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Review

The modulatory role of dopamine receptors in brain neuroinflammation

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ABSTRACT

Neuroinflammation is a general pathological feature of central nervous system (CNS) diseases, primarily caused by activation of astrocytes and microglia, as well as the infiltration of peripheral immune cells. Inhibition of neuroinflammation is an important strategy in the treatment of brain disorders. Dopamine (DA) receptor, a significant G protein-coupled receptor (GPCR), is classified into two families: D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptor families, according to their downstream signaling pathways. Traditionally, DA receptor forms a wide variety of psychological activities and motor functions, such as voluntary movement, working memory and learning. Recently, the role of DA receptor in neuroinflammation has been investigated widely, mainly focusing on nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, renin-angiotensin system, αB-crystallin, as well as invading peripheral immune cells, including T cells, dendritic cells, macrophages and monocytes. This review briefly outlined the functions and signaling pathways of DA receptor subtypes as well as its role in inflammation-related glial cells, and subsequently summarized the mechanisms of DA receptors affecting neuroinflammation. Meaningfully, this article provided a theoretical basis for drug development targeting DA receptors in inflammation-related brain diseases.

1. Introduction

Neuroinflammation is defined as an inflammatory response mediated by astrocytes, microglia, and endothelial cells in central nervous system (CNS), which disturbs homeostasis and is a typical manifestation of many neurological diseases. The main causes of neuroinflammation contain the response of brain and spinal cord cells to infections and cell death, together with the infiltration of cells from the innate and adaptive immune systems into the brain and spinal cord [1]. As some emerging evidence, it is accepted that neuroinflammation is an important characteristic of brain diseases. For example, activated adaptive immune cells and inflammatory processes contribute to neuronal cell death and formation of α-synuclein (α-syn) oligomers in animal models of Parkinson's disease (PD) [2,3]. The widespread aggregation of α-syn in the form of Lewy bodies is a neuropathological hallmark of PD [4]. Besides, Multiple Sclerosis (MS) is an autoimmune inflammatory disease characterized by the progressive loss of neuronal function, which is driven by infiltrating peripheral immune cells [3,5]. It is known that PD and MS are two common neurodegenerative diseases, which affect an increasing number of people worldwide. In addition to neurodegeneration, neuroinflammation is also an important pathological feature in other brain diseases. There is converging evidence indicating a potentially chronic and/or exaggerated neuroimmune response in the process of schizophrenia, such as intensive levels of pro-inflammatory mediators and activation of microglia [6]. Moreover, neuroinflammation after intracerebral hemorrhages (ICH) contains the early activation of resting microglia, the influx of peripheral leukocytes and release of pro-inflammatory factors, which has a significant impact on the pathological process of secondary brain damage [7]. In particular, neuroinflammation is associated with not only neuropathological progression but also normal brain function. For example, it is demonstrated that pro-inflammatory mediators produced by lesioned neurons can disrupt blood-brain barrier (BBB) permeability [8] and decrease synaptic function plasticity [9]. Therefore, inhibition of neuroinflammation represents an important therapeutic strategy to treat neurological diseases and maintain normal brain functions.

Dopamine (DA) receptor, a significant G protein-coupled receptor (GPCR), is classified into two families: D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptor families, according to their downstream signaling pathways. DA receptor forms a wide variety of psychological activities and motor functions, such as voluntary movement, working memory and learning [10]. Historically, the significance of the dopaminergic (DAergic) system in the brain was emphasized attributing to the investigation of PD, which was caused by degeneration of the DAergic neurons in substantia nigra pars compacta (SNc) [11,12]. Thus, an increased amount of highly efficient compounds activating DA

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receptors were synthesized and developed for the symptomatic therapy of this disease, such as pramipexole, apomorphine and ropinirole. In addition, it is observed that dopamine D2 receptor (D2R) antagonists, including chlorpromazine, sultopride, and other compounds, have potent antipsychotic activity in patients with schizophrenia [10]. To sum up, DA receptor is an important drug target in treating brain disorders.

Certainly, the relationship of DA receptor and inflammation has been investigated widely and deeply in recent years. DA, a neurotransmitter, was also proposed to have immunoregulatory and anti-inflammatory effects in previous studies [13,14]. In peripheral DAergic system, activation of DA receptor is able to control tissue inflammation and injury [15], such as acute pancreatitis and renal inflammation [16,17]. The anti-inflammatory effect of DA receptor is closely related to the inhibition of NF-κB activation through protein phosphatase 2A (PP2A)-dependent Akt pathway [16], which is an important downstream signaling pathway of DA receptor. More importantly, the stimulation of DA receptor was confirmed to weaken neuroinflammation happened in brain disorders, such as ischemic stroke and neurodegenerative processes [18,19]. For instance, Yan Y et al. (2015) illustrated that DA prevented nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) inflammasome-dependent neuroinflammation via regulating dopamine D1 receptor (D1R)/cAMP signaling pathway and suggested D1R as a potential therapeutic target for the inflammation-related CNS diseases [20]. Another study accomplished by Shao W et al. (2013) demonstrated that activation of astrocytic D2R suppressed neuroinflammation through αB-crystallin-dependent mechanism in the brain during aging and some neurodegenerative disorders [21]. Here, we reviewed studies of the roles and signaling pathways of DA receptors, as well as some important DA receptor agonists/antagonists applied in clinic. And the critical inflammatory glial cells in CNS, including astrocytes and microglia, were also introduced in this review. Significantly, we discussed the mechanism of DA receptors affecting neuroinflammation, which is observed in recent studies. Meaningfully, DA receptors may be developed as potential therapeutic targets for brain inflammatory diseases.

2. Dopamine receptor

2.1. Classification and functions

D1-like receptors stimulate the activity of AC and consequently promote the production of the second messenger cAMP through activating the $G\alpha_{s/olf}$ family of G proteins, while D2-like receptors family are coupled to the $G\alpha_{i/o}$ family which can suppress AC activity and cAMP production [22,23].

Because DA is associated with multiple physiological processes, the significant roles of DA receptor subtypes have been widely investigated. For example, D1Rs are critical for regulating expression of brain-derived neurotrophic factor (BDNF) in prefrontal cortex (PFC) which is related to spatial working learning and memory processes [24]. Besides, activation of D1Rs in the hippocampus dentate gyrus (DG) promotes the formation of evident contextual representations of novel environments which is closely related to memory [25]. D2Rs are reported to play an important role in controlling locomotor activity. There is evidence that the specific inhibition of D2R blocks amphetamine-induced reduction of locomotor activity [26]. On the other hand, D2R deficiency or inhibition attenuates spontaneous locomotor activity, while withdrawal of D2R blockade leads to a distinct increase of activity, indicating that D2R dysfunction reduces motor activity [27]. D3Rs are demonstrated to inhibit cocaine-induced alterations in signaling transduction, synaptic ultra-structure, and behavioral responses, all of which play vital roles in cocaine addiction, whereas D1Rs have the opposite effects in cocaine-induced alterations [28]. Furthermore, upregulated D3Rs in striatum is associated with tardive dyskinesia (TD) in non-human primate models [29]. As for D4Rs, it is known that D4R activation is necessary for the effects of neuregulin-1 on network activity, and D4R agonist increases γ oscillation power induced by kainite [30]. Additionally, selective D4R activation increased long-term potentiation (LTP) in Schaffer collateral (SC)-CA1 of aged mice, providing novel strategies for the prevention of cognitive decline in aging as well as age-related diseases [31]. Therefore, D4R modulators have potential benefits for ameliorating psychiatric disorders and cognitive functions. It seems that D5Rs have some of the same functions as the D1Rs. Both D1Rs and D5Rs control hippocampal LTP and memory in the brain, and play critical roles in conferring the properties of reward and novelty to information processed by the hippocampus [32]. Recently, selective D5Rs agonists are demonstrated to have neuroprotective effects against apoptosis and ameliorate cognitive impairment in amyloid β_{1-42}-induced mice [33].

2.2. Drugs targeting dopamine receptors

DA receptors have been developed as therapeutic targets for several pathological conditions in brain, such as PD and schizophrenia. For instance, DA receptor agonists, including pramipexole, ropinirole, apomorphine, bromocriptine (BRC) and other compounds, have been widely used clinically to treat PD [34–37]. Moreover, compared with bromocriptine, pramipexole or ropinirole treatment has milder adverse reactions, and can reduce L-DOPA-induced motor complications [34]. D2R antagonists were certified to have potent antipsychotic activity in patients with schizophrenia, which contributed to the development of antipsychotic drugs based on D2R. Antipsychotic drugs are divided into two major categories, first-generation antipsychotics, such as chlorpromazine and haloperidol, and second-generation antipsychotics, such as clozapine and risperidone [38,39]. Generally speaking, second-generation antipsychotics, also defined as atypical antipsychotics, possess the ability not only to restrain D2R, but also to target other neurotransmitter receptors, most notably of which is serotonin 5-HT_{2A} receptor. Furthermore, second-generation antipsychotics commonly have a lower propensity to develop extrapyramidal reactions. The representative DA receptor agonists/antagonists used in clinic are concluded in Table 1.

Table 1
Clinical application of drugs targeting DA receptors.

Drugs	DA receptors[a]	Clinical application	References
Bromocriptine	D2R (+)	PD, hyperprolactinemia, pituitary tumors, type 2 diabetes	[34,35]
Pramipexole	D2R (+), D3R (+)	PD, depression, restless legs syndrome	[34,36,37]
Ropinirole	D2R (+), D3R (+)	PD, restless legs syndrome	[34,37]
Chlorpromazine	D2R (−)	Schizophrenia	[38]
Risperidone	D2R (−)	Schizophrenia, bipolar disorder	[39]
Fenoldopam	D1R (+)	Hypertension	[40]
Metoclopramide	D2R (−), D3R (−)	Nausea, gastroparesis	[41]
Brexpiprazole	D2R (−)	Schizophrenia, major depressive disorder	[42]
Cariprazine	D3R (+), D2R (+)	Schizophrenia, type I bipolar disorder	[42]
Flibanserin	D4R (−)	Hypoactive sexual desire disorder	[43]

[a] + indicates agonism; − indicates antagonism.

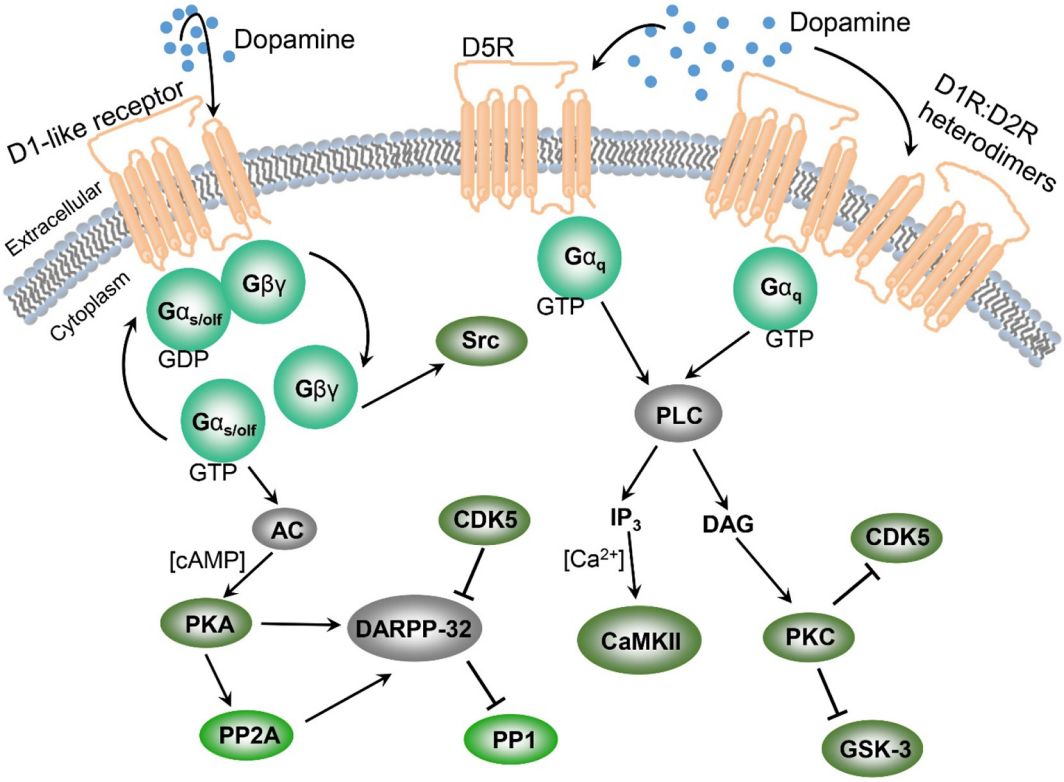

Fig. 1. Signaling pathways regulated by dopamine D1-like receptor.
$G\alpha_{s/olf}$/cAMP/PKA signaling regulated by D1-like receptor phosphorylates DARPP-32. It depends on phosphorylation of DARPP-32 at threonine 34, which suppresses protein dephosphorylation via inhibition of PP-1. PP2A activated by PKA also leads to the phosphorylation of DARPP-32 at Thr^{34}. In contrast, CDK5 is shown to prevent the suppression of PP1 by DARPP-32 and result in PKA inhibition through phosphorylating DARPP-32 at Thr^{75}. On the other hand, Src family kinase members, including Src and Fyn are activated by D1Rs via Gβγ subunits of heterotrimeric G proteins. In addition, both D5Rs and D1R:D2R heterodimers regulate $G\alpha_q$/PLC signaling. Activation of PLC results in the production of DAG and IP_3 which are derived from PIP_2, contributing to a raised mobilization of intracellular calcium in response to IP_3 and the activation of PKC by DAG. The up-regulation of cytoplasmic calcium leads to the activation of calcium-regulated enzymes, such as the CaMKII. PKC may inactivate GSK-3 and decrease CDK5 activity, and then reduce the phosphorylation of DARPP-32 by CDK5. AC, adenylyl cyclase; CaMKII, calcium/calmodulin-dependent kinase II; CDK5, cyclin-dependent kinase 5; DAG, diacylglycerol; DARPP-32, DA- and cAMP-regulated phosphoprotein of 32 kDa; GSK-3, glycogen synthase kinase 3; IP_3, inositol trisphosphate; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PP-1, protein phosphatase-1; PP2A, protein phosphatase 2A.

2.3. Dopamine receptor family signaling pathways

As described above, the D1-like receptors are usually coupled to $G\alpha_{s/olf}$, which further increase the production of cAMP and the activity of protein kinase A (PKA). The DA- and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32) has been extensively studied among PKA substrates, which is a multifunctional phosphoprotein basically expressed in medium spiny neurons (MSNs). It is proposed that DARPP-32 affects gene transcription via binding to nuclear targets, including histone H3 and the cAMP response element-binding protein (CREB) [44–46]. In addition to D1Rs effects on cAMP-regulated signaling and Src family kinase (SFK) pathway, D1R/D2R heterodimers or D5Rs are also demonstrated to couple to $G\alpha_q$ to modulate phospholipase C (PLC). Activation of PLC promotes the production of diacylglycerol (DAG) and inositol trisphosphate (IP_3) from phosphatidylinositol 4,5-bisphosphate (PIP_2). It is possible that protein kinase C (PKC) activated by DAG may decrease cyclin-dependent kinase 5 (CDK5) activity and then diminish the phosphorylation of DARPP-32 induced by CDK5. Besides, PKC has previously been shown to inactivate glycogen synthase kinase 3 (GSK-3) associated with embryonic development, and cell differentiation, survival, and apoptosis (Fig. 1).

D2-like receptors are coupled to $G\alpha_{i/o}$ and then modulate the production of cAMP negatively through inhibiting AC, leading to a reduction of PKA activity. After D2Rs activation, Gβγ subunits divided from Gα subunits have been identified to activate PLC leading to the production of DAG and IP_3. In addition to activating PLC, D2R-mediated activation of Gβγ subunits also participates in the modulation of ion channels, including G protein-coupled inwardly rectifying potassium channels (GIRKs) and L-type calcium channels. G protein-independent D2R signaling is represented by β-Arrestin 2 (βArr2)-mediated mechanisms. The mechanism underlying the regulation of Akt by βArr2 has shown that activation of the D2-like receptors contributes to the constitution of a protein complex composed of PP2A, Akt, and βArr2 [10,47]. Then, PP2A increases the dephosphorylation and inactivation of Akt, leading to the activation of GSK-3 (Fig. 2). Besides what is described in D1Rs signaling, GSK-3 also plays a critical role in synaptic plasticity and receptor trafficking. GSK-3α and GSK-3β, two isoforms of GSK-3, are closely related kinases initially involved in the modulation of glycogen synthesis in response to insulin. In addition, the phosphorylation of a single residue at serine 21 of GSK-3α or serine 9 of GSK-3β results in the inactivation of GSK-3α or GSK-3β which is constitutively active [48]. Akt has been demonstrated to suppress GSK-3α and GSK-3β in response to insulin, insulin-like growth factor (IGF), and neurotrophins such as BDNF and neurotrophin 3 [10,48,49].

3. Glial cells and dopamine receptor

In CNS, inflammatory responses primarily involve microglia and astrocytes, which are the main types of glial cells. They are effectors and regulators of neurodevelopment, acting through neuronal-glial interactions in brain development and function. Glial cells have multiple functions in the brain, including ensuring electrical conduction of

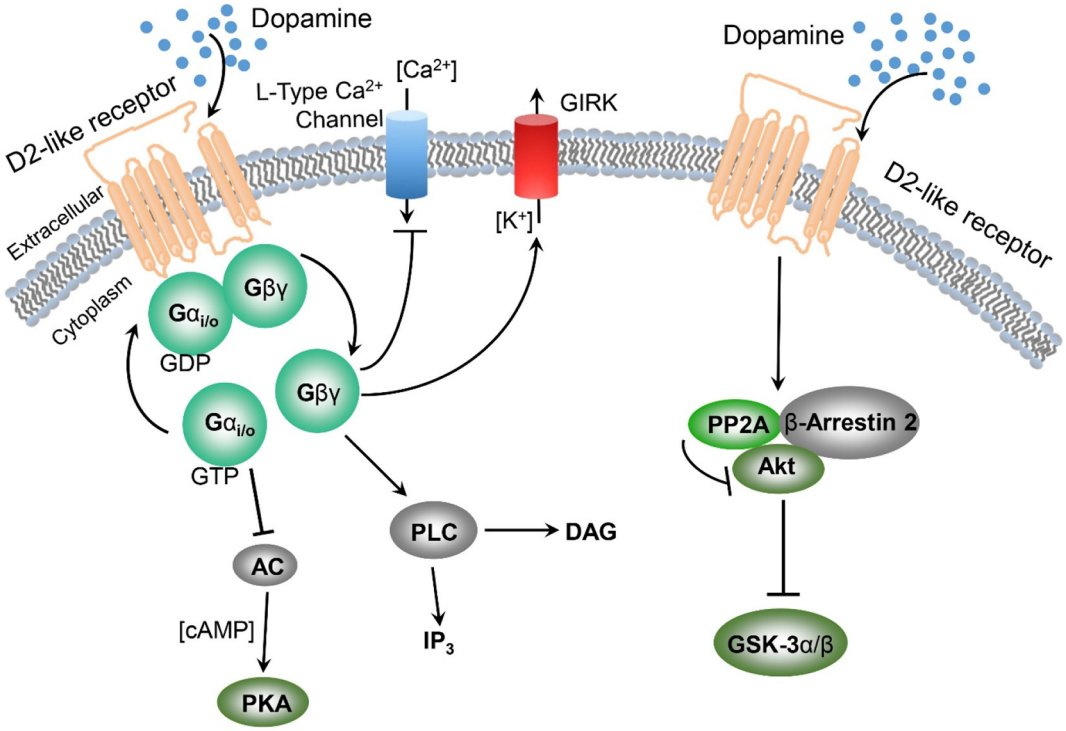

Fig. 2. Signaling pathways regulated by dopamine D2-like receptor.
D2-like receptors are coupled to $G\alpha_{i/o}$ and modulate the production of cAMP negatively through inhibiting AC, leading to a reduction of PKA activity. After D2Rs activation, Gβγ subunits separated from Gα subunits have been identified to activate PLC leading to the production of DAG and IP_3. In addition to activating PLC, D2R-regulated Gβγ subunits also participate in the modulation of ion channels, such as GIRKs and L-type calcium channels. G protein-independent D2R signaling is represented by βArr2-mediated pathways. Stimulation of the D2-like receptors contributes to the formation of a protein complex that is composed of PP2A, Akt, and βArr2. And then, PP2A promotes the dephosphorylation and inactivation of Akt, leading to the activation of GSK-3α/β. βArr2, β-Arrestin 2; AC, adenylyl cyclase; DAG, diacylglycerol; GIRKs, G protein-coupled inwardly rectifying potassium channels; GSK-3, glycogen synthase kinase 3; IP_3, inositol trisphosphate; PKA, protein kinase A; PLC, phospholipase C; PP2A, protein phosphatase 2A.

neurons, structural and functional support of neurons, regulation of synaptic function, immune response, etc. [50,51]. The anti-inflammatory effects mediated by DA receptors are closely related to activation status of microglia or/and astrocytes.

3.1. Microglia

Microglia are regarded as phagocytic cells located in the CNS and are responsible for the innate immune responses. Evidence has suggested that the activated microglia produce pro-inflammatory cytokines, such as interleukin (IL)-6, interferon (IFN)-γ, tumor necrosis factor α (TNF-α), and IL-1β, as well as reactive oxygen species (ROS), participating in immune responses in the brain. Furthermore, microglia are able to eliminate dead cells, modulate neuronal migration, promote angiogenesis, affect the activation and proliferation of other glial cells, and participate in the stability of internal environment [52,53]. Therefore, controlled activity of microglia is significant to sustain normal brain function. Classically, microglia are often categorized as two functional states (i.e., activated and resting microglia), also called M1 (classical) and M2 (alternative) phenotypes [52]. M1 microglia produce pro-inflammatory cytokines and chemokines, resulting in progressive neuronal death and brain diseases. Conversely, M2 activation facilitates the release of anti-inflammatory factors, such as transforming growth factor-beta (TGF-β) and IL-10. Appropriate transformation of the microglial response from M1 to M2 phenotype is required for an efficient treatment of inflammatory diseases.

DA receptor families are predominantly expressed in microglia [54], which appear to modulate inflammatory response and neuronal survival (Table 2) [55]. For example, D1R activated by acetyl-L-carnitine attenuates microglial activation and release of inflammatory mediators, eventually ameliorates cognitive deficits and neurodegeneration in PD rats [56]. It was found that acetyl-L-carnitine inhibited microglial activation-mediated inflammatory response and diminished TNF-α level by increasing the production of IL-10, which led to improved neuronal survival [56]. IL-10 is a critical anti-inflammatory cytokine that effectively modulates inflammatory response by inhibiting the production of inflammatory cytokines including IL-6 and TNF-α. Besides, D5R activated by DA-reuptake inhibitor bupropion promotes a shift of microglial M1 toward M2 polarization via stimulating the transcription factor CREB, which is clinically effective in anti-depression [57]. Depression is a common psychiatric disorder associated with neuroinflammation and microglial activity [58]. Moreover, bupropion decreases the levels of TNF-α, IL-1β, IFN-γ, and nitric oxide, while it elevates IL-10 levels in LPS-induced microglia M1 polarization. However, this effect is partly abolished by D5R antagonist SCH23390 [57].

Notably, the expression of D2R was not detectable in resident microglia in the healthy brain, while activated microglia expressed all DA receptor subtypes, indicating that DA receptor expression probably depends on activation status of microglia [59]. Similarly, DA has a differential role in influencing cellular functions of resting and activated microglia, such as phagocytosis and adhesion, depending on the activation states of microglia [60]. D2R is expressed on activated microglia as well as peripherally derived macrophages after cerebral ischemia in mice. And D2R/D3R agonist, pramipexole, increases the release of nitrite from LPS-induced activated murine microglia, which has an important role in regulating neuroinflammation [59]. Pramipexole can be a potential therapeutic drug for ischemic stroke patients. Moreover, it seems that activation of D2R is involved in suppressing microglia of low activity in basal conditions [55]. Conversely, the D3R-selective antagonist PG01037 reduces the acquisition and activation of

Table 2
The functions of DA receptors expressed on neuroimmune-related cells.

Inflammatory cells	DA receptors[a]	Functions	Diseases	References
Microglia	D1R (+), D2R (+), D4R (−)	Inhibit microglial activation	PD, ischemic stroke, ALS	[56,59,62]
	D5R (+), D3R (−)	Reduce microglial M1 polarization	Depression, PD	[57,61]
Astrocytes	D2R (+)	Decrease astrocytic proliferation and activation	PD, ALS	[21,55,66–68]
	D1R (+), D3R (−)	Modulate astrogliosis	PD	[56,61,70]
$CD4^+$ T cells	D3R (+)	Promote Th1 inflammatory phenotype differentiation	PD	[102,103]
	D5R (−)	Reduce the proportion of Th17 cells	MS	[102,107,108]
	D1-like receptors (+)	Result in dysfunction of Treg cells	MS	[109–111]
$CD8^+$ T cells	D3R (+)	Induce selective adhesion, migration and homing of cytotoxic $CD8^+$ cells	PD, MS	[116,117]
Dendritic cells	D5R (+), D3R (+)	Modulate the differentiation and activation of T cells	MS	[106,107,118]
	D1-like and D2-like receptors (−)	Regulate DC-mediated Th17 and Th2 phenotypes differentiation	MS	[124,125,127]
Monocytes and macrophages	D2-like receptors (+)	Promote the phagocytic activity of macrophages	Neurocognitive disorders	[129]
	D2R (+), D1R (+)	Attenuate macrophages and monocytes-mediated neuroinflammation	ICH, PD	[20,95,130]

[a] + indicates activation; − indicates inhibition.

M1 phenotype microglia, contributing to an anti-inflammatory effect and displaying a significant therapeutic effect in PD mice model [61]. Furthermore, in amyotrophic lateral sclerosis (ALS) model, D4R antagonist, L-745,870 inhibits microglial activation and reduces the production of TNF-α, thereby preventing spinal cord motor neuronal loss [62]. These opposite effects may attribute to the types of antagonists and the differences of disease models.

3.2. Astrocytes

The functions of astrocytes are found in many aspects, including providing nutrient supports for neurons, controlling extracellular water and electrolyte balance, producing various extracellular trophic factors, and modulating neurotransmitters. Furthermore, astrocytes can produce cytokines modulating immune responses. Activation of astrocytes can release ROS and other substances (e.g., matrix metalloprotease), which are involved in inflammatory reactions [63,64]. Activation of astrocytic detrimental signaling pathway is identified to trigger neuronal death and BBB damage through immune cell recruitment and cytokine or chemokine release [65].

DA receptors are also expressed in astrocytes, and several studies indicate that DA receptors play a major role in modulating the astrocytic activity (Table 2). It is known that astrocytic D2R generally suppresses neuroinflammation through different mechanisms, such as αB-crystallin and βArr2-dependent mechanisms [21,66]. Activation of astrocytic D2R by quinpirole prevents neuroinflammation-mediated degeneration of DAergic neurons in LPS-induced PD model [67]. However, the anti-inflammatory effects of quinpirole is abolished in α-Syn overexpressed mouse brain via decreasing the expression of βArr2 and promoting Toll-like receptor 4 (TLR4)/NF-κB axis in astrocytes [67]. Another study also found quinpirole reduced astrocytic proliferation and astrogliosis via stimulating D2R, which was related to its anti-inflammatory effects in the early stage of PD [55]. Furthermore, D2R agonist BRC significantly inhibits the activation of astrocytes and reduces the production of TNF-α in the spinal cord of ALS mice, thus preventing loss of motor neuron [68]. Blockade of D2R with sulpiride attenuates the activation of astrocytes and the release of IL-1β and TNF-α induced by chronic treatment with morphine, which provides an opportunity for the treatment of morphine-induced anti-nociceptive tolerance clinically [69].

In addition to D2R, the lack of D3R expression in astrocytes prefers to a beneficial astrogliosis with anti-inflammatory functions on microglia [61]. The beneficial astrogliosis may refer to the increase of anti-inflammatory and neuroprotective astrocytes, M2 phenotype astrocytes, similar to M2 microglia. Likewise, D1R is able to modulate astrogliosis and inflammation factors secretion in PFC and SNc of PD [56,70]. Moreover, DA can also facilitate the release of astrocytic TNF-α through activation of TLR4/NF-κB signaling pathway, contributing to TNF-α-mediated neuronal apoptosis and subsequent progressive neurodegeneration in minimal hepatic encephalopathy [71]. Non-selective activation of DA receptors by apomorphine triggers reactive astrocytes and inflammatory response in the hippocampus, related to dysfunction of learning and memory [72]. In conclusion, DA receptors on glial cells or neurons can be potential targets in regulating inflammatory response and neuronal damage.

4. The mechanism of dopamine receptor affecting neuroinflammation

In recent studies, the effects of DA receptors on neuroinflammation have been universally investigated in PD, MS, stroke and other brain diseases. Although the mechanisms of DA receptors on neuroinflammation are diverse and even not fully illuminated, it is found that NLRP3 inflammasome, renin-angiotensin system and αB-crystallin are investigated more deeply and can be promising targets. More importantly, DA receptors influence neuroinflammatory process through modulating invading peripheral immune cells, such as $CD4^+$ T cells, dendritic cells, monocytes and macrophages (Table 2). In this section, we concluded previous studies relevant to the following mechanisms, which might provide possible therapeutic targets for inflammation-related brain diseases in clinic.

4.1. NLRP3 inflammasome

Inflammasomes are important multi-protein complexes, which can promote the cleavage and activation of inflammatory caspases and IL-1β maturation. The inflammasome contains a cytosolic pattern recognition receptor, particularly a nucleotide-binding oligomerization domain-like receptor (NLR). NLRP3 inflammasome is the most typical inflammasome among various NLR inflammasome complexes, and has been related to multiple human immune and inflammatory diseases [73]. Activation of NLRP3 inflammasome results in the cleavage of procaspase-1 into caspase-1, leading to the maturation of several pro-inflammatory factors, such as IL-1β and IL-18 [73]. As a result, the NLRP3 inflammasome may be a hopeful target for anti-inflammatory treatment.

It is demonstrated that NLRP3 inflammasome participates in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced loss of the DAergic neurons [20,74]. Moreover, DA is considered to inhibit NLRP3 inflammasome activation via regulating D1R/cAMP signaling pathway, and D1R signaling can protect against MPTP-induced neuroinflammation via suppression of NLRP3 inflammasome in vivo [20]. NLRP3

inflammasome is also assembled and activated in PD patients, which is characterized by the elevated caspase-1 activity and IL-1β level in the serum of PD patients, compared to age-matched healthy controls [75]. Therefore, DA restricts the progression of inflammatory diseases, and D1R can be a significant target for the therapy of NLRP3-driven brain inflammatory diseases, including stroke, PD and other neurodegenerative diseases. Consistently, A-68930, a D1R specific agonist, inhibits NLRP3-mediated neuroinflammation by increasing the expression of IFN-β in ICH mice, and thereby improve neurological outcome [76]. ICH injury is a devastating subtype of stroke which is characterized by activation and accumulation of inflammatory cells, such as microglia, astrocytes and infiltration of macrophage. And IFN-β is known as an immunomodulatory cytokine partly controlling the inflammatory process. Therefore, D1R/IFN-β/NLRP3 signaling pathway plays a key role in attenuating neuroinflammation in ICH injury. In addition, the levels of NLRP3 inflammasome and both IL-1β and IL-18 are also increased in brain tissues obtained from ischemic stroke patients [77]. A-68930 can also alleviate tissue damage and promote locomotion recovery in spinal cord injury, the mechanism of which may be associated with the inhibition of NLRP3 inflammasome activity [78].

In addition to D1R, D2R can also regulate NLRP3 inflammasome activation. For instance, it was found that selective D2R agonist LY171555 inhibited the activation of NLRP3 inflammasome in the SNc of MPTP-induced PD mice [66]. The results of positron emission tomography (PET) imaging revealed that D2R binding in the cortex and striatal of memory-impaired PD patients was significantly reduced compared to healthy controls [79]. Moreover, it was observed that caspase-1 cleavage and IL-1β release were decreased in the midbrain of normal mice, while D2R anti-inflammasome effect was deficient in βArr2 knockout mice under agonist of astrocytic D2R. As a result, astrocytic D2R is convinced to inhibit NLRP3 inflammasome activity via modulating βArr2 [66]. Moreover, LY171555 enhances the interaction of βArr2 and NLRP3, which will further suppress the inflammasome assembling process. This provides a new approach for targeting the astrocytic NLRP3-induced inflammatory reaction in the therapy of PD and other neurodegenerative diseases. It is known that an increasing number of immunotherapeutic strategies are being applied to neurodegenerative diseases, which have been successful in MS [80].

Similarly, there are investigations manifesting that DA receptors can also control inflammation in the peripheral tissues via inhibiting NLRP3 inflammasome. A-68930 presents a protective role on spinal cord injury-induced acute lung injury by the inhibition of NLRP3 inflammasome in the lung tissues [81]. Furthermore, previous study revealed that DA had potential improvement effects for ventilator-induced lung injury by suppressing the production of pro-inflammatory cytokines IL-6, IL-18, IL-1β and TNF-α, which was mediated by the negatively regulation of NLRP3 inflammasome [82]. In conclusion, DA receptor is an underlying therapeutic target for the treatment of NLRP3 inflammasome-induced neuroinflammatory diseases. To develop more effective drugs, future studies should focus on exploring more specific mechanisms of DA receptors on NLRP3.

4.2. Renin-angiotensin system

Renin-angiotensin system (RAS) was firstly regarded as a humoral circulation system that regulated sodium and water homeostasis as well as blood pressure. However, an independent and local RAS has been discovered in the brain, where angiotensinogen is primarily derived from astrocytes [83]. Angiotensinogen is the precursor glycoprotein of angiotensin II (AII) that is the most significant effector of the RAS. The function of AII is modulated by two major receptors: AII type 1 (AT1) and type 2 (AT2) receptors. Generally, AT2 receptor exerts directly opposed actions compared to those mediated by AT1 receptor. And AT1 and AT2 receptors are expressed in both astrocytes and microglia [84]. A number of investigations have confirmed that the brain RAS is closely associated with neuroinflammatory response and progression of neuronal death in CNS diseases, such as PD [85] and AD [86]. Hyperactivation of brain RAS, by stimulating AT1 receptor and NADPH oxidase, regulates inflammatory processes and oxidative stress that play an important role in certain aging-related diseases. For instance, a clinical study confirmed that the general loss of AT1 receptor in surviving DA neurons in substantia nigra correlated with neuronal dysfunction and neurodegenerative progression of PD patients [87]. It supports the idea that AII/AT1/NADPH oxidase axis-mediated oxidative stress contributes to DA neurons death and neuropathological and clinical manifestations of PD. Furthermore, RAS may play a primary role in DA-mediated alterations of neuroinflammation and neuronal oxidative stress. Moreover, a counter regulatory pathway between DA and AT receptors is also discovered in the substantia nigra and striatum of mice [83].

The results of a previous study indicate that up-regulation of AT1/AT2 receptor ratio promotes inflammatory state and DAergic vulnerability in brain [88]. Both D1R and D2R-deficient mice overexpress AT1 receptor in the striatum and substantia nigra of young mouse brain, thereby modulating oxidative stress and neuroinflammation. The suppression of inflammatory response mediated by DAergic system is impaired by aging, which is a prominent risk factor for PD [89]. Interestingly, a compensatory effect is observed in young adult DA receptor-deficient mice. The expression of AT2 receptor is remarkably increased in D2R-deficient mice, while angiotensinogen levels and angiotensin converting enzyme (ACE) activity are downregulated in D1R-deficient mice [88]. The mechanism accounting for counteracted AT1 receptor overexpression by the different compensatory effects remains to be clarified. Moreover, L-DOPA treatment inhibits microglia-mediated inflammatory reaction and neuronal oxidative stress induced by overactivation of RAS in young DA-declined rats, while is useless in aged rats. More specifically, DA is demonstrated to inhibit production of angiotensinogen/AII in astrocytes via D2R [55]. D2R agonist quinpirole increases AT2 receptor expression but decreases AT1 receptor expression in cultured astrocytes, which reduces astrocytic proliferation and astrogliosis related to inflammation. However, both D1R and D2R agonists, SKF-38393 and quinpirole, inhibit the pro-inflammatory AT1/NADPH-oxidase/superoxide pathway in LPS-treated microglia. An initial reduction of striatal DA levels induced by MPP^+, similar to early stages of PD, may result in an augment of angiotensinogen and AII, which accelerates the neuroinflammatory reaction as well as process of DAergic degeneration [55]. Therefore, DA receptor agonists may attenuate neuroinflammation and disease development through suppression of glial RAS in early stages of PD and aging.

There are possible interactions between DA and AT receptors, which regulate inflammatory microglial response and neuroinflammation collectively, constituting an effective neuroprotective strategy for PD [83]. AT1 receptor and D2R are identified to form heteromers in both rat striatum and co-transfected cells, by using in situ proximity ligation assays and bioluminescence resonance energy transfer [90]. The selective AT1 receptor antagonist, candesartan, is able to block D2R-mediated effects on cAMP levels and βArr2 recruitment in co-transfected cells, primary cultures of neurons and brain slices, namely cross-antagonism [90], exerting opposite effects on neuroinflammation. Accordingly, perindopril, ACE inhibitor, enhanced the effect of L-DOPA while reducing dyskinesias in a proof-of-concept, randomized, double-blind crossover study in PD patients [91]. Therefore, drugs targeting RAS selectively may be beneficial for PD and/or dyskinesia via altering the functional response of DA receptor. Additionally, D4R agonist, PD168077, has been shown to decrease AT1 receptor expression in peripheral tissues, such as vascular smooth muscle cells [92] and renal proximal tubule cells [93], related to cardiovascular diseases and hypertension respectively.

4.3. αB-crystallin (CRYAB)

αB-crystallin, also called CRYAB, is known as a small heat-shock

protein (HSP) with neuroprotective and anti-inflammatory activities. For example, in a 48-week randomized controlled Phase IIa trial, after repeated intravenous administrations of the lower doses of αB-crystallin, a progressive decline in MS lesion activity as monitored by magnetic resonance imaging (MRI) became apparent, and they were not seen in the placebo group [94]. It is confirmed that αB-crystallin is required for D2R-mediated inhibition of inflammatory response in astrocytes, which is related to aging and multiple neurodegenerative disorders [21]. D2R-deficient mice display prominent neuroinflammatory response and result in severe neurodegeneration of nigral DAergic neurons induced by neurotoxin MPTP, together with a significant decline in the level of αB-crystallin. Moreover, overexpression of αB-crystallin suppresses the production of pro-inflammatory cytokines IL-1β and IFN-γ caused by a lack of D2R in PD model [21]. Activation of D2R by quinpirole decreases the levels of pro-inflammatory mediators in the substantia nigra of 6-hydroxydopamine (6-OHDA) or MPTP-treated PD mice through increasing αB-crystallin expression [21].

In the process of brain injury induced by ICH, D2R has an important role in controlling inflammatory response mediated by αB-crystallin, which will improve neurological outcomes and attenuate brain injury. For example, D2R agonists, quinpirole and ropinirole, limit microglial activation and inflammatory cytokine IL-1β production in ICH mice, which is related to intensive cytoplasmic binding activity between NF-κB and αB-crystallin and reduces NF-κB nuclear translocation [95]. However, a randomized, placebo-controlled, double-blind study indicated that there was no difference between ropinirole + physiotherapy and physiotherapy alone in gait/motor effects of patients with chronic stroke [96]. Stimulation of astrocytic D2R by Sinomenine, a bioactive alkaloid extracted from the medicinal herb *Sinomenium acutum*, inhibits neuroinflammation as well as alleviates neuronal apoptosis and cerebral infarction in ischemic stroke via enhancing αB-crystallin expression [97]. Sinomenine promotes nuclear translocation of αB-crystallin in astrocytes, and prevents signal transducer and activator of transcription 3 (STAT3) activity by reinforcing the interaction between αB-crystallin and STAT3, which further blocks DNA-binding activity of STAT3 [97]. As a result, NF-κB and STAT3 are considered to be potential pathways in D2R-targeted neuroinflammatory injury via regulating αB-crystallin. However, there are only a few studies investigating the mechanisms of D2R regulating αB-crystallin. Thus, future research should clarify whether DA receptors in addition to D2R have an impact on αB-crystallin in brain disorders.

4.4. Peripheral immune cells

4.4.1. T cells

As important cells of the adaptive immune system, T lymphocytes can be subdivided into $CD4^+$ T cells and $CD8^+$ T cells, depending on their functions: help and guide other immune cells ($CD4^+$) and eliminate infected somatic cells ($CD8^+$). It is known that CNS-infiltrated T cells contribute to the pathogenesis of neurodegenerative diseases, including PD and MS [3]. Moreover, targeting DA receptors expressed on T cells by using DA or agonists/antagonists is able to regulate the activation of T cells and cytokine secretion [13,14,98].

4.4.1.1. $CD4^+$ T cells. $CD4^+$ T cells infiltrating the CNS have a crucial impact on microglial activation, inflammatory responses and subsequent neuronal damage, which depends largely upon the differentiation functional phenotypes of these cells. The differentiation of $CD4^+$ T cells toward the T-helper 1 (Th1) and Th17 phenotypes, the main pro-inflammatory phenotypes, is able to strongly trigger chronic neuroinflammation [99]. In contrast, anti-inflammatory functional phenotypes, Th2 and T-regulatory (Treg) phenotypes, are involved in the decrease of microglial inflammatory functions, attenuate neuroinflammatory processes and promote neuronal survival [99]. For instance, a clinical study reported that, compared with control group, Th1 cells were increased and the Th1/Th2 balance was shifted toward Th1 in PD patients, which were associated with motor function scores. Moreover, it was also found that Th17 cells were increased and Tregs were decreased in PD patients [100].

It is confirmed that DA receptors expressed on brain-infiltrating $CD4^+$ T cells exhibit a major function in the inflammatory reaction involved in brain diseases [101], especially D3R and D5R on $CD4^+$ T cells. D3R stimulation triggers the decrease of cAMP levels further facilitating activation of $CD4^+$ T cell, and the stimulation of D3R also inhibits extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation leading to efficient Th1 phenotype differentiation. By contrast, activation of D5R results in an efficient T cell receptor-caused ERK1/2 phosphorylation, thereby stimulating $CD4^+$ T cells, but without effect on Th1 differentiation [102]. For instance, D3R expressed on $CD4^+$ T cells is probably essential in promoting microglial activation and destruction of DAergic neurons during MPTP-induced PD [103]. The lack of D3R prevents microglial activation as well as degeneration of DAergic neurons in the lesion location of PD mice. Furthermore, activation of D3R on $CD4^+$ T cells promotes T cell stimulation, differentiation toward Th1 inflammatory phenotype and production of inflammatory factors, including TNF-α and IFN-γ [103]. It was found that D3R expression was selectively reduced in peripheral blood $CD4^+$ T cells obtained from PD patients and selective antagonism of D3R exerted therapeutic effects in PD mice [104]. D3R expressed on $CD4^+$ T cells may be developed as a novel therapeutic target for PD. Another study observed that increased expression of D3R on intestinal $CD4^+$ T cells enhanced the acquirement of Th1 phenotype and the expansion of Th17 cells, while impaired the generation of Th2 phenotype, which promoted the chronic inflammatory colitis conditions [105].

Apart from D3R expressed on $CD4^+$ T cells, D5R may be also involved in regulating $CD4^+$ T cells activation and differentiation. In the animal model of MS, experimental autoimmune encephalomyelitis (EAE), DA facilitates $CD4^+$ T cell activation and differentiation through stimulating D5R expressed on dendritic cells (DCs), thereby leading to the development of $CD4^+$ T cell-mediated immune responses [106]. D5R-deficient DCs emerge a significant role in reducing the proportion of Th17 cells infiltrating the CNS, which is capable to alleviate the severity of EAE in mice [106]. Furthermore, D5R-deficiency in DCs can also restrict the production and release of the inflammatory mediators IL-12 and IL-23 in CNS mediated by Th1 and Th17 cells [107]. However, a recent study reported that activation of D5R in naive $CD4^+$ T cell favored the suppressive impact of Treg cells on neuroinflammation just once the severity stage of EAE manifestation, although Th17-driven inflammatory response was stimulated by D5R in the early stage of this disease [108]. Thus, there are two opposite roles of D5R in $CD4^+$ T cell at different stages during the development of MS.

Moreover, dysfunction of Treg cells in MS patients is probably caused by increased expression of D1-like receptors in Treg cells, which eventually leads to effector T cells proliferation and activation [109]. In clinic, IFN-β treatment is able to abolish the inhibitory effect of DA on Tregs function and reduces the expression of D5R in Tregs from MS patients compared to healthy controls, which further promotes the suppression of effector T cells proliferation mediated by Tregs [110]. Catecholamine-dependent down-regulation of Treg function is also mediated primarily by D1-like receptors [111]. It is observed that both D1-like and D2-like receptors are functionally active in reduced regulatory functions of Treg cells; however, D1-like receptors stimulation may result in stronger effects than D2-like receptors [112].

Haloperidol, a typical antipsychotic drug, is an antagonist of D2-like receptor. It is observed that haloperidol affects neuroimmune function through inhibiting DC-induced differentiation of $CD4^+$ T cell toward Th1 phenotype in the brain, which is mediated by D2-like receptor [113]. Besides, the response of $CD4^+$ T cell is also regulated by α-syn in a dose-dependent manner in serum of mouse with α-syn vaccination, which is associated with expression levels of D2R and D3R on $CD4^+$ T cell [114]. In vitro, both monomeric and fibrillar α-syn increase $CD4^+$

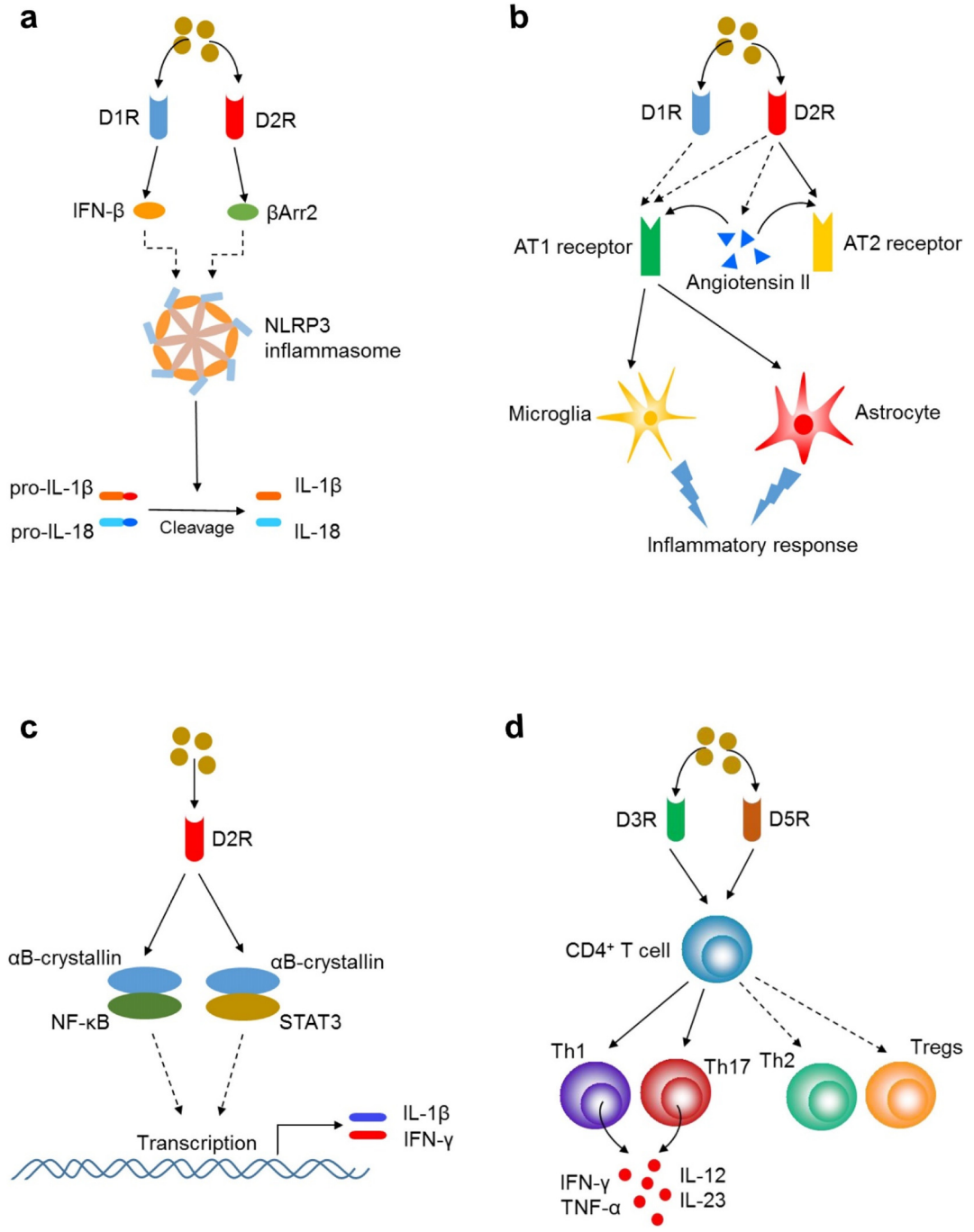

Fig. 3. The mechanism of dopamine receptors regulating neuroinflammation.
(a) The pathway of DA receptors inhibiting neuroinflammation via NLRP3 inflammasome. NLRP3 inflammasome is an important multi-protein complex, which can lead to the maturation of several pro-inflammatory factors, such as IL-1β and IL-18. Activation of D1R inhibits NLRP3-mediated neuroinflammation by increasing the expression of IFN-β, while D2R suppresses NLRP3 inflammasome activity via modulating βArr2. **(b)** The role of DA receptors in RAS-mediated neuroinflammatory response. As the most significant effector of the RAS, angiotensin II regulates inflammatory processes through two major receptors: AT1 and AT2 receptor. Generally, AT2 receptor exerts directly opposed actions compared to those mediated by AT1 receptor. Stimulation of D1R or D2R decreases AT1 receptor expression, thereby inhibiting astrocytes and microglia-mediated inflammatory response. Besides, D2R can also inhibit the production of angiotensin II and increase AT2 receptor expression. **(c)** αB-crystallin involved in DA receptors and neuroinflammation. Activation of D2R enhances the interaction of αB-crystallin with NF-κB or STAT3, which further blocks DNA-binding activity of NF-κB or STAT3. NF-κB and STAT3 are two common transcription factors promoting transcription of inflammatory cytokines, such as IL-1β and IFN-γ. **(d)** The mechanism of DA receptors modulating neuroinflammation mediated by $CD4^+$ T cells. Activation of D3R or D5R expressed on $CD4^+$ T cells promotes T cell stimulation, differentiation toward Th1 or Th17 inflammatory phenotype and release of pro-inflammatory factors. In addition, increased expression of D3R on $CD4^+$ T cells impairs anti-inflammatory effect of Th2 phenotype, and D5R can also regulate the suppressive impact of Treg cells on neuroinflammation. βArr2, β-Arrestin 2; AT1/2, angiotensin II type 1/2; IFN, interferon; IL, interleukin; RAS, renin-angiotensin system; STAT3, signal transducer and activator of transcription 3; Th, T-helper; TNF-α, tumor necrosis factor α; Tregs, T-regulatory cells.

T cells and affect expression of DA receptors on $CD4^+$ T cells in peripheral blood mononuclear cells obtained from PD patients [115].

4.4.1.2. $CD8^+$ T cells. Activation of DA receptors, primarily D3R, induces selective adhesion, migration and homing of cytotoxic $CD8^+$ cells, which may have important therapeutic implications on neurological and psychiatric diseases [116]. In animal experiments, D3R antagonist U-99194A significantly decreases homing of naive $CD8^+$ T cells into lymph nodes [117]. Conversely, another study found that the lack of D3R-signaling in DCs potentiated the activation of cytotoxic responses mediated by $CD8^+$ T cells [118]. A prominent inflammatory response involving both infiltration of $CD4^+$ and $CD8^+$ T cells and activation of resident microglia was observed in α-syn-induced PD model and PD patients [3,119]. In addition to D3R, stimulation of D1-like receptor was also demonstrated to inhibit the proliferation of $CD8^+$ T cells via elevating intracellular cAMP in vitro [120,121].

4.4.2. Dendritic cells

A major role of dendritic cells (DCs) recruited to the CNS is to present antigen to invading T cells in order to determine the outcome of neuroinflammation, which is a potential drug target of CNS diseases, especially MS [122]. For instance, it was found that DC density was increased in patients with MS via corneal confocal microscopy, which was involved in the inflammatory conditions of MS [123]. As described above, stimulation of D5R or D3R expressed on DCs is able to modulate the differentiation and cytotoxicity of CNS-infiltrating $CD4^+$ and $CD8^+$ cells [106,107,118]. Besides, DCs pre-treated with D1-like receptor antagonists are enabled to ameliorate EAE in mouse model, which is possibly due to the promotion of DC-dependent inhibition of the pathogenic Th17-effector phenotype [124]. Similarly, D2-like receptor antagonists, such as sulpiride and nemonapride, induce a significant human monocyte-derived DC-mediated Th2 phenotype differentiation and suppress secretion of inflammatory cytokines [125,126]. Another D2R antagonist, risperidone can modulate the immune function of DCs and increase the production of pro-inflammatory cytokines, such as IL-6, IL-8 and TNF-α [127].

4.4.3. Monocytes and macrophages

Monocytes and macrophages are known as critical effectors and regulators of the innate immune response and inflammation, where DA receptor is expressed and plays important modulatory functions [128]. For example, activation of D2-like receptor regulates the phagocytic activity of macrophages, which contributes to scavenging of apoptotic cells and cell debris in neurocognitive disorders [129]. In ICH mice model, treatment with D2R agonists, quinpirole and ropinirole, attenuates activation of macrophages and microglia, thereby inhibiting neuroinflammation and ameliorating brain injury [95]. It was shown that macrophages-mediated inflammatory process was mitigated by the action of DA on D1R, through the inhibition of NLRP3 inflammasome [20]. Activation of D1R with fenoldopam prevents activity of LPS-stimulated macrophages and monocytes and production of inflammatory cytokines [130]. However, D5R-signaling in monocytes obtained from MS patients involves the attenuation of STAT3-activation, a transcription factor that limits the production of the inflammatory cytokines IL-12 and IL-23 [107]. Additionally, depletion of DA content can also reduce the infiltration of peripheral macrophages as well as the activation of microglia induced by 6-OHDA, which is associated with the pathogenesis of PD [131].

5. Conclusions

DA receptors are modulators and effectors of brain disorders through complex signaling pathways interaction and can be affected by different ligands. Although D1-like and D2-like receptor families have different downstream signaling pathways, it seems that they are consistent in regulating inflammatory response. Targeting DA receptors with specific agonists and antagonists provides an opportunity to control neuroinflammation, which may be related to the amelioration of various CNS diseases, such as PD, MS and stroke. As we stated in this review, neuroinflammation is recognized to be a ubiquitous pathological feature of these diseases, involving glial cells activation (astrocytes and microglia) and consequently release of pro-inflammatory cytokines. It is well known that microglia and astrocytes are crucial glial cells involved in inflammatory response, where DA receptors play important roles in regulating the production and release of inflammatory mediators and subsequently the pathological symptoms of diseases. In addition to microglia and astrocytes, neuroinflammation is also modulated by CNS-infiltrated peripheral immune cells, where DA receptors are expressed and display diverse effects (Table 2). The suppression of neuroinflammation represents a promising strategy in the clinical treatment of brain diseases.

In general, activation of DA receptors exerts inhibitory effects in the progression of neuroinflammation through modulating NLRP3 inflammasome, RAS or αB-crystallin (Fig. 3). However, activation of DA receptors on $CD4^+$ T cells, primarily D3R and D5R, contributes to the development of $CD4^+$ T cell-mediated inflammatory reactions via promoting Th1 and Th17 phenotypes while inhibiting Treg and Th2 cells (Fig. 3). In DCs, suppression of DA receptors mainly prefers to attenuate $CD4^+$ and $CD8^+$ T cells-mediated neuroinflammation in brain diseases, especially MS. By contrast, in most studies, DA receptors expressed on astrocytes and microglia possess anti-inflammatory functions mediated by different mechanisms in brain inflammatory diseases. Moreover, stimulation of D2R and D1R regulates the phagocytosis of macrophages and reduces the activity of macrophages and monocytes, eventually mitigating neuroinflammation. Therefore, it is convinced that the role of DA receptors on neuroinflammation depends on different immune cells, receptor subtypes and disease models. In summary, a comprehensive understanding of the connection between DA receptor and neuroinflammation will provide novel insights into the suppression of inflammatory response by targeting DA receptor and, finally, help develop therapeutic drugs for brain diseases.

Declaration of competing interest

There is no conflict of interest among the authors.

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