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THE GUT-BRAIN AXIS: THE ROLE OF NUTRITION

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The gut-brain axis (GBA) refers to the bi-directional communication that occurs between the gut and the brain. Recently, studies have highlighted the important role of nutrition in modulating the GBA. We will delve into this exciting area of research and understand how certain diets and foods may be linked to mood and mental health.

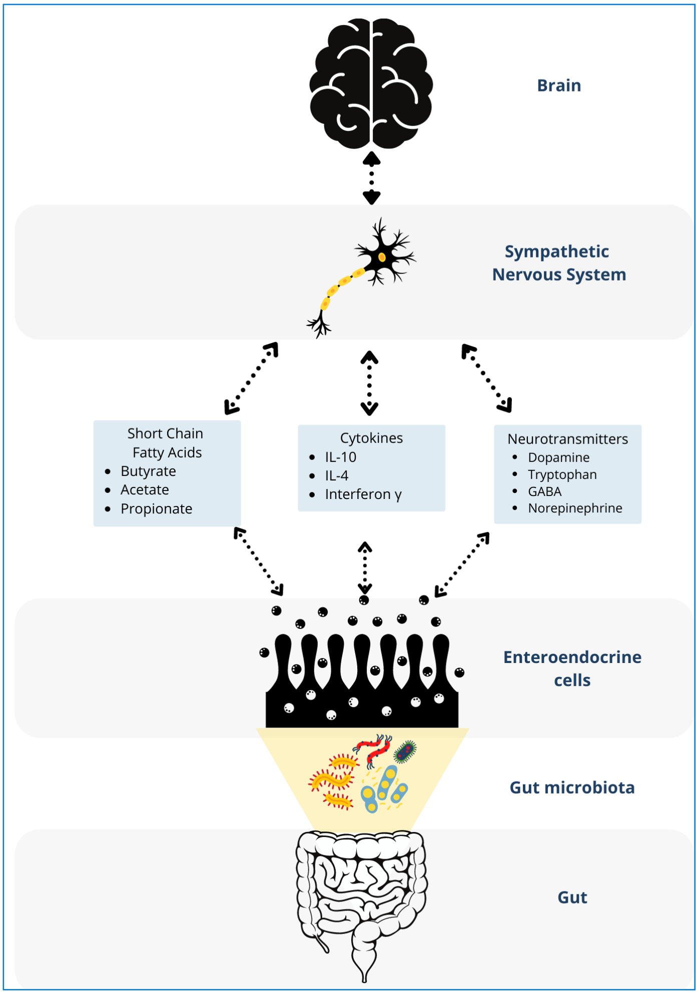
We have all experienced the feeling of 'butterflies in our stomach' or had a 'gut feeling' about something. But why is this? For centuries, scientists have endeavoured to understand the links between digestion and emotions, behaviour and cognition.[1] In recent decades, research has shown that the gut and brain are in constant bi-directional communication with one another via the gut-brain axis (GBA). The health of our gastrointestinal tract and microbiome can affect neurocognitive function and vice versa. This research is revealing new possibilities for dietetic and cognitive-based therapies to target both mental health and gastrointestinal conditions.

THE GUT AND THE BRAIN

The term 'gut' is not clearly defined. It may refer to just the intestines, the entire gastrointestinal tract, or the gastrointestinal system including accessory organs. It was originally thought that the sole purpose of the gut was to digest and excrete food. However, we now know that the gut is also responsible for hormone, enzyme and antimicrobial peptide production, immune system homeostasis, and is home to our gut microbiome.[2] Live microbes are found throughout the gastrointestinal tract but are most densely populated within the large intestine.

Our brains contain billions of neurons that, together with the spinal cord, comprise the central nervous system (CNS). The CNS is linked to the other organs of the body through the peripheral nervous system (PNS).[3] Contained within the PNS is the enteric nervous system (ENS); a network of neurons and nerves lining the gastrointestinal mucosa. The ENS controls mucosal contractions, secretions, and blood flow, and is capable of functioning independently of the CNS. Therefore, the ENS is often termed 'the second brain'.[4]

Figure 1: Communication pathways and metabolites within the GBA



CROSS-TALK BETWEEN THE GUT AND THE BRAIN

The brain and gut appear to have many lines of communication, including neural innervation, inflammatory and immune responses, enteroendocrine signalling and production of microbial metabolites[4-6] (see Figure 1).

The gut is directly linked to the CNS via the vagus nerve, extending from the brain stem to the abdomen.[7] Signals from the brain to the gut are sent through efferent fibres; however, most communication (up to 90%) is sent from the gut to the brain via afferent fibres.[8] Afferent fibres detect physical (eg, stretch and distention) and chemical (eg, microbial metabolites and neurotransmitters) stimuli in the gut.[8]

Neuropeptides and neurotransmitters play a part in the GBA by relaying messages to other biologically active peptides within the nervous system, many of which are found in the gut.[9,10] The gut microbiota can modulate the release of biologically active peptides from enteroendocrine cells.[10] Several studies suggest that the gut microbiota may have a role in the metabolism of tryptophan into neuroactive compounds including serotonin.[11] Microbial species like *Lactobacillus* and *Bifidobacterium* are known to produce gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter.[10] Some studies suggest a link between GABA levels and the gut microbiota, as certain species are found to increase GABA levels.[10] This is potentially beneficial as GABA is known for its calming effect.[10]

The immune system is another communication pathway between the gut and the brain. Within the gastrointestinal mucosa lies the gut-associated lymphoid tissue which hosts up to 70% of the immune cells in our body.[12] There are two types of immune responses: innate and adaptive (or acquired) immunity. Innate immunity is considered the 'first line of defence', Yakult

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Some dietary approaches have demonstrated beneficial outcomes for gastrointestinal and brain disorders (both neurological and psychiatric); these include the Mediterranean diet, high-fibre diet, probiotic and prebiotic supplementation and more recently, the 'psychobiotic diet

whereas adaptive immunity is a more specific response, which develops following exposure to a pathogen.[13] The gut microbiota interacts directly and indirectly (i.e. through the secretion of chemokines and cytokines) with these immune cells and 'trains' them to fight pathogens. Cellular and chemical messengers produced by the immune system enter circulatory and lymphatic systems to relay information to the brain. These messengers may also be recognised by afferent neurons to confer information about the health and immune status of the gut to the brain.[12]

Lastly, many gastrointestinal microbes produce short-chain fatty acids (SCFA) that stimulate the sympathetic nervous system and cross the blood-brain barrier.[14] SCFAs may stimulate the release of hormones influencing hunger and satiety, enhance mucous production, strengthen the gastrointestinal barrier and protect against diseases like bowel cancer.[14]

ROLE OF DIET WITHIN THE GBA

Diet plays a major role in shaping the gut microbiota. Many clinical studies have investigated the role of diet on the gut microbiota and the incidence of diseases. However, relatively few have explored how diet-induced changes in the gut microbiota affect the brain. Some dietary approaches have demonstrated beneficial outcomes for gastrointestinal and brain disorders (both neurological and psychiatric); these include the Mediterranean diet, high-fibre diet, probiotic and prebiotic supplementation and more recently, the 'psychobiotic diet'.

DIETARY PATTERNS

Cohort studies have revealed that certain dietary patterns affect mental health. For example, a systematic review and meta-analysis showed that a diet high in fruits, vegetables and wholegrains is associated with a reduced risk of depression.[15] Indeed, diets high in plant-based foods, such as the Mediterranean diet, have been linked to beneficial microbial profiles.[16] Improved mental health outcomes associated with plant-based diets may be in part attributed to altered microbial signalling along the GBA; however, evidence to date is lacking.[17] Conversely, the western diet, characterised by an excessive intake of fats, sugars and animal protein, is often associated with higher mortality rates and increased risk of disease, including gastrointestinal disorders.[18]

Interventional studies for the treatment of depression support the above findings. The 'SMILES' trial was the first randomised controlled trial (RCT) to study the effect of dietary intervention in the treatment of depression. This study reported a significant improvement in depressive symptoms when participants (with moderate to severe depression) followed a modified Mediterranean diet.[19] Likewise, the GEICO study found that the vegan diet improved symptoms of anxiety and depression.[20] While the underlying mechanisms are unclear, it has been suggested that these dietary interventions may aid the recovery from gut dysbiosis, a commonly observed condition in depressive patients.[21]

MACRONUTRIENTS

It is well-established that the macronutrient composition of our diet will alter our gastrointestinal microbes and their metabolite profile, which may in turn affect the GBA. Carbohydrates, particularly dietary fibre, have been extensively studied for their beneficial effects on the gut microbiota. The characteristics of dietary fibre (i.e. solubility, fermentability and viscosity) are often overlooked, despite being metabolised differently by the gut microbiota. For example, soluble fermentable fibres such as β-glucans promote the growth of beneficial *Lactobacillus* and *Bifidobacterium* genera which metabolise fibre to release SCFAs.[22] Diets high in polyunsaturated fatty acids are also associated with increased microbial diversity and high relative abundance of *Bifidobacterium*, *Roseburia* and *Lactobacillus*.[23]

Conversely, low-carbohydrate diets (with or without controlled fibre intake) have been shown to reduce SCFA production and butyrate-producing bacteria.[24] Likewise, a high-protein, low-carbohydrate diet has been associated with increased colonic protein fermentation: a process that releases toxic and carcinogenic by-products such as branched-chain fatty acids and n-nitroso compounds.[25] Finally, some evidence suggests that excessive intake of saturated fatty acids may reduce microbial diversity.[26]

PROBIOTICS AND PREBIOTICS

As previously discussed, the composition of the gastrointestinal microbiota may influence neurologic and mental health via the GBA. Therefore, the inclusion of live, beneficial dietary microbes (i.e. probiotics) and carbohydrates that are selectively fermented by beneficial bacteria (i.e. prebiotics) are two commonly studied dietary interventions.

Several studies have investigated the effect of consuming beneficial bacterial strains, mainly species of *Lactobacillus* and *Bifidobacterium*, on mental health and neurological conditions. In one such study, healthy medical students consumed 100mL of the *Lactobacillus paracasei* Shirota-containing fermented milk drink or a placebo for eight weeks leading up to examination day.[27] This pilot study found significantly higher faecal serotonin levels post-intervention and reduced stress-related abdominal symptoms among participants in the intervention group.[24] Similar outcomes were also observed with *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 formulations.[28]

Recent studies have investigated the use of probiotic strains of *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Bifidobacterium breve* in cognitive function, anxiety and depressive symptoms. While results are mixed, some studies have reported positive outcomes.[29,30] Overall, it appears that probiotics have a small but significant effect on depression and anxiety.[31]

Regular intake of prebiotics, such as inulin-type-fructans (ITF), may have a mediating effect on satiety and eating behaviours via the GBA. Consumption of ITF-rich foods has been shown to increase satiety, reduce cravings for 'unhealthy foods',[32] and increase *Bifidobacterium* genera in the gut. Authors suggest that the gut microbiota may affect appetite and eating behaviours by regulating ghrelin (appetite hormone) receptor signalling.[33] Exciting research is also being conducted in neurodegenerative disorders such as Parkinson's and Alzheimer's, to determine whether probiotic and prebiotic supplementation may affect disease rating scores and metabolic changes.[34-36]

PSYCHOBIOTICS

Psychobiotics – a term established by Professor Ted Dinan in 2013 – initially referred to bacterial species and strains which, when administered in adequate amounts, played a beneficial role in mental health.[37] However, this term has since evolved to include exogenous factors, particularly dietary components like fermentable fibres and fermented foods, that positively influence the GBA. An ongoing study by researchers at University College Cork is investigating the effect of a psychobiotic diet on stress responses in healthy individuals.

Preliminary findings of this study suggest that this dietary approach may improve stress response.[38] However, further research is required to consolidate these findings.

CONCLUSION

Our understanding of the gut-brain axis has rapidly advanced over the past decade – from analysing observational data to investigating physiochemical aspects and nutritional modulation of the axis. However, there are many questions researchers are investigating. Which species and strains of bacteria help with certain neuropsychological conditions? Which foods and dietary components can promote the growth of these 'psychobiotic' strains? How effective is a psychobiotic diet when compared with already existing clinical approaches?

The authors are excited about the prospect of research around the gut microbiota connecting these dots, and helping translate concrete scientific evidence into practical advice.

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Questions relating to: *The gut-brain axis: the role of nutrition*
Type your answers below, download and save or print for your records, or print and complete by hand.

Q.1	List the main pathways through which the gut and the brain interact.
A	
Q.2	Explain the role of the gut microbiota within these pathways.
A	
Q.3	What is the importance of the vagus nerve and the ENS within the gut-brain axis?
A	
Q.4	What are some metabolites produced by the gut microbiota that may directly or indirectly impact the gut-brain axis?
A	
Q.5	What is the evidence around plant-based dietary patterns, gut microbiota and mental health?
A	
Q.6	Explain the aim and main outcome of the 'SMILES' trial.
A	
Q.7	What dietary components are generally linked to positive mental health outcomes?
A	
Q.8	Outline some of the observed effects of high-protein low-carbohydrate diets on the gut (and the gut-brain axis).
Q.9	What do the results of the meta-analysis (2019) on the effect of probiotics on mental health conditions suggest?
Q.10	What does the term 'psychobiotics' mean?

Please type additional notes here.