Research Article

Molecular Mechanisms of Glial Cells Related Signaling Pathways Involved in the Neuroinflammatory Response of Depression

Junhui Wang, Jie Qin, Peng Wang, Yu Sun, and Qi Zhang

1The Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
2Department of Ultrasound, Qingdao Municipal Hospital, Qingdao, Shandong, China
3School of Basic Medicine, Qingdao University Medical Center, Qingdao, Shandong, China
4Department of Endocrinology, Qilu Hospital of Shandong University, Jinan, Shandong, China
5Department of Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Correspondence should be addressed to Yu Sun; sunyujinan@gmail.com and Qi Zhang; qi.zhang@lhsc.on.ca

Received 20 May 2020; Revised 17 September 2020; Accepted 28 September 2020; Published 10 October 2020

Academic Editor: Phileen Pinge-Filho

Dysfunction of the glial cells, such as astrocytes and microglia, is one of the pathological features in many psychiatric disorders, including depression, which emphasizes that glial cells driving neuroinflammation is not only an important pathological change in depression but also a potential therapeutic target. In this review, we summarized a recent update about several signaling pathways in which glial cells may play their roles in depression through neuroinflammatory reactions. We focused on the basic knowledge of these signaling pathways by elaborating each of them. This review may provide an updated image about the recent advances on these signaling pathways that are essential parts of neuroinflammation involved in depression.

1. Introduction

Depression is one of the most common disability diseases in human beings, affecting approximately 16% of the world’s population. In addition to major depressive disorder (MDD) patients, there are many diseases associated with depression, such as Alzheimer’s disease, epilepsy, cerebrovascular disease, cancer, and Parkinson’s disease [1–3]. So far, the mechanisms of depression are understood to be serotonin deficits, stress, and the hypothalamic-pituitary-adrenal axis theory [4–6]. In recent years, the theory of inflammation is attracting much more attention. Clinical and basic studies have revealed that immunological abnormalities and cytokines could significantly affect depressive symptoms, the neuroendocrine system, neurotransmitters, neurodegeneration, and neurogenesis [7–9].

Microglia and astrocytes are important immune regulatory cells in the central nervous system (CNS). Usually, microglia is named as “resting” cells, with long branching processes and a small cellular body, which keep monitoring immune threats while maintaining homeostasis in the CNS [10]. When activated, ramified microglia could turn into ameboid morphology, phagocyte-like cell, and secrete immune-molecules, including a series of cytokines [10]. During this course, the activated microglial cells could be transformed to either M1 type (toxic) or M2 type (protective) microglia, depending on the variety of external or internal insults [11]. Astrocytes, key components of the blood-brain barrier (BBB), serve as a functional barrier that regulates and restricts CNS inflammation [12]. In addition, astrocytes could regulate and keep the balance of the glutamate system and significantly contribute to synaptic plasticity [13].

Patients with MDD showed elevated microglial density in the frontal cortex, temporal cortex, and hippocampus from a positron emission tomography (PET) study [14]. In the same study, the expressions of some genes in astrocytes were decreased in the prefrontal cortex of MDD patients, which reflected an astrocytic dysfunction, such as GFAP, ALDH1L1, SOX9, GLUL, SCL1A3, GJA1, and GJB6 [15]. The findings from human beings are consistent with results
from animal models of depression [16]. Neuroinflammation with increased expression of proinflammatory cytokines in CNS contributes to the etiology of depression. Animals with proinflammatory cytokines injection exhibit depression-like behavior [17]. Intraperitoneal injection of lipopolysaccharide (LPS) that could trigger systemic inflammation led mice to show obvious depressive-like behaviors, with activated microglia and astrocytes in the hippocampus and medial prefrontal cortex (mPFC) [17]. Previous reports also found that rats under the chronic unpredictable mild stress (CUMS) model exerted depressive-like behavior with obvious hippocampus and mPFC microglia activation and reactive astrogliosis [18, 19]. After maternal deprivation, the level of glial fibrillary acidic protein (GFAP) immunopositive cells decreased in the hippocampus of offspring rats in early developmental phases but increased in late developmental phases [20]. Iba-1 (microglial marker) immunopositive cells increased in both early and late developmental phases [20]. These data suggested that microglia and astrocytes might play key roles in MDD. Maternal deprivation is a well-established predisposing factor for the development of anxiety and depression [21].

Therefore, microglia and astrocytes could be extensively involved in the pathogenesis of both MDD patients and animal models. The underlying mechanisms by which these glial cells trigger the neuroinflammatory response, and how they are orchestrated and regulated by each other, are quite important in order to understand the significance of these events of glial cells during the development of depression. Therefore, we summarized the recent research findings of this field and presented the updated profile of the network of glial cells, neuroinflammation, and depression.

2. Signaling Pathways of Neuroinflammation in Depression

2.1. Kynurenine Pathway. The kynurenine pathway is regulated by inflammatory cytokines in CNS diseases [22]. Tryptophan (TRP) is transformed to kynurenine (KYN) by tryptophan dioxygenase or indoleamine 2, 3-dioxygenase (IDO). With the help of kynurenine aminotransferase (KAT), KYN is transformed into kynurenic acid (KYNA), which is an antagonist of N-methyl-D-aspartic acid (NMDA) receptor and α7-nicotinic acetylcholine receptor [23]. KYN can also be transformed into 3-hydroxykynurenine (3-HK) with the kynurenine monoxygenase (KMO). Then, 3-HK is transformed to quinolinic acid (QUIN), which is an agonist of the NMDA receptor [24]. Since literatures have shown kynurenine signaling could significantly impact glutamate, acetylcholine, and serotonin pathways, the above KYN pathways of tryptophan are considered to play important roles in the pathophysiology of inflammation and depression [25]. A study showed that IDO and KMO were significantly activated to produce large amounts of 3-HK and QUIN in microglial cells exposed to IFN-γ stimulation [26]. Combination treatment of IFN-γ and LPS in microglial cells leads to significant IDO upregulation, which was not inhibited by nitric oxide (NO) [27]. In another study with an animal model, results suggested that LPS injection induced the microglial and IDO activation, and the activation could be exacerbated in CX3CR1 (-/-) deficient mice, which implied that CX3CR1 could inhibit the activation of IDO [28]. A previous report also validated that suppression of the KYN pathway in microglia could significantly reduce the neurite branching and complexity of cortical neurons [29]. By combination with L-KYN and LPS, L-KYN exerted a significant inhibitory effect on the microglia response to LPS, which suggested that the KYN pathway might play a direct role in regulating microglia activity [30].

While astrocytes have limited expression profiles of the above enzymes, IDO was activated by IFN-γ in astrocytes, which only resulted in large amounts of KYN and KYNA, but not the generation of 3-HK and QUIN [26, 31]. However, KYN and KYNA in astrocytes could be released and absorbed by surrounding microglia, which would further promote the neuroinflammatory response. LPS increased the expression of IDO-11-FL in both astrocytes and microglia in the mice brains, but IDO-2-v6 was only induced in astrocytes [32]. The different profiles of this signaling pathway in astrocytes and microglia should be taken into account in future studies.

2.2. Inflammasome. The activation of the inflammasome participates in the innate immune reaction in depression [33]. The NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome, which includes the NLRP3 protein, adapter protein apoptosis-associated speck-like protein (ASC), and procaspase-1, is the most studied member of the inflammasome [34]. In an in vitro study, primary human microglial cells contained the expression profile of inflammasome-related genes and the expression of these genes could be regulated functionally [35]. LPS-induced activation of NLRP3 and caspase-1 could be detected in microglia, and this may be correlated to microglia polarization to the M1 phenotype [36]. In primary cultures of astrocytes, oxygen-glucose deprivation and reoxygenation could induce the upregulation of NLRP3, caspase-1, and the extra cellular release of IL-1β and high mobility group box 1 (HMGB1) [37]. Furthermore, the NLRP3 inflammasome complex could be expressed in astrocytes induced by HMGB1, and IL-4 could inhibit this effect through a negative regulation of NF-κB activity and promotion of peroxisome proliferator-activated receptor γ (PPARγ) activation [38]. In MDD patients and depressive rodents, assembly of the NLRP3 complex, the subsequent proteolysis, and release of the proinflammatory cytokines interleukin-1β (IL-1β) and IL-18 have been widely reported [39]. LPS-injected mice displayed elevated expressions of NLRP3, ASC, and caspase-1 in the hippocampus, and this was correlated with long-term depression-like behaviors [40]. In the CUMS rat model, NLRP3 inflammasome was activated in microglial cells of the PFC area, and subsequently, IL-1β was elevated as well [41].

2.3. Purinergic Pathway. Purinergic receptors are divided into ionotropic P2X (for ATP) and metabotropic P1 (for adenosine) or P2Y. The P2X7 receptor (P2X7R) is increasingly recognized as an important cell surface regulator of
some key inflammatory molecules, including IL-1β, IL-18, IL-6, and tumor necrosis factor-alpha (TNF-α). Moreover, a study has proven that the generation of P2X7R-dependent cytokines is driven by the activation of NLRP3 inflammasome and antagonists of P2X7R, which is likely to possess therapeutic potential as novel anti-inflammatory therapies [42]. In depressive mouse models induced by LPS or CUMS, the P2X7/NF-κB pathway was activated in the hippocampus or mPFC of the mouse brain, and the expressions of NF-κB, p-IKKα, p-IKKβ, p-IκBα, p-NF-κB, p65, IL-6, IL-1β, and TNF-α were elevated as well [43, 44]. The activation of P2X7R was accompanied by the inflow of Ca2+, followed by the activation of MAPK kinases (ERK, JNK, p38), transcriptional factors (NF-κB, CREB, AP-1) into the nucleus, and the boosted expression of series of inflammatory genes (TNF-α, IL-6, COX-2, iNOS, IL-1β, IL-12, IL-6, IL-23, etc.). Likewise, the activation of P2Y1 receptor (Gq-coupled proteins) could lead to the activation of PLC and subsequently mobilize intracellular calcium, which could cause the activation of PKC, p38 MAPK, and transcriptional factor CREB, thus regulating the expression of inflammatory genes [45].

In cultured microglia, the release of IL-6, IL1α, IL1β, IL18, and chemokine CC motif ligand 2 (CCL2) was P2X7R-dependent, and benzoyl-benzoyl ATP (Bz-ATP) could also induce microglial cell death [46, 47]. IL-1β release was P2X7R-pore-dependent, and IL-1β had trophic effects on surrounding microglia in terms of their activation and proliferation [48]. In astrocyte cultures, ATP increased Ser-727 phosphorylation of signal transducer and activator of transcription 3 (STAT3), which played an important role in astrocyte proliferation and reactive astrogliosis [49]. Selective P2X7R agonist, Bz-ATP, increased monocyte chemoattractant protein-1 (MCP-1) expression through the activation of ERK1/2 and p38, which would make leukocyte infiltration in the CNS after inflammation [50].

2.4. Nicotinic Acetylcholine Pathway. In depression, central alpha7 nicotinic acetylcholine receptor (α7 nAChR) is a key player in regulating the cholinergic mediated anti-inflammatory pathway [51]. The α7 nAChR positive allosteric modulator (PAM), PNU120596, prevented LPS-induced depression-like behaviors in mice, hindered activation of microglia and astrocytes, and inhibited the upregulation of IL-1β and TNF-α in the hippocampus and prefrontal cortex [52]. The α7 nAChR-signaling pathway was involved in the process of nicotine regulation of microglial activation with a neuroprotective role. In cultured microglia, nicotine suppressed LPS-induced TNF-α release via the activation of α7 nAChRs, a signaling process involved the activation of PLC and Ca2+ release from intracellular Ca2+ stores, and associated with the suppression of ERK, JNK, and p38 activation [53]. Meanwhile, nicotine enhanced P2X7-receptor-mediated TNF-α release from microglia [53]. The activation of α7 nAChRs by nicotine caused the upregulated expression of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) in microglial cultures [54] and elevated the expression of glutamate/aspartate transporter (GLAST) and glutamate uptake [55].

The expression of α7nAChR was detected in human astrocytes as well. In cultured astrocytes, pretreatment with nicotine could suppress MPP or LPS-induced TNF-α expression and activation of ERK1/2 and p38 [56]. After stimulation by IL-1β, nicotine could inhibit the proinflammatory cytokines, such as IL-6, IL-1β, TNF-α, IL-8, and IL-13, and the activation of butyrylcholinesterase that was induced by COX-2 [57]. In addition, α7 nAChR partial agonist (GTS21) significantly reduced LPS-induced secretion of inflammatory cytokines (TNF-α and IL-6), inhibited the NF-κB pathway, and upregulated canonical Nrf2 antioxidant genes (HO1, TXNRD1, and GCLC) in cultured astrocytes.

2.5. Mitochondria. Evidences has suggested that the dysfunction of mitochondria may play an important role in the pathogenesis of MDD [58]. In depressive rodents, mitochondrial perturbation and mitochondrial component release were reported to promote cytokine generation and neuroinflammation. Meanwhile, cytokines were able to influence several mitochondrial functions, including oxidative phosphorylation and oxidative stress, and thus facilitate the neuroinflammation [58].

In microglial cells exposed to LPS, mitochondrial fission regulated mitochondrial ROS production and promoted the expression of TNF-α, IL-1β, IL-6, IL-23, iNOS, and COX-2 through the activation of NF-κB and MAPK [59]. Rotenone and tebufenpyrad could induce mitochondrial impairment, enhance mitochondrial ROS generation, and amplify LPS-induced upregulation of the NLRP3 inflammasome and the generation of IL-1β [60]. Since the synthesis of mitochondrial DNA (mtDNA) was crucial for NLRP3 signaling in macrophages, the oxidized mitochondria may facilitate the microglia-derived inflammation [61]. The activation peripheral benzodiazepine receptor (PBR), a component of the mitochondrial permeability transition pore (PTP), significantly inhibited the LPS-induced upregulation of COX-2 and TNF-α [62]. Translocator protein (TSPO), an outer mitochondrial membrane protein, was upregulated in LPS-challenged microglial cells. TSPO could reverse the LPS-triggered production of the proinflammatory mediators CCL2, IL-6, and iNOS [63]. Mitochondrial uncoupling protein 2 (UCP2) knockout mice demonstrated depressive-like behaviors and lost more astrocytes in the hippocampus when exposed to chronic mild stress. UCP2 decreased ROS, negatively regulated the activation of NLRP3 inflammasome, and inhibited the production of IL-1β in astrocytes exposed to LPS in primary cultures [64].

2.6. Steroid Hormone Pathway. Steroid hormones, such as glucocorticoids (GCs) and estrogens, are well-established regulators of immune responses. Dysfunction of steroid hormones has been found in MDD. Usually, stress leads to the elevation of GCs, the subsequent activation of the hypothalamus-pituitary-adrenal (HPA) axis, and the activation of the glucocorticoid receptor (GR) in the brain, which exerts a negative feedback. However, prolonged exposure to stress leads to a defective feedback of GR [65, 66]. GR, mineralocorticoid receptor (MR), and estrogen receptor alpha (ERα) were all expressed in microglia. After LPS challenge, the expressions of GR, MR, and ERα were significantly downregulated. Corticosterone application inhibited the
upregulation of TNF-α, IL-6, and NO induced by LPS and INF-γ, while 17 beta-estradiol had little effect, which suggested GR and MR were the primary steroid hormone regulators in microglial inflammatory activity [67]. Corticosterone inhibited the upregulation of excitatory amino acid transporter, GLUT-1, and glutamate uptake capacity in microglia induced by LPS [68]. Chronic corticosterone exposure increased the gene expression of NLRP3 and NF-κB in microglia, and even chronic corticosterone exposure potentiated the microglial proinflammatory response (TNFα, IL-1β, IL-6, and NLRP3) to LPS [69]. In microglial cells, the administration of 17 beta-estradiol (E2) or progesterone (P) dampened IL-1β, ASC, and NLRP3 expression after hypoxia [70]. Glucocorticoids enhanced the release of ATP from astrocytes by opening the pannexin-1 hemi-channels, which was regulated by glucocorticoid-inducible kinase-1 (SGK-1) [71]. Glucocorticoids decreased the expression of GR and AMP-activated protein kinase (AMPK) activation in cultured astrocytes. The activation of AMPK could prevent the dexamethasone-induced downregulation of GR and depression-like behavior in rats [72]. Estradiol (E2) could repress astrocyte GFAP protein expression, reorganize laminin, and enhance neurite outgrowth [73]. Corticosterone downregulated the biosynthesis of connexin43 (Cx43) but increased the degradation of Cx43 in the prefrontal cortical and hippocampus astrocyte, suggesting stress-induced dysfunction of gap junctions [74, 75].

2.7. Connexin in Glial Cells. Connexin (Cx)43, Cx30, Cx26, Cx40, and Cx45 are expressed in astrocytes [76, 77], while Cx43 and Cx30 are the most important Cx species contributing to gap junction channels (GJs) or hemi-channels (HCs) [78, 79]. Energetic metabolites can be released by astrocytes through the gap-junction channels and hemi-channels that are usually used by neurons to maintain their functions [80, 81]. Also, Cx plays a role in postnatal BBB maturation [82] and neural synaptic plasticity [83]. In the gap junction protein Cx43, its carboxyl-terminal domain could modulate the function of astrocyte P2Y1 receptors [84].

![Figure 1: A schematic graph demonstrates the role of glial cells and the relevant signaling pathway. The surrounding microglia (upper left) and astrocyte (upper right) impact the function of neuron (middle) in multiple ways. The nuclear mechanisms of some of the pathways are graphed at the bottom.](image-url)
### Table 1: Summary of the pathways in depression.

| Pathway          | Reports                                                                 |
|------------------|-------------------------------------------------------------------------|
| Kynurenine       | The neurite branching and complexity of cortical neurons was facilitated by the IFNγ stimulated kynurenine pathway induction in microglia [29]. |
| Inflammasome     | Assembly of the NLRP3 complex in microglia activated proinflammatory response and contributed to depression [39]. |
| Purinergic       | Modulation of P2X7/NF-κB pathway in microglia could attenuate the depressive-like behaviors in mice [43]. |
| Neuropeptide     | Neuropeptide Y inhibited the inflammation in microglia, which was one of key processes in depression [97]. |

**2.9. Glial Cells, Pain, and Depression.** The fact that some of the abovementioned pathways are closely involved in the pain promote us to discuss the cooccur condition of depression, pain. Pain could exacerbate the symptom of depression but the common mechanisms behind them remain to be identified [102]. Inflammation activated KYN pathway could potentially modulate neuropathic and inflammatory pain sensitivity [103]. Meanwhile, inflammasome, NFκB, and NMDA receptors are known or potential target of pain therapy [104–106]. The crosstalk between pain and depression could be mediated with these signaling pathways. Further investigation of how the crosstalk is modulated may decipher the complex relationship between pain and depression.

**3. Conclusions**

Taken together, neuroinflammation is a very important pathological component of depression. There are many important signaling pathways woven together to form the network of astrocytes and microglia in the context of depression. Here, we summarized the recent progress on several signaling pathways, including the kynurenine pathway, the inflammasome, the purinergic pathway, the nicotinic acetylcholine pathway, mitochondria, and steroid hormone pathways, by focusing on their molecular mechanisms, respectively (Figure 1). The purpose of this summary is to update the information on the recent advances in molecular mechanisms and may provide useful information to further understand the whole picture of the interactions between neuroinflammation, glial cells, and depression (Table 1).

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

**Conflicts of Interest**

The authors declare that there are no conflicts of interests in this study.
Authors’ Contributions

J Wang, Y Sun, and Q Zhang designed the structure and the idea, and J Wang wrote the manuscript. J Wang, Y Sun, and P Wang edited the manuscript before submission. Jie Qin and J Wang revised the manuscript during revision.

Acknowledgments

We thank the critical comments from Dr. Jing Sun (Department of Pathology, Capital Medical University) during the manuscript preparation. Dr. Yu Sun is supported by the grant of “the Fundamental Research Fund of Shandong University, China (2018JC015).”

References

[1] C. P. C. Galts, L. E. B. Bettio, D. C. Jewett et al., “Depression in neurodegenerative diseases: common mechanisms and current treatment options,” *Neuroscience and Biobehavioral Reviews*, vol. 102, pp. 56–84, 2019.

[2] W. Cai, C. Mueller, Y. J. Li, W. D. Shen, and R. Stewart, “Post-stroke depression and risk of stroke recurrence and mortality: a systematic review and meta-analysis,” *Aging Research Reviews*, vol. 50, pp. 102–109, 2019.

[3] J. A. Salpekar and M. Mula, “Common psychiatric comorbidities in epilepsy: how big of a problem is it?,” *Epilepsy & Behavior*, vol. 98, Part B, pp. 293–297, 2019.

[4] A. Menke, “Is the HPA axis as target for depression outdated, or is there a new hope?,” *Frontiers in Psychiatry*, vol. 10, p. 101, 2019.

[5] S. Yatham, S. Shivathan, R. Yoon, T. L. da Silva, and A. V. Ravindran, “Depression, anxiety, and post-traumatic stress disorder among youth in low and middle income countries: a review of prevalence and treatment interventions,” *Asian Journal of Psychiatry*, vol. 38, pp. 78–91, 2018.

[6] C. N. Yohn, M. M. Gergues, and B. A. Samuels, “The role of 5-HT receptors in depression,” *Molecular Brain*, vol. 10, no. 1, p. 28, 2017.

[7] C. H. Liu, G. Z. Zhang, B. Li et al., “Role of inflammation in depression relapse,” *Journal of Neuroinflammation*, vol. 16, no. 1, p. 90, 2019.

[8] A. C. Liberman, E. Trias, L. da Silva Chagas et al., “Neuroimmune and inflammatory signals in complex disorders of the central nervous system,” *Neuroimmunomodulation*, vol. 25, no. 5–6, pp. 246–270, 2019.

[9] S. W. Jeon and Y. K. Kim, “Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness?,” *World J Psychiatry*, vol. 6, no. 3, pp. 283–293, 2016.

[10] D. Mattei and T. Notter, “Basic concept of microglia biology and neuroinflammation in relation to psychiatry,” *Current Topics in Behavioral Neurosciences*, vol. 44, pp. 9–34, 2020.

[11] Y. Tang and W. Le, “Differential roles of M1 and M2 microglia in neurodegenerative diseases,” *Molecular Neurobiology*, vol. 53, no. 2, pp. 1181–1194, 2016.

[12] M. V. Sofroniew, “Astrocyte barriers to neurotoxic inflammation,” *Nature Reviews. Neuroscience*, vol. 16, no. 5, pp. 249–263, 2015.

[13] C. Murphy-Royal, J. Dupuis, L. Groc, and S. H. R. Oliet, “Astrogial glutamate transporters in the brain: regulating neurotransmitter homeostasis and synaptic transmission,” *Journal of Neuroscience Research*, vol. 95, no. 11, pp. 2140–2151, 2017.

[14] H. Li, A. P. Sagar, and S. Kéri, “Microglial markers in the frontal cortex are related to cognitive dysfunctions in major depressive disorder,” *Journal of Affective Disorders*, vol. 241, pp. 305–310, 2018.

[15] C. Nagy, M. Suderman, J. Yang et al., “Astrocytic abnormalities and global DNA methylation patterns in depression and suicide,” *Molecular Psychiatry*, vol. 20, no. 3, pp. 320–328, 2015.

[16] C. Ménard, G. E. Hodes, and S. J. Russo, “Pathogenesis of depression: insights from human and rodent studies,” *Neuroscience*, vol. 321, pp. 138–162, 2016.

[17] M. Adzic, Z. Brkic, M. Mitic et al., “Therapeutic strategies for treatment of inflammation-related depression,” *Current Neuropsychopharmacology*, vol. 16, no. 2, pp. 176–209, 2018.

[18] Y. L. Wang, Q. Q. Han, W. Q. Gong et al., “Microglial activation mediates chronic mild stress-induced depressive- and anxiety-like behavior in adult rats,” *Journal of Neuroinflammation*, vol. 15, no. 1, p. 21, 2018.

[19] C. Fan, Q. Song, P. Wang, Y. Li, M. Yang, and S. Y. Yu, “Neuroprotective effects of ginsenoside-Rg1 against depression-like behaviors via suppressing glial activation, synaptic deficits, and neuronal apoptosis in rats,” *Frontiers in Immunology*, vol. 9, p. 2889, 2018.

[20] G. Z. Réus, R. H. Silva, A. B. de Moura et al., “Early maternal deprivation induces microglial activation, alters glial fibrillary acidic protein immunoreactivity and indoleamine 2,3-dioxygenase during the development of offspring rats,” *Molecular Neurobiology*, vol. 56, no. 2, pp. 1096–1108, 2019.

[21] A. S. Miragaia, G. S. de Oliveira Wertheimer, A. C. Consoli et al., “Maternal deprivation increases anxiety- and depressive-like behaviors in an age-dependent fashion and reduces neuropeptide Y expression in the amygdala and hippocampus of male and female young adult rats,” *Frontiers in Behavioral Neuroscience*, vol. 12, p. 159, 2018.

[22] B. M. Campbell, E. Charych, A. W. Lee, and T. Möller, “Kynurenines in CNS disease: regulation by inflammatory cytokines,” *Frontiers in Neuroscience*, vol. 8, p. 12, 2014.

[23] G. Tuboly, L. Tar, Z. Bohar et al., “The inimitable kynurenic acid: the roles of different ionotropic receptors in the action of kynurenic acid at a spinal level,” *Brain Research Bulletin*, vol. 112, pp. 52–60, 2015.

[24] T. L. da Silveira, D. C. Zamberlan, L. P. Arantes et al., “Quinolinic acid and glutamatergic neurodegeneration in Caenorhabditis elegans,” *Neurotoxicology*, vol. 67, pp. 94–101, 2018.

[25] S. W. Jeon and Y. K. Kim, “Inflammation-induced depression: its pathophysiology and therapeutic implications,” *Journal of Neuroimmunology*, vol. 313, pp. 92–98, 2017.

[26] G. J. Guillemin, S. J. Kerr, G. A. Smythe et al., “Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection,” *Journal of Neurochemistry*, vol. 78, no. 4, pp. 842–853, 2001.

[27] Y. Wang, M. A. Lawson, K. W. Kelley, and R. Dantzer, “Primary murine microglia are resistant to nitric oxide inhibition of indoleamine 2,3-dioxygenase,” *Brain, Behavior, and Immunity*, vol. 24, no. 8, pp. 1249–1253, 2010.

[28] A. W. Corona, Y. Huang, J. C. O’Connor et al., “Fractalkine receptor (CX3CR1) deficiency sensitizes mice to the behavioral
Mediators of Inflammation

changes induced by lipopolysaccharide,” *Journal of Neuroinflammation*, vol. 7, no. 1, p. 93, 2010.

[29] K. O’Farrell, E. Fagan, T. J. Connor, and A. Harkin, “Inhibition of the kynurenine pathway protects against reactive microglial-associated reductions in the complexity of primary cortical neurons,” *European Journal of Pharmacology*, vol. 810, pp. 163–173, 2017.

[30] A. M. Garrison, J. M. Parrott, A. Tuñon, J. Delgado, L. Redus, and J. C. O’Connor, “Kynurenine pathway metabolic balance influences microglia activity: targeting kynurenine monoxygenase to dampen neuroinflammation,” *Psychoneuroendocrinology*, vol. 94, pp. 1–10, 2018.

[31] G. J. Guillemin, G. Smythe, O. Takikawa, and B. J. Brew, “Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons,” *Glia*, vol. 49, no. 1, pp. 15–23, 2005.

[32] C. R. Dostal, M. Carson Sulzer, K. W. Kelley, G. G. Freund, and R. H. McCusker, “Gliaal and tissue-specific regulation of kynurenine pathway dioxygenases by acute stress of mice,” *Neurobiol Stress*, vol. 7, pp. 1–15, 2017.

[33] M. Fleschner, M. Frank, and S. F. Maier, “Danger signals and inflammasomes: stress-evoked sterile inflammation in mood disorders,” *Neuropsychopharmacology*, vol. 42, no. 1, pp. 36–45, 2017.

[34] B. Z. Shao, Q. Cao, and C. Liu, “Targeting NLRP3 inflammasome in the treatment of CNS diseases,” *Frontiers in Molecular Neuroscience*, vol. 11, p. 20, 2018.

[35] V. Ramaswamy, J. G. Walsh, D. B. Sinclair et al., “Inflammation induction in Rasmussen’s encephalitis: cortical and associated white matter pathogenesis,” *Journal of Neuroinflammation*, vol. 10, no. 1, p. 152, 2013.

[36] J. Ślusarczyk, E. Trojan, K. Głombik et al., “Targeting the NLRP3 inflammasome-related pathways via tianetine treatment-suppressed microglia polarization to the M1 phenotype in lipopolysaccharide-stimulated cultures,” *International Journal of Molecular Sciences*, vol. 19, no. 7, p. 1965, 2018.

[37] Z. Jian, S. Ding, H. Deng et al., “Probencid protects against oxygen-glucose deprivation injury in primary astrocytes by regulating inflammasome activity,” *Brain Research*, vol. 1643, pp. 123–129, 2016.

[38] X. Yao, Q. Jiang, W. Ding et al., “Interleukin 4 inhibits high mobility group box 1-protein-mediated NLRP3 inflammasome formation by activating peroxisome proliferator-activated receptor-y in astrocytes,” *Biochemical and Biophysical Research Communications*, vol. 509, no. 2, pp. 624–631, 2019.

[39] F. N. Kaufmann, A. P. Costa, G. Ghisleni et al., “NLRP3 inflammasome-driven pathways in depression: clinical and preclinical findings,” *Brain, Behavior, and Immunity*, vol. 64, pp. 367–383, 2017.

[40] W. Zhu, F. S. Cao, J. Feng et al., “NLRP3 inflammasome activation contributes to long-term behavioral alterations in mice injected with lipopolysaccharide,” *Neuroscience*, vol. 343, pp. 77–84, 2017.

[41] Y. Pan, X. Y. Chen, Q. Y. Zhang, and L. D. Kong, “Microglial NLRP3 inflammasome activation mediates IL-1β-related inflammation in prefrontal cortex of depressive rats,” *Brain, Behavior, and Immunity*, vol. 41, pp. 90–100, 2014.

[42] M. F. Lister, J. Sharkey, D. A. Savatzky et al., “The role of the purinergic P2X7 receptor in inflammation,” *Journal of Inflammation*, vol. 4, no. 1, p. 5, 2007.

[43] K. Zhang, J. Liu, X. You et al., “P2X7 as a new target for chrysophanol to treat lipopolysaccharide-induced depression in mice,” *Neuroscience Letters*, vol. 613, pp. 60–65, 2016.

[44] W. J. Su, T. Zhang, C. L. Jiang, and W. Wang, “Clemastine alleviates depressive-like behavior through reversing the imbalance of microglia-related pro-inflammatory state in mouse hippocampus,” *Frontiers in Cellular Neuroscience*, vol. 12, p. 412, 2018.

[45] Y. D. Potucek, J. M. Crain, and J. J. Watters, “Purinergic receptors modulate MAP kinases and transcription factors that control microglial inflammatory gene expression,” *Neurochemistry International*, vol. 49, no. 2, pp. 204–214, 2006.

[46] C. H. Shieh, A. Heinrich, T. Serchov, D. van Calker, and K. Biber, “P2X7-dependent, but differentially regulated release of IL-6, CCL2, and TNF-α in cultured mouse microglia,” *Glia*, vol. 62, no. 4, pp. 592–607, 2014.

[47] Y. He, N. Taylor, L. Fourgeaud, and A. Bhattacharya, “The role of microglial P2X7: modulation of cell death and cytokine release,” *Journal of Neuroinflammation*, vol. 14, no. 1, p. 135, 2017.

[48] M. Monif, C. A. Reid, K. L. Powell, K. J. Drummond, T. J. O’Brien, and D. A. Williams, “Interleukin-1β has trophic effects in microglia and its release is mediated by P2X7R pore,” *Journal of Neuroinflammation*, vol. 13, no. 1, p. 173, 2016.

[49] K. B. Washburn and J. T. Neary, “P2 purinergic receptors signal to STAT3 in astrocytes: difference in STAT3 responses to P2Y and P2X receptor activation,” *Neuroscience*, vol. 142, no. 2, pp. 411–423, 2006.

[50] W. Panenka, H. Jijon, L. M. Herx et al., “P2X7-like receptor activation in astrocytes increases chemokine monocyte chemoattractant protein-1 expression via mitogen-activated protein kinase,” *The Journal of Neuroscience*, vol. 21, no. 18, pp. 7135–7142, 2001.

[51] H. O. Kalkman and D. Feuerbach, “Modulatory effects of α7 nAChRs on the immune system and its relevance for CNS disorders,” *Cellular and Molecular Life Sciences*, vol. 73, no. 13, pp. 2511–2530, 2016.

[52] S. Alzarea and S. Rahman, “α7 nicotinic receptor allosteric modulator PNU120596 prevents lipopolysaccharide-induced anxiety, cognitive deficit and depression-like behaviors in mice,” *Behavioural Brain Research*, vol. 366, pp. 19–28, 2019.

[53] T. Suzuki, I. Hide, A. Matsubara et al., “Microglial alpha7 nicotinic acetylcholine receptors drive a phospholipase C/IP3 pathway and modulate the cell activation toward a neuroprotective role,” *Journal of Neuroscience Research*, vol. 83, no. 8, pp. 1461–1470, 2006.

[54] R. De Simone, M. A. Ajmone-Cat, D. Carnevale, and L. Minghetti, “Activation of alpha7 nicotinic acetylcholine receptor by nicotine selectively up-regulates cyclooxygenase-2 and prostaglandin E2 in rat microglial cultures,” *Journal of Neuroinflammation*, vol. 2, no. 1, p. 4, 2005.

[55] N. Moriooka, M. Tokuhara, Y. Nakamura et al., “Primary cultures of rat cortical microglia treated with nicotine increases in the expression of excitatory amino acid transporter 1 (GLAST) via the activation of the α7 nicotinic acetylcholine receptor,” *Neuroscience*, vol. 258, pp. 374–384, 2014.

[56] Y. Liu, J. Hu, J. Wu et al., “α7 nicotinic acetylcholine receptor-mediated neuroprotection against dopaminergic neuron loss in an MPTP mouse model via inhibition of astrocyte activation,” *Journal of Neuroinflammation*, vol. 9, no. 1, p. 98, 2012.
[57] P. Revathikumar, F. Bergqvist, S. Gopalakrishnan et al., “Immunomodulatory effects of nicotine on interleukin 1β activated human astrocytes and the role of cyclooxygenase 2 in the underlying mechanism,” Journal of Neuroinflammation, vol. 13, no. 1, p. 256, 2016.

[58] C. Culmsee, S. Michels, S. Scheu, V. Arolt, U. Dannlowski, and J. Alferink, “Mitochondria, microglia, and the immune system—how are they linked in affective disorders?,” Frontiers in Psychiatry, vol. 9, p. 739, 2019.

[59] J. Park, H. Choi, J. S. Min et al., “Mitochondrial dynamics modulate the expression of pro-inflammatory mediators in microglial cells,” Journal of Neurochemistry, vol. 127, no. 2, pp. 221–232, 2013.

[60] S. Sarkar, E. Malovic, D. S. Harishchandra et al., “Mitochondrial impairment in microglia amplifies NLRP3 inflammasome proinflammatory signaling in cell culture and animal models of Parkinson’s disease,” NPJ Parkinsons Disease, vol. 3, no. 1, p. 30, 2017.

[61] Z. Zhong, S. Liang, E. Sanchez-Lopez et al., “New mitochondrial DNA synthesis enables NLRP3 inflammasome activation,” Nature, vol. 560, no. 7717, pp. 198–203, 2018.

[62] H. B. Choi, C. Khoo, J. K. Ryu, E. van Bremen, S. U. Kim, and J. G. McLarnon, “Inhibition of lipopolysaccharide-induced cyclooxygenase-2, tumor necrosis factor-alpha and [Ca2+]i responses in human microglia by the peripheral benzodiazepine receptor ligand PK11195,” Journal of Neurochemistry, vol. 83, no. 3, pp. 546–555, 2002.

[63] M. Karlstetter, C. Nothdurfter, A. Aslanidis et al., “Translocator protein (18 kDa) (TSPO) is expressed in reactive retinal microglia and modulates microglial inflammation and phagocytosis,” Journal of NeuroInflammation, vol. 11, no. 1, p. 3, 2014.

[64] R.-H. Du, F.-F. Wu, M. Lu et al., “Uncoupling protein 2 modulation of the NLRP3 inflammasome in astrocytes and its implications in depression,” Redox Biology, vol. 9, pp. 178–187, 2016.

[65] M. Belvederi Murri, C. Pariente, V. Mondelli et al., “HPA axis and aging in depression: systematic review and meta-analysis,” Psychoneuroendocrinology, vol. 41, pp. 46–62, 2014.

[66] M. J. Szpunar and B. L. Parry, “A systematic review of cortisol, thyroid-stimulating hormone, and prolactin in peripartum women with major depression,” Archives of Women’s Mental Health, vol. 21, no. 2, pp. 149–161, 2018.

[67] A. Sierra, A. Gottfried-Blackmore, T. A. Milner, B. S. McEwen, and K. Bulloch, “Steroid hormone receptor expression and function in microglia,” Glia, vol. 56, no. 6, pp. 659–674, 2008.

[68] J. Jacobsson, M. Persson, E. Hansson, and L. Rönnbäck, “Corticosterone inhibits expression of the microglial glutamate transporter GLT-1 in vitro,” Neuroscience, vol. 139, no. 2, pp. 475–483, 2006.

[69] M. G. Frank, S. A. Hershman, M. D. Weber, L. R. Watkins, and S. F. Maier, “Chronic exposure to exogenous glucocorticoids primes microglia to pro-inflammatory stimuli and induces NLRP3 mRNA in the hippocampus,” Psychoneuroendocrinology, vol. 40, pp. 191–200, 2014.

[70] A. Slowik, L. Lammerding, A. Zendedel, P. Habib, and C. Beyer, “Impact of steroid hormones E2 and P on the NLRP3/ASC/Casp1 axis in primary mouse astroglia and BV-2 cells after in vitro hypoxia,” The Journal of Steroid Biochemistry and Molecular Biology, vol. 183, pp. 18–26, 2018.

[71] S. Koyanagi, N. Kusunose, M. Taniguchi et al., “Glucocorticoid regulation of ATP release from spinal astrocytes underlies diurnal exacerbation of neuropathic mechanical allodynia,” Nature Communications, vol. 7, no. 1, p. 13102, 2016.

[72] S.-Y. Yuan, J. Liu, J. Zhou et al., “AMPK mediates glucocorticoids stress-induced Downregulation of the glucocorticoid Receptor in cultured rat prefrontal cortical astrocytes,” PLoS One, vol. 11, no. 8, article e0159513, 2016.

[73] I. Rozovsky, M. Wei, D. J. Stone et al., “Estradiol (E2) enhances neurite outgrowth by repressing glial fibrillary acidic protein expression and reorganizing laminin,” Endocrinology, vol. 143, no. 2, pp. 636–646, 2002.

[74] C. Y. Xia, S. F. Chu, S. Zhang et al., “Ginsenoside Rg1 alleviates corticosterone-induced dysfunction of gap junctions in astrocytes,” Journal of Ethnopharmacology, vol. 208, pp. 207–213, 2017.

[75] C. Y. Xia, Z. Z. Wang, Z. Zhang et al., “Corticosterone impairs gap junctions in the prefrontal cortical and hippocampal astrocytes via different mechanisms,” Neuropharmacology, vol. 131, pp. 20–30, 2018.

[76] R. Dermietzel, Y. Gao, E. Scemes et al., “Connexin43 null mice reveal that astrocytes express multiple connexins,” Brain Research. Brain Research Reviews, vol. 32, no. 1, pp. 45–56, 2000.

[77] J. I. Nagy, B. D. Lynn, O. Tress, K. Willecke, and J. E. Rash, “Connexin26 expression in brain parenchymal cells demonstrated by targeted connexin ablation in transgenic mice,” The European Journal of Neuroscience, vol. 34, no. 2, pp. 263–271, 2011.

[78] A. Wallraff, R. Köhling, U. Heinemann, M. Theis, K. Willecke, and C. Steinhäuser, “The impact of astrocytic gap junctional coupling on potassium buffering in the hippocampus,” The Journal of Neuroscience, vol. 26, no. 20, pp. 5438–5447, 2006.

[79] N. Rouach, A. Koulakoff, V. Abudara, K. Willecke, and C. Giaume, “Astrogial metabolic networks sustain hippocampal synaptic transmission,” Science, vol. 322, no. 5907, pp. 1551–1555, 2008.

[80] G. Perez and A. Araque, “GLIA modulates synaptic transmission,” Brain Research Reviews, vol. 63, no. 1–2, pp. 93–102, 2010.

[81] E. Decrock, M. De Bock, N. Wang et al., “Connexin and panxenin signaling pathways, an architectural blueprint for CNS physiology and pathology,” Cellular and Molecular Life Sciences, vol. 72, no. 15, pp. 2823–2851, 2015.

[82] P. Ezan, P. André, S. Cistermino et al., “Deletion of astroglial connexins weakens the blood-brain barrier,” Journal of Cerebral Blood Flow and Metabolism, vol. 32, no. 8, pp. 1457–1467, 2012.

[83] U. Pannasch, L. Vargova, J. Reingruber et al., “Astrogial networks scale synaptic activity and plasticity,” Proceedings of the National Academy of Sciences of the United States of America, vol. 108, no. 20, pp. 8467–8472, 2011.

[84] E. Scemes, “Modulation of astrocyte P2Y1receptors by the carboxyl terminal domain of the gap junction protein Cx43,” Glia, vol. 56, no. 2, pp. 145–153, 2008.

[85] K. Dobrenis, H. Y. Chang, M. H. Pina-Benabou et al., “Human and mouse microglia express connexin36, and functional gap junctions are formed between rodent microglia and neurons,” Journal of Neuroscience Research, vol. 82, no. 3, pp. 306–315, 2005.
Mediators of Inflammation

[86] I. Maezawa and L. W. Jin, “Rett syndrome microglia damage dendrites and synapses by the elevated release of glutamate,” The Journal of Neuroscience, vol. 30, no. 15, pp. 5346–5356, 2010.

[87] E. A. Eugenin, D. Eckardt, M. Theis, K. Willecke, M. V. L. Bennett, and J. C. Saez, “Microglia at brain stab wounds express connexin 43 and in vitro form functional gap junctions after treatment with interferon- and tumor necrosis factor-,” Proceedings of the National Academy of Sciences of the United States of America, vol. 98, no. 7, pp. 4190–4195, 2001.

[88] S. K. Wassell and S. S. Scherer, “Activated microglia do not form functional gap junctions in vivo,” Journal of Neuroimmunology, vol. 269, no. 1–2, pp. 90–93, 2014.

[89] H. Takeuchi, S. Jin, J. Wang et al., “Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner,” The Journal of Biological Chemistry, vol. 281, no. 30, pp. 21362–21368, 2006.

[90] T. Mika and N. Prochnow, “Functions of connexins and large pore channels on microglial cells: the gates to environment,” Brain Research, vol. 1487, pp. 16–24, 2012.

[91] J. D. Sun, Y. Liu, Y. H. Yuan, J. Li, and N. H. Chen, “Gap junction dysfunction in the prefrontal cortex induces depressive-like behaviors in rats,” Neuropsychopharmacology, vol. 37, no. 5, pp. 1305–1320, 2012.

[92] C. Ernst, C. Nagy, S. Kim et al., “Dysfunction of astrocyte connexins 30 and 43 in dorsal lateral prefrontal cortex of suicide completers,” Biological Psychiatry, vol. 70, no. 4, pp. 312–319, 2011.

[93] J. A. Orellana, R. Moraga-Amaro, R. A. Dáaz-Galarce et al., “Restraint stress increases hemichannel activity in hippocampal glial cells and neurons,” Frontiers in Cellular Neuroscience, vol. 9, p. 102, 2015.

[94] A. Tanti, P. E. Lutz, J. Kim et al., “Evidence of decreased gap junction coupling between astrocytes and oligodendrocytes in the anterior cingulate cortex of depressed suicides,” Neuropsychopharmacology, vol. 44, no. 12, pp. 2099–2111, 2019.

[95] C. Y. Xia, Z. Z. Wang, T. Yamakuni, and N. H. Chen, “A novel mechanism of depression: role for connexins,” European Neuropsychopharmacology, vol. 28, no. 4, pp. 483–498, 2018.

[96] V. Kormos and B. Gaszner, “Role of neuropeptides in anxiety, stress, and depression: from animals to humans,” Neuropeptides, vol. 47, no. 6, pp. 401–419, 2013.

[97] M. Golyszny and E. Obuchowicz, “Are neuropeptides relevant for the mechanism of action of SSRIs?,” Neuropeptides, vol. 75, pp. 1–17, 2019.

[98] R. Ferreira, S. Kapelli, T. Santos et al., “Neuropeptide Y modulation of interleukin-1[beta] (IL-1[beta])-induced nitric oxide production in microglia,” The Journal of Biological Chemistry, vol. 285, no. 53, pp. 41921–41934, 2010.

[99] R. Ferreira, T. Santos, L. Cortes et al., “Neuropeptide Y inhibits interleukin-1 beta-induced microglia motility,” Journal of Neurochemistry, vol. 120, no. 1, pp. 93–105, 2012.

[100] A. R. Burmeister, M. B. Johnson, V. S. Chauhan et al., “Human microglia and astrocytes constitutively express the neurokinin-1 receptor and functionally respond to substance P,” Journal of Neuroinflammation, vol. 14, no. 1, p. 245, 2017.

[101] M. Ifuku, Y. Okuno, Y. Yamakawa et al., “Functional importance of inositol-1,4,5-triphosphate-induced intracellular Ca2+ mobilization in galanin-induced microglial migration,” Journal of Neurochemistry, vol. 117, no. 1, pp. 61–70, 2011.  

[102] W. W. IsHak, R. Y. Wen, L. Naghdechi et al., “Pain and depression: a systematic review,” Harvard Review of Psychiatry, vol. 26, no. 6, pp. 352–363, 2018.

[103] A. S. Pires, V. X. Tan, B. Heng, G. J. Guillemin, and A. Latini, “Kynurenine and tetrahydrobiopterin pathways crosstalk in pain hypersensitivity,” Frontiers in Neuroscience, vol. 14, p. 620, 2020.

[104] H. Zhang, F. Li, W. W. Li et al., “The inflammasome as a target for pain therapy,” British Journal of Anaesthesia, vol. 117, no. 6, pp. 693–707, 2016.

[105] X. L. Zhou, C. J. Zhang, Y. N. Peng, Y. Wang, H. J. Xu, and C. M. Liu, “ROR2 modulates neuropathic pain via phosphorylation of NMDA receptor subunit GluN2B in rats,” British Journal of Anaesthesia, vol. 123, no. 2, pp. e239–e248, 2019.

[106] A. C. Abraham, S. A. Shah, M. Golman et al., “Targeting the NF-kB signaling pathway in chronic tendon disease,” Science Translational Medicine, vol. 11, no. 481, article eaav4319, 2019.