Dysbiosis and Neurological Conditions

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The prevalence of neurological conditions which manifest with chronic pain is increasing globally, where the World Health Organisation has now classified chronic pain as a risk factor for death by suicide. While many chronic pain conditions have a definitive underlying aetiology, non-somatic conditions represent difficult-to-diagnose and difficult-to-treat public health issues. The interaction of the immune system and nervous system has become an important area in understanding the occurrence of neuroinflammation, nociception, peripheral and central sensitisation seen in chronic pain.

Keywords: microbiota ; intestinal ; chronic pain ; neuroinflammation

1. Introduction

Chronic pain is pain which persists longer than 3 months past the normal healing time of the tissue [1], as associated with somatic injury. The International Association for the Study of Pain (IASP) now defines chronic pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [2]. While pain is associated with many chronic conditions, the most recent update of the International Classification of Diseases (ICD-11), however, now lists chronic pain as its own health condition [3]. There are many categories and types of pain, including neuropathic, nociceptive, musculoskeletal, inflammatory, psychogenic and mechanical [4]. Additional types of chronic pain are categorised into functional somatic syndromes (FSS) where chronic pain persists in the absence of any physical or structural defect in the body or absence of a somatic condition [5]. Chronic pain is multifaceted, having a significant impact on the suffering individual socially, economically and physically, and affects approximately 20% of the global population [2]. Chronic pain is also associated with opioid addiction, mental health conditions, social isolation and reduced quality of life [6]. Importantly, there is a significant rate of moderate and severe mental health conditions associated with chronic or persistent pain [7]. Chronic co-morbidities—either physical and/or mental—are present in 88% of chronic pain patients [1]. Risk factors associated with chronic pain include sociodemographic, clinical, psychological and biological factors (females are more prone than males) [1]. Treatment protocols typically include pain therapy, such as non-steroidal anti-inflammatory drugs, opioids, psychological therapy, physical therapy, or alternative non-pharmacological treatments [8]. Additional therapeutics often prescribed include antiepileptic drugs (gabapentin or pregabalin), antidepressants, e.g., tricyclic antidepressants amitriptyline and serotonin-norepinephrine reuptake inhibitor duloxetine, topical analgesics, e.g., lidocaine, muscle relaxers, N-methyl-d-aspartate receptor antagonists and alpha 2 adrenergic agonists [4]. Nonpharmacological treatment regimens include heat and cold therapy, cognitive behavioural therapy, relaxation therapy, counselling, ultrasound stimulation, acupuncture, aerobic exercise, chiropractic, physical therapy, osteopathic manipulative medicine and occupational therapy [4]. The widespread prescription of opioids raises addiction issues as ca. 20% of chronic pain patients are prescribed opioid pain relief for acute and chronic pain.

2. Dysbiosis—Imbalance in the Gut

2.1. Causation of Dysbiosis

The gut microbiota is unique to each individual and influenced by mode of birth, infant feeding, lifestyle and dietary choices, medication and the genetics of the host. A healthy gut microbiota is, however, evident as having microbial diversity, microbial gene richness and microbial functional activity [9]. Alterations in gut microbiota relate to antibiotic use, food preservatives, diet, and improvement in standards of living and hygiene [10]. Antibiotic use depletes the resident microbes, where exposure to antibiotic therapy in early life leads to long-term immune dysregulation and visceral hypersensitivity [11]. Dietary compounds, e.g., flavonoids, exert a major impact on the gut microbiome diversity typically in a positive manner, stimulating the growth of beneficial bacteria [9]. Importantly, the Western diet, which is low in fibre and high in a complex mixture of fats and simple sugars, is believed to reduce the microbial diversity or remove essential taxa from the human microbiota in Western populations [12]. Rodent-based studies demonstrated that a high-fat diet (60% fat) decreases the number of bacterial species and alters the diversity of the intestinal microbiota [13]. Such a diet is

associated with obesity, low grade inflammation and metabolic disorders, such as type 2 diabetes (T2D). Indeed, more than 80% of patients with T2D in the Western world are obese with altered gut microbiota, inflammation, and gut barrier disruption [13]. The pro-inflammatory bacterial lipopolysaccharide (LPS) toxin has been identified in the systemic circulation of obese and type 2 diabetic patients and is believed to originate from the intestinal microbiota [13]. Importantly, the LPS toxin release from Gram negative bacteria impacts on gut-barrier function, adipose inflammation, intestinal glucose absorption, blood glucose, insulin and incretins, impacting on the prevalence of metabolic disorders [14]. Reduced levels of intestinal *Firmicutes* species has been reported in persons with T2D and obesity [15]. Studies demonstrate the reduced diversity evident in obese hosts where alterations in relative abundance of the major phyla *Firmicutes* and *Bacteroidetes* is present often with an overabundance of pathogenic microorganisms [16]. Studies have shown that in cases of severe intestinal inflammation, as observed in IBD and cancer, increased abundance of *Enterobacteriaceae* are present [14]. Low or non-calorie artificial sweeteners, e.g., saccharin, sucralose and aspartame also negatively impact microbial diversity [17] and have been associated with the induction of glucose intolerance in mice [9]. Non-antimicrobial therapeutics are also known to impact the resident microbiota. Indeed, studies have shown that commonly used drugs, including antipsychotics, proton-pump inhibitors (PPIs), hormones and anticancer drugs have a deleterious impact on microbial species of the GIT [9]. Opioid-induced dysbiosis has been associated with dysbiosis associated disease states and opioid tolerance [18]. Interestingly, Metformin, a therapeutic for the treatment of T2D, has recently been shown to alter the gut microbial diversity [9]. The impact of environmentally polluting chemicals, including heavy metals (mercury and lead), antimicrobial nanoparticles (silver) and endocrine disrupting chemicals (bisphenol A, phthalates) may also contribute to gut dysbiosis [19]. Studies have demonstrated that chronic exposure to low doses of the insecticide Chlorpyrifos altered the gut diversity in rodents and simulated human intestinal microbiota preparation [9].

2.2. How the Microbiota Interacts with the Nervous System and Induces Pain

The brain is known to regulate gastrointestinal function via the enteric nervous system and the vagal nerve (VN). The VN connects the internal organs (visceral organs) with the brain and is composed of sensory (afferent) and motor (efferent) neurons being part of the parasympathetic branch of the autonomic nervous system (ANS) where it regulates many critical bodily functions including mood, immune response, inflammation, digestion and heart rate [20]. This gut-brain axis (GBA) relies on bidirectional communication between the GIT enteric nervous system, hypothalamic pituitary adrenal (HPA) axis and the CNS [21]. The GBA has varied routes of communication utilising endocrine, immune and neural mechanisms, which the microbiota is capable of agonising to influence the CNS and can lead to pain associated with neuroinflammation [22]. The GBA is influenced by the resident microbiota via the secretion of neuroactive biologics, including serotonin, dopamine, acetylcholine and γ-aminobutyric acid (GABA) [5]. Specifically, intestinal species, including *Escherichia* spp. and *Lactobacillus* spp., are known to synthesize GABA [23] and acetylcholine [24]. Intestinal *E. coli* can produce norepinephrine, 5-hydroxytryptamine (5-HT) and dopamine, while *Streptococci* and *Enterococci* produce 5-HT [24]. Enterochromaffin cells allow for communication between the microbes and the CNS as they are agonised by microbial products and secrete 5-HT into the lamina propria and blood system [25]. Some microbial species present in the gut can also induce the release of intestinal peptides and hormones from host enteroendocrine cells and immune modulators, including cytokine and chemokines [22]. Central sensitization is associated with neuroinflammation via the activation of inflammatory immune cells and inflammatory molecules (cytokine, chemokines). Such immune mediators interact with nociceptors on the CNS and PNS, allowing for alterations in pain pathways resulting in neurological pain [5].

The afferent fibres of the vagal nerve present in the gastrointestinal wall are also stimulated by bacterial metabolites sugars, short chain fatty acids and GABA [5]. The HPA axis is a part of the limbic system of the brain associated with memory and emotional processing and is responsible for stress responses being activated by pro-inflammatory cytokines [21]. In response to stress triggers, the HPA axis stimulates the secretion of the corticotropin-releasing factor (CRF) from the hypothalamus, which in turn stimulates adrenocorticotropic hormone (ACTH) secretion from the pituitary gland, ultimately leading to the release of cortisol from the adrenal glands [26]. Pro-inflammatory cytokines can stimulate the HPA axis [27]. Microbiota produce the SCFAs propionate, butyrate and acetate in the GIT, which are absorbed by the intestinal epithelial cells or colonocytes and regulate cellular processes, including gene expression, chemotaxis, differentiation, proliferation and apoptosis [28]. SCFAs act as an energy source in the body, but can also act as agonists of G protein-coupled receptors, free fatty acid receptor 2 (FFAR2, GPR43) and FFAR3 (GPR41) inducing a signalling response, regulating metabolism and satiety [29]. Studies show that microbial SCFAs may impact neurotransmitters, including glutamate, glutamine and GABA, the synthesis of dopamine, noradrenaline and adrenaline, and also to regulate the expression of tryptophan 5-hydroxylase essential for serotonin synthesis. [25]. Tryptophan crosses the BBB and is available for serotonin synthesis in the brain [30]. Serotonin over-production is believed to lead to a dysregulation of the GBA involving the CNS and PNS, resulting in chronic pain conditions including IBS [5]. Additionally, SCFAs stimulate mucosal release of endocrine agents from the intestinal endocrine cells and inhibit histone deacetylase activity which has effects in the peripheral and central nervous systems [25]. Butyrate inhibits pro-inflammatory pathways and also plays a

key role in preventing systemic exposure to intestinal antigens [30]. Importantly, studies in germ-free mice have shown that the diversity of the microbiota is essential for neurological processes, including development, myelination, neurogenesis and microglia activation [31]. Intestinal bacterial species may also produce neurotoxic molecules, e.g., d-lactate, ammonia and neurotoxins, e.g., *Clostridium tetani* producing botulinum, which can enter the CNS via systemic or extrinsic afferent nerve fibres, leading to neuronal damage [24]. Additionally, the LPS toxin, which is a constituent of the cell membrane of gram-negative bacteria, may induce neuro-inflammatory reactions if it gains entry to the systemic circulation from the GIT; however, LPS is unable to penetrate the BBB in healthy persons [15].

3. Chronic Pain Conditions

As chronic pain conditions increase globally, it is imperative to determine causative mechanisms of pain conditions. While somatic conditions of chronic pain are somewhat more readily treated, certain chronic pain conditions lacking an obvious cause are difficult to treat and manifest as life-long conditions having a drastic impact on the patient. Additionally, due to the co-morbid nature of pain conditions, the multifaceted nature of the immune system, nervous system and commensal microbiota, it is important to develop a better understanding of their interconnected relationship.

3.1. Neurological Conditions

The relationship between the gut microbiota on many chronic conditions, particularly neurodegenerative disease, is an area of interest as studies have shown that the microbiota can modulate the endocrine, nervous and immune systems [16]. The crosstalk between the gut and the brain helps maintain a healthy neurological state as the enteric bacteria impact on brain development and behaviour [23]. Neurological degenerative diseases include Parkinson disease (PD), Alzheimer disease (AD), multiple sclerosis (MS), Motor neuron disease, Amyotrophic lateral sclerosis (ALS) and Huntington's disease, amongst others [31][32]. Neurodegenerative diseases are caused by a progressive loss of neurons in the CNS, with no cure and limited treatment options available. Interestingly the BBB displays increased permeability in neurodegenerative diseases [15][33]. An abundance of pro-inflammatory microbial species in the gut has been associated with the inflammation and neuroinflammation present in neurodegenerative diseases [34][35]. Drastic alterations in gut commensal bacteria have been seen in patients suffering from AD, PD, MS and additional neurological conditions of Autism, schizophrenia and major depression disorder (MDD) [16]. The intestinal microbiota also modulates a range of neurotrophins, e.g., brain-derived neurotrophic factor (BDNF) and proteins involved in brain development and plasticity [11]. GIT dysbiosis can induce local immune activation leading to systemic inflammation, neuroinflammation and changes in CNS functioning [36]. Activation of neurogenic inflammation via innate immune mechanisms initiates and maintains neuropathic pain as afferent nociceptive nerves communicate with the immune system [37]. Importantly, chronic pain, including radicular neuropathic pain and central neuropathic pain is present in many neurological diseases, affecting 20–40% of neurology patients [38].

3.1.1. Parkinson's Disease

Studies have shown that alterations in the composition of the microbiota is present in patients with PD [31]. The gastric organism *H. pylori* and the aetiological agent of gastric ulcers has been associated with PD since the 1960s, where the successful treatment of infection alleviates PD symptoms [23]. Alterations in intestinal microbiota in PD patients can lead to the accumulation of the protein α-synuclein and the elevated activation of microglia in brain neurons [16]. Genetic studies on stool samples from PD patients determined a lower diversity of SCFA-producing bacteria, including *Blauia*, *Coprococcus* and *Roseburia*, compared to healthy controls [30]. Furthermore, an increase in *Enterobacteriaceae* species was established to be directly proportional to the severity of symptoms associated with stability, gait and rigidity [39]. Importantly, when germ-free mice were colonised via faecal transplantation with samples from PD patients, they developed classic PD symptoms, including motor issues, behavioural issues and neuroinflammation, which improved with antibiotic therapy [31]. Studies have also demonstrated that some GIT species, including *Lactobacillus* and *Enterococcus faecalis*, can affect the metabolism of the therapeutic Levodopa through increased tyrosine decarboxylase gene expression [40]. The diversity of non-bacterial species, such as the eukaryotic yeast, is also impaired in PD patients, with important species lacking as identified by genetic analysis [24]. Inflammation in the GIT is recognised as a contributor to PD, where IBD patients are at higher risk of developing PD. Biomarkers of intestinal inflammation calprotectin and zonulin, a biomarker of intestinal permeability, are elevated in PD patients [24].

3.1.2. Alzheimer's Disease

While the exact aetiology of AD has yet to be established, it is known that AD is a manifestation of cell loss, increased activation of signalling pathways, amyloid-β (Aβ) deposits, mitochondrial dysfunction, chronic oxidative stress, impaired energy metabolism and DNA damage [35]. Studies have determined that AD patients possess gut microbiota with

significant changes in the composition of the intestinal microbiome or dysbiosis compared to healthy persons, where reduced levels of *Actinobacteria* (*Bifidobacterium*) and *Firmicutes* phylum's were evident [15]. Gut permeability and leaky gut induced by dysbiosis is speculated to impact on disease development in obese AD persons leading to the systemic inflammation and neuroinflammation seen in AD patients [15]. Importantly, the relationship between pathogenic *E. coli* and *Shigella* species inducing inflammation and a reduced presence of anti-inflammatory *E. rectale* has been associated with peripheral inflammation, cognitive issues and brain amyloidosis, which may induce neurodegeneration in AD patients [41]. AD patients also display lower diversity of butyrate-producing bacteria and increased presence of proinflammatory species [42]. Post-mortem studies on AD patients have shown that the hippocampus and cortex possess LPS toxin levels up to 3 times that of non-AD patients, indicating a causative link between BBB permeability to LPS toxin in AD patients [15]. Gut microbiota-derived amyloids produced by intestinal *Streptomyces*, *Bacillus*, *Pseudomonas*, *Klebsiella* and *Staphylococcus* species, which are similar to CNS amyloids, may contribute to the pathology of AD. Such bacterial amyloids can induce cytokine production, inflammation, phagocytosis and innate immune reactions impacting CNS homoeostasis and pathology in persons with an increased permeability of the GIT and BBB [35].

3.1.3. Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis is a neuromuscular disease due to the progressive death of motor neurons and muscle atrophy [43]. Compared to PD and AD, there is less research available on the impact of dysbiosis on ALS. This fatal neurodegenerative disease does, however, also display evidence of altered gut biodiversity, as studies show dysbiosis leading to an increased prevalence of proinflammatory organisms in ALS patients [44]. Animal studies have demonstrated the impact of dysbiosis on ALS, where a reduced content of butyrate-producing bacteria resulted in gut permeability [31]. Animal studies have demonstrated intestinal dysbiosis in rodents prior to ALS manifestation, where leaky gut was also present [43]. Furthermore, alleviating dysbiosis improved ALS progression with worsening dysbiosis associated with more severe clinical symptoms [43]. The *Firmicutes* to *Bacteroidetes* ratio in ALS patients is an area of much investigation, of which, studies, however, report contracting results as described by Boddy et al. (2021) [45].

3.1.4. Multiple Sclerosis

Multiple sclerosis is an inflammatory disease of the central nervous system where host T cells are involved in the destruction of nerve tissue or demyelination and disease progression. MS is both an autoimmune disease and neurodegenerative condition, with ca. 75% of patients suffering chronic pain [38]. Studies have shown that a reduced quantity of butyrate-producing bacteria, particularly *Firmicutes*, are associated with the pathogenesis of MS [30]. Loss of integrity and increased permeability of the BBB is also a characteristic of MS and may be resultant from dysbiosis-induced intestinal permeability or leaky gut [31]. Studies assessing bacterial diversity in MS patients identified variations in species, including *Bacteroides* (butyrate-producing), *Prevotella* and *Sutterella* with bacterial species *Streptococcus thermophilus* and *Eggerthella lenta* significantly increased in MS patients [46].

3.2. Autoimmune Conditions

Autoimmune diseases are diseases manifesting when a patient's immune system attacks self-cells and tissues leading to inflammation, tissue damage and chronic pain. Autoimmunity is therefore, a failure of self vs. non-self-recognition with the synthesis of autoantibodies (antibodies specific to self-tissues) or by the generation of autoreactive T lymphocytes [47]. Currently, there are approximately 100 listed autoimmune diseases, with the most common being Coeliac disease, Rheumatoid arthritis (RA), Inflammatory bowel disease (Crohn's and colitis), Graves' disease, Hashimoto thyroiditis, MS, Systemic lupus erythematosus (SLE) and type 1 diabetes (T1D) [48]. Studies assessing the role of the GIT microbiota on local and systemic (gut-distal autoimmunity) autoimmune disease have established that dysbiosis contributes to many of the disease states in this category [16]. The production of anti-inflammatory SCFAs by resident bacteria is one pathway where a shortage of SCFA production has been identified in MS [48]. Immuno-mediated encephalitis, which manifests as inflammation of the CNS, is an emerging group of syndromes which are non-MS autoimmune diseases of the brain and CNS associated with high mortality [49]. Encephalitis manifest due to an abnormal antibody response against cell-surface, intracellular synaptic, or intraneuronal antigens [50]. Studies have shown that the microbiota of encephalitis patients differed from that of healthy controls with alterations in SCFA production evident [49]. A decrease in butyrate- and propionate-producing species, including *Faecalibacterium prausnitzii* and *A. muciniphila*, is common in autoimmune diseases [51]. Systemic autoimmune diseases, e.g., RA, SLE and dermatological diseases (psoriasis) are characterized by an unusual adaptive immune response to autoantigens, specifically autoreactive T cells, which are a main driver of disease pathogenesis [52]. The microbiota influences the development of T lymphocytes, including Th-2/Th-1 lymphocytes, where the balance of effector T cells is altered in dysbiosis and results in T cell mediated autoimmune reactions [47]. Molecular mimicry which results from shared epitopes between GIT microbes and self-proteins may also lead to autoreactive T cell activation and autoimmunity [53]. As such, cross-reactivity of the immune system to microbial antigens

may trigger autoimmune activity [54]. Molecular mimicry can also result in pain via direct IgG-induced injury of nociceptive fibres [37]. Additionally, the GIT microbiota is associated with the development of B lymphocytes and the synthesis of antibodies particularly immunoglobulin A (IgA) which is targeted against thymus-dependent and independent antigens [47]. Importantly, both autoreactive T cells and autoantibody-producing B cells have been associated with the pathogenesis of SLE [53]. In SLE, patient's periodontitis is an issue with ca. 65% of patients affected, periodontitis is associated with dysbiosis of oral microbiota where pathogenic species of *Fusobacterium nucleatum* and *Actinomyces naeslundii*, amongst others, are present [47]. Additionally, the pathogenic *Enterococcus gallinarum* has been detected in the livers of patients with SLE and autoimmune hepatitis related to translocation from the GIT [54]. In RA patients, studies have shown a deficit of *Haemophilus* spp., which negatively correlates with the quantity of serum autoantibodies; furthermore, *Lactobacillus salivarius* was over-abundant and correlated with increased severity of symptoms [53]. The autoimmune disease of the pancreas T1D is associated with increased intestinal permeability and leaky gut with an excess presence of pro inflammatory species in the GIT microbiota [55].

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