Received: 22 January 2021 | Accepted: 15 March 2021

DOI: 10.1002/prp2.766

REVIEW

Nuclear receptors of NR1 and NR4 subfamilies in the regulation of microglial functions and pathology

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Abstract

This review provides an overview of researches on the NR1 and NR4 nuclear receptors involved in the regulation of microglial functions. Nuclear receptors are attractive candidates for drug targets in the therapies of the central nervous system disorders, because the activation of these receptors is expected to regulate the functions and the phenotypes of microglia, by controlling the expression of specific gene subsets and also by regulating the cellular signaling mechanisms in a nongenomic manner. Several members of NR1 nuclear receptor subfamily have been examined for their ability to regulate microglial functions. For example, stimulation of vitamin D receptor inhibits the production of pro-inflammatory factors and increases the production of anti-inflammatory cytokines. Similar regulatory actions of nuclear receptor ligands on inflammation-related genes have also been reported for other NR1 members such as retinoic acid receptors, peroxisome proliferator-activated receptors (PPARs), and liver X receptors (LXRs). In addition, stimulation of PPARγ and LXRs may also result in increased phagocytic activities of microglia. Consistent with these actions, the agonists at nuclear receptors of NR1 subfamily are shown to produce therapeutic effects on animal models of various neurological disorders such as experimental allergic encephalomyelitis, Alzheimer's disease, Parkinson's disease, and ischemic/hemorrhagic stroke. On the other hand, increasing lines of evidence suggest that the stimulation of NR4 subfamily members of nuclear receptors such as Nur77 and Nurr1 also regulates microglial functions and alleviates neuropathological events in several disease models. Further advancement of these research fields may prove novel therapeutic opportunities.

KEYWORDS
apolipoprotein E, CD36, interleukin, mitogen-activated protein kinase, NF-kappa B, suppressor of cytokine signaling protein, toll-like receptor

Abbreviations: 6-OHDA, 6-hydroxydopamine; ABCA1, ATP-binding cassette transporter A1; ApoE, apolipoproein E; APP, amyloid precursor protein; CCL, C-C motif chemokine ligand; CNS, central nervous system; CXCL, C-X-C motif chemokine ligand; ERK, extracellular signal-regulated kinase; IFN, interferon; IL, interleukin; iNOS, inducible form of nitric oxide synthase; JAK, Janus kinase; LPS, lipopolysaccharide; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF, nuclear factor; NGFIB, nerve growth factor IB; NO, nitric oxide; Nur77, nuclear receptor 77; Nurr1, nuclear receptor related 1; Pdia3, protein disulfide isomerase family member 3; PPAR, peroxisome proliferator-activated receptor; RAR, retinoic acid receptor; RXR, retinoid X receptor; SOCS, suppressor of cytokine signaling; STAT, signal transducers and activators of transcription; TLR, toll-like receptor; TNF, tumor necrosis factor; VDR, vitamin D receptor.

1 | INTRODUCTION

Accumulating lines of evidence indicate that microglia play versatile roles in the physiology/pathophysiology of the central nervous system (CNS). Particularly under various pathological conditions, microglia represent the major cell population in the CNS that regulates inflammatory responses. The roles of microglia in inflammation are bidirectional: on the one hand, these cells produce pro-inflammatory cytokines and reactive oxygen/nitrogen species involved in the progression of inflammation, but on the other hand, they can produce anti-inflammatory cytokines and also exhibit the phagocytic activity that contributes to the resolution of inflammation. These properties of microglia have been conveniently designated as pro-inflammatory "M1" phenotype and anti-inflammatory "M2" phenotype, respectively, in analogy with two-faced functions of macrophages in the peripheral tissues.[1,2] However, this classification is under debate because the phenotypes of microglia are far more complicated than the postulated M1/M2 polarization.[3,4] In any case, pharmacological interventions that modify the phenotypes and the functions of microglia may provide novel therapeutic opportunities for various CNS disorders accompanied by inflammatory events. In this context, nuclear receptors are considered the attractive candidates for drug targets, because ligand-induced activation of these receptors regulates gene expression by interacting with the specific response elements in DNA sequences, thereby alters the phenotypes and the functions of cells.[5,6] Besides, several kinds of nuclear receptors may regulate cellular signal transduction pathways in a nongenomic manner, as discussed below.

Human genome encodes 48 members of nuclear receptor superfamily, which are divided into seven subfamilies (Table 1). The expression of many nuclear receptor superfamily members has been detected in cells of macrophage lineage, as previously reported.[7] Estrogen receptor-like receptors are categorized as the members of NR3 subfamily that includes the receptors for steroid hormones such as the sex steroids estrogens (NR3A1, NR3A2), androgens (NR3C4), and progesterone (NR3C3), as well as the adrenal steroids glucocorticoids (NR3C1) and aldosterone (NR3C2). Regulation of microglial functions by these steroid hormone receptors has been investigated by many studies, which are summarized in recent reviews.[8-10] On the other hand, NR1 subfamily is comprised of a larger number of group members including retinoic acid receptors (RARs), peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), and vitamin D receptor (VDR). Another nuclear receptor subfamily of recent interest is nerve growth factor IB (NGFIB)-like subfamily designated as NR4 subfamily, which includes nuclear receptor 77 (Nur77)/NGFIB and nuclear receptor related 1 (Nurr1). Regulatory roles in microglia of these nuclear receptors mentioned above, among others, have been proposed by a substantial number of researches. This review aims to provide an overview of the advancement of researches on the nuclear receptor members of NR1 and NR4 subfamilies, as potential therapeutic targets based on the regulation of microglial functions.

2 | VITAMIN D AND VDR

Vitamin D is a lipophilic vitamin derived from diet mainly as cholecalciferol (vitamin D_3) of the animal origin and partly as ergocalciferol (vitamin D_2) of the mushroom origin. In addition, the *de novo* biosynthetic pathway of vitamin D is present in human body, provided that sufficient exposure of the skin to ultraviolet-B light enables the conversion of 7-dehydrocholesterol into vitamin D_3.[11] Hydroxyl groups are then added sequentially to vitamin D_3 by CYP2R1/CYP27A1 (25-hydroxylases) in the liver and CYP27B1 (1α-hydroxylase) in the kidney, resulting in the generation of 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$; calcitriol), the active form of vitamin D (Figure 1A). 1,25-$(OH)_2D_3$ binds to VDR (NR1I1), and ligand-bound VDR in combination with retinoid X receptors (RXRs) as a heterodimer partner regulates the expression of various target genes.[12,13] Besides these classical actions as a nuclear receptor, VDR may produce rapid nongenomic actions by modulating the activities of various kinases in the cytosol that mediate intracellular signaling.[14] Vitamin D is best known for its role in calcium homeostasis and bone metabolism, via the facilitation of calcium absorption from the intestine and via the actions on osteoblasts/osteoclasts. However, VDR is also distributed in other organs and cells, and 1,25-$(OH)_2D_3$ produces a wide range of biological actions including the regulation of the immune system[15,16] and the CNS.[12]

An early study demonstrated that primary microglia obtained from rat brain produced 1,25-$(OH)_2D_3$ from 25-hydroxyvitamin D_3 (25-$(OH)D_3$), when activated by lipopolysaccharide (LPS) or interferon (IFN)-γ.[17] A later study on the expression of vitamin D-related genes showed that the enzymes involved in the production of 1,25-$(OH)_2D_3$ from vitamin D_3 (CYP27A1 and CYP27B1) were expressed in rat cerebral cortex and hippocampus, although the amounts of expression were lower than those in the liver and the kidney.[18] Neurons and to a lesser amount microglia are the major cell types expressing CYP27B1 (that produces 1,25-$(OH)_2D_3$ from 25-$(OH)D_3$) in the brain. On the other hand, within the CNS, VDR expression is most abundant in astrocytes and lower expression is found in other cell types such as neurons, microglia, oligodendrocytes, and endothelial cells.[18] Notably, the same study demonstrated that the expression levels of protein disulfide isomerase family member 3 (Pdia3) were higher in the brain than in the liver and the kidney and that Pdia3 was expressed in all the major cell types in the brain. Because Pdia3 is a presumed membrane-associated enzyme involved in the nongenomic actions of 1,25-$(OH)_2D_3$,[19,20] the actions of 1,25-$(OH)_2D_3$ in the brain might be mediated in part by Pdia3.

Several studies using microglia-like cell lines or primary microglia have shown that exogenous application of 25-$(OH)D_3$ or 1,25-$(OH)_2D_3$ directly affects the phenotypes of these cells, with regard to the expression of pro-inflammatory/anti-inflammatory factors and the phagocytic activities. For example, 25-$(OH)D_3$ suppressed nitric oxide (NO) production from microglial BV-2 cells and primary microglia, and this effect was abrogated by the knockdown of VDR.[21] 1,25-$(OH)_2D_3$ has also been shown to inhibit the expression of several pro-inflammatory cytokines including tumor necrosis

TABLE 1 Members of nuclear receptor superfamily encoded by human genome

Subfamily	Group	Nomenclature	Common name (Abbreviation)
1. Thyroid hormone receptor-like	A	NR1A1	Thyroid hormone receptor α (TRα)
		NR1A2	Thyroid hormone receptor β (TRβ)
	B	**NR1B1**	**Retinoic acid receptor α (RARα)**
		NR1B2	**Retinoic acid receptor β (RARβ)**
		NR1B3	Retinoic acid receptor γ (RARγ)
	C	**NR1C1**	**Peroxisome proliferator-activated receptor α (PPARα)**
		NR1C2	**Peroxisome proliferator-activated receptor β/δ (PPARβ/δ)**
		NR1C3	**Peroxisome proliferator-activated receptor γ (PPARγ)**
	D	NR1D1	Rev-erbAα
		NR1D2	Rev-erbAβ
	F	NR1F1	RAR-related orphan receptor α (RORα)
		NR1F2	RAR-related orphan receptor β (RORβ)
		NR1F3	RAR-related orphan receptor γ (RORγ)
	H	**NR1H2**	**Liver X receptor β (LXRβ)**
		NR1H3	**Liver X receptor α (LXRα)**
		NR1H4	Farnesoid X receptor (FXR)
	I	**NR1I1**	**Vitamin D receptor (VDR)**
		NR1I2	Pregnane X receptor (PXR)
2. Retinoid X receptor-like	A	NR2A1	Hepatocyte nuclear factor-4α (HNF4α)
		NR2A2	Hepatocyte nuclear factor-4γ (HNF4γ)
	B	NR2B1	Retinoid X receptor α (RXRα)
		NR2B2	Retinoid X receptor β (RXRβ)
		NR2B3	Retinoid X receptor γ (RXRγ)
	C	NR2C1	Testicular receptor 2 (TR2)
		NR2C2	Testicular receptor 4 (TR4)
	E	NR2E1	Homolog of the Drosophila tailless gene (TLX)
		NR2E3	Photoreceptor cell-specific nuclear receptor (PNR)
	F	NR2F1	Chicken ovalbumin upstream promoter-transcription factor I (COUP-TFI)
		NR2F2	Chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII)
		NR2F6	ErbA-related (EAR-2)
3. Estrogen receptor-like	A	NR3A1	Estrogen receptor α (ERα)
		NR3A2	Estrogen receptor β (ERβ)
	B	NR3B1	Estrogen-related receptor α (ERRα)
		NR3B2	Estrogen-related receptor β (ERRβ)
		NR3B3	Estrogen-related receptor γ (ERRγ)
	C	NR3C1	Glucocorticoid receptor (GR)
		NR3C2	Mineralocorticoid receptor (MR)
		NR3C3	Progesterone receptor (PR)
		NR3C4	Androgen receptor (AR)

(Continues)

TABLE 1 (Continued)

Subfamily	Group	Nomenclature	Common name (Abbreviation)
4. Nerve growth factor-inducible B protein-like	A	**NR4A1**	**Nuclear receptor 77/Nerve growth factor IB (Nur77/NGFIB)**
		NR4A2	**Nuclear receptor related 1 (Nurr1)**
		NR4A3	Neuron-derived orphan receptor 1 (Nor1)
5. Steroidogenic factor-like	A	NR5A1	Steroidogenic factor 1 (SF1)
		NR5A2	Liver receptor homolog-1 (LRH1)
6. Germ cell nuclear factor-like	A	NR6A1	Germ cell nuclear factor (GCNF)
0. Miscellaneous	B	NR0B1	Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1 (DAX1)
		NR0B2	Small heterodimer partner (SHP)

Note: Receptors highlighted in bold are discussed in detail in the main text.

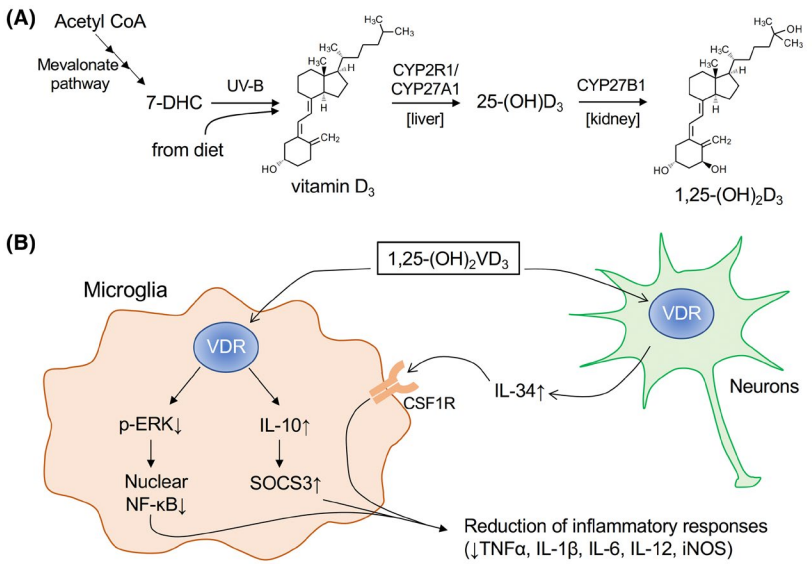

FIGURE 1 Vitamin D receptor (VDR) stimulation reduces the inflammatory responses in microglia. (A) The biosynthetic pathway of the active form of vitamin D_3 (1,25-$(OH)_2D_3$). Vitamin D_3 is derived either from diet or from *de novo* synthesis dependent on ultraviolet-B (UV-B)-induced conversion of 7-dehydrocholesterol (7-DHC), an intermediate product of the mevalonate pathway. 1,25-$(OH)_2D_3$ is produced by the sequential hydroxylation of vitamin D_3 by CYP2R1/CYP27A1 (25-hydroxylases) in the liver and CYP27B1 (1α-hydroxylase) in the kidney. (B) Proposed actions of 1,25-$(OH)_2D_3$ on microglial phenotype. Activation of VDR inhibits extracellular signal-regulated kinase (ERK) phosphorylation and arrests nuclear translocation of NF-κB that mediates the production of pro-inflammatory factors in microglia. In addition, VDR activation increases the expression of an anti-inflammatory cytokine IL-10 that induces the expression of SOCS3, an inhibitor of Janus kinase (JAK)/ signal transducers and activators of transcription (STAT) signaling. VDR is also expressed in neurons and triggers the upregulation of IL-34, which activates its receptor (colony stimulating factor-1 receptor; CSF1R) in microglia to suppress the inflammatory responses

factor (TNF)-α, interleukin (IL)-1β and IL-6 as well as inducible NO synthase (iNOS) in LPS-stimulated microglial EOC13 cells and BV-2 cells.[22,23] In addition, 1,25-$(OH)_2D_3$ inhibited the phosphorylation of extracellular signal-regulated kinase (ERK) and nuclear translocation of nuclear factor (NF)-κB in LPS-stimulated BV-2 cells, which may contribute to its anti-inflammatory effect.[23] Another study on IFN-γ-stimulated mouse primary microglia showed that 25-$(OH)D_3$ and 1,25-$(OH)_2D_3$ reduced the expression of pro-inflammatory factors such as TNF-α, IL-6, IL-12, and iNOS while increased the expression of an anti-inflammatory cytokine IL-10 and that IL-10-induced up-regulation of suppressor of cytokine signaling (SOCS)3 expression was responsible for the reduction of pro-inflammatory factors[24] (Figure 1B). Enhanced expression of anti-inflammatory cytokine/chemokine such as IL-10 and C-C motif chemokine ligand (CCL)17 has also been demonstrated in HMO6 human microglial cells treated with 1,25-$(OH)_2D_3$.[25] Taken together, these results suggest that vitamin D directly regulates the properties of microglia to induce anti-inflammatory reactions. It should be noted that the direct evidence for the involvement of VDR is lacking except for a limited number of cases,[21] and vitamin D might also exert its anti-inflammatory actions via VDR-independent pathways.[12,19,20] Concerning the phagocytic activity of microglia, vitamin D may have complex effects. A recent

study on human primary microglia showed that 1,25-$(OH)_2D_3$ downregulated the expression of MerTK, a receptor tyrosine kinase involved in the phagocytic clearance of dead cells and myelin debris.[26] On the other hand, the phagocytic and intracellular killing activities were significantly lower in primary microglia obtained from vitamin D-deficient mice than in those from control mice, indicating that vitamin D may be important for the resistance of the brain against bacterial infections.[27]

Several lines of evidence in vivo also suggest anti-inflammatory actions of vitamin D. The expression of iNOS induced in monocytes and microglia by injection of LPS into rat hippocampus was inhibited by locally delivered 1,25-$(OH)_2D_3$.[28] Inhibition of microglial activation and iNOS expression by 1,25-$(OH)_2D_3$ has also been demonstrated in rats with experimental allergic encephalomyelitis, an animal model of multiple sclerosis.[29,30] These anti-inflammatory actions were accompanied by alleviated neurological symptoms.[29,31] In spontaneous hypertensive rats, continuous infusion of 1,25-$(OH)_2D_3$ into the paraventricular nucleus of the hypothalamus inhibited the upregulation of various inflammatory parameters including microglial activation and also reduced the systolic blood pressure, heart rate, and cardiac hypertrophy.[32] Another study on spontaneous hypertensive rats suggested the regulation of brain renin–angiotensin system by VDR via the actions on microglia. That is, 1,25-$(OH)_2D_3$ induced the expression of angiotensin converting enzyme 2 and Mas receptor in microglia, both of which negatively regulated the actions of angiotensin-II.[33] Anti-inflammatory and neuroprotective effects of vitamin D have also been demonstrated in the experimental models of Parkinson's disease based on 6-hydroxydopamine (6-OHDA)- or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced degeneration of dopaminergic neurons in the substantia nigra.[34,35] It should be noted that the indirect actions via other cell types may be involved in the effect of 1,25-$(OH)_2D_3$ on microglial activities in vivo. For example, the protective effect of 1,25-$(OH)_2D_3$ against 6-OHDA, 1-methyl-4-phenylpyridinium, glutamate, and reactive oxygen species has been demonstrated in primary cultures of midbrain dopaminergic neurons.[36] Therefore, the prevention of microglial activation in the experimental models of Parkinson's disease might be a secondary phenomenon as a consequence of direct neuroprotection by 1,25-$(OH)_2D_3$. In this context, 1,25-$(OH)_2D_3$ induces the production of IL-34 in neurons, and neuron-derived IL-34 directs microglia toward anti-inflammatory phenotype[37] (Figure 1B).

3 | RETINOIC ACID AND RARS

RARs, to which a vitamin A metabolite all-*trans* retinoic acid binds as an endogenous agonist, consist of three subtypes RARα (NR1B1), RARβ (NR1B2), and RARγ (NR1B3). These receptors constitute heterodimers with RXRs and act as ligand-dependent transcription factors by binding to the retinoic acid response element of their target genes, although nongenomic functions of RARs have also been proposed.[38-40]

Retinoic acid signaling is well known to play essential roles in embryonic development, but the expression of RARα and RARβ is also detected in several discrete regions of the brain and the spinal cord of adult mice and rats.[41] In addition, the enzymes involved in retinoic acid synthesis (retinaldehyde dehydrogenases) and the proteins regulating the functions and the transport of retinoic acid (such as cellular retinol binding protein I and cellular retinoic acid binding protein I) are expressed in adult CNS.[38,41] These expression patterns imply that endogenous retinoic acid signaling plays important physiological and pathophysiological roles in the CNS. Indeed, ample evidence indicates that endogenous retinoic acid regulates synaptic plasticity by binding to RARα and regulating the local protein synthesis in neuronal dendrites.[39,40] After spinal cord injury in rats, stimulation of neuronal RARβ prevents the formation of glial scar and promotes axon regrowth.[42]

Microglia also express RARα particularly under several pathological conditions,[43,44] providing the opportunities for RAR ligands to regulate microglial functions. In primary rat microglia, all-*trans* retinoic acid inhibited the expression of TNF-α and iNOS induced by LPS or amyloid β peptide (Aβ), which was accompanied by enhanced expression of RARβ and reduced nuclear translocation of NF-κB.[45] We have demonstrated that an RARα/β agonist Am80 inhibits the production of a chemokine C-X-C motif chemokine ligand (CXCL)2 as well as several pro-inflammatory factors such as TNF-α, IL-1β and iNOS in LPS-treated BV-2 cells. The mechanisms of the action of Am80 may involve the reduced expression of NF-κB p65 subunit and CD14, a co-receptor for toll-like receptor (TLR)4, in addition to the reduced nuclear translocation of NF-κB [46] (Figure 2). The anti-inflammatory effects of Am80 were further validated in vivo in a mouse model of intracerebral hemorrhage. Daily oral administration of Am80 alleviated neurological deficits, which was associated with the inhibition of microglial activation in the perihematoma region.[44,47] Am80 also suppressed the expression of several cytokines and chemokines such as IL-1β, IL-6, and CXCL2 in the brain after intracerebral hemorrhage. Because reparixin, a C-X-C motif chemokine receptor antagonist that blocks the action of CXCL2, also alleviated neurological deficits, the therapeutic effect of Am80 on intracerebral hemorrhage may be attributable, at least in part, to the suppression of CXCL2 induction.[48]

Potential therapeutic effects of RAR agonists have also been explored on the experimental models of Alzheimer's disease. In Tg2576 mice overexpressing amyloid precursor protein (APP) with Swedish mutation, an RAR agonist AM580 reduced amyloid deposition in the cerebral cortex and the hippocampus, which may result from increased Aβ uptake via the upregulation of apolipoprotein E (ApoE) as well as from increased Aβ degradation via the upregulation of neprilysin and insulin-degrading enzyme, in microglia.[49] In a study using another line of mice overexpressing APP with Swedish mutation (APP23 mice), Am80 in combination with an RXR agonist HX630 improved the cognitive functions of mice and reduce the amount of insoluble Aβ in the brain.[50] The latter study proposed that the therapeutic effect of RAR/RXR stimulation may be attributable to the increased expression of IL-4 receptors in microglia and

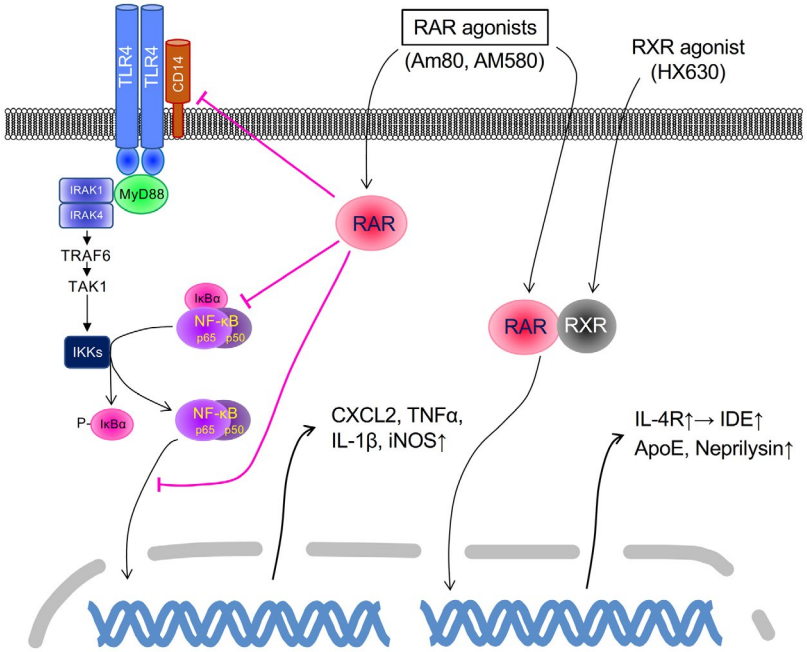

FIGURE 2 Retinoic acid receptor (RAR) stimulation reduces the inflammatory responses while enhances the Aβ-degrading activity of microglia. Activation of RAR in microglia inhibits TLR4-mediated inflammatory signaling by decreasing the expression of CD14 and NF-κB p65 subunit as well as by inhibiting nuclear translocation of NF-κB. On the other hand, RAR in combination with retinoid X receptor (RXR) upregulates the expression of IL-4 receptor (IL-4R), and the enhanced IL-4 signaling leads to the increased expression of insulin-degrading enzyme (IDE). RAR stimulation also upregulates the expression of ApoE and neprilysin. These upregulated molecules contribute to Aβ clearance

the resultant augmentation of IL-4 signaling, which leads to the increased degradation of Aβ by microglia through the upregulation of insulin-degrading enzyme.[50] (Figure 2).

4 | PPARS

NR1C subfamily of nuclear receptors include PPARα (NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3). Each of these receptors forms a heterodimer complex with RXR and binds to the peroxisome proliferator response element of DNA. Upon binding of specific agonists, PPAR/RXR recruits the coactivator complex and activates the transcription of downstream genes, thereby producing various biological actions.

PPARα is abundantly expressed in several tissues and organs including the liver and the brown adipose tissue and regulates lipid metabolism. Several studies examined the effect of PPARα agonists on microglial responses. In mouse primary microglia, various PPARα agonists including fenofibrate and WY14,643 suppressed NO production stimulated by IFN-γ/TNF-α or LPS and also suppressed LPS-induced production of pro-inflammatory cytokines such as TNF-α and IL-1β.[51] Fenofibrate and GW7647, another PPARα agonist, also suppressed γ-irradiation-induced expression of TNF-α, IL-1β, and cyclooxygenase-2 (COX-2) in BV-2 cells, possibly via the inhibition of nuclear translocation of NF-κB p65 and via the inhibition of c-Jun phosphorylation[52] (Figure 3). Suppression of microglial activation and pro-inflammatory cytokine production by PPARα agonists was confirmed in mouse cerebral cortex in vivo after local injection of LPS.[53] Fenofibrate was also shown to diminish global cerebral ischemia-reperfusion injury in rats, which was associated with the inhibition of microglial activation and pro-inflammatory cytokine production.[54] In mouse experimental allergic encephalomyelitis, PPARα agonists gemfibrozil and fenofibrate decreased the clinical score,[55] which may result from suppressed production of IL-12 family cytokines, along with suppressed expression of TLR4 and related adaptor molecules CD14 and MyD88 in microglia[56] (Figure 3).

PPARβ/δ is ubiquitously expressed in the body. This receptor is thought to regulate fatty acid metabolism, but a few studies addressed the role of PPARβ/δ in the regulation of microglial functions. For example, a PPARβ/δ agonist L-165,041 inhibited γ-irradiation-induced expression of pro-inflammatory factors TNF-α, IL-1β, CCL2, and COX-2 in BV-2 cells. These effects may be mediated by the inhibition of NF-κB activation via physical interaction of PPARβ/δ with NF-κB p65 and also by the prevention of the recruitment of protein kinase Cα-mediated MEK/ERK/AP-1 signaling pathway.[57] In another study, a PPARβ/δ agonist GW501,516 was shown to increase the expression of SOCS1, thereby inhibit Janus kinase (JAK)/ signal transducers and activators of transcription (STAT) signaling that mediates NADPH oxidase 2 expression in and glutamate release from LPS-treated BV-2 cells.[58]

Much larger number of studies have been concerned with PPARγ, a well-known target of anti-diabetic drugs that improve the insulin sensitivity of several tissues such as the muscle, the liver, and the adipose tissue. PPARγ is constitutively expressed in rat primary microglia, and application of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), a natural ligand of PPARγ, inhibits the expression of iNOS and TNF-α induced by LPS and/or IFN-γ.[59] Similar effects were observed with synthetic PPARγ agonists such as rosiglitazone and pioglitazone in mouse primary microglia.[60] The mechanisms of the actions of PPARγ agonists may include the induction of SOCS1 expression and the resultant inhibition of JAK/STAT signaling[61] and the blockade of p38 mitogen-activated protein kinase (MAPK) activation.[62,63] In addition, similar to the case with PPARα agonists,[56] PPARγ agonists suppressed the production of IL-12 family cytokines such as

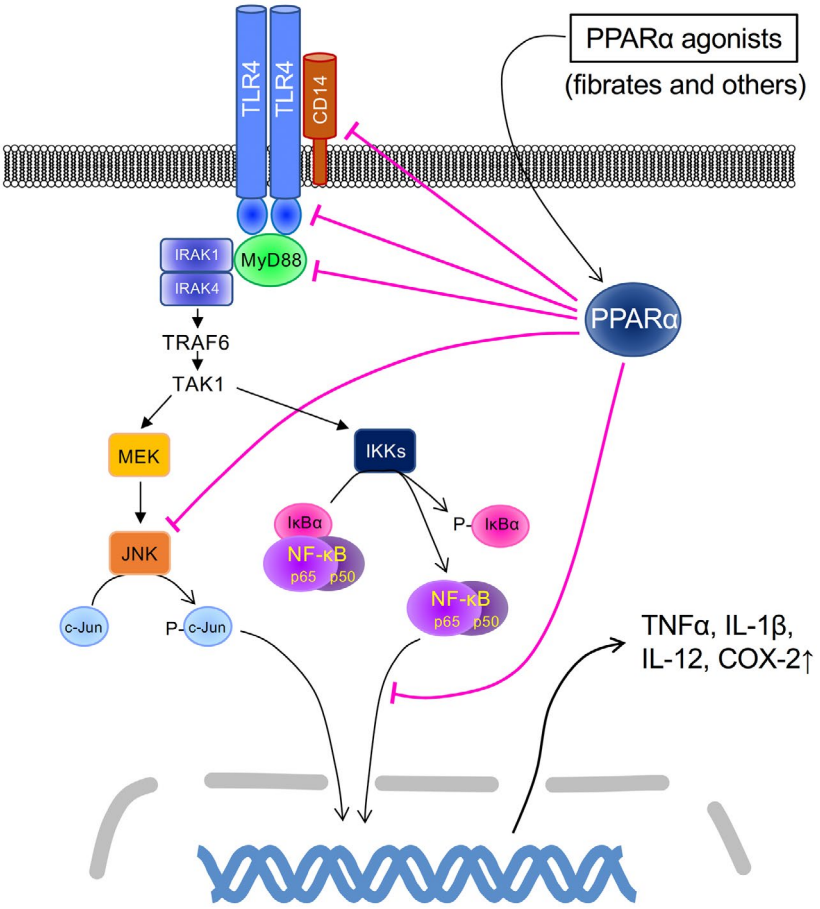

FIGURE 3 Peroxisome proliferator-activated receptor (PPARα) stimulation reduces the inflammatory responses in microglia. Activation of PPARα in microglia inhibits TLR4-mediated signaling by decreasing the expression of signaling components such as toll-like receptor (TLR4), CD14, and MyD88. In addition, PPARα prevents c-Jun *N*-terminal kinase (JNK)-dependent c-Jun phosphorylation and nuclear translocation of NF-κB, both of which mediate the transcription of pro-inflammatory factors

IL-12, IL-23, and IL-27 in mouse primary microglia stimulated by LPS or IFN-γ/TNF-α.[64] CD200R1 expressed in microglia restrains microglial activation via the interaction with CD200 expressed in neurons, and Dentesano et al[65] showed that 15d-PGJ_2 prevented the downregulation of CD200R1 in LPS/ IFN-γ-stimulated mouse primary microglia. Taken together, these findings suggest that PPARγ agonists produce anti-inflammatory actions in microglia (Figure 4A). By contrast, Ji et al[66] reported beneficial effects of a PPARγ antagonist T0070907. That is, T0070907 inhibited the expression of pro-inflammatory factors including iNOS, IL-1β, and TNF-α, while increasing the expression of IL-4, insulin-like growth factor-1 and transforming growth factor-β, in LPS-stimulated rat primary microglia. These effects of the PPARγ antagonist may be related to the enhancement of autophagic responses via the activation of LKB1/Akt signaling pathway.[66]

Potential anti-inflammatory effects of PPARγ agonists demonstrated in vitro have promoted investigations of the therapeutic effects of these compounds on various CNS disorders. Ischemic brain injury has been one of the main focuses,[67] and thiazolidine analogs including pioglitazone were shown to inhibit microglial activation and brain tissue damage induced by transient focal ischemia in rats[68,69] and mice.[70] The therapeutic effects were associated with the inhibition of IL-1β upregulation in microglia/macrophages.[68] Later studies suggested that the conversion of microglial phenotypes into anti-inflammatory states contributed to the effects of PPARγ agonists under ischemic conditions (Figure 4A,B). For example, PPARγ in the hippocampal CA1 region after transient ischemia was mainly expressed in microglia, and rosiglitazone increased the expression of anti-inflammatory cytokines IL-4 and IL-13.[71] Rosiglitazone was also found to induce microglial expression of a scavenger receptor CD36 (via the induction of 5-lipoxygenase expression and lipoxin A_4 production in neurons) involved in the resolution of inflammation after permanent focal ischemia in mice.[72] Rosiglitazone-induced "M2" polarization of microglia characterized by CD206 expression may also contribute to the promotion of oligodendrogenesis and the long-term maintenance of white matter integrity after transient focal ischemia in mice.[73] The effects of PPARγ agonists have also been examined in hemorrhagic stroke models in neonatal rats[74] as well as adult mice and rats.[75] In these studies, the upregulation of CD36 expression in microglia/macrophages and the resultant enhancement of hematoma resolution by phagocytosis are considered to mediate the therapeutic effects of rosiglitazone and 15d-PGJ_2. Physical trauma is another cause of acute brain injury, and PPARγ agonists such as rosiglitazone and pioglitazone were effective in inhibiting microglial activation and preventing brain tissue lesion after cortical impact-induced traumatic brain injury in mice and rats.[76,77]

Neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease are also important subjects of PPARγ research. When transgenic mice with APP mutation (APPV717I mice) were treated with pioglitazone, the number of activated microglia in the

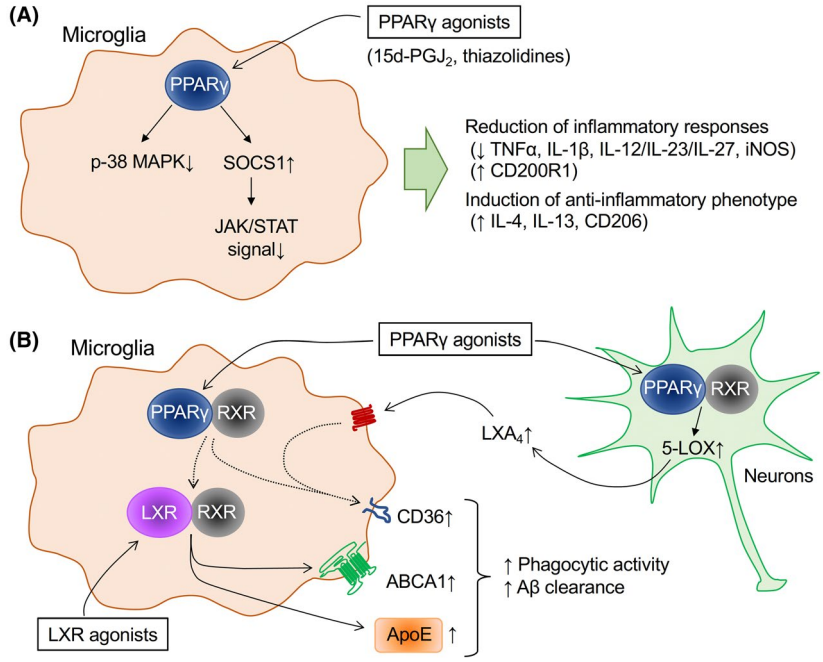

FIGURE 4 Peroxisome proliferator-activated receptor (PPARγ) stimulation reduces the inflammatory responses while enhances the phagocytic activity of microglia. (A) Activation of PPARγ inhibits p38 MAPK activation and also induces the expression of SOCS1, an inhibitor of Janus kinase (JAK)/ signal transducers and activators of transcription (STAT) signaling, which leads to the induction of anti-inflammatory phenotype as well as the reduction of inflammatory responses of microglia. (B) PPARγ agonists increase the expression of CD36 in microglia, via neuronal PPARγ -mediated induction of 5-lipoxygenae (5-LOX) expression and resultant production of lipoxin A_4 (LXA_4) as well as via microglial PPARγ stimulation. PPARγ stimulation in microglia also increases the expression of ABCA1 and ApoE in an LXR-dependent manner. Direct stimulation of LXR is similarly effective in upregulating ABCA1 and ApoE in microglia. These upregulated molecules promote the phagocytic clearance of Aβ

hippocampus and the cortex decreased. Concomitantly, amyloid deposits in these brain regions and the amount of soluble $A\beta_{1\text{-}42}$ also decreased.[78] Examinations of the mechanisms of the actions of pioglitazone in primary microglia showed that the upregulation of CD36 induced by PPARγ in cooperation with RXRα may promote the phagocytic clearance of Aβ by microglia.[79] Another study using transgenic mice with the mutations in APP and presenilin 1 (APPswe/PS1Δe9 mice) suggested that the recruitment of LXR-regulated genes such as ApoE and ATP-binding cassette transporter A1 (ABCA1) via PPARγ stimulation by pioglitazone promoted the degradation of Aβ by microglia. At the same time, PPARγ stimulation promoted the phenotype conversion of microglia from a pro-inflammatory state into an anti-inflammatory state, which allowed the phagocytic clearance of Aβ.[80] Potential therapeutic effects of PPARγ agonists on Parkinson's disease have been examined in MPTP-treated mice or 6-OHDA-treated rats. Dehmer et al[81] showed that PPARγ was expressed in the striatum and the substantia nigra of vehicle- and MPTP-treated mice and that pioglitazone reduced microglial activation in both brain regions and abrogated the loss of dopaminergic neurons in the substantia nigra. Similar effect of PPARγ agonist on MPTP-treated mice was demonstrated by a study using rosiglitazone.[82] In addition, a partial PPARγ agonist GW610742X as well as a full PPARγ agonist pioglitazone attenuated microglial activation and protected dopaminergic neurons in the substantia nigra of 6-OHDA-treated rats.[83] The mechanisms of the therapeutic effect of PPARγ agonists on Parkinson's disease model may include the reduced production of pro-inflammatory cytokines,[84,85] the enhanced production of anti-inflammatory cytokines,[85,86] and the enhanced phagocytic activity[86] in microglia.

5 | LXRS

LXRα and LXRβ (NR1H3 and NR1H2, respectively), together with farnesoid X receptor (NR1H4), are comprised in NR1H subfamily of nuclear receptors. As the receptors for oxysterols, LXRs are known to regulate lipid homeostasis including the synthesis and the transport of cholesterol in the body,[87] but these receptors may also have other physiological functions. Indeed, both LXRα and LXRβ are expressed in rat primary microglia,[88] and stimulation of microglial LXRs by oxidized low-density lipoprotein or by the agonists such as 7-ketocholesterol and TO901317 suppressed the production of pro-inflammatory factors by LPS[88,89] and Aβ fragment.[90] The effect of LXR stimulation was enhanced by the copresence of RXR agonists, and the mechanisms of the action of LXR agonists involve the suppression of inhibitor of κB phosphorylation and degradation, followed by the inhibition of NF-κB recruitment.[88,89] Similarly, tormentic acid was shown to inhibit LPS-induced nuclear translocation of NF-κB p65 and expression of pro-inflammatory cytokines,

iNOS, and COX-2 in BV-2 cells, which was canceled by the knockdown of LXRα.[91] In another study, the inhibitory effect of an LXR agonist GW3965 on LPS-induced iNOS expression was shown to be mediated by the inhibition of histone 4 acetylation and the inhibition of NF-κB p50 binding to the iNOS promoter.[92] Moreover, transcriptomic profiling revealed that LXRβ is one of the key transcription factors regulating the expression of pro-inflammatory and anti-inflammatory gene clusters in disease-associated microglia.[93]

Based on the regulatory roles in brain lipid metabolism and brain inflammation, LXRs have been considered the potential therapeutic targets for several neurodegenerative disorders.[94] Particularly, Alzheimer's disease has been a focus of attention of LXR research, because the expression of ApoE is regulated by LXRs and also because the specific ApoE isoforms are associated with the occurrence of Alzheimer's disease.[95] Although LXRs expressed in neurons and astrocytes may contribute to the regulation of Alzheimer's disease pathology,[95] LXRs in microglia play critical roles in the clearance and the degradation of Aβ. Indeed, the phagocytic activity of Aβ-stimulated BV-2 cells was facilitated by an LXR agonist GW3965.[96] In addition, stimulation of LXRs by GW3965 increased the expression of ApoE and ABCA1 and also enhanced intracellular degradation of Aβ in microglia.[97] The effects of LXR agonists GW3965 and TO901317 were also tested in the mouse models of Alzheimer's disease such as Tg2576 mice and high-fat diet-loaded APP23 mice, respectively, and both drugs were effective in reducing Aβ burden in the brain and improving the behavioral performance of mice.[97,98] Conversely, APP/presenilin 1 transgenic mice displayed increased amyloid deposition in the brain, when either LXRα gene or LXRβ gene was deleted.[96]

Deletion of LXRβ gene was also shown to exacerbate the degeneration of dopaminergic neurons associated with the activation of microglia and astrocytes in the substantia nigra of the MPTP mouse model of Parkinson's disease.[99] On the other hand, GW3965 and TO901317 attenuated the inflammatory responses and rescued dopaminergic neurons from degeneration in MPTP-treated wild-type mice.[99,100] The effects of LXR agonists have also been tested in the experimental models of retinal disease. When TO901317 was administered to rd1 mice, an established model of retinitis pigmentosa, the drug suppressed the activation of microglia in the retina and delayed the apoptosis of photoreceptors.[101] TO901317 also inhibited the activation of microglia and the expression of pro-inflammatory cytokines after retinal ischemia-reperfusion in mice, although these effects may be indirectly mediated by the retained expression of ABCA1 in retinal ganglion cells.[102] Other examples demonstrating the anti-inflammatory and/or therapeutic effects of LXR agonists against CNS disorders include the effects of GW3965 and TO901317 on experimental allergic encephalomyelitis[92,103] and the effect of TO901317 on intracerebral hemorrhage[104] in mice.

6 | NUR77/NGFIB AND NURR1

NR4A subfamily of nuclear receptors includes Nur77/NGFIB (NR4A1), Nurr1 (NR4A2), and neuron-derived orphan receptor 1 (NR4A3). They have been classified as orphan nuclear receptors that do not have endogenous ligands for activation and are constitutively active. But several compounds with novel molecular entities or some kinds of old drugs were found to bind to these receptors and enhance their transcriptional activities, which facilitated the progress of researches on the pathophysiological roles of these nuclear receptors. Moreover, prostaglandins E_1 and A_1 were recently identified as the potential endogenous ligands for Nurr1.[105]

6-Mercaptopurine is a purine derivative with anticancer and immunosuppressant activities based on the inhibition of DNA replication and cellular proliferation. Besides these actions, this drug was reported to activate NR4A nuclear receptors.[106,107] In rat primary microglia and BV-2 microglial cells, 6-mercaptopurine inhibited LPS-induced production of TNF-α, and the mechanisms of this action involved the upregulation of Nur77 expression and the resultant inhibition of NF-κB recruitment as well as of histone H3 acetylation.[108] Proteomic analysis of LPS-stimulated primary microglia obtained from wild-type and Nur77-deficient mice revealed that various signaling pathways including TLRs, MAPKs, chemokines, and FcγR-mediated phagocytosis were modified by Nur77.[109] Indeed, microglia from Nur77-deficient mice exhibited enhanced production of pro-inflammatory cytokines such as IL-1β and IL-6 in response to LPS,[110] and Nur77 deficiency resulted in exacerbated inflammation and demyelination and worsened the clinical scores of experimental allergic encephalomyelitis.[110,111] Conversely, administration of a Nur77 agonist cytosporone B to wild-type mice alleviated the demyelination, inflammation, and neurological symptoms.[110] Cytosporone B was also found to attenuate the inflammatory responses and alleviate the pathology of MPTP-induced Parkinson's disease model in mice.[112] On the other hand, the role of Nur77 in the regulation of stroke pathology is controversial. The involvement of Nur77 in the suppression of NF-κB signaling has been demonstrated by small interfering RNA-mediated knockdown of Nur77 in an experimental model of intracerebral hemorrhage in mice,[113] whereas a study on ischemia-reperfusion injury in Nur77-deficient mice claimed that Nur77 interacted with NF-κB to promote its target gene transcription and exacerbated neuroinflammation.[114]

Nurr1 was initially identified as a Nur77-related nuclear receptor whose expression was predominant in the brain.[115] Nurr1 plays an essential role in the development of midbrain dopaminergic neurons,[116] but its expression is also found in various other regions of the adult CNS and is upregulated under several pathological conditions.[117,118] Nurr1 expression in normal brain is mainly found in neurons, but its expression in microglia was shown to increase after transient global ischemia in Mongolian gerbils[119] and intracerebral hemorrhage in mice,[120] suggesting the involvement of this nuclear receptor in the regulation of microglial functions. Indeed, Nurr1 knockdown in BV-2 cells enhanced LPS-induced production of inflammatory factors such as TNF-α, IL-1β and iNOS. Detailed examinations on the roles of Nurr1 in microglia revealed that Nurr1 interacted with the p65 subunit of NF-κB phosphorylated by glycogen synthase kinase 3β and recruited the CoREST complex to repress the transcription of NF-κB-dependent pro-inflammatory

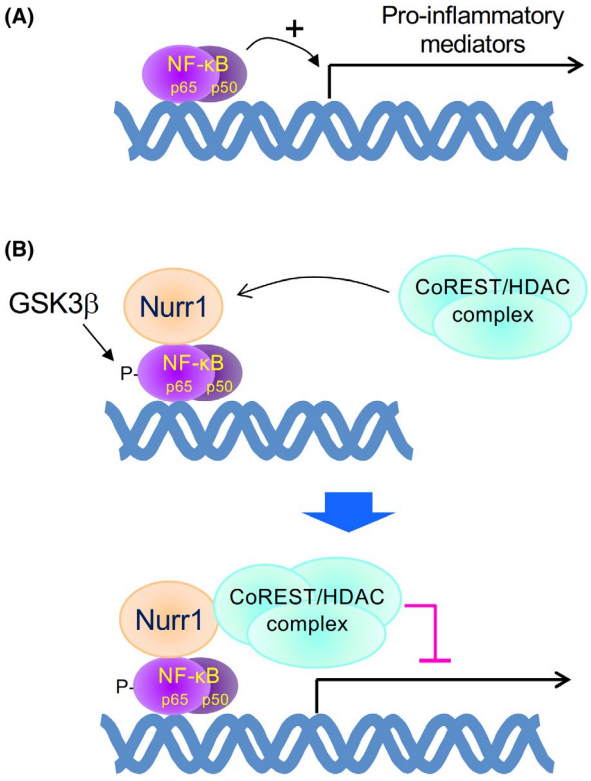

FIGURE 5 Nurr1 suppresses NF-κB-mediated inflammatory responses in microglia. (A) NF-κB complex composed of p65 and p50 subunits initiates the transcription of pro-inflammatory factors such as TNF-α, IL-1β and iNOS. (B) Nurr1 binds to the NF-κB p65 subunit phosphorylated by glycogen synthase kinase (GSK)3β and recruits the CoREST/histone deacetylase (HDAC) complex to repress the transcription of pro-inflammatory genes. Modified from Saijo et al[121] and De Miranda et al[130]

genes[121] (Figure 5). Interaction of Nurr1 with NF-κB p65 was also shown to inhibit α-synuclein-induced TNF-α production in BV-2 cells.[122] A recent study using BV-2 cells proved another mechanism of the action, in that Nurr1 directly bound to the RasGRP1 intron to reduce its expression, thereby inhibited the recruitment of Raf/MEK/ERK signaling and inflammatory cytokine production.[123] The regulatory roles of Nurr1 in microglia-mediated inflammation in vivo have been demonstrated by the findings that short hairpin RNA-mediated knockdown or conditional knockout of Nurr1 exacerbated the inflammatory pathology and the degeneration of dopaminergic neurons in the substantia nigra.[121,124] Xie et al[125] found that microRNA miR-145-5p negatively regulated the expression of Nurr1 in microglia. Intracerebroventricular infusion of anti-miR-145-5p upregulated the expression of Nurr1, inhibited the production of pro-inflammatory cytokines, and rescued rat brain from ischemia-reperfusion injury.[125]

Although Nurr1 has been considered a constitutively active nuclear receptor that does not require ligand binding for its activation,[126] several distinct classes of compounds were recently reported to act as Nurr1 agonists. These compounds were tested for their potential therapeutic effects against several CNS disorders.[127] For example, daily oral administration of a Nurr1 agonist SA00025 inhibited the degeneration of dopaminergic neurons and the activation of microglia in a rat model of Parkinson's disease model based on intranigral injection of poly(I:C) and intrastriatal injection of 6-OHDA.[128] Several 3,3′-diindolylmethane derivatives have been reported to exhibit the specific activity on NR4A subfamily, and particularly, 1,1-bis(3′-indolyl)-1-(*p*-chlorophenyl)methane (C-DIM12) is a high-affinity agonist of Nurr1.[129] In fact, C-DIM12 inhibited LPS-induced expression of NF-κB-regulated genes in BV-2 cells, at least in part by stabilizing the binding of Nurr1 with the CoREST complex.[130] In the MPTP-induced mouse model of Parkinson's disease, daily oral administration of C-DIM12 normalized the expression of NF-κB-regulated genes, inhibited the proliferation and the activation of microglia, and prevented the degeneration of dopaminergic neurons.[131,132] Another study has identified 4-amino-7-chloroquine derivatives such as amodiaquine and chloroquine as Nurr1 agonists.[133] As expected, amodiaquine inhibited LPS-induced inflammatory gene expression in BV-2 cells and prevented microglial activation in the substantia nigra and ameliorated the neurological functions of 6-OHDA hemi-parkinsonian mice.[133] We have demonstrated that daily intraperitoneal administration of amodiaquine after the induction of intracerebral hemorrhage in mice suppressed microglial activation around the hematoma, inhibited the upregulation of several inflammatory factors such as IL-1β, CCL2 and CXCL2, and alleviated the neurological deficits.[120] A study using HX600, an agonist of RXR-Nurr1 heterodimer complex, demonstrated that the compound inhibited the production of various inflammatory mediators in LPS-stimulated BV-2 cells. The same study also demonstrated that the compound suppressed the activation of microglia and reduced the brain injury after permanent middle cerebral artery occlusion in mice.[134] Overall, these findings suggest that Nurr1 is a promising candidate for the therapeutic drug targets that regulate inflammatory responses in the brain.

7 | CLOSING REMARKS

Nuclear receptors are well known to regulate the gene expression and alter the functions of various tissues and organs in response to vitamins (such as vitamin D and vitamin A derivatives), hormones (such as thyroid hormone and steroid hormones), and other endogenous/exogenous substances. Based on these properties, the ligands of several nuclear receptors are widely used for the treatments of systemic disorders, such as glucocorticoids for immune and inflammatory diseases, PPARα agonists for hyperlipidemia, and PPARγ agonists for diabetes. On the other hand, the last two decades have seen a remarkable progress in the understanding of the roles of nuclear receptors in the regulation of pathological events in the CNS via the regulation of microglial functions. Various findings summarized in this article are consistent with the idea that nuclear receptor ligands can modify the phenotypes of microglia and afford the therapeutic effects on neurological disorders. Although clinical translation of the potential therapies for CNS disorders with nuclear

receptor ligands has been unsuccessful so far, various unexplored approaches including reconsideration of the experimental design and introduction of novel research strategies may lead to the effective therapies.[135] Elucidation of the roles of nuclear receptors and their endogenous ligands may also help understanding the regulatory mechanisms of the divergent phenotypes of microglia in the CNS.[3,4]

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[136,137]

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

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REFERENCES

1. Jha MK, Lee WH, Suk K. Functional polarization of neuroglia: Implications in neuroinflammation and neurological disorders. *Biochem Pharmacol*. 2016;103:1-16.
2. Du L, Zhang Y, Chen Y, Zhu J, Yang Y, Zhang HL. Role of microglia in neurological disorders and their potentials as a therapeutic target. *Mol Neurobiol*. 2017;54(10):7567-7584.
3. Holtman IR, Skola D, Glass CK. Transcriptional control of microglia phenotypes in health and disease. *J Clin Invest*. 2017;127(9):3220-3229.
4. Mesquida-Veny F, Del Río JA, Hervera A. Macrophagic and microglial complexity after neuronal injury. *Prog Neurogibol*. 2020;101970.
5. Saijo K, Crotti A, Glass CK. Regulation of microglia activation and deactivation by nuclear receptors. *Glia*. 2013;61(1):104-111.
6. Skerrett R, Malm T, Landreth G. Nuclear receptors in neurodegenerative diseases. *Neurobiol Dis*. 2014;72:104-116.
7. Barish GD, Downes M, Alaynick WA, et al. A nuclear receptor atlas: macrophage activation. *Mol Endocrinol*. 2005;19(10):2466-2477.
8. Liberman AC, Budziñski ML, Sokn C, Gobbini RP, Steininger A, Arzt E. Regulatory and mechanistic actions of glucocorticoids on T and inflammatory cells. *Front Endocrinol (Lausanne)*. 2018;9:235.
9. Yilmaz C, Karali K, Fodelianaki G, et al. Neurosteroids as regulators of neuroinflammation. *Front Neuroendocrinol*. 2019;55:100788.
10. Acosta-Martínez M. Shaping microglial phenotypes through estrogen receptors: relevance to sex-specific neuroinflammatory responses to brain injury and disease. *J Pharmacol Exp Ther*. 2020;375(1):223-236.
11. Holick MF, MacLaughlin JA, Clark MB, et al. Photosynthesis of previtamin D_3 in human skin and the physiologic consequences. *Science*. 1980;210(4466):203-205.
12. Cui X, Gooch H, Petty A, McGrath JJ, Eyles D. Vitamin D and the brain: genomic and non-genomic actions. *Mol Cell Endocrinol*. 2017;453:131-143.
13. Carlberg C, Bendik I, Wyss A, et al. Two nuclear signalling pathways for vitamin D. *Nature*. 1993;361(6413):657-660.
14. Hii CS, Ferrante A. The non-genomic actions of vitamin D. *Nutrients*. 2016;8(3):135.
15. Morgan JW, Kouttab N, Ford D, Maizel AL. Vitamin D-mediated gene regulation in phenotypically defined human B cell subpopulations. *Endocrinology*. 2000;141(9):3225-3234.
16. von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C. Vitamin D controls T cell antigen receptor signaling and activation of human T cells. *Nat Immunol*. 2010;11(4):344-349.
17. Neveu I, Naveilhan P, Menaa C, Wion D, Brachet P, Garabédian M. Synthesis of 1,25-dihydroxyvitamin D_3 by rat brain macrophages in vitro. *J Neurosci Res*. 1994;38(2):214-220.
18. Landel V, Stephan D, Cui X, Eyles D, Feron F. Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. *J Steroid Biochem Mol Biol*. 2018;177:129-134.
19. Nemere I, Garbi N, Hämmerling GJ, Khanal RC. Intestinal cell calcium uptake and the targeted knockout of the 1,25D_3-MARRS (membrane-associated, rapid response steroid-binding) receptor/PDIA3/Erp57. *J Biol Chem*. 2010;285(41):31859-31866.
20. Chen J, Olivares-Navarrete R, Wang Y, Herman TR, Boyan BD, Schwartz Z. Protein-disulfide isomerase-associated 3 (Pdia3) mediates the membrane response to 1,25-dihydroxyvitamin D_3 in osteoblasts. *J Biol Chem*. 2010;285(47):37041-37050.
21. Hur J, Lee P, Kim MJ, Cho YW. Regulatory effect of 25-hydroxyvitamin D_3 on nitric oxide production in activated microglia. *Korean J Physiol Pharmacol*. 2014;18(5):397-402.
22. Lefebvre d'Hellencourt C, Montero-Menei CN, Bernard R, Couez D. Vitamin D3 inhibits proinflammatory cytokines and nitric oxide production by the EOC13 microglial cell line. *J Neurosci Res*. 2003;71(4):575-582.
23. Dulla YA, Kurauchi Y, Hisatsune A, Seki T, Shudo K, Katsuki H. Regulatory mechanisms of vitamin D_3 on production of nitric oxide and pro-inflammatory cytokines in microglial BV-2 cells. *Neurochem Res*. 2016;41(11):2848-2858.
24. Boontanrart M, Hall SD, Spanier JA, Hayes CE, Olson JK. Vitamin D3 alters microglia immune activation by an IL-10 dependent SOCS3 mechanism. *J Neuroimmunol*. 2016;292:126-136.
25. Verma R, Kim JY. 1,25-Dihydroxyvitamin D_3 facilitates M2 polarization and upregulates TLR10 expression on human microglial cells. *NeuroImmunoModulation*. 2016;23(2):75-80.
26. Clarke J, Yaqubi M, Futhey NC, et al. Vitamin D regulates MerTK-dependent phagocytosis in human myeloid cells. *J Immunol*. 2020;205(2):398-406.
27. Djukic M, Onken ML, Schütze S, et al. Vitamin D deficiency reduces the immune response, phagocytosis rate, and intracellular killing rate of microglial cells. *Infect Immun*. 2014;82(6):2585-2594.
28. Garcion E, Sindji L, Montero-Menei C, Andre C, Brachet P, Darcy F. Expression of inducible nitric oxide synthase during rat brain inflammation: regulation by 1,25-dihydroxyvitamin D_3. *Glia*. 1998;22(3):282-294.
29. Nataf S, Garcion E, Darcy F, Chabannes D, Muller JY, Brachet P. 1,25 Dihydroxyvitamin D_3 exerts regional effects in the central nervous system during experimental allergic encephalomyelitis. *J Neuropathol Exp Neurol*. 1996;55(8):904-914.
30. Garcion E, Nataf S, Berod A, Darcy F, Brachet P. 1,25-Dihydroxyvitamin D_3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis. *Brain Res Mol Brain Res*. 1997;45(2):255-267.
31. Garcion E, Sindji L, Nataf S, Brachet P, Darcy F, Montero-Menei CN. Treatment of experimental autoimmune encephalomyelitis in

rat by 1,25-dihydroxyvitamin D_3 leads to early effects within the central nervous system. *Acta Neuropathol*. 2003;105(5):438-448.
32. Xu ML, Yu XJ, Zhao JQ, et al. Calcitriol ameliorated autonomic dysfunction and hypertension by down-regulating inflammation and oxidative stress in the paraventricular nucleus of SHR. *Toxicol Appl Pharmacol*. 2020;394:114950.
33. Cui C, Xu P, Li G, et al. Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: role of renin-angiotensin system. *Redox Biol*. 2019;26:101295.
34. Kim JS, Ryu SY, Yun I, et al. 1α,25-Dihydroxyvitamin D_3 Protects Dopaminergic Neurons in Rodent Models of Parkinson's Disease through Inhibition of Microglial Activation. *J Clin Neurol*. 2006;2(4):252-257.
35. Calvello R, Cianciulli A, Nicolardi G, et al. Vitamin D treatment attenuates neuroinflammation and dopaminergic neurodegeneration in an animal model of Parkinson's Disease, shifting M1 to M2 microglia responses. *J Neuroimmune Pharmacol*. 2017;12(2):327-339.
36. Ibi M, Sawada H, Nakanishi M, et al. Protective effects of 1α,25-$(OH)_2D_3$ against the neurotoxicity of glutamate and reactive oxygen species in mesencephalic culture. *Neuropharmacology*. 2001;40(6):761-771.
37. Lee PW, Selhorst A, Lampe SG, Liu Y, Yang Y, Lovett-Racke AE. Neuron-specific vitamin D signaling attenuates microglia activation and CNS autoimmunity. *Front Neurol*. 2020;11:19.
38. Maden M. Retinoic acid in the development, regeneration and maintenance of the nervous system. *Nat Rev Neurosci*. 2007;8(10):755-765.
39. Masiá S, Alvarez S, de Lera AR, Barettino D. Rapid, nongenomic actions of retinoic acid on phosphatidylinositol-3-kinase signaling pathway mediated by the retinoic acid receptor. *Mol Endocrinol*. 2007;21(10):2391-2402.
40. Aoto J, Nam CI, Poon MM, Ting P, Chen L. Synaptic signaling by all-trans retinoic acid in homeostatic synaptic plasticity. *Neuron*. 2008;60(2):308-320.
41. Zetterström RH, Lindqvist E, Mata de Urquiza A, et al. Role of retinoids in the CNS: differential expression of retinoid binding proteins and receptors and evidence for presence of retinoic acid. *Eur J Neurosci*. 1999;11(2):407-416.
42. Goncalves MB, Malmqvist T, Clarke E, et al. Neuronal RARβ signaling modulates PTEN activity directly in neurons and via exosome transfer in astrocytes to prevent glial scar formation and induce spinal cord regeneration. *J Neurosci*. 2015;35(47):15731-15745.
43. Schrage K, Koopmans G, Joosten EA, Mey J. Macrophages and neurons are targets of retinoic acid signaling after spinal cord contusion injury. *Eur J Neurosci*. 2006;23(2):285-295.
44. Matsushita H, Hijioka M, Hisatsune A, Isohama Y, Shudo K, Katsuki H. A retinoic acid receptor agonist Am 80 rescues neurons, attenuates inflammatory reactions, and improves behavioral recovery after intracerebral hemorrhage in mice. *J Cereb Blood Flow Metab*. 2011;31(1):222-234.
45. Dheen ST, Jun Y, Yan Z, Tay SS, Ling EA. Retinoic acid inhibits expression of TNF-α and iNOS in activated rat microglia. *Glia*. 2005;50(1):21-31.
46. Takaoka Y, Takahashi M, Kurauchi Y, et al. Retinoic acid receptor agonist Am 80 inhibits CXCL2 production from microglial BV-2 cells via attenuation of NF-κB signaling. *Int Immunopharmacol*. 2016;38:367-376.
47. Matsushita H, Hijioka M, Hisatsune A, Isohama Y, Shudo K, Katsuki H. Natural and synthetic retinoids afford therapeutic effects on intracerebral hemorrhage in mice. *Eur J Pharmacol*. 2012;683(1–3):125-131.
48. Matsushita H, Hijioka M, Ishibashi H, et al. Suppression of CXCL2 upregulation underlies the therapeutic effect of the retinoid Am 80 on intracerebral hemorrhage in mice. *J Neurosci Res*. 2014;92(8):1024-1034.
49. Goncalves MB, Clarke E, Hobbs C, et al. Amyloid β inhibits retinoic acid synthesis exacerbating Alzheimer disease pathology which can be attenuated by an retinoic acid receptor α agonist. *Eur J Neurosci*. 2013;37(7):1182-1192.
50. Kawahara K, Suenobu M, Ohtsuka H, et al. Cooperative therapeutic action of retinoic acid receptor and retinoid x receptor agonists in a mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2014;42(2):587-605.
51. Xu J, Storer PD, Chavis JA, Racke MK, Drew PD. Agonists for the peroxisome proliferator-activated receptor-α and the retinoid X receptor inhibit inflammatory responses of microglia. *J Neurosci Res*. 2005;81(3):403-411.
52. Ramanan S, Kooshki M, Zhao W, Hsu FC, Robbins ME. PPARα ligands inhibit radiation-induced microglial inflammatory responses by negatively regulating NF-κB and AP-1 pathways. *Free Radic Biol Med*. 2008;45(12):1695-1704.
53. Wang G, Namura S. Effects of chronic systemic treatment with peroxisome proliferator-activated receptor α activators on neuroinflammation induced by intracerebral injection of lipopolysaccharide in adult mice. *Neurosci Res*. 2011;70(2):230-237.
54. Xuan AG, Chen Y, Long DH, et al. PPARα agonist fenofibrate ameliorates learning and memory deficits in rats following global cerebral ischemia. *Mol Neurobiol*. 2015;52(1):601-609.
55. Lovett-Racke AE, Hussain RZ, Northrop S, et al. Peroxisome proliferator-activated receptor α agonists as therapy for autoimmune disease. *J Immunol*. 2004;172(9):5790-5798.
56. Xu J, Racke MK, Drew PD. Peroxisome proliferator-activated receptor-alpha agonist fenofibrate regulates IL-12 family cytokine expression in the CNS: relevance to multiple sclerosis. *J Neurochem*. 2007;103(5):1801-1810.
57. Schnegg CI, Kooshki M, Hsu FC, Sui G, Robbins ME. PPARδ prevents radiation-induced proinflammatory responses in microglia via transrepression of NF-κB and inhibition of the PKCα/MEK1/2/ERK1/2/AP-1 pathway. *Free Radic Biol Med*. 2012;52(9):1734-1743.
58. Lee WJ, Ham SA, Yoo H, et al. Activation of PPARδ attenuates neurotoxicity by inhibiting lipopolysaccharide-triggered glutamate release in BV-2 microglial cells. *J Cell Biochem*. 2018;119(7):5609-5619.
59. Bernardo A, Levi G, Minghetti L. Role of the peroxisome proliferator-activated receptor-γ (PPAR-γ) and its natural ligand 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 in the regulation of microglial functions. *Eur J Neurosci*. 2000;12(7):2215-2223.
60. Storer PD, Xu J, Chavis J, Drew PD. Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: implications for multiple sclerosis. *J Neuroimmunol*. 2005;161(1–2):113-122.
61. Park EJ, Park SY, Joe EH, Jou I. 15d-PGJ_2 and rosiglitazone suppress Janus kinase-STAT inflammatory signaling through induction of suppressor of cytokine signaling 1 (SOCS1) and SOCS3 in glia. *J Biol Chem*. 2003;278(17):14747-14752.
62. Xing B, Xin T, Hunter RL, Bing G. Pioglitazone inhibition of lipopolysaccharide-induced nitric oxide synthase is associated with altered activity of p38 MAP kinase and PI3K/Akt. *J Neuroinflammation*. 2008;5:4.
63. Ji H, Wang H, Zhang F, Li X, Xiang L, Aiguo S. PPARγ agonist pioglitazone inhibits microglia inflammation by blocking p38 mitogen-activated protein kinase signaling pathways. *Inflamm Res*. 2010;59(11):921-929.
64. Xu J, Drew PD. Peroxisome proliferator-activated receptor-γ agonists suppress the production of IL-12 family cytokines by activated glia. *J Immunol*. 2007;178(3):1904-1913.
65. Dentesano G, Serratosa J, Tusell JM, et al. CD200R1 and CD200 expression are regulated by PPAR-γ in activated glial cells. *Glia*. 2014;62(6):982-998.
66. Ji J, Xue TF, Guo XD, et al. Antagonizing peroxisome proliferator-activated receptor γ facilitates M1-to-M2 shift of microglia by

enhancing autophagy via the LKB1-AMPK signaling pathway. *Aging Cell*. 2018;17(4):e12774.
67. Ding Y, Kang J, Liu S, Xu Y, Shao B. The protective effects of peroxisome proliferator-activated receptor gamma in cerebral ischemia-reperfusion injury. *Front Neurol*. 2020;11:588516.
68. Sundararajan S, Gamboa JL, Victor NA, Wanderi EW, Lust WD, Landreth GE. Peroxisome proliferator-activated receptor-γ ligands reduce inflammation and infarction size in transient focal ischemia. *Neuroscience*. 2005;130(3):685-696.
69. Zhao Y, Patzer A, Gohlke P, Herdegen T, Culman J. The intracerebral application of the PPARγ -ligand pioglitazone confers neuroprotection against focal ischaemia in the rat brain. *Eur J Neurosci*. 2005;22(1):278-282.
70. Luo Y, Yin W, Signore AP, et al. Neuroprotection against focal ischemic brain injury by the peroxisome proliferator-activated receptor-γ agonist rosiglitazone. *J Neurochem*. 2006;97(2):435-448.
71. Lee CH, Park OK, Yoo KY, et al. The role of peroxisome proliferator-activated receptor γ, and effects of its agonist, rosiglitazone, on transient cerebral ischemic damage. *J Neurol Sci*. 2011;300(1–2):120-129.
72. Ballesteros I, Cuartero MI, Pradillo JM, et al. Rosiglitazone-induced CD36 up-regulation resolves inflammation by PPARγ and 5-LO-dependent pathways. *J Leukoc Biol*. 2014;95(4):587-598.
73. Han L, Cai W, Mao L, et al. Rosiglitazone promotes white matter integrity and long-term functional recovery after focal cerebral ischemia. *Stroke*. 2015;46(9):2628-2636.
74. Flores JJ, Klebe D, Rolland WB, Lekic T, Krafft PR, Zhang JH. PPARγ-induced upregulation of CD36 enhances hematoma resolution and attenuates long-term neurological deficits after germinal matrix hemorrhage in neonatal rats. *Neurobiol Dis*. 2016;87:124-133.
75. Zhao X, Sun G, Zhang J, et al. Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor γ in microglia/macrophages. *Ann Neurol*. 2007;61(4):352-362.
76. Yi JH, Park SW, Brooks N, Lang BT, Vemuganti R. PPARγ agonist rosiglitazone is neuroprotective after traumatic brain injury via anti-inflammatory and anti-oxidative mechanisms. *Brain Res*. 2008;1244:164-172.
77. Sauerbeck A, Gao J, Readnower R, et al. Pioglitazone attenuates mitochondrial dysfunction, cognitive impairment, cortical tissue loss, and inflammation following traumatic brain injury. *Exp Neurol*. 2011;227(1):128-135.
78. Heneka MT, Sastre M, Dumitrescu-Ozimek L, et al. Acute treatment with the PPARγ agonist pioglitazone and ibuprofen reduces glial inflammation and Aβ1-42 levels in APPV717I transgenic mice. *Brain*. 2005;128(Pt 6):1442-1453.
79. Yamanaka M, Ishikawa T, Griep A, Axt D, Kummer MP, Heneka MT. PPARγ/RXRα-induced and CD36-mediated microglial amyloid-β phagocytosis results in cognitive improvement in amyloid precursor protein/presenilin 1 mice. *J Neurosci*. 2012;32(48):17321-17331.
80. Mandrekar-Colucci S, Karlo JC, Landreth GE. Mechanisms underlying the rapid peroxisome proliferator-activated receptor-γ-mediated amyloid clearance and reversal of cognitive deficits in a murine model of Alzheimer's disease. *J Neurosci*. 2012;32(30):10117-10128.
81. Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB. Protection by pioglitazone in the MPTP model of Parkinson's disease correlates with IκBα induction and block of NFκB and iNOS activation. *J Neurochem*. 2004;88(2):494-501.
82. Schintu N, Frau L, Ibba M, et al. PPAR-gamma-mediated neuroprotection in a chronic mouse model of Parkinson's disease. *Eur J Neurosci*. 2009;29(5):954-963.
83. Sadeghian M, Marinova-Mutafchieva L, Broom L, et al. Full and partial peroxisome proliferation-activated receptor-γ agonists, but not δ agonist, rescue of dopaminergic neurons in the 6-OHDA parkinsonian model is associated with inhibition of microglial activation and MMP expression. *J Neuroimmunol*. 2012;246(1–2):69-77.
84. Carta AR, Frau L, Pisanu A, Wardas J, Spiga S, Carboni E. Rosiglitazone decreases peroxisome proliferator receptor-γ levels in microglia and inhibits TNF-α production: new evidences on neuroprotection in a progressive Parkinson's disease model. *Neuroscience*. 2011;194:250-261.
85. Pisanu A, Lecca D, Mulas G, et al. Dynamic changes in pro- and anti-inflammatory cytokines in microglia after PPAR-γ agonist neuroprotective treatment in the MPTPp mouse model of progressive Parkinson's disease. *Neurobiol Dis*. 2014;71:280-291.
86. Lecca D, Janda E, Mulas G, et al. Boosting phagocytosis and anti-inflammatory phenotype in microglia mediates neuroprotection by PPARγ agonist MDG548 in Parkinson's disease models. *Br J Pharmacol*. 2018;175(16):3298-3314.
87. Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. *Nat Rev Endocrinol*. 2018;14(8):452-463.
88. Kim OS, Lee CS, Joe EH, Jou I. Oxidized low density lipoprotein suppresses lipopolysaccharide-induced inflammatory responses in microglia: oxidative stress acts through control of inflammation. *Biochem Biophys Res Commun*. 2006;342(1):9-18.
89. Zhang-Gandhi CX, Drew PD. Liver X receptor and retinoid X receptor agonists inhibit inflammatory responses of microglia and astrocytes. *J Neuroimmunol*. 2007;183(1–2):50-59.
90. Lefterov I, Bookout A, Wang Z, Staufenbiel M, Mangelsdorf D, Koldamova R. Expression profiling in APP23 mouse brain: Inhibition of Abeta amyloidosis and inflammation in response to LXR agonist treatment. *Mol Neurodegener*. 2007;2:20.
91. Ma A, Wang Y, Zhang Q. Tormentic acid reduces inflammation in BV-2 microglia by activating the liver X receptor alpha. *Neuroscience*. 2015;287:9-14.
92. Secor McVoy JR, Oughli HA, Oh U. Liver X receptor-dependent inhibition of microglial nitric oxide synthase 2. *J Neuroinflammation*. 2015;12:27.
93. Gao T, Jernigan J, Raza SA, et al. Transcriptional regulation of homeostatic and disease-associated-microglial genes by IRF1, LXRβ, and CEBPα. *Glia*. 2019;67(10):1958-1975.
94. Courtney R, Landreth GE. LXR regulation of brain cholesterol: from development to disease. *Trends Endocrinol Metab*. 2016;27(6):404-414.
95. Kang J, Rivest S. Lipid metabolism and neuroinflammation in Alzheimer's disease: a role for liver X receptors. *Endocr Rev*. 2012;33(5):715-746.
96. Zelcer N, Khanlou N, Clare R, et al. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. *Proc Natl Acad Sci USA*. 2007;104(25):10601-10606.
97. Jiang Q, Lee CY, Mandrekar S, et al. ApoE promotes the proteolytic degradation of Aβ. *Neuron*. 2008;58(5):681-693.
98. Fitz NF, Cronican A, Pham T, et al. Liver X receptor agonist treatment ameliorates amyloid pathology and memory deficits caused by high-fat diet in APP23 mice. *J Neurosci*. 2010;30(20):6862-6872.
99. Dai YB, Tan XJ, Wu WF, Warner M, Gustafsson JÅ. Liver X receptor beta protects dopaminergic neurons in a mouse model of Parkinson disease. *Proc Natl Acad Sci USA*. 2012;109(32):13112-13117.
100. Paterniti I, Campolo M, Siracusa R, et al. Liver X receptors activation, through TO901317 binding, reduces neuroinflammation in Parkinson's disease. *PLoS One*. 2017;12(4):e0174470.
101. He X, Sun D, Chen S, Xu H. Activation of liver X receptor delayed the retinal degeneration of rd1 mice through modulation of the immunological function of glia. *Oncotarget*. 2017;8(19):32068-32082.
102. Li L, Xu L, Chen W, et al. Reduced annexin A1 secretion by ABCA1 causes retinal inflammation and ganglion cell apoptosis in a murine glaucoma model. *Front Cell Neurosci*. 2018;12:347.
103. Hindinger C, Hinton DR, Kirwin SJ, et al. Liver X receptor activation decreases the severity of experimental autoimmune encephalomyelitis. *J Neurosci Res*. 2006;84(6):1225-1234.

104. Wu CH, Chen CC, Lai CY, et al. Treatment with TO901317, a synthetic liver X receptor agonist, reduces brain damage and attenuates neuroinflammation in experimental intracerebral hemorrhage. *J Neuroinflammation*. 2016;13(1):62.
105. Rajan S, Jang Y, Kim CH, et al. PGE1 and PGA1 bind to Nurr1 and activate its transcriptional function. *Nat Chem Biol*. 2020;16(8):876-886.
106. Ordentlich P, Yan Y, Zhou S, Heyman RA. Identification of the antineoplastic agent 6-mercaptopurine as an activator of the orphan nuclear hormone receptor Nurr1. *J Biol Chem*. 2003;278(27):24791-24799.
107. Wansa KD, Harris JM, Yan G, Ordentlich P, Muscat GE. The AF-1 domain of the orphan nuclear receptor NOR-1 mediates trans-activation, coactivator recruitment, and activation by the purine anti-metabolite 6-mercaptopurine. *J Biol Chem*. 2003;278(27):24776-24790.
108. Huang HY, Chang HF, Tsai MJ, Chen JS, Wang MJ. 6-Mercaptopurine attenuates tumor necrosis factor-alpha production in microglia through Nur77-mediated transrepression and PI3K/Akt/mTOR signaling-mediated translational regulation. *J Neuroinflammation*. 2016;13(1):78.
109. Chen Y, Jin Y, Zhan H, et al. Proteomic analysis of the effects of Nur77 on lipopolysaccharide-induced microglial activation. *Neurosci Lett*. 2017;659:33-43.
110. Rothe T, Ipseiz N, Faas M, et al. The nuclear receptor Nr4a1 acts as a microglia rheostat and serves as a therapeutic target in autoimmune-driven central nervous system inflammation. *J Immunol*. 2017;198(10):3878-3885.
111. Wang LM, Zhang Y, Li X, et al. Nr4a1 plays a crucial modulatory role in Th1/Th17 cell responses and CNS autoimmunity. *Brain Behav Immun*. 2018;68:44-55.
112. Liu TY, Yang XY, Zheng LT, Wang GH, Zhen XC. Activation of Nur77 in microglia attenuates proinflammatory mediators production and protects dopaminergic neurons from inflammation-induced cell death. *J Neurochem*. 2017;140(4):589-604.
113. Wu X, Fu S, Liu Y, et al. NDP-MSH binding melanocortin-1 receptor ameliorates neuroinflammation and BBB disruption through CREB/Nr4a1/NF-κB pathway after intracerebral hemorrhage in mice. *J Neuroinflammation*. 2019;16(1):192.
114. Zhang YJ, Song JR, Zhao MJ. NR4A1 regulates cerebral ischemia-induced brain injury by regulating neuroinflammation through interaction with NF-κB/p65. *Biochem Biophys Res Commun*. 2019;518(1):59-65.
115. Law SW, Conneely OM, DeMayo FJ, O'Malley BW. Identification of a new brain-specific transcription factor, NURR1. *Mol Endocrinol*. 1992;6(12):2129-2135.
116. Zetterström RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T. Dopamine neuron agenesis in Nurr1-deficient mice. *Science*. 1997;276(5310):248-250.
117. Xing G, Zhang L, Zhang L, et al. Rat nurr1 is prominently expressed in perirhinal cortex, and differentially induced in the hippocampal dentate gyrus by electroconvulsive vs. kindled seizures. *Brain Res Mol Brain Res*. 1997;47(1–2):251-261.
118. Honkaniemi J, States BA, Weinstein PR, Espinoza J, Sharp FR. Expression of zinc finger immediate early genes in rat brain after permanent middle cerebral artery occlusion. *J Cereb Blood Flow Metab*. 1997;17(6):636-646.
119. Park JH, Ahn JH, Kim DW, et al. Altered Nurr1 protein expression in the hippocampal CA1 region following transient global cerebral ischemia. *Mol Med Rep*. 2020;21(1):107-114.
120. Kinoshita K, Matsumoto K, Kurauchi Y, Hisatsune A, Seki T, Katsuki H. A Nurr1 agonist amodiaquine attenuates inflammatory events and neurological deficits in a mouse model of intracerebral hemorrhage. *J Neuroimmunol*. 2019;330:48-54.
121. Saijo K, Winner B, Carson CT, et al. A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. *Cell*. 2009;137(1):47-59.
122. Shao QH, Yan WF, Zhang Z, et al. Nurr1: A vital participant in the TLR4-NF-κB signal pathway stimulated by alpha-synuclein in BV-2 cells. *Neuropharmacology*. 2019;144:388-399.
123. Oh M, Kim SY, Gil JE, et al. Nurr1 performs its anti-inflammatory function by regulating RasGRP1 expression in neuro-inflammation. *Sci Rep*. 2020;10(1):10755.
124. Dong J, Liu X, Wang Y, Cai H, Le W. *Nurr1*^{Cd11bcre} conditional knockout mice display inflammatory injury to nigrostriatal dopaminergic neurons. *Glia*. 2020;68(10):2057-2069.
125. Xie X, Peng L, Zhu J, et al. miR-145-5p/Nurr1/TNF-α signaling-induced microglia activation regulates neuron injury of acute cerebral ischemic/reperfusion in rats. *Front Mol Neurosci*. 2017;10:383.
126. Wang Z, Benoit G, Liu J, et al. Structure and function of Nurr1 identifies a class of ligand-independent nuclear receptors. *Nature*. 2003;423(6939):555-560.
127. Jakaria M, Haque ME, Cho DY, Azam S, Kim IS, Choi DK. Molecular Insights into NR4A2(Nurr1): an emerging target for neuroprotective therapy against neuroinflammation and neuronal cell death. *Mol Neurobiol*. 2019;56(8):5799-5814.
128. Smith GA, Rocha EM, Rooney T, et al. A Nurr1 agonist causes neuroprotection in a Parkinson's disease lesion model primed with the toll-like receptor 3 dsRNA inflammatory stimulant poly(I:C). *PLoS One*. 2015;10(3):e0121072.
129. Inamoto T, Papineni S, Chintharlapalli S, Cho SD, Safe S, Kamat AM. 1,1-Bis(3'-indolyl)-1-(p-chlorophenyl)methane activates the orphan nuclear receptor Nurr1 and inhibits bladder cancer growth. *Mol Cancer Ther*. 2008;7(12):3825-3833.
130. De Miranda BR, Popichak KA, Hammond SL, et al. The Nurr1 activator 1,1-Bis(3'-Indolyl)-1-(p-Chlorophenyl)methane blocks inflammatory gene expression in BV-2 microglial cells by inhibiting nuclear factor κB. *Mol Pharmacol*. 2015;87(6):1021-1034.
131. De Miranda BR, Popichak KA, Hammond SL, Miller JA, Safe S, Tjalkens RB. Novel para-phenyl substituted diindolylmethanes protect against MPTP neurotoxicity and suppress glial activation in a mouse model of Parkinson's disease. *Toxicol Sci*. 2015;143(2):360-373.
132. Hammond SL, Popichak KA, Li X, et al. The Nurr1 ligand, 1,1-bis(3'-Indolyl)-1-(p-Chlorophenyl)methane, modulates glial reactivity and is neuroprotective in MPTP-induced Parkinsonism. *J Pharmacol Exp Ther*. 2018;365(3):636-651.
133. Kim CH, Han BS, Moon J, et al. Nuclear receptor Nurr1 agonists enhance its dual functions and improve behavioral deficits in an animal model of Parkinson's disease. *Proc Natl Acad Sci USA*. 2015;112(28):8756-8761.
134. Loppi S, Kolosowska N, Kärkkäinen O, et al. HX600, a synthetic agonist for RXR-Nurr1 heterodimer complex, prevents ischemia-induced neuronal damage. *Brain Behav Immun*. 2018;73:670-681.
135. Moutinho M, Codocedo JF, Puntambekar SS, Landreth GE. Nuclear receptors as therapeutic targets for neurodegenerative diseases: lost in translation. *Annu Rev Pharmacol Toxicol*. 2019;59:237-261.
136. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS Guide to pharmacology in 2019: Updates and expansion to encompass the new guide to immunopharmacology. *Nucleic Acids Res*. 2018;46(D1):D1091-D1106.
137. Alexander SPH, Cidlowski JA, Kelly E, et al. The concise guide to pharmacology 2019/20: nuclear hormone receptors. *Br J Pharmacol*. 2019;176(Suppl 1):S229-S246.

How to cite this article: Katsuki H. Nuclear receptors of NR1 and NR4 subfamilies in the regulation of microglial functions and pathology. *Pharmacol Res Perspect*. 2021;9:e00766. https://doi.org/10.1002/prp2.766