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Review

When Gut Hormones Influence Brain Function in Depression

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Abstract: The literature on the crosstalk between the brain and the gut has increased considerably in recent years. It is widely accepted now that the microbiome plays a significant role in several brain disorders, neurodevelopment, neurocognitive stages, and physiological functions. However, the mechanisms that influence such crosstalk are still not well elucidated. In this sense, one of the possible mechanisms by which the microbiome could influence brain function is through gut hormones released by enteroendocrine cells: ghrelin, cholecystokinin (CCK), peptide YY (PYY), vasoactive intestinal polypeptide (VIP), glucagon-like peptide (GLP1-2), corticotropin-releasing factor (CRF), glucose-dependent insulinotropic polypeptide (GIP), secretin, serotonin (5-HT), and oxytocin. Especially when one considers that the brain expresses receptors for these hormones in areas important to the neurobiology of brain disorders (e.g., depression), such as the hippocampus, amygdala, hypothalamus, and suprachiasmatic nucleus. To strengthen this hypothesis, gastrointestinal dysfunction (such as altered motility or pain) is relatively common in depressive patients, and changes in diet (low-carbohydrate diets, for example) positively affect mood. Additionally, alterations in the gut microbiome are relatively common in depressive patients and are related to the levels of *Akkermansia*, *Lactobacillus*, *Bifidobacteria*, *Faecalibacterium*, *Roseburia* and *Clostridium*. Finally, concerning the gut-released hormones, the literature reports that ghrelin can be a peripheral marker for the antidepressant treatment success rate and has elevated levels during depression. GLP-1 is tightly correlated with HPA axis activity being decreased by high cortisol levels. CCK seems to be altered in depression due to increased inflammation and activation of Toll-like receptor 4. Such finds allow the postulation that hormones, the microbiome and mood are intertwined and co-dependent. VIP is correlated with circadian rhythms. There is a bidirectional connection of the circadian rhythms between the host and the microbiota. Circadian rhythm disruption is associated with both poor outcomes in mental health and alterations in the microbiota composition. In sum, in the past year, more and more research has been published showing the tight connection between gut and brain health and trying to decipher the feedback in play. Here, we focus on depression.

Keywords: microbiome; brain; hormones; depression; circadian rhythm

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1. Introduction

The gut–brain axis is now well established, but the microbiome production of different metabolites and hormones that can influence locally and in the brain, has only in recent years started to be explored. The literature links the microbiome and several brain conditions, such as neurodevelopmental disorders [1,2], depression [3,4], anxiety [5,6], Parkinson's [7,8], Alzheimer's [9], and schizophrenia [10], among others. Additionally, bacterial metabolites could be key players in these multifactorial diseases by influencing the availability of neurotransmitters, the induction of the inflammatory response, and/or the production of hormones. However, at the moment, very little has been researched in this regard, although the literature is filled with correlations between microbiome alterations and various developmental/psychiatric conditions. Such lack of research may be due to the

complexity of bacterial ecology since this ecological complexity makes it hard to disentangle and correlate the molecular pathway alterations and specific profiles of dysbiosis. It is worth pointing out that the receptors for peptides produced in the gut by enteroendocrine cells (EE cells) are also found in several brain areas and could therefore be one of the links which explain the influence of gut homeostasis in brain health [2,11].

In fact, some animal work can corroborate such a hypothesis. Most of the current mechanistic literature at the moment comes from germ-free (GF) animals in comparison to specific pathogen-free (SPF) mice or control animals (with normal microbiomes) [12]. For instance, Fröhlich and co-workers [13] showed that antibiotic treatment in adult mice could cause alterations in the colonic microbiome followed by alterations in the levels of metabolites (SCFA—short chain fatty acids, trimethylamine, adenine and uracil) and cognitive impairment. Crumeyrolle-Arias and co-workers [14] showed that changes in the microbiome (comparing GF and SPF rats) were correlated with altered levels of corticosterone (CORT) and dysfunctional dopamine turnover in brain areas critical to the stress response. Additionally, Fan and co-workers [4] observed depressive-like behaviour in mice after treatment with antibiotics, followed by increased corticosterone levels, disruption in neurotransmitter levels and changes in the relative abundance of *Bacteroides thetaiotaomicron*, *Klebsiella oxytoca*, and *Klebsiella aerogenes* after stress. Additionally, Luczynski and co-workers [12] reported changes in stress hormone signalling, such as adrenocorticotropic hormone (ACTH) and CORT, alterations in microglia function and neuronal function, accompanied by behavioural changes. Additionally, an increasing numbers of clinical studies show correlational findings [6,15]. For instance, a recent work correlated pre-existing individual differences in host–microbiome with the susceptibility to be resilient or responsive to traumatic stress [16].

Interestingly, studies also report that gastrointestinal (GI) dysfunction or some level of distress has a higher prevalence in individuals with some brain/psychiatric disorder when compared to controls and that the GI symptom severity can be correlated with the severity of the neurological/psychiatric condition [17–19]. In the autism spectrum, an increased intestinal permeability and altered motility in patients were reported, and such findings were replicated in animal tests where it was also shown that treatment with *Bacteroides fragilis* was capable of reversing such stereotypic behaviours [1]. Additionally, in Parkinson's disease, it was shown that infection with *H. pylori*, as well as small intestine microbial overgrowth, were correlated with the intensity of motor symptoms [7,19], while a decrease in bacteria groups related to SCFA production was correlated with cognitive decline and a low BMI (body mass index). Additionally, Saji and co-workers [20] showed a correlation between specific enterotypes (I and III specifically) and dementia. Finally, studies showed that patients suffering from depression and/or anxiety frequently present changes in colonic motility, which can, in turn, alter intestinal physiology and the microbiome constitution [21,22].

Moreover, obesity and a Western diet have been reported to be associated, at some level, with psychiatric disorders, although the directionality of the association is not entirely defined [23–25]. Goldbacher and Matthews [23], and Hawkins and Steawart [24] wrote reviews showing an association between psychological characteristics and metabolic dysfunction and between excess adiposity and depression symptoms, respectively. At the same time, the work of Gowey and colleagues [25] reported that elevated depressive symptoms and/or perceived stress were generally associated with increased waist circumference, higher C-reactive protein, and lower high-density cholesterol, while the practice of physical activity and healthy diet seemed to attenuate this association.

In sum, in the past year, more and more research has been conducted showing the tight connection between gut and brain health and pointing out the tight interplay between the health of the microbiome and brain function. In this regard, there are some literature reporting the trans-kingdom symbiosis between the microbiome and the host and the influence of microbial metabolites in brain function, but this is out of the scope of the present paper, for a detailed review on the topic please refer to [26,27]. This review will

focus on the main gut hormones (released by enteroendocrine cells) that may influence the brain, focusing primarily on depressive states (see summary Figure 1). Additionally, since the role of circadian rhythm in depression has also gained strength in the past few years, the connection between circadian rhythm and the microbiome will also be explored in the following sections.

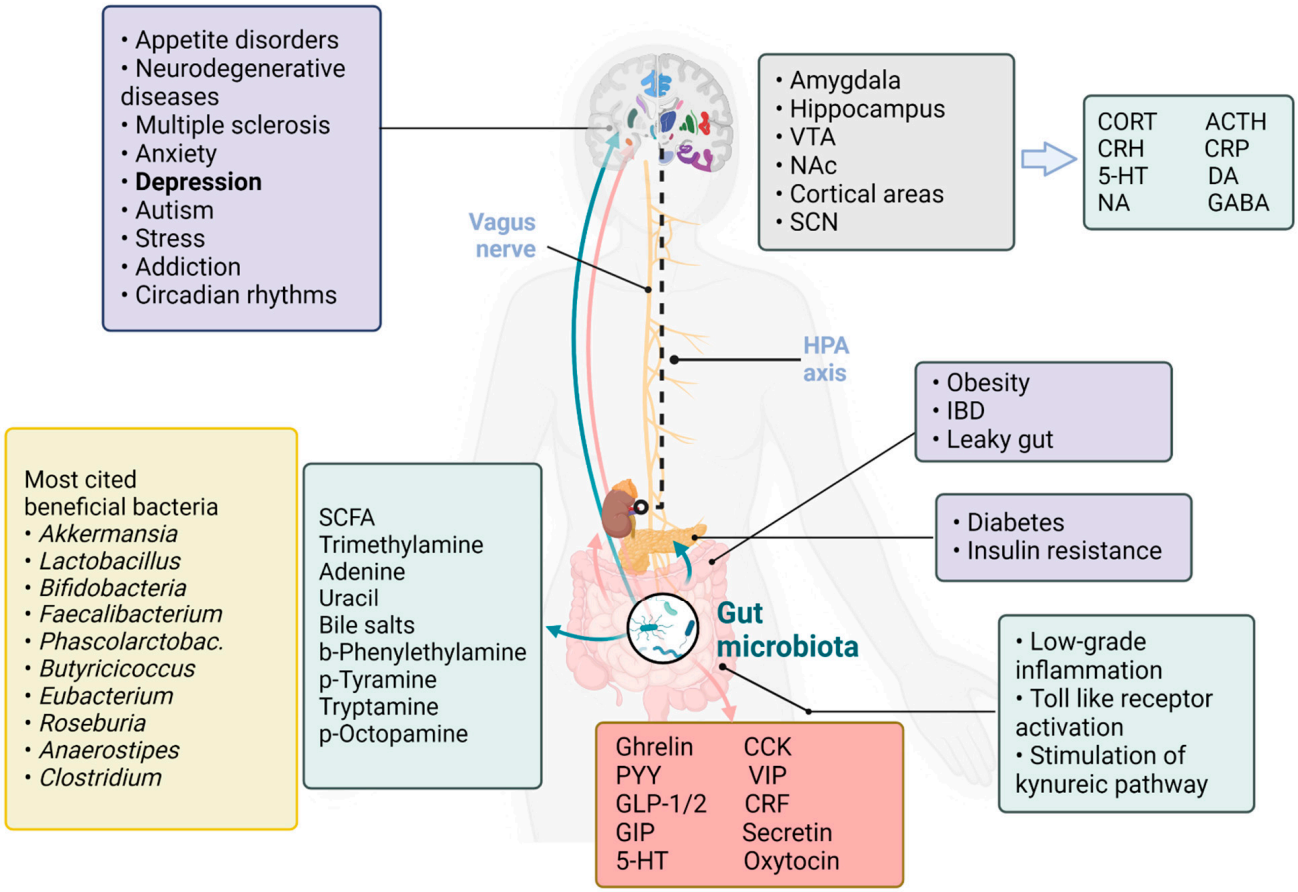

Figure 1. Summary of the crosstalk between the microbiome, gut, brain and gut hormones. SCFA: short-chain fat acids; PYY: peptide YY; GLP-1/2: glucagon-like peptide 1 and 2; GIP: glucose-dependent insulinotropic polypeptide; 5-HT: serotonin; CCK: cholecystokinin; VIP: vasoactive intestinal polypeptide; CRF: corticotropin-releasing factor; VTA: ventral tegmental area; NAc: nucleus accumbens; SCN: suprachiasmatic nucleus; CORT: cortisol; CRH: corticotropin-releasing hormone; NA: noradrenaline; ACTH: adrenocorticotropic hormone; CRP: C-reactive protein; DA: dopamine; GABA: gamma-aminobutyric acid; HPA axis: hypothalamic-pituitary-adrenal axis.

2. Literature Search Method

In this review, the search was divided into separate search terms grouped as follows: "(microbiota[Title/Abstract]) AND (depress* or bipolar or mania or anxiety or addiction or schizophrenia or psychiatr* or "mental health"[Title/Abstract])) AND (circadian[Title/Abstract])", "((microbiota or microbiome)[Title/Abstract]) AND (hormone[Title/Abstract])) AND (depression[Title/Abstract])" or "((microbiota or microbiome)[Title/Abstract]) AND (hormone[Title/Abstract])) AND ((brain disease or mental disorder) [Title/Abstract])". Searches were performed on PubMed (Bethesda, MD, USA) between September and 30 October 2022. The total number of papers obtained was 230, and papers were further filtered to remove manuscripts that were not directly related to the review topic.

3. Gut Hormones

Approximately 1% of the total number of cells in the mucosal lining are EE cells responsible for synthesizing and secreting hormones. Although in low percentage among the epithelial cell population, this is the largest endocrine organ in the human body. The hormones produced are essential players in the control of metabolism and behaviour [28]. Reports have shown that the microbiome can influence the release of hormones in EE cells and, therefore, can influence the host's physiological and disease progression states [28,29], but this is still a field not well explored.

Hormones produced by enteroendocrine cells include ghrelin, cholecystokinin (CCK), peptide YY (PYY), vasoactive intestinal polypeptide (VIP), glucagon-like peptide (GLP-1), corticotropin-releasing factor (CRF), glucose-dependent insulinotropic polypeptide (GIP), secretin, serotonin (5-HT), and oxytocin. This expression presents anatomical variation (see Figure 2): ghrelin and orexigenic peptides are produced in the stomach; the proximal part of the small intestine producing CCK, secretin, GIP and GLP-1; the distal small and large intestines producing GLP-1/2 and PYY; and the large intestine producing CRF and the majority of 5-HT; while mesenteric neurons produce oxytocin and VIP [11,30–34]. In this review, the main focus will be ghrelin, CCK, PYY and VIP due to their known role in behaviour and brain function [2,11,35,36].

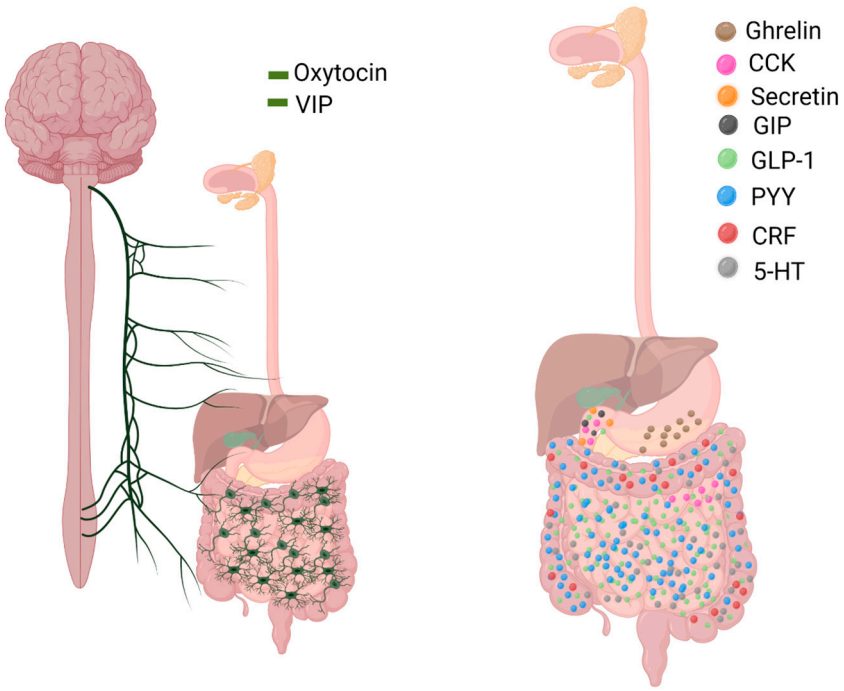

Figure 2. Schematic representation of the cell's anatomical location producing gut hormones. CCK: cholecystokinin; PYY: peptide YY; VIP: vasoactive intestinal polypeptide; GLP-1/2: glucagon-like peptide 1 and 2; CRF: corticotropin-releasing factor; GIP: glucose-dependent insulinotropic polypeptide; 5-HT: serotonin.

3.1. Ghrelin

The hormone ghrelin is produced in the stomach by A (X-like) cells, has 28 amino acids, and binds to the growth hormone secretagogue receptor type 1a [35,37]. Ghrelin is a hormone that controls orexigenic and adipogenic signals in the body, and it is released by the stomach when it is empty to signal to the brain to eat. While in the brain, ghrelin contributes to stress responses. Due to its location in the brain, it is not of surprise that ghrelin would play a role in depression and anxiety. The receptors for the peptide are found in the amygdala, hippocampus, ventral tegmental area and nucleus accumbens [37,38]. Moreover, ghrelin may also affect arousal states, helping regulate sleep–wake patterns [38,39].

It is not yet completely understood whether the microbiome influences ghrelin levels or if the central activity of ghrelin, through vagal stimulation, affects the microbiome. The literature shows that ghrelin levels are depleted in GF mice compared to the control [40]. Khosravi and co-workers [41] showed that *H. pylori* infection in GF mice increased ghrelin levels and inflammation during fasting, while other bacteria protected SPF mice, indicating that ghrelin is independent of the microbiome, increasing in the presence of a single pathogen. In opposition, Hamamah and Covasa [40] showed decreased levels of leptin, GLP-1, PYY, and ghrelin in GF mice and that microbiome restoration could restore the hypothalamic and hindbrain neuropeptides deficits present in the mice, indicating that the microbiome could control such levels. Finally, Fetissov and co-workers [42] described decreased levels of ghrelin in the plasma of autistic children, accompanied, or not, by increased ratios of *Firmicutes* to *Bacteroidetes*.

In fact, several bacteria have been correlated with ghrelin levels; *Clostridium* and *Ruminococcus* have been positively associated; increased levels of *Faecalibacterium* and *Prevotellaceae* are negatively correlated; and finally, the data is controversial regarding the levels of *Bacteroides*, *Bifidobacterium*, *Lactobacillus* [11,43].

Nonetheless, the importance of ghrelin in the control of stress is well established, and it has become a candidate target for treating mental disorders in the past few decades [44–46]. In fact, according to the review presented by Horne and Foster [45], ghrelin could be taken as a peripherical biomarker for chronic stress, and it seems to be a possible marker for responsiveness to antidepressant treatment. However, the triad microbiome, ghrelin, and elevated chronic stress levels have not yet been explored mechanistically.

Additionally, increased ghrelin levels seem to have beneficial effects for Parkinson's patients. According to Chu and co-workers [47], elevated ghrelin levels induced by fasting have neuroprotective effects through AMPK signalling in dopamine neurons, accompanied by an increase in the relative abundance of *Lactobacillus*. Additionally, it is also important to notice that since ghrelin is involved in lipid and glucose metabolism, which in turn affects mitochondrial respiration, it may play a neuroprotective role against neurodegeneration conditions, such as Alzheimer's disease [48,49].

3.2. Cholecystokinin (CCK)

CCK has a 115 precursors, and was first isolated and described in 1960; the release of CCK happens postprandially after the ingestion of fat or protein [35]. The biologically active forms of this peptide include Gly-extended and amidated CCK-33, -58, -22, and -8 [50]. CCK can bind to two receptors (CCK1 and CCK2) that are rhodopsin-like G protein-coupled receptors, the first more abundant in the intestine and the second in the brain [11]. In the intestine, CCK is produced by I-cells in the proximal small intestine [35].

In the brain, the CCK hormone seems to regulate appetite and food intake [2,51], social behaviour and emotional processing [52–54]. Researchers have also correlated the elevation of CCK levels with increased levels of anxiety behaviour in both humans and animals and believe that the brain areas affected are the amygdala, hippocampus and cortical areas [55,56].

According to Del-Bel and co-workers [52], social isolation can increase CCK mRNA expression in the amygdala, hippocampus, cortex and ventral tegmental area (VTA) of rats. While target mutations in CCK receptors can alter social behaviour in mice [57]. Interestingly, genetic changes have been observed in the CCK gene in patients with Asperger's syndrome (AS), which is part of the autistic spectrum [58]. Changes in CCK levels were also reported in depression [53], anxiety and schizophrenia [56]. Additionally, concerning neurodegeneration, CCK may reduce the activity of glycogen synthase kinase-3 and have a protective effect on memory loss in Alzheimer's disease [59].

However, despite being a very abundant gut peptide in the brain, the role of the microbiome in this peptide is not yet well explored. Very few studies exist regarding the microbiome's effects on CCK levels. Bogunovic and co-workers [60], showed that treatment with LPS can stimulate the release of CCK in cell models through Toll-like receptor 4 (TLR-4)

activation. According to Duca and co-workers [61], this hormone is lower in GF mice, independently of the expression of EE cells in the intestine. Additionally, the only study performed in humans correlated the observed changes in the microbiome with CCK levels after bariatric surgery and did not find any correlations [62].

3.3. Glucagon-like Peptide (GLP-1, GLP-2)

The glucagon-like peptide is 30 amino acid long produced in the distal part of the small intestine and the colon by L-cells [35]. It has two forms, peptides 1 and 2, and it is released in response to the ingestion of carbohydrates and fat in a 1:1 proportion. The role of these two peptides is distinct (for a review, see [63]), and here we will focus only on GLP-1, which the receptors are expressed in the brain. In the brain, GLP-1R (glucagon-like receptor 1) is present in the brainstem and the hypothalamus and presents an anorexigenic function.

Regarding the stress response, GLP-1 seems to activate the HPA response, having a positive role in activating the hypothalamus–pituitary–adrenocortical response to stress. The literature also reports that elevated levels of glucocorticoids reduce the bioavailability of GLP-1, as a negative feedback loop [64]. Regarding GLP-1 and anxiety, the data shows opposite results when evaluating animals versus humans. According to the literature, central injection of GLP-1 in mice decreases exploration time on anxiety tests, while in humans, the elevated levels of this hormone seem to have an anxiolytic effect [65,66]. According to Diz-Chaves and co-workers [67], the possible antidepressant and anxiolytic effects of GLP-1 would be related to the decreased activation of TREK in the HPA axis. Additionally, some studies have suggested a neuroprotective activity of GLP-1 in neurodegenerative disorders [68,69].

Finally, the gut microbiome can elicit the secretion of GLP-1 through three distinct pathways. Firstly, LPS can bind to TLR-4 in L cells and increase GLP-1 production [60,70]. Secondly, SCFA can activate G protein-coupled free fatty acid receptors 2 and 3 (FFAR2-3) in L-cells, increasing intracellular calcium and GLP-1 [71,72]. Lastly, indole can increase calcium influx and promote GLP-1 production [73]. New evidence from Ren and co-workers [74] shows that a low-carbohydrate diet can lessen depressive symptoms while increasing GLP-1 through increased SCFA and relative abundance of SCFA-producing bacteria *Roseburia*, *Ruminococcus* and *Eubacterium* in diabetic patients. Additionally, according to Leeuwendaal and co-workers [43] a decrease in *Firmicutes* and *Bacteroidetes* and an increase in *Proteobacteria* were related to increased levels of GLP-1. However, mechanistic data correlating bacteria and GLP-1 in different brain diseases is still scarce.

3.4. Peptide YY (PYY)

Peptide YY (PYY) is a 36 amino acid peptide produced by L cells in the ileum and colon. The production of this peptide happens especially in response to lipids, carbohydrates and proteins [11,75]. PYY is part of the neuropeptide YY family, comprising NPY, PYY and PP (neuropeptide Y, peptide YY and pancreatic polypeptide, respectively) [75]. In the brain, it can be found in the hypothalamus, nucleus tractus solitarii, spinal cord, and pons. This peptide can bind to four different receptors Y1, Y2, Y4, and Y5, with different levels of affinity depending on which family member is in question (for review, see [76]). The Y4 receptor seems to be involved in depressive and anxiety states [75,77], and most literature reports point out that PYY binds to Y2 but not Y4 [11], decreasing its importance in the pathology of depression and anxiety. However, there are some pieces of evidence of the role of these hormones in hedonic states, although most of the literature for this family of peptides is related to NPY (for review, see [78]).

Batterham and co-workers [79] showed that administration of PYY promoted hedonic states, while Painsipp and co-workers [80] showed that knockout of PYY increased depressive-like behaviour in animals independent of sex, while anxiety behaviour would be sex-dependent and induced by NPY. Interestingly, Stadbauer and co-workers [81] showed that Y2 receptor agonism produces behavioural and cognitive symptoms similar to schizophrenia and related psychotic disorders in mice.

Additionally, according to Leeuwendaal and co-workers [43], antibiotic-induced fluctuations in *Enterococci*, *Coliforms*, and *Bifidobacteria* were correlated to an increased PYY secretion. Hassan and co-workers [82] showed that antibiotic treatment could increase the levels of PYY and GLP-1 while depleting microbiota and inhibiting the anhedonic effect of a high-fat diet. However, most of the literature explores the role of NPY, not PYY, in such states, which is out of the scope of the present review.

3.5. Vasoactive Intestinal Polypeptide (VIP)

The vasoactive intestinal polypeptide (VIP) is a 28 amino acids peptide which interacts with two distinct class B GPCRs (G protein-coupled receptors), namely VIP receptor 1 (VIPR1) and 2 (VIPR2) [83]. Among the many activities of this peptide are vasodilation, immune activation and circadian rhythm control. It is important to notice that VIP receptors can also bind PACAP (pituitary adenylyl cyclase-activating peptide), which has its own receptor to which VIP has a low affinity [33]. VIP is produced mainly by mesenteric neurons but also can be produced by activated T cells [84], and endogenous VIP is released by numerous stimuli such as acetylcholine, serotonin, substance P and GLP-2 [33].

Regarding circadian rhythm, neurons that express this hormone can be found in the ventral area of the suprachiasmatic nucleus (SCN) and it seems to play a role in controlling motor activity. Moreover, according to Vosko and co-workers [85], VIP through vasoactive intestinal peptide receptor 2 (VPAC2R) plays a pivotal role in synchronizing SCN to light cues and helps maintain the synchronicity between oscillating neurons.

Additionally, Mosley and co-workers [86] recently showed the neuroprotective and immunomodulatory effect of a vasoactive intestinal peptide receptor-2 peptide agonist (LBT-3627). In this study, treatment with LBT3627 could prevent neurodegeneration induced by a 6-hydroxydopamine (6-OHDA) and α-synuclein (α-Syn). Additionally, the neuroprotective role of this hormone has already been reported by other groups [87], as well as the immune-modulatory role [88]. Finally, the literature reports that an increase in PYY led to an elevation in the levels of BDNF after administration of a diet rich in non-digestible carbohydrates [89].

However, although much research has been done to try to understand the role of the microbiome in the development of psychiatric disorders, very little is known about how the microbiome can alter gut hormones and consequently influence brain function, as discussed in this section. Therefore, more efforts are needed to elucidate how the microbiome can influence hormones and vice versa.

In the next section, a more detailed revision of what is known regarding the microbiome's influence on depression will be explored.

4. Depression, Gut Microbiome and Hormones

Depression is one of the most prevalent psychiatric illnesses that affect the population. It is estimated that at least 16% of the general population will suffer from this disorder at some point in their lives, and its consequences are, to some extent, permanent [90,91]. The most prevalent type of depression is unipolar or major depressive disorder (MDD), in which the core symptoms are anhedonia (lack of pleasure) and depressed mood (DSM-V), but the phenotypic expressions of this disorder vary [92]. MDD neurobiology is complex and multifactorial encompassing genetic, epigenetic and environmental factors [93]. However, an imbalance in the microbial environment (dysbiosis) is commonly observed in depressive patients and may be a key player in disease development [94]. Several studies have shown a correlation between depressive states and changes in specific gut microbiome species, mainly *Actinobacteria*, *Firmicutes*, *Bacteroidetes* and *Proteobacteria*. However, the directionality of such a relation is not yet possible to define [95,96]. Due to these observations, the gut flora became a novel target for the treatment of depression, and several studies focus on improving the richness and diversity of the gut microbiome population [97].

In fact, the relationship between the gut and brain axis (called GBA, or more recently MGBA for microbiome–gut–brain axis) consists of three pathways that produce

a bidirectional flow of information [11,98–100]. This link occurs through hormonal components, including the HPA axis, gut hormones and anatomical connections such as the vagus nerve [11,99]. Another relevant factor to account for is the effect of early life disturbances and stress on brain development and function, correlated with depression in late life stages [101]. Additionally, in this lane, there is also growing evidence that the gut microbiome at the beginning of life (from conception to the two years of life) has a crucial role in shaping health outcomes [99]. Animal studies showed the gut microbiome's essential role in regulating early brain development [102–104]; for example, *Bifidobacterium infantis* has been shown to elevate plasma tryptophan and thus influence 5-HT transmission [99]. Therefore, the presence of a healthy microbiome early in life is fundamental to brain health. In this regard, gut microbiota composition is determined by several perinatal factors [105,106], and as for the prenatal period, there is no consensus regarding the existence of a placental microbiome in healthy full-term pregnancies [107,108]. Therefore, since infant gut colonization begins at birth [106,109,110], the delivery mode plays a critical role in microbiome colonization. While vaginal delivery exposes the infant to its mother vaginal microbiota, in which *Lactobacillus*, *Prevotella* or *Sneathia* spp. are predominant [111], the caesarean section results in an altered microbial composition in the neonate which is enriched for skin bacteria (prevalence of *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp.) [99,111–113]. Additionally, the type of feeding seems to be important in bacterial colonization as breastfed infants have a higher amount of *Bifidobacterium* and high microbiome diversity than formula-fed infants [106,114]. Such richness could be explained by the nutritional value of human breast milk, which is rich in non-digestible oligosaccharides [115,116]. Other factors can disturb the bacterial profile, such as antibiotic exposure, gestational age (which seems to be correlated with caesarean section) and environmental factors. However, the bacterial composition tends to revert to its previous level of diversity with the removal of the disturbing factor, except for dietary patterns, which tend to be relatively permanent [99,117] and creates lasting disturbances for brain development.

Going back to the bidirectional flow of information that occurs on the MGBA, preclinical and clinical studies involving HPA axis disturbance presented a relationship between the depressive phenotype, diminished variety and richness of the microbiome, and an increased amount of Gram-negative bacterium [96,118]. One of the forms by which the brain can influence the microbiome is through the HPA axis, which regulates intestinal peristalsis and the control of epithelial cell functions. Dysfunctional states of this axis, such as stress-related hyperactivity, can modify the permeability of the intestinal epithelium through the reduced expression of claudins [9]. As a result, an increased inflammatory response is observed [119]. Additionally, several pieces of evidence show that psychological or physical stress can significantly dysregulate the MGBA, as observed in irritable bowel syndrome (IBS). Additionally, individuals with this condition generally present comorbidities such as depression and anxiety [120,121].

Furthermore, studies reported that the growth and function of bacteria (such as adhesion to the intestinal mucosa) could be affected by mammalian neuroendocrine hormones and catecholamines [122]. For example, the absence of neuronal 5-HT in an animal model negatively impacted gut microbiome composition, which can be worsened by chronic corticosterone treatment [123]. Additionally, rats chronically treated with ACTH presented a higher relative abundance of *Desulfovibrio* [124], which is known to promote a pro-inflammatory environment by up-regulating interleukin 6 (IL-6), interleukin 8 (IL-8) and tumour necrosis factor-alpha (TNF-α) [96,125]. In Addition, the overgrowth of Gram-negative bacteria, such as the *Enterobacteriaceae* family, which promotes systemic inflammation through increased gut barrier permeability and bacterial translocation, was observed in women with postpartum depression (PPD) [118,126]. It is important to note that such changes in inflammatory states could, in turn, increase VIP levels (through increased levels of T-activated cells), which would promote changes in circadian rhythms and sleep disturbance, a common complaint among depressive patients [33,84]. Moreover, GLP-1 seems to be part of the feedback loop activating the HPA axis [64] and seems to be involved in the peripheral

activation of VIP [33]. The literature also points to a possible antidepressant and anxiolytic effect of GLP-1 activation [67] by the depletion of TREK activation in the HPA axis. In Addition, anti-inflammatory drugs can increase the levels of GLP-1 [74], while chronically elevated corticosterone levels seem to inhibit its production [64]. HPA hyperactivity and increased corticosterone also increase CCK levels, and blockage of CCK seems to decrease such hyperactivation [53,127]. In sum, it is possible to theorize that the crosstalk between GLP-1 and VIP could be fundamental in maintaining euthymic states and that the sleep disturbance and HPA hyperactivation observed in depressive states could, in part, be caused by inflammatory states that would disrupt such peptides, while increasing levels of CCK. Such intricate relationships between the HPA axis and gut peptides could explain, at least in part, the high prevalence of intestinal dysfunction in depressive patients and also the depressive states of patients suffering from intestine complications, such as IBD.

Additionally, tight crosstalk between gut microbiota metabolism and host health has been demonstrated, making this interaction important to developing depressive phenotype in animal models [96] and humans [118]. Microbial metabolism generates diverse compounds, such as cytokines, neurotransmitters (serotonin (5-HT), dopamine (DA), gamma-aminobutyric acid (GABA), and melatonin), SCFAs, tryptophan and bile salt metabolites [128]. In Addition, these metabolites have an autocrine and paracrine influence on the enteric nervous system (ENS), the vagus nerve, and central nervous system (CNS) activity [129]. Correlation analysis between microbial composition and metabolite expression showed that active metabolites from *Akkermansia* and *Lactobacillus* were intimately related to host inositol metabolism and biosynthesis of phenylalanine, tyrosine and tryptophan [130]. *Lactobacillus* produces pyruvic acid, hippurate and d-arabitol, which correlates with an increased richness in the gut microbiome [96,131]. *Akkermansia muciniphila* plays an important role in mucosal barrier homeostasis, besides producing metabolites such as acetic acid, propionic acid and oligosaccharides, which are used as substrates for *Faecalibacterium prausnitzii*. In Addition, *Faecalibacterium*, *Phascolarctobacterium* and *Butyricicoccus* (which are significantly decreased in PPD patients), are butyrate producers [118,132]. Elevating butyrate production is correlated with a healthy gut since these short-chain fatty acids inhibit inflammation and consequent disruption in intestinal permeability. Increased gut permeability is linked to increased levels of LPS in circulation, which in turn can activate Toll-like receptors (such as TLR-4) and stimulate the release of CCK [60], which is reported to be elevated in depression [53]. Reinforcing the importance of CCK in depressive states, the literature reports that repeated social defeat increases CCK [127], which can be reversed by antidepressant treatment.

Studies in a GF mice model demonstrate the direct influence of the gut microbiome on host behaviour, brain development and hormonal function [99,133,134]. For instance, GF rats inoculated with a faecal transplant (FT) from depressive patients developed depression-like behaviours and molecular changes similar to depressive patients [134]. These depressed rats presented reduced hippocampal levels of neurotransmitters (5-HT, noradrenalin (NA) and DA), HPA axis hyperactivity accompanied by high levels of CORT, ACTH and corticotropin-releasing hormone (CRH), increased inflammatory markers (TNF-α, IL-6, IL-1 and interferon-gamma (IFN-γ)) and reduced levels of anti-inflammatory cytokines (IL-4, IL-10). High levels of pro-inflammatory cytokines contribute to the inhibition of the negative feedback of the HPA axis, increasing blood–brain barrier permeability and reducing 5-HT synthesis [135]. Beyond such alterations, dysbiosis can also induce mitochondrial structure damage (change in shape, size, and presence of vacuoles) in small intestinal cells. Mitochondrial damage often results in multiorgan and multi-system lesions, especially in high-energy demand and metabolism organs, such as the brain, contributing to an increased inflammatory response [136], and stimulating kynurenine synthesis. In this sense, it is relevant to mention that increased ghrelin levels can decrease mitochondrial damage and have been proposed as a target for treating neurodegenerative conditions where mitochondrial damage is high [48,49]. However, in opposition, high levels of ghrelin have been linked to the hyperactivation of the HPA axis and MDD [45], and ghrelin seems to

inhibit the release of 5-HT while increasing its turnover in animal models [137]. Moreover, kynurenine and 5-HT pathways depend on tryptophan metabolism and a shift towards the kynurenic pathway, as in dysbiotic states, has been associated with depression and neuronal damage [138,139]. For example, in the study by Zhao and co-workers [139], the depressive phenotype in rats was accompanied by a high relative abundance of *Lactobacillus* and *Bacteroides*, which was negatively correlated with 5-HT levels and positively correlated with kynurenine, while *Ruminococcus* and *Clostridium IV* were positively correlated with 5-HT levels. It is important to emphasize that the metabolism of 5-HT is closely connected to the gut microbiome, and 90% of produced 5-HT arises from the intestinal microbiota; therefore, shifts in the activation of the gut 5-HT production will significantly affect the brain as well [140]. Finally, returning to the role of diet in controlling the microbiome, hyperglycaemic states can cause dysbiosis through the disruption of tryptophan metabolism [141]. At the same time, patients suffering from MDD can develop metabolic syndrome, and patients with metabolic syndrome have a high incidence of depression [141–144]. Interestingly, a decreased abundance of *Clostridia phylum* was seen in anhedonic-depressed patients with a simultaneous increase in *Bacteroides* enterotype, which can increase insulin callousness through high LPS and TNF-α levels [145,146].

4.1. Gut Microbiome, Depression and Nutrition

Food ingestion is highly related to gut microbiota composition. A healthy gut microbiome is fundamental for the host's metabolic functions, facilitating energy extraction from food through their enzymes, increasing vitamin synthesis, preserving nutrients and modifying taste receptors [61,110,147]. Epidemiological studies report that imbalanced nutrition, eating (EDs), and alcohol/substance disorders increase the risk of depression [82,148]. In addition, such disorders share neurobiological mechanisms that regulate depressive behaviours (such as disturbed reward processing) and related neural circuitries [149,150]. EDs are a multifactorial health problem that depends on diet composition, genetic, and environmental factors, including the gut microbiota [151,152]. Such influence may be due to the modulatory effects of the gut microbiome (per transcriptome regulation) on hormones such as GLP-1, PYY, GIP and leptin [153,154].

The regulation of appetite depends on ghrelin (orexigenic hormone) promoting food intake and leptin (anorexigenic hormone) inducing satiety. The activation of ghrelin triggers an increase in PYY, while leptin induces the production of GLP-1 and α-melanocyte-stimulating hormone (α-MSH) [155]. This peptide (α-MSH) plays a role in the activation of immunoglobulins, which can be linked to the inflammatory profiles observed in EDs and depressive disorders [152,156,157]. Interestingly, food restriction as a mild stressor increased the levels of α-MSH auto-antibodies [158]. Such auto-antibodies are present in healthy people to avoid immune complex formation by neutralizing neuropeptides. Additionally, patients with depressive disorders showed decreased levels of acylated ghrelin (IgM class) and NPY (IgG class) auto-antibodies [152,159]. Furthermore, decreased NPY IgG plasma levels seem to have a protective role in depression, higher levels were associated with a lower body mass index (BMI) and reduced appetite, often observed in some EDs, such as anorexia [152,160]. Connecting this alteration in NPY to the microbiome, clinical features of eating disorders have been associated with some specific gut bacterial strains, e.g., *Escherichia coli K12*. Interestingly, this strain has a bacterial protein (caseinolytic protease B—ClpB) that triggers the production of auto-antibodies cross-reacting with appetite-regulating hormones. Additionally, ClpB is homologous with α-MSH, a neuropeptide involved in regulating mood and emotion [158,161,162].

Among several compounds present in food and produced by the microbiota, trace amines are of particular importance in depression [163,164]. This group of endogenous monoamines, in particular, b-phenylethylamine (PEA), p-tyramine (TYR), tryptamine (TRP), and p-octopamine (OCT), bind to the TAAR1 receptor. Additionally, TAAR1 acts as a rheostat of dopaminergic, glutamatergic, and serotonergic neurotransmission and regulates hormonal and inflammatory responses. Clinical data shows deficits in PEA are

associated with depression, whereas MAO inhibitors are known to elevate trace amine levels. Furthermore, the underlying antidepressant effects of exercise have been shown to increase the levels of PEA [165,166].

Fermentation by intestinal bacteria can also produce SCFAs from dietary carbohydrates and amino acids (such as glutamate, asparagine, and others) [167,168]. SCFAs are thought to play a critical role in microbial–endocrine communication and influence behaviour. Such actions are believed to be due to their neuroactive properties and involvement in neurodevelopmental processes, CNS immune system homeostasis, microglial maturation and blood–brain barrier integrity [82,168]. According to Sittipo and co-workers [168], the main bacteria synthesizing SCFAs are *Faecalibacterium*, *Clostridium*, *Eubacterium*, *Roseburia*, *Anaerostipes*, *Bifidobacterium* and *Akkermasia*. In addition, SCFAs stimulate the release of leptin from adipocytes, a hormone associated with the anhedonic behaviour observed in obese mice [82] and regulates GLP production [168]. Depletion of the gut microbiota by antibiotic treatment (ABT) attenuated the caloric intake in HFD (high-fat diet)obese rats and reduced the intestinal faecal amounts of fatty acids and metabolites (including SCFAs and tryptophan), glucose and other aromatic amino acids [82,169]. Additionally, ABT prevented HFD-inducing anhedonic behaviours and increased plasmatic levels of leptin. There is a correlation between leptin levels and anhedonic behaviour in obese rats, so the gut microbiome is essential in triggering such behaviours under a HFD [82].

Based on the presented studies, a diet rich in fermented foods and fibre can support a healthy microbiota which in turn can have a protective effect against the development of mental and eating disorders and is fundamental in the homeostasis of gut hormones.

4.2. Gut Microbiome, Depression and Pro/Prebiotics

Due to the modulatory effects of the gut microbiome on the brain, several studies have shown the beneficial effects of pro- and prebiotics on depressive-like behaviours. Probiotics comprise supplementation with beneficial bacteria or oligosaccharides that promote the growth of indigenous gut bacteria, such as *Lactobacilli* and *Bifidobacteria*. Both are described to have neurotropic effects [170]. Animal studies also report a modulatory effect of probiotics on behaviour and HPA activity, and such effects are strain-specific [171]. In animal studies, *Lactobacillus* strains effectively prevented depressive-like behaviours and lowered plasma CORT and ACTH levels [171–173]. Moreover, the literature also reports the effects of *Lactobacillus* in increasing plasma IL-10 levels and restoring neurotransmitter (5-HT, DA, NE) and glucocorticoid receptor (GR) levels [171–173]. Furthermore, *Lactobacillus* supplementation is reported to increase the mRNA expression of BDNF through membrane-derived extracellular vesicles (EV) released from gut bacteria [171,172]. Additionally, such a mechanism seems to be mediated by sirtuin 1 (Sirt1) [174,175]. Another bacterium considered a candidate for treating depressive states is the Gram-negative bacteria *Akkermansia muciniphila*. Similar to *Lactobacillus*, supplementation with this bacterium had a positive effect on behaviour and a modulatory effect on CORT, catecholamines and BDNF [176]. Finally, probiotic treatment also may increase gut microbiota richness and diversity, combined with decreased HPA axis activity and lower levels of inflammatory cytokines, as reported with *Akkermansia*, *Lactobacillus* and *Saccharomyces boulardii* [177]. In sum, probiotics seem to positively affect depressive disorder treatment. Still, the mechanisms need to be further elucidated. However, considering their modulatory effect on the HPA axis, it can be hypothesized that they indirectly affect levels of CCK, GLP and VIP.

Finally, prebiotic supplementation (with oligosaccharides) diminished waking salivary cortisol reactivity in health participants [89,178], increased the levels of probiotic bacteria (*Bifidobacteria* and *Lactobacillus*), and certain butyrate-producing microbes, such as *Faecalibacterium*, *Ruminococcus* and *Oscillospira*, in animals and humans [179,180]. Furthermore, individuals showed increased attentional vigilance to positive versus negative stimuli, which could be interpreted as an early anxiolytic-like profile and a decrease in negative bias observed in depression [180]. Additionally, prebiotics decreased ghrelin and C-reactive

protein in obese and overweight adults [181], and these markers are also reported to be increased in depressive patients.

5. Circadian Rhythms, Gut Microbiome and Hormones

Circadian rhythm disruption is associated with psychiatric disorders, such as MDD and bipolar disorder. Animal models such as social defeat and alterations in the light/dark cycle can induce a depressive phenotype in animals, reinforcing rhythmicity's role in mental health [182–185]. Additionally, a reduced amplitude of the skin temperature rhythm was found in untreated, self-reported depressed patients [186], and a reduced amplitude of circadian activity was found in patients wearing an actigraph [187]. Depression severity is associated with a misalignment between rhythms. For example, the larger the difference between the midsleep phase and the time of minimum core body temperature, the more intense depressive symptoms [92]. Moreover, individuals classified as evening-types self-report an impaired overall quality of life [188] and are more likely to be diagnosed with major depression [189]. Since circadian rhythms can be observed in most physiological variables of the mammalian body, some reciprocal relationships between circadian rhythms and microbiota could be expected. Additionally, the gut microbiota also expresses circadian rhythms, both in its species abundance and metabolome, influencing the host's circadian pattern of the transcriptome [190] while also being affected by the host's circadian rhythms [191].

There are some indirect associations between the microbiota, circadian rhythms and mental health. For example, (i) lithium has been used to treat bipolar disorders [192], (ii) lengthening the locomotor circadian period in rats [193], and (iii) promoting changes in the microbiota [194]. However, a cause–relationship cannot be established from these separate data. In fact, while the relationship between circadian rhythms and the microbiota and the relationship between circadian rhythms and mental health is well studied, fewer published studies have addressed the relationship between the microbiota, circadian rhythms and mental health.

According to Ma and co-workers [195], seven days of REM sleep deprivation using the multiple platforms method led to depressive-like behaviours in the forced swim and sucrose preference tests and decreased alpha diversity of the microbiota in Wistar rats. Their data also reported a decreased in the relative abundance of *Akkermansia* and an increase in *Oscillospira*, *Parabacteroides*, *Ruminococcus*, *Phascolarctobacterium* and *Aggregatibacter*. In another study, microbiota-derived SCFAs were found to have a diurnal rhythm in participants' guts [196]. However, this rhythmicity was absent in both night workers and individuals diagnosed with alcohol-use disorders.

Finally, a promising study was reported as a protocol involving bipolar patients and a 2-year follow-up design [197]. The researchers aimed to collect data during three distinct mood phases: euthymia, depression and mania. The stool was collected to analyse the microbiota composition, and blood samples were collected for the analysis of melatonin, its metabolite levels and variants of genes related to the melatonin pathway, such as the MT1 and MT2 receptors and the enzyme aralkylamine N-acetyltransferase.

6. Conclusions

Based on the data presented and summarised in this review, it is possible to conclude that further studies are needed to elucidate the gut microbiome's influence on hormonal balance. However, based on the current literature, it is possible to conclude that dysbiosis and the presence of high inflammation in depressive patients play a role in hormonal dysfunction. For instance, increased levels of T-activated cells increases VIP levels, and VIP balance is necessary to keep circadian rhythmicity [33,84]. Increased cortisol disrupts the homeostasis of GLP-1 [33,84], which may have antidepressant properties. Increased cortisol and inflammation also change CCK levels, and high CCK levels are present in depressive and anxious patients [53,127]. Finally, the shift from the serotonin to the kynurenine pathway observed in inflammatory states can influence ghrelin levels [45,48,49]. Such

intricate relationships between the HPA axis, inflammation, the microbiome and gut peptides could explain, at least in part, the high prevalence of intestinal dysfunction in depressive patients and could be one pathway by which dysbiosis could lead to mood disorders.

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Abbreviations

5-HT	Serotonin
ABT	Antibiotic Treatment
ACTH	Adrenocorticotropic Hormone
AS	Asperger's Syndrome
BMI	Body Mass Index
CCK	Cholecystokinin
CNS	Central Nervous System
CORT	Cortisol (or Corticosterone)
CRF	Corticotropin-Releasing Factor
CRH	Corticotropin-Releasing Hormone
CRP	C-Reactive Protein
DA	Dopamine
DSM-V	Diagnostic and Statistical Manual of Mental Disorders V
EDs	Eating Disorders
EE cells	Enteroendocrine cells
ENS	Enteric Nervous System
EV	Extracellular Vesicles
FT	Faecal Transplant
GABA	Gamma-Aminobutyric Acid
GF	Germ-Free
GIP	Glucose-Dependent Insulinotropic Polypeptide
GLP-1/2	Glucagon-Like Peptide 1 and 2
GR	Glucocorticoid Receptor
HFD	High-Fat Diet
HPA axis	Hypothalamic–Pituitary–Adrenal Axis
IBS	Irritable Bowel Syndrome
IFN-γ	Interferon Gamma
IL	Interleukin
MDD	Major Depressive Disorder
NA	Noradrenaline
NAc	Nucleus Accumbens
NPY	Neuropeptide Y
OCT	p-Octopamine
PEA	b-Phenylethylamine
PP	Pancreatic Polypeptide
PPD	Postpartum Depression
PYY	Peptide YY
REM	Rapid Eye Movement
SCFA	Short-Chain Fat Acids
SCN	Suprachiasmatic Nucleus
SPF	Specific Pathogen-Free
TRP	Tryptamine
TYR	p-Tyramine
VIP	Vasoactive Intestinal Polypeptide
VTA	Ventral Tegmental Area

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