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Review article

The role of orphan G protein-coupled receptors in the pathophysiology of multiple sclerosis: A review

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ABSTRACT

G protein-coupled receptors (GPCRs) are a large family of transmembrane proteins that are expressed in many organs and serve as important drug targets. A new subgroup, namely orphan GPCRs, comprising many of these receptors has been discovered. These receptors exhibit diverse physiological functions and have been considered in many neurological disorders including Alzheimer's disease, Parkinson's disease, and multiple sclerosis (MS). GPR17, GPR30, GPR37, GPR40, GPR50, GPR54, GPR56, GPR65, GPR68, GPR75, GPR84, GPR97, GPR109, GPR124, and GPR126 are orphan GPCRs that have been reported with considerable effects in the prevention and/or treatment of MS in preclinical studies. In the present article, we reviewed the most recent findings regarding the role of orphan GPCRs in the treatment of MS.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) [1]. It is characterized by infiltration of inflammatory leukocytes to the CNS followed by oligodendrocyte cell death, myelin sheath destruction, and axonal injury. These effects lead to neurological deficits including visual and sensory disruption, tremor, motor weakness, bladder impairment, and clinical disability [2,3]. Patients with MS have enhanced cytokine production including interferon-γ (IFN-γ) and interleukin-17 (IL-17) *via* activation of Th1 and Th17 cells [4]. The increased secretion of IFN-γ and IL-17 has been associated with the abnormal generation of IL-12 and IL-23 by pro-inflammatory dendritic cells [5,6]. Since the pathogenesis of MS is not completely understood and current medications have various side effects, a great deal of effort has been devoted to understanding the pathological mechanisms of MS and finding new therapeutic approaches for this disease.

G-protein coupled receptors (GPCRs) constitute a large family of 7 trans-membrane-spanning proteins that activate internal signal transduction cascades through binding to different ligands including neurotransmitters, peptides, and lipids [7]. This family of receptors has therapeutic potentials in the treatment of MS [8,9]. The rhodopsin-like or class A family of GPCRs has been recognized as the largest source of therapeutic targets [7,9,10]. Although a large number of rhodopsin-like receptors are called “orphans” and mostly have no known ligand(s) [11]. In this review article, for the first time, we present an overview of the effect(s) of selected orphan GPCRs in the initiation and progression of MS.

2. Methods

The present review was performed using relevant keywords such as ‘multiple sclerosis’, ‘oligodendrocyte precursor cells’, ‘myelin’, ‘glial cells’, ‘Schwann cells’, ‘GPCRs’, ‘demyelination models’, orphan receptors, ‘cuprizone’, and ‘EAE’ in the following databases: PubMed (U.S. National Library of Medicine, Bethesda, MD), Web of Science (Thomson Reuters, Eagan, MN), and Scopus and ScienceDirect (Elsevier Properties S.A, USA). No time limitation was applied in this review and both *in vitro* and *in vivo* studies were included. Firstly, we will give a brief explanation of each selected orphan GPCR and will then discuss its role in the pathophysiology of MS.

3. Orphan GPCRs and multiple sclerosis

3.1. GPR17

GPR17 is an orphan GPCR that is expressed in oligodendrocyte precursor cells (OPCs) and premature oligodendrocytes [12]. It has a

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role in developmental myelination and OPC differentiation [6,13]. GPR17 or P2Y-like membrane receptor responds to both uracil nucleotides and cysteinyl leukotrienes such as uridine diphosphate glucose (UDP-glucose) and leukotriene D4 as endogenous ligands [14]. Some synthetic ligands such as MDL29951 and pranlukast have been developed that are able to activate or antagonize GPR17, respectively [15,16]. Qu et al. evaluated the role of GPR17 in the survival and differentiation of oligodendrocytes using *in vitro* biochemical and *in vivo* mutagenesis models [17]. They found that lysolecithin (LPC) in GPR17 deficient C57BL/6 mice induced demyelinating injury. Overexpression or pharmacological activation of GPR17 by MDL29951 reduced survival of oligodendrocytes and blocked myelinogenesis in transgenic mice. In addition, pharmacological inhibition with pranlukast enhanced oligodendrocyte survival and remyelination after LPC treatment [17]. It was reported that GPR17 negatively regulated oligodendrocyte differentiation by inactivation of intracellular protein kinase A (PKA) and cAMP-activated GTP exchange factor Epac1 [18]. Interestingly, a study by Raff showed that remyelination is faster in GPR17 knock-out (KO) mice than in wild-type mice after LPC injection in the corpus callosum. This effect was mediated *via* extracellular signal-regulated kinase (ERK1/2) activation [19]. Also, McGeachy et al. indicated that GPR17 acts as a potent negative modulator for oligodendrocyte myelination by inducing nuclear localization of differentiation inhibitors ID2 and 4 and opposing *Olig1* function [6].

On the other hand, the role of GPR17 in stroke has been evaluated [20]. The researchers induced stroke by permanent middle cerebral artery occlusion (MCAO) in the first inducible GPR17 reporter mouse line for fate-mapping studies (GPR17-iCreERT2xCAG-eGFP (enhanced green fluorescent protein) transgenic mice). In this mouse line, tamoxifen treatment makes cells expressing GPR17 green and distinguishable for their entire life. [21]. The results demonstrated that GFP^+ cells noticeably accumulated near the ischemic region. Interestingly, it has been shown that GPR17 promoted OPCs migration in an *in vitro* preparation and has a role in oligodendrogliogenesis *via* modulation of K^+ currents [22]. Indeed, GPR17 has been reported as a necessary component for initiation of OPC differentiation. However, GPR17 needs to be turned down for final maturation of oligodendrocyte [23]. In another study, using tamoxifen-induced GFP-labeling transgenic mice, two demyelination models including experimental autoimmune encephalomyelitis (EAE) and cuprizone-induced demyelination were compared [23]. In both models, demyelination induced a strong increase of fluorescent GFP1 cells at damaged areas. In the cuprizone model, these activated GFP1 cells reached final differentiation and expressed myelin proteins. However, in the EAE model, GFP1 cells were stopped at immature stages and did not express mature myelin markers [23]. It was proposed that overexpression of GPR17 in OPCs was responsible for irreversible demyelination in EAE but not the cuprizone model. Nyamoya and her colleagues, to evaluate mRNA and protein expression of GPR17 in the corpus callosum, employed two different models of toxin-induced demyelination: cuprizone and LPC [24]. After acute cuprizone-induced demyelination, a strong endogenous remyelination response occurred in the white matter corpus callosum but not in the gray matter cortex region. This effect was accompanied with a robust GPR17 expression that was absent in the gray matter cortex. After LPC-induced focal white matter demyelination, higher numbers of $GPR17^+$ cells were observed. In contrast, in the chronic cuprizone-induced demyelination model, $GPR17^+$ cell densities were comparable to control animals. Also, pharmacological inhibition of the GPR17 signaling cascade accelerated the remyelination process similar to GPR17 null mice [18,24].

3.2. GPR30

GPR30 or G-protein coupled estrogen receptor (GPER), has been reported to be expressed in the basal forebrain cholinergic neurons and may be involved in the modulation of cognition [25]. Two distinct classes of estrogen receptors have been identified so far: the nuclear estrogen receptors alpha (ERα) and beta (ERβ), and GPR30. Although ERα and ERβ are estrogen-responsive nuclear receptors that act as transcriptional modulators [26], it has been demonstrated that estrogen is able to provoke rapid responses *via* activation of GPR30 [27,28]. GPR30 is selective for the physiologically active 17α and 17β isomers of estradiol but does not bind other steroids including progesterone, testosterone, or cortisol [29]. It has been demonstrated that 17β-estradiol has protective effects in the onset of EAE [30]. Researchers used mice lacking ERα and GPR30 to explore the efficacy of ethinyl estradiol in the treatment of mice with EAE. Based on their findings, ethinyl estradiol decreased disease severity in wild-type and ERα KO mice but did not change disease severity in the GPR30 KO group. They also showed the levels of anti-inflammatory IL-10 were higher in ethinyl estradiol-ERα KO mice but not in ethinyl estradiol-GPR30 KO mice [31]. It seems that expression of GPR30 is a determinant factor in the ability of ethinyl estradiol in the remyelination process. In another study, to evaluate the role of GPR30 signaling as a pro-myelination process, researchers administrated G-1, as a specific agonist for GPR30, to demyelinated rats. Histological examination of the corpus callosum with oligodendrocyte differentiation stage-specific markers showed that G-1 enhanced remyelination by oligodendrocytes following demyelination [32].

Blasko and his co-workers showed that GPR30 was expressed in both human and mouse immune cells [29]. They showed that G-1, *via* activation of GPR30 signaling, inhibited the generation of lipopolysaccharide (LPS)-induced cytokines such as tumor necrosis factor-α (TNF-α) and IL-6 in human primary and murine macrophages dose-dependently. Their results also revealed that G-1 could reduce the severity of the disease in both active and passive EAE models in SJL mice by pro-inflammatory cytokine reduction, including IFN-ϒ and IL-17 [29].

Tamoxifen is an estrogen receptor modulator that has been used for breast cancer treatment since the 1970s [33]. Gonzalez and his team showed that tamoxifen acts as a potent inducer of OPC differentiation *in vitro* [34]. They also demonstrated that tamoxifen relies on modulation of the estrogen receptors ERα, ERβ, and GPR30. Moreover, they unveiled that administration of tamoxifen to ethidium bromide-induced demyelination rats increased remyelination in demyelinated lesions without change in macrophage response [34].

The role of vitamin D in the initiation and progression of MS has been evaluated and discussed in many studies [35–37]. Most of these studies consider this vitamin an important protective factor in MS. The mechanism behind the role of vitamin D in MS has been the subject of recent studies. In accordance, Subramanian et al. showed that vitamin D3-mediated protection in female mice with EAE was related to the 17β-estradiol level. For understanding the role of estrogen receptors in beneficial effects of vitamin D3 on EAE, researchers compared disease severity and immunological responses in calcitriol-treated wild-type C57BL/6 mice and GPR30 KO mice [38]. They found that the preventive effects of vitamin D3 on clinical signs, CNS lesions, and demyelination in wild-type mice were abolished in EAE-GPR30 KO mice (Fig. 1) [38].

3.3. GPR37

GPR37 and G protein-coupled receptor 37 like-1 (GPR37L1) act as parkin substrates [39]. They are expressed in different CNS areas such as the corpus callosum, caudate nucleus, putamen, substantia nigra, and hippocampus [10]. Also, GPR37 is mostly expressed in oligodendroglia [40] and in Schwann cells (SCs). It has been reported that fingolimod, as a standard medication for MS, caused GPR37 downregulation [41].

Proteomic analysis of brain tissue from mice lacking GPR37 showed changes in the expression of oligodendroglial proteins such as myelin-associated glycoprotein (MAG), which contribute to brain insults [42]. These findings revealed that GPR37 KO mice exhibited increased loss of myelin in response to cuprizone but not increased loss of OPCs or

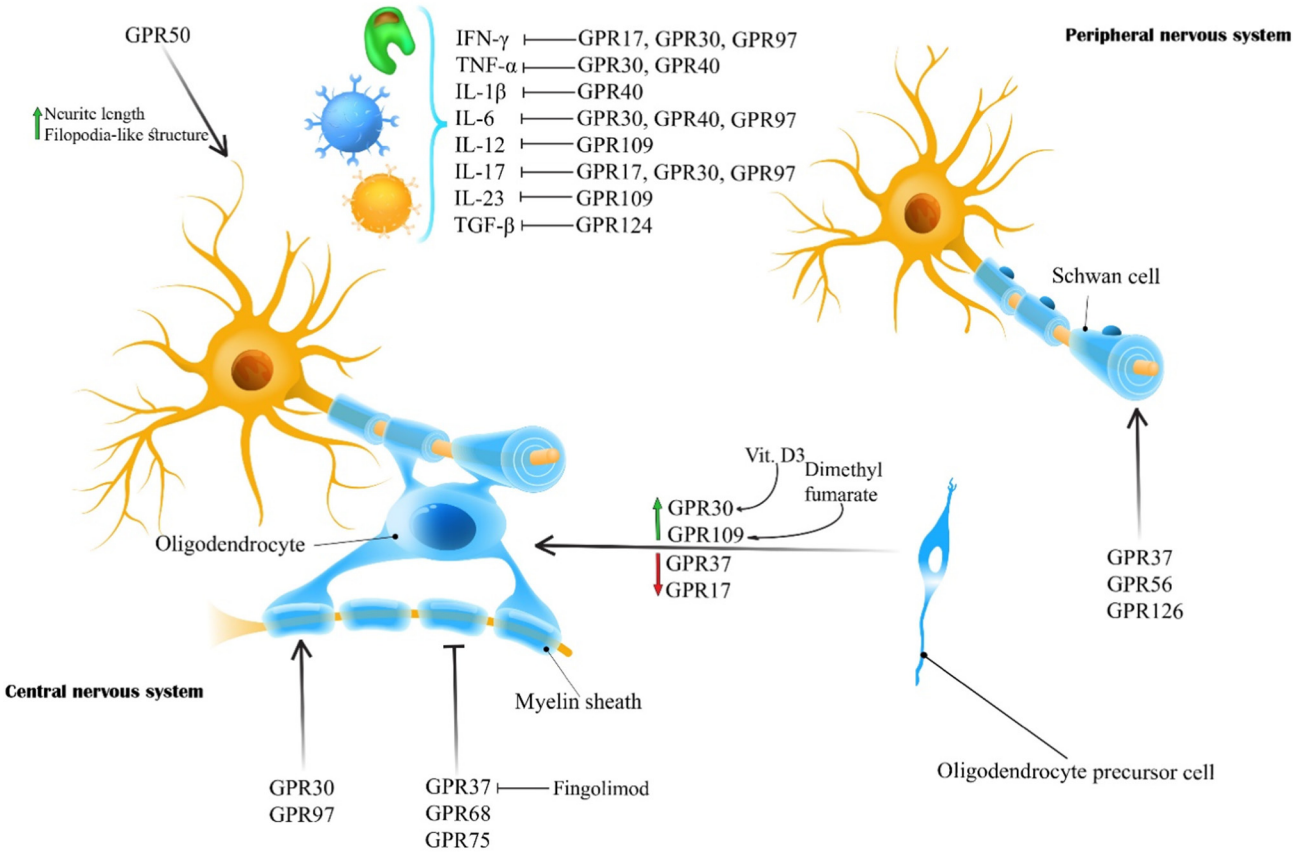

Fig. 1. A schematic illustration of the orphan GPCRs targets involved in the modulation of multiple sclerosis. ↑ and → represent promote/activate, ⊥ and ↓ represent the inhibitory/suppressive effects.

mature oligodendrocytes in the cuprizone model of demyelination. They also showed enhancement of ERK phosphorylation *via* a cAMP-dependent mechanism following loss of GPR37 [42]. Yang et al. identified that GPR37 was as an inhibitor of late-stage oligodendrocyte differentiation and myelination. Although genetic deletion of GPR37 did not affect the number of OPCs, mice lacking GPR37 had myelination during development and increased thickness of myelin sheaths in adulthood [40]. An alternative target for cAMP other than protein kinase A is the exchange protein activated by cAMP (EPAC) [43]. A recent study showed that GPR37 activation inhibited oligodendrocyte differentiation *via* suppression of EPAC-dependent activation of Raf-MAPK-ERK1/2 signaling and nuclear translocation of ERK1/2 [40].

3.4. GPR40

Free fatty acid receptor1 (FFA1) or GPR40 is activated by long-chain fatty acids such as docosahexaenoic acid and is expressed in different human brain areas such as the midbrain, hippocampus, hypothalamus, cerebellum, cerebral cortex, olfactory bulb, medulla oblongata, and the spinal cord [44]. GPR40-polyunsaturated fatty acids (PUFAs) complex has been reported with promising therapeutic potential in neuropathological conditions such as apoptosis, inflammatory pain, and Alzheimer's and Parkinson's diseases [44]. GPR40 has been reported to have a significant role during epileptogenesis [45]. It is a lauric acid (LA), a major component of coconut oil, receptor on the plasma membrane. Researchers examined the effects of LA on hyper-activated microglia induced by LPS in primary cultured rat microglia and the mouse microglial cell line namely BV-2 [46]. LA inhibited LPS-stimulated nitric oxide (NO) generation and expression of the inducible NO synthase protein without affecting cell viability. This effect was reversed in the presence of GW1100 as a GPR40 selective antagonist. LA also reduced LPS-induced phagocytosis, which was completely reversed by GW1100 co-treatment. Moreover, LA suppressed LPS-induced reactive oxygen species and pro-inflammatory cytokine production (IL-1β, IL-6, TNF-α), as well as phosphorylation of p38 mitogen-activated protein kinase and c-Jun *N*-terminal kinase. Nishimura et al. findings suggested that suppression of microglial activation by LA may occur *via* the GPR40-dependent cascade [46].

3.5. GPR50

GPR50, the melatonin-related receptor, is an X-linked receptor with high expression levels in the hypothalamus, pituitary, and locus coeruleus. It has a crucial role in the modulation of stress and anxiety-related disorders [47]. NOGO-A is a membrane protein and myelin-associated neurite outgrowth inhibitor. Inhibition of NOGO-A or its receptors has been reported to be involved in neuronal integrity, axonal sprouting, and regeneration in autoimmune insults such as MS [48]. In yeast two-hybrid screening, researchers identified a correlation between GPR50 and NOGO-A [49]. They confirmed the correlation in mammalian cells and found an enrichment of both GPR50 and neuronal NOGO-A at the primary cortical neurons. GPR50, but not neuronal NOGO-A, overexpression enhanced neurite length and filopodia- and lamellipodia-like structures in differentiated Neuroscreen-1 cells [49].

3.6. GPR54

GPR54 has been found in the dentate gyrus of the hippocampus and amygdala and has an endogenous ligand that was named as kisspeptin [50]. In addition to its role in anxiety-related behaviors, reproductive system, and food intake [51], it also has immunoregulatory functions. A previous study showed that GPR54 deficiency led to a reduction in the

number of peripheral regulatory T cells and elevated autoimmunity both in pre-pubertal mice and bone marrow (BM) chimeric mice [52]. In the EAE model, GPR54 KO (*GPR54*$^{-/-}$) mice showed severe encephalomyelitis compared to the wild-type and heterozygous (*GPR54*$^{+/-}$) mice. Although the EAE scores for heterozygous and WT mice were similar [52].

3.7. GPR56

GPR56 or ADGRG1 is a regulator of oligodendrocyte development in humans. It was found that microglia-derived transglutaminase 2 (TG2) is a novel GPR56 ligand. Based on Giera et al. findings, TG2/laminin (glia-to-glia) signaling *via* GPR56 on OPCs enhanced remyelination in two experimental models of demyelination including cuprizone and LPC [53]. They demonstrated that during SCs development, the GPR56-dependent RhoA signaling pathway increased radial sorting of axons in zebrafish and rodent models. The results showed that in the peripheral nervous system, GPR56 is localized to distinct SCs and is required to promote proper myelin thickness and facilitate organization of the myelin sheath [54]. Interestingly, they identified plectin as a novel binding protein to the GPR56 complex in SCs. Plectin is a large cytoskeletal linker scaffolding protein that induces multiple diseases (plectinopathies) in humans when mutated [54].

3.8. GPR65

The GPR65 gene has been related to several autoimmune diseases, such as MS. It is expressed in lymphoid organs and is activated by extracellular protons [55]. Using a murine EAE model of MS, it was reported that GPR65-deficient mice had exacerbated disease development. Moreover, GPR65 expression levels were found to be highest on invariant natural killer T (iNKT) cells. Surprisingly, EAE severity in GPR65 KO mice was reported as normal in the absence of iNKT cells. Accordingly, it was suggested that GPR65 signaling in iNKT cells is essential for suppressing autoimmune diseases [56].

3.9. GPR68

GPR68 or ovarian cancer G protein-coupled receptor 1 (OGR1) acts as a sensor for mild reduction in extracellular pH that occurs under inflammatory conditions [57]. It has a pro-inflammatory function and is expressed by various immune cells such as macrophages, dendritic cells, and T cells [57,58]. D'Souza et al. used the EAE model to determine the role of GPR68 in modulating autoimmunity development and the underlying mechanisms. They observed that GPR68 ablation led to extreme inhibition of EAE that was connected to a significant decrease in the expansion of myelin oligodendrocyte glycoprotein peptide 35–55 (MOG35–55)-reactive T helper 1 (Th1) and Th17 cells in the periphery and reduced accumulation of Th1 and Th17 effectors in the CNS [59]. The study also revealed that the impaired T cell responses in GPR68-KO mice were related to decreased frequency and number of dendritic cells in draining lymph nodes during EAE and higher NO generation by macrophages [59].

3.10. GPR75

GPR75 is a deorphanized receptor for the chemokines CCL5 (RANTES) and CCL3 that is expressed in the CNS [60]. Previous studies showed that RANTES/CCL5 protected the mouse hippocampal cell line from amyloid-β induced toxicity, which is not related to binding chemokine receptors such as CCR3 and CCR5 but mediated by GPR75 activation [60,61]. Using the EAE model, it was demonstrated that CCR1-KO mice developed a far less severe form of experimental MS [62]. In these animals, administration of anti-macrophage inflammatory protein-1-α antibody (MIP-1α or CCL3) reduced disease severity [63].

3.11. GPR84

Under inflammatory conditions such as EAE, cuprizone-induced demyelination, and endotoxemia, microglia cells express GPR84, an orphan receptor whose pathophysiological role is unidentified [64,65]. Elevated GPR84 expression by endotoxin has been linked to pro-inflammatory cytokines including TNF-α and IL-1. A study by Bouchard et al. showed that mice lacking either one or both of these cytokines had lower GPR84-expressing cells in the cerebral cortex during the early phase of endotoxemia [64]. They also showed that recombinant TNF provoked GPR84 expression *via* a dexamethasone-insensitive mechanism. Furthermore, it was demonstrated that microglia produced GPR84 not only during endotoxemia but also during EAE [64]. In agreement with previous findings, Audoy-Remus et al. demonstrated that GPR84 was upregulated in microglia of APP/PS1 transgenic mice, a model of Alzheimer's disease [66]. According to this study, lack of GPR84 did not change plaque formation or hippocampal neurogenesis while it enhanced dendritic degeneration [66].

3.12. GPR97

GPR97 is expressed in leukocytes and has a role both in macrophage-related inflammation and obesity-induced metabolic syndrome [67]. This orphan receptor is expressed in the spinal cord and endothelial cells of wild-type mice and is upregulated in the spinal cord-infiltrating CD4^{+} T cells and spinal cord endothelial cells of EAE mice [68]. GPR97 has been reported to modulate the nuclear factor-κB (NF-κB) activity. The role of GPR97 in the development of EAE in mice has been investigated [69]. GPR97-KO mice with EAE exhibited a notable increase of leukocyte infiltration, extensive demyelination, and increased severity of disease when compared to wild-type EAE animals. Also, the Th1/Th17 ratio in the CNS was extremely increased in GPR97-KO mice and accompanied by high levels of IL-6, INF-γ, TNF-α, and IL-17. This finding was further verified by an *in vitro* culture assay that showed GPR97 affected pro-inflammatory cytokine generation [69].

3.13. GPR109

GPR109A or hydroxycarboxylic acid receptor 2 (HCA_2) is highly expressed in neutrophils, macrophages, monocytes, and dermal dendritic cells [70]. It is activated by both monomethyl fumarate (MMF) and nicotinic acid (niacin or vitamin B3). Dimethyl fumarate (DMF) was approved as a first-line oral therapy to treat relapsing forms of MS [71]. It has been demonstrated that the mechanism of action of DMF/MMF is related to activation of the nuclear factor erythroid-derived 2-related factor 2 (Nrf2) pathways [72]. Recently researchers showed MMF/DMF could also downregulate the immune response through a non-Nrf2 related pathway (GPR109A signaling pathway) because MMF acts as an HCA_2 agonist [73]. In the EAE model, Chen et al. demonstrated that, at least, part of the beneficial effect of DMF is associated with activation of HCA_2/GPR109A [73]. *In vivo* administration of DMF significantly reduced CNS neutrophil infiltration, neurological damage, and demyelination in intact mice, but not in GPR109 KO mice [73]. Binding of DMF or MMF to HCA2/GPR109A on dendritic cells inhibits the generation of pro-inflammatory cytokines such as IL-12 and IL-23 *in vitro* and in EAE [74].

3.14. GPR124

GPR124 or tumor endothelial marker 5 (TEM5), is expressed in the forebrain and spinal cord. It is the first essential endothelial receptor which acts as a regulator for brain angiogenesis [75]. GPR124 is one of the crucial molecules for blood brain barrier (BBB) differentiation and maturation. BBB dysfunction is linked to many neurological diseases including stroke, MS, and brain tumors [75].

Genetic deletion of GPR124 has been involved in transforming

Table 1
An overview of the role of the orphan GPCRs in the modulation of multiple sclerosis.

Receptor	Alternative name(s)	Expression in the brain	Endogenous ligand or selective agonist	*In vitro/in vivo* model of multiple sclerosis	Effect	Ref.
GPR17	P2Y-like receptor damage sensor	Premature oligodendrocyte and OPCs	Uracil nucleotides and cysteinyl-leukotrienes	Activation of GPR17 by MDL29951 in primary cultured LPC model	Decreased oligodendrocytes survival	[17]
				Inhibition with pranlukast in primary cultured LPC model	Increased oligodendrocytes survival	
				GPR17 ablation in mice lysolecithin (LPC) model	Enhanced remyelination	[88]
				GPR17 overexpressing transgenic mice	Increased myelinating disorders	[6]
				GPR17-KO mice with EAE	Early onset of oligodendrocyte myelination	
GPR30	G-protein coupled estrogen receptor (GPER)	Oligodendrocytes, corpus callosum, forebrain	Estradiol	Ethinyl estradiol in intact animals with EAE	Reduction in disease severity	[31]
				GPR30-KO mice with EAE	No significant effect	
				Administration of G-1 (GPR30 agonist) to SJL mice with EAE	Reduced disease severity in both active and passive EAE models	[29]
				Using tamoxifen in cultured OPCs	Induced OPCs differentiation	[34]
				Tamoxifen administration in ethidium bromide model	Accelerated remyelination	
				G-1 administration to cuprizone-induced demyelination in rats	Accelerated remyelination in	[32]
GPR37	Pael receptor (Pael-R)	Oligodendroglia	E3 ubiquitin ligase, Parkin	GPR37-KO mice	Increased thickness of myelin sheaths	[42]
				GPR37 Ablation	Accelerated oligodendrocyte differentiation and exhibited hypermyelination	[40]
GPR40	Free fatty acid receptor 1 (FFA1),	Olfactory bulb, midbrain, hippocampus, hypothalamus, cerebral cortex, cerebellum, spinal cord	Free fatty acids	Microglial cell line (BV-2)	Lauric acid alleviated neuroinflammatory responses by activated microglia	[46]
GPR54	Kisspeptin receptor (KISS1R)	Cortical and medial nucleus of the amygdala, dentate gyrus	Kisspeptins	GPR54-KO mice	Developed severe EAE	[52]
GPR56	Adhesion G protein-coupled receptor G1 (ADGRG1)	Neural progenitor cells	Microglia-derived transglutaminase 2 (Tgm2)	Tgm2-KO mice	Reduced myelination and oligodendrocyte numbers	[53]
GPR65	T-cell death-associated gene 8 (TDAG8)	Hippocampus		GPR65-KO mice	Developed severe EAE	[56]
GPR68	Ovarian cancer G protein-coupled receptor 1 (OGR1)	Hippocampus		OGR1-deficient mice	Ameliorated EAE	[59]
GPR84		Microglia	Medium-chain FFAs	GPR84 deficient mice	Reduced microgliosis	[66]
GPR97		Spinal cord Endothelial cells		Adgrg3 deficient mice	Ameliorated EAE	[69]
GPR124	Tumor endothelial marker 5 (TEM5)	Forebrain spinal cord		GPR124 ablation	TGF-β activation disturbance Lack expression of GLUT-1	[76]
GPR126		Mature SCs	Type IV collagen	Inducible GPR126 mutant mice	Impaired remyelination	[81]

growth factor-beta (TGF-β) signaling modulation in a brain-specific manner [76,77]. TGF-β signaling pathway in endothelial cells has been characterized in CNS angiogenesis. Lack of TGF-β pathway leads to vascular sprouting and hemorrhages [78]. Kuhnert et al. showed that GPR124 ablation decreased the expression of the glucose transporter 1 (Glut-1) and BBB marker [77]. According to these studies, it is a possibility that this orphan receptor participates in MS pathology.

3.15. GPR126

GPR126 is expressed in adult SCs and plays roles in nerve functions [79]. GPR126 has been reported as an essential component for SCs development and myelination [80]. Mogha et al., by using an inducible SC-specific GPR126-KO mouse model, reported that GPR126 possesses SC-autonomous and SC-non-autonomous functions in remyelination and peripheral nerve repair [81]. Similarly, Monk et al. showed that GPR126 is required for SC development and myelination in zebrafish and mice [82,83]. It has been reported that axonal signals provoke the expression of the transcription factor Oct6 in SCs, which will produce myelin for a limited time [83]. In addition, Oct6 regulates Krox20 expression [84]. So, both these transcription factors are necessary for the myelination process in SCs. Monk et al., by employing GPR126 mutational analysis in zebrafish, showed that SCs did not express Oct6 and Krox20 and were arrested at the promyelinating phase. Their study also showed that cAMP augmentation in GPR126 mutants, but not in Krox20 mutants, restored myelination [82]. It has been suggested that, at the beginning of myelination, GPR126 and protein kinase A (PKA) act as switches that permit SCs to initiate Krox20 expression and myelination. After myelination initiation, Krox20 expression is maintained and myelin maturation proceeds independently of GPR126 signaling [85]. In addition, it was reported that GPR126 ablation diminished expression of differentiated SCs markers such as Oct6, Krox20, and myelin basic protein and induced severe congenital hypomyelinating peripheral neuropathy in mice [83]. Table 1 represents an overview of the effects of the orphan GPCRs in the modulation of MS.

4. Conclusion

Our knowledge regarding the physiological role of orphan GPCRs is very limited. However, various studies show that this group of receptors has important roles in the pathophysiology of neurodegenerative disorders including MS. The present review unveiled the role of orphan GPCRs in the initiation and progression of MS. Some of these receptors including GPR30 and GPR97 have pro-myelination effects while some others have inhibitory actions on myelination, both in the peripheral and central nervous systems. Orphan GPCRs, *via* mechanisms other than myelination, may also affect MS including modulation of immune cell responses and cytokine release. For example, some of them were able to decrease INF-γ, TNF-α, IL-1β, IL-6, IL-12, IL-17, and IL-23 and some were able to affect T helper cell function. In addition, GPR50 increased neurite length and filopodia- and lamellipodia-like structures implying that some of these receptors may even change the structure of the neurons. Involvement of GPR37 and GPR109 in the therapeutic effects of fingolimod and dimethyl fumarate, as two oral medications for the treatment of MS, even further highlights the therapeutic potentials of these receptors in the treatment of MS. As mentioned, orphan GPCRs are involved in the modulation of various neurological and psychological disorders [9,10]. It is well known that patients with MS have various concomitant diseases including anxiety, depression, psychosis, and pain [86,87]. Considering these findings, it may be suggested that these receptors can be targeted for the treatment of MS and concomitant diseases. However, many more studies are needed for this aim.

Conflicts of interest

The authors declare no conflicts of interest.

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