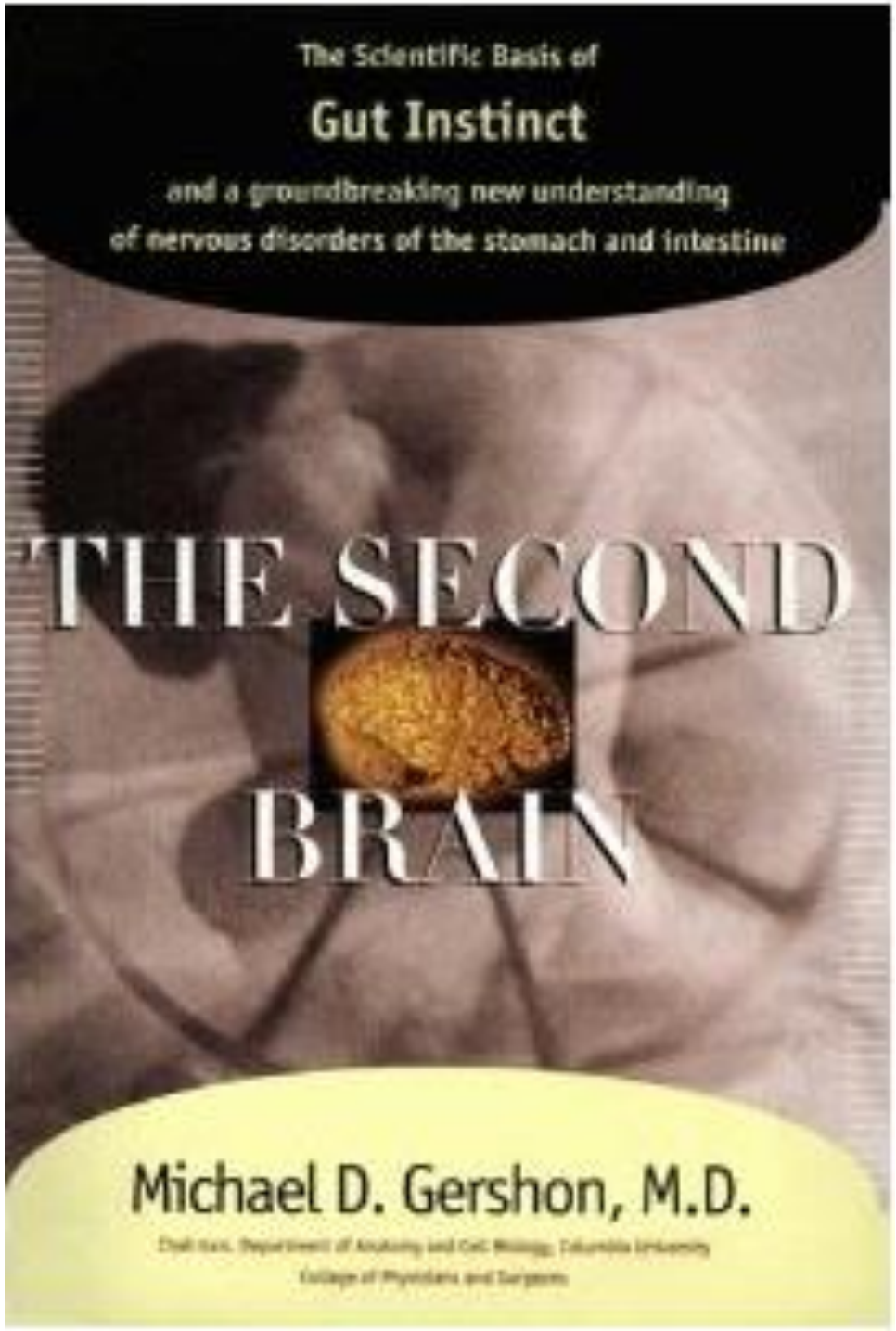
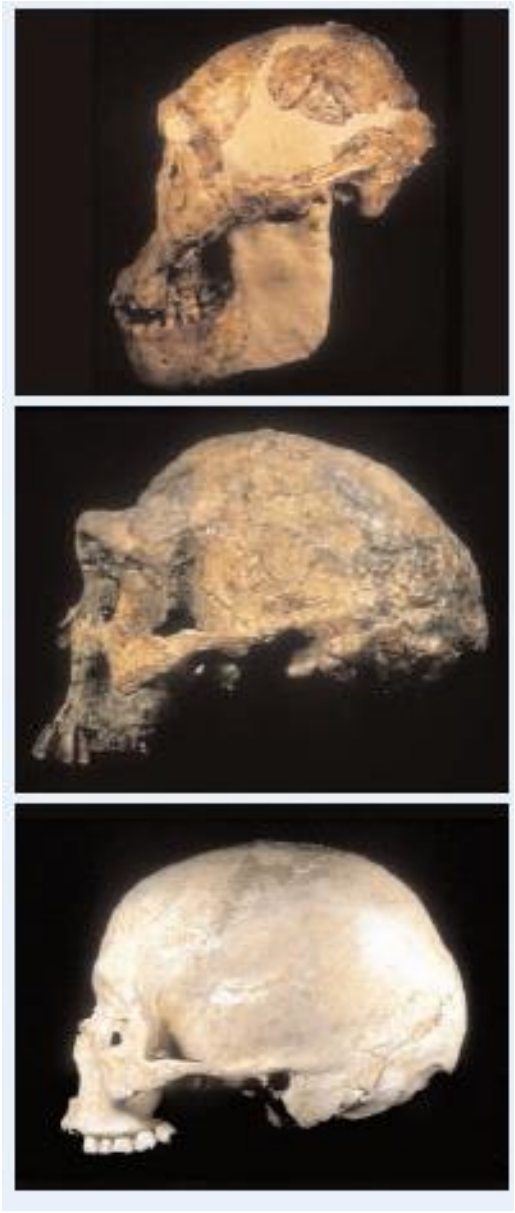
Thank you, Prof. Subrata Sinha



Swapping guts for brain

Expensive tissue hypothesis
Leslie Aiello

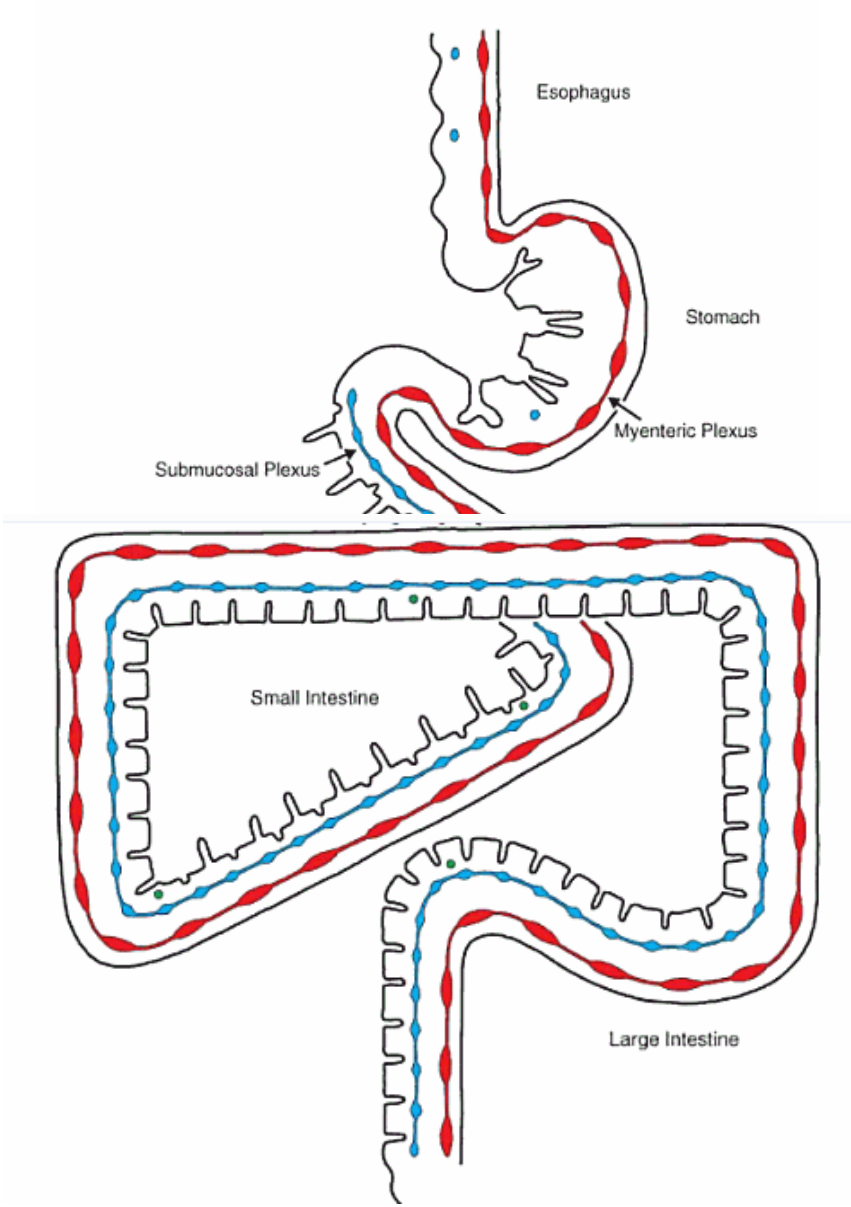


Australopithecus

Homo erectus

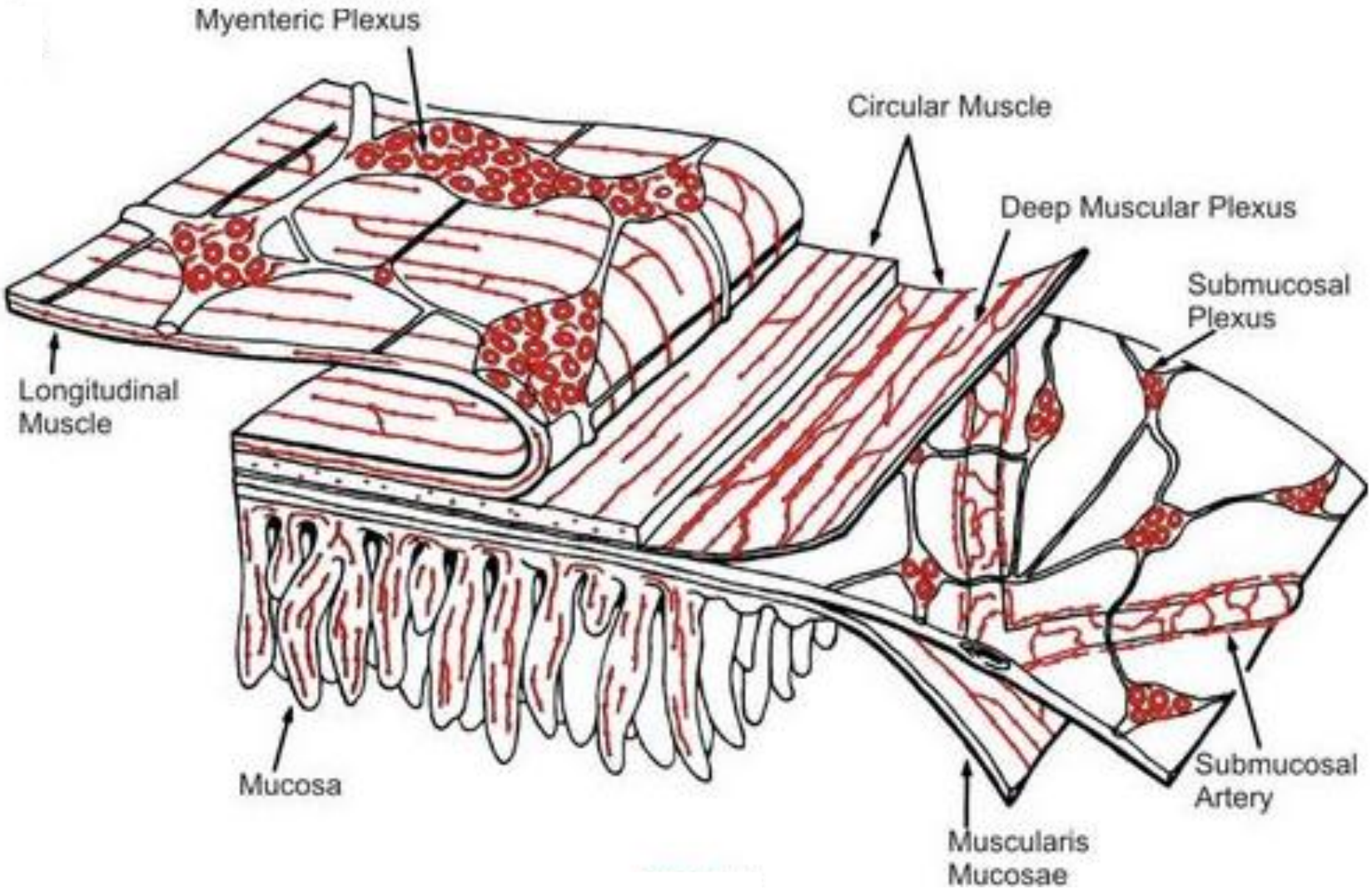
Homo sapiens

Gut: dynamic muscular tube

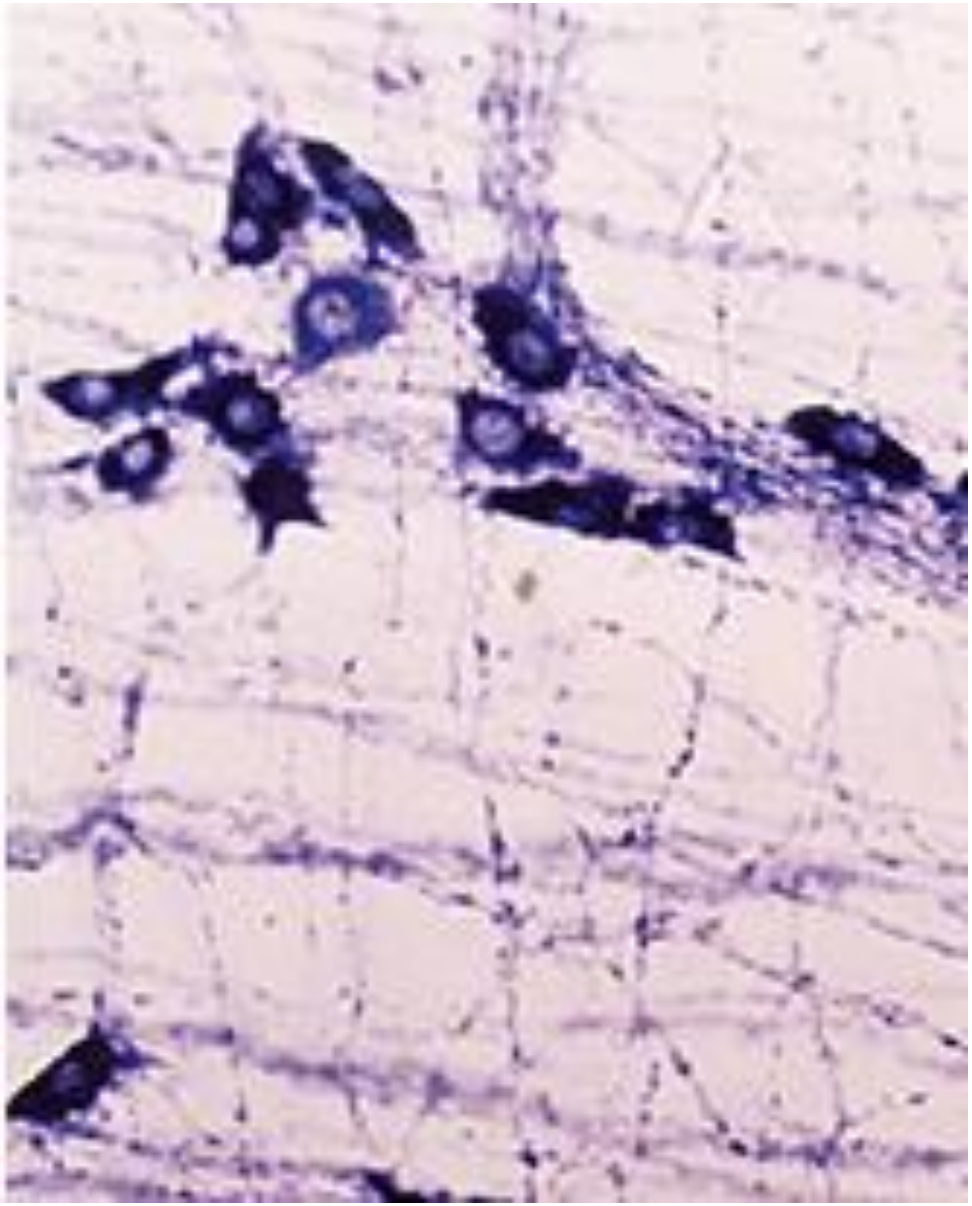


Enteric Nervous System
JB Furness

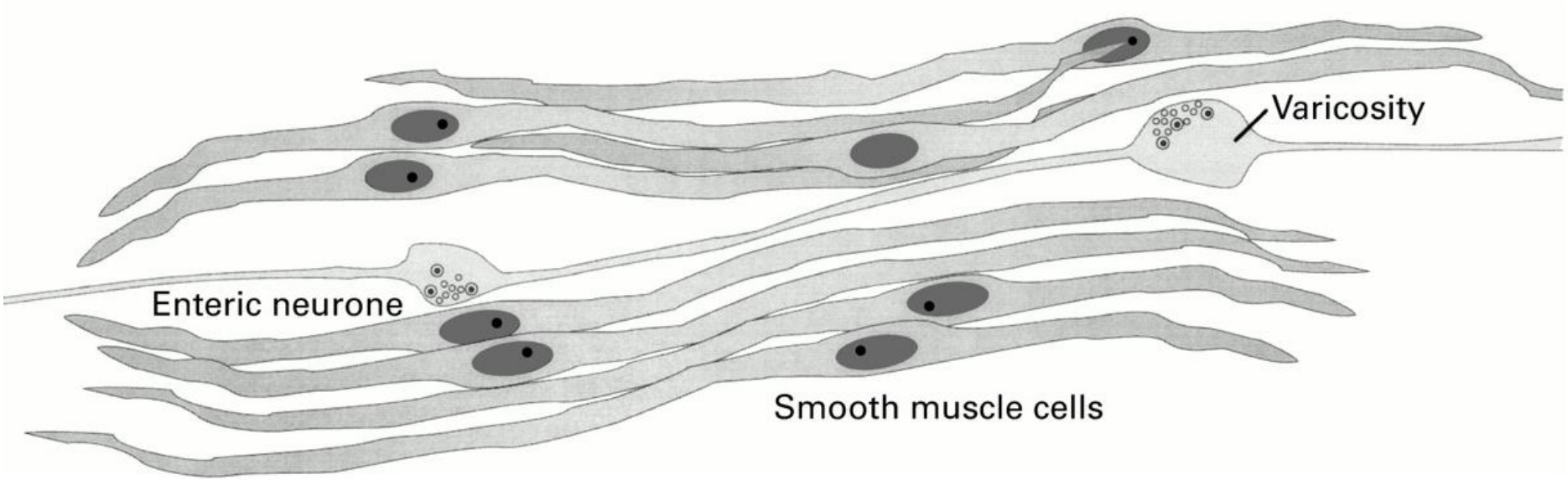
Rather monotonous architecture: enteric nervous system



Nerve terminal in laminar preparation



Neuro-Smooth muscle neuromuscular junction



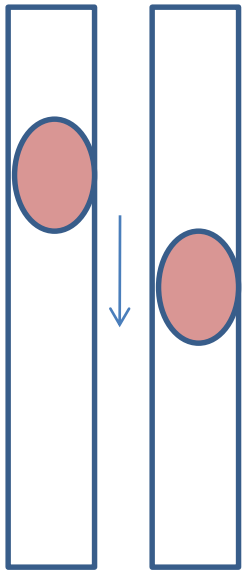
Who is a Longshoreman?

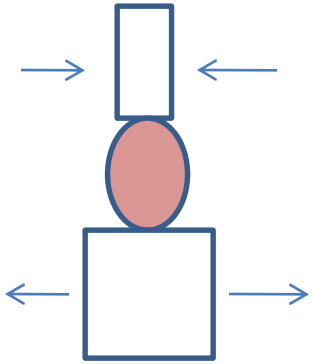
A longshoreman in enteric nerve terminal

Arun Chaudhury
Harvard Medical School

Law of intestine: peristalsis

Can we swallow during *shirshasan?*



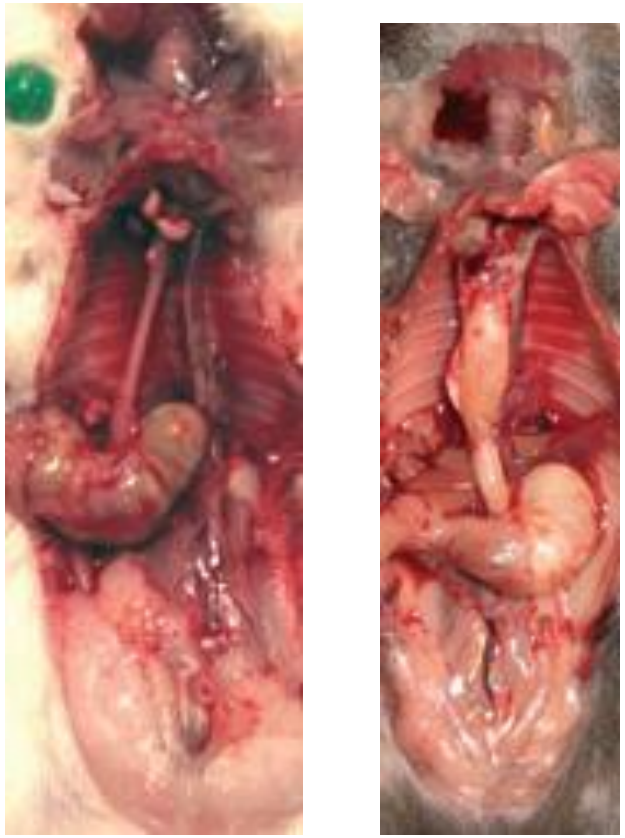


Major NM neurotransmitters in gut

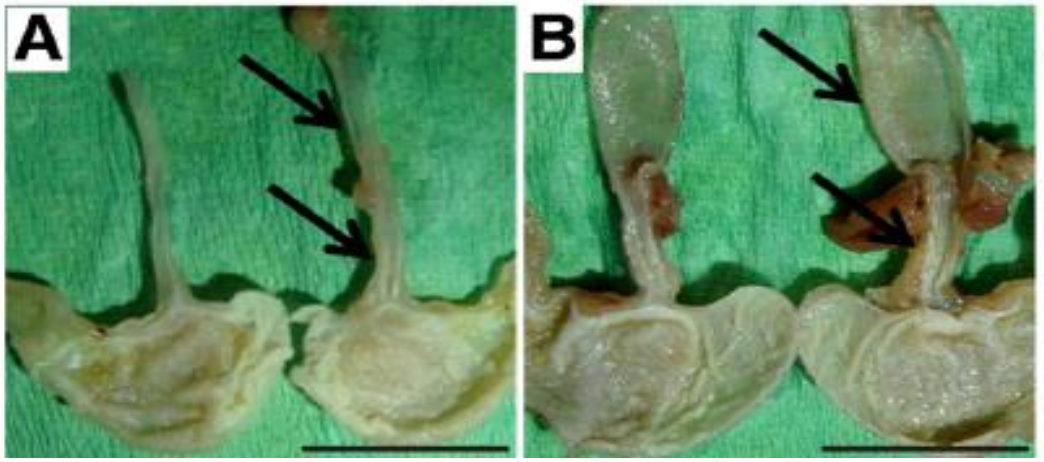
- Excitatory: ACh, Substance P
- Inhibitory: ATP, VIP, NO

Inhibitory neurotransmission critical in gut NMJ

Achalasia: Failure of LES to relax

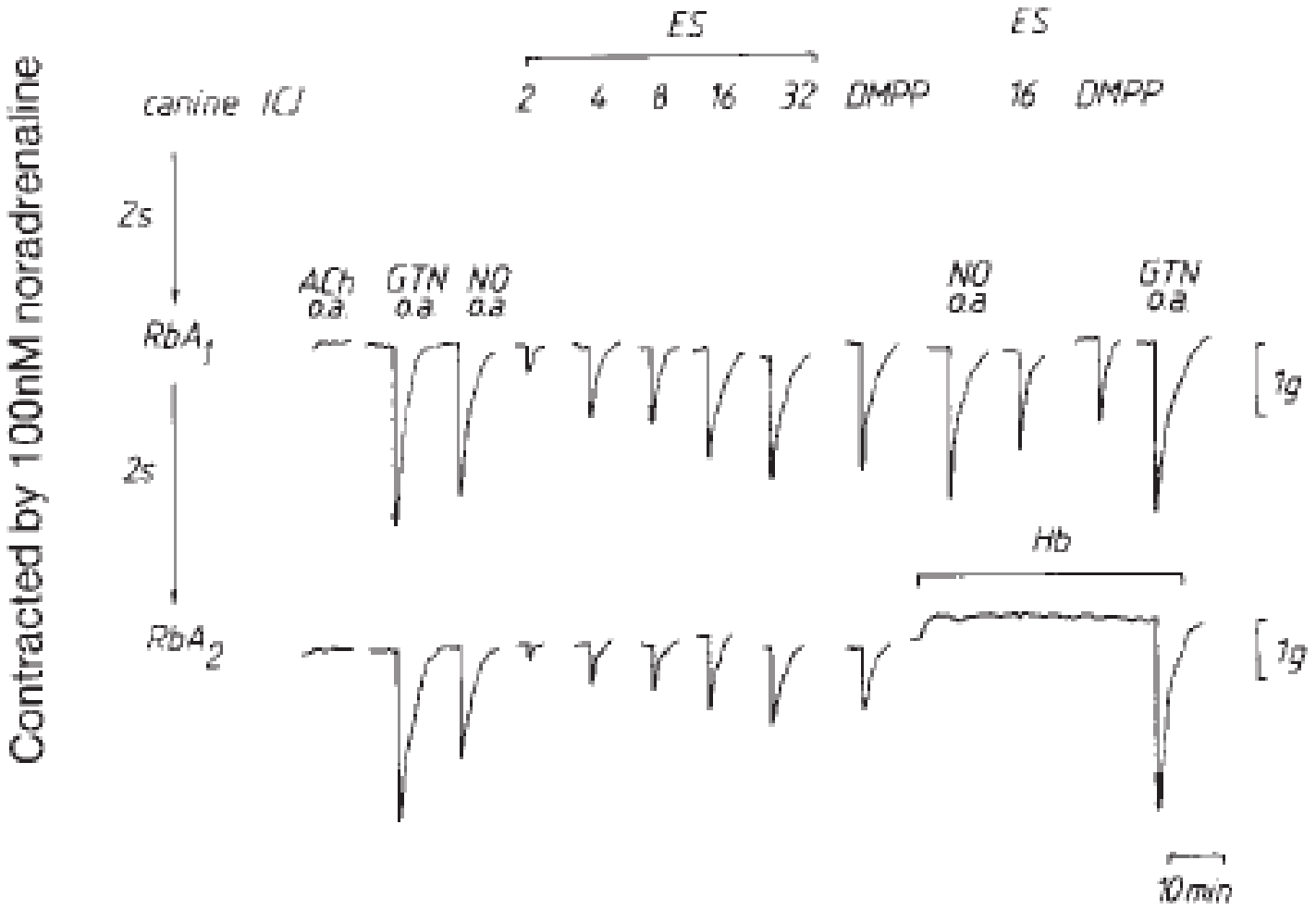


van der Weyden 2009



Zizer 2010

NO is a NT released from nerves in gut



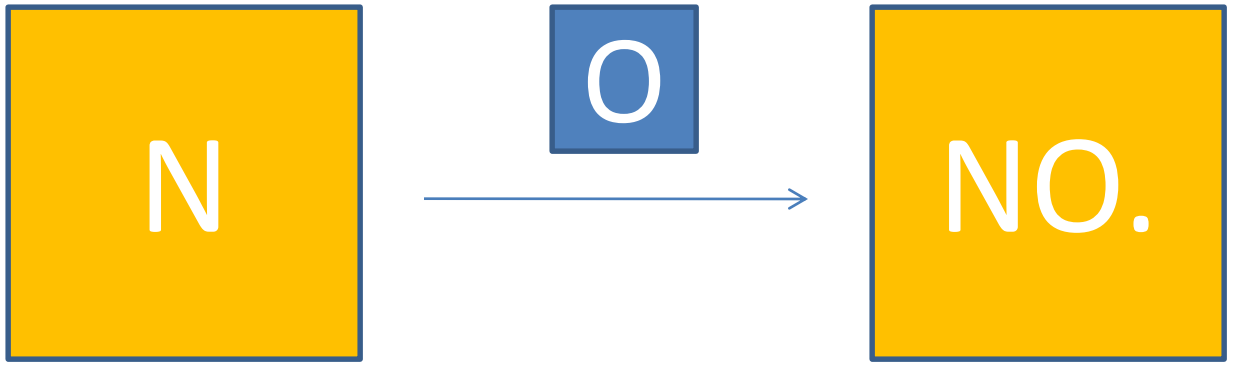
Bult et al 1990 Nature

Neurotransmitter identity doubt

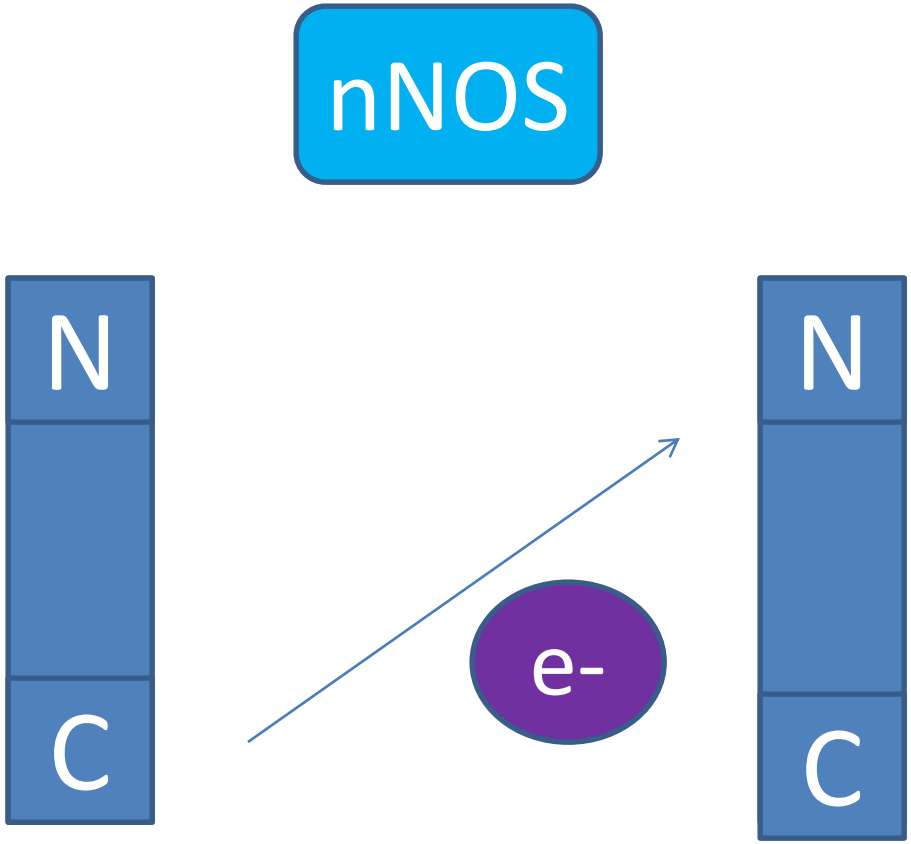
SIR—In a recent Letter[1], Bult *et al.* showed that stimulation by an electric field of the isolated and perfused canine ileocolonic junction pretreated with adrenergic and cholinergic blocking agents results in the release of nitric oxide. The authors concluded that nitric oxide is released from the nonadrenergic–noncholinergic neurons innervating this tissue and, therefore, that nitric oxide is the inhibitory transmitter for these neurons. An alternative explanation entirely consistent with these data is that stimulation of these neurons causes release of an unknown neurotransmitter

Ignarro et al 1990

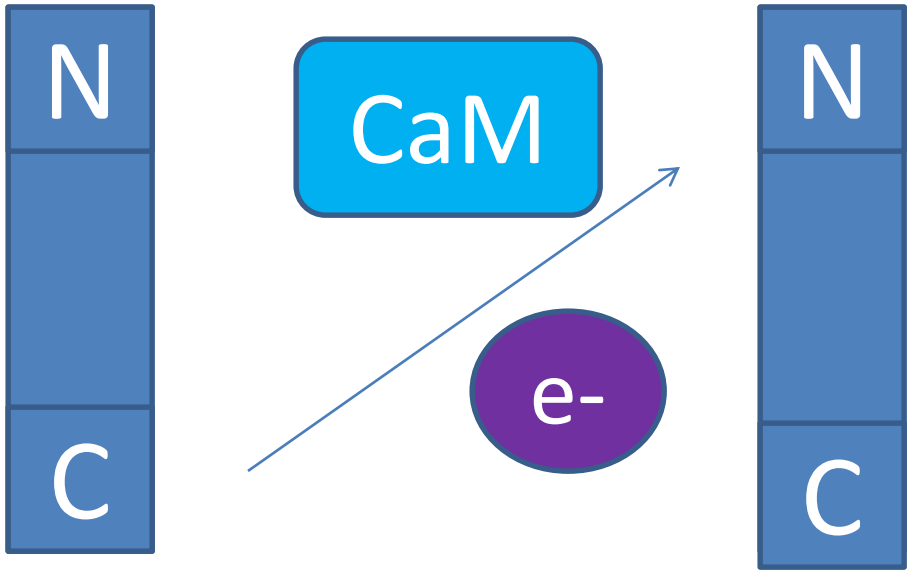
Synthesis of NO



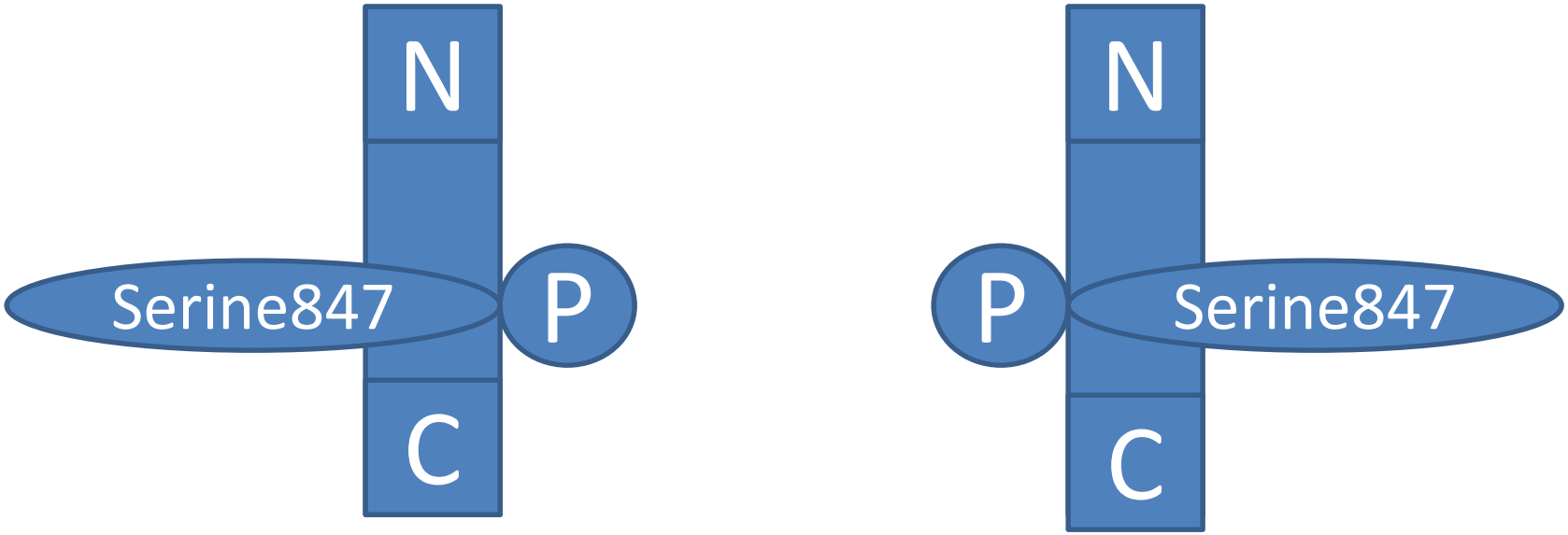
Catalytic synthesis of NO



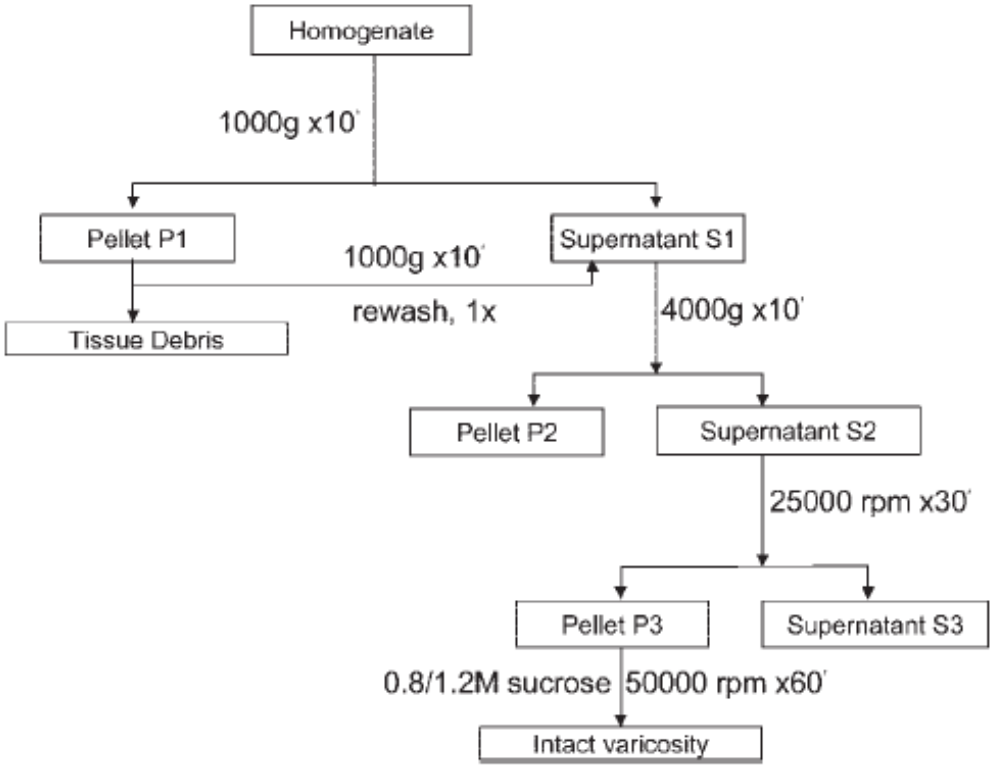
Facilitation of electron transfer

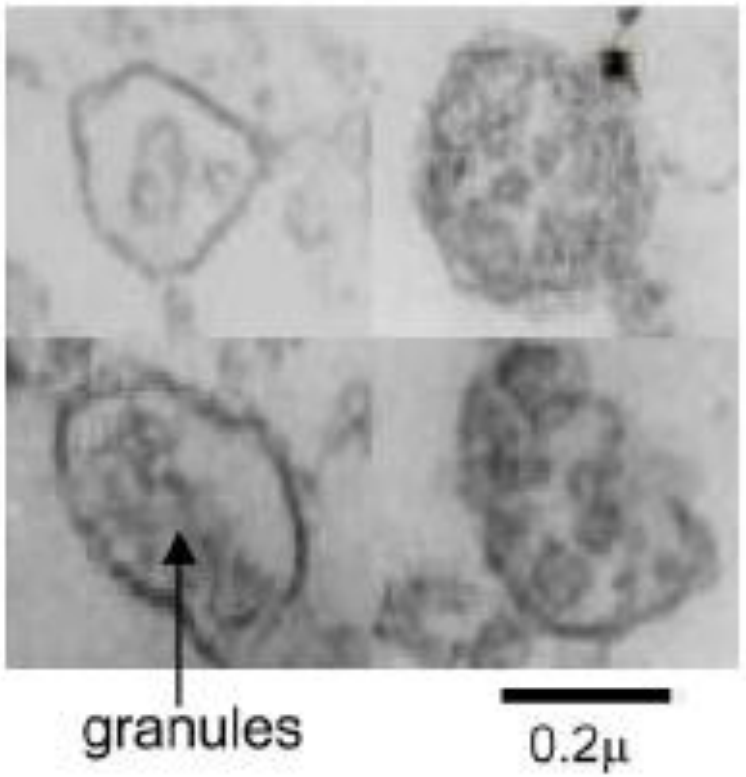


Inhibition of electron transfer



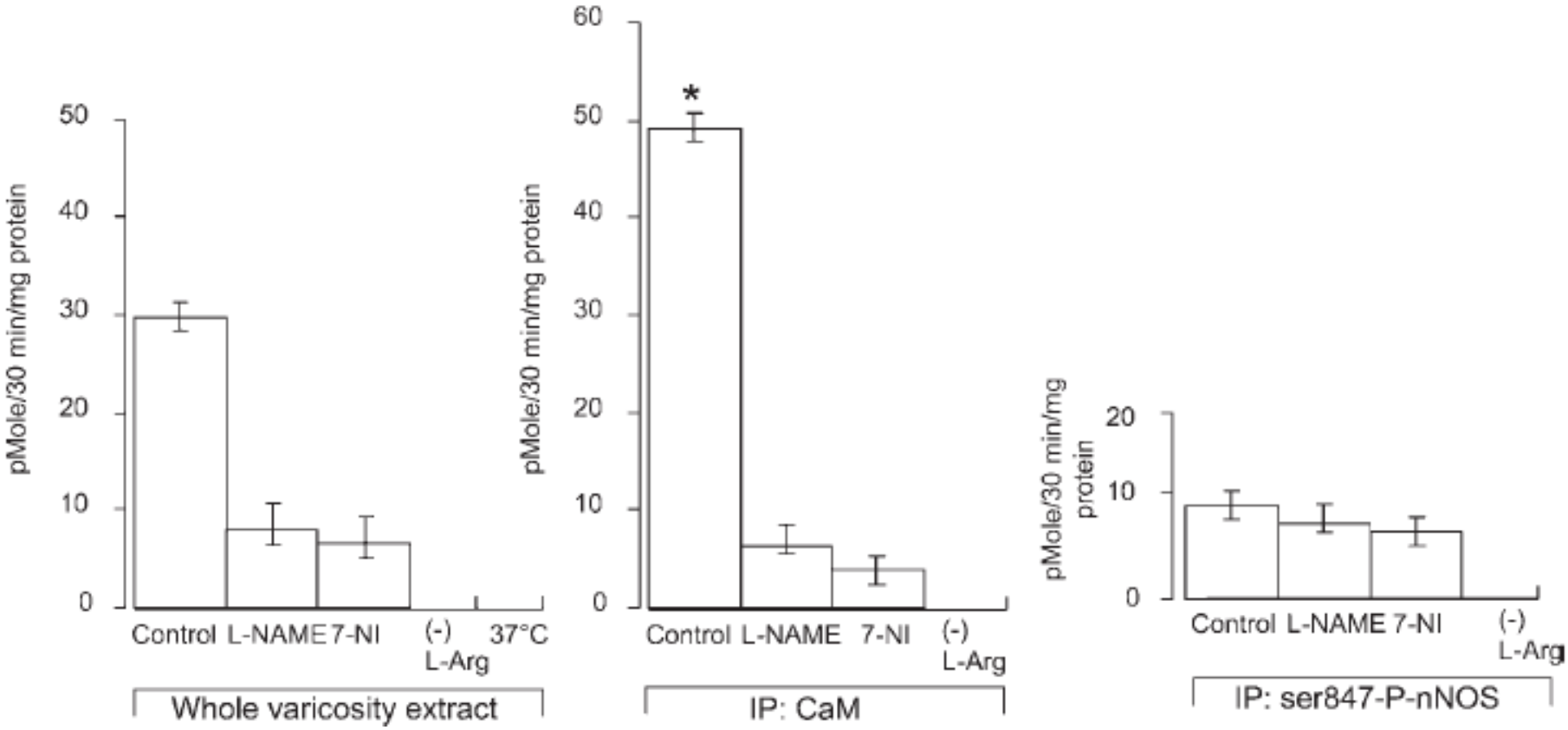
Obtaining enteric varicosities





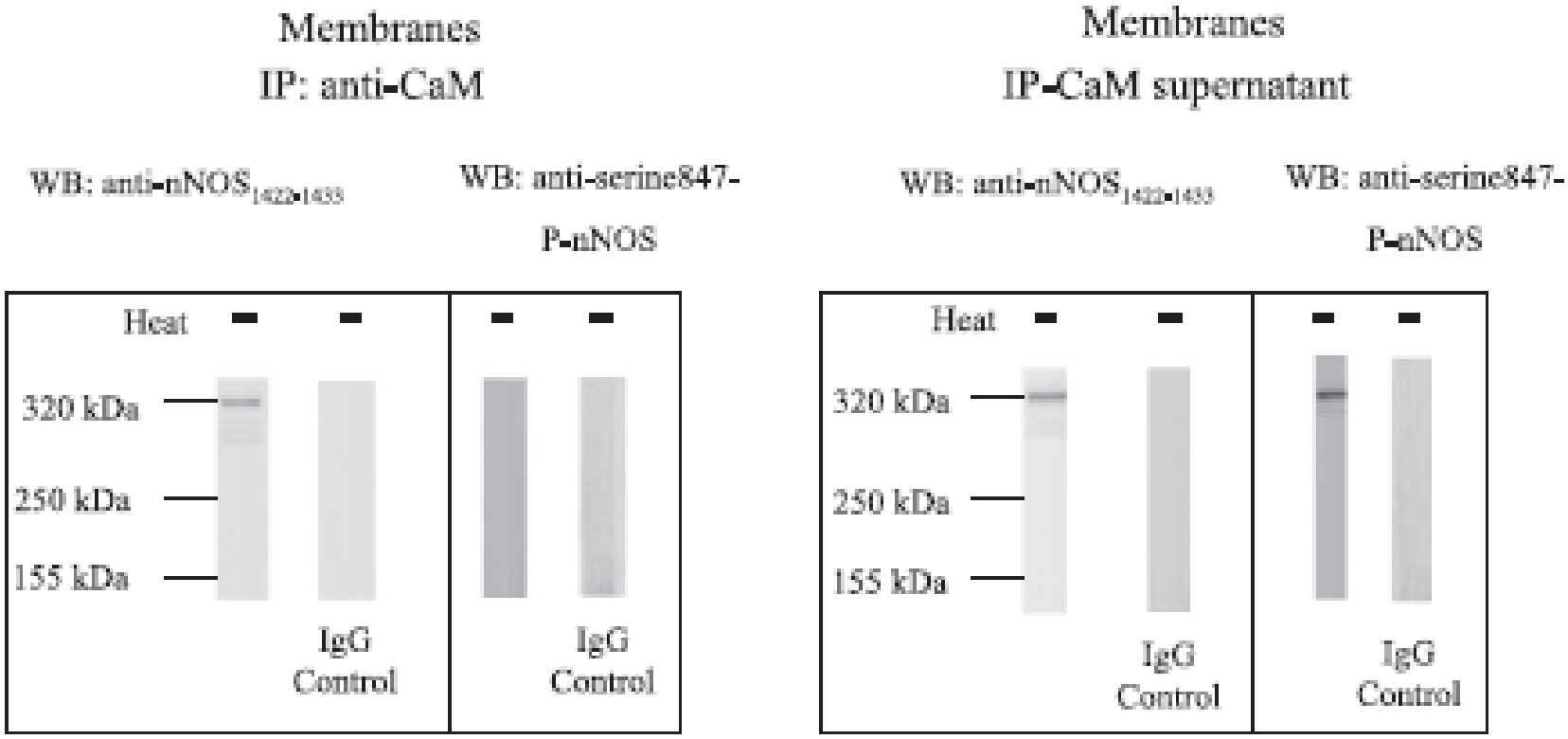
Rao, Chaudhury, Goyal, 2008, AJP Gastro

Active and inactive nNOS present in varicosities



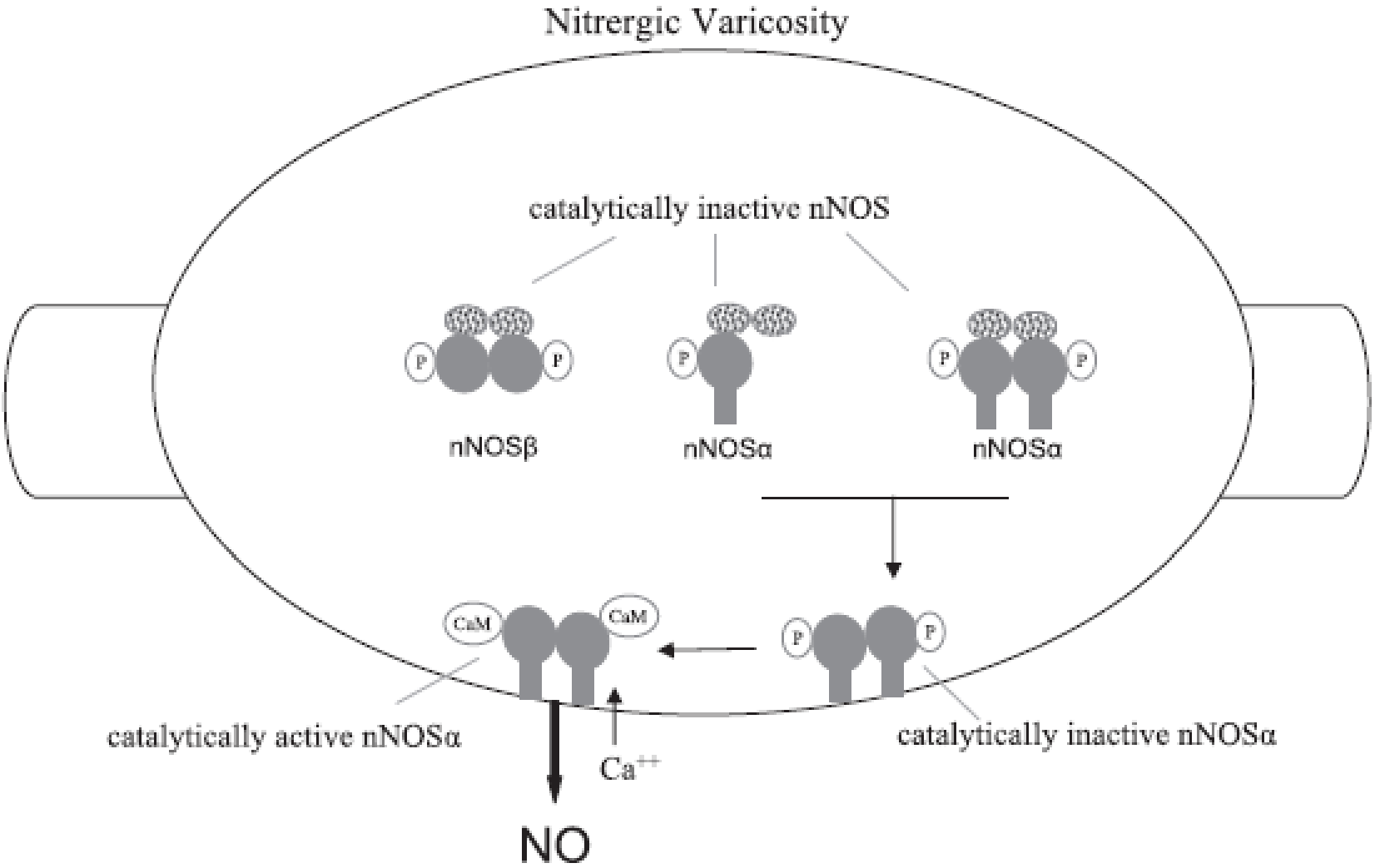
Rao, Chaudhury, Goyal, 2008, AJP Gastro

Both active and inactive nNOSα in varicosity membrane



Chaudhury, Rao, Goyal, 2008, AJP Gastro

How active nNOS transported to varicosity membrane?

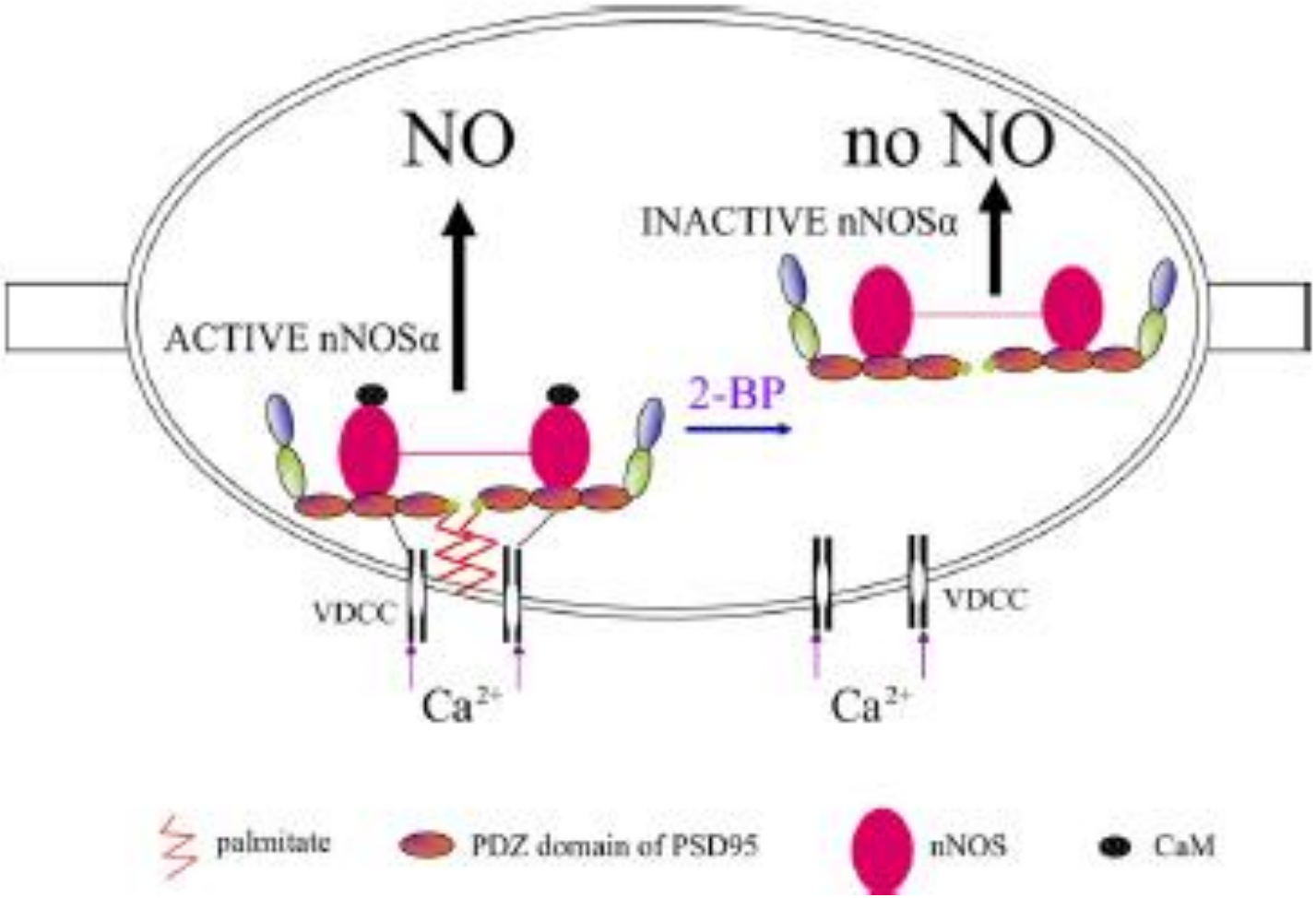


Chaudhury, Rao, Goyal, 2008, AJP Gastro

Possible modes of transport

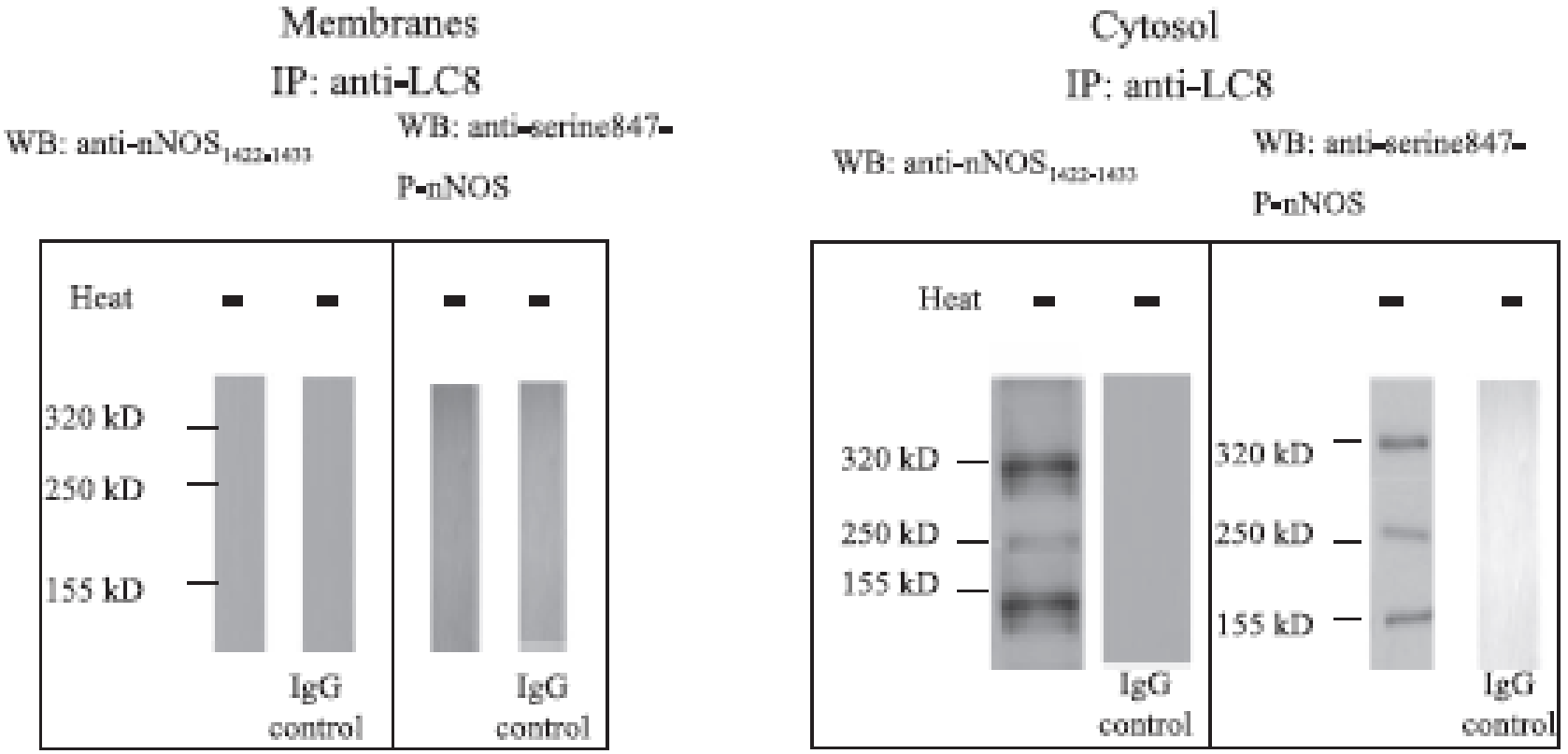
- Passive diffusion
- Molecular adaptors

Molecular adaptor for membrane binding: PSD95



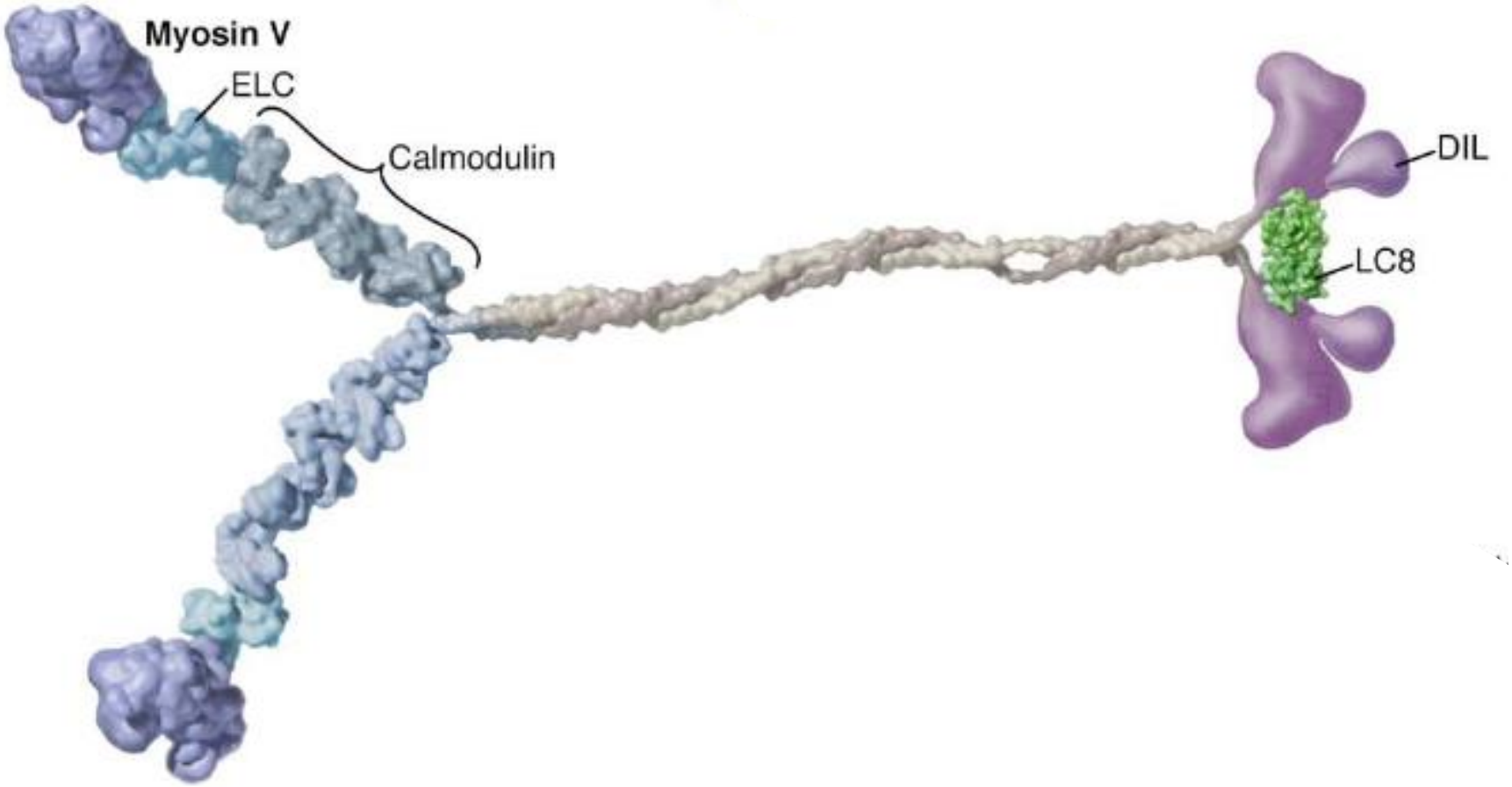
Chaudhury, He, Goyal, 2009, AJP Gastro

Cytosolic nNOS bound to PIN (DLC8 or LC8)



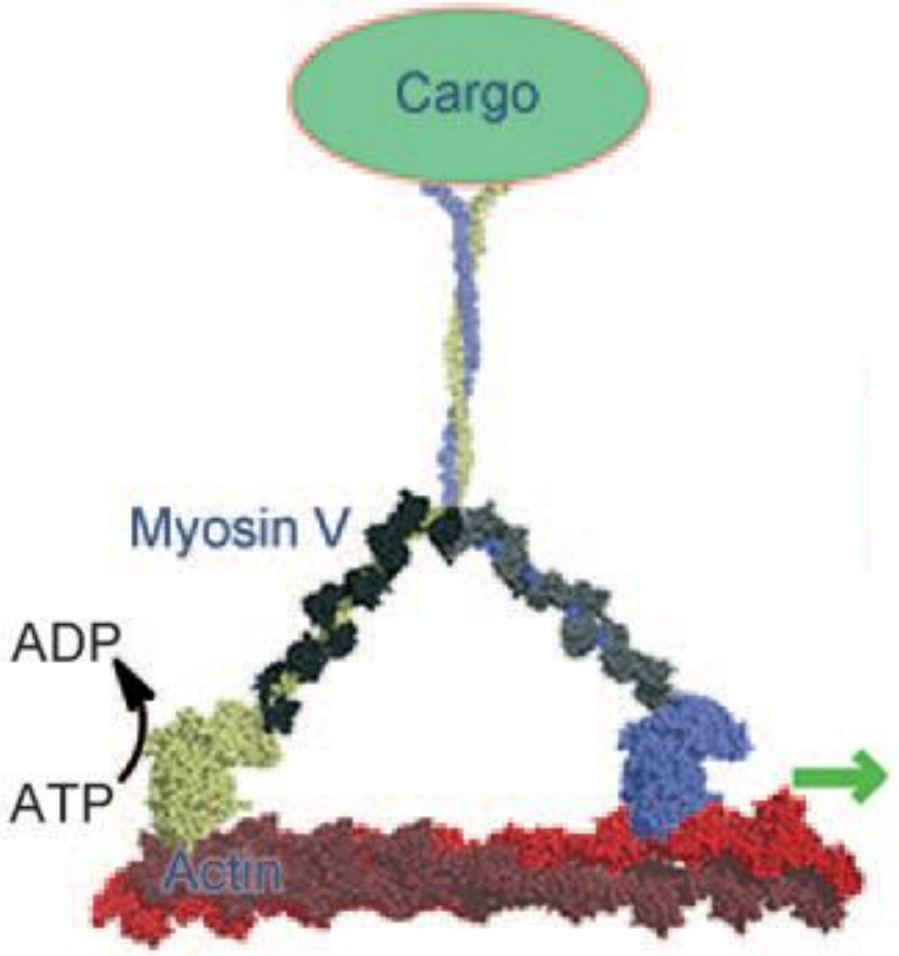
Chaudhury, Rao, Goyal, 2008, AJP Gastro

LC8 is light chain of myosin Va



Vale RD, 2003

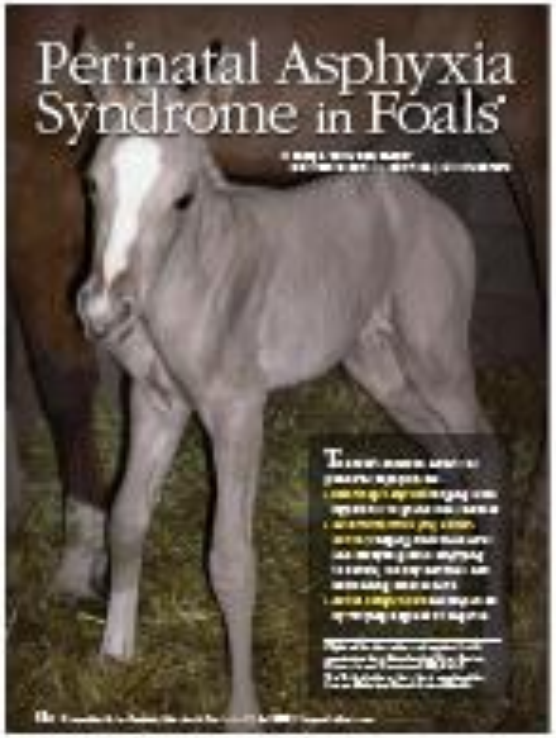
Myosin Va is a possible candidate for cargo transport in varicosity



Examine hypothesis if myosin Va facilitates enteric neurotransmission

‘Dilute’

DBA/2J



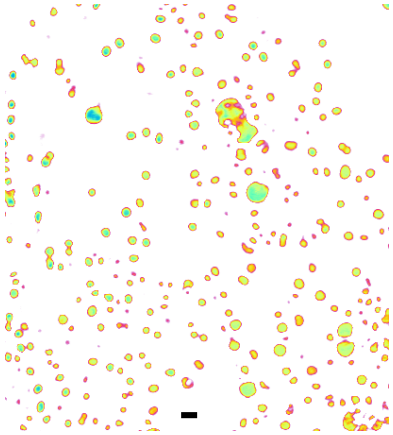
Lavender foal syndrome

Griscelli syndrome

Myosin Va present in enteric varicosities

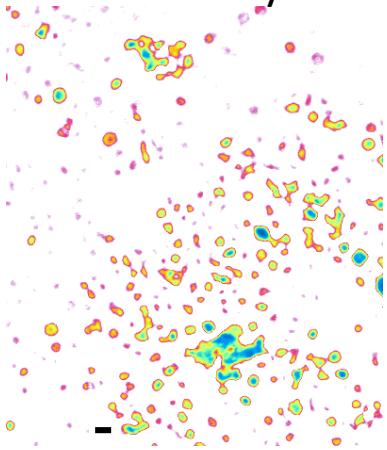
a.

WT (C57BL/6J) varicosity



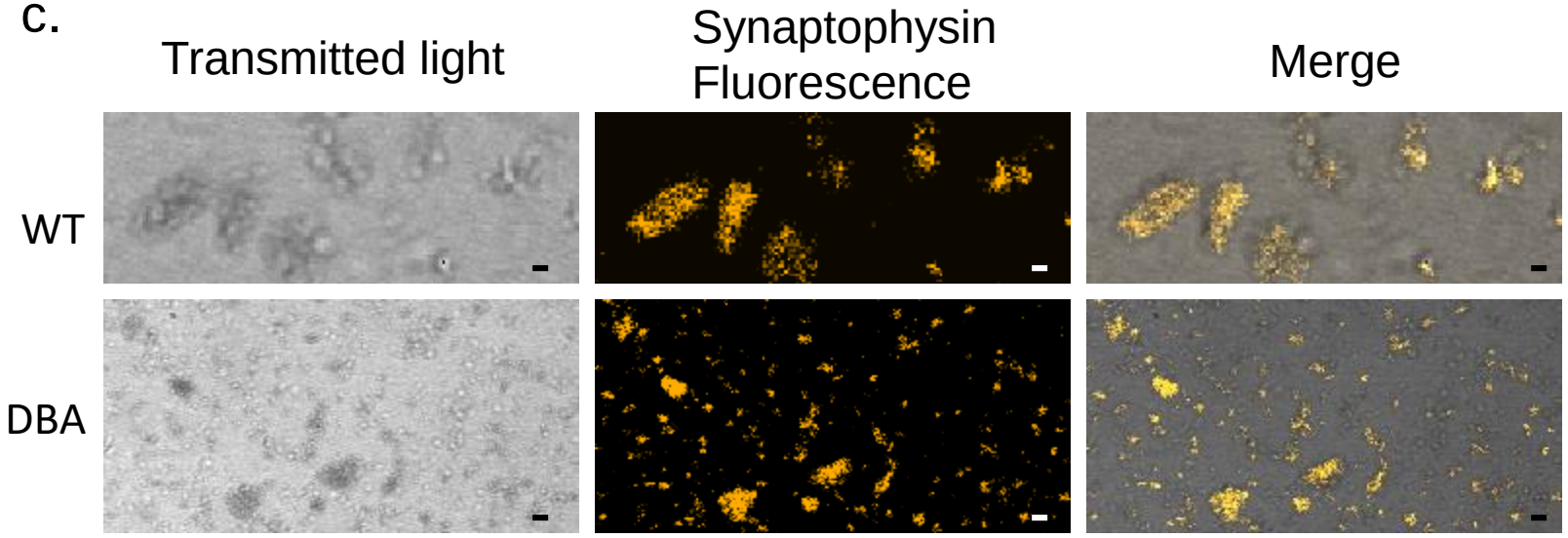
b.

Dilute (DBA/2J) varicosity

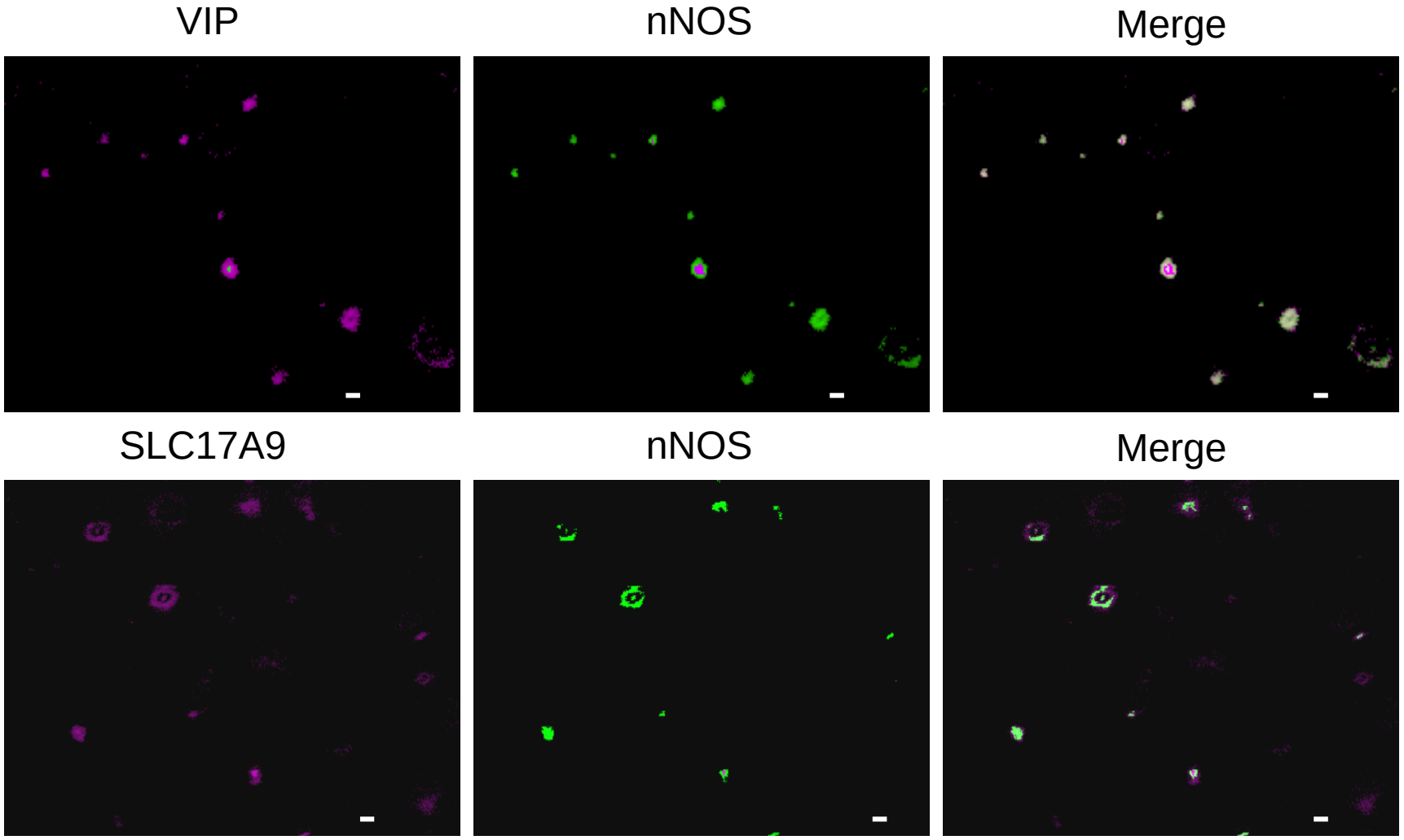


Pseudocolored DIC image of gut varicosities

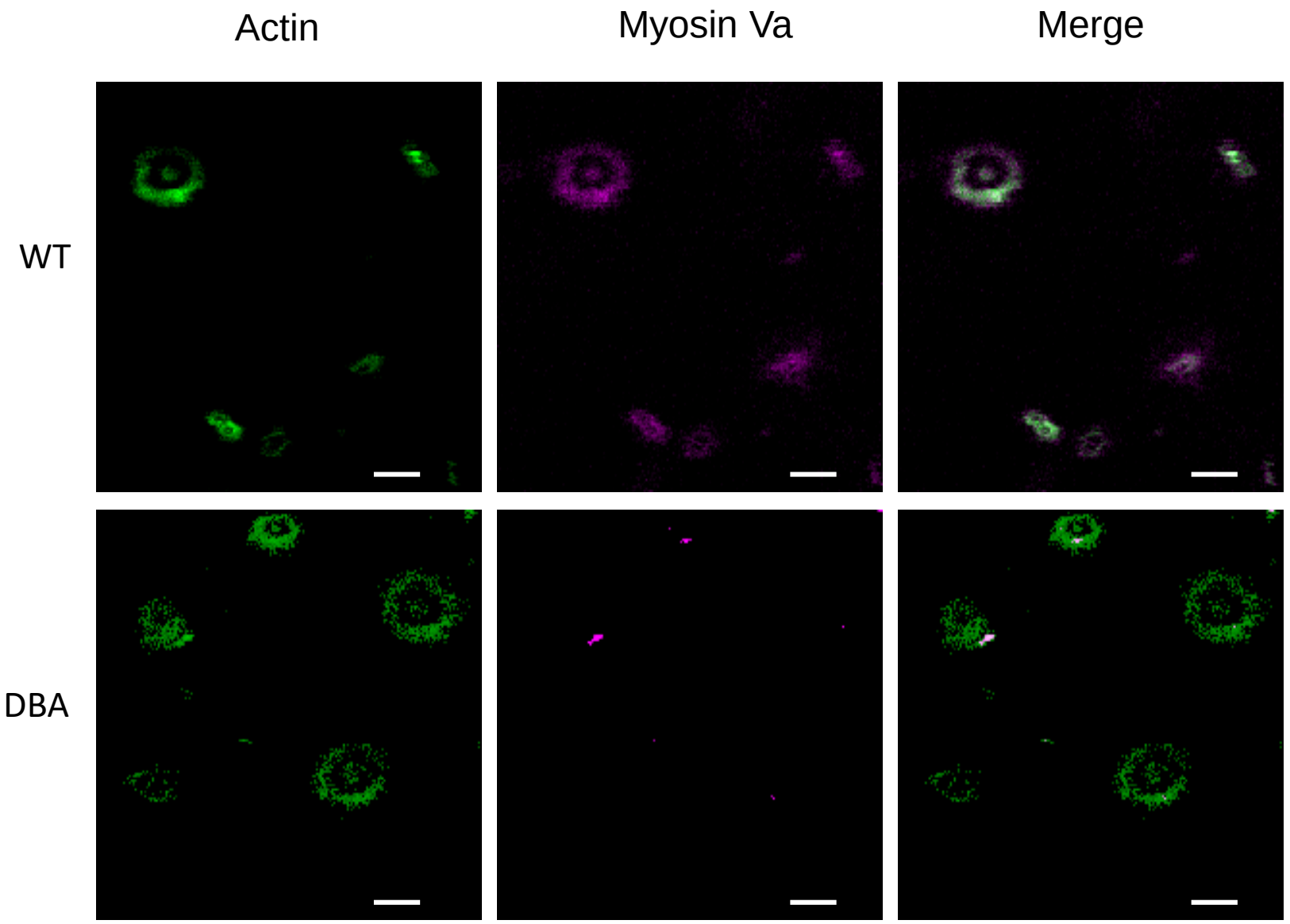
c.



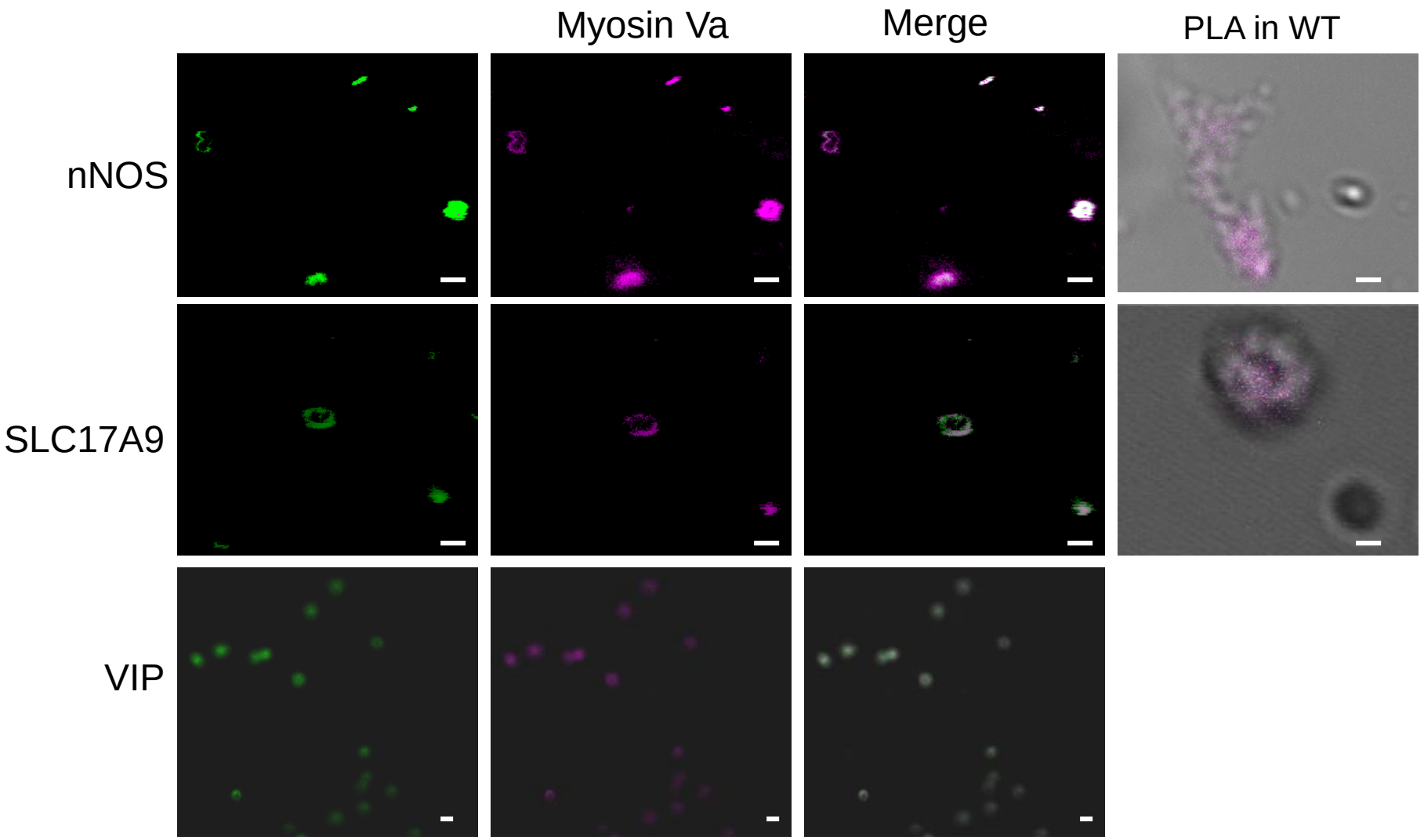
Inhibitory neurotransmitter systems present in enteric varicosities



Myosin Va reduced in DBA/2J varicosities



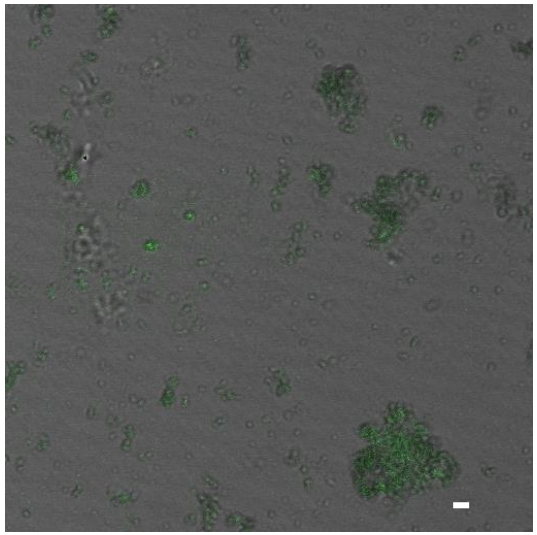
Myosin Va present in inhibitory varicosities



FM1-43 loading reduced in DBA/2J varicosities

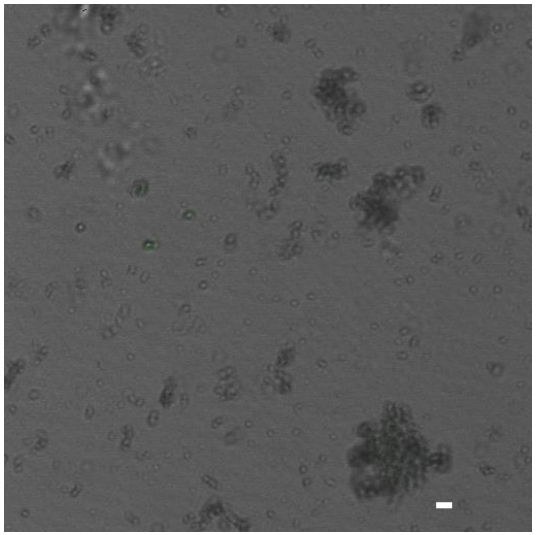
FM1-43 WT

0 min



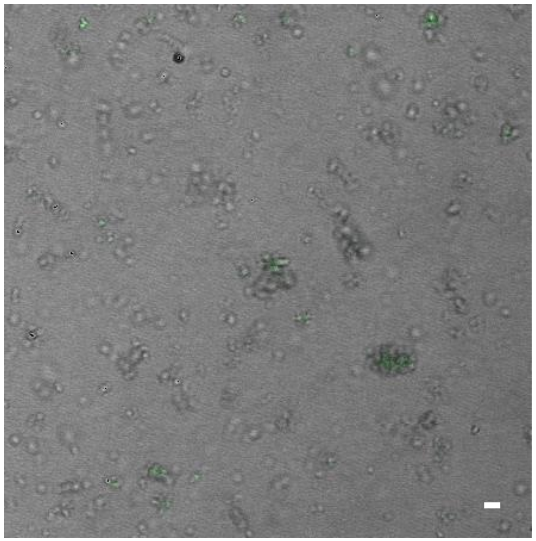
FM1-43 WT

10 min



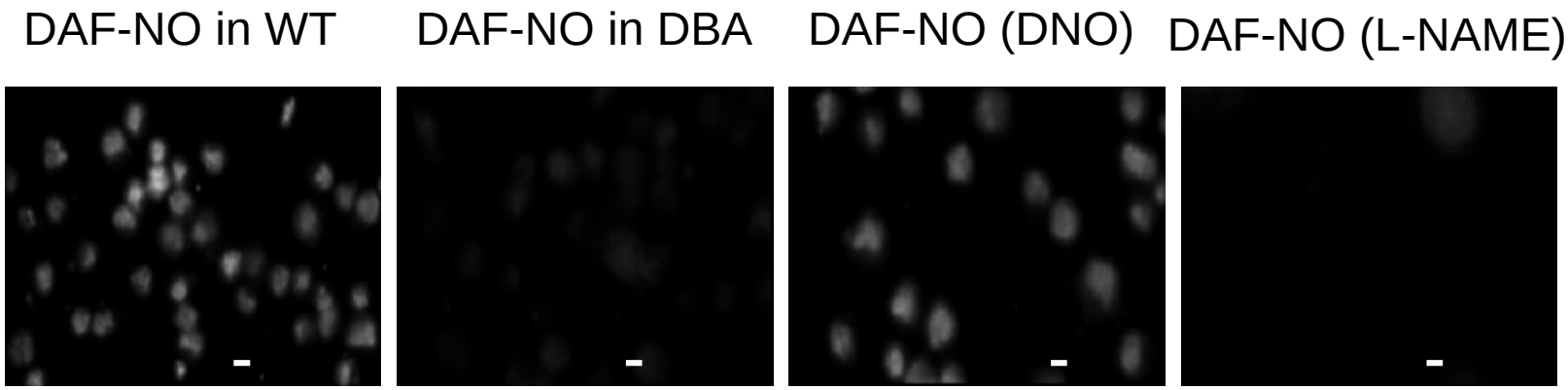
FM1-43 DBA

10 min



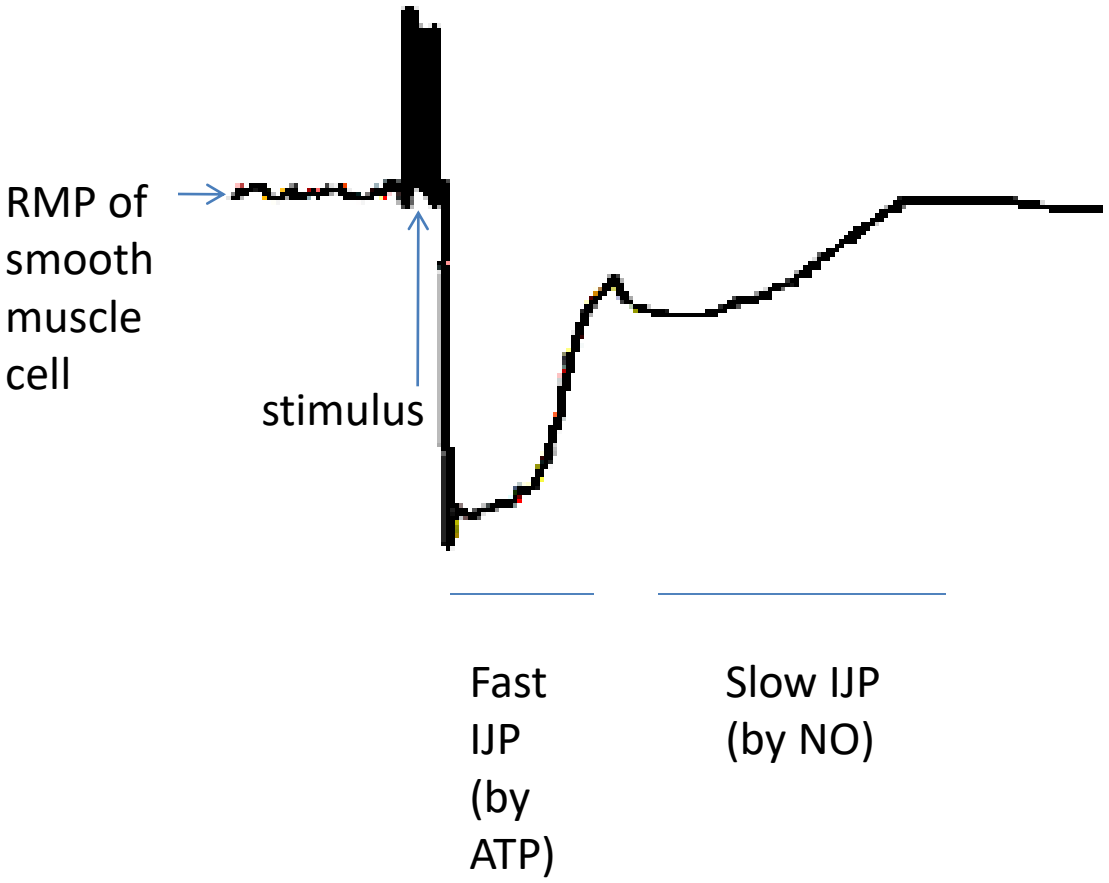
Chaudhury, He, Goyal, 2011, myosin Va and purinergic neurotransmission, Gastroenterology Manuscript, Peer review

in vitro NO production reduced in DBA varicosities



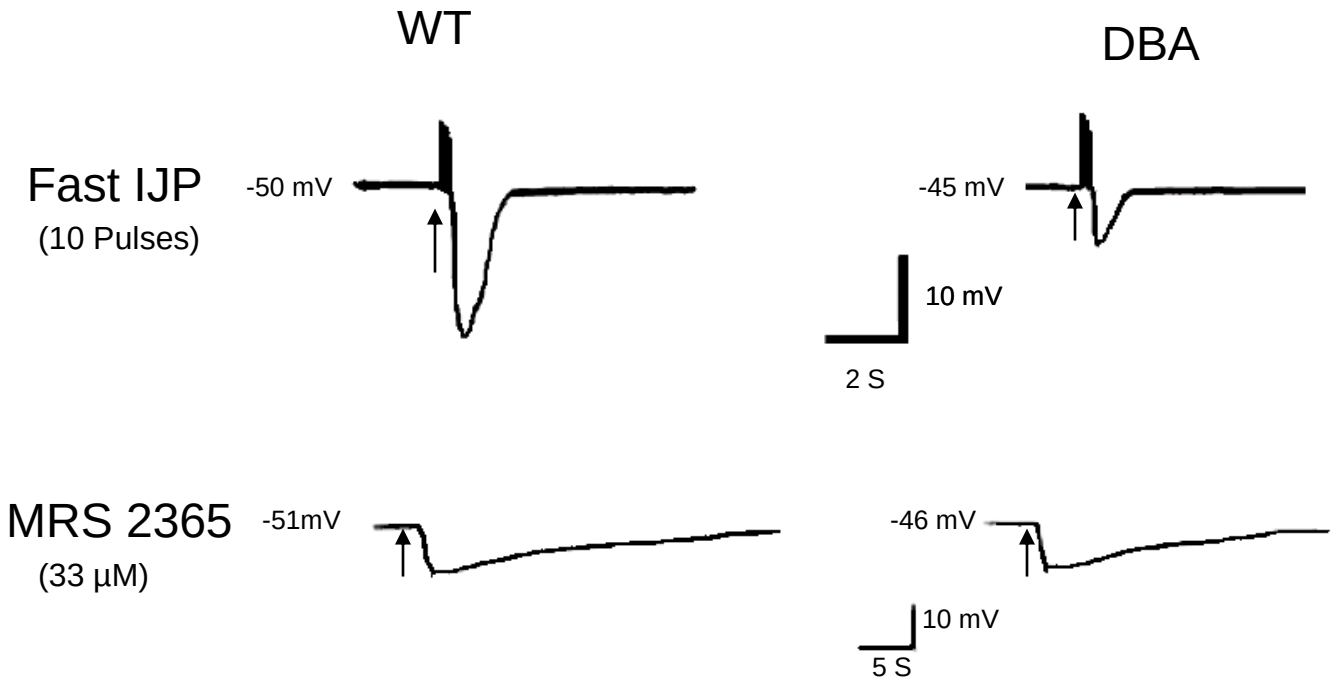
Chaudhury, He, Goyal, 2011, myosin Va and nitrergic neurotransmission, Gastroenterology Manuscript, Peer review

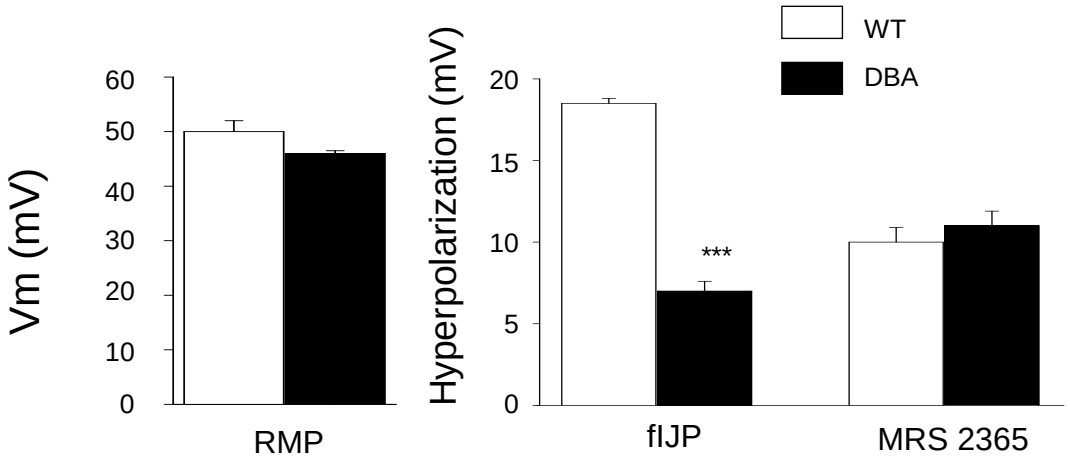
Inhibitory Junction Potential (IJP)



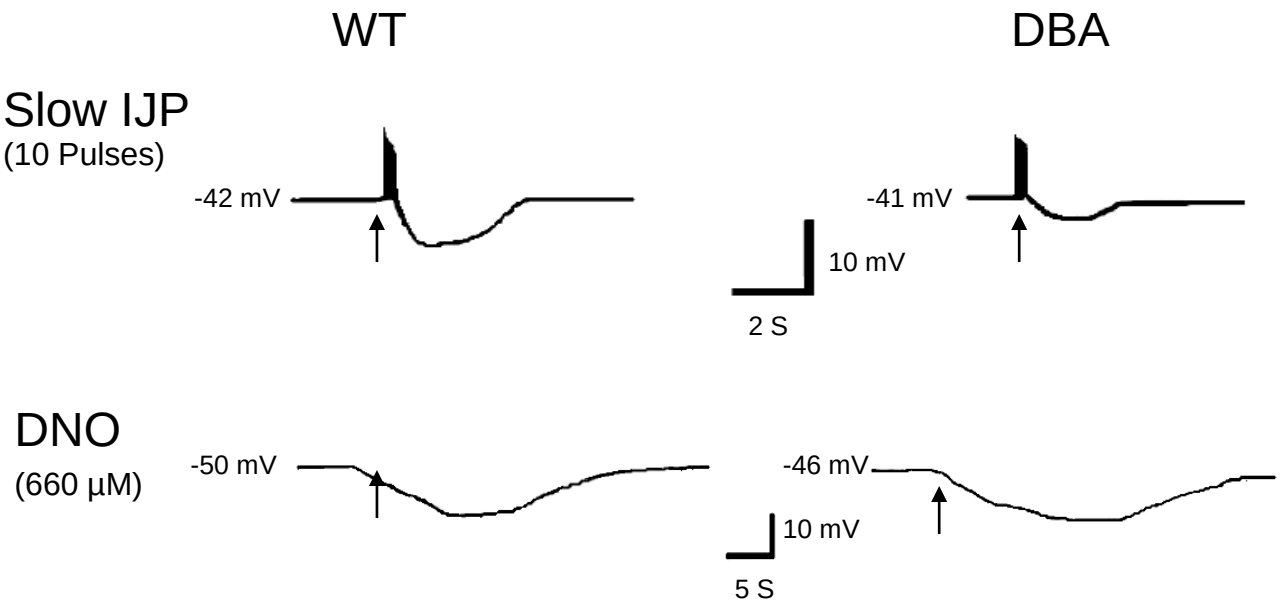
Responses can be pharmacologically separated by ATP blocker apamin or NO synthesis inhibitor L-NAME.

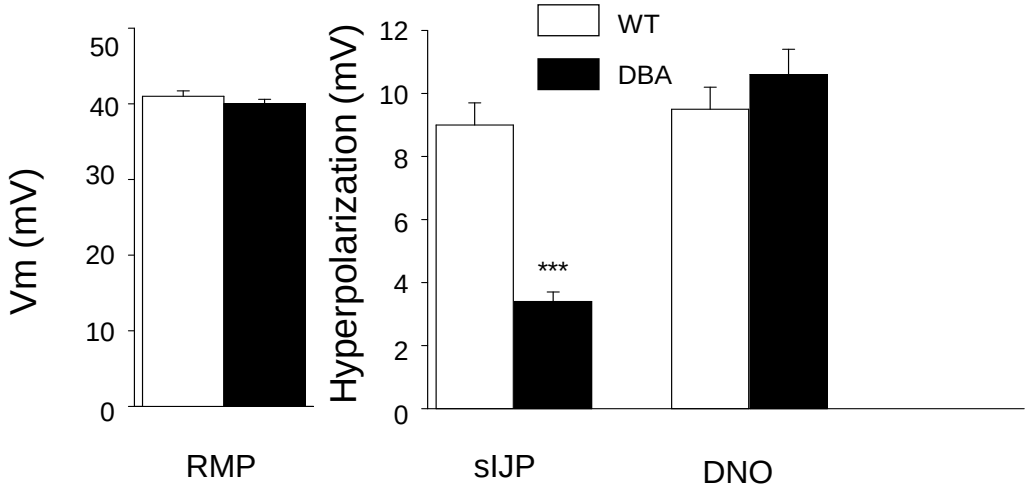
Fast IJP reduced in DBA



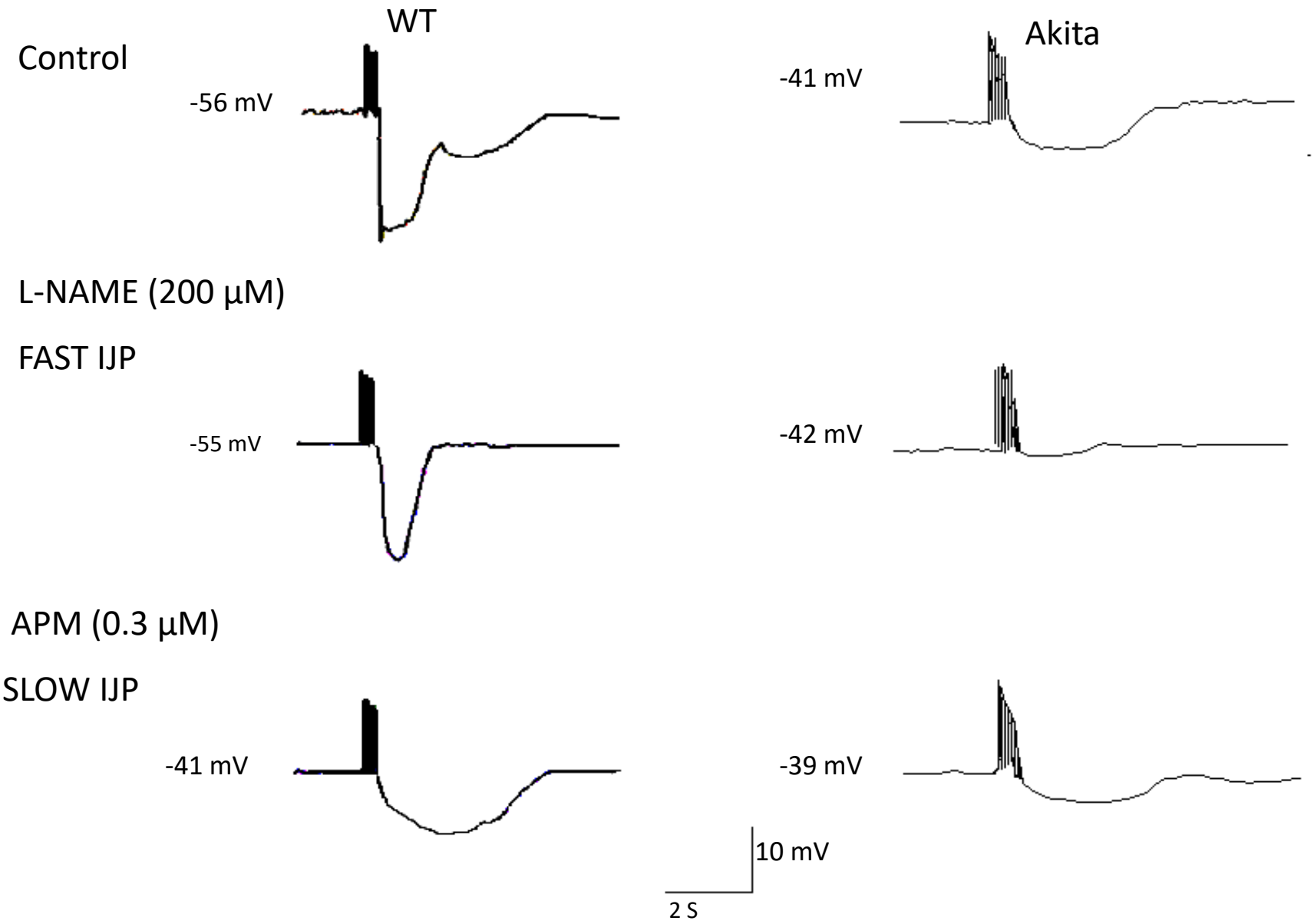


Slow IJP reduced in DBA





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



Translational directions: Pathophysiology of functional bowel diseases without apparent neuropathy

Insulin dependent regulation of myosin Va in enteric terminals

Acknowledgements

- Raj K Goyal
- Xue-Dao He
- Mary Beth Shertick
- Frances Achee
- NIDDK & NCI

No conflicts

Mini Mintzmeat: The ‘Dilute cat’