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Short Communication

Therapeutically Targeting the Microbiota-Gut-Brain Axis to Treat Mental Diseases

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The National Institutes of Health (NIH) started the Human Microbiome Project (NIH Human Microbiome Project-Home) after interest in the understanding of microbiome-based effects on health and physiopathology of diseases.

In many people worldwide it is common to find both intestinal and mental disorders and this suggests a strong correlation between the centrale nervous system (CNS) and the gastrointestinal (GI) tract. This bidirectional relationship between these two organs is named the gut-brain axis, it is at the base of correlation among mental diseases and inflammatory bowel diseases (IBD). It is possible to link cognitive and emotional functions of the brain with peripheral intestinal functions such as enteric reflex, intestine permeability, immune system stimulation and enter-endocrine signaling [1].

There is evidence of the enteric microbiome's pivotal role in the cross talking of gut-brain axis. The gut microbiota is composed of 10^{14} microorganisms whose composition reflects the evolution of both host and microbe cells. Although each person has a specific microbiota, the GI tract of healthy adult is usually inhabited from Bacteroidetes, Firmicutes, Proteobacteria and Actinobacteria and the balance of this is responsible for many essential functions. Basically, there is a two-way communication that leads the microbiota to interact with the brain and subsequently the brain with the gut. In fact, an imbalance of its composition, called *dysbiosis*, leads surely to gastroenteric disease and as soon as these affect the CNS and cognitive functions there will be also mental disorders symptoms and vice-versa [2].

The communication between the gut and the CNS passes through afferent pathways of the autonomic nervous system and consequently the nervous system responds on the intestinal walls or lumen and their functions. The microbiota-gut-brain axis (MGBA) is formed by different communication pathways: descending pathways include the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamic-pituitary-adrenal (HPA) axis, while ascending pathways include the vagus nerve (VN) and reflex arc, cytokines, immunological mediators, microbiota, and intestinal metabolites. The main metabolites of intestinal bacterial fermentation, in both colon and small intestine, are the short-chain fatty acids (SCFAs). These are considered regulators of many physiological processes such as *acetate* that allows the acetylation of histones and methylation of DNA, *butyrate* which influences the immune system by arising T cells number in the colon, and *acetate* or *propionate* that influence lipid, glucose, and cholesterol metabolism in various tissues. The lipophilic nature of these SCFAs permits them to cross the blood-brain-barrier (BBB) reaching the brain, where they are able to interact with neurons and to regulate the function of the microglia. The microbiome is capable of production also of neuroactive molecules such as tryptamine, serotonin, GABA, noradrenalin, dopamine, and acetylcholine [3].

Instead, the CNS directly or indirectly induced the release of signaling molecules, cytokines, and antimicrobial peptides into the gastrointestinal lumen. Moreover, the immune system plays a key role in signal transduction of intestinal bacteria on the CNS by pro- and

anti-inflammatory cytokines levels. The gut macrophages act in the gut-brain axis through toll-like receptors (TLRs) and interleukin-1 receptor (IL-1R), whose continuous expression causes an inflammatory state in the host [4]. The latter communicates immediately with the brain activating HPA axis inducing the corticotrophin-releasing and then the release of cortisol that alter gut permeability, barrier function and communicate with immune cells for release of cytokines. It is thought that the mental disorders are caused by above mentioned alterations, especially an neurotransmitters imbalance and HPA axis disfunction.

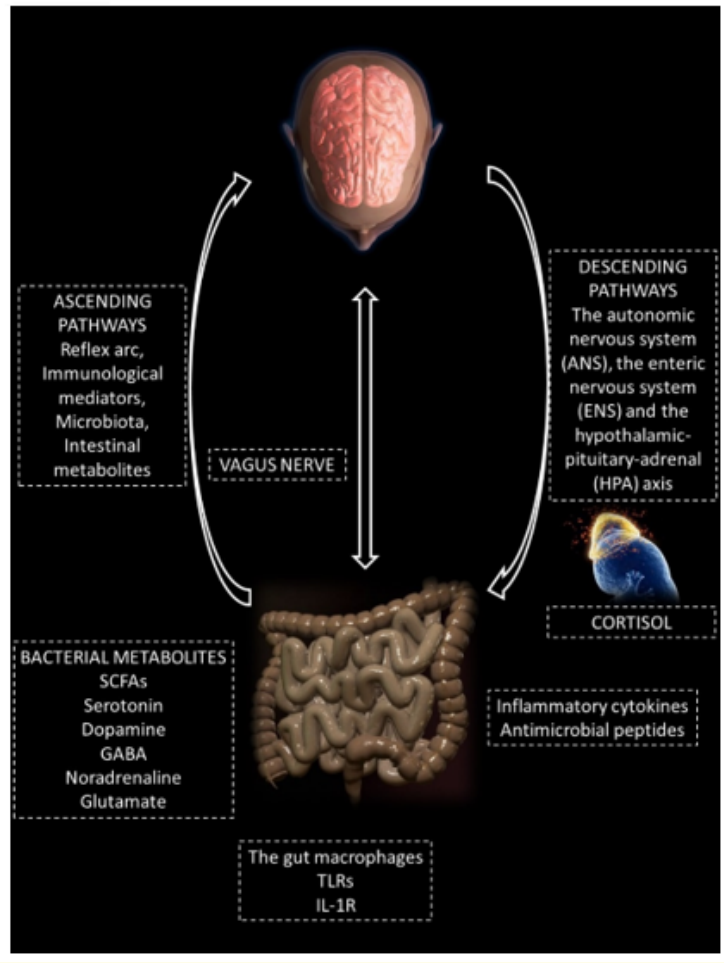

Figure 1: *Overview of the microbiota-gut-brain axis and its bidirectional crosstalk.*

Many experimental studies reported how the microbiota-gut profile is changed in patients suffering from mental illness. Hence, the pivotal role of bacterial strains in the microbiota has been highlighted towards mental diseases like stress, anxiety, depression, Alzheimer's disease, Parkinson's disease, and many psychiatric disorders, among them schizophrenia, attention deficit hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD) and many others. Maybe the gut microbiota also plays a key role in some Long-COVID symptoms. It is known how these mental illnesses are based on altered levels of neurotransmitters and since these are influenced by the gut microbiota it is possible to include the MGBA as therapeutic target and to act on its pathways to treat the aforementioned disease.

Serotonin (5-HT, 5-hydroxytryptamine), the main neurotransmitter implicated in physiopathology of depression, is produced over 90% in the gut by the enterochromaffin cells (ECs) and neurons of the ENS and it plays a key role in the gastrointestinal functions such as motility, absorption, and transit. The gut microbiota (GM) acts on serotoninergic production by ECs through the short-chain fatty acid (SCFA) butyrate which allows the hydroxylation of tryptophan to 5-hydroxytriptophan and then its decarboxylation to 5-hydroxytryptmine [5]. For example, the production of 5-HT was reported by *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus* and other strains [6].

Dopamine (DA), noradrenaline (NA), and adrenaline (AD) are biogenic amines derived from the amino acid tyrosine and they play a crucial role in many biological functions such as prefrontal-cortex input, including motor control, learning, attention and inhibitory control, effects on the cardiovascular system and on the metabolism. The GM acts on catecholaminergic production in the CNS, thanks to the production of L-phenylalanine, the precursor of tyrosine [7]. A dysbiosis of bowel microbiota can alternate the DA levels causing different physio pathological process such as Parkinson's disease, with its decrease, or psychotic disorder, with its increase [8]. Biosynthetic pathways of L-phenylalanine and DA were described in *Corynebacterium glutamicum* or *Escherichia coli* [9] and *Bacillus*, *Serratia*, *Lactobacillus*, *Klebsiella*, *Morganella* or *Escherichia coli* [10] respectively.

Gamma-Aminobutyric Acid (GABA) is the primary neurotransmitters of the mammalian CNS to have an inhibitory control, its decrease is correlate with depressive and anxiety behavior. The GABAergic receptors are in the autonomic and central nervous system and also in many organs including the gastro-enteric tract. The GM acts on GABAergic production so much so that with a disrupted GM one altered metabolite is GABA, in particular *Lactobacillus rhamnosus* altered the central mRNA expression of $GABA_A$ and $GABA_B$ receptors reducing the anxiety though the vagus nerve [11]. There are many bacteria strains (both *Lactobacillus* and *Bifidobacterium*) with ability to produce this neurotransmitter via the enzyme glutamate decarboxylase[1] as well as there are also microorganisms which consume GABA with depressive/anxious effect.

Glutamate (GLU) is the main copious excitatory neurotransmitter in the CNS and its level is controlled by glutamate-glutamine cycle. The latter is alterate in patients with depression and the frequency with which there are often inflammatory bowel syndrome (IBS) among patients affected by depressive behavior led to think of a correlation between the gut and this mental illness, in particular an alterate glutamatergic activity in ENS could be a major cause of IBS [13].

Acetylcholine (ACh), the main neurotransmitters implicated in physiopathology of Alzheimer's disease, is the primary excitatory neurotransmitters in the periphery and it plays a key role in many biological processes such as synaptic plasticity, cortical dynamics, and neuronal excitability in addition to other effect via cholinergic receptors. ACh and enzyme involved in its synthesis have been discovered in bacteria, in particular in *Lactobacillus plantarum* [14]. Also, an alteration in the gut microbiota composition could be associated with Alzheimer's disease, for example in *Firmicutes*: *Bacteroidetes* ratio [15].

Many studies attempt the ability to directly modulate the gut microbiota by the ingestion of living microorganism or other products to gain a healthy state on the patient. There are many products on the market that are therapeutically effective on the gut microflora composition. *Probiotics* are defined as live microbes which, when administered in satisfactory quantities, perform a health benefit on the host and its gut microbiota. *Prebiotics* are instead an appropriate substrate for the gut microorganisms which is able to utilize it causing a health effects on the host. As an alternative there are *synbiotics* that are a combination of probiotics and prebiotics, in this way the latter is important to improve the capability of live microbes to lead a change in commensal bacteria composition/function and as a result in the host. At least there is a possibility to ingest fermented food or nonviable entities, including bacteria fragments or cellular extract

[1]The gene encoding the glutamate decarboxylase, gadB, was identified in the genome of many bacterial species (*Lactobacillus plantarum, Lactobacillus brevis, Bifidobacterium adolescentis, Bifidobacterium angulatum, Bifidobacterium dentium*) [12] which also need another gene, gadC, to emit the neurotransmitter.

called "inactivated probiotics" or *parabiotics* and metabolites of microorganisms fermentation which are equally bioactive products and are named *postbiotics*. This plethora of products on the market each one with a specific strains composition suggests using the gut-microbiota-brain axis as a new target to obtain beneficial results in the brain and mental disorders. Consequently, the term psychobiotic was coined to name live organisms that, when ingested in adequate doses, provide healthy improvement of emotional state and cognitive functions in patients suffering from psychiatric disorders.

Hence, the use of the microbiota-gut-brain axis as therapeutical target could bring the psychobiotics to provide safer therapeutic alternatives in mental disorders avoiding the sides effects due to known psychotropic drugs.

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