Emerging roles of GPR109A in regulation of neuroinflammation in neurological diseases and pain

Kyle Taing, Lawrence Chen, Han-Rong Weng

Abstract
Neuroinflammation plays a critical role in the pathological process of multiple neurological disorders and pathological pain conditions. GPR109A, a G protein-coupled receptor, has emerged as an important therapeutic target for controlling inflammation in various tissues and organs. In this review, we summarized current data about the role of GPR109A in neuroinflammation. Specifically, we focused on the pharmacological features of GPR109A and signaling pathways used by GPR109A to ameliorate neuroinflammation and symptoms in Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, stroke, and pathological pain conditions.

Key Words: β-hydroxybutyrate, cytokines, HCAR2; lupus; neuroinflammation; neuropathic; niacin; nociception; synaptic

Introduction
Neuroinflammation, characterized by infiltration of leukocytes, activation of microglia and astrocytes, and overproduction of pro-inflammatory mediators in the nervous system, is a key pathological feature shared by numerous neurological diseases (D'Sabato et al., 2016; Bachiller et al., 2018). Controlling neuroinflammation has become an important approach to the prevention and treatment of cell death in Alzheimer’s disease (AD) (Muzio et al., 2021; Ahmad et al., 2022), Parkinson’s disease (PD) (Badanjak et al., 2021; Muzio et al., 2021), multiple sclerosis (Thompson and Ciccarelli, 2020; Healy et al., 2022), and stroke (Ahmad et al., 2014; Tschoe et al., 2020). Neuroinflammation is also implicated in abnormal neuronal activation along with the pain signaling pathway in pathological pain conditions (Chen et al., 2018; Lacagnina et al., 2021). Targeting microglial receptors or signaling molecules has been proven to be a powerful means to control neuroinflammation in neurological diseases and chronic pain (Bachiller et al., 2018; Chen et al., 2018; Muzio et al., 2021).

Accounting for approximately 10–15% of all cells in the brain, microglia have long been known to act as macrophages, the first line of immune defense, within the central nervous system by actively surveying their surrounding microenvironment (Nimmenjmer et al., 2005; Bachiller et al., 2018; Chen et al., 2018; Muzio et al., 2021). Microglial cells are activated upon the stimulation of a host of pro-inflammatory receptors, including chemokine receptors (CX3CR1), purinergic receptors (P2X4R, P2X7R, P2Y12, P2Y13), Toll-like receptor 4 (Kobayashi et al., 2008; Taves et al., 2013; Tsuda et al., 2013; Grace et al., 2014), and colony-stimulating factor 1 receptor (Guan et al., 2016; Yan et al., 2017). Activation of such receptors results in the production of pro-inflammatory mediators and microglial proliferation (Kobayashi et al., 2008; Taves et al., 2013; Tsuda et al., 2013; Grace et al., 2014; Guan et al., 2016; Yan et al., 2017). Much less is known about the anti-inflammatory receptors expressed on microglial cells. Emerging studies suggest that G-protein-coupled receptor 109A (GPR109A), an anti-inflammatory G-inhibitory (G-) protein-coupled receptor, regulates neuroinflammation in neurological diseases and chronic pain by regulating microglial activation. In this review, we will first introduce the history and pharmacological features of GPR109A. We will then discuss mechanisms and molecular pathways involving GPR109A within the microglia as well as how GPR109A may play a role in regulating neuroinflammation in neurological diseases and pathological pain conditions.

Search Strategy
PubMed and Google Scholar databases with default settings and no restrictions were used to search the literature in this review. “GPR109A” and each of its aliases (“Acid Receptor 2 (HCAR2)”, “Niacin Receptor 1 (NIACR1)”, “HM74a”, “HM74b”, and “PUMA-G”) were used as key words to search the literature regarding the nature of GPR109A on the databases. To obtain the literature specific to the roles of GPR109A in neurological disorders and pain, we searched the databases with “GPR109A” or one of its aliases (“Acid Receptor 2 (HCAR2)”, “Niacin Receptor 1 (NIACR1)”, “HM74a”, “HM74b”, and “PUMA-G”) in combination with “Alzheimer’s”, or “Parkinson’s”, or “multiple sclerosis”, or “stroke”, or “ischemia or ischemic”, or “Huntington’s”, or “epilepsy or epileptic”, or “neuropathy or neuropathic”, or “neuroinflammation or inflammatory”, or “cytokine”, or “glial”, or “astrocyte”, or “microglia”, or “pain”. Since no literature was found regarding the role of GPR109A in Huntington’s disease or epilepsy, our review focuses on its role in Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, stroke, and pathological pain conditions.

History and the Pharmacological Features of GPR109A
In 2003, three research groups independently discovered that GPR109A, an orphan G-protein-coupled receptor (GPCR), has a high affinity for niacin (also known as nicotinic acid and Vitamin B3) (Soga et al., 2003; Tunaru et al., 2003b; Wise et al., 2003b; Offermanns et al., 2011). This receptor was deorphanized two years later when the endogenous ligand ketone body β-hydroxybutyrate (BHB) was found (Taggart et al., 2005). This receptor is also known as hydroxycarboxylic acid receptor 2 (HCAR2), niacin receptor 1 (NIACR1), HM74a, HM74b, and PUMA-G (Tunaru et al., 2003a; Chai et al., 2013). The gene coding GPR109A (HCAR2) is located on chromosome 12 (Band 12q24.31) in humans (Zeilner et al., 2005). It has been shown in human embryonic kidney 293 (HEK293) cells that GPR109A forms either homo-dimers or hetero-dimers with GPR109B in both the plasma membrane and endoplasmic reticulum (Mandrika et al., 2010). GPR109B has more than 95% sequence homology with GPR109A with a difference in only 16 amino acids across their sequences (Wise et al., 2003b). The homo- or hetero-dimerization state is not altered by ligand binding. There is no significant difference in agonist-mediated cAMP signaling between cells with homo- and hetero-dimerization, and the dimerization is a constitutive process occurring early during biosynthesis (Mandrika et al., 2010). GPR109A embodies a highly conservative GPCR structure coupled with an inhibitory G protein (Wise et al., 2003a; Tuteja et al., 2017). GPR109A is localized to the cellular membranes of cells and expressed in multiple tissues and cell types (Table 1).

The most notable agonist for GPR109A is niacin, which lends its name to one of the receptor’s aliases (niacin receptor 1). The other endogenous agonists of GPR109A are BHB and butyrate, which are ketone bodies produced during ketosis (Tunaru et al., 2003a; Lee et al., 2020). BHB has a higher potency of BHB required...
Roles of GPR109A in Neurological Diseases

GPR109A was originally recognized to perform three key functions in the body: (1) inhibiting lipolysis (breakdown of fats) in adipocytes (Digby et al., 2016), (2) mediating mcA-II-induced apoptosis in mature neutrophils (Kostylina et al., 2008), and (3) suppressing atherogenesis in patients with type 2 diabetes (Dobbins et al., 2010). More recently, GPR109A agonists have been demonstrated to modify Aβ metabolism and neuroinflammation (Muzio et al., 2021). Recent studies have reported the beneficial effects of BHB and niacin in the management of PD in animal models and clinical studies. Specifically, BHB improves the motor dysfunction and dopamine depletion of the PD rat model induced by intranigral injection of lipopolysaccharide (LPS) (Fu et al., 2015). These beneficial effects are accompanied by the inhibition of microglial over-activation as well as the promotion of anti-inflammatory and anti-apoptotic signaling pathways in the substantia nigra (SJW et al., 2018). In primarily mesencephalic mixed neuron-glial cultures, activation of GPR109A with niacin attenuates microglial activation and levels of phosphorylated nuclear factor kappa B (NF-κB) (Park et al., 2019). Further, niacin induces the LPS-induced protein and mRNA expression of various pro-inflammatory mediators, such as interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6) in cultures of monocytes (Liu et al., 2014). Treatment of GPR109A knock-out mice with niacin induces the LPS-induced protein and mRNA expression of various pro-inflammatory mediators and increases the LPS-induced protein and mRNA expression of various pro-inflammatory mediators (Fu et al., 2015). Further study on the changes in molecular signaling pathways in patients receiving niacin supplements have a higher improvement ratio of M2:M1 macrophages as well as improved quality of life (Wakade et al., 2018). Multiple sclerosis (MS) is an autoimmune-initiated inflammatory demyelination of the central nervous system, commonly presenting with various neurologic symptoms (Healy et al., 2022). Most treatments are disease-modifying agents aimed to decrease the likelihood of relapses and delay the progression of neurodegeneration. A recent study has recognized that activation of glial cells plays an important role in the disease progressive process (Healy et al., 2022). One specific medicine approved by the FDA in 2013 for treating patients with relapsing MS is dimethyl fumarate (DMF) (Venci and Gandhi, 2013), which was previously used to treat psoriasis (Venci and Gandhi, 2013). DMF is converted to its active metabolite, monomethyl fumarate (MMF), which is known to be a nicotinic receptor agonist (Tang et al., 2008; Hanson et al., 2010). Furthermore, the authors found that HT22 hippocampal cells treated with BHB have an improved mitochondrial respiratory function and increased adenosine 5'-triphosphate production. The beneficial effects of GPR109A were further demonstrated in mouse neuroinflammation models (Fu et al., 2015). In this study, sodium butyrate was used to activate GPR109A. The authors found that sodium butyrate produces protective effects on Aβ-induced cell injury. Aβ levels and production of Aβ-induced reactive oxygen species (ROS) are suppressed in cells treated with sodium butyrate. Sodium butyrate treatment increases the amount of NEP, GPR109A, and brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family that confers protective effects against AD. These effects are attenuated when the Gi protein is inhibited by pertussis toxin, consistent with the nature of Gi GPCRs (Sun et al., 2020). Table 1 summarizes the beneficial effects of GPR109A agonists as a promising scaffold for therapeutic development.

Parkinson’s disease PD clinically manifests with tremors, rigidity, gait abnormalities, and late-onset cognitive dysfunction. The PD pathology is characterized by decreased dopamine neuronal density due to the degeneration of dopamine neurons in the substantia nigra (SN) and ventral tegmental area (VTA) (Brown et al., 2003; Won et al., 2013). BHB have an improved mitochondrial respiratory function and increased adenosine 5'-triphosphate production. The beneficial effects of GPR109A were further demonstrated in mouse neuroinflammation models (Fu et al., 2015). In this study, sodium butyrate was used to activate GPR109A. The authors found that sodium butyrate produces protective effects on Aβ-induced cell injury. Aβ levels and production of Aβ-induced reactive oxygen species (ROS) are suppressed in cells treated with sodium butyrate. Sodium butyrate treatment increases the amount of NEP, GPR109A, and brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family that confers protective effects against AD. These effects are attenuated when the Gi protein is inhibited by pertussis toxin, consistent with the nature of Gi GPCRs (Sun et al., 2020). Table 1 summarizes the beneficial effects of GPR109A agonists as a promising scaffold for therapeutic development.

Multiple sclerosis (MS) is an autoimmunity-initiated inflammatory demyelination of the central nervous system, commonly presenting with various neurologic symptoms (Healy et al., 2022). Most treatments are disease-modifying agents aimed to decrease the likelihood of relapses and delay the progression of neurodegeneration. A recent study has recognized that activation of glial cells plays an important role in the disease progressive process (Healy et al., 2022). One specific medicine approved by the FDA in 2013 for treating patients with relapsing MS is dimethyl fumarate (DMF) (Venci and Gandhi, 2013), which was previously used to treat psoriasis (Venci and Gandhi, 2013). DMF is converted to its active metabolite, monomethyl fumarate (MMF), which is known to be a nicotinic receptor agonist (Tang et al., 2008; Hanson et al., 2010). Furthermore, the authors found that HT22 hippocampal cells treated with BHB have an improved mitochondrial respiratory function and increased adenosine 5'-triphosphate production. The beneficial effects of GPR109A were further demonstrated in mouse neuroinflammation models (Fu et al., 2015). In this study, sodium butyrate was used to activate GPR109A. The authors found that sodium butyrate produces protective effects on Aβ-induced cell injury. Aβ levels and production of Aβ-induced reactive oxygen species (ROS) are suppressed in cells treated with sodium butyrate. Sodium butyrate treatment increases the amount of NEP, GPR109A, and brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family that confers protective effects against AD. These effects are attenuated when the Gi protein is inhibited by pertussis toxin, consistent with the nature of Gi GPCRs (Sun et al., 2020). Table 1 summarizes the beneficial effects of GPR109A agonists as a promising scaffold for therapeutic development.

Table 1: GPR109A expression in tissues and cellular types

| Immune system | Nervous system | Others |
|---------------|---------------|--------|
| Keratinocytes (Hanson et al., 2010) | Astrocytes* (Rezq and Abdul-Rahman, 2016) | Adipocytes (Digby et al., 2016) |
| Langerhans cell (Maciejewski-Lenoir et al., 2006) | Microglia (Fu et al., 2014; Rahman et al., 2014; Viatzenko-Karpinski et al., 2022) | Hepatocytes (Jadeja et al., 2013) |
| Lymphocytes (Liu et al., 2014) | Neurons (Rezq and Abdul-Rahman, 2016; Boccella et al., 2019) | Intestinal epithelial cells (Ghimire et al., 2021) |
| Macrophages (Knowles et al., 2006; Wakade et al., 2018) | Retinal pigment epithelial cells (Martin et al., 2009) | Kidney podocytes (Felizardo et al., 2019) |
| Monocytes (Liu et al., 2014) | Schwann cells (Boccella et al., 2019) | Mammary epithelial cells (Guo et al., 2021b) |
| Multinucleated osteoclasts (Chen et al., 2021) | Satellite cells (Boccella et al., 2019) | |
| Neutrophils (Kostyla et al., 2008) | | |

*Microglia in the cortex (Rahman et al., 2014), rostral ventrolateral medulla (Rezq and Abdul-Rahman, 2016) and spinal dorsal horn (Viatzenko-Karpinski et al., 2022), and BV-2 microglial cell line (Fu et al., 2014),* astrocytes in rostral ventrolateral medulla (Rezq and Abdul-Rahman, 2016); *Neurons in rostral ventrolateral medulla (Rezq and Abdul-Rahman, 2016)* and dorsal root ganglions (Boccella et al., 2019).
neurons in mice with EAE (Parodi et al., 2015). MMF reduces monocyte transendothelial migration and adhesion to inflamed human brain endothelial cells (Lim et al., 2016). Activation of mRNA nuclear factor (erythroid-derived) related factor 2 (Nrf2) has been linked to mechanisms of action of DMF/MMF with discrepant reports. DMF was found to produce protective effects on oligodendrocytes, myelin, axons, and neurons in mice with EAE, and reduce oxidative stress via activation of the Nrf2 antioxidant pathway (Chen et al., 2014). Nrf2 has been found in the spinal cord in mice receiving BHB via a mini-osmotic pump reaches a concentration of 250 mg/ml, and the production of prostaglandin D2 (PGD2) by cyclooxygenase 1 (COX-1) and the molecular pathways of inflammasomes are completely suppressed (Schulze-Topphoff et al., 2016). Further investigation is required to resolve such discrepancies.

**Stoke**

Stoke refers to a blockage or bleeding of the blood vessels that either interrupts or reduces the supply of blood to the brain. After acute stroke episodes, neuroinflammation further injures neurons, glia, vascular cells, and extracellular matrix scaffolding (Jayara et al., 2019). In an ischemic mouse model induced by the distal middle cerebral artery occlusion, it has been shown that infarcts in mice on ketogenic diets or receiving BHB or nicotinic acid are significantly smaller than those in control groups (Ramharter et al., 2014). More importantly, this study demonstrated that activation of GPCR109A on monocytes and/or macrophages produces such protective effects via the production of prostaglandin D2 (PGD2) by cyclooxygenase 1 (COX-1) and the molecular pathways of inflammasomes (Yan et al., 2017). The binding site of GPCR109A in stroke is in line with other studies where the effects of BHB, niacin or DMF/MMF were tested on animal middle cerebral artery occlusion stroke models. It was reported that intravenous injection of BHB improves neurological scores and reduces infarct volume after ischemia via upregulating the BHB transporter (sodium-coupled monocarboxylate transporter 1) and activating the extracellular-signal-regulated kinase/cyclic AMP-response element-binding protein/endothelial nitric oxide synthase pathway (Yan et al., 2021). Intravenous injection of BHB significantly reduces cerebral infarct area, edema formation, lipid peroxidation, and neurological deficits (Suzuki et al., 2002). Animals treated with Niapsan, an extended-release formulation of niacin, have reduced infarct areas and improved functional recovery after stroke (Shehadah et al., 2010). Niapsan treatment reduces levels of apoptotic markers (TUNEL and cleaved caspase-3) and TNFα but raises levels of vascular endothelial growth factor and phosphorylated phosphatidylinositol-3 kinase in the ischemic brain (Rahman et al., 2016). Synaptic plasticity and motor axon growth are also promoted by niacin treatment (Cui et al., 2010). Many studies have shown that DMF/MMF ameliorates areas of infarct and functional recovery (Cui et al., 2010). Neuroinflammation and oxidative stress are both attenuated by niacin treatment (Safari et al., 2019; Li et al., 2021b). Such protective effects are associated with upregulation of the Nrf2 anti-oxidative and anti-inflammatory signaling pathway (Yan et al., 2019; Li et al., 2021b). Interestingly, GPCR109A mRNA levels were elevated in both the treated and untreated groups, suggesting that the upregulation in GPCR109A does not come with MMF therapy but with the initial stroke itself (Clausen et al., 2017).

**Roles of GPR109A in Pathological Pain**

Pain is one of the most common reasons people seek medical treatment, as well as a leading cause of disability and disease burden globally (Disease et al., 2018). Clinical management of chronic pain remains a challenge because currently available analgesics (including NSAIDs, antidepressants, anticonvulsants, and opioids) (Israel et al., 2021) are neither potent nor safe (Gregus et al., 2021; Israel et al., 2021). Accordingly, the development of novel analgesics with high potency and safety features is in great demand. It is widely accepted that pathologic pain occurs when neurons along the pain signals pathway are abnormally activated. Neurons in the spinal dorsal horn are part of the pain signaling pathway. Excessive activation of spinal dorsal horn neurons, termed central sensitization, is known to be the hallmark of pathologic pain (Woolf, 2011). Studies over the past two decades have demonstrated that neuroinflammation greatly modulates neuronal activities in the spinal dorsal horn. Glial cells can enhance neuronal activities through releasing pro-inflammatory cytokines [such as TNF-α (Kawasaki et al., 2008), IL-1β (Kawasaki et al., 2008; Yan and Weng, 2013), IL-6 (Kawasaki et al., 2008), IL-18 (Viatchenko-Karpinski et al., 2022)], and IL-1β leads to suppression of spinal glutamate transporter activity (Yan et al., 2017). So inhibition of GPCR109A reduces the activity of cathepsin B and the production of mature IL-1β and interleukin-18 (IL-18) in the spinal dorsal horn (Yan et al., 2017). In neuroinflammation, cathepsin B is critically engaged in the production of pro-inflammatory cytokines and the molecular pathways regulating the protein expression of GPCR109A is warranted.
Concluding Remarks

Neuroinflammation is a critical pathological process implicated in multiple neurological disorders including Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, stroke, and pathological pain conditions. Accumulating data have suggested that activation of GPR109A receptors ameliorates symptoms in these neurological disorders and chronic pain via suppressing pro-inflammatory signaling pathways and the production of pro-inflammatory mediators as well as enhancing anti-inflammatory signaling pathways (Table 2). The majority of available data on the role of GPR109A in neuroinflammation were derived from experiments where non-specific GPR109 agonists (such as niacin, BHB, and MMF) were used in combination with GPR109A knockout techniques to determine the contribution of GPR109A signaling. Upon administration of non-specific agonists, however, the compounding effects induced by signaling pathways other than the GPR109A signaling cannot be ruled out. Future studies to understand the in-depth biology of GPR109A will open new avenues to identify and develop novel therapeutic targets for the treatment of neuroinflammation-related neurological diseases and chronic pain.

Author contributions: Conception and design: HRW; literature search and manuscript writing: KT, LC, and HRW. All authors approved the final manuscript.

Conflicts of interest: The authors declare no conflicts of interest.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons AttributionNonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

References

Ahmad M, Dar NJ, Bhat ZS, Hussain A, Shah A, Liu H, Graham SH (2014) Inflammation in ischemic stroke: mechanisms, consequences and possible drug targets. CNS Neurol Disord Drug Targets 13:1378-1396.

Ahmad MA, Kareem O, Khutthar M, Akbar M, Haque MR, Iqubal A, Haider MF, Pottoo FH, Abulila FS, Al-Haidar MB, Alhajri N (2022) Neuroinflammation: a potential risk for dementia. Int J Mol Sci 23.

Bachiller S, Jimenez-Ferrer I, Paulus A, Yang Y, Swanberg M, Deierborg T, Boza-Serrano A (2018) Microglia in neurological diseases: a roadmap to brain disease-dependent-inflammation response. Front Cell Neurosci 12:488.

Badanjak K, Fiesmer S, Smajic S, Skupin A, Grunewald A (2021) The contribution of microglia to neuroinflammation in Parkinson’s disease. Int J Mol Sci 22:4676.

Boatman PD, Laurant B, Schrader TO, Kasem M, Johnson BR, Skinner P, Jung JK, Xu J, Cherrier MC, Webb PJ, Semple G, Sage CR, Knudsen J, Chen R, Luo WL, Caro L, Cote J, Lai E, Wagner J, Taggart AK, et al. (2012) (1aR,5aR)-1a,3,5,5a-Tetrahydro-1H-2,3-diazas-cyclopenta[4-carboxylic acid (MK-1903): a potent GPR109a agonist that lowers free fatty acids in humans. J Med Chem 55:3644-3666.

Boccella S, Guida F, De Logu F, De Gregorio D, Mazzitelli M, Belardo C, Iannotta M, Serra N, Nassi R, de Novellis V, Geppetti P, Maloiu S, Luongo L (2019) Ketones and pain: unexplored role of hydroxyl carboxylic acid receptor type 2 in the pathophysiology of neuropathic pain. FASEB J 33:1062-1073.

Table 2 | Summary of signaling molecules regulated by GPR109A

| Molecules enhanced by GPR109A activation | References |
|----------------------------------------|------------|
| SOD2 Pathologic pain                   | Qian et al., 2017 |
| FOXO3a Pathologic pain                | Qian et al., 2017 |
| PI3K Stroke                           | Shehadah et al., 2010 |
| VEGF Stroke                           | Shehadah et al., 2010 |
| PGD2 Stroke                           | Rahman et al., 2014 |
| HSP72 Stroke                          | Clausen et al., 2017 |
| IL-10 Stroke                          | Clausen et al., 2017 |
| NAD⁺ Multiple sclerosis               | Parodi et al., 2015 |
| AMPK Multiple sclerosis               | Parodi et al., 2015 |
| SIRT1 Multiple sclerosis              | Parodi et al., 2015 |
| Nrf-2 Multiple sclerosis              | Chen et al., 2014 |
| Ca²⁺ Multiple sclerosis               | Parodi et al., 2015 |
| NEP Alzheimer’s disease               | Wu et al., 2020 |
| BDNF Alzheimer’s disease              | Sun et al., 2020 |

| Molecules suppressed by GPR109A activation | References |
|-------------------------------------------|------------|
| IL-1β Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, pathologic pain | Fu et al., 2015; Parodi et al., 2015; Qian et al., 2017; Wu et al., 2020; Viatchenko-Karpinski et al., 2022 |
| TNF-α Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, pathologic pain | Shehadah et al., 2010; Fu et al., 2015; Parodi et al., 2015; Wu et al., 2020 |
| NF-κB Parkinson’s disease, multiple sclerosis, pathologic pain | Parodi et al., 2015 |
| IL-6 Alzheimer’s disease, Parkinson’s disease | Fu et al., 2015; Wu et al., 2020 |
| NLRP3 Pathologic pain                    | Qian et al., 2017 |
| p38 MAPK Pathologic pain                 | Viatchenko-Karpinski et al., 2022 |
| NR4a2 Multiple sclerosis                 | Parodi et al., 2015 |
| IL-18 Alzheimer’s disease, Parkinson’s disease | Qian et al., 2017; Viatchenko-Karpinski et al., 2022 |
| COX-2 Parkinson’s disease                | Fu et al., 2015 |
| lNOS Parkinson’s disease                 | Fu et al., 2015 |
| APP Alzheimer’s disease                  | Sun et al., 2020 |
| ROS Alzheimer’s disease                  | Sun et al., 2020 |
| Caspase 3 Stroke                        | Shehadah et al., 2010 |
| TUNEL                                   | Shehadah et al., 2010 |
| Hmx1 Multiple sclerosis                  | Parodi et al., 2015 |

APP: Amyloid precursor protein; BDNF: brain-derived neurotrophic factor; COX-2: cyclooxygenase 2; FOXO3a: transcription factor Fkh-related box class O 3a; GSK-3β: glycogen synthesis kinase-3β; HMox1: heme oxygenase 1; Hsp72: heat shock protein 72; IL: interleukin; iNOS: inducible nitric oxide synthase; NADPH oxidase (NQO): nicotinamide adenine dinucleotide phosphate; p38 MAPK: mitogen-activated protein kinase; NMDA-R: N-methyl-D-aspartic acid receptor; SLE: systemic lupus erythematosus.
