Review Article

THE IMMUNOLOGY OF MIND CONTROL: EXPLORING THE RELATIONSHIP BETWEEN THE MICROBIOME AND THE BRAIN (PART V)

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ABSTRACT

The final part of this series concludes the evaluation of the relationship between the human species and the human gut microbiome, focusing on whether their relationship is symbiotic, parasitic or somewhere in between. The possibilities based on animal studies are explored and compared to scientific facts proven in human beings. In particular, close attention is paid to the relationship between the gut microbiome and central nervous system, and the effect of this on human behaviour. This relationship is termed the 'microbiome–gut–brain axis'. The gut microbiome has an influence on stress (both acute and chronic), anxiety, loneliness and depression, as well as odour and attraction, through a number of pathways. It has also been associated with the development of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and with associated cognitive decline. It has also been postulated to play a role in schizophrenia. Since the common treatments used for these conditions are not equally effective in all patients, it is vital for clinicians to explore other avenues to be used as therapeutic targets. The gut microbiome, in particular, requires further research in order to aid the development of future therapies for certain conditions. The role of vitamin D in relation to the gut microbiome and the brain, and the impact of the gut microbiome on autoimmunity and systemic disease and how this affects the brain is explored. Randomised controlled trials in human beings are greatly needed to prove or disprove the effects of the gut microbiome on complex psychiatric diseases.

Keywords: immunology, mind control, relationship, microbiome, brain

INTRODUCTION

The gut microbiome is a biologically diverse ecosystem that is established early in life. It contains 100 times the number of genes in the human genome and is highly impacted upon by environmental factors. The influence of the gut microbiome extends far beyond the enteric system; including substantial impact on the development and functioning of the central nervous system (CNS).[1] In concluding this five-part series, we explore the role of the gut microbiome in schizophrenia, the role of vitamin D in relation to the gut microbiome and the brain, as well as the impact of the gut microbiome on autoimmunity and systemic disease and how this affects the brain.

SCHIZOPHRENIA

Schizophrenia is a complex disorder of the brain characterised by disorganised cognition, delusions and hallucinations. A genetic basis for the disease has been under scrutiny for decades but genetic models have failed in reproducibility and the results are confounding. However, an autoimmune aetiology has always been suspected and was supported by the fact that there was a co-association between schizophrenia and coeliac disease.[2] An increased incidence of autoimmune diseases in patients with schizophrenia has since been established.[3]

Several risk factors can be linked by a common pathway in the gastrointestinal tract (GIT) which can precipitate CNS disease and, in particular, schizophrenia. Therefore schizophrenia can serve as a model to illustrate the close ties between the gut and the brain. Enteric barrier dysfunction, food antigen hypersensitivity (gluten, casein) and gastrointestinal inflammation are all characterised by this disorder. It is postulated that some patients may even benefit from antimicrobial and probiotic interventions as well as dietary intervention in the form of gluten and casein-free diets as future treatment modalities to combat this disease.[4]

Schizophrenia tends to aggregate in families and the gut microbiome between family members also retains great similarity. The human brain is underdeveloped at birth. The baby is exposed to its mother's microbiota via passage through the birth canal. This initial colonisation plays a fundamental role in the development of the immature brain. Interestingly, premature

delivery increases the risk of developing schizophrenia as the premature gut lacks microbial diversity.[1]

Increasing evidence proposes that maternal immune activation affects fetal brain development via inflammatory mediators in both the cerebrospinal fluid and blood of mothers with schizophrenia. Immunological abnormalities including abnormal cellular and humoral reactivity, increased inflammatory cytokine production, the presence of brain-directed antibodies and increased numbers and responsiveness of peripheral lymphocytes are associated with schizophrenia. Communication between neurons and microglia regulates neural circuits and conveys essential peripheral information, including microbiome signals. Animal studies suggest that maternal infection with schizophrenia in early pregnancy results in microglial abnormalities in the developing fetus. During adolescence these highly sensitised microglia result in behavioural and cognitive changes. This process has been coined the 'microglia hypothesis' of schizophrenia. Prenatal therapies, including short-chain fatty acids, probiotics and fibre-rich diets are currently being investigated with the aim of preventing schizophrenia in offspring with genetic risk factors.[5]

The widespread inflammation encountered in schizophrenia affects the whole body, including the brain. Local barrier dysfunction results in mass accumulation of lymphocytes and a pro-inflammatory environment which spreads to the CNS.[6] Neuroactive protein products (gluten, casein), which access the blood stream, induce an autoimmune response inside the brain. In the case of schizophrenia, this attack is directed specifically against the hippocampus (essential for memory storage and the generation of long-term memory), the amygdala (important for emotional regulation) and the frontal cortex (which regulates impulsivity). This results in disorganised cognitive processing and a distorted view of the world.[2,7]

This milieu of disordered cognition can also be directly affected by neurotransmitters which are produced by bacteria in the gut. Gamma aminobutyric acid (GABA), norepinephrine, serotonin, acetylcholine and dopamine are all produced by bacteria and are passed to the brain by the vagus nerve. We are all pivotally dependant on the neuroactive substances made by these bacteria.[1] Commensals also circulate neurotrophins such as brain-derived neurotrophic factor (BDNF), synaptophysin and postsynaptic density protein 95 (PSD-95), which build and maintain neural networks at the synaptic level. Bacteria can even upregulate glutaminergic N-Methyl-D-aspartate (NMDA) receptors in the hippocampus and cerebral cortex – two critical areas for memory retention and emotional regulation.[6] NMDA receptor hypofunction and a lack of BDNF are both central to the pathophysiology of schizophrenia. The cognitive dysfunction results from diminished synaptic plasticity and an inability of the brain to regulate itself. Post-mortem evidence supports alterations in several neurotransmitter systems including GABA, glutamate, serotonin and dopamine.[8]

As with Parkinson's disease, evidence which links the gut microbiome to schizophrenia is mounting. The parasite *Toxoplasma gondii* is a recognised environmental risk factor for schizophrenia and causes major perturbations to the gut microbiome.[9] It has been suggested that specific infectious processes that occur at an early neurodevelopmental and immature immune system stage predispose individuals to autoimmune processes. This results in direct damage to various anatomical structures and neurodevelopmental processes. Confirming this theory, several studies in patients with schizophrenia have reported increased serum or cerebrospinal fluid antibodies against herpes simplex virus, cytomegalovirus, borna virus and Epstein-Barr virus.[7]

The fact that at least 30 per cent of patients will not respond to conventional antipsychotics is again cause for concern. Forty-one per cent of these treatment-resistant individuals have been found to display biological signs of immune activation.[10] A mind-shift may be required in establishing future therapeutics, including possible auto-antibody screening.[10,11] Immunotherapy may be of value in modifying the immune system which may have beneficial effects on the management of patients with autoimmune diseases and neuropsychiatric diseases, including schizophrenia.[7] However, it is important to keep in mind that schizophrenia is most likely a heterogeneous disorder, resulting from interactions between multiple factors.[11]

Further studies evaluating the effects of the gut microbiome and the immune system on the development of schizophrenia are required prior to any conclusions being made in this regard. Future effective management of this heterogeneous disorder will require treatment modalities targeting all aspects of its pathophysiology.[12]

VITAMIN D AND ITS EFFECT ON THE BRAIN

Gut microbiome microorganisms act as biochemical factories, aiding the host in acquiring nutrients, producing vitamins and degrading toxins. Impairment in gut homeostasis has been associated not only with many gastrointestinal diseases, but also with extra-intestinal diseases such as diabetes mellitus, obesity, autoimmune and neurological diseases.[13]

Vitamin D plays a vital role in bone mineralisation; it also has major effects on the cardiovascular and immune systems and acts as a host defence against pathogenic microorganisms.[13] Vitamin D has been well researched for its anti-inflammatory properties. Its hormonal activity has been linked to vitamin D receptor (VDR) expression (of which is at its highest in $CD8^+$ T cells) and to the vitamin D activating enzyme CYP27B1. Both VDR and CYP27B1 are found in various cell types including the prostate, kidneys, muscles and cells of the immune system. This supports the prominent role of vitamin D in immunity and gut homeostasis.[13]

Recent studies have demonstrated that the gut microbiome composition may be altered by vitamin D levels. The direct effects of vitamin D on bacteria is still under investigation. Minimal evidence shows that vitamin D inhibits the growth of specific mycobacterial species *in vitro*. Vitamin D deficiency results in an increase in Bacteriodetes and Proteobacteria phyla.[14] One study assessing the effects of vitamin D3 on the phyla of the gut microbiome, revealed a reduction in opportunistic pathogens, particularly Proteobacteria in the upper GIT (with significant reductions in *Pseudomonas* and *Escherichia/*

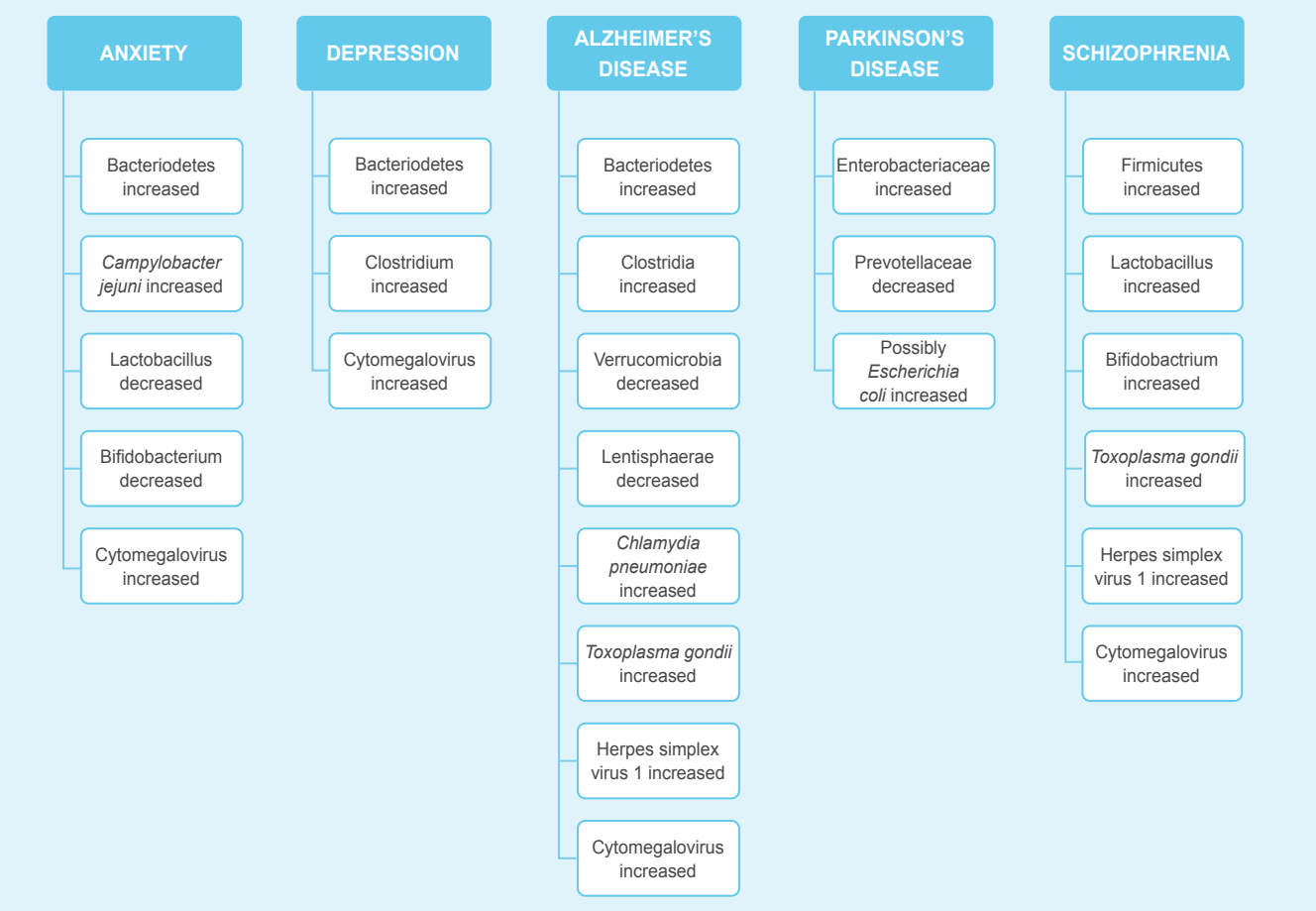

Figure 1: Bacterial, viral and parasitic species in the gut microbiome relevant to CNS disorders (adapted from Ghaisas et al[12])

Shigella species) and increases in bacterial richness.[13] This illustrates the antimicrobial effects of vitamin D consistent with its immunoregulatory properties.[14]

There is also some evidence supporting the concept that bacteria influence vitamin D metabolism by expressing enzymes necessary for steroid hydroxylation and vitamin D activation. Further studies are required to understand the relationship between the gut microbiome and vitamin D.[14]

The physiological effects of vitamin D on calcium and phosphate homeostasis have been thoroughly studied, however, recent experimental and pre-clinical data suggest a link between vitamin D and cognitive function. It has been estimated that approximately 1 billion people worldwide suffer from vitamin D insufficiency or deficiency.[15] Vitamin D deficiency is therefore an extremely common problem worldwide for all age groups (neonates to the elderly). Evidence suggests that vitamin D deficiency *in utero* and throughout life has marked long-lasting mental-health sequelae.[16]

At a molecular level, the brain has the ability to synthesise the active form of vitamin D (1.25 dihydroxyvitamin D) within many cell types and regions, predominantly in the hypothalamus and substantia nigra.[17] A well-designed rat model of prenatal vitamin D deficiency found that vitamin-D-deficient rat pup's brains were larger and longer with increased ventricular volume with a thinner neocortex compared to controls. Therefore vitamin D plays an important role in brain development.[16]

The elderly population display a higher prevalence of vitamin D deficiency than other age groups. This is due to a number of factors:

- decreased dairy and vitamin D ingestion;
- decreased sun exposure and reduced 7-dehydrocholestrol epidermal levels resulting in decreased vitamin D production;
- altered metabolism of vitamin D as a result of hepatic or renal failure; and
- increased catabolism from various medications (gluco-corticoids, immunosuppressants and anti-epileptics).

Studies in human beings support a correlation between decreased levels of circulating 25-hydroxyvitamin D and cognitive impairment in aging populations.[15]

It is well known that vitamin D has numerous functions in the nervous system and plays a vital role in neuroprotection.[15] This vitamin plays a role in the release of neurotransmitters, regulation of the production of neurotrophic factor, calcium homeostasis, reducing oxidant activity, regulating apoptosis, contributing to synaptic plasticity as well as immune system and inflammatory process modulation.[15,16] These processes are altered during aging and in the pathology of Alzheimer's disease, making vitamin D a fascinating preventative or therapeutic

implement. Animal studies have already demonstrated the pleiomorphic action of vitamin D in the brain and its versatility as a neurosteroid.[15]

It has been demonstrated that individuals with dementia have reduced vitamin D levels (±16.2 ng/mL) compared to those with mild cognitive impairment (±20 ng/mL) or those with normal memory (±19.7 ng/mL).[18] Reduced vitamin D levels were associated with increased difficulty remembering general information (semantic memory), visiospatial ability and executive functioning. Over a five-year period, vitamin-D-deficient individuals demonstrated a more rapid decline in overall executive function.[18] A systematic review summarised the results of studies evaluating cognition and 25-hydroxyvitamin D levels.[17] The meta-analysis showed that patients with Alzheimer's disease had decreased 25-hydroxyvitamin D levels compared to those without Alzheimer's disease. The Mini-Mental State Examination (MMSE) scores were also found to be lower in individuals with decreased 25-hydroxyvitamin D concentrations.[17]

It is now well established that Alzheimer's disease patients have reduced circulating 25-hydroxyvitamin D levels when compared to matched controls. However, clinical interventional studies in human beings have shown disappointing results regarding increasing 25-hydroxyvitamin D levels with improved cognitive outcomes.[15] These results may also have been impacted by other factors affecting vitamin D concentrations such as genetic factors, higher skin pigmentation, older age and female gender.[15,17]

Animal studies have, however, shown that vitamin D supplementation is protective against Alzheimer's disease and increases memory and learning. Latimer et al showed that a diet high in vitamin D3 (10 000 IU/kg/day) for five to six months prevented cognitive decline in aging rats. Further studies in human beings are required before conclusions can be made in this regard, specifically looking at whether vitamin D insufficiency triggers Alzheimer's disease or whether it removes protection of the CNS against Alzheimer's disease.[15]

Vitamin D acts not only as a neurosteroid for regulating neuronal differentiation and maturation by regulating neurotrophic factor production, but also acts as a neuroprotective agent by diminishing amyloid-beta accumulation by stimulation of amyloid-beta peptide phagocytosis.[16] As mentioned, the establishment of a chronic inflammatory process is an important component of neurodegenerative diseases.[19] Vitamin D has been shown to be an effective immune modulator and can regulate the inflammatory pathology in Alzheimer's disease by various processes, namely:

- upregulation of several neurotrophin's expression;
- increased anti-inflammatory cytokine IL-4 secretion;
- decreased pro-inflammatory cytokine (TNF-α, IL-1β) secretion; and
- inhibition of dendritic cell differentiation.[15]

Vitamin D is a potent antioxidant through free radical generation inhibition via nitric oxide synthase and gamma-glutamyl transpeptidase.[16] Vitamin D3 supplementation for five months impacts inflammatory and immune gene expression profiles resulting in improved functional cognitive outcomes in animal models. Interestingly, a 21-day administration of 1,25 dihydroxyvitamin D induced a change in the amyloid burden and inflammatory state of aged rats, however, this had no significant effect in younger rats.[15]

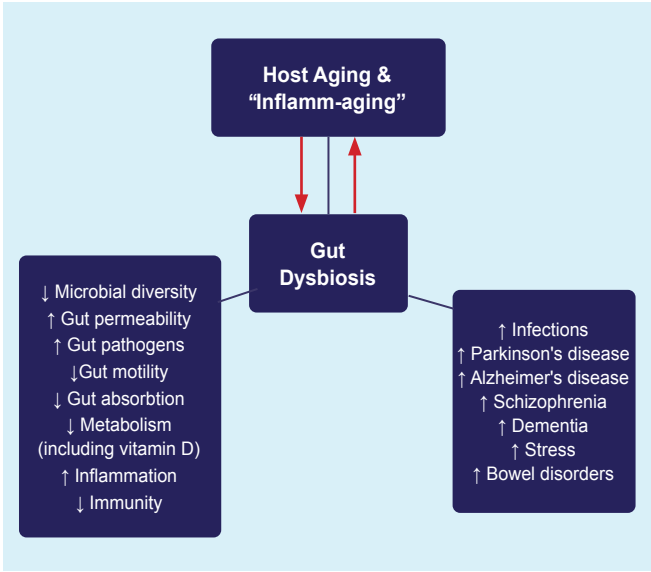

Figure 2: The relationship between the gut microbiome and ageing (adapted from Nagpal et al[19])

Vitamin D also plays a vital role in brain vascular health. Studies on vitamin-D-deficient adult rodents revealed increased stroke severity, including higher impairments in post-stroke sensorimotor behaviour and larger infarct volumes compared to controls. Vitamin D deficiency has been shown to reduce insulin-like growth factor 1 production. Insulin-like growth factor 1 is a neuroprotectant that limits infarct size and increases neuronal regrowth.[16]

Some cross-sectional studies have found that decreased vitamin D concentrations are associated with a higher risk of neuroimaging abnormalities, such as white matter hyperintensities, enlarged ventricular volume, lacunar infarcts and large-vessel infarcts, whereas other studies have not found this association. However, they did find an association between severe vitamin D deficiency with increased risk of prevalent infarcts. Interestingly, decreased vitamin D concentrations are associated with lacunar and large-vessel infarcts but not small-vessel infarcts.[20]

Vitamin D deficiency has also been shown to be more common in individuals after traumatic brain injury, with 46.5% being vitamin D deficient and 33.7% vitamin D insufficient. Therefore, an overall 80.2% having decreased vitamin D concentrations. In agreement with other studies in non-traumatic brain-injury patients, low vitamin D levels negatively correlated with cognition (even after adjustment for factors such as gender, age, time since traumatic brain injury and severity of brain injury).[21] With correction of these factors, vitamin D deficiency was also associated with more depressive symptoms in these patients.[21]

The association between vitamin D deficiency and neuro-psychiatric illness, including schizophrenia and major depressive

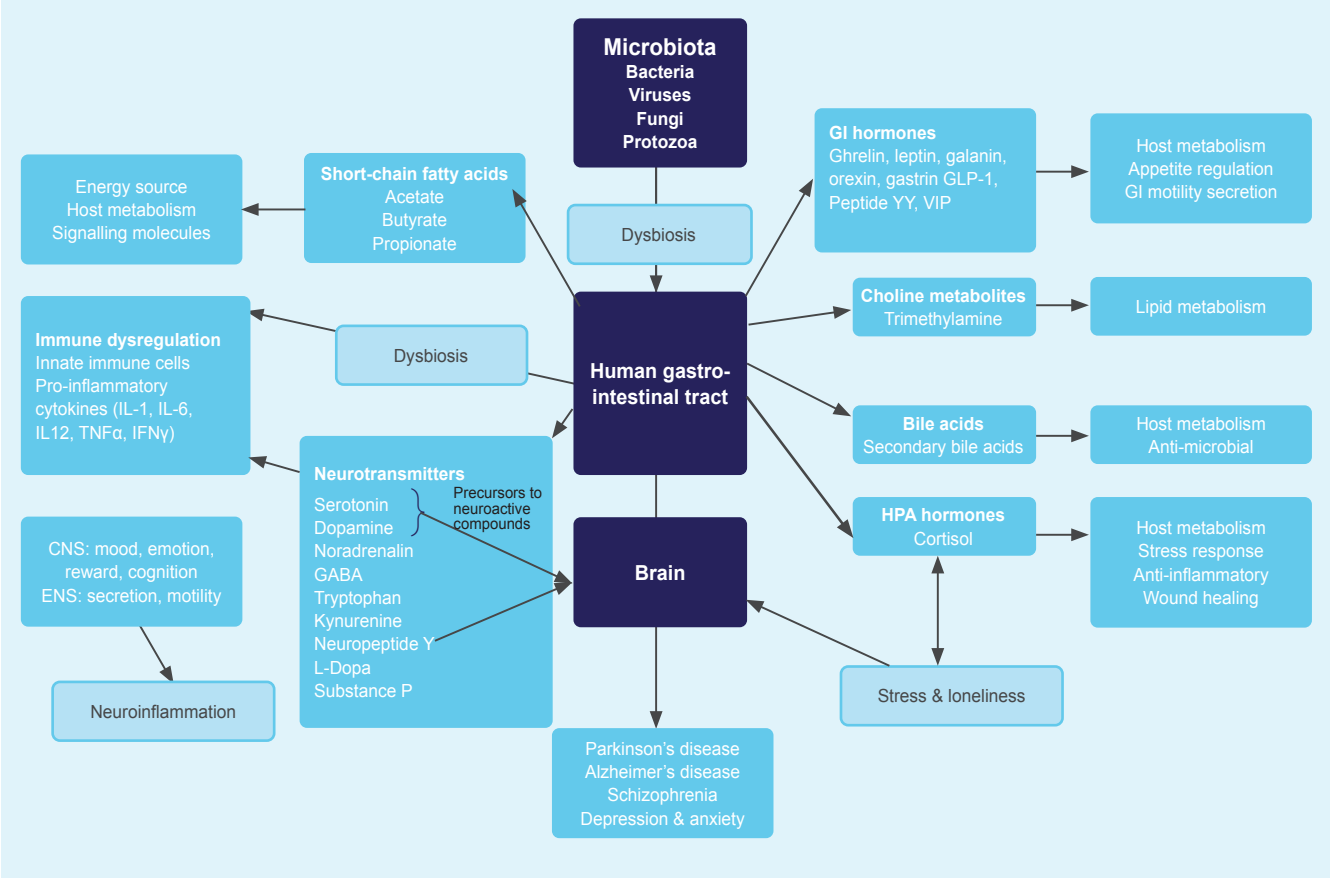

Figure 3: The microbiome-gut-brain axis and its effects (adapted from Forsythe & Kunze;[33] Panduro et al;[34] O'Callaghan et al[35] and Ramezani & Raj[36])

disorder has also been researched. A Dutch study found that although the type of psychiatric disorder was not a predictor of decreased vitamin D levels, vitamin D deficiency was found to be 4.7 times more common in a Dutch population of 320 outpatients with schizoaffective disorder (SAD), schizophrenia or bipolar mood disorder when compared to the general population.[22] Researchers have therefore suggested that these patient populations be screened regularly for vitamin D deficiency.[22]

Currently, the World Health Organisation (WHO) has determined that depression is ranked fourth on the global burden of disease list. It is a leading cause of disability worldwide. Treatment for depression is successful in only 60–80% of cases. Due to this and the high rate of patient medication discontinuation (because of high side-effect profiles) and high relapse rates, other avenues for treatment of depression need to be considered. Studies conducted have revealed an association between vitamin D deficiency and the presence of an active mood disorder with depressive symptoms.[23] Hoogendijk et al showed that 25-hydroxyvitamin D levels were 14% reduced in individuals with minor depression and 14% reduced in those with major depressive disorder when compared to controls. This was shown to be a significant reduction ($p < 0.001$).[24] The mechanism is not clearly understood but is reported to be linked to vitamin D receptors in the hypothalamus that are important for neuroendocrine functioning. Studies on the use of supplemental vitamin D for treatment of mood symptoms have conflicting results and further research is required in this area. Individuals most at risk for vitamin D deficiency include the elderly, adolescents, obese persons and those with chronic illnesses, especially malabsorption syndromes – namely, coeliac disease, chronic diarrhoea and inflammatory bowel disease. Interestingly, these groups are also noted to be at risk for depression.[23]

Vitamin D supplementation has been shown to be beneficial for general health and a variety of diseases. Increasing vitamin D levels to approximately 42 ng/mL reduces disease rates in diabetes mellitus, various cancers, cardiovascular disease and infections by 10–50% and reduces overall mortality rate by 18% per year.[13]

Therefore, there is sufficient evidence to warrant further studies to determine the cause-and-effect relationship between vitamin D and cognitive impairment. To date, no treatment study has examined this question.[17] Epidemiological evidence supports the theory that modifiable lifestyle-related factors are linked to cognitive decline. Diet specifically has become an intense research avenue in relation to neurodegenerative disease and cognitive aging.[25] Early and effective detection and treatment of vitamin D deficiency and insufficiency in individuals with depression and other mental disorders may be a cost-effective and easy therapy to improve both quality of life (QoL) and long-term morbidity.[23]

GUT MICROBIOME AND AUTOIMMUNITY

Females are 2–10 times more susceptible to a wide range of autoimmune disorders than their male counterparts. Androgens and oestrogens strongly modulate Th1/Th2 balance. Androgens down regulate natural killer cells, TNF-α production and Toll-like receptor 4 but increase anti-inflammatory IL-10 production. Oestrogens, however, enhance cell-mediated and humoral immune responses, NK cell cytotoxicity and pro-inflammatory cytokine production (namely, IL-1, IL-6 and TNF-α). This aids in explaining the enhanced immune reactivity in females, who are therefore inherently more resistant to infections than males. Females, however, are more susceptible to autoimmune diseases.[26]

Hormone-dependant regulation of auto-immunity was studied in a mouse model. In non-obese type 1 diabetic mice, females were significantly more susceptible (2:1) to disease than males.[27] However, interestingly, the opposite was seen in germ-free mice where more male mice became diabetic. It was noted that testosterone levels were higher in germ-free females compared to their control female counterparts (who were only specific pathogen-free), whereas testosterone levels were lower in germ-free males compared to their control male counterparts. Fascinatingly, the gut microbiome components were noted to be identical in nursing mice, started diverging in pubescent mice and became distinct in adulthood for males and females. The study also showed that transfer of cecal contents from male non-obese diabetic mice to female non-obese diabetic mice prior to the onset of disease protected the females against pancreatic islet cell inflammation, autoantibody production and development of diabetes. This protective effect was associated with increased testosterone levels in the female mice. Blocking androgen receptor activity revoked the protective effect. The gut microbiome may therefore be able to regulate sex hormones and influence one's susceptibility to autoimmune conditions.[27]

Recent research has evaluated the role of the gut microbiome or 'second genome' and its influence on autoimmunity. In studies of type 1 diabetes mellitus (DM) patients, shifts in ratios of the main phyla within the gut microbiome have been shown, with reduced Bacteriodets : Firmicute ratios, decreased bacterial diversity and decreased abundance of potential butyrate producers. A recent study in children demonstrated that decreased abundance of lactate and butyrate-producing bacteria are linked with β cell autoimmunity. Butyrate is reported to wield immunomodulatory effects on intestinal macrophages and induce T-cell regulatory differentiation inhibiting IFN-γ-mediated inflammation. Other studies have also shown higher abundance of Clostridium with less Bifidobacterium and Lactobacillus in type 1 DM when compared to healthy controls.[26]

Further studies are essential to explore the relationship between the gut microbiome and autoimmunity as this may have a substantial impact on brain development and in the development of neurocognitive disorders.

GUT AND SYSTEMIC DISEASE

Various systemic diseases, including obesity and diabetes, show significant changes in both resident gut microbiome composition as well as the host's gut homeostasis and metabolic processes.[12]

Both type 1 and type 2 DM have been associated with dysbiosis of the gut.[28] Individuals with type 2 DM have been shown to have higher proportions of Betaproteobacteria than healthy individuals. This correlated with higher plasma glucose levels than with body mass index (BMI), implying that this species may be involved in glucose metabolism. Preliminary studies have also shown an increased association with type 2 DM and the development of Parkinson's disease. Although the mechanistic link between both these conditions is unknown, chronic inflammation, oxidative stress and mitochondrial dysfunction are shared pathophysiological mechanisms amongst both.[12]

Since individuals with type 2 DM have a higher risk of developing Parkinson's disease, the effect of anti-diabetic drugs on Parkinson's disease. has also been evaluated. An individual's risk of developing Parkinson's disease increases 2.2-fold when they are diagnosed with type 2 DM, however, with oral anti-hyperglycaemic agents the risk is decreased to 1.3-fold. This suggests that oral anti-hyperglycaemic agents may have a protective effect against the development of neurodegenerative diseases such as Parkinson's disease.[12]

Interestingly, minor sleep restriction sufficiently alters the composition of the gut microbiome. These alterations affect learning, memory, β-amyloid deposition in the cortex and cognitive flexibility. Further studies are essential to investigate the interplay between sleep, gut microbiome composition, cognitive flexibility and systemic inflammation (ultimately resulting in systemic disease).[29]

Further human studies are essential to ascertain the link between the gut microbiome and the development of systemic disease and the potential impact of this relationship on the development of neurocognitive disorders. This maybe be an important avenue to explore in the future treatment of these conditions.

CONCLUSION

Gut microbiota play a crucial role in the bidirectional interaction between the CNS and the intestines.[30] There is a long history of co-evolution between human beings and the microorganisms in our gut microbiome. This co-evolution may have effects on mental and physical health. The effects of imbalances in gut microbiota composition at different stages of life and their subsequent short- and long-term impact on behaviour and brain modulation, require extensive consideration.[31] However, premature conclusions in extrapolating these findings to human beings should be avoided.

As seen in this five-part series, the gut microbiome plays a role in stress and anxiety, depression, loneliness and odour and attraction. It plays a role in the development of neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease and in schizophrenia. It also plays a role in vitamin D metabolism, in autoimmunity and may impact systemic diseases that may all in turn affect the brain.

The extrapolation of findings in studies based on laboratory animal models to human beings is unwise as laboratory animals live under abnormally hygienic conditions. Animals living in less hygienic conditions, as well as humans, encounter different

immune responses. Human beings also exhibit cognition and adaptive behaviour that is different from other species.

More studies (including carefully designed translational and clinical studies) need to be conducted to investigate the aftermath of imbalances in gut microbiota composition. Investigations also need to be launched into possible avenues of prevention and treatment in the clinical sector to avoid long-term or permanent effects.[31] Infant studies are of particular importance, first, to ascertain the effects of alterations in the gut microbiome early in life on brain development and gut-brain interactions and, secondly, to assess whether interventions aimed at reducing gut dysbiosis can alter such effects.[32]

Several other areas need further consideration, such as obesity, the hygiene or microbiota hypothesis for allergic disease, and the possible association between gut microbiota and psychiatric conditions. Of further relevance is the role of probiotic or commensal strain exposure to certain inflammatory conditions – such as rheumatoid arthritis, asthma, inflammatory bowel disease and chronic obstructive pulmonary disease – all of which have strong associations with mood disorders and depression.[33] Further studies in human beings are therefore essential before any conclusive remarks regarding the effect of the gut microbiome on complex psychiatric disorders can be made.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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