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The microbiota-gut-immune-glia (MGIG) axis in major depression

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Abstract

There is robust evidence that major depression (MDD) is accompanied by a low-grade activation of the immune-inflammatory response system, which is involved in the pathophysiology of this disorder. It is also becoming apparent that glia cells are in reciprocal communication with neurons and orchestrate various neuromodulatory, homeostatic, metabolic, and immune mechanisms and have a crucial role in neuroinflammatory mechanisms in MDD. Those cells mediate the central nervous system (CNS) response to systemic inflammation and psychological stress, but at the same time, they may be an origin of the inflammatory response in the CNS. The sources of activation of the inflammatory response in MDD are immense, however, in recent years, it is becoming increasingly evident that the gastrointestinal tract with gut-associated lymphoid tissue (GALT) and increased intestinal permeability to bacterial LPS and food-derived antigens contribute to activation of low-grade inflammatory response with subsequent psychiatric manifestations. Furthermore, an excessive permeability to gut-derived antigenic material may lead to subsequent autoimmunities which are also known to be comorbid with MDD. In this review, we discuss fascinating interactions between the gastrointestinal tract, increased intestinal permeability, intestinal microbiota, and glia-neuron crosstalk, and their roles in the pathogenesis of the inflammatory hypothesis of MDD. To emphasize those crucial intercommunications for the brain functions, we propose the term of *microbiota-gut-immune-glia (MGIG) axis.*

Keywords:
depression, leaky gut, microbiota, cytokines, neuroimmunomodulation, oxidative stress

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1. Introduction

In recent years, there has been growing evidence regarding abnormal glial functions and quantity in various psychiatric disorders such as schizophrenia, bipolar disorder, attention deficit hyperactivity disorder (ADHD), anxiety disorders, dementia, and major depressive disorder (MDD) (1) (Figure 1). It is becoming clear that glia abnormalities have a crucial role in the neuroinflammatory pathophysiology of those disorders. MDD is also accompanied by volumetric brain reduction and a decrease in metabolic activity mostly in the hippocampus and medial prefrontal cortex (mPFC) and it is becoming evident that those changes are not only due to neuronal atrophy but also abnormalities in non-neuronal glial cells contribute to those changes (2).

Within the central nervous system (CNS), glial cells include astrocytes, microglia, oligodendrocytes, and ependymal cells, that are in the constant reciprocal communication with neurons and orchestrate neuromodulatory, homeostatic, metabolic, and immune mechanisms. Glia are also highly involved in neurogenesis, neuronal plasticity, neuronal pruning, and stripping. Given such complex involvement of glia in brain functions and psychiatric pathology, it is valuable to study the mechanisms and origins of glial activation and abnormalities. Moreover, further exploration of how to modulate those non-neuronal constituents of the nervous system might improve psychiatric prophylactics and treatment.

There is robust evidence that MDD is accompanied by activation of the immune-inflammatory response that manifests with increased levels of pro-inflammatory cytokines, mostly IL-1β, TNF-α, IL-6, activation of oxidative and nitrosative stress (O&NS) with subsequent autoimmunity against O&NS generated neoepitopes (3-5). Moreover, abnormalities in the metabolism of tryptophan (TRP) and its catabolites (TRYCATs) via the kynurenine pathway were also observed in this disorder (6, 7). All the above processes take place both in the periphery and within CNS and glia mediate central response to systemic inflammation. On the other hand, glia may also be an origin of central inflammatory response when the abnormality is located in the CNS or when influenced by psychological stress - a well-known precipitating and exacerbating factor of the first episodes, reoccurrence, and deterioration of psychiatric disorders' symptoms (Figures 1, 2).

The activation of the inflammatory response system in MDD may often be derived from various comorbid inflammatory and autoimmune diseases, which are known risk factors of MDD. The question, however, arises, what is the source of the inflammatory response in the periphery and CNS without a specific comorbid inflammatory disorder? First, it is worth

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differentiating inflammation from parainflammation since both accompany MDD. The first one could be considered as a "classic inflammation" caused by pathogens, more precisely by pathogen-associated molecular patterns (PAMPs) including bacterial lipopolysaccharides (LPS)/endotoxin, bacterial lipoproteins, flagellins, peptidoglycans and other. The second type – parainflammation, is considered as a "sterile inflammation" and is triggered by psychological stress or by Danger/Damage Associated Molecular Patterns (DAMPs), otherwise defined as alarmins. Those biomolecules are released as a result of tissue injury and include heat-shock proteins, HMGB1 (high-mobility group box 1), hyaluronan fragments, ATP, uric acid, DNA, RNA and heparin sulfate. Both PAMPs and DAMPs are recognized by pattern recognition receptors (PRRs) including Toll-like receptors (TLRs). For instance, activation of TLR4 with bacterial LPS triggers so-called inflammasomes – innate immune system receptors, which further activate intracellular pro-inflammatory caspases what results with the release of proinflammatory cytokines.

Further, psychological stress may increase expression of TLRs on macrophages and amplifies NF-κB activation induced by LPS, and through activation of hypothalamic-pituitary-axis (HPA) and sympathetic nervous system (SNS) may up-regulate the expression of nuclear factor kappa beta (NF-κB) in mononuclear cells with subsequent increase of pro-inflammatory cytokines release (8-10). Also, catecholamines are known to play a crucial role in the stress-induced release of central and peripheral pro-inflammatory cytokines, microglial activation, and increased macrophages trafficking to the brain. Consequently, β-adrenergic receptor antagonist propranolol prevented stress-induced microglial activation and pro-inflammatory cytokines gene expression in those cells with subsequent decrease of anxiety-like behaviors (11, 12).

In recent years it is becoming increasingly evident that the gastrointestinal tract with gut-associated lymphoid tissue (GALT) contributes to activation of low-grade inflammatory response with subsequent psychiatric manifestations (13). GALT is the source of 70-80% of immune cells in the human organism and the gastrointestinal tract is the largest surface of contact between the human body and the external environment. GI tract is also the interaction site of the immune system with an enormous number of intestinal microbiota which constitutes the primary source of PAMPs. However, this selective barrier may be compromised by multiple factors ranging from psychological stress to environmental, immune and intestinal microbiota-related factors (Figure 1). Disruption of this barrier and increase of its permeability leads to the activation of immune-inflammatory responses due to the influx of antigenic material including

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LPS and food-derived antigens. Because of that GI tract could be considered as the "immune gate" of the psychopathology (13).

Interestingly, increased intestinal permeability accompanies various psychiatric disorders, including chronic fatigue syndrome (CFS) (14, 15), MDD (16-21), schizophrenia, bipolar disorder, and autism (13). The role of gut-derived inflammation and increased intestinal permeability in the pathogenesis of psychiatric disorders is not a new concept, and almost 70 years ago Buscaino demonstrated various inflammatory changes in post mortem studies of patients with schizophrenia (22, 23) while Henri Baruk indicated a compelling role of gastrointestinal tract, infections and intestinal toxins in schizophrenia and catatonia (24-27). Also, Asperger recognized the association between coeliac disease and psychotic disorders (28). In 1979 Dohan proposed an intriguing hypothesis that *"Basic biological defect in schizophrenia is genetic impairment (e.g., via defective enzymes or, receptors) of the gut and other barrier systems which eases the passage of food-derived neuroactive polypeptides from the gut lumen to brain cells"* (29). Currently, it is becoming increasingly clear that indeed, besides compromised intestinal barrier, increased permeability of BBB, might be a part of the clinical picture of schizophrenia, bipolar disorder, MDD, and autism (30).

Latterly, another player emerged in this multidimensional milieu of gut-brain interactions. Intestinal microbiota, for which we are talking, due to its vast, not yet well-explored functions in human health and disease, are considered as "forgotten organ." This fascinating symbiont exceeds the number of cells of the human body by ten times, and it is estimated that the combined set of intestinal microbiota's genes is 150 times larger than that of the human genome (31). These organisms, through the endocrine and neural mechanisms, including vagal nerve mediation, may influence immunity, brain functions and behavior. Microbiota could be considered as guardians of the intestinal epithelium and its permeability. Due to their close interaction with GALT, those bacteria may exert anti-inflammatory effects via a decrease of peripheral and central pro-inflammatory cytokines concentrations or increase of anti-inflammatory cytokines concentrations. Furthermore, they modulate the HPA axis, tryptophan and TRYCATs metabolism in kynurenine and serotoninergic axes and are the source of multiple neurotransmitters and neuroactive compounds, including GABA, 5-HT, dopamine, norepinephrine, histamine, acetylcholine and short-chain fatty acids (SCFA) (Figure 1). Intestinal microbiota are involved in microglia maturation, neurogenesis and shape regulation of the expression of neurotransmitters' receptors in the brain, regulate blood-brain barrier (BBB) permeability and take part in other fascinating microbiota-gut-brain axis interactions, which we will explore in this review (32-35). Accordingly, various abnormalities

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of intestinal microbiota were demonstrated in psychiatric disorders including MDD (36-39), schizophrenia and bipolar disorder (40), autism (41-44), dementia (45) CFS (46), alcoholism (47). Furthermore, growing clinical data confirms the therapeutic effects of so-called psychobiotics in those disorders (32, 48-64).

In this review, we will take a "step back" to take a broader look at those intriguing interactions between GI tract, inflammation and mental health with particular emphasis on how microbiota-gut-brain axis and increased intestinal permeability, so-called "leaky-gut," may affect glia functions and contribute to MDD pathophysiology.

Furthermore, to emphasize increasingly evident, vast, and essential interactions between intestinal microbiota, gastrointestinal tract, and glia, we propose the term of *microbiota-gut-immune-glia (MGIG) axis.*

2. Glia-neuron crosstalk and depression

2.1 Astrocytes-neuron crosstalk and depression

Astrocytes are the most numerous glial cells within human CNS constituting 20-40% of glia, and it is estimated that a single astrocyte may interact with up to two million synapses (65). These cells have critical roles in the regulation of neuronal activity, growth, and survival, synapse formation, integration of synaptic information, synaptic transmission and plasticity. Astrocytes perform critical for neurons metabolic functions including regulation of fluid and ion balance, provision of energy and growth factors (66). They produce various gliotransmitters including glutamate, ATP and D-serine (67), and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and inducible nerve growth factor (VGF) which are involved in neurogenesis, synaptic plasticity and promotion of excitatory synaptic transmission. These glial cells are equipped in multiple receptors for monoamines including adrenoreceptors and 5-HT receptors, and glia are highly responsive to changes of monoamines extracellular concentration. Moreover, the release of the above tropic factors by astrocytes is dependent on extracellular monoamines concentration. Given that, it was proposed that antidepressant medication may also act via this pathway, which incorporates astrocytes into the classical monoamine hypothesis of antidepressants' action (2). For instance, secretion of BDNF, VEGF and VGF are increased by monoamines and by antidepressants which increase monoamines levels (68). It is worth mentioning that astrocytic response to 5-HT may be interfered with by glutamate what in turn may be improved by serotonin reuptake inhibitors (SSRI) treatment (68). Additionally, astrocytes are equipped in transporters for

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serotonin (SERT) and noradrenaline (NERT). Further, astrocytes are the site of TRP metabolism via the kynurenine pathway and they generate kynurenic acid (KYNA) which may exert neuroprotective effect due to its antagonism to glutamate receptors. KYNA is also an antagonist of the alpha7 nicotinic receptor for acetylcholine (α7 nAChR) what indicates functionally significant crosstalk between the nicotinic cholinergic system, astrocytes and the kynurenine pathway (69).

Astrocytic endfeets provide almost complete sheath covering the brain's microvessels, which has critical implications in the regulation of blood-brain barrier (BBB) function including its permeability (70).

Those glial cells play a pivotal role in the regulation of CNS immunity and inflammatory response via the release of cytokines, chemokines, regulation of adaptive immune responses, and regulation of immune cells trafficking into CNS, and they influence microglia functions. Depending on the stimuli, astrocytes may exert anti-inflammatory, protective *modus operandi* through the release of anti-inflammatory cytokines, involvement in immunosuppression, promotion of cell survival, myelin preservation and reduction of BBB permeability. Contrary, in highly activated detrimental mode, these cells exert potent pro-inflammatory functions via the release of pro-inflammatory cytokines and chemokines, immune cells recruitment, oxidative and nitrosative stress, promotion of neuronal death, demyelination and BBB impairment (71). For instance, the pro-inflammatory cytokine IL-1β, broadly involved in inflammatory processes in depression, stimulates astrocytes to generate VEGF which contributes to increased permeability of BBB and leucocytes extravasation (72, 73).

Another crucial aspect is that human astrocytes express TLR4 to recognize bacterial LPS (74), and exposure of astrocytes to LPS contributes to activation of their pro-inflammatory and cytotoxic profiles (75). Subsequently, in the lipopolysaccharide (LPS)-induced model of depression (with LPS administered intraperitoneally), inhibition of activated astrocytes prevented depressive-like behaviors and attenuated neuroinflammation and decreased expression of hippocampal IL-1β, TNF-α, iNOS, and GFAP. This was also accompanied by an improvement of hippocampal BDNF expression, a recognized biomarker for antidepressant treatment efficacy (76). Furthermore, activation of astrocytic LTR4 by systemic LPS challenge in the early postnatal period led to neurodevelopmental abnormality and excessive formation of excitatory synapses that resulted in the increase of seizure activity (77). Interestingly, lithium, which is a well-known potent mood stabilizer, ameliorated LPS-induced activation of astrocytes, partially by inhibition of TLR4 expression (78).

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Formation of *glia limitans* – a functional borders separating neural from non-neural tissue along meninges, perivascular space, and tissue lesions within CNS, is another crucial role of astrocytes in the context of CNS immunity and autoimmunity (75). When facing CNS insults, astrocytes react with astrogliosis and scar formation, wound closure, and restriction of inflammatory processes. These processes also support BBB restoration (75). Astrogliosis however, may also contribute to the aggravation of the inflammation.

The most acknowledged mechanism of astrocytes' involvement in MDD pathophysiology relates to their regulation of glutamate and γ-aminobutyric acid (GABA) levels and balance between those neurotransmitters. The former is the primary and most abundant excitatory neurotransmitter in the human brain, and the latter is the main inhibitory one. Astrocytes are responsible for removal of over 90% of glutamate in the glutamatergic synapses and they are also the site of glutamate conversion to glutamine with glutamine synthetase. Because of that, initially, the model of the tripartite synapse was proposed which incorporated pre and postsynaptic membranes accompanied by astrocyte regulating glutamate turnover. However, as a result of growing evidence of reciprocal interactions between astrocytes, microglia and neurons a term of the quad-partite synapse was proposed (79-81).

MDD is accompanied by astrogliosis characterized by astrocyte morphological changes and a decrease in their numbers and/or density, and those abnormalities were demonstrated both in humans and in animal models of MDD (65). As well, psychological stress can induce significant structural remodeling of astrocytes and microglia (79), and MDD patients have decreased number and density of astrocytes in the hippocampus, prefrontal cortex (PFC) and amygdala (65). Post mortem studies demonstrated that MDD and schizophrenia are characterised by a decreased expression of the glial fibrillary acidic protein (GFAP) in PFC, a parameter characteristic for astrocytes activation (82). Also, post mortem studies revealed astrocytic hypertrophy in anterior cingulate white matter in depressed suicides and those changes could reflect local inflammation in the white matter of MDD patients (83). Consistently, treatment with SSRI and a tricyclic antidepressant (TCA) had a beneficial effect on astrocytes' morphology and number, similarly to nonpharmacological treatment with electroconvulsive therapy (ECT) and transcranial magnetic stimulation (65).

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2.2 Microglia-neuron crosstalk and depression

Pathologies of microglia, namely microgliopathy, with either activation or suppression and decline of microglial functions in specific brain areas were demonstrated in depressed patients, and it was proposed that some forms of MDD could be considered as a microglial disease (84). These glial cells are the first-line defense resident macrophages in neural parenchyma providing constant surveillance of the surrounding environment (85). They modulate neuronal functions and numerous immune processes and perform key roles in synaptogenesis, synapse elimination, and plasticity through synaptic pruning and synapse sampling. These brain resident macrophages closely and reciprocally crosstalk with neurons via multiple soluble factors and contact-dependent mechanisms. Microglia release proinflammatory cytokines (IL-1β, TNF-α), prostaglandin E2 (PGE2), neurotrophins (BDNF), chemokines, nitric oxide (NO), neurotransmitters, such as glutamate and ATP. They are also the site of tryptophan metabolism via the "neurotoxic branch" of the kynurenine pathway and generate TRYCATs involved in the inflammatory pathophysiology of MDD. Those include 3-hydroxykynurenine (3OHKYN), which can induce oxidative damage and cell death, and quinolinic acid (QUIN), an NMDA receptor agonist that stimulates synaptosomal glutamate release and inhibits its uptake into astrocytes what may result with neurotoxicity (86). Furthermore, there are reciprocal astrocytes-microglia interactions in the context of glutamate, and it was demonstrated that stimulation of astrocytes with LPS resulted in the release of ATP from microglia, which bound to astrocytic P2Y receptor. This subsequently led to increased release of glutamate by astrocytes and increased excitatory neurotransmission (87).

On the other hand, neurons regulate microglial functions and viability through soluble factors such as chemokines, including crucial in neurodevelopment fractalkine (CX3CL1), cytokines, such as transforming growth factor β (TGFβ), colony-stimulating factor-1 (CSF1), interleukin-34. In addition, neurons release neurotransmitters, including glutamate, GABA, norepinephrine and nucleotides - uridine diphosphate (UDP) and adenosine triphosphate (ATP) which bind to microglia and regulate microglial motility and phagocytosis (88). For example, excessive release of glutamate induces microglial chemotaxis towards the source of glutamate release (89).

Microglia, depending on their environment, may present various modes of action, which could be divided into "resting microglia" or rather "surveying/steady-state microglia" since, precisely speaking, it is never resting, and activated or reactive microglia. In its surveying mode microglia remain stationary and express ramified morphology with motile

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processes that continuously monitor their territory (90). However, it is worth mentioning that those cells do not function in clearly defined dichotomy and they may also exist in transitional forms between highly activated and surveying modes. Microglia, as the brain resident macrophages, are equipped in the plethora of receptors for DAMPs and PAMPs, including TLR4 for bacterial LPS, receptors for cytokines, chemokines, prostaglandins, various neurotransmitters, ATP and complement system. Subsequently, psychological stress and different immune challenges both in the CNS and in the periphery such as infection, trauma, increased load of peripheral LPS, autoimmune processes, oxidative and nitrosative stress (O&NS), significant changes in glutamatergic and noradrenergic neurotransmission can activate those glial cells. Activated microglia release pro-inflammatory, cytokines, adopt an enlarged soma, ameboid morphology and phagocytic activity, and migrate towards the source of infection, injury, abnormal neuronal activity, or neuroinflammation etc. Moreover, it is particularly important in the context of MDD, that activation of microglia leads to activation of IDO and synthesis of detrimental TRYCATs, activation of glutamate transmission, decrease in brain synthesis of BDNF and other tropic factors and subsequently decreased neurogenesis (84).

Accordingly, morphological changes of microglia due to exposure to stress were demonstrated in brain regions, namely the prefrontal cortex, hippocampus, hypothalamus, amygdala and nucleus accumbens, which are known to be involved in MDD and anxiety (88). In an elegant post-mortem study of depressed suicides, Torres-Platas et al. demonstrated no difference in the number of microglial cells in the dorsal anterior cortex (dACC), a region known for its implication in major depression. However, depressed suicides had a higher proportion of primed vs. resting microglia. The authors also demonstrated twice a higher number of macrophages surrounding blood vessels along with increased gene expression of macrophage-specific marker (IBA1) and monocyte chemoattractant protein-1 (MCP-1 or CCL2), a chemokine involved in the recruitment of circulating monocytes. Depressed suicides had also increased mRNA of CD45 cells, a marker enriched in perivascular macrophages (91).

Furthermore, treatment with TCA imipramine attenuated LPS induced depressive-like behaviors and IL-6 level in mice (92) and treatment with SSRIs potently inhibited microglial TNF-α and NO production (93), and fluoxetine, and citalopram decreased microglial release of glutamate and D-serine (94) in LPS stimulated microglial cell cultures. Minocycline, a tetracycline antibiotic, is known for anti-neuroinflammatory properties and the ability to inhibit microglial activity. This medication attenuated LPS-induced neuroinflammation by reducing cortical and hippocampal mRNA levels of IL-1β, IL-6 and IDO what was accompanied by

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improvement in sickness behavior and anhedonia in laboratory animals (95). Consequently, minocycline exhibits antidepressant properties (96). Interestingly, it was demonstrated that the anti-inflammatory effects of minocycline in human microglia-like cells were mediated by retinoid signaling (97) (for further reading regarding microglia in MDD see (84)).

2.3 Oligodendrocytes-neuron crosstalk and depression

Oligodendrocytes are the third group of glial cells which abnormalities were demonstrated in MDD (98-100). Those cells received much attention in the context of their involvement in the formation of myelin; however, oligodendrocytes also have multiple immune functions, and they cross-talk with microglia and astrocytes, and this communication may be for those myelin-forming cells both protective or detrimental (101). Quiescent astrocytes and steady-state microglia are involved in the maturation of oligodendrocytes, maintenance and production of myelin via the release of IL-10, TGF-β, growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF2), insulin-like growth factor 1 (IGF-1) and other (101, 102). However, activated microglia can induce damage of oligodendrocytes and myelin via the release of pro-inflammatory cytokines including TNF-α, IL-1β and IFN-γ, the release of glutamate and through activation of O&NS. LPS-induced activation of microglia and astrocytes resulted in hypomyelination with the involvement of pro-inflammatory cytokines (103) and it was demonstrated that already maternal exposure to LPS might lead to hypomyelination in the offspring (104). On the other hand, oligodendrocytes can produce immune-regulatory factors that modulate microglia and astrocyte and those include a broad range of cytokines, chemokines. Additionally, oligodendrocytes express receptors for complement system, glutamate, heat shock proteins and TLR2 and TLR3 receptors what indicates their immunomodulatory importance (102).

3. From gut-derived lipopolysaccharides to depression via the “Immune Gate” of psychopathology

Our bodies have quite stunning defense mechanisms, which for the host may be often unpleasant but lifesaving. As an example, sickness behaviors are a plethora of immune driven processes, a kind of “hibernation mode,” which helps to endure difficult sickness periods. Those could be fatigue, circadian rhythms dysregulation, loss of appetite, decreased sexual drive, a need for isolation and solitude and so on (105). Those evolutionary, adaptive behaviors

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have various precise roles. Decreased appetite which results in reduced absorption of nutrients, including tryptophan and iron, may prevent bacterial growth and their multiplication. A need for isolation could be considered as the first evolutionary quarantine, which reduces the likelihood of further infection spread. Further, cachexia is a rapid muscle wasting during cancer or other severe inflammatory disorders. This process is mediated by pro-inflammatory cytokine, TNF-α, alias cachexine, which due to its catabolic effects, is contributing to the "recycling" of resources generated in muscle and adipose tissues for the benefit of the immune system during its ongoing challenge. Finally, increased intestinal permeability is becoming a well-recognized process accompanying stress and inflammation.

It is tempting to propose a perspective that this process could have developed as another defense mechanism and that evolution, in its wisdom, found another way, with the involvement of GI, the largest immune organ, to activate and alert the immune system in response to various broadly speaking stressors, to prepare for a confrontation with a potential threat. If this reaction is time-limited, then it serves its purpose; however, when it is becoming chronic or excessive, it may lead to severe pathologic processes, including multiple inflammatory and autoimmune disorders with behavioral consequences. Moreover, intestinal milieu may have significantly different characteristics among individuals in the context of GALT's equilibrium between Th1 and Th2 cell polarization, oral tolerance or the composition of intestinal microbiota what may lead to exacerbated inflammatory and autoimmune responses in certain susceptible individuals. Also, there seem to be reciprocal interactions between the abovementioned mechanisms and increased intestinal permeability.

3.1 Various *stressors* are the cause of the "leaky gut"

Intestinal one-layer epithelium, the crucial component of the intestinal barrier, is composed of enterocytes interconnected by junctional complexes consisting of tight junctions (zonulae occludentes), adherens junctions and desmosomes which regulate the paracellular pathway. Absorption of molecules takes place also through the transcellular route (106). Animal and human studies demonstrated that psychological stress increases intestinal permeability via corticotropin-releasing hormone (CRH)-mediated mast cell activation, and this leads to translocation of luminal antigens, including bacterial and food-derived antigens. Such translocation subsequently leads to the activation of the immune-inflammatory response (107-112) (Figure 1). For instance, acute psychological stress increased permeability of antigenic protein horseradish peroxide (HRP) in intestinal villus and follicle associated

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epithelium which is specialized in antigen uptake. Further, chronic stress increased the translocation of *Escherichia coli* in follicle associated epithelium by more than 30 times and permeability to HRP increased by almost fourfold (109). Interestingly, the administration of disodium cromoglycate, mast cells "stabilizer," prevented stress-induced intestinal permeability in human subjects (107). Moreover, disruption of the intestinal barrier and its increased permeability may be caused by broad range of other *stressors* including immune, intestinal microbiota-related and environmental factors namely, pro-inflammatory cytokines, i.e., IFN-γ (113), TNF-α (114, 115), IL-1β (116), further, NF-κB (117), O&NS (112, 118), infections (119, 120), abnormalities in gut flora composition such as dysbiosis and small intestine bacterial overgrowth (SIBO) (47, 121, 122), alcohol (47, 123-125), heat stress (126), food additives and pesticides (127-132), prolonged strenuous exercise (133, 134), specific medication including non-steroidal anti-inflammatory drugs (NSAID) (135, 136) or antibiotics (137-140) (Figure 1). Furthermore, psychological stress, MDD and chronic inflammatory disorders are often accompanied by hypercortisolemia which when prolonged, may lead to glucocorticoid (GKK) receptors resistance (141). This might be another crucial aspect in the context of increased intestinal permeability in MDD since it has been demonstrated that GKK treatment-induced retightening of the intestinal tight junctions barrier defect in patients with Crohn's disease (142).

Interestingly, there are many structural and functional similarities between the intestinal barrier and BBB and the latter's permeability may be compromised by analogous factors compromising the gut barrier. Accordingly, psychological stress via (CRH)–mediated mast cell activation increases BBB permeability and this was also inhibited by disodium cromoglycate (143). Pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ), O&NS, immune products including CCL11 (eotaxin) and LPS may also compromise BBB (144-149).

3.2 Bacterial LPS cause depressive symptoms

But how could an increase in gut permeability lead to depressive symptoms and how glia could be involved in this process? Bacterial LPS is a glycolipid complex found in the outer membrane of G (-) bacteria, and it interacts with Toll-like 4 (TLR4) transmembrane receptor, which belongs to the pattern recognition receptor (PRR) family. Activation of TLR4 due to bacterial intestinal translocation leads to activation of innate immune response and proinflammatory cytokines productions via intracellular NF-κB signaling pathway. Since we, as holobionts, are in constant relation with an immense amount of symbiotic and potentially

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threatening microbes, we are broadly equipped with microbial sensing machinery and already maternal microbiome regulates embryos' expression of microglial genes involved in LPS processing and response. This suggests that microbiome, in very early stages of life, regulates the expression of genes that are involved in their own detection and response to inflammatory stimuli and dysregulations in intestinal microbiota composition may lead to an abnormal reaction of microglia to bacterial LPS (150). TLR4 are present in a broad range of immune and non-immune cells including monocytes, macrophages, granulocytes, dendritic cells, lymphocytes, microglia, astrocytes, oligodendrocytes and various tissues including intestines (151). Peripheral LPS challenge has substantial effects on the brain's immunity and behavior and leads to an increase of central proinflammatory cytokines expression and glial activation. Furthermore, bacterial LPS, glucocorticoids, O&NS and proinflammatory cytokines such as IFNγ, TNF-α, IL-1β, IL-6 can activate indoleamine 2,3 dioxygenase (IDO) and tryptophan 2,3 dioxygenase (TDO) which are the first step enzymes converting tryptophan (serotonin precursor) towards TRYCATs depleting tryptophan from the conversion to 5-HT and melatonin. Kynurenine pathway metabolism in CNS is mostly compartmentalized within glia. In astrocytes, kynurenine (KYN) is converted into kynurenic acid (KYNA) and in microglia, kynurenine is converted into more neurotoxic metabolites including 3-hydroxykynurenine (3OHKYN), 3-hydroxyanthranilic acid (3HAA) and quinolinic acid (QUIN) and for this reason, it is considered as the neurotoxic branch. It was demonstrated that in MDD, there is an imbalance between neuroprotective and neurotoxic branches of the kynurenine pathway with increased metabolism of TRP towards neurotoxic branch what may lead to increased glutamate neurotransmission (7, 152). Previously it was also demonstrated that LPS-induced depressive-like behaviors are mediated by IDO activation in mice (153). Consequently, LPS induced low-grade inflammation with subsequent transient changes in behavior, a decrease in cognitive functions, depressed mood and anxiety is a well-known laboratory model in both human and animal studies (154, 155). For instance, a peripheral challenge with bacterial endotoxin increased central mRNA expression of IL-1β, TNF-α, IL-6 in brain areas involved in MDD such as hippocampus, amygdala and striatum. This was accompanied by central microglia and astrocytes activation and increased central metabolism of TRP via kynurenine pathway (156). Another negative aspect of kynurenine pathway activation is decreased conversion of tryptophan towards melatonin which besides its circadian rhythm regulating role, also has various immune-regulatory functions and has beneficial influence on intestinal permeability (157-159). Furthermore, it was demonstrated that increased intestinal LPS translocation in

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AIDS patients led to increased peripheral monocyte activation and increased trafficking into the brain, and it is believed that this mechanism contributes to HIV-associated dementia (160).

It is noteworthy that even single activation of microglia due to peripheral LPS is priming those cells towards exacerbated inflammatory response in the future. Similarly, microglia could be primed by other inflammatory processes, trauma, and injury, aging, psychological stress in different stages of life, including early-life, prenatal stress and adulthood (Figure 2). Psychological stressors in this context may also act with the involvement of NLRP3 inflammasome (161-164). Furthermore, within CNS or systemic exposure to different inflammatory factors including IL-1β, TNF-alfa, PGE2, NO or ROS result with the heightened neuroinflammatory response of microglia (161). This mechanism is crucial in the context of MDD pathophysiology since the above microglia-priming factors may also trigger MDD onset or they coincide with a depressive episodes. For instance, there is a 7.9 times higher incidence of MDD in patients after traumatic brain injury (TBI) and 53.1% patients in the first year after TBI met criteria for MDD (165). Moreover, peripheral LPS challenge 30 days after TBI resulted in an exaggerated inflammatory response in primed microglia and induced microglial reactivity what was accompanied by the onset of depressive behaviors (166).

Increased expression of TLRs, including TLR4, was observed in depressed and suicidal patients both in the periphery and in the CNS and antidepressant treatment and cognitive-behavioral psychotherapy (CBT) decreased expression of TLR4 in peripheral mononuclear blood cells (167, 168). In particular, CBT decreased plasma expression of TLR-4 RNA and protein, NF-κB RNA and decreased 16S rRNA subunit (16S rDNA) of intestinal microbiota which is the parameter characterizing bacterial translocation. Also, clinical improvement in this study was associated with a decrease in inflammatory parameters.

LPS-induced astrocytes activation also plays a role in MDD symptomatology. Animal studies revealed that peripheral administration of LPS resulted in depressive-like behaviors and an increased in the hippocampal and cortical expression of IL-1β, TNF-α, inducible nitric oxide synthase (iNOS) and GFAP. Furthermore, the LPS challenge resulted in the decreased expression of BDNF in the hippocampus and cortex. Inhibition of activated astrocytes resulted in a decrease in neuroinflammation and reversed decreased in BDNF expression. Those changes were accompanied by amelioration of depressive-like behaviors induced by LPS (76). It was also demonstrated that lithium can ameliorate LPS-induced astrocytes activation via inhibition of TLR4 expression (78). It is also noteworthy, in the context of discussed above LPS involvement of MDD, that female microglia have higher expression of genes associated

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with response to LPS, inflammatory response and apoptotic process (169), and there is 1.7-fold greater incidence of MDD in women compared to men (170).

3.3 The evidence of the "leaky gut" in depression

There is growing evidence that MDD is accompanied by increased intestinal permeability, so-called "leaky gut" (Figure 1). It is difficult to specify when it is a cause and when effect, however, it seems that all possible combinations between those two, in a vicious circle manner, may represent different stages and/or types of the gut-derived inflammatory response in major depression (Figure 2). It is tempting to propose a distinction that increase of intestinal barrier permeability could be "gut-originated," "CNS-originated," and "periphery-originated." As discussed above, various stressors – psychological, inflammatory and environmental may compromise the gut barrier which becomes a source for systemic and central inflammatory response and autoimmunity (Figure 1). For instance, the "flagship" gut-brain axis disorders including celiac disease (CD), inflammatory bowel disorders (IBD) and irritable bowel syndrome (IBS) are the common comorbidities of MDD and anxiety and are accompanied by increased intestinal permeability which may be both the source, and a consequence of inflammation and autoimmunity (171). Also, various non-intestinal inflammatory disorders, including type 1 diabetes, obesity, food allergy, asthma, atopic eczema, multiple sclerosis (MS), rheumatoid arthritis, ankylosing spondylitis are accompanied by increased intestinal permeability and are comorbid with MDD (171-173). Those are the sources of inflammation which via peripheral and CNS-dependant manner could contribute to increased intestinal permeability and further activate the inflammatory response.

Maes and colleagues presented the first evidence of increased intestinal permeability in MDD, and two consecutive studies demonstrated that increased translocation of Gram (-) bacteria might play a role in the inflammatory pathophysiology of MDD. In those studies, the serum concentration of immunoglobulins A and M were measured against LPS of commensal enterobacteria: *Hafnia alvei, Pseudomonas aeruginosa, Morganella morganii, Pseudomonas putida, Citrobacter koseri and Klebsiella pneumonia.* Levels of immunoglobulins were higher in depressed patients' group compared to controls. Furthermore, higher IgM responses were demonstrated in chronically depressed patients (duration > two years) compared to non-chronic depression and control groups (16, 17). Besides, it was shown that translocation of intestinal commensals had activated O&NS processes, and autoimmune responses directed against O&NS generated neoantigenic epitopes in depressed patients. This suggests that bacterial

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translocation also via activation of O&NS and involvement in the autoimmunity, plays a role in MDD pathophysiology (18). In another study patients with depressive and anxiety symptoms without any gastrointestinal symptoms had increased plasma levels of zonulin and intestinal fatty acid-binding protein-2 (FABP2), a marker of impaired intestinal epithelium integrity, and those abnormalities were linked to dysbiosis in patients' group. It is worth mentioning that zonulin is a crucial regulator of epithelial and endothelial barrier permeability and its upregulation has been demonstrated in multiple chronic inflammatory, autoimmune and metabolic disorders which are frequent comorbidities of MDD (174). Also, MDD patients had increased levels of intestinal microbiota 16S rDNA in the peripheral blood as a marker of increased bacterial translocation, which was accompanied by increased expressions of TLR-4 RNA and protein in peripheral mononuclear blood cells, increased expression of NF-κB and increased concentration of IL-6. Interestingly, sixteen weeks of CBT significantly decreased all the above parameters besides IL-6 level, and authors demonstrated more pronounced clinical improvement in Hamilton Depression Rating Scale (HAM-D) in the group with greater decrease in pro-inflammatory parameters (168).

Gut permeability may be assessed by measurement of ratio in urine concentration of a disaccharide lactulose and monosaccharide mannitol after their oral administration. Since lactulose is a larger particle compared to mannitol, in the situation of increased intestinal permeability, the lactulose/mannitol (LMR) ratio increases. It was demonstrated that LMR correlated with MDD severity in adolescents, particularly with neurovegetative symptoms. In the same study, authors assessed sympathetic (SNS) and parasympathetic (PNS) nervous systems activities and provided preliminary evidence which suggested that increased intestinal permeability could mediate the association between depressive symptoms and SNS activity (20). Further, in the year 2012, the role of increased intestinal permeability to food antigens with subsequent type III hypersensitivity with the formation of IgG complexes was proposed as a source of activation of the inflammatory response in MDD (175, 176). The first study in this subject, however, failed to demonstrate a significant difference in mean IgG concentration against food antigens between patients and controls. Interestingly, there were significant positive correlations of IgG concentration to 11.36% of food products with the length of a depressive episode (months) (176). It is worth noting that almost 60% of patients in this study experienced weight loss due to decreased appetite what might have significantly reduced exposure to food antigens, and food deprivation on its own has an immune suppressive effect also on immunoglobulins production. Furthermore, most of the patients in this study experienced a first depressive episode, and only one patient had chronic depression, and it was

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previously noted that length and chronicity of depression might contribute to the intensity of the inflammatory response and intestinal permeability (17). Still, the concept of food-derived inflammatory response and autoimmunity in MDD seems valuable for further exploration, and possibly patients with chronic, recurrent depression, with gastrointestinal and/or extra-intestinal autoimmune diseases, might be a subgroup of patients where food-derived IgG hyperreactivity might contribute to the inflammatory response in MDD. In the subsequent study, it was revealed that out of 39 selected food antigens, patients with MDD had significantly higher serum levels of total IgG antibodies and IgG against celery, garlic, and gluten compared with healthy control (177).

Also, gut-derived immune-inflammatory responses and increased gut permeability may play a part in suicidality, and patients with recent suicidal attempts had increased plasma levels of LPS and antibodies to gliadin and *Saccharomyces cerevisiae* (ASCA). The latter is a yeast mannan and is a marker of GI inflammation typically increased in ulcerative colitis and Crohn's disease; however, its increased level was also previously demonstrated in patients with mood disorders (178, 179).

4. Gut-derived autoimmunity and depression

There is significant comorbidity of MDD with inflammatory and autoimmune disorders, and scientific data indicate a role of autoantibodies in the pathogenesis of MDD. A large, nationwide, population-based Danish study revealed that prior hospital contact due to autoimmune disorder increased the risk of subsequent MDD by 45%, and any history of hospitalization due to infection increased the risk of depression in the future by 62% (180). Moreover, various autoimmune disorders are often comorbid with psychotic disorders and increase the risk of schizophrenia by 45% (181). Still, the source of the autoimmunity is mostly unknown and in recent years there is a growing evidence that increased permeability of gut barrier, as the gate of entry of antigenic material, may contribute to pathogenesis of autoimmune disorders including MS, CD, type 1 diabetes, asthma, IBD and ankylosing spondylitis (171). Such peripheral and within-CNS inflammatory processes would involve broad immune machinery, including elevation of proinflammatory cytokines with subsequent activation of the kynurenine pathway, a shift in glia functions towards the inflammatory mode of action with its negative influence on brain functions including mood and cognition (Figure 1). Also, there is a growing evidence that both intestinal and non-intestinal autoimmune disorders including Grave's disease, Hashimoto's thyroiditis, multiple sclerosis (MS), systemic

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lupus erythematosus (SLE), psoriasis, psoriatic arthritis, scleroderma, type 1 diabetes and vitiligo are accompanied by alterations in the intestinal microbiota composition (182). It is worth mentioning that appropriate intestinal microflora plays a crucial role in the preservation of intestinal barrier and oral tolerance due to promoting intestinal regulatory T cells and increased levels of immune-suppressive IL-10 and TGF-β. This prevents abnormal intestinal permeability to bacterial and food-derived antigens and subsequent food immune reactivities and autoimmunities (183).

There are two well-recognized mechanisms that are believed to contribute to gut-derived autoimmunity and those are molecular mimicry (cross-reactivity), and covalent binding (Figure 1). For instance, in MS, molecular mimicry between myelin oligodendrocyte glycoprotein and milk protein - butyrophilin was demonstrated and as a consequence, due to structural similarities between those structures, there is an autoimmune reaction against host's cells and tissues, in this instance against myelin (184). As an example of second scenario – covalent binding, a new antigenic epitope is generated when food-derived antigenic material, for instance, agglutinins and lectins bind with human tissue, what leads to the formation of neoepitopes and autoimmune reaction. There are various examples of autoimmunity in MDD. As an example, patients with this disorder had higher frequency of elevation of serum anti-nuclear (ANA), anti-thyroid gland (TGA) and anti-parietal cell (PCA) antibodies and anti-brain including those against hypothalamus, hippocampus and cerebellum (185, 186) (for broader review of autoantibodies in MDD refer to (187)). Also, increased frequency in the presence of anti-5-HT antibody activity was significantly higher in depressed patients (188). In an animal study, intracerebroventricular injection of anti–ribosomal P antibodies, which are involved in neuropsychiatric symptoms of systemic lupus erythematosus (SLE), resulted in depressive-like behavior in mice what was significantly inhibited with fluoxetine treatment (189).

Interestingly, Lambert and Vojdani explored correlations between antibodies against food antigens, commonly triggering autoimmune reactions in humans, such as gluten proteins, diary and lectins/agglutinins with the presence of antibodies against different tissues (190). In patients' group negative for IgG against gluten family proteins, 35% of patients were positive for antibodies against one or more tissues, and in gluten, positive patients' group, 64% of patients reacted to one or more tissue. In patients' group negative for IgG+IgA against dairy family proteins, 30% of patients were positive for antibodies against one or more tissues, and in the dairy positive patients' group, 73% of patients reacted to one or more tissue. In patients' group negative for IgG+IgA against lectin/agglutinin proteins, 22% were positive for antibodies against one or more tissues, and in lectin/agglutinin positive patients' group 76% of

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patients reacted to one or more tissue. Impressively, in all three groups of patients positive for food-derived antigens, neurological tissues including myelin basic protein, asialoganglioside, α+β-tubulin, cerebellum and/or synapsin had the highest immune reactivity.

Previously cross-reactivities between casein and milk butyrophilin with myelin, cerebellum, and glutamic acid decarboxylase-65 (GAD65) were demonstrated (191-194). L-glutamic acid decarboxylase is a key enzyme responsible for the synthesis of gamma-aminobutyric acid (GABA), a primary inhibitory neurotransmitter, and its decreased level is believed to be involved in the symptomatology of MDD and anxiety. Interestingly, high levels of autoantibodies against GAD65 and reduced levels of GAD67 were demonstrated in MDD (195, 196). Abnormalities in brain GABA levels can also have significant immunomodulatory consequences. There is an interesting GABA-related crosstalk between astrocytes and microglia. Astrocytes are equipped in GABA synthesizing enzyme GAD 67 and in GABA A and B receptors, but microglia only express GABA receptors without an ability of synthesis of this neurotransmitter what makes them "GABA receptive cells" (197). It was demonstrated that when astrocytes and microglia were stimulated with LPS, GABA suppressed inflammatory response via inhibiting NFκB and P38 MAP kinase pathways what resulted in the reduction of TNFα and IL-6 release and decreased neurotoxicity (197). To add to this exciting gut-brain axis GABA-related reciprocity, Bravo et al. demonstrated that probiotic bacteria *L. rhamnosus* (JB-1) altered expressions of central GABA receptors in laboratory animals and this was accompanied by reduction of anxiety and depression-related behaviors, and those effects were mediated via the vagus nerve (198).

There is also a structural homology between plant aquaporin (AQP) and human aquaporin-4, and such homology may lead to molecular mimicry and autoimmunity. Those channel proteins regulate the water flow both in humans and plants, and they are present in astrocyte's endfeets, which constitute BBB. When BBB remains intact then circulating antibodies against plant-derived AQP would not interact with astrocytes which reside on the neuronal side of BBB. However, in the circumstances of disrupted BBB due to various environmental, stress-related or inflammatory factors circulating antibodies against AQP may react with astrocytes' endfeets leading to autoimmunity and further disruption of BBB (199). Interestingly, patients with MS have higher levels of serum antibodies against human and plant AQP what is believed to contribute to increased BBB and autoimmunity in MS (200). Also, autoimmunity against AQP4 is a clinical feature of another demyelinating inflammatory disorder - neuromyelitis optica (NMO) restricted to the spinal cord and optic nerves. Similarly to MS, binding of IgG

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to AQP4 is accompanied by activation of the complement system with subsequent tissue damage and demyelination (201).

The process of demyelination, however, is not limited to demyelinating diseases *per se*, and there is a piece of strong evidence that abnormalities in myelin content also accompany MDD. This is supported by a post-mortem, neuroimaging, and genetic studies (98, 99). For instance, the main feature in post-mortem studies is the decrease of oligodendrocytes concentration in prefrontal brain regions and imaging studies demonstrated that the extent of myelin abnormalities correlated with MDD symptoms severity and resistance to the antidepressant treatment (99). Quantitative magnetic resonance imaging (qMRI) revealed that MDD patients had decreased myelin level in the whole brain and patients who experienced more depressive episodes had a more significant reduction of myelin in the lateral prefrontal cortex (LPFC) (100). There are various hypotheses why patients with MDD may experience myelin abnormalities; however, the mechanism remains not fully understood and explored. It was demonstrated that neuronal activity increases myelin formation hence social isolation, which is a common feature of depression, decreased myelin content if the prefrontal cortex in mice model. Intriguingly, if mice were socially isolated very early (2 weeks after weaning), the myelination did not recover after reintroduction to the social environment (202). Further, oligodendrocytes express receptors for glutamate and it was demonstrated that those cells are highly sensitive to excitotoxicity due to glutamate excess (203). Consequently, experimental autoimmune encephalomyelitis (EAE) treatment with AMPA/kinaite glutamate receptors antagonist resulted in improvement in EAE, improved survival of oligodendrocytes and decreased axonal damage (204). It is worth mentioning that MDD is accompanied by impaired glutamate turnover by astrocytes in the quad-partite synapse and subsequent increased extracellular glutamate concentration could contribute to myelin damage. Finally, in view of the above-mentioned gut-derived autoimmunity processes in the context of demyelination, it seems reasonable to speculate that also in MDD, similar autoimmune processes could take place leading to loss of myelin.

Autoimmunity against N-methyl-D-aspartate (NMDA) receptors currently is mainly associated with anti-NMDA receptor encephalitis and its psychotic and neurologic presentation; however, the association between the presence of antibodies against this receptor and depressive symptoms were also demonstrated (205-207). Particularly this autoimmunity is a fascinating example of how gastrointestinal infection may lead to increased intestinal permeability and immune response to food antigens and subsequent development of autoimmunity against neuronal surface antigens and receptors. Severance with colleagues

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demonstrated that patients with schizophrenia had significantly increased anti-*Saccharomyces cerevisiae* IgG (ASCA) which correlated with antibodies against gluten and casein. Additionally, patients with schizophrenia had increased intestinal microbial translocation what manifested with increased levels of soluble CD14. There was also a significant correlation between *Toxoplasma gondii* infection and measures of antibodies to food antigens. In the second part of the study, which was performed on a mouse model, authors demonstrated that mice infected with *T.gondii* had elevated IgG against casein and gluten compared to noninfected controls and this correlated with measures of *T.gondii* seropositivity. Finally, infected mice had significantly increased anti-NMDA autoantibodies what was accompanied by activation of the complement system. It is worth mentioning that Toxoplasmosis is a known risk factor of schizophrenia and the recent large-scale serological study confirmed a causal relationship between *T. gondii* and schizophrenia (208).

Further, it was proposed that bacterial translocation in patients with MDD led to an autoimmune reaction in those patients. It was demonstrated that MDD was accompanied by increased intestinal permeability to commensal bacteria and that there were significant positive associations between IgM/IgA responses against bacterial LPS and various parameters of O&NS processes and autoimmune processes against neoepitopes (18). More precisely, IgM/IgA responses to LPS correlated with IgG antibody levels against oxidized LDL (oxLDL), IgM responses against malondialdehyde (MDA), azetaic acid, phophatidyl Inositol (Pi), NO-tryptophan and NO-tyrosine. Furthermore, IgA responses to LPS correlated with lysozyme, a glycoside hydrolase with antibacterial properties which is found in monocytes, macrophages and neutrophils. Those results demonstrate that bacterial translocation may induce oxidative processes and hypernitrosylation with subsequent autoimmune processes against O&NS-modified neoepitopes due to the denaturation of endogenous molecules. Also, there are structural similarities between antigenic sites of commensal bacteria and the lipid structures of neuronal tissues, for example, gangliosides, which may lead to the molecular mimicry (18). Furthermore, *Campylobacter jejuni*, a common cause of gastroenteritis in humans, exhibits mimicry of their LPS structure with myelin sheath of peripheral axons what may lead to Guillain-Barré syndrome and its neurologic manifestations (209). It was also proposed that dysbiosis may trigger autoimmune diseases via inappropriate post-translational modification of host proteins (210). More precisely, intestinal microbes express broad enzymatic machinery which is involved in post-translational modification of proteins (PTMP) within GI, however abnormal PTMP due to abnormalities in microbiota composition may result in the production of neoepitopes and subsequent autoimmunity. It is also believed that this mechanism may

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contribute to the development of various autoimmune disorders, which are accompanied by dysbiosis, such as IBD, rheumatoid arthritis, type 1 diabetes, celiac disease, and MS (182, 210).

5. Intestinal microbiota modulate glia functions

There are various mechanisms of how intestinal microbiota can interact with the central nervous system and there is a broad outstanding literature covering microbiota-gut-brain axis interactions (32, 211). In this article, we will approach this topic from the microbiota-gut-immune-glia (MGIG) axis perspective, and we will explore the role of microbiota in intestinal and BBB permeability in the regulation of microglial, oligodendrocyte and BBB maturation and functions (Figure 1). Furthermore, we will discuss the role of the aryl hydrocarbon receptor (AHR) in the communication within the MGIG axis and finally, we will summarize the involvement of gut bacteria in the modulation of serotonin and kynurenine axes.

5.1 Microbiota as modulators of intestinal and blood-brain barrier permeability

Intestinal microbiota as natural „guardians" of intestinal epithelium and regulators of GALT play a crucial role in maintaining this barrier's integrity (35, 212). Gut microbiota are able to lower the concentration of zonulin and pro-inflammatory cytokines levels, inhibit the expression of NF-κB transcription factor, increase the concentration of anti-inflammatory cytokines and regulate tryptophan and kynurenin metabolism (35, 213-216) (Figure 1). As proinflammatory cytokines, NF-κB and zonulin play a crucial role in increasing intestinal permeability, various microbes, due to their ability to regulate these parameters, show a protective effect on the intestinal barrier (35, 213, 214, 217). These bacteria have a beneficial impact on the function of intestinal tight junctions, they prevent the adherence of numerous pathogens to the intestinal epithelium, increase mucin production by epithelial goblet cells, increase the level of the secretory form of immunoglobulin A (sIgA) and antimicrobial β-defensin, which are all beneficial in maintaining intestinal barrier (218). For instance, pretreatment of animals with probiotics *Lactobacillus rhamnosus* and *Lactobacillus helveticus* completely prevented bacterial adhesion to the intestinal epithelium and stress-induced bacterial translocation to mesenteric lymph nodes and improved intestinal barrier function following psychological stress (212). *Lactobacillus* species also prevented stress-induced bacterial translocation and reduced HPA activity (219). Further, *Lactobacillus rhamnosus* GG attenuated IFNγ and TNF-α induced intestinal permeability via inhibiting NF-kB signaling

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(35). In a group of endurance-trained men, a multispecies probiotic treatment resulted in decreased zonulin in feces and beneficially affected plasma TNF-α concentration (217).

Microbiota also modulate BBB permeability, and it was demonstrated that germ-free (GF) mice displayed increased BBB permeability due to the disorganization of endothelial tight junctions and decreased expression of their proteins, namely occludin and claudin-5. In addition, embryos from GF mice displayed more permeable BBB. Exposure of GF mice to gut microbiota led to the upregulation of BBB tight junctions' proteins and decreased permeability. Finally, it was demonstrated that the administration of SCFA - sodium butyrate increased expression of occludin in the frontal cortex and hippocampus of GF mice and decreased BBB permeability. The authors also demonstrated decreased BBB permeability after monocolonisation of GF mice with bacterial strains *Clostridium tyrobutyricum*, known for its ability to synthesize butyrate, and with *Bacteroides thetaiotaomicron,* known for its ability to synthesize acetate and propionate (220).

5.2. MGIG axis in the regulation of microglial maturation and function

Another key aspect of the microbiota-gut-brain axis or, more precisely, MGIG axis is the ability of intestinal microbiota to control maturation and functions of microglia (Figure 1). It was demonstrated that GF mice displayed abnormal morphology, immature phenotype and increased number of brain microglia what was accompanied by impaired innate immune responses. Further, the limited complexity of gastrointestinal microbiota was related to defective microglia and the recolonization of intestinal flora improved features of those glial cells. Interestingly, in this study, eradication of microbiota with antibiotics led to similar impairments in microglia functions to those of GF animals, and abnormalities of microglia were also reversed by SCFA administration what indicates the crucial role of SCFA in microglial functions (221). One of the mechanisms of how microglia respond to their environment is the expression of sensome genes what was initially demonstrated in adult microglia (222). Recently, Thion and colleagues, in their elegant study, showed that microglia begin to express sensome genes already *in utero* and subsequently, authors revealed that microbiome influences prenatal and adult microglia in a sex-dependant manner (223). For instance, the absence of maternal microbiome from fetal stages resulted in dysregulation of genes related to microglia morphogenesis, regulation of transcription, adaptive immune responses, cell migration and chemotaxis and these effects were sex-dependent. Also, GF mice demonstrated an increased density of microglia in their embryos' somatosensory cortex, the

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striatum and preoptic area. In this study authors also revealed that microbiome regulates expression of genes affecting LPS processing and response and interestingly concluded that "*microbiome regulates the early expressions of genes controlling its own detection and response to inflammation*" and that "*maternal microbiota might prime microglia to their challenges in postnatal period*."

5.3 MGIG axis influences oligodendrocyte function and myelination

The intestinal microbiota also has a crucial role in myelination. It was demonstrated that appropriate cortical myelination is dependent on the intestinal microbiota during critical windows of neurodevelopment and that microbiota determined the expression of genes involved in myelination (224). Furthermore, SCAF butyrate suppressed demyelination and enhanced remyelination. In the mice model of cuprizone-induced demyelination, oral administration of antibiotics significantly increased demyelination that was prevented by butyrate administration. In this study, butyrate did not decrease microglia accumulation in a demyelinated lesion, which indicates that this SCFA had a direct influence on oligodendrocytes (225).

5.4 The aryl hydrocarbon receptor (AHR) - a mean of communication MGIG axis

Aryl hydrocarbon receptor (AHR) is another piece of exciting microbiota-gut-immune-glia axis puzzle. Until recently, its role was mostly discussed in the context of GI immunity; however, recent findings confirm its involvement in the regulation of glial functions and neuroinflammation by diet and intestinal microbiota. AHR is a ligand-activated transcription factor and various immune cells are equipped with this receptor, for instance, intraepithelial lymphocytes (IEL) and mucosal T helper 17 cells in the gastrointestinal tract, and astrocytes, and microglia in the CNS. Ligands of this receptor include environmental toxins, i.e. dioxins which by means of binding to this receptor, activate enzymes such as cytochrome P450 involved in dioxins metabolism.

Also, dietary products including vegetables from cabbage family such as broccoli, cauliflower, Brussel sprouts, cabbage, watercress or kale, are the source of indole-3-carbinol which along with its metabolites exhibit a strong affinity for the AHR (226) (Figure 1). Furthermore, vegetables and fruits are the sources of other AHR ligands such as flavonoids, carotenoids and stilbenes (227). Intestinal microbiota, for instance, probiotic bacteria

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Lactobacillus reuteri, are involved in the synthesis of AHR ligands from dietary tryptophan and GF mice have attenuated expression of AHR receptor (228). Because of that, AHR seems to be a crucial point of interaction between gut microbiota and the immune system. In the GI tract due to affinity to the abovementioned lymphocytes, AHR ligands are broadly speaking involved in intestine immune function regulation since AHR deficient mice have increased intestinal inflammation and permeability (183).

This receptor is also involved in interactions between diet, intestinal microbiota, microglia, and astrocyte functions. Rothhammer and colleagues demonstrated that transforming growth factor-alpha (TGF-α) and Vascular endothelial growth factor B (VEGF-B) produced by microglia are involved in the regulation of astrocyte functions in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) and human samples (229). Further, the authors demonstrated that intestinal microbes utilize dietary TRP for the synthesis of AHR agonists, including indoxyl-3-sulfate (I3S), to regulate the production of TGF-α and VEGF-B and subsequently CNS inflammation through AHR. For instance, *Lactobacillus reuteri* is a probiotic bacteria that can transform TRP into AHR agonists (230). AHR may directly influence astrocytes' functions. Type I interferon signaling along with TRP metabolites synthesized by intestinal flora activated AHR what resulted in suppression of CNS inflammation in the course of EAE (231). Further, AHR plays a crucial role in microglial response to bacterial LPS and its response may be both anti-inflammatory and pro-inflammatory depending on the availability of AHR ligands. More precisely, AHR when activated by its ligands, such as formylindolo[3,2-b]carbazole (FICZ) or 3-methylcholanthrene (3MC), attenuated LPS-induced microglial immune responses via limitation of NF-κB activity (232). Finally, microbiota-derived SCFA including butyrate and propionate, enhance AHR activities in the presence of their ligands (227).

5.5 Modulation of serotonin and kynurenine axes by microbiota

A robust clinical data is indicating the crucial role of tryptophan and TRYCATs in psychiatric disorders, including MDD. TRYCATs have various immunomodulatory functions, influence glutamate transmission and exert both neurotoxic and neuroprotective roles in CNS and their metabolism is compartmentalized within glia. Both peripheral and central inflammation drives the metabolism of tryptophan via the kynurenine pathway with the subsequent synthesis of various TRYCATs. It was demonstrated that peripheral LPS challenge was accompanied by central microglia and astrocytes activation, and increased central, and

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peripheral metabolism of TRP in kynurenine pathway via neurotoxic branch (156), and peripheral LPS challenge is a well-known laboratory model leading to depressive-like behaviors both in human and animals (154, 155). Given that, mechanisms influencing the kynurenine pathway both central and, in the periphery, may modify microglia and astrocytes function with detrimental consequences in neurotransmission.

The growing amount of evidence indicates intestinal microbes' significance in the metabolism of tryptophan and kynurenines. For instance, it was recently demonstrated that augmentation of SSRI treatment with psychobiotic *Lactobacillus plantarum 299v* decreased plasma kynurenin level in depressed patients what was accompanied by improvement of cognitive functions in those patients (233). Animal studies revealed an elevated plasma tryptophan level in GF animals, which normalized after colonization of the gastrointestinal tract bacterial flora (234). Also, GF animals had elevated plasma levels of both tryptophan and 5-HT compared to animals raised in the conventional conditions (235). GF mice also had reduced kynurenine:tryptophan ratio (KYN:TRP) and this parameter can characterize the activity of IDO and TDO - the first step kynurenine pathway enzymes. Moreover, KYN:TRP ratio normalized after colonization with bacterial flora (234). Besides, gastrointestinal infection with *Trichuris muris* increased TRP: KYN and this infection was accompanied by anxiety symptoms in infected mice, a decrease in hippocampal BDNF (BDNF mRNA), and an increase in peripheral TNF-α, IFN-γ levels. Anti-inflammatory treatment of infected animals with etanercept and budesonide decreased KYN and proinflammatory cytokines levels along with improvement in anxiety symptoms. Also, the administration of probiotic *Bifidobacterium longum* normalized BDNF levels and reduced anxiety symptoms in those animals (236). Desbonnet with colleagues were the first to demonstrate the antidepressant properties of the psychobiotic *Bifidobacterium infantis* in an animal model. These bacteria increased plasma tryptophan and KYNA levels. Also, *Bifidobacterium infantis* had a beneficial effect on the HPA axis, proinflammatory cytokine levels of IFN-γ, IL-6, TNFα and monoamine levels in the brain of the animals studied, e.g. by normalizing the level of noradrenaline in the brainstem, lowering the level of 5-HIAA (5-hydroxyindole acetic acid - product of TRP metabolism and 5-HT breakdown) in the frontal cortex and reduction of DOPAC (3.4 dihydroxyphenylacetic acid - product of dopamine metabolism) in the cortex of the amygdala of examined animals. Furthermore, this probiotic reversed behavioral deficits in the maternal separation model of depression (215, 216).

Intestinal microbiota have also the capacity to modulate the activity of different enzymes of the kynurenine pathway thanks to their ability to synthesize different enzymatic

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cofactors. For instance, the administration of probiotic *Lactobacillus johnsonii* resulted in a decrease in plasma KYN levels. Interestingly, these bacteria also reduced IDO activity in vitro in HT-29 intestinal epithelial cells. The authors also observed that *L. johnsonii* increased the synthesis of H_2O_2 in the intestinal lumen and that H_2O_2 reduced IDO activity (237). This result is consistent with previous studies that have shown that H_2O_2 reduces IDO activity. Since many probiotic bacteria can produce H_2O_2, this could highly likely be a "universal" mechanism through which probiotics and intestinal microbiota can modulate the kynurenine pathway.

Moreover, intestinal microbiota are able to produce various vitamins including vitamin K and vitamins of group B, such as folates, nicotinic acid, biotin, pyridoxine, thiamine, cobalamin and pantothenic acid (238, 239) and some of those vitamins including vitamin B2 and B6 are cofactors in kynurenine pathway (240). More precisely, an active form of riboflavin (vitamin B2) - flavin adenine dinucleotide (FAD), is a cofactor for kynurenine 3-monooxygenase (KMO) and an active form of pyridoxine (vitamin B6) - pyridoxal 5'-phosphate (PLP), is a cofactor for kynurenine aminotransferase (KAT) and kynureninase (240, 241). Furthermore, riboflavin is required for the conversion of pyridoxine and folate to bioavailable forms. Consequently, the administration of vitamin B6 decreased KYN levels due to increased activity of kynurenine pathway enzymes (242, 243). It is worth mentioning that appropriate levels of above enzymatic cofactors are crucial to prevent the accumulation of detrimental kynurenines and both inflammation and psychological stress contribute to more rapid utilization of those cofactors (244, 245).

There are also direct ways of how intestinal microbiota may influence TRP and 5-HT metabolism. An example of the direct effect of bacteria on TRP metabolism is that some bacteria have the tryptophanase enzyme that converts indole to TRP (246). Moreover, bacteria also can synthesize TRP with the participation of the tryptophan synthase and *Lactobacillus plantarum* has also been shown to have the ability to synthesize 5-HT from TRP (247).

6. Diet and glia functions in the context of depression

It is well recognized that there is a reciprocal connection between depression and obesity and that obesity increases the risk of MDD and cognitive decline. Furthermore, the western diet, high consumption of fat and sugar, excess in alcohol consumption are associated with MDD, and abnormal intestinal barrier function (248-251) (Figures 1,2).

Obesity may also be accompanied by volumetric brain changes, for instance, in the prefrontal cortex (PFC), the area related to MDD pathophysiology (252). Low-grade

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inflammation, which is associated with obesity and MDD, seems to be one of the factors contributing to the relations as mentioned above and the adipose tissue is a source of proinflammatory cytokines including IL-1β, TNF-α, and IL-6. On the other hand, interactions between diet, weight, inflammation and mental health are not yet fully understood.

Recently another perspective emerges that diet may modulate microbial composition and permeability of intestinal and BBB, and this may influence humoral and immune mechanisms, including glia functions with subsequent effects on mental and physical health. Human and animal studies confirmed that obesity is associated with changes in the composition of intestinal microbiota (253), increased intestinal and BBB permeability (254, 255). For instance, animal studies demonstrated that prolonged high-fat diet (HFD) might lead to gut dysbiosis characterized by an increased ratio of *Firmicutes* to *Bacteroidetes* bacterial phyla and increased growth of *Proteobacteria* – mainly G(-) lipopolysaccharide containing bacteria. Those abnormalities were accompanied by increased levels of peripheral cytokines and LPS, induction of TLR4 receptors and nitrosative stress and reduction of tight-junction proteins claudin-1 and occludin in the colon. Furthermore, HFD exacerbated inflammation and obesity via the TLR4 signaling pathway (256) and chronic HFD led to the dysfunction of microglia morphology in PFC what was accompanied by cognitive deficits (257). Dietary obesity due to HFD led to impairment of hippocampal-dependent memory, increased hippocampal IL-1β, induced synaptic stripping by microglia and impaired hippocampal plasticity. Interestingly, those abnormalities were reversible with a low-fat diet (258). Furthermore, chronic HFD induced gut dysbiosis, gut and systemic inflammation including increased LPS level in sera. Moreover, HFD led to the activation of microglia, hippocampal dysplasticity, mitochondrial dysfunctions and impairment of cognitive functions. Consumption of prebiotic (xyloolidosaccharide), probiotic (*Lactobacillus paracasei* HII01) or symbiotic significantly decreased above abnormalities. Interestingly, probiotic and symbiotic also reduced plasma insulin levels (259). Contrary, in obese women, caloric restriction and weight loss resulted in a decrease of intestinal permeability and reduction of peripheral inflammation parameters, including plasma high-sensitivity C-reactive protein (hsCRP) and lipopolysaccharide-binding protein (LBP) (260). Also, in rodents, a low-fat diet with caloric restriction reduced activation of microglia activated by aging (261). Probiotic mixture VSL#3 decreased the effect of peripheral inflammation on brain immunity. More precisely, it reduced microglial activation and cerebral monocyte activation with a simultaneous decrease in sickness behaviors and level of circulation TNF- α (262).

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7. Conclusions and future perspectives

Ronald S. Smith, in the early nineties, proposed *The Macrophage Theory of Depression* (263). In his sadly unfinished book, "Cytokines & Depression. How your immune system *causes* depression", in a mind-provoking way, he referred to the First Edition of Encyclopaedia Britannica published in 1771, in which thirty-seven different subtypes of fever disease were described as separate disorders.

Smith wrote: *"Eventually it was understood that fever is not one disease nor 37 kinds of fever diseases, but rather it is a trustworthy* ***universal sign of acute immune system activation****. Fever is a sign of* ***acute*** *immune system activation, regardless of any other signs, symptoms or diseases that it may be associated with. After this realization, fewer was no longer a bewildering and complex disease, but instead, a simple, direct and easily understood signal of acute immune activation"* (264).

Given such significant progress in the field of psychoneuroimmunology in the last three decades, we are coming to an understanding, analogically to Smith's forethought, that symptoms of major depression are manifestations of a broad range of immune-mediated and inflammatory processes. However, we are still building our knowledge about the mechanisms and sources of such inflammatory response, and it is reasonable to believe that the gastrointestinal tract with GALT and the vast surface of contact with antigenic material, together with intestinal microbiota play a crucial role in psychiatric psychopathology including the one of MDD. In this review, we discussed increasingly evident interactions between gastrointestinal tract, increased intestinal permeability, intestinal microbiota, and glia functions, and to emphasize those crucial intercommunications for the brain functions, we propose the term of *microbiota-gut-immune-glia (MGIG) axis.*

Also, promoting the knowledge regarding inflammatory mechanisms underlying psychiatric symptoms could be of high significance for patients and their families. Currently, still, the common stigmatizing understanding is that symptoms of depression, schizophrenia, bipolar disorder, and other psychiatric disorders are "just something in suffering person's head," or that "there is something wrong with this person," etc., and usually, patients are very much identified with the symptoms of their illness believing that "they are their depression or psychosis." Similarly, their environment, family, and friends often identify the person with their symptoms. There is usually a significant relief for patients and their families when they start to realize that the mechanisms underlying psychiatric symptoms could be immune-mediated and that, after all, they have distinct organic background with manifestations in their

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behavior, emotions, distorted perception of reality, and in various physical aspects including changes in their energy level, appetite, circadian rhythms, and other.

Also, bringing more attention to the GI tract in the context of psychiatric treatment and diagnosis is desirable. This includes further development and broader implementation of easily accessible markers of increased intestinal permeability and gut-derived inflammatory response, such as measurements of the immune response to bacterial and food-derived antigens, assessment of autoimmunities, for example, cross-reactivities between food antigens and tissues. Moreover, evaluations of intestinal microbiota composition with subsequent "targeted" supplementation of probiotics will be valuable.

Dietary interventions are another aspect that is receiving recognition in depression treatment and prevention, and recently we are observing a growing interest in an exciting field of the Nutritional Psychiatry (265). There are reports which indicate that specific diets for instance, Western diet (249, 266, 267), high-fat (256) and high-carbohydrate diets (250), contribute to depression and neuroinflammation. Contrary, the Mediterranean diet (268), calorie restriction (260, 269-271), anti-inflammatory diet (272, 273), and, in general, improvement of quality of diet and nutrition (274, 275) may benefit MDD prevention and treatment. Also, taking into consideration that food-derived antigens may also contribute to inflammation and autoimmunity, further research regarding the role of an elimination diet and implementation of such diets for MDD patients might be valuable. Particularly, food elimination diet based on IgG antibodies had beneficial effects in neurologic and GI disorders such as irritable bowel syndrome, Crohn's disease and migraine, and improvement in those symptoms is believed to be related to decreased levels of food-specific IgG response due to decreased exposure to food antigens (276-281).

Additionally, it is relevant to incorporate in psychiatric treatment easily accessible and well-tolerated supplementation of nutraceuticals, prebiotics, probiotics, antioxidants, minerals and vitamins which have anti-inflammatory mechanisms of action and beneficially influence GI tract. As an example, curcumin and zinc are known for their antidepressant, anti-inflammatory mechanisms of action and beneficial influence on intestinal permeability (282-287). Curcumin decreases the level of TNFα, a pro-inflammatory cytokine that negatively influences tight junctions and increases intestinal and BBB permeability (288), decreases IDO activity (289) and inhibits NF-κβ signaling involved in increased permeability of both intestinal and BBB barriers (290). Interestingly, curcumin decreases the permeability of BBB and microglial activation (291, 292), and this herb also has a positive influence on astrocyte functions. It was shown that curcumin had a neuroprotective effect on LPS-activated astrocytes

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and prevented of GFAP and NF-κB upregulation (293), and alleviated oxidative stress, and mitochondrial dysfunction in those glial cells (294).

Finally, we also propose that the mechanism of increase of intestinal permeability could have evolved as a way of activation of the immune system in response to various broadly speaking stressors, to prepare for a confrontation with a potential threat. However, this mechanism functions in a "double edge sword" manner that, in general, is quite common for the immune system. Consequently, if increased gut permeability is chronic or excessive, it may lead to severe pathologic processes including multiple inflammatory and autoimmune disorders with psychiatric manifestations.

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Figure 1. **The role of MGIG in the pathogenesis of MDD**
(Image generated using Servier Medical Art. Partially adapted and modified from (13))

1: Factors compromising the intestinal barrier lead to increased intestinal permeability to bacterial LPS and food antigens. **2**: Increased intestinal permeability is a source of bacterial LPS and food-derived antigens which lead to activation of peripheral and within CNS immune-inflammatory response with involvement of i.e., pro-inflammatory cytokines, increased O&NS, activation of HPA, activation of TLR4 by bacterial LPS, activation of kynurenine pathway with subsequent diversion of tryptophan from 5-HT synthesis towards synthesis of detrimental TRYCATs, development of type III hypersensitivity to food antigens and development of peripheral and central autoimmunity. **3**: Gut-derived antigens lead to peripheral and within CNS autoimmunity via molecular mimicry and covalent binding, and bacterial translocation may induce oxidative processes and hypernitrosylation with subsequent autoimmune processes against O&NS-modified neoepitopes due to the denaturation of endogenous molecules. **4**: Abnormalities in glia functions contributing to the pathogenesis of MDD. **5**: Microbiota regulate glia functions via humoral and neural routes (n. X). **6**: Microbiota regulate peripheral inflammation i.e., via decreasing intestinal permeability, decreasing levels of pro-inflammatory cytokines, modulation of tryptophan, 5HT and TRYCATs metabolism. **7**: Diet modulates glia functions. **8**: Factors increasing blood-brain-barrier permeability.

A: astrocyte; Ach: acetylcholine; AHR: aryl hydrocarbon receptor; BBB: blood-brain-barrier; BDNF: brain-derived neurotrophic factor; CNS: central nervous system; CRH: corticotropin-releasing hormone; GABA: γ-aminobutyric acid; HPA: hypothalamic–pituitary–adrenal axis; IDO: indoleamine 2,3 dioxygenase; M: microglia; MDD: major depressive disorder; MGIG: the microbiota-gut-immune-glia axis; N: neuron; NE: norepinephrine; NF-κB: nuclear factor kappa B; NSAIDs: Nonsteroidal anti-inflammatory drugs; O: oligodendrocyte; O&NS: oxidative and nitrosative stress; SCFAs: short-chain fatty acids; SIBO: small intestinal bacterial overgrowth; TLR: toll-like receptors; TRYCATs: tryptophan catabolites; 5-HT: serotonin

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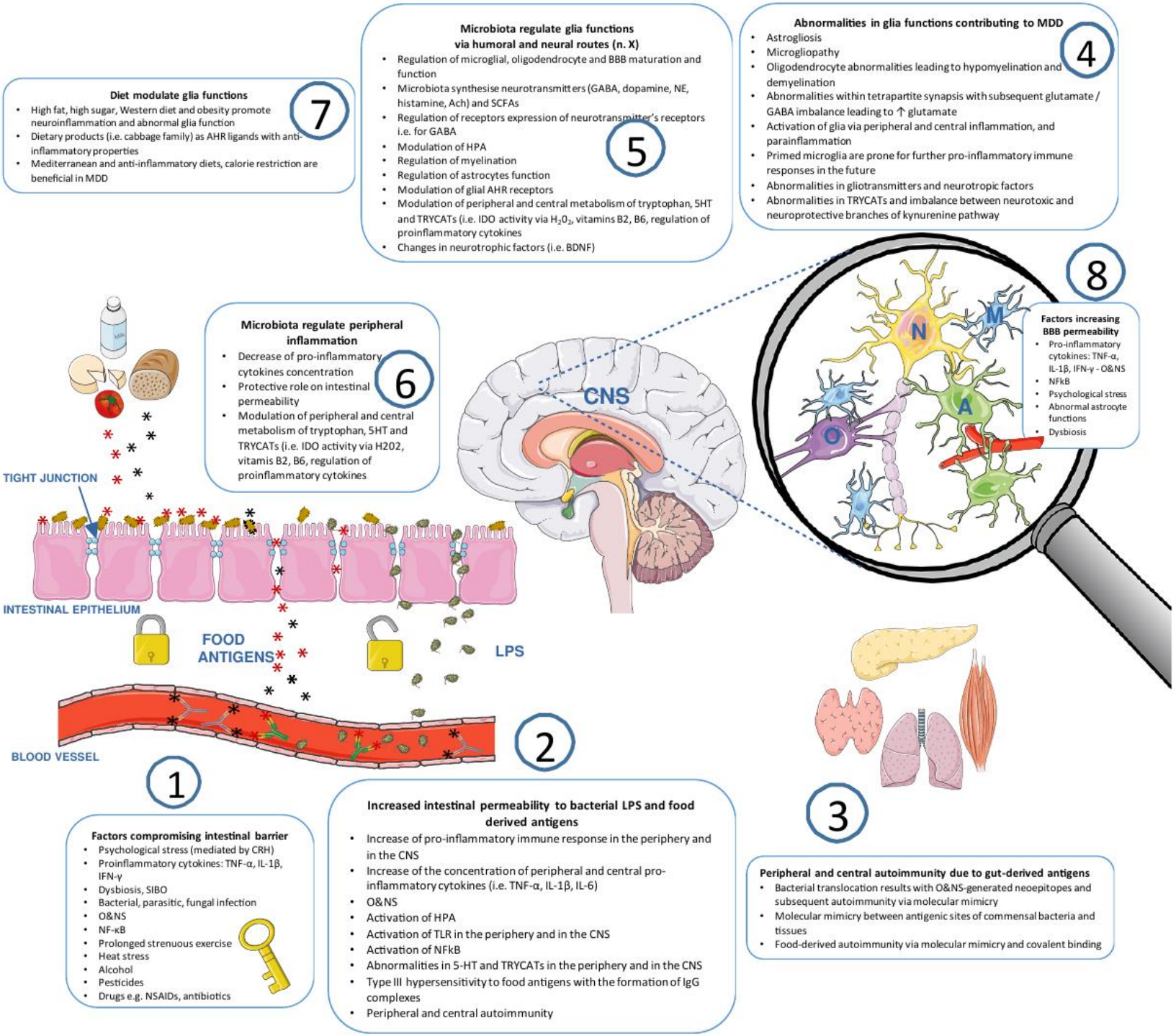

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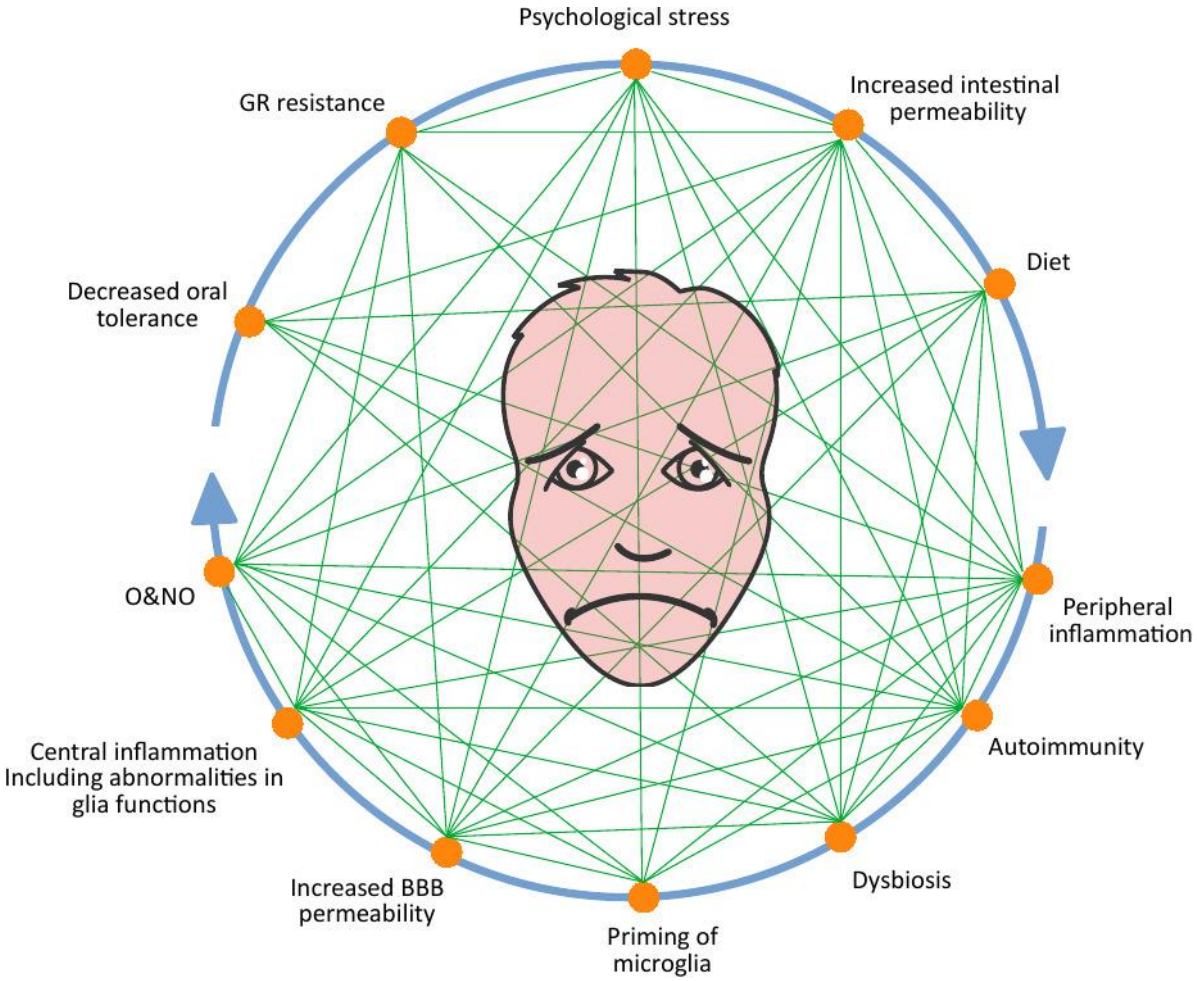
Figure 2. **The vicious circle of the reciprocal immune-inflammatory and MGIG interactions contributing to depression pathophysiology**
(*Image generated using Servier Medical Art*)



Immune-inflammatory mechanisms that take part in the pathogenesis of major depression may have various origins, and there are reciprocal interactions between above-presented components. For instance, psychological stress may lead to increased intestinal permeability, which contributes to inflammation in the periphery and/or within CNS what contributes to symptoms of MDD. Alternatively, inflammatory processes in the periphery i.e., in the course of IBD, may lead to increased intestinal permeability and inflammatory processes (an increase of proinflammatory cytokines, O&NO, increase in TRYCATs etc.) what contributes to depressive symptoms. As another example, dysbiosis may lead to increased intestinal permeability and subsequent translocation of bacterial and food-derived antigens which further activation of immune-inflammatory response and autoimmunity. Also, microglia can be primed with peripheral LPS and other immune-inflammatory processes, trauma, and injury, aging, psychological stress in different stages of life, including early-life, prenatal stress and adulthood. Priming of microglia results with the exacerbated glial pro-inflammatory response when in the future, there is an exposure to similar factors including psychological stress, inflammation etc. that may contribute to the first episode or reoccurrence of the depressive episode. Various other sequences of immune-inflammatory and MGIG interactions are possible with shared outcome in the form of depressive symptoms.

BBB: blood-brain-barrier; IBD: inflammatory bowel diseases; LPS: bacterial lipopolysaccharides; GR: glucocorticoid receptor; MDD: major depressive disorder; MGIG: microbiota-gut-immune-glia axis; O&NO: oxidative and nitrosative stress; TRYCATs: tryptophan catabolites via the kynurenine pathway