Anxiety, Acuity, Attention: Heading off Neuro Dysfunction Pt. II

A Biogenetix Clinical Presentation

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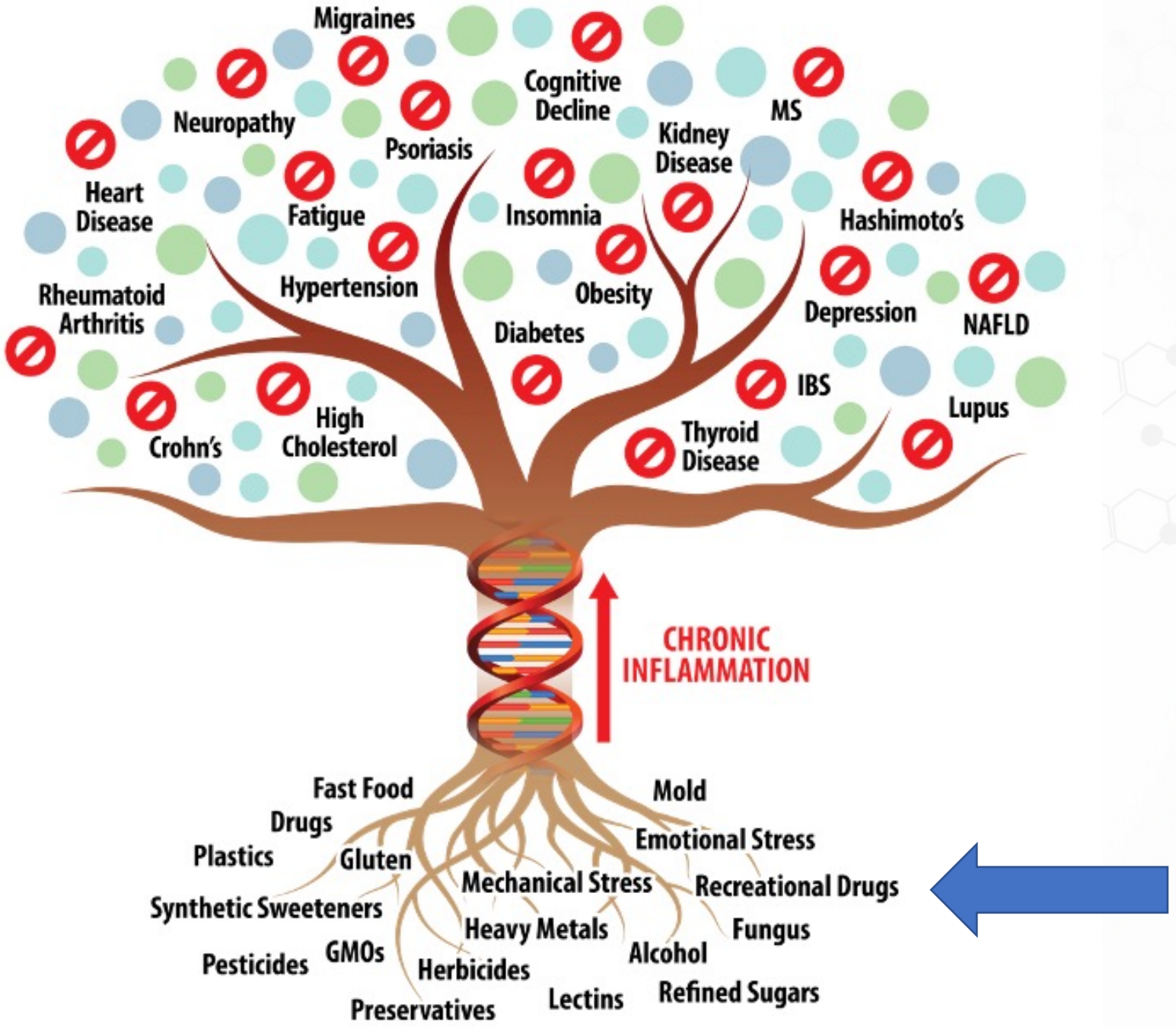
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*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Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
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Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives

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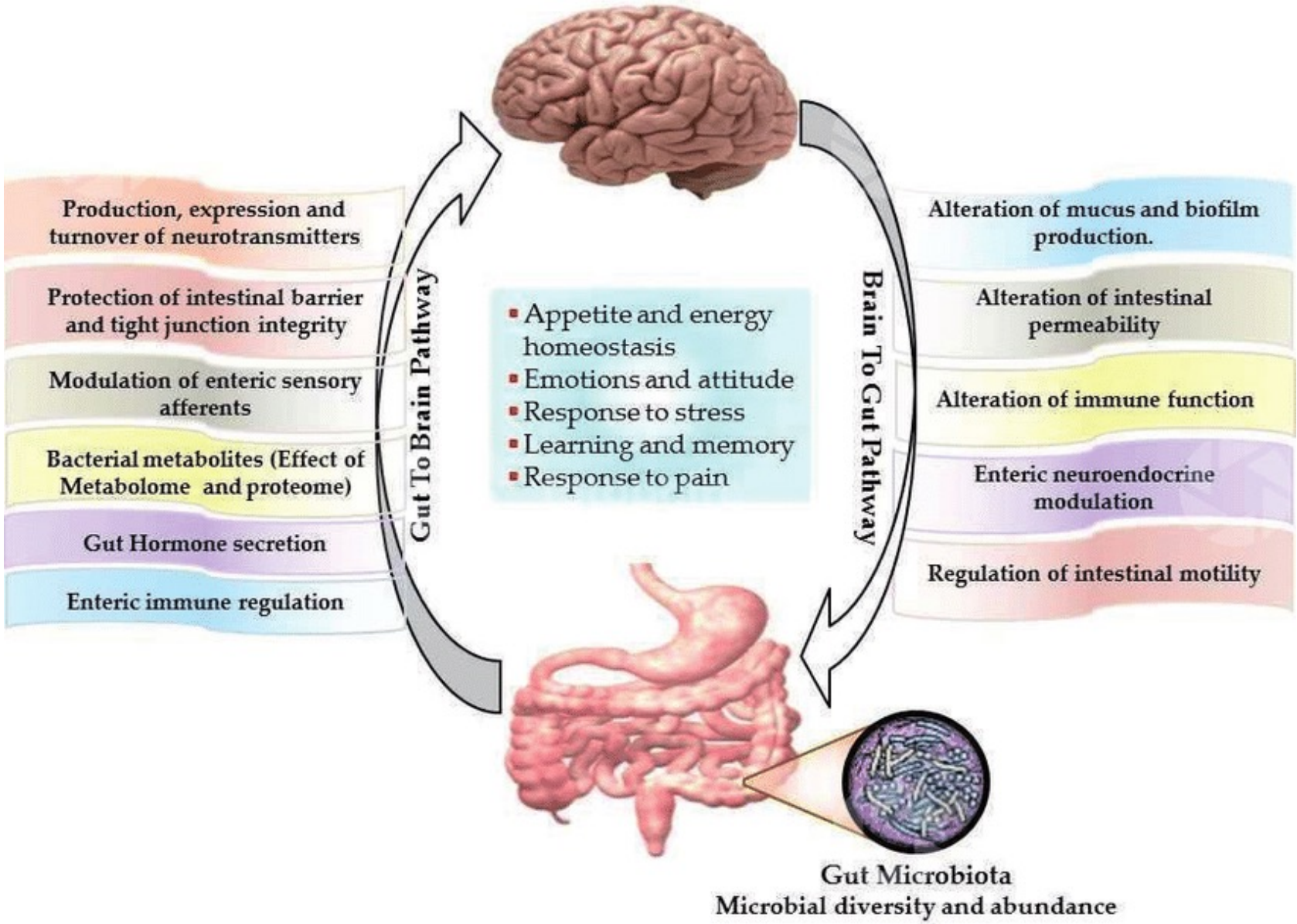
PMID: 37111321

Gut Microbiota in Anxiety and Depression: Unveiling the Relationships and Management Options

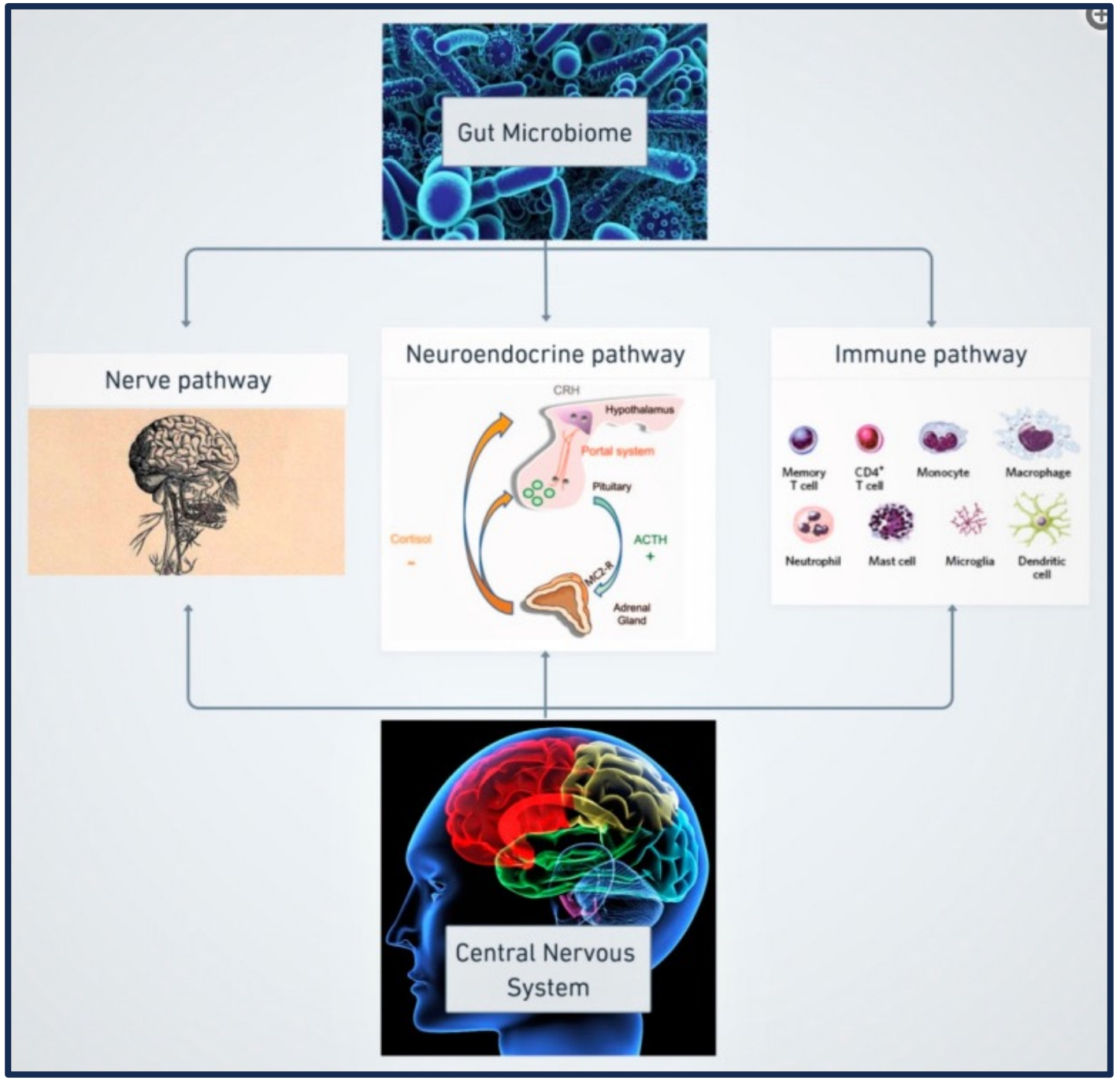
Akash Kumar,[1] Jhilam Pramanik,[2] Nandani Goyal,[3] Dimple Chauhan,[4] Bhagavathi Sundaram Sivamaruthi,[5,6] Bhupendra G. Prajapati,[7,*] and Chaiyavat Chaiyasut[6,*]

Woo-Yang Kim, Academic Editor

The gut microbiota is critical for maintaining human health and the immunological system. Several neuroscientific studies have shown the significance of microbiota in developing brain systems. The gut microbiota and the brain are interconnected in a bidirectional relationship, as research on the microbiome–gut–brain axis shows. Significant evidence links anxiety and depression disorders to the community of microbes that live in the gastrointestinal system. Modified diet, fish and omega-3 fatty acid intake, macro- and micro-nutrient intake, prebiotics, probiotics, synbiotics, postbiotics, fecal microbiota transplantation, and 5-HTP regulation may all be utilized to alter the gut microbiota as a treatment approach. There are few preclinical and clinical research studies on the effectiveness and reliability of various therapeutic approaches for depression and anxiety. This article highlights relevant research on the association of gut microbiota with depression and anxiety and the different therapeutic possibilities of gut microbiota modification.



https://www.researchgate.net/publication/337361132/figure/fig1/AS:826950981525513@1574171886318/The-bidirectional-pathways-of-the-gut-to-brain-axis-and-their-effects-Modulation-of-the.ppm



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7830868/

Medscape Medical News

ADHD Symptoms Linked With Physical Comorbidities

Anne-Gaëlle Moulun
January 15, 2024

Investigators from the French Health and Medical Research Institute (INSERM), University of Bordeaux, and Charles Perrens Hospital, alongside their Canadian, British, and Swedish counterparts, have shown that attention deficit disorder hyperactivity disorder (ADHD) or attention deficit disorder without hyperactivity is linked with physical health problems. Cédric Galéra, MD, PhD, child and adolescent psychiatrist and epidemiologist at the Bordeaux Population Health Research Center (INSERM/University of Bordeaux) and the Charles Perrens Hospital, explained these findings to *Medscape Medical News*.

A Bilateral Association

ADHD is a neurodevelopmental condition that develops in childhood and is characterized by high levels of inattention or agitation and impulsiveness. Some studies have revealed a

Long-Term Use of ADHD Meds and CVD Risk: New Data

Megan Brooks
November 22, 2023

Added to Email Alerts

17

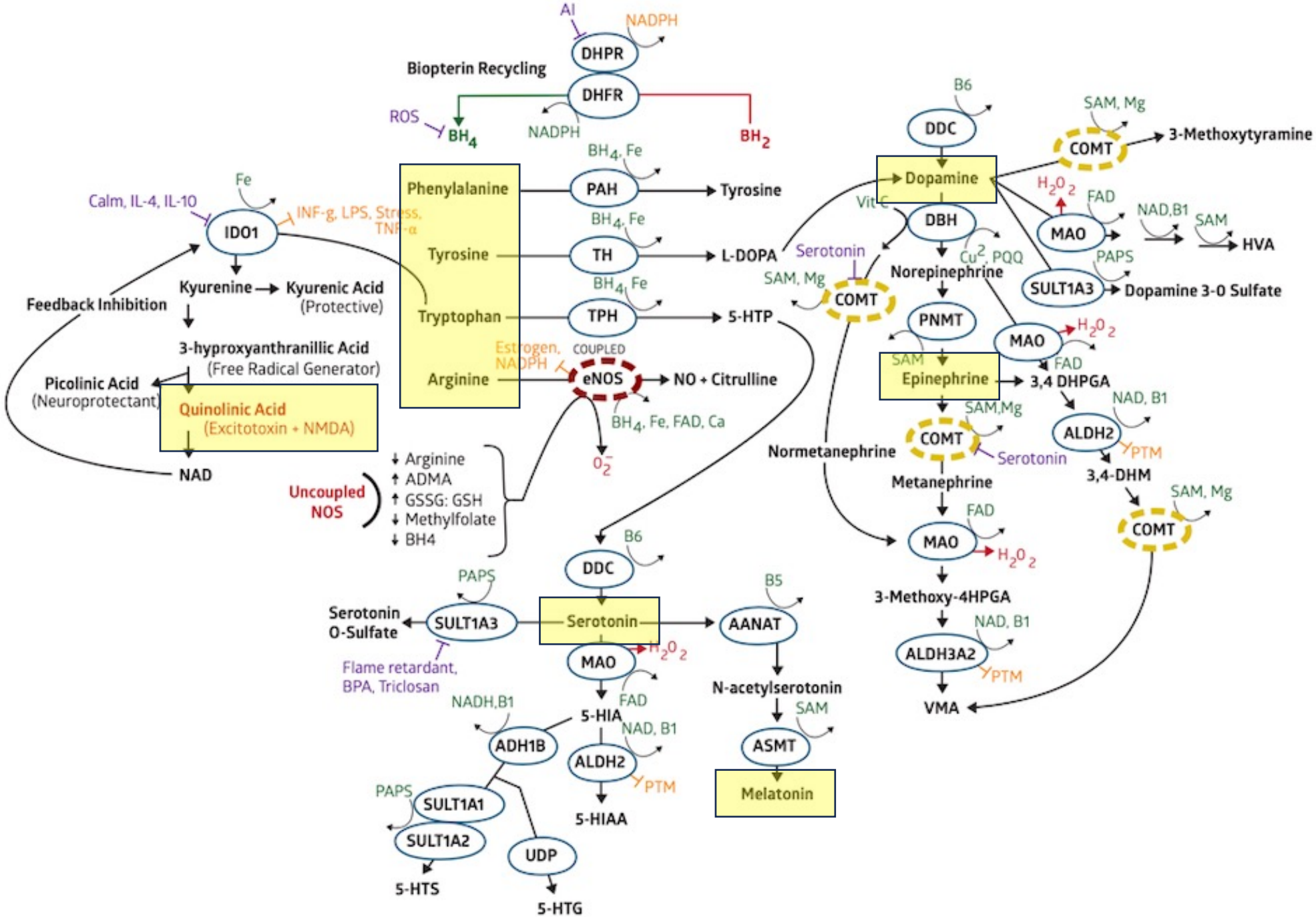
113

Longer cumulative use of medication to treat attention-deficit/hyperactivity disorder (ADHD) is associated with a small, but statistically significant, increased risk for cardiovascular disease (CVD), results of a large Swedish nested case-control study suggest.

The increased risk was evident only for hypertension and arterial disease, was dose-dependent, and was higher for stimulant than nonstimulant ADHD medications.

"Clinicians should be vigilant in monitoring signs and symptoms of cardiovascular diseases, particularly among those receiving higher doses," Zheng Chang, PhD, principal researcher, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, told *Medscape Medical News*.

https://www.medscape.com/viewarticle/998745?ecd=WNL_trdalrt_pos1_231125_etid6095385&uac=356271PT&impID=6095385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Biopterin Recycling
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ROS
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Tyrosine
Phenylalanine
Fe
Calm, IL-4, IL-10
IDO1
INF-g, LPS, Stress, TNF-α
BH4, Fe
TH
L-DOPA
Tyrosine
Kyurenine
Kyurenic Acid
(Protective)
Feedback Inhibition
BH4, Fe
TPH
5-HTP
Tryptophan
3-hyproxyanthranillic Acid
(Free Radical Generator)
Estrogen, NADPH
COUPLED
Arginine
eNOS
NO + Citrulline
Picolinic Acid
(Neuroprotectant)
Quinolinic Acid
(Excitotoxin + NMDA)
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Serotonin
O-Sulfate
Serotonin
B5
AANAT
Flame retardant,
BPA, Triclosan
MAO
H2O2
FAD
NADH,B1
5-HIA
N-acetylserotonin
SAM
NAD, B1
ADH1B
ALDH2
ASMT
PTM
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NAD, B1
ALDH3A2
PTM
VMA

Nutrients. 2021 Jan; 13(1): 249.
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PMID: 33467150

Current Evidence on the Role of the Gut Microbiome in ADHD Pathophysiology and Therapeutic Implications

Ana Checa-Ros,[1,2,3,*] Antonio Jeréz-Calero,[4] Antonio Molina-Carballo,[3,4] Cristina Campoy,[3] and Antonio Muñoz-Hoyos[3,4]

ADHD is the most common neurodevelopmental disorder in children and adolescents, affecting 5% of individuals younger than 18 years [104,105]. It is characterized by the permanent and impairing presence of inattention and/or hyperactivity and impulsivity. These core symptoms must appear before the age of 12 in accordance with the new diagnostic criteria (DSM-5) [106]. The course of this disorder is variable, and some symptoms may persist into adulthood in around 40–60% of cases [107]. ADHD impacts on many aspects of an individual's wellbeing, including physical health and academic, social and occupational functioning. It is frequently comorbid with other psychiatric and neurological conditions, such as ASD, mood disorders, epilepsy or sleep problems, creating a substantial burden for the individual, their family and the community [108]. Psychostimulants, and methylphenidate (MPH) in particular, represent the first-line medication for moderate and severe cases of ADHD in children from 5 years and over and in young patients [109]. Its efficacy mainly lies in increasing the extracellular levels of DA and norepinephrine (NE) [110], although it has additional effects on other neurotransmitter systems also involved in ADHD pathophysiology, such as 5-HT [111] and even Glu [112]. However, the long-term use of psychostimulants is often limited by poor compliance and tolerability problems derived from the combination of adverse effects, ADHD-related stigma and social resistance to medication, particularly in adolescents [113,114].

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Numerous etiological factors have been attributed to ADHD: genetic factors, which represent around 70–80% [115]; and diverse environmental factors, including perinatal factors (prematurity, low birthweight) and psychosocial determinants (adoption, child neglect) [116,117,118]. The pathophysiology of ADHD is yet to be clarified. ADHD symptoms are associated with deficits in executive functions, such as behavioral inhibition, working memory, set-shifting, planning and organization [119]. The neuroanatomical basis for this impairment has traditionally been located in the prefrontal cortex [120,121]. However, several large neural networks have also been implicated in ADHD recently, particularly the dopaminergic mesolimbic system, which is associated with motivated behaviors, anticipated outcomes and reinforced learning [108,119]. In fact, it has been suggested that the alteration of the catecholaminergic neurotransmission system could be the main pathophysiological factor for ADHD [122,123].

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Nowadays, there is increasing evidence that the aforementioned etiological factors and catecholaminergic dysfunction may lead to a neuronal state predominantly characterized by oxidative stress and inflammation, which could perpetuate the neurochemical alterations responsible for ADHD [124]. Increased levels of oxidative and nitrosative (NO) stress markers, together with a decrease in the concentrations of antioxidants, have been found in ADHD [125,126]. Furthermore, an alteration in the mitochondrial number and function in the dopaminergic neurons have been reported in individuals with ADHD in comparison with controls [127,128]. A dysregulation of the mitochondrial function provokes an uncontrolled production of reactive oxygen species (ROS) and reactive oxygen nitrogen species (RONS), which are by-products of the oxidative reactions leading to the production of adenosine triphosphate (ATP) [129]. Excessive levels of ROS/RONS harm the integrity of neurons by oxidating the polyunsaturated fatty acids (PUFAs) that constitute their membranes, as well as alter the apoptotic mechanisms. ROS/RONS also

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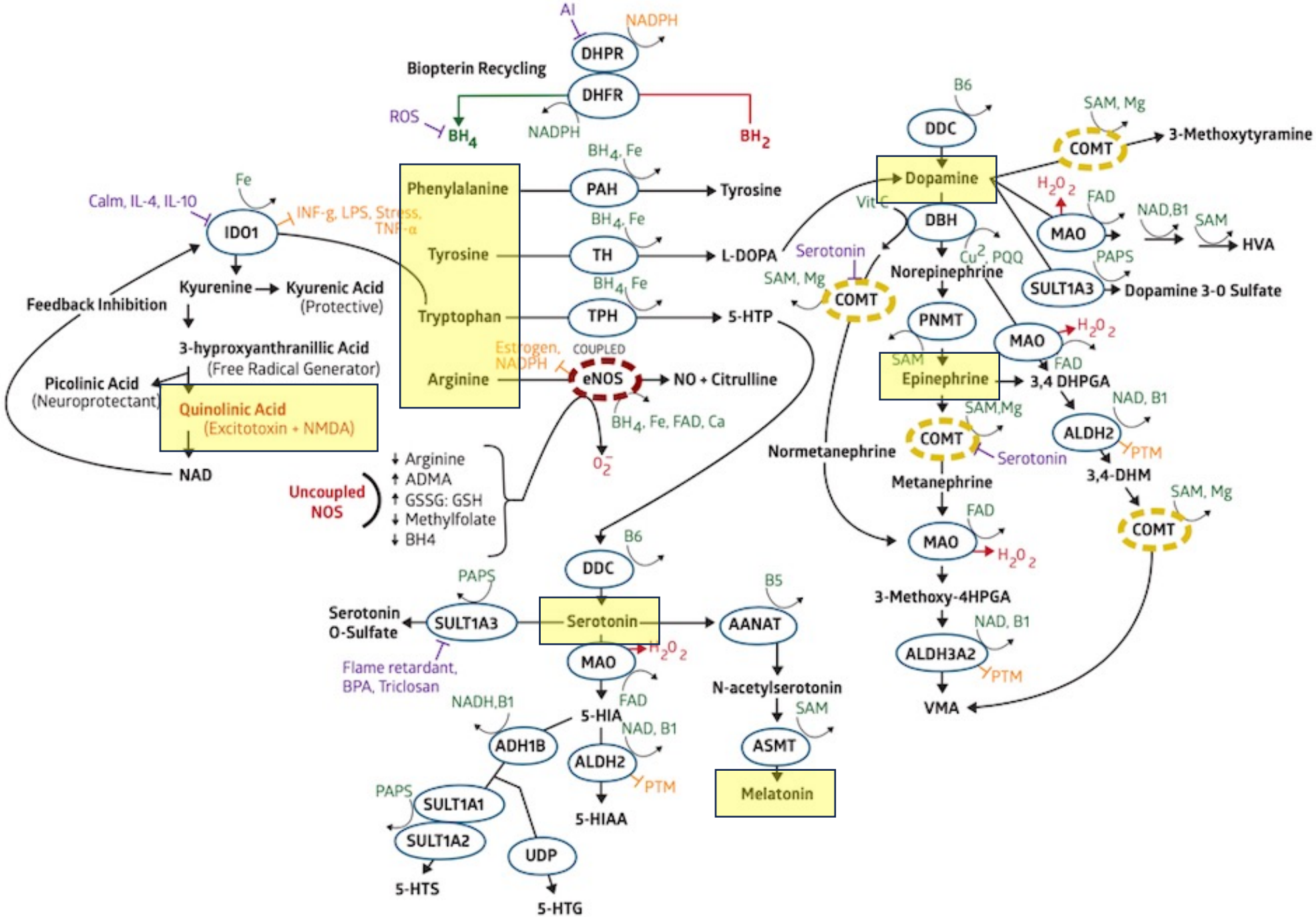
Aarts et al. [133] were the first authors to report microbial composition differences in Dutch young adult patients with ADHD using the next-generation sequencing of 16S rDNA in fecal samples. No significant differences in either alpha diversity (within-sample), which accounts for species richness, or beta diversity (between-sample), which indicates differences in diversity between the two cohorts, were found between ADHD patients and healthy controls. However, within the phylum Actinobacteria, the genus *Bifidobacterium* was significantly increased in the ADHD cohort. The authors also predicted bacterial gene function in relation to the metabolic pathways involved in the synthesis of phenylalanine, tyrosine and tryptophan. Interestingly, the relative abundance in the genus *Bifidobacterium* was correlated with a significant increase in the enzyme cyclohexadienyl dehydratase (CDT), which is involved in the synthesis of a dopaminergic precursor (phenylalanine). In a subset of 28 participants, independent of diagnosis, Aarts et al. also performed functional magnetic resonance imaging (fMRI) analysis to correlate the differences in microbial composition with neural reward responses. They observed a negative association between the relative abundance of CDT and reward anticipation responses in bilateral ventral striatum. Reward anticipation, which is dependent on DA neurotransmission [134], is crucial to direct actions towards positively balanced stimuli and has been reported to be reduced in ADHD patients [135]. Aarts et al. highlighted that the differential microbiome composition found between patients with ADHD and controls in their study may account for altered reward anticipation responses, which is a neural hallmark of ADHD.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IDO1
INF-g, LPS, Stress, TNF-α
BH4, Fe
TH
L-DOPA
Tyrosine
Kyurenine
Kyurenic Acid
(Protective)
Feedback Inhibition
BH4, Fe
TPH
5-HTP
Tryptophan
3-hyproxyanthranillic Acid
(Free Radical Generator)
Estrogen, NADPH
COUPLED
Arginine
eNOS
NO + Citrulline
Picolinic Acid
(Neuroprotectant)
Quinolinic Acid
(Excitotoxin + NMDA)
BH4, Fe, FAD, Ca
O2-
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↑ GSSG: GSH
↓ Methylfolate
↓ BH4
Uncoupled NOS
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Melatonin
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adults with ADHD, revealed a significant increase of a genus from the family Ruminococcaceae. However, in this case the genus was *Ruminococcaceae_UGC_004*, which was found to be associated with inattention symptoms. This association was not affected by the intake of ADHD medication. Szopinska-Tokov et al. compared the ADHD population with other two cohorts of patients: subthreshold ADHD group, composed of individuals who did not reach the criteria for ADHD but scored too high to be considered healthy controls; and the control group, which included unaffected siblings of ADHD patients, although the family relatedness was a factor considered in the statistical analysis. The alpha diversity was not significantly different between groups, although the beta diversity was reported to be significantly reduced among patients with ADHD, and this correlated with inattention scores. The Basic Local Alignment Search Tool (BLAST) available at the National Center for Biotechnology Information (NCBI) was used to search for similarities between protein and nucleotide regions. Consequently, the authors found that the genus *Ruminococcaceae_UGC_004* shared sequences with microbial species with the ability to consume the GABA neurotransmitter. The novelty of this study was to provide new evidence on the role of the gut

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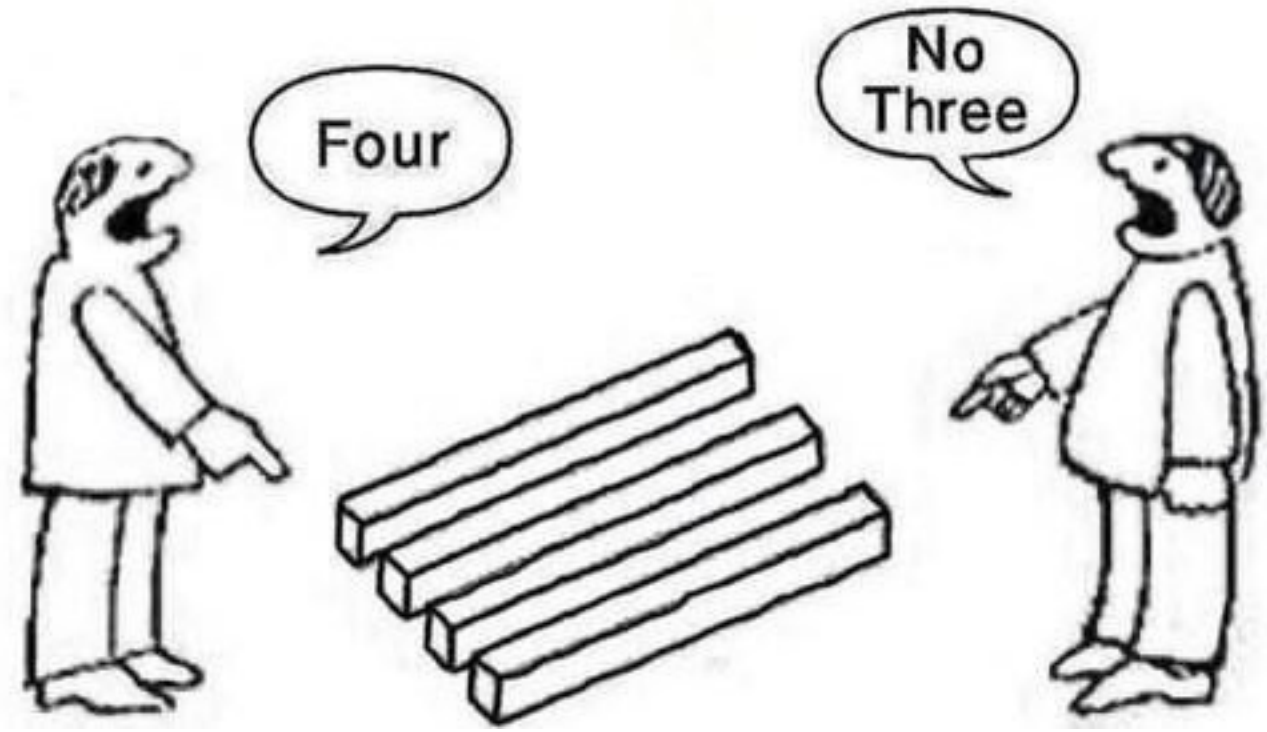
supplementation in comparison with placebo. Micronutrient supplementation caused a significant decrease of the phylum Actinobacterium, particularly a 25% reduction in the order *Bifidobacteriales*, which was attributed to the genus *Bifidobacterium*. This was accompanied by higher levels of the genus *Collinsella*. A pairwise correlation was detected between lower ADHD-RS-IV scores and decreased Actinobacteria abundance, as well as between lower concentrations of Actinobacteria and higher scores in the CGAS (in which higher results indicate better functioning). The results highlight a potential effect of micronutrient supplementation to modulate the abundance of putative probiotic bacterial species. Nevertheless, the role of *Bifidobacterium* in ADHD is contradictory. Several studies reported a protective effect of *Bifidobacterium longus* on several neuropsychiatric disorders, including ADHD [136,152]. On the contrary, Aarts et al. [133] found an association between higher abundances of Bifidobacterium species and ADHD. These opposing results may account for differences between studies in sample sizes, dietary patterns, diagnostic heterogeneity of neuropsychiatric disorders and the interpretation of compositional datasets in general. The strengths of this study lie in the quality of its methodology: detailed description of

1. Diet
2. Probiotics
3. Omega 3 products
4. Stim vs non-stim medications



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The Wedge Protocol