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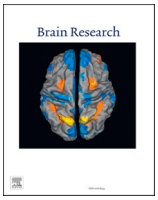

Review

NLRP3 inflammatory pathway. Can we unlock depression?

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ABSTRACT

Depression holds the title of the largest contributor to worldwide disability, with the numbers expected to continue growing. Currently, there are neither reliable biomarkers for the diagnosis of the disease nor are the current medications sufficient for a lasting response in nearly half of patients. In this comprehensive review, we analyze the previously established pathophysiological models of the disease and how the interplay between NLRP3 inflammasome activation and depression might offer a unifying perspective. Adopting this inflammatory theory, we explain how NLRP3 inflammasome activation emerges as a pivotal contributor to depressive inflammation, substantiated by compelling evidence from both human studies and animal models. This inflammation is found in the central nervous system (CNS) neurons, astrocytes, and microglial cells. Remarkably, dysregulation of the NLRP3 inflammasome extends beyond the CNS boundaries and permeates into the enteric and peripheral immune systems, thereby altering the microbiota-gut-brain axis. The integrity of the brain blood barrier (BBB) and intestinal epithelial barrier (IEB) is also compromised by this inflammation. By emphasizing the central role of NLRP3 inflammasome activation in depression and its far-reaching implications, we go over each area with potential modulating mechanisms within the inflammasome pathway in hopes of finding new targets for more effective management of this debilitating condition.

1. Introduction

Over the past three decades, in hopes of finding novel treatment options, we probed deeper into many diseases' cellular pathophysiology to obtain a complete understanding of the exact mechanism taking place and whether we can reverse or hinder any of the steps. For several seemingly unrelated diseases, including atherosclerosis (Karasawa and Takahashi, 2017), Inflammatory Bowel Disease (Opipari and Franchi, 2014), and Alzheimer's (Ising and Heneka, 2018; Tan et al., 2014; Halle et al., 2008), a recurrent theme of inflammation via the action of inflammasomes kept emerging. Inflammasomes, discovered in 2002 (Martinon et al., 2002), are cytoplasmic polyprotein complexes involved in the activation of inflammatory mediators of innate immunity as a response to pathogen invasion or damage signals, the cascade of events that can lead to pyroptosis, the release of interleukin (IL)-1β and IL-18 (Kanneganti, 2020), which can result in different diseases depending on the tissue which has been involved.

Each inflammasome is often composed of three major subunits: first, numerous pattern recognition receptors (PRRs) of the same type that sense the insulting signal and come together to make the body of this cytoplasmic complex, second adaptor protein ASC (apoptosis-associated specklike protein) that connects the receptors to the effector enzymes and third effector protein caspase-1 that brings the downstream inflammatory response. From the PPR proteins discovered absent, melanoma 2 (AIM2), pyrin, and part of the NOD-like receptor (NLR) family, namely NLRP1, NLRP2, NLRP3 (pyrin domain containing), and NLRC4 (CARD domain containing) are well recognized to be capable of constructing these formations, and other PPRs depending on the context, might also arrange likewise (Kanneganti, 2020).

In addition, in the central nervous system (CNS), participating inflammasomes, including NLRP1 (Tan et al., 2014; Walsh et al., 2014; Abulafia et al., 2009), NLRP2 (Minkiewicz et al., 2013; Burm et al., 2015), NLRP3 (Halle et al., 2008; Johann et al., 2015), AIM2 (Adamczak et al., 2014), and NLRC4 (Burm et al., 2015) that have been found in

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neurons (Tan et al., 2014; Adamczak et al., 2014), microglial cells (Halle et al., 2008; Walsh et al., 2014; Burm et al., 2015) and astrocytes (Minkiewicz et al., 2013; Johann et al., 2015) have demonstrated their role in many pathologies like Parkinson (Zella et al., 2019), Amyotrophic Lateral Sclerosis (Johann et al., 2015), Multiple Sclerosis (Malhotra et al., 2020) and depression (Iwata et al., 2013).

Depression, the most common mental health disorder and the single largest contributor to worldwide disability according to World Health Organization (WHO), can have devastating consequences both psychologically and physically (Smith, 2014). It affects many of us at least once during our lifetime (1 in every 3 women and 1 in every 5 men (Luppa et al., 2012). Moreover, following the Coronavirus disease 2019 (COVID-19) pandemic, its global prevalence reached its peak of 28.18 % (Mahmud et al., 2022). Needless to say, with this overwhelming impact, there is a call for more sophisticated solutions. Of the mentioned inflammasomes, NLRP3 is the most extensively studied, and we strive to investigate the full picture of related pathways as well as treatment options according to the present literature.

2. Disease theories

2.1. Current theories

Depression is still described and diagnosed through psychological symptoms, such as at least 2 weeks of presence of either depressed mood or loss of interest and pleasure (anhedonia) accompanied by other symptoms, namely disturbance in sleep, apatite, loss of concentration, fatigue, a sense of worthlessness and suicidal ideation lasting most of the days (Diagnostic and Statistical Manual of Mental Disorders fifth Edition (DSM-5)). Even so, the multifactorial influence of environmental stress, which is a major risk factor (Humphreys et al., 2020; Hammen, 2005; First, 2013), along with genetic predisposition, plus the various types of disease presentations, make it challenging to narrow the root of this disorder (Lohoff, 2010; Dean and Keshavan, 2017).

Some of the proposed theories include Neurotransmitter dysfunction, commonly described as a pathological deficiency in the brain monoamine, norepinephrine, dopamine, and serotonin neurotransmitters. Moreover, this theory is possibly the first and basis of the majority of pharmacological treatments (Schildkraut, 1965; Bunney and Davis, 1965; Prange, 1964; Hamon and Blier, 2013). The endocrine disturbance is usually referred to as chronic hyper and/or subsequent hypoactivation of the hypothalamic–pituitary–adrenal axis (HPA axis) (Fries et al., 2005; Gillespie and Nemeroff, 2005). The neuroplasticity hypothesis is quoted as neurotrophic factor deficiency and structural alterations in brain networks (Dean and Keshavan, 2017; Jesulola et al., 2018; Otte et al., 2016). On top of that, according to estimates, 40–50 % of cases inherit Major depressive disorder (MDD) (Lohoff, 2010). Cortical abnormalities, such as thinning in certain regions have also been reported (Schmaal et al., 2017; Li et al., 2020). Yet none of these are fully conclusive of what happens during the disease.

2.2. Emerging theories

The latest hypothesis that could link more pieces of the puzzle is the inflammatory theory. This theory first caught attention after it was observed that chronic treatment with interferon in those suffering from hepatitis C could evoke the development of MDD (Schaefer et al., 2005). Furthermore, previously diagnosed MDD patients exhibited high levels of inflammatory cytokines, i.e., IL-6, tumor necrosis factor (TNF), and C reactive protein (CRP) in their blood (Dowlati et al., 2010; Köhler et al., 2017; Osimo et al., 2019). Further detection of MDD as a recurrent comorbidity of chronic inflammatory-based illnesses, such as cardiovascular disease and rheumatoid arthritis supported this idea (Vaccarino et al., 2007; Dougados et al., 2014). In fact, American Heart Association now recognizes MDD as a risk factor for cardiovascular disease (Goldstein et al., 2015). Behavioral manifestations, also referred to as sickness behaviors, include a range of symptoms: fatigue, loss of appetite, psychomotor retardation, and social-behavioral withdrawal, which overlap with frequent symptoms of MDD. This can be demonstrated by using pro-inflammatory cytokines (Brys et al., 2020).

Although the rise in inflammatory marker levels is not consistent in all depressed patients (Osimo et al., 2019), research has shown its possible use in detecting the severity of the disease and its resistance to treatment (Gasparini et al., 2022). This is important considering 20–30 % of patients do not respond to current available pharmacological treatments, and only 50 % of cases experience full remission, and for those who do respond to treatment, there is still a need for long-term therapy, and also, side effects are common (Johnston et al., 2019; Arioz et al., 2019). In addition, not only many well-known anti-depressants have shown anti-inflammatory properties (Zhang et al., 2020; Kopschina Feltes et al., 2017) but also other agents that mitigate inflammation, e.g., Monoclonal antibodies against TNF-α and IL-12/23 (infliximab and ustekinumab) and Nonsteroidal anti-inflammatory drugs (NSAIDs) (cyclooxygenase-2 (COX-2) inhibitor celecoxib) can alleviate depressive symptoms (Raison et al., 2013; Langley et al., 2010; Müller et al., 2006).

The reason behind this inflammatory activation has been hypothesized to be beneficial from an evolutionary standpoint. Conserving energy (referring to the physical hypoactivity in acute illness) and strengthening the immune system, which in our ancestral environment where we were constantly attacked by pathogens could have helped us to increase our survival (Miller and Raison, 2016). Nevertheless, inflammation plays a hugely beneficial role when it is transient, and the problem arises when it persists. Incidentally, inflammation is detected in patients with depression peripherally and in the CNS. This cytokine cascade can dysregulate both neurotransmitters and neuroendocrine functions. It can contribute to epigenetic gene expressions and, over time, damages the cortical tissue.

2.3. How the inflammatory theory encompasses previous findings

Let us delve into the potential role of inflammation in the neurotransmitter dysfunction theory of depression, with a particular focus on the deficiency of monoamine neurotransmitters. Inflammatory activation of indoleamine 2,3 dioxygenase (IDO) enzyme in patients with depression, degrades tryptophan (TRP) to kynurenine (KYN) (Kim et al., 2012). As TRP is the precursor to serotonin, this leads to a drop in its level. Accordingly, kynurenine monooxygenase (KMO), also induced by pro-inflammatory cytokines, transforms KYN into quinolinic acid (QUIN), a potent agonist of the N-methyl-D-aspartate (NMDA) receptor. This causes glutaminergic neurotransmission, not to mention that it could consequently enhance the KYN pathway resulting in a vicious positive feedback loop (Arteaga-Henriquez et al., 2021; Zhang et al., 2021). Restriction of monoamine synthesis due to a pro-inflammatory environment could likewise prevent synaptic monoamine reuptake along with amplifying pre-synaptic monoamine transporters' action (Fig. 1 section A) (Into et al., 2017).

As we shift our attention to endocrine disturbances, particular emphasis must be placed on the dysregulation of the HPA axis. Bear in mind that stress, whether physical or psychological, has been proven to prompt inflammation (Herbison et al., 2017). From a neuroendocrine perspective, stress activates the HPA axis, during which it releases glucocorticoids. In a study incorporating dexamethasone, it was demonstrated that this glucocorticoid induces inflammation via the nuclear factor-kappa-B (NF-kB)/NLRP3 pathway and activates pro-inflammatory genes and cytokines (Feng et al., 2019). This may seem contradictory to the notion of immune suppression by the HPA axis; however, chronic inflammation drives glucocorticoid resistance both in the immune system as well as target cells, eventually decreasing inhibitory feedback on the production of the corticotropin-releasing hormone that could stir up stress response (Fig. 1 section B) (Nikkheslat et al., 2015).

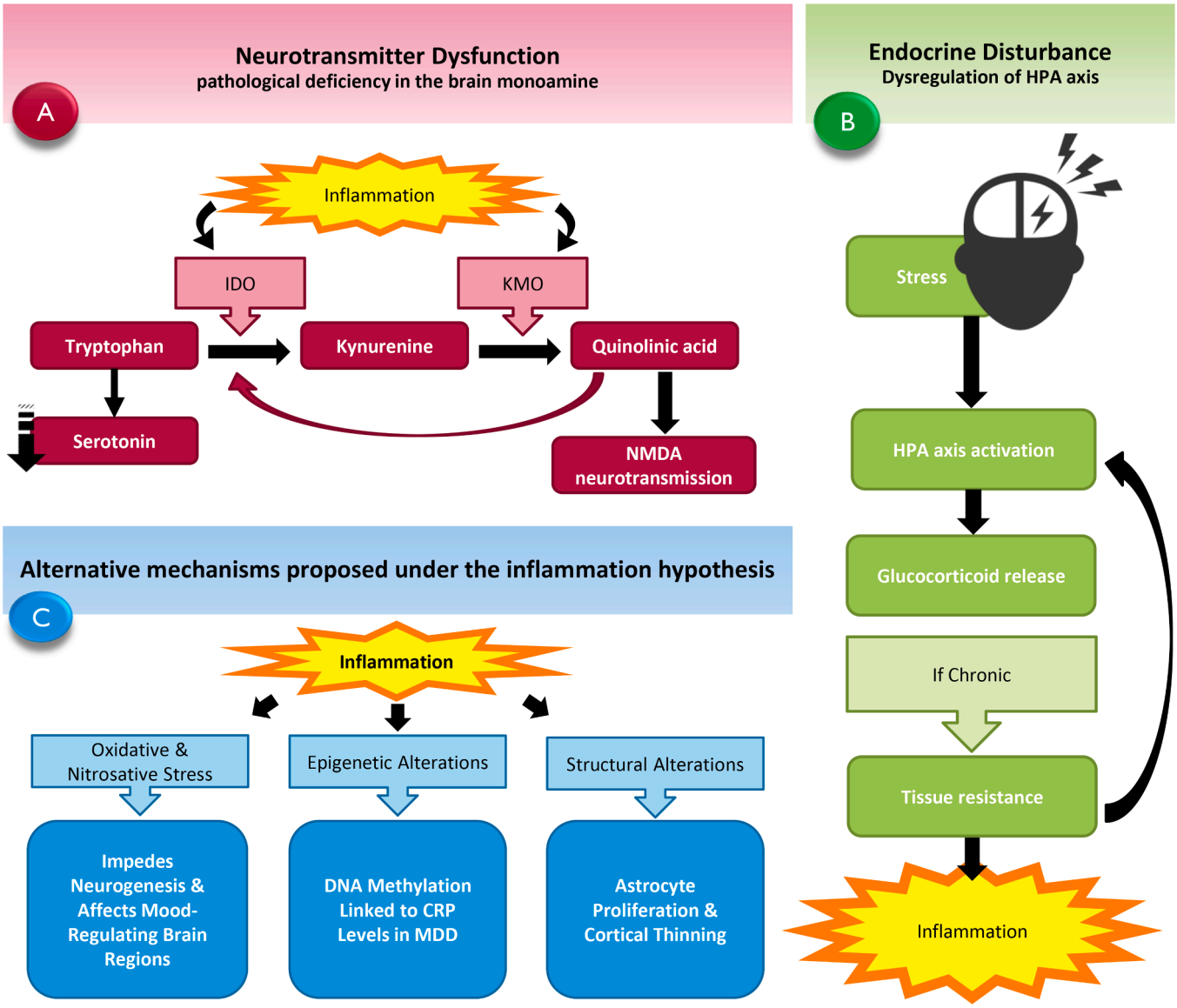

Fig. 1. Diagram depicting the involvement of inflammation in different proposed theories of depression pathophysiology. Section A focuses on the most well-known theory, the deficiency in monoamines. During inflammation enzymes like IDO break down tryptophan, the precursor to the monoamine neurotransmitter serotonin, depleting its production. The byproducts of this pathway exacerbate this disintegration. Section B illustrates the dysregulation of the HPA axis that is initiated by physical or psychological stress but can turn detrimental if chronically activated prompting tissue resistance and inflammatory response. Section C gives a brief overview of alternative mechanisms involved in depression. Oxidative and nitrosative stress emitted during inflammatory processes interrupt neurogenesis and impair the mood regulatory sites in the brain. DNA methylation in depressed patient is observed in conjunction with their level of inflammation along with structural changes like cortical thinning of certain regions and astrocyte proliferation. IDO: Indoleamine 2,3-dioxygenase; KMO: Kynurenine monooxygenase; NMDA: N-Methyl-D-aspartate; HPA axis: Hypothalamic-Pituitary-Adrenal axis; CRP: C-reactive protein; MDD: Major Depressive Disorder.

Other processes proposed for depression pathophysiology align with the inflammatory hypothesis. Specifically, mechanisms under this hypothesis involve the actions of reactive oxygen species (ROS) and nitrosative stress, which hinder neurogenesis and damage mood-regulatory brain sites. (Qiu et al., 2020). Epigenetic DNA methylation has been shown to be relevant to the CRP level in MDD patients (Green et al., 2021). Astrogliosis and thinning of some cortical areas have also been observed (Fig. 1 section C) (Han et al., 2020). Despite the fact that animal models may not be sophisticated enough to demonstrate the complexity of depression, both chemically and stress-induced models present increased inflammation compared to healthy controls (Wang et al., 2022).

3. NLRP3 inflammasome

In depression, the inflammatory response emerges from an interplay between the CNS and peripheral immune system processes. Inflammasomes, a vital component of innate immunity may have a pivotal role in mediating this inflammation (Kaufmann et al., 2017). Originally proposed in 2002 (Martinon et al., 2002), they are cytoplasmic protein complexes in charge of detecting possible threats or stress, thereby triggering the immune response (Martinon et al., 2002). NLRP3 inflammasome has one of the widest sensory spectrums through the detection of molecular patterns indicating pathogen invasion, cellular damage, and physical or psychological stress, also referred to as damage-associated molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPs) (Han et al., 2018). NLRP3′s involvement in MDD is well-established and extensively explored.

This supramolecular complex is made up of 3 major components: first, the NLRP3 protein itself is formed by triple domains appertaining to N-terminal pyrin domain (PYD), the effector domain for supramolecular complex configuration; central triple-ATPase NACHT domain, moderating protein oligomerization upon activation; and carboxyterminal leucine-rich repeat (LRR) domains, the sensor for the upcoming signals (Duncan et al., 2007); second, the ASC molecule that is composed of CARD and PYD domains, and third, the pro-caspase-1, including the caspase-1 (cysteine-dependent aspartate-directed protease) enzyme attached to a CARD domain (Sharma and de Alba, 2021). These major components and their corresponding domains allow alignment, as demonstrated in Graphical abstract section A. This oligomerization is necessary for the caspase-1 enzyme maturation, which then goes on to convert pro-IL-1 to IL-1, pro-IL-18 to IL-18, and induce gasdermin D (GSDMD) cleavage (Walsh et al., 2014). When inactive, it exists as an ADP-bound NLRP3 decamer in the cytoplasm (Hochheiser et al., 2022).

NlRP3 has two different activation pathways: canonical and non-canonical. The canonical pathway is a two-step concurrent process. The step termed "priming" is regulated by receiving the DAMPs/PAMPs signaling under the aegis of toll-like receptor (TLR)-adaptor molecule myeloid differentiation primary response 88 (MyD88) and/or cytokine receptors, including but not limited to TNF and INF-α/β receptors. Consequently, nuclear factor-κB (NF-κB) is activated, thus, amplifying transcription of inflammasome substrates i.e., pro-caspase-1, pro-IL-1β, NLRP3, and ASC. After these proteins reach a threshold level, the second activation step can occur by triggering the NLRP3 cytosolic sensor to initiate oligomerization and, in turn, caspase-1 activation. The outputs would be pro-inflammatory cytokines IL-1β, IL-18, and also GSDMD, which mediates pyroptosis cell death (Graphical abstract section B) (Bauernfeind et al., 2009; Latz et al., 2013; Shi et al., 2017). While caspase-1 and GSDMD mark the canonical pathway, the non-canonical pathway lunches by means of caspase-3/-4/-5/-11. They can either directly carry out pyroptosis or facilitate caspase-1 activation (Wang et al., 2019; Xu et al., 2018).

Clinical findings have revealed mRNA and protein expression of NLRP3 and caspase-1, along with an increment of IL-1β and IL-18 levels in peripheral blood mononuclear cells of MDD patients that were treated with Amitriptyline (Alcocer-Gómez et al., 2014; Syed et al., 2018). Complementarily, in multiple post-mortem studies of suicidal MDD patients, the NLRP3 levels were altered in the prefrontal cortex (Pandey et al., 2021; Pandey et al., 2018). Others report a correlation between NLRP3 gene methylated position and brain structure differences in MDD compared to healthy controls (Han et al., 2022). On top of that, its concentration can drive disease progression, simultaneously preventing recovery from stress (Yang et al., 2021; Wan et al., 2022).

Preclinical studies describe NLRP3 neuroinflammation in chronic unpredictable mild stress (CUMS) induced depressive behavior and other animal models (Iwata et al., 2016; Pan et al., 2014; Xu et al., 2016). More importantly, NLRP3-knockout mice were resistant and showed no depressive behavior (Alcocer-Gómez et al., 2016). Likewise, the antidepressant mechanism of well-known medications like Fluoxetine is shown to directly inhibit NLRP3 inflammasome activation (Ambati et al., 2021). This makes it a desirable target for treatment (Kaufmann et al., 2017). Mounting evidence is indicative of a pathogenic mechanism for NLRP3 Inflammasome in depressive disease. By integrating its recognized pathological course, we hope to highlight the potential treatment targets.

4. CNS

4.1. Astrocytes

Congregating proof points to Astrocyte's participation in depression pathophysiology. It has been reported that the number of astrocytes was reduced in depressed patients (Qi et al., 2019). Similarly, mice demonstrated depressive-like behaviors following a drug-induced glial loss (Banasr and Duman, 2008). NLRP3 activation in these cells is thought to execute a form of programmed cell death labeled as pyroptosis. Pyroptosis is a form of cellular death mediated by GSDM family proteins. GSDMD is a downstream product of the NLRP3 pathway. Multiple GSDMD proteins come together to construct oligomer pores in the cellular membrane letting the intracellular content leak. Secondary electrolyte osmotic imbalance swells up the cell, eventually bursting it, releasing all its content along with the inflammatory components produced, such as IL-1β, IL-18, high mobility group box-1 (HMGB1) protein, and heat shock proteins, exacerbating the inflammation and the damage generated (Graphical abstract section B&C) (Xu et al., 2018; Bergsbaken et al., 2009). The phenomenon has been reported in the brain of suicidal depressed patients (Pandey et al., 2021). Compelling evidence illustrates that selective serotonin reuptake inhibitors (SSRIs) reduce the pyroptosis of astrocytes in the CUMS models (Li et al., 2021). Depression-like manifestations improve when GSDMD, caspase-1, and astrocyte NLRP3 inflammasome genes are knocked out (Li et al., 2021).

Kir4.1 and Kir6.1-containing K-adenosine triphosphate (ATP) channels (Kir6.1/K-ATP) are widely expressed in astrocytes (Thomzig et al., 2001; Cui et al., 2018). Studies showed that the NLRP3 activation is fulfilled using the Kir4.1 and NMDAR/calpain-1 pathways. N-Methyl-D-aspartate receptor (NMDAR) is a membrane-bound receptor that participates in the flux of calcium ions. It is partially regulated by Kir4.1, another membrane K + channel. Calpain-1 is the outcome of NMDAR activation that goes on to activate NLRP3 (Cui et al., 2018; Song et al., 2021;429:115711.). Song Z et al. showed that astrocytes' specific reduction of Kir4.1 prohibited calpain-1 expression, and NLRP3 was activated in LPS-induced depression-like behaviors in mice (Song et al., 2021;429:115711.). Memantine is an NMDAR antagonist that has shown promising results in reducing NLRP3 inflammasome and astrocyte inflammatory activation, ultimately attenuating LPS-induced depressive-like behavior (Song et al., 2021;429:115711.).

Kir6.1 has illustrated a vital role in limiting astrocytic pyroptosis and the development of depression. Located at the cell membranes and mitochondrial organelles, they interact with NLRP3 and prevent inflammasome assembly (Li et al., 2022). The mitochondrial membrane coupled channel regulates mitochondrial ROS, a common NLRP3 trigger (Lin et al., 2019; Wang et al., 2021). Iptakalim is an ATP-sensitive K (K-ATP) channel opener with antidepressant effects. It has also been revealed that it could inhibit the expression of NLRP3, and furthermore, it can stabilize the HPA axis (Zhao et al., 2017).

4.2. Microglial cells

Microglial cells are credited as CNS resident macrophages so this makes it logical to look for them as the source of depressive neuroinflammation (Bachiller et al., 2018). Indeed, they are activated and express abundant NLRP3 during depressive symptoms (Pan et al., 2014). In a simplified manner, we could say that activated microglial cells differentiate into M1, which can aggravate neuroinflammation by releasing pro-inflammatory cytokines, and M2, which can alleviate inflammation by secreting anti-inflammatory cytokines (Wolf et al., 2017). NLRP3 activation directs microglia activation, and pushes it toward M1 polarization (Zhang et al., 2018). This is significant because some traditional medications, such as SSRIs as well as Tricyclic antidepressants (TCAs), and repurposed antidepressants, such as melatonin, Pioglitazone, NSAIDs, and Minocycline, a semisynthetic tetracycline antibiotic, have demonstrated their effectiveness by preventing microglial activation (Kopschina Feltes et al., 2017; Köhler et al., 2014; Pae et al., 2008; Nieto-Quero et al., 2021).

Thus far, these activated pro-inflammatory microglial cells exacerbate the condition by virtue of three known mechanisms other than the direct NLRP3 activation (Wang et al., 2022). One we previously mentioned, is the Kynurenine pathway that consumes the precursor to serotonin neurotransmitter and produces neurotoxic metabolites (Zhang

et al., 2020). Microglial cells also assist the proliferation of neural progenitor cells (NPCs). Their chronic activation prohibits neurogenesis and differentiation, risking the survival of newly formed neurons (Wang et al., 2022). Moreover, they have a bidirectional interaction with neurons to maintain functional stability. Neurons express CX3CL1 and CD200; microglial cells express receptors for those, CX3CR1 and CD200R (Chamera et al., 2020). It has been demonstrated in human and animal research that overexpression of CX3CL1 promotes inflammatory polarization, and on the contrary, its deficiency impairs neuron-microglia reaction to chronic stress (Tang et al., 2018; Merendino et al., 2004).

Pyroptosis is found in microglial cells as well, but the fall in their number is mostly displayed in the late stages of depression and correlates with severity. Interestingly, at this level, microglial cell activation actually improves the symptoms (Jia et al., 2021). Paeoniflorin was revealed to attenuate some LPS-induced depressive behavior by restricting caspase-11-dependent pyroptosis of hippocampal microglia (Tian et al., 2021).

Purinergic signaling utilizes membrane-bound ATP receptor P2X7 (P2X7R). It also facilitates microglial and macrophage inflammatory activation. The gene for this receptor is found to be associated with depressive symptoms in mice and humans (Czamara et al., 2018; Andrejew et al., 2020). When it binds to a designated target, the ATP, it allows K efflux and Na and Ca influx. Intracellular K concentration decline results in the NIMA-related kinase 7 (NEK7) dependent assembly of the NLRP3 inflammasome (He et al., 2016). There are studies suggesting that P2X7 up-regulates NFκB and can activate caspase-1, independent of the inflammasome (Garrosa-Jiménez et al., 2021; von Muecke-Heim et al., 2021). In this regard, Simvastatin exerts some antidepressant effects as it suppresses NLRP3 inflammasome activation and inhibits P2X7, TLR2, and TLR4 expression (Menze et al., 2021).

Results from targeting Nuclear factor erythroid 2-related factor 2 (Nrf2)/Silent information regulator 2 homolog 1 (SIRT1) as a treatment possibility are encouraging. Nrf2 is a redox-sensitive transcription factor regulating the antioxidant response (Yamamoto et al., 2018). According to post-mortem studies, its level was reduced in the hippocampus, prefrontal cortex, and parietal cortex of MDD patients (Martín-Hernández et al., 2018; Zhang et al., 2018). Dimethyl fumarate saves microglial from pyroptosis, alleviates LPS-induced symptoms, and diminishes IL-1β, IL-18, caspase-1, and NLRP3 levels all by Nrf2/NF-κB signaling pathway (Tastan et al., 2021). Nrf2 knockout mice with neuroinflammation and heightened NLRP3, IL-1β mRNA levels show depressive behavior (Arioz et al., 2019; Bouvier et al., 2017). Nrf2 regulates ROS degradation, an activator of NlRp3 inflammasome. This makes it a logical mood gatekeeper, having said that constant crosstalk with SIRT1, a NAD-dependent deacetylase enzyme, was demonstrated in LPS-induced depression models (Arioz et al., 2019). Inhibition of SIRT1 increased NLRP3 inflammasome concentration (Arioz et al., 2019). Melatonin, a naturally produced hormone mainly in charge of the circadian rhythm, utilizes the SIRT1/Nrf2 signaling pathway to inhibit NLRP3 inflammasome activation and pyroptosis of murine microglia (Arioz et al., 2019).

4.3. Neurons

Neuronal pyroptosis plays an essential role in many CNS pathologies, depression included (Li et al., 2020). Neurons are a predominant site for Kir6.2 expression. Kir6.2 knockout mice accentuate depression-like behaviors as a consequence of neuronal death (Fan et al., 2016). Both in humans and mice, miRNA-27a serum concentration illustrates a negative correlation with depressive symptoms. Isoliquiritin is a phenolic flavonoid with an antidepressant effect on LPS and ATP-induced neuroinflammation. It was found to be involved in miRNA-27a/SYK/NF-κB cascade, NLRP3-mediated neuronal pyroptosis, and inflammation (Li et al., 2021). What's more, Minocycline demonstrates anti-pyroptosis properties. It attenuates NLRP3 and GSDM hippocampal neuronal pyroptosis in the monosodium glutamate-induced depression rat models. VX-765, a caspase-1-specific inhibitor, does the same and improves the depressive-like performance of rats (Yang et al., 2020).

4.4. Brain blood barrier (BBB)

The brain blood barrier (BBB) guards the CNS environment and keeps it in a very tightly regulated manner. This is a great advantage in terms of any unwanted antigens that could cause a harmful immune response. Its integrity is compromised by both systemic and local inflammation (Ménard et al., 2016). When BBB is impaired a bidirectional relationship between the activation of NLRP3 and raised endothelin (ET)-1 is established (Gora et al., 2021). Intriguing results show that the anti-diabetic sodium–glucose co-transporter-2 (SGLT2) inhibitor, Dapagliflozin, exhibits anti-depressant properties as it could normalize both miR-125a-5p and ETBR (ET B receptor) expression and enhance the tight junctions of BBB by the NLRP3/TNF-α/miR-501-3p/zonula occludens 1 axis in chronic unpredictable stress (CUS) rats. It also can promote neuroplasticity and prevent neuronal death by the means of brain-derived neurotrophic factors (Muhammad et al., 2021).

5. Peripheral immunity

Activated microglial cells recruit other peripheral innate and adaptive immunity cells, such as macrophages and B-cells, through BBB, intensifying the inflammation (Wang et al., 2022). CD36 B-cells are involved in neuroinflammation. CD36 (-/-) mice have shown better resistance to chronic stress-induced depressive symptoms by expressing less NLRP3 inflammasome signaling (Bai et al., 2021). The IDO enzyme and the kynurenine pathway are present in macrophages as well, generating neurotransmitter imbalance and pro-inflammatory cytokines (O'Connor et al., 2009). Peripheral levels of IL-1β can result in the expansion of encephalitogenic T cells (Dinarello, 2011).

Autophagy is an important function of cells for scavenging unnecessary or damaged components. During NRPP3 activation, caspase-1 cleaves the autophagy signaling molecule, Toll/IL1R domain-containing adaptor-inducing IFN-β (TRIF), thus inhibiting the process. Autophagy negatively regulates the NLRP3 inflammasome activation. This is achieved through clearing endogenous activators, such as ROS, that can leak from the damaged mitochondria (Biasizzo and Kopitar-Jerala, 2020). Although autophagy may be disturbed in all cells, this function is particularly important in phagocytes like macrophages since host defense is dependent on the production of ROS, at the same time, the balance needs to be maintained to prevent excessive inflammation (Biasizzo and Kopitar-Jerala, 2020; Cao et al., 2019). Evidence has emerged that autophagy inhibitor 3MA builds up ROS that is released into the cytosol by defective mitochondria, accordingly activating the NLRP3 inflammasome (Ma et al., 2018). Studies have displayed that ROS might activate the inflammasome by NF-κB or mitogen-activated protein kinases (MAPK) pathways (Bakunina et al., 2015). Another observation is that chronic glucocorticoid administration can increase cerebral ROS concentration (Uchihara et al., 2016), facilitate NF-κB transcription (Pace and Miller, 2009, 1179), and promote both mRNA and protein levels of NLRP3 in macrophages and microglia (Frank et al., 2014).

6. Microbiome

Growing evidence is proving the significance of the Microbiota-gut-brain axis in the pathophysiology of MDD. Though it is still not clear whether the dysbiosis of the gut microbiome causes the depressive manifestation or vice versa, the hypothesis states that the enteric bacteria and their products leak into the lamina propria, and subsequently, the bloodstream, triggering the enteric and peripheral immune response, all as a result of loss of intestinal epithelial barrier (IEB) integrity that is modulated by the enteric bacteria (Pellegrini et al.,

2018). In fact, MDD patients' composition of colonic bacteria has been found to be distinct from healthy individuals (Pellegrini et al., 2018). Antigens' secretion from the microbiome can induce depressive pathology as a consequence of promoting M1 microglial-induced pyroptosis (Rutsch et al., 2020). NLRP3 inflammasome has been linked to the preservation of IEB immune reaction to bacterial flora (Pellegrini et al., 2017). When activated, it alters the composition of gut microbiota. Likewise, when NLRP3 is knocked out (-/-) in mice, there is a shift in the composition of normal flora (Chung and Kasper, 2010; Hirota et al., 2011). It is believed that canonical NLRP3 inflammasome signaling regulates Firmicutes/Bacteroidetes ratio (Pellegrini et al., 2020). The scale tilts toward inflammation by a rise in Firmicutesand and a subsequent fall of Bacteriodetes and Proteobacteria (Guo et al., 2018). It is noteworthy that pro-inflammatory states seem to include NLRP3′s reduced activity at the level of epithelial and endothelial cells, which damages the IEB, while the NLRP3 is hyperactivated in the immune cells (Pellegrini et al., 2020). In CRS mice, Minocycline improved depressive manifestation by modulating the gut microbiota and inhibiting caspase-1 (Wong et al., 2016). Microbiota transplantation is now being explored as a potential treatment. In rats, it significantly improved depressive behavior and decreased NLRP3 expression in the frontal cortex and hippocampus, all while it inhibited the activation of microglia and astrocytes (Rao et al., 2021). As well as transplant, even housing with the other NLRP3 (-/-) knocked out mice has shown improvement in the depressive manifestation of CUS mice (Zhang et al., 2019).

7. Non-pharmacological strategies

So far, we mentioned many previously used anti-depressants and other repurposed medications with anti-depressant effects that tend to also modulate the NLRP3 pathway. Perhaps the latest breakthrough in the pharmacological aspect of depression treatment is the use of a sub-anesthetic dose of Ketamine, which generates anti-depressant effects within hours of administration with long-lasting effects even in treatment-resistant patients (Berman et al., 2000; DiazGranados et al., 2010; Zarate et al., 2006). It can also create resistance against stress and inflammatory-induced depression (Dolzani et al., 2018; Camargo et al., 2020; Mastrodonato et al., 2020; McGowan et al., 2018). Although this medication modulates the NLRP3 pathway and microglial activation (Li et al., 2019; Camargo et al., 2021) due to its psychotomimetic side effects, its clinical use is limited (Gao et al., 2016). Additionally, findings on non-pharmacological strategies that we can implement in our lives today are compelling, in view of the fact that they likewise fine-tune the NLRP3 pathway. First off, Aerobic exercise suppresses NLRP3 inflammasome activation in the hippocampus and prefrontal cortex, improving depressive-like behavior (Liu et al., 2015; Wang et al., 2016; Carneiro et al., 2015), and it can inhibit microglial activation (Andoh and Koyama, 2020). Some studies suggest that aerobic exercise achieves these by TLR regulation (Mee-Inta et al., 2019) or balancing leptin secretion and sensitivity (Liu et al., 2015).

What is more, aerobic exercise has the same restricting effect on vascular endothelial NLRP3 inflammasome activation, improving endothelial function (Lee et al., 2020). Whilst there is no direct evidence of NLRP3 activation in CNS vascular endothelial cells as of yet, aerobic exercise boosts the expression of junction proteins zonula occludin-1 (ZO-1) and ZO-2, thereby, protecting the controlled permeability of vessels (Wang et al., 2016). Accordingly, we could hypothesize it protects BBB permeability.

Administration of Eicosapentaenoic acid (EPA), an ω3 long-chain polyunsaturated fatty acid that is inadequately synthesized by the body and is predominantly found in seafood (Zhang et al., 2019; Ahmmed et al., 2020), has proven its anti-depressant effects according to randomized controlled trials (Lin and Su, 2007; Hallahan et al., 2016; Grosso et al., 2014). It can limit neuroinflammation as it prohibits the activation of microglia and astrocytes and restricts the expression of NLRP3 pathway elements. In parallel, it also regulates the HPA axis (Larrieu et al., 2014; Wang et al., 2021).

Evidence validates the therapeutic impact of the ketogenic diet and supplementation (as in ketone salt, ketone esters, and medium-chain triglycerides) in depression (Brietzke et al., 2018; Bostock et al., 2017; Ari et al., 2016). This is attained in part as per inhibition of the NLRP3 pathway and microglial activation (Bae et al., 2016; Youm et al., 2015; Kovács et al., 2019). On top of that ketone bodies enhance mitochondrial respiration that prevents excessive oxidative stress (Maalouf et al., 2007).

8. Conclusion

Modern living demands have reformed our susceptibility to depression (Marx et al., 2021; Camell et al., 2015). The discovery of NLRP3 inflammasome involvement is a major step in following the biological source of depression upstream. It is spotted in both patients and animal model simulators. It looks to correlate with depressive epigenetic changes, and many pharmacological approaches that improve the mood, alter its pathway one way or another. We aimed to paint the bigger picture of its activation in various areas with mechanisms involved. The inflammation can occur both peripherally and centrally. It can affect the function of hormones, neurotransmitters and derail neuroplasticity. Furthermore, it can go as far as to kill the cells through the pyroptosis phenomenon creating perpetual damage.

No matter how promising the results are so far, there are still shortcomings that need to be addressed. For one, there are different categories for depressive illness with their own symptomology, responsiveness to medication, gender, and age distributions that need to be taken accounted for in research (van Doeselaar et al., 2021; Yanguas-Casás et al., 2020). Biological and behavioral responses strongly rely on the animal model that differs from study to study and is hard to replicate a human psychological impairment (Stephan et al., 2019; Bale et al., 2019). There is great heterogeneity in the relationship between inflammation and its biomarkers in patients (Gasparini et al., 2022; Liu et al., 2020). Thus far, other inflammasomes have had limited research focusing on them could open up new possibilities. Also, the mechanism by which stress translates to activation of the inflammasomes could hold beneficial clues for optimal treatment and elucidate the specific involvement and significance of each activation pathway.

Nevertheless, NLRP3 inflammasome is not the be-all, and end-all target in this disease as its deletion demonstrated deterioration of synaptic transmission, anxiety-like behavior, and struggle in fear-based learning, corresponding to low-level NLRP3 dependent inflammation in memory consolidation. Breaking the vicious inflammatory overdrive is the goal, yet balancing the inflammatory pathway is delicate pursuit.

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No data was used for the research described in the article.

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