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Personalized Nutrition for Depression: Impact on the Unholy Trinity

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Abstract
Major depressive disorder (MDD) is a chronic affective disorder that has a strong neuroinflammatory component underpinning its etiology. Recent studies indicate that MDD is also associated with changes in the gut microbiota and that the latter is mainly modulated by diet. Microbiota-based personalized nutrition aims to provide an individual-specific diet that will yield the maximum benefit from a given diet since the gut microbiota is accounted for the variations that individuals present in response to a given food. In this review, we present and discuss 5 possible outcomes of using microbiota-based personalized nutrition. Harnessing this approach is essential to design more accurate therapies to prevent and treat MDD or to even help in drug metabolism, especially in the case of antidepressants.

Introduction

The gut microbiota encompasses an ecosystem of microorganisms that include not only bacteria, but also viruses and fungi that provides benefits to the host while warranting their own survival in a symbiotic manner [1]. Interestingly, over the last 2 decades, studies have shown that perturbations in the gut microbiota are associated with a plethora of diseases, such as metabolic, neurodegenerative, and also neuropsychiatric diseases, such as major depressive disorder (MDD) [1]. MDD is a chronic affective disorder characterized by a set of symptoms including anhedonia, cognitive deficits, and suicidal thoughts [2]. Interestingly, research has shown that depressed patients have alterations in the composition of the gut microbiota in comparison to healthy controls [3] and that the transplantation of the gut microbiota of depressed subjects to rats subjected to microbiota depletion via antibiotics induce depressive-like behavior [4]. Notably, some gut microorganisms have shown to be depleted

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depressed in subjects, such as *Coprococcus* and *Dialister* [5]. Advances in the field resulted in the demonstration that MDD is a neuroimmune disorder, in which neuroinflammation plays a critical pathogenetic role [6]. More recently, depression was described as being caused by an *unholy trinity*, namely, dysregulated stress, immunity, and gut microbiome [7].

Since diet is an important determinant of the gut microbiota's profile after the transition to a solid diet [8], dietary interventions were developed as an approach to prevent or treat MDD. However, the issue relies on proposing one single type of diet to a heterogeneous population without any *previous* information about their gut microbiota. This fact does not take into consideration that there are inter-individual variations determined by the intersection between the gut microbiota and host physiology and metabolism. In other words, any effect of a given diet should be regarded as dependent of 3 complex and interconnected systems: the diet itself, the gut microbiota and the host physiology [8]. In this regard, personalized nutrition aims to identify key gut microbiota features that would help in the prediction of a response to food and subsequently in the design of a gut microbiome-based, person-specific diet [8]. In this sense, knowing the gut microbiota landscape *previous* to the intervention is of key importance, since this knowledge could predict and/or determine if the intervention will succeed or not. In this review, we propose that a microbiota-based nutritional personalized nutrition is likely the most viable and modern approach to treat depression and defeat its unholy trinity. However, to maximize efficiency, this approach should yield the 5 following outcomes: (1) gut microbiota modulation, (2) immunomodulation, (3) increased epithelial barrier function, (4) enhancement of stress resilience, and (5) improved response to antidepressants (ADs). Here, we briefly revise and discuss the aforementioned outcomes, explaining how their management may consequently contribute to improvements in depressive behavior. Harnessing the knowledge of personalized nutrition and its outcomes may lead to the development of a depression's Holy Grail in the future.

Gut Microbiota Modulation: Achieving Richness and Diversity

The gut microbiota-based personalized nutrition should increase richness and diversity of the species of the microbial community or even sustain the growth of specific species, allowing the host to benefit from a healthy microbiota. When comparing the effects of a westernized diet (rich in animal protein and sugars) versus a non-westernized diet (rich in fibers that are used as prebiotics) and its health outcomes, non-westernized diet has more beneficial effects because it leads to increased production of short-chain fatty acids (SCFAs), key microbial molecules that are used as messengers to regulate the gut-brain axis [9]. For instance, secretion of 5-HT by enterochromaffin cells, which is essential for the regulation of gut motility, gut microbes and for the signaling in the vagus afferents, is triggered by SCFAs and secondary bile acids [10]. Interestingly, Western diet was associated with lower gut microbiota diversity [11] and the latter is related to stress reactivity, known to be altered in depression [12]. Unsurprisingly, depressed subjects who consumed a Mediterranean diet for 12 weeks had improved depressive symptoms when compared to subjects who received only social support [13].

Exploring the Gut Microbiota to Promote Stress Resilience

Studies now acknowledge that the gut microbiota is associated with stress resilience. For example, decreased levels of *Bifidobacterium* [14] as well as increased levels of *Lactobacillus*, *Clostridium* cluster III, and *Anaerofustis* [15] were detected in the feces of stress-susceptible mice. Furthermore, the possibility that some microorganisms can produce mental health benefits when ingested in appropriate amounts (*psychobiotics*) is gaining traction [16, 17]. Therefore, microbiota-based personalized nutrition is likely to regulate a core etiological factor in MDD – *stress*. This would probably be a revolution in psychiatry in terms of prevention of new cases of MDD and of relapses due to stress in depressed patients. Therefore, the employment of the proposed approach should aim at increasing the number of psychobiotics or stress resilience-promoting microorganisms.

Immunomodulation via Aryl Hydrocarbon Receptor

MDD has a strong immune-inflammatory component underpinning its pathophysiology. Humoral factors, such as the tryptophan catabolytes, as well as immune cells, such as T helper (Th)-17 [18] cells are associated with MDD, as well as oxidative and nitrosative stress (O&NS) pathways [19]. In this regard, the aryl hydrocarbon receptor (AHR) plays a key role in the modulation of

the immune system. Gut microbes possess the enzyme tryptophanase, which is responsible for the conversion of tryptophan, the 5-HT precursor, to indole, that is, metabolized in the liver into indoxyl-3-sulfate (I3S), a natural agonist of AHR [20]. After crossing the BBB, I3S binds to AHR in activated astrocytes and inhibit the secretion of pro-inflammatory cytokines, such as IL-6, TNF, CCL2, and NOS2 [21]. Moreover, AHR signaling is implicated in the recruitment of inflammatory monocytes to the CNS and in the activation of monocytes and microglia [21]. Furthermore, by binding to AHR in microglia, I3S induces the secretion of TGF-α AND VEGF-B, which limits astrocytes activation [22]. Therefore, increasing AHR activity has immunomodulatory effects via inhibition of brain inflammation. Accordingly, identifying and characterizing AHR agonists-producers hold promise in the treatment of MDD. For example, *Lactobacillus reuteri* is a known producer of indole-3-aldehyde [23], which was proven to exert anti-inflammatory effects [24]. Therefore, future studies should explore the effects of I3S and other AHR agonists in vitro and in vivo, especially focusing on AD effects, either by means of personalized nutrition, which should aim at increasing the numbers of AHR agonists-producers or even by drug design.

Increased Barrier Function: Gut Epithelia

Gut epithelial integrity is essential for a proper gut functioning. When a diet is deprived of fibers, microorganisms present in the outer mucus layer of the colon rely on degrading mucus as means of energy source [25]. As a consequence of a thin mucus layer, penetration of microbes into the gut is favored. Besides, expression of tight junction proteins in epithelial cells limits the access of microbes into the tissue, but reduced expression of these proteins also due to increased oxidative stress [19] and reduced numbers of bacteria that help in the maintenance of barrier function, such as SCFA producers which induce the expression of tight junction proteins, lead to leaky gut and translocation of bacteria and microbial molecules, such as *E. coli* and LPS, respectively, to the bloodstream. This leads to *metabolic endotoxemia* and systemic low grade inflammation [8]. Therefore, personalized nutrition should aim to increase the numbers of mucin-and epithelial barrier function-modulators, thus preventing the exit of detrimental gut-derived molecules and their facilitated entry into the CNS, which subsequently triggers CNS inflammation and behavioral changes relevant to MDD.

Improved Response to ADs

The treatment of depression with ASs faces a major problem: almost half of the patients do not respond to standard treatments [26]. This general approach, which generates responders and non-responders, will be progressively replaced by *personalized psychiatry*. Interestingly, the gut microbiota may be responsible for the determinations in inter-individual variations in response to such treatments [27]. Interestingly, the improved insulin sensitivity observed after fecal microbiota transplantation in mice depended on the baseline gut microbiota composition, which supports the previous notion of gut microbiota and inter-individual variations in response to a given treatment [28]. If that is also the case for ADs, then microbiota-based personalized nutrition would be of key importance to normalize the response to ADs. On the one hand, studies have suggested that the gut microbiota modulates the effects of ADs [29, 30]. Furthermore, it is becoming clear that gut microbes takes part in the metabolism of xenobiotics, and the effect of a given drug depends on the baseline gut microbiota composition [31]. On the other hand, evidence shows that ADs have antimicrobial effects, which could be positive (modulating beneficial microorganisms) or detrimental (e.g., depleting beneficial strains and favoring pathobionts) [32, 33]. As a consequence, the following question arises and deserves to be answered in future studies: Does baseline gut microbiota composition explains why some patients do not respond to ADs (probably because of a distinct metabolism of ADs with pharmacokinetic and/or pharmacodynamic consequences, rendering the drugs ineffective in them) and some features of treatment-resistant depression? Here, we hypothesize that a gut microbiota-based personalized nutrition approach changes gut microbiota and, as a consequence, ADs metabolism in the host. As a result, the patient now responds to ADs and their depressive symptoms are improved. Furthermore, once ADs themselves have direct and indirect effects on the gut microbiota (for instance, by reducing inflammation in the CNS and in the intestine), we hypothesize that a strong modulation of depressive symptoms could be achieved via the gut-brain axis. However, these 2 hypotheses are yet to be corroborated by future research and will add much to *nutritional psychiatry* and will likely change the way neuropsychiatric disorders are tackled. Nonetheless, a recent study with the selective serotonin reuptake inhibitor fluoxetine showed that 5-HT modulates the colonization of *Turicibacter sanguinis* (Turicibacteriaceae family), a bacterium that regulates gut 5-HT and thus can

potentially modulate mood [34]. Treatment with fluoxetine inhibited bacterial reuptake of 5-HT and altered bacterial gene expression, limiting *T. sanguinis* to colonize the intestine. Interestingly, *T. sanguinis* is able to modulate lipid metabolism [34] and is associated with inflammation and cancer [35]. Furthermore, decreased abundance of *T. sanguinis* was associated with selective serotonin reuptake inhibitors use in humans [36]. Interestingly, treatment with fluoxetine was associated with a reduction in the abundance of *Lactobacillus johnsoni* and *Bacteroidales S24-7* and increase in *Alistipes*, which were related to weight gain and gut dysbiosis [37]. Moreover, preliminary data from MDD patients suggest that treatment-resistant depression is associated with a changed gut microbiota in comparison to patients who responded to ADs treatment. Notably, patients with the resistant form of MDD had higher levels of *Proteobacteria, Tenericutes,* and *Peptostreptococcaceae* [27]. However, the precise link between ADs, gut microbiota and its impact in host physiology, gut-brain axis, and mood remains unknown.

Conclusion

In this review, we discussed how the knowledge generated by gut microbiota-based personalized nutrition, together with the field of nutritional psychiatry, is of key importance to the development of new approaches to prevent and treat depression. The 5 outcomes that this approach generates, when combined, are likely to serve as depression's Holy Grail, thereby dismantling depression's unholy trinity.

Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Author Contributions

E.D.-S. conceived the study; performed literature search, data collection, and data analysis; and wrote the manuscript under the supervision of C.A.P., G.K., and T.G. All authors approved the final version of this paper.

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