Functional Role of Prebiotic Supplement in Brain Signalling

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Abstract

Prebiotics are a class of nutrients, typically non-digestible fibre compounds observed in food which may induce the growth of beneficial microorganisms with greater influence in the gastrointestinal tract and gut microbiota. Prebiotics may pass through the upper part of the gastrointestinal tract and stimulate advantageous bacterial growth. The function and composition of gut microbiota can be altered using prebiotics. Gut bacteria are involved in the physiological processes including immunomodulation, adiposity, energy balance and electrophysiological activity of the central nervous system. Prebiotics not only possess its activity against infectious agents but also have actions on brain-derived neurotrophic factors, neurotransmitters and synaptic proteins. Prebiotics hold greater influence on cognition and psychiatric disorders. Prebiotics like wheat fibre can be considered as a treatment option for autism. In this regimen, the proposed book chapter will focus towards gut microbiota, probiotics, role of prebiotics and its supplements in supporting gut microbial growth, brain signalling, abnormalities in brain signalling, clinical and preclinical findings related to psychiatric changes and in overcoming abnormal psychiatric changes.

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9.1 Introduction

The majority of microorganisms in the gastrointestinal tract are collectively known as human gut microbiota (Xifra et al. 2016). Gut microbiota function as basic physiological processes and at the same time alter the host susceptibility to diseases (Yang et al. 2020). About three million microorganisms and thousands of bacterial phylotypes are involved in a different function of host metabolism. The gut microbiota consists of more than 150 genes. About 80–90% of the bacterial phylotypes include both gram-negative bacteria (Bacteroidetes, Proteobacteria) and gram-positive bacteria (Actinobacteria, Proteobacteria) (Xifra et al. 2016).

The gut microbiome comprises all microorganisms and their genome present in the intestinal tract and contributes towards the development of the hypothalamic-pituitary-adrenal (HPA) axis. Gut bacteria are greatly involved in the regulation of various physiological processes such as immunomodulation, adiposity, energy balance and electrophysiological activity of the enteric nervous system (ENS) (Sarkar et al. 2016). Gut microbiota composition can be altered in patients with both metabolic and neuropsychiatric symptoms. Studies reported that the gut microbiota has a major role in regulating the functions of the gut-brain axis. The functions of the gut-brain axis include metabolism, inflammation, brain function and behaviour (Fernandez et al. 2017).

A core gut microbiota was seen among family members, but there are inter-individual variations in the presence of gut microbiota in each patient (Xifra et al. 2016). High-throughput and low-cost sequencing methods are an effective technique to find the composition and structure of gut microbiota, and hypervariable regions (V1–V9) of the ribosomal RNA present in bacteria may help to find the species easily. It is reported that the microbiota of each individual is varying after birth because the gastrointestinal (GI) tract is getting colonized rapidly and changes in the microbiota occur due to disease, diet and drugs such as antibiotics. The presence of *lactobacilli* is higher in the microbiota of vaginally delivered infants as compared to caesarean section which slowed down and diminished the colonization of the *Bacteroides* genus but colonized by facultative anaerobes like *Clostridium* species. The development of microbiota in its initial stage is controlled by two phyla, such as Actinobacteria and Proteobacteria, with low microbial diversity. The microbiota of infants resembles that of adults, and the composition of the microbiota will be stable in adulthood. The changes in microbiota are expected due to various life events. In geriatric cases (age over 65), the presence of Bacteroidetes phyla and *Clostridium* cluster IV is reported as compared to that of younger subjects. In elderly patients, the metabolic process such as short-chain fatty acid (SCFA) production and amylolysis

is reduced, and thereby the proteolytic activity gets increased (Elizabeth and Nathalie 2017). The intestinal mucosa is vital for health management since it is important in the growth and maintenance of the physiological system. Altered intestinal mucosa significantly affects the development and functions of the brain. Infections or paralytic ileus, prolonged hospitalization and death post stroke are the major clinical complications reported for brain injury (Houlden et al. 2016).

The major beneficial gut microbiome are fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) (Burokas et al. 2017). Some of the reported factors which regulate the microbiota are prebiotics, probiotics, antibiotics, bacterial infection, genetically modified bacteria and faecal microbiota transplantation (Burokas et al. 2015). Antimicrobials, prebiotics, probiotics and diet are some of the modulators of the gut microbiome which function according to the type and phase of the disease (Kao et al. 2019).

9.2 Probiotics

Probiotics are living microorganisms that support humans as well as animals when administered adequately. The most commonly used probiotics are different species of *lactobacilli* and *bifidobacteria*. They provide beneficial effects on CNS dysfunction during neurological disorders by increasing microbiota diversity and beneficial bacteria compositions (Bagheri et al. 2019). Probiotics with various gut microbiota such as strains of *bifidobacteria* and *lactobacilli* have shown anxiolytic and procognitive effects in rodents and humans; therefore, this can be used for the treatment of brain disorders (Alexandra et al. 2018). Probiotics are reported to exhibit preventive activity against the neurodegenerative disease such as Alzheimer's disease. The probiotic mixture of *L. acidophilus*, *B. bifidum* and *B. longum* and another combination of *L. acidophilus*, *L. casei*, *B. bifidum* and *L. fermentum* has positive effects on the treatment of Alzheimer's disease. A mixture of probiotics (*L. acidophilus*, *L. fermentum*, *B. lactis and B. longum*) has shown effects on modulating gut microbiota and improves memory deficits and oxidative stress in β-amyloid (1–42)-injected rats (Yang et al. 2020). The abnormal reactions were reversible through probiotic-induced bacterial recolonization (Sarkar et al. 2016). Thus, the probiotics can be used as an agent for regulating the gut microbiome and thereby modifying the health (Kazemi et al. 2019a, b).

9.3 Prebiotics

Prebiotics are selectively fermented ingredients first defined in the mid-1990s. Prebiotics help to improve the health of an organism by specific alterations in the composition and/or activity of the gastrointestinal microbiota (Alexandra et al. 2018; Brownawell et al. 2012). Glenn Gibson and Marcel Roberfroid in 1995 proposed the concepts of prebiotics initially. Prebiotics were described as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth

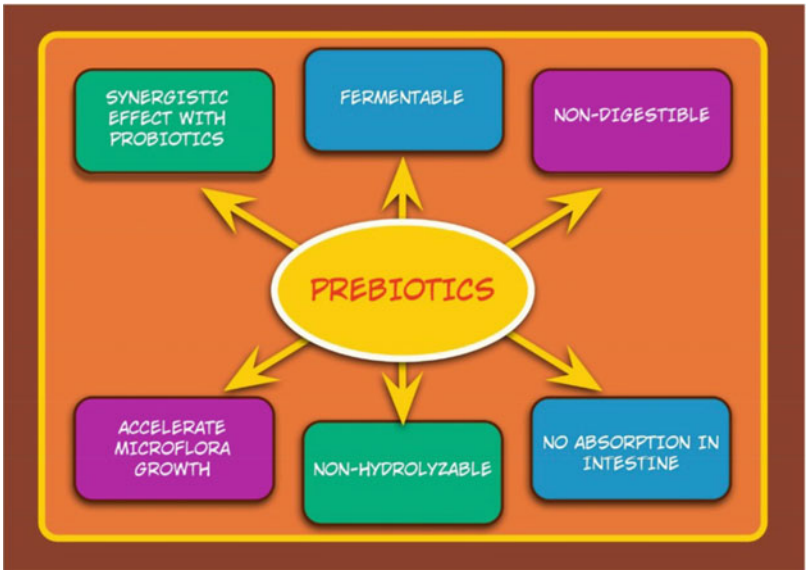

Fig. 9.1 Salient features of prebiotics

and/or activity of one or a limited number of bacteria in the colon and thus improving the host's health". Short- and long-chain fructans (FOS, inulin), lactulose and GOS are some of the prebiotics classified under this definition. The sixth meeting of International Scientific Association of Probiotics and Prebiotics held in 2008 had defined "dietary prebiotics" as "a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host's health". The various types of prebiotics are fructans (inulin and fructo-oligosaccharide or oligofructose), galacto-oligosaccharides, starch, glucose-derived oligosaccharides, non-carbohydrate oligosaccharides and other oligosaccharides. Small amounts of FOS and GOS are present in foods. An ideal prebiotic should not be degraded in stomach pH and enzymes, absorbed in the gastrointestinal tract and can also be fermented by the gut microbiota (Davani-Davari et al. 2019). The salient features of prebiotics are shown in Fig. 9.1.

9.4 Prebiotics Role in Supporting Gut Microbial Growth

Prebiotics are a group of beneficial nutrients which stimulate some of the bacterial species in the gut microbiota to produce beneficial effects on the host. Its degradation products (short-chain fatty acids) are released into the systemic circulation which affects the functions of the gastrointestinal tract and other organs (Kazemi et al. 2019a, b). The carbohydrates which are not digested in the small intestine may undergo fermentation in the large intestine by the gut microbiota and produce short-

chain fatty acids and lactic acids which may stimulate the bacteria (*bifidobacteria* and *lactobacilli*). These bacteria are beneficial to improve the health (Alexandra et al. 2018). Several studies reported the effective role of prebiotics in reducing the risk and severity of GI infections and inflammations such as diarrhoea, inflammatory bowel disease, ulcerative colitis and bowel function disorders like irritable bowel syndrome. Prebiotics promote mineral absorption and lower the risk of obesity (Brownawell et al. 2012).

Prebiotics support the growth and activity of probiotics (Davani-Davari et al. 2019). The use of prebiotics is a better choice for the maintenance of brain health and adjunctive treatment for neuropsychiatric disorders. The central expression of brain-derived neurotrophic factor (BDNF) and *N*-methyl-D-aspartate receptor (NMDAR) subunits is reduced in the absence of gut bacteria. The oral probiotics increase the brain-derived neurotrophic factor (BDNF) and impart significant anxiolytic effects. Prebiotics did not alter glutamate, glutamine, L-serine, L-alanine or D-alanine levels in the brain. The effect of galacto-oligosaccharides on the components of central NMDAR signalling was greater than fructo-oligosaccharides and reflects the proliferative potency of galacto-oligosaccharides on microbiota (Savignac et al. 2013). Some disruptions in the normal gut microbiota may cause depression (Kazemi et al. 2019a, b). Little amounts of prebiotics are usually present in our daily diet, and they have an extensive role in improving health. FOS and GOS are the main source for manufacturing prebiotics (Davani-Davari et al. 2019).

9.5 Brain Signalling (Microbiome-Gut-Brain Axis)

There are considerable interactions between the gut microbiota and the CNS through the gut-brain axis which maintains the health of an organism (Tarr et al. 2015; Sarkar et al. 2016). The mechanisms which are proposed for the effects of microbiota on the gut-brain axis are the regulation of the functions of the autonomic nervous system, the neuroendocrine system and the immune system (Yang et al. 2020). The abnormalities associated with brain signalling are shown in Fig. 9.2.

Usually, the gut microbiome and the CNS get matured during the early period of life; hence, this period is influential for the growth and development of normal physiology of an individual. The gut microbiome helps to improve the neurodevelopmental process through the regulation of neuronal, hormonal and immunological pathways. Interruptions to the gut microbiome may cause abnormalities in the responses of the HPA axis and brain-derived neurotrophic factors which may crucially affect the normal behaviour of an individual (Loughman et al. 2020). The gut microbiome has extensive effects on the functioning of the brain such as psychological processing, behaviour, neurodevelopmental process and during changes in gene expression in particular brain regions (Burokas et al. 2017).

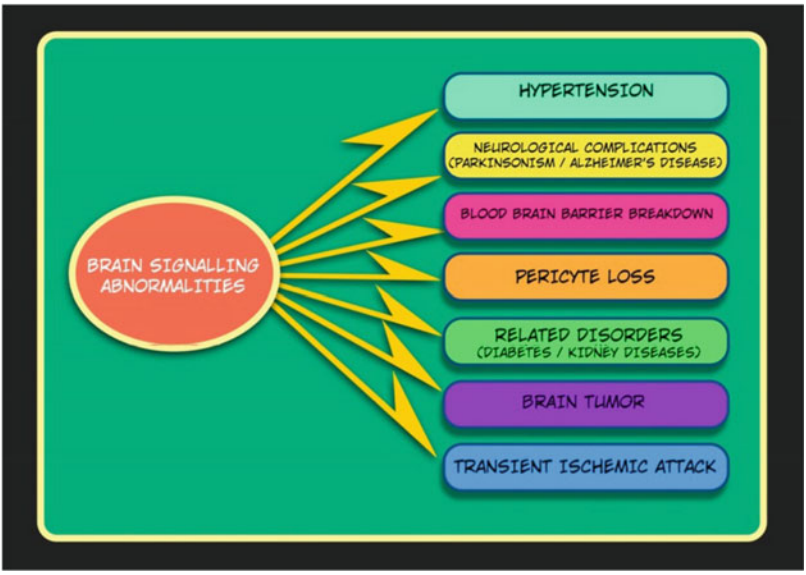

Fig. 9.2 Brain signalling abnormalities

9.5.1 Neural Pathway

The enteric nervous system (ENS) has a significant role in controlling gut functions to maintain the general homeostasis by regulating the neurotransmitters and thereby acts as the "brain of the gut". The active participation of the major parasympathetic nerve (vagus nerve) is essential. With the help of the vagus nerve (a major nerve in the parasympathetic system), dorsal root ganglia and somatosensory afferents, the afferent signals from the GI tract are transmitted to the brain stem (periaqueductal grey) and finally allow the distribution to the brain areas such as the hypothalamus, thalamus, limbic system and somatosensory cortex. The efferent signals are sent back to the enteric nervous system (ENS) through the spinal or vagal efferents (Burokas et al. 2015). The mode of communication of the gut to the brain is through vagus nerve innervation, immune system activation by cytokine/chemokine activity and release of neuropeptides, hormone, cortisol secretion and microbial metabolites. Studies have shown that the vagus nerve has effects on the bidirectional communication of the microbiota-gut-brain axis (Davani-Davari et al. 2019).

9.5.2 Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis is a group of structures which include the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland and the adrenal gland. The HPA axis plays a vital role in the regulation of stress responses (Smith and Vale 2006). Alterations in the gut

microbiota activate the HPA axis by the release of various mediators (pro-inflammatory cytokines, small bioactive molecules, prostaglandins, microbial antigens, ileal corticosterone and short-chain fatty acids). Some bacterial species interact with the vagus nerve and produce vagal signals which activate the HPA axis that may lead to gut dysbiosis and altered permeability (Misiak et al. 2020). Noradrenaline is the main neurotransmitter in the sympathetic nervous system which can alter the goblet cell function and influences the gut microbiota indirectly. The sympathetic nervous system is activated when nor-adrenaline is released and it circulates in stroke conditions (Houlden et al. 2016).

9.5.3 Tryptophan and 5-Hydroxytryptamine Metabolism

Tryptophan is an essential amino acid usually present in protein-rich diet. It gets absorbed from the gut to the systemic circulation and exists as free and albumin-bound fractions through large amino acid transport, and it can cross the BBB easily for participating in the biosynthesis of 5-hydroxytryptamine (5-HT). The mucosal 5-HT can activate the peristaltic movement of the gastrointestinal tract. *Clostridium* bacteria have been reported for its active role in the activation of 5-HT synthesis and the regulation of peristaltic movement of the GI tract (Golubeva et al. 2017). Both probiotics and prebiotics or its combination can be used for curing GI symptoms and autism spectrum disorder (ASD)-related symptoms. An increased level of *Clostridium* bacterial species with its corresponding increase in plasma 5-hydroxytryptamine was reported in children affected with ASD, and the treatment with a combination of probiotics and fructo-oligosaccharides (FOS) has shown marked reduction in the 5-HT level (Wang et al. 2020). The hippocampal monoamine neurotransmitter gene plays an important role in regulating brain activities such as behaviour and its functions. Derangements in the functions of monoamine neurotransmitter during childhood alter the development of brain functions which leads to the development of brain-related disorders such as neuropsychiatric disorders, pyramidal and extra-pyramidal motor disorders, epilepsy, etc. A study with anxiety and depression-induced germ-free mice models administered with commensal microbiota reported a significant increase in the level of serotonin and dopamine in the striatum which reveals the positive impact of probiotic role in modulating behavioural changes (Pan et al. 2019). The presence of microbiota associated tryptophan metabolites such as 5-hydroxy indoleacetate, melatonin, N-acetyl tryptophan, tryptamine, indol-3-acetate, methyl indole-3-acetate, and methyl indole-3-propionate in urine has also been linked to a direct role of the human metabolome in gut microbial metabolism (Pavlova et al. 2017). An isoquinoline alkaloid, palmitin, is reported for its activity against ulcerative colitis, protecting from gut microbiota dysbiosis and modulating tryptophan catabolism (Zhang et al. 2018).

9.5.4 Immune System

The development and functions of both innate and adaptive immune systems can be regulated by the gut microbiota (Dhar and Mohanty 2020). After injury, a rapid tissue reaction was seen, including the generation of reactive oxygen species, purine metabolites, mitochondrial and polysaccharide components. These factors then bind to pattern recognition receptors (PPRs) such as toll-like receptors (TLRs) and nucleotide binding receptors (NODs), presenting innate cells with gut microbial ligands that help defend against secondary infections (Sabin and Echeverri 2020). TLRs can recognize the microorganism-associated molecular patterns and pathogen-associated molecular patterns and activate the immune responses. Microorganisms such as *Bacteroides*, *Lactobacillus* and *Bifidobacterium* may bind to the innate cell receptors and secrete some metabolites such as short-chain fatty acids (butyrate, acetate, propionate and secondary bile acids) (Dhar and Mohanty 2020). The mood and cognition get altered directly (toll-like receptors) and indirectly (immune activation) through mechanisms involved in some bacterial products such as gram-negative endotoxins (Beilharz et al. 2016). Brain-derived neurotrophic factor (BDNF) which is widely distributed in the nervous system has effect on pro-inflammatory cytokines and regulates the neuroplasticity and inflammation and inhibits the cell apoptosis during gut inflammation. The reduced expression of BDNF is related to inflammation and stress. Studies reported that gut microbiota have effects on BDNF levels and behaviours in mice (Li et al. 2018). Lipopolysaccharides are toll-like receptor ligands that activate the nuclear factor-k (NF-k) pathway, resulting in dysbacteriosis of the gut microbiota, associated low grade chronic systemic inflammation during ageing, and cognitive impairment (Yang et al. 2020). Toll-like receptors, NOD-like receptors (NLRs) and RIG-I-like receptors are some of the pattern recognition receptors which can identify the cell components of gut microbiota such as lipopolysaccharides, peptidoglycan and flagellin and can activate cytokines, hormones and some molecular signals to the CNS (Davani-Davari et al. 2019).

9.5.5 Gut Hormonal Response

The pancreatic hormone GLP-1 is classified as an incretin which can bind to its receptor GLP-1R. in the enteric nervous system and stimulates the vagus nerve to activate the gut-brain-periphery axis. As a result, insulin secretion is stimulated while glucagon release is inhibited. GLP-1 has effects on both the peripheral and central nervous systems. Dysbacteriosis of gut microbiota may lead to degeneration of nerves and muscles in the digestive system and also shows that GLP-1 resistance G proteins, adenylate cyclase, cyclic AMP (cAMP), protein kinase C (PKC), cAMP response element binding protein (CREB), nitric oxide (NO) and NO synthase (NOS) are the main signalling molecules responsible for GLP-1 intracellular action for neurons and B cells (Grasset et al. 2017).

9.6 Factors Affecting the Microbiome-Gut-Brain Axis

The factors affecting the microbiome-gut-brain axis are diet, age, sex and some drugs such as antibiotics. Any changes in the structure of gut microbiota may affect the normal functioning of the host (An et al. 2020).

9.6.1 Role of Diet in the Microbiome-Gut-Brain Axis

The composition of microbiota varies according to the daily diet (Fulling et al. 2020). Intake of high levels of saturated fats and processed sugars leads to obesity, and its short-term exposure impairs memory and causes neurological diseases. Varying diet is independent of hippocampal, hypothalamic and neuroplasticity markers and brain-derived neurotrophic factors. However, it changes the microbial composition in a variety of ways, including memory, inflammation-related hippocampus genes, and the gut microbiome (Burokas et al. 2015). The microbiota-colon-brain axis plays an important role in the regulation of energy metabolism. A study has also reported the importance of gut microbiota in the development of obesity and the memory loss associated with the diet containing high saturated fatty acids (Zhang et al. 2019). Feed deprivation in fish showed dangerous effects in their behaviour and stress physiology, which consequently leads to disease outbreak. Functional ingredients in diet affect the physiology and stress responses of host organism. Feed deprivation in some cases influenced anxiety-like behaviours (Forsatkar et al. 2017). The role of macronutrients in the complete diet is greater and can be considered as a better treatment option for diet-induced memory deficits (Beilharz et al. 2016).

9.6.2 Role of Age in the Microbiome-Gut-Brain Axis

Any exposure to environmental factors causes permanent impact on brain function during adolescence and early adulthood. Mental uneasiness due to the lack of gut bacteria affects gut-brain communication and brain development which may cause psychiatric disorders. A study has reported the effects of gut bacterial depletion from weaning onwards on adult cognitive, social and emotional behaviours. Any depletion in the gut microbiota affects the adult brain by reduced anxiety-induced cognitive deficits, changes in the tryptophan metabolic pathway and reduction in brain-derived neurotrophic factor (BDNF), oxytocin and vasopressin expression (Desbonnet et al. 2015). Adolescence is a critical period of growth that is marked not only by changes in behaviour and the neuroimmune system, and also based on the development of gut microbiota (Fulling et al. 2020). Traumatic brain injury (TBI) is highly reported in children and adolescents. The combination of resveratrol, prebiotic fibre and omega-3 fatty acids can be used for the treatment of TBI which may support to prevent injury-related deficits in medial prefrontal cortex (mPFC) spine density (Salberg et al. 2017). Ageing may alter the composition of gut

microbiota which may lead to inflammation and dementia through the suppression of TLR4- and RIG-I-mediated NF-κβ signalling. Activation of microglia and neuro-inflammation occurs not only due to neuronal loss and oxidative changes but also due to age-related dementia (Yang et al. 2020). An increase in pathogenic bacteria was observed in the gut microbiota of aged persons than beneficial microbiota. An impaired microbiota may cause a chronic inflammation and enhance the upregulation of neurotrophic factors such as neurotrophins and neuropoietic cytokines. Both prebiotic and probiotic supplements can modulate gut microbiota and improve the physiological state and thereby serve as a best therapeutic tool for age-related cognitive impairment (Romo-Araiza and Ibarra 2020).

9.6.3 Role of Sex in the Microbiome-Gut-Brain Axis

Sex differences should be examined in neurogastroenterology and psychiatric research with significant changes in behaviour due to changes in gut microbiota in sex differences. Gut microbiota has a great influence in the expression of genes in the medial prefrontal cortex. Any changes in the digestive system during childhood may affect the composition of the gut microbiome, resulting in microbial imbalance, improper functioning of the intestinal barrier and disruptions in brain development owing to dysfunction of gut-brain axis(Rincel et al. 2019).

9.6.4 Role of Drugs in the Microbiome-Gut-Brain Axis

Antibiotics may alter the structure and composition of the gut microbiota (Desbonnet et al. 2015). Triptolide, a plant constituent used for the treatment of autoimmune disease, can produce major hepatic toxicity by destroying the Firmicutes and reducing the short-chain fatty acids. The triptolide toxicity can be reduced using the intake of prebiotics, probiotics and short-chain fatty acids such as propionate (Huang et al. 2020).

9.7 Abnormalities in Brain Signalling

Both the central nervous system and the digestive system are interconnected with neuroendocrine and humoral pathways (MacLaren et al. 2019). Studies reported that stressor exposure and acid suppression significantly alter gut microbiota community (Tarr et al. 2015). Early life stress is a widely reported risk factor for the development of psychiatric disorders and may cause enduring changes in the gut microbiota that lead to the development of abnormal neuronal and endocrine functions. The gut microbiota influence the brain development and function by affecting inflammatory mediators, the hypothalamic-pituitary-adrenal axis and neurotransmission. Early life stress from social isolation can lead to alterations in gut microbiota, anxiety,

learning/memory impairment, low levels of hippocampal IL-6, IL-10, and neurogenesis (Doherty et al. 2017).

Gut bacteria can influence appetite by participating in the hunger pathway both locally and centrally through the use of molecular derivatives generated during its various phases of growth. A combination of altered social and feeding behaviours is common in children with autism spectrum disorder (ASD). The α-melanocyte-stimulating hormone (α-MSH) is a specific anorexigenic neuropeptide in the brain acting on melanocortin receptor type 4 (MC4R) which is also involved in the feeding behaviour. Oxytocin is another neuropeptide which is critically involved in the social behaviour. The brain-derived neurotrophic factor (BDNF) signalling produced by the neurons has been observed in the pathophysiology of ASD and contributes to the anorexigenic effects. It has been reported that the release of β-endorphin independent of α-MSH in response to endocannabinoids blocks the proopiomelanocortin (POMC) neurons. Leptin, obtained from adipose tissue and stomach, can directly and indirectly trigger POMC neurons by controlling the energy homeostasis and blocking the inhibitory γ-aminobutyric acid from adjacent neuropeptide Y of the arcuate nucleus (Fetissov et al. 2019).

Gut microorganisms have a major role in the biotransformation of phospholipids. In the presence of the enzyme phospholipase D, certain bacteria in the gut may hydrolyze phosphatidylcholine to choline, and the released choline will be converted in to trimethylamine (Chittim et al. 2019). Trimethylamine (TMA) found in gut microbiota may be oxidised to Timethylamine N-oxide, which can affect the inflammatory process and induce cardiovascular disorders. Choline, L-carnitine and ergothioneine are the main precursors of TMA. Choline is present in many foods in its free and combined forms such as phosphatidylcholine, phosphocholine and sphingomyelin (Janerio et al. 2018). The neural excitation and inhibition balance can be regulated by some neurotransmitters such as γ-aminobutyric acid (GABA) and glutamate (Sarkar et al. 2016).

9.8 Disease Occurring Due to Abnormalities in Brain Signalling

Disorders affecting the microbiota-gut-brain axis are metabolic disorders (obesity, diabetes), functional gastrointestinal disorders (irritable bowel syndrome), stress, anxiety, depression, neurodegenerative disorders (Alzheimer's disease, multiple sclerosis, Parkinson's disease), neurodevelopmental disorders (autism, schizophrenia) and also addiction (alcohol dependence) (Burokas et al. 2015). A drastic change in the social and feeding behaviours of children having autism spectrum disorder was reported. Some neuropeptides such as α-MSH and oxytocin have a pivotal role in controlling the social and feeding behaviour (Fetissov et al. 2019). The human infant gut microbiota has enduring significance in the neurodevelopmental process. The cross-sectional connections between behaviour and gut microbiota in 77 human babies aged 18–27 months revealed a link between phylogenetic diversity and temperamental issues, especially in boys (Loughman et al. 2020). The correlation between prebiotics role and brain signalling is shown in Fig. 9.3.

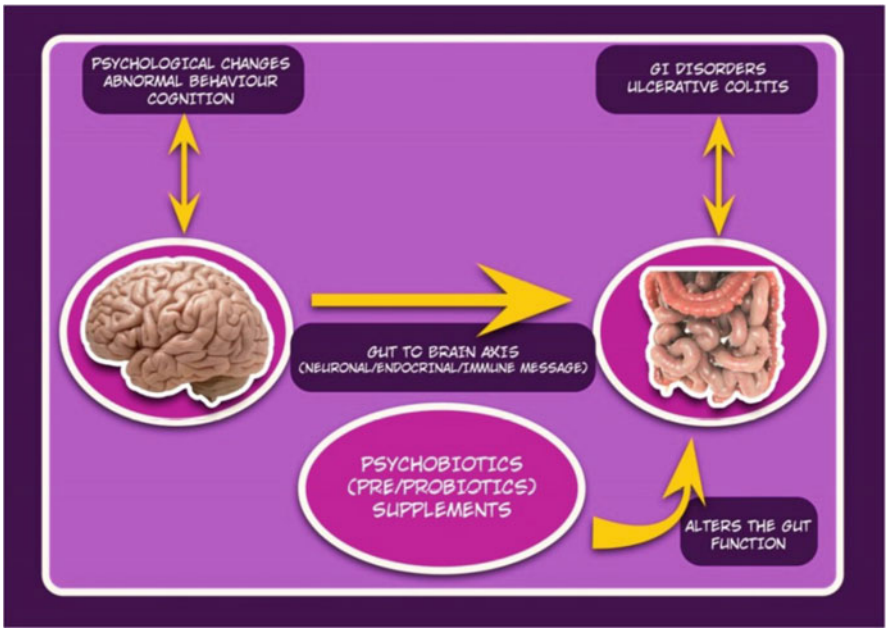

Fig. 9.3 Prebiotics role and brain signalling

Chronic Periodontitis (CP) is an infectious disease caused by inflammation in periodontal tissues, which is followed by the invasion of bacteria, endotoxins, and cytokines into the bloodstream with response to inflammation. Studies reported that CP can alter the normal oral and gut microbiota through the generation of plaque microorganisms and this may lead to the formation of various diseases in both the digestive system and the central nervous system (Xue et al. 2020).

The microbiota-gut-brain axis is extensively involved in the pathology of major depressive disorder (MDD) and regulates the functions of the brain. An increased expression of immune-modulating microbiota such as *Clostridia* was reported in experimental mice exposed to social defeat stress. An increased level of *Lactobacillus*, *Clostridium cluster III*, *Anaerofustis* and *Corynebacterium* was also reported in rats exposed to uncontrolled stress. The increased plasma adrenocorticotrophin and corticosterone levels in response to restraint stress in germ-free mice establish the direct link between the hypothalamic-pituitary-adrenal (HPA) axis and the microbiota (Sarkar et al. 2016).

Traumatic brain injury (TBI) is highly reported in civilians, military personnel and veterans and further aggravates to the symptoms of co-morbid post-traumatic stress disorder (Brenner et al. 2017). Probiotics can be used to treat human allergic diseases such as asthma and atopic diseases. Probiotics use has been shown to minimise the need of antibiotics, improve immune-related illnesses such as inflammatory bowel disease, metabolic syndrome, and diabetes, and to have positive health benefits on anxiety, depression, and gut discomfort (Davani-Davari et al. 2019).

The role of prebiotics in the management of metabolic and central nervous system-related diseases is reported in many studies (Ahmadi et al. 2019). Gut microbiota dysbiosis might be implicated in the pathophysiology of depression. Hence, probiotics, prebiotics and synbiotics have been administered in clinical trials with an attempt to relieve depressive symptoms (Vaghef-Mehrabany et al. 2020). Recent studies reported the significance of gut microbiota in the management of tumour growth (Li et al. 2020).

9.9 Clinical and Preclinical Findings Related to Psychiatric Changes

The role of the microbiota-gut-brain axis in health and diseases such as neuropsychiatric disorders is gaining much importance. The understanding on the composition of prebiotics and the microbiota-derived metabolites acting on signalling of cellular pathways is much interesting (Neri-Numa and Pastore 2020). An altered composition of caecal microbiota with specific changes in Peptococcaceae and Prevotellaceae was observed in experimental stroke models, and the changes in the gut microbiota were observed in traumatic brain injury. To treat individuals with brain damage, altering the gut mucosa is a better alternative (Houlden et al. 2016). In a preclinical experiment, the behavioural, physiological and caecal microbiota profile of aged male mice was studied and reported the role of gut microbiota in increasing gut permeability and peripheral inflammation that cause the deterioration of behavioural, affective and cognitive functions in ageing (Scott et al. 2017).

Altered Schaedler flora (ASF) mice represent a unique model to elucidate mechanisms governing microbiota-gut-brain communication. ASF mice displayed marked anxiogenic behaviour as compared to conventionally reared mice (Lyte et al. 2019). A preclinical study reported the effects of stress and acid suppression on the distribution of gastrointestinal microbiota. The cognitive functions are regulated through several key biological processes in the hippocampus. Neurocognition may alter due to dysbiosis caused by acid suppression during stress (MacLaren et al. 2019).

The cerebrovascular disease like cerebral ischaemic stroke can alter the normal functions of gut microbiota including *Bacteroides*, *Escherichia*, *Shigella*, *Haemophilus*, *Eubacterium nodatum*, *Collinsella*, *Enterococcus*, *Proteus*, *Alistipes*, *Klebsiella*, *Shuttleworthia* and *Faecalibacterium*. The combination therapy for the treatment of cerebrovascular diseases with *Puerariae Lobatae Radix* (PLR) and *Chuanxiong Rhizoma* (CXR) has strong effects on the gut microbiome and cured the cerebral infarction and modified the nerve functions (Chen et al. 2019). It has been reported that child compound Endothelium corneum (CCEC) is effective for the therapy of functional dyspepsia (FD). Further, CCEC significantly enhanced gastric emptying and small intestinal transit of FD-affected rats and prominently suppressed gastrointestinal microinflammation. CCEC supressed over-activated POMC/Stat3/Akt pathway in the hypothalamus. CCEC enhanced gastrointestinal

motility probably through rebalancing the homeostasis of the brain-gut-microbiota axis (He et al. 2019).

Clinical investigations comparing standard enteral formula (SEF) against enteric formula with prebiotic content (EFPC) in terms of nutrition treatment-related outcomes in neurocritical care patients revealed the relevance of nutrition therapy in preventing protein debt. The use of EFPC compared to SEF was associated with significant higher total energy, carbohydrate, protein, lipid, enteral volume and fluid intake during each day of nutrition therapy (Tuncay et al. 2018).

A double-blind clinical trial was conducted to compare the effect of probiotic (*Lactobacillus helveticus* and *Bifidobacterium longum*) and prebiotic (galacto-oligosaccharide) supplementation, and an improvement in the BDI score, a decline in the kynurenine/tryptophan ratio and a rise in the tryptophan/isoleucine ratio were observed in MDD subjects who are supplemented with probiotics for 8 weeks as compared to the placebo who are not supplemented with probiotics (Kazemi et al. 2019a, b).

A double-blind placebo-controlled trial reported the effect of prebiotic and probiotic on serum inflammatory cytokines (TNF-α, IL-1ß, IL-6 and IL-10). A reduced BDI score in the prebiotic-treated group, a reduced cortisol level and an equilibrium in the cytokine levels were observed in both groups which are treated with prebiotics and probiotics. Probiotics have marked effects on improving the symptoms of depression (Kazemi et al. 2019a, b).

9.10 Prebiotics Role in Overcoming the Abnormal Psychiatric Changes

Prebiotics possess a greater role in overcoming the brain-related disease associated with the gut microbiota. Sialyllactose is a prebiotic which can alter the colonic and gut microbiota composition and reduce the stress and anxiety by regulating the immune and endocrine functions. The prebiotic combination of FOS and GOS can reduce the level of corticosterone and L-tryptophan in stress conditions (Burokas et al. 2017). ProBiotic-4 is a probiotics product made up of Bifidobacterium lactis, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus acidophilus, which have effects on the microbiota-gut-brain axis. A study reported that ProBiotic-4 can be used for the management of cognitive impairments in senile mice having impaired gut microbiota and can also reduce the age-related dysfunction of the intestinal and blood-brain barrier (Yang et al. 2020).

It has been reported that there is a relationship between the effect of prebiotic (oligofructose) treatment on dentate gyrus neurons and spatial memory but prebiotic administration did not improve behavioural alterations and associated reduction of hippocampal neurogenesis. Prebiotic administration improved excessive food intake and glycaemic dysregulations (glucose tolerance and insulin resistance) (Fernandez et al. 2017). Preclinical studies reported the beneficial effect of galacto-oligosaccharide for improving learning and memory deficits. Probiotics can raise the activity of anorexigenic gut hormones (peptide tyrosine tyrosine, glucagon-like

peptide 1 and leptin) and can decline the level of orexigenic hormones (ghrelin). Prebiotics are a better option for the treatment of schizophrenia (Kao et al. 2018). Both prebiotics and probiotics can be used for the management of the enteric nervous system (Davani-Davari et al. 2019).

9.11 Prebiotic Supplement in Overcoming the Psychiatric Changes

The lactic acid bacteria present in yogurts can modify the memory deficits during ageing (Scott et al. 2017). Resveratrol ameliorates the hepatic steatosis by modulating the gut microbiota. It increases the gene expression of fasting-induced adipose factor, decreases the expression of lipogenesis-related genes and proteins (SREBP-1, FAS and ACC) and reverses high-fat diet (HFD)-induced gut microbiota dysbiosis, with an increase in the relative abundance of Bacteroidetes and a decrease in that of Firmicutes and Proteobacteria (Xiaohan et al. 2020). A dihydroquinoline analog of agomelatine, *N*-(2-(7-methoxy-3,4-dihydroisoquinolin-1-yl)ethyl) acetamide hydrochloride (NMDEA), has reduced the depression in chronic unpredictable mild stress-induced mice models. NMDEA is involved in regulating the neuro-inflammatory markers (IL-1β, IL-6 and iNOS) and gut microbiota by acting on the microbiota-inflammasome-brain axis and can be used for the treatment of dysbiosis of bacterial species (An et al. 2020). Milk oligosaccharides such as 3′ Sialyllactose and 6′ Sialyllactose support normal microbial communities and behavioural responses during exposure to stress, potentially through effects on the microbiota-gut-brain axis. Milk oligosaccharides helped to maintain normal behaviour on tests of anxiety-like behaviour and normal numbers of DCX+ immature neurons (Tarr et al. 2015). The various prebiotic supplements in overcoming psychiatric changes are shown in Table 9.1.

The role of chronic prebiotic (combination of fructo-oligosaccharides and galacto-oligosaccharides) treatment (for 3 weeks) in anxiety, depression, cognition, stress response and social behaviour using C57BL/6J male mice was evaluated in plasma corticosterone, microbiota composition and caecal short-chain fatty acids and reported for its efficient antidepressant and anxiolytic actions. Prebiotics can regulate the gene expression in the hippocampus and the hypothalamus (Burokas et al. 2017). Bimuno™ galacto-oligosaccharide (B-GOS) is a prebiotic that can activate *N*-methyl-D-aspartate (NMDA) and promote the growth of useful gut bacteria (Gronier et al. 2018). Bimuno™ galacto-oligosaccharide (B-GOS) can reduce the weight gained through olanzapine intake and modify the memory (Kao et al. 2019). Nutrient supplements are essential for the proper development of the brain. Prebiotics and bioactive milk fractions are some of the agents which can act on the microbiota-gut-brain axis and can supplement nutrients for the brain to enhance the memory and maintain the emotional behaviours (Mika et al. 2018). Prebiotics which are supplemented through food undergo biotransformation in the presence of colonic microorganisms and release some metabolites such as short-chain fatty acids into the lumen of the gastrointestinal tract and alter the composition of host (Neri-Numa and

Table 9.1 Prebiotic supplements in overcoming psychiatric changes

Supplement name	Mode of action	Therapeutic benefit	References
Prebiotics inulin or mucin	Mucin fails to inhibit tumour growth in germ-free mice	For colon cancer	Li et al. (2020)
	Inulin enhances the efficacy of a MEK inhibitor against melanoma		
Resveratrol	Increases the gene expression of fasting-induced adipose factor	Ameliorates the hepatic steatosis	Xiaohan et al. (2020)
N-(2-(7-methoxy-3,4-dihydroisoquinolin-1-yl)ethyl)acetamide hydrochloride	Regulating the neuro-inflammatory markers (IL-1β, IL-6 and iNOS)	Antidepressant action	An et al. (2020)
Soybean peptides Maillard reaction products (SMRPs)	Modulating gut microbiota to alleviate ageing-related disorders in D-galactose-induced ICR mice	Flavour enhancer and potential prebiotic which retard the ageing process	Zhang et al. (2020)
Ethanol-precipitated glycans from the softwood hemicellulose autohydrolysate	Stimulate in vitro growth of *Bifidobacterium adolescentis*	Cardioprotective	Deloule et al. (2020)
Bimuno™ galacto-oligosaccharides (B-GOS)	Activate *N*-methyl-D-aspartate (NMDA) and promote the growth of useful gut bacteria	Memory enhancer, treatment option for neuro-inflammation	Gronier et al. (2018), Kao et al. (2019)
Water-soluble, non-digestible polysaccharides isolated from sago and acorn	Reduce high-fat diet-induced defects	Type 2 diabetes mellitus	Ahmadi et al. (2019)
Phenylethanoid glycosides (magnoloside A)	Modulate the composition of gut microbiota	Used for abdominal bloating, pain and indigestion	Xue et al. (2019)
Prebiotics and bioactive milk fractions	Enhance memory and maintain the emotional behaviours	Nutrient supplements for brain development	Mika et al. (2018)
Combination of fructo-oligosaccharides and galacto-oligosaccharides	Regulate the gene expression in the hippocampus and the hypothalamus	Antidepressant and anxiolytic	Burokas et al. (2017)
Lactic acid bacteria present in yogurts	–	Modify the memory deficits during ageing	Scott et al. (2017)
Psychobiotics	Beneficial bacteria have greater influence on the gut	Better anxiolytic and antidepressant agents	Sarkar et al. (2016)

(continued)

Table 9.1 (continued)

Supplement name	Mode of action	Therapeutic benefit	References
	microbiome and the immune system		
Milk oligosaccharides (3′ Sialyllactose and 6′ Sialyllactose)	Support normal microbial communities and behavioural responses during exposure to stress	Maintain normal behaviour on tests of anxiety-like behaviour and normal numbers of DCX+ immature neurons	Tarr et al. (2015)

Pastore 2020). Water-soluble, non-digestible polysaccharides isolated from sago and acorn have shown positive effects to reduce the high-fat diet-induced defects in the biotransformation of glucose through the effect on the microbiota-gut-brain axis and can be used as a better therapeutic tool against type 2 diabetes mellitus (Ahmadi et al. 2019). Soybean peptides Maillard reaction products (SMRPs) as a flavour enhancer were reported as a potential prebiotic on modulating gut microbiota to alleviate ageing-related disorders in D-galactose-induced ICR mice. SMRPs have been reported to elevate the diversity of gut microbiota and ameliorate microbial community structure (Zhang et al. 2020).

The ethanol-precipitated glycans from the softwood hemicellulose autohydrolysate were able to stimulate in vitro growth of *Bifidobacterium adolescentis*, but to a much lesser extent than that of adherent-invasive *E. coli*, *B. adolescentis* was the best producer of SCFA. When mice were fed with the ethanol-precipitated fraction, the relative abundance of Bacteroidetes raised while that of Proteobacteria diminished, suggesting change towards a less obesogenic microbiome. Following treatment, lipid analysis showed a decrease in cholesterol, bile acids and free fatty acids, indicating a potential cardioprotective role (Deloule et al. 2020). The importance of gut microbiota in anti-tumour immunity and the potential therapeutic role for prebiotics were studied by the addition of the prebiotics inulin or mucin to the diet of C57BL/6 mice. Mucin fails to inhibit tumour growth in germ-free mice, indicating that the gut microbiota is required for the activation of the anti-tumour immune response. Inulin limits tumour growth in syngeneic mouse models of colon cancer and NRAS mutant melanoma and enhances the efficacy of a MEK inhibitor against melanoma (Li et al. 2020). Magnoloside A, a phenylethanoid glycoside, was isolated from the traditional Chinese medication 'Hou Po,' which is frequently used to alleviate stomach bloating, discomfort, and indigestion. Magnoloside A can modulate the composition of gut microbiota. Preclinical studies reported that magnoloside A has activity against functional dyspepsia through the activation of peptide hormones such as gastrin, motilin and calcitonin and reducing the rate of 5-hydroxytryptamine and nitric oxide synthase (Xue et al. 2019).

Psychobiotics are also beneficial bacteria that have greater influence on the gut microbiome, the brain, the enteric nervous system and the immune system and can be used as better anxiolytic and antidepressant agents (Sarkar et al. 2016).

9.12 Conclusion

Prebiotics are selectively fermented non-digestible food ingredient that helps to maintain the host's health by stimulating the growth or activity of the gastrointestinal microbiota. The gut microbiota has strongly interacted with the central nervous system (CNS) through the gut-brain axis and maintains the health of an organism. Prebiotics play a major role in overcoming the abnormal psychiatric changes such as anxiety-like behaviour, impairment in learning and memory, depression, cognition, stress response, social behaviour, synaptic injuries and neurodegeneration. Non-digestible oligosaccharides with prebiotic properties are extensively used for stimulating the beneficial bacteria such as *bifidobacteria* and *lactobacilli*. Several studies have proven the effect of prebiotics in the central nervous system and its effective role in the management of psychiatric disorders in connection with the gut microbiota. Human microbiota is a potential diagnostic and therapeutic tool for many disorders affecting the gut-brain axis, and the function of prebiotics in the treatment of such diseases is now the most intensive area of study. The future works should be required for understanding the mechanisms involved in microbiota and brain functions, development of novel prebiotics for the regulation of altered gut microbiota and treatment of neurological diseases.

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