

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Involvement of Astrocytes in the Process of Metabolic Syndrome

*Ana Karolina Santana Nunes, Haniel Soares Fernandes
and Sura Wanessa Santos Rocha*

Abstract

Astrocytes constitute a very heterogeneous population of cells, which regulate pH, extracellular levels of ions and neurotransmitters, and energy metabolism in addition to actively participating in neurotransmission. In situations of damage to the CNS, the typical response is the degree of reactive gliosis, which can form glial scars. On the other hand, chronic diseases such as obesity, type 2 diabetes, hypertension, and atherosclerosis have been causally related to low-grade chronic inflammation in various metabolic tissues. It has been pointed out that the identification of hypothalamic inflammatory alterations are triggered by overnutrition, orchestrated by the hypothalamic immune system, and sustained by the pathophysiology associated with the metabolic syndrome. We discuss here the effects of astrocytes and the main astrocyte mechanisms involved in the metabolic syndrome and its comorbidities.

Keywords: astrocytes, neuroinflammation, metabolic syndrome, metabolism

1. Introduction

The cases of metabolic syndrome (MetS) in adults are increasing, due to several factors such as aging population, physical inactivity, obesity and chronic overnutrition [1]. Metabolic abnormalities are involved in the metabolic syndrome, such as diabetes mellitus, hypercholesterolemia and dyslipidemia, hypertension, and central obesity [2]. Several studies in neuroscience and immunology are linked to overnutrition to neuroinflammation, particularly in the hypothalamus and in the hippocampus, due to interaction between accelerated adiposity, hyperglycemia, and cognitive decline [3–5].

The primary risk of cognitive decline in both obese and hyperglycemic individuals is the systemic and chronic inflammatory component of MetS, due to preparation of the resident population of glial cells to establish a form of low-grade neuroinflammation [6].

Astrocytes are active agents of the dynamic central nervous system (CNS) signaling. The astrocytes participate in a variety of essential physiological processes in the healthy brain, such as providing structural support to neurons, participating in the formation and maturation of synapses, control of homeostasis of ions and metabolites, receptor trafficking, neurotransmitter clearance, and modulating the synaptic plasticity moment by moment [7]. Many studies have shown their contribution to information processing and memory formation in the brain, thus pointing to a role for astrocytes in higher integrated brain functions [8, 9].

A vast arsenal at the disposal of astrocytes is being defined, as in the determination of functions and mechanisms of reactive astrogliosis, cellular hypertrophy, and glial scar formation with preservation of the cellular domains and rearrangement of the tissue structure as well as contributing to specific CNS disorders and lesions [9]. Neuroinflammation in the enteric system occurs due to the activation of enteric glial cells (EGCs) which are the most abundant cells within the enteric nervous system (ENS). EGCs are located adjacent to the neurons within the enteric ganglia and along the interganglionic connections of the myenteric and submucosal plexus but also protrude into the extraganglionic mucosal layer [10–13]. Their morphology and the expression of markers such as calcium-binding protein S100 and glial fibrillary acidic protein (GFAP) [14] resemble central nervous system astrocytes.

The EGCs can exert immunomodulatory functions; they can secrete inflammatory signaling molecules such as interleukins IL-1 β and IL-6 [10, 15] as well as other mediators, including nerve growth factor (NGF), S-nitrosoglutathione (GSNO), nitric oxide (NO), and S100B [16], and express class II major histocompatibility (MHC) complex molecules [16, 17]. CNS astrocytes activated by inflammation are characterized by hypertrophy and proliferation, coupled with a positive regulation of the GFAP's cytoskeleton [18], due metabolic syndrome and inflammatory conditions of the intestinal disease (IBD) [19].

Many studies have shown that multiple connections between peripheral and cerebral changes involving inflammatory, metabolic, and neural components have been identified under conditions associated with obesity [20–22]. Therefore, identifying and treating these conditions is of primary importance to people worldwide. Obesity-related chronic inflammation provides an important link to metabolic derangements including insulin resistance, cognitive impairment affecting the hypothalamus, and other brain regions [20].

The present study was designed to discuss the effects of astrocytes and the main astrocyte and neuroinflammatory mechanisms involved in the metabolic syndrome and their comorbidities, which gave rise to the field of immunometabolism.

2. Neuroimmunologic mechanisms and role of glial cells

Until recently the CNS was considered to be immunologically privileged, since many antibodies and peripheral immune system cells are usually blocked through the blood-brain barrier (BBB), a specialized structure composed of endothelial cells (ECs), pericytes, astrocytes, and microglia [23]. The BBB maintains the chemical composition of the neuronal microenvironment, which is necessary for the proper functioning of neuronal circuits, synaptic transmission, synaptic remodeling, angiogenesis, and neurogenesis [24].

The immune system influences the functioning of BBB, which in turn affects the functioning of the CNS in both physiological and pathological conditions. In some cases, the BBB separates the CNS from the immune system; in others it acts as a mediator of neuroimmune interactions, and in others it may act as a target for immune system attacks [25]. In physiological conditions, immune cells cross the BBB at a very low rate, through specific interactions, promoting the endothelial junctions that control the flow of cells through them [26–28]. On the other hand, neuropathological diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), lateral amyotrophic sclerosis (LAS), multiple sclerosis (MS), and BBB destruction or damage, can be induced or mediated by LPS (lipopolysaccharide), cytokines, prostaglandins, and nitric oxide. The BBB is capable of responding to LPS due to the presence of Toll-like receptor 4 (TLR4) and other Toll-like receptors on the membranes of the BBB cells [29]. Similarly, these cells have receptors for

cytokines, chemokines, and other immunological molecules [30, 31]. As a result, the immune system is able to affect the functions of the BBB beyond those of disruption.

Perivascular cells (astrocytes and microglia) in addition to endothelial cells produce several inflammatory factors, such as the release of cytokines and chemokines that affect the BBB permeability and the expression of adhesion molecules. Cytokines (TNF- α , IL1- β , IFN- γ) can stimulate the expression of adhesion molecules (vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1)) in endothelial cells allowing the passage of activated leukocytes into the CNS [32]. Immune cell (macrophages, lymphocytes) traffic through the BBB should initiate or contribute to a vicious cycle resulting in progressive synaptic dysfunction and neuronal loss in neurodegenerative disorders [20, 24].

On the other hand, a specific subset of T cells is essential to suppress autoimmunity and maintain immune homeostasis. T regulatory cells (Treg) have been characterized with important functions. Emerging evidence shows that Treg cells are not only important for maintaining immune balance at the periphery but also contribute to the self-tolerance and immune privilege in CNS [33]. Leukocyte extravasation requires interactions between adhesion molecules in endothelial cells and leukocytes. Leukocyte adhesion molecules (LAMs) expressed by ECs include P-selectin, E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1) [34]. Selectin binds to P-selectin-binding glycoprotein (PSGL-1), while ICAM-1 and VCAM-1 bind to α 4-integrins in leukocytes. After the initial binding event, immune cells roll along the vessel wall releasing chemokines that strengthen their binding interactions, promoting the state of neuroinflammation [35].

Neuroinflammation is recognized as a prominent feature of various pathological conditions [36]. Thus, several lines of evidence strongly suggest that neuroinflammation is a crucial process involved in the progression of neuronal degeneration, a common feature observed in several neurodegenerative disorders such as degenerative neuropathologies [36]. In the inflammatory process, the main cellular events are observed, such as increased blood flow and vascular permeability with consequent venular dilation and recruitment of cells to the inflamed site. A significant role played by reactive oxygen species has been observed to develop inflammation, causing endothelial cell damage and increased microvascular permeability, chemotactic factor production, neutrophil recruitment, oxidation, and lipid peroxidation [37]. Such inflammatory mediators play a regulatory role in the growth, differentiation, and activation of immune cells [38]. Glial cells (microglia, astrocytes, and oligodendrocytes) define cerebral homeostasis and are responsible for defense and preservation against neural tissue injury [14].

3. The role of astrocytes in neuroinflammation

Astrocytes are an important group of heterogeneous cells and play key roles in the physiology of the nervous system, including regulation of pH, extracellular levels of ions and neurotransmitters, and energy metabolism. In addition, it plays an important role in the formation and functioning of the BBB [39] and also actively participates in neurotransmission [27]. In pathological situations in the CNS, the typical response of astrocytes is the state of reactive gliosis involving positive gene regulation of cytoskeletal proteins (e.g., glial fibrillary acidic protein (GFAP)) and corresponding to the change in morphology reaching a state of hypertrophy, hyperplasia, and glial scar formation [40–42].

In addition, astrocytes play an important role in central immunity. The innate immune response is accurately adjusted by identifying the type of threat that is present. The molecular structures that are associated with threats are recognized by Pattern Recognition Receptors (PRRs). PRRs recognize molecular patterns associated with pathogens (PAMPs) are expressions such as microorganisms such as bacteria, viruses and viruses, and damage-associated diseases (DAMPs) that signal cellular damage and are therefore responsible for a state of stress or injury [14]. Among PRRs, one of the main classes is the family of transmembrane proteins of Toll-like receptors (TLRs). Generally pathogen response and tissue damage happen quickly, assuming some roles of the cells of the immune system, releasing cytokines (IL-1 β , IL-6, TNF- α) and chemokines (MCP-1, CCR-2, COX-2), influencing other cells of the immune system (macrophages and lymphocytes), and modulating the BBB [14].

Among glial cells, astrocytes play a role in the release of Toll-like receptors [43]. Since the TLRs are expressed and detected by the binding of their binding genes, a signaling mediated by the myeloid differentiation gene 88 (Myd88) is initiated, having an activation of the nuclear transcription factor NF κ B. In the activation of NF κ B, the inflammatory process is released through the secretion of pro-inflammatory molecules (1 β , IL-6, TNF- α , IL-12). In addition, there is no state of activation of astrocytes to recruit microorganisms, lymphocytes, and dendritic cells to the lesion site [44].

4. Implications of metabolic syndrome in the central nervous system: the role of the bowel-brain axis

The increased obesity in the last 40 years is considered a consequence of the sedentary lifestyle and adherence to diets rich in saturated fat and refined carbohydrates that induce changes in the microbiota and underlying metabolic and psychological complications [45]. Bacteria, viruses, protozoa, archaea, and fungi represent the microorganisms that inhabit the intestinal tract of mammals, with bacteria composing the majority [46, 47] in concentrations between 10^1 to 10^3 cells per gram in the upper intestine and 10^{11} to 10^{12} cells per gram in the colon [48].

These microorganisms play a role in human physiology through various mechanisms, such as the metabolism of nutrients and the regulation of immunological and neuroendocrine functions, as they bind to the CNS through the enteric nervous system (ENS) [49]. From the microbiota, the active metabolite LPS (lipopolysaccharide), in addition to short-chain fatty acids (SCFA), from invasive and commensal bacteria, respectively [50, 51], can be expressed in the intestinal lumen and influence the integrity of BBB [52], especially butyrate, in which it positively induces the expression of junction proteins, including claudin-2, occludin, cingulin, and occludens-1 and occludens-2 (ZO-1 and ZO-2), forming protein structures in the gut, like tight junction [53, 54]. These proteins form a mechanical link between epithelial cells and establish paracellular diffusion of fluids and solutes in the barrier [55]. Where high fiber and fruit meals were shown to reduce the increases induced by meals with high saturated fat and high carbohydrate content in levels inflammatory response [56].

In mammals, colon epithelial cells, adipocytes, and peripheral blood mononuclear cells express a pair of G-protein-coupled receptors (GPR41 and GPR43) that are activated by SCFAs through the receptors on the T enteroendocrine cells [57]. They sense the amount of AGCC produced by bacteria in the colon and secrete the glucagon-like peptide 1 (GLP-1) and the tyrosine tyrosine peptide (PYY), allowing inhibition of intestinal motility and increased absorption of nutrients, respectively [58]. Thus, the

composition of the diet determines the type of nutrient that reaches the gastrointestinal tract (GI) that can alter the composition of the intestinal microbiota and the production of metabolites to, consequently, influence intestinal permeability [59].

Bacterial products, such as LPS, can display a variety of PAMPs recognized by TLRs and nucleotide-binding oligomerization domain receptors (NOD) on macrophages and dendritic cells in the innate immune system, such as flagellin, recognized by TLR5 to induce α -defensin secretion through Paneth cells, a NOD-dependent antimicrobial protein [60]. All TLRs recognize protein, lipid, or nucleotide PAMPs. TLR2, TLR4, and TLR6 recognize fungal PAMPs, while TLR9 and TLR11 recognize protozoan PAMPs [61]. Although TLRs can activate immune cell proliferation through an Akt-dependent pathway, they will all induce the expression and secretion of cytokines [61]. Although TLRs may activate immune cell proliferation via an Akt-dependent pathway, all but TLR3 will induce the expression and secretion of tumor necrosis factor- α (TNF- α), interleukin 1 β (IL-1 β), and interferon- γ (IFN- γ), recruiting the primary myeloid differentiation response 88 (MYD88), which recruits the kinase family associated with the interleukin-1 receptor (IRAK), leading to phosphorylation of the inhibitory protein kappa B (I- κ B) to induce translocation of nuclear factor kappa B (NF- κ B) and influence the expression of inflammation [62, 63]. In addition, the activation of TLRs participates in the proliferation of epithelial cells and IgA secretion in the intestinal lumen, essential for intestinal barrier integrity and bacterial population balance, respectively [61]. Deregulation of these processes, or excessive activation of TLRs, can result in chronic inflammatory responses and exuberant repair [64].

In the epithelium, segmented bacterial filaments (SFB) and other commensal microbes activate dendritic cells (DCs) and macrophages in the lamina propria, inducing T helper 17 (TH17) cells through the production of interleukins IL-1 β , IL-6, and IL-23 and helper T cells (TH1) by the possible production of interleukin-12 (IL-12) [21]. TH17 cells regulate the gut microbiota community by secreting the IL-22-dependent antimicrobial lectin regenerating islet-derived 3 gamma (REGIII γ). One of the microbial derivatives, polysaccharide A (PSA), stimulates intestinal epithelial cells to secrete growth factor and β transformation (TGF β), inducing DCs and macrophages to secrete retinoic acid and interleukin 10 (IL-10) to promote activation of regulatory T cells and forkhead box P3 (FOXP3) and, subsequently, inactivation of TH17 and TH1 cells, in a type of negative feedback between the cells of defense in relation to the balance of the gut bacteria [65]. Activation of TLRs induces B cell-activating factor (BAFF) secretion, which differentiates B cells by increasing activation-induced cytidine deaminase (AID) expression and promotes differentiation of IgA-producing plasma cells, by maturing antibodies and casting in the intestinal lumen to alter the composition and function of the microbiota [65].

In obese individuals, due to imbalance of the microbiota (dysbiosis) and oxidative stress, TLR4 is activated and recognizes the bacterial LPS and the flagellin of commensal bacteria, activating TLR5 for dendritic cell signaling and activation of innate lymphoid cells (ILCs), both processes to secrete REGIII γ [66]. ILCs communicate with the microbiota through cytokines, aryl hydrocarbon (AhR) receptors, and antimicrobial peptides and participate in the cross-talk of epithelial cells with the intestinal microbiota [67]. Divided into three groups, group ILCs (ILC1) are activated by interleukin-12 (IL-12) derived from myeloid cells, which in response secrete IFN- γ , whereas group ILCs (ILC2) interact with mast cells, eosinophils, basophils, and macrophages, and group 3 (ILC3) ILCs interact with cells of both innate and adaptive immune systems to secrete IL-22 and initiate an antimicrobial program along with restoration of the intestinal barrier [68].

5. Neuroinflammation from the intestine

The gut-brain axis is composed of the central nervous system, innervated by afferents and efferents of the vagus nerve and extrinsic fibers of the autonomic nervous system (ANS) interconnecting it to the hypothalamic-pituitary-adrenal (HPA) axis, in addition to the intrinsic neurons of the enteric nervous system and the intestinal microbiota. Intrinsic intestinal innervations connect the intestine to the brain via vagal and spinal fibers, whereas the brain sends efferent sympathetic and parasympathetic fibers to the intestine [69, 70]. The HPA axis is part of the limbic system and is the main regulator of stress response and intestinal function during digestion which, due to the corticotrophin releasing factor (CRF) secreted by the hypothalamus, can influence the motility, permeability, and level of intestinal inflammation [47, 71]. Therefore stress and emotions can influence the microbial composition of the intestine by bacterial products that gain access through the bloodstream and the postrema area and due to the release of glucocorticoids and/or sympathetic neurotransmitters that influence the physiology of the intestine and alter the habitat of the microbiota, such as noradrenaline, which may even influence bacterial gene expression or signaling among bacteria, altering the composition and activity of the microbiota [72].

After bacterial colonization, increased production of neurotransmitters, such as serotonin (5-HT) and γ -aminobutyric acid (GABA), and the expression of various cytokines are physiological implications essential for intestinal homeostasis and HPA axis programming, which plays an important role in stress responses [73]. The attention is focused on the stress due to serotonin, which is synthesized through tryptophan, in enterochromaffin cells (EC), about 90%, and in autonomic nerves, about 10%, i.e., at the level of the gastrointestinal tract [74].

Stress, corticosterone, and inflammation are the cornerstones of the catabolism of L-tryptophan (TRP) to kynurenine (KYN) and, subsequently, to quinolinic acid (QUIN) [75, 76]. TRP catalysis occurs through the enzymes indoleamine 2,3-dioxygenase (IDO), kynurenine monooxygenase (KMO), and tryptophan 2,3-dioxygenase (TDO), where stress results in the production of corticotropin-release hormone (CRH) by the hypothalamus, which induces the synthesis of adrenocorticotrophic hormone (ACTH) by corticotrope cells in the anterior pituitary to target by blood the adrenal cortex and synthesize glucocorticoids for induction of TDO and activation of intracellular glucocorticoid receptors (GR) and subsequent TRP catalysis in KYN and kynurenic acid (KYNA) by kynurenine aminotransferase (KAT) or in 3-hydroxyquinurenine (3OH-KYN), both with neurotoxic potential of catabolizing 5-HT in 5-hydroxyindoleacetic acid (5-HIAA) by kynurenine monooxygenase [77]. On the other hand, stress induced by β -adrenergic receptors on the MSA axis (medullary sympathetic- adrenal) activates lymphoid cells and induces the release of proinflammatory cytokines IL-1 β , IL-6 and IFN- γ and catecholamines [76].

These events induce the barrier permeability and increase of bacterial endotoxin through the gut, which stimulates immune cells in the lamina propria to secrete proinflammatory cytokines and prostaglandins (PGE2) to communicate the brain via afferent nerves, compromising the intestinal barrier and creating a cycle, where inflammatory cytokines will activate the SAM and HPA axes, resulting in barrier rupture, increased endotoxin translocation, and an inflammatory and stress state [78]. Where, one of the causes of this translocation, from the intestinal point of view, concerns LPS of invasive bacteria and their arrival in the intestinal lumen, in which it will induce a pro-inflammatory response in lymphoid and innate immune cells, and subsequent release of cytokines such as IL-1 β , IL-6 and TNF- α , in the bloodstream to the brain, from the axis of the gut-brain, affecting BBB integrity, causing a pro-inflammatory stress cycle in CNS cells inducing neuroinflammation [79] **Figure 1**.

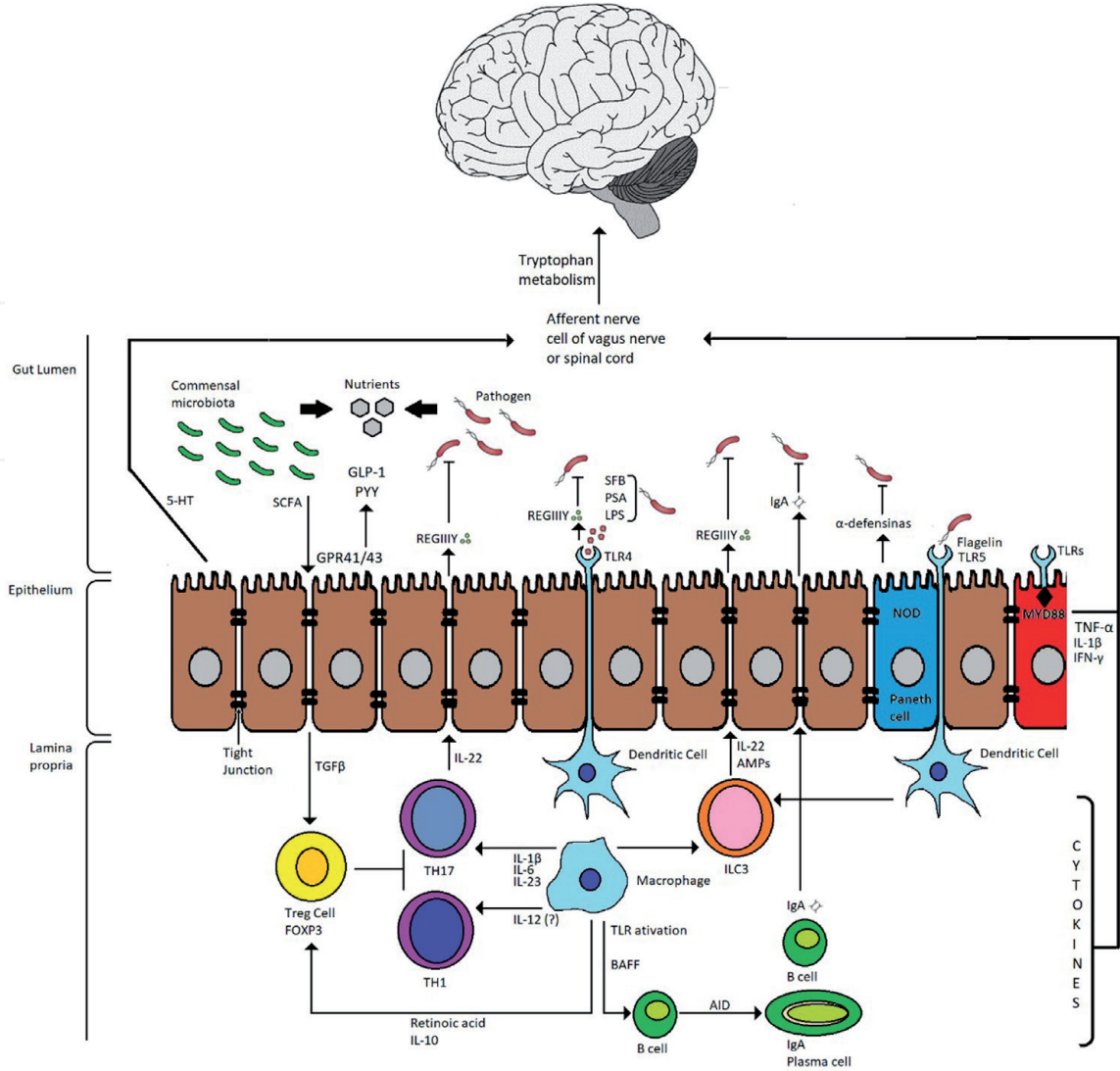


Figure 1.
Mechanisms by which the intestine is able to influence actions in the central nervous system (Fernandes, HS and Nunes, AKS).

6. Mechanisms of neuroinflammation and the process of metabolic syndrome

The proinflammatory cytokines (IL-1 β , IL-6 and IFN- γ) and catecholamines, are able to induce IDO within CNS, exactly within the astrocyte and microglia, so the uptake and metabolism of L-tryptophan into these cells leads to the production of KYNA, which has neuroprotective actions in the CNS, but the catabolism of L-tryptophan in the microglia gives rise to metabolites with reactive oxidative properties, such as 3OH-KYN, 3-HAA and QUIN, that can be transported through the BBB to serve as substrates and contribute to the kynurenine pathway in the CNS, where macrophages and microglia represent the main sources of QUIN, an agonist on NMDA receptor subtype methyl-D-aspartate (NMDA) that acts as being able to contribute to excitotoxicity and neurotoxicity [80, 81].

The astrocytes do not appear to have KMO, which favors the formation of KYNA, which after being released in the presynaptic area preferentially inhibits the NMDARs and $\alpha 7$ nicotinic acetylcholine receptors (nAChRs) in the extra-synaptic [81] **Figure 2.**

This leads to more leukocyte inflammation and infiltration at the BBB, since tight junction proteins, including claudins, ZO-1, and occludins, are downregulated [82].

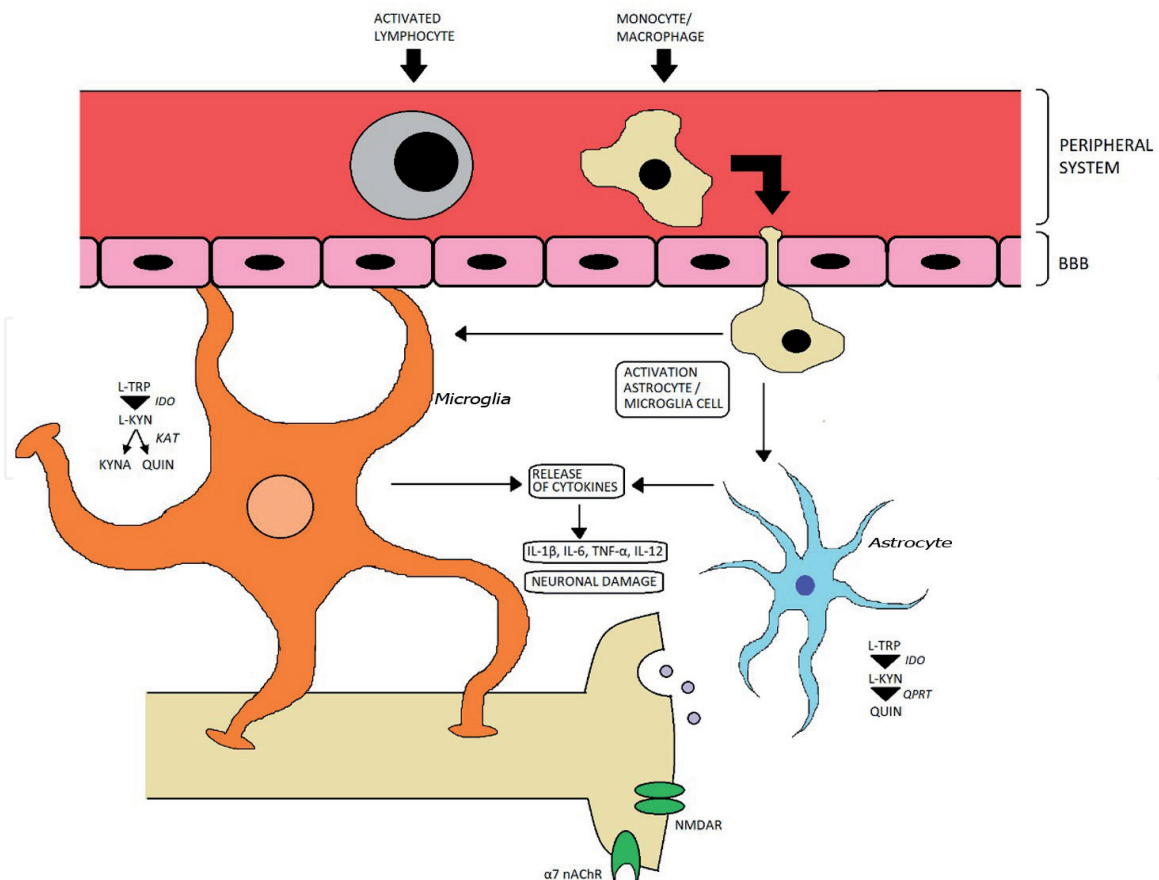


Figure 2. Mechanism of astrocytes and microglia during the metabolic syndrome. Increased BBB allows the invading cells of the peripheral immune system and promotes the activation of glial cells, with consequent release of cytokines. In parallax, description of the KYN mechanism (Fernandes, HS and Nunes, AKS).

In response to inflammation, leukocyte extravasation increases with positive regulation of VCAM-1 and ICAM-1 [39]. Once the functional capacity of astrocytes is compromised, BBB is impaired, resulting in a significant increase in BBB permeability rate, a promotion of leukocytes in cerebrospinal fluid (CSF), and increased immune response, including pathogens and toxins in the CNS. This process favors the activation of astrocytes and microglia, which stimulates the continuous symptoms in the CNS, including the hypothalamus, with consequent response to the stress of insulin symptoms, as well as cognitive injury [83].

Within the metabolic syndrome, diabetes mellitus involves the CNS, and insulin signal transduction involves the activation of phosphatidyl-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways [84]. The insulin receptor (IR) has two subunits (α and β). The α -subunit is directed toward the extracellular medium. Insulin binding to the IR receptor promotes autophosphorylation of the receptor on β subunits, located within the plasma membrane. A phosphorylation cascade of the insulin receptor substrates (IRS) 1 to 4 is then followed, and PI3K is then recruited into the membrane and induces the insertion of the GLUT glucose transporter into the plasma membrane [85]. In addition, PI3K also phosphorylates AKT, which in turn phosphorylates the glycogen synthase kinase 3 (GSK3) protein by inactivating it. This inactivation decreases the phosphorylation of Tau, which is present in neurons and has the function of stabilizing the microtubules for the transport of synaptic vesicles and other cellular components [86]. Therefore, the neuroinflammatory process comprises several mechanisms through the activation of the glial cells that leads to neuronal damage and consequent damages to the CNS.

7. Conclusion

In metabolic syndrome and obesity-associated conditions, immune and metabolic dysregulation results in chronic systemic inflammation, neuroinflammation, cognitive impairment, and other pathological manifestations. An understanding of this complex pathology requires providing new insight into the regulatory role of the astrocytes.

Although research to date in the fields of immunometabolism and neuroinflammation has produced encouraging preliminary results, there remains a vast expanse of unexplored questions requiring the interdisciplinary knowledge of metabolism, neuroscience, and immunology.

In summary, the descriptions of this study indicate that astrocytes play an important role in immunity by triggering neuroinflammation mediated by metabolic syndrome associated with obesity. Elucidating these mechanisms by binding the metabolism syndrome, inflammation, and CNS by astrocytes could generate potential new therapeutic targets or specific strategies to combat metabolic syndrome and obesity.

Abbreviation

ACTH	adrenocorticotrophic hormone
ANS	autonomic nervous system
CNS	central nervous system
DAMPs	damage-associated diseases
EGCs	enteric glial cells
ENS	enteric nervous system
GFAP	glial fibrillary acidic protein
GI	gastrointestinal tract
GPR	G-protein-coupled receptors
GR	glucocorticoid receptors
GSNO	nitrosoglutathione
I- kB	inhibitory protein kappa B
IBD	intestinal disease
ICAM	intercellular adhesion molecules 1
ILCs	innate lymphoid cells
IRS	insulin receptor substrates
KMO	kynurenine monooxygenase
KYN	kynurenine
KYNA	kynurenic acid
MAPK	mitogen-activated protein kinase
MetS	metabolic syndrome
MHC	class II major histocompatibility
Myd88	myeloid differentiation gene 88
NF-kB	nuclear factor kappa B
NGF	nerve growth factor
NMDA	methyl-D-aspartate
NO	nitric oxide
NOD	oligomerization domain receptors
PAMPs	molecular patterns associated with pathogens
PRRs	pattern recognition receptors
QUIN	kynolinic acid
SCFA	short-chain fatty acids

SFB	segmented bacterial filaments
TLR4	Toll-like receptor 4
VCAM	vascular cell adhesion molecule 1

IntechOpen

Author details

Ana Karolina Santana Nunes^{1,2*}, Haniel Soares Fernandes³
and Sura Wanessa Santos Rocha^{2,4}

1 Federal University of Pernambuco, Recife, Pernambuco, Brazil

2 Ultrastructure Laboratory, Aggeu Magalhães Research Center (FIOCRUZ),
Recife, Pernambuco, Brazil

3 Estacio de Sa University, Fortaleza, Ceará, Brazil

4 University of Pernambuco, Recife, Pernambuco, Brazil

*Address all correspondence to: nunes.aks@gmail.com

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] James AM, Collins Y, Logan A, Murphy MP. Mitochondrial oxidative stress and the metabolic syndrome. *Trends in Endocrinology and Metabolism*. 2012;**23**(9):429-434
- [2] Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease. Risk factor, paradox, and impact of weight loss. *Journal of the American College of Cardiology*. 2009;**53**(21):1925-1932
- [3] Cai D. Neuroinflammation and neurodegeneration in overnutrition-induced diseases. *Trends in Endocrinology and Metabolism*. 2013;**24**(1):40-47
- [4] Moreno-Navarrete JM, Blasco G, Puig J, Biarnés C, Rivero M, Gich J, et al. Neuroinflammation in obesity: Circulating lipopolysaccharide-binding protein associates with brain structure and cognitive performance. *International Journal of Obesity*. 2017;**41**(11):1627-1635
- [5] Wanrooy BJ, Kumar KP, Wen SW, Qin CX, Ritchie RH, Wong CHY. Distinct contributions of hyperglycemia and high-fat feeding in metabolic syndrome- induced neuroinflammation. *Journal of Neuroinflammation*. 2018;**8**:1-13
- [6] Drake C, Boutin H, Jones MS, Denes A, McColl BW, Selvarajah JR, et al. Brain inflammation is induced by co-morbidities and risk factors for stroke. *Brain, Behavior, and Immunity*. 2011;**25**(6):1113-1122
- [7] Unger JW. Glial reaction in aging and Alzheimer's disease. *Frontiers in Aging Neuroscience*. 1998;**28**:24-28
- [8] Hatten ME, Liem RKH, Shelanski ML, Mason CA. Astroglia in CNS injury. *Glia*. 1991;**243**:233-243
- [9] Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. *Acta Neuropathologica*. Jan 2010;**119**(1): 7-35. DOI: 10.1007/s00401-009-0619-8. [Epub 2009 Dec 10]
- [10] Ruhl A. Glial cells in the gut. *Neurogastroenterology and Motility. Acta Neuropathologica*. 2005;**17**(6):777-790
- [11] Opazo MC, Ortega-Rocha EM, Coronado-Arrázola I, Bonifaz LC, Boudin H, Neunlist M, et al. Intestinal microbiota influences non-intestinal related autoimmune diseases. *Frontiers in Microbiology*. 2018;**9**:1-20
- [12] Bohórquez DV, Samsa LA, Roholt A, Medicetty S, Chandra R, Liddle RA. An enteroendocrine cell-enteric glia connection revealed by 3D electron microscopy. *PLoS One*. 26 Feb 2014;**9**(2):e89881. DOI: 10.1371/journal.pone.0089881.eCollection 2014
- [13] Boesmans W, Lasrado R, Vanden Berghe P, Pachnis V. Heterogeneity and phenotypic plasticity of glial cells in the mammalian enteric nervous system. *Glia*. 2015;**63**(2):229-241
- [14] Jessen K, Mirsky R. Astrocyte-like glia in the peripheral nervous system: An immunohistochemical study of enteric glia. *The Journal of Neuroscience*. 2018;**3**(11):2206-2218
- [15] Murakami M, Ohta T, Ito S. Lipopolysaccharides enhance the action of bradykinin in enteric neurons via secretion of interleukin-1 β from enteric glial cells. *Journal of Neuroscience Research*. 2009;**87**(9):2095-2104
- [16] Cirillo C, Sarnelli G, Turco F, Mango A, Grosso M, Aprea G, et al. Proinflammatory stimuli activates human-derived enteroglia cells

and induces autocrine nitric oxide production. *Neurogastroenterology and Motility*. 2011;**23**(9):10-12

[17] Cirillo C, Sarnelli G, Esposito G, Grosso M, Petruzzelli R, Izzo P, et al. Increased mucosal nitric oxide production in ulcerative colitis is mediated in part by the enteroglia-derived S100B protein. *Neurogastroenterology and Motility*. Nov 2009;**21**(11):1209-e112. DOI: 10.1111/j.1365-2982.2009.01346.x. [Epub 2009 Jun 24]

[18] Reyes RC, Verkhratsky A, Parpura V. Plasmalemmal $\text{Na}^+/\text{Ca}^{2+}$ exchanger modulates Ca^{2+} -dependent exocytotic release of glutamate from rat cortical astrocytes. *ASN Neuro*. 2012;**4**(1):AN20110059

[19] Chan KL, Cathomas F, Russo SJ. Central and peripheral inflammation link metabolic syndrome and major depressive disorder. *Acta Neuropathologica. Physiology* (Bethesda). 1 Mar 2019;**34**(2):123-133. DOI: 10.1152/physiol.00047.2018

[20] Guillemot-Legris O, Muccioli GG. Obesity-induced neuroinflammation: Beyond the hypothalamus. *Trends in Neurosciences*. 2017;**40**(4):237-253 . DOI: 10.1016/j.tins.2017.02.005. [Epub 2017 Mar 18]

[21] Schwartz MW, Porte D Jr. Diabetes, obesity, and the brain. *Science*. 2005;**307**:375-380

[22] Pavlov VA, Tracey KJ. The vagus nerve and the inflammatory reflex—Linking immunity and metabolism. *Nature Reviews. Endocrinology*. 2012;**8**(12):743-754

[23] Disabato D, Quan N, Godbout JP. Neuroinflammation: The devil is in the details. *Journal of Neurochemistry*. 2017;**139**(Suppl. 2):136-153

[24] Zlokovic BV. New therapeutic targets in the neurovascular pathway in

Alzheimer's disease. *Neurotherapeutics*. 2008;**5**(3):409-414

[25] Erickson MA, Banks WA. Blood-brain barrier dysfunction as a cause and consequence of Alzheimer's disease. *Journal of Cerebral Blood Flow and Metabolism*. 2013;**33**(10):1500-1513

[26] Jagim AR, Harty PS, Camic CL. Common ingredient profiles of multi-ingredient pre-workout supplements. *Nutrients*. 2019;**11**(2):4-11

[27] Banks WA. The blood-brain barrier in neuroimmunology: Tales of separation and assimilation. *Brain, Behavior, and Immunity*. 2015;**44**:1-8

[28] Xu H, Manivannan A, Liversidge J, Sharp PF, Forrester JV, Crane IJ. Requirements for passage of T lymphocytes across non-inflamed retinal microvessels. *Journal of Neuroimmunology*. 2003;**142**(1-2):47-57

[29] Siednienko J, Halle A, Nagpal K, Golenbock DT, Miggin SM. TLR3-mediated IFN- β gene induction is negatively regulated by the TLR adaptor MyD88 adaptor-like. *European Journal of Immunology*. 2010;**40**(11):3150-3160

[30] Łabuzek K, Liber S, Gabryel B, Okopień B. Metformin has adenosine-monophosphate activated protein kinase (AMPK)-independent effects on LPS-stimulated rat primary microglial cultures. *Pharmacological Reports*. 2010;**62**(5):827-848

[31] Paintlia AS, Paintlia MK, Singh I, Singh AK. IL-4-induced peroxisome proliferator-activated receptor gamma activation inhibits NF-kappaB trans activation in central nervous system (CNS) glial cells and protects oligodendrocyte progenitors under neuroinflammatory disease conditions: Implication for CNS-demyelinating diseases. *Journal of Immunology*. 1 Apr 2006;**176**(7):4385-4398

- [32] Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Homeostatic control of the thyroid-pituitary axis: Perspectives for diagnosis and treatment. *Frontiers in Endocrinology*. 2015;**6**:1-17
- [33] Amor S, Woodroffe MN. Innate and adaptive immune responses in neurodegeneration and repair. *Immunology*. 2014;**141**(3):287-291
- [34] Lee KS, Kim J, Kwak SN, Lee KS, Lee DK, Ha KS, et al. Functional role of NF- κ B in expression of human endothelial nitric oxide synthase. *Biochemical and Biophysical Research Communications*. 2014;**448**(1):101-107
- [35] Gieske BT, Stecker RA, Smith CR, Witherbee KE, Harty PS, Wildman R, et al. Metabolic impact of protein feeding prior to moderate-intensity treadmill exercise in a fasted state: A pilot study. *Journal of the International Society of Sports Nutrition*. 2018;**15**(1):1-12
- [36] Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell*. 2010;**140**(6):918-934
- [37] Menegazzi M, Di Paola R, Mazzon E, Genovese T, Crisafulli C, Dal Bosco M, et al. Glycyrrhizin attenuates the development of carrageenan-induced lung injury in mice. *Pharmacological Research*. 2008;**58**(1):22-31
- [38] Schins RPF, McAlinden A, MacNee W, Jimenez LA, Ross JA, Guy K, et al. Persistent depletion of I kappa B alpha and interleukin-8 expression in human pulmonary epithelial cells exposed to quartz particles. *Toxicology and Applied Pharmacology*. 2000;**167**(2):107-117
- [39] Figley CR, Stroman PW. The role(s) of astrocytes and astrocyte activity in neurometabolism, neurovascular coupling, and the production of functional neuroimaging signals. *The European Journal of Neuroscience*. 2011;**33**(4):577-588
- [40] Jessen R, Wood PM, Wanner INAB, Mahoney J, An K, Bates M, et al. Invariant mantling of growth cones by Schwann cell precursors characterize growing peripheral nerve fronts. *Glia*. 2006;**438**:424-438
- [41] Rothermundt M, Peters M, Prehn JHM, Arolt V. S100B in brain damage and neurodegeneration. *Microscopy Research and Technique*. 2003;**60**(6):614-632
- [42] Nagayach A, Patro N, Patro I. Astrocytic and microglial response in experimentally induced diabetic rat brain. *Metabolic Brain Disease*. 2014;**29**(3):747-761
- [43] Owen JA, Kehoe SJ, Oliver SJ. Influence of fluid intake on soccer performance in a temperate environment. *Journal of Sports Sciences*. 2013;**31**(1):1-10
- [44] González H, Elgueta D, Montoya A, Pacheco R. Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases. *Journal of Neuroimmunology*. 2014;**274**(1-2):1-13
- [45] Portune KJ, Benítez-Páez A, Del Pulgar EM, Cerrudo V, Sanz Y. Gut microbiota, diet, and obesity-related disorders-The good, the bad, and the future challenges. *Molecular Nutrition & Food Research*. Jan 2017;**61**(1). DOI: 10.1002/mnfr.201600252. [Epub 2016 Sep 20]
- [46] Xu J, Mahowald MA, Ley RE, Lozupone CA, Hamady M, Martens EC, et al. Evolution of symbiotic bacteria in the distal human intestine. *PLoS Biology*. 2007;**5**(7):1574-1586
- [47] Gill SR, Pop M, Deboy RT, Eckburg PB, Peter J, Samuel BS, et al. Metagenomic analysis of the human

distal gut microbiome Steven. *Science*. 2011;**312**(5778):1355-1359

[48] Derrien M, van Hylckama Vlieg JET. Fate, activity, and impact of ingested bacteria within the human gut microbiota. *Trends in Microbiology*. 2015;**23**(6):354-366

[49] Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine - supplemental materials. *Science*. 2005;**307**(5717):1915-1920

[50] Bernat O. Medicines from microbiota. *Nature Biotechnology*. 2013;**31**(4):309-315

[51] Russell WR, Hoyles L, Flint HJ, Dumas ME. Colonic bacterial metabolites and human health. *Current Opinion in Microbiology*. 2013;**16**(3):246-254

[52] Vijay N, Morris M. Role of monocarboxylate transporters in drug delivery to the brain. *Current Pharmaceutical Design*. 2014;**20**(10):1487-1498

[53] Plöger S, Stumpff F, Penner GB, Schulzke JD, Gäbel G, Martens H, et al. Microbial butyrate and its role for barrier function in the gastrointestinal tract. *Annals of the New York Academy of Sciences*. 2012;**1258**(1):52-59

[54] Dörfel MJ, Huber O. Modulation of tight junction structure and function by kinases and phosphatases targeting Occludin. *Journal of Biomedicine & Biotechnology*. 2012;**2012**:1-14

[55] Ivanov AI, Parkos CA, Nusrat A. Cytoskeletal regulation of epithelial barrier function during inflammation. *The American Journal of Pathology*. 2010;**177**(2):512-524

[56] Ghanim H, Abuaysheh S, Sia CL, Korzeniewski K, Chaudhuri A, Fernandez-Real JM, et al. Increase in

plasma endotoxin concentrations and the expression of toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal: Implications for insulin resistance. *Diabetes Care*. 2009;**32**(12):2281-2287

[57] Ang Z, Ding JL. GPR41 and GPR43 in obesity and inflammation - protective or causative? *Frontiers in Immunology*. 2016;**7**:1-5

[58] Fukui H, Xu X, Miwa H. Role of gut microbiota-gut hormone axis in the pathophysiology of functional gastrointestinal disorders. *J. Neurogastroenterol. Motil*. 2018;**24**(3):367-386

[59] Oriach CS, Robertson RC, Stanton C, Cryan JF, Dinan TG. Food for thought: The role of nutrition in the microbiota-gut-brain axis. *Clinical Nutrition Experimental*. 2016;**6**:25-38

[60] Zhang M, Sun K, Wu Y, Yang Y, Tso P, Wu Z. Interactions between intestinal microbiota and host immune response in inflammatory bowel disease. *Frontiers in Immunology*. 2017;**8**:1-13

[61] Abreu MT. Toll-like receptor signalling in the intestinal epithelium: How bacterial recognition shapes intestinal function. *Nature Reviews Immunology*. 2010;**10**(2):131-143

[62] Hanke M, Keilian T. Toll-like receptors in health and disease in the brain: Mechanisms and therapeutic potential. *Clinical Science*. 2011;**121**(9):367-387

[63] McCusker RH, Kelley KW. Immune - neural connections: How the immune system's response to infectious agents influences behavior. *The Journal of Experimental Biology*. 2012;**216**(1):84-98

[64] Moyano-Porcile V, Olavarria-Ramírez L, González-Arancibia C,

- Bravo JA, Julio-Pieper M. Short-term effects of poly(I:C) on gut permeability. *Pharmacological Research*. 2015;**101**: 130-136
- [65] Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology*. 2013;**13**(5):321-335
- [66] Milanski M, Degasperi G, Coope A, Morari J, Denis R, Cintra DE, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: Implications for the pathogenesis of obesity. *The Journal of Neuroscience*. 2009;**29**(2):359-370
- [67] Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. *The Lancet Gastroenterology & Hepatology*. 2017;**2**(2):135-143
- [68] Thaïss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature*. 2016;**535**(7610):65-74
- [69] Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Comprehensive Physiology*. 2014;**4**(4):1339-1368
- [70] Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*. 2017;**7**:124-136
- [71] Manuscript A. Permeability in a region-specific manner. *Neurogastroenterology & Motility*. 2014;**25**(2):1-21
- [72] Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. *Nature Reviews Microbiology*. 2012;**10**(11):735-742
- [73] Diaz Heijtz R, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America*. 2011;**108**(7):3047-3052
- [74] Barbara G, Feinle-Bisset C, Ghoshal UC, Santos J, Vanner SJ, Vergnolle N, et al. The intestinal microenvironment and functional gastrointestinal disorders. *Gastroenterology*. 2016;**150**(6):1305-1318.e8
- [75] Del Vecchio M, Procopio G, Cassata A, Pozzi P, Busto G, Celio L, et al. Stress-induced immune dysfunction implications for health. *Tumori*. 1999;**85**(1):6-11
- [76] O'Farrell K, Harkin A. Stress-related regulation of the kynurenine pathway: Relevance to neuropsychiatric and degenerative disorders. *Neuropharmacology*. 2017;**112**:307-323
- [77] Dantzer R. Role of the kynurenine metabolism pathway in Inflammation-induced depression: Preclinical approaches. In *Inflammation-Associated Depression: Evidence, Mechanisms and Implications*. Current Topics in Behavioral Neurosciences; Cham, Switzerland: Springer; 2016. pp. 117-138. ISBN: 978-3-319-51152-8
- [78] De Punder K, Pruimboom L. Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. *Frontiers in Immunology*. 2015;**6**:1-12
- [79] Schachter J, Martel J, Lin CS, Chang CJ, Wu TR, Lu CC, et al. Effects of obesity on depression: A role for inflammation and the gut microbiota. *Brain, Behavior, and Immunity*. 2018;**69**:1-8
- [80] Smythe GA, Kapoor V, Kerr SJ, Guillemin GJ, Croitoru J, Brew BJ, et al. Kynurenine pathway metabolism

in human astrocytes: A paradox for neuronal protection. *Journal of Neurochemistry*. 2003;**78**(4):842-853

[81] Vécsei L, Szalárdy L, Fülöp F, Toldi J. Kynurenines in the CNS: Recent advances and new questions. *Nature Reviews Drug Discovery*. 2013;**12**(1):64-82

[82] Xu Z, Zeng W, Sun J, Chen W, Zhang R, Yang Z, et al. The quantification of blood-brain barrier disruption using dynamic contrast-enhanced magnetic resonance imaging in aging rhesus monkeys with spontaneous type 2 diabetes mellitus. *NeuroImage*. 2017;**158**:480-487

[83] Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neuroscience and Biobehavioral Reviews*. 2017;**74**:277-286

[84] Unger JW, Livingston JN, Moss AM. Insulin receptors in the central nervous system: Localization, signalling mechanisms and functional aspects. *Progress in Neurobiology*. 1991;**36**(5):343-362

[85] Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*. 2018;**10**(11):1618

[86] Cho J-H, Johnson GVW. Primed phosphorylation of tau at Thr231 by glycogen synthase kinase 3 β (GSK3 β) plays a critical role in regulating tau's ability to bind and stabilize microtubules. *Journal of Neurochemistry*. 2010;**88**(2):349-358