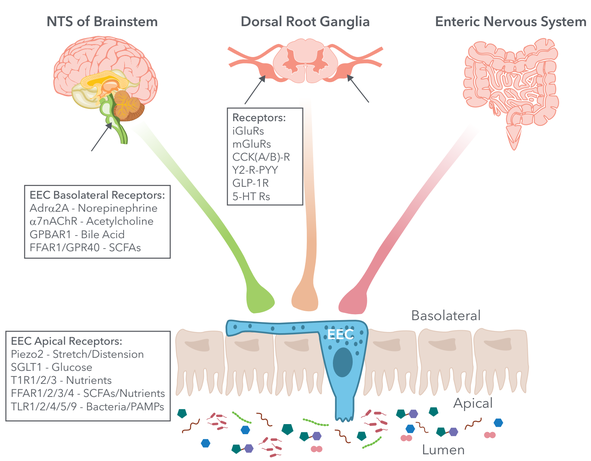
bio-techne® | GUT-BRAIN AXIS

Timothy Sampson[1], Adam Hamilton[2], and Maria Elizabeth de Sousa Rodrigues[3]

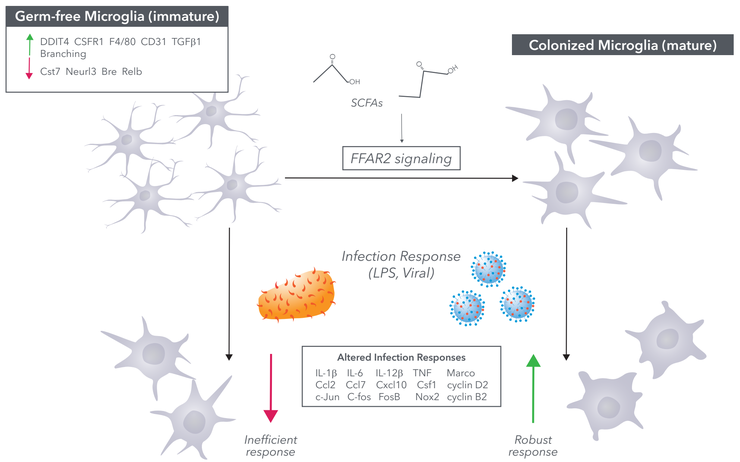
Enteroendocrine Cells (EEC) Facilitate Gut-to-Brain Signaling



SELECT EEC SIGNALING MOLECULES:		
SIGNALING MOLECULE	SECRETING EEC SUBTYPE (LOCATION)	FUNCTION
5-HT	EC-cell (Stomach, Proximal SI, Distal SI, Proximal LI, Distal LI), L-cell (Distal SI, Proximal LI, Distal LI), I-cell (Proximal SI), K-cell (Proximal SI)	Multifunctional, promotes GI motility. Activates 5-HT receptors (5-HT3 and 5-HT4) on vagal afferents.
CCK	I-cell (Proximal SI)	Increases satiety, delays gastric emptying. Short-chain fatty acid (SCFA) responsive.
GASTRIN	G-cell (Stomach, Proximal SI)	Stimulates stomach acid and enzyme secretion, promotes gastric emptying.
GHRELIN	A-cell (Stomach, Proximal SI)	Promotes appetite, increases motility.
GLP-1	L-cell (Distal SI, Proximal LI, Distal LI)	Inhibits motility, emptying, and promotes satiety. Receptors expressed in gut, pancreas, kidney, ENS, vagus nerve, and CNS.
GLUTAMATE	Throughout intestinal tract	Synaptic signaling to sensory afferents.
LEPTIN	Gastric Chief-cell (Stomach), P-cell (Stomach)	Signals satiety. Synergistic with CCK on the vagus nerve.
PYY	L-cell (Distal SI, Proximal LI, Distal LI)	Inhibits food intake, triggers ileal break. Acts directly on vagal afferents and crosses the blood-brain barrier (BBB) to act via NPY receptors (Y1-5 receptors), primarily through NPY2R.
SOMATOSTATIN	D-cell (Stomach, Proximal SI)	Inhibits stomach secretion, decreases gastric emptying, slows motility.

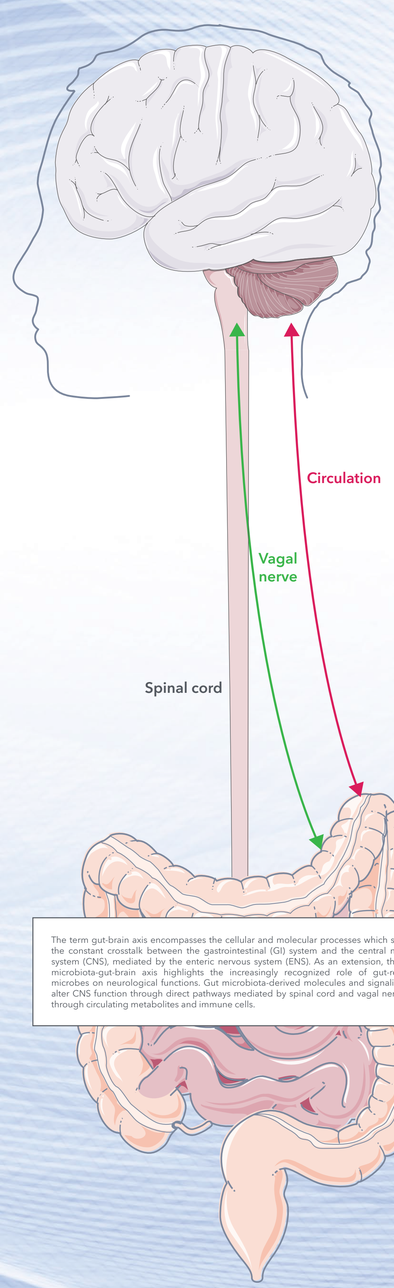
Enteroendocrine cells (EECs) reside along the length of the GI epithelium, where they play a role in regulating gut motility and secretions, food intake, postprandial glucose levels, and metabolism. Activation of EECs induces the release of a range of signaling molecules including hormones, neuroactive peptides and neurotransmitters, which reach the circulation or act on local circuits. Within the enteric neuroepithelial circuit, EECs are innervated by sensory afferents originating from the brainstem (vagus nerve, nucleus tractus solitarius [NTS]), the spinal cord's dorsal root ganglia (DRG, primary sensory afferents), and the ENS (intrinsic primary afferent neurons [IPANs]). EECs contain presynaptic and postsynaptic proteins and are in extremely close proximity to sensory neurons from the vagus nerve, DRGs, and ENS. Tracing/imaging studies have revealed axon-like basal cytoplasmic processes (neuropods) involved in functional synaptic connections. Through these tight interactions with vagal sensory afferents, EECs function as conduits for gut microbiome-CNS communication by sensing microbial metabolites and associated molecules and relaying appropriate responses.

Microbiome-Derived Signals Drive Microglia Maturation



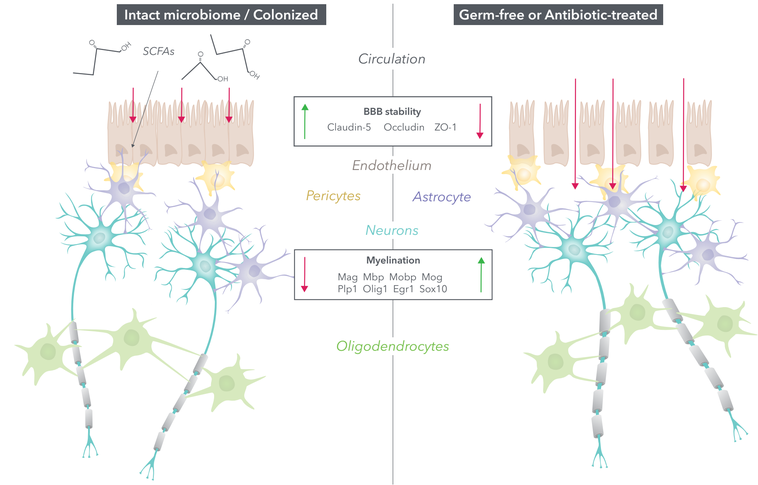
Microglia, brain-resident myeloid cells, play a central role in brain homeostasis in both health and disease. These cells have essential roles in synaptic development and in immune functions, including detection of foreign bodies / pathogens and scavenging of dead and dying cells. Microglia homeostasis is complexly regulated and is, in part, modulated by peripheral factors, including those derived from the gut microbiota. Microbiota derived short-chain fatty acids (SCFAs), products of bacterial fermentation, signal through FFAR2 and promote microglia development.

Germ-free (GF) mice have slightly immature microglia, paused in an adult-like state but without achieving a fully mature phenotype and characterized by increased expression of DDIT and CsfR1 genes. E18.5 embryos from GF mothers show increased microglial density in various brain regions, with increased numbers of microglia exhibiting a ramified morphology, indicative of a resting state. Offspring of GF dams immediately after birth, a time when microglia typically exhibit an activated phenotype, show altered microglial morphology and density, as well as attenuated inflammatory responses. Additionally, microglia from adult GF mice, lacking constant postnatal input from gut microbiota, show distinct differences in density and morphology compared with those derived from specific pathogen-free (SPF) mice. This leads to altered immune responses in the brain following a challenge by viral pathogens or bacterial stimuli (LPS), including decreased IL-1β, IL-6, TNF, and Nox2, in microglia derived from GF animals compared to those from colonized mice.



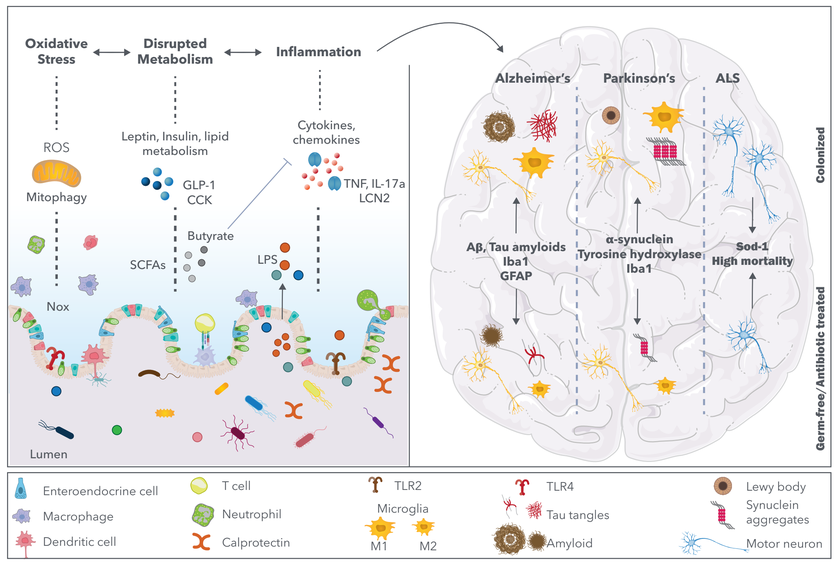
The term gut-brain axis encompasses the cellular and molecular processes which support the constant crosstalk between the gastrointestinal (GI) system and the central nervous system (CNS), mediated by the enteric nervous system (ENS). As an extension, the term microbiota-gut-brain axis highlights the increasingly recognized role of gut-resident microbes on neurological functions. Gut microbiota-derived molecules and signaling can alter CNS function through direct pathways mediated by spinal cord and vagal nerves, or through circulating metabolites and immune cells.

Brain Structure is Modulated by the Microbiome



The blood-brain barrier (BBB) is comprised of endothelial cells, pericytes, astrocytes, neurons, and extracellular matrix components that together function in the maintenance of CNS homeostasis. The BBB of GF mice is more permeable, with decreased tight junction protein expression and disorganized tight junctions. Colonization of GF mice with pathogen-free microbiota increases the expression of tight junction proteins such as transmembrane claudin-5 and occludin, and cytoplasmic zonula occludens-1 (ZO-1), stabilizing the BBB. Additionally, microbiota-derived SCFAs, specifically butyrate, restore BBB stability in GF mice. The vasculature and pericyte coverage are unaffected by changes in microbiota. GF mice also show increased myelination and myelin production in the prefrontal cortex, with alterations in the corpus callosum and other regions. These changes are associated with increased transcription of oligodendrocyte myelin-associated genes as indicated, and unrelated to oligodendrocyte number.

Impact of the Microbiome on Neurodegenerative Diseases.



Gut dysbiosis is associated with neurodegenerative diseases. Modulation of peripheral inflammatory status by inflammatory molecules, such as LPS or anti-inflammatory butyrate, can contribute to CNS neurodegenerative pathologies.
Alzheimer's disease (AD)- GF and antibiotic-treated AD animal models, such as APP/PS1 mice, have reduced cerebral amyloid, decreased microgliosis (indicated through Iba1 abundance) and overall changes in pro-inflammatory cytokine profile compared to control mice. Recolonization with microbiota derived from conventionally raised APP transgenic mice increases cerebral amyloid pathology.
Parkinson's disease (PD)- GF PD animal models, such as mice overexpressing α-synuclein, have reduced α-synuclein inclusions, neuroinflammatory markers (including Iba1), and motor dysfunction compared to controls. Treatment of mice with LPS or particular microbes enhances susceptibility to PD-inducing toxins, including MPTP, leading to rapid loss of tyrosine hydroxylase in the GI tract and CNS.
Amyotrophic lateral sclerosis (ALS)- GF or antibiotic-treated SOD1 mice, show exacerbated ALS pathology with increased motor symptoms, and substantially increased mortality.

NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.

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GUT-BRAIN AXIS POSTER

ABBREVIATIONS

ENTEROENDOCRINE CELLS (EEC) FACILITATE GUT-TO-BRAIN SIGNALING	
5-HT (R)	5-hydroxytryptamine (receptor)
α7nAChR	Alpha-7 nicotinic receptor
Adrα2A	Alpha-2A-adrenergic receptor
CCK(A/B)-R	Cholecystokinin (A/B) receptor
DRG	Dorsal root ganglia
EEC	Enteroendocrine cell
ENS	Enteric nervous system
FFAR1/2/3/4	Free fatty acid receptor 1/2/3/4
GI	Gastrointestinal
GLP-1(R)	Glucagon-like peptide 1 (receptor)
GPBAR1	G protein-coupled bile acid receptor 1
GPR40	G-protein-coupled receptor 40
iGluRs	Ionotropic glutamate receptors
IPAN	Intrinsic primary afferent neuron
LI	Large intestine
mGluRs	Metabotropic glutamate receptors
NPY (2R)	Neuropeptide Y (receptor Y2)
NTS	Nucleus tractus solitarius
PAMPs	Pathogen-associated molecular patterns
PYY	Peptide YY
SCFA	Short chain fatty acid
SGLT1	Sodium-glucose cotransporter 1
SI	Small intestine
T1R1/2/3	Taste receptor type 1, member 1/2/3
TLR1/2/4/5/9	Toll-like receptor 1/2/4/5/9
Y2-R - PYY	Y receptor type 2 - Peptide YY

MICROBIOME-DERIVED SIGNALS DRIVE MICROGLIA MATURATION	
Bre	Brain and reproductive organ-expressed
Ccl2	Chemokine (C-C motif) ligand 2
Ccl7	Chemokine (C-C motif) ligand 7
Csf1	Colony stimulating factor 1
CsfR1	Colony stimulating factor 1 receptor
CD31	Platelet endothelial cell adhesion molecule-1 (PECAM-1)
Cst7	Cystatin F
Cxcl10	C-X-C motif chemokine ligand 10
DDIT	DNA-damage inducible transcript
DDIT4	DNA-damage inducible transcript 4
F4/80	EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1)
FFAR2	Free fatty acid receptor 2
FosB	FBJ murine osteosarcoma viral oncogene homolog B
GF	Germ-free
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-12β	Interleukin 12 beta
LPS	Lipopolysaccharide
Marco	Macrophage receptor with collagenous structure
Neurl3	Neuralized E3 ubiquitin protein ligase 3
Nox2	NADPH oxidase 2
Relb	V-rel reticuloendotheliosis viral oncogene homolog B
SPF	Specific pathogen-free
TGFβ1	Transforming growth factor beta 1
TNF	Tumor necrosis factor

BRAIN STRUCTURE IS MODIFIED BY THE MICROBIOME	
BBB	Blood-brain barrier
CNS	Central nervous system
Egr1	Early growth response 1
GF	Germ-free
Mag	Myelin-associated glycoprotein
Mbp	Myelin basic protein
Mobp	Myelin-associated oligodendrocyte basic protein
Mog	Myelin oligodendrocyte glycoprotein
Olig1	Oligodendrocyte transcription factor 1
Plp1	Proteolipid protein 1
SCFA	Short-chain fatty acid
Sox10	SRY-related HMG-box 10
ZO-1	Zonula occludens-1

IMPACT OF THE MICROBIOME ON NEURODEGENERATIVE DISEASES	
Aβ	Beta-amyloid peptide
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APP	Amyloid precursor protein
CCK	Cholecystokinin
CNS	Central nervous system
GF	Germ-free
GFAP	Glial fibrillary acidic protein
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
Iba1	Ionized calcium binding adapter molecule 1
IL-17a	Interleukin 17A
LCN2	Lipocalin-2
LPS	Lipopolysaccharide
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Nox	NADPH oxidase
PD	Parkinson's disease
PS1	Presenilin 1
ROS	Reactive oxygen species
SCFA	Short-chain fatty acid
SOD1	Superoxide dismutase 1
TLR2	Toll-like receptor 2
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor

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