Gastrointestinal microbiota, diet and brain functioning

A growing interest for research in the relationship between the gastrointestinal (GI), GI microbiota, health and disease is due to the potential for research identifying intervention strategies. Preclinical and clinical studies have indicated that initial colonisation of bacteria in the GI tract can affect the individual’s health condition in later life. Diet is an influential factor in modulating this complex ecosystem and consequently can help to modulate physiological conditions. The broader role of the GI microbiota in modulation of pathology and physiology of various diseases has pointed to the importance of bidirectional communication between the brain and the GI microbiota in maintaining homeostasis. An association of diet with metabolic diseases is well known and there are dietary supplements reported to improve brain function and cognitive decline. In addition to the plausible mechanisms of inflammation and oxidative stress for psychological conditions, more research into the role of the GI microbiota in combination with dietary factors as a component in psychological condition is warranted. From this work, targeted interventions could result.

Although a link between GI function and health or disease in an individual has been determined, the underlying mechanisms are not clearly understood. The GI tract of a newborn is rapidly colonised by microbiota during the birth process through maternal contact and from the surrounding environment. This microbial ecosystem stabilises in first 2–3 years of life and reaches maturity in the human adult1. By adulthood, the intestine contains approximately $10^{12}$ bacteria per gram of colonic content2, which is 10 times the number of cells in the human body. Based on 16S rRNA gene analyses, it was estimated that an adult GI tract harbours between 500 to 1000 different species3 from three major bacterial phyla, Bacteroidetes (Gram-negative), Firmicutes (Gram-positive) and Actinobacteria (Gram-positive). The proportion of these phyla in any individual depends upon that individual’s genetic makeup, dietary habits and surrounding environment.

The initial inoculation then colonisation of the GI impacts the GI microbiota throughout life and the dynamic microbial ecosystem is highly influenced by the surrounding environment and dietary factors. Any modifications in this highly organised and complex ecosystem have the potential to influence the normal physiological functions and are suspected to play a role in obesity, fatty liver disease, inflammation, diabetes and also psychological conditions4–8.

Diet that impacts GI microbiota: from infancy to elderly

Upon ageing, weakening of dentition, salivary function, digestion and intestinal transit time may affect the intestinal microbiota9,10. One manageable environmental factor is diet, which has been shown to significantly impact the GI microbial composition. The types of bacteria present are dependent on the type of substrates available, with some bacteria prospering on a specific substrate while others are unable to utilise that compound11. This selective substrate usage therefore enables modulation of the composition of GI microbiota via the diet, which can occur at any stage of life. However, diet in infancy can greatly affect the maturation process of the microbial profile, gastrointestinal health and immune system.

Human milk is normally the first dietary exposure to an infant. This is fermented in the colon, stimulating the growth of specific bacteria...
(including Gram positive Bifidobacterium spp.). Infants fed with breast milk and those on milk formula developed and harboured different and diverse bacterial populations in their GI tract. Moreover, the composition of different milk formula facilitates different types of bacterial colonisation. Infants fed with oligosaccharide enriched formula harbour higher counts of Bifidobacterium spp. and Lactobacillus spp. compared to infants fed on unsupplemented formulae. This prebiotic effect of infant food could be of a major concern as it plays a role in shaping the GI microbiota that is believed to influence an individual’s health for their entire life. A significant shift in the GI microbial ecology occurs when infants switch to a more solid and varied diet, including substantial reduction in the percentage of Bifidobacterium spp. and Lactobacillus spp. in the total microbiota. Throughout adulthood GI microbiota appears to become more stable as with more stable dietary habits. The final shift in composition and function of gut microbiota occurs during the older age of lifespan. In general, aging is associated with a decline in physiological function including in the immune system and metabolism that consequently affects the microbial composition, or vice versa. Human age-related changes reported in the GI microbiota composition include a numerical decrease in Bifidobacterium spp. and Lactobacillus spp. and an increase in Enterobacteriaceae and obligate anaerobes such as Clostridium spp.

Numerous dietary components have been identified as having positive or negative effect on brain function and behaviour, this effect can be improved by GI microbiota. Animal studies and human clinical trials have well demonstrated the role of omega-3 polyunsaturated fatty acid in normal brain functioning. Administration of Bifidobacterium spp. in combination with a substrate for eicosapentaenoic acid (EPA), alpha-linolenic acid results in increased concentration of EPA in liver tissue and docosahexaenoic acid in brain tissues. In wild mice model, probiotics such as L. helveticus prevented high fat diet-induced anxiety-like behaviour. Diet can modulate the GI microbial composition by providing a favourable environment while the contrary is also true that GI microbiota can modulate the effect of diet and in turn host physiological and psychological function.

**Activity of GI microbiota**

The GI microbiota can produce a vast range of metabolites and/or structural components whose generation depends on the availability of nutrients and the luminal environment. These metabolites are subsequently taken up by GI tissues, potentially reach circulation and other distant tissues and can be excreted in urine and breath. GI microbiota have been linked to very important health functions such as development and role of the immune system, resistance to infection by preventing pathogen colonisation, bioactivation of beneficial constituents such as polyphenols, detoxification of xenobiotics and metabolism of luminal components leading to formation of a variety of metabolites such as short chain fatty acids (SCFA), vitamins and several gases. SCFAs such as n-butyrate, acetate and propionate act as key sources of energy for tissues and promote cellular mechanisms that maintain tissue integrity. When SCFAs reach the circulatory system, they impact immune function and inflammation. SCFAs are also involved in host-microbe signalling and control of colonic pH with subsequent effects on microbial composition, intestinal motility and epithelial cell proliferation. Microbes have also been involved in enzymatic degradation of complex substrates particularly many forms of polysaccharides from ingested food. For example Bacteroides thetaiotaomicron, produces an array of enzymes for carbohydrate breakdown. During metabolism some gases such as methane, hydrogen, hydrogen sulfide and carbon dioxide are produced within the GI tract. Excess production of these gases may cause GI problems such as bloating and pain. These gases may serve useful purposes however, it is debatable whether hydrogen sulfide for example, is largely beneficial or harmful.

Furthermore, GI microbiota can influence behaviour and brain function by influencing the expression of certain body chemicals such as hormones, neurotransmitters and neurotrophic factors. Commensal bacteria such as Bifidobacteria infantis can modulate tryptophan metabolism, this suggest that GI microbiota may influence the precursor pool for serotonin (5-HT). Animal studies have demonstrated that GI microbioa can also modulates brain chemistry such as Brain-Derived Neurotropic Factor (BDNF) expression in the hypothalamus and the brainstem. BDNF is crucially involved in neurogenesis, brain development and neural circuit formation. BDNF has also been recognised as an important antiobesity factor. GI microbiota maintain communication with the host using metabolic, neural, immune and endocrine pathways. For health, homeostasis between the GI microbiota and the host system is essential, since any imbalance in this arrangement may result in a disease condition.

**Interaction between GI microbiota and brain functioning**

The evidence is increasing for a bidirectional route of communication between brain, gut and GI microbiota which use immune, neural and endocrine pathways and by this means influence gut-brain communication, brain function and even human behaviour. The top-down mechanism of the effect of stress and psychological condition on the GI functions is known from extensive research, in
particular with Inflammatory Bowel Disease, Irritable Bowel Syndrome and Crohn’s disease. However, the role of GI microbiota in brain functions such as stress, cognition and mood need to be explored more comprehensively.

The GI microbiota influences the release of the major neurotransmitters tryptophan, serotonin, endocannabinoïd ligands, ghrelin and cholecystokinin, which can influence food intake, energy balance and some brain tasks such as emotion, cognition and motor functions. Changes in microbial composition and metabolism correlate with the concept of ‘inflamm-ageing’, a low-grade chronic pro-inflammatory status as a common basis for a broad spectrum of age associated pathologies including cognitive decline and immunosenescence. Age-associated changes may increase intestinal permeability and ease the passage of bacterial lipopolysaccharides (LPS) into circulation, resulting in an elevated systemic LPS level. When LPS binds to pattern recognition receptors such as toll-like receptor 4 on immune cells, there is induction of inflammation by production and release of cytokines, leukotrienes and prostaglandin. Animal studies with probiotic supplementation demonstrated that probiotics can normalise immune responses, reverse behavioural deficits and restore basal noradrenaline level in response to stress. The probiotics also normalise central nervous system (CNS) biochemistry and improve behaviour in a mouse model of colitis, through vagal nerve pathways for gut-brain communication. Psychological responses to the GI microbiome composition may be an important factor in understanding the increasing prevalence of psychological conditions in the community and research into this topic should be promoted.

Conclusion

Clinically, a psychological condition does not stand alone since there are frequently immune system and GI comorbidities. Antidepressants are the commonest treatment, and as such are focused on a top-down approach. However, growing evidence from increasing numbers of animal studies and human trials suggest that the GI microbiota composition can be correlated with the incidence of complex conditions such as cognitive decline, anxiety and depression. Detailed clinical interpretation is warranted so that novel interventions in neuropsychological conditions can be employed. Preclinical research combining detailed exploration of the GI microbiota in well-designed human cohort studies investigating the impact of antibiotics, probiotics and diet on the brain and CNS functions will inform us of the importance of bottom-up mechanisms in neuropsychological conditions. Further research in this emerging area will provide novel targets for interventions in psychological disorders.

References


**Biographies**

**Shakuntla Gondalia** is as Postdoctoral Fellow at Swinburne University of Technology, Victoria and her research interest incorporates gastrointestinal microbial ecology and nutritional intervention with the potential to improve the health and cognitive performance. Her research aims to better understand the effective mechanisms of GI microbiota, nutritional and dietary intervention on individual’s physiological and psychological health condition.

**Professor Andrew Scholey** is director of the Centre for Human Psychopharmacology at Swinburne University, Melbourne. He is a leading international researcher into the neurocognitive effects of natural products, supplements and food components, having published over 160 peer-reviewed journal articles, books and book chapters. Scholey has been lead investigator in a series of studies into the human biobehavioural effects of natural products, and their neurocognition-enhancing and anti-stress/anxiolytic properties (including first-into human neurocognitive assessment of Ginseng, Sage and Lemon balm among others). His current research focuses on neuroimaging and biomarker techniques to better understand the mechanisms of cognitive enhancement.