INE INSTITUTE OF NUTRITIONAL ENDOCRINOLOGY

Digestion: The Gut-Brain Connection in Clinical Practice

Excerpt from SHINE 2015, Day 1

The Microbiome and The Vagus Nerve: The Impact of Food and Mood

Dr. Ritamarie Loscalzo

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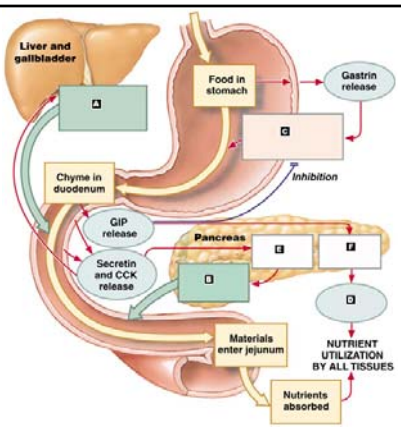
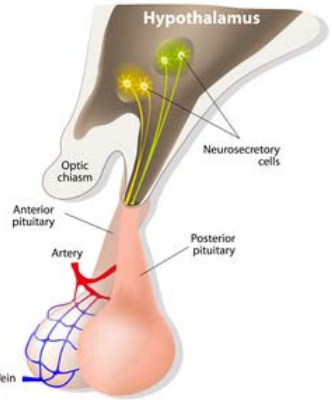


Gut Hormones

Hormone	Produced by	Action
Leptin	Fat cells	Signals satiety
Ghrelin	Stomach lining	Signals hunger
Gastrin	Stomach	Production of stomach acid
Cholecystokinin (CCK)	Small intestine	Production of pancreatic juices and emptying of gall bladder
Secretin	Duodenum	Stimulates bicarbonate production by pancreas, bile production by liver, and pepsin by stomach
Peptide YY	Mainly ileum and colon, but a little in other parts of GI tract	Inhibits gastric motility, increases water and electrolyte absorption in colon, may suppress pancreatic secretion, increases efficiency of digestion
Incretins: GIP: Gastric Inhibitory Peptide and GLP: Glucagon-Like Peptide	Small intestine	Increases insulin, inhibits glucagon release, slows rate of absorption of nutrients by reducing gastric emptying
Somatostatin	Stomach, intestine, pancreas	Inhibits gastrin, CCK, secretin, GIP and also growth hormone, TSH, glucagon and insulin
Dopamine	Brain and GI mucosa	Reduces motility and protects mucosa
Serotonin	Brain and GI mucosa	Inhibits gastric acid and stimulates mucus



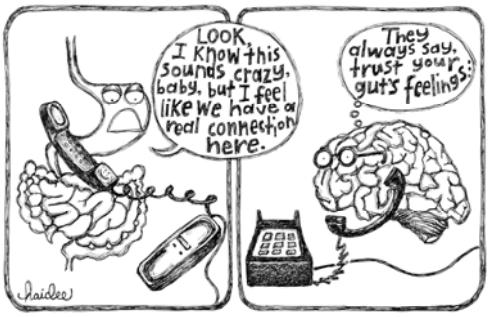
Brain Hormones - Hypothalamus

Hormone	Produced by	Actions
Thyrotropin-releasing hormone (TRH)	Parvocellular neurosecretory cells of the paraventricular nucleus	Stimulate thyroid-stimulating hormone (TSH) release from anterior pituitary (primarily).
Prolactin-releasing hormone (PRH)	Parvocellular neurosecretory cells of the paraventricular nucleus	Stimulate prolactin release from anterior pituitary.
Corticotropin-releasing hormone (CRH)	Parvocellular neurosecretory cells of the paraventricular nucleus	Stimulate adrenocorticotropic hormone (ACTH) release from anterior pituitary.
Dopamine aka Prolactin-inhibiting hormone (DA or PIH)	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary.
Growth hormone-releasing hormone (GHRH)	Neuroendocrine neurons of the arcuate nucleus	Stimulate growth hormone (GH) release from anterior pituitary.
Gonadotropin-releasing hormone (GnRH)	Neuroendocrine cells of the preoptic area	• Stimulate follicle-stimulating hormone (FSH) release from anterior pituitary. • Stimulate luteinizing hormone (LH) release from anterior pituitary.
Somatostatin, aka growth hormone-inhibiting hormone (GHiH)	Neuroendocrine cells of the periventricular nucleus	• Inhibit growth hormone (GH) release from anterior pituitary. • Inhibit (moderately) thyroid-stimulating hormone (TSH) release from anterior pituitary.

Brain Hormones - Pituitary

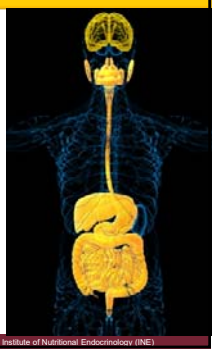
Hormone	Produced by	Actions
Thyroid Stimulating Hormone (TSH)	Anterior lobe of Pituitary	Stimulates thyroid gland to produce T4.
Adrenocorticotropic Hormone (ACTH)	Anterior lobe of Pituitary	Stimulates adrenal glands to respond in times of stress.
Follicle-Stimulating Hormone (FSH)	Anterior lobe of Pituitary	In women, stimulates the growth of ovarian follicles before the release of the egg at ovulation. It also increases estrogen production. In men, acts on the Sertoli cells of the testes to stimulate sperm production.
Luteinizing Hormone (LH)	Anterior lobe of Pituitary	In men, stimulates Leydig cells in the testes to produce testosterone. In women, stimulates ovarian follicles to produce estrogen, and causes the follicle to rupture and release a mature egg.
Prolactin (PRL)	Anterior lobe of Pituitary	Promotes lactation in response to the suckling of young after birth. (It's inhibited by dopamine)
Growth Hormone (GH)	Anterior lobe of Pituitary	Promotes growth in children and helps to maintain normal body structure and metabolism by promoting the deposition of protein and burning of fat.
Alpha Melanocyte-Stimulating Hormone (α-MSH)	Anterior lobe of Pituitary	Bind to melanocytes to stimulate the production of melanin, a skin pigment.
Anti-diuretic Hormone aka Vasopressin (ADH)	Hypothalamus, stored and secreted by Posterior lobe of Pituitary	Regulates the body's retention of water by acting to increase water reabsorption in the kidney's collecting ducts.
Oxytocin (OT)	Hypothalamus, stored and secreted by Posterior lobe of Pituitary	Stimulates contraction of the uterus during childbirth and promotes the movement of milk into the breast. In men, stimulates sperm movement and production of testosterone by the testes.

The Gut-Brain Axis



Connections Between the Gut and Brain

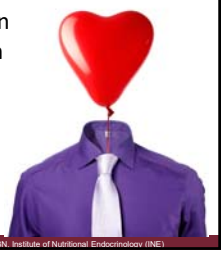
- ✓ Vagus nerve
- ✓ Neurotransmitters: *dopamine, serotonin, GABA*
- ✓ Leaky gut
- ✓ Microbiome: *Lactobacillus helveticus, Bifidobacterium longum*
- ✓ Allergens
- ✓ Inflammation
- ✓ Mood, memory, and focus



The Psychology of Digestion

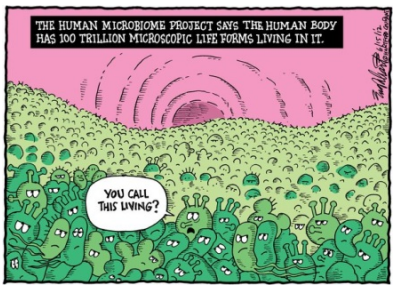
Digestion Begins in your HEAD and HEART
-- Not Your Gut!!!

- Impact of thoughts
- Fight/flight effects on digestion
- Relaxation effects on digestion
- Role of breathing on digestion
- Pre-meal ritual



The Human Body Is Mostly Non-Human

- ✓ 50 trillion human cells
- ✓ 500 trillion non-human cells
- ✓ 10% human, and 90% bacterial



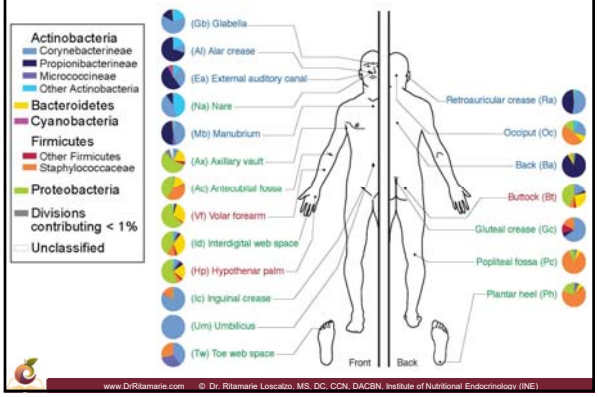
The Microbiome

- Microbial cells found to exceed human cells by a factor of ten-to-one.
- Total number of genes associated with the microbiome could exceed the total number of human genes by a factor of 100-to-one.
- Microbes contribute more genes responsible for human survival than humans' own genes.

Gut Microbiome

Genomes of the Gut Microbes

Microbiome Body Wide Distribution



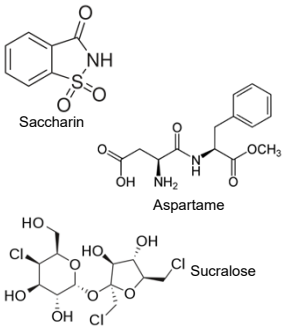
Microbes in the Gut

- ✓ Types: **beneficial, opportunistic, pathogenic**
- ✓ **Protection from foreign microbes by:**
  - ✓ Acidic stomach pH
  - ✓ Saliva and bile
  - ✓ Immune system
- ✓ **Functions:**
  - ✓ Digestion
  - ✓ Synthesis of B vitamins and vitamin K
  - ✓ Making neurotransmitters
  - ✓ Metabolism of bile acids, sterols, and xenobiotics
  - ✓ Fermentation of undigested carbohydrates to short-chain fatty acids
    - ✓ Butyrates: colon epithelium
    - ✓ Propionates: liver
    - ✓ Acetates: muscle tissue

Gut Microbiome Variability

Firmicutes vs Bacteriodetes

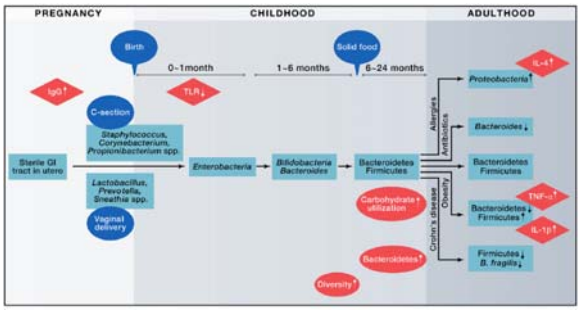
Non-Caloric Sweeteners and Gut Microbes



Credit: Weizmann Institute of Science

Nature **514**, 181–186 (09 October 2014)

Gut Microbiome Timeline



Goals:

- ✓ Develop a reference set of microbial genome sequences
- ✓ Preliminary characterization of the human microbiome
- ✓ Explore the relationship between and changes in the human microbiome
- ✓ To develop new technologies and tools for computational analysis
- ✓ To establish a resource repository
- ✓ To study the ethical, legal, and social implications of human microbiome research

HUMAN MICROBIOME PROJECT

Methods and Findings

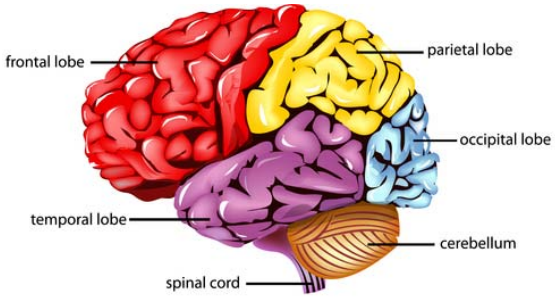
HUMAN MICROBIOME PROJECT

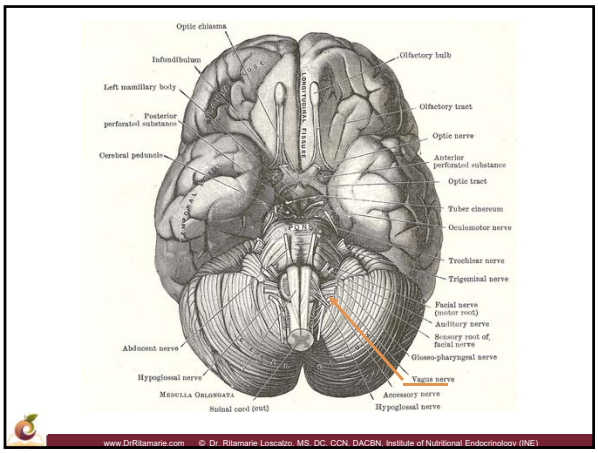
- ✓ 242 healthy U.S. volunteers
- ✓ More than 5,000 samples collected from body sites such as mouth, nose, skin, lower intestine, and vagina
- ✓ Microbial genome data extracted by identifying the bacterial specific ribosomal RNA, 16S rRNA
- ✓ More than 10,000 microbial species found
- ✓ Bacterial components of the microbiome were found to change over time, affected by disease and medication
- ✓ Eventually it returns to equilibrium

The Second Brain

Enteric Nervous System (ENS)

- Embedded in the wall of the gut
- 500 million neurons
- Responsible for cravings under stress
- Important in physical and mental well-being
- Can work both independently of and in conjunction with the brain
- Helps sense environmental threats and then influences response




Optic chiasma
Infundibulum
Left mamillary body
Posterior perforated substance
Cerebral peduncle
Olfactory bulb
Olfactory tract
Optic nerve
Anterior perforated substance
Optic tract
Tuber cinereum
Oculomotor nerve
Trochlear nerve
Trigeminal nerve
Facial nerve (motor root)
Auditory nerve
Sensory root of facial nerve
Glosso-pharyngeal nerve
Vagus nerve
Accessory nerve
Hypoglossal nerve
Abducent nerve
Hypoglossal nerve
Medulla Oblongata
Spinal cord (cut)
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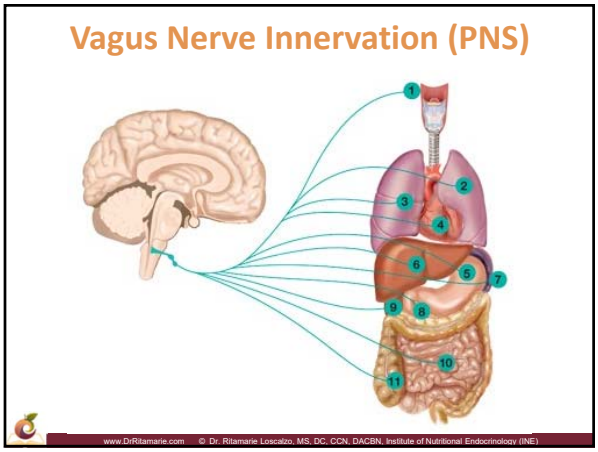
Vagus Nerve Innervation (PNS)
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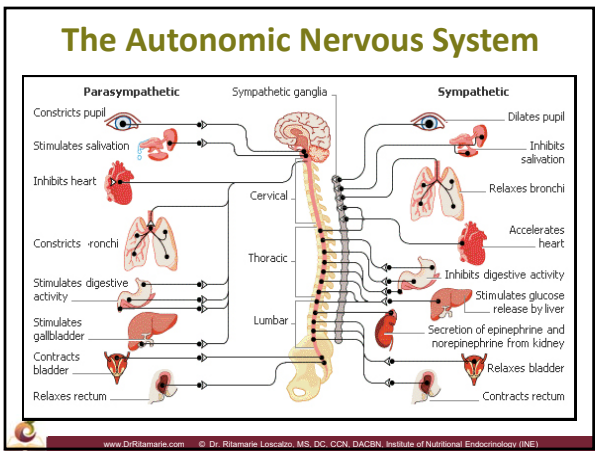
The Autonomic Nervous System
Parasympathetic
Sympathetic ganglia
Sympathetic
Constricts pupil
Stimulates salivation
Inhibits heart
Constricts bronchi
Stimulates digestive activity
Stimulates gallbladder
Contracts bladder
Relaxes rectum
Cervical
Thoracic
Lumbar
Dilates pupil
Inhibits salivation
Relaxes bronchi
Accelerates heart
Inhibits digestive activity
Stimulates glucose release by liver
Secretion of epinephrine and norepinephrine from kidney
Relaxes bladder
Contracts rectum
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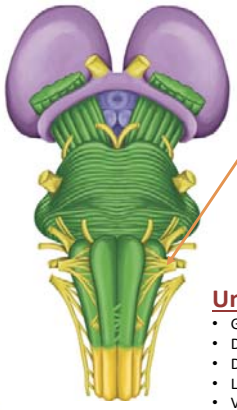


The Vagus Nerve

Main Functions

- Heart rate
- Breathing – acetylcholine, blocked by mercury
- Digestion

Overactivity

- Drop in blood pressure and heart rate
- Vasovagal syncope

Underactivity

- Gastroparesis
- Difficulty swallowing
- Decreased enzyme production
- Loss of gag reflex
- Voice changes

Manifestations of Underactive Vagus Nerve

Symptoms

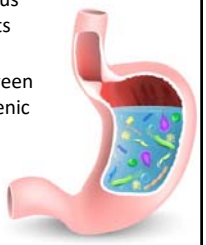
- ✓ SIBO
- ✓ Constipation
- ✓ Gall bladder contraction problems
- ✓ Loss of ability to make digestive enzymes and HCl
- ✓ Chronic intestinal permeability
- ✓ Depression

Causes

- ✓ Hiatal hernia
- ✓ Poor posture
- ✓ Muscular imbalances
- ✓ Alcohol
- ✓ Spicy foods
- ✓ Stress
- ✓ Fatigue
- ✓ Anxiety

The Vagus Nerve and Gut Microbiome

- ❑ Gut microorganism can activate the vagus nerve ➔ critical role in mediating effects on the brain and behavior
- ❑ The vagus appears to differentiate between non-pathogenic and potentially pathogenic bacteria
- ❑ Immunomodulatory role regulating mood: Signals from the gut can instigate anti-inflammatory mediators including acetylcholine



Adv Exp Med Biol. 2014;817:115-33. doi: 10.1007/978-1-4939-0897-4_5. ***Vagal pathways for microbiome-brain-gut axis communication.*** Forsythe P[1], Bienenstock J, Kunze WA.

Neurology of Gastrointestinal Activity

Frontal Cortex
Excites vagal nerve to activate gut motility and enzyme secretion

Insular Cortex
Somatic map of viscera – lets brain know where gut is

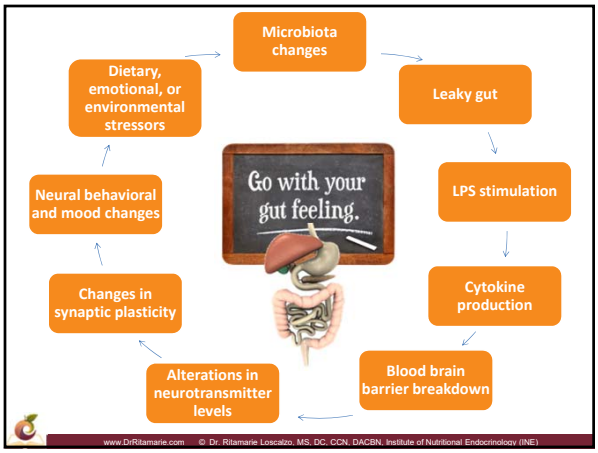
Vagus
- Activates intestinal motor cells for gut motility
- Modulates blood flow to gut
- Activates release of digestive enzymes

Enteric Nervous System (ENS)
- Generates intestinal motility
- Generates enzyme release
- Provides sensory input to vagus

The Enteric Nervous System (ENS)

- **First discussed** by American physician Byron Robinson in 1907 in *The Abdominal and Pelvic Brain*, and named by British physiologist Johannis Langley
- Gut contains 100 million neurons - more than the spinal cord
- **Neurochemicals in gut:** serotonin, dopamine, glutamate, norephinephrine, nitric oxide, neuropeptides, enkephalins benzodiazepines
- **90% of signals along the vagus nerve come from the ENS**
- Pathogens crossing the gut lining stimulate immune cells in the gut wall to secrete histamine and other inflammatory chemicals which triggers diarrhea or alerts the brain in the head via the vagus nerve, which may trigger vomiting
- **Bacterial lipopolysaccharides,** aka postbiotics, can lead to depression, irritability, anger, and violence
- Nerve signals from the gut to the brain via the vagus nerve affect mood
- Research in the *British Journal of Psychiatry* in 2006: **Stimulation of the vagus nerve found to be effective for chronic, non-responsive depression**

http://www.drritamarie.com/go/GutInstincts2ndBrain
American Journal of Physiology - Gastrointestinal and Liver Physiology, vol 283, p G1217.



Brain Imbalance → Vagus Nerve Suppression

- ✓ Impaired gut motility → yeast overgrowth, constipation, and liver stress
- ✓ Decreased ileocecal valve tone → SIBO, transit time disruption
- ✓ Decreased gallbladder contraction → _____
- ✓ Decreased HCl → _____
- ✓ Decreased digestive enzyme secretion → _____
- ✓ Decreased bile → _____
- ✓ Reduced blood flow to intestines → leaky gut

Gut Impact on Brain

Gut Imbalances	Brain Symptoms
✓ Flora disruption	✓ Depression, anxiety
✓ Lipopolysaccarides	✓ Changes in appetite
✓ Cytokines	✓ Damage to receptors
✓ Imbalanced gut peptides	✓ Blood brain barrier damage
	✓ Neurochemistry changes

Ghrelin and Mood

- ✓ Stress leads to increased Ghrelin
- ✓ Ghrelin stimulates dopamine
- ✓ Stimulates quest for fatty food
- ✓ Chronic stress or depression can lead to chronically elevated ghrelin and obesity

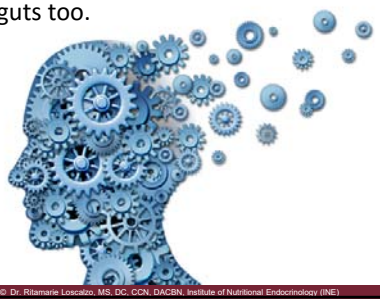
Journal of Clinical Investigation, vol 121, p 2684

Parkinson's and the Gut

- ✓Heiko Braak at the University of Frankfurt, Germany believes it begins in the gut
- ✓Constipation may be an early sign

Alzheimer's and the Gut

The characteristic plaques or tangles found in the brains of people with Alzheimer's are present in neurons in their guts too.



Vagus Nerve Activation

Activities

- ✓Gargling
- ✓Gag reflex
- ✓Singing loudly
- ✓Coffee enemas

Results

- ✓Increased motility
- ✓Increased contraction of sphincters
- ✓Increased release of digestive enzymes
- ✓Increased blood flow to intestines