Role of Intestinal Microbiota in Major Depression

Subjects: Neurosciences

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A major depressive disorder is a serious mental illness characterized by a pervasive low mood that negatively concerns personal life, work life, or education, affecting millions of people worldwide. Due to the complexity of the disease, the most common and effective treatments consist of a multi-therapy approach, including psychological, social, and pharmacological support with antidepressant drugs. Evidence has underlined the pivotal role of gut microbiota (GM) also in the regulation of their pharmacokinetics/pharmacodynamics, through indirect or direct mechanisms.

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1. Introduction

Major depressive disorder (MDD), commonly known as depression, is a serious mental illness characterized by a pervasive low mood that persists for at least two weeks. MDD determines the loss of interest or pleasure in normally enjoyable activities, which can negatively affect personal life, work life, or education, leading to social impairment followed by general health problems and the risk of suicide [1]. The World Health Organization (WHO, Geneva, Switzerland) has estimated that about 350 million people are affected by MDD and considering its incidence of 6%, it is considered the second leading cause of disability worldwide, with high economic and social costs [2]. In addition, this scenario has been exacerbated by the COVID-19 pandemic, with an increased burden of 25% mainly related to isolation and fear of infection [3].

Generally, depression is believed to be caused by a combination of genetic, environmental, and psychological factors, including family history, major life changes, certain treatments, chronic health problems, and substance use disorders [4]. However, the etiology of MDD is still unknown.

Due to the complexity of the disease, the current most common treatment consists of a multi-therapy approach, including psychological, social, and pharmacological support to relieve the manifestations and restore the health state. Antidepressant drugs, in particular, are recommended as an initial treatment choice in people with mild, moderate, and severe depression [1]. Antidepressants, which act by correcting chemical imbalances of neurotransmitters in the brain, are usually very effective; however, their use requires caution [5]. In fact, antidepressant drugs must be taken daily for 1 or 2 weeks to exert their beneficial clinical effects [6], and about 10–

30% of the patients show a partial response or do not respond to treatment [7], losing the therapeutic effects with long-term administration (tachyphylaxis) [8]. Lastly, toxicity, side effects, and interactions with other drugs can also limit patients' compliance [1]. Considering that, to date, antidepressants are among the most prescribed drugs, the establishment of targeted and personalized antidepressant treatments is necessary to improve their safety and efficacy [9][10]. In general, the advancement of pharmacokinetics/pharmacodynamics studies of antidepressant drugs can improve both the quality of life of patients and the sustainability of healthcare systems [11].

In the last few years, scientific evidence has been reported suggesting that a normal composition of the gut microbiota (GM) is required to preserve host health, whereas its alteration may have a role in determining local and systemic pathological conditions, including mood disorders [12]. In addition, GM may represent the first contact point between oral medications and the host body and may regulate both pharmacokinetics/pharmacodynamics pathways through indirect or direct mechanisms; the study of these complex interactions between GM and drugs is currently under the spotlight, and it has been recently named "pharmacomicrobiomics" [12][13].

2. Types, Symptoms, and Causes of Depression

MDD is a heterogeneous and complex disease that can have devastating effects on an individual's function and life quality. It is characterized by several symptoms, including a sad mood, pessimistic worries, anhedonia, sleep alterations, poor focus, changes in appetite, fatigue, psychomotor agitation or retardation, and the risk of suicide. To be diagnosed with depression, the aforementioned symptoms must be present for at least two weeks. Different types of depression are usually classified as major depression, persistent depressive disorder, perinatal depression, seasonal affective disorder, and depression with symptoms of psychosis. All these forms of depression may be categorized as mild, moderate, or severe based on the frequency and intensity of the symptoms. The disorder's course widely varies from one episode lasting months to a lifelong disorder with recurrent major depressive episodes [1].

Even though the depression mechanisms have not been completely elucidated yet, dysfunctions in serotoninergic (5-hydroxytryptamine, 5-HT), dopaminergic (DA), noradrenergic (NE), and gamma-aminobutyric acid (GABAergic) neurotransmissions have been considered a plausible explanation of the pathophysiology of depression over several decades [14][15]. Furthermore, several factors, such as the hypothalamic-pituitary axis, host genetic polymorphisms, environmental factors, but also neurological, hormonal, immunological, and neuroendocrinological mechanisms, seem to play a role in the development of the depression phenotype. Psychological stress and adversity associated with genetic variants of monoaminergic transporter genes or defined receptor genes also appear to play a specific role in vulnerability to depression [16]. Some studies suggest that a predisposition to the disease occurs early in infancy and even in utero (perinatal depression). Indeed, the deprivation of maternal care can reflect itself in the epigenetic alteration of glucocorticoid receptors in the hippocampus, increasing the activation of the hypothalamic–pituitary–adrenal axis in response to stress factors and predisposing to depression later in life [17]. Another attractive theory on the development of depression is the "cytokines model," which supposes that immunity plays a role in the modulation of brain structure and function through the cytokines' production. Indeed, depressed patients often show a high circulating level of proinflammatory cytokines such as

interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP), supporting the hypothesis that a chronic production of proinflammatory cytokines may provoke neurotransmitter imbalance leading to neuropsychiatric diseases [18][19].

In this scenario, considering the documented capability of the GM to modulate the immune system and regulate brain functions through the so-called "gut-brain axis" [20], it has been proposed that the GM has a role in the pathogenesis of depression [21]. Indeed, it has been demonstrated that fecal microbiota transplantation (FMT) from depressed patients to microbiota-depleted rats can induce behavioral and physiological features characteristic of depression in the recipient animals [19]. In addition, several studies have documented a profound GM dysbiosis in depressed patients [22][23] and some authors have suggested that a predisposition to depression occurs early in infancy and even in utero. Indeed, during pregnancy, stress-induced changes to both maternal vaginal and intestinal microbiota are associated with changes in reproductive hormones, stress hormones, and neurosteroids that can be transferred to offspring in utero or during parturition, determining a long-term risk for neurobehavioral disorders [24].

3. The Role of the Gut-Brain Axis in Depression

The GM is composed of more than 100 trillion microorganisms carrying three times the number of human genes and, under normal conditions, is involved in several physiological processes such as food digestion, vitamin synthesis, the regulation of intestinal barrier homeostasis, and immunity modulation [25].

Conversely, harmful changes in the GM function and composition determine an intestinal dysbiosis that may contribute to the genesis of local or systemic diseases and eventually result in a possibly permanent alteration in the physiological response in a way that is mainly dependent on inflammatory processes [26][27]. Interestingly, a recent body of evidence documented the existence of the "gut-brain axis," a complex bidirectional system in which communication occurs through three parallel and interplaying pathways that involve nervous, endocrine, and immune signals [28]. Different preclinical and observational studies have documented that GM has a prominent role in mediating brain functions via the gut-brain axis [20], and its importance in the pathogenesis of brain disorders, including depression, has been proposed [21][29].

The main mechanism responsible for the effect exerted by alterations in GM on distant body districts, including the brain, is the modification of intestinal permeability. In fact, in GM dysbiosis, pathogens' overgrowth promotes the loss of the intestinal barrier, determining a "leaky gut" condition that allows intestinal microorganisms, and especially their metabolites, to enter the systemic circulation by crossing the intestinal barrier [30].

Thus, regarding the gut-brain crosstalk, microbial-derived metabolites are also involved in the afferent input of the vagus nerve [31], in the stimulation of the enteric nervous system and in the regulation of the hypothalamic-pituitary-adrenal axis [32].

Overall, the main metabolic products involved in the communication between the gut and brain and whose alterations may have a role in the genesis of MDD are neurotransmitters, short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), and formyl peptides, as shown in Figure 1.

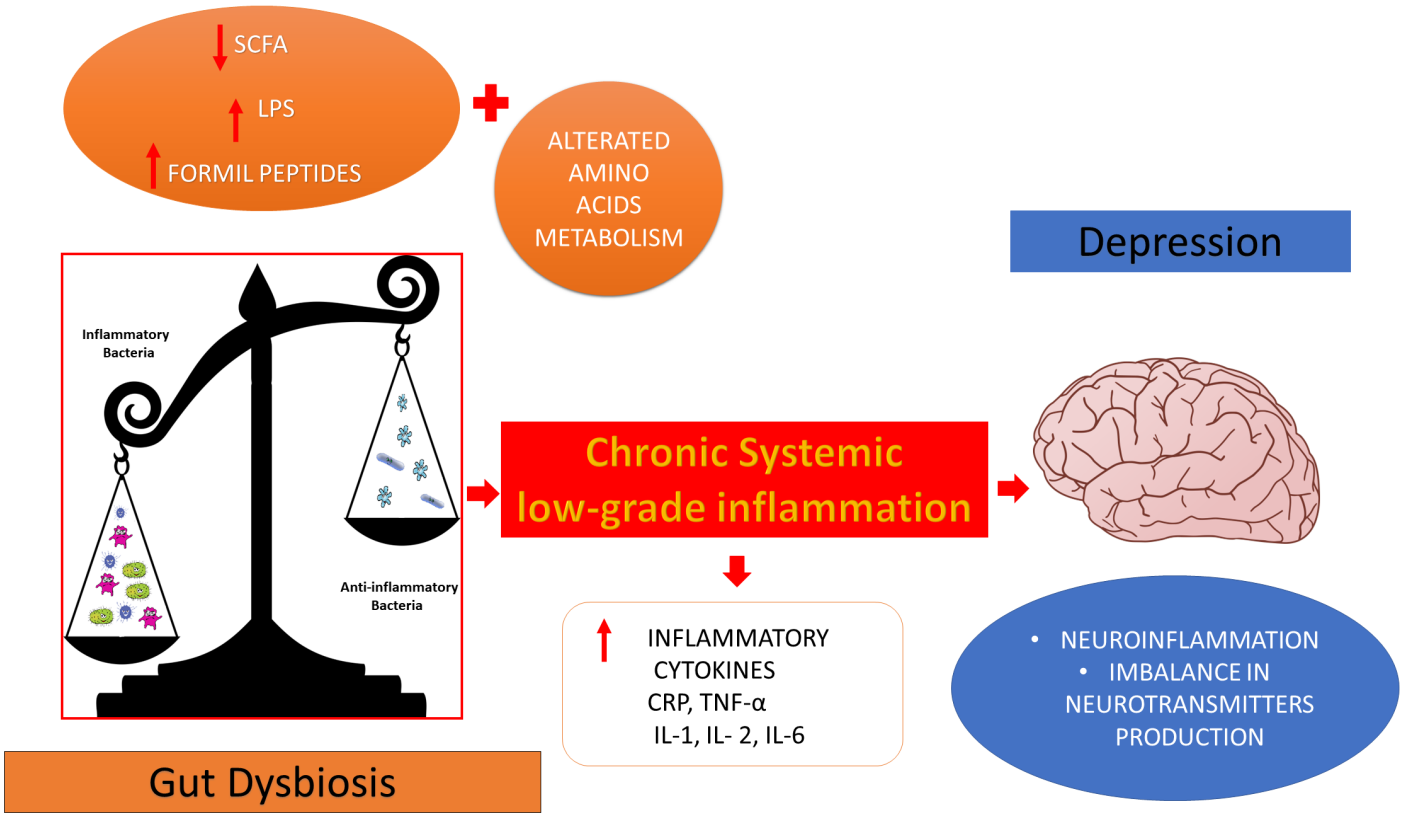

Figure 1. The gut-microbiota-brain axis.

3.1. Neurotransmitters

Neurotransmitters play a fundamental role in “gut-brain axis” signaling, and intestinal bacteria may react to the host’s neurochemical compounds or produce their own. It was largely demonstrated that GM can produce 5-HT, NE, DA, melatonin, histamine, tyramine, phenylethylamine, glutamate, and GABA neurotransmitters [33][34][35]. In vitro studies have documented the existence of a great number of microbes producing neurotransmitters [35]. On the other hand, experimental evidence showed that germ-free mice exhibited a severe imbalance in cerebral neurotransmitters, with high noradrenaline and reduced GABA and serotonin levels [36]. In addition, preclinical and clinical studies have also confirmed that the GM manipulation of probiotics, especially *Lactobacillus* and *Bifidobacterium* strains, can improve depressive symptoms by increasing 5-HT levels in the brain [37][38].

An essential element in neurotransmitter synthesis is the availability of precursors, usually represented by amino acids (AAs), whose levels are strictly related to the diet [39]. During their path, particularly in the colon, the AAs undergo various stages and are directly metabolized by gut bacteria [40][41]. For example, the fermentation of basic AAs leads mainly to decarboxylate metabolites, while the catabolism of arginine can lead to agmatine, putrescine, spermidine, and spermine through the polyamine pathways [33]. Arginine can also enter the arginase pathway of

some bacteria, where it is converted into urea and ornithine and subsequently catalyzed into glutamate [42]. Afterwards, the glutamate can be deaminated by the intracellular enzyme glutamate decarboxylase into GABA [33][42]. Instead, histidine metabolism can produce histamine, a neurotransmitter implicated in allergic reactions but also neurological and psychiatric diseases, while the catabolism of tyrosine determines the production of tyramine, phenols, and p-coumarate. Importantly, tyrosine is a precursor of catecholamines, and tyramine is a neurotransmitter involved in the side effects of MAOI antidepressants [33]. In addition, phenylalanine catabolism can produce phenylethylamine [43] (PEA) and trans-cinnamic acid. In particular, PEA has been found in the brain in low concentration and seems to stimulate the release of 5-HT by acting on its transporter [44].

Anyway, the most important AA for gut-brain communication is tryptophan, an essential aromatic AA that can be transformed into several metabolites such as serotonin, kynurenine, or indole. Approximately 90% of tryptophan is degraded in the liver through the “kynurenine pathway,” but several gut bacteria can modulate this process, mainly through gut metabolites, for instance SCFAs, resulting in higher tryptophan levels [45]. About 5% of tryptophan can be converted directly by GM into indole compounds through the indole pathway [46]. In detail, the indole is produced by specific bacteria, such as *Echerichia coli*, through a transformation dependent on tryptophan-catabolizing enzymes [47]. In the liver, the indole is subsequently converted into several metabolites, some of which, e.g., indoxyl sulphate, show anxiogenic effects, while others, such as isatin, have an anxiolytic effect. Indeed, isatin activates the vagus nerve and travels to the brain, where it acts as a potent MAO-B inhibitor, increasing DA levels [47][48]. Finally, a tryptophan fraction is converted into 5-HT and melatonin through the serotonin pathway [49].

In conclusion, the control of the neurotransmitters’ production by GM involves an intricate network of pathways, mostly under exploration, that will require deeper investigation in the future.

3.2. Short Chain Fatty Acids

The SCFAs are monocarboxylic acids predominantly produced in the colon through the fermentation of dietary polysaccharides by the GM, mainly from anaerobic bacteria [50][51][52]. Locally, they represent an energy source for colonocytes and regulate intestinal barrier integrity; however, unmetabolized SCFAs can cross the intestinal barrier and enter the systemic circulation, acting as signals for host metabolic, immune, and neurocognitive functions [53]. In detail, growing evidence suggests that an alteration of the intestinal SCFA abundance is associated with the reduction of several neurotransmitters in the brain, determining a depressive phenotype [54][55]. In general, the SCFAs affect brain functions through several direct and indirect pathways. Firstly, they directly contribute to maintaining the integrity of the brain-blood barrier (BBB) and enhance the Claudin5 expression, both of which are essential to protect the brain from inflammatory cytokines and toxins derived from systemic circulation [51][56]. Recent findings have documented that a loss of BBB integrity is evident in germ-free mice and mood disorders, suggesting that normal BBB tightness is fundamental to protecting against depression [56]. Moreover, after crossing the BBB, the SCFAs can stimulate the microglia, regulating their functions [57]. In addition, SCFAs can display indirect activity on the brain through the gut. For instance, the SCFAs bind to free fatty acid receptor 2 (FFA2) expressed on the colonic enteroendocrine L-cells, stimulating the release of gut hormones such as glucagon-like

peptide 1 (GLP-1), which may interact with GLP-1 receptors, which have been recently identified in neurons of the amygdala, hippocampus, and dorsal raphe nucleus [58]. Importantly, the activation of these receptors can exert an antidepressant effect through several mechanisms, including inhibition of neuroinflammation, promotion of neurogenesis, and neurotransmitter production [59].

3.3. Lipopolysaccharides

Lipopolysaccharides (LPS) are structural components of Gram-negative bacteria walls that exert pro-inflammatory effects by activating the Toll-like receptor (TLR)-4 and by triggering NF-kB (nuclear factor kappaB) [60]. The gut is the main LPS source in the human body, and, while in physiological conditions the LPS load is well tolerated, its high content, determined by the disruption of gut barrier integrity, leads to “metabolic endotoxiemia”, which is associated with a chronic systemic low-grade inflammation and several related pathologies [61]. In detail, several reports have demonstrated the association between high LPS levels and depression, especially for its ability to stimulate the production of proinflammatory cytokines and to activate indole and GluN2B receptors [62][63].

3.4. Formyl Peptides

The formyl-peptide receptors (FPRs) are transmembrane G protein-coupled receptors that can be considered pattern recognition receptors, interacting with chemotactic factors released by bacteria or damaged host tissues. The FPRs are located on the surface of immune cells and are correlated with host innate defense mechanisms [64]. To date, three types of FPR have been identified (FPR1, FPR2 and FPR3), which can have pro-inflammatory or anti-inflammatory effects depending on ligands and the environment [65]. Particularly, the microbial-derived formyl peptides can activate FPRs, which are expressed by both the enteric nervous system and the central nervous system. Interestingly, recent evidence showed that formyl peptides regulate neuroinflammation and emotional behaviors, preventing neurodegenerative diseases and mental disorders such as anxiety and depression [65][66][67].

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