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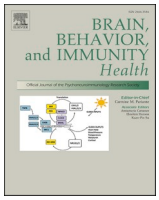

P2X7 receptors from the perspective of NLRP3 inflammasome pathway in depression: Potential role of cannabidiol

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ABSTRACT

Many patients with depressive disorder do not respond to conventional antidepressant treatment. There is an ongoing interest in investigating potential mechanisms of treatment resistance in depression to provide alternative treatment options involving inflammatory mechanisms. Increasing evidence implicates the NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome as a critical factor in neuroinflammation. ATP-induced P2X7 receptor (P2X7R) activation is a major trigger for inflammation, activating the canonical NLRP3 inflammatory cascade. Psychosocial stress, the primary environmental risk factor for depression, is associated with changes in ATP-mediated P2X7R signaling. Depression and stress response can be alleviated by Cannabidiol (CBD). CBD has an anti-inflammatory activity related to the regulation of NLRP3 inflammasome activation. However, CBD's effects on the inflammasome pathway are poorly understood in central nervous system (CNS) cells, including microglia, astrocytes, and neurons. This review will emphasize some findings for neuroinflammation and NLRP3 inflammasome pathway involvement in depression, particularly addressing the ATP-induced P2X7R activation. Moreover, we will underline evidence for the effect of CBD on depression and address its potential impacts on neuroinflammation through the NLRP3 inflammasome cascade.

1. Introduction

Depressive disorder (DD) is characterized by depressed mood, anhedonia, low self-esteem, feelings of worthlessness, sleep and eating disturbances, and impaired cognitive function (APA, 2013). DD is one of the most common chronic, relapsing psychiatric disorders and is expected to be the leading cause of global disease burden by 2030 (Mathers and Loncar, 2006). Suicidal thoughts and attempts can lead to death in people with DD (APA, 2013). The monoamine hypothesis in the pathogenesis of depression has been accepted for many years (Schildkraut, 1965). However, about one-third of patients do not respond to the current pharmacological treatments that act on the monoaminergic system. This finding suggests that the monoamine hypothesis alone is not sufficient to explain the pathogenesis of depression (Sanacora et al., 2012). After the classic monoaminergic theory, new theories have been introduced, such as the neuroplastic (Pittenger and Duman, 2008), glutamatergic (Sanacora et al., 2012), and inflammatory theories (Hall et al., 2016), which could contribute to depression (Pitsillou et al., 2020). Many studies have drawn attention to increased inflammatory responses in depression and other stress-related pathologies (Slavich and Irwin, 2014; Stein et al., 2018).

Individuals with depressive disorder, particularly those with severe and treatment-resistant depression (Eller et al., 2008; Maes et al., 1993; O'Brien et al., 2007), exhibit all of the cardinal features of an inflammatory response, including increased expression of pro-inflammatory cytokines and their receptors and higher levels of acute-phase reactants and chemokines in peripheral blood and cerebrospinal fluid (Felger and Lotrich, 2013; Maes, 1995; Miller et al., 2009). Some research suggests that viral infections such as influenza, cytomegalovirus, SARS-CoV-1 and SARS-CoV-2 are associated with an increased incidence of depression (Jeon and Kim, 2018; Mazza et al., 2020). Also, inflammation markers are related to depression severity in COVID-19 survivors in the long term (Akçay et al., 2022; Mazza et al., 2021). A recent meta-analysis has highlighted the significant associations between concurrent depression and inflammatory factors (Colasanto et al., 2020). Although there is considerable evidence that peripheral and central inflammation plays a role in the pathophysiology of DD, the mechanisms underlying activation are not fully understood (Stein et al., 2018).

In recent years, stimulation of the Nucleotide-binding and

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oligomerization domain (NOD)-like receptor pyrin domain containing 3 (NLRP3) inflammasome has been reported to contribute to the pathogenesis of many neuropsychiatric disorders including DD (Alcocer-Gómez and Cordero, 2014; Burak et al., 2022; Cakir-Aktas et al., 2023; Kaufmann et al., 2017; Kursun et al., 2021). It is emphasized that the NLRP3 inflammasome may be a target for DD treatment in patients (Alcocer-Gómez et al., 2017; Arioz et al., 2019). In addition to elevated levels of interleukin 1β (IL-1β) and IL-18 in patients diagnosed with DD, increased levels of the NLRP3 inflammasome have been reported in mononuclear cells isolated from peripheral blood (Alcocer-Gómez et al., 2014). Additionally, postmortem brain samples from suicide victims with depression have shown an increased expression of various innate immune genes and proteins, such as IL-1β, IL-6, tumor necrosis factor (TNF), and altered Toll-like receptor 4 immune response (Martín-Hernández et al., 2018). However, a recent meta-analysis did not find a consistent association between TNF-α and IL-1β and major depression, which could be related to inconsistencies between subgroups of the patients (Haapakoski et al., 2015). A recent postmortem study has reported that the protein and mRNA expression levels of NLRPs, including NLRP1, NLRP3, NLRP6, and caspase-3, were increased in patients who were depressed and died by suicide, compared to control (Ghanshyam et al., 2021). The canonical NLRP3 inflammatory cascade is activated when ATP binds to P2X7R. This leads to the activation of caspase-1 and the production of active IL-1β and IL-18 (Guo et al., 2015). The possible relationship between P2X7R and the pathogenesis of depression has recently begun to be discussed (Bhattacharya and Jones, 2018; Deussing and Arzt, 2018; Silberstein et al., 2021). Psychosocial stress, the primary environmental risk factor for depression, is associated with changes in ATP-mediated P2X7R signaling. Therefore, P2X7R involvement in innate and adaptive immunity is important in stress-related depression (Iwata et al., 2013; Ribeiro et al., 2019). Riberio et al. have proposed that increased extracellular ATP evoked by SARS-CoV-2 infection may trigger P2X7 receptor hyperactivation, leading to NLRP3 inflammasome stimulation as a critical mediator of neuroinvasion and subsequent neuroinflammatory processes as in psychiatric disorders (Ribeiro et al., 2021). The number of studies drawing attention to the relationship between P2X7 receptor activation and depression is increasing (von Mücke-Heim and Deussing, 2023).

Cannabidiol (CBD) is a non-stimulant phytocannabinoid found in Cannabis sativa and related species, comprising around 50% of their content. Tetrahydrocannabinol (THC), cannabis's main bioactive compound, is psychoactive and addictive. However, CBD is not addictive or psychotomimetic (Oberbarnscheidt and Miller, 2020). CBD has various pharmacological effects, including anti-diabetic, antioxidant, anti-cancer, neuroprotective, and anti-inflammatory properties (Crippa et al., 2018). However, the molecular pathway of its anti-inflammatory activity is still poorly understood. Recently published data indicate that the anti-inflammatory effects of CBD are associated with the regulation of NLRP3 inflammasome activation (Chu et al., 2024; Huang et al., 2019; Libro et al., 2016). Also, Hartman et al. suggest that the NLRP3 inflammasome in microglia could be a target for CBD in stress response (Hartmann et al., 2023). Two recent *in vitro* studies in microglial cell lines have examined CBD's anti-inflammatory effects experimentally (Rodrigues et al., 2024; Yndart Arias et al., 2023). The mechanisms of action of CBD on the NLRP3 inflammasome complex in microglial, astrocyte, and neuronal cells remain unclear.

This review examines the role of P2X7R signaling in depression from the perspective of the NLRP3 inflammasome pathway. Furthermore, we explore the potential of cannabidiol as an anti-inflammatory target for the treatment of depression.

2. NLRP3 inflammasome pathway

The NLRP3 inflammasome is a multiprotein complex that contains a cytosolic pattern recognition receptor (PRR), an adaptor protein called apoptosis-associated speck-like protein (ASC), and the effector enzyme caspase-1 (Li et al., 2021). This inflammasome complex detects various endogenous and exogenous danger signals and responds by promoting IL-1β and IL-18 maturation (Guo et al., 2015). The canonical mechanism of NLRP3 inflammasome formation consists of two steps: priming and activation. First, stress conditions induce the release of damage-associated molecular patterns (DAMPs), detected by membrane-associated pattern recognition receptors (PRRs) like Toll-like receptors (TLRs)(Newton and Dixit, 2012). This initial step is controlled by innate immune signaling, primarily mediated by toll-like receptor (TLR)-adaptor molecules myeloid differentiation primary response 88 (MyD88) and/or cytokine receptors, such as the tumor necrosis factor receptor (TNF-R). These receptors activate pro-IL-1β, pro-IL-18, and NLRP3 inflammasome-related transcriptions (NLRP3, ASC, pro-Caspase-1) through nuclear factor-κB (NF-κB) activation (Bauernfeind et al., 2009; Pellegrini et al., 2017). Aside from the NF-kB pathway, various other signals and potential binding sites (such as c-Myb, Ahr, ETS family, and Sp-1) have been reported to play a role in regulating NLRP3 (Anderson et al., 2008). Furthermore, NLRP3 expression may also be regulated through post-transcriptional mechanisms. Various micro-RNAs (miR) have been identified as inhibitors of NLRP3 mRNA (Tezcan et al., 2019; Zamani et al., 2020), while HIF-2a triggers NLRP3 activation by producing Long non-coding (Lnc) RNA (Zhang et al., 2019). However, the roles of miR and Lnc RNAs are not yet fully understood. Proteins associated with the NLRP3 inflammasome are still inactive in the cellular cytoplasm after translation. This phase is considered the priming process.

The second signal that enables the formation of the NLRP3 complex is required for the activation step. The NLRP3 cytosolic receptor detects cytosolic damage through the P2X7 receptor. Extracellular ATP molecules bind directly to the P2X7 receptor and promote K+ efflux from the cytosol (Perregaux and Gabel, 1994; Surprenant et al., 1996). NLRP3 receptors sense this K^+ efflux, which leads to oligomerization and activation of the NLRP3 inflammasome. Although K^+ efflux is a crucial mechanism in the ATP-induced activation of the NLRP3 inflammasome, P2X7R activation leads to an open conformation, causing also Na^+ and Ca^{+2} influx (Habermacher et al., 2016; Kaufmann et al., 2017). This triggers the formation of the intracellular NLRP3 inflammasome and subsequent caspase-1 activation. Effector caspase-1 cleaves inactive pro-IL-1β and pro-IL-18 into their active forms. These pro-inflammatory cytokines are then secreted from the cell, producing their inflammatory effects in other cells and tissues (Swanson et al., 2019). Although the consequences of canonical and non-canonical activation of the inflammasome are similar, a non-canonical NLRP3 activation has also been characterized (Accogli et al., 2023; Pellegrini et al., 2017). Caspase-11 (in mice) and Caspases-4 and 5 (in humans) are proteins capable of recognizing intra-cytosolic LPS and bacterial mRNA and triggering the activation of NLRP3 inflammasome (Accogli et al., 2023; Kayagaki et al., 2011). Caspase-11 promotes pyroptosis by cleaving Gasdermin D (GSDMD), leading to pore formation, ion efflux, NLRP3 activation, and ultimately cell death by pyroptosis (Kayagaki et al., 2015; Shi et al., 2015). To further understand how caspase-1 and -11 interact to promote both canonical and non-canonical NLRP3 inflammasome activation, additional experiments should be carried out to clarify the molecular mechanisms involved (Viganò and Mortellaro, 2013).

3. P2X7R and depression from the perspective of neuroinflammation

The P2X7 receptor is expressed throughout the body, including in immune and central nervous system (CNS) cells, primarily microglia, astrocytes, and oligodendrocytes (Junger, 2011; Sluyter, 2017; Zhao et al., 2021). Although the neuronal expression of P2X7R is controversial, an increasing number of studies support its presence in neurons (Kopp et al., 2019). The P2X7 purinergic receptors are ionotropic receptors with a structure comprising various domains. These domains

include the C-terminal cytoplasmic tail, the first transmembrane domain, the extracellular domain, the second transmembrane domain, and the N-terminal cytoplasmic tail (Junger, 2011; Sluyter, 2017). ATP binds to sites situated in the extracellular domain and promotes pore opening. Additionally, the C-terminus is the most unique domain in the P2X family and determines the biological properties of P2X7R (Kopp et al., 2019). The P2X7R receptor, unlike other members of the P2X family, requires a higher concentration of extracellular ATP (2–4 mM) (Jacobson and Müller, 2016; Khakh and North, 2012). P2X7R's high activation threshold and relatively slow desensitization are crucial in chronic inflammatory diseases (Andrejew et al., 2020).

P2X7R is an important link between mood disorders and immune dysregulation. Previous studies suggest that P2X7R signaling acts as a translator of psychosocial stress in the CNS (Iwata et al., 2013, 2016). Psychosocial stress induces the release of the DAMP molecule ATP in the prefrontal cortex and hippocampus. ATP-induced P2X7R pathways lead to inflammatory cytokine production (IL-1β, IL-18, IL-6, and TNFα) via the NLRP3 and NF-kB pathways primarily in microglia and probably to a lesser extent in astrocytes (Franklin et al., 2018; Iwata et al., 2013; Iwata et al., 2016; von Mücke-Heim and Deussing, 2023). The P2RX7 gene has previously been associated with a higher risk for depression and is implied as a candidate gene for depression (McQuillin et al., 2009). Studies have shown that there may be a relationship between some polymorphisms in the P2X7 receptor gene and the development of depression (Halmai et al., 2013; Hejjas et al., 2009). In a recent study, peripheral blood mRNA expression of a cluster of six inflammatory genes (P2X7R, IL-1β, IL-6, TNFα, glucocorticoid receptor, CXCL12) was found to identify treatment-resistant patients (Cattaneo et al., 2020). The authors described an association between P2X7R, inflammatory cytokines, and FKBP5 mRNA levels. Moreover, P2X7R was the best discriminator between treatment-resistant and all other depressed patients in the cohort (Cattaneo et al., 2020). The occurrence of antidepressant-like behaviors in mice with genetic deletion of the P2X7 receptor or administration of some selective/non-selective P2X7 receptor antagonists shows the importance of P2X7 receptors in the development and treatment of depression (Boucher et al., 2011; Pereira et al., 2013).

JNJ-54175446 is a CNS-penetrant high-affinity and selective P2X7R antagonist in development for the treatment of unipolar mood disorder. Recently, a double-blind, placebo-controlled, randomized study has been conducted to assess its safety, pharmacokinetics, and effects in patients with DD (Recourt et al., 2023). DD patients tolerated a single dose of 600 mg of the drug, followed by once-daily doses of 150 mg of the drug. It did not have a significant effect on mood as assessed using the self-rated depression scales; however, it decreased ex-vivo IL-1β release by lipopolysaccharide (LPS)-stimulated peripheral white blood cells in the presence of the P2X7 receptor agonist 3′-O-(4-benzoylbenzoyl)-ATP (BzATP). Recourt et al. have hypothesized that total sleep deprivation (TSD) is a behavioral challenge model that allows for concurrent demonstration of mood modulation and changes in cytokine release by JNJ-54175446 following P2X7 stimulation (Recourt et al., 2023). However, CSD (combined with light therapy) reduced depressive symptoms on both self-reported and clinician-rated rating instruments, which lasted until the end of the observation period (day 10). This improvement duration on mood is longer than previously reported in the literature, which may have affected the ability to evaluate its potential antidepressant effect when administered post-TSD. Furthermore, when the P2X7R is activated under elevated neuronal activity and pathology, pharmacological antagonism is only expected to elicit an effect when sufficiently high ATP concentrations activate the channels (Bodin and Burnstock, 2001). It is challenging to translate its mood-modulating effects observed in animal models of depression to a human context. It is under phase II clinical trial as a potential antidepressant agent. This phase II trial is a multi-center, randomized, double-blinded, placebo--controlled study and is still carried out across five centers in the United Kingdom (https://clinicaltrials.gov/study/NCT04116606).

4. CBD and depression

The isolation and structure of CBD were first described in 1940 (Adams et al., 1940) and remained largely unexplored for many years. Due to worldwide legal restrictions, there are limited studies on the therapeutic potential of CBD (Leonard and Aricioglu, 2023). In the early 1990s, the discovery of the CB1 and CB2 cannabinoid receptors in the central nervous system and the identification of endocannabinoids renewed interest in researching cannabinoid compounds (Zuardi, 2008). This led to increased studies on CBD, driven by exploring its potential therapeutic benefits. Research has shown that it has anticonvulsant, anxiolytic, analgesic, and neuroprotective properties and also does not have the addictive effects associated with THC (Crippa et al., 2018). Unlike THC and related phytocannabinoids, CBD has very weak activity at CB1 and CB2 receptors (Leonard and Aricioglu, 2023). Although CBD has a low affinity for CB1 and CB2 receptors, it can function as an allosteric modulator at these receptors. CBD inhibits the enzymatic breakdown and uptake of anandamide, thereby raising anandamide levels and promoting endocannabinoid signaling through CB1, CB2, and the vanilloid receptor 1 (TRPV1) (Silote et al., 2019). CBD affects not only the endocannabinoid and endovanilloid systems but also the serotonergic system. It can enhance 5-HT1A-mediated neurotransmission (Russo et al., 2005), and many of CBD's behavioral effects appear to be influenced by 5-HT1A receptors (Campos et al., 2012; Resstel et al., 2009; Sartim et al., 2016; Zanelati et al., 2010). In addition to the serotonergic system, CBD can also regulate many other different transmitter systems. CBD is also a weak antagonist of mu and delta opioid receptors and a partial agonist of dopamine 2 receptors (Mlost et al., 2020). These interactions with many different types of molecular processes demonstrate its complex pharmacology.

Preclinical studies have shown that CBD may be useful in treating a variety of psychiatric disorders, such as schizophrenia, post-traumatic stress disorder, substance abuse, obsessive-compulsive disorder, anxiety, and depression (Campos et al., 2017). Potential mechanisms for the antidepressant effects of CBD have been suggested, including 5-HT1A receptor agonism, neuroplasticity (mTOR, BDNF, and synaptogenesis), and epigenetic mechanisms (Campos et al., 2017; Silote et al., 2019). The initial experimental evidence regarding CBD's antidepressant-like effects in rats indicated that the impact of CBD was inhibited when WAY100635, a 5HT1A antagonist, was used as a pre-treatment in this study (Resstel et al., 2009). Zanelati et al. investigated the antidepressant effects of CBD and also whether these responses depended on the activation of 5-HT1A receptors and on hippocampal expression of brain-derived neurotrophic factor (BDNF). Systemic CBD treatment reduced immobility time in the forced swimming test in mice, and WAY100635 pretreatment blocked CBD-induced effects. However, CBD treatment failed to change hippocampal BDNF levels (Zanelati et al., 2010). A single CBD injection induced a rapid antidepressant-like effect in the olfactory bulbectomy mouse model, this acute effect was associated with increased extracellular 5-HT and glutamate levels in the ventromedial prefrontal cortex (vmPFC). Moreover, the 5HT1A-receptor antagonist WAY100635 prevented the behavioral and neurochemical effects of CBD (Linge et al., 2016). CBD's acute antidepressant effects were associated with increased expression of synaptophysin and PSD95 in the medial prefrontal cortex (mPFC) and elevated BDNF levels in both mPFC and hippocampus (Sales et al., 2019). The behavioral effects of CBD were eliminated when the TrkB antagonist or the mTOR inhibitor rapamycin was injected into the intracerebroventricular area. Its antidepressant-like effects may be related to rapid changes in synaptic plasticity in the mPFC through activation of the BDNF-TrkB signaling pathway. Regarding the effects of CBD's hippocampal neurogenesis, a CBD-rich diet led to increased neural progenitor cell proliferation in the hippocampus of mice over six weeks. This effect seemed to depend on CB1 receptors, as it was absent in animals lacking these receptors (Wolf et al., 2010). Campos et al. showed that CBD reversed the anxiogenic effect and decreased neurogenesis in wild-type mice exposed to chronic

unpredictable stress (CUS) (Campos et al., 2013). However, the anti-stress properties of CBD were not seen in transgenic GFAP/thymidine kinase mice, in which neurogenesis was suppressed. The effects of CBD were attenuated by the administration of pharmacological antagonists targeting CB1 and CB2 receptors (Campos et al., 2013). These findings suggest that CBD's capacity to alleviate stress is contingent upon its facilitation of hippocampal neurogenesis. However, the involvement of neurogenesis in the behavioral effects of CBD appears to depend on the duration of treatment and the behavioral paradigm utilized. For instance, Schiavon et al. (2016) confirmed that acute (single injection, 3 and 30 mg kg^{-1}) and chronic (15d, 3, 30 mg kg^{-1}) treatment with CBD causes an antidepressant-like effect; however, the chronic treatment resulted in different findings that neurogenesis increased at 3 mg kg^{-1}, but decreased at 30 mg kg^{-1} dose (Schiavon et al., 2016). CBD can also affect epigenetic mechanisms by regulating DNA methylation in brain regions relevant to depression neurobiology (Domingos et al., 2022). Sales et al. found that stress decreases DNA methylation and DNA methyltransferase (DNMT) activity in the hippocampus while increasing it in the prefrontal cortex. However, treatment with CBD and a DNMT inhibitor prevented these alterations in both brain regions (Sales et al., 2020). In a current study, the effects of early stress on mitochondrial damage and oxidative stress in female mice were examined in the maternal separation (MS) mouse model (Martín-Sánchez et al., 2022). It was determined that female mice in the MS-exposed and CBD-applied group had significantly less immobility time in the tail suspension test than the MS group that did not receive CBD. Although the antidepressant effect of CBD has been determined behaviorally, it has not been shown to reverse mitochondrial metabolic changes (Martín-Sánchez et al., 2022). The antidepressant effect of CBD was examined in a chronic stress depression model in rats, and it was found that there was a hedonic effect with increased sucrose preference after three weeks of treatment (Gáll et al., 2020). All these results show that CBD has an antidepressant effect, but its mechanism of action is still unclear.

5. The role of CBD in NLRP3 inflammasome pathway

Published studies have reported that CBD provides an improvement in various inflammatory-related diseases, including neurodegenerative diseases, through modulation of important pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and a transcription factor, NF-kB (Chu et al., 2024; Dos-Santos-Pereira et al., 2020; Huang et al., 2019; Liu et al., 2020). In the LPS model of depression, CBD reduced immobility time in the tail suspension test and increased sucrose preference (Florensa-Zanuy et al., 2021). CBD reduced cortical NF-kB activation and IL-6 levels in both plasma and brain in mice. Additionally, CBD decreased the kynurenine/tryptophan and kynurenine/serotonin ratios in the hippocampus and cortex in the LPS model with mice (Florensa-Zanuy et al., 2021). The recently published data further support the notion that CBD possesses anti-inflammatory properties, which are closely linked to its ability to regulate the activation of inflammasomes (Huang et al., 2019; Libro et al., 2016). For example, CBD has been reported to exert hepatoprotective effects against nonalcoholic steatohepatitis in a mouse model and has shown that the antihepatitis effect of CBD is associated with the NLRP3 inflammasome pathway (Huang et al., 2019). A recent *in vitro* study showed that CBD inhibited NLRP3 inflammasome activation following LPS + ATP stimulation, resulting in reduced IL-1β levels in THP-1 macrophages and primary human bronchial epithelial cells (Suryavanshi et al., 2022). Moreover, CBD treatment reduced pain, inflammation, and the levels of NLRP3, ASC, caspase-1, IL-1β/18, and TNF-α in mice with oral ulcers (Qi et al., 2022). An *in vitro* study with a SARS-CoV-2 recombinant human novel coronavirus spike glycoprotein model suggested that CBD decreased the protein levels of NLRP3 inflammasome components (Corpetti et al., 2021). A recent study has shown that the effects of CBD on the inflammasome complex in human THP-1 monocytes and CBD inhibited K^+ output and reduced inflammasome formation by directly binding to P2X7 receptors (Liu et al., 2020). The authors stated that further examination of CBD's effects on P2X7 receptors is needed to elucidate the mechanisms of CBD's anti-inflammasome activity (Liu et al., 2020). A recent study has compared the anti-inflammatory effects of CBD and Δ(9)-tetrahydrocannabinol in human microglial cells infected with HIV (Yndart Arias et al., 2023). CBD reduced the production of various inflammatory cytokines and chemokines such as MIF, SERPIN E1, IL-6, IL-8, GM-CSF, MCP-1, CXCL1, CXCL10, and IL-1 β compared to Δ(9)-THC. Additionally, CBD deactivated caspase 1 and reduced NLRP3 gene expression, which plays a crucial role in the inflammasome cascade. Rodrigues et al. have recently investigated the effects of CBD treatment on pro-inflammatory markers in lipopolysaccharide (LPS)-challenged BV2 microglia (Rodrigues et al., 2024). They found that CBD inhibited the LPS-induced pro-inflammatory responses by suppressing iNOS and NLRP3/Caspase-1-dependent signaling cascades, reducing nitric oxide, IL-1β, and TNF-α concentrations (Rodrigues et al., 2024). Although there is recent evidence regarding CBD's anti-inflammasome activity in human microglial cells, no study has investigated CBD's effects on P2X7 receptors in the NLRP3 inflammasome cascade in microglial cells. Furthermore, there is currently no molecular-level evidence regarding the interaction between CBD and the NLRP3 pathway in animal stress models. It is important to investigate the effects of CBD treatment on P2X7 receptors in microglial cells and other CNS cells, such as astrocytes and neuronal cells, through in vivo experiments.

6. Conclusion

Neuroinflammation plays a crucial role in the pathophysiology of many CNS disorders, including depressive disorders. The NLRP3 inflammasome is a critical participant in neuroinflammation and is responsible for releasing pro-inflammatory cytokines and triggering the inflammatory response. Based on the evidence mentioned in this review, the relationship between depression and neuroinflammation is apparent. In addition, current antidepressants are both inadequate in reducing depressive symptoms and have a slow onset of action. Thus, new treatment strategies involving inflammasome pathways are an area of interest. Considering the antidepressant effects of CBD and its effects on NLRP3 inflammasome pathways, it may be a potential antidepressant agent. In vitro studies in microglial cell lines have recently experimentally examined the effects of CBD anti-inflammasome; however, it is still unclear how these effects are caused. Also, in vivo experiments are needed to show CBD treatment and its neuropsychiatric effects at both molecular and behavioral levels. CBD's broad therapeutic effects in neuropsychiatric disorders may be explained by its general anti-stress response due to ATP-mediated P2X7R. Considering that P2X7R plays an important role in mood disorders and the NLRP3 inflammasome pathway, CBD's anti-inflammasome effects in depression may related to P2X7R. It's crucial to study the effects of CBD treatment on P2X7 receptors in CNS cells like microglial, astrocytes, and neuronal cells through in vivo experiments. In conclusion, we highlight the capacity of CBD to suppress inflammation by modulating the NLRP3 inflammasome pathway, suggesting that CBD may have a potential therapeutic role in depressive disorders.

CRediT authorship contribution statement

Elif Akcay: Writing – original draft, Investigation, Conceptualization. **Hulya Karatas:** Writing – review & editing, Supervision.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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