The Brain-Gut Axis: Implications in Developmental Neurogastroenterology and the Critical Roles of Serotonin

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Introduction

• Similarities between the enteric nervous system and central nervous system
  – Link between brain and gut in brain-gut axis disorders

• Disorders of the brain-gut axis
  – Stress during development
  – Serotonin signaling abnormalities during development
    • Irritable bowel syndrome (IBS)
    • Autism

ENS: “The Brain in the Gut”

• Similar to CNS:
  – complex integrated circuits
    – Several hundred million neurons
    – Reflexes
    – Same neurotransmitters

• Factors that affect CNS affect ENS
  – Genetics
  – Environment
  – Interact
Brain-Gut Axis and Defecation Disorders


Brain-Gut Axis, Functional Disorders and IBS


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Effect of Antidepressants and Psychological Therapies, Including Hypnotherapy, in Irritable Bowel Syndrome: Systematic Review and Meta-Analysis

Alexander C Ford, Eamonn M M Quigley, Brian S Lacy, Anthony J Lembo, Yuri A Salto, Lawrence R Schiller, Eddy E Soffer, Brennan M & Speigel and Paul Moayyedi


Hypnosis and Guided Imagery Treatment for Gastrointestinal Disorders: Experience With Scripted Protocols Developed at the University of North Carolina. Tolson L. Am J Gastroenterol. 2014 Jul;109(7):1048-52. [Author Information]
A scientific consensus is emerging that the origins of adult disease are often traceable to developmental and biological disruptions occurring in the early years of life.

Stress alters the brain-gut axis

Altered neural circuitry in the gut-brain axis in IBS

- Neuroimaging studies identify key areas in CNS in IBS
- Salience network
  - Intrinsic brain network
  - Gut: chronic abdominal pain, visceral hypersensitivity, altered bowel habits
  - Extensive connections to hypothalamus (amongst others)
fMRI & the Salience Network in Children

Excessive coupling of the salience network with intrinsic neurocognitive brain networks during rectal distension in adolescents with Irritable bowel syndrome: a preliminary report

Xinna Lin1, Alan Silverman1, Mark Kem1, B. Douglas Ward1, Shi-Jiang Li1, Reza Shaker2

• Brain responses to rectal distension similar between adolescents and adults with IBS
• Excessive coupling of the salience network with the major networks
  – emotion and pain perception

Reduced Functional Connectivity Between the Hypothalamus and Cortex in Pediatric Patients with Irritable Bowel Syndrome

Manu R. Sood, Xiaolin Liu1, Gisela Chelimsky, Douglas Ward1, Shi-Jiang Li1, Reza Shaker2

• IBS patients demonstrate reduced hypothalamus connectivity
• Disrupted hypothalamus functioning may contribute to IBS

Stress Impacts Brain Development Similarly in Mice and Humans

• Altered brain signaling
  – Enhanced stress response
• Altered gut function
  – Colonic transit
  – Intestinal permeability
  – Visceral hypersensitivity

Maternal Separation Impacts IBS

• Altered brain signaling
  – Enhanced stress response
• Altered gut function
  – Colonic transit
  – Intestinal permeability
  – Visceral hypersensitivity
Maternal Separation Results in Visceral Hypersensitivity

Environmental Stress and Development

Autism Spectrum Disorder (ASD)

• Autism Spectrum Disorder (ASD)
  - Symptoms:
    - Abnormal social interactions
    - Impaired communication
    - Repetitive behaviors
  - 1/68 nationally
  - Huge number of GI disorders!
  - A brain-gut axis disorder???
Brain-Gut Links in ASD

- Genetic
  - c-Met
  - CHD8

- Serotonin
  - Genetic
    - SERT G56A (genetic defect in serotonin reuptake)
  - Environmental
    - Selective Serotonin Reuptake Inhibitors (SSRIs)


- c-MET as a Brain-Gut Connection in Autism

  - Expression altered in the brains of
  - c-MET promoter variant rs18588301, a single nucleotide polymorphism that increases the risk for ASD
  - Distinctively associated with individuals with ASD & GI dysfunction


- CHD8 Mutations Define a Subtype of Autism in Early Development

  - Chromodomain Helicase DNA Binding Protein 8
    - Vertebrate early development
  - First mutation to demonstrate direct link with autism subtype
  - 6,176 children with ASD
  - 15 had a CHD8 mutation
    - All had similar characteristics in appearance
      - Large heads and wide set eyes
  - Interviewed families
    - Gastrointestinal problems
  - Disrupted CHD8 gene in zebrafish
    - Developed large heads & wide set eyes
    - Fewer enteric neurons
    - Constipated

Serotonin Connects the Brain and Gut in Autism

- 3% Sleep, mood, appetite
- 95%

Serotonin is Critical for Brain Development

- One of the most widely distributed & earliest systems to develop
  - Innervates almost all areas of the brain
  - Serotonergic neurons in human brain from fifth gestational week

Serotonin Signaling is Abnormal in the CNS in Autism

- Important for pre- and postnatal human brain development
  - Changes in serotonergic signaling associated with ASD
    - Increased # serotonin axon branching in temporal cortex
  - PET scans show diminished serotonin synthesis
Serotonin is Critical for Gut Function!

- Serotonin inactivation is SERT-dependent.
- Increases in SERT activity decrease the effects of serotonin.
- Decreases in SERT activity increase the effects of serotonin.

SERT Variants are Overexpressed in ASD

- Serotonin plays critical roles in brain & gut development and function.
- GI problems 4-fold more common in children with ASD.
- Does abnormal serotonin homeostasis cause brain-gut dysfunction in ASD?
  - GWAS: SERT variants overexpressed in ASD.
  - All result in overactive serotonin transporter activity.

Hypothesis

Genetic abnormalities in the serotonin transporter (SERT), of the kind found in autism, also cause abnormalities in gut development & function.

Could the G56A mutation be a brain-gut link in ASD?
Total and late-born enteric neurons are deficient in G56A (SuperSERT) mice

- **Total neurons** — HuC/D
- **Late born neurons** — CGRP and TH

Motility is Diminished in G56A Mice

Gut Dysfunction is Preventable in the G56A Mice

- G56A mouse model represents a brain-gut link in autism:
  - ASD-associated features
  - Defects in ENS development
  - Abnormal gut movement
- Is there a way to prevent the ENS & motility defects?
  - 5-HT4 is a major receptor for intestinal serotonin
    - 5-HT4 stimulation increases the number of neurons in cell culture
    - G56A mice have less neurons
  - Increases gastrointestinal movement
  - G56A mice have slower GI transit

5-HT4 levels lower in children with ASD & GI dysfunctions

- Prucalopride: selective, high affinity 5-HT4 receptor agonist
- Approved in Europe and Canada
- Treatment for chronic constipation

Prucalopride rescues G56A mice

**Antenatal SSRI Exposure**

- Selective serotonin reuptake inhibitors (SSRIs):
  - SSRIs inhibit SERT
  - Increase serotonergic neurotransmission
  - Used to treat depression during pregnancy
    - 6%
  - 2-fold risk of congenital malformations
    - After CNS development
    - Increased risk of autism in males exposed
  - Effects of antenatal SSRI exposure on GI unknown
    - Children exposed in utero to SSRIs require laxatives 10-fold more than non-exposed
    - Exposure may lead to abnormal ENS development and GI motility

Will Fluoxetine alter ENS development and GI function?

- Hyperplasia of the ENS
- Slower *in vivo* motility
- Faster *in vitro* motility
  - Excess sympathetic activation from the brain
Conclusions

• Bidirectional communication between the brain & the gut
  – Starts in utero
• Developmental insults lead to brain-gut disorders
  – Present at all stages of life
    • Autism, constipation, IBS
    • Parkinson’s, Alzheimer’s
• Serotonin plays critical roles in brain and gut development
  – Genetics, environmental
    – Critical to disorders of the brain-gut axis
• Can the brain be fixed via the gut?
  – Gut-focused target therapies

Future Opportunities

Microbiota-Gut-Brain Axis
Spinal Neurons Play a Role in Brain-Gut Communication

NMDA receptor mediates chronic visceral pain induced by neonatal nociceptive somatic stimulation
Adrian Miranda, K., Aarne Miskie, J. Mitchell Brussert, T. Pradeep Kannappuli, M., Nazanin Isaez, J., Jyoti M. Sengupta, M. B.

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