Esophagogastrointestinal Motility Disorders

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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
Nitric oxide (NO)
Acetylcholine (ACh)

Principal Neurotransmitters

neurons

glia
Sandwiched!

Myenteric Ganglia
(Auerbach’s Plexi)
Dogiel neurons: IPANs (intrinsic primary afferent neurons) & interneurons

Chaudhury et al, 2014, *Frontiers in Medicine (Gastroenterology)*
Can one drink during *sirshasan*?
Simultaneous Fluoroscopy & Esophageal Manometry

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

Figure 5. Relative potencies of purine compounds in causing relaxation of the isolated guinea-pig tenia coli. Ordinate: amplitude of relaxation as a percentage of the response to ATP \((10^{-4})\). 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.

Superfusion assay, Sir John Vane

Burnstock et al Br J Pharmacol 1970
[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.

PMID: 14293445
[Indexed for MEDLINE]
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
One neurone, one neurotransmitter
Multiplicity of neurotransmitters during enteric neuro-smooth muscle neurotransmission
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

Achalasia

Diffuse Esophageal Spasm

NCCP, Non-cardiac chest pain
Proventricular dilation disease

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

Last et al 2012, JSAVA
Bioelectronics of Nitric Oxide (NO) synthesis

Synthesis of NO

Catalytic synthesis of NO

Facilitation of electron transfer

Inhibition of electron transfer

Active nNOS

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

Chaudhury 2014

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

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

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

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

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

Diabetes

Image J, NIH

Chaudhury et al 2014
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

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Chaudhury et al 2017

Enhanced methylation
Tetrahydrobiopterin metabolism in mental disorders


Abstract
Changes in DHPR activity in those aged 12 and under with a variety of mental disorders were investigated using dried blood spots on Guthrie cards. DHPR activity was found to be lowered in autism and Rett's syndrome. DHPR activity was unaffected in non specific mental retardation suggesting that the deficit seen in autism and Rett's syndrome does not arise secondary to the mental dysfunction. In Down's syndrome blood biopterin levels correlated with blood spot DHPR activity. Human brain BH4 synthetic activity was investigated in aging and senile dementia of the Alzheimer type (SDAT). BH4 synthetic activity and DHPR activity decline with age in non demented controls. In SDAT, decreases in BH4 synthetic activity were seen in temporal and visual cortices and locus coeruleus. The site of the defect is probably at 6-pyruvoyl-tetrahydropterin synthase. Aluminium inhibits human brain BH4 synthesis in vitro and produces an 'Alzheimeresque' pattern
Ogilvie’s syndrome

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

INTACT fIJP + sIJP

Intact IJP in ICC genomic knockout mice

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

**Bristol Stool Chart**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>Type 2</td>
<td>Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
<td>Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>Type 4</td>
<td>Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
<td>Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>Type 6</td>
<td>Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
<td>Watery, no solid pieces. Entirely Liquid</td>
</tr>
</tbody>
</table>

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
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
Insights from Mother Nature

Alapaca

Do humming birds develop gastroparesis?

Gastric emptying mechanisms of sloth

Low amplitude IJP in stomach, Szurszewski, abstract

Chaudhury, 2017

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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Mutter Museum, Philadelphia
Importance in Medicine & Medical Research

Independent validation
Changes in nitrergic innervation of defunctionalized rat colon after diversion colostomy

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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).
Changes in cholinergic and nitric systems of defunctionalized colons after colostomy in rabbits

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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; relaxation responses were detected using propranolol, sodium nitroprusside, sodium nitrite, and

![Graph](image)

**Fig. 3** -- Effects of colostomy on the increasing effect of L-NAME (3 x 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