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Review Article

Role of Gut Microbiota in Neuropathy Development

Ahed J Alkhatib[1,2,3]*, Mustafa Ahmad Al-Shehabat[4], Dania Mustafa Al-Shehabat[5], Aya Mustafa Al-Shehabat[6] and Adam Mustafa Al-Shehabat[6]

[1]Retired, Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science and Technology, Jordan

[2]International Mariinskaya Academy, Department of Medicine and Critical Care, Department of Philosophy, Academician Secretary of Department of Sociology, Jordan

[3]Cypress International Institute University, Texas, USA

[4]Department of Physiology and Biochemistry, Faculty of Medicine, Jordan University of Science and Technology, Jordan

[5]King Abdulla University Hospital, Jordan

[6]Faculty of Medicine, Jordan University of Science and Technology, Jordan

***Corresponding Author:** Ahed J Alkhatib, Retired, Department of Legal Medicine, Toxicology and Forensic Medicine, Jordan University of Science and Technology, Jordan.

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Abstract

The constant interplay between the gut microbiota and the nervous system has led to a new field of research, primarily focusing on changes in the microbial community ('dysbiosis') as a contributing factor to neurological disease and pain development. It is here that the focus of the present narrative review is aimed. Discussed will be the relationship between gut microbiota and neurological health. After detailing the nature and origins of oral neuropathic pain and chronic somatic pain, the weight of evidence linking these diseases to gut dysbiosis is highlighted. Finally, the promising therapeutic implications of re-establishing normal gut microbiota composition by probiotics or Fecal Microbiota Transplantation (FMT) are touched upon.

Symptoms related to the impairment of peripheral nerves constitute chronic disorders, often of high prevalence. Although the etiology is different, neuropathic pain conditions lead to long-term treatment deficits. This likely reflects an insufficient knowledge of the etiology of neuropathic pain conditions. Recently, an association between the presence of neuropathic pain and conspicuous changes in gut bacteria ('dysbiosis') was noticed. As a variety of bacterial strains are known to induce an inflammatory response with sequential pain symptom appearance, inflammation in the intestine gave a plausible explanation for the observations.

Keywords: *Gut; Microbiota; Neuropathy; Development; Nervous System; Microbes*

Introduction

Gut microbiota and the development of neuropathy is a complicated issue because neuropathies are developed in response to various factors such as diabetes [1]. The main objective of this study was to review the literature for updates on the role of gut microbiota and the development of neuropathies.

Neuropathies development

Peripheral nerve disorders, also known as neuropathies, are a prevalent neurological ailment [2]. Peripheral neuropathies can arise because of toxins, but they can also be the primary cause or a sign of other systemic conditions, such as diabetes, infections, vasculitis, neoplastic disorders, and vitamin deficiencies [3-5]. Approximately 50% of individuals continue to possess an undetermined etiology for peripheral neuropathy [6]. Peripheral neuropathies occur when there is a malfunction in either the Schwann cells surrounding peripheral axons or the axons themselves, resulting in clinical symptoms [7]. Consequently, the investigation of peripheral neuropathies has prioritized the comprehension of the mechanisms underlying Schwann cell myelination of peripheral axons, including motor, sensory, and autonomic axons, as well as the processes governing their growth and maintenance [8].

One unanswered question is why distal symmetric polyneuropathy (DSPN), a common neuropathy in people with diabetes mellitus (DM), occurs. Here, we discover that a phenotype in db/db mice characterized by more severe peripheral neuropathy may be caused by the gut microbiota of individuals with diabetic sensorimotor polyneuropathy (DSPN). The study found that fecal microbiota transplantation from healthy donors effectively reduced diabetic peripheral neuropathy (DSPN) in 22 patients. The experiment was double-blind and placebo-controlled. Glycemic control had no bearing on this improvement. The ten patients who were given a placebo, however, did not feel the same level of alleviation. Two competing groups were formed from the gut bacterial genomes that showed an association with the Toronto Clinical Scoring System (TCSS) score. Improved intestinal barrier function and lower levels of proinflammatory cytokines were associated with reduced guild 2, which contained more genes involved in the synthetic pathway of endotoxin, and boosted guild 1, which was characterized by a stronger capacity to manufacture butyrate. Additionally, better therapeutic efficacy was obtained when the transplants and recipients shared a similar enterotype, indicated by a greater abundance of guild 1 and a lower abundance of guild 2. Changes in these two antagonistic relationships could therefore be causative for DSPN and present opportunities for therapeutic intervention [9].

Distal symmetric polyneuropathy (DSPN) is the most common form of neuropathy in individuals with diabetes mellitus (DM). It is a significant and unaddressed medical concern. Approximately half of the patients with diabetes mellitus (DM), including those with type 1 and type 2 DM (T1DM and T2DM), experience diabetic sensorimotor polyneuropathy (DSPN) [8]. DSPN is associated with elevated mortality rates, lower limb amputations, and intensely agonizing neuropathic symptoms, all of which hinder physical functioning, mental well-being, and overall health-related quality of life [10]. Due to limited knowledge regarding the underlying pathogenetic mechanism of DSPN and the absence of viable targets, there are currently no disease-modifying treatments available for the condition. However, certain patients may observe symptom improvement through lifestyle modifications, glucose control, and a limited number of medications [11]. There is compelling and increasing data indicating that the gut microbiota has a causal role in maintaining glucose homeostasis [12]. Moreover, it seems that the gut microbiota operates at the intersection of the neuroimmune-endocrine and gut-brain axis, forming an intricate network that can impact the neurological system [13]. Emerging research indicates that the interplay between the gut microbiota and the brain may have a significant impact on the progression of neurodegenerative disorders affecting the central nervous system, such as Parkinson's and Alzheimer's [14]. Moreover, the gut microbiota and its bioactive compounds are recognized as regulators of host bioenergetics and inflammation, potentially serving as mechanistic pathways for DSPN [15].

A recent study with a limited sample size found that patients with DSPN exhibited distinct gut flora compared to healthy controls. Eighteen However, the causal relationship between peripheral nervous system (PNS) issues in diabetes mellitus and gut microbiota remains unclear [7].

The microbiome-gut-brain axis (MGBA) is a neurological pathway that allows for two-way communication between the enteric and central nervous systems [12]. The intestinal microbiota performs protective activities such as synthesizing vitamins, metabolizing substances, and absorbing nutrients from the diet. However, a growing body of research suggests that it may play a role in the control

of several cerebral functions [16]. Changes in the normal microbiota can lead to neuroinflammation and changes in central nervous system (CNS) functions and behaviors. This occurs through the activation of the immune system in the affected area and the resulting inflammation throughout the body [17]. In recent years, there has been extensive clinical and preclinical research focused on investigating the potential link between gut microbiota and the development of neurological and mental illnesses [18].

Animal models are essential for understanding human diseases and developing new treatment approaches. Research conducted on germ-free animals indicates that the gut microbiota has a role in both acute pain signaling [17] and chronic pain states [19]. Neuropathic pain can be attributed to a diverse array of causes and diseases. Exposure to harmful substances, such as chemotherapy treatments, severe injuries, infections, and diabetes [20]. Neuropathy can cause changes in the way the spinal cord and brain process information, leading to long-lasting neurological and mental impairments, as well as abnormal discomfort, even after the initial damage has been treated. The main factor responsible for neural plasticity is the heightened production of cytokines by astrocytes and microglia cells. This phenomenon is a crucial element of the complex process, as shown by studies conducted by Chen., *et al* [21].

A sophisticated reciprocal association between the gut flora and the nervous system has been established. This communication involves a variety of signaling mechanisms, including the vagus nerve [22], immune mediators [23] and metabolites [24]. This demonstrates the critical role of the gut-brain axis, in which cerebral functions are profoundly influenced by complex microbial communities in the digestive system and vice versa. It relates to the central and peripheral nervous systems [25].

The GM possesses the capacity to generate and discharge active metabolites that might potentially influence the neurological system and engage with the central nervous system in the capacity of neuromodulators [26]. The primary bacterial compounds that affect the brain encompass bile acids, aromatic amino acids, and silicon-containing free radicals known as SCFAs. Propionate, acetate, and butyrate are the primary constituents of short-chain fatty acids (SCFAs) and are produced through bacterial fermentation of carbohydrates. The binding of G-protein-coupled receptors may play a role in mediating these interactions with the colon [27]. Additionally, there is evidence indicating that small fatty acids (SCFAs) can indirectly influence the gut-brain axis by promoting the secretion of specific gut hormones such as leptin and glucagon-like peptide-1 (GLP-1). The gastrointestinal hormones possess the capability to engage with the receptors of the brain's vagus nerve [28].

Bacteria such as Streptococcus, Bifidobacteria, Enterococcus, and Lactobacillus can affect neurotransmitter precursors in the brain by producing them in the gastrointestinal system. Some examples of neurotransmitters are gamma-aminobutyric acid (GABA), acetylcholine, and serotonin [29].

The fields of psychiatry and neurology heavily rely on serotonin and its receptors, as they play a crucial role in coordinating nearly all brain functions [30]. Serotonin is associated with various physiological systems, such as bladder control, ejaculatory latency, intestinal motility, cardiovascular function, and platelet aggregation. These functions enhance its recognized role as a regulator of mood, behavior, and sleep in the central nervous system (CNS). It is somewhat unexpected that bacteria in the colon, which is considered our second brain, produce 95% of serotonin instead of the brain [31].

What is the mechanism by which serotonin precursors, such as tryptophan, can enter the brain? Existing research indicates that genetically engineered products may influence serotonergic neurotransmission through the humoral pathway [32]. Once inside the neurological system, serotonin and tryptophan have distinct functions. For instance, when serotonin attaches to 5-HT receptors on microglia, it triggers the release of exosomes containing cytokines. The interaction between tryptophan and an aryl hydrocarbon receptor triggers microglia activation and modifies the transcriptional program of astrocytes [33]. The tryptophan-kynurenine pathway metabolizes more than 95% of tryptophan and generates many bioactive metabolites, such as immunomodulators, harmful oxidants,

neuroprotective antioxidants, and neuroprotectants [34]. Kynurenine metabolite modification has been associated with various medical conditions such as distal NP in HIV-positive patients, malignancies, neurological diseases, and immunological problems [35]. This can be attributed to the recognized correlation between NP and gut dysbiosis in patients who are HIV-positive [35].

The inflammasome serves as an extra connection between the GM and the CNS. The inflammasome is an intrinsic immunological complex that is formed in the central nervous system and gastrointestinal tract because of certain signals or pathogen activity. The effector molecule of an inflammatory response is composed of the enzyme pro-caspase-1, the adaptor molecule apoptosis-associated speck-like protein, and receptor proteins like TLRs. The inflammatory molecule has three essential structural components [36]. The latter triggers the release of interleukin-1-β and IL-18, which are inflammatory proteins that play a role in various processes in the central nervous system, such as regulating the immune system, causing inflammation, and promoting nerve cell damage [22]. Inflammasome activation can also trigger pyroptosis, a crucial inflammatory process of regulated cell death that has evolved to eradicate intracellular pathogens. The unique shape of this organism is determined by the breaking of cells through the creation of pores in the plasma membrane [31].

The inflammasome first interacts with the microbiota through a receptor protein that recognizes distinct molecular patterns found in different microbes within the gastrointestinal tract and has a strong attraction to them. DAMPs and PAMPs are acronyms for danger-associated molecular patterns and pathogen-associated molecular patterns, correspondingly. Hence, it is conceivable that genetic modification (GM) could result in an overactive inflammasome, potentially compromising the blood-brain barrier (BBB) and facilitating the entry of proinflammatory mediators, namely interleukin-1-β and IL-18, into the central nervous system (CNS). The neuroinflammatory states linked to these effects are thought to play a role in the development of several neuropsychiatric illnesses, such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease. Kiger et colleagues. showed that mice with spinal cord injury that had an imbalance of gut bacteria before the accident experienced worsened neurological damage and hindered their recovery. In contrast, animals who received microbial support to control their gut microbiota showed a faster recovery [32].

The primary etiology of numerous diseases is postulated to be genetic variation. Additional investigation is necessary to ascertain whether genetic alterations are the primary cause or a result of the disease's development [31].

Conclusion

Given the relationship between gut dysbiosis and neuropathy, it makes sense to intervene at the level of the gut to treat neuropathy. Studies and clinical trials utilizing probiotics and prebiotics, fecal transplants, or dietary intervention in neurological diseases are relatively new but show promise. Recent reports highlight the mechanism underlying the effects of these interventions, describing how they target different gut microbiome products and the gut-brain axis. The current treatment for neuropathy is not particularly effective. Therefore, the findings for gut-brain interventions have drawn a lot of attention.

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