INFLUENCE OF NUTRIENTS ON THE INTERPLAY BETWEEN THE PNEI SYSTEM AND GUT MICROBIOTA

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Abstract

Gut microbiota is considered one of the regulators of homeostasis of the host. Its communications with the psycho-neuro-endocrine-immunology (PNEI) system of the host could be described in several ways, including the HPA axis coordination, a direct effect on the immune system and inflammation and secretion of neurotransmitters that aid microbiota`s development and adaptation to various conditions.

All of this is achieved through the vagal nerve, which is depicted as a connective unit between PNEI system and gut microbiota.

Microbial status also depends on nutrition. There are several dietary patterns that vary on the amount and type of nutrients consumed. The Meditteranean and the plant-based diet can have a positive impact on microorganisms in the gut and induce the proper implementation of physiological functions of the body. Despite the abundance of diets, not all of them are considered healthy for the microbiome populations. Refined sugars and saturated fat, which form the Western diet, can reason in predispositions to the development of diseases.

Keywords: *microbiota, gut, PNEI system, neurotransmitters, nutrients.*

Introduction

The psycho-neuro-endocrine-immunology, also known as PNEI, is a study investigating four systems which are tight bonded and affect physical health altogether – the psychic, the nervous, the endocrine, on one side and the immune system, on another. This complex interplay is mediated by a wide variety of signaling (or messenger) molecules. Such cross-talk among systems are carefully trimmed by feedback loops that simultaneously act in order to maintain the homeostatic equilibrium (França, K. et al., 2017).

The whole PNEI system has a vital connection with gut microbiota. Gut microbiota consists of microbe cells in the gastrointestinal tract that are crucial for providing for the human health (Del Toro-Barbosa, M. et al., 2020). They help to calibrate the innate and adaptive responses (Donia, M. S. et al., 2015).

Nutritional habits have also become an inseparable topic of discussion as they are recognized as one of the drivers of microbial composition and diversity. The role of both nutrients and dietary patterns on the microbiota have been extensively researched and there are several proved explanations about this relationship (Berding, K. et al., 2021).

In this review, we are aiming to focus on understanding the function of these microorganisms as well as finding their influence on other systems. We are going to explain the importance of eating

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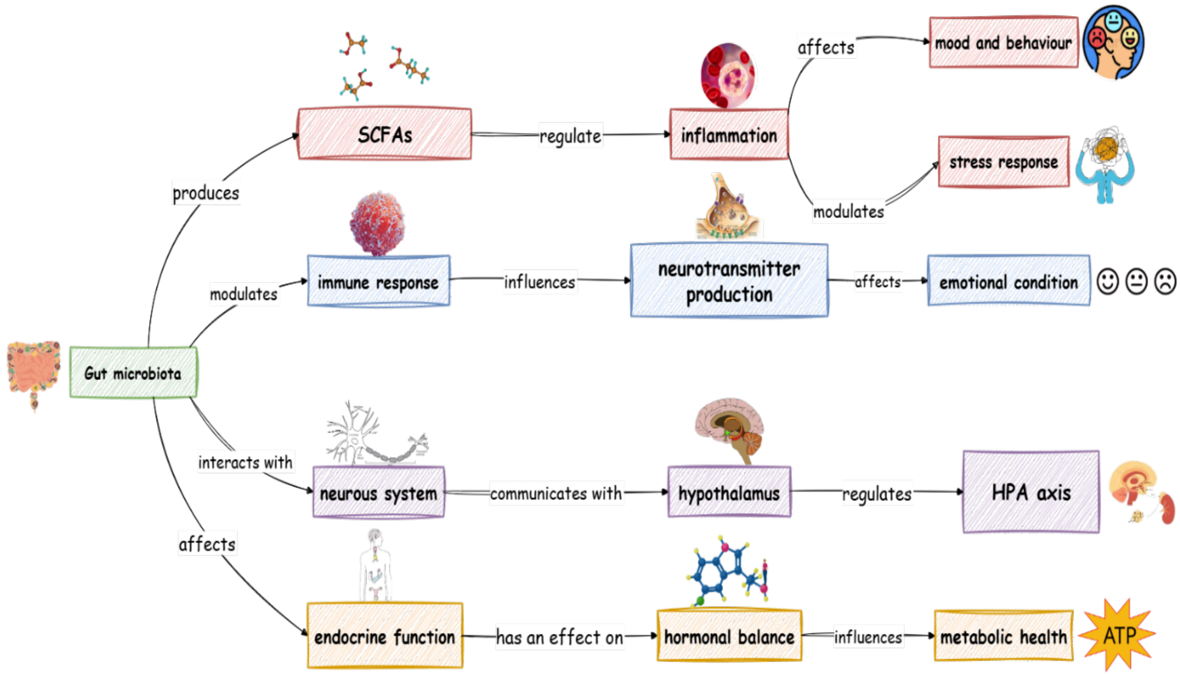
habits and why accustoming to some of them may or may not help maintaining a healthy gut microbiota.

Effects of the gut microbiota on the PNEI system

It has been reported that the enteric microbiome plays an eminent role in the gut-brain axis communication (Del Toro-Barbosa, M. et al., 2020**)**. This interaction may cause changes in both human physiological behavior and pathogenesis, including the proper work of the gastrointestinal tract and the central nervous system (Du, Y. et al., 2020).

It has been discovered that these bacteria provide their psychobiotic potential through the enteric nervous system or the immune system's stimulation. This can happen in three different pathways: first, by influencing the hypothalamic-pituitary-adrenal (HPA) axis stress response; second, by a direct effect on the immune system; third, by secretion of different molecules (Sarkar, A. et al., 2016), (Fig.1).

Fig.1: Pathways of influence of gut microbiota.



The HPA axis is the main neuroendocrine response system to physiological and physical stress in the human body. When a stressful event is experienced, the HPA axis is activated, and as a result, the secretion of cortisol is increased. Cortisol adapts the body for the 'fight or flight' response. This happens by the elevation in blood sugar through gluconeogenesis (De Weerth, C, 2017; Kinlein, S. A. et al., 2019), suppressed immune function (Mayer, E. A., 2000) and enhanced fat and protein metabolism (De Weerth, C, 2017; Kinlein, S. A. et al., 2019). Microbial balance can decrease the activation of the HPA axis. However, disturbance in the microbial equilibrium may lead to a negative impact of this axis and even to overproduction of cortisol. In such concentration, cortisol cannot exert its anti-inflammatory properties (Silverman, M. N. et al., 2012).

Microorganisms in the gut have a significant impact on the immune system. Some publications have shown the way the gut microorganisms modulate immune responses at the mucosal surface during infection, inflammation, and autoimmunity; (Cassel, S. L. et al., 2008; El Aidy, S. et al., 2014; Kamada, N. et al., 2013; Mazmanian, S. K. et al., 2005; Round, J. L. et al., 2009). As a result, metabolites produced from the microbiome can traverse the intestinal barrier and enter the circulatory system, where they directly activate imuune cells (Schirmer, M. et al., 2016) and define their population, migration and function (Dorrestein, P. C. et al., 2014).

Different neuroactive compounds which alter the PNEI system can be produced by the gut microbiota. Inseparable relationships between the psyche and serotonin have been depicted. Serotonin (5-HT; 5-hydroxytryptamine) plays essential roles in the regulation of neuronal differentiation and migration, as well as axonal outgrowth, myelination and synapse formation (Gaspar, P. et al., 2003). 5-HT is mainly found in the intestinal mucosa, 90%–95% of it is stored in two primary reservoirs: in the intestinal epithelium, where it is induced by enterochromaphin cells (ECs), and in neurons of the enteric nervous system (Gershon, M.D., 2013).

Gut microbiota plays a critical role in the generation of free catecholamines in the gut lumen. (Asano, Y. et al., 2012). Catecholamine (CA) neurotransmitters (dopamine (DA), norepinephrine (NE), and epinephrine (EP)) are crucial for motor control, learning, memory formation, and in stress response (Kobayashi, K., 2001). NE and DA are distinguished as regulators of prefrontal cortex-dependent function, such as attention, decision making, and inhibitory control (Xing, B. et al., 2016).

Normal production mechanisms of gamma-aminobutyric acid (GABA) and glutamate in microbiota are also of importance in controlling excitatory and inhibitory neurotransmission (Petroff, O. A. C., 2002). Coordination between these two neurotransmitters is essential for implementation of complex brain processes such as neuronal excitability, synaptic plasticity, and cognitive functions such as learning and memory (Foster, A. et al., 2006).

Microbiota influences neurous system directly by secretion of acetylcholine (Ach). Ach is a primary excitatory neurotransmitter in the periphery. It influences synaptic plasticity, reinforces neuronal loops and cortical dynamics during learning, modulates neuronal excitability (Picciotto, M. R. et al., 2012), and can also alter the firing of neurons on a rapid time scale in response to changing environmental conditions (Letzkus, J. J. et al., 2011).

Short-chain fatty acids (SCFAs) are saturated aliphatic organic acids that include one to six carbons. SCFAs are produced by gut bacteria through saccharolytic fermentation of carbohydrates that have not been digested and absorbed in the small intestine (Den Besten, G. et al., 2013). Regarding its role in the organism, SCFAs are defined as substrates modifying host cellular metabolism. They are very efficient in regulating the integrity of the epithelial barrier, the immune system and inflammatory response and inserts effects on lipid metabolism and adipose tissue at several levels (Morrison, D. J. et al, 2016). Moreover, SCFAs might directly affect neural function by strengthening blood-brain barrier integrity, modulating neurotransmission, influencing levels of neurotrophic factors, and improving memory consolidation (Silva, Y. P. et al., 2020).

The classic trio modulates gut microbiota

The microorganisms located in the gut are involved in metabolic actions through the extraction of beneficial compounds, such as carbohydrates, fats and proteins, for the cells of the host. These macronutrients which are being processed have a different impact of the microbial profile because of the individual functions of the microbial taxa (Berding, K. et al., 2021). Their proportional ratio is essential for microbiota development.

Carbohydrates are well-studied dietary compounds. Digestible ones are enzymatically decomposed in the small intestine and include starches and sugars, such as glucose, fructose, sucrose, and lactose (Singh, R. K. et al., 2017). Studies have proved that these natural carbohydrates have a controversial effect on the microbiome. The artificial sweeteners such as saccharin, sucralose, and aspartame are also being widely discussed due to their negative effects. They have been originally marketed as a non-calorie alternative option replacing natural sugars. However, their consumption is more likely to reason in glucose intolerance than the consumption of pure glucose and sucrose. They might have mediated this effect through alteration of the gut microbiota (Suez, J. et al., 2014).

On the contrary, undigestible carbohydrates, like fibers, tend to positively impact the microorganisms. Chemical characteristics (polymerization, solubility, and viscosity) of different fibers determine the placement of metabolism within the gastrointestinal tract, leading therefore to specific microbial changes in response to their ingestion. Besides changing microbial composition, different dietary fibers also influence microbial enzymatic capacity and metabolite concentration. Both solubility and fermentability determine the degree and location of microbial fermentation as well as the type of metabolite produced, which supports the crucial action of fibers in the gut (Berding, K. et al., 2021).

Despite most fatty acids being absorbed in the small intestine, dietary lipids and fat also mark an impact on the microbial profile. They are known to exert a mixed effect, depending on the type of fat. Different degrees of saturation have been proven to specifically shape microbial composition. For example, high saturated fatty acid (SFA) intake has been reported to reduce in total bacterial abundance in humans, as well as decreasing the microbial diversity and richness (Roytio, H. et al., 2017). For instance, ω-3 (omega-3) fatty acids have been proposed to restore the eubiotic state in pathological conditions by increasing the amount of beneficial bifidobacteria and decreasing enterobacteria, which in turn results in providing an anti-inflammatory environment through the production of SCFAs and suppression of endotoxemia (Watson, H. et al., 2018; Costantini, L. et al., 2017).

The third group of macronutrients affecting the gut microbiota are the proteins. The source, concentration, and amino acid balance of dietary protein are primary factors influencing the composition, structure, and function of gut microbes, as well as the availability of different microbial metabolites (Berding, K. et al., 2021). Bigger ratio between proteins and carbohydrates increases colonic protein fermentation and the production of branched-chain fatty acids (BCFAs) phenylacetic acid and N-nitroso compounds (Russell, W. R. et al., 2011).

Examples of dietary patterns

Macronutrients participate in various dietary patterns. The Meditteranean and the plant-based diet are significant for abundant microbial status in the gut. They consist of high intake of fiber and other low glycemic carbohydrates, and relatively greater intake of plant-based than animal-based proteins. They also include a beneficial fatty acid profile that is rich in both monounsaturated and polyunsaturated fatty acids, high levels of polyphenols and other antioxidants (Kromhout, D. et al., 1989). Western, omnivore-type diet, shifts the composition of the microbiota to a more disease associated type. It is distinguished from other healthy diets by including critically low amounts of dietary fibers and high percentage of saturated fat and refined carbohydrates and animal-based proteins, which have been associated with a disturbance with the abundance of specific bacteria (Albenberg, L. G. et al., 2014; Singh, R. K. et al., 2017).

Conclusion

The interaction between microorganisms in the gut and the PNEI system has received the deserved attention. Questions about the understanding of this expansive microbe population have received an answer. The impact of the gut flora on the development and the adapting mechanisms of human beings is well depicted, and yet discussible. Microbiome plays an eminent role in the gut-brain axis communication by secretion of biologically active molecules. These molecules regulate CNS development, hormone concentrations, psychological and immune response and therefore, maintenance of microbial equilibrium is of huge importance. This is known to be achieved by different dietary patterns whose effects are analyzed depending on the ratio between macronutrients. Fibers are significant in achieving the processes in the gut, proteins provide the structure and function of microbiota and lipids decrease inflammation. However, clarity of adapting mechanisms of gut microbiota during physiological and pathological conditions is yet to be improved with greater discoveries and implications.

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