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

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Abstract

Neuroinflammation plays a critical role in the pathological process of multiple neurological disorders and pathological pain conditions. GPR109A, a Gi 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 (DiSabato 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 (Nimmerjahn 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 indicate that G-protein-coupled receptor 109A (GPR109A), an anti-inflammatory G-inhibitory (G$_i$) 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 neuroinflammatory", 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 B$_3$) (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 (Zellner 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$_i$ 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 to GPR109A than butyrate (Taggart et al., 2005). The EC$_{50}$ of BHB required

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Table 1 | GPR109A expression in tissues and cellular types

Immune system	Nervous system	Others
Keratinocytes (Hanson et al., 2010)	Astrocytes[s] (Rezq and Abdel-Rahman, 2016)	Adipocytes (Digby et al., 2010)
Langerhans cell (Maciejewski-Lenoir et al., 2006)	Microglia[*] (Fu et al., 2014; Rahman et al., 2014; Viatchenko-Karpinski et al., 2022)	Hepatocytes (Jadeja et al., 2019)
Lymphocytes (Liu et al., 2014)	Neurons[+] (Rezq and Abdel-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 (Kostylina et al., 2008)		

*Microglia in the cortex (Rahman et al., 2014), rostral ventrolateral medulla (Rezq and Abdel-Rahman, 2016) and spinal dorsal horn (Viatchenko-Karpinski et al., 2022), and BV-2 microglial cell line (Fu et al., 2014); [s]astrocytes in rostral ventrolateral medulla (Rezq and Abdel-Rahman, 2016); [+]Neurons in rostral ventrolateral medulla (Rezq and Abdel-Rahman, 2016) and dorsal root ganglions (Boccella et al., 2019).

for the activation of GPR109A is approximately 700 μM (Gille et al., 2008) while the concentration of BHB is 44 μM in the cerebrospinal fluid and 62 μM in the blood under physiological conditions in rats (Wang et al., 2017). Thus, the concentration of BHB in the body under normal conditions is not sufficient to activate GPR109A. However, short-term starvation was found to induce activation of GPR109A due to elevated endogenous BHB levels through ketosis (Boccella et al., 2019), as ketone body levels rise in individuals undergoing fasting. BHB levels can be raised to approximately 5 mM concentration also by nutritional ketosis (Koppel and Swerdlow, 2018). It is noteworthy that niacin, BHB, and butyrate are not selective agonists for GPR109A. In addition to having a high-affinity for GPR109A, niacin also shows a low-affinity for GPR109B. Furthermore, niacin is an NAD^{+} precursor, which is required for over 500 enzymatic reactions and plays key roles in the regulation of mitochondrial metabolism, inflammation, meiosis, autophagy, and apoptosis (Rajman et al., 2018). Besides binding to GPR109A, butyrate and BHB respectively activate GPR41 and GPR43 (Brown et al., 2003; Won et al., 2013). BHB also inhibits class I and IIa histone deacetylases to regulate gene expression (Shimazu et al., 2013), and it acts as a metabolite to increase mitochondrial adenosine 5'-triphosphate production (Sato et al., 1995) and bolster antioxidant defenses (McCarty et al., 2015).

Synthetic agonists for GPR109A include drugs such as acipimox and acifran, both of which are niacin derivatives and hypolipidemic agents (Pike, 2005; Jung et al., 2007; Kamanna and Kashyap, 2007). Both acipimox and acifran have a high affinity for GPR109A and a low affinity for GPR109B (Kamanna and Kashyap, 2007). Monomethyl fumarate (MMF), an active metabolite of dimethyl fumarate (DMF), has been demonstrated to be an agonist of GPR109A (Hanson et al., 2010; Venci and Gandhi, 2013). More recent synthetic selective GPR109A agonists include MK-1903, which was developed for the treatment of dyslipidemia (Boatman et al., 2012), and GSK2560743, which reduces glucose levels in patients with type 2 diabetes (Dobbins et al., 2013). Finally, mepenzolate bromide, a synthetic antimuscarinic drug, is a GPR109A receptor blocker (Singh et al., 2012).

Roles of GPR109A in Neurological Diseases

GPR109A was originally recognized to perform three key functions in the cells expressing this receptor: (1) inhibiting lipolysis (breakdown of fats) in adipocytes (Plaisance et al., 2009), (2) mediating niacin-induced apoptosis in mature neutrophils (Kostylina et al., 2008), and (3) suppressing atherogenesis in arteries (Digby et al., 2012; Chai et al., 2013; Zhang et al., 2021). Moreover, this receptor is also implicated in mitigating many other pathophysiological processes, including the reduction of chemokine and proinflammatory cytokine production (Digby et al., 2012), suppression of mammary tumorigenesis by inhibiting cancer cell survival (Elangovan et al., 2014), and attenuation of colonic inflammation and carcinogenesis by communicating with the gut microbiome (Thangaraju et al., 2009). The beneficial effects induced by activation of microglial GPR109A in neuroinflammation-related neurological diseases, such as Alzheimer's disease, PD, stroke, multiple sclerosis, and pathological pain conditions, have been revealed in recent years.

Alzheimer's disease
AD patients present with the progressive and irreversible decline of cognitive, behavioral, and sensorimotor functions (Knopman et al., 2021). AD is pathologically characterized by the accumulation of extracellular deposits of insoluble amyloid-β (Aβ) and intracellular aggregates of hyperphosphorylated tau (Knopman et al., 2021). Although there is currently no cure for AD, studies have shown that this disease is correlated with increased levels of microglial and astrocytic activation and increased production of proinflammatory

cytokines (Knopman et al., 2021; Leng and Edison, 2021; De Sousa, 2022). Activating GPR109A with ketone bodies was reported to produce protective effects in animal models and *in vitro* culture cells. In the 5XFAD AD mouse model, BHB treatment significantly improves passive avoidance behaviors and responses to the Morris water maze test and nest construction (Wu et al., 2020). These are accompanied by attenuation of Aβ accumulation and senile plaques in the brain. Microglial activation and the production of interleukin 1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6) in the brain are also reduced (Wu et al., 2020). BHB suppresses the expression of amyloid precursor protein (APP) but increases the amount of neprilysin (NEP), a degradation enzyme for Aβ (Wu et al., 2020). In GPR109A knock-out mice, BHB failed to modulate APP and NEP levels (Wu et al., 2020). 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 *in vitro* mouse neuroblastoma N2a cells (Sun et al., 2020). In this study, sodium butyrate was used to activate GPR109A. The authors found that sodium butyrate produces protective effects on Aβ-induced N2a cell injury. APP 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). Together, these findings strongly suggest 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 dopamine deficiency due to loss of neurons in the substantia nigra as well as intracellular alpha-synuclein aggregation (Poewe et al., 2017). Microglial activation in the substantia nigra was found in post-mortem studies (Hartmann, 2004). It is believed that the pathogenesis of PD may involve various mechanisms, including oxidative stress, mitochondrial dysfunction, 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 protection of dopaminergic neurons in the substantia nigra (Fu et al., 2015). In primarily mesencephalic mixed neuron-glial cultures, activation of GPR109A with BHB attenuates microglial activation and levels of phosphorylated nuclear factor kappa B (NF-κB) induced by LPS, which, in turn, dampens the LPS-induced protein and mRNA expression of various pro-inflammatory mediators [e.g., inducible nitric oxide synthase, cyclooxygenase-2 (COX-2), TNF-α, IL-1β, and IL-6] (Fu et al., 2015). Activation of GPR019A with niacin reduces the production of the pro-inflammatory cytokines IL-1β and IL-6 induced by LPS in BALB/c murine macrophage RAW264.7 cells (Giri et al., 2019). Niacin produces this anti-inflammatory effect by suppressing the nuclear translocation of phosphorylated NF-κB induced by LPS (Giri et al., 2019). Interestingly, PD patients receiving niacin supplements have a higher ratio of M2:M1 macrophages as well as improved quality of life (Wakade et al., 2018). Further study on the changes in molecular signaling pathways in patients receiving niacin would provide a rationale for the application of niacin in PD treatment.

Multiple sclerosis
Multiple sclerosis (MS) is 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). Although the mechanisms underlying the beneficial effects induced by DMF remain not clearly understood, it was demonstrated that GPR109A at least in part mediates the beneficial effects of MMF. In mice with experimental autoimmune encephalomyelitis, a murine model of MS, Chen's group in 2014 reported that DMF treatment improves motor function, reduces immune cell infiltration, and decreases demyelination of the spinal cord in wild-type mice. These beneficial effects are abolished in GPR109A knockout mice, providing evidence for the dependence of DMF on GPR109A (Chen et al., 2014). In murine microglial cell line N9, Parodi et al showed that through activation of GPR109A, MMF switches the LPS-activated microglia from a classically activated, pro-inflammatory type to an alternatively activated, neuroprotective one (Parodi et al., 2015). MMF elevates Ca^{2+} levels and increases the activity of AMPK (phosphorylated AMPK) in microglia. The authors demonstrated that AMPK activation results in the activation of sirtuin 1 (SIRT1) via NAD^{+} generation. SIRT1, in turn, inhibits NF-κB via acetylation and suppresses the production of pro-inflammatory molecules such as TNF-α, IL-1β, and heme oxygenase 1, and nuclear receptor subfamily 4 group A member 2 (Parodi et al., 2015). At the synaptic levels, DMF treatment normalizes the increased frequency of excitatory postsynaptic currents in corticostriatal

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 associated with 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). However, another study later found in the EAE model that DMF treatment ameliorates disease signs in Nrf2 knockout mice, both clinically and histologically (Schulze-Topphoff et al., 2016). DMF treatment did not change the total count of CD4^{+} T cells in either WT or Nrf2 knockout mice, but it did lower the amount of both Th1 and Th17 cells in both mice models (Schulze-Topphoff et al., 2016). Further investigation is required to resolve such discrepancies.

Stroke

Stroke 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 (Jayaraj 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 (Rahman et al., 2014). More importantly, this study demonstrated that activation of GPR109A on monocytes and/or macrophages produces such protective effects via the production of prostaglandin D2 (PGD2) by cyclooxygenase 1 (COX-1) and the hematopoietic PGD2 synthase (Rahman et al., 2014). The beneficial role of GPR109A 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 intraventricular 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-responsive element-binding protein/endothelial nitric oxide synthase pathway (Li et al., 2021a). Intravenous injection of BHB significantly reduces cerebral infarct area, edema formation, lipid peroxidation, and neurological deficits (Suzuki et al., 2002). Animals treated with Niaspan, an extended-release formulation of niacin, have smaller infarct areas and improved functional recovery after stroke (Shehadah et al., 2010). Niaspan 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 (Shehadah et al., 2010). Synaptic plasticity and neuronal 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 in mice with middle cerebral artery occlusion (Safari et al., 2019; Li et al., 2021b). DMF and its breakdown product, MMF, alleviate oxidative stress and inflammation after ischemic stroke (Lin et al., 2016; Safari et al., 2019; Li et al., 2021b). Such protective effects are associated with suppression of glial activation (Yao et al., 2016) and glycogen synthase kinase-3β expression, and increased expression of heat shock protein 72 and interleukin 10 (IL-10), an anti-inflammatory cytokine (Clausen et al., 2017). Nrf2 is suggested to mediate the anti-oxidative and anti-inflammatory role induced by DMF/MMF (Zhao et al., 2015; Lin et al., 2016; Yao et al., 2016; Safari et al., 2019; Li et al., 2021b). Interestingly, GPR109A mRNA levels were elevated in both the treated and untreated groups, suggesting that the upregulation in GPR109A 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 signaling 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 spinal central sensitization, is known to play a critical role in the genesis 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 chemokines (Cao et al., 2014; Chen et al., 2018), as well as reducing glial glutamate transporter activity (Yan et al., 2014). For example, IL-1β enhances spinal excitatory synaptic activity by increasing presynaptic glutamate release (Yan and Weng, 2013), postsynaptic AMPA (Yan and Weng, 2013), and NMDA receptor activity (Kawasaki et al., 2008), as well as reducing glial glutamate transporter activity (Yan et al., 2014). In addition, IL-1β also suppresses GABAergic inhibitory synaptic activity by reducing both presynaptic synthesis of GABA transmitter and postsynaptic GABA receptor activity (Yan et al., 2015). Glial activation and production of pro-inflammatory mediators are controlled by either receptors on the cell plasma membrane or intracellular signaling molecules in microglia. GPR109A has emerged as an important target for regulating neuroinflammation in the pain signaling pathway and conquering chronic pain (Boccella et al., 2019;

Viatchenko-Karpinski et al., 2022).

Studies in recent years have shown that the administration of DMF and BHB, both GPR109A agonists, in animals produces analgesic effects. Oral DMF administration strongly prevents thermal and mechanical hypersensitivity induced by tibial bone fracture (Guo et al., 2021a), intervertebral disc degeneration (Zhu et al., 2020), complete Freund's adjuvant-induced arthritis (Lal et al., 2021), and nerve injury (Li et al., 2020). Mechanistically, DMF treatment blocks the increased protein expression of IL-1β and IL-6 in the hind paw skin of mice with a bone fracture (Guo et al., 2021a). In rats with complete Freund's adjuvant-induced arthritis, oral treatment of DMF reduces protein levels of IL-1β, TNF-α, COX-2, and NF-κb in the joint tissue (Lal et al., 2021). Protein expression levels of IL-1β and monocyte chemoattractant protein-1 in the dorsal root ganglion in rats with nerve injury are attenuated by DMF treatment (Li et al., 2020). In Nrf2 knockout mice, the beneficial effects induced by DMF in chronic pain induced by the tibial bone fracture are abolished (Guo et al., 2021a). Moreover, Nrf2 is considered to mediate the antioxidant and anti-inflammatory signaling by DMF in the complete Freund's adjuvant-induced arthritis (Lal et al., 2021) and neuropathic pain (Li et al., 2020).

Qian et al. (2017) reported that BHB treatment improves functional recovery and neuropathic pain in mice with spinal cord injuries. BHB was continuously administered to mice via a subcutaneous mini-osmotic pump following a mid-thoracic spinal contusion injury at the T9–T10 level. BHB Treatment significantly improves locomotor function and attenuates mechanical and thermal hypersensitivity induced by spinal cord injury (Qian et al., 2017). Mechanistically, BHB treatment prevents loss of motor neuron function and suppresses microglia activation induced by spinal cord injury via (1) enhancing histone acetylation and protein expression of the transcription factor Forkhead box class O 3a, catalase, and superoxide dismutase 2; (2) suppressing the nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3 inflammasome activation; (3) reducing IL-1β and IL-18 cytokine levels; and (4) ameliorating mitochondrial function and oxidative stress (Qian et al., 2017). The authors reported that BHB concentration in the spinal cord in mice receiving BHB via a mini-osmotic pump reaches a level of approximately 1.6 mmol (Qian et al., 2017), a concentration that is higher than the EC$_{50}$ (approximately 700 μmol) for BHB to activate GPR109A. Although the authors in their report did not study the involvement of GPR109A in experiments, it is conceivable that activation of GPR109A at least mediates in part the effects induced by BHB in their experiments.

Recently, the role of GPR109A in the regulation of pathological pain was directly addressed in mice with neuropathic pain and mice with chronic pain caused by systemic lupus erythematosus (SLE). At the periphery, GPR109A was found in Schwann cells in the sciatic nerve, and neurons and satellite cells in the dorsal root ganglia (Boccella et al., 2019). In the spinal dorsal horn, GPR109A is expressed in spinal microglia but not in astrocytes or neurons (Viatchenko-Karpinski et al., 2022). GPR109A protein expression is significantly increased in the dorsal root ganglia in mice with peripheral nerve injury, and in the spinal dorsal horn in mice with chronic pain caused by SLE (Viatchenko-Karpinski et al., 2022). In mice with neuropathic pain induced by chronic constriction of the sciatic nerve or spared nerve injury, it was reported that single and repeated oral administration of DMF attenuates pre-existing mechanical allodynia in both male and female mice (Boccella et al., 2019). BHB given intraperitoneally or raised by 60-hour starvation in mice also produces similar effects. These effects are abolished in GPR109A knockout mice, indicating that GPR109A mediates the analgesic effects induced by DMF and BHB on chronic pain induced by nerve injury (Boccella et al., 2019). More recently, we defined the role of GPR109A in chronic pain induced by SLE in MRL/lpr (lupus-prone) mice, a SLE mouse model. MRL/lpr mice spontaneously develop chronic pain at the age of 11 weeks and older (Yan et al., 2017; Viatchenko-Karpinski et al., 2022). This is concurrently accompanied by increased activation of microglia and astrocytes, as well as increased p38 mitogen-activated protein (MAP) kinase activity and production of IL-1β and IL-18 in the spinal dorsal horn (Yan et al., 2017; Viatchenko-Karpinski et al., 2022). At the synaptic level, mice with chronic pain induced by SLE have increased glutamate release from primary afferent terminals (Viatchenko-Karpinski et al., 2022) and reduced activity and protein expression of glial glutamate transporters (Yan et al., 2017) in the spinal dorsal horn. It has been demonstrated that IL-18 enhances glutamate release from the presynaptic terminals (Viatchenko-Karpinski et al., 2022) while IL-1β leads to suppression of glial glutamate transporter activity in the spinal dorsal horn (Yan et al., 2017). Intrathecal administration of a GPR109A specific agonist (MK1903) attenuates chronic pain induced by SLE in the male and female SLE mouse model (Viatchenko-Karpinski et al., 2022). The enhanced activity of p38 MAP kinase in mice with chronic pain is suppressed upon activation of GPR109A receptors in the microglia. Furthermore, activation of GPR109A receptors reduces the activity of cathepsin B and the production of mature IL-1β and interleukin-18 (IL-18) in the spinal dorsal horn in MRL/lpr mice with chronic pain (Viatchenko-Karpinski et al., 2022). Cathepsin B is critically engaged in the production of mature IL-1β and IL-18 from pro-IL-1β and IL-18 (Sun et al., 2012). These findings indicate that activation of spinal GPR109A produces analgesic effects in MRL/lpr mice with chronic pain through suppressing p38 MAP Kinase activity, mitigating production of IL-18 and IL-1β, and reducing glutamatergic activity at the spinal dorsal horn (**Figure 1**). Further investigation into the molecular pathways used by GPR109A to suppress the production of pro-inflammatory cytokines and the molecular pathways regulating the protein expression of GPR109A is warranted.
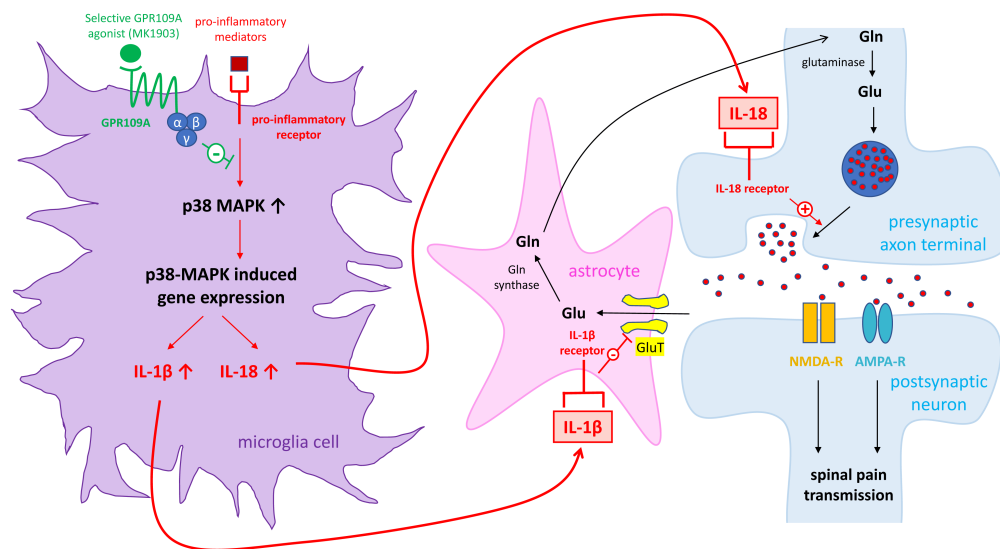
Figure 1 │ Molecular signaling pathways used by GPR109A to attenuate spinal neuroinflammation and chronic pain induced by SLE in mice.
Mice with chronic pain caused by SLE have increased p38 MAPK activity and production of IL-1β and IL18 in the spinal dorsal horn. IL-18 enhances glutamate release from the primary afferent terminals (presynaptic terminals), while IL-1β reduces glial glutamate uptake by suppressing glial glutamate transporter activity. Activation of microglial GPR109A attenuates glutamatergic synaptic activity and chronic pain by suppressing p38 MAPK activity and production of IL-1β and IL-18. AMPA-R: Aminomethylphosphonic acid receptor; Gln: glutamine; Glu: glutamate; GluT: glutamate transporter; IL: interleukin; MAPK: mitogen-activated protein kinase; NMDA-R: N-methyl-D-aspartic acid receptor; SLE: systemic lupus erythematosus.

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.

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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, Khushtar M, Akbar M, Haque MR, Iqubal A, Haider MF, Pottoo FH, Abdulla 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 road map to brain-disease dependent-inflammatory response. Front Cell Neurosci 12:488.

Badanjak K, Fixemer 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, Lauring 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-diaza-cyclopropa[a]pentalene-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, Nassini R, de Novellis V, Geppetti P, Maione 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	Disease(s)	References
Molecules enhanced by GPR109A activation		
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
GSK-3β	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		
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	Pathologic pain	Qian et al., 2017; Viatchenko-Karpinski et al., 2022
COX-2	Parkinson's disease	Fu et al., 2015
iNOS	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	Stroke	Shehadah et al., 2010
Hmox1	Multiple sclerosis	Parodi et al., 2015

APP: Amyloid precursor protein; BDNF: brain-derived neurotrophic factor; COX-2: cyclooxygenase 2; FOXO3a: transcription factor Forkhead box class O 3a; GSK-3β: glycogen synthase kinase-3β; HMOX1: heme oxygenase 1; Hsp72: heat shock protein 72; IL: interleukin; iNOS: inducible nitric oxide synthase; NEP: neprilysin; NF-κB: nuclear factor kappa B; NLRP3: the nucleotide-binding oligomerization domain (NOD)-like receptor pyrin domain containing 3; Nr4a2: nuclear receptor subfamily 4 group A member 2; Nrf-2: mRNA nuclear factor (erythroid-derived) related factor-2; PGD2: prostaglandin D2; PI3K: phosphatidylinositol 3-kinase; ROS: reactive oxygen species; SIRT1: sirtuin 1; SOD2: superoxide dismutase 2; TNF-α: tumor necrosis factor alpha; VEGF: vascular endothelial growth factor.

Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Steplewski KM, Murdock PR, Holder JC, Marshall FH, Szekeres PG, Wilson S, Ignar DM, Foord SM, et al. (2003) The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem 278:11312-11319.

Cao DL, Zhang ZJ, Xie RG, Jiang BC, Ji RR, Gao YJ (2014) Chemokine CXCL1 enhances inflammatory pain and increases NMDA receptor activity and COX-2 expression in spinal cord neurons via activation of CXCR2. Exp Neurol 261:328-336.

Chai JT, Digby JE, Choudhury RP (2013) GPR109 and vascular inflammation. Curr Atheroscler Rep 15:325.

Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR (2018) Microglia in pain: detrimental and protective roles in pathogenesis and resolution of pain. Neuron 100:1292-1311.

Chen H, Assmann JC, Krenz A, Rahman M, Grimm M, Karsten CM, Kohl J, Offermanns S, Wettschureck N, Schwaninger M (2014) Hydroxycarboxylic acid receptor 2 mediates dimethyl fumarate's protective effect in EAE. J Clin Invest 124:2188-2192.

Chen JR, Zhao H, Wankhade UD, Chintapalli SV, Li C, Gai D, Shankar K, Zhan F, Lazarenko OP (2021) GPR109A mediates the effects of hippuric acid on regulating osteoclastogenesis and bone resorption in mice. Commun Biol 4:53.

Clausen BH, Lundberg L, Yli-Karjanmaa M, Martin NA, Svensson M, Alfsen MZ, Flaeng SB, Lyngso K, Boza-Serrano A, Nielsen HH, Hansen PB, Finsen B, Deierborg T, Illes Z, Lambertsen KL (2017) Fumarate decreases edema volume and improves functional outcome after experimental stroke. Exp Neurol 295:144-154.

Cui X, Chopp M, Zacharek A, Roberts C, Buller B, Ion M, Chen J (2010) Niacin treatment of stroke increases synaptic plasticity and axon growth in rats. Stroke 41:2044-2049.

De Sousa RAL (2022) Reactive gliosis in Alzheimer's disease: a crucial role for cognitive impairment and memory loss. Metab Brain Dis 37:851-857.

Digby JE, McNeill E, Dyar OJ, Lam V, Greaves DR, Choudhury RP (2010) Anti-inflammatory effects of nicotinic acid in adipocytes demonstrated by suppression of fractalkine, RANTES, and MCP-1 and upregulation of adiponectin. Atherosclerosis 209:89-95.

Digby JE, Martinez F, Jefferson A, Ruparelia N, Chai J, Wamil M, Greaves DR, Choudhury RP (2012) Anti-inflammatory effects of nicotinic acid in human monocytes are mediated by GPR109A dependent mechanisms. Arterioscler Thromb Vasc Biol 32:669-676.

DiSabato DJ, Quan N, Godbout JP (2016) Neuroinflammation: the devil is in the details. J Neurochem 139 Suppl 2:136-153.

Disease GBD, Injury I, Prevalence C (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1789-1858.

Dobbins RL, Shearn SP, Byerly RL, Gao FF, Mahar KM, Napolitano A, Nachbaur GJ, Le Monnier de Gouville AC (2013) GSK256073, a selective agonist of G-protein coupled receptor 109A (GPR109A) reduces serum glucose in subjects with type 2 diabetes mellitus. Diabetes Obes Metab 15:1013-1021.

Elangovan S, Pathania R, Ramachandran S, Ananth S, Padia RN, Lan L, Singh N, Martin PM, Hawthorn L, Prasad PD, Ganapathy V, Thangaraju M (2014) The niacin/butyrate receptor GPR109A suppresses mammary tumorigenesis by inhibiting cell survival. Cancer Res 74:1166-1178.

Felizardo RJF, de Almeida DC, Pereira RL, Watanabe IKM, Doimo NTS, Ribeiro WR, Cenedeze MA, Hiyane MI, Amano MT, Braga TT, Ferreira CM, Parmigiani RB, Andrade-Oliveira V, Volpini RA, Vinolo MAR, Marino E, Robert R, Mackay CR, Camara NOS (2019) Gut microbial metabolite butyrate protects against proteinuric kidney disease through epigenetic- and GPR109a-mediated mechanisms. FASEB J 33:11894-11908.

Fu SP, Li SN, Wang JF, Li Y, Xie SS, Xue WJ, Liu HM, Huang BX, Lv QK, Lei LC, Liu GW, Wang W, Liu JX (2014) BHBA suppresses LPS-induced inflammation in BV-2 cells by inhibiting NF- kappa B activation. Mediators Inflamm 2014:983401.

Fu SP, Wang JF, Xue WJ, Liu HM, Liu BR, Zeng YL, Li SN, Huang BX, Lv QK, Wang W, Liu JX (2015) Anti-inflammatory effects of BHBA in both in vivo and in vitro Parkinson's disease models are mediated by GPR109A-dependent mechanisms. J Neuroinflammation 12:9.

Ghimire S, Weber D, Hippe K, Meedt E, Hoepting M, Kattner AS, Hiergeist A, Gessner A, Matos C, Ghimire S, Wolff D, Edinger M, Hoffmann P, Poeck H, Herr W, Holler E (2021) GPR expression in intestinal biopsies From SCT patients is upregulated in GvHD and is suppressed by broad-spectrum antibiotics. Front Immunol 12:753287.

Gille A, Bodor ET, Ahmed K, Offermanns S (2008) Nicotinic acid: pharmacological effects and mechanisms of action. Annu Rev Pharmacol Toxicol 48:79-106.

Giri B, Belanger K, Seamon M, Bradley E, Purohit S, Chong R, Morgan JC, Baban B, Wakade C (2019) Niacin ameliorates neuro-inflammation in Parkinson's disease via GPR109A. Int J Mol Sci 20:4559.

Grace PM, Hutchinson MR, Maier SF, Watkins LR (2014) Pathological pain and the neuroimmune interface. Nat Rev Immunol 14:217-231.

Gregus AM, Levine IS, Eddinger KA, Yaksh TL, Buczynski MW (2021) Sex differences in neuroimmune and glial mechanisms of pain. Pain 162:2186-2200.

Guan Z, Kuhn JA, Wang X, Colquitt B, Solorzano C, Vaman S, Guan AK, Evans-Reinsch Z, Braz J, Devor M, Abboud-Werner SL, Lanier LL, Lomvardas S, Basbaum AI (2016) Injured sensory neuron-derived CSF1 induces microglial proliferation and DAP12-dependent pain. Nat Neurosci 19:94-101.

Guo TZ, Shi X, Li W, Wei T, Kingery WS, Clark JD (2021a) Dimethyl fumarate reduces oxidative stress and pronociceptive immune responses in a murine model of complex regional pain syndrome. Anesth Analg 132:1475-1485.

Guo W, Li W, Su Y, Liu S, Kan X, Ran X, Cao Y, Fu S, Liu J (2021b) GPR109A alleviate mastitis and enhances the blood milk barrier by activating AMPK/Nrf2 and autophagy. Int J Biol Sci 17:4271-4284.

Hanson J, Gille A, Zwykiel S, Lukasova M, Clausen BE, Ahmed K, Tunaru S, Wirth A, Offermanns S (2010) Nicotinic acid- and monomethyl fumarate-induced flushing involves GPR109A expressed by keratinocytes and COX-2-dependent prostanoid formation in mice. J Clin Invest 120:2910-2919.

Hartmann A (2004) Postmortem studies in Parkinson's disease. Dialogues Clin Neurosci 6:281-293.

Healy LM, Stratton JA, Kuhlmann T, Antel J (2022) The role of glial cells in multiple sclerosis disease progression. Nat Rev Neurol 18:237-248.

Israel JE, St Pierre S, Ellis E, Hanukaai JS, Noor N, Varrassi G, Wells M, Kaye AD (2021) Ketamine for the treatment of chronic pain: a comprehensive review. Health Psychol Res 9:25535.

Jadeja RL, Jones MA, Fromal O, Powell FL, Khurana S, Singh N, Martin PM (2019) Loss of GPR109A/HCAR2 induces aging-associated hepatic steatosis. Aging (Albany NY) 11:386-400.

Jayaraj RL, Azimullah S, Beiram R, Jalal FY, Rosenberg GA (2019) Neuroinflammation: friend and foe for ischemic stroke. J Neuroinflammation 16:142.

Jung JK, Johnson BR, Duong T, Decaire M, Uy J, Gharbaoui T, Boatman PD, Sage CR, Chen R, Richman JG, Connolly DT, Semple G (2007) Analogues of acifran: agonists of the high and low affinity niacin receptors, GPR109a and GPR109b. J Med Chem 50:1445-1448.

Kamanna VS, Kashyap ML (2007) Nicotinic acid (niacin) receptor agonists: will they be useful therapeutic agents? Am J Cardiol 100:S53-61.

Kawasaki Y, Zhang L, Cheng JK, Ji RR (2008) Cytokine mechanisms of central sensitization: distinct and overlapping role of interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha in regulating synaptic and neuronal activity in the superficial spinal cord. J Neurosci 28:5189-5194.

Knopman DS, Amieva H, Petersen RC, Chetelat G, Holtzman DM, Hyman BT, Nixon RA, Jones DT (2021) Alzheimer disease. Nat Rev Dis Primers 7:33.

Knowles HJ, te Poele RH, Workman P, Harris AL (2006) Niacin induces PPARgamma expression and transcriptional activation in macrophages via HM74 and HM74a-mediated induction of prostaglandin synthesis pathways. Biochem Pharmacol 71:646-656.

Kobayashi K, Yamanaka H, Fukuoka T, Dai Y, Obata K, Noguchi K (2008) P2Y12 receptor upregulation in activated microglia is a gateway to p38 signaling and neuropathic pain. J Neurosci 28:2892-2902.

Koppel SJ, Swerdlow RH (2018) Neuroketotherapeutics: a modern review of a century-old therapy. Neurochem Int 117:114-125.

Kostylina G, Simon D, Fey MF, Yousefi S, Simon HU (2008) Neutrophil apoptosis mediated by nicotinic acid receptors (GPR109A). Cell Death Differ 15:134-142.

Lacagnina MJ, Heijnen CJ, Watkins LR, Grace PM (2021) Autoimmune regulation of chronic pain. Pain Rep 6:e905.

Lal R, Dhaliwal J, Dhaliwal N, Dharavath RN, Chopra K (2021) Activation of the Nrf2/HO-1 signaling pathway by dimethyl fumarate ameliorates complete Freund's adjuvant-induced arthritis in rats. Eur J Pharmacol 899:174044.

Lee AK, Kim DH, Bang E, Choi YJ, Chung HY (2020) Beta-hydroxybutyrate suppresses lipid accumulation in aged liver through GPR109A-mediated signaling. Aging Dis 11:777-790.

Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157-172.

Li J, Ma J, Lacagnina MJ, Lorca S, Odem MA, Walters ET, Kavelaars A, Grace PM (2020) Oral dimethyl fumarate reduces peripheral neuropathic pain in rodents via NFE2L2 antioxidant signaling. Anesthesiology 132:343-356.

Li Y, Zhang X, Ma A, Kang Y (2021a) Rational application of beta-hydroxybutyrate attenuates ischemic stroke by suppressing oxidative stress and mitochondrial-dependent apoptosis via activation of the Erk/CREB/eNOS pathway. ACS Chem Neurosci 12:1219-1227.

Li Y, Chu L, Liu C, Zha Z, Shu Y (2021b) Protective effect of GSK-3beta/Nrf2 mediated by dimethyl fumarate in middle cerebral artery embolization reperfusion rat model. Curr Neurovasc Res 18:456-464.

Lim JL, van der Pol SM, Di Dio F, van Het Hof B, Kooij G, de Vries HE, van Horssen J (2016) Protective effects of monomethyl fumarate at the inflamed blood-brain barrier. Microvasc Res 105:61-69.

Lin R, Cai J, Kostuk EW, Rosenwasser R, Iacovitti L (2016) Fumarate modulates the immune/inflammatory response and rescues nerve cells and neurological function after stroke in rats. J Neuroinflammation 13:269.

Liu F, Fu Y, Wei C, Chen Y, Ma S, Xu W (2014) The expression of GPR109A, NF-kB and IL-1beta in peripheral blood leukocytes from patients with type 2 diabetes. Ann Clin Lab Sci 44:443-448.

Maciejewski-Lenoir D, Richman JG, Hakak Y, Gaidarov I, Behan DP, Connolly DT (2006) Langerhans cells release prostaglandin D2 in response to nicotinic acid. J Invest Dermatol 126:2637-2646.

Mandrika I, Petrovska R, Klovins J (2010) Evidence for constitutive dimerization of niacin receptor subtypes. Biochem Biophys Res Commun 395:281-287.

Martin PM, Ananth S, Cresci G, Roon P, Smith S, Ganapathy V (2009) Expression and localization of GPR109A (PUMA-G/HM74A) mRNA and protein in mammalian retinal pigment epithelium. Mol Vis 15:362-372.

McCarty MF, DiNicolantonio JJ, O'Keefe JH (2015) Ketosis may promote brain macroautophagy by activating Sirt1 and hypoxia-inducible factor-1. Med Hypotheses 85:631-639.

Muzio L, Viotti A, Martino G (2021) Microglia in neuroinflammation and neurodegeneration: from understanding to therapy. Front Neurosci 15:742065.

Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308:1314-1318.

Offermanns S, Colletti SL, Lovenberg TW, Semple G, Wise A, AP IJ (2011) International union of basic and clinical pharmacology. LXXXII: nomenclature and classification of hydroxy-carboxylic acid receptors (GPR81, GPR109A, and GPR109B). Pharmacol Rev 63:269-290.

Parodi B, Rossi S, Morando S, Cordano C, Bragoni A, Motta C, Usai C, Wipke BT, Scannevin RH, Mancardi GL, Centonze D, Kerlero de Rosbo N, Uccelli A (2015) Fumarates modulate microglia activation through a novel HCAR2 signaling pathway and rescue synaptic dysregulation in inflamed CNS. Acta Neuropathol 130:279-295.

Pike NB (2005) Flushing out the role of GPR109A (HM74A) in the clinical efficacy of nicotinic acid. J Clin Invest 115:3400-3403.

Plaisance EP, Lukasova M, Offermanns S, Zhang Y, Cao G, Judd RL (2009) Niacin stimulates adiponectin secretion through the GPR109A receptor. Am J Physiol Endocrinol Metab 296:E549-558.

Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE (2017) Parkinson disease. Nat Rev Dis Primers 3:17013.

Qian J, Zhu W, Lu M, Ni B, Yang J (2017) D-beta-hydroxybutyrate promotes functional recovery and relieves pain hypersensitivity in mice with spinal cord injury. Br J Pharmacol 174:1961-1971.

Rahman M, Muhammad S, Khan MA, Chen H, Ridder DA, Muller-Fielitz H, Pokorna B, Vollbrandt T, Stolting I, Nadrowitz R, Okun JG, Offermanns S, Schwaninger M (2014) The beta-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages. Nat Commun 5:3944.

Rajman L, Chwalek K, Sinclair DA (2018) Therapeutic potential of NAD-boosting molecules: the in vivo evidence. Cell Metab 27:529-547.

Rezq S, Abdel-Rahman AA (2016) Central GPR109A activation mediates glutamate-dependent pressor response in conscious rats. J Pharmacol Exp Ther 356:456-465.

Safari H, Badeli-Sarkala H, Namavar MR, Kargar-Abarghouei E, Anssari N, Izadi S, Borhani-Haghighi A (2019) Neuroprotective effect of dimethyl fumarate in stroke: the role of nuclear factor erythroid 2-related factor 2. Iran J Neurol 18:108-113.

Sato K, Kashiwaya Y, Keon CA, Tsuchiya N, King MT, Radda GK, Chance B, Clarke K, Veech RL (1995) Insulin, ketone bodies, and mitochondrial energy transduction. FASEB J 9:651-658.

Schulze-Topphoff U, Varrin-Doyer M, Pekarek K, Spencer CM, Shetty A, Sagan SA, Cree BA, Sobel RA, Wipke BT, Steinman L, Scannevin RH, Zamvil SS (2016) Dimethyl fumarate treatment induces adaptive and innate immune modulation independent of Nrf2. Proc Natl Acad Sci U S A 113:4777-4782.

Shehadah A, Chen J, Zacharek A, Cui Y, Ion M, Roberts C, Kapke A, Chopp M (2010) Niaspan treatment induces neuroprotection after stroke. Neurobiol Dis 40:277-283.

Shimazu T, Hirschey MD, Newman J, He W, Shirakawa K, Le Moan N, Grueter CA, Lim H, Saunders LR, Stevens RD, Newgard CB, Farese RV, Jr., de Cabo R, Ulrich S, Akassoglou K, Verdin E (2013) Suppression of oxidative stress by beta-hydroxybutyrate, an endogenous histone deacetylase inhibitor. Science 339:211-214.

Singh V, Jamwal S, Jain R, Verma P, Gokhale R, Rao KV (2012) Mycobacterium tuberculosis-driven targeted recalibration of macrophage lipid homeostasis promotes the foamy phenotype. Cell Host Microbe 12:669-681.

Soga T, Kamohara M, Takasaki J, Matsumoto S, Saito T, Ohishi T, Hiyama H, Matsuo A, Matsushime H, Furuichi K (2003) Molecular identification of nicotinic acid receptor. Biochem Biophys Res Commun 303:364-369.

Sun J, Yuan B, Wu Y, Gong Y, Guo W, Fu S, Luan Y, Wang W (2020) Sodium butyrate protects N2a cells against Abeta toxicity in vitro. Mediators Inflamm 2020:7605160.

Sun L, Wu Z, Hayashi Y, Peters C, Tsuda M, Inoue K, Nakanishi H (2012) Microglial cathepsin B contributes to the initiation of peripheral inflammation-induced chronic pain. J Neurosci 32:11330-11342.

Suzuki M, Suzuki M, Kitamura Y, Mori S, Sato K, Dohi S, Sato T, Matsuura A, Hiraide A (2002) Beta-hydroxybutyrate, a cerebral function improving agent, protects rat brain against ischemic damage caused by permanent and transient focal cerebral ischemia. Jpn J Pharmacol 89:36-43.

Taggart AK, Kero J, Gan X, Cai TQ, Cheng K, Ippolito M, Ren N, Kaplan R, Wu K, Wu TJ, Jin L, Liaw C, Chen R, Richman J, Connolly D, Offermanns S, Wright SD, Waters MG (2005) (D)-Beta-Hydroxybutyrate inhibits adipocyte lipolysis via the nicotinic acid receptor PUMA-G. J Biol Chem 280:26649-26652.

Tang H, Lu JY, Zheng X, Yang Y, Reagan JD (2008) The psoriasis drug monomethylfumarate is a potent nicotinic acid receptor agonist. Biochem Biophys Res Commun 375:562-565.

Taves S, Berta T, Chen G, Ji RR (2013) Microglia and spinal cord synaptic plasticity in persistent pain. Neural Plast 2013:753656.

Thangaraju M, Cresci GA, Liu K, Ananth S, Gnanaprakasam JP, Browning DD, Mellinger JD, Smith SB, Digby GJ, Lambert NA, Prasad PD, Ganapathy V (2009) GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. Cancer Res 69:2826-2832.

Thompson A, Ciccarelli O (2020) Towards treating progressive multiple sclerosis. Nat Rev Neurol 16:589-590.

Tschoe C, Bushnell CD, Duncan PW, Alexander-Miller MA, Wolfe SQ (2020) Neuroinflammation after intracerebral hemorrhage and potential therapeutic targets. J Stroke 22:29-46.

Tsuda M, Masuda T, Tozaki-Saitoh H, Inoue K (2013) Microglial regulation of neuropathic pain. J Pharmacol Sci 121:89-94.

Tunaru S, Kero J, Schaub A, Wufka C, Blaukat A, Pfeffer K, Offermanns S (2003a) PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. Nat Med 9:352-355.

Tunaru S, Kero J, Schaub A, Wufka C, Blaukat A, Pfeffer K, Offermanns S (2003b) PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. Nat Med 9:352-355.

Tuteja S, Wang L, Dunbar RL, Chen J, DerOhannessian S, Marcovina SM, Elam M, Lader E, Rader DJ (2017) Genetic coding variants in the niacin receptor, hydroxyl-carboxylic acid receptor 2, and response to niacin therapy. Pharmacogenet Genomics 27:285-293.

Venci JV, Gandhi MA (2013) Dimethyl fumarate (Tecfidera): a new oral agent for multiple sclerosis. Ann Pharmacother 47:1697-1702.

Viatchenko-Karpinski V, Kong L, Weng HR (2022) Activation of microglial GPR109A alleviates thermal hyperalgesia in female lupus mice by suppressing IL-18 and glutamatergic synaptic activity. Glia 70:634-649.

Wakade C, Giri B, Malik A, Khodadadi H, Morgan JC, Chong RK, Baban B (2018) Niacin modulates macrophage polarization in Parkinson's disease. J Neuroimmunol 320:76-79.

Wang X, Liu Q, Zhou J, Wu X, Zhu Q (2017) beta hydroxybutyrate levels in serum and cerebrospinal fluid under ketone body metabolism in rats. Exp Anim 66:177-182.

Wise A, Foord SM, Fraser NJ, Barnes AA, Elshourbagy N, Eilert M, Ignar DM, Murdock PR, Steplewski K, Green A, Brown AJ, Dowell SJ, Szekeres PG, Hassall DG, Marshall FH, Wilson S, Pike NB (2003a) Molecular identification of high and low affinity receptors for nicotinic acid. J Biol Chem 278:9869-9874.

Wise A, Foord SM, Fraser NJ, Barnes AA, Elshourbagy N, Eilert M, Ignar DM, Murdock PR, Steplewski K, Green A, Brown AJ, Dowell SJ, Szekeres PG, Hassall DG, Marshall FH, Wilson S, Pike NB (2003b) Molecular identification of high and low affinity receptors for nicotinic acid. J Biol Chem 278:9869-9874.

Won YJ, Lu VB, Puhl HL, 3rd, Ikeda SR (2013) beta-Hydroxybutyrate modulates N-type calcium channels in rat sympathetic neurons by acting as an agonist for the G-protein-coupled receptor FFA3. J Neurosci 33:19314-19325.

Woolf CJ (2011) Central sensitization: implications for the diagnosis and treatment of pain. Pain 152:S2-15.

Wu Y, Gong Y, Luan Y, Li Y, Liu J, Yue Z, Yuan B, Sun J, Xie C, Li L, Zhen J, Jin X, Zheng Y, Wang X, Xie L, Wang W (2020) BHBA treatment improves cognitive function by targeting pleiotropic mechanisms in transgenic mouse model of Alzheimer's disease. FASEB J 34:1412-1429.

Yan X, Weng HR (2013) Endogenous interleukin-1beta in neuropathic rats enhances glutamate release from the primary afferents in the spinal dorsal horn through coupling with presynaptic N-methyl-D-aspartic acid receptors. J Biol Chem 288:30544-30557.

Yan X, Yadav R, Gao M, Weng HR (2014) Interleukin-1 beta enhances endocytosis of glial glutamate transporters in the spinal dorsal horn through activating protein kinase C. Glia 62:1093-1109.

Yan X, Jiang E, Weng HR (2015) Activation of toll like receptor 4 attenuates GABA synthesis and postsynaptic GABA receptor activities in the spinal dorsal horn via releasing interleukin-1 beta. J Neuroinflammation 12:222.

Yan X, Maixner DW, Li F, Weng HR (2017) Chronic pain and impaired glial glutamate transporter function in lupus-prone mice are ameliorated by blocking macrophage colony-stimulating factor-1 receptors. J Neurochem 140:963-976.

Yao Y, Miao W, Liu Z, Han W, Shi K, Shen Y, Li H, Liu Q, Fu Y, Huang D, Shi FD (2016) Dimethyl fumarate and monomethyl fumarate promote post-ischemic recovery in mice. Transl Stroke Res 7:535-547.

Zellner C, Pullinger CR, Aouizerat BE, Frost PH, Kwok PY, Malloy MJ, Kane JP (2005) Variations in human HM74 (GPR109B) and HM74A (GPR109A) niacin receptors. Hum Mutat 25:18-21.

Zhang SJ, Li ZH, Zhang YD, Chen J, Li Y, Wu FQ, Wang W, Cui ZJ, Chen GQ (2021) Ketone body 3-hydroxybutyrate ameliorates atherosclerosis via receptor Gpr109a-mediated calcium influx. Adv Sci (Weinh) 8:2003410.

Zhao X, Sun G, Zhang J, Ting SM, Gonzales N, Aronowski J (2015) Dimethyl fumarate protects brain from damage produced by intracerebral hemorrhage by mechanism involving Nrf2. Stroke 46:1923-1928.

Zhu H, Chen G, Wang Y, Lin X, Zhou J, Wang Z, Suo N (2020) Dimethyl fumarate protects nucleus pulposus cells from inflammation and oxidative stress and delays the intervertebral disc degeneration. Exp Ther Med 20:269.