ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatr 2021 December 19; 11(12): 1167-1424

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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Editorial Board Member of *World Journal of Psychiatry*, Subho Chakrabarti, MD, FRCP, FAMS, Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 16002, India. chakrabarti.subho@pgimer.edu.in

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Production Editor: *Xu Guo*; **Production Department Director:** *Yu-Jie Ma*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
December 19, 2021

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World J Psychiatr 2021 December 19; 11(12): 1191-1205

DOI: 10.5498/wjp.v11.i12.1191

ISSN 2220-3206 (online)

REVIEW

Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder

Han Wang, Wei-Jing Kan, Yuan Feng, Lei Feng, Yang Yang, Pei Chen, Jing-Jie Xu, Tian-Mei Si, Ling Zhang, Gang Wang, Jing Du

ORCID number: Han Wang 0000-0001-9366-1817; Wei-Jing Kan 0000-0002-1538-7047; Yuan Feng 0000-0003-4172-4024; Lei Feng 0000-0001-7810-5070; Yang Yang 0000-0001-8425-6633; Pei Chen 0000-0002-6396-1031; Jing-Jie Xu 0000-0001-8311-2355; Tian-Mei Si 0000-0001-9823-2720; Ling Zhang 0000-0002-9713-1458; Gang Wang 0000-0003-3949-1188; Jing Du 0000-0003-3128-9997.

Author contributions: Wang H wrote the first draft of the manuscript; Kan WJ, Feng Y, Feng L, Yang Y, Chen P, and Xu JJ managed the systematic literature search; Du J supervised the study; Si TM, Zhang L, and Wang G critically revised the manuscript; and all authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest for this manuscript.

Supported by the National Natural Science Foundation of China, No. 31650005.

Country/Territory of origin: China

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Han Wang, Wei-Jing Kan, Yuan Feng, Lei Feng, Yang Yang, Pei Chen, Jing-Jie Xu, Ling Zhang, Gang Wang, Jing Du, The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, Beijing 100088, Beijing Province, China

Tian-Mei Si, Department of Clinical Psychopharmacology, Peking University Institute of Mental Health, Beijing 100191, Beijing Province, China

Jing Du, State Key Laboratory for Conservation and Utilization of Bio-resources in Yunnan, Yunnan University, Kunming 650091, Yunnan Province, China

Corresponding author: Jing Du, PhD, Professor, The National Clinical Research Center for Mental Disorders & Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital, No. 5 Ankanghutong, Western City District, Beijing 100088, Beijing Province, China. 2648215772@qq.com

Abstract

Major depressive disorder (MDD) is highly prevalent and is a significant cause of mortality and morbidity worldwide. Currently, conventional pharmacological treatments for MDD produce temporary remission in < 50% of patients; therefore, there is an urgent need for a wider spectrum of novel antidepressants to target newly discovered underlying disease mechanisms. Accumulated evidence has shown that immune inflammation, particularly inflammasome activity, plays an important role in the pathophysiology of MDD. In this review, we summarize the evidence on nuclear receptors (NRs), such as glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, in modulating the inflammasome activity and depression-associated behaviors. This review provides evidence from an endocrine perspective to understand the role of activated NRs in the pathophysiology of MDD, and to provide insight for the discovery of antidepressants with novel mechanisms for this devastating disorder.

Key Words: Major depressive disorder; Immune inflammation; Inflammasome; Nuclear receptors

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 1, 2021
Peer-review started: March 1, 2021
First decision: July 15, 2021
Revised: July 29, 2021
Accepted: November 2, 2021
Article in press: November 2, 2021
Published online: December 19, 2021

P-Reviewer: Kotzalidis GD
S-Editor: Wang JJ
L-Editor: Wang TQ
P-Editor: Wang JJ

Core Tip: We summarize the evidence on nuclear receptors (NRs), such as glucocorticoid receptor, mineralocorticoid receptor, estrogen receptor, aryl hydrocarbon receptor, and peroxisome proliferator-activated receptor, in modulating inflammasome activity and depression-associated behaviors. This review provides evidence from an endocrine perspective to understand the role of activated NRs in the pathophysiology and treatment of major depressive disorder. Hopefully, the modulation of NRs with hormones and metabolites may become one of the key endocrinologic mechanisms for the development of novel therapeutics to increase the likelihood of therapeutic efficacy.

Citation: Wang H, Kan WJ, Feng Y, Feng L, Yang Y, Chen P, Xu JJ, Si TM, Zhang L, Wang G, Du J. Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder. *World J Psychiatr* 2021; 11(12): 1191-1205
URL: https://www.wjgnet.com/2220-3206/full/v11/i12/1191.htm
DOI: https://dx.doi.org/10.5498/wjp.v11.i12.1191

INTRODUCTION

Major depressive disorder (MDD) is common, has a high recurrence rate and disability rate, and affects approximately 300 million people worldwide[1]. However, the underlying pathophysiological mechanisms of MDD have yet to be completely understood. Although effective treatments are available, market-approved antidepressants have many problems, such as a single mechanism of action, delayed effect [2], and numerous side effects[3], and approximately one third of all patients fail to respond to conventional antidepressants[4]. Accordingly, there is an urgent need for new conceptual frameworks and perspectives to understand the occurrence and development of depression to develop better treatments. As another important hypothesis of depression, several lines of evidence have established an association between MDD and the neuroimmune pathway, although some psychiatrists have argued about the causal relationship between inflammation and depression[5-7]. In this review, we outline emerging data that point to nuclear receptors (NRs) as potentially important contributors to the pathophysiology of depression. We first review the current research on the inflammatory hypothesis of depression, and investigate the role of inflammasomes in the neuroimmune pathway of depression. The regulatory roles of NRs [including glucocorticoid receptor (GR), mineralocorticoid receptor (MR), estrogen receptor (ER), aryl hydrocarbon receptor (AHR), and peroxisome proliferator-activated receptor (PPAR)] in inflammasome activation and pathophysiology of depression are also investigated. Finally, these interactions are discussed as a foundation for new therapeutics that target the NRs to treat depression.

INFLAMMATION AND MDD

Inflammatory response is a survival mechanism in human self-protection, which is the defensive response of the body to various traumatic stimuli. Endogenous or exogenous pathogens and tissue damage are initially detected by pattern recognition receptors (PRRs), such as Toll-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors, mainly expressed by cells that participate in the innate immune response[8]. Following the activation of such receptors, signals are then transmitted to activate transcription factors. These factors regulate hundreds of genes that increase the initial inflammatory response. The brain has its own highly complex immune regulation system and is closely connected with the peripheral immune system[9]. Crosstalk between the immune system and the central nervous system (CNS) is very important for the establishment of appropriate immunity against infection and injury, the maintenance of mental health, and the influence of behavioral response[10].

The role of inflammation in the causation and exacerbation of MDD is supported by the findings from clinical studies that patients with chronic inflammation (*e.g.*, asthma [11,12] and meningitis[13,14]), tumors, and autoimmune diseases (*e.g.*, multiple

sclerosis[15,16], Guillain-Barre syndrome[17], and systemic lupus erythematosus[18,19]) are more likely to suffer from depression, the secretion of inflammation-activated cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor α (TNFα), and C-reactive protein] in the peripheral blood and cerebrospinal fluid of patients with depression is increased[20,21], microglial activation and neuro-inflammation were found in the brain of patients with depression examined post mortem[22], and both nonsteroidal anti-inflammatory drugs and cytokine inhibitors have an active therapeutic effect on depression[23-25]. Preclinical studies have demonstrated that repeated stress events cause neurobiological changes including synaptic plasticity deficits[26] and neurotransmitter system dysregulation[27,28], leading to depressive-like behavior. Apart from these neurobiological responses, exposure to stress also has physiological and immunological consequences such as increased expression of inflammatory cytokines (such as IL-1β, TNFα, and IL-6) in the blood and brain[29]. Although cumulative evidence supports that immune inflammation plays a very important role in the pathogenesis of depression, the exact mechanism remains unclear.

INFLAMMASOMES IN THE NEUROIMMUNE PATHWAY OF MDD

The term 'inflammasome' was first proposed by the Tschopp research group in 2002 [30]. Inflammasomes are multiprotein complexes (-700 KD) composed of intracellular PRRs, and are an important part of the innate immune system. They can recognize pathogen-associated molecular patterns (PAMPs, such as lipopolysaccharide and bacteria) or host-derived danger signaling molecular patterns [DAMPs, including adenosine triphosphate (ATP), heat shock proteins (Hsp), glucose, uric acid, high mobility group box 1, and molecules associated with oxidative stress], and can recruit and activate pro-caspase-1. Activated caspase-1 cleaves the precursors of IL-1β and IL-18 to produce corresponding mature cytokines[31]. Activated inflammasomes can also induce apoptosis. Over the past 18 years, extensive research in this area has illustrated the key components of inflammasome activation and its role in disease processes. To date, five receptor proteins have been found to assemble inflammasomes, consisting of the NOD, leucine rich repeat (LRR)-containing protein (NLR) family members NLRP1, NLRP3, and NLRC4, as well as the proteins absent in melanoma 2 and pyrin[32]. The existing evidence suggests that NLRP1 and NLRP3 inflammasomes, especially NLRP3, play an important role in the neuroimmune pathway of MDD[33].

NLRP1 inflammasome

NLRP1 is the first identified inflammasome sensor protein[31]. Humans only have one NLRP1 protein, containing PYD, NOD, and LRRs domains, a function-to-find domain, and a carboxy-terminal caspase-associated recruitment domain[31]. The NLRP1 inflammasome, mainly expressed in neurons, is predominantly implicated in pathologies of neuronal injury and cognitive impairment, which are core features of MDD[34,35]. Although no clinical studies have reported the NLRP1 inflammasome changes in the pathogenesis of MDD patients, animal studies suggest that the NLRP1 inflammasome may play an important regulatory role in depressive-like behavior. Li *et al*[36] found that inhibiting the product of NLRP1 inflammasome could eliminate the depression-like behaviors caused by a chronic constriction injury. Recent studies showed that chronic unpredictable mild stress (CUMS) increased the expression of NLRP1 inflammasome complexes and pro-inflammatory cytokines. Hippocampal *Nlrp1a* knockdown prevented the NLRP1 inflammasome-driven inflammatory response and improved CUMS-induced depressive-like behaviors[37]. The above results suggest that NLRP1 inflammasome may be a potential antidepressant target, and further mechanisms need to be clarified.

NLRP3 inflammasome

Unlike NLRP1, NLRP3, mostly expressed in microglia cells, is activated by the most diverse array of danger signals[33,34]. NLRP3 has been reported to participate in the pathophysiology of depression in animal models and MDD patients. Supporting the hidden role of the NLRP3 inflammasome in MDD patients are data demonstrating that NLRP3 activation is increased in peripheral blood mononuclear cells[38,39]. Preclinical evidence linking the NLRP3 inflammasome to depressive-like behaviors has been found in numerous animal models, including an acute model of systemic lipopolysaccharide administration[40], chronic stress models[33], and ovariectomy and estrogen-deficient mice. These models can lead to depressive-like behavior and up-regulation of NLRP3 expression in rodents. Down-regulation of the expression of NLRP3 by some

biological methods can reverse depression-like behavior[41]. NLRP3 inflammasome-driven pathways in depression have been widely reviewed[42]. In brief, psychological stress and danger substances can activate the NLRP3 inflammasome, which may lead to the release of pro-inflammatory cytokines and induction of depression. Next, we will focus on the role of NRs in the activation of inflammatory bodies in the following chapters.

ROLE OF NRS IN REGULATION OF INFLAMMASOMES AND DEPRESSION

The NR superfamily is a family of ligand-regulated transcription factors that are widely expressed throughout the body[43]. NRs are activated by steroid hormones, such as androgen, estrogen, and progesterone, and other lipid-soluble signals, including oxysterols, retinoic acid, and thyroid hormone, and regulate the expression of a wide range of genes linked to metabolism and inflammation. There are 49 known members in humans[43]. All NR superfamily members have a common architecture, containing a variable N-terminal domain, a central DNA binding domain (DBD), a hinge region, a carboxy-terminal ligand-binding domain (LBD), and a variable C-terminal domain[44]. Of these, the DBD and LBD are the two most highly conservative binding domains. The DBD contains two zinc-fingers, which act as a hook, that provide base-specific binding to sequences in the vicinity of target genes. The LBD of NRs consists of a three-layered, antiparallel, helical sandwich and is connected to the DBD by a flexible hinge domain. According to the key characteristics of dimerization, DNA binding motifs, and ligand binding, NRs can be broadly divided into four classes [steroid receptors, retinoid X receptor (RXR) heterodimers, homodimeric orphan receptors, and monomeric orphan receptors][45]. There are some obvious structural and functional differences between different classes, and the role of different NRs in the neuroimmune mechanism of MDD are described.

NRs in MDD

GR

GR is a member of the steroid receptors, and is activated by the endogenous steroid hormone cortisol[46]. Unliganded GR is predominantly localized within the cytoplasm [47]. Glucocorticoid (GC) binding causes conformational changes of the GR and activates multiple functional domains, including the hinge and LBD regions. After rapidly and efficiently being transported to the nucleus, the GR binds to the specific GC response elements of the genome to form a nuclear complex containing the GR and co-regulatory factors, which jointly activate or inhibit the transcription of GC responsive genes[48].

The participation of GR down-regulation in the pathophysiology of MDD has been demonstrated in clinical and preclinical studies. Drug-free MDD patients have reduced *GR* mRNA expression together with increased expression of the FK506 binding protein 5[49,50], which reduces GR function and promotes inflammation by coordinating with Hsp90. Kang *et al*[51] found an association between the methylation of GRs and depression later in life. A meta-analysis demonstrated that the *NR3C1* (GR) rs41423247 homozygous mutation may be a risk factor for MDD [odds ratio (OR): 0.77, 95% cumulative incidence (CI): 0.64-0.94, $P = 0.01$][52]. Studies on transgenic mice and a mouse stress model found that the down-regulation of GR expression is significantly related to depressive-like behavior[53]. Exogenous GC exacerbates depressive-like behavior, and down-regulates GR expression. In addition, accumulating evidence has illustrated that GR antagonists, such as mifepristone, ameliorate psychotic symptoms and cognitive deficits in MDD and bipolar disorder[54,55]. However, this seems to contradict the hypothesis of enhanced immune inflammatory response in MDD, as GC is one of the most effective anti-inflammatory hormones in the body.

It is also understandable that the effect of GR on the immune system and synapse is highly dependent on the time and dose. Mounting data indicate that innate immune cytokines cause insufficient GC signals by decreasing GR expression, blocking translocation of the GR from the cytoplasm to the nucleus, and disrupting GR-DNA binding through nuclear protein-protein interactions, which may be a reasonable explanation for this problem. Escoter-Torres *et al*[56] have reviewed the mechanisms of inflammatory gene regulation by the GR. Here, we will mainly explore the relationship between GR and inflammasomes in the pathophysiological mechanism of MDD.

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction was assumed to be due to aberrant adrenal GC secretion and disorderly hormone feedback loops in MDD patients[57]. GC-induced activation of the NLRP3 inflammasome may mediate the potentiated neuroinflammation[58]. However, whether the effects of inflammasome activation and the HPA axis are regulated through GR-related pathways is still unclear. Nevertheless, some evidence suggests that the GR is closely related to inflammasomes, which play an important regulatory role in some immune inflammatory diseases, such as MDD and acute-on-chronic hepatitis B liver failure[59]. In chronic obstructive pulmonary disease-induced depression, GR dysfunction mediates activation of the NLRP3 inflammasome. Preclinical evidence has shown that activation of the GR-NF-κB-NLRP3 pathway in microglia mediated chronic stress-induced neuroinflammation and depressive-like behavior[60]. Chronic corticosterone (CORT) treatment can increase Txnip and upregulate Txnip-NLRP3 binding, which activated the NLRP3 inflammasome, and induced the activation of caspase-1 and the release of IL-1β[61]. In addition, chronic GC exposure may increase neuroinflammation through NLRP1 inflammasome activation and induce neurodegeneration[62]. In conclusion, subsequent studies should be devoted to exploring how GR regulates the activation of inflammatory bodies and thus regulates the neuroimmune response.

MR

Negative feedback regulation of the HPA axis requires the participation of the dual-receptor system of MR and GR[63]. Similar to GR, MR is another member of steroid receptor and ligand-inducible transcription factors. In the brain, MR has approximately 10-fold higher affinity for CORT than the GR[64]. Due to the differences in affinity, CORT at the basal level largely occupies the MR, whereas higher hormone levels progressively occupy the GR after stress and circadian/ultradian peaks[65]. Early research results showed that brain MRs did not play an important role in the regulation of the stress response; however, subsequent studies demonstrated that MRs were essential for nongenomic regulation of glutamate transmission in the hippocampus by CORT. Based on this, considering that MRs are expressed abundantly in the limbic circuitry, a number of studies have focused on their regulatory role in depression and cognitive dysfunction[66].

The expression of MRs was decreased in the hippocampus, inferior frontal gyrus, and cingulate gyrus in depressed patients[67,68]. In addition, neuroendocrine studies also indicated abnormal MR function in MDD[63]. Otte C *et al*[69] found that the administration of an MR agonist (fludrocortisone) in drug-free patients with depression effectively reduced cortisol secretion and improved their verbal memory and executive function. In MDD patients treated with escitalopram, fludrocortisone accelerated the treatment response by 6 d. Furthermore, *MR* gene variants[70,71] and haplotypes[72,73] have been associated with depression symptoms and stress-induced reward-related learning deficits, and MR haplotypes may be potential biomarkers for a subgroup of patients with atypical depression[73]. In addition, MR malfunction and abnormal DNA methylation level have been demonstrated in treatment-resistant depression, depression during pregnancy, and in adolescence[74,75]. In preclinical studies, the role of the MR in the regulation of HPA-axis activity, executive function, and memory performance has been well demonstrated. In contrast to the effect of GR antagonists on long-term potentiation (LTP), MR antagonists inhibited the LTP process, suggesting that the MR and GR have opposite effects on the adjustment of synaptic plasticity after stress exposure[76]. The results from transgenic mice with forebrain knockout or overexpression of *MR* confirmed the role of MR in learning and memory[77]. After loss of the *MR* gene in the forebrain, mice displayed an aberrant basal and stress-induced CORT secretion and deficits in learning and memory[78]. In contrast, overexpression of MR in the forebrain improved spatial memory and behavior performance[79].

Research on the role of MR in the pathogenesis of depression is still in its infancy, and its possible mechanism has not been fully explained. Chen *et al*[80] reviewed the possible mechanism of MR in regulating depression, learning, and memory from different perspectives, such as HPA-axis activity, 5-HT transmitter system, adult-neurogenesis, and inflammation. Considering that MR can participate in the regulation of other and immune-related diseases by activating NLRP3 inflammasome[81,82], whether the role of MR in the pathogenesis of depression is involved in inflammasomes and modulation of inflammasomes will be important research directions in the future.

ER

Given that the prevalence of depression in women is 2-3 times higher than that in men and changes in mood are simultaneously associated with estrogen levels[83], a potential role for estrogen in the pathophysiology of depression has generated substantial interest. It is well documented that estrogen can regulate neurotransmission, enhance the levels of serotonin and noradrenaline, and plays a vital role in emotion processing, cognition regulation, and motivation triggers[84,85]. The data from clinical and preclinical research show that estrogen is involved in modulation of depression and anxiety. For example, cumulative clinical studies found that menopausal declines in estrogen levels were associated with an increase in mood disturbances in women[86,87]. Moreover, premenopausal women with depression had lower levels of 17β-estradiol (E_2) than non-depressed women[88]. In rodents, ovariectomy, resulting in estrogen deficiency, induced an increase in depression and anxiety-like behavior[89] which was improved by E_2 replacement[90].

Estrogen plays its biological role mainly through activating ERs. The ERs including ERα (ESR1) and ERβ (ESR2) are members of a superfamily of hormone-regulated transcription factors, and regulate the gene transcription of estrogen by binding to specific DNA sequences[91]. Genetic variation in ERs may therefore modify estrogen signaling, such as altering binding efficiency and disrupting normal gene regulation, thus increasing susceptibility to developing depression in women. Ryan J *et al*[87] carried out a detailed review and pointed out that there was a significant correlation between *ESR1* gene polymorphism and severe depression in women. Preclinical research has demonstrated that ERα and ERβ agonists can reverse stress-induced depressive behavior and cognitive deficits[92]. However, the specific mechanism of ER in stress-induced depression remains unclear. Some studies have found that NLRP3 inflammasome activation mediates estrogen deficiency-induced depressive-like behavior and neuroinflammation in the hippocampus of mice[93]. In other inflammation-related diseases, such as endometriosis and breast cancer, the ER regulates the activation of NLRP3, which leads to inflammation[94,95].

AHR

AHR is a ligand-activated transcription factor which was first identified as a contaminant of the chemical herbicide Agent Orange[96]. However, AHR has been proved to be a crucial modulator of host-environment interactions in recent years, espe-cially for immune and inflammatory responses. As an NR, AHR is bound by co-chaperones Hsp90 and XAP that maintain its localization in the cytoplasm. After ligand binding, AHR is released from its co-chaperones and is transferred to the nucleus, where it forms a heterodimer with AHR nuclear translocator (ARNT) and binds to DNA to regulate target gene expression[97]. AHR can bind to many diverse ligands, including exogenous synthetic aromatic hydrocarbons [*e.g.*, benzo (a) pyrene], exogenous natural chemicals [*e.g.*, tryptophan (Trp) and norisoboldine], and endogenous ligands (*e.g.*, tryptamine and kynurenine)[98]. Specifically, compounds from the Trp metabolic pathway, especially the kynurenine pathway (~95% of Trp metabolism), provide many ligands for the AHR and play an important role in the regulation of immune and inflammatory responses. A large body of studies have shown that the AHR is associated with many diseases driven by immune/inflammatory processes, including MDD, asthma, multiple sclerosis, rheumatoid arthritis, and allergic reactions[97].

Increased kynurenine (KYN) production from Trp metabolism, mediated by indoleamine 2,3-dioxygenase (IDO), is a biomarker of immune dysregulation in depression [99]. Clinical and preclinical data have consistently shown an elevated KYN level with depressive behavior after immune disturbance. The activation of AHR signaling may play an important role in immune regulation. Preclinical evidence has shown that blocking the AHR can reverse KYN-induced monocyte trafficking, neuroimmune disorder, and depression-like behavior in mice[99]. Recent clinical studies have also confirmed that the AHR is related to the individual difference in plasma KYN concentration in MDD patients[100]. The AHR regulates the expression of Trp-2,3-dioxygenase 2 (TDO2) and IDO1/2, and downstream enzymes kynurenase and kynurene 3-monooxygenase (KMO). The results of *in vitro* cell culture showed that AHR knockdown resulted in a decrease of KYN concentration in the cell culture medium, which may be due to the increase in quinolinic acid, a downstream metabolite of KYN[97]. Quinolinic acid is a neurotoxic NMDA receptor agonist and contributes to MDD symptoms[100]. Although cumulative data have confirmed the regulatory role of AHR in depression-like behavior induced by an abnormal KYN metabolic pathway, the specific mechanism has not been clearly elucidated. A

significant result showed that AHR can regulate the activity of NLRP3 inflammasome by inhibiting the transcription of *NLRP3*[101]. The proposed model is as follows: Following engagement by AHR cognate ligands, it forms a heterodimer with ARNT in the nucleus, binds to the xenobiotic response element (XRE) regions located at the NF-κB site in the promoter of *NLRP3* and then inhibits NF-κB transcription activity, finally decreasing *NLRP3* transcription and subsequent inflammasome activation[101]. In view of the role of NLRP3 in the neuroimmune mechanism of depression, this may be the potential mechanism of AHR in regulating depressive episodes. In addition, the AHR acts as a potential crosstalk mediator between the adaptive immune system in the gut and gut microbiota-derived metabolites. Whether AHR has a certain role in the brain-gut axis dysfunction of MDD should be investigated in subsequent research.

PPARs

PPARs are ligand-activated transcription factors and members of the NR receptor superfamily. Three isotypes of PPARs have been identified, namely, PPARα, PPARβ/δ, and PPARγ[102]. Despite the three PPAR isoforms having a high degree of structural homology, they have distinct tissue distribution, ligand-binding properties, and functional roles. Endogenous and natural ligands of PPARs mainly include fatty acids and fatty-acid derivatives. PPARs translocate into the nucleus upon ligand binding, where they form heterodimers with the RXR and then bind to peroxisome proliferator response elements to regulate transcriptional target genes. The physiological characteristics of PPARα, β/δ, and γ and their role in other diseases have been extensively reviewed[103,104], and will not be elaborated here. Next, we will discuss the role of PPARs in depression.

PPARα

PPARα is distributed in many peripheral tissues which catabolize high amounts of fatty acids. In the CNS, PPARα is highly expressed in the basal ganglia, prefrontal cortex, thalamic nuclei, hippocampus, and ventral and tegmental areas[105]. In these regions, the distribution of PPARα in neurons is higher than that in glial cells. Recent research found that PPARα modulates the stress response, neurotransmission, neuroinflammation, and neurogenesis and plays an important regulatory role in some neuropsychiatric diseases, such as depression, post-traumatic stress disorder, and neurodegenerative diseases[106]. Preclinical studies found that knockout or overexpression of PPARα in rodent brain could imitate or reverse the depressive-like behavior induced by chronic stress. In addition, PPARα selective agonists (WY14643 and fenofibrate) have been associated with antidepressant effects in stress-induced depression models[107,108]. Some antidepressants, such as venlafaxine and fluoxetine, need PPARα to play an antidepressant role[109]. The antidepressant effect may be mediated by acting on the cAMP response element-binding (CREB)-mediated biosynthesis of brain-derived neurotrophic factor (BDNF)[109-111]. Some studies have also indicated that PPARα can modulate mesolimbic dopamine transmission and improve depression-related behavior[112]. Furthermore, N-palmitoylethanolamine, which stimulates PPARα, induced a dose-dependent antidepressant effect by engaging neurosteroid biosynthesis[113]. In summary, PPARα may play an important role in the pathogenesis of MDD and the effects of antidepressant medications, and it may be a new target for developing novel antidepressants.

PPARβ/δ

PPARβ/δ is the most widely expressed isoform in the brain, with particularly high levels in the hippocampus, entorhinal cortex, and hypothalamus[105]. Compared with the other two subtypes, PPARβ/δ showed a higher expression level in neurons, and had neuroprotective effects in some CNS disease models[114]. Recent studies have found that overexpression of PPARβ/δ in the hippocampus can inhibit depressive-like behavior induced by chronic stress in rats, which corresponds to a significant down-regulation of PPARβ/δ expression in the hippocampus when rats experience chronic unpredictable stress[115]. Subsequent studies have found that when PPARβ/δ is knocked down, rats show depressive-like behavior[116]. Similar to the antidepressant effect of PPARα, the CREB-BDNF pathway may also be involved in the antidepressant effect of PPARβ/δ. Furthermore, chronic stress can increase the expression of TWIST1, which will lead to mitochondrial damage and ATP deficiency by down-regulating PPARβ/δ expression, and eventually leads to depression-like behavior in mice[116]. How overexpression of PPARβ/δ and its agonists play an antidepressant role is still unclear.

PPARγ

PPARγ is highly expressed in the amygdala, dental gyrus, prefrontal cortex, ventral tegmental area, and basal ganglia[105]. Under normal physiological conditions, PPARγ can co-localize with neurons and astrocytes in human and mouse brain, but not with microglia. However, PPARγ can also be expressed in microglia when the functional status of microglia changes. PPARγ agonists have been synthesized for the treatment of metabolic diseases, especially dyslipidemia and type 2 diabetes mellitus, as well as non-metabolic diseases including neurodegenerative diseases, cancer, and inflammatory diseases due to their important metabolic regulation and excellent druggability[117,118]. Compared with the above two subtypes, the relationship between PPARγ and depression has been more widely recognized, and clinical trials on the antidepressant effects of PPARγ agonists are in full swing. Some gratifying results have been found and were well reviewed[117].

In conclusion, all isotypes of PPAR may participate in the pathophysiology of depression, and even antidepressants based on PPAR agonists have been developed. However, how PPARs play an antidepressant role seems unclear, although some studies have shown that this occurs by regulating the biosynthesis of BDNF and regulating the 5-HT neurotransmitter system. Activation of PPARs inhibits the activation of inflammasomes (in particular NLRP3) and the release of inflammatory cytokines, which is similar to the changes in patients with depression and in depressive models[119,120]. Therefore, whether and how PPARs play an antidepressant role by regulating the inflammatory response will be an important future research direction. In fact, some studies have found a link between them. Liu *et al*[121] found that oridonin, mediated through the PPARγ receptor signaling pathway, modulated excitatory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the prefrontal cortex, and showed fast and significant antidepressant efficacy. In addition, Song *et al*[122] found that, astragaloside IV, which exhibited PPARγ agonist activity, ameliorated stress and neuroinflammation-induced depressive-like behaviors *via* the PPARγ/NF-κB/NLRP3 inflammasome axis in mice. Apigenin exhibits antidepressant-like effects by inhibiting NLRP3 inflammasome activation through the upregulation of PPARγ in rats with CUMS[123]. Moreover, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease, PPARβ/δ agonist alleviates NLRP3 inflammasome-mediated neuroinflammation[120].

CONCLUSION

Given the relatively low overall response rates and the wide range of 'adverse' events associated with current antidepressants, there is an urgent need for novel therapeutics to treat specific underlying disease mechanisms that are not addressed by the antidepressants targeting the serotonergic and/or noradrenergic system. Hopefully, the modulation of NRs with hormones and metabolites may become one of the key endocrinologic mechanisms for the development of novel therapeutics to increase the likelihood of therapeutic efficacy. Here, we reviewed the regulatory role of NRs (including the GC, MR, ER, AHR, and PPAR) in inflammasome activation and the pathophysiology of depression (Figure 1). Indeed, a major breakthrough in the pathophysiology of depression was the discovery that DAMPs and PAMPs activate inflammasomes, which enhance caspase-1 activity, and subsequently inhibit excitatory AMPA receptor synaptic plasticity in the brain circuitry to change mood-associated behaviors[124,125]. Cumulative studies have shown that activation of the NRs may directly change the activity of inflammasomes to modulate the levels of mature forms of caspase-1 and IL-1β. Caspase-1-mediated programmed cell death and surface stability of the AMPA receptor in the hippocampus, are essential for depression-like behavior[125]. Current data suggest that direct modulation of NRs may offer new opportunities to mitigate depressive disorders. However, several directions are warranted for future studies: (1) To identify more NR activators for the treatment of MDD; (2) To address the detailed mechanism of how NRs modulate inflammasomes; and (3) To perform clinical trials to prove the role of NR modulators in the treatment of MDD. These NR modulators can be safely used in combination with currently available antidepressants to simultaneously target multiple disease mechanisms and increase the likelihood of therapeutic success.

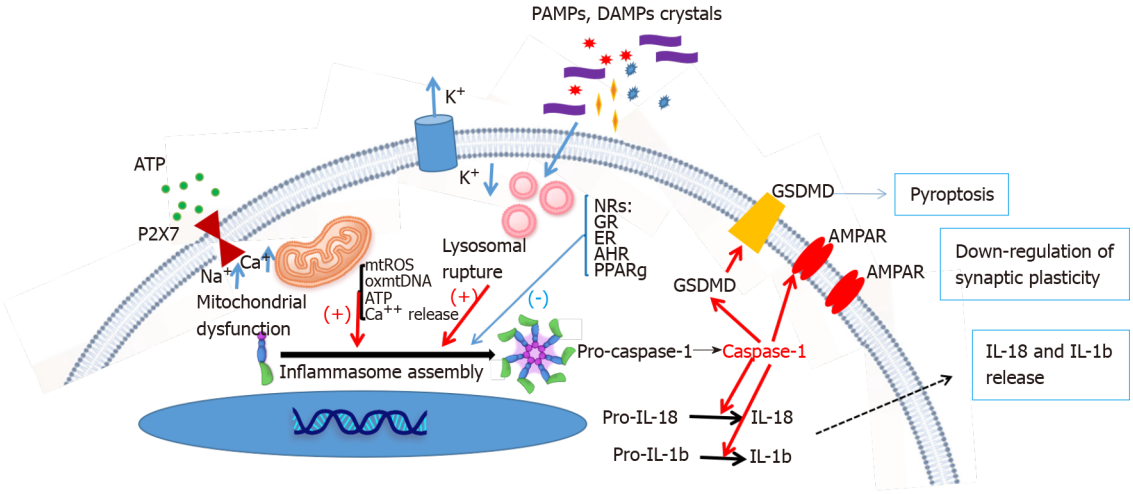

Figure 1 Inflammasome activation in the pathophysiology of major depressive disorder - roles of the nuclear receptors. NLRP3 inflammasome activation, which includes canonical and noncanonical activation pathways, is induced by a number of pathogen-associated molecular patterns and danger signaling molecules patterns. The canonical activation pathway involves stimulation-mediated activation signals such as ion fluxes, lysosomal rupture, mitochondrial dysfunction, and so on. Mitochondrial dysfunction leads to the production of mitochondrial reactive oxygen species, damaged mitochondrial DNA, and calcium release from the mitochondria, and all these changes facilitate the assembly of inflammasomes. Activation of the inflammasome causes caspase-1 activation, leading to the maturation and release of interleukin (IL)-1/IL-18 and pyroptosis. In addition, caspase-1 modulates the membrane stability of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which leads to the down-regulation of AMPA receptors at the synapses. Nuclear receptors inhibit the assembly of NLRP3 inflammasome, which will finally protect the excitatory AMPA receptor synaptic activity and contribute to the antidepressant mechanism of the nuclear receptor activators. ROS: Reactive oxygen species; PAMPS: Pathogen-associated molecular patterns; DAMPS: Danger associated molecular patterns; GSDMD: Gasdermin D; AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; IL: Interleukin; NRs: Nuclear receptors; GR: Glucocorticoid receptor; ER: Estrogen receptor; AHR: Aryl hydrocarbon receptor; PPAR: Peroxisome proliferator-activated receptor; ATP: Adenosine triphosphate.

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