Stress, Gut and Our Health

Stop the Madness

Tereza Hubkova, MD

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The Maternal Gut Microbiome during Pregnancy

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Solveig A. Cunningham, PhD [Assistant Professor],
Rollins School of Public Health, Emory University

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Abstract

The gut microbiome is a critical component of an individual's metabolism and overall health. The prenatal period is marked by unique inflammatory and immune changes that alter maternal gut function and bacterial composition as the pregnancy advances. The composition of the maternal gut microbiome contributes to obstetric outcomes with long-term health sequelae for mother and child. Estrogen and progesterone also impact gut function, especially during the prenatal period. These physiologic changes in pregnancy allow for adjustments in maternal metabolism and weight necessary to support the pregnancy. This article will review the normal hormonal, metabolic and immunologic changes to the maternal gut microbiome throughout the prenatal period, in addition to relevant implications for nurses providing care for pregnant women.

Livina in Vitality

ORIGINAL ARTICLE

The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior

T Arentsen[1], Y Qian[1], S Gkotzis[1,2], T Femenia[1], T Wang[1], K Udekwu[2], H Forssberg[3] and R Diaz Heijtz[1]

Recent studies have revealed that the gut microbiota modulates brain development and behavior, but the underlying mechanisms are still poorly understood. Here, we show that bacterial peptidoglycan (PGN) derived from the commensal gut microbiota can be translocated into the brain and sensed by specific pattern-recognition receptors (PRRs) of the innate immune system. Using expression-profiling techniques, we demonstrate that two families of PRRs that specifically detect PGN (that is, PGN-recognition proteins and NOD-like receptors), and the PGN transporter PepT1 are highly expressed in the developing brain during specific windows of postnatal development in both males and females. Moreover, we show that the expression of several PGN-sensing molecules and PepT1 in the developing striatum is sensitive to manipulations of the gut microbiota (that is, germ-free conditions and antibiotic treatment). Finally, we used the PGN-recognition protein 2 (Pglyrp2) knockout mice to examine the potential influence of PGN-sensing molecules on brain development and behavior. We demonstrate that the absence of Pglyrp2 leads to alterations in the expression of the autism risk gene *c-Met*, and sex-dependent changes in social behavior, similar to mice with manipulated microbiota. These findings suggest that the central activation of PRRs by microbial products could be one of the signaling pathways mediating the communication between the gut microbiota and the developing brain.

Molecular Psychiatry (2017) **22,** 257–266; doi:10.1038/mp.2016.182; published online 15 November 2016

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Peptidoglycan and the brain

- important for brain development in utero
- important for the growth of nerve cells, differentiation, synaptogenesis, myelinization and blood brain barrier development
- affects motor, cognitive, social and emotional function
- important for gut brain connection for the rest of our life
- reduces stress induced inflammatory response in the brain

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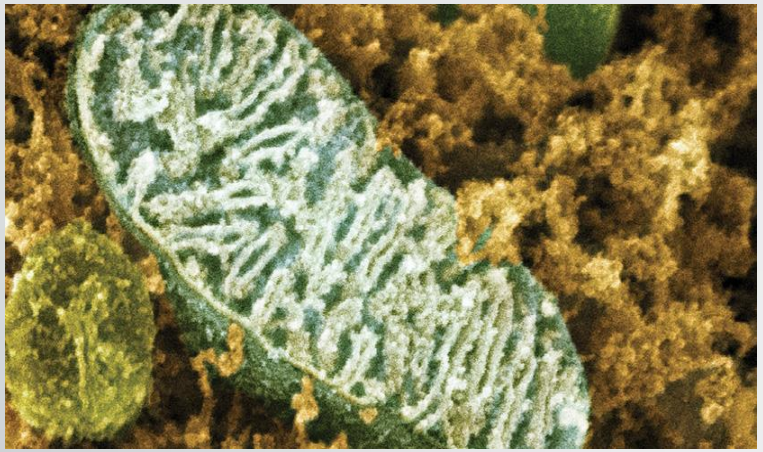

"Life did not take over the globe by combat, but by networking."
Dr. Lynn Margulis

"Symbiotic relationships are the major driving force behind evolution."

Symbiogenesis

- **Men and their microbiota can be considered as holobionts – the fitness of the host depends on and cannot be seen separate from its microbiota.**

Gordon et al. 2013, Carrier et al. 2017

van de Guchte *et al. Microbiome* (2018) 6:81
https://doi.org/10.1186/s40168-018-0466-8

Microbiome

COMMENTARY Open Access

Humans as holobionts: implications for prevention and therapy

Maarten van de Guchte[1*], Hervé M. Blottière[1,2] and Joël Doré[1,2]

Abstract

The human gut microbiota is increasingly recognized for its important or even decisive role in health. As it becomes clear that microbiota and host mutually affect and depend on each other in an intimate relationship, a holistic view of the gut microbiota–host association imposes itself. Ideally, a stable state of equilibrium, homeostasis, is maintained and serves health, but signs are that perturbation of this equilibrium beyond the limits of resilience can propel the system into an alternative stable state, a pre-disease state, more susceptible to the development of chronic diseases. The microbiota–host equilibrium of a large and growing proportion of individuals in Western society may represent such a pre-disease state and explain the explosive development of chronic diseases such as inflammatory bowel disease, obesity, and other inflammatory diseases. These diseases themselves represent other alternative stable states again and are therefore hard to cure. The holistic view of the microbiota–host association where feedback loops between microbiota and host are thought to maintain the system in a stable state—be it a healthy, pre-disease, or disease state—implies that integrated approaches, addressing host processes and microbiota, should be used to treat or prevent (pre-)disease.

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Published: 27 July 2017

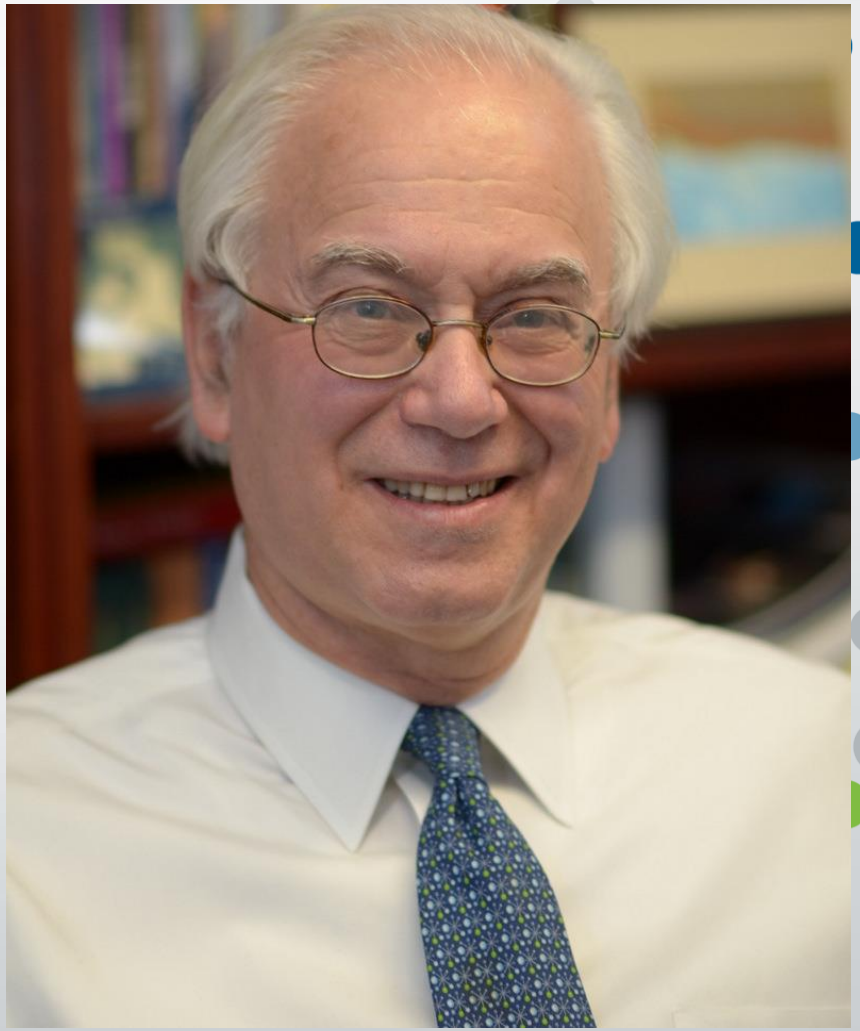
The theory of disappearing microbiota and the epidemics of chronic diseases

Martin J. Blaser

Nature Reviews Immunology **17**, 461–463 (2017) | Cite this article

Abstract

In recent decades, the incidence of many apparently unrelated chronic diseases has markedly increased. Here, I theorize that losses of particular bacterial species of our ancestral microbiota have altered the context in which immunological, metabolic and cognitive development occur in early life, which results in increased disease. This ominous trend suggests that we must refocus efforts to understand and reverse the underlying circumstances that are responsible for our disappearing microbiota.



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J Clin Psychiatry. 2015 Nov;76(11):1522-8. doi: 10.4088/JCP.15m09961.

Antibiotic exposure and the risk for depression, anxiety, or psychosis: a nested case-control study

Ido Lurie [1] [2], Yu-Xiao Yang, Kevin Haynes, Ronac Mamtani, Ben Boursi

Affiliations + expand

PMID: 26580313 DOI: 10.4088/JCP.15m09961

Treatment with a single course of antibiotics was associated with higher risk of depression (23% -25% increased risk).

Recurrent treatment with antibiotics increased the risk of depression by 40-56% (from 2-5 to > 5 courses).

The risk of anxiety goes up by 17% after a single course of penicillin and 44% with > courses.

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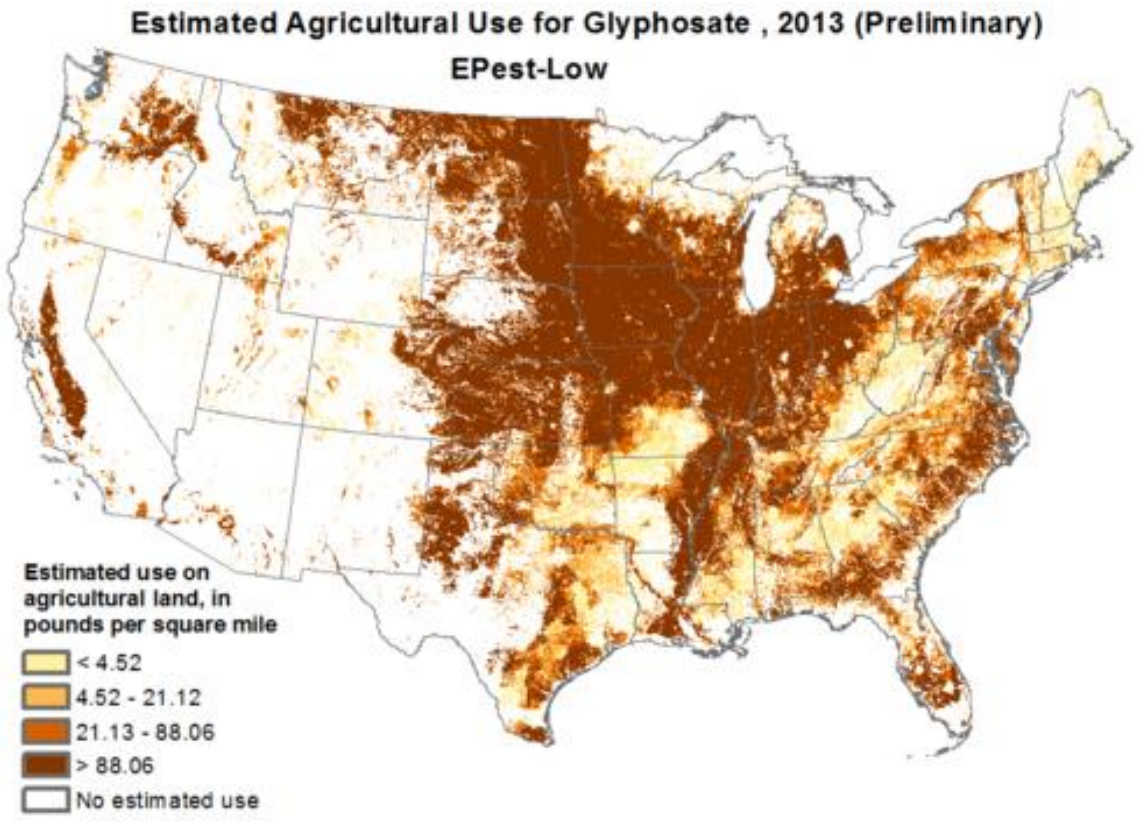

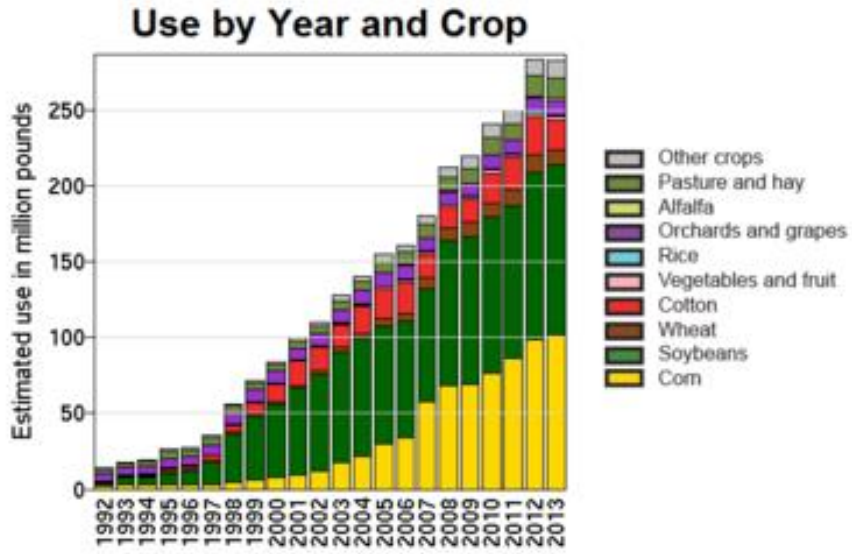

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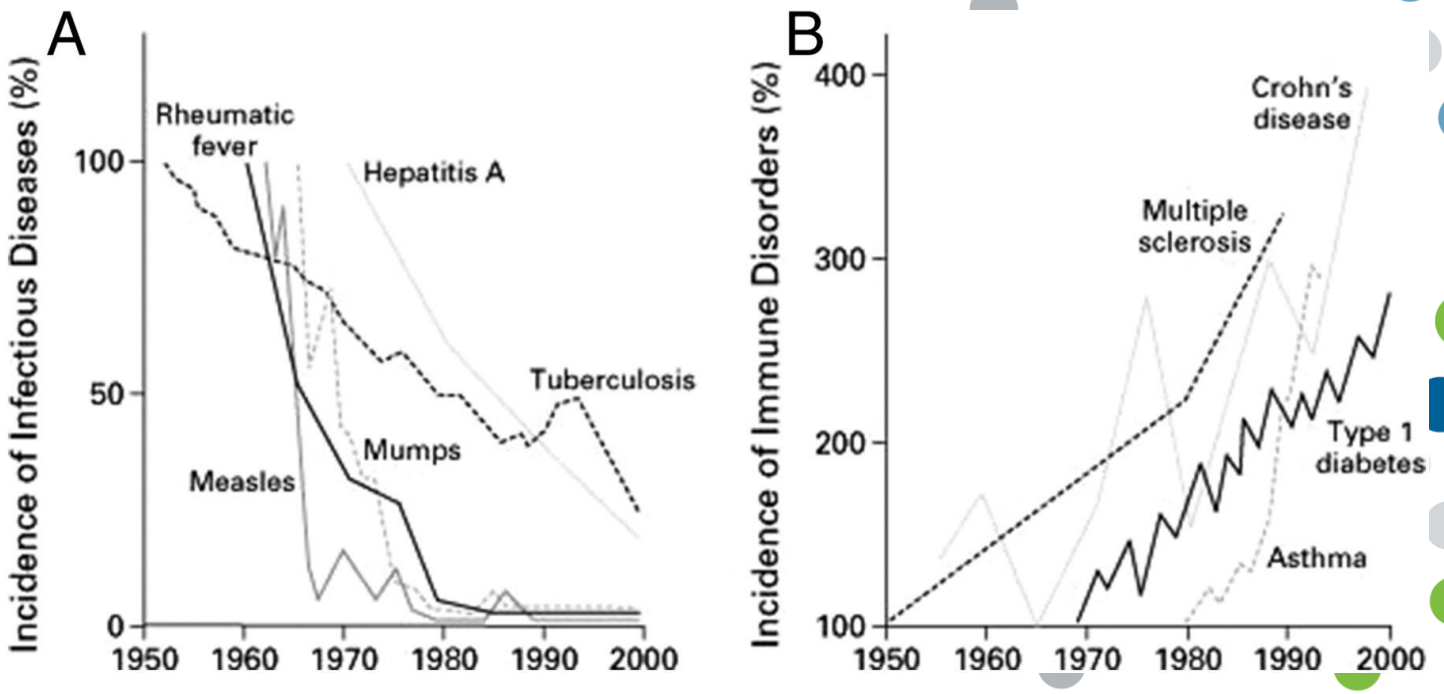
Rise of chronic inflammatory diseases



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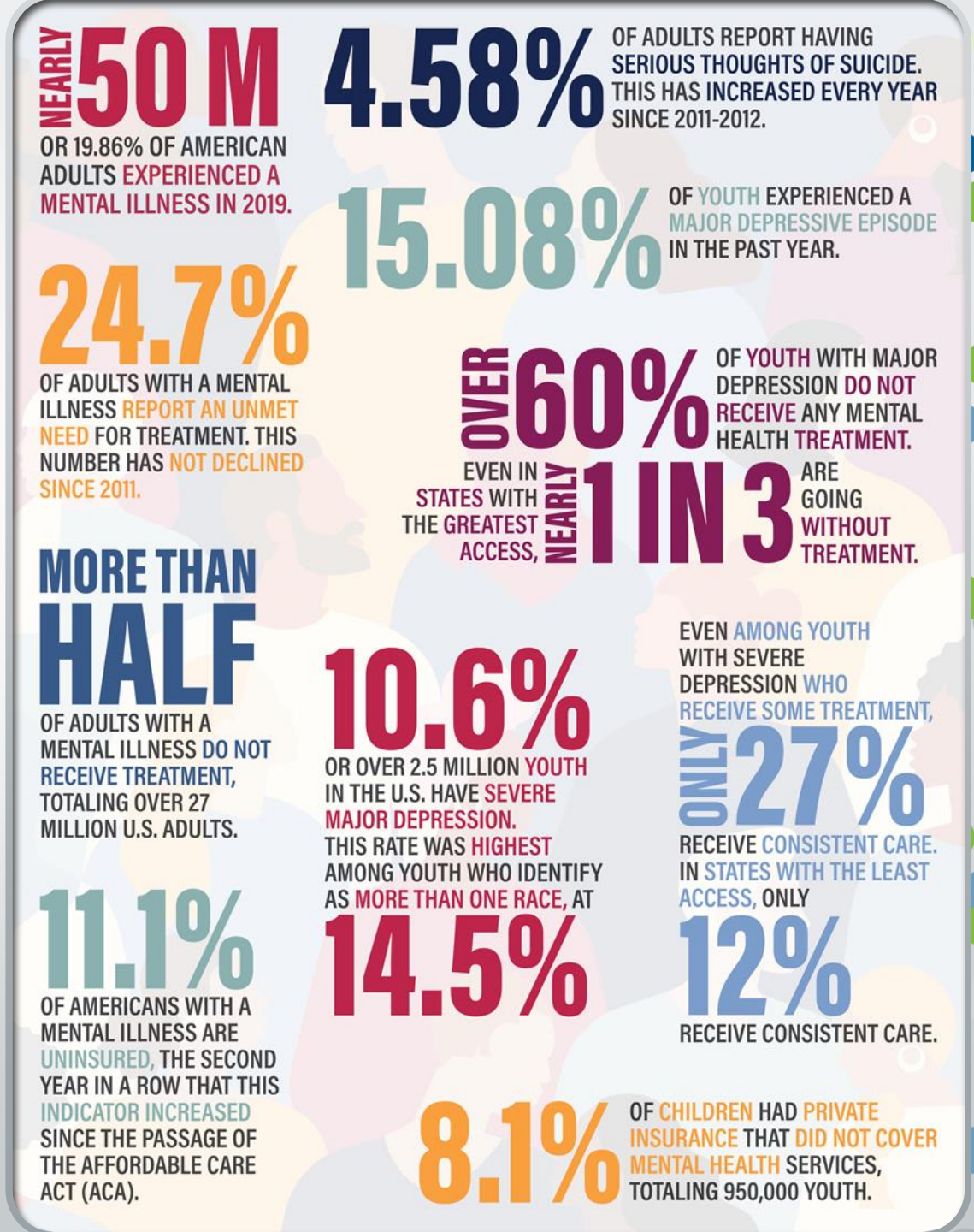
Concerning stats

- 1 in 4 people are affected by mental health illness at some point in their life
- 1 in 5 children / youth has mental health illness
- In the past 12 months, around 26.2% of Americans met criteria for any mental health disorder – anxiety 18.1%, depression 9.5% , impulse control disorder 8.9%.
- Between 2005 and 2015, the number of people living with depression increased by 18%.

MHA Mental Health America



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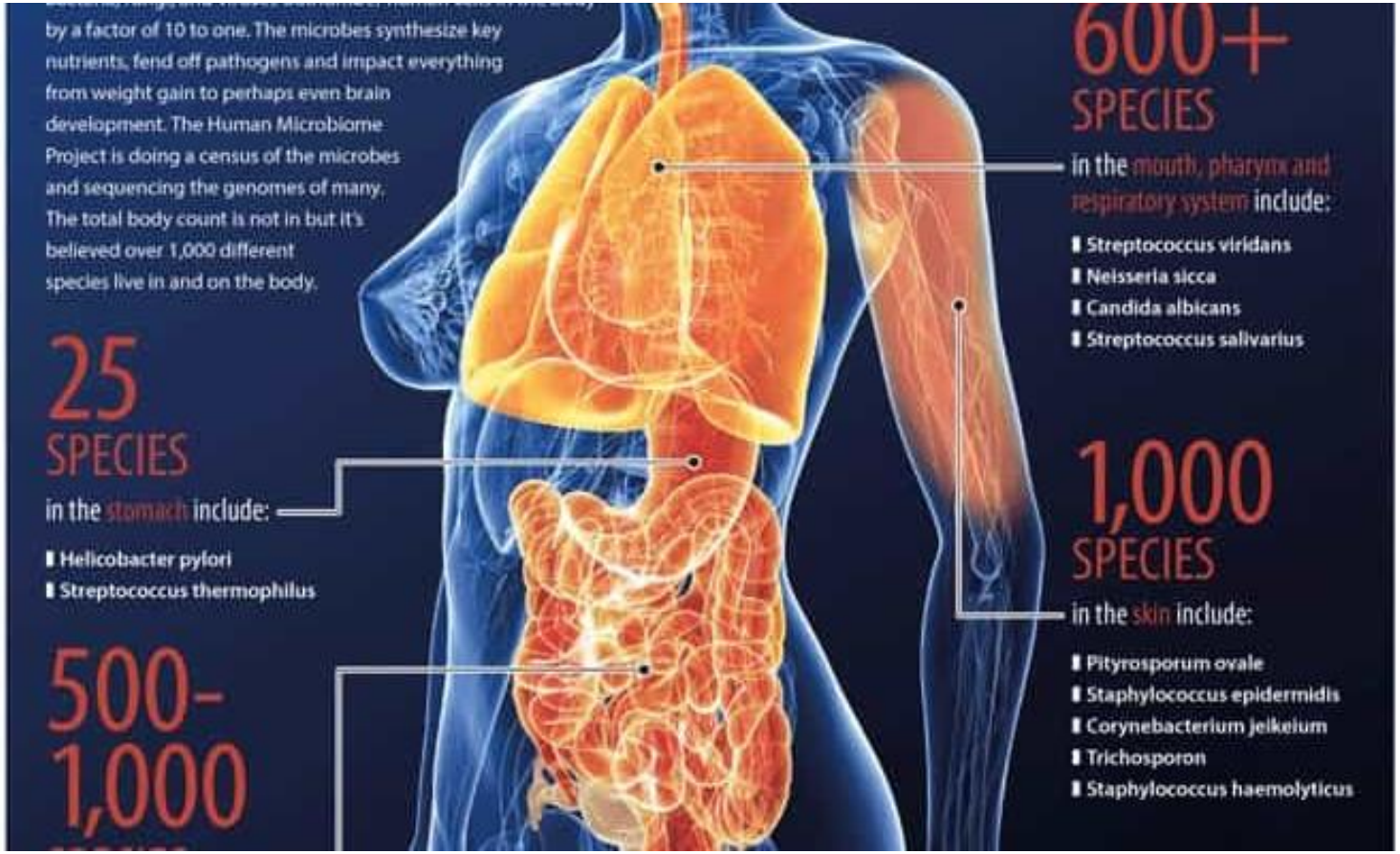

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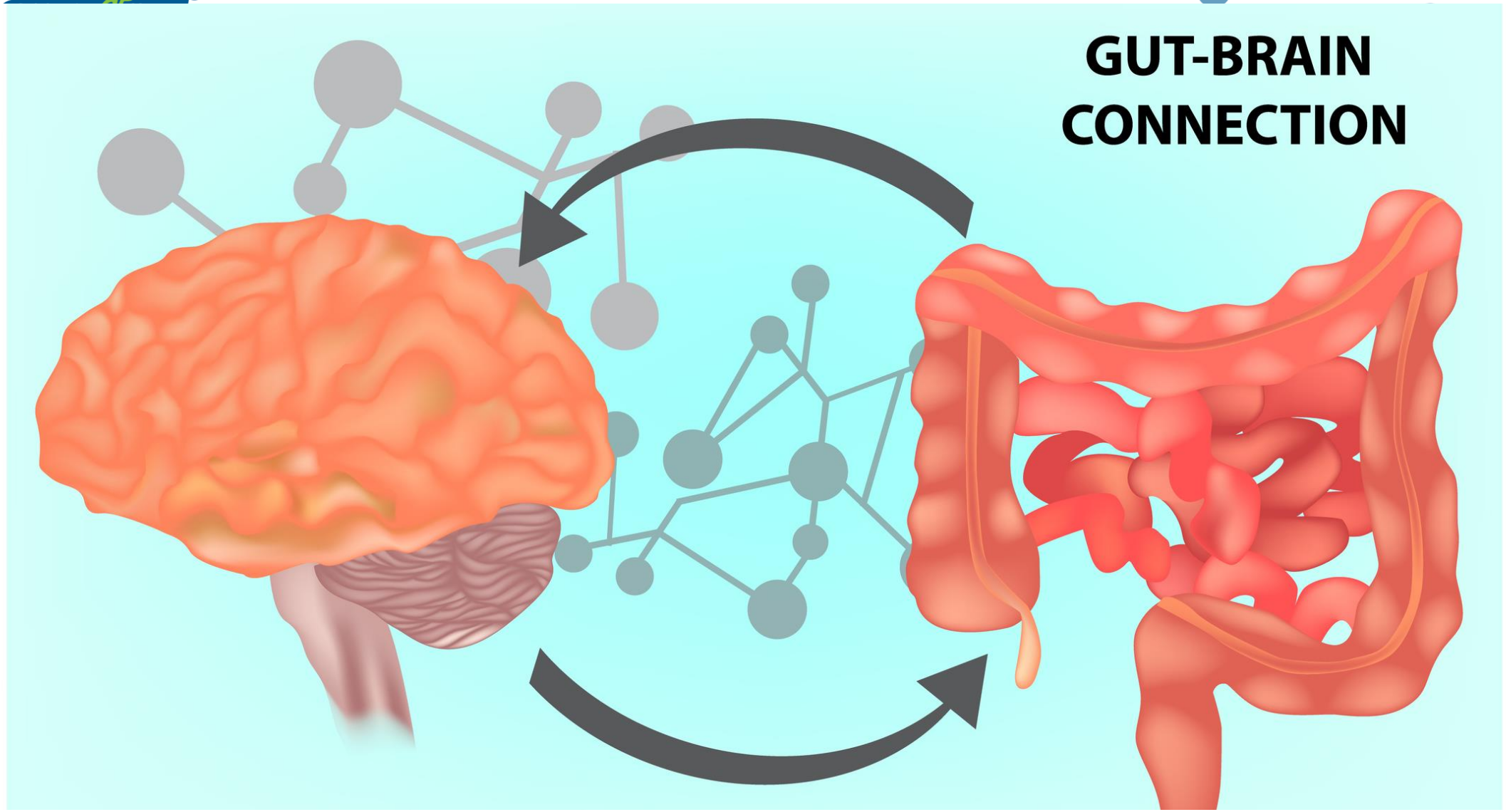


Microbiota as a source of neuroprotective nutrients

- Some essential vitamins—such as **vitamins K, B2, B9, and B12**, synthesized by microbiota—have a neuroprotective effect on the CNS.

Parker A., Fonseca S., Carding S.R. Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. *Gut Microbes.* 2019;11:135–157.

- **Vitamin K** is produced by *Escherichia coli*, *Klebsiella pneumoniae*, *Propionibacterium*, and *Eubacterium*;
- **B2** (riboflavin) by *Bacillus subtilis* and *E. coli*;
- **B9** (folic acid) by *Bifidobacterium*, *Lactococcus lactis* and *Streptococcus thermophilus*;
- **B12** (cobalamin) by *Lactobacillus reuteri* and *Propionibacterium freudenreichii*.

B vitamins and the brain

- Randomized, controlled trial (**VITACOG**) assessing the effect of B-vitamin treatment (folic acid 0.8 mg/d, vitamin B12 0.5 mg/d, vitamin B6 20 mg/d) on elderly volunteers with mild cognitive impairment (MCI) over a period of 24 mo.
- Subjects receiving B vitamins showed a **significant reduction of atrophy** compared with the placebo group in posterior brain regions including bilateral hippocampus and para-hippocampal gyrus, retro-splenial precuneus, lingual and fusiform gyrus, as well as in the cerebellum - regions most affected in AD, and also in MCI subjects who later convert to AD

Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, Smith AD. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci U S A*. 2013;110:9523–9528.

Vitamin K and the brain

- Low levels of vitamin K have been correlated with apolipoprotein Eϵ4 allele, a risk factor linked to Alzheimer's dementia.
- Allison AC. The possible role of vitamin K deficiency in the pathogenesis of Alzheimer's disease and in augmenting brain damage associated with cardiovascular disease. *Med Hypotheses*. 2001
- Vitamin K has been shown to have a beneficial role in the modulation of α-synuclein fibrillization, associated with Parkinson's disease.
- Da Silva FL, Coelho Cerqueira E, de Freitas MS, Goncalves DL, Costa LT, Follmer C. Vitamins K interact with N-terminus alpha-synuclein and modulate the protein fibrillization in vitro. Exploring the interaction between quinones and alpha-synuclein. *Neurochem Int*. 2013
- Increased dietary vitamin K intake has been associated with less severe subjective memory complaints in the elderly.
- Soutif-Veillon A, Ferland G, Rolland Y, Presse N, Boucher K, Feart C, Annweiler C. Increased dietary vitamin K intake is associated with less severe subjective memory complaint among older adults. *Maturitas*. 2016

Short Chain Fatty Acids

Acetate

- Affects body weight via appetite regulation, insulin sensitivity, increased energy expenditure and fat oxidation
- Binds to GPR 41 and GPR 43, able to enter TCA cycle, important for blood pressure regulation,
- Cross talk between muscle, liver and adipose tissue

Butyrate

- Anti-inflammatory and anti-depressant effect on brain
- Increases non-REM sleep
- Epigenetic effect – helps with transcription of pro-survival, pro-regeneration and pro-neuroplasticity genes

Propionate

- Increased levels associated with gingivitis and periodontal disease
- Low levels associated with asthma
- Excess propionate associated with motor impairments, brain atrophy, cognitive impairments and dementia

Gut microbiome and sleep

The brain sleep mechanisms and the gut flora are linked through a dynamic bidirectional relationship. Depletion of intestinal microbiota induces significant reduction in sleep suggesting that the **gut flora is a source of sleep-inducing signals**, while circadian disruption and chronic sleep fragmentation promote intestinal dysbiosis.

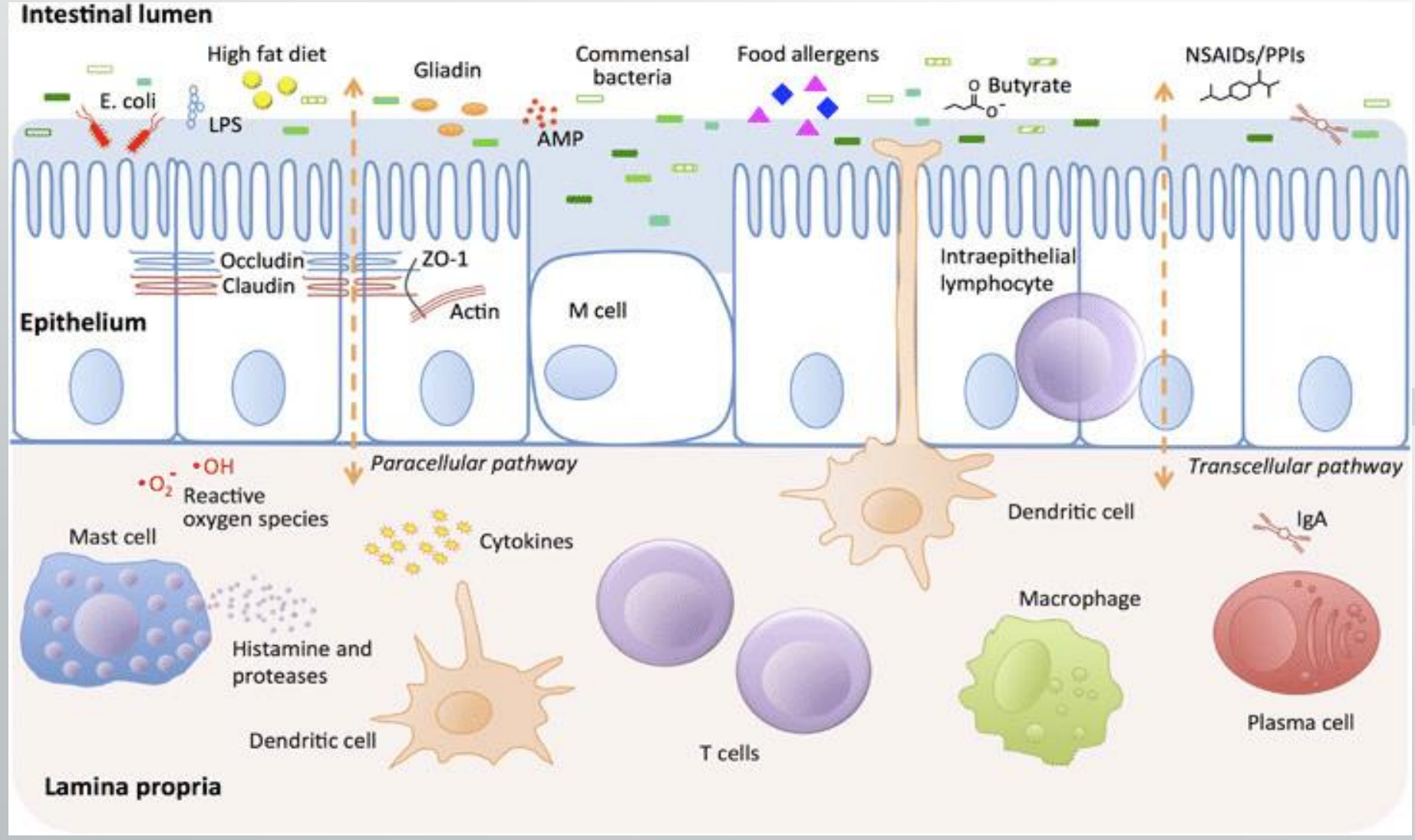
Benedict C, Vogel H, Jonas W, et al. Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. *Mol Metabol*. 2016;**5**(12):1175–1186.

Wang Z, Yuan K, Ji YB, Li SX, Shi L, Wang Z, Zhou XY, Bao YP, Xie W, Han Y, Shi J, Lu L, Yan W, Chen WH. Nature and Science of Sleep. 2022 Jan 25; 14: 121-133

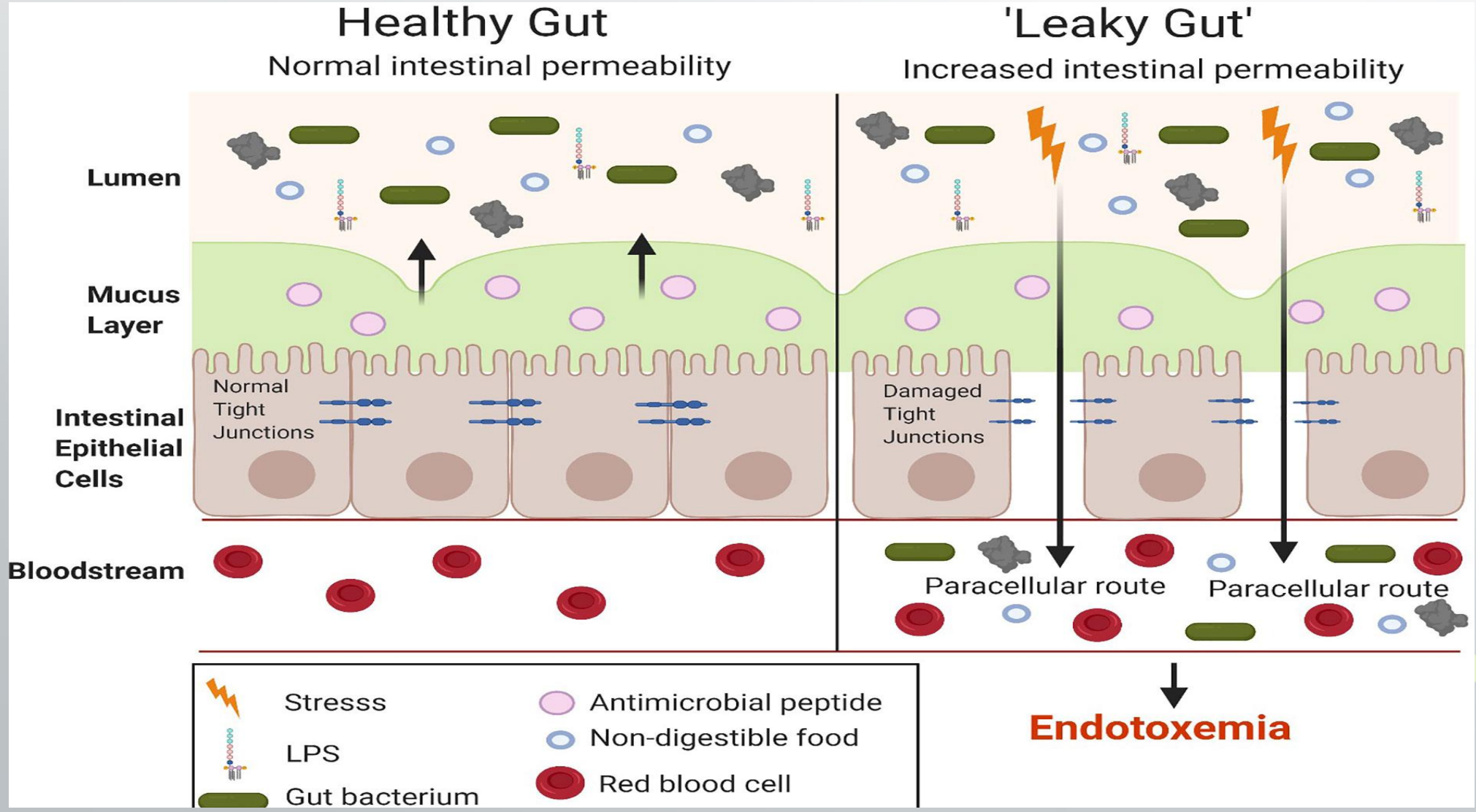
Other neuroactive microbial metabolites:

- Short-chain fatty acids (SCFAs)
- Gamma-Aminobutyric acid (GABA)
- BDNF
- Histamine
- Acetylcholine
- Serotonin
- Melatonin
- Catecholamines
- Nitric oxide

Intestinal Lining



Leaky Gut > Endotoxemia



“Leaky gut” leads to “Inflamed brain”

- In rodents, a single injection of LPS causes acute **immune activation in the brains that persists for at least 12 months**, and results in loss of dopaminergic neurons in the substantia nigra 10 months later. (Qin 2007)
- Endotoxin stimulates microglia in the brain to produce nitric oxide and pro-inflammatory cytokines. (Kinsner, 2006)
- High plasma levels of endotoxin can **increase permeability of the blood-brain barrier,** allowing toxic plasma components, including **amyloid β** and **α-synuclein** into the brain. (Vutukuri, 2018)

3 times more LPS

- Blood LPS levels in Alzheimer's patients are 3-fold the levels in control (Zhang et al, 2006)

Front Aging Neurosci. 2018; 10: 42.
Published online 2018 Feb 22. doi: 10.3389/fnagi.2018.00042
PMCID: PMC5827158
PMID: 29520228

Lipopolysaccharide Associates with Amyloid Plaques, Neurons and Oligodendrocytes in Alzheimer's Disease Brain: A Review

Xinhua Zhan,* Boryana Stamova, and Frank R. Sharp

Abstract

Go to:

This review proposes that lipopolysaccharide (LPS, found in the wall of all Gram-negative bacteria) could play a role in causing sporadic Alzheimer's disease (AD). This is based in part upon recent studies showing that: Gram-negative *E. coli* bacteria can form extracellular amyloid; bacterial-encoded 16S rRNA is present in all human brains with over 70% being Gram-negative bacteria; ultrastructural analyses have shown microbes in erythrocytes of AD patients; blood LPS levels in AD patients are 3-fold the levels in control; LPS combined with focal cerebral ischemia and hypoxia produced amyloid-like plaques and myelin injury in adult rat cortex. Moreover, Gram-negative bacterial LPS was found in aging control and AD brains, though LPS levels were much higher in AD brains. In addition, LPS co-localized with amyloid plaques, peri-vascular amyloid, neurons, and oligodendrocytes in AD brains. Based upon the postulate LPS caused oligodendrocyte injury, degraded Myelin Basic Protein (dMBP) levels were found to be much higher in AD compared to control brains. Immunofluorescence showed that the dMBP co-localized with β amyloid (Aβ) and LPS in amyloid plaques in AD brain, and dMBP and other myelin molecules were found in the walls of

LPS higher in Parkinson's, ALS and Autism

- Parkinson's disease patients have increased gastrointestinal and a proportion of Parkinson's patients have elevated blood endotoxin.(Forsyth et al. 2011)

  - Serum endotoxin levels are elevated in patients with severe autism (Emanuele et al, 2010)
  - LPS higher in amyotrophic lateral sclerosis (Zhang et al. 2009)

Journal List › J Neuroinflammation › v.16; 2019 › PMC6744684

Journal of Neuroinflammation BMC

J Neuroinflammation. 2019; 16: 180.
Published online 2019 Sep 13. doi: 10.1186/s12974-019-1564-7

PMCID: PMC6744684
PMID: 31519175

The endotoxin hypothesis of neurodegeneration

Guy C. Brown

Author information · Article notes · Copyright and License information Disclaimer

This article has been cited by other articles in PMC.

Associated Data

Data Availability Statement

Abstract

Go to:

The endotoxin hypothesis of neurodegeneration is the hypothesis that endotoxin causes or contributes to neurodegeneration. Endotoxin is a lipopolysaccharide (LPS), constituting much of the outer membrane of gram-negative bacteria, present at high concentrations in gut, gums and skin and in other tissue during bacterial infection. Blood plasma levels of endotoxin are normally low, but are elevated during infections, gut inflammation, gum disease and neurodegenerative disease. Adding endotoxin at such levels to blood of healthy humans induces systemic inflammation and brain microglial activation. Adding high levels of endotoxin to the blood or body of rodents induces microglial activation, priming and/or tolerance, memory deficits and loss of brain synapses and neurons. Endotoxin promotes amyloid β and tau aggregation and

Serum LPS, depression and anxiety

- LPS predictive of depression/anxiety disorders as well as severity of depression and anxiety.

Published in final edited form as:
Gut. 2018 August ; 67(8): 1555–1557. doi:10.1136/gutjnl-2017-314759.

Increased human intestinal barrier permeability plasma biomarkers zonulin and FABP2 correlated with plasma LPS and altered gut microbiome in anxiety or depression

Bruce R Stevens[1,2], **Ruby Goel**[1], **Kim Seungbum**[1], **Elaine M Richards**[1], **Richard C Holbert**, **Carl J Pepine**[3], and **Mohan K Raizada**[1]

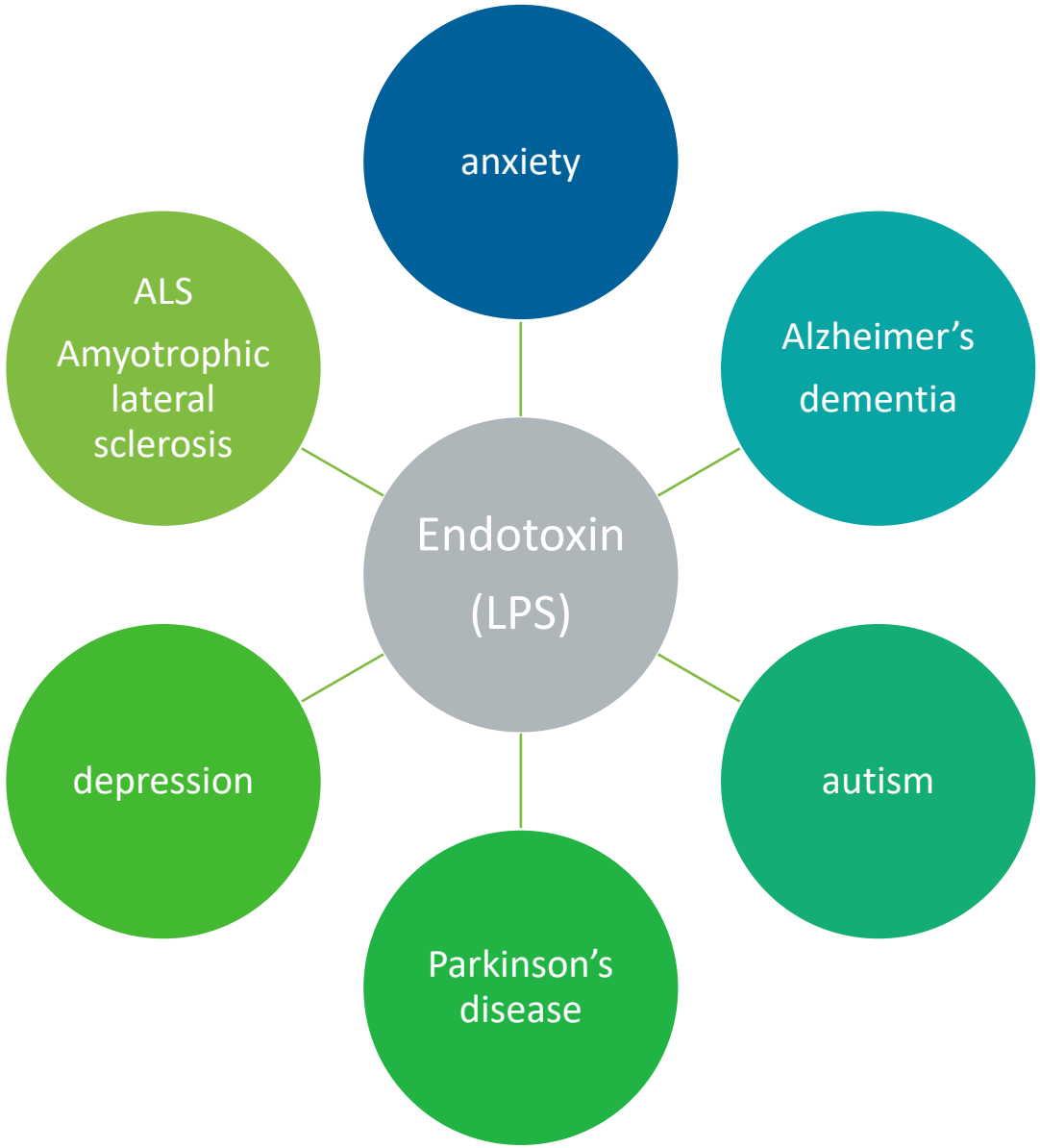
[1]Department of Physiology & Functional Genomics, University of Florida College of Medicine, Gainesville, Florida, USA

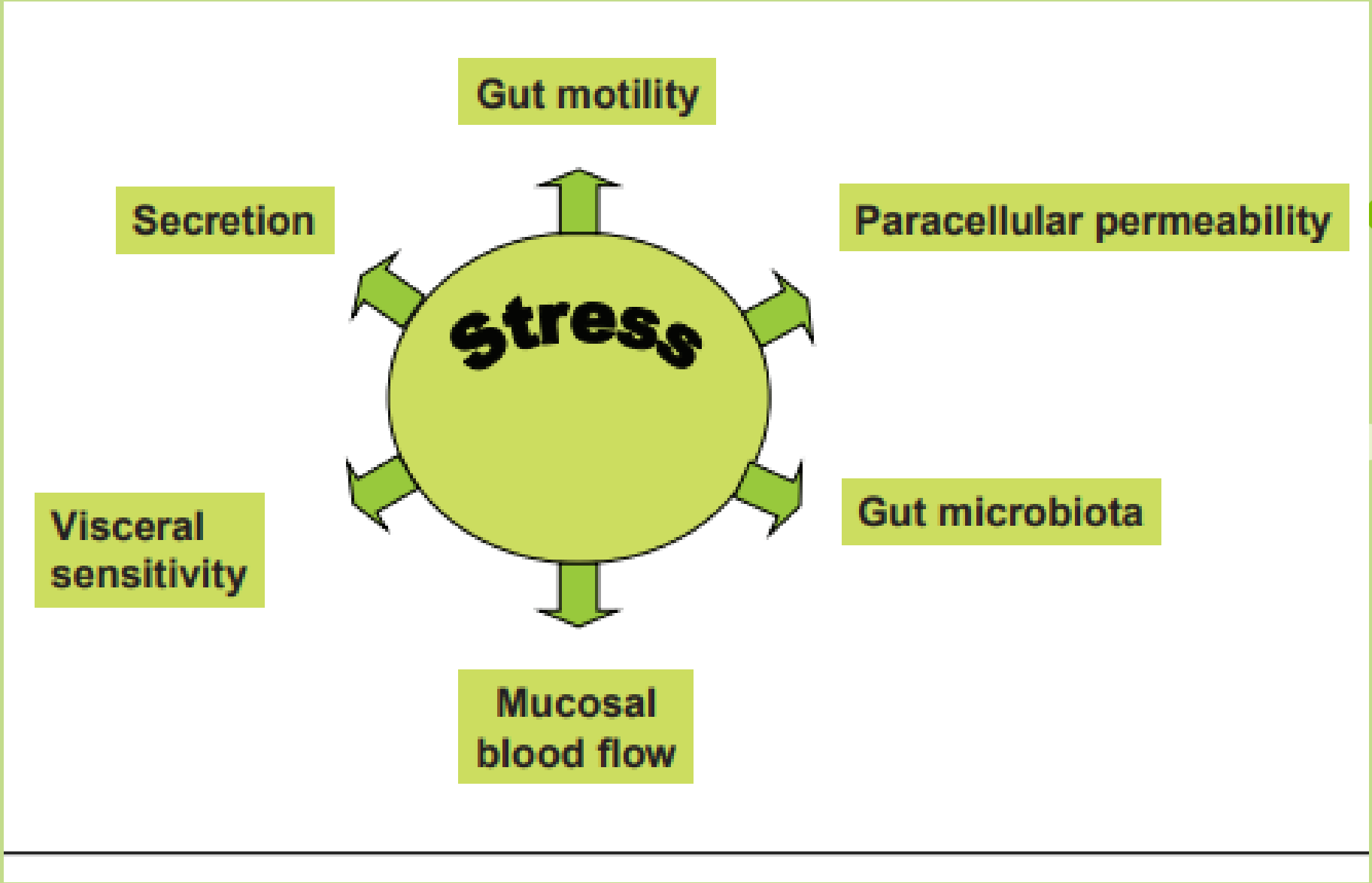
[2]Department of Psychiatry, University of Florida College of Medicine, Gainesville, Florida, USA

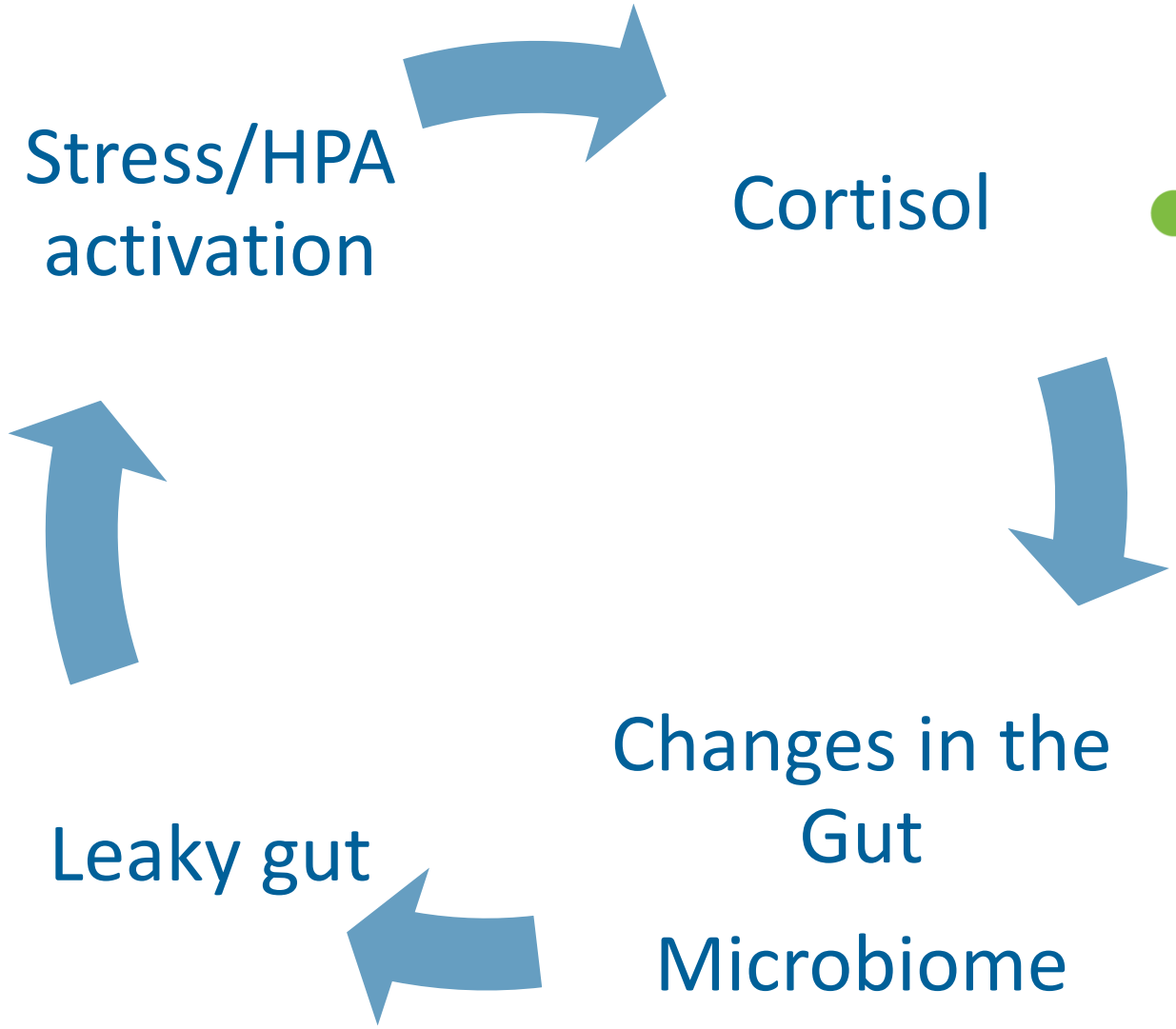
[3]Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, Florida, USA

We read with interest the recent work by Uhde *et al*,[1] which demonstrated that physically asymptomatic non-coeliac gluten/wheat sensitivity involves compromised intestinal epithelium barrier dysfunction in conjunction with systemic immune activation events. We also read with interest the recent work by Marchesi *et al*,[2] which comprehensively reviewe the role of microbiota in physical disorders of the gut and extra-gut organs.

But common to these *Gut* papers was the lack of accounting for anxiety and depression, comorbidities often experienced in gastroenterology clinics. Patients who are otherwise physically asymptomatic often do not explicitly divulge these mental disorders, or the disorders are unintentionally overlooked, yet they report ‘diminished quality of life’.


anxiety
ALS
Amyotrophic lateral sclerosis
Alzheimer's dementia
Endotoxin (LPS)
depression
autism
Parkinson's disease


Gut motility
Secretion
Paracellular permeability
Stress
Visceral sensitivity
Gut microbiota
Mucosal blood flow


Stress/HPA activation
Cortisol
Changes in the Gut Microbiome
Leaky gut

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Stress and intestinal permeability

Gut. 2014 Aug;63(8):1293-9. doi: 10.1136/gutjnl-2013-305690. Epub 2013 Oct 23.

Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism

Tim Vanuytsel [1], Sander van Wanrooy [2], Hanne Vanheel [2], Christophe Vanormelingen [2], Sofie Verschueren [2], Els Houben [2], Shadea Salim Rasoel [2], Joran Tóth [2], Lieselot Holvoet [2], Ricard Farré [2], Lukas Van Oudenhove [2], Guy Boeckxstaens [1], Kristin Verbeke [2], Jan Tack [1]

Affiliations + expand

PMID: 24153250 DOI: 10.1136/gutjnl-2013-305690

Abstract

Objective: Intestinal permeability and psychological stress have been implicated in the pathophysiology of IBD and IBS. Studies in animals suggest that stress increases permeability via corticotropin-releasing hormone (CRH)-mediated mast cell activation. Our aim was to investigate the effect of stress on intestinal permeability in humans and its underlying mechanisms.

Design: Small intestinal permeability was quantified by a 2 h lactulose-mannitol urinary excretion test. In a first study, 23 healthy volunteers were subjected to four different conditions: control; indomethacin; public speech and anticipation of electroshocks. In a second study, five test conditions were investigated in 13 volunteers: control; after pretreatment with disodium cromoglycate (DSCG); administration of CRH; DSCG+CRH and DSCG+public speech.

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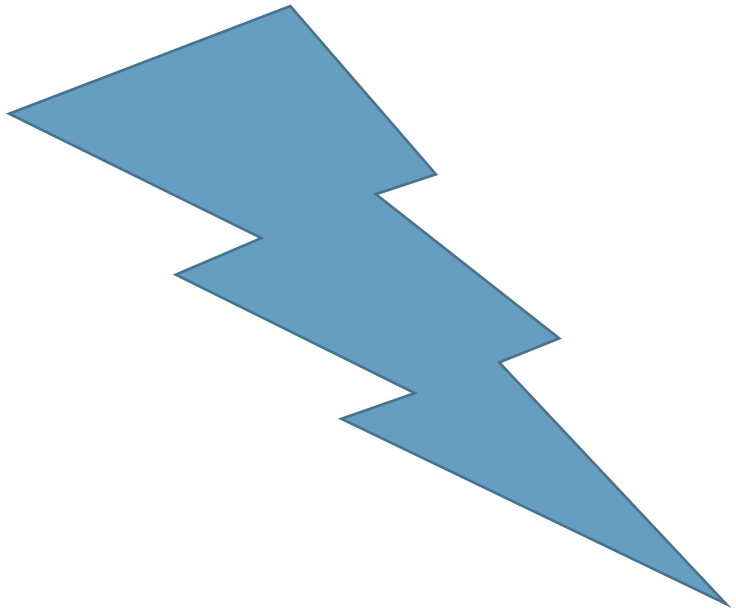
Stress



Review > Neurosci Biobehav Rev. 2020 Oct;117:26-64. doi: 10.1016/j.neubiorev.2017.07.003. Epub 2017 Jul 28.

Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy

Bea R H Van den Bergh [1], Marion I van den Heuvel [2], Marius Lahti [3], Marijke Braeken [4], Susanne R de Rooij [5], Sonja Entringer [6], Dirk Hoyer [7], Tessa Roseboom [8], Katri Räikkönen [9], Suzanne King [10], Matthias Schwab [11]

Affiliations + expand

PMID: 28757456 DOI: 10.1016/j.neubiorev.2017.07.003

Abstract

Accumulating research shows that prenatal exposure to maternal stress increases the risk for behavioral and mental health problems later in life. This review systematically analyzes the available human studies to identify harmful stressors, vulnerable periods during pregnancy, specificities in the outcome and biological correlates of the relation between maternal stress and offspring outcome.

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Front Psychol. 2011 Jan 19;1:223. doi: 10.3389/fpsyg.2010.00223. eCollection 2010.

Prenatal Maternal Stress Associated with ADHD and Autistic Traits in early Childhood

Angelica Ronald [1], Craig E Pennell, Andrew J O Whitehouse

Affiliations + expand

PMID: 21833278 PMCID: PMC3153828 DOI: 10.3389/fpsyg.2010.00223

Free PMC article

ADHD

Abstract

Research suggests that offspring of mothers who experience high levels of stress during pregnancy are more likely to have problems in neurobehavioral development. There is preliminary evidence that prenatal maternal stress (PNMS) is a risk factor for both autism and attention deficit hyperactivity disorder (ADHD), however most studies do not control for confounding factors and no study has investigated PNMS as a risk factor for behaviors characteristic of these disorders in early childhood. A population cohort of 2900 pregnant women were recruited before their 18th week of pregnancy and investigated prospectively. Maternal experience of stressful life events was assessed during pregnancy. When offspring were age 2 years, mothers completed the child behavior checklist. Multiple regression showed that maternal stressful events during pregnancy significantly predicted ADHD behaviors in offspring, after controlling for autistic traits and other confounding variables, in

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Psychiatry Res. 2014 Oct 30;219(2):353-60. doi: 10.1016/j.psychres.2014.04.034. Epub 2014 May 10.

Prenatal maternal stress predicts autism traits in 6½ year-old children: Project Ice Storm

Deborah J Walder [1], David P Laplante [2], Alexandra Sousa-Pires [2], Franz Veru [3], Alain Brunet [3], Suzanne King [4]

Affiliations + expand

PMID: 24907222 DOI: 10.1016/j.psychres.2014.04.034

Autism

LT

Abstract

Research implicates prenatal maternal stress (PNMS) as a risk factor for neurodevelopmental disorders; however few studies report PNMS effects on autism risk in offspring. We examined, prospectively, the degree to which objective and subjective elements of PNMS explained variance in autism-like traits among offspring, and tested moderating effects of sex and PNMS timing in utero. Subjects were 89 (46F/43M) children who were in utero during the 1998 Quebec Ice Storm. Soon after the storm, mothers completed questionnaires on objective exposure and subjective distress, and completed the Autism Spectrum Screening Questionnaire (ASSQ) for their children at age 6½. ASSQ scores were higher among boys than girls. Greater objective and subjective PNMS predicted higher

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Anxiety

Psychoneuroendocrinology. 2020 Aug;118:104716. doi: 10.1016/j.psyneuen.2020.104716. Epub 2020 May 16.

Disaster-related prenatal maternal stress, and childhood HPA-axis regulation and anxiety: The QF2011 Queensland Flood Study

Mia A McLean [1], Gabrielle Simcock [2], Guillaume Elgbeili [3], David P Laplante [4], Sue Kildea [5], Elizabeth Hurrion [6], Belinda Lequertier [1], Vanessa E Cobham [1], Suzanne King [7]

Affiliations + expand

PMID: 32479967 DOI: 10.1016/j.psyneuen.2020.104716

Abstract

Background: The fetal programming hypothesis suggests that prenatal maternal stress (PNMS) influences aspects of fetal development, such as the Hypothalamic Pituitary Adrenal (HPA) axis, enhancing susceptibility to emotional problems. No study (to our knowledge) has investigated this pathway considering development of preschool anxiety symptoms. Using data from the Queensland Flood study (QF2011), our objective was to determine whether toddler HPA-axis functioning mediated the association between aspects of flood-related PNMS and child anxiety symptoms at 4-years, and whether relationships were moderated by the timing of the stressor in utero or by the child's sex.

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Review > Int Rev Neurobiol. 2020;150:17-40. doi: 10.1016/bs.irn.2019.11.002. Epub 2019 Dec 14.

Prenatal stress: Effects on fetal and child brain development

Alexandra Lautarescu [1], Michael C Craig [2], Vivette Glover [3]

Affiliations + expand

PMID: 32204831 DOI: 10.1016/bs.irn.2019.11.002

Depression

Abstract

The impact of stress on brain health begins in the womb. Both animal and human studies have found that prenatal maternal stress affects the brain and behavior of the offspring. Stressful life events, exposure to a natural disaster, and symptoms of maternal anxiety and depression increase the risk for the child having a range of emotional, behavioral and/or cognitive problems in later life. These include depression, anxiety, Attention Deficit Hyperactivity Disorder (ADHD), and/or conduct disorders. There is an increased risk for other outcomes also, including preterm delivery and reduced telomere length, possibly indicative of an accelerated life history. The causal role of prenatal maternal stress on the etiology of the neurodevelopmental disorders is supported by large population cohorts, which have controlled for a wide range of potential confounders, including postnatal maternal mood.

Developmental **O**rigins of **H**ealth **a**nd **D**isease (DOHaD)

- DOHaD postulates that adverse events during gestation/early postnatal life are responsible for fetal programming of the structure and function of cells, tissues, and organs, leading to permanent alterations in the individual's physiology that then predispose the individual to a plethora of health conditions, including behavioral and cognitive disorders.

Gluckman PD, Buklijas T, Hanson MA, 2016. Chapter 1 - The Developmental Origins of Health and Disease (DOHaD) Concept: Past, Present, and Future, In: Rosenfeld CS (Ed.), *The Epigenome and Developmental Origins of Health and Disease*


Help!

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What we feed our babies…

- Breast milk is crucial for the gut microbiome

What we Feed Ourselves…

- The MIND dietary pattern is a combination of the Mediterranean diet and the DASH diet and is based on dietary components that have been shown to be neuroprotective. The MIND diet **emphasizes natural plant-based foods** and limited intakes of animal foods and foods high in saturated fat. Uniquely, the MIND diet also specifies the consumption of **berries** and **green leafy vegetables**

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Review > Neurosci Lett. 2016 Jun 20;625:56-63. doi: 10.1016/j.neulet.2016.02.009.
Epub 2016 Feb 8.

Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health?

Megan W Bourassa [1], Ishraq Alim [1], Scott J Bultman [2], Rajiv R Ratan [3]

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PMID: 26868600 PMCID: PMC4903954 DOI: 10.1016/j.neulet.2016.02.009

Free PMC article

Fiber, Prebiotics

Abstract

As interest in the gut microbiome has grown in recent years, attention has turned to the impact of our diet on our brain. The benefits of a high fiber diet in the colon have been well documented in epidemiological studies, but its potential impact on the brain has largely been understudied. Here, we will review evidence that butyrate, a short-chain fatty acid (SCFA) produced by bacterial fermentation of fiber in the colon, can improve brain health. Butyrate has been extensively studied as a histone deacetylase (HDAC) inhibitor but also functions as a ligand for a subset of G protein-coupled receptors and as an energy metabolite. These diverse modes of action make it well suited for solving the wide array of imbalances frequently encountered in neurological disorders. In this review, we will integrate evidence from the disparate fields of gastroenterology and neuroscience to hypothesize that the metabolism of a high fiber diet in the gut can alter gene expression in the brain to prevent neurodegeneration and promote regeneration.

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Probiotics to the rescue!

Brain Behav Immun. 2019 Oct;81:198-212. doi: 10.1016/j.bbi.2019.06.016. Epub 2019 Jun 15.

Probiotic consumption during puberty mitigates LPS-induced immune responses and protects against stress-induced depression- and anxiety-like behaviors in adulthood in a sex-specific manner

Emma Murray [1], Rupali Sharma [1], Kevin B Smith [1], Kendall D Mar [1], Rudra Barve [1], Matthew Lukasik [1], Atiqa F Pirwani [1], Etienne Malette-Guyon [1], Sanjeevani Lamba [2], Bronwen J Thomas [2], Homa Sadeghi-Emamchaie [1], Jacky Liang [1], Jean-François Mallet [3], Chantal Matar [4], Nafissa Ismail [5]

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PMID: 31212008 DOI: 10.1016/j.bbi.2019.06.016

Abstract

Puberty/adolescence is a significant period of development and a time with a high emergence of psychiatric disorders. During this period, there is increased neuroplasticity and heightened vulnerability to stress and inflammation. The gut microbiome regulates stress and inflammatory responses and can alter brain chemistry and behaviour. However, the role of the gut microbiota during pubertal development remains largely uninvestigated. The current study examined gut manipulation with probiotics during puberty in CD1 mice on lipopolysaccharide (LPS)-induced immune responses and enduring effects on anxiety- and depression-like behaviours and stress-reactivity in adulthood. Probiotics reduced LPS-induced sickness behaviour at 12 h in females and at 48 h following LPS treatment in males. Probiotics also reduced LPS-induced changes in body weight at 48 h post-treatment in females. Probiotic treatment also prevented LPS-induced increases in pro- and anti-inflammatory peripheral cytokines at 8 h following LPS treatment, reduced central cytokine

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Psycho biotics

Review > Prog Neuropsychopharmacol Biol Psychiatry. 2021 Mar 8;105:110142.
doi: 10.1016/j.pnpbp.2020.110142. Epub 2020 Oct 15.

The effects of psychobiotics on the microbiota-gut-brain axis in early-life stress and neuropsychiatric disorders

Annie Tremblay [1], Lucie Lingrand [2], Morgane Maillard [2], Berengere Feuz [2], Thomas A Tompkins [3]

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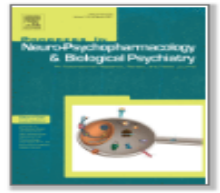
PMID: 33069817 DOI: 10.1016/j.pnpbp.2020.110142

Free article

Abstract

Psychobiotics are considered among potential avenues for modulating the bidirectional communication between the gastrointestinal tract and central nervous system, defined as the microbiota-gut-brain axis (MGBA). Even though causality has not yet been established, intestinal dysbiosis has emerged as a hallmark of several diseases, including neuropsychiatric disorders (NPDs). The fact that the microbiota and central nervous system are co-developing during the first years of life has provided a paradigm suggesting a potential role of psychobiotics for earlier interventions.

Progress in Neuro-Psychopharmacology and Biological Psychiatry
Volume 105, 8 March 2021, 110142



The effects of psychobiotics on the microbiota-gut-brain axis in early-life stress and neuropsychiatric disorders

Annie Tremblay [a], Lucie Lin

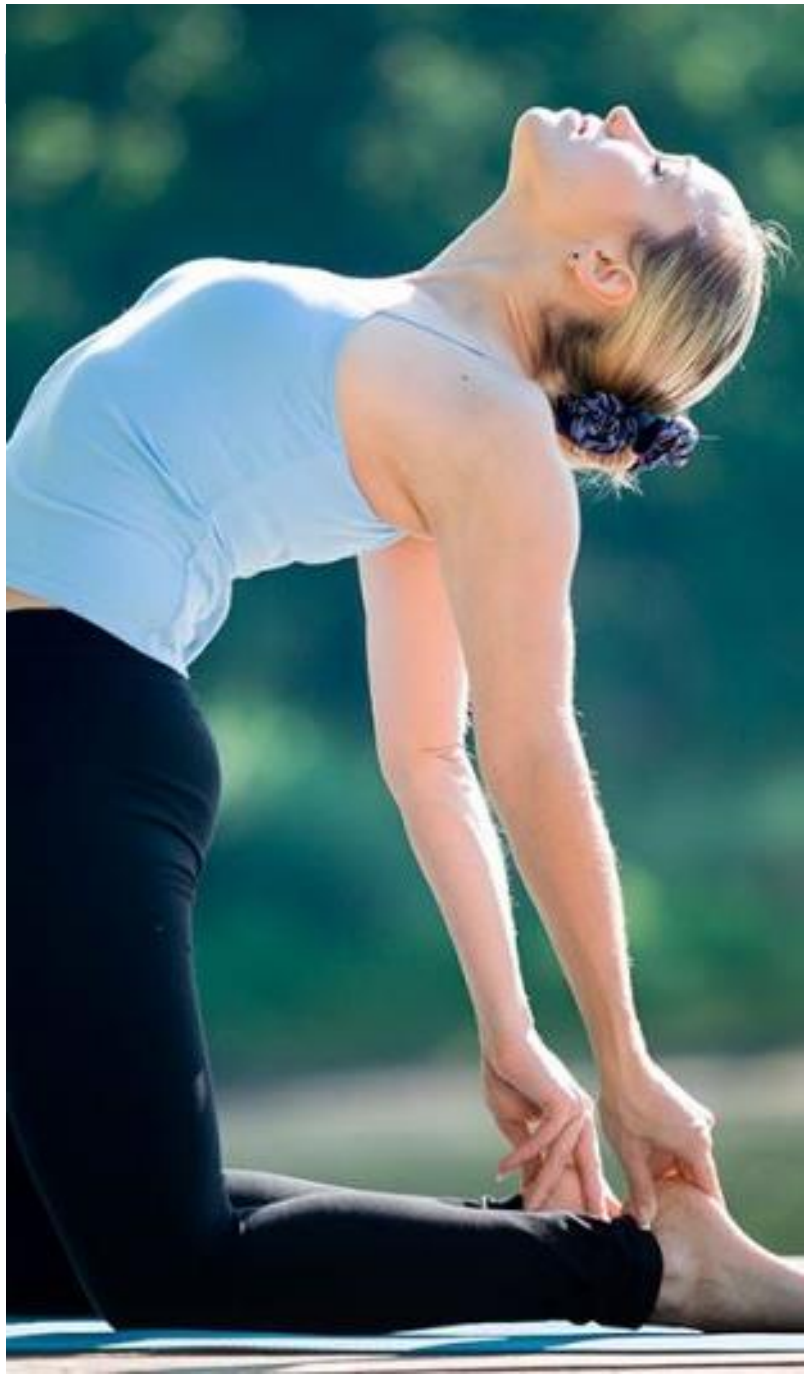
Review > Nutrients. 2019 Apr 20;11(4):890. doi: 10.3390/nu11040890.

From Probiotics to Psychobiotics: Live Beneficial Bacteria Which Act on the Brain-Gut Axis

Luis G Bermúdez-Humarán [1], Eva Salinas [2], Genaro G Ortiz [3], Luis J Ramirez-Jirano [4], J Alejandro Morales [5], Oscar K Bitzer-Quintero [6]

Affiliations + expand

PMID: 31010014 PMCID: PMC6521058 DOI: 10.3390/nu11040890



Thank you!

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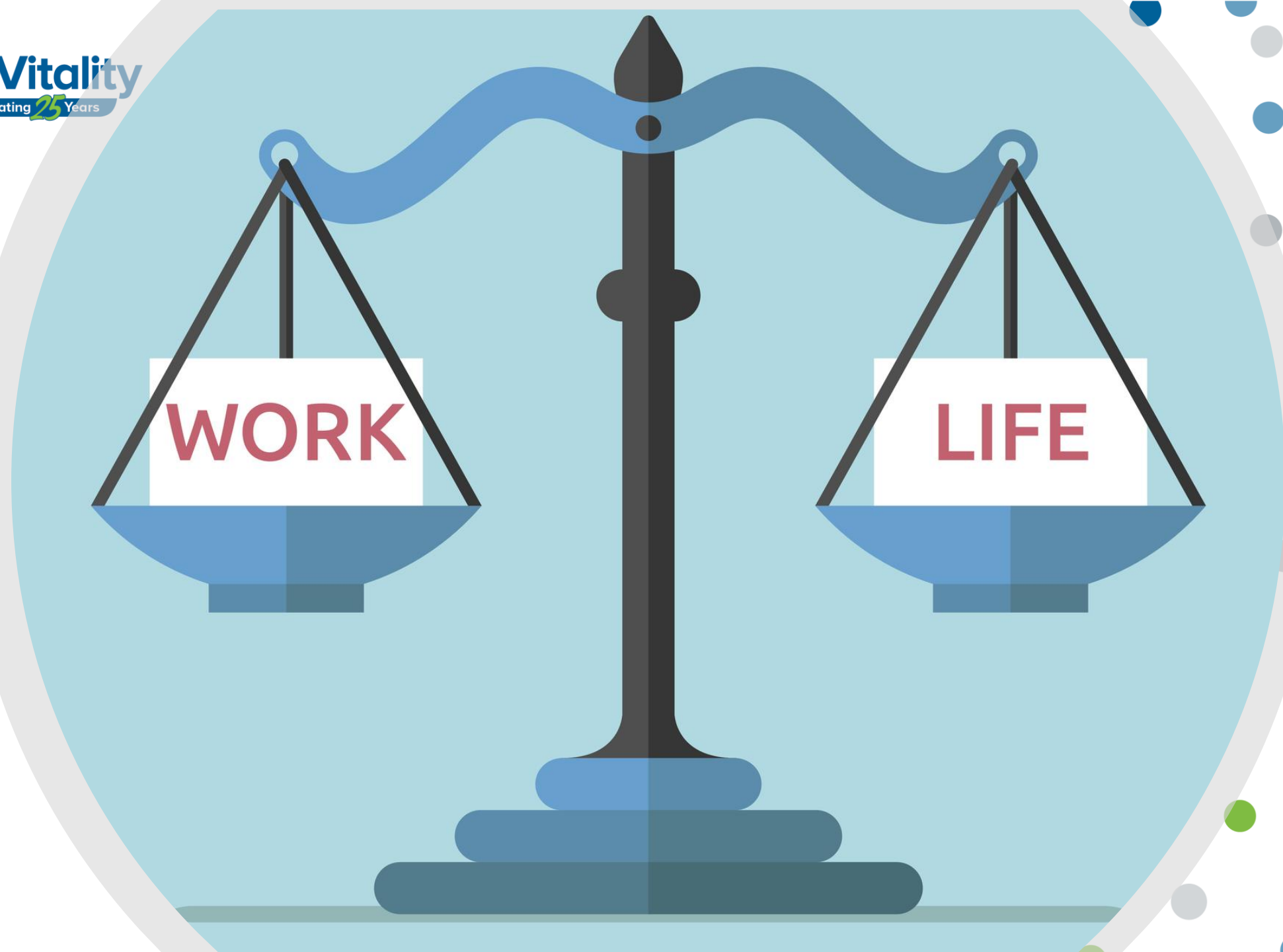

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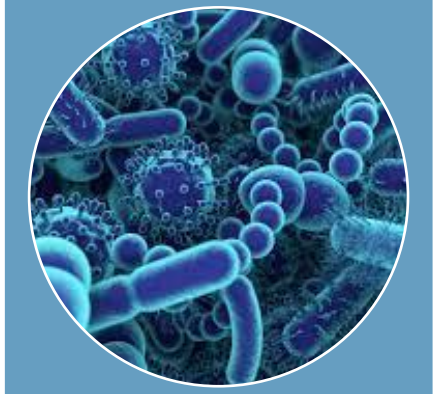
Diet, Lifestyle and Environment



Microbiome

Gut permeability

Brain

Artificial sweeteners cause leaky gut

- Intestinal epithelial homeostasis is established by equilibrium between cell proliferation and cell death, with dysregulated or excessive epithelial cell death associated with diseases of impaired barrier integrity and leakage across the paracellular space.
- Diseases associated with a leaky gut, such as Crohn's disease and ulcerative colitis, have been demonstrated to impact the expression of claudins in the small and large intestine
- **At high concentrations, aspartame and saccharin were found to induce apoptosis and cell death in intestinal epithelial cells**, while **at low concentrations, sucralose and aspartame increased epithelial barrier permeability and down-regulated claudin 3 at the cell surface**. (Aparna Shil, Nutrients 2020)

Fillers in artificial sweeteners (AS)

- There is evidence that artificial sweeteners influence inflammation pathways. Owing to the potent sweetening effect of most AS and bitterness/lingering aftertaste, most commercial products contain a commercial proprietary blend of two or more AS. Commercial AS also contain fillers such as **maltodextrin** comprising 95–99% of the product to add weight and volume, or anti-caking agents such as **silica**. While these substances are considered innocuous in small quantities, several studies indicate that such fillers could also promote intestinal inflammation and changes in gut microbiota.

Western diet > leaky gut

- There is increasing evidence that the **consumption of a high-fat diet and excessive alcohol intake leads to increased intestinal permeability and metabolic endotoxemia.** (Moreira A.P., Texeira T.F., Ferreira A.B., Peluzio Mdo C., Alfenas Rde C. Influence of a High-Fat Diet on Gut Microbiota, Intestinal Permeability and Metabolic Endotoxaemia. *Br. J. Nutr.* 2012;108:801–809.)

Dysbiosis

- Microbial-derived toxins like 4EPS and cresol are found to be related to autism, and recently to inhibit myelin gene expression. This shows a correlation of the microbiome to neuroplasticity and early as well as long-term brain development