GUT.BRAIN.AXIS

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- **The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions.**
- Recent advances in research have described the **importance of gut microbiota in influencing these interactions.**
- This interaction between microbiota and GBA appears to **be *bidirectional***, namely through signaling from **gut-microbiota to brain and from brain to gut-microbiota by means of *neural*, *endocrine*, *immune*, *and humoral links***.

Microbiota

- **A major advance in understanding the function of the intestinal microbiota** has been the development of **techniques that permit a detailed assessment of the composition of the flora** and its distribution throughout the alimentary tract.
- One of the methods to visualize single bacterial species within complex communities is called **ribosomal RNA fluorescence in situ hybridization (FISH).**

BACTERIA IN THE UPPER GASTROINTESTINAL TRACT

- **Mouth** — Microorganisms from the external world first contact the alimentary tract in the mouth. **Bacteria can be found in high concentrations on food remnants, the dental surface and within or attached to desquamated epithelial cells, and suspended in oral secretions.** There are also high concentrations of bacteria in saliva .
- Despite the high concentration of bacteria in the oral cavity, samples taken from the stratified epithelium of the mouth and saliva taken directly from the salivary duct are virtually sterile in healthy persons.
- This reflects defensive mechanisms working in concert to suppress bacterial adhesion and growth.

- **Stomach and duodenum** — Cultures of fluid from the stomach or duodenum of healthy volunteers contain **bacterial concentrations of 10^3 to 10^4/mL**, depending in part upon the composition of digested food.
- Fluorescence in situ hybridization (FISH) demonstrates that bacteria in the stomach and duodenum are **localized strictly within the intestinal lumen and separated from the mucosa by a mucus layer**.
- Their composition is variable, reflecting the heterogeneous composition of the ingested flora. In healthy individuals, the mucosa and the mucus layer of the stomach and duodenum are free of bacteria.
- In patients with *Helicobacter pylori* infection, the mucosal surface of the stomach is covered with a bacterial biofilm in which *H. pylori* is predominant.

Pancreatic tract

- **The microflora of the normal pancreatic duct has not been extensively studied**, since samples available from healthy individuals are not readily available.
- FISH analysis of pancreatic duct biopsies obtained during endoscopic retrograde cholangiopancreatography **from patients with benign or malignant obstruction of the pancreatic duct have demonstrated islands of bacterial adhesion in approximately 70 percent of the biopsies .**
- **The anatomically normal pancreatic duct epithelium is generally sterile.** Thus, bacterial islands appear to be located in regions of disturbed duct anatomy.
- Bacterial species in the pancreatic duct are diverse and highly variable among individuals.

Biliary tract

- **The situation is different in the presence of foreign bodies such as biliary stents. The colonization of the biliary stents by polymicrobial biofilm can be documented within a week after implantation** . Both aerobic and anaerobic bacteria, which are commonly found in the intestine, can be identified. The microbial colonization starts with the distal end of the biliary stent and advances proximally. **Bacteria are located mainly on the inner surface of plastic stents**. By contrast, the surface of biliary stents facing normal epithelium is not colonized, indicating that the healthy epithelial layer efficiently resists microbial colonization .
- The rapid development of biofilms at the inner surface of the biliary stents indicates that the ***biliary and pancreatic secretions alone are unable to prevent the development of bacterial biofilms on foreign bodies***. ***Interestingly, the bacterial biofilm disappears as soon as the stent is occluded by sludge***, **suggesting that organic substances in sludge help prevent bacterial growth.**

Small intestine

- **The epithelial surface of the small intestine in a healthy human is not colonized**. Occasional groups of bacteria can be found in low concentrations of 10^5 or less within the lumen. Bacteria do not form conglomerates and spatial structures and the luminal contents **are separated from the mucosa by a mucus layer.**
- **In humans, the adherence of segmented filamentous bacteria has not been observed either in health or disease.** Pathologic conditions with altered microbiota in the small intestine include acute and chronic infections, bacterial overgrowth, and inflammatory bowel disease.
- Common to all of these conditions are a disruption of the mucus barrier, loss of bacterial separation between mucosa and lumen, bacterial adherence, invasion, and translocation.

The role of microbiota in colonic function

- Bacteria in the human colon are mainly responsible for the reduction of the fecal mass. Which bacterial species are responsible for these processes are not well known.
- **However, a reasonable assumption is that the numerically predominant bacteria are indispensable for the biochemical processes that occur in the colon.**
- ***Eubacterium rectale* (*Roseburia* spp), *Faecalibacterium prausnitzii*, and *Bacteroides* groups comprise each 10 to 30 percent and cumulative 70 percent of the total microbiota in humans .**
- **Strict anaerobic species predominate**, although the diversity of bacteria is high and consists of approximately **3000 to 5000 species.**

The role of microbiota in colonic function

- In the colon, bacteria reach concentrations of **up to the 10^{11}/mL** and **compose up to 90 percent of the fecal mass.** Such high bacterial concentrations can be achieved only under active facilitation of bacterial growth.
- Bacterial growth is facilitated by **peristalsis** (which extensively mixes bacteria with fibers), and **maintenance of optimal viscosity and temperature.**
- However, the most astonishing feature promoting colonic bacterial growth is the virtual **lack of mechanisms to suppress** it.

The role of microbiota in colonic function

- **However, it is increasingly recognized that bacterial residents of the large bowel cannot be easily divided as being pathogenic or nonpathogenic.** Many of indigenous bacteria are known pathogens. As examples, *Escherichia coli* cause sepsis, *Bacteroides* cause abscesses, Enterococci cause endocarditis, and *Clostridium histolyticum* causes gas gangrene. These bacterial groups are considered normal inhabitants of the human colon because they can be found in every healthy person.
- **Fluorescence in situ hybridization (FISH) analysis of the mucosal flora has clearly demonstrated that the host does not tolerate the indigenous microbiota but separates them from contact with the mucosa.**

Mucus barrier

- **Colonic and ileal biopsies from healthy persons are covered with mucus that is free of bacteria.**
- The separation of fecal bacteria from the mucosa by mucus can be seen in sections of normal appendices, which were resected for suspected acute appendicitis and found to be normal.

Biostructure of fecal microbiota

- The term "habitual" as used in this context is not synonymous with "commensal". Commensal bacteria include certain bacterial groups such as Bifidobacteriaceae, Enterobacteriaceae, Clostridia, Lactobacilli, and Enterococci, which are often present, but not obligatory for the healthy human intestine, and whose presence, absence, or alteration in number do not reflect whether the colon is healthy or diseased.
- Studies evaluating 86 different bacterial groups have demonstrated that *E. rectale* (*Roseburia* spp.), *Bacteroides*, and *F. prausnitzii* groups are habitual and each comprise 20 to 50 percent of the fecal flora and together at least 70 percent of all bacteria present in feces . All other bacterial groups occur only in a subset of patients.
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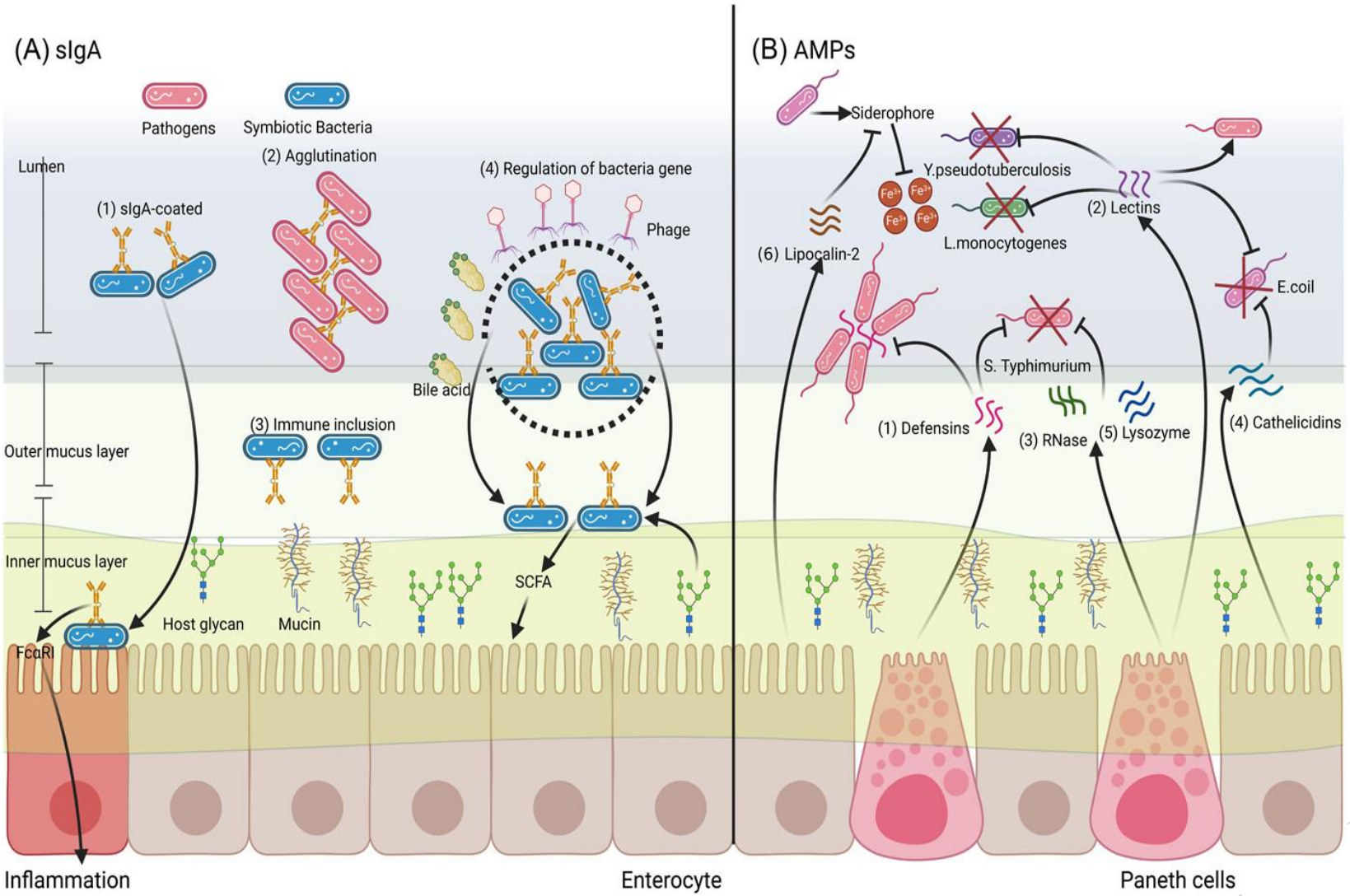

(A) sIgA
Pathogens
Symbiotic Bacteria
Lumen
(2) Agglutination
(1) sIgA-coated
(4) Regulation of bacteria gene
Phage
Bile acid
(3) Immune inclusion
Outer mucus layer
Inner mucus layer
SCFA
Host glycan
Mucin
FcαRI
Inflammation
Enterocyte
(B) AMPs
Siderophore
Y.pseudotuberculosis
(2) Lectins
L.monocytogenes
(6) Lipocalin-2
E.coil
S. Typhimurium
(1) Defensins
(3) RNase
(5) Lysozyme
(4) Cathelicidins
Paneth cells

Biostructure of fecal microbiota

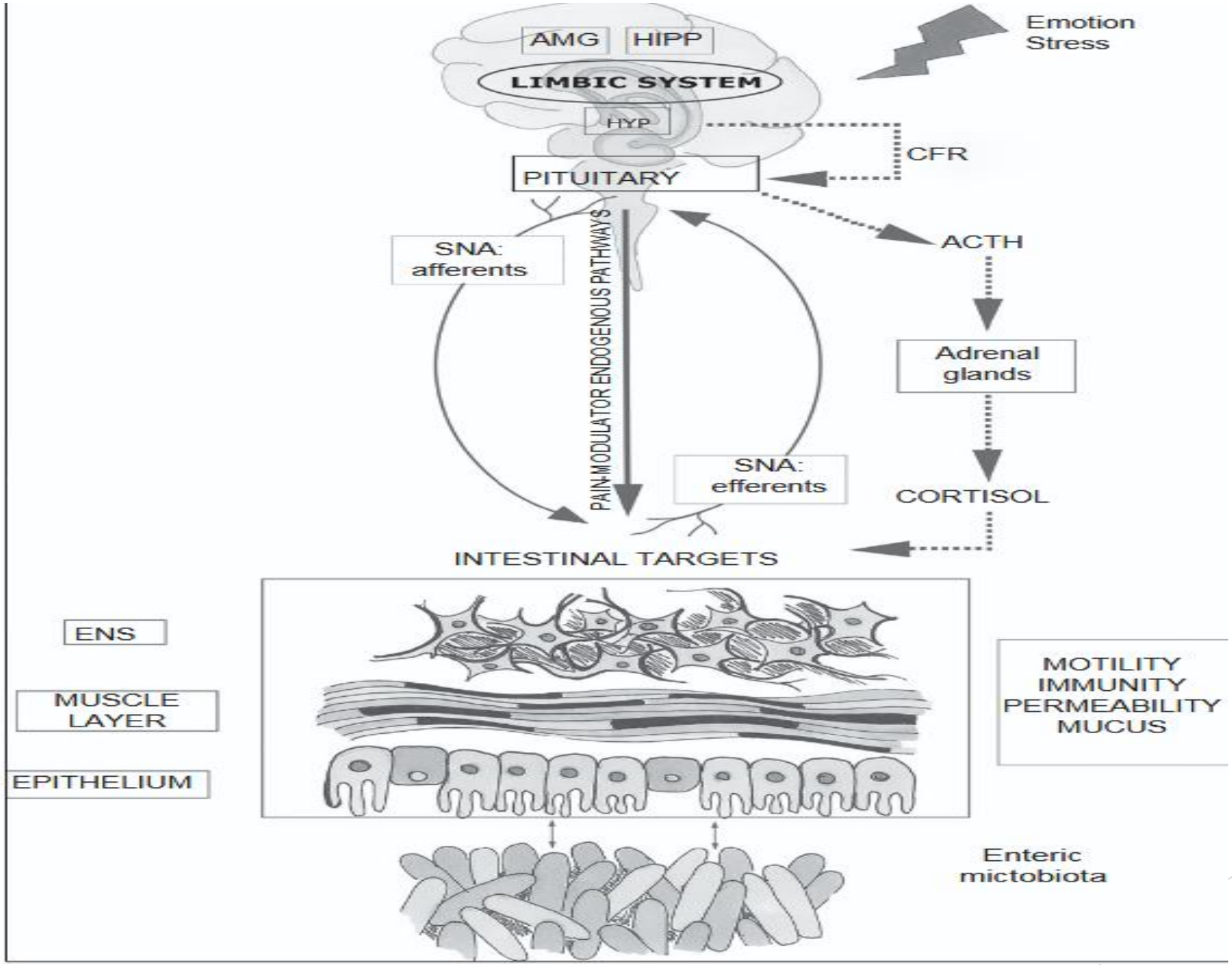
- With regard to the mucus layer, **bacteria can be divided in fecomucous (bacteria that tend to live within feces), mucophob (bacteria that tend to avoid mucus), and mucotroph (bacteria that tend to live within mucus).**
- **All habitual bacteria are fecomucous**; their highest concentrations are within feces, although they also enter mucus. Their concentrations diminish with increasing distance from the fecal surface.
- **The mucophob bacteria (such as the Bifidobacteriaceae group) avoid mucus.**
- **Mucotroph bacteria (such as Enterobacteriaceae and Verucomicriaceae) are located on the border between feces and mucus.**

GBA

- The exponential growth of evidence detailing the **bidirectional interactions** between **the gut microbiome and the brain** **supports a comprehensive** model that integrates the **central nervous, gastrointestinal, and immune systems** with this newly discovered organ.
- Data from preclinical and clinical studies have shown remarkable **potential for novel treatment targets not only in functional gastrointestinal disorders but in a wide range of psychiatric and neurologic disorders, including Parkinson's disease, autism spectrum disorders, anxiety, and depression, among many others.**
- **This interaction between microbiota and GBA appears to be bidirectional**, namely through signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links.

Introduction

- **This bidirectional communication network includes the *central nervous system (CNS), both brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamic pituitary adrenal (HPA) axis*.**
- **The autonomic system**, with the sympathetic and parasympathetic limbs, drives both afferent signals, arising from the lumen and transmitted though enteric, spinal and vagal pathways to CNS, and efferent signals from CNS to the intestinal wall.
- **The HPA axis** is considered the core stress efferent axis that coordinates the adaptive responses of the organism to stressors of any kind.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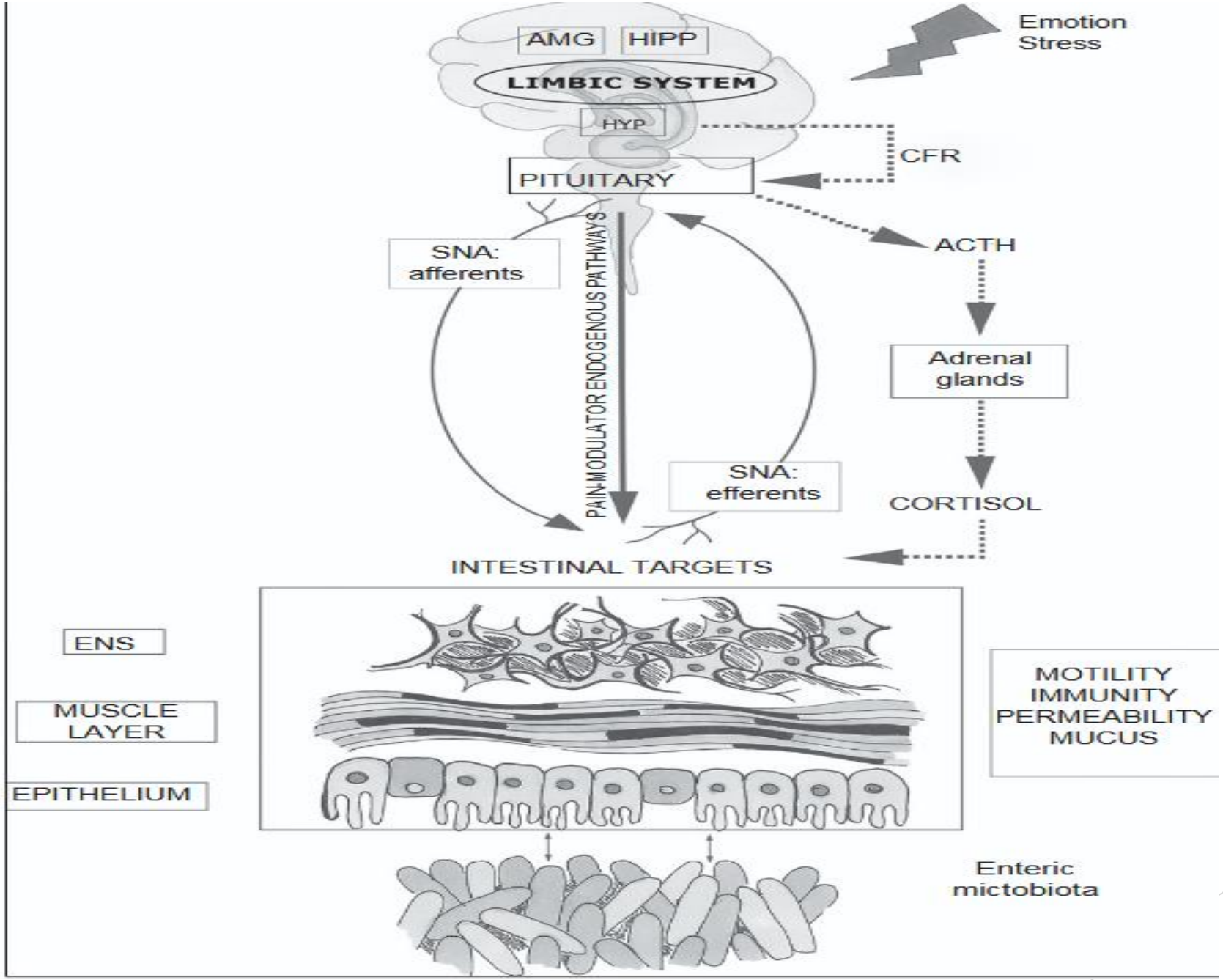
Adrenal
glands
SNA:
efferents
CORTISOL
INTESTINAL TARGETS
ENS
MUSCLE
LAYER
EPITHELIUM
MOTILITY
IMMUNITY
PERMEABILITY
MUCUS
Enteric
mictobiota

Introduction

- **Environmental stress**, as well as elevated systemic pro-inflammatory cytokines, **activate this system that, through secretion of the corticotropin-releasing factor (CRF) from the hypothalamus, stimulates adrenocorticotropic hormone (ACTH) secretion from pituitary gland that, in turn, leads to cortisol release from the adrenal glands.**
- **Cortisol is a major stress hormone** that affects many human organs, including the brain.
- ***Thus, both neural and hormonal lines of communication*** **combine to allow brain to influence the activities of intestinal functional effector cells**, such as immune cells, epithelial cells, enteric neurons, smooth muscle cells, interstitial cells of Cajal and enterochromaffin cells.
- These same cells, on the other hand, are under the influence of the gut microbiota.

Introduction

- **The enteric microbiota is distributed in the human gastrointestinal tract and, although each person's microbiota profile is distinct**, relative abundance and distribution along the intestine of these bacterial phylotypes is similar among healthy individuals.
- **The two more prominent phyla are Firmicutes and Bacteroides accounting for at least ¾ of the microbiome.**
- This microbial community has important metabolic and physiological functions for the host and contributes to its homeostasis during life.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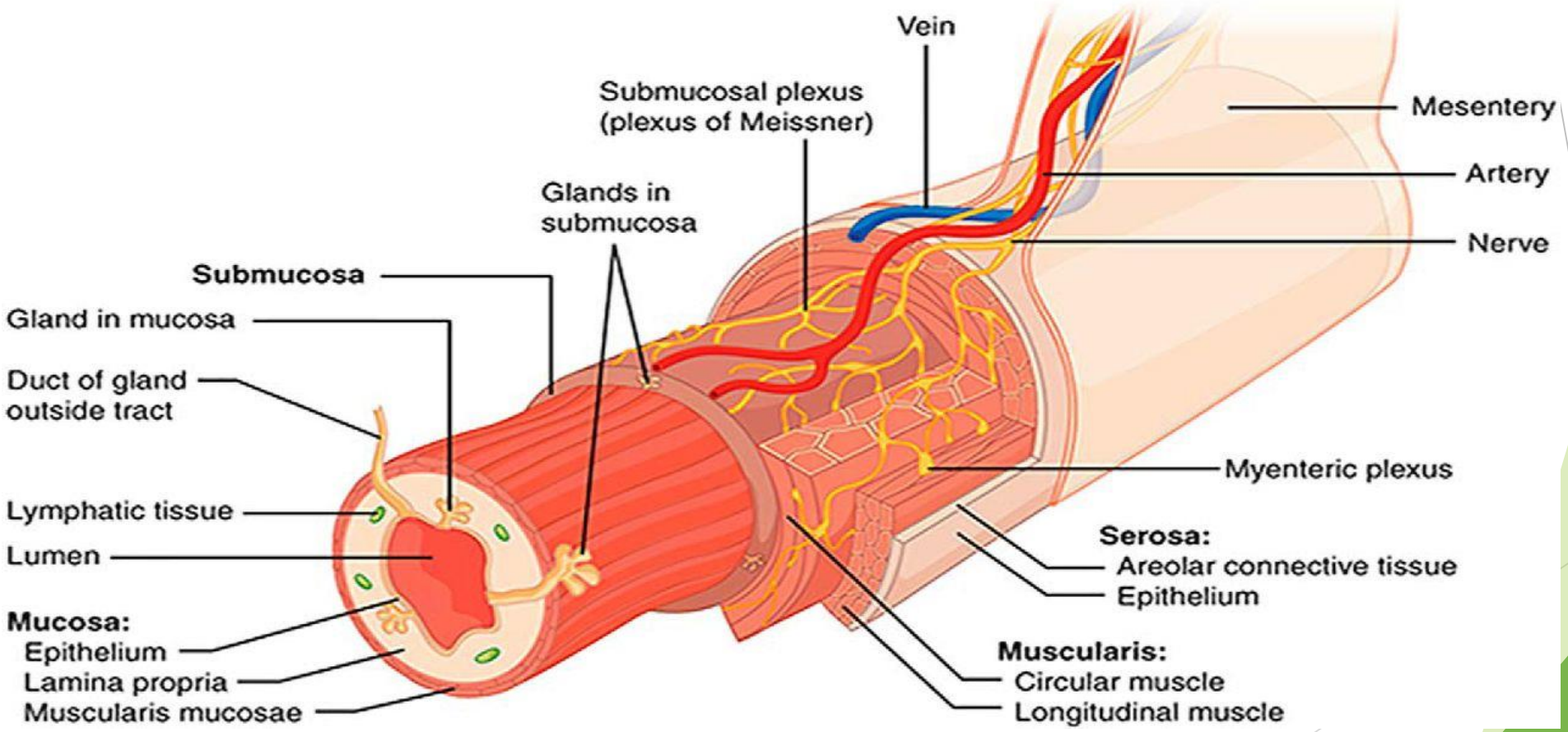
The two major plexuses of the ENS are the myenteric plexus, located between the circular and longitudinal muscle layers in the muscularis externa, and the submucosal plexus, located in the submucosa



Role of microbiota in GBA

- **Both clinical and experimental evidence suggest that enteric microbiota has an important impact on GBA**, interacting not only locally with **intestinal cells and ENS, but also directly with CNS** through neuroendocrine and metabolic pathways.
- **In humans, the most compelling evidence of a gastrointestinal microbe-brain interaction** arose more than 20 years ago from the observation of the often dramatic improvement in patients **with *hepatic encephalopathy***, after the administration of oral antibiotics.
- In the meantime, emerging data support **the role of microbiota in influencing anxiety and depressive-like behaviors and, more recently, of dysbiosis in autism.** ***In fact, autistic patients present specific microbiota alterations according to the severity of the disease***.

Role of microbiota in GBA

- **Dysbiosis occurs also in functional gastrointestinal disorders (FGID)** that are highly associated with **mood disorders** and are linked to a disruption of GBA.
- **The disruption occurring in the GBA determines changes** in intestinal motility and secretion, **causes visceral hypersensitivity and leads to cellular alterations of the entero-endocrine and immune system.**
- Both clinical and experimental evidence suggest that **enteric microbiota** has an important impact on GBA, **interacting not only locally with intestinal cells and ENS, but also directly with CNS through neuroendocrine and metabolic pathways.**

From gut microbiota to brain

- Different technical strategies have been used, consisting in the **use of germ-free (GF) animals, probiotics, antibiotics and infection studies .**
- Studies on GF animals have shown that bacterial **colonization of the gut is central to development and maturation of both ENS and CNS .**
- The absence of microbial colonization is associated to an altered expression and turnover of neurotransmitters in both nervous systems and also to alterations of gut sensory-motor functions, consisting in delayed gastric emptying and intestinal transit reduced migrating motor complex cyclic recurrence and distal propagation and enlarged cecal size .
- Studies conduced on GF animals have also demonstrated that **microbiota influences stress reactivity and anxiety-like behavior, and regulates the set point for HPA activity.**

Table 1 Main principal mechanisms of the bidirectional brain-gut-microbiota axis

From gut microbiota to brain:
Production, expression and turnover of neurotrasmitters (i.e. serotonin, GABA) and neurotrophic factor (BDNF)
Protection of intestinal barrier and tight junction integrity
Modulation of enteric sensory afferents
Bacterial metabolites
Mucosal immune regulation
From brain to gut microbiota:
Alteration in mucus and biofilm production
Alteration in motility
Alteration of intestinal permeability
Alteration in immune function

From gut microbiota to brain

- The impact of microbiota on GBA has been further supported by studies finalized to **the manipulation of gut microbiota through the use of probiotics and/or antibiotics.**
- These studies also confirm that microbiota affects anxiety and HPA system by influencing brain neurochemistry . **Chronic treatment with Lactobacillus rhamnosus JB-1 induced region-dependent alterations in GABA mRNA in the brain.**
- Similarly, transient alteration of microbiota composition, obtained by **administration of oral antimicrobials (neomycin, bacitracin, and pimaricin) in specific-pathogen- free mice, increased exploratory behavior and hippocampal expression of BDNF.**

From gut microbiota to brain

- Evidence indicates that **microbiota communication with the brain involves the vagus nerve, which transmits information from the luminal environment to CNS.**
- In a model of **chronic colitis associated to anxiety- like behavior, the anxiolytic effect obtained with a treatment with Bifidobacterium longum**, was absent in mice that were vagotomized before the induction of colitis.

From gut microbiota to brain

- The disruption occurring in the GBA determines changes in intestinal motility and secretion, causes **visceral hypersensitivity and leads to cellular alterations of the entero-endocrine and immune system.**
- **Microbiota may interplay with multiple of these different pathophysiological IBS targets**, and its role is supported by varying lines of evidence: the presence in IBS patients of alterations in microbiota composition with defects both in its stability and diversity, **the development of post-infectious IBS,** the possible coexistence with small intestinal bacterial overgrowth and the efficacious treatment of certain probiotics and non-systemic antibiotics.

From gut microbiota to brain

- Studies conduced on GF animals have also demonstrated that **microbiota influences stress reactivity and anxiety-like behavior, and regulates the set point for HPA activity.**
- These animals generally show a decreased anxiety and an increased stress response with augmented levels of ACTH and cortisol .

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Microbiota may interact with GBA through different mechanisms

- **The principal one** likely being modulation of the **intestinal barrier, whose perturbation can influence all the underlying compartments**.
- **Probiotic species- specific central effects** are indeed associated with restoration of **tight-junction integrity and the protection of intestinal barrier**, as recently reported in an animal model of water avoidance stress . Pre-treatment of animals with probiotic combined formulation of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 restored tight junction barrier integrity and attenuated HPA axis and autonomic nervous system activities, assessed through plasma cortisol and catecholamine measurements.
- **Probiotics** also prevented changes in **hippocampal neurogenesis** and expression in hypothalamic genes involved in synaptic plasticity.

Microbiota may interact with GBA through different mechanisms

- **Microbiota can interact with GBA** also through the modulation of **afferent sensory nerves as reported for Lactobacillus reuteri** that, enhancing their excitability by inhibiting calcium-dependent potassium channels opening, modulates gut motility and pain perception. **Furthermore, microbiota can influence ENS activity by producing molecules that can act as local neurotransmitters, such as GABA, serotonin, melatonin, histamine and acetylcholine** and by generating a biologically active form of catecholamines in the lumen of the gut .
- **Lactobacilli also utilize nitrate and nitrite to generate nitric oxide .and to produce hydrogen sulfide that modulates gut motility** by interacting with the vanilloid receptor on capsaicin-sensitive nerve fiber.

Microbiota may interact with GBA through different mechanisms

- **The ENS represents also the target of bacterial metabolites.**
- **One of the main product of bacterial metabolism are short-chain fatty acid (SCFAs), such as butyric acid, propionic acid and acetic acid, that are able to stimulate sympathetic nervous system, mucosal serotonin release** and to ***influence memory and learning process*** .
- In this context, it is interesting to report that diet manipulation of microbiota may influence behavior.

Microbiota may interact with GBA through different mechanisms

- Last but not least, **microbiota affects mucosal immune activation**. The enhanced mucosal inflammation induced in mice after treatment with oral antimicrobials, increases **substance P expression** in ENS, an effect normalized by the administration of Lactobacillus paracasei which also attenuates antibiotic-induced visceral hypersensitivity.
- **The effects of microbiota on immune activation might be in part mediated by proteases**. These enzymes are upregulated in intestinal- immune mediated disorders and become the end-stage effectors of mucosal and enteric nervous damage.

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From brain to gut microbiota

- Different types of **psychological stressors modulate the composition and total biomass of the enteric microbiota, independently from duration**. In fact, also the use of short stressors impact the microbiota, being the exposure to social stressor for only 2 h significantly able to change the community profile and to reduce the relative proportions of the main microbiota phyla .
- **These effects may be mediated, through the parallel neuroendocrine output efferent systems (i.e. autonomic nervous system and HPA),** both directly via host-enteric microbiota signaling and indirectly via changes in the intestinal milieu.

From brain to gut microbiota

- **The direct influence is mediated by the secretion, under the regulation of brain, of signaling molecules by neurons, immune cells and enterocromaffin cells, which might affect microbiota.** Communication between CNS effectors and bacteria relies **on the presence of neurotransmitter receptors on bacteria.**
- **Several studies have reported that binding sites for enteric neurotransmitters produced by the host are present on bacteria and can influence the function of components of the microbiota**, contributing to increase predisposition to inflammatory and infection stimuli.

From brain to gut microbiota

- **Stress induces variation in size and quality of mucus secretion .Acoustic stress affects gastric and intestinal postprandial motility in dogs, delaying the recovery of the migrating motor complex pattern and inducing a transient slowing of gastric emptying.**
- **Mental stress too increases the frequency of cecocolonic spike-burst activity** through the central release of CRF. Regional and global changes in gastrointestinal transit can have profound effects on the delivery of important nutrients, mainly prebiotics and dietary fibers, to the enteric microbiota.

From brain to gut microbiota

- **Brain might also affect microbiota composition and function by alteration of intestinal permeability**, allowing bacterial antigens to penetrate the epithelium and stimulate an immune response in the mucosa.
- **Acute stress increased colonic paracellular permeability involving overproduction of interferon-γ and decrease in mRNA expression of ZO-2** .Finally, it is important to remark that **gut alterations associated to stress facilitate the expression of virulent bacteria.**
- **Norepinephrine released during surgery induces the expression of Pseudomonas aeruginosa, which might result in gut sepsis .** Besides, norepinephrine can also stimulate proliferation of several strains of enteric pathogens and increase the virulent properties of Campylobacter jejuni and might favor overgrowth of non-pathogenic isolates of Escherichia coli,as well as of pathogenic Escherichia coli 0157:H7:3.

From brain to gut microbiota

- Given the ability of gut microbiota to alter nutrient availability and the **close relationship between nutrient sensing and peptide secretion by enteroendocrine cells**, the interaction of microbiota and GBA might also occur through the release of biologically active peptides from enteroendocrine cells that can affect the GBA .
- For example, **galanin stimulates the activity of the central branch of the HPA axis (i.e. the release of CRF and ACTH), thereby enhancing glucocorticoid secretion from the adrenal cortex.**
- **Galanin also is able to stimulate directly cortisol secretion from adrenocortical cells**, and norepinephrine release from adrenal medulla . **Ghrelin too possesses a marked ACTH/cortisol-releasing** effect in humans and it is probably involved in the modulation of the HPA response to stress and nutritional/metabolic variations.

From brain to gut microbiota

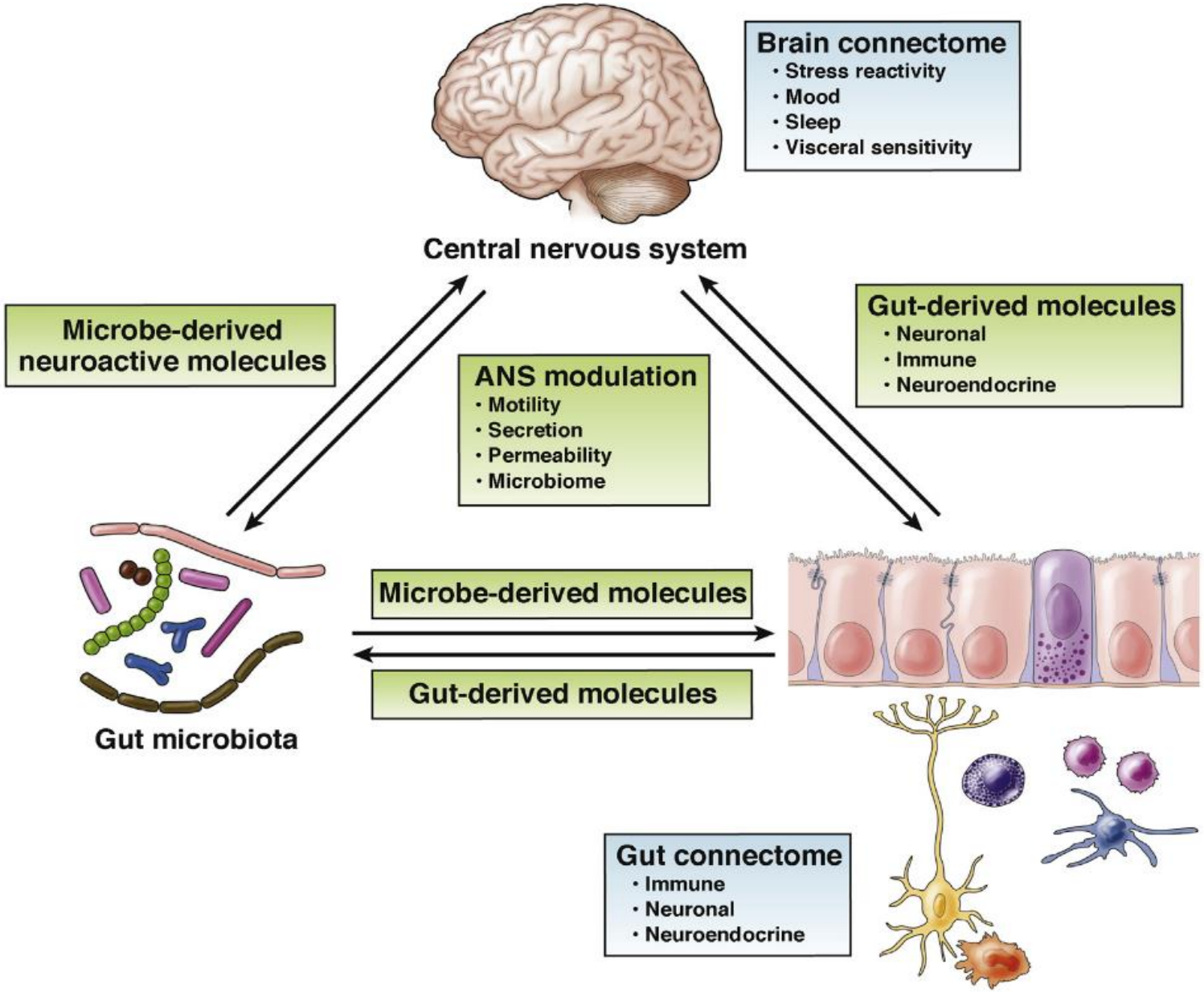
- **The enhanced mucosal inflammation** induced in mice after treatment with oral antimicrobials**, increases substance P expression in ENS**, an effect normalized by the administration of Lactobacillus paracasei which also attenuates **antibiotic-induced visceral hypersensitivity** .
- **The effects of microbiota on immune activation might be in part mediated by proteases.** These enzymes are upregulated in intestinal- immune mediated disorders and become the end-stage effectors of mucosal and enteric nervous damage .
- Increased concentration of proteases have been detected in fecal samples of IBS patients associated to specific intestinal bacterial species.

From brain to gut microbiota

- **The direct influence is mediated by the secretion**, under the regulation of brain, of signaling molecules by neurons, immune cells and enterocromaffin cells, which might affect microbiota.
- Communication between CNS effectors and bacteria relies on the presence of neurotransmitter receptors on bacteria. ***Several studies have reported that binding sites for enteric neurotransmitters produced by the host are present on bacteria and can influence the function of components of the microbiota, contributing to increase predisposition to inflammatory and infection stimuli*** . High affinity for GABA system has been reported in Pseudomonas fluorescens with binding properties similar to those of a brain receptor.
- Escherichia coli O157:H7 possesses a receptor for host-derived epinephrine/norepinephrine that can be blocked specifically by adrenergic antagonists.

From brain to gut microbiota

- Besides, brain has a prominent role in the modulation of gut functions, such as motility, secretion of acid, bicarbonates and mucus, intestinal fluid handling and mucosal immune response, all important for the maintenance of the mucus layer and biofilm where individual groups of bacteria grow in a multiplicity of different microhabitats and metabolic niches associated with the mucosa .
- **Brain, through the ANS, may also modulate immune function**. The sympathetic branch **modulates number, degranulation and activity of mast cells with consequent imbalance in tryptase and histamine release in stress-related muscle dysfunction** . Other mast cell products, such as CRF, in turn, can increase epithelial permeability to bacteria, which facilitates their access to immune cells in the lamina propria


Brain connectome
• Stress reactivity
• Mood
• Sleep
• Visceral sensitivity
Central nervous system
Microbe-derived neuroactive molecules
ANS modulation
• Motility
• Secretion
• Permeability
• Microbiome
Gut-derived molecules
• Neuronal
• Immune
• Neuroendocrine
Microbe-derived molecules
Gut-derived molecules
Gut microbiota
Gut connectome
• Immune
• Neuronal
• Neuroendocrine

Concluding Functional Intestinal Disorders remarks

- Recent studies have suggested that there are at least 2 subgroups of patients who meet Rome criteria for IBS, based on gut microbial community structure, 1 sub- group not differing from healthy control subjects, despite similar GI symptoms.
- In one of these studies, the dysbiotic IBS subgroup also differed in regional brain volumes from the eubiotic group,suggesting a relationship between microbial community structure and brain structure.

- Based on analysis of fecal samples, regardless of the analytical methodology used, a number of studies reported a decreased relative abundance of the genera Bifidobacterium and Lactobacillus, and an increased Firmicutes:Bacteroidetes ratios at the phylum level. Because stress has been associated with a reduction in Lactobacilli in preclinical and clinical studies,132,171,172 one may speculate that the reported IBS-related changes in community structure and resulting metabolism are in part owing to altered ANS modulation of the gut as described earlier.

Obesity/Food Addiction

- **The gut microbiota and its metabolites play an crucial role in the modulation of satiety signals and eating behaviors.** In preclinical studies, fecal transplantation from hyperphagic obese mice to germ-free mice was able to induce hyperphagic behavior and weight gain in the recipients.
- **The gut micro-biome produces several neuroactive compounds; these bioactive products include several indole-containing metabolites and 5-HT.** The administration of probiotics modifies brain function and even brain metabolites including-aminobutyric acid and glutamate.A handful of studies point to a dramatic change in gut microbial composition after bariatric surgery.

Depression and Anxiety

- Preclinical studies have shown the microbiota's capacity to **modulate emotional behaviors, and influence parameters significant to depression pathogenesis and severity.**
- Although studies characterizing the gut microbiome of major depressive disorder vs health have yielded marginally distinct assemblage correlations, 3 different types of studies suggest causality: depressed human-to-rodent fecal microbial transplants have induced depressive behaviors in the animal Models.

Parkinson's Disease

- The risk of Parkinson's disease development increases with infrequency of bowel movement and constipation severity, and there is a significant comorbidity of Parkinson's disease and IBS-like symptoms.
- Moreover, constipation is among the earliest features, appearing as early as 15.3 years before motor dysfunction.
- **Early gastrointestinal symptoms, thus, may be prodromal, making the gut microbiota a promising source of information for diagnosis, prognosis, and, potentially, pathogenesis.**

Autism Spectrum Disorder

- **GI symptom severity is correlated strongly to ASD symptom severity, as well as anxiety and sensory over-responsivity conditions modulated by gut microbiota in preclinical models .**
- Gut dysbiosis is an increasingly documented symptom of ASD but, similar to other clinical conditions, causality remains limited to intriguing, albeit untested, hypotheses and results from uncontrolled clinical studies.