Chapter 7
Microbiota-Gut-Brain Axis in Neurological Disorders

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1 Introduction

The human body accommodates a multitude of microorganisms that inhabit various anatomical sites, such as skin, mucosa, gastrointestinal tract, respiratory tract, urogenital tract and mammary glands, and are collectively defined as the microbiome, the composition and functions of which are crucial to health and survival (Moos et al. 2016). Among the different organ systems that coordinate the functions of the human body, central nervous system comprising the brain and spinal cord, plays a primary role in controlling awareness, movements, sensations, thoughts, speech and memory by integrating sensory information and responding accordingly. Furthermore, the microbiome engages in complex interactions with the organ systems of the human body thereby regulating the functions of both the entities. Such relationships between the central nervous system (CNS) and the gut microbiome have been explored in detail and is termed as microbiome-gut-brain (MGB) axis, a complex bidirectional inter-communication that exists between the gut microbiome and the crucial areas of the CNS (Malan-Muller et al. 2018; Cryan 2019). Various neuroactive compounds such as neurotransmitters, metabolites, cytokines, and hormones are synthesised by the gut microbiota and the host as a result of this interaction. These neuromodulatory substances gain access to the brain by different pathways, thus affecting the local homeostasis. Dysregulation of the MGB axis has been implicated in the pathogenesis of various

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neuroinflammatory, neurodevelopmental and neurodegenerative diseases which is mediated by either a direct line of communication through vagus nerve or immune system activation or both (Cryan 2019). In turn, gut microbiota composition is influenced by the brain in response to stress and endocrine factors (Tremlett et al. 2017).

The specific aetiology and trigger for many of the neurodevelopmental and neurodegenerative diseases remain elusive to the scientific community. An intricate interplay of genetic and environmental factors is attributed to their pathogenesis (Tremlett et al. 2017). There is accumulating evidence suggesting a definitive role of human gut microbiome in the pathogenesis of Parkinson's disease (PD), multiple sclerosis (MS) and autism spectrum disorders (ASD) whereas animal and human studies are ongoing to elucidate the role of microbiome in Alzheimer disease (AD), stroke, traumatic brain injury, amyotrophic lateral sclerosis and glioma (Cryan 2019). Prebiotics, probiotics, diet modifications, aerobic exercises and microbial transplantation are the few interventions employed for targeting gut dysbiosis in neurological disorders, subject to critical screening and evaluation (Tremlett et al. 2017; Kang et al. 2017; Gubert et al. 2018; Yang et al. 2019).

2 Microbiome-Gut-Brain Axis

The bidirectional interactions in the MGB axis are perpetuated through direct and indirect pathways. These pathways are mediated by the following components, (i) endocrine (hypothalamic-pituitary-adrenal [HPA] axis); (ii) immune-reactive molecules (cytokines and chemokines); (iii) metabolic pathways; (iv) limbic system; and (v) neural system (afferent and efferent pathways) (Malan-Muller et al. 2018). The communication is also dependent on the permeability of the blood-brain barrier (BBB) and the intestinal epithelial barrier (IEB) (Lyte and Cryan 2014).

2.1 Gut Microbiota

The microbiota colonising the human gastrointestinal tract is a collection of bacteria, archaea and eukaryotes which have co-evolved in a mutual relationship over the years. An estimated 10^{14} organisms inhabit the gastrointestinal tract which supersedes the number of human cells in the body (Cani 2018). Recent genomic studies suggest that the ratio of bacterial to human cells is 1.3:1 (Gill et al. 2006; Sender et al. 2016). The inherited human genome is non-modifiable, while the microbiome composition is highly dynamic and diverse at various stages of life, with the changes being driven by extraneous factors like diet, physical activity and stress. Earlier studies had classified the gut microbiota into 3 enterotypes—*Bacteriodes* (Enterotype 1), *Prevotella* (Enterotype 2) and *Ruminococcus* (Enterotype 3) which is currently considered obsolete (MetaHIT Consortium et al. 2011). The gut microbiota is primarily composed of 2 major phyla, Bacteroidetes (largely composed of

Bacteroides and *Prevotella* species) and Firmicutes (comprised of *Clostridium*, *Lactobacillus* and *Ruminococcus* species). Bacteria in the human gut belong to either of these phyla, although a few gut pathogens from phylum Proteobacteria are also present (Gill et al. 2006).

2.2 Bi-directional Pathways between Gut and Brain

The bidirectional interaction pathways existing between the CNS and the gut micro-biome have also been termed and referred to as microbial endocrinology (Lyte and Cryan 2014). Many neuroactive compounds (gamma-aminobutyric acid [GABA], acetylcholine, serotonin, dopamine and norepinephrine) are produced by both the host and the microbiota. Food consumed by humans contains pre-existing functional neuroactive components as well as substrates required to produce these compounds. Gut microbiota can directly produce neuroactive compounds from these substrates (Wall et al. 2014; Strandwitz 2018).

Neuroactive compounds produced in the gut are known to influence the host behavioural functions via two pathways. These compounds are either taken up from the gut into the portal circulation and then to systemic circulation, ultimately reaching the brain or they directly interact with the G protein-coupled receptors (GPCR-43)/neurokinin (NK)1R or NK2R receptors expressed on the enteric nervous system (ENS) which innervates the gastrointestinal tract (Aresti Sanz and El Aidy 2019). The brain functions influenced by these pathways can result in alteration of behaviour or cognition and also determine the food preferences and appetite. The brain also regulates the composition of the microbiota through the specific release of certain neurochemicals like substance P, calcitonin gene-related peptide, neuropeptide Y, somatostatin and vasoactive intestinal polypeptide into the gut lumen. This leads to the bidirectional vicious axis between the CNS and the gut microbiome (Fig. 7.1) (Holzer and Farzi 2014; Lyte and Cryan 2014).

2.3 Role of Neurotransmitters in MGB Axis Homeostasis

Numerous neurotransmitters secreted by a wide spectrum of microbial species have been identified in the human gut which can impact the CNS. These neurotransmitters can potentially enter the brain from gut through portal circulation, but is limited by the intact BBB. Neurotransmitters like serotonin, dopamine, GABA and norepinephrine cannot typically breach the BBB. Yet, their precursors have the capability to cross the BBB and subsequently get converted to active neurotransmitters. For example, tryptophan is the serotonin precursor and tryptophan concentration in the blood plasma has been shown to correlate with brain serotonin levels (Strandwitz 2018). The alternate hypothesis is that the microorganism-derived neurotransmitters affect the brain through the vagus nerve and its afferent neurons. Vagus nerve
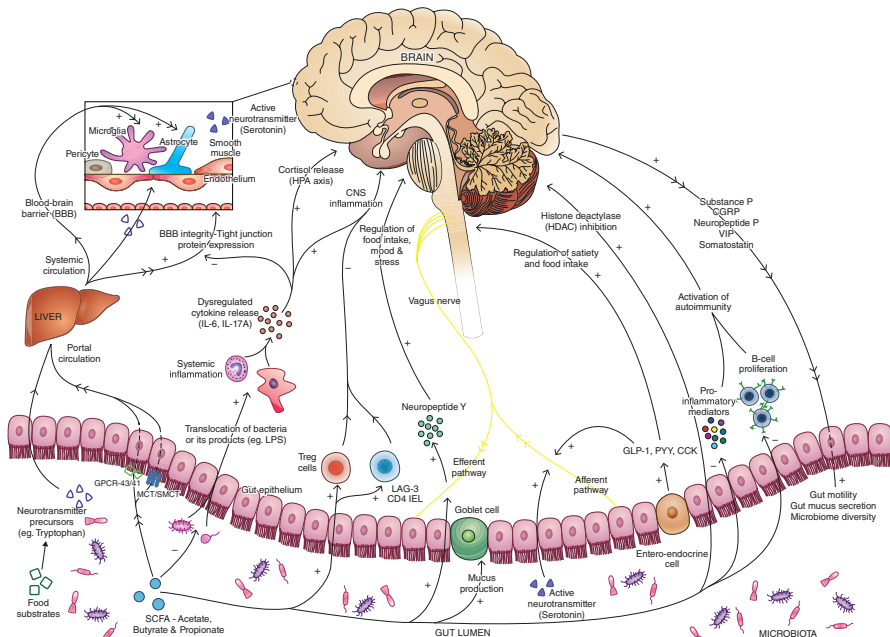
Fig. 7.1 Microbiome-gut-brain (MGB) axis. *BBB* blood-brain barrier, *CCK* cholecystokinin, *CD4* cluster differentiation-4, *CGRP* calcitonin gene-related peptide, *CNS* central nervous system, *GLP-1* glucagon-like peptide-1, *GPCR43/41* G protein-coupled receptor 43/41, *HDAC* histone deacetylase, *HPA* hypothalamic-pituitary-adrenal axis, *IEL* intra-epithelial lymphocyte, *IL* interleukin, *LAG-3* lymphocyte activation gene-3, *LPS* lipopolysaccharide, *MCT* monocarboxylate transporter, *PYY* peptide YY, *SCFA* short-chain fatty acid, *SMCT* sodium-coupled monocarboxylate transporter, *Treg* regulatory T cell, *VIP* vasoactive intestinal peptide

signalling plays a crucial role in mediating stress, mood and satiety (Browning et al. 2017).

2.4 Role of Gut Neuroactive Metabolites in MGB Axis

Among the various bacterial metabolic by-products, short-chain fatty acids (SCFAs) have been identified as the key mediators of the brain-gut interaction. SCFAs are composed of up to 6 carbon atoms and are produced by the anaerobic fermentation of dietary fibres and resistant starches by the large intestine microbiota (Pascale et al. 2018). The predominant SCFAs produced are acetate (60%), propionate (20%) and butyrate (20%). They are absorbed by colonocytes via H^+ or sodium-dependent monocarboxylate transporters into the portal circulation and are metabolised in the liver (Vijay and Morris 2014). Butyrate is primarily consumed as a preferred fuel

source by colonocytes. A minor fraction reaches the systemic circulation and crosses the BBB thereby impacting CNS functions (Silva et al. 2020).

SCFAs play a key role in maintaining the gut-brain axis which includes preserving the integrity of colonocytes and IEB, preventing the translocation of bacteria or their toxic products, maintaining colonic mucus production, regulation of gut mucosal immunity and systemic inflammation via inhibition of histone deacetylation and T regulatory cells (Tregs) differentiation and regulation of appetite, sleep and whole-body homeostasis (Arpaia et al. 2013; Smith et al. 2013). Histone deacetylase (HDAC) inhibitors like butyrate and other SCFAs are emerging as promising therapeutic options due to their effects on transcription activation and gene regulation in the CNS (Dietz and Casaccia 2010).

2.5 Role of Gut Microbiota in Modulation of Microglia and Astrocyte Biology

Early microbiome studies to determine the influence of gut microbiota on CNS modulation was performed on germ-free (GF) or gnotobiotic animals. These gnotobiotic animals have been a powerful tool to determine causation and to study the effect of a particular bacteria or a dietary intervention on the MGB axis. A few animal studies have shown the role of gut microbiota on biological changes in microglia and astrocyte (Erny et al. 2015; Fung et al. 2017). Microglia constitute 10–15% of all cells in the CNS and as scavenger cells of brain, remove apoptotic nerve cells, kill invasive pathogens and trim redundant synaptic connections (Nayak et al. 2014). Microglial maturation and function are affected by the gut microbiota. Compared to conventionally colonised (specific pathogen-free, SPF) controls, GF mice have microglia with abnormal morphology, altered gene expression and impaired functional response to stimulation. The microglial changes were observed to revert to normal morphology once the diet for GF mice was supplemented with SCFAs (Erny et al. 2015). Similar changes in astrocyte morphology and functions due to the gut microbiota have been reported. Astrocytes are the major glial cells in the CNS that provide physical and metabolic support to the neurons. They take part in synaptogenesis and maintain the integrity of BBB by supporting the lining endothelial cells. Animal studies have shown that microbial metabolites bind to the aryl hydrocarbon receptor (AHR) in astrocytes, reducing symptoms of experimental autoimmune encephalitis (EAE) by inhibiting type I interferon signalling. This effect was reversed when mice were treated with antibiotics. Microbiota-dependent metabolism of tryptophan into AHR ligands engages AHR on astrocytes, thus leading to an increase in astrocyte expression of the inhibitor protein SOCS2 and consequently inhibiting activation of the transcription factor NF-κB and thereby limiting CNS inflammation (Rothhammer et al. 2016).

2.6   Role of Immune System in MGB Axis

Inflammation in the gut has been shown to mirror systemic and CNS inflammation. Peripheral gut insults like antibiotic use and unbalanced diet disrupt the IEB leading to translocation of bacteria and bacterial products like lipopolysaccharide (LPS) into the bloodstream creating a systemic inflammatory response by cytokine release. Dysregulated cytokine release can impact the permeability of BBB, thereby allowing entry of preformed neurotransmitters and pro-inflammatory cells and molecules to initiate a CNS inflammatory milieu (Pan et al. 2011).

Several studies suggest that local and systemic immune activation has critical effects on neural plasticity and behavioural effects, thereby confirming the contribution of immune system in the MGB axis homeostasis (Blander et al. 2017). Recognition of microbe-associated molecular patterns (MAMPs) in microbes and their metabolic by-products (SCFAs) can activate distinct immunological pathways for maintaining the CNS homeostasis (Thursby and Juge 2017). The mode of delivery (caesarean section) and antibiotic use have been linked with immune activation phenomenon in the newborn due to gut dysbiosis (Moos et al. 2016). These early gut dysbiotic changes have been positively correlated with defective neuronal plasticity and behavioural development, classically observed in ASD (Dzidic et al. 2018). The gut colonisers, Lactobacillus and Bifidobacterium, produce the neurotransmitter, acetylcholine, modulating the vagal nerve signalling, thereby attenuating the release of harmful cytokines (IL-1β, IL-6 and TNF-α) (El Aidy et al. 2014). A potential mechanism by which immune activation affects physiology and behaviour is via actions on the serotonergic system. As observed in mice studies by Lowry et al., serotonergic neurons in the dorsal raphe regulate mood and behaviour in response to the immune stimuli. Vagal afferent nerve fibres are also involved in transferring signals from peripheral immune activation to the CNS (Lowry et al. 2007). In addition, microbial infections can trigger antibody-mediated CNS autoimmunity and consequent neurodegeneration (Wu and Wu 2012). Altogether, peripheral immune response regulation by the gut microbiota and exogenous microbial challenges are critical in moulding CNS function and behaviour.

2.7   Composition and Correlation of Dysbiosis with Brain Behaviour

Increase in the members of the phylum Firmicutes or decrease in the members of phylum Bacteroidetes or their subclasses (altered Bacteroidetes/Firmicutes ratio) has been consistently observed in individuals with CNS disorders. In addition to the ratio, relative abundance or deficiency of certain genera in gut microbiota have been strongly linked with CNS disorders (Gill et al. 2006). Colonic bacterial spp. *Faecalibacterium prausnitzii* (Clostridial cluster IV), *Coprococcus*, *Roseburia* (Clostridial cluster XIV), *Eubacterium* and *Anaerostipes* have been identified to produce high concentrations of butyrate, an HDAC inhibitor. Butyrate-producing

Faecalibacterium and *Coprococcus* were consistently associated with high mental quality-of-life (QOL) indicators (Cheung et al. 2019). The genera *Akkermansia*, *Oscillospira* and *Lactococcus* were found to be relatively abundant in individuals with higher sociability, less anxiety or depression (Johnson 2020). A relative abundance of *Desulfovibrio* and *Sutterella* was associated with less sociable behaviour and autism (Wang et al. 2011; De Angelis et al. 2013).

3 Impact of MGB Axis in Neurological Disorders

The dysregulation of gut microbiome composition is attributed to the pathomechanism of several neurological disorders (Fig. 7.2). In the next section, we will discuss the role of gut microbiome in a few neurological conditions based on the current evidence obtained from animal and human studies.
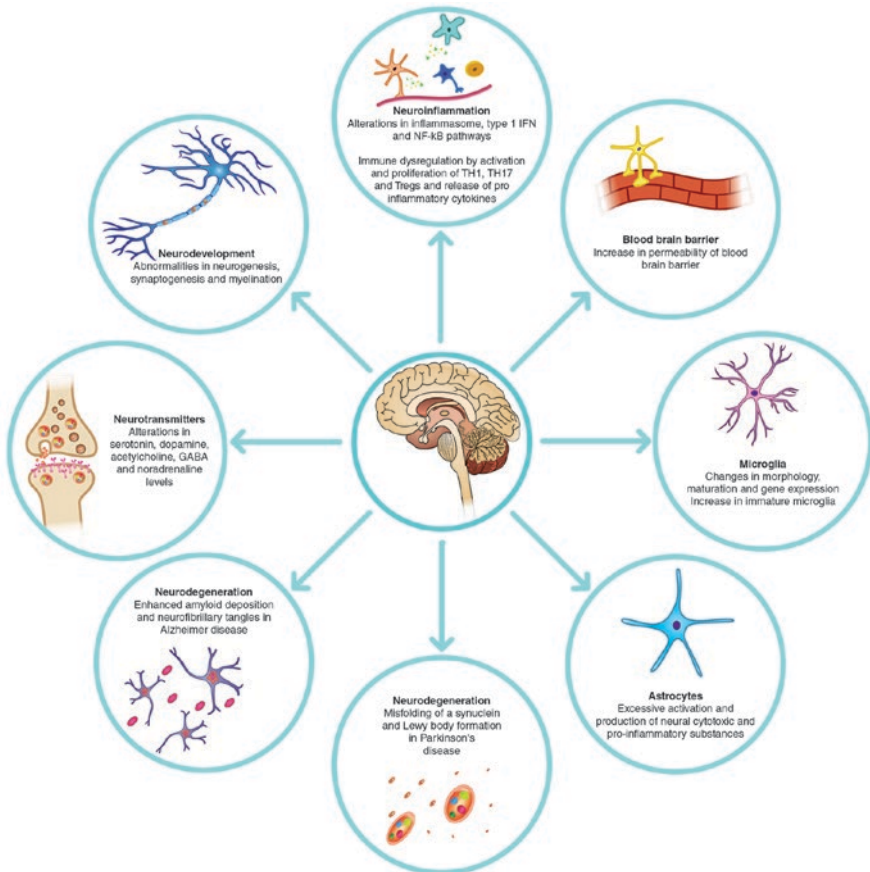
Fig. 7.2 Pathophysiological mechanisms in the central nervous system due to gut dysbiosis. *GABA* Gamma aminobutyric acid; *IFN* interferons; *NF-kB* nuclear factor kappa light chain enhancer of activated B cells; *Tregs* regulatory T cells; *TH1* T helper type 1 cells; *TH17* T helper 17 cells

3.1   Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the CNS characterised by the presence of widespread 'plaques' in the brain, spinal cord and optic nerve. MS plaques are pathologically heterogeneous revealing combinations of demyelination, inflammation, gliosis, axonal loss and remyelination (Reich et al. 2018). The commonest clinical phenotype of the disease at onset is the relapsing-remitting MS (RRMS) which occurs in more than 85%, while the remaining have progressive onset MS. The therapeutic approach is centred around immunomodulatory disease-modifying therapies (DMTs) which reduce the relapses but have unsatisfactory effect on the disease progression and long-term disability (Rae-Grant et al. 2018).

Immune dysregulation and pro-inflammatory immune shift are the hallmarks of MS, and active research is ongoing to identify the trigger for this. The pathogenesis is thought to be multifactorial with environmental influence prevailing over genetic factors. Evidence for the role of gut dysbiosis in MS susceptibility, pathogenesis, and disease course is compelling. Studies in animal models and persons with MS show alteration of gut microbiota which contribute to the change in immune homeostasis. CNS inflammation simulating MS can be induced in experimental animals by priming and activating the immune system with injection of myelin peptides and this is referred to as the EAE model. EAE can also be spontaneously generated in transgenic mice which express myelin-specific immune receptors (Glatigny and Bettelli 2018). Gut microbiota is essential for EAE induction as was evidenced by low frequency and reduced severity of EAE in GF mice. These mice had concomitant decreased pro-inflammatory TH17 differentiation, low levels of pro-inflammatory cytokines and enhanced Tregs. EAE could be re-established in them by allowing gut colonisation with segmented filamentous bacteria (Ivanov et al. 2009). Transfer of gut microbiota from MS patients could also induce EAE. In a study of 34 sets of monozygotic twins who were discordant for MS, transfer of gut microbiota from an affected twin induced spontaneous EAE more frequently in GF mice compared to the healthy twin (Berer et al. 2017). Conversely, administration of normal gut commensal bacteria, particularly those belonging to phyla Bacteroidetes and Firmicutes, was shown to reduce the incidence of EAE and the inflammatory response in susceptible models (Mowry and Glenn 2018).

In human studies, no difference was noted in the overall diversity and abundance of bacteria in MS and non-MS guts (Mowry and Glenn 2018; Mirza et al. 2020). The composition and relative richness of bacterial groups at sub-phylum level in MS were different from controls across multiple studies (Mirza et al. 2020). Members of phylum Bacteroidetes (*Bacteroidaceae, Bacteroides* and *Prevotella*) and phylum Firmicutes (*Fecalibacterium*) were reduced in MS gut (Cantarel et al. 2015; Miyake et al. 2015; Chen et al. 2016). These bacteria have key role in the generation of SCFAs which are anti-inflammatory. Studies also showed an increased abundance of methanogenic bacterial genera, *Methanobrevibacter* and *Akkermensia* (Tremlett et al. 2016; Jangi et al. 2016). They have pro-inflammatory effects related

to respectively recruiting and activating immune cells and altering genes involved in immune responses. However, methanogenic bacteria may be increased secondary to constipation in MS and hence their abundance may result from MS than cause it. A recent study noted that the profile of gut microbiota in treatment-naïve MS varies across different ethnic groups with relative abundance of *Clostridia* being a common observation in all the groups (Ventura et al. 2019). Exposure to DMT can result in significant alterations in the beta diversity of gut microbiota (Tremlett et al. 2016; Mirza et al. 2020).

Studies in paediatric MS are of particular interest as children have fewer exposure to environmental stimuli and hence could shed light on the pathogenic role of the gut microbiota. Phylum Actinobacteria and genus *Desulfovibrio* were more abundant in MS gut. (Tremlett et al. 2016). These bacteria are also increased in other autoimmune inflammatory diseases including inflammatory bowel disease (Tremlett and Waubant 2018). A three-fold higher risk of an early relapse was noted among paediatric MS with Fusobacteria being absent in stool samples (Tremlett et al. 2016).

3.2 Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder (NMSOD) is a severe multiphasic demyelinating disease driven by autoantibodies against aquaporin-4 water channels (AQP4). The B-cell responses in NMOSD are strongly influenced by T-cell-mediated cytotoxicity. Gut microbiota studies in NMOSD patients revealed over-abundance of *Clostridium perfringens* (Cree et al. 2016). This is of particular interest in the pathogenesis of the disease as AQP4 displays high degree of homology to an adenosine triphosphate-binding cassette transporter permease of *C. perfringens* and can show cross-reaction (Varrin-Doyer et al. 2012). A recent study from Indian NMOSD demonstrated increase in *Clostridium boltea* which also shares sequence similarity with AQP4 (Pandit et al. 2021).

3.3 Parkinson's Disease

Parkinson's disease (PD), a progressive neurodegenerative disease, is characterised by degeneration of the dopaminergic neurons projecting from the substantia nigra. PD is an alpha-synucleinopathy and its pathological hallmark is the presence of alpha-synuclein (α-synuclein) immunoreactive inclusions called Lewy bodies within neurons. Mutations of the gene for α-synuclein can cause familial forms of PD (Kalia and Lang 2016). Though the dominant clinical presentations of PD are motor disability, a range of non-motor signs have been described in PD with olfactory, sleep, gastrointestinal, autonomic, neuropsychiatric and sensory dysfunction

(Poewe 2008). These non-motor symptoms often precede the neurological manifestations and have severe impact on the QOL (Pfeiffer 2016).

Gastrointestinal symptoms are frequent in PD among which constipation and delayed intestinal motility are the most common and distressing (Poewe 2008). Gut dysbiosis influences the gastrointestinal manifestations of PD as well as has role in the pathogenesis and severity of the disease. Mice transplanted with faecal microbiota from PD patients developed the classical motor symptoms of PD and neuroinflammation (Sampson et al. 2016). Neuroinflammation is being increasingly recognised as being integral to PD pathogenesis (Hirsch and Hunot 2009). The main mechanisms proposed for the influence of gut on PD include activation of the ENS through interactions with gut microbiota, activation of the local immune system and increase in gut permeability (Mulak 2015).

The contribution of gut in the pathogenesis was suggested by the detection of α-synuclein in the ENS in early PD (Hilton et al. 2014). Misfolding of α-synuclein could be induced by damage to enteric neurons and enteric glial cells leading to the accumulation of the inclusion bodies (Mulak 2015; Yang et al. 2019). Gut dysbiosis or an alternate environmental factor initiates the neuronal damage. Vagus nerve can transmit the α-synuclein pathology from the ENS to the dorsal vagal nucleus (Holmqvist et al. 2014). This hypothesis is supported by evidence from truncal vagotomy which prevented the spread of α-synuclein from gut to brain and the subsequent neurodegeneration in mouse models (Kim et al. 2019). Changes in gut flora and small intestinal bacterial overgrowth in PD contribute to inflammation and leaky gut which are hypothesised as substrates for the subsequent neurodegeneration (Tan et al. 2014; Yang et al. 2019).

In general, colonic biopsies and faecal analysis have revealed non-uniform data on gut microbiota in PD compared to controls. An increased diversity of bacterial species in PD gut was recorded in one study (Keshavarzian et al. 2015). Two studies showed a reduced abundance of Prevotellaceae species which reduced SCFAs implicated in PD pathogenesis. Other microbials noted to be decreased are Lachnospiraceae, Firmicutes, *Clostridium coccoides, Bacteroides fragilis, Faecalibacterium prausnitzii,* Enterococcaceae and Bacteroidetes, whereas Verrucomicrobiaceae species were increased in PD guts (Cryan et al. 2019). Enterobacteriaceae was associated with increased severity of postural instability and gait dysfunction in PD (Scheperjans et al. 2015).

Absorption and metabolism of levo-dopa which is the primary treatment for PD is influenced by the gut microbiota. Tyrosine decarboxylase from gut microbiota in mice reduced the plasma concentration of L-dopa (van Kessel et al. 2019). Conversely, PD medications have been linked to change in gut microbial status. Bacillaceae species was relatively abundant in patients who received levo-dopa compared to alternate therapy (Heintz-Buschart et al. 2018). A combination of monoamine oxidase inhibitors and amantadine also resulted in an increased microbial richness in PD (Bedarf et al. 2017).

3.4 Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disease which manifests clinically as progressive loss of episodic memory and other neurocognitive functions. The typical pathological substrates in the brain are extracellular deposition of amyloid plaques and dystrophic neurites containing hyperphosphorylated tau protein (DeTure and Dickson 2019). More recent evidence has linked neuroinflammation and systemic inflammation with AD pathogenesis (Heneka et al. 2015). Genetic and environmental factors play key roles in AD pathogenesis, the best understood being increasing age and the presence of the high-risk ε4 allele of apolipoprotein E gene (Xu and Wang 2016). Studies in animal models and gut microbiota in AD patients suggest a strong influence of the latter in AD pathogenesis. GF mice had reduced neuroinflammation and lower amyloid burden in brain. Antibiotics were shown to alter the neuropathology in transgenic mice by reducing accumulation of amyloid plaques (Jiang et al. 2017; Bostanciklioğlu 2019).

In human studies, alpha (within sample) and beta (between sample) diversities were reduced in AD compared to controls. Bacterial flora was different in AD compared to healthy controls with reduced abundance of Firmicutes in AD. Proinflammatory Escherichia and Shigella were increased with increase in inflammatory markers NLRP3, CXCL2, IL-6, and IL-1β in amyloid positive and cognitively impaired patients compared to cognitively preserved patients. AD gut also demonstrated reduced anti-inflammatory strain *Bifidobacterium breve* strain A1 and *Escherichia rectale* (Vogt et al. 2017; Cattaneo et al. 2017).

3.5 Autism Spectrum Disorder

Autism spectrum disorder (ASD) manifests in early childhood and is defined by the clinical features of stereotyped behaviours and rituals and deficits in communication and social interaction. The cause of ASD is largely attributed to the genetic and environmental factors and their interplay (Lord et al. 2018). Neuro-inflammation and gut microbiota has also been implicated as a cause for ASD in the recent studies (Li et al. 2017). Maternal factors including vaginal infections, periodontitis, prescription drug usage (sodium valproate), diet and obesity, mode of delivery (caesarean section vs vaginal delivery) and postnatal factors such as antibiotics and breastfeeding, host genetics and environment shape the gut microbiota in early life (Tamburini et al. 2016). Various human and animal studies have shown that these factors can alter the composition of gut microbiota and their metabolic products thus predisposing a child for autism (Li et al. 2017).

Many clinical and physiological changes seen in ASD including diarrhoea, constipation, gaseous distension, gastroesophageal reflux disease, intolerance to certain food, abnormal metabolites and neuro-inflammation are attributed to the less diverse gut microbiota in the ASD children (Pulikkan et al. 2019). Aberrant behaviours of

irritability, hyperactivity, social withdrawal and stereotypy were found to be more in ASD children with gastrointestinal problems (Chaidez et al. 2014; Moradi et al. 2021). Histopathology from ASD subjects with gastrointestinal symptoms was inconsistent with some showing lymphoid nodular hyperplasia, follicular lymphoid hyperplasia, ulcerative colitis and others with either non-specific inflammation or normal findings (Kang et al. 2014). From pyrosequencing study of faecal micro-flora, higher counts of microbial organisms belonging to Bacteroidetes and Proteobacterium phyla in children with ASD were detected as compared to neuro-typical children in whom Firmicutes and Actinobacterium were predominant (Finegold et al. 2010). Similar findings were also observed in a recent study in ASD children between age group 2–4 years which showed higher colonisation by Bacteroidetes, Proteobacteria and butyrate producing *Faecalibacterium prausnitzii*, whereas a significant reduction of *Bifidobacterium longum* was observed (Coretti et al. 2018). Contradictory to the above findings, an increase in the ratio of Firmicutes/Bacteroidetes in ASD was reported in some studies (Strati et al. 2017; Moradi et al. 2021). In ASD subjects with constipation, high levels of Escherichia, Shigella and Clostridium cluster XVIII were found (Strati et al. 2017).

As mentioned in the initial part of this chapter, gut microbiota and their metabo-lites play a central role in brain behaviour modulated via immune, neural and endo-crine pathways originating from leaky intestines. In ASD, metabolites from the transformed gut microbiome metabolism lead to increased production of SCFAs including acetate, propionate and butyrate (Li et al. 2017). A decrease in the gut colonisation by *E. coli* affects the catabolism of 3,3 phenylpropionate. SCFAs acti-vate inflammasomes, innate immune system receptors and sensors thereby modulat-ing downstream inflammatory pathways involving Tregs and TH17 cells contributing to aberrant behaviour in ASD. Levels of pro-inflammatory markers such as TNFα, IL-10, TGFβ, NT and SORT-1 were found to be significantly higher in ASD patients as compared to controls thus confirming that the immune pathways were altered in them (Carissimi et al. 2019). Desulfovibrio sp. and *B. fragilis*, a predominant gut coloniser in ASD, produce LPS which is an important antigenic component trigger-ing immunological response (Finegold et al. 2010). Thus, intestinal dysbiosis has effects on immunological, biochemical and neuroendocrine system which ulti-mately influences the brain and behaviour.

3.6 Glioma

Table 7.1 provides a summary of the pattern in gut dysbiosis observed in major neurodegenerative diseases as per reliable research studies conducted in the recent past.

Tumours of CNS cause substantial morbidity and mortality, and the most com-mon histologic type is glioma (Patel et al. 2019). The gut microbiota was recently implicated in the pathogenesis of glioma since the microbiota exert pleiotropic effects in tumour progression, growth, survival, transformation and response to

Table 7.1 Gut dysbiosis in neurological disorders

Study	Study population	Results
Multiple sclerosis (MS)		
Jangi et al. (2016)	60 patients with MS and 43 healthy controls	↑*Methanobrevibacter* and *Akkermansia* & ↓ *Butyricimonas* ↑*Prevotella* and *Sutterella* and ↓ *Sarcina* in MS patients treated with DMT compared with untreated patients
Chen et al. (2016)	31 RRMS patients and 36 healthy controls	MS patients showed ↑*Pseudomonas*, *Mycoplana*, *Haemophilus*, *Blautia*, and *Dorea* genera ↑*Parabacteroides*, *Adlercreutzia* and *Prevotella* genera in healthy controls
Tremlett et al. (2016)	18 paediatric RRMS patients and 17 controls	↑*Desulfovibrionaceae* (*Bilophila*, *Desulfovibrio* and *Christensenellaceae*) and ↓ *Lachnospiraceae* and *Ruminococcaceae* in MS patients
Parkinson's disease (PD)		
Hill-Burns et al. (2017)	197 PD cases and 130 controls	↑*Bifidobacteriaceae*, *Christensenellaceae*, *Lachnospiraceae*, *Lactobacillaceae*, *Pasteurellaceae* and *Verrucomicrobiaceae* families
Li et al. (2019)	51 PD patients and 48 healthy controls	↑*Akkermansia* and ↓ *Lactobacillus* in PD patients
Lin et al. (2019)	80 PD patients and 77 healthy controls	↑*Verrucomicrobia, Mucispirillum*, *Porphyromonas*, *Lactobacillus*, and *Parabacteroides* ↑*Prevotella* in controls
Autism spectrum disorder (ASD)		
Coretti et al. (2018)	11 ASD children and 14 healthy controls	↑*Faecalibacterium prausnitzii* and ↓ *Bifidobacterium longum* in ASD
Pulikkan et al. (2018)	30 ASD children and 24 healthy controls	↑*Lactobacillaceae*, *Bifidobacteraceae*, and *Veillonellaceae* ↑*Prevotellaceae* in controls
Ma et al. (2019)	45 ASD and 45 healthy children	↓in relative abundance of *Lachnoclostridium*, *Tyzzerella* subgroup 4 and *Flavonifractor* in ASD Firmicutes/Bacteroidetes ratio not significantly different between the ASD and healthy controls
Zurita et al. (2020)	25 ASD cases and 35 controls	↑*Bacteroides*, *Akkermansia*, *Coprococcus* and *Ruminococcus* in ASD

Note: This table includes only the recent and larger studies published after 2016
DMT disease-modifying therapy; *RRMS* relapsing-remitting multiple sclerosis.

therapeutic agents. A recent study of tumours involving breast, lung, brain, ovary, pancreas, melanoma and bone revealed presence of intracellular bacteria in both cancer and immune cells (Nejman et al. 2020). In the mouse glioma models, reduction in Bacteroidetes and Firmicutes were seen with an abundance of Verrucomicrobia especially of Akkermansia genus after tumour growth was observed. The metabolites such as dihydroxy phenylacetic acid (DOPAC), 5-hydroxy indole acetic acid (5-HIAA), adenosine, histamine, acetate, propionate, butyrate, norepinephrine, GABA, tryptophan, valerate and aspartic acid levels were found to be reduced in them (Dono et al. 2020). The circulating immune cells such as T and B cells and macrophages cross the BBB and play a role in gliomagenesis. Tumour survival and

growth is promoted by an immunosuppressed microenvironment created by immune cells and cytokine profile in which Tregs play a crucial role (Mehrian-Shai et al. 2019).

4   Therapeutic Interventions

The gut microbiome composition can be manipulated by the application of probiotics, prebiotics, diet modifications and faecal microbial transplantation. Relying on such alternative interventions to augment the gut microbiome, post proper evaluation and trials will reduce the huge burden on complex drugs and associated side effects, and promote the QOL of patients suffering from neurological disorders.

Probiotics are lactic acid-producing bacteria (Lactococci, Lactobacilli, Bifidobacteria and Saccharomycetes) that augment the IEB and may prevent intestinal inflammatory diseases. Prebiotics are non-digestible oligosaccharides that encourage the growth of beneficial bacteria. A few studies have reported beneficial effects of probiotics/prebiotics in neuropsychiatric symptoms such as anxiety and depression (Li et al. 2017).

Two studies in MS compared outcomes of probiotic preparations with *Lactobacillu*s species versus placebo and noted improvement in markers of inflammation; however, intestinal bacterial loads were not assessed in them (Kouchaki et al. 2017; Tamtaji et al. 2017). Another study showed an anti-inflammatory shift of the flora with an increased abundance of *Lactobacillus*, and decreased abundance of *Akkermansia, Dorea* and *Blautia* with probiotic therapy (Tankou et al. 2018). Probiotics/prebiotics can potentially alter the gut dysbiosis in PD and have been tried as therapeutic strategies. Increased complete bowel movements were reported in one study in PD patients with probiotics/prebiotics compared to placebo (Barichella et al. 2016). Treatment with probiotics (*Lactobacillus* and *Bifidobacterium* species) produced an increase in mini-mental status examination (MMSE) scores in a small cohort of patients with AD (Akbari et al. 2016). Larger studies looking into changes in the gut flora and cognitive scores with therapy are needed to assess therapeutic effects further. In a recent systemic review of eight clinical trials that involved the use of pre/probiotic supplementation in children with ASD, prebiotics combined with a gluten and casein-free diet was found to improve certain gastrointestinal symptoms along with significant reduction in anti-sociability scores. But probiotics have limited evidence in alleviating the gastrointestinal or neurobehavioral symptoms in ASD children (Ng et al. 2019).

There is currently no standardised pre/probiotics regimen with regard to type and concentration of different strains, duration of treatments and monitoring parameters in the management of neurological disorders.

Potential therapeutic approaches sought for modification of microbiota in MS also include vitamin D3 supplementation and diet modifications. Vitamin D3 supplementation in a small sample of MS patients improved immune tolerance and reduced inflammation with anti-inflammatory shift of gut microbiota in the

subgroup who were not on immunotherapy (Cantarel et al. 2015). Dietary modifications have also been shown to impact the inflammatory profile. A diet rich in simple sugars, saturated fat, salt and high calorie content has been associated with increased risk for autoimmune demyelinating diseases. This has been shown to increase inflammatory cells in the gut and induce gut dysbiosis (Thorburn et al. 2014). A shift to normal gut flora can be induced by a calorie-restricted diet rich in fruits, vegetables and fish although robust studies for the utility in MS are lacking (Mowry et al. 2018).

Faecal microbiota transplantation (FMT) is a procedure wherein the faecal microbiota from a healthy person is transferred to a patient with gut-microbiome dysbiosis. FMT in patients with PD improved constipation and non-gastrointestinal manifestations (Yang et al. 2019). It was also tried in ASD; however, the safety profile and efficacy of this intervention needs to be established (Li et al. 2017). The principle of microbiota transfer therapy (MTT) is based on FMT protocol with minor modifications. Oral vancomycin treatment is given for 14 days followed by fasting (12–24 h) and bowel cleansing. Standardised Human Gut Microbiota (SHGM) either orally or rectally is then administered to repopulate the gut microbiota for a period of 7–8 weeks. Gastrointestinal and behavioural symptoms in ASD subjects significantly improved with MTT (Kang et al. 2017). There is insufficient evidence to translate FMT and MTT to clinical practice at present.

5 Conclusion

The bi-directional pathways involving gut microbiome and human brain connect host behaviour with the gut function thereby subserving a major role in health and disease. The marked differences in the composition of gut microbiota across various studies suggest a strong role for ethnicity, dietary patterns and other environmental influences (Cryan et al. 2019). Nevertheless, the perturbations in the gut microbiota have been linked to disease risk and progression in various neurological disorders including neurodegenerative, neurodevelopmental and autoimmune diseases, tumours and stroke. Gut microbiome dysregulation may not be directly causative, but when combined with other risk factors can be responsible for various neurological disorders (Tremlett et al. 2017). Many of these studies are limited by small sample size and the wide variability in the methods for collection, storage and analysis of samples (Cryan et al. 2019). Therefore, in-depth, standardised and multicentric studies at a global level are highly warranted to substantiate the relationship between gut microbiota and the numerous neurological diseases in which they have been implicated. Such studies possess the potential to identify biomarkers for disease onset, activity and co-morbid conditions. Simultaneously, the role of physiotherapy and non-strenuous, aerobic exercises in alleviating the symptoms in neurological disorders by strengthening the gut-brain axis can be further explored to gauge its potency as a promising intervention strategy in the future.

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