

From "leaky gut" to impaired glia-neuron communication in depression

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Abstract

In the last three decades, the robust scientific data emerged, demonstrating that the immune-inflammatory response is a fundamental component of the pathophysiology of major depressive disorder (MDD). Psychological stress and various inflammatory comorbidities contribute to such immune activation. Still, this is not uncommon that patients with depression do not have defined inflammatory comorbidities, and alternative mechanisms of immune activation need to take place. The gastrointestinal (GI) tract, along with gut-associated lymphoid tissue (GALT), constitutes the largest lymphatic organ in the human body and forms the biggest surface of contact with the external environment. It is also the most significant source of bacterial and food-derived antigenic material. There is a broad range of reciprocal interactions between the GI tract, intestinal microbiota, increased intestinal permeability, activation of immune-inflammatory response, and the CNS that has crucial implications in brain function and mental health. This intercommunication takes place within the microbiota-gut-immune-glia (MGIG) axis, and glial cells are the main orchestrator of this communication. A broad range of factors, including psychological stress, inflammation, dysbiosis and other, may compromise the permeability of this barrier. This leads to excessive bacterial translocation and the excessive influx of food-derived antigenic material that contributes to activation of the immune-inflammatory response and depressive psychopathology. This chapter summarizes the role of increased intestinal permeability in MDD and mechanisms of how the "leaky gut" may contribute to immune-inflammatory response in this disorder.

1. Introduction

For over four decades, the monoaminergic hypothesis mostly defined our understanding of major depressive disorder (MDD). This hypothesis postulated that deficits in certain neurotransmitters, including serotonin (5-HT), noradrenaline, and dopamine, contribute to MDD symptomatology and that antidepressant treatment improves depressive symptoms due to the restoration of the appropriate neurotransmission. However, in the last two decades, a piece of robust scientific evidence emerged indicating that MDD is accompanied by the low-grade immune-inflammatory response, which has a crucial role in the pathophysiology of this disorder. Consequently, various immune hypotheses of this disorder emerged, including the macrophage hypothesis of depression (1), the monocyte-T-lymphocyte hypothesis (2), a neurodegeneration hypothesis (3), the cytokine hypothesis (4) the glutamate hypothesis (5), "leaky gut" hypothesis (6, 7), or depression as a glial-based synaptic dysfunction (8), to name a few. Those hypotheses reciprocally complement each other and represent a continuum of evolving understanding of depression. It also became clear that the monoaminergic paradigm is just a part of the much bigger and intriguingly complicated psycho-neuro-immunological picture.

Some of the crucial aspects of immune-inflammatory response in MDD include increased levels of pro-inflammatory cytokines i.e., IL-1 β , TNF- α , IL-6 (4, 9), activation of oxidative and nitrosative stress (O&NS) and decreased levels of crucial antioxidants and total antioxidant capacity in depressed patients (10-13). Also, it has been demonstrated that O&NS may generate neoepitopes with subsequent autoimmunity in depressed patients (14). Furthermore, MDD is accompanied by abnormalities in the metabolism of tryptophan and its catabolites in the kynurenine pathway (TRYCATs / kynurenines) what manifests with the decreased amount of tryptophan available for conversion to 5-HT and increased conversion of tryptophan to TRYCATs. Those kynurenines may exert neurotoxic, pro-oxidative effects on the CNS, and increase glutamate neurotransmission (3, 15-18). Moreover, MDD is often comorbid with various inflammatory and autoimmune disorders, which could contribute to the activation of the inflammatory response in MDD. Those, for instance, include inflammatory bowel diseases (IBD) i.e., Crohn's disease, ulcerative colitis or irritable bowel syndrome (IBS), further, rheumatoid arthritis, multiple sclerosis (MS), coronary artery disease, chronic obstructive pulmonary disease (COPD), HIV infection (human immunodeficiency virus), Alzheimer's disease and other, and their comorbidity reciprocally worsens the course and prognosis. Still, this is not uncommon that patients with MDD do not have defined inflammatory comorbidities, and alternative mechanisms of immune activation in this disorder need to take place.

One of the major contributors to activation of immune-inflammatory response is psychological stress, which with the involvement of hypothalamic-pituitary-adrenal (HPA) axis and the activation of the sympathetic nervous system (SNS), upregulates the expression of nuclear factor kappa beta (NF- κ B) in mononuclear cells what results with an increase of pro-inflammatory cytokines release (19-21). Moreover, catecholamines induce activation of microglia, the release of pro-inflammatory cytokines in

the periphery and within the CNS, and increase the trafficking of macrophages to the CNS. Psychological stress also upregulates the TLR-4 pathway and exacerbates response to bacterial LPS (21-24).

Another crucial element that links the effects of psychological stress and immunity is the gastrointestinal (GI) tract with the gut-associated lymphoid tissue (GALT). GI tract, along with GALT, constitutes the largest lymphatic organ in the human body, and it is responsible for the production of 70-80% of immune cells. Given that, in the last decade, there is a growing interest in reciprocal interactions between the GI tract, intestinal microbiota, increased intestinal permeability, activation of immune-inflammatory response, and the CNS. This intercommunication takes place within the microbiota-gut-brain axis or recently proposed the microbiota-gut-immune-glia (MGIG) axis (25), since glial cells are the main orchestrator of the immune response within CNS, and mediate the central response to the systemic inflammation. GI tract forms the biggest surface of contact of the human body with the external environment, and it is the most significant source of bacterial and food-derived antigenic material.

Bacterial LPS/endotoxin, which is a cell wall component of Gram-negative bacteria, along with other bacterial-derived antigenic material including flagellins, lipoproteins, peptidoglycans belong to so-called pathogen-associated molecular patterns (PAMPs) and are recognized by pattern recognition receptors (PRRs) including Toll-like transmembrane receptors (TLRs). TLRs constitute broad antigen sensing "machinery" and, of particular interest, TLR4 are responsible for recognizing bacterial LPS. Those receptors are expressed on various immune and non-immune cells both in the periphery and within the CNS, such as dendritic cells, lymphocytes, monocytes, macrophages, granulocytes, astrocytes, microglia, oligodendrocytes and tissues including intestinal tissue (26). LPS can also activate receptors for advanced glycation end products (RAGE) which can lead to endothelial hyperpermeability (27). The second group of gut-derived antigens, which could play a significant part in the immune-inflammatory mechanism in MDD are food-derived antigens.

Permeability of the intestinal barrier is the main determinant of the extent of bacterial translocation from the intestinal lumen and subsequent activation of TLR4 receptors. Importantly, this barrier's permeability may be compromised by a broad range of factors, including psychological stress with the involvement of HPA axis activation and corticotropin-releasing hormone (CRH)-mediated mast cells activation (Fig.1) (28-34). Also, psychological stress may contribute to increased intestinal permeability via activation of SNS and activation of β 2-adrenergic receptors expressed on epithelial cells (33, 35, 36). Moreover, factors compromising gut barrier include pro-inflammatory cytokines such as IFN- γ (37), TNF- α (38, 39), IL-1 β (40), O&NS (30, 41), NF- κ B (42), alcohol (43-46), high-fat diet (47) and obesity (48), traumatic brain injury (49), food additives and pesticides (50-55), prolonged strenuous exercise (56, 57), heat stress (58), infections (59, 60), some medications for instance, antibiotics (61-64) and non-steroidal anti-inflammatory drugs (NSAID) (65, 66). Finally, since gut microbes are the "natural guardians" and modulators of this barrier's integrity, abnormalities in their

composition, including dysbiosis and small intestine bacterial overgrowth (SIBO), contribute to increased intestinal permeability (46, 67, 68). Importantly, MDD is accompanied by changes in the intestinal microbiota composition (69-73), and dysbiosis was also demonstrated in other psychiatric disorders, including chronic fatigue syndrome (CFS) (74), schizophrenia and bipolar disorder (75, 76), autism (77-81) and alcoholism (46). Additionally, psychological stress has a detrimental influence on intestinal microbiota composition what has a negative impact on mucosal immunity and results with an increase of parameters of peripheral and central inflammation (82-84). In view of the above, growing scientific data demonstrates that various psychiatric disorders including MDD (6, 7, 14, 76, 85-87), schizophrenia (88-90), bipolar disorder (76), CFS (91, 92), autism (93-95), alcohol dependence (44-46) are accompanied by increased intestinal permeability. Furthermore, numerous inflammatory disorders, which are comorbid with MDD, including celiac disease, IBD, IBS, rheumatoid arthritis, ankylosing spondylitis, MS, type 1 and type 2 diabetes, asthma, atopic eczema, are also accompanied by increased intestinal permeability (96-99).

Finally, glial cells, which are non-neuronal and most abundant cell types in the CNS, play a crucial role in the brain's immune response to both systemic and central inflammation, and reciprocally cross-talk with neurons. Those cells include astrocytes, microglia, oligodendrocytes, ependymal cells, Schwann cells, and satellite cells. In particular, astrocytes, microglia, and oligodendrocytes are mainly involved in psychiatric manifestations of gut-derived immune-inflammatory response, and various glial abnormalities accompany MDD. It is noteworthy that these cells express TLR4 receptors for endotoxin, and subsequently, bacterial translocation influenced their functions and structure. Astrocytes are involved in different metabolic processes, including ion and fluids balance and energetic metabolism. Those cells produce a broad range of gliotransmitters, including glutamate, adenosine triphosphate (ATP), D-serine, and are the source of different neurotrophic factors involved in neurotransmission and synaptic plasticity. Astrocytes play a significant part in the regulation of glutamate and gamma-aminobutyric acid (GABA) neurotransmission and are responsible for the reuptake of about 90% of the glutamate. Subsequently, their dysfunction leads to glutamate excess and inappropriate balance between excitatory and inhibitory neurotransmission (Fig.1). Astrocytes also have a pivotal role in the blood-brain-barrier (BBB) function and its permeability (100). Abnormalities in astrocytes function and structure, namely astrogliosis, accompanies MDD, and depressed patients have decreased number and density of those cells in brain regions involved in MDD such as the hippocampus, amygdala and prefrontal cortex (101-103). Also, psychological stress has a negative influence on the structure and functions of astrocytes and microglia (104). Consequently, antidepressant treatment, including antidepressant medication, lithium, and electroconvulsive therapy (ECT) has a beneficial influence on the structure and functions of astrocytes (101, 105).

Microglia is another group of glial cells involved in MDD. Those brain resident-macrophages are mainly participating in immune regulation, and they are "the first line" immune defense of the CNS. Those cells are equipped with a broad plethora of pro-inflammatory mechanisms, including cytokines,

chemokines, nitric oxide (NO), prostaglandins, pro-oxidative kynurenes, such as 3-hydroxykynurenine (3OHKYN) and quinolinic acid (QUIN). These immune mechanisms can be life-saving, but when excessively and chronically triggered, can be detrimental to brain functions and mental health. Microglia release neurotrophins, including brain-derived neurotrophic factor (BDNF) and neurotransmitters, i.e., ATP and glutamate, and are involved in synaptogenesis, synaptic pruning, sampling, and elimination. Interestingly, glutamate influences microglial chemotaxis, and microglia migrate towards the origin of increased glutamate release (106). Consequently, abnormalities in microglia proportions (primed v.s resting cells), functions, and morphology, namely microgliopathy, were demonstrated in MDD and suicidality (107, 108). It was also shown that antidepressant treatment attenuates microglial activation, including the release of glutamate and pro-inflammatory cytokines (109-111). Moreover, psychological stress has a negative impact on microglia morphology, particularly in brain areas related to MDD and anxiety, such as the hippocampus, prefrontal cortex, amygdala, hypothalamus, and nucleus accumbens (112).

Last but not least are oligodendrocytes, which are mainly involved in myelin formation. Astrocytes and microglia profoundly influence these glial cells. Pro-inflammatory cytokines, O&NS, and glutamate may compromise functions of oligodendrocytes, particularly myelin formation and abnormalities in oligodendrocytes function and myelin formation were demonstrated in MDD (113-115).

In this chapter will summarise the role of increased intestinal permeability in major depression and mechanisms of how the "leaky gut" may contribute to immune-inflammatory response in this disorder.

2. The evidence of increased intestinal permeability in depression

Increased intestinal permeability to bacterial antigens

It is becoming increasingly evident that MDD is accompanied by increased intestinal permeability, which could contribute to the low-grade immune-inflammatory response in patients with MDD (Fig.1). The first evidence of the "leaky gut" in depression was demonstrated in two consecutive studies, which revealed that MDD patients had increased serum levels of immunoglobulins A (IgA) and M (IgM) against LPS of enteric commensal bacteria. Additionally, patients with chronic depression (duration > two years) had higher IgM responses compared to non-chronically depressed patients (6, 7). It was also demonstrated that patients with melancholic versus non-melancholic depression had higher IgA to gut commensal *Citrobacter Koseri*, and Hamilton Depression Rating Scale (HAM-D) score was significantly associated with IgA to *Citrobacter Koseri* (76). Moreover, IgG to oxidized LDL (oxLDL) was significantly associated with increased bacterial translocation what is consistent with earlier results, which demonstrated that increased translocation of gut microbes might drive oxidative and nitrosative stress and autoimmune responses against O&NS generated neoepitopes in depressed

patients (14, 76). Another research demonstrated increased plasma levels of bacterial LPS along with increased levels of zonulin and intestinal fatty acid-binding protein-2 (FABP2) in patients with anxiety and depressive symptoms (85). Zonulin is a regulator of intestinal permeability, and FABP2 is a marker of the defective intestinal barrier. It should be noted that increased zonulin levels were also revealed in various inflammatory and autoimmune disorders, which are often comorbid with MDD (116). In the same study, patients with depression and anxiety presented with gut dysbiosis and their abnormal intestinal bacterial flora composition was correlated with levels of LPS, zonulin, and FABP2 what indicates that dysbiosis may contribute to increased intestinal permeability in MDD. In another study, patients with MDD had significantly elevated plasma level of 16S ribosomal RNA (rRNA) subunit (16S rDNA) of intestinal microbiota, and this parameter is an indicator of bacterial translocation (117). Furthermore, patients had increased plasma expression of TLR-4 RNA and protein and increased expression NF-kb RNA, and increased concentration of IL-6. Strikingly, sixteen weeks of cognitive-behavioral therapy (CBT) significantly decreased expressions of TLR-4 RNA and protein, NF-kb RNA, and reduced level of 16S rDNA what indicates that CBT contributed to decrease of intestinal permeability. Additionally, greater decrease in pro-inflammatory parameters during CBT was associated with more pronounced clinical improvement in Hamilton Depression Rating Scale (HAM-D). Using another approach of intestinal barrier assessment, namely measurement of the lactulose/mannitol ratio (LMR), a positive association between intestinal permeability and depressive symptoms severity in unmediated adolescents, particularly neurovegetative symptoms, was demonstrated (86). Authors also revealed the association between sympathetic nervous system (SNS) activity and the gut permeability and suggested that intestinal permeability could mediate the association between MDD symptoms and the activity of SNS.

Increased intestinal permeability to food-derived antigens

Another aspect of "leaky gut" in MDD is an increased gut permeability to food-derived antigens (Fig.1). It was proposed that increased intestinal permeability to food antigens with subsequent type III hypersensitivity and formation of IgG complexes may contribute to low-grade immune-inflammatory response in MDD (118, 119). Recently Tao et al. demonstrated that depressed adolescents had a higher rate of serum food-specific IgG that was accompanied by increased serum levels of histamine, S100 calcium-binding protein B (S100B), and homocysteine (120). S100B is considered as a marker of increased permeability of BBB and is primarily expressed in astrocytes. Authors concluded that IgG-mediated type III hypersensitivity against food antigens could be the principal cause of increased histamine level, which in turn contributed to increased BBB permeability in depressed patients. It is worth noting that increased histamine release from i.e., mast cells is not exclusively mediated by IgE and that binding of IgG with receptors for the Fc portion of immunoglobulins (FcR), for instance, FcγRIII, also contributes to histamine release (121). Another study revealed that when depressed

patients were tested for IgG levels against 39 selected food antigens, patients had significantly higher serum total IgG and IgG against celery, garlic and gluten compared to the control group (122). It was also previously demonstrated that IgG concentration against 5 out of 44 food products (11.36%) positively correlated with the length of depressive episodes (119). Those results could indicate that the longer duration of depressive symptoms could be related to more pronounced intestinal permeability and subsequent inflammatory response. This seems consistent with the previous report that patients with chronic depression had significantly higher IgM responses against commensal bacteria compared to healthy controls (7). Still, two scenarios seem plausible regarding the activation of low-grade immune-inflammatory response and "leaky gut" in depression. On the one hand, activation of the immune-inflammatory response can be secondary to increased intestinal permeability. On the other hand, increased intestinal permeability can be secondary to inflammatory factors i.e., activation of HPA axis, pro-inflammatory cytokines, Nf-kb, and O&NS which all are the essence of the immune response in various inflammatory disorders.

To summarise, the current literature demonstrates that increased intestinal permeability to bacterial and food-derived antigens accompanies MDD. However, what are the immune consequences and mechanisms which may lead to gut-derived psychiatric manifestations, particularly depressive symptomatology?

3. Crossing the barriers beyond the brain's privileged immunity

Central consequences of peripherally LPS-induced immune-inflammatory response

There are various mechanisms of how bacterial LPS contribute to the activation of the immune-inflammatory response both in the periphery and in the CNS (Fig.1). It is, however, important to emphasize that activation of the immune-inflammatory response due to an increase of LPS level in the circulation is not restricted to the periphery but also results with activation of inflammatory response within the CNS and glial cells are primarily involved in this process. Therefore, it is well established that peripheral LPS challenge leads to sickness behaviors, depressed mood, anxiety, and a decline in the cognitive functions both in humans and animals (123, 124). Peripheral LPS administration also led to robust activation of brain microglia in humans what was assessed using PET brain imaging (125). This was accompanied by an elevation of circulating cytokines TNF- α , IL-6, IL-8, and IL-10 and sickness behaviors, including fatigue and reduction in social interest. In addition, peripheral stimulation with LPS induced microglial proliferation in the circumventricular organs, hypothalamus, limbic system and medulla oblongata (126). Consequently, it was demonstrated that peripheral administration of LPS led to increased expression of cortical and hippocampal IL-1 β , TNF- α , GFAP and iNOS. This was accompanied by decreased expression of BDNF and depressive-type behaviors in laboratory animals. Inhibition of astrocytes resulted in a decrease in above mentioned neuroinflammatory

parameters, reversed LPS-induced decreased in BDNF and attenuated depressive-like behaviors (127). Consistently, antidepressant treatment with tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), transcranial magnetic stimulation and electroconvulsive therapy had a beneficial effect on number and morphology of those glial cells (101). Similarly, TCA and SSRIs inhibited LPS-induced depressive-like behaviors and IL-6 release in laboratory animals (109), attenuated the release of TNF- α , NO (110), and glutamate, and D-serine release by activated microglia (111). Also, lithium prevented LPS-induced activation of astrocytes, TLR4 expression and pro-inflammatory cytokine production and this mood stabilizer also has a strong antidepressant and antisuicidal properties (105). Furthermore, minocycline, which is a tetracycline antibiotic with antidepressant properties, has known anti-neuroinflammatory and microglia modulatory properties (128). In LPS-stimulated brain microglial cells, minocycline blocked the secretion of pro-inflammatory cytokines. In the second part of this study minocycline reduced mRNA levels of IL-1 β , IL-6, and IDO in the cortex and hippocampus of laboratory animals, which were peripherally stimulated with LPS. This was accompanied by a reduction in anhedonia and sickness behaviors (129). Furthermore, LPS have a detrimental influence on oligodendrocytes maturation and myelination (130).

Bacterial LPS after translocation binds to PAMP, such as TLR4 and activate MyD88-dependent and MyD88-independent pathways of the innate immune response through NF- κ B signaling what leads to increased release of pro-inflammatory cytokines including IL-1b, TNF- α , IL-6 and type I interferons (IFNs). Endotoxin can also activate RAGE what can lead to endothelial hyperpermeability (27). Moreover, this bacterial molecule can activate the classical component system what may lead to neuropathology, including dopaminergic neurons loss (131, 132).

LPS-induced release of pro-inflammatory cytokines can influence brain and behavior via humoral, neural and cellular pathways (133). The humoral pathway includes passage of cytokines through more permeable areas of BBB such as choroid plexus and circumventricular organs, activation of BBB endothelium and subsequent release of second messengers including prostaglandins and nitric oxide which further activate inflammatory cascade within the brain parenchyma. Moreover, some cytokines do have specific transport molecules in the endothelium, which allows for active transport via BBB. Cytokines can also act through neural route, for example, by activating afferent fibers of the vagal nerve. Furthermore, cytokines contribute to the entry to the brain parenchyma of monocytes activated in the periphery. During peripheral inflammation, cerebral microglia recruit monocytes into the brain via the release of cerebral monocyte chemoattractant protein (MCP)-1 and increased numbers of circulating CCR2-expressing monocytes. Also, peripheral TNF- α is required to stimulate microglia to produce chemokine MCP-1/CCL2 (133, 134). It was also recently demonstrated that peripheral LPS challenge results with the influx of leucocytes to the brain parenchyma. Respectively, prolonged, repeated exposure to peripheral LPS resulted in microglia activation and increased expression of various chemokines, which attracted neutrophils, monocytes to the brain parenchyma. This led to increased BBB permeability and transient recruitment of neutrophils and monocytes and sustained infiltration of

monocytes, T-cells, NK cells and NK T cells to the brain parenchyma. Interestingly, following consecutive challenges, peripheral tolerance to LPS developed, which manifested with not as pronounced inflammatory response in the periphery, however in the brain, the inflammatory process progressed and manifested with increased transcription of inflammatory cytokines and chemokines (135).

"The TLRs perspective"

There is a broad presence of the TLR4 microbe sensing "machinery" in different brain cells, including astrocytes, microglia, oligodendrocytes, neurons, perivascular macrophage, endothelium, meninges and circumventricular organs (136). Those receptors are also expressed on dendritic cells, lymphocytes, monocytes, granulocytes, and tissues, including intestinal tissue (26). Such a broad expression of PAMPs within-CNS and periphery surely have to serve its purpose and indicate that brain tissue is well familiar with the endotoxin molecule (137). It is even more so in MDD and various neurodegenerative disorders. However, the latter are beyond the scope of this chapter. When it comes to depression, *post mortem* study revealed over-expression of TLR3 and TLR4 in the dorsolateral prefrontal cortex of depressed suicide victims and depressed non-suicide subjects, compared with controls (138). Animal studies demonstrated that exposure to LPS (139, 140) and psychological stress (141) enhances expression of TLR4 and higher expression of TLR3, 4, 5, and 7 mRNA was demonstrated in peripheral blood of depressed patients (137). TLR4 mRNA expression was associated with the severity of MDD measured with the Hamilton Depression Rating Scale (HAM-D-17). Moreover, it was demonstrated that four weeks of antidepressant treatment of MDD patients significantly decreased expression of TLRs (1-9) in peripheral blood mononuclear cells (PBMCs) (142) and lithium inhibited LPS-induced astrocytes activation via inhibition of TLR4 expression (105). Also, sixteen weeks of cognitive CBT significantly decreased the expressions of TLR-4 RNA and protein, which was accompanied by the improvement of intestinal barrier function (117).

LPS and kynurenines

Another essential element in this depression-related inflammatory puzzle is the kynurenine pathway. Bacterial lipopolysaccharides, O&NS and pro-inflammatory cytokines, including IFN γ , IL-1 β , IL-6, TNF- α , and cortisol, can activate the first step enzymes in the kynurenine pathway particularly indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) (Fig.1). The former is expressed in antigen-presenting cells during immune reactions, and TDO is mostly expressed in the liver and neurons. Those enzymes are involved in the conversion of tryptophan (5-HT and melatonin precursor) to kynurenine and its further catabolites (TRYCATs) what subsequently decreases the amount of tryptophan available for conversion to 5-HT. TRYCATs perform numerous critical physiological roles, including immunomodulatory functions however, their excess may have an adverse

effect on the CNS functions. For instance, quinolinic acid (QUIN) is an N-methyl-D-aspartate (NMDA) receptor agonist and has neurotoxic activity due to stimulation of synaptosomal glutamate release and inhibition of its reuptake by astrocytes. This results in an increase in its concentration in the synapse and excessive stimulation of the NMDA receptors (143, 144), and increased oxidative stress (145). This is particularly important in the context of glutamate hypothesis of depression where due to dysfunction and decreased number of astrocytes, there is not sufficient reuptake of glutamate what leads to an imbalance between glutamate and GABA neurotransmission. Therefore, it was demonstrated that activation of microglia resulted in IDO activation, the elevation of detrimental kynurenines, and an increase in glutamate neurotransmission (107). This also resulted in inhibition of the brain's tropic factors synthesis, including BDNF, and in decreased neurogenesis.

Another kynurenine metabolite - 3-hydroxykynurenine (3HKYN) has neurotoxic, neuroapoptotic and pro-oxidative effects and is further metabolized to pro-oxidative 3-hydroxyanthranilic acid (3HAA). In contrast, kynurenic acid (KYNA) is an NMDA receptor antagonist and modulates acetylcholine 7 alpha nicotinic receptor ($\alpha 7$ -nACh) functions, and it is believed that KYNA counteracts the neurotoxic effects of the above-mentioned QUIN (146, 147). Accordingly, Myint and Kim proposed the neurodegeneration hypothesis of MDD and demonstrated that an imbalance between neuroprotective and neurodegenerative metabolites in the kynurenine pathway contributes to MDD (3, 15). Still, it is important to keep in mind that despite "neuroprotective" effects of KYNA and its antagonism to QUIN, those kynurenines, when in excess, contribute to neurodegeneration and cognitive decline, in schizophrenia, bipolar disorder, Alzheimer's, Parkinson's and Huntington's diseases, dementia related to HIV infection, amyotrophic lateral sclerosis (ALS), post-surgical cognitive decline and other (148-150). The negative impact of QUIN and KYNA on cognitive functions is mainly due to their ability to modulate glutamate and acetylcholine neurotransmission (148). It is noteworthy that the brain's glial cells are the site of TRYCATs metabolism and tryptophan, and kynurenine after crossing BBB became substrates for further TRYCATs synthesis within CNS. More precisely, the "neuroprotective" KYNA synthesizing branch is located in astrocytes and neurotoxic QUIN synthesizing branch is compartmentalized in microglia. Peripheral LPS challenge influences the metabolism of TRYCATs in the brain and in the periphery. LPS challenge increased kynurenine/tryptophan ratio both in the periphery and in the CNS. It resulted in increased expression of pro-inflammatory cytokines IL-1 β , TNF- α , and IL-6 in the hippocampus, amygdala, and striatum, and was accompanied by an increase of neuroinflammatory glial cellular markers. In addition, kynurenine metabolism in the hippocampus was skewed toward the neurotoxic branch (151). Also, peripheral chronic, intermittent administration of LPS in laboratory animals resulted in depressive-like behaviors assessed by levels of anhedonia and despair. This was accompanied by hippocampal microglia activation and increased expression of IDO, increased levels of NF-kB p65 and IL-1 β levels, elevated QUIN/tryptophan ratio, increased levels of kynurenine and QUIN, and decreased hippocampal levels of tryptophan, and 5-HT (152). Importantly kynurenine, besides being a precursor for TRYCATs, also

has various immunomodulatory roles. For instance, it activates monocytes and astrocytes and is involved in the trafficking of monocytes to the brain, and those neuroimmune mechanisms are accompanied by depressive-like symptoms in laboratory animals (153). Above mentioned effects of kynurenine on monocyte chemotaxis take place with the involvement of the aryl hydrocarbon receptor (AhR). Moreover, kynurenine is involved in mast cell activation, also through AhR (154).

Numerous studies indicate the crucial role of kynurenine pathway activation in the pathogenesis of depressive disorders. For example, the interferon- α treatment of hepatitis C patients resulted in depressive symptoms along with changes in the kynurenine:tryptophan (KYN:TRP) concentration ratio and this ratio can indirectly characterize the activity of the enzymes of the IDO and TDO (155). Besides, the peripheral supply of interferon- α led to an increase in the concentration of KYN in cerebrospinal fluid (CSF) of patients, which was associated with a significant increase in the concentration of QUIN and KYNA in CSF. Also, the levels of these kynurenines correlated with the severity of depressive symptoms (156). Interestingly, it has been suggested that kynurenines may also play an important role in suicidal behavior. *Post mortem* study of severely depressed patients, who died due to suicide, demonstrated a significant upregulation of microglial QUIN in the anterior cingulate gyrus (18). Also, suicide attempters in the course of depression had a significantly increased level of QUIN but not KYNA in CSF (157). The CSF QUIN level was associated with higher CSF IL-6 levels, and QUIN correlated with suicidality. Moreover, MDD patients who attempted suicide had elevated KYN levels compared to MDD patients who did not have suicidal attempts (158). Another study demonstrated that adolescents with suicidal tendencies had a reduced level of TRP and an increased ratio of KYN:TRP (159).

LPS and blood-brain-barrier

Another essential aspect is the interaction of peripheral LPS with BBB. Crucial questions that call for the answer in this context are whether peripheral LPS can increase BBB permeability and whether BBB is penetrable for those bacterial antigens? And if so, does disruption of BBB integrity accompanies MDD?

Through decades the common consensus was that the CNS and particularly the brain is an immune-privileged organ well protected by highly selective BBB. However, recent years of research revealed another side to it demonstrating that this barrier might be compromised by multiple factors, including psychological stress via (CRH)-mediated mast cell activation (160), bacterial LPS, O&NS, pro-inflammatory cytokines (TNF- α , IL-1 β , IFN- γ) and CCL11 (eotaxin) (90, 161-165). Interestingly, those factors also compromise the intestinal barrier. Additionally, intestinal microbiota modulate BBB permeability and short-chain fatty acids (SCFAs) produced by those bacteria, including butyrate and propionate, have a protective effect on BBB and decrease its permeability (166, 167). Furthermore, a

relatively recent discovery that the central nervous system is equipped with the lymphatic system additionally advocates re-evaluation of the above consensus (168).

A respective number of in vivo animal studies demonstrated that peripheral LPS challenge results in disruption of BBB permeability (for review of the mechanisms see (169, 170)). Varatharaj and Galea, in their systematic review, concluded that 60% of studies included in analysis revealed disrupted BBB after LPS challenge (169). Authors noted that variability in those results might be attributed to different LPS doses and dosing protocol used in studies, different species, age, health status, the gender of experimental animals, the time course of permeability estimation, and finally, types of solutes used as markers of BBB permeability. Vargas-Caraveo et al. were the first who revealed that LPS could penetrate BBB under physiological conditions and proposed mechanisms for that (171). The authors demonstrated the presence of two distinct LPS domains, namely, lipid A and core LPS in circumventricular organs, choroid plexus, meningeal cells, astrocytes, tanycytes, and endothelial cells and those domains were co-localized with CD14, TLR-4, and NF- κ B. The results of the study also suggest that LPS crossed BBB via a lipoprotein-mediated transport mechanism.

Regarding human studies, so far, the field of neurodegenerative disorders, which are often comorbid with MDD, gives us the most compelling data indicating that translocation of LPS and other bacterial molecules via BBB is possible and, interestingly, this accounts for not only patients with dementia but also healthy individuals. There is a piece of strong evidence from *post mortem* studies of patients suffering from Alzheimer's disease, which demonstrated the increased LPS levels in grey and white matter compared to controls (172). Interestingly, LPS and *Escherichia coli* K99 pili protein were also present in the control group but in a much lower concentration. Moreover, *E coli* DNA was present in the brain tissues of patients and controls. This indicates that besides increased BBB to LPS in the course of the illness, highly likely, there are also physiological mechanisms of bacterial molecules translocation via BBB. Also, another study of brain lysates from patients with Alzheimer's disease demonstrated significantly higher LPS concentrations in the hippocampus and neocortex, which in the most severe case reached a 26-fold higher level compared to the control (173).

Regarding MDD, recently, it was demonstrated that depressed adolescents had a higher S100B serum level, and this parameter is considered as a marker of increased BBB permeability and is primarily expressed in astrocytes. Moreover, patients had a higher rate of serum food-specific IgG, and this was accompanied by increased serum levels of histamine and homocysteine (120). The authors of this study suggested that IgG-mediated type III hypersensitivity against food antigens could be the principal cause of increased histamine level, which in turn contributed to increased BBB permeability in depressed patients. It was also demonstrated in the course of bipolar disorder, that patients with increased BBB permeability had more significant symptoms of depression and anxiety and a more chronic course of the illness (174).

Still, it seems that the permeability of BBB in major depression is not a "black or white" scenario. Likely, it might vary depend on various factors, including genetic ones, the severity of the illness and

the level, and the source of immune-inflammatory response accompanying the MDD and other. Moreover, the disruption of BBB is highly dependent on astrocyte function, and their abnormal function was reported in MDD. It also seems likely that interaction between peripheral inflammation, astrogliosis, and abnormal BBB permeability may progress in a vicious cycle manner where progressive dysfunction of those glial cells contributes to increased BBB permeability and subsequent, further neuroinflammatory changes contribute to astrocytic dysfunction and psychopathology.

Lipoproteins – regulators of the peripheral endotoxin load

As reviewed above, Vargas-Caraveo et al. suggested that LPS can cross BBB via lipoprotein-mediated transport (171). When discussing the role of lipoproteins in the context of LPS transport, it is also important to point out lipoproteins' crucial homeostatic role in neutralizing LPS and their elimination in the liver (175, 176). For instance, high-density lipoprotein cholesterol (HDL-C) and its apolipoprotein A-I (ApoAI) have anti-inflammatory properties and high affinity to LPS and are involved in LPS neutralization, and transport to hepatocytes for their degradation. This mechanism prevents further LPS activation of inflammatory response and synthesis of pro-inflammatory cytokines (171, 177). Consequently, lipoproteins are one of the major determinants of LPS load in the circulation, and likely in CNS, and abnormal lipoproteins concentration may contribute to increased LPS-derived immune-inflammatory response both in the periphery and CNS. Interestingly, the connection between abnormal lipoproteins levels and MDD has been previously established. For instance, MDD patients had decreased HDL-C levels compared to controls, and patients with a history of serious suicide attempts had significantly lower HDL-C compared to MDD patients without such attempts (178-180). Moreover, patients with chronic depression had significantly lower HDL-C compared to healthy controls, or patients with shorter duration of depression (181, 182), and melancholic features of MDD were independently associated with lower HDL-C (180). The data above indicates an intriguing connection between increased intestinal permeability, adverse lipoprotein patterns, and depressive symptoms. Further exploration of this area might have implications for MDD treatment.

LPS and glucocorticoids

Another vital connection between LPS and depression is the involvement of endotoxin in glucocorticoid (GKK) functions and the immune response to those anti-inflammatory hormones. So far, there is compelling scientific data that suggests that LPS may contribute to GCC resistance what could also highly likely have a negative impact on intestinal barrier function. It is well established that hyperactivity of the HPA axis accompanies MDD, and 50% to 80% of patients experience hypercortisolemia with the highest rates in severe depression (183), and the severity of depression correlates with cortisol plasma levels (119). Consistently, it was also proposed that the modulation of glucocorticoid receptors (GR) is one of the mechanisms involved in antidepressants' action (183).

Furthermore, psychological stress and chronic inflammation are known to contribute to GCC resistance (184, 185). It was previously demonstrated, particularly in patients with Crohn's disease, that GCC treatment decreased intestinal permeability and retightened intestinal tight junctions (TJ) via inhibition of TNF- α – induced increase in myosin light chain kinase (MLCK) protein expression, and GCC beneficial influence on the intestinal barrier was mediated by GR (186, 187). Unfortunately, it is not uncommon that the longer time of GCC treatment, the less effective it is due to the gradual development of resistance to those anti-inflammatory hormones. Consequently, the deletion of intestinal epithelial GR receptor NR3C1 led to increased intestinal permeability (188). It was demonstrated that exposure to LPS increases the expression of GR β in macrophage what contributed to GR resistance and inhibited the anti-inflammatory action of GCC (189, 190). Furthermore, LPS led to the loss of the GCC inhibitory effect on the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) (191). However, the effect of LPS on expression of GR isoforms is not consistent and may vary depending on the cell types (191). Still, this seems an intriguing direction for further investigations whether the mechanism of GR resistance (due to i.e., LPS, pro-inflammatory cytokines, and cortisol) also contributes to intestinal GR resistance and subsequent increased intestinal permeability. This could, for example, take place due to the lack of GCC inhibitory role on TNF- α – induced increased intestinal permeability. Finally, it is worth mentioning that BBB is highly influenced by GCC, which decrease its permeability. There are many analogies between structure and functions of BBB and intestinal barrier, and both those barriers and their permeabilities are susceptible to analogous immune detrimental factors, including TNF- α , IL-1 β , IFN- γ , O&NS, and LPS.

Increased intestinal permeability – the source of autoimmunity in MDD

Another crucial aspect of how the "leaky-gut" may contribute to MDD, is the involvement of the compromised intestinal barrier in the autoimmunity (Fig.1). This is a very interesting and broad topic which introduction in-depth is beyond the scope of this chapter (for further reading see (25)). However, it is briefly worth mentioning that highly likely it is not an epidemiological coincidence that autoimmune disorders increase the risk of major depression and other psychiatric disorders (192, 193), and that there is growing evidence of increased intestinal permeability and dysbiosis in various autoimmune disorders, comorbid with MDD, such as IBD, MS, coeliac disease, diabetes, to name a few (96, 194-196). On the one hand, bacterial translocation leads to increased O&NS, hypernitrosylation and generation of immunogenic neoepitopes (14). On the other hand, food-derived antigenic material, for instance, lectins and agglutinins, bind with the tissue and form neoepitopes in a covalent-binding mechanism what leads to autoimmunity. Another mechanism is a molecular mimicry/cross-reactivity, where due to unfortunate molecular coincidence, there is a structural homology between antigenic material (i.e., gut-derived or newly O&NS/hypernitrosylation-formed) and own structure of the organisms what leads to the autoimmune reaction against this structure i.e., cell membrane, tissue etc.

For instance, molecular mimicry between casein and butyrophilin with myelin, cerebellum or even a key enzymes responsible for GABA synthesis were demonstrated (197-200). Those fascinating, but concerning interactions clearly indicate to a substantial role of a healthy intestinal barrier, well balanced intestinal microbiota and a diet, in the context of inflammation, autoimmunity and mental health.

4. Conclusions

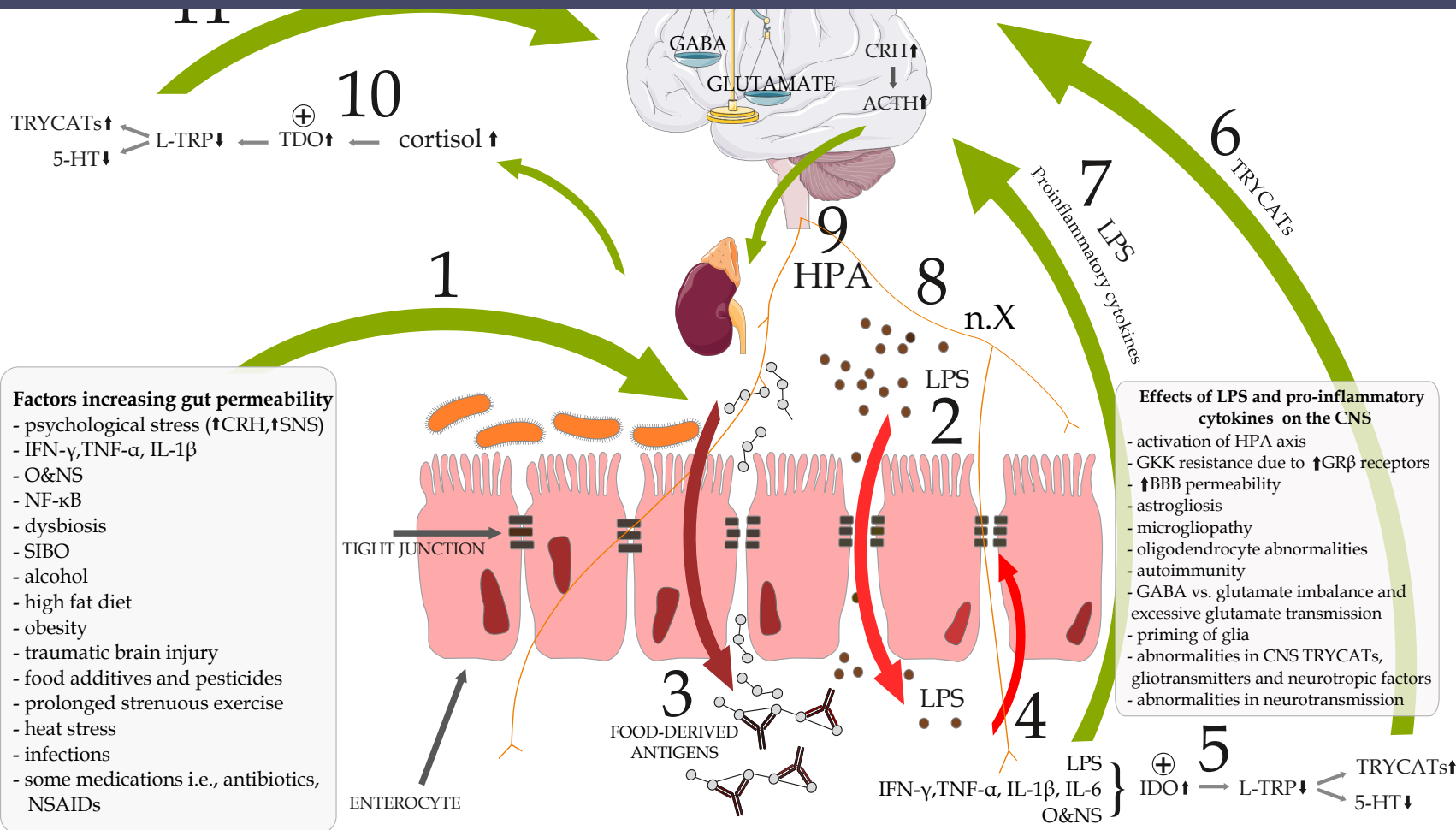
We are facing exciting times in neuroscience and psychiatry research and it is becoming evident that the mind-body connection takes place on the sites of interaction between the immune, endocrine, and nervous systems. Given that it is also becoming clear that a more holistic approach in the context of mental health diagnosis and treatment is required to warrant its truly efficient and long-term effects. Surely, the intestinal barrier with GALT and intestinal microbiota, which until quite recently remained the "forgotten organ" do play a major part in the above mind-body interactions. It is crucial to promote this knowledge among medical professionals and patients and to implement accessible and cost-effective markers of intestinal permeability, gut-derived inflammation, and autoimmunities driven by bacterial and food-derived antigens. It is also important to bring more attention to the prophylactics and the treatment focusing on the improvement of the integrity of the intestinal barrier. This could include specific supplementation and dietary interventions with known benefits to the gut barrier, and those include, for example, probiotics, prebiotics, turmeric, zinc, glutamine and other. Diet is another crucial factor contributing to mental health and the field of nutritional psychiatry is recently receiving growing attention. A diet when is not well balanced i.e., Western, high-fat, high-carbohydrate diet, contributes to neuroinflammation and depression. Contrary, a good quality diet rich in antioxidants, polyphenols, fiber, pre and probiotics, healthy fats will have a therapeutic value. Making those healthy and conscious choices may be the first step towards wellbeing and a healthy body and mind.

Figure 1. The Overview of mechanisms involved in increased intestinal permeability and subsequent activation of the immune-inflammatory response in depression

(Image generated using Servier Medical Art. Partially adapted and modified from Rudzki et al. 2012 (201))

1) Various factors contribute to increased intestinal permeability (i.e., psychological stress, inflammation, dysbiosis, O&NS, diet and other); 2) Increased translocation of bacterial LPS through the intestinal epithelium and subsequent activation of the immune-inflammatory response (i.e., via activation of TLR4, RAGE, NF- κ B) and increase levels of pro-inflammatory cytokines, O&NS peripherally and within the CNS, LPS may contribute to the peripheral and within the CNS autoimmunity; 3) Increased translocation of food-derived antigens and formation of IgG immune complexes and IgG-mediated type III hypersensitivity; food antigens-associated molecular mimicry and covalent binding may lead to peripheral and within the CNS inflammatory response and autoimmunity); 4) Further disruption of the gut barrier due to released pro-inflammatory cytokines, O&NS and activation of NF- κ B; 5) Activation of IDO by LPS, pro-inflammatory cytokines, O&NS with subsequent increased synthesis of TRYCATs and decreased availability of tryptophan for conversion to 5-HT and melatonin; 6) Detrimental influence of TRYCATs on the CNS; 7) Influence of pro-inflammatory cytokines and LPS on CNS by humoral route with subsequent: activation of HPA axis, increase expression of GR β leading to GCC resistance; increase of BBB permeability, astrogliosis, microgliopathy, oligodendrocyte abnormalities, priming of glia, abnormalities in CNS TRYCATs, gliotransmitters and neurotropic factors, imbalance between GABA and glutamate and increased glutamate neurotransmission, abnormalities in 5-HT, NA and DA neurotransmission; 8) Peripheral LPS and pro-inflammatory cytokines activate the CNS inflammatory response via neural route (n.X); 9) Activation of HPA axis and subsequent increase in cortisol level; 10) Activation of TDO by elevated cortisol with subsequent increase in synthesis of TRYCATs and decreased availability of tryptophan for conversion to 5-HT and melatonin; 11) Further detrimental influence of TRYCATs on the CNS

BBB: blood-brain-barrier; BDNF: brain-derived neurotrophic factor; CNS: the central nervous system; CRH: corticotropin-releasing hormone; DA: dopamine; IgG: immunoglobulin G; GABA: γ -aminobutyric acid; HPA: hypothalamic-pituitary-adrenal axis; GCC: glucocorticoids; GR β : glucocorticoid receptor β ; IDO: indoleamine 2,3 dioxxygenase; LPS: bacterial lipopolysaccharides; L-TRP: tryptophan; NA: noradrenaline; NF- κ B: nuclear factor kappa B; NSAIDs: nonsteroidal anti-inflammatory drugs; n.X: vagal nerve; O&NS: oxidative and nitrosative stress; RAGE: receptors for advanced glycation end products; SIBO: small intestinal bacterial overgrowth; SNS: the sympathetic nervous system; TLR: toll-like receptors; TRYCATs: tryptophan catabolites; 5-HT: serotonin



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