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Psychobiotics as Modulators of Gut-Brain Influences

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Abbreviations: PYY: Polypeptide Tyrosine; CCK: Cholecystokinin; GLP-1: glucagon-like peptide-1; Pit: Pituitary; Adr: Adrenal; IL-1, -6, -10: Interleukins -1, -6, -10; TNF-α: Tumor Necrosis Factor Alpha

ABSTRACT

Psychobiotics, first defined as live bacteria (probiotics) provide mental health benefits through their interactions with intestinal commensal bacteria. To date, this definition has been extended to prebiotics that also influence commensal bacteria in combination with probiotics. Psychobiotics, either in animals or in humans, are capable of modifying the imbalance produced by stress i.e., a decrease in neuronal activity to emotion-related information and a decrease in "cortisol wakefulness," which is a marker of stress. Regarding communication, the reported results provide evidence for a local bacteria-induced modulation of the enteric nervous system. Moreover, microbiome-brain communications may also run through the microbiota metabolization to short chain fatty acids (SCFAs) which, in turn, trigger the satiety peptide secretion. The microbiome-brain communications also contribute to the reduction in pro-inflammatory cytokines, which can permeate the blood-brain barrier and permit the brain access to pathogenic entities. In this sense, the pneumogastric, tenth cranial nerve activity also exerts anti-inflammatory and anxiolytic effects. For the brain-microbiome influences, the stress-related production of corticoids, in reducing the gut epithelium integrity, permits the release of bacteria, which, in turn, triggers an inflammatory response through cell elements such as lipopolysaccharides. Psychobiotics cannot be limited to probiotics and prebiotics only, any substance that exerts a microbiome-mediated effect is potentially a psychobiotic. Antipsychotics and antibiotics, at least, may also be classified as psychobiotics. Finally, according to the clinical effects reported for psychobiotics, presently they can offer a natural low-risk and first line alternative to psychotropic medications.

Introduction

Psychobiotics are bacteria beneficial to the body, including probiotic and prebiotic components, capable of influencing gut-brain relationships [1]. This evidence is supported by a pivotal study reporting that mice raised in sterile environments (germ-free animals), exhibited excessive physiological reactions to stress compared to normal controls. These abnormal reactions were reversible by recolonization through probiotic-induced bacteria [2]. Thus, the microbiome appears capable of exerting a causal involvement in the maintenance of general homeostasis (body and brain), as well as in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, a marker of stress. It is now also reported that the vectors of communication between bacteria and brain, to which psychobiotics exert an effect, include the enteric nervous system, the immune system and the vagal nerve. Besides the above considerations, it must be further specified that the nature of psychobiotics, could also be extended to any exogenous influence whose brain effect is bacteria-mediated [1,3].In the present review,

we have considered successively: the microbiota of the gut-brain axis; the psychophysiological influences exerted by probiotics and prebiotics; the microbiome-brain-microbiome communications; the psychobiotics different from probiotics and prebiotics; the role of psychobiotics in patient care.

The Microbiota of the Gut-Brain Axis

The gut microbiota includes all microorganisms and their genomes located in the intestinal tract. The bidirectional communications, brain-gut-brain, regulate several important functions (immunity, digestion, metabolism, satiety, and stress) [4,5].

Probiotics

Bacteria beneficial to health, probiotics, when ingested in appropriate amounts, may lead to positive psychiatric effects in some psychopathologies [6]. The bacteria most frequently employed as probiotics are Gram-positive bacteria Bifidobacterium, Lactobacillus [7]. These bacteria do not possess pro-inflammatory lipopolysaccharide chains in the gut and their propagation does not trigger immunological inflammatory reactions. With such bacteria, the immune system learns to distinguish between pro- or anti-inflammatory entities and to develop adapted immune responses (Figures 1& 2) [8].

Prebiotics

They can also be included in the definition of psychobiotics since they are compounds that, by fermentation in the gut, produce specific changes in bacterial composition and activity. Moreover, prebiotics also support the growth of commensal bacteria and the majority of them are fructans and oligosaccharides (Figures 1 & 2) [1].

Psychophysiological, Immune and Clinical Influences of Psychobiotics

Probiotics in Rodents

According to the great variety of reports available in literature, to limit redundancy, only two relevant approaches are reported here. In one of them, a maternal separation was achieved to induce an early-life stress. Rat pups were left undisturbed or administered with a neutral vehicle substance or the probiotic Bifidobacterium infantis. Vehicle rats showed psychophysiological patterns corresponding to maternal separation, i.e., poorer performance on the forced swim test; an increased inflammation with heightened peripheral pro-inflammatory cytokines (Interleukin-6, IL-6); decreased presence of brain noradrenaline; elevated concentrations of corticotrophin releasing factor (CRF) mRNA. These indices were normalized in probiotic-fed rats. In this model, probiotics appear thus capable of correcting the imbalance produced by the maternal separation [9]. In the other approach selected, probiotic effects during stressful experiences have been examined [10]. Healthy adult male Sprague-Dawley rats were administered with Lactobacillus helveticus while exposed to chronic-restraint stress or no intervention. Relative to control group, the animals fed with probiotics showed lower levels of post-restraint anxiety as well as an enhanced memory. At the biochemical level, rats supplemented with probiotic displayed lower levels of adrenocorticotropic hormone and corticosterone [11]. The probiotic group also showed increases in anti-inflammatory cytokines (IL-10), noradrenaline and serotonin. Again, probiotics, through influences similar to those reported for maternal separation, appear capable of correcting the imbalance produced by the chronic restraint stress [10].

Probiotics in Humans

While the clinical studies available are much more current than those reported for rodents, they also appear robust [12]. Here, we consider three relevant reports of probiotic effects in healthy medical student athletes [13], in patients with an irritable bowel syndrome and in healthy patients subjected to an emotional situation [1].

Healthy Student Athletes: These subjects fed with Lactobacillus gasseri showed, relative to placebo, elevated mood and reduced natural killer cell activity after strenuous exercise, with some additional alleviation of fatigue when the probiotic α-lactalbumin was consumed [13]. These results suggest that probiotics may have relevant ecological benefits and the potential to improve some life activities.

Patients with an Irritable Bowel Syndrome: Such patients, in addition to the irritable bowel disease [14], also exhibited disturbances in the gut-brain axis [15] and in the composition of their microbiota [16]. The foregoing disturbances were also often associated with anxiety and depressive syndrome [17], and an aberrant ratio of IL-10 and IL-12 suggesting a generalized pro-inflammatory state. Finally, patients who consumed Bifidobacterium infantes had a normalization of the interleukin's ratio after treatment [1]. These results show that probiotics can induce changes in cytokines and therefore exert immunological effects.

Stressful Situations: Over four weeks, healthy human female participants took either a placebo or a combination of probiotics (Bifidobacterium animalis, Streptococcus thermophiles, Lactobacillus bulgaricus, Lactococcus). They further received a functional Magnetic Resonance Imaging (MRI) to determine how ingestion of probiotics could affect their neurophysiological activity. During the image acquisition phase, faces with emotions

(expressions of fear) were presented to the participants. Compared to placebo, participants on probiotics showed a decrease in neuronal activity and emotional response, somatosensory and interoceptive processing in the somatosensory cortex, the insula and the periaqueductal gray [18]. These results may represent a probiotic-induced reduction in the neuronal reactivity to stressful situations. Indeed, the exertion of stress has an important influence on the functional and structural aspects of the microbiome. Glucocorticoids can impair the intestinal barrier function, allowing in this way the migration of bacteria, which in turn generate an inflammatory immune response (Figure 1 & 2) [1, 2].

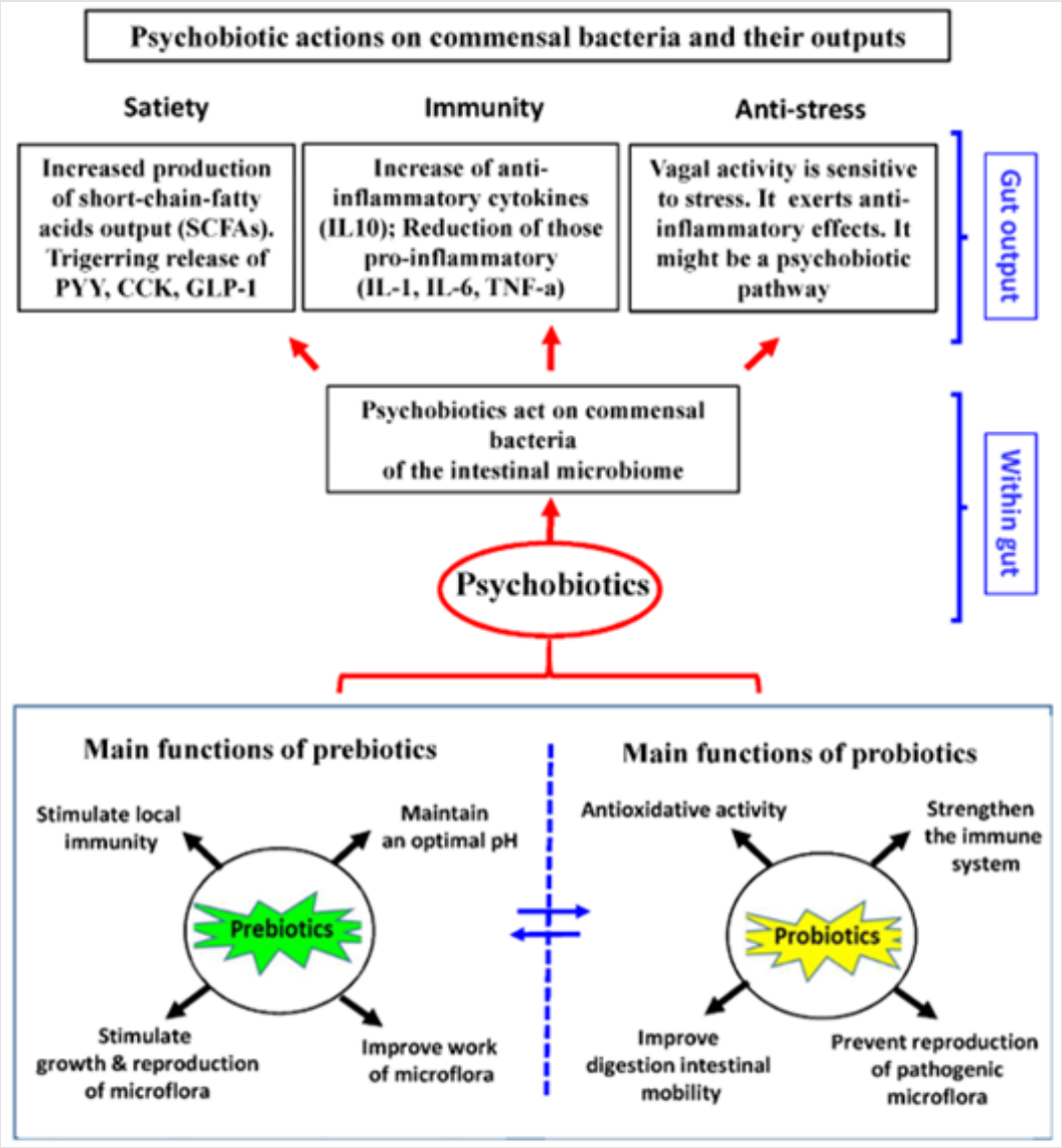

Figure 1: Psychobiotics actions on commensal bacteria within the gut. Psychobiotics, primarily defined as probiotics, are bacteria involved in the general homeostasis maintenance. They act, at first, through their interactions with normal intestinal flora bacteria (various synergistic effects). These bacteria do not possess the pro-inflammatory lipopolysaccharide chain and their propagation does not trigger immunological inflammatory reactions. Prebiotics can also be included in the definition of psychobiotics since they are compounds that, by fermentation in the gut, produce specific changes in bacterial composition and activity (various pleiotropic effects). Prebiotics are fructans and oligosaccharides that support the growth of normal flora bacteria (double harrows probiotics/probiotics). Psychobiotic communications. Within the gut, they regulate the enteric nervous system either directly or through various neurotransmitters (mainly aminergic). The outputs from the gut include the short-chain fatty acids (SCFAs) capable of influencing the secretions of satiety peptides (PYY, CCK, GLP-1). Psychobiotics also influence the immune system in triggering the release of anti-inflammatory cytokines (IL-10) and in reducing that of pro-inflammatory (IL-1, IL-6, TNF-a). Finally, the vagus nerve possesses abundant sensory fibers conveying information from body organs to the brain. It is sensitive to nutrition, activity and stress and might be a psychobiotic pathway.

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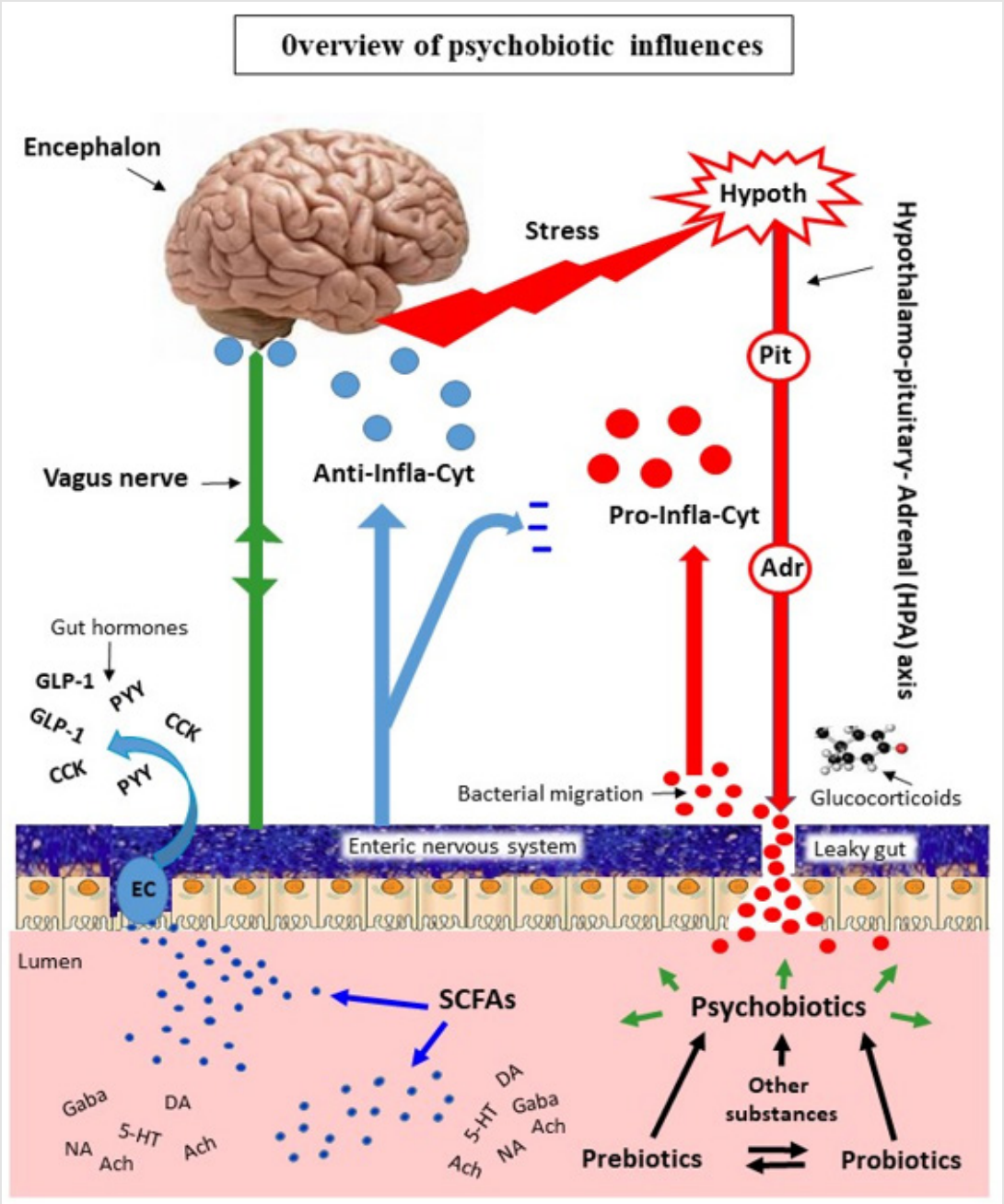

Figure 2: Psychobiotics influences within the gut. They are mainly produced by probiotics and prebiotics. Probiotics introduce beneficial bacteria like lactobacilli and bifidobacteria into the gut. Prebiotics support the growth of such bacteria. Psychobiotics cannot be limited to probiotics and prebiotics only. Any substance that exerts a microbiome effect is potentially also a psychobiotic (other substances). Psychobiotics regulate the enteric nervous system either directly or through various neurotransmitters including, dopamine (DA), noradrenaline (NA), serotonin (5-HT), gamma-aminobutyric acid (GABA) and acetylcholine (Ach). Short-chain fatty acids (SCFAs), issued from the metabolization, in anaerobic conditions, of indigestible polysaccharides are produced by the microbiota in the large intestine. Outside of the gut. Psychobiotics may contribute to eliminating pathogens in decreasing the inflammation (Anti-Infla-Cyt, anti-inflammatory cytokines) that causes the reduction of circulating pro-inflammatory cytokines (Pro-Infla-Cyt). In stressful situations, the hypothalamic-pituitary-adrenal gland (HPA) axis releases glucocorticoids capable of inducing a leaky gut. In this situation, a bacterial migration takes place leading to an inflammatory situation through pro-inflammatory cytokines. Anti-Infla-Cyt counteract this process. SCFAs, in interacting with the gut endocrine cells (EC), catalyze the release of gut hormones such as CCK, PYY and GLP-1. The vagus nerve also plays an important role since it is sensitive to nutrition, exercise and stress. It may exert anti-inflammatory and anxiolytic effects.

Prebiotics in Rodent

A small number of studies have examined the psychophysiological effects of prebiotics. These include investigations of galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS), which are a source of nutrition for microbiota bacteria of Bifidobacterium and Lactobacillus genera and stimulate their activity and propagation in the gut [19]. Proportional to the prebiotic exposure, male rodents (both Sprague-Dawley rats and C57BL/6 mice) showed enhanced learning and working memory, a higher expression in the hippocampal and striatal brain-derived neurotrophic factor (BDNF), and an increased hippocampal long-term potentiation. Moreover, in relationship to the administration, rats fed the prebiotics during lactation showed substantially enhanced maze learning and object recognition one year later [20]. These findings point out the influence of prebiotics on memory processes and have important implications for assessing the long-lasting effects of prebiotics.

Prebiotics in Humans

A very small number of studies have examined the effects of prebiotics in humans. These studies include investigations on GOS and FOS (non-digestible oligosaccharides with prebiotic properties), that are sources of nutrition for microbiota bacteria by stimulating their activity and spread within the intestine. The first human study considering the psychophysiological effects of prebiotics [21] was conducted in healthy participants who consumed either GOS or FOS or placebo. Compared to other groups, participants who consumed GOS had a significantly decreased response in "cortisol wakefulness" which is a biomarker of emotional disturbances [1,3]. Further studies are necessary to document the time course of prebiotic effects.

Microbiome-Brain Communications

Mechanisms of the effects exerted by psychobiotics are still poorly understood. The crucial step remaining in this field of research lies in the understanding of the processes through which microbiome and brain communicate.

Bacteria-Enteric Nervous System Inter-Influences

Gut bacteria regulate electrophysiological thresholds in enteric nervous system neurons. Neurons exposed to Bifidobacterium longum showed reduced generation of action potentials when they were electrically stimulated [22]. In the same sense, in germ-free mice, these neurons showed lower levels of excitability compared to their normally colonized counterparts [23]. Thus, the above results provide evidence for a direct bacteria-induced modulation of the enteric nervous system. Gut-derived bacteria, through the metabolism of non-digestible fibbers, also provide various neurotransmitters like dopamine, noradrenaline, serotonin, gamma-aminobutyric acid (GABA) and acetylcholine [1]. Regarding GABA, it is now well known that it is the chief inhibitory neurotransmitter in the central nervous system (CNS). Found in large amounts, it regulates many processes, including anxiety and depression, blood pressure, pain and epilepsy [24,25]. Interest in the role of GABA as an antihypertensive dietary component has recently increased in Japan, due to the high sodium intake in that country. This aspect led to an increase in the research surrounding the development of fermented products containing GABA [24]. This transmitter is produced primarily from the decarboxylation of L-glutamate by glutamate decarboxylase and is found in animals as well as in higher plants and bacteria [26]. One way to increase its concentration in the gut may include the ingestion of probiotic bacteria containing dietary monosodium glutamate (MSG) to generate GABA [27]. In this way, the ingestion of human intestinally derived bifidobacteria and lactobacilli, the most efficient way to produce GABA [24], appears now as an efficient and new pathway to produce GABAbiotic (Figure 1&2).

Short Chain Fatty Acids

The human gut cannot digest macronutrients such as plant polysaccharides since the human genome does not code the enzymes necessary for their digestion [28]. The metabolization, by anaerobic fermentation, of indigestible polysaccharides is produced by the microbiota in the large intestine [28] and produces short-chain fatty acids (SCFAs) [29]. The greater proportion of SCFA is directed into the liver and muscle, through the circulatory system. While it is unclear to what extent the SCFAs enter the CNS, there is some evidence for their psychotropic properties. For instance, systemic sodium butyrate injections in rats produce antidepressant effects, an increase the central serotonin neurotransmission and a brain-derived neurotrophic factor (BDNF) expression [30]. SCFAs also stimulate the HPA axis [31] or directly affect the mucosal immune system [32], which may indirectly affect central neurotransmission. SCFAs also influence secretion of satiety peptides, including cholecystokinin (CCK), peptide tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) [33]. They also promote pleiotropic effects including stress and immunity (Figure 1 & 2).

Bacteria and Immune System Interactions

The key function of the immune system is to detect and eliminate pathogens. Psychobiotics may contribute in this process by decreasing the inflammation that conduces to a reduction in circulating pro-inflammatory cytokines. These cytokines can increase the permeability of the blood-brain barrier, permitting, in this way, the brain access to potential pathogenic entities [34]. Then, cytokines alter the neurotransmitters (serotonin, dopamine, and glutamate) involved in brain communication [35]. Finally, cytokines can also enter the brain through active uptake, stimulating

secretion of pro-inflammatory substances such as prostaglandins [36], precipitating further inflammation (cytokine storm). In this situation, cytokines produce an excessive host-inflammatory response comprising of the induction of various interleukins (IL-6, IL-17A, tumor necrosis factor alpha, interferon gamma and free radicals related to nitric oxide (NO) [37]. Here, it must be further documented that when exposed to pro-inflammatory cytokines, the inducible NO-synthase (iNOS) enzyme is expressed and triggers the release of large amounts (Figure 1 & 2) of NO. This compound reacts avidly with oxygen and superoxide radicals to form NO derivatives including peroxynitrite (ONOO-). The latter has a long half-life and is a powerful oxidant that perpetuates acute systemic and CNS damages including inflammation, protein deterioration, cell membrane destruction, DNA/RNA lesions, and cell death [38-41]. Above NO-related mechanism observed with pathogens invasion (bacteria, viruses and parasites), is also present throughout the aging process and neurodegenerative pathologies [39-41].

Vagal Communications

The vagus nerve plays an important role in coordinating parasympathetic activity, including the regulation of heart rate and gut motility. It also possesses abundant sensory fibbers capable of conveying rich information from body organs to the brain [42]. The vagal activity is sensitive to nutrition, exercise, and stress [1]. Stimulating the vagus nerve exerts anti-inflammatory [43] and anxiolytic effects [1] and is used therapeutically for refractory depression and epilepsy [44,45]. Here, it must be recalled that stimulation of the afferent large diameter fibbers of the vagus and aortic nerves (vago-aortic stimulation) can evoke slow wave sleep (SWS) and paradoxical sleep (or rapid eye movement sleep, REM sleep) [46]. Thus, it must be questioned whether the anti-inflammatory and anxiolytic effect observed with stimulation of the vagus nerve [44] or the administration of psychobiotics, might run both through the vagus nerve afferents to the brain (Figure 2).

Brain-Microbiome Influences

Stress and Glucocorticoids

While stress cannot be considered per se as a signaling pathway, it may play important influences on structural and functional aspects of the microbiome [47]. During stress, through the HPA axis, a hyper-production of glucocorticoids takes place. Such a production, while contributing substantially to the maintenance of resting and stress-related homeostasis, deregulates gut barrier function, in reducing the epithelium integrity [48]. Such an impairment permits the outward migration of bacteria, triggering inflammatory immune responses. Bacterial translocation from the gut can also modulate inflammation by raising the concentrations of pro-inflammatory cell elements such as lipopolysaccharides, a process associated with human depression [49]. Moreover, probiotic supplementation with the Bifidobacterium or Lactobacillus genera can restore in turn the gut-barrier integrity [50]. These mechanisms illustrate the pleiotropy of the effects that can be exerted by these compounds in healthy or pathological conditions (Figure 1 & 2).

Psychobiotics Different from Probiotics and Prebiotics

Antipsychotics and Antibiotics

Psychobiotics cannot be limited to probiotics and prebiotics only. Any substance that exerts a microbiome-mediated psychological effect is potentially also a psychobiotic. In this sense, the ingestion of an antipsychotic like olanzapine increases the abundance of actinobacteria and proteobacteria. Moreover, a mixture of antibiotics, containing neomycin, metronidazole, and polymyxin, also ameliorate the effects of olanzapine on bacteria [51]. Antibiotic mixtures (bacitracin, neomycin, and pimaricin) have been shown to induce neurochemical and behavioral changes through the microbiome [52]. Therefore, both antibiotics and antipsychotics may also be classified as psychobiotics. Moreover, many other substances may exert secondary psychobiotic effects in addition to their primary intended effect. The study of the above substances (pharmacomicrobiomics) represents a new and open field of research (Figure 1 & 2) [53].

Psychobiotics for Patient Care

Psychobiotics an Alternative to Psychotropic Medications

Through an important volume of scientific approaches, the role of probiotics appears of particular interest since significant evidence indicates that microbiota can maintain or even restore health. In nutritional psychiatry, significant reports also link human intestinal microbiota to mental health giving rise to the concept of psychobiotics. Research conducted with this focus suggests that CNS and gut have bidirectional communications through neuronal, endocrine, and immune pathways. Thus, psychobiotics could offer a natural, low-risk alternative to psychotropic medications. This area needs, however, to be further explored. Clinicians should continue to examine effective strains and doses of probiotics as this information becomes available. The abundance of favorable research conducted to date, with no reported adverse reactions, supports the use and continued investigation of psychobiotics [54,55].

Conclusion

At the completion of this review, it appears that psychobiotics, including probiotics, prebiotics and different other compounds, exert microbiome-mediated psychological effects. Psychobiotics are capable of influencing the microbiota-brain relationships and exert anxiolytic effects characterized by changes in emotional, cognitive and neural parameters. Channels through which psychobiotics

exert their effects include the enteric nervous system, the immune system and the vagal nerve. In nutritional psychiatry, experimental evidence suggests that the human intestinal microbiota could be directly linked to mental health, giving rise to the concept of psychobiotics. In the management of patients, psychobiotics may offer a natural, low-risk alternative to psychotropic medications. Finally, regarding the perspectives in the inflammatory conditions of depressive or neurodegenerative pathologies, the use of antioxidants like superoxide dismutase (SOD) and glutathione peroxidase (GPx), or NO-synthase inhibitors (iNOS) should be considered.

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