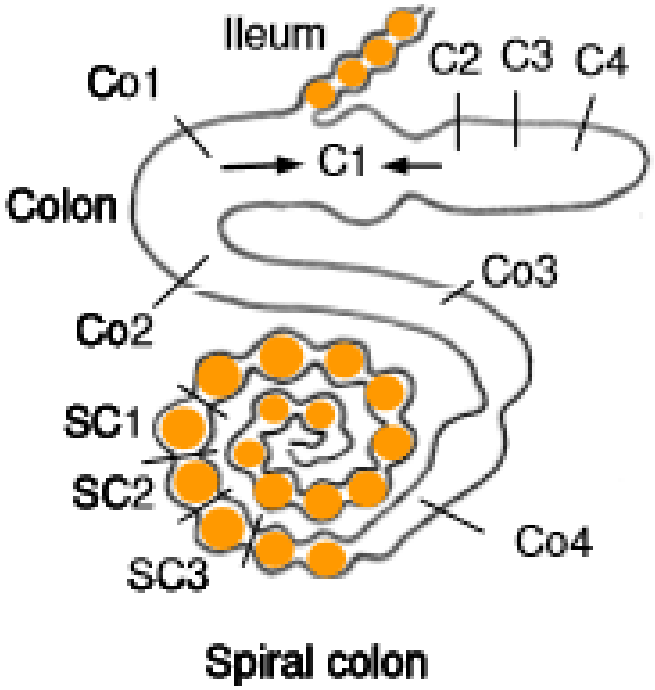
Klein et al 2013

Chaudhury 2013; Chaudhury 2016

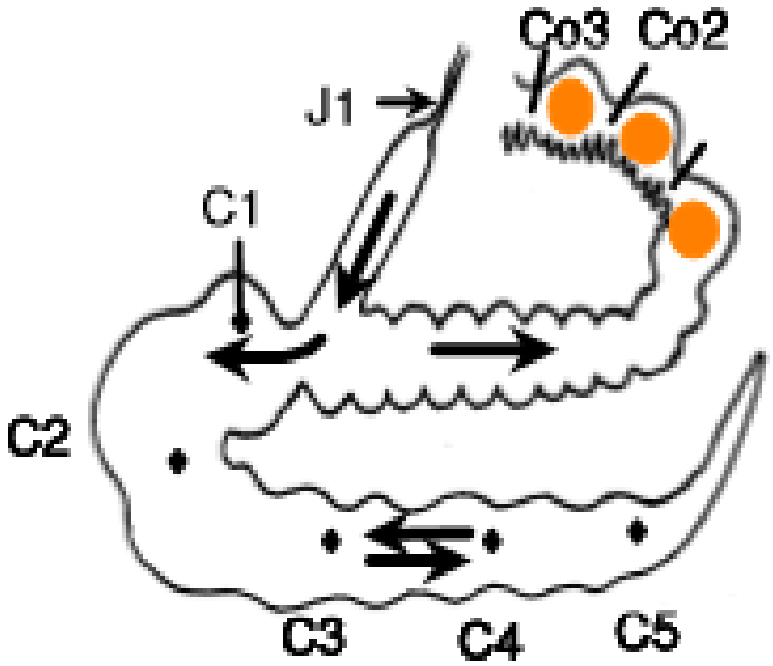
Mechanisms of retropulsion: Toggling of the prospective circuit



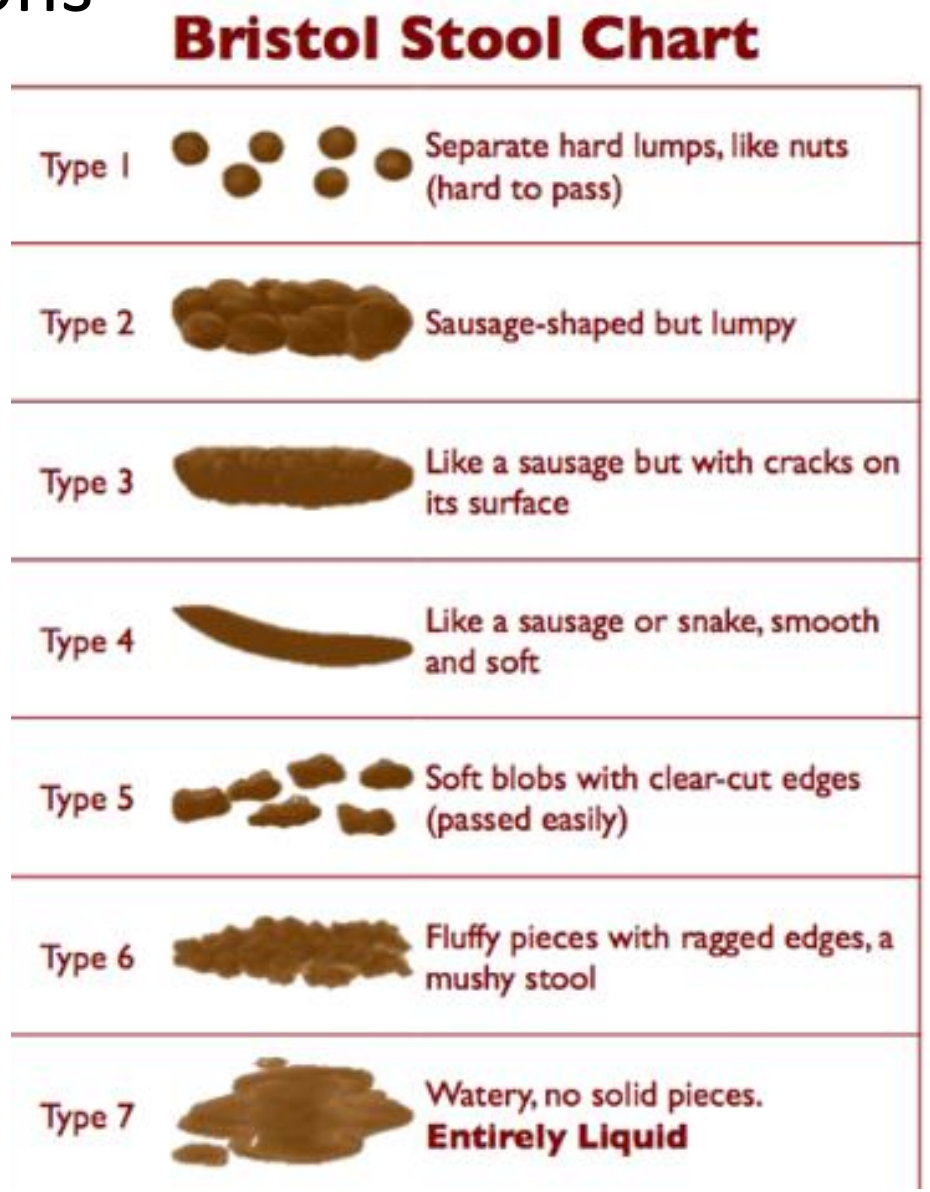
Lessons in motility from fecal pellet shapes & intestinal segmentations



sheep

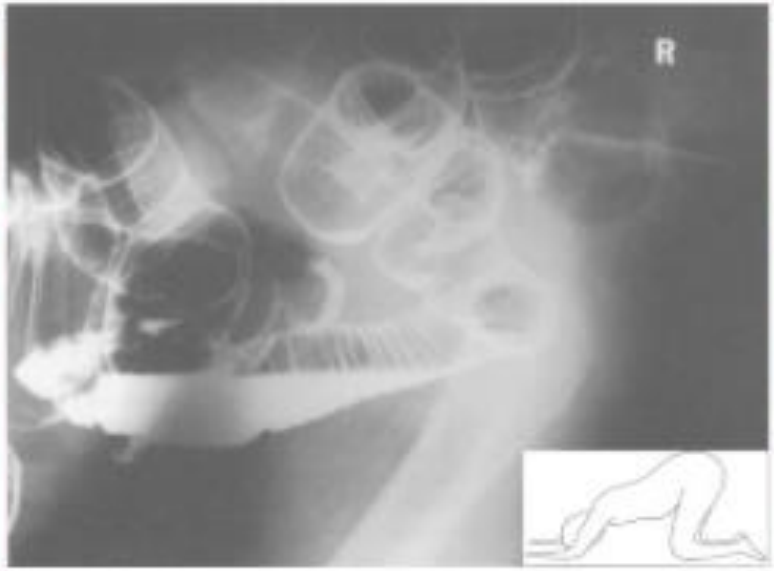


rabbit



Human Megacolon

Chagas disease

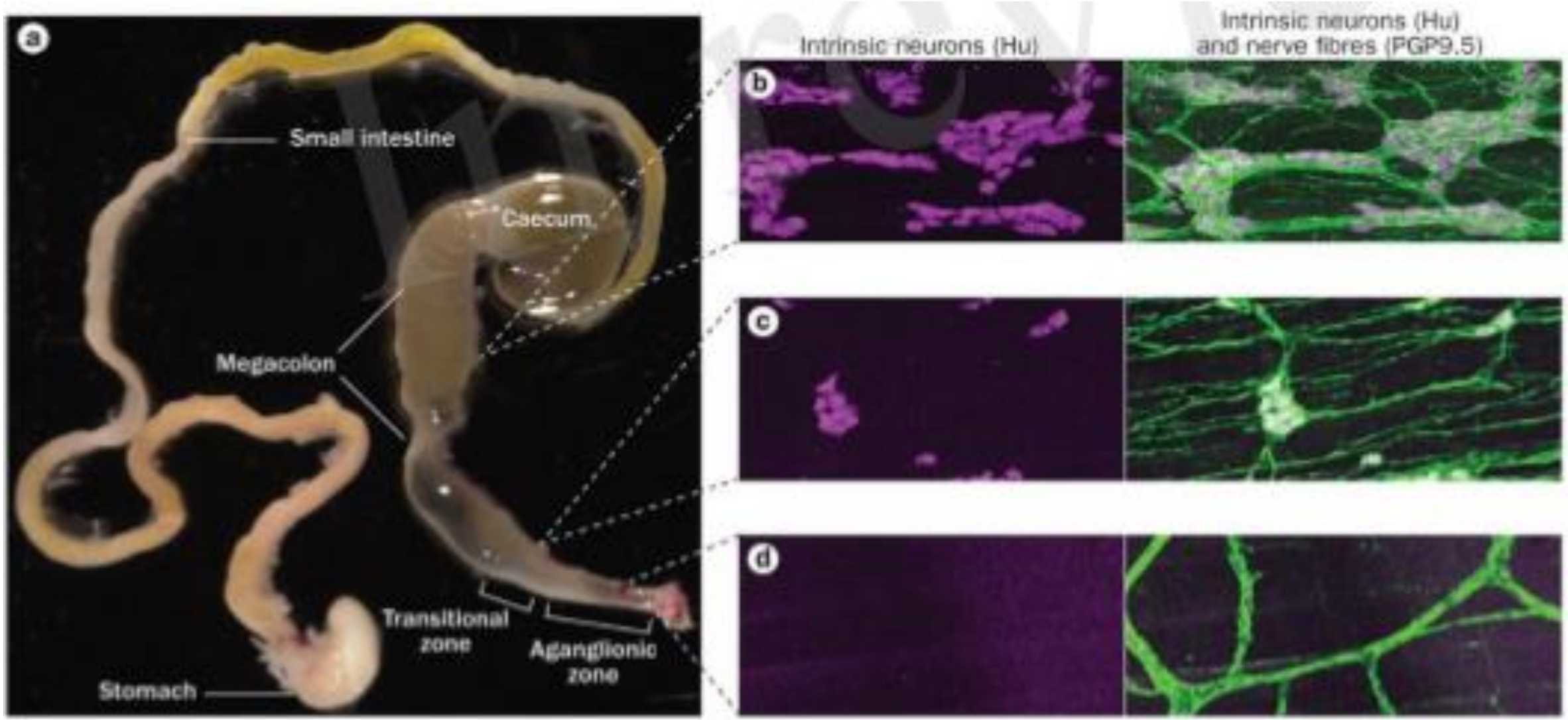


Knee-elbow position

Listless colon

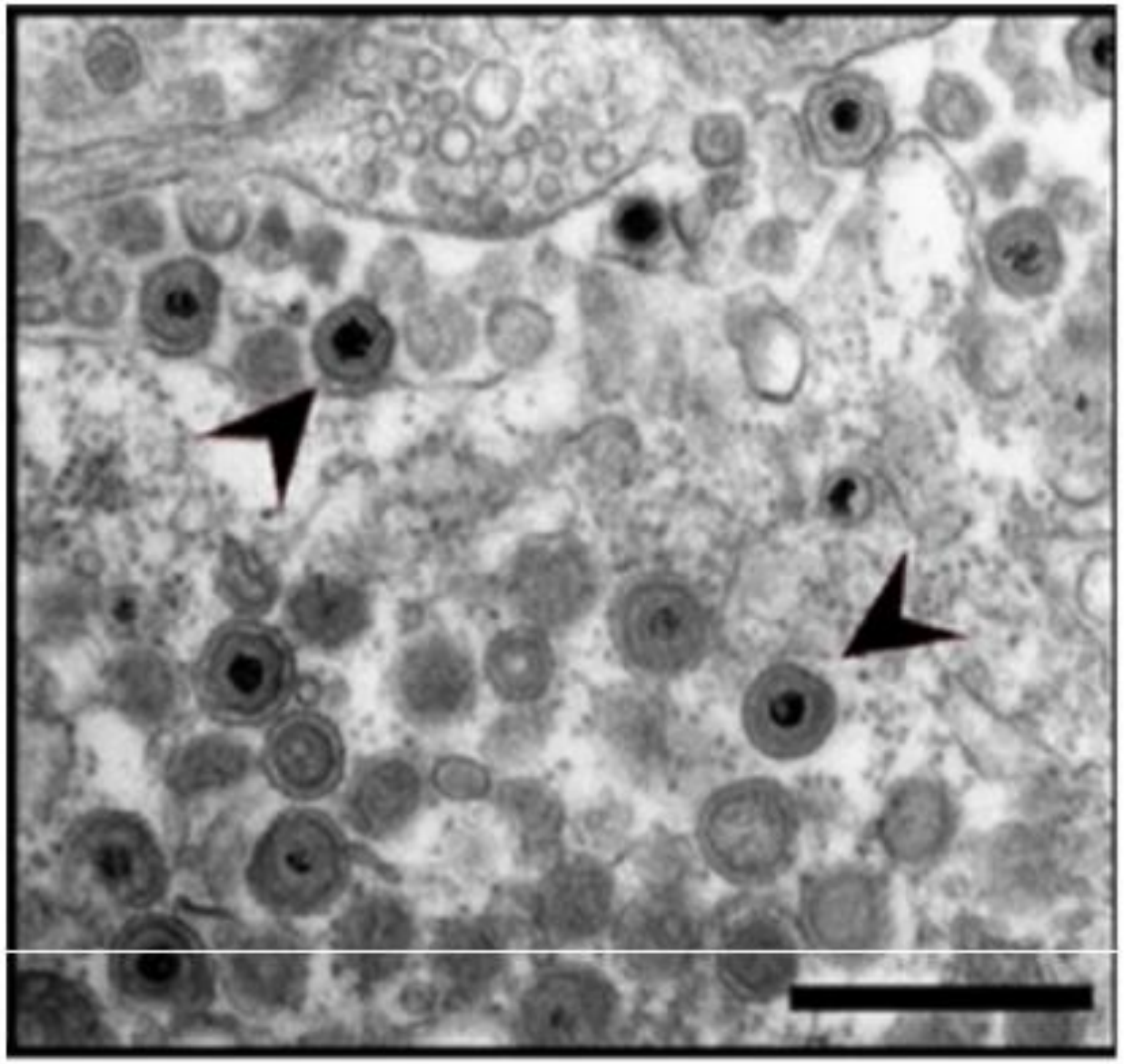
Chaudhury, Srinivas, et al,
Frontiers in Pathology, Peer review, 2017

Animal model of Hirschsprung's disease

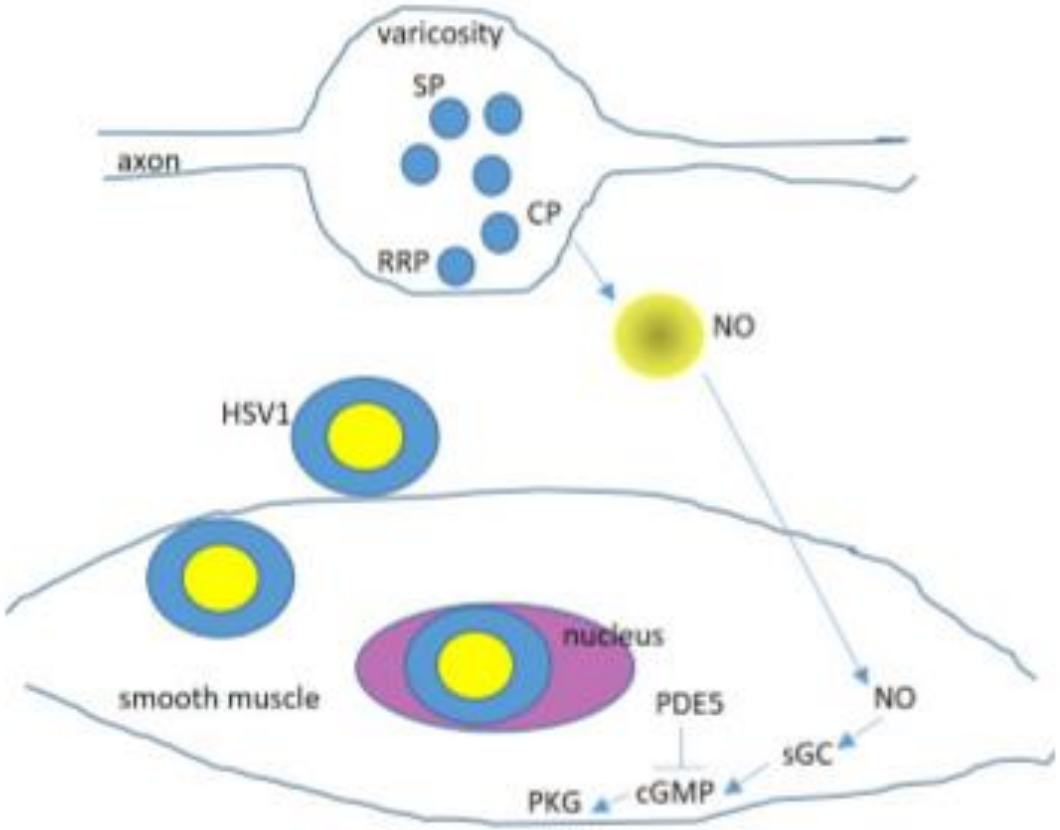


Chaudhury, Srinivas, et al,
Frontiers in Pathology, Peer review, 2017

HSV2 intestinal myopathy: A Model for constipation



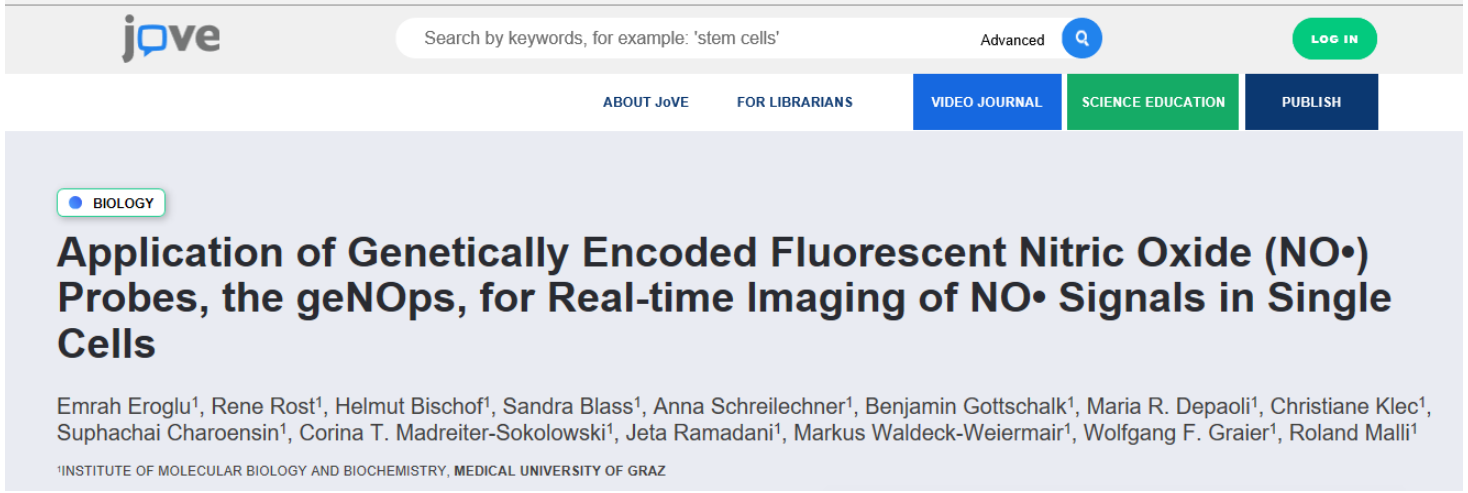
Khoury-Hanold et al, Cell Host & Microbe, 2016



Chaudhury, Srinivas, et al,
Frontiers in Pathology, Peer review, 2017

What is the basis for multisystem involvement?

- 2 siblings from Ecuador, 11 and 14 yrs old
- Seizure disorders, pervasive neurodevelopmental disorder
- Achalasia
- Tuberculosis and recurrent fungal infections



Pedroza, Chaudhury 2017

Microbiome (virus, bacteria, fungus, prion)

& ENS

Neuroimmune interactions…an unexplored area

In ancient China, the first meal of a child was mother's fecal pellet

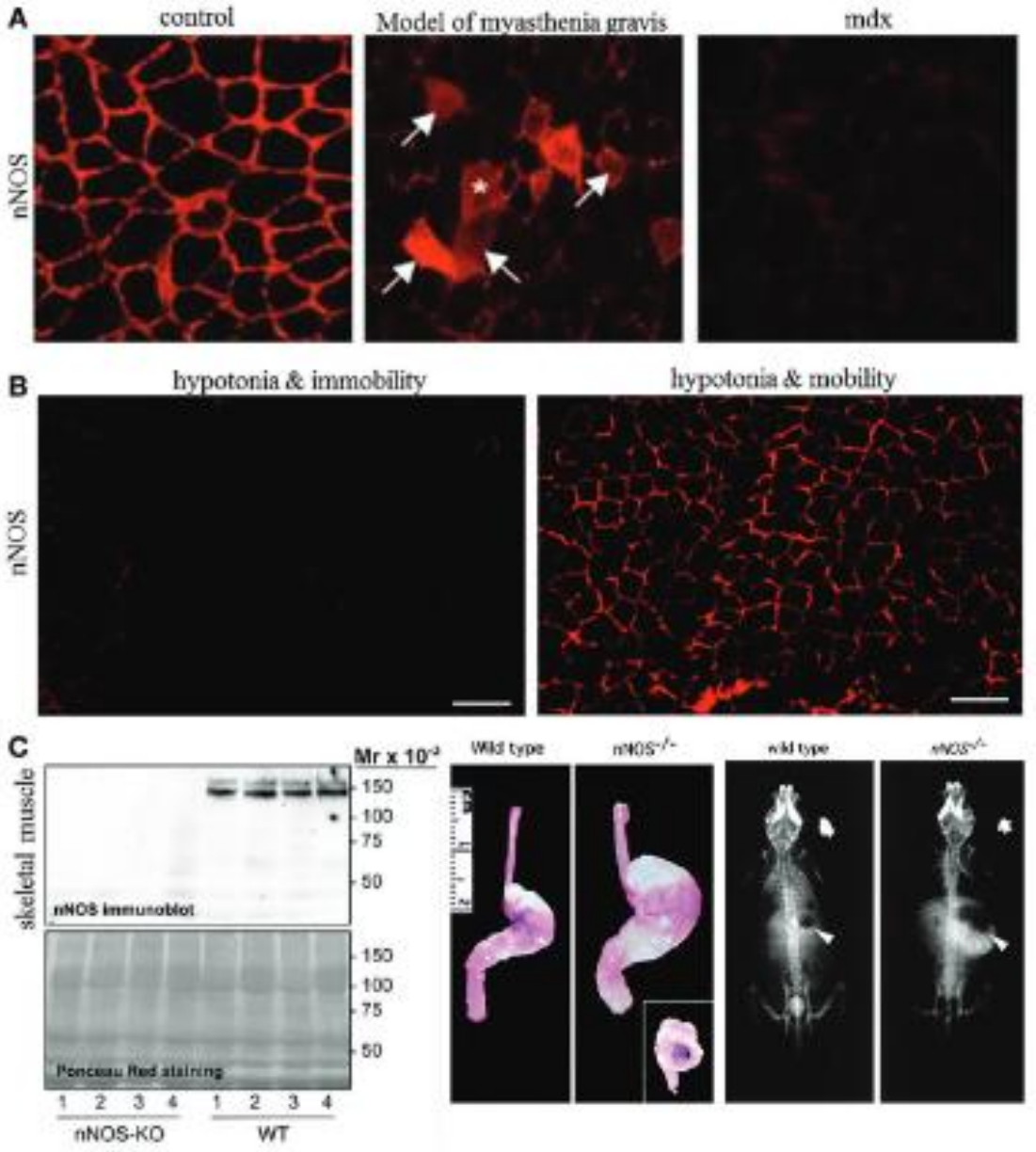
Necrotizing enterocolitis, etc….antibiotic overuse in NICU

Intestinal gas, bloating, SIBO

Rational approaches to identification of pathophysiology

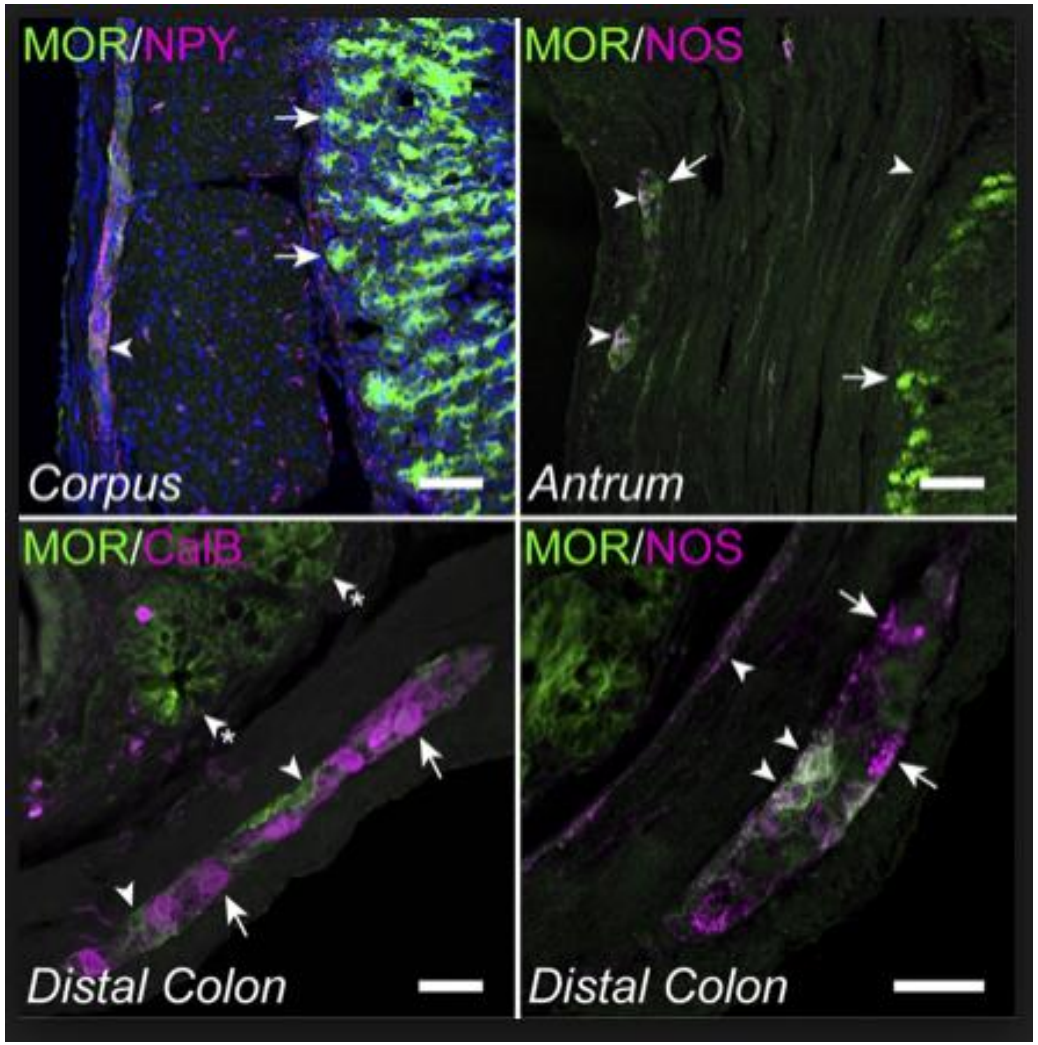
- Skeletal muscle biopsy…nNOS location
- nNOS in neutrophil…dimer assay
- Defects in secretory capacity…platelet assay
- Skin melanosome assay for myosin Va
- Whole thickness intestinal bx and over the scope clipping is still not a reality

Patent worthy



Chaudhury 2016

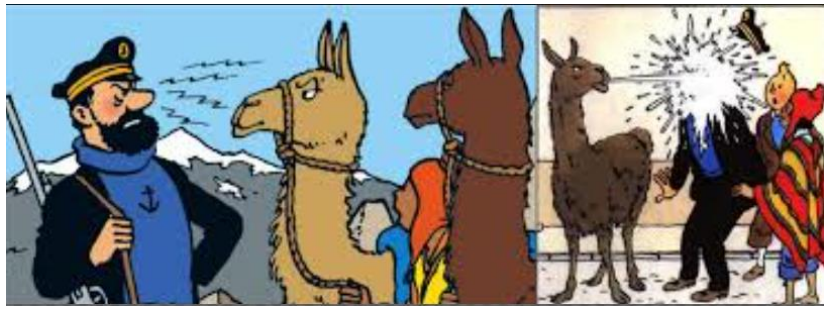
Enteric musculomotor transmission & The Opioid Epidemic



MOR = μ-opioid receptor
NOS = neuronal nitric oxide synthase

Lay et al, 2016, G252-G266, American Journal of Physiology Gastrointestinal and Liver

Insights from Mother Nature



Alapaca

Do humming birds develop gastroparesis?

Chaudhury, 2017

Gastric emptying mechanisms of sloth

Low amplitude IJP in stomach, Szurszewski, abstract

Chaudhury, 2017

Phenotype reversal in Ulcerative Colitis

- Role of nicotinic receptors?

Satish Rao

SLC17A9 (Vesicular nucleotide transporter, VNUT) knockout mice have apparently normal appearing GI tract and normal fecal pellet output

Delve to figure out the molecular basis of FUNCTIONAL BOWEL DISORDERS

Find BIOMARKERS of FUNCTIONAL BOWEL DISORDERS

Summary

- Pathophysiology of esophagogastrointestinal motility disorders often difficult to discern
- Obtain detailed **HISTORY**, ask patients to maintain diary, do NOT discount symptoms
- Detailed communication and empathy with patients, along with expert dietary consult (regarding FODMAP diet, fibers etc)
- Subtle molecular defects, mostly involving neurotransmission at multiple levels
- The defects may involve both upper and lower GI tract (for example, alternating constipation and diarrhea may co-exist with refractory GERD in an irritable bowel syndrome patient)
- All defects of GI motility affects the final common pathway of IJP
- Lot remains to be known
- Think physiology and pathology (e.g., why do we belch after a coke…?any relation to TLESR, reflux disease and biliary reflux)

Lessons for other organ systems from enteric neurotransmission

- Similarity in mechanisms of insulin release with fast and slow IJP
- Aortic stiffening, widening of pulse pressure and nNOS-mediated NO release in tunica intima
- Flow through low pressure system..pancreatic/cystic duct, portal vein, pulmonary vein, fallopian tube

Bioelectronic medicine for ameliorating gastrointestinal motility disorders

- Lessons from **sex medicine**
- **Bioelectronic medicine**…on demand de novo synthesis of NO…very very difficult challenge in pharmacology for functional bowel disorders

Yartsa gunbu

cordycepin

Patent worthy

Chaudhury 2017

Look for pharmacology everywhere!

Chikoo & Myosin V; Chaudhury, 2017, patent worthy

Outstanding research questions

- Though tonic, LES and pylorus differ…LES relax with a sweep of primary peristaltic wave….NO synthesis in pylorus is stochastic…what is the luminal stimulus that drive gastric emptying?
- Segmentation…what determines the ends and the length of the segment
- What is the luminal sensor
- How millions of food molecules with different structures distinguished from few thousands toxins, also of different structures…is there a quantal difference in serotonin release
- Street food and ENS
- ENS of hyena
- Milk Oligosaccharide and neurotransmission
- DIETARY FIBERS and neurotransmission

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- Raj K Goyal, Mallinckrodt Professor of Medicine, Harvard Medical School
- Luis Alberto Pedroza

Dean Srinivas, for your kind invitation

Faculty & Staff, ESIC Medical College

ESIC Medical College SanathNagar

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- NIH

Thank you all!

Mutter Museum, Philadelphia

Importance in Medicine & Medical Research

Independent validation

Neurogastroenterol Motil (2004) **16,** 475–487 doi: 10.1111/j.1365-2982.2004.00565.x

Changes in nitrergic innervation of defunctionalized rat colon after diversion colostomy

A. CHAUDHURY,* A. SHARIFF,* M. SRINIVAS† & U. SABHERWAL*

*Department of Anatomy, All India Institute of Medical Sciences (AIIMS), New Delhi, India
†Department of Pediatric Surgery, All India Institute of Medical Sciences (AIIMS), New Delhi, India

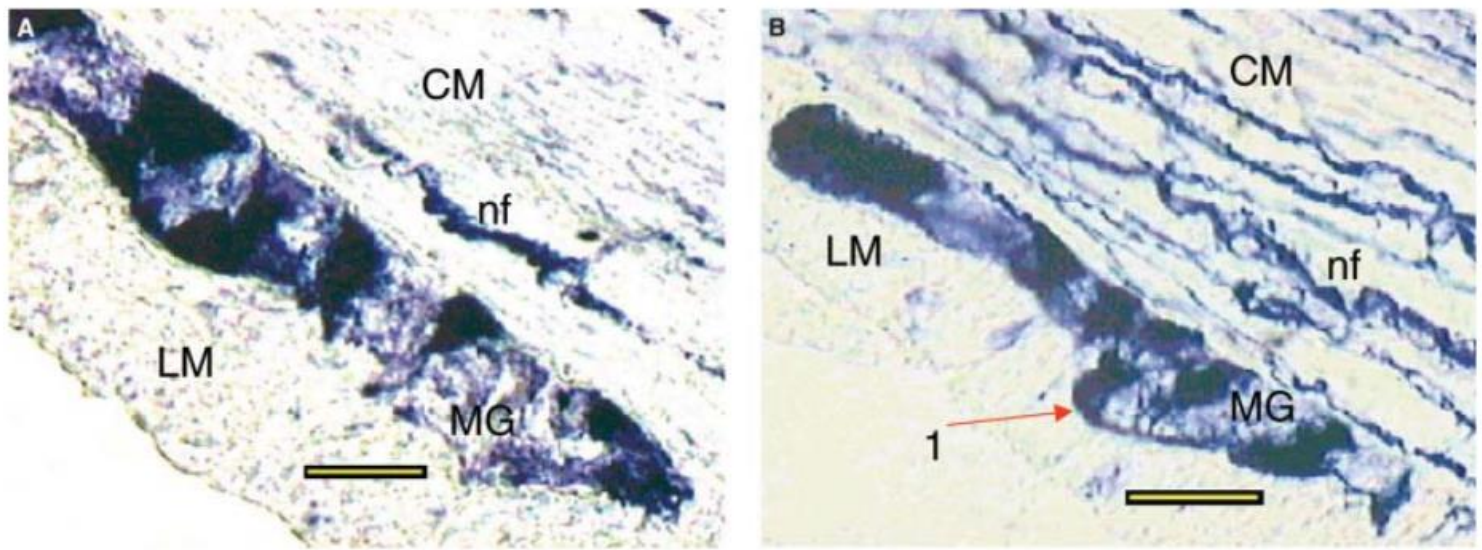

Figure 2 NADPH diaphorase stained light micrographs of myenteric ganglia. Marked reduction in size of neuronal soma and nuclei of nitrergic neurones (1) of myenteric plexus in the defunctionalized colon of rats (B) after diversion colostomy; (A) sham operated, (B) diversion colostomy. Note that the topographic distribution of diaphorase positive nerve cells and fibres was similar in the experimental as well as in sham-operated rats. nf, NADPH diaphorase positive varicose nerve fibres in the circular muscle layer; LM, longitudinal muscle; CM, circular muscle; MG, myenteric ganglia (scale bar 50 μm).

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Changes in cholinergic and nitrergic systems of defunctionalized colons after colostomy in rabbits

Serdar Moralıoğlu, MD,[a,*] *İsmail Mert Vural, MD,*[b] *İbrahim Onur Özen, MD,*[a] *Gökçe Öztürk, MD,*[b] *Yusuf Sarıoğlu, MD,*[c] *and Abdullah Can Başaklar, MD*[a]

[a] *Faculty of Medicine, Department of Pediatric Surgery, Gazi University, Ankara, Turkey*
[b] *Faculty of Medicine, Department of Pharmacology, Gazi University, Ankara, Turkey*
[c] *Department of Pharmacology, Faculty of Medicine, Istinye University, Istanbul, Turkey*

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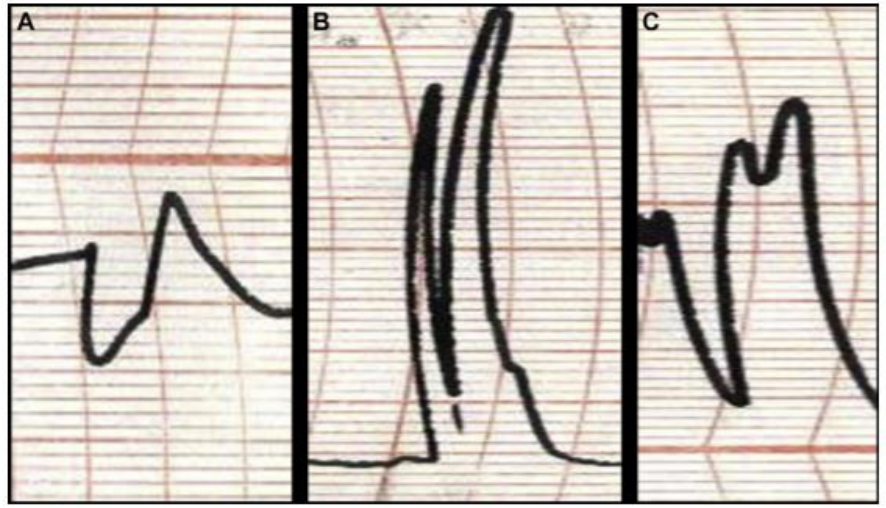
ABSTRACT

Background: This study was designed to assess smooth muscle function and motility in defunctionalized colonic segments and subsequent changes in pathways responsible for gastrointestinal motility.

Methods: Two-month-old New Zealand rabbits were randomly allocated into control and study groups. Sigmoid colostomies were performed in the study group. After a 2-month waiting period, colonic segments were harvested in both groups. For the *in vitro* experiment, the isolated circular muscle strips which were prepared from the harvested distal colon were used. First, contraction responses were detected using KCl and carbachol;



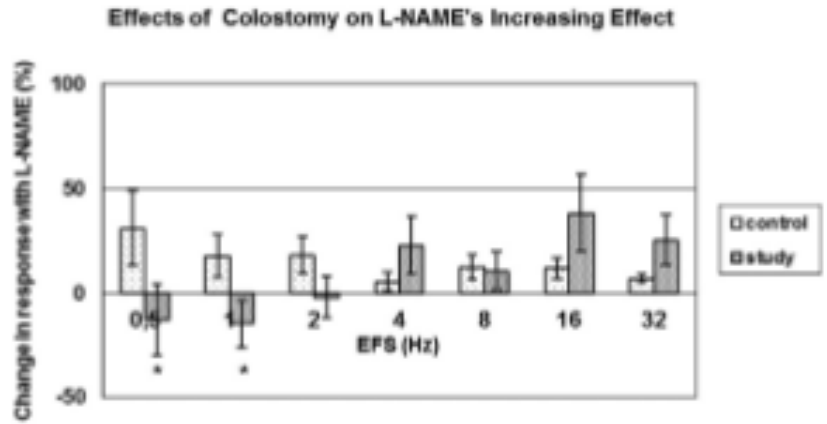


Fig. 3 — Effects of colostomy on the increasing effect of L-NAME (3×10^{-4} M) on EFS-induced responses in the control and study groups (number of animals = 6 and number of tissue samples = 10 in both groups). *P < 0.05.

Slides will be uploaded to

www.arunchaudhury.org