

Review

The Role of the Adrenal–Gut–Brain Axis on Comorbid Depressive Disorder Development in Diabetes

Thalita Mázala-de-Oliveira ¹, Bruna Teixeira Silva ^{1,2}, Paula Campello-Costa ² and Vinicius Frias Carvalho ^{1,2,3,*}
¹ Laboratório de Inflamação, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro 21040-360, Brazil; tha.mazala@hotmail.com (T.M.-d.-O.); bruna_teixeira@id.uff.br (B.T.S.)

² Programa de Pós-Graduação em Neurociências, Instituto de Biologia, Universidade Federal Fluminense, Niterói 24210-201, Brazil; paulacampello@id.uff.br

³ Laboratório de Inflamação—INCT-NIM, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro 21040-360, Brazil

* Correspondence: vfrias@ioc.fiocruz.br; Tel.: +55-21981828679

Abstract: Diabetic patients are more affected by depression than non-diabetics, and this is related to greater treatment resistance and associated with poorer outcomes. This increase in the prevalence of depression in diabetics is also related to hyperglycemia and hypercortisolism. In diabetics, the hyperactivity of the HPA axis occurs in parallel to gut dysbiosis, weakness of the intestinal permeability barrier, and high bacterial-product translocation into the bloodstream. Diabetes also induces an increase in the permeability of the blood–brain barrier (BBB) and Toll-like receptor 4 (TLR4) expression in the hippocampus. Furthermore, lipopolysaccharide (LPS)-induced depression behaviors and neuroinflammation are exacerbated in diabetic mice. In this context, we propose here that hypercortisolism, in association with gut dysbiosis, leads to an exacerbation of hippocampal neuroinflammation, glutamatergic transmission, and neuronal apoptosis, leading to the development and aggravation of depression and to resistance to treatment of this mood disorder in diabetic patients.

Keywords: treatment-resistant depression; depression; diabetes; glucocorticoids; gut microbiota; TLR4



Citation: Mázala-de-Oliveira, T.; Silva, B.T.; Campello-Costa, P.; Carvalho, V.F. The Role of the Adrenal–Gut–Brain Axis on Comorbid Depressive Disorder Development in Diabetes. *Biomolecules* **2023**, *13*, 1504. <https://doi.org/10.3390/biom13101504>

Academic Editor: Declan McKernan

Received: 4 July 2023

Revised: 15 August 2023

Accepted: 26 August 2023

Published: 10 October 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by disturbances in the homeostasis of carbohydrate metabolism that result in hyperglycemia. Currently, diabetes is one of the most serious and common chronic diseases worldwide. Patients with uncontrolled diabetes develop several disabling complications that reduce their life expectancy, and which can even be fatal. In 2021, the global prevalence of diabetes reached pandemic proportions with 537 million people with the disease worldwide, accompanied by a global health expenditure of US \$966 billion [1]. Furthermore, future projections suggest that by 2045 the number of people with diabetes will increase by 46% [1], and the estimated health expenditure for the care of this disease that will exceed USD one trillion.

Diabetic patients are more susceptible to developing mood disorders, including depression, than non-diabetic individuals. Diabetic patients who have mood disorders have a high risk of mortality from micro- and macrovascular complications when compared to diabetic patients who do not develop these comorbidities [2–4]. In addition, diabetes-related mood disorders culminate in a large economic burden for patient care and are associated with more treatment-resistant depression [5,6]. Therefore, knowledge of the mechanisms underlying the establishment of mood disorders in diabetics is fundamental for the early diagnosis and/or treatment of patients. The pathophysiology of mood disorders in diabetics is complex and multifactorial, and includes factors inherent to diabetes itself, such as hyperglycemia and diabetes-related microvascular dysfunction. Furthermore, changes in hippocampal homeostasis, including neuroinflammation, oxidative stress, imbalance in

neurotransmitter levels, and decrease in brain-derived neurotrophic factor (BDNF), are key to the evolution of mood disorders in diabetic patients [7–10].

It is well known that there is a bidirectional communication between the neuroendocrine system, including the hypothalamus–pituitary–adrenal (HPA) axis, which is the central stress-response system, and gut microbiota [11–13]. The HPA axis is a neuroendocrine system responsible for the stress response triggered by both internal and external stimuli. Activation of the HPA axis triggers neurons in the paraventricular nucleus (PVN) of the hypothalamus to release corticotropin-releasing hormone (CRH), which subsequently induces secretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary and, finally, glucocorticoids from the adrenal cortex. Due the metabolic effects of chronic exposure to high glucocorticoids levels, the HPA axis needs to be finely regulated. Therefore, rising levels of glucocorticoids activate their receptors (GRs) in the hypothalamus and pituitary, inhibiting further release of CRH and ACTH, in a classic endocrine negative feedback loop, which enables the HPA axis to return to a physiological state following acute activation [14].

The human gut microbiota is composed of up to 100 trillion complex microorganisms, such as commensal, symbiotic, and pathogenic bacteria, as well as archaea, fungi, and viruses that colonize the intestine [15]. Exogenous chronic treatment with glucocorticoids, the major effector hormone produced by the HPA axis, shifted the composition of gut microbiota and the profile of fecal metabolites in rats [11], reducing the fecal production of short-chain fatty acids (SCFAs). In addition, chronic stress promotes changes in the gut microbiota profile and leaks in the epithelial–intestinal barrier [16]. In addition, maternal separation, a powerful stressor in early life, increases plasma corticosterone and leads to changes in the microbiota and systemic immune response, revealing alterations in the intestine–microbiota–brain axis [17]. On the other hand, the gut microbiome composition can regulate the activity of the HPA axis. The lower diversity and higher relative abundance of pathogenic bacteria induced by maternal precarity were positively correlated with hyperactivity of the HPA axis [18]. Furthermore, germ-free mice, those with no commensal microbiota, exhibited higher systemic ACTH and corticosterone levels after acute stress response than specific pathogen-free (SPF) mice [19,20] and pre-treatment with probiotic *Lactobacillus farciminis* inhibited acute psychological stress-induced HPA axis hyperactivity in rats [19,20].

Since patients with both diabetes and depression showed a hyperactivity of the HPA axis accompanied by gut dysbiosis [21–24], a term commonly used to describe a bloom of pathobionts, loss of commensals, and/or loss of diversity [25], we hypothesized that disturbance in the adrenal–gut–brain axis is a crucial factor in diabetes-induced comorbid depressive disorder development and treatment-resistant depression.

2. Diabetes, the HPA Axis, and Microbiota

It is well known that diabetic patients present a hyperactivity of the HPA axis, evidenced by an increase in the circulating levels of ACTH and cortisol as well as elevated urinary free cortisol levels [26–28]. In diabetic patients, the hyperactivity of the HPA axis was related to both a failure in the negative feedback of the axis, attested by the dexamethasone suppression test [28], and a higher reactivity of adrenal to CRH stimulation [29]. We and others have shown that diabetic animals exhibit high levels of ACTH and corticosterone in the circulation [30–33], and an impairment in the negative feedback of the HPA axis [34]. We previously demonstrated that the exacerbation of glucocorticoid production by diabetic animals was related to overexpression of ACTH receptor (MC2R) and steroidogenic enzymes, including steroidogenic acute regulatory protein (StAR) and 11 β -Hydroxysteroid dehydrogenase 1 (11 β -HSD1), in the adrenal gland [33,35], while the failure in the negative feedback of the HPA axis was associated with a downregulation of GRs and mineralocorticoid receptors (MRs) in the pituitary. In addition, we showed that the reduction in the GR expression in the pituitary gland of diabetic rats occurred 24 h after the onset of hyperglycemia, suggesting that the lack of glycemic control in diabetics may be involved with the downregulation of GR in the pituitary gland [33,36].

Furthermore, we noted that diabetic animals showed a reduction in the anti-inflammatory receptor peroxisome proliferator-activated receptor γ (PPAR- γ) expression and an increase in the pro-inflammatory receptor angiotensin II type 1 receptor (AT1R) expression in the adrenal gland. In addition, the blocked of Ang-II/AT1R axis, which is a pro-inflammatory pathway, with captopril or olmesartan inhibited the exacerbation of corticosterone production by adrenal glands of diabetic mice through a mechanism dependent of a reduction in the expression of Ang-II and ACTH receptors, AT1R and MC2R, respectively, and steroidogenic enzymes StAR and 11 β -HSD1. On the other hand, the activation of anti-inflammatory receptors PPAR- γ and AT2R with rosiglitazone and CGP42112A, respectively, inhibited the hypercortisolism in diabetic mice. Rosiglitazone induced a reduction in the circulating corticosterone levels which was related to a decrease in the systemic ACTH levels and in the expression of MC2R in the adrenal gland. Furthermore, the inhibitory effect of rosiglitazone on the hyperactivity of the HPA axis observed in diabetic rats was related to an upregulation of PI3K expression in the pituitary and adrenal glands. However, the exact mechanisms by which CGP42112A reduced the exacerbation of corticosterone production by adrenal glands of diabetic mice still remain elusive [35,36]. As observed in the adrenal gland, diabetic patients and animals showed a pro-inflammatory profile in their circulation [37,38]. In diabetics, the composition of the gut microbiota is altered and has been appointed as a driver of chronic low-grade systemic metabolic inflammation [39,40].

Patients with diabetes, both type 1 and type 2, presented a gut microbial dysbiosis [39,41,42]. In general, diabetic patients showed an increase in the ratio of Bacteroidetes/Firmicutes [41,43]. In addition, in all diabetic groups, a significant increase in the abundance of Gram-negative and potentially opportunistic pathogenic bacteria, such as *Pseudomonas* and *Prevotella*, in contrast to a reduction in the commensal bacteria, including *Turicibacter*, *Terrisporobacter*, and *Clostridium* was observed [44]. Patients with type 1 diabetes presented a clear depletion of species like *Prevotella copri* and *Bifidobacterium longum*, probiotic bacteria, and enrichment of families like *Ruminococcaceae*, *Clostridiaceae*, *Clostridiales*, and *Oscillibacter*, bacteria associated with infection and inflammation [45]. Furthermore, type 1 and type 2 diabetic patients presented a decrease in the abundance of SCFA-producing bacteria [46].

SCFAs are important to the maintenance of epithelial–intestinal barrier permeability, reducing the translocation of bacteria and their products from the gut to the bloodstream [47]. The reduction in the abundance of SCFA-producing bacteria in the gut microbiota is possibly involved with the breakdown of the intestinal epithelial barrier observed in diabetic patients, attested by the measure of circulating levels of lipopolysaccharide (LPS) and/or intestinal fatty acid binding protein [48,49]. Furthermore, LPS, a component of the cell wall of Gram-negative bacteria and potentially opportunistic pathogenic bacteria found in the gut microbiota of diabetic patients, enhanced intestinal permeability in vitro and in vivo [50,51]. Additionally, the levels of LPS, which has been proposed as a source for chronic low-grade systemic metabolic inflammation [52,53], LPS-binding protein (LBP) [52], and/or bacterial DNA, including *Proteobacteria*, are increased in the circulation of diabetic patients [54].

The maintenance of homeostasis in the gut environment is important not only in slowing down diabetes development but it is also central in the control of its complications [55], suggesting that dysbiosis may have an important role in diabetes-induced comorbid depressive disorder development and treatment-resistant depression.

3. Depression, the HPA Axis, and Microbiota

Depression, also known as major depression or major depressive disorder (MDD), is a psychiatric disease that affects how a person feels, thinks, and handles daily activities, such as sleeping, eating, or working. Currently, depression is the leading cause of disability worldwide, and is associated with an increased risk of suicide [56,57]. Furthermore, about 30% of patients with depression fail to respond to conventional treatment, leading to treatment-resistant depression [58,59]. The pathophysiology of depression is associated with genetic and environment factors [60,61]. It also emerges as a comorbidity of chronic

and systemic medical illnesses such as diabetes mellitus [62,63]. Patients with depression showed a reduction in the hippocampal volume [64–66], which is associated with a decrease in the size of pyramidal neurons, retraction of dendrites, reduction of neurogenesis in the hippocampal dentate gyrus, and a drop in the astrocyte counts [67–69]. In animal models of depression, treatment with antidepressants restored the hippocampal volume by restoring neurogenesis and cell differentiation [70,71].

At the molecular level, several alterations in the homeostasis of hippocampal function are involved in the development and/or aggravation of depression, including impairment in the biogenic amines and glutamate (Glu) signaling [72], decrease in the BDNF levels [73], imbalance in the neurogenesis, apoptosis, and autophagia [74], and increase in oxidative stress and neuroinflammation [75,76] (Figure 1).

Interestingly, depression is anticipated by chronic exposure to stress [77,78], suggesting that activation of the HPA axis may be involved in the development of depression that cannot be explained only by imbalance in the hippocampal neurotransmitter levels. In fact, around 50% of depressed patients and 80% of severely depressed patients showed hyperactivity of the HPA axis [79,80]. In addition, depressive patients presented adrenal hypertrophy and an increase in the circulating levels of both ACTH and cortisol [81–84]. Furthermore, repeated exposure to short-term stress or injection of glucocorticoids induced depressive-like behavior in mice [85]. Dexamethasone inhibited the proliferation of rodent neural stem cells, suggesting that glucocorticoids can impact neurogenesis, as observed in depressed patients [86]. Both chronic severe stress, which caused increased glucocorticoid levels, and direct glucocorticoid administration induced neural cell death, atrophy of neuronal processes, and decrease in the hippocampal neurogenesis [87–89]. Furthermore, glucocorticoid-receptor-impaired (GR-i) mice, a transgenic mouse model of reduced GR-induced negative feedback regulation of the HPA axis, exhibited changes in depressive-like behaviors, together with a reduction in cell proliferation and imbalanced levels of neuroplastic and epigenetic markers in the hippocampus. The treatment of GR-i mice with agomelatine, an antidepressant drug that acts as a melatonin receptor agonist and a serotonin (5-HT) 2C receptor antagonist, improved depressive-like behaviors and reversed the deficit in hippocampal cell proliferation in GR-i mice [90]. Altogether, these data suggest that hyperactivity of the HPA axis can be a trigger for depression development and worsening.

Additionally, patients with post-traumatic stress disorder (PTSD) showed a decrease in serum 5-HT levels and an increase in circulating cortisol levels [91,92]. This imbalance in 5-HT and cortisol levels in patients with PTSD was associated with a dysregulation in the immune response, attested by high levels of circulating pro-inflammatory cytokines, such as IL-1 β , IL-6, and TNF- α [92–96], and low levels of anti-inflammatory cytokines, including IL-4 and IL-10 [97]. It is noteworthy that elevated serum IL-6 and TNF- α levels, as well as increased levels of salivary cortisol, are also associated with treatment-resistant depression [98–100]. Treatment-resistant depression is a subset of MDD, which affects approximately 30% of patients and is diagnosed when MDD patients show an inadequate response to at least two trials of antidepressant pharmacotherapy [101]. Treatment-resistance depression occurs when patients develop the same underlying neurobiology as the treatment-responsive illness; however, the pathophysiological alterations are more severe such that standard treatment is inadequate, and/or patients present progressive neurobiological changes or iatrogenic effects compared to treatment-sensitive patients treated with first-choice antidepressants [102].

A subgroup of PTSD patients with cirrhosis exhibited lower microbial diversity in the gut microbiota, as well as an increase in the levels of pathobiontic bacteria, including *Enterococcus* and *Escherichia-Shigella* genera, and a reduction in the levels of *Lachnospiraceae* and *Ruminococcaceae* families [103]. Although the enterochromaffin cells, with the cooperation of gut microbiota, are responsible for most of the 5-HT production by humans [104], there is no correlation between the drop in 5-HT and gut dysbiosis in these patients. In addition, rats that have been induced to a PTSD-like phenotype showed changes in the levels of phyla Firmicutes, Bacteroidetes, Cyanobacteria, and Proteobacteria and a significant reduction in the 5-HT concentrations in the cerebral cortex [105]; however, there is no evidence that the decrease in the 5-HT levels in the brain was caused by a lower production of this neurotransmitter by enterochromaffin cells. A possible

explanation for the reduction in 5-HT levels in the brain of patients with PTSD is an alteration in the activity of monoamine oxidase A (MAO-A), which is the major enzyme responsible for the metabolism of monoamines. In fact, the 5-HT concentration in the hippocampi decreased in parallel to an increase in the MAO-A activity in rats that had been induced to a PTSD-like phenotype [106]. Recently, it was shown that the treatment with the probiotic *Bacillus coagulans* Unique IS-2[®] reduced chronic stress-induced depression in rats by a mechanism related to an increase in BDNF and 5-HT levels and a decrease in TNF- α , IL-1 β , and dopamine levels in the hippocampus and frontal cortex. Also, probiotic treatment restored systemic levels of L-tryptophan, L-kynurenine, kynurenic-acid, and 3-hydroxyanthranilic acid, villi/crypt ratio, goblet-cell count, Firmicutes to Bacteroides ratio, and levels of acetate, propionate, and butyrate in fecal samples of rats subjected to chronic stress, suggesting that the antidepressive-like effect of probiotics may be due to a remodeling of the intestine–microbiota–brain axis [107].

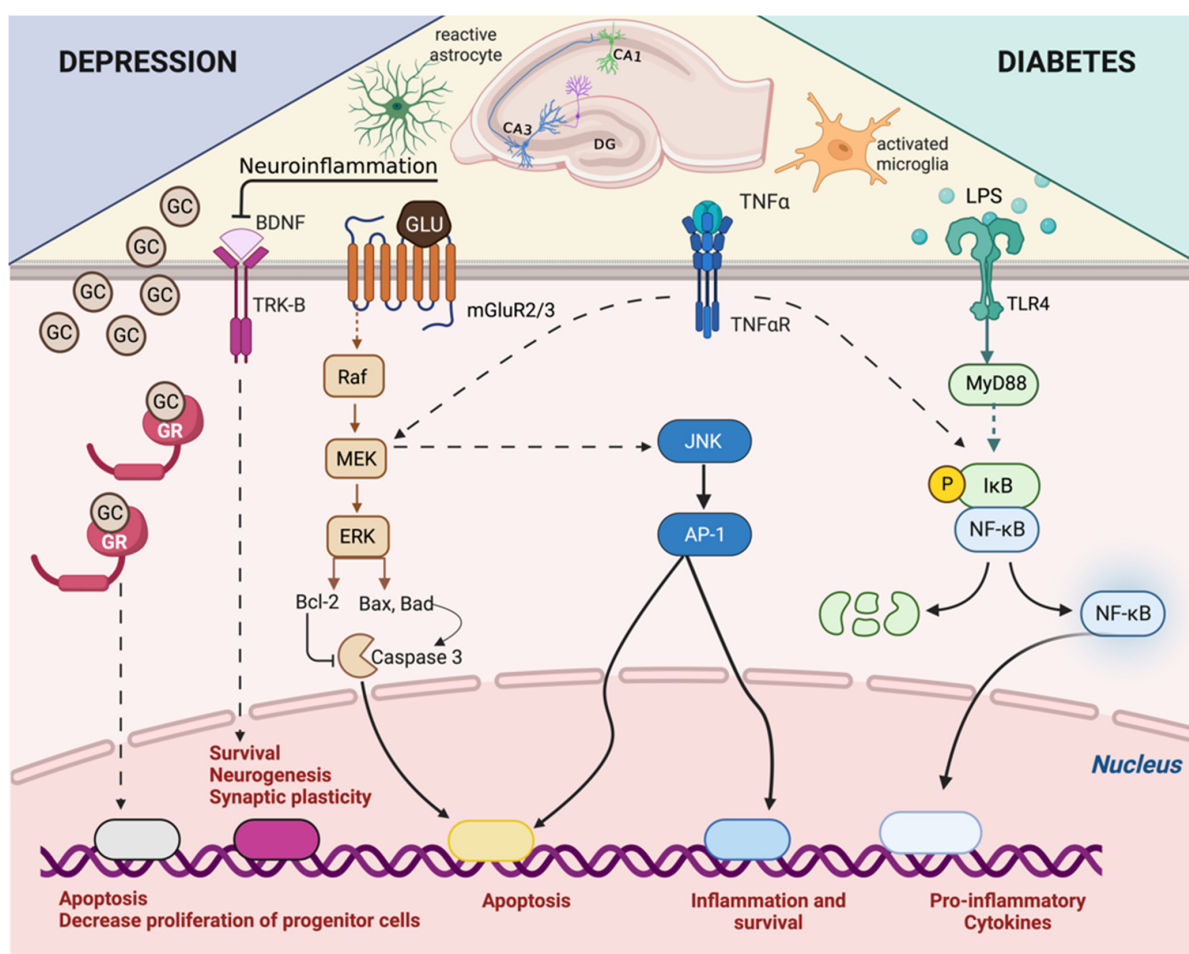


Figure 1. Scheme illustrating the main hippocampal mechanisms observed in the diabetes-related depression. The hippocampus represents a site of convergence for cellular and molecular changes observed in diabetes-associated depression. At the cellular level, there is an increase in the reactivity of astrocytes and microglia, a reduction in hippocampal neurogenesis, apoptosis of pyramidal neurons, and synaptic plasticity with dendritic retraction. At the molecular level, there is an increase in glucocorticoid signaling, a reduction in BDNF production, an increase in mGluR2/3 activity leading to caspase 3 activation and an increase in the TLR4/MyD88/NF- κ B signaling pathway, with an augmentation in reactive oxygen species and transcription of pro-inflammatory cytokines, such as TNF- α , production. Together these pathways regulate gene transcription, increasing inflammation and apoptosis and decreasing progenitor proliferation, which in turn promotes a decrease in the hippocampal size.

The use of two approaches to avoid glucocorticoid action, the removal of adrenal glands, or treatment with GR antagonist RU486 (mifepristone), increased hippocampal neurogenesis [108–110], strongly suggesting that hypercortisolism is important to the development and/or aggravation of depression. In fact, treatment with mifepristone improved neurocognitive impairment in bipolar depressed patients [111]. Nevertheless, in other studies, this treatment leads to improvement in psychotic but not in depressive symptoms in patients with psychotic major depression [112,113].

In addition to neuroendocrine imbalance, modifications in the gut microbiome have also been correlated with depression. For instance, several studies have shown an imbalance in the Firmicutes/Bacteroidetes ratio in patients with MDD [113–116]. Furthermore, the fecal microbiota of patients with MDD presented a significant reduction in the diversity of commensal bacteria genera, such as *Clostridium* [117,118], the vast majority of whose species are butyrate-producing bacteria [119], *Bifidobacterium* and *Lactobacillus* [120], and an increase in the Gram-negative and opportunistic pathogenic bacterium, such as *Prevotella* and *Klebsiella* [114], indicating that these patients exhibited gut dysbiosis. Furthermore, the use of ketamine, a N-methyl-D-aspartate (NDMA) antagonist with an antidepressant effect [121], also increased the number of butyrate-producing bacteria [122] in a chronic social defeat stress model of depression in mice.

Interestingly, germ-free mice exhibited depressive-like behaviors when receiving fecal microbiota transplantation derived from depressive patients [123]. In addition, chronic unpredictable mild stress mice treated with *Clostridium butyricum* improved depressive-like behavior, upregulating 5-HT and BDNF levels in the brain [124]. Another study showed that the administration of *C. butyricum* in association with antidepressants reduced 70% of depressive symptoms in patients with treatment-resistant depressive disorder [125]. This evidence strongly suggests that as well as HPA axis hyperactivity, gut dysbiosis promotes the development and/or worsening of the depressive condition.

4. Adrenal–Gut Axis Imbalance Is Central to Depressive Disorder Development and Aggravation in Diabetes

In diabetes, the development of depressive disorder is related to hyperglycemia and an increase in the circulating pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α , known as low-grade inflammation [126–128]. It is well known that alterations in hippocampal homeostasis, such as neuroinflammation, oxidative stress, and imbalance in neurotransmitter and BDNF levels, are crucial to the progression of mood disorders during diabetes. Indeed, type-2-diabetes-induced depression was accompanied by an increase in pro-inflammatory cytokines, including TNF- α , and a reduction in the BDNF content in the hippocampus. Interestingly, the levels of agmatine, an arginine metabolite involved in the regulation of insulin secretion and neuroprotection, were reduced in the hippocampus of type 2 diabetic rats. However, a chronic systemic treatment with agmatine improved depressive-like symptoms and inhibited neuroinflammatory markers [129].

The hyperactivity of the HPA axis and the consequent elevated systemic glucocorticoid levels is the potential second hit in the comorbid depression observed in diabetic patients [23,130,131]. Diabetes induced an increase in the levels of both corticosterone and its receptor in the hippocampus of rats [132,133]. Since the hippocampus is the major region of the central nervous system affected by depression, these data suggest that depressive disorder development and aggravation in diabetes may be related to hypercortisolism. In an in vitro model of diabetes-induced depression, using a hippocampal neurovascular unit (NVU) that contained hippocampal neurons, astrocytes, and microvascular endothelial cells from rats incubated in a hyperglycemic milieu, the activation of GR by corticosterone caused an impairment in the barrier function in clear association with neuronal apoptosis in the hippocampal NVU. This neuronal apoptosis in hippocampal NVU after the induction of diabetes-related depression in vitro was related to an activation of both GR and metabotropic glutamate receptor 2/3 (mGluR2/3) [4]. Interestingly, the treatment of *db/db* mice, a spontaneously murine model of type 2 diabetes, with metyrapone, which is a

corticosterone synthesis inhibitor, reduced systemic corticosterone levels in parallel to a decrease in hippocampal levels of pro-inflammatory cytokines IL-1 β and TNF- α and IBA1+ cells [134]. In addition, streptozotocin-induced diabetic mice showed a reduction in the astrocytic reactivity, attested by GFAP expression, in the hippocampus, which was sensitive to GR antagonist treatment [135]. Altogether, these data indicate that depressive disorder evoked by diabetes is related to a hypercortisolism-induced increase in the neuronal apoptosis and a reduction in astrocytic reactivity in the hippocampus (Figure 1).

In diabetic patients, hyperglycemia and low-grade inflammation are capable of disrupting the BBB, especially in the hippocampus region, and the epithelial–intestinal barrier [136–139]. Furthermore, glucocorticoid-induced brain damage is related to neuroinflammation. Although glucocorticoids suppress inflammation systemically, they can realize either pro- or anti-inflammatory actions in the brain, depending on the degree and duration of exposure, external factors preceding injury, injury characteristics, and the specific brain region [140,141]. For instance, if stress or glucocorticoid administration occurred prior to LPS injection directly into the hippocampus, it potentiated pro-neuroinflammatory effects of the LPS [142]. Chronic exposure to stress or glucocorticoid administration also potentiated LPS-induced neuroinflammation [143,144]. Glucocorticoids can also induce dysbiosis in parallel with a disruption in the epithelial–intestinal barrier, as observed in diabetics [11,135,145]. Altogether, the leak in both the epithelial–intestinal barrier and the BBB allows endotoxins, including LPS, present in the pathogenic bacteria that make up the intestinal microbiota of diabetics, to reach the hippocampus. In addition, the hippocampal neuronal apoptosis observed in diabetic mice was related to an increase in the expression of TLR4 [146] (Figure 1).

The biguanide metformin, which is a first-line drug for the treatment of type 2 diabetic patients, was effective in reducing depressive symptoms in non-diabetic and diabetic patients [147,148]. Interestingly, patients with type 2 diabetes treated with metformin showed alterations in the diversity of gut microbiota compared with those treated with a placebo, and the treatment significantly increased the concentrations of fecal SCFA, including propionate and butyrate, and plasma bile acids, such as primary, secondary, and unconjugated bile acids. The metformin-induced increase in these gut microbiota metabolites in type 2 diabetic patients was related to its antidiabetic effects [149]. The treatment with metformin also reduced the serum corticosterone levels in high-fat-diet-induced obese rats [150]. Furthermore, metformin improved LPS-induced depression in mice, through normalization of glutamatergic transmission in the hippocampal CA1 pyramidal neurons [151], suggesting that TLR4 activation in the hippocampus of diabetics by pathogenic products from the gut microbiota can be crucial for the aggravation of depression disorder. In addition, high glucose enhanced LPS-induced microglia activation in vitro, in clear association with an increase in TLR4 expression [152,153]. Interestingly, stimulation with LPS induced neuroinflammation, resulting in profound changes in the ultrastructure of NVU [154], as observed in diabetic mice [155,156], suggesting that TLR4 activation-induced neuroinflammation can increase the breakdown of BBB observed in diabetics. Moreover, diabetes increased LPS-induced depression behaviors and neuroinflammation in mice [157].

Finally, there is a close association between HPA axis disruption [158], uncontrolled inflammatory response [98,159], increased glutamate signaling [160] and, more recently, gut dysbiosis [161,162] in the development antidepressant therapy failure. Remarkably, some studies have suggested that hypercortisolism is an important factor associated with treatment-resistant unipolar depression. Furthermore, the highly resistant depressed patients showed an impaired response of the HPA axis to prednisolone and mineralocorticoid receptor antagonist, suggesting that there was a malfunctioning of the GRs and MRs [163,164]. Importantly, the increase in bacterial translocation, attested by measurement of 16S rRNA subunits of intestinal microbiota in the blood plasma, and in the immune response to LPS, including a rise in circulating pro-inflammatory cytokine levels and up-regulation of TLR4 signaling in peripheral mononuclear blood cells, was observed in patients with MDD [165–167]. Altogether, this evidence strongly suggests that both

HPA axis hyperactivity and gut dysbiosis play an important role in the development of treatment-resistant depression observed in diabetic patients who have developed depressive disorders.

5. Conclusions

We postulate that hypercortisolism acts as a second hit in the onset of comorbid depression observed in diabetic patients, through an induction of neuroinflammation and an increase in glutamatergic transmission in the hippocampus. Furthermore, hypercortisolism in diabetes may be important to the development of dysbiosis and the break-down of the epithelial–intestinal barrier with consequent translocation of pathogenic bacterial products, such as LPS, into the bloodstream. Possibly, the activation of TLR4 in the hippocampus of diabetics induces an exacerbation in the neuroinflammation and glutamatergic transmission, resulting in the aggravation of depressive symptoms and in the development of the treatment-resistant depression (Figure 2). In this respect, new therapeutic strategies founded on the normalization of HPA axis activity and/or gut microbiota seem to be potentially practical approaches for adjuvant treatment of comorbid depressive disorder in diabetic patients.

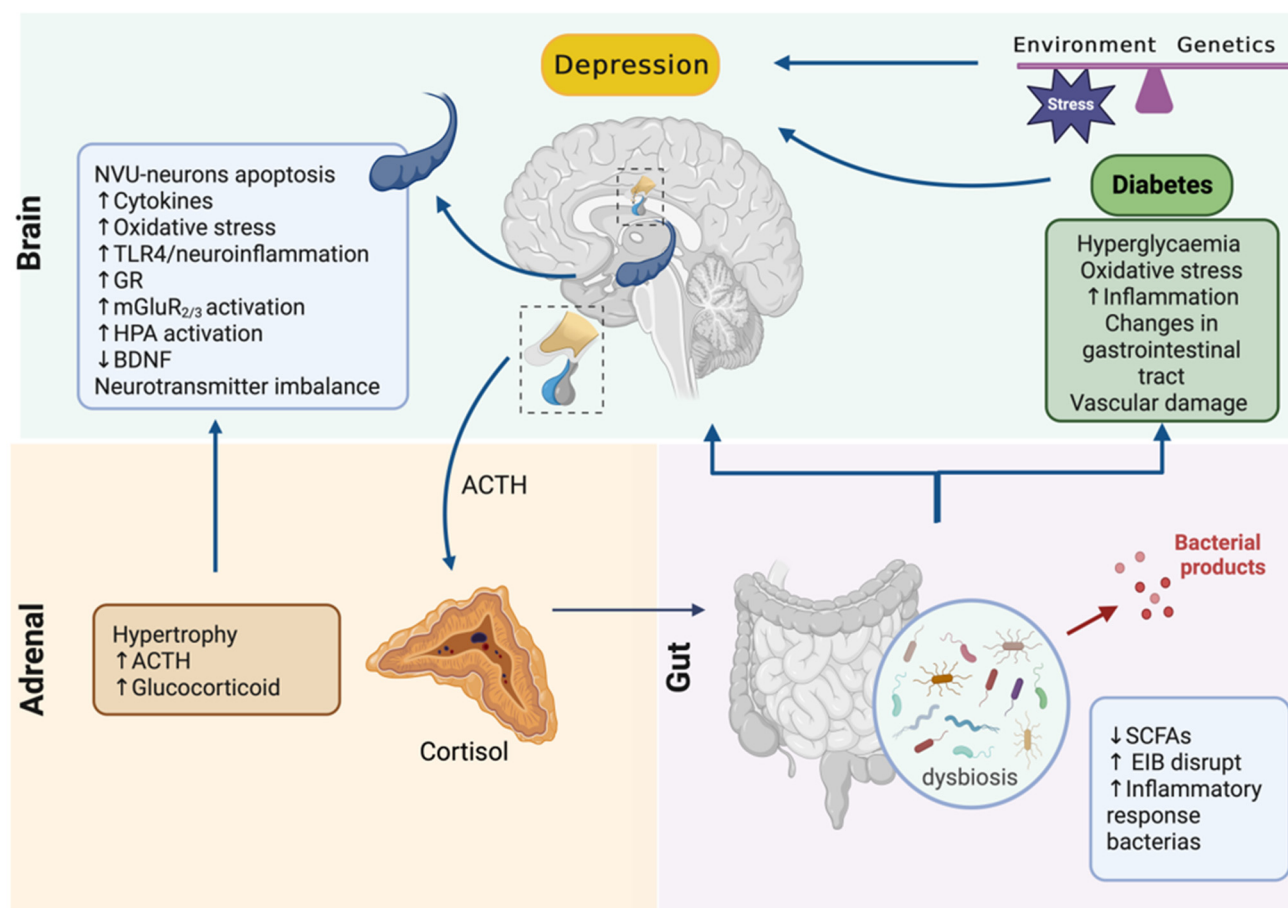


Figure 2. Adrenal–gut–brain axis imbalance contributes to aggravation of diabetes-related depression. In diabetes, hyperglycemia and hypercortisolism are associated with gut microbiota dysbiosis, as well as with changes in the central nervous system. Furthermore, the dysbiosis favors disruption of the endothelial intestinal barrier and the translocation of bacterial products into the blood, activating inflammatory signaling pathways. In the central nervous system, alterations in the physiology of the hippocampus are observed, associated with an imbalance in the neurotransmitters and a decrease in BDNF levels. Together, the exacerbation of neuroinflammation and glutamatergic transmission in the brain results in the worsening of depressive symptoms and the development of the treatment-resistant depression in diabetic patients.

Author Contributions: V.F.C. conceived of the presented idea; T.M.-d.-O., B.T.S., P.C.-C. and V.F.C. wrote the manuscript; and T.M.-d.-O. and P.C.-C. designed the figures. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by CNPq (302791/2022-1) and Faperj (E-26/200.951/2022 and E-26/200.341/2023) and the APC was funded by Oswaldo Cruz Institute/Fiocruz.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sun, H.; Saeedi, P.; Karuranga, S.; Pinkepank, M.; Ogurtsova, K.; Duncan, B.B.; Stein, C.; Basit, A.; Chan, J.C.N.; Mbanya, J.C.; et al. IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045. *Diabetes Res. Clin. Pract.* **2022**, *183*, 109119. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Fiedorowicz, J.G.; Palagummi, N.M.; Forman-Hoffman, V.L.; Miller, D.D.; Haynes, W.G. Elevated Prevalence of Obesity, Metabolic Syndrome, and Cardiovascular Risk Factors in Bipolar Disorder. *Ann. Clin. Psychiatry* **2008**, *20*, 131–137. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Fiedorowicz, J.G.; He, J.; Merikangas, K.R. The Association between Mood and Anxiety Disorders with Vascular Diseases and Risk Factors in a Nationally Representative Sample. *J. Psychosom. Res.* **2011**, *70*, 145–154. [\[CrossRef\]](#)
4. Liu, J.; Han, Y.-S.; Liu, L.; Tang, L.; Yang, H.; Meng, P.; Zhao, H.-Q.; Wang, Y.-H. Abnormal Glu/MGluR2/3/PI3K Pathway in the Hippocampal Neurovascular Unit Leads to Diabetes-Related Depression. *Neural Regen. Res.* **2021**, *16*, 727–733. [\[CrossRef\]](#)
5. Borbély, É.; Simon, M.; Fuchs, E.; Wiborg, O.; Czéh, B.; Helyes, Z. Novel Drug Developmental Strategies for Treatment-Resistant Depression. *Br. J. Pharmacol.* **2022**, *179*, 1146–1186. [\[CrossRef\]](#)
6. Bryan, C.; Songer, T.; Brooks, M.M.; Rush, A.J.; Thase, M.E.; Gaynes, B.; Balasubramani, G.K.; Trivedi, M.H.; Fava, M.; Wisniewski, S.R. The Impact of Diabetes on Depression Treatment Outcomes. *Gen. Hosp. Psychiatry* **2010**, *32*, 33–41. [\[CrossRef\]](#)
7. Zhou, X.-Y.; Zhang, F.; Hu, X.-T.; Chen, J.; Tang, R.-X.; Zheng, K.-Y.; Song, Y.-J. Depression Can Be Prevented by Astaxanthin through Inhibition of Hippocampal Inflammation in Diabetic Mice. *Brain Res.* **2017**, *1657*, 262–268. [\[CrossRef\]](#)
8. Ergenc, M.; Ozacmak, H.S.; Turan, I.; Ozacmak, V.H. Melatonin Reverses Depressive and Anxiety Like-Behaviours Induced by Diabetes: Involvement of Oxidative Stress, Age, Rage and S100B Levels in the Hippocampus and Prefrontal Cortex of Rats. *Arch. Physiol. Biochem.* **2022**, *128*, 402–410. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Gupta, D.; Thangaraj, D.; Radhakrishnan, M. A Novel 5HT3 Antagonist 4i (N-(3-Chloro-2-Methylphenyl)Quinoxalin-2-Carboxamide) Prevents Diabetes-Induced Depressive Phenotypes in Mice: Modulation of Serotonergic System. *Behav. Brain Res.* **2016**, *297*, 41–50. [\[CrossRef\]](#)
10. Moosaie, F.; Mohammadi, S.; Saghaideh, A.; Dehghani Firouzabadi, F.; Rezaei, N. Brain-Derived Neurotrophic Factor in Diabetes Mellitus: A Systematic Review and Meta-Analysis. *PLoS ONE* **2023**, *18*, e0268816. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Zhang, J.; Feng, D.; Law, H.K.-W.; Wu, Y.; Zhu, G.-H.; Huang, W.-Y.; Kang, Y. Integrative Analysis of Gut Microbiota and Fecal Metabolites in Rats after Prednisone Treatment. *Microbiol. Spectr.* **2021**, *9*, e0065021. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Wu, T.; Yang, L.; Jiang, J.; Ni, Y.; Zhu, J.; Zheng, X.; Wang, Q.; Lu, X.; Fu, Z. Chronic Glucocorticoid Treatment Induced Circadian Clock Disorder Leads to Lipid Metabolism and Gut Microbiota Alterations in Rats. *Life Sci* **2018**, *192*, 173–182. [\[CrossRef\]](#)
13. Ergang, P.; Vagnerová, K.; Hermanová, P.; Vodička, M.; Jágr, M.; Šrůtková, D.; Dvořáček, V.; Hudcovic, T.; Pácha, J. The Gut Microbiota Affects Corticosterone Production in the Murine Small Intestine. *Int. J. Mol. Sci.* **2021**, *22*, 4229. [\[CrossRef\]](#)
14. Speer, K.E.; Semple, S.; Naumovski, N.; D’Cunha, N.M.; McKune, A.J. HPA Axis Function and Diurnal Cortisol in Post-Traumatic Stress Disorder: A Systematic Review. *Neurobiol. Stress* **2019**, *11*, 100180. [\[CrossRef\]](#)
15. Sekirov, I.; Russell, S.L.; Antunes, L.C.M.; Finlay, B.B. Gut Microbiota in Health and Disease. *Physiol. Rev.* **2010**, *90*, 859–904. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Deng, Y.; Zhou, M.; Wang, J.; Yao, J.; Yu, J.; Liu, W.; Wu, L.; Wang, J.; Gao, R. Involvement of the Microbiota-Gut-Brain Axis in Chronic Restraint Stress: Disturbances of the Kynurenine Metabolic Pathway in Both the Gut and Brain. *Gut Microbes* **2021**, *13*, 1869501. [\[CrossRef\]](#) [\[PubMed\]](#)
17. O’Mahony, S.M.; Marchesi, J.R.; Scully, P.; Codling, C.; Ceolho, A.-M.; Quigley, E.M.M.; Cryan, J.F.; Dinan, T.G. Early Life Stress Alters Behavior, Immunity, and Microbiota in Rats: Implications for Irritable Bowel Syndrome and Psychiatric Illnesses. *Biol. Psychiatry* **2009**, *65*, 263–267. [\[CrossRef\]](#)
18. Jahnke, J.R.; Roach, J.; Azcarate-Peril, M.A.; Thompson, A.L. Maternal Precarity and HPA Axis Functioning Shape Infant Gut Microbiota and HPA Axis Development in Humans. *PLoS ONE* **2021**, *16*, e0251782. [\[CrossRef\]](#)
19. Clarke, G.; Grenham, S.; Scully, P.; Fitzgerald, P.; Moloney, R.D.; Shanahan, F.; Dinan, T.G.; Cryan, J.F. The Microbiome-Gut-Brain Axis during Early Life Regulates the Hippocampal Serotonergic System in a Sex-Dependent Manner. *Mol. Psychiatry* **2013**, *18*, 666–673. [\[CrossRef\]](#)

20. Sudo, N.; Chida, Y.; Aiba, Y.; Sonoda, J.; Oyama, N.; Yu, X.-N.; Kubo, C.; Koga, Y. Postnatal Microbial Colonization Programs the Hypothalamic-Pituitary-Adrenal System for Stress Response in Mice: Commensal Microbiota and Stress Response. *J. Physiol.* **2004**, *558*, 263–275. [\[CrossRef\]](#)
21. Chan, O.; Chan, S.; Inouye, K.; Vranic, M.; Matthews, S.G. Molecular Regulation of the Hypothalamo-Pituitary-Adrenal Axis in Streptozotocin-Induced Diabetes: Effects of Insulin Treatment. *Endocrinology* **2001**, *142*, 4872–4879. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Allin, K.H.; Nielsen, T.; Pedersen, O. Mechanisms in Endocrinology: Gut Microbiota in Patients with Type 2 Diabetes Mellitus. *Eur. J. Endocrinol.* **2015**, *172*, R167–R177. [\[CrossRef\]](#)
23. Joseph, J.J.; Golden, S.H. Cortisol Dysregulation: The Bidirectional Link between Stress, Depression, and Type 2 Diabetes Mellitus. *Ann. N. Y. Acad. Sci.* **2017**, *1391*, 20–34. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Farzi, A.; Hassan, A.M.; Zenz, G.; Holzer, P. Diabetes and Mood Disorders: Multiple Links through the Microbiota-Gut-Brain Axis. *Mol. Asp. Med.* **2019**, *66*, 80–93. [\[CrossRef\]](#)
25. Levy, M.; Kolodziejczyk, A.A.; Thaïs, C.A.; Elinav, E. Dysbiosis and the Immune System. *Nat. Rev. Immunol.* **2017**, *17*, 219–232. [\[CrossRef\]](#)
26. Sagara, R.; Inoue, T.; Sonoda, N.; Yano, C.; Motoya, M.; Umakoshi, H.; Sakamoto, R.; Ogawa, Y. Association between Cortisol and Left Ventricular Diastolic Dysfunction in Patients with Diabetes Mellitus. *J. Diabetes Investig.* **2022**, *13*, 344–350. [\[CrossRef\]](#)
27. Roy, M.S.; Roy, A.; Brown, S. Increased Urinary-Free Cortisol Outputs in Diabetic Patients. *J. Diabetes Its Complicat.* **1998**, *12*, 24–27. [\[CrossRef\]](#)
28. Chiodini, I.; Adda, G.; Scillitani, A.; Coletti, F.; Morelli, V.; Di Lembo, S.; Epaminonda, P.; Masserini, B.; Beck-Peccoz, P.; Orsi, E.; et al. Cortisol Secretion in Patients With Type 2 Diabetes. *Diabetes Care* **2007**, *30*, 83–88. [\[CrossRef\]](#)
29. Roy, M.S.; Roy, A.; Gallucci, W.T.; Collier, B.; Young, K.; Kamilaris, T.C.; Chrousos, G.P. The Ovine Corticotropin-Releasing Hormone-Stimulation Test in Type I Diabetic Patients and Controls: Suggestion of Mild Chronic Hypercortisolism. *Metabolism* **1993**, *42*, 696–700. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Chan, O.; Inouye, K.; Vranic, M.; Matthews, S.G. Hyperactivation of the Hypothalamo-Pituitary-Adrenocortical Axis in Streptozotocin-Diabetes Is Associated with Reduced Stress Responsiveness and Decreased Pituitary and Adrenal Sensitivity. *Endocrinology* **2002**, *143*, 1761–1768. [\[CrossRef\]](#)
31. Kim, S.; Park, E.S.; Chen, P.R.; Kim, E. Dysregulated Hypothalamic-Pituitary-Adrenal Axis Is Associated With Increased Inflammation and Worse Outcomes After Ischemic Stroke in Diabetic Mice. *Front. Immunol.* **2022**, *13*, 864858. [\[CrossRef\]](#)
32. Carvalho, V.F.; Barreto, E.O.; Diaz, B.L.; Serra, M.F.; Azevedo, V.; Cordeiro, R.S.B.; Martins, M.A.; Silva, P.M.R.E. Systemic Anaphylaxis Is Prevented in Alloxan-Diabetic Rats by a Mechanism Dependent on Glucocorticoids. *Eur. J. Pharmacol.* **2003**, *472*, 221–227. [\[CrossRef\]](#)
33. Torres, R.C.; Prevatto, J.P.; Martins, M.A.; Carvalho, V.F. From Type-1 Diabetes HPA Axis to the Disease Complications. *J. Diabetes Metab.* **2013**, *S12*, 1–8. [\[CrossRef\]](#)
34. Silva, P.M.R.E.; Carvalho, V.F.; Cordeiro, R.S.B.; Martins, M.A. Down-Regulation of Allergic Responses in Conditions of Experimental Diabetes: A Role for Glucocorticoids? *Neuroimmunomodulation* **2009**, *16*, 13–18. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Chaves, A.D.S.; Magalhães, N.S.; Insuela, D.B.R.; Silva, P.M.R.E.; Martins, M.A.; Carvalho, V.F. Effect of the Renin-Angiotensin System on the Exacerbation of Adrenal Glucocorticoid Steroidogenesis in Diabetic Mice: Role of Angiotensin-II Type 2 Receptor. *Front. Endocrinol.* **2022**, *13*, 1040040. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Torres, R.C.; Magalhães, N.S.; Silva, P.M.R.E.; Martins, M.A.; Carvalho, V.F. Activation of PPAR- γ Reduces HPA Axis Activity in Diabetic Rats by up-Regulating PI3K Expression. *Exp. Mol. Pathol.* **2016**, *101*, 290–301. [\[CrossRef\]](#)
37. Donath, M.Y.; Dinarello, C.A.; Mandrup-Poulsen, T. Targeting Innate Immune Mediators in Type 1 and Type 2 Diabetes. *Nat. Rev. Immunol.* **2019**, *19*, 734–746. [\[CrossRef\]](#)
38. Scheithauer, T.P.M.; Rampanelli, E.; Nieuwdorp, M.; Vallance, B.A.; Verchere, C.B.; Van Raalte, D.H.; Herrema, H. Gut Microbiota as a Trigger for Metabolic Inflammation in Obesity and Type 2 Diabetes. *Front. Immunol.* **2020**, *11*, 571731. [\[CrossRef\]](#)
39. Qin, J.; Li, Y.; Cai, Z.; Li, S.; Zhu, J.; Zhang, F.; Liang, S.; Zhang, W.; Guan, Y.; Shen, D.; et al. A Metagenome-Wide Association Study of Gut Microbiota in Type 2 Diabetes. *Nature* **2012**, *490*, 55–60. [\[CrossRef\]](#)
40. Karlsson, F.H.; Tremaroli, V.; Nookaew, I.; Bergström, G.; Behre, C.J.; Fagerberg, B.; Nielsen, J.; Bäckhed, F. Gut Metagenome in European Women with Normal, Impaired and Diabetic Glucose Control. *Nature* **2013**, *498*, 99–103. [\[CrossRef\]](#)
41. Larsen, N.; Vogensen, F.K.; Van Den Berg, F.W.J.; Nielsen, D.S.; Andreasen, A.S.; Pedersen, B.K.; Al-Soud, W.A.; Sørensen, S.J.; Hansen, L.H.; Jakobsen, M. Gut Microbiota in Human Adults with Type 2 Diabetes Differs from Non-Diabetic Adults. *PLoS ONE* **2010**, *5*, e9085. [\[CrossRef\]](#)
42. Durazzo, M.; Ferro, A.; Gruden, G. Gastrointestinal Microbiota and Type 1 Diabetes Mellitus: The State of Art. *J. Clin. Med.* **2019**, *8*, 1843. [\[CrossRef\]](#)
43. Demirci, M.; Bahar Tokman, H.; Taner, Z.; Keskin, F.E.; Çağatay, P.; Ozturk Bakar, Y.; Özyazar, M.; Kiraz, N.; Kocazeybek, B.S. Bacteroidetes and Firmicutes Levels in Gut Microbiota and Effects of Hosts TLR2/TLR4 Gene Expression Levels in Adult Type 1 Diabetes Patients in Istanbul, Turkey. *J. Diabetes Complicat.* **2020**, *34*, 107449. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Radwan, S.; Gilfillan, D.; Eklund, B.; Radwan, H.M.; El Menofy, N.G.; Lee, J.; Kapuscinski, M.; Abdo, Z. A Comparative Study of the Gut Microbiome in Egyptian Patients with Type I and Type II Diabetes. *PLoS ONE* **2020**, *15*, e0238764. [\[CrossRef\]](#)
45. Zhou, H.; Zhao, X.; Sun, L.; Liu, Y.; Lv, Y.; Gang, X.; Wang, G. Gut Microbiota Profile in Patients with Type 1 Diabetes Based on 16S rRNA Gene Sequencing: A Systematic Review. *Dis. Markers* **2020**, *2020*, 3936247. [\[CrossRef\]](#)

46. Ejtahed, H.-S.; Hoseini-Tavassol, Z.; Khatami, S.; Zangeneh, M.; Behrouzi, A.; Ahmadi Badi, S.; Moshiri, A.; Hasani-Ranjbar, S.; Soroush, A.-R.; Vaziri, F.; et al. Main Gut Bacterial Composition Differs between Patients with Type 1 and Type 2 Diabetes and Non-Diabetic Adults. *J. Diabetes Metab. Disord.* **2020**, *19*, 265–271. [\[CrossRef\]](#)
47. Guilloteau, P.; Martin, L.; Eeckhaut, V.; Ducatelle, R.; Zabielski, R.; Van Immerseel, F. From the Gut to the Peripheral Tissues: The Multiple Effects of Butyrate. *Nutr. Res. Rev.* **2010**, *23*, 366–384. [\[CrossRef\]](#)
48. Ochocińska, A.; Wysocka-Mincewicz, M.; Groszek, A.; Rybak, A.; Konopka, E.; Bierła, J.B.; Trojanowska, I.; Szalecki, M.; Cukrowska, B. Could I-FABP Be an Early Marker of Celiac Disease in Children with Type 1 Diabetes? Retrospective Study from the Tertiary Reference Centre. *Nutrients* **2022**, *14*, 414. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Yuan, J.-H.; Xie, Q.-S.; Chen, G.-C.; Huang, C.-L.; Yu, T.; Chen, Q.-K.; Li, J.-Y. Impaired Intestinal Barrier Function in Type 2 Diabetic Patients Measured by Serum LPS, Zonulin, and IFABP. *J. Diabetes Its Complicat.* **2021**, *35*, 107766. [\[CrossRef\]](#)
50. Nighot, M.; Rawat, M.; Al-Sadi, R.; Castillo, E.F.; Nighot, P.; Ma, T.Y. Lipopolysaccharide-Induced Increase in Intestinal Permeability Is Mediated by TAK-1 Activation of IKK and MLCK/MYLK Gene. *Am. J. Pathol.* **2019**, *189*, 797–812. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Guo, S.; Al-Sadi, R.; Said, H.M.; Ma, T.Y. Lipopolysaccharide Causes an Increase in Intestinal Tight Junction Permeability in Vitro and in Vivo by Inducing Enterocyte Membrane Expression and Localization of TLR-4 and CD14. *Am. J. Pathol.* **2013**, *182*, 375–387. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Gomes, J.M.G.; de Assis Costa, J.; Alfenas, R.d.C.G. Metabolic Endotoxemia and Diabetes Mellitus: A Systematic Review. *Metabolism* **2017**, *68*, 133–144. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Jayashree, B.; Bibin, Y.S.; Prabhu, D.; Shanthirani, C.S.; Gokulakrishnan, K.; Lakshmi, B.S.; Mohan, V.; Balasubramanyam, M. Increased Circulatory Levels of Lipopolysaccharide (LPS) and Zonulin Signify Novel Biomarkers of Proinflammation in Patients with Type 2 Diabetes. *Mol. Cell. Biochem.* **2014**, *388*, 203–210. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Amar, J.; Chabo, C.; Waget, A.; Klopp, P.; Vachoux, C.; Bermúdez-Humarán, L.G.; Smirnova, N.; Bergé, M.; Sulpice, T.; Lahtinen, S.; et al. Intestinal Mucosal Adherence and Translocation of Commensal Bacteria at the Early Onset of Type 2 Diabetes: Molecular Mechanisms and Probiotic Treatment. *EMBO Mol. Med.* **2011**, *3*, 559–572. [\[CrossRef\]](#)
55. Snelson, M.; De Pasquale, C.; Ekinci, E.I.; Coughlan, M.T. Gut Microbiome, Prebiotics, Intestinal Permeability and Diabetes Complications. *Best Pract. Res. Clin. Endocrinol. Metab.* **2021**, *35*, 101507. [\[CrossRef\]](#)
56. Lim, G.Y.; Tam, W.W.; Lu, Y.; Ho, C.S.; Zhang, M.W.; Ho, R.C. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Sci. Rep.* **2018**, *8*, 2861. [\[CrossRef\]](#)
57. Friedrich, M.J. Depression Is the Leading Cause of Disability around the World. *JAMA* **2017**, *317*, 1517. [\[CrossRef\]](#)
58. McIntyre, R.S.; Millson, B.; Power, G.S. Burden of Treatment Resistant Depression (TRD) in Patients with Major Depressive Disorder in Ontario Using Institute for Clinical Evaluative Sciences (ICES) Databases: Economic Burden and Healthcare Resource Utilization. *J. Affect. Disord.* **2020**, *277*, 30–38. [\[CrossRef\]](#)
59. Arnaud, A.; Benner, J.; Suthoff, E.; Werneburg, B.; Reinhart, M.; Sussman, M.; Kessler, R.C. The Impact of Early Remission on Disease Trajectory and Patient Outcomes in Major Depression Disorder (MDD): A Targeted Literature Review and Microsimulation Modeling Approach Based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study. *J. Affect. Disord.* **2023**, *325*, 264–272. [\[CrossRef\]](#)
60. Zajkowska, Z.; Walsh, A.; Zonca, V.; Gullett, N.; Pedersen, G.A.; Kieling, C.; Swartz, J.R.; Karmacharya, R.; Fisher, H.L.; Kohrt, B.A.; et al. A Systematic Review of the Association between Biological Markers and Environmental Stress Risk Factors for Adolescent Depression. *J. Psychiatr. Res.* **2021**, *138*, 163–175. [\[CrossRef\]](#)
61. Gonda, X.; Petschner, P.; Eszlari, N.; Baksa, D.; Edes, A.; Antal, P.; Juhasz, G.; Bagdy, G. Genetic Variants in Major Depressive Disorder: From Pathophysiology to Therapy. *Pharmacol. Ther.* **2019**, *194*, 22–43. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Bădescu, S.V.; Tătaru, C.; Kobylinska, L.; Georgescu, E.L.; Zăhău, D.M.; Zăgrean, A.M.; Zăgrean, L. The Association between Diabetes Mellitus and Depression. *J. Med. Life* **2016**, *9*, 120–125. [\[PubMed\]](#)
63. OuYang, H.; Chen, B.; Abdulrahman, A.-M.; Li, L.; Wu, N. Associations between Gestational Diabetes and Anxiety or Depression: A Systematic Review. *J. Diabetes Res.* **2021**, *2021*, 9959779. [\[CrossRef\]](#)
64. Barch, D.M.; Tillman, R.; Kelly, D.; Whalen, D.; Gilbert, K.; Luby, J.L. Hippocampal Volume and Depression among Young Children. *Psychiatry Res. Neuroimaging* **2019**, *288*, 21–28. [\[CrossRef\]](#)
65. Bremner, J.D.; Narayan, M.; Anderson, E.R.; Staib, L.H.; Miller, H.L.; Charney, D.S. Hippocampal Volume Reduction in Major Depression. *Am. J. Psychiatry* **2000**, *157*, 115–118. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Stockmeier, C.A.; Mahajan, G.J.; Konick, L.C.; Overholser, J.C.; Jurjus, G.J.; Meltzer, H.Y.; Uylings, H.B.M.; Friedman, L.; Rajkowska, G. Cellular Changes in the Postmortem Hippocampus in Major Depression. *Biol. Psychiatry* **2004**, *56*, 640–650. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Czéh, B.; Lucassen, P.J. What Causes the Hippocampal Volume Decrease in Depression? Are Neurogenesis, Glial Changes and Apoptosis Implicated? *Eur. Arch. Psychiatry Clin. Neurosci.* **2007**, *257*, 250–260. [\[CrossRef\]](#)
68. Willard, S.L.; Riddle, D.R.; Forbes, M.E.; Shively, C.A. Cell Number and Neuropil Alterations in Subregions of the Anterior Hippocampus in a Female Monkey Model of Depression. *Biol. Psychiatry* **2013**, *74*, 890–897. [\[CrossRef\]](#)
69. Chen, F.; Bertelsen, A.B.; Holm, I.E.; Nyengaard, J.R.; Rosenberg, R.; Dorph-Petersen, K.-A. Hippocampal Volume and Cell Number in Depression, Schizophrenia, and Suicide Subjects. *Brain Res.* **2020**, *1727*, 146546. [\[CrossRef\]](#)

70. Beauquis, J.; Roig, P.; De Nicola, A.F.; Saravia, F. Neuronal Plasticity and Antidepressants in the Diabetic Brain. *Ann. N. Y. Acad. Sci.* **2009**, *1153*, 203–208. [\[CrossRef\]](#)
71. Czéh, B.; Michaelis, T.; Watanabe, T.; Frahm, J.; de Biurrun, G.; van Kampen, M.; Bartolomucci, A.; Fuchs, E. Stress-Induced Changes in Cerebral Metabolites, Hippocampal Volume, and Cell Proliferation Are Prevented by Antidepressant Treatment with Tianeptine. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 12796–12801. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Li, Y.-F. A Hypothesis of Monoamine (5-HT)-Glutamate/GABA Long Neural Circuit: Aiming for Fast-Onset Antidepressant Discovery. *Pharmacol. Ther.* **2020**, *208*, 107494. [\[CrossRef\]](#)
73. Zhang, K.; Wang, F.; Zhai, M.; He, M.; Hu, Y.; Feng, L.; Li, Y.; Yang, J.; Wu, C. Hyperactive Neuronal Autophagy Depletes BDNF and Impairs Adult Hippocampal Neurogenesis in a Corticosterone-Induced Mouse Model of Depression. *Theranostics* **2023**, *13*, 1059–1075. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Jung, S.; Choe, S.; Woo, H.; Jeong, H.; An, H.-K.; Moon, H.; Ryu, H.Y.; Yeo, B.K.; Lee, Y.W.; Choi, H.; et al. Autophagic Death of Neural Stem Cells Mediates Chronic Stress-Induced Decline of Adult Hippocampal Neurogenesis and Cognitive Deficits. *Autophagy* **2020**, *16*, 512–530. [\[CrossRef\]](#)
75. Wang, Y.-L.; Wu, H.-R.; Zhang, S.-S.; Xiao, H.-L.; Yu, J.; Ma, Y.-Y.; Zhang, Y.-D.; Liu, Q. Catalpol Ameliorates Depressive-like Behaviors in CUMS Mice via Oxidative Stress-Mediated NLRP3 Inflammasome and Neuroinflammation. *Transl. Psychiatry* **2021**, *11*, 353. [\[CrossRef\]](#)
76. Troubat, R.; Barone, P.; Leman, S.; Desmidt, T.; Cressant, A.; Atanasova, B.; Brizard, B.; El Hage, W.; Surget, A.; Belzung, C.; et al. Neuroinflammation and Depression: A Review. *Eur. J. Neurosci.* **2021**, *53*, 151–171. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Herbison, C.E.; Allen, K.; Robinson, M.; Newnham, J.; Pennell, C. The Impact of Life Stress on Adult Depression and Anxiety Is Dependent on Gender and Timing of Exposure. *Dev. Psychopathol.* **2017**, *29*, 1443–1454. [\[CrossRef\]](#)
78. Wulsin, A.C.; Wick-Carlson, D.; Packard, B.A.; Morano, R.; Herman, J.P. Adolescent Chronic Stress Causes Hypothalamo-Pituitary-Adrenocortical Hypo-Responsiveness and Depression-like Behavior in Adult Female Rats. *Psychoneuroendocrinology* **2016**, *65*, 109–117. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Young, E.A.; Haskett, R.F.; Murphy-Weinberg, V.; Watson, S.J.; Akil, H. Loss of Glucocorticoid Fast Feedback in Depression. *Arch. Gen. Psychiatry* **1991**, *48*, 693–699. [\[CrossRef\]](#)
80. Anacker, C.; Zunszain, P.A.; Carvalho, L.A.; Pariante, C.M. The Glucocorticoid Receptor: Pivot of Depression and of Antidepressant Treatment? *Psychoneuroendocrinology* **2011**, *36*, 415–425. [\[CrossRef\]](#)
81. Kahl, K.G.; Schweiger, U.; Pars, K.; Kunikowska, A.; Deuschle, M.; Gutberlet, M.; Lichtinghagen, R.; Bleich, S.; Hüper, K.; Hartung, D. Adrenal Gland Volume, Intra-Abdominal and Pericardial Adipose Tissue in Major Depressive Disorder. *Psychoneuroendocrinology* **2015**, *58*, 1–8. [\[CrossRef\]](#)
82. Druzhkova, T.A.; Yakovlev, A.A.; Rider, F.K.; Zinchuk, M.S.; Guekht, A.B.; Gulyaeva, N.V. Elevated Serum Cortisol Levels in Patients with Focal Epilepsy, Depression, and Comorbid Epilepsy and Depression. *Int. J. Mol. Sci.* **2022**, *23*, 10414. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Sorgdrager, F.J.H.; Doornbos, B.; Penninx, B.W.J.H.; de Jonge, P.; Kema, I.P. The Association between the Hypothalamic Pituitary Adrenal Axis and Tryptophan Metabolism in Persons with Recurrent Major Depressive Disorder and Healthy Controls. *J. Affect. Disord.* **2017**, *222*, 32–39. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Jia, Y.; Liu, L.; Sheng, C.; Cheng, Z.; Cui, L.; Li, M.; Zhao, Y.; Shi, T.; Yau, T.O.; Li, F.; et al. Increased Serum Levels of Cortisol and Inflammatory Cytokines in People With Depression. *J. Nerv. Ment. Dis.* **2019**, *207*, 271–276. [\[CrossRef\]](#)
85. Lee, E.-H.; Park, J.-Y.; Kwon, H.-J.; Han, P.-L. Repeated Exposure with Short-Term Behavioral Stress Resolves Pre-Existing Stress-Induced Depressive-like Behavior in Mice. *Nat. Commun.* **2021**, *12*, 6682. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Kim, J.B.; Ju, J.Y.; Kim, J.H.; Kim, T.-Y.; Yang, B.-H.; Lee, Y.-S.; Son, H. Dexamethasone Inhibits Proliferation of Adult Hippocampal Neurogenesis in Vivo and in Vitro. *Brain Res.* **2004**, *1027*, 1–10. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Sapolsky, R.M. The Possibility of Neurotoxicity in the Hippocampus in Major Depression: A Primer on Neuron Death. *Biol. Psychiatry* **2000**, *48*, 755–765. [\[CrossRef\]](#)
88. David, D.J.; Samuels, B.A.; Rainer, Q.; Wang, J.-W.; Marsteller, D.; Mendez, I.; Drew, M.; Craig, D.A.; Guiard, B.P.; Guilloux, J.-P.; et al. Neurogenesis-Dependent and -Independent Effects of Fluoxetine in an Animal Model of Anxiety/Depression. *Neuron* **2009**, *62*, 479–493. [\[CrossRef\]](#)
89. Tanapat, P.; Galea, L.A.; Gould, E. Stress Inhibits the Proliferation of Granule Cell Precursors in the Developing Dentate Gyrus. *Int. J. Dev. Neurosci.* **1998**, *16*, 235–239. [\[CrossRef\]](#)
90. Boulle, F.; Velthuis, H.; Koedam, K.; Steinbusch, H.W.; van den Hove, D.L.A.; Kenis, G.; Gabriel, C.; Mocaer, E.; Franc, B.; Rognan, D.; et al. Behavioral and Neurochemical Characterization of TrkB-Dependent Mechanisms of Agomelatine in Glucocorticoid Receptor-Impaired Mice. *Eur. Neuropsychopharmacol.* **2016**, *26*, 65–77. [\[CrossRef\]](#)
91. Oglodek, E.A. Changes in the Serum Concentration Levels of Serotonin, Tryptophan and Cortisol among Stress-Resilient and Stress-Susceptible Individuals after Experiencing Traumatic Stress. *Int. J. Environ. Res. Public Health* **2022**, *19*, 16517. [\[CrossRef\]](#) [\[PubMed\]](#)
92. D'Elia, A.T.D.; Jurueña, M.F.; Coimbra, B.M.; Mello, M.F.; Mello, A.F. Increased Immuno-Inflammatory Mediators in Women with Post-Traumatic Stress Disorder after Sexual Assault: 1-Year Follow-Up. *J. Psychiatr. Res.* **2022**, *155*, 241–251. [\[CrossRef\]](#) [\[PubMed\]](#)
93. Oganessian, L.P.; Mkrtchyan, G.M.; Sukiasyan, S.H.; Boyajyan, A.S. Classic and Alternative Complement Cascades in Post-Traumatic Stress Disorder. *Bull. Exp. Biol. Med.* **2009**, *148*, 859–861. [\[CrossRef\]](#) [\[PubMed\]](#)

94. Wang, W.; Wang, L.; Xu, H.; Cao, C.; Liu, P.; Luo, S.; Duan, Q.; Ellenbroek, B.; Zhang, X. Characteristics of Pro- and Anti-Inflammatory Cytokines Alteration in PTSD Patients Exposed to a Deadly Earthquake. *J. Affect. Disord.* **2019**, *248*, 52–58. [\[CrossRef\]](#) [\[PubMed\]](#)
95. Küffer, A.; Straus, L.D.; Prather, A.A.; Inslicht, S.S.; Richards, A.; Shigenaga, J.K.; Madden, E.; Metzler, T.J.; Neylan, T.C.; O'Donovan, A. Altered Overnight Levels of Pro-Inflammatory Cytokines in Men and Women with Posttraumatic Stress Disorder. *Psychoneuroendocrinology* **2019**, *102*, 114–120. [\[CrossRef\]](#)
96. Koirala, R.; Aass, H.C.D.; Søggaard, E.G.I.; Dhakal, H.P.; Ojha, S.P.; Hauff, E.; Thapa, S.B. Association of Pro-Inflammatory Cytokines with Trauma and Post-Traumatic Stress Disorder Visiting a Tertiary Care Hospital in Kathmandu. *PLoS ONE* **2023**, *18*, e0281125. [\[CrossRef\]](#)
97. Wang, Z.; Mandel, H.; Levingston, C.A.; Young, M.R.I. An Exploratory Approach Demonstrating Immune Skewing and a Loss of Coordination among Cytokines in Plasma and Saliva of Veterans with Combat-Related PTSD. *Hum. Immunol.* **2016**, *77*, 652–657. [\[CrossRef\]](#)
98. Strawbridge, R.; Hodsoll, J.; Powell, T.R.; Hotopf, M.; Hatch, S.L.; Breen, G.; Cleare, A.J. Inflammatory Profiles of Severe Treatment-Resistant Depression. *J. Affect. Disord.* **2019**, *246*, 42–51. [\[CrossRef\]](#)
99. Maes, M.; Bosmans, E.; De Jongh, R.; Kenis, G.; Vandoolaeghe, E.; Neels, H. Increased Serum IL-6 and IL-1 Receptor Antagonist Concentrations in Major Depression and Treatment Resistant Depression. *Cytokine* **1997**, *9*, 853–858. [\[CrossRef\]](#)
100. Murata, S.; Murphy, M.; Khanna, R.; Hoppensteadt, D.; Fareed, J.; Halaris, A. Elevated Salivary Cortisol Predicts Response to Adjunctive Immune Modulation in Treatment-Resistant Bipolar Depression. *J. Affect. Disord. Rep.* **2021**, *4*, 100117. [\[CrossRef\]](#)
101. Voineskos, D.; Daskalakis, Z.J.; Blumberger, D.M. Management of Treatment-Resistant Depression: Challenges and Strategies. *Neuropsychiatr. Dis. Treat.* **2020**, *16*, 221–234. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Howes, O.D.; Thase, M.E.; Pillinger, T. Treatment Resistance in Psychiatry: State of the Art and New Directions. *Mol. Psychiatry* **2022**, *27*, 58–72. [\[CrossRef\]](#) [\[PubMed\]](#)
103. Bajaj, J.S.; Sikaroodi, M.; Fagan, A.; Heuman, D.; Gilles, H.; Gavis, E.A.; Fuchs, M.; Gonzalez-Maeso, J.; Nizam, S.; Gillevet, P.M.; et al. Posttraumatic Stress Disorder Is Associated with Altered Gut Microbiota That Modulates Cognitive Performance in Veterans with Cirrhosis. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2019**, *317*, G661–G669. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Wei, L.; Singh, R.; Ghoshal, U.C. Enterochromaffin Cells–Gut Microbiota Crosstalk: Underpinning the Symptoms, Pathogenesis, and Pharmacotherapy in Disorders of Gut-Brain Interaction. *J. Neurogastroenterol. Motil.* **2022**, *28*, 357–375. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Zhou, Q.; Sun, T.; Wu, F.; Li, F.; Liu, Y.; Li, W.; Dai, N.; Tan, L.; Li, T.; Song, Y. Correlation of Gut Microbiota and Neurotransmitters in a Rat Model of Post-Traumatic Stress Disorder. *J. Tradit. Chin. Med. Sci.* **2020**, *7*, 375–385. [\[CrossRef\]](#)
106. Lee, B.; Choi, G.M.; Sur, B. Antidepressant-Like Effects of Hesperidin in Animal Model of Post-Traumatic Stress Disorder. *Chin. J. Integr. Med.* **2021**, *27*, 39–46. [\[CrossRef\]](#)
107. Satti, S.; Palepu, M.S.K.; Singh, A.A.; Jaiswal, Y.; Dash, S.P.; Gajula, S.N.R.; Chaganti, S.; Samanthula, G.; Sonti, R.; Dandekar, M.P. Anxiolytic- and Antidepressant-like Effects of Bacillus Coagulans Unique IS-2 Mediate via Reshaping of Microbiome Gut-Brain Axis in Rats. *Neurochem. Int.* **2023**, *163*, 105483. [\[CrossRef\]](#)
108. Gould, E.; Cameron, H.A.; Daniels, D.C.; Woolley, C.S.; McEwen, B.S. Adrenal Hormones Suppress Cell Division in the Adult Rat Dentate Gyrus. *J. Neurosci.* **1992**, *12*, 3642–3650. [\[CrossRef\]](#)
109. Mayer, J.L.; Klumpers, L.; Maslam, S.; de Kloet, E.R.; Joëls, M.; Lucassen, P.J. Brief Treatment with the Glucocorticoid Receptor Antagonist Mifepristone Normalises the Corticosterone-Induced Reduction of Adult Hippocampal Neurogenesis. *J. Neuroendocrinol.* **2006**, *18*, 629–631. [\[CrossRef\]](#)
110. Oomen, C.A.; Mayer, J.L.; de Kloet, E.R.; Joëls, M.; Lucassen, P.J. Brief Treatment with the Glucocorticoid Receptor Antagonist Mifepristone Normalizes the Reduction in Neurogenesis after Chronic Stress. *Eur. J. Neurosci.* **2007**, *26*, 3395–3401. [\[CrossRef\]](#)
111. Young, A.H.; Gallagher, P.; Watson, S.; Del-Estal, D.; Owen, B.M.; Ferrier, I.N. Improvements in Neurocognitive Function and Mood Following Adjunctive Treatment with Mifepristone (RU-486) in Bipolar Disorder. *Neuropsychopharmacology* **2004**, *29*, 1538–1545. [\[CrossRef\]](#) [\[PubMed\]](#)
112. DeBattista, C.; Belanoff, J.; Glass, S.; Khan, A.; Horne, R.L.; Blasey, C.; Carpenter, L.L.; Alva, G. Mifepristone versus Placebo in the Treatment of Psychosis in Patients with Psychotic Major Depression. *Biol. Psychiatry* **2006**, *60*, 1343–1349. [\[CrossRef\]](#) [\[PubMed\]](#)
113. Flores, B.H.; Kenna, H.; Keller, J.; Solvason, H.B.; Schatzberg, A.F. Clinical and Biological Effects of Mifepristone Treatment for Psychotic Depression. *Neuropsychopharmacology* **2006**, *31*, 628–636. [\[CrossRef\]](#) [\[PubMed\]](#)
114. Lin, P.; Ding, B.; Feng, C.; Yin, S.; Zhang, T.; Qi, X.; Lv, H.; Guo, X.; Dong, K.; Zhu, Y.; et al. Prevotella and Klebsiella Proportions in Fecal Microbial Communities Are Potential Characteristic Parameters for Patients with Major Depressive Disorder. *J. Affect. Disord.* **2017**, *207*, 300–304. [\[CrossRef\]](#)
115. Liu, Y.; Zhang, L.; Wang, X.; Wang, Z.; Zhang, J.; Jiang, R.; Wang, X.; Wang, K.; Liu, Z.; Xia, Z.; et al. Similar Fecal Microbiota Signatures in Patients With Diarrhea-Predominant Irritable Bowel Syndrome and Patients With Depression. *Clin. Gastroenterol. Hepatol.* **2016**, *14*, 1602–1611.e5. [\[CrossRef\]](#)
116. Chen, J.-J.; Zheng, P.; Liu, Y.-Y.; Zhong, X.-G.; Wang, H.-Y.; Guo, Y.-J.; Xie, P. Sex Differences in Gut Microbiota in Patients with Major Depressive Disorder. *Neuropsychiatr. Dis. Treat.* **2018**, *14*, 647–655. [\[CrossRef\]](#)
117. Jiang, H.; Ling, Z.; Zhang, Y.; Mao, H.; Ma, Z.; Yin, Y.; Wang, W.; Tang, W.; Tan, Z.; Shi, J.; et al. Altered Fecal Microbiota Composition in Patients with Major Depressive Disorder. *Brain Behav. Immun.* **2015**, *48*, 186–194. [\[CrossRef\]](#)

118. Mason, B.L.; Li, Q.; Minhajuddin, A.; Czysz, A.H.; Coughlin, L.A.; Hussain, S.K.; Koh, A.Y.; Trivedi, M.H. Reduced Anti-Inflammatory Gut Microbiota Are Associated with Depression and Anhedonia. *J. Affect. Disord.* **2020**, *266*, 394–401. [\[CrossRef\]](#)
119. Vital, M.; Howe, A.C.; Tiedje, J.M. Revealing the Bacterial Butyrate Synthesis Pathways by Analyzing (Meta)Genomic Data. *mBio* **2014**, *5*, e00889. [\[CrossRef\]](#)
120. Leinonen, L.; Joutsiniemi, S.L. Auditory Evoked Potentials and Magnetic Fields in Patients with Lesions of the Auditory Cortex. *Acta Neurol. Scand.* **1989**, *79*, 316–325. [\[CrossRef\]](#)
121. Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S.; Krystal, J.H. Antidepressant Effects of Ketamine in Depressed Patients. *Biol. Psychiatry* **2000**, *47*, 351–354. [\[CrossRef\]](#)
122. Yang, C.; Qu, Y.; Fujita, Y.; Ren, Q.; Ma, M.; Dong, C.; Hashimoto, K. Possible Role of the Gut Microbiota-Brain Axis in the Antidepressant Effects of (R)-Ketamine in a Social Defeat Stress Model. *Transl. Psychiatry* **2017**, *7*, 1294. [\[CrossRef\]](#)
123. Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X.; et al. Gut Microbiome Remodeling Induces Depressive-like Behaviors through a Pathway Mediated by the Host's Metabolism. *Mol. Psychiatry* **2016**, *21*, 786–796. [\[CrossRef\]](#) [\[PubMed\]](#)
124. Sun, J.; Wang, F.; Hu, X.; Yang, C.; Xu, H.; Yao, Y.; Liu, J. Clostridium Butyricum Attenuates Chronic Unpredictable Mild Stress-Induced Depressive-Like Behavior in Mice via the Gut-Brain Axis. *J. Agric. Food Chem.* **2018**, *66*, 8415–8421. [\[CrossRef\]](#)
125. Miyaoka, T.; Kanayama, M.; Wake, R.; Hashioka, S.; Hayashida, M.; Nagahama, M.; Okazaki, S.; Yamashita, S.; Miura, S.; Miki, H.; et al. Clostridium Butyricum MIYAIRI 588 as Adjunctive Therapy for Treatment-Resistant Major Depressive Disorder: A Prospective Open-Label Trial. *Clin. Neuropharmacol.* **2018**, *41*, 151–155. [\[CrossRef\]](#) [\[PubMed\]](#)
126. Thummasorn, S.; Apichai, S.; Chupradit, S.; Sirisattayawong, P.; Chaiwong, P.; Sriwichain, S.; Pratchayasakul, W.; Chattipakorn, N.; Chattipakorn, S.C. T2DM Patients with Depression Have Higher Levels of Hyperglycemia and Cognitive Decline than T2DM Patients. *PLoS ONE* **2022**, *17*, e0273327. [\[CrossRef\]](#) [\[PubMed\]](#)
127. Nguyen, M.M.; Perlman, G.; Kim, N.; Wu, C.-Y.; Daher, V.; Zhou, A.; Mathers, E.H.; Anita, N.Z.; Lanctôt, K.L.; Herrmann, N.; et al. Depression in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Blood Inflammatory Markers. *Psychoneuroendocrinology* **2021**, *134*, 105448. [\[CrossRef\]](#)
128. Wang, J.; Zhou, D.; Dai, Z.; Li, X. Association Between Systemic Immune-Inflammation Index and Diabetic Depression. *Clin. Interv. Aging* **2021**, *16*, 97–105. [\[CrossRef\]](#)
129. Kale, M.; Nimje, N.; Aglawe, M.M.; Umekar, M.; Taksande, B.; Kotagale, N. Agmatine Modulates Anxiety and Depression-like Behaviour in Diabetic Insulin-Resistant Rats. *Brain Res.* **2020**, *1747*, 147045. [\[CrossRef\]](#)
130. Gragnoli, C. Depression and Type 2 Diabetes: Cortisol Pathway Implication and Investigational Needs. *J. Cell. Physiol.* **2012**, *227*, 2318–2322. [\[CrossRef\]](#)
131. Kokkinopoulou, I.; Diakoumi, A.; Moutsatsou, P. Glucocorticoid Receptor Signaling in Diabetes. *Int. J. Mol. Sci.* **2021**, *22*, 11173. [\[CrossRef\]](#)
132. Marissal-Arvy, N.; Campas, M.-N.; Semont, A.; Ducroix-Crepy, C.; Beauvieux, M.-C.; Brossaud, J.; Corcuff, J.-B.; Helbling, J.-C.; Vancassel, S.; Bouzier-Sore, A.-K.; et al. Insulin Treatment Partially Prevents Cognitive and Hippocampal Alterations as Well as Glucocorticoid Dysregulation in Early-Onset Insulin-Deficient Diabetic Rats. *Psychoneuroendocrinology* **2018**, *93*, 72–81. [\[CrossRef\]](#) [\[PubMed\]](#)
133. Shin, J.H.; Seong, J.K.; Yi, S.S. Sequential Alterations of Glucocorticoid Receptors in the Hippocampus of STZ-Treated Type 1 Diabetic Rats. *J. Vet. Sci.* **2014**, *15*, 19. [\[CrossRef\]](#) [\[PubMed\]](#)
134. Dey, A.; Hao, S.; Erion, J.R.; Wosiski-Kuhn, M.; Stranahan, A.M. Glucocorticoid Sensitization of Microglia in a Genetic Mouse Model of Obesity and Diabetes. *J. Neuroimmunol.* **2014**, *269*, 20–27. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Zuo, Z.-F.; Wang, W.; Niu, L.; Kou, Z.-Z.; Zhu, C.; Wang, W.; Zhao, X.-H.; Luo, D.-S.; Zhang, T.; Zhang, F.-X.; et al. RU486 (Mifepristone) Ameliorates Cognitive Dysfunction and Reverses the down-Regulation of Astrocytic N-Myc Downstream-Regulated Gene 2 in Streptozotocin-Induced Type-1 Diabetic Rats. *Neuroscience* **2011**, *190*, 156–165. [\[CrossRef\]](#) [\[PubMed\]](#)
136. Thaiss, C.A.; Levy, M.; Grosheva, I.; Zheng, D.; Soffer, E.; Blacher, E.; Braverman, S.; Tengeler, A.C.; Barak, O.; Elazar, M.; et al. Hyperglycemia Drives Intestinal Barrier Dysfunction and Risk for Enteric Infection. *Science* **2018**, *359*, 1376–1383. [\[CrossRef\]](#)
137. Rom, S.; Heldt, N.A.; Gajghate, S.; Seliga, A.; Reichenbach, N.L.; Persidsky, Y. Author Correction: Hyperglycemia and Advanced Glycation End Products Disrupt BBB and Promote Occludin and Claudin-5 Protein Secretion on Extracellular Microvesicles. *Sci. Rep.* **2020**, *10*, 18828. [\[CrossRef\]](#)
138. Martín, R.; Miquel, S.; Chain, F.; Natividad, J.M.; Jury, J.; Lu, J.; Sokol, H.; Theodorou, V.; Bercik, P.; Verdu, E.F.; et al. Faecalibacterium Prausnitzii Prevents Physiological Damages in a Chronic Low-Grade Inflammation Murine Model. *BMC Microbiol.* **2015**, *15*, 67. [\[CrossRef\]](#)
139. Stranahan, A.M.; Hao, S.; Dey, A.; Yu, X.; Baban, B. Blood-Brain Barrier Breakdown Promotes Macrophage Infiltration and Cognitive Impairment in Leptin Receptor-Deficient Mice. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 2108–2121. [\[CrossRef\]](#)
140. Sorrells, S.F.; Caso, J.R.; Munhoz, C.D.; Sapolsky, R.M. The Stressed CNS: When Glucocorticoids Aggravate Inflammation. *Neuron* **2009**, *64*, 33–39. [\[CrossRef\]](#)
141. Bolshakov, A.P.; Tret'yakova, L.V.; Kvichansky, A.A.; Gulyaeva, N.V. Glucocorticoids: Dr. Jekyll and Mr. Hyde of Hippocampal Neuroinflammation. *Biochemistry* **2021**, *86*, 156–167. [\[CrossRef\]](#) [\[PubMed\]](#)

142. Espinosa-Oliva, A.M.; De Pablos, R.M.; Villarán, R.F.; Argüelles, S.; Venero, J.L.; Machado, A.; Cano, J. Stress Is Critical for LPS-Induced Activation of Microglia and Damage in the Rat Hippocampus. *Neurobiol. Aging* **2011**, *32*, 85–102. [\[CrossRef\]](#) [\[PubMed\]](#)
143. Munhoz, C.D.; Lepsch, L.B.; Kawamoto, E.M.; Malta, M.B.; Lima, L.D.S.; Werneck Avellar, M.C.; Sapolsky, R.M.; Scavone, C. Chronic Unpredictable Stress Exacerbates Lipopolysaccharide-Induced Activation of Nuclear Factor-KB in the Frontal Cortex and Hippocampus via Glucocorticoid Secretion. *J. Neurosci.* **2006**, *26*, 3813–3820. [\[CrossRef\]](#)
144. Frank, M.G.; Herselman, S.A.; Weber, M.D.; Watkins, L.R.; Maier, S.F. Chronic Exposure to Exogenous Glucocorticoids Primes Microglia to Pro-Inflammatory Stimuli and Induces NLRP3 MRNA in the Hippocampus. *Psychoneuroendocrinology* **2014**, *40*, 191–200. [\[CrossRef\]](#)
145. Shukla, P.K.; Meena, A.S.; Pierre, J.F.; Rao, R. Central Role of Intestinal Epithelial Glucocorticoid Receptor in Alcohol- and Corticosterone-Induced Gut Permeability and Systemic Response. *FASEB J.* **2022**, *36*, e22061. [\[CrossRef\]](#)
146. Guo, X.; Shi, Y.; Du, P.; Wang, J.; Han, Y.; Sun, B.; Feng, J. HMGB1/TLR4 Promotes Apoptosis and Reduces Autophagy of Hippocampal Neurons in Diabetes Combined with OSA. *Life Sci.* **2019**, *239*, 117020. [\[CrossRef\]](#) [\[PubMed\]](#)
147. Guo, M.; Mi, J.; Jiang, Q.-M.; Xu, J.-M.; Tang, Y.-Y.; Tian, G.; Wang, B. Metformin May Produce Antidepressant Effects through Improvement of Cognitive Function among Depressed Patients with Diabetes Mellitus. *Clin. Exp. Pharmacol. Physiol.* **2014**, *41*, 650–656. [\[CrossRef\]](#)
148. Abdallah, M.S.; Mosalam, E.M.; Zidan, A.-A.A.; Elattar, K.S.; Zaki, S.A.; Ramadan, A.N.; Ebeid, A.M. RETRACTED ARTICLE: The Antidiabetic Metformin as an Adjunct to Antidepressants in Patients with Major Depressive Disorder: A Proof-of-Concept, Randomized, Double-Blind, Placebo-Controlled Trial. *Neurotherapeutics* **2020**, *17*, 1897–1906. [\[CrossRef\]](#)
149. Wu, H.; Esteve, E.; Tremaroli, V.; Khan, M.T.; Caesar, R.; Mannerås-Holm, L.; Ståhlman, M.; Olsson, L.M.; Serino, M.; Planas-Félix, M.; et al. Metformin Alters the Gut Microbiome of Individuals with Treatment-Naive Type 2 Diabetes, Contributing to the Therapeutic Effects of the Drug. *Nat. Med.* **2017**, *23*, 850–858. [\[CrossRef\]](#)
150. Shin, A.C.; Balasubramanian, P.; Suryadevara, P.; Zyskowski, J.; Herdt, T.H.; MohanKumar, S.M.J.; MohanKumar, P.S. Metformin Effectively Restores the HPA Axis Function in Diet-Induced Obese Rats. *Int. J. Obes.* **2021**, *45*, 383–395. [\[CrossRef\]](#)
151. Chen, J.; Zhou, T.; Guo, A.-M.; Chen, W.-B.; Lin, D.; Liu, Z.-Y.; Fei, E.-K. Metformin Ameliorates Lipopolysaccharide-Induced Depressive-Like Behaviors and Abnormal Glutamatergic Transmission. *Biology* **2020**, *9*, 359. [\[CrossRef\]](#) [\[PubMed\]](#)
152. Hung, H.-C.; Tsai, S.-F.; Sie, S.-R.; Kuo, Y.-M. High Glucose Enhances Lipopolysaccharide-Induced Inflammation in Cultured BV2 Microglial Cell Line. *Immun. Inflamm. Dis.* **2022**, *10*, e610. [\[CrossRef\]](#) [\[PubMed\]](#)
153. Zhang, X.; Dong, H.; Zhang, S.; Lu, S.; Sun, J.; Qian, Y. Enhancement of LPS-Induced Microglial Inflammation Response via TLR4 Under High Glucose Conditions. *Cell. Physiol. Biochem.* **2015**, *35*, 1571–1581. [\[CrossRef\]](#)
154. Erickson, M.A.; Shulyatnikova, T.; Banks, W.A.; Hayden, M.R. Ultrastructural Remodeling of the Blood-Brain Barrier and Neurovascular Unit by Lipopolysaccharide-Induced Neuroinflammation. *Int. J. Mol. Sci.* **2023**, *24*, 1640. [\[CrossRef\]](#) [\[PubMed\]](#)
155. Hayden, M.R.; Grant, D.G.; Aroor, A.R.; DeMarco, V.G. Empagliflozin Ameliorates Type 2 Diabetes-Induced Ultrastructural Remodeling of the Neurovascular Unit and Neuroglia in the Female Db/Db Mouse. *Brain Sci.* **2019**, *9*, 57. [\[CrossRef\]](#)
156. Hayden, M.R.; Banks, W.A. Deficient Leptin Cellular Signaling Plays a Key Role in Brain Ultrastructural Remodeling in Obesity and Type 2 Diabetes Mellitus. *Int. J. Mol. Sci.* **2021**, *22*, 5427. [\[CrossRef\]](#)
157. Lin, K.-I.; Johnson, D.R.; Freund, G.G. LPS-Dependent Suppression of Social Exploration Is Augmented in Type 1 Diabetic Mice. *Brain Behav. Immun.* **2007**, *21*, 775–782. [\[CrossRef\]](#)
158. Fischer, S.; Strawbridge, R.; Vives, A.H.; Cleare, A.J. Cortisol as a Predictor of Psychological Therapy Response in Depressive Disorders: Systematic Review and Meta-Analysis. *Br. J. Psychiatry* **2017**, *210*, 105–109. [\[CrossRef\]](#)
159. Haroon, E.; Daguan, A.W.; Woolwine, B.J.; Goldsmith, D.R.; Baer, W.M.; Wommack, E.C.; Felger, J.C.; Miller, A.H. Antidepressant Treatment Resistance Is Associated with Increased Inflammatory Markers in Patients with Major Depressive Disorder. *Psychoneuroendocrinology* **2018**, *95*, 43–49. [\[CrossRef\]](#)
160. Zarate, C.A.; Singh, J.B.; Carlson, P.J.; Brutsche, N.E.; Ameli, R.; Luckenbaugh, D.A.; Charney, D.S.; Manji, H.K. A Randomized Trial of an N-Methyl-D-Aspartate Antagonist in Treatment-Resistant Major Depression. *Arch. Gen. Psychiatry* **2006**, *63*, 856–864. [\[CrossRef\]](#)
161. Siopi, E.; Chevalier, G.; Katsimpardi, L.; Saha, S.; Bigot, M.; Moigneu, C.; Eberl, G.; Lledo, P.-M. Changes in Gut Microbiota by Chronic Stress Impair the Efficacy of Fluoxetine. *Cell Rep.* **2020**, *30*, 3682–3690.e6. [\[CrossRef\]](#)
162. Fontana, A.; Manchia, M.; Panebianco, C.; Paribello, P.; Arzedei, C.; Cossu, E.; Garzilli, M.; Montis, M.A.; Mura, A.; Pisanu, C.; et al. Exploring the Role of Gut Microbiota in Major Depressive Disorder and in Treatment Resistance to Antidepressants. *Biomedicines* **2020**, *8*, 311. [\[CrossRef\]](#)
163. Juruena, M.F.; Cleare, A.J.; Papadopoulos, A.S.; Poon, L.; Lightman, S.; Pariante, C.M. The Prednisolone Suppression Test in Depression: Dose-Response and Changes with Antidepressant Treatment. *Psychoneuroendocrinology* **2010**, *35*, 1486–1491. [\[CrossRef\]](#)
164. Juruena, M.F.; Pariante, C.M.; Papadopoulos, A.S.; Poon, L.; Lightman, S.; Cleare, A.J. The Role of Mineralocorticoid Receptor Function in Treatment-Resistant Depression. *J. Psychopharmacol.* **2013**, *27*, 1169–1179. [\[CrossRef\]](#)
165. Maes, M.; Kubera, M.; Leunis, J.-C.; Berk, M.; Geffard, M.; Bosmans, E. In Depression, Bacterial Translocation May Drive Inflammatory Responses, Oxidative and Nitrosative Stress (O&NS), and Autoimmune Responses Directed against O&NS-Damaged Neopeptides. *Acta Psychiatr. Scand.* **2013**, *127*, 344–354. [\[CrossRef\]](#)

166. Kéri, S.; Szabó, C.; Kelemen, O. Expression of Toll-Like Receptors in Peripheral Blood Mononuclear Cells and Response to Cognitive-Behavioral Therapy in Major Depressive Disorder. *Brain Behav. Immun.* **2014**, *40*, 235–243. [[CrossRef](#)]
167. Kelly, J.R.; Borre, Y.; O’ Brien, C.; Patterson, E.; El Aidy, S.; Deane, J.; Kennedy, P.J.; Beers, S.; Scott, K.; Moloney, G.; et al. Transferring the Blues: Depression-Associated Gut Microbiota Induces Neurobehavioural Changes in the Rat. *J. Psychiatr. Res.* **2016**, *82*, 109–118. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.