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The Possible Role of Metformin and Fibroblast Growth Factor-21 in Multiple Sclerosis Neuropathology: Birds of a Feather Flock Together

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ABSTRACT

Multiple sclerosis (MS) is a progressive demyelinating disease of the CNS, characterized by inflammation, the formation of CNS plaques, and damage to the neuronal myelin sheath (Graphical abstract). Fibroblast growth factor 21 (FGF21) is involved in various metabolic disorders and neurodegenerative diseases. FGF21 and its co-receptor β-Kloth are essential in the remyelination process of MS. Metformin, an insulin-sensitizing drug that is the first-line treatment for type 2 diabetes mellitus (T2DM), may have a potential neuroprotective impact by up-regulating the production of FGF21, which may prevent the onset of neurodegenerative diseases including MS. The purpose of this review is to clarify how metformin affects MS neuropathology mechanistically via modifying FGF21. Metformin increases the expression of FGF21. Metformin also increases the expression of β-Klotho, modulates oxidative stress, reduces glutamate-induced excitotoxicity, and regulates platelet function and coagulation cascades. In conclusion, metformin can enhance the functional activity of FGF21 in countering the development and progression of MS. Preclinical and clinical studies are warranted in this regard.

1 | Introduction

Multiple sclerosis (MS) is a demyelinating illness of the central nervous system (CNS) (Dobson and Giovannoni 2019). MS is the most common inflammatory disease that impairs motor and sensory neural signal transmission (Dobson and Giovannoni 2019; Kumar et al. 2011; Vecchio et al. 2017). MS is presented clinically by unilateral visual loss, double vision, muscular weakness, and motor-sensory incoordination (Kumar et al. 2011; Vecchio et al. 2017). MS affects 2.8 million subjects globally, with prevalence varying among different populations (Dutta and Trapp 2014; Buscarinu et al. 2019; Lane et al. 2022). In 2022, about one million people in the United States were living with MS (McGinley et al. 2021). The disease is more common in women, typically affecting individuals between the ages of 20 and 50 (Zeydan and Kantarci 2020).

The central pathophysiology of MS is failure of myelin production or damage to the myelin sheath by immune cells (Buscarinu et al. 2019). In genetically susceptible individuals, abnormal immune responses to certain environmental factors can trigger cell-mediated, leading to axonal demyelination (Derada Troletti et al. 2019). CNS plaque development, which is a hallmark of MS neuropathology, is characterized by inflammation and damage to the neuronal myelin sheath (Derada Troletti et al. 2019). Sunlight exposure and adequate levels of vitamin D have been found to protect against the development of MS (Derada Troletti et al. 2019).

Multiple focal patches of demyelination scattered across the cerebral cortex, deep gray matter, spinal cords, and white matter of the brain are characteristics of these plaques (Al-Kuraishy, Al-Gareeb, et al. 2024; Al-Kuraishy, Jabir, et al. 2024; Al-Kuraishy et al. 2023a; Al-Kuraishy, Sulaiman, et al. 2024; Alruwaili et al. 2023; Khatir et al. 2020; Lassmann et al. 2001). In MS, oligodendrocytes, which are responsible for producing the myelin sheath, are principally impacted (Lan et al. 2017; Sedel et al. 2016). Partial remyelination can occur during the remission phase, while demyelination often recurs during the relapse stage, leading to plaque formation at multiple sites within the CNS (Ponath et al. 2018). MS is considered as an immune-mediated disease involving both the humoral and cellular arms of the immune system (Martino et al. 2002). Auto-reactive T lymphocytes in the peripheral system initiate inflammatory alterations in MS (Liu et al. 2007). It has been shown that molecular mimicry triggers polyclonal activation of peripheral auto-reactive T cells (Elsayed et al. 2022). Auto-reactive T cells have the ability to cross through the blood–brain barrier (BBB) via attaching to VCAM-1 on endothelial cells and integrins on immune cells (Rice et al. 2005). Inflammation and pro-inflammatory cytokines (Gerdes et al. 2020; Hedström et al. 2020; Aloisi and Cross 2022; Coles 2008; Marrie 2004; Sf 2021) lead to an up-regulation of VCAM-1 and integrin expression (Dyment et al. 2004). In addition, T cells stimulate the production and secretion of matrix metalloproteinase (MMPs), which promote the entry of T cells and contribute to the myelin degeneration (Mohammadhosayni et al. 2020; Martin et al. 2021; Balasa et al. 2020; James et al. 2020).

These neuropathological changes induce axonal damage and injury of the myelin sheath (Figure 1).

Acute attacks of MS are treated with high doses of corticosteroids such as methylprednisolone either orally or intravenously (Hauser and Cree 2020; Pitt et al. 2022; Makhani and Tremlett 2021; Granziera et al. 2021; Sakakibara 2019; Mayo et al. 2019; Alhossan et al. 2022; Teoli et al. 2021). Plasmapheresis is recommended when corticosteroid therapy is ineffective. Disease-modifying therapies for chronic MS management include mitoxantrone, glatiramer, and interferons (Tintore et al. 2019). Additionally, about 50% of MS patients use alternative and complementary medicine, including biotin, vitamin D, and cannabis (Vespignani 2020). Earlier studies have demonstrated that metformin can attenuate the inflammatory reactions in MS (Xu et al. 2007; Zhou et al. 2012). Moreover, fibroblast growth factor 21 (FGF21), a growth factor involved in various metabolic disorders and neurodegenerative diseases (Kliewer and Mangelsdorf 2010), is affected by metformin (M. Zhang et al. 2013). Conferring to these findings, this review aims to discuss the immunoinflammatory effect of metformin in MS in relation to the expression of FGF21.

2 | The Physiological Role of FGF21: An Overview

FGF21 is a peptide hormone synthesized by hepatocytes (Al-Kuraishy et al. 2023b). Along with FGF19 and FGF21, FGF23 forms part of the FGF family, which is involved in regulating angiogenesis, cell mitosis, and differentiation (Al-kuraishy et al. 2023c). FGF21 is highly expressed in the liver, adipose tissues, and pancreas (Nygaard et al. 2014). It is also produced by skeletal muscles and other tissues, with its expression enhanced by phosphoinositol 3 kinase (PI3K) (Sun et al. 2021). The expression of FGF21 is influenced by various cellular signaling; for example, the liver X receptor (LXR) inhibits the expression of FGF21 (Pérez-Martí et al. 2017; Rodgers et al. 2019; Uebanso et al. 2012). FGF21 improves glucose, lipid metabolism and energy expenditure (Pérez-Martí et al. 2017). FGF21 binds four types of FGF receptors (FGFR1–4), and its interaction with these receptors is enhanced by β-Klotho, a transmembrane protein that serves as a co-receptor for FGF21 (Min et al. 2018). The expression of FGF21 varies under different pathophysiological conditions, for example, exercise and fasting increase muscular and hepatic FGF21 expression, correspondingly (Cuevas-Ramos et al. 2010; K. Li et al. 2012). Interestingly, low-protein diet enhances FGF21 expression, thereby improving the metabolic profile (Larson et al. 2019). In addition, peroxisome proliferator-activated receptor alpha (PPAR-α) induces the expression of FGF21 in the liver, whereas PPAR gamma (PPAR-γ) induces the expression of FGF21 in adipose tissue (Yu 2015). Moreover, FGF21 expression is induced by sirtuin-1 (SIRT1) and mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2) (Li et al. 2014).

It has been shown that FGF21 exhibits neuroprotective effects against numerous neurodegenerative diseases. For instance, it reduces the neurotoxicity caused by amyloid beta (Aβ) in Alzheimer's disease (AD) (Chen et al. 2019). In vitro and in vivo studies have confirmed that FGF21 inhibits tau protein hyperphosphorylation-induced neuronal injury and apoptosis through its antioxidant effects (Chen et al. 2019). Moreover, FGF21 has neuroprotective effects against Parkinson's disease (PD) by promoting the anti-inflammatory phenotype (Yang
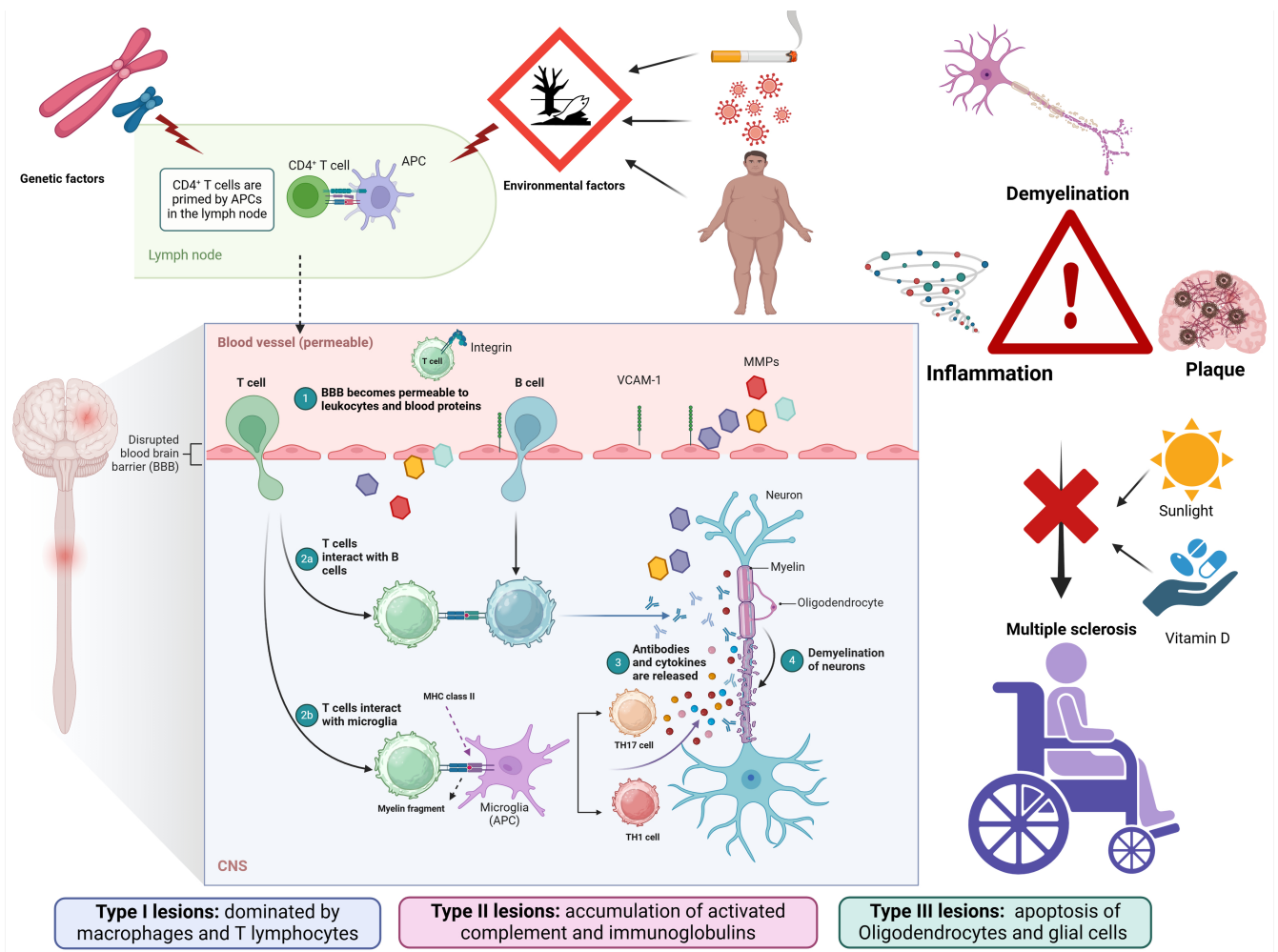
FIGURE 1 | Pathophysiology of MS.

et al. 2021). This anti-inflammatory effect of FGF21 is primarily mediated by increasing the expression of SIRT1 and inhibiting of inflammatory signaling pathways such as NF-κB (Yang et al. 2021). Sun et al. (2020) found that FGF21 modulates the neuronal-astrocyte lactate shuttle pathway, which is dysregulated in AD. FGF21 also attenuates neuroinflammation and promotes neurogenesis in various neurodegenerative diseases including AD and PD (Woodbury and Ikezu 2014). Furthermore, FGF21 inhibits mitochondrial dysfunction by up-regulating the production of peroxisome proliferator-activated-γ coactivator 1 α (PGC-1α) (Restelli et al. 2018; Mäkelä et al. 2014). Furthermore, FGF21 reduces angiotensin II (AngII)-induced cerebrovascular aging and related oxidative stress and inflammatory conditions (X.-M. Wang et al. 2016). These verdicts indicated that FGF21 significantly protects neurons from the development and progression of neurodegenerative disorders (Figure 2).

3 | Role of FGF21 in MS

FGF21 is an important growth factor that promotes the differentiation and proliferation of oligodendrocyte precursor cells, which is crucial for the remyelination process (Kurosu et al. 2007; Adams et al. 2012). Of note, FGF21 and its co-receptor β-Kloth are essential for remyelination in MS (Kuroda

et al. 2017). It has been reported that the CSF level of FGF21 is approximately 40% of its level in circulation in healthy subjects (Tan et al. 2011) due to limited entry of FGF21 into the CNS through the BBB, suggesting that peripheral administration of FGF21 may not effectively effective in the management of MS. However, disruption of BBB integrity in neurodegenerative diseases facilitates the entry of FGF21 into CNS (Chen et al. 2018). Nonetheless, peripherally administration FGF21 has been proven to be effective in promoting remyelination in MS (Kuroda et al. 2017). Disruption of BBB is a critical factor in the pathogenesis of MS as it prevents the entry of immune and inflammatory cells to the CNS (Ortiz et al. 2014). Interestingly, FGFR1 and FGFR1 are prominently expressed in oligodendrocyte precursor cells, suggesting a significant role in the remyelination process (Fortin et al. 2005). In addition, FGF21 protects neurons from glutamate-induced excitotoxicity, which involved in the pathogenesis of MS via inhibition of oxidative and inflammatory reactions (Linares et al. 2020; Xu et al. 2021). As well, FGF21 attenuates AD-induced neuroinflammation by inhibiting NF-κB, TLR4, and heat shock protein 90 (Amiri et al. 2018). Neuroinflammation is closely linked with progressive neurodegeneration and demyelination in MS (Koudriavtseva and Mainero 2016). Therefore, FGF21 can attenuate MS neuropathology by targeting both glutamate-induced excitotoxicity and neuroinflammation. A case–control study involving 50 MS
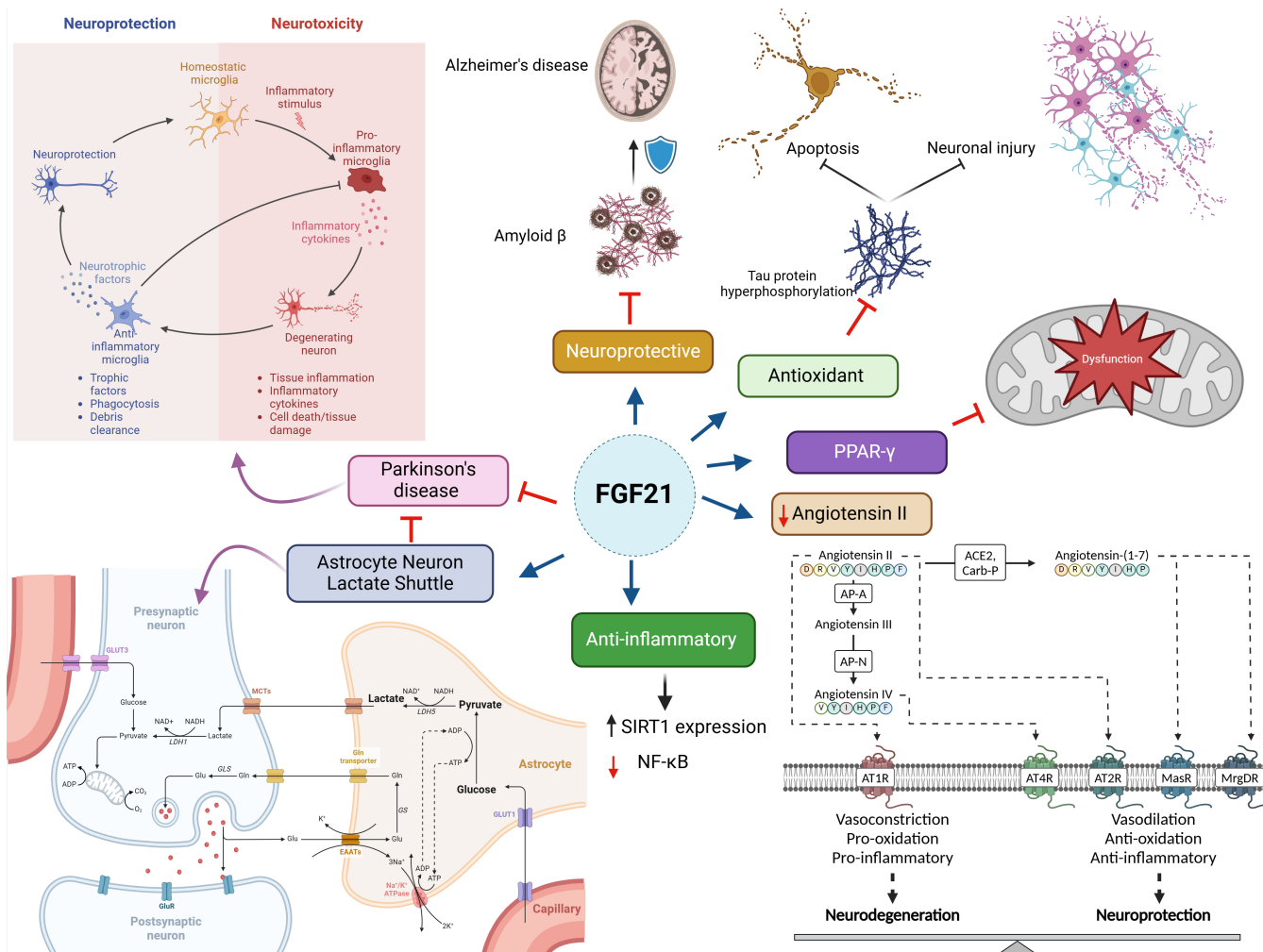
FIGURE 2 | Neuroprotective effects of FGF21.

patients and 33 healthy controls revealed increased serum levels of FGF21 and vascular endothelial growth factor (VEGF) in MS patients compared to healthy controls (Su et al. 2006). These findings underscore the potential significance of FGF21 and VEGF in the pathophysiology of MS.

In MS, the distribution and progression of sclerotic lesions in the brain stem and spinal cord can compromise the integrity of the autonomic nervous system, leading to severe autonomic dysfunction (Autonomic 2003). Research has indicated that FGF21 improves sympathetic drive and enhances autonomic function in mice (Douris et al. 2015). FGF21 plays a versatile role in regulating energy expenditure by activating the sympathetic nervous system (BonDurant and Potthoff 2018). Furthermore, FGF21 improves cognitive function by promoting hippocampal neurogenesis in mouse models with traumatic brain injury (Shahror et al. 2020). Yu et al. (2015) revealed that FGF21 attenuates D-galactose-induced aging in mice by boosting hippocampal neurogenesis and preventing of oxidative stress. FGF21 also improves synaptic plasticity, thereby improving memory and learning capabilities (Reuss and Bohlen und Halbach 2003). In the context of MS, auto-reactive T lymphocytes trigger inflammatory changes in the MS (Singhal et al. 2016), and inhibition of these cells could mitigate MS neuropathology. FGF21 has the remarkable ability to suppress the activity and growth

of T lymphocytes in mice. This suppression is accompanied by a decrease in the production of pro-inflammatory cytokines (Singhal et al. 2016). FGF21 can suppress NF-κB, which is a key regulator of B and T lymphocytes (Yu et al. 2016). Therefore, FGF21 plays a crucial role in regulating immunoinflammatory response in MS neuropathology.

FGF21 binds to FGF receptors, a process that enhanced by β-Klotho, a transmembrane protein that acts as a co-receptor for FGF21 (Yu 2015). This co-receptor exerts differential neuroprotective effects against neurodegenerative diseases, including MS. β-Klotho agonists mimic the action of FGF21 (Min et al. 2018), suggesting a potential role of this receptor in MS. A study conducted by Aleagha et al. (2015) showed that CSF level of β-Klotho was reduced in MS patients compared to controls. β-Klotho promotes the maturation of oligodendrocyte precursor cells and improves myelination in MS patients (Scazzone et al. 2019). Similarly, a case–control study revealed that β-Klotho mRNA expression in the peripheral blood mononuclear cells was reduced in MS patients compared to controls (Karami et al. 2017). Notably, Klotho protein improves and maintains vitamin D metabolism, which acts as a neurosteroid mitigating different neurodegenerative diseases, mainly MS (Dërmaku-Sopjania et al. 2021). Vitamin D deficiency is regarded as a risk factor for the development and progression of MS (Miclea
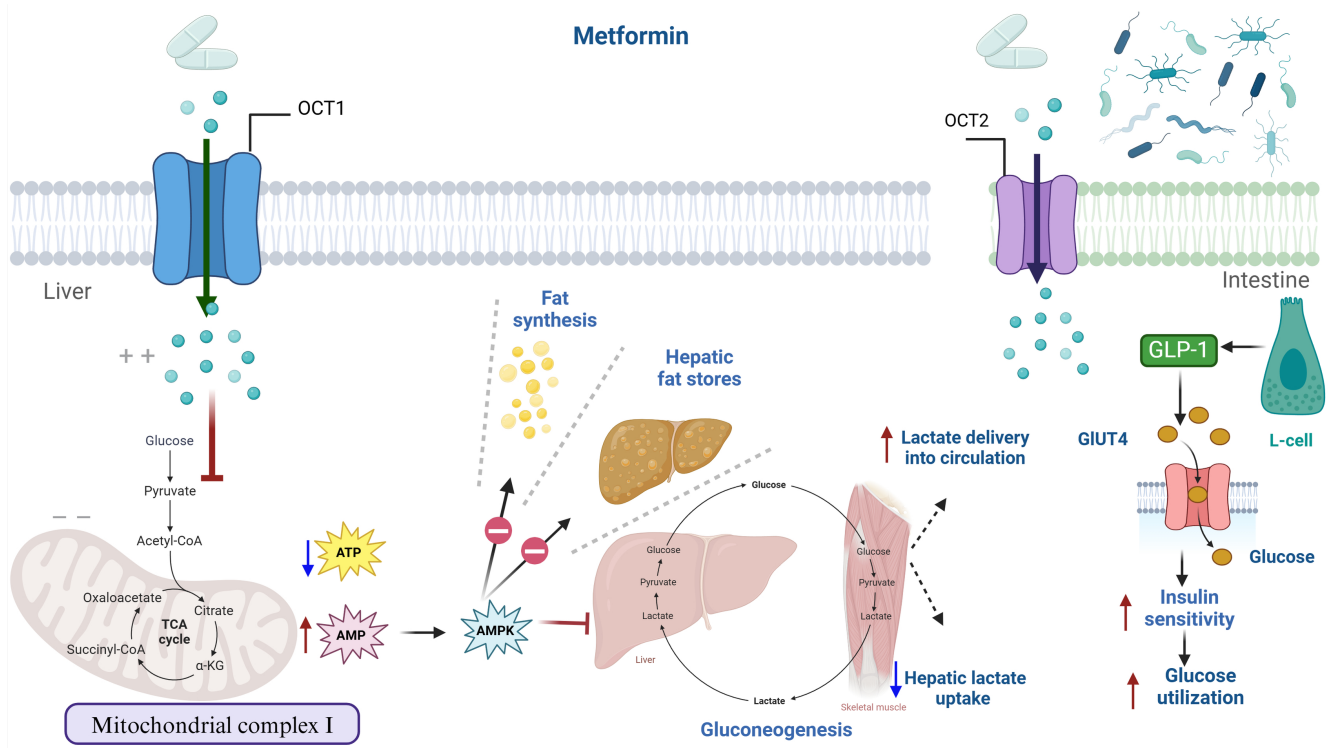
FIGURE 3 | Pharmacology of metformin.

et al. 2020). Therefore, Klotho protein and FGF21 regulate different inflammatory and metabolic pathways implicated in MS neuropathology.

4 | The Neuroprotective Effects of Metformin

Metformin is an insulin-sensitizing drug belonging to the biguanide class; it is used as first-line therapy in the management of T2DM due to its ability to decrease peripheral insulin resistance (IR) (Al-Kuraishy, Sami, et al. 2020; Al-Kuraishy, Al-Gareeb, Saad, and Batiha 2023). Metformin is an orally administered medication, absorbed in the small intestine through the highly expressed plasma membrane monoamine transporter (PMAT) in enterocytes (Al-Kuraishy, Al-Gareeb, Alblihed, Cruz-Martins, et al. 2021; Al-Kuraishy, Al-Gareeb, Waheed, and Al-Maiahy 2018; Al-Kuraishy et al. 2019; Al-Kuraishy et al. 2016; Al-Kuraishy, Al-Gareeb, Alexiou, et al. 2022; He 2020). By inhibiting mitochondrial complex I, metformin prevents the synthesis of ATP, which raises adenosine monophosphate protein kinase levels and increases the AMP:ATP ratio (AMPK). AMPK enhances anaerobic glucose metabolism and insulin sensitivity in enterocytes (Abdul-Hadi, Naji, Shams, et al. 2020) (Figure 3). It also encourages the gut microbiota to utilize glucose by stimulating the release of glucagon-like peptide 1 (GLP-1) from intestinal L cells (Al-Kuraishy, Al-Gareeb, Albogami, et al. 2022). Moreover, it has pleiotropic properties such as antioxidant and anti-inflammatory effects (Al-Kuraishy, Al-Gareeb, Alblihed, Guerreiro, et al. 2021; Al-Kuraishy, Al-Gareeb, Albogami, et al. 2022; Foretz et al. 2019; Al-Kuraishy and Al-Gareeb 2016; Rasheed et al. 2019; Al-Nami et al. 2020; Al-kuraishy et al. 2016; Flory and Lipska 2019; Abdul-Hadi, Naji, Shams, Sami, et al. 2020; Al-Kuraishy, Al-Gareeb, Alsayegh, et al. 2023;

Trueck et al. 2019; LaMoia and Shulman 2021; Tarry-Adkins et al. 2021).

Metformin has potential neuroprotective effects against numerous neurodegenerative diseases such as AD and PD. Mounting evidence suggests that metformin decreases the risk of AD in T2DM patients (Nath et al. 2009; Herath et al. 2016). Compared with other diabetic treatments, metformin has been reported to enhance working memory and executive brain functions in T2DM patients (Luchsinger et al. 2016; Imfeld et al. 2012). It has been shown that prolonged metformin treatment > 4 years reduces the risk of AD, PD, and Huntington's disease (Herath et al. 2016). Conversely, numerous studies showed an increased risk of cognitive impairment and AD with long-term metformin therapy (Imfeld et al. 2012; Moore et al. 2013). The neuroprotective effect of metformin is primarily mediated through AMPK, which mitigates the aggregation of Aβ and hyperphosphorylation of tau proteins (J. Li et al. 2012). In addition, metformin enhances neurogenesis, angiogenesis, and synaptic plasticity and induces autophagy (Venna et al. 2014). Metformin improves the levels of brain-derived neurotrophic factor (BDNF), which inhibit neuroinflammation and protect neurons from oxidative stress (Chen et al. 2016). C. Wang et al. (2016) showed that metformin exerted a neuroprotective effect via inhibiting apoptosis and activating autophagy in mice with experimental spinal cord injury. It has been reported that chronic AMPK activation by metformin has protective effects against ischemic stroke. However, acute metformin treatment exacerbates acute ischemic stroke (Turkistani et al. 2024; Mima et al. 2016; Sharma et al. 2021). Consequently, timing of metformin administration and its duration are crucial factors in mitigating acute ischemic stroke. Notably, in T2DM patients, metformin usage lowers the risk and severity of ischemic stroke (Mima et al. 2016). A
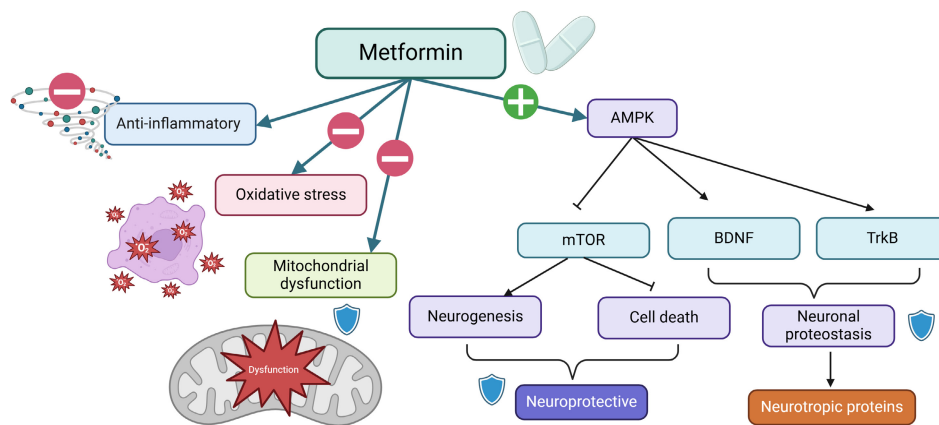
FIGURE 4 | Anti-epileptic effect of metformin.

prospective study demonstrated that treatment with metformin before the onset of acute ischemic stroke decreases the disease severity in T2DM patients (Mima et al. 2016). In recent years, metformin has been repurposed for the management of age-related neurodegenerative disorders and ischemic stroke via the modulation of AMPK and different signaling pathways (Sharma et al. 2021).

Additionally, metformin has beneficial effects against the development of epilepsy and exhibits anti-epileptic properties by ameliorating oxidative stress, inhibiting mTOR-induced neuroinflammation, and modulating of neuronal AMPK signaling (Alnaaim et al. 2023). Metformin attenuates abnormal neurogenesis, neuronal cell deaths, and neuroinflammation in epilepsy (Sanz et al. 2021). AMPK improves neuronal proteostasis by modulating BDNF and tropomyosin receptor tyrosine kinase B (TrkB), which play roles in epileptogenesis (Sanz et al. 2021). Singh et al. emphasized that metformin is a promising anti-epileptic agent by modulating epileptogenesis process via inhibiting oxidative stress, mTOR, and inflammatory signaling pathways (Singh et al. 2022). An experimental study established the efficacy of metformin in attenuating pilocarpine-induced seizure in rats (Mehrabi et al. 2018). These findings propose that metformin may exert anti-epileptic effects through modulation of TrkB, BDNF, oxidative stress, and inflammatory signaling pathways. Furthermore, metformin boosts the expression of the neuroprotective protein progranulin, which helps to reduce neuronal excitability and prevent seizure development in temporal lobe epilepsy (Alrouji et al. 2024; Paudel et al. 2020; Vazifehkhah et al. 2020). Thus, metformin exhibits anti-epileptic effects by regulating astrogliosis and the release of progranulin (Figure 4).

Certainly, *PARKIN* is recognized as a gene that protects against mitochondrial damage in PD and other neurodegenerative brain disorders (Mehrabi et al. 2018). The neuroprotective benefits of metformin are attributed to its enhancement of *PARKIN* gene expression (Mehrabi et al. 2018). Furthermore, metformin modulates several genes implicated in neurodegenerative brain diseases such as leucine-rich repeat kinase 2 (*LRRK2*) and PD-like Parkinson's disease kinase 1 (*PIK1*) genes (Alrouji et al. 2024; Paudel et al. 2020).

Overall, metformin offers a wide range of neuroprotective benefits by promoting neurogenesis, regulating cognitive dysfunction, counteracting aging processes, mitigating mitochondrial dysfunction and oxidative stress, enhancing autophagy, and modulating the expression of neuroprotective genes.

5 | Role of Metformin in MS

It has been reported that metformin attenuates autoimmune response in the CNS in an animal model of MS. Metformin is effective against experimental autoimmune encephalomyelitis (EAE) via the inhibition of T cell-mediated inflammation through AMPK-dependent pathway in mice (Nath et al. 2009). Metformin attenuates the induction of EAE by restricting the infiltration of mononuclear cells into the CNS, downregulating the expression of pro-inflammatory cytokines, cell adhesion molecules, matrix metalloproteinase 9, and chemokine (Onohuean et al. 2021; El-Saber Batiha et al. 2022; Al-Kuraishy, Al-Gareeb, Alsayegh, et al. 2023; Hasan Khudhair et al. 2022; Al-Kuraishy, Al-Gareeb, Alqarni, et al. 2021; Al-Kuraishy, Al-Gareeb, Waheed, and Al-Maiahy 2018). Moreover, the AMPK activity and lipids alterations (total phospholipids and in free fatty acids) are restored by metformin treatment in the CNS of treated EAE animals, suggesting the possible involvement of AMPK. Metformin activated AMPK in macrophages and thereby inhibited biosynthesis of phospholipids as well as neutral lipids and also down-regulated the expression of endotoxin-induced pro-inflammatory cytokines and their mediators such as iNOS and cyclooxygenase 2. It also attenuated IFN-gamma and IL-17-induced iNOS and cyclooxygenase 2 expression in RAW267.4 cells, further supporting its anti-inflammatory property. Metformin inhibited T cell-mediated immune responses including Ag-specific recall responses and production of Th1 or Th17 cytokines, while it induced the generation of IL-10 in spleen cells of treated EAE animals (Nath et al. 2009). It has been revealed that metformin via AMPK can inhibit T cell-mediated autoimmunity in EAE (Paintlia et al. 2013). The expressions of neurotrophic factors and of signatory genes of oligodendrocytes lineages were increased in the CNS of metformin-treated EAE animals. Similarly, metformin protects oligodendrocytes via AMPK activation in mixed glial cultures. Therefore, AMPK activators, including metformin, have the potential to limit neurologic deficits in MS and related neurodegenerative disorders. Metformin can limit the infiltration of immunoinflammatory cells into the CNS and inhibit

the expression of pro-inflammatory cytokines, matrix metalloproteinase 9 (MMP9), chemokines, and adhesion molecules (Sag et al. 2008; Alsubaie et al. 2022; Al-Kuraishy, Al-Gareeb, Al-Niemi, et al. 2022; Moubarak et al. 2021; Al-Kuraishy and Al-Gareeb 2016; Babalghith et al. 2022; Al-Kuraishy, Al-Gareeb, and Batiha 2022; Al-Kuraishy, Al-Naimi, et al. 2020; Rasheed et al. 2019). Furthermore, metformin blocks the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 via inhibiting the IL-17 and INF-γ signaling pathway, as well as T cell-mediated Th1 cytokines (Sag et al. 2008). These findings indicated that metformin in virtue of its anti-inflammatory could be effective against MS neuropathology, as documented recently (Dziedzic et al. 2020).

Metformin has a potent remyelinating effect by enhancing the activity and differentiation of oligodendrocyte precursor cells (OPCs) in rats (Neumann et al. 2019; Alorabi et al. 2022; Al-Kuraishy, Al-Gareeb, Qusti, et al. 2021; Alkuraishy, Al-Gareeb, and Waheed 2018; Batiha et al. 2021; Al-Kuraishy, Al-Gareeb, Abdullah, et al. 2021; Al-Kuraishy, Al-Gareeb, Qusty, et al. 2022). Of note, the differentiation potential of adult rodent OPCs decreases with age. Aged OPCs become unresponsive to pro-differentiation signals, signifying intrinsic constraints on therapeutic approaches aimed at enhancing OPC differentiation. This decline in functional capacity is associated with hallmarks of cellular aging, including decreased metabolic function and increased DNA damage. Fasting or treatment with metformin can reverse these changes and restore the regenerative capacity of aged OPCs, improving remyelination in aged animals following focal demyelination. Aged OPCs treated with metformin regain responsiveness to pro-differentiation signals, suggesting synergistic effects of rejuvenation and pro-differentiation therapies (Neumann et al. 2019). These findings provide insight into aging-associated remyelination failure and suggest therapeutic interventions for backing such declines in chronic disease. Furthermore, metformin can inhibit gliosis in MS by reducing the functional activity of microglia and astrocytes, thereby enhancing oligodendrocytes' function and myelination process (Largani et al. 2019; Al-Kuraishy, Al-Gareeb, et al. 2020; Al-Kuraishy, Hussien, et al. 2020; Al-Kuraishy, Al-Maiahy, et al. 2020; Batiha et al. 2023; Al-Thomali et al. 2022; Mostafa-Hedeab et al. 2022; Hussien et al. 2018; Al-Kuraishy, Al-Gareeb, Saad, and Batiha 2023; Al-Kuraishy, Al-Gareeb, Elekhnawy, and Batiha 2022). Furthermore, it has been suggested that metformin exerts its beneficial influence through AMPK pathway. Metformin up-regulates the expression of mitochondrial biogenesis genes and ameliorates the oxidative stress in the cuprizone-induced demyelination. As well, metformin reduces astrogliosis and microgliosis via AMPK signaling (Largani et al. 2019). Consistently, Largani et al. (2019) illustrated that metformin has a protective effect on the oligodendrocytes by reducing oxidative stress and mitochondrial dysfunction in the cuprizone-induced MS model in mice. Metformin also enhances myelin recovery and mitigates behavioral deficits in animal models of MS by modulating oligodendrogenesis via an AMPK-dependent pathway (Sanadgol et al. 2020).

On the other hand, metformin exerts a neuroprotective effect against MS pathogenesis through AMPK-independent mechanism. Metformin is not only a great regenerating and remyelinating agent to activate endogenous neural precursors but also

a promising candidate as a preconditioning reagent to maximize the grafting and differentiation potential of transplanted exogenous neural stem cells in vivo. It has been shown that pre-treatment of human induced pluripotent stem cell-derived neural stem cells with metformin before transplantation into the rat stroke brain can enhance their capability to graft and differentiate into neurons, astrocytes, and oligodendrocytes in vivo (Ould-Brahim et al. 2018). Metformin has been shown to promote the proliferation and differentiation of neuroblasts, formation of oligodendrocytes and impact pericyte maturity and coverage following ischemic stroke. Interestingly, metformin's ability to promote neural regeneration following stroke may be sex-dependent (Ruddy et al. 2019). Studies have confirmed the beneficial efficacy of metformin on fibrinolysis (Krysiak et al. 2013). Inhibitors of hemostasis proteases, such as plasminogen activator inhibitor 1 (PAI-1), tissue factor inhibitor (TFPI), and thrombomodulin (TM), are the key regulators of fibrinolysis and coagulation. The PAI-1 level has been reported to be higher in MS patients during exacerbations. The genetic polymorphisms of PAI-1 are linked to lower PAI-1 plasma levels and are associated with increased risk of developing MS syndrome (Lovrecic et al. 2008). Furthermore, there is a statistically positive correlation between expanded disability status scale (EDSS) scores and TM levels in MS patients (Balkuv et al. 2016). Studies conducted on 138 MS patients (85 RRMS and 53 P-MS) have demonstrated higher PAI-1 and TFPI levels in MS patients compared to healthy individuals. Studies have shown that metformin decreases coagulation factor VII and the circulating level of PAI-1. Furthermore, it interferes with factor XIII, cross-linking activity and fibrin polymerization (Standeven et al. 2002). Interestingly, metformin inhibits inflammation-induced neurodegeneration and demyelination in MS by inhibiting the expression of NF-κB and the expression of pro-inflammatory cytokines (Sanadgol et al. 2020). Moreover, metformin increases the expression of PPARα (Maida et al. 2011), which is dysregulated in MS (Storer et al. 2005). Activation of PPARα has been shown to have beneficial effects in MS models. For instance, fenofibrate, a PPARα agonist, attenuates LPS-induced expression and the release of pro-inflammatory cytokines from activated astrocytes in EAE (Xu et al. 2007). Fenofibrate achieves this by inhibiting MyD88-mediated TLR4 signaling and the expression of IL-12 (Xu et al. 2007). Therefore, metformin, through the activation of PPARα, can potentially reduce MS neuropathology by modulating inflammatory pathways and reducing the pro-inflammatory cytokine burden. This AMPK-independent mechanism adds to the multifaceted approach of metformin in ameliorating MS-related neuroinflammation and promoting neuroprotection.

Furthermore, metformin affects adipokines, including leptin and adiponectin (Dludla et al. 2021), which are involved in the pathogenesis of autoimmunity and MS (Harroud et al. 2021). Leptin promotes pro-inflammatory signaling whereas adiponectin enhances anti-inflammatory cytokines in MS (Nygaard et al. 2012). A case–control study included 25 MS patients and 25 healthy controls observed that plasma leptin and adiponectin were increased and decreased respectively in MS patients compared to controls (Nygaard et al. 2012). Metformin has been observed to increase adiponectin levels and reduce leptin levels (Dludla et al. 2021), thereby potentially modulating adipokines-mediated MS neuropathology. A placebo-controlled clinical trial investigating the possible role of metformin in

MS neuropathology has been initiated (Li et al. 2020; Aatsinki et al. 2014), and we await the outcomes. A cohort study revealed that metformin use for 6–24 months in MS patients reduced brain sclerotic lesions by lowering levels of IL-17 and INF-γ, while augmenting AMPK activity and anti-inflammatory regulatory T cells (Negrotto et al. 2016).

Moreover, imeglimin, which has a chemical structure close to metformin, is a novel oral antidiabetic drug modulating mitochondrial functions, has a neuroprotective effect against ischemia-induced brain damage and neurological deficits (Zemgulyte et al. 2022). Findings from preclinical study observed that imeglimin by inhibiting of mitochondrial permeability transition pore (mPTP) and microglial activation attenuates ischemia-induced brain damage in rats (Zemgulyte et al. 2022). In addition, imeglimin reduces LPS-induced NLRP3 inflammasome activation by inhibiting mPTP opening in THP-1 macrophages (Lee et al. 2024). NLRP3 inflammasome activation is linked with development and progression of MS (Olcum et al. 2020). Therefore, the structural similarity between metformin and imeglimin may explain the neuroprotective effect of imeglimin.

Therefore, metformin through modulation of adipocytokines and PPARα/AMPK signaling pathway could be effective in MS management.

6 | Interaction of Metformin With FGF21 in MS

Of note, FGF21 is highly down-regulated in MS (Su et al. 2006); therefore, restoring FGF21 levels by metformin administration could be a therapeutic strategy in the management of MS. Metformin has been shown to increase the expression of hepatocyte FGF21 via AMPK-dependent pathway in rats (Nygaard et al. 2012). FGF21 mRNA and protein expression are reduced in both rat and human hepatocytes treated with metformin when incubated with Compound C (an AMPK inhibitor) (Nygaard et al. 2012). Therefore, metformin is a potent inducer of hepatic FGF21 expression and that the effect of metformin seems to be mediated through AMPK activation. In addition, activated FGF21 enhances the expression of AMPK, which regulates mitochondrial function (Md 2010). Consequently, both FGF21 and metformin accelerate the expression of AMPK, a critical factor in the remyelination process in MS (Largani et al. 2019). In addition, FGF21 promotes the expression of SIRTI and PGC-1α signaling pathways (Md 2010), which are down-regulated in MS (Li et al. 2020; Witte et al. 2013). This dual activation by metformin and FGF21 suggests a synergistic potential in modulating mitochondrial function and promoting remyelination, making it a promising approach in the treatment of MS.

6.1 | SIRTI and PGC-1α

SIRTI regulates various signal transductions to control gene expression involved in the regulation of energy metabolism, inflammation, and oxidative stress during neuronal injury (Li et al. 2020). SIRTI signaling is reduced in different neurological disorders, including MS (Li et al. 2020; Sharma et al. 2021). SIRTI dysregulation affects transcription factors, and other

molecular alterations such as gene expression modification influence neuronal plasticity inhibit Th17 cells, and interleukin-1β can aggravate brain diseases. However, up-regulation of SIRT-1 reduces autoimmunity, neurodegeneration, and neuroexcitation (Sharma et al. 2021). The expression of SIRT1 in MS brains and in peripheral blood mononuclear cells (PBMCs) obtained from patients with RRMS was significant decrease during relapses when compared with the levels in controls and stable MS patients (Tegla et al. 2014). It has been shown that genetic variations in *SIRT1* rs3818292, rs3758391, and rs7895833 are related with MS, with possible differences in gender and age, as well as lower serum SIRT1 levels (Kaikaryte et al. 2023). Thus, SIRT1 may represent a biomarker of relapses and understanding the SIRT-1 signaling and identifying immune-mediated neuron deterioration can detect major therapeutic interventions that could prevent neuro complications in MS. Similarly, PGC-1α, a master regulator of mitochondrial function, is highly reduced in pyramidal neurons of the MS cortex (Witte et al. 2013). Reduction of PGC-1α enhances the development of oxidative stress and mitochondrial dysfunction in the frontal cortex of MS patients (Witte et al. 2013). Recent proof proposes that ROS produced by inflammatory cells drive axonal degeneration in active MS lesions by inducing mitochondrial dysfunction. Mitochondria are endowed with a variety of antioxidant enzymes, including peroxiredoxin-3, thioredoxin-2 and PGC-1α, which are involved in limiting ROS-induced damage. Immunohistochemical analysis of a large cohort of MS patients discovered a prominent up-regulation of PGC-1α and downstream mitochondrial antioxidants in active demyelinating MS lesions. Enhanced expression was predominantly observed in reactive astrocytes as a compensatory mechanism (Nijland et al. 2014). Intriguingly, neuronal cells co-cultured with PGC-1α-overexpressing astrocytes were protected against an exogenous oxidative attack compared to neuronal cells co-cultured with control astrocytes. Enhanced astrocytic PGC-1α levels markedly reduced the production and secretion of the pro-inflammatory mediators IL-6 and chemokine (Nijland et al. 2014). Thus, increased astrocytic PGC-1α in active MS lesions might initially function as an endogenous protective mechanism to dampen oxidative damage and inflammation thereby reducing neurodegeneration. Activation of PGC-1α therefore represents a promising therapeutic strategy to improve mitochondrial function and repress inflammation. In addition, up-regulation of neuronal PGC-1α protected neurons from apoptosis in EAE mouse model (Dang et al. 2019).

Notably, metformin promotes the expression of neuroprotective PGC-1α and SIRT1 signaling (Aatsinki et al. 2014; Ren et al. 2020). Metformin promotes the expression of hepatic PGC-1α in mice (Duan et al. 2019) and SIRTI signaling in diabetic rats (Ren et al. 2020). Findings from preclinical study illustrated that metformin protected dopaminergic neurons and improved dopamine-sensitive motor performance in an MPTP-induced PD animal model via ATF2/CREB-PGC-1α pathway (Kang et al. 2017). Likewise, metformin protects oligodendrocytes via activation of AMPK/PGC-1α signaling pathway in mixed glial cultures (Paintlia et al. 2013). Furthermore, metformin improves mitophagy in neurodegenerative diseases by activating neuronal SIRT1 signaling (Chen et al. 2021). Besides, FGF21 increases the expression of neuronal PGC-1α and SIRTI (Fang et al. 2025; Katsu-Jiménez and Giménez-Cassina 2019). Thus, metformin increases the expression of PGC-1α and SIRTI

signaling either directly or indirectly through activation of FGF21. This dual mechanism suggests that metformin could be beneficial in mitigating the neuropathology of MS by enhancing mitochondrial function and reducing oxidative stress and inflammation.

6.2 | Glutamate-Induced Excitotoxicity

Glutamate-induced excitotoxicity and associated oxidative stress are linked with oligodendrocytes injury and neurodegeneration in MS (Xu et al. 2021; Gardón et al. 2022). It has been shown that the interaction between metformin and FGF21 is highly beneficial in mitigating neuronal injury induced by oxidative stress and glutamate-induced excitotoxicity (Kar et al. 2022). Of note, FGF21 defends neurons from glutamate-induced excitotoxicity by inhibiting oxidative and inflammatory reactions (Linares et al. 2020). FGF-21 plays a crucial role in protecting mesenchymal stem cells from apoptosis induced by oxidative stress and inflammation (Linares et al. 2020). Furthermore, metformin attenuates LPS-induced oxidative stress and inflammation by increasing the expression of FGF21 (Xu et al. 2021). Various studies highlighted the potential of metformin in amelioration oxidative stress and neuronal injury across neurological disorders (Wang et al. 2020; Hassan et al. 2020). Besides, metformin attenuates glutamate-induced excitotoxicity in experimental stroke model (Zhou et al. 2016). Metformin promotes neuronal viability in neurodegenerative disorders by directly inhibiting glutamate-induced excitotoxicity and neurotoxicity (Zhou et al. 2016). In this state, metformin through induction expression of FGF21 can potentiate its neuroprotective effect against oxidative stress and glutamate-induced excitotoxicity in MS.

6.3 | β-Klotho

β-Klotho, a transmembrane protein, functions as a co-receptor for FGF21 (Yu 2015), contributing to its neuroprotective effects against MS (Kuroda et al. 2017). Mechanistically, leakage of circulating FGF21 which is predominantly expressed by the pancreas drives proliferation of oligodendrocyte precursor cells through interactions with β-Klotho, an essential coreceptor of FGF21. Notably, human oligodendrocyte precursor cells expressed β-Klotho and proliferated in response to FGF21 in vitro (Kuroda et al. 2017). It has been shown that elevating the expression of β-Klotho could potentially enhance the neuroprotective effects of FGF21. An experimental study demonstrated that diabetic mice exhibited reduced FGF21 sensitivity due to elevated levels of circulating miR34a (Majeed et al. 2016). Up-regulation of FGF-21 and β-Klotho in livers with a concomitant reduction in its downstream effectors, ERK and Sirt1 may lead to compromised FGF-21 sensitivity (Majeed et al. 2016). Interestingly, RNA binding motif 3 (RBM3) is a powerful neuroprotectant that inhibits neurodegenerative cell death in vivo and is a promising therapeutic target in brain ischemia. RBM3 is increased by the FGF21 in rat cortical neurons. FGF21 receptor binding is controlled by the transmembrane protein β-Klotho, which is mostly absent in the adult brain. However, RBM3/β-Klotho is unexpectedly high in the human infant vs. adult brain (hippocampus/prefrontal cortex). RBM3/β-Klotho is enriched in neurons in the developing brain (Jackson et al. 2019). Therefore, β-Klotho

has a neuroprotective effect against MS, and activating of this co-receptor could be a therapeutic strategy in MS. It has been shown that metformin increase β-Klotho and its downstream effectors, SIRT1 and ERK, thereby improving FGF21 sensitivity (Majeed et al. 2016). However, overexpression of FGF21 in T2DM can lead to FGF21 resistance (So and Leung 2016). In addition, IR and elevated levels of pro-inflammatory cytokines such as TNF-α suppress β-Klotho expression, resulting in FGF21 resistance in adipocytes and exacerbating inflammatory disorders (Díaz-Delfín et al. 2012). Moreover, recombinant human FGF21 (rhFGF21) activates PPARγ in TNF-α-induced HBMECs through formation of an FGF21/FGFR1/β-Klotho complex which up-regulated TJ and AJ proteins (Chen et al. 2018). Therefore, FGF21 by protecting of the BBB attenuates the progression of MS neuropathology. Thus, metformin alleviates IR by regulate β-Klotho expression and counteract FGF21 resistance. These findings suggest that metformin may enhance FGF21′s functional activity against the development and progression of MS by increasing β-Klotho expression.

6.4 | Immune Response

FGF21 inhibits the activity of T lymphocytes and the expression of pro-inflammatory cytokines (Singhal et al. 2016), and blocks NF-κB, a master regulator of B and T lymphocytes (Yu et al. 2016). In vitro, FGF21 reduced the expression of TNF-α, IL-1β, IL-6, and IFN-γ and increased the level of IL-10 in a dose-dependent manner in LPS-stimulated RAW 264.7 macrophages. FGF21 also suppresses ROS production and oxidative stress by restoring the activities of antioxidant enzymes in LPS-stimulated RAW 264.7 macrophages. Furthermore, FGF21 inhibits LPS-induced NF-κB activation, including degradation of I-κB and nuclear translocation of p65. As well, FGF21 induced heme oxygenase-1 (HO-1) expression and increased the nuclear transcription factor-E2-related factor 2 (Nrf2) levels in a dose-dependent manner in LPS-stimulated RAW 264.7 macrophages (Yu et al. 2016). Thus, FGF21 exerts an anti-inflammatory effect by enhancing Nrf2-mediated antioxidant capacity and suppressing NF-κB signaling pathway. Accordingly, FGF21 attenuates the immunoinflammatory response in MS neuropathology. The augmentation of FGF21 expression by metformin further inhibits autoreactive T cells in MS (Nath et al. 2009). Metformin also inhibits T cell-mediated immune responses by inducing the expression of FGF21 mRNA in the brain of EAE model (Nath et al. 2009). Furthermore, metformin, through an AMPK-dependent mechanism, enhances anti-inflammatory regulatory T and inhibits the progression of the Th1 and Th17 immune response (Duan et al. 2019). Remarkably, the inhibition of glucose metabolism suppresses T helper lymphocytes involved in the production of autoantibodies. Therefore, the modulation of glucose metabolism by metformin can eliminate autoreactive T helper lymphocytes and prevent the development of systemic autoimmunity (Choi et al. 2018). In addition, metformin inhibits systemic autoimmunity in mice by suppressing the differentiation of B lymphocytes into plasma cells (Lee et al. 2017). Likewise, FGF21 can block the differentiation of B lymphocytes into plasma cells (Wan 2013), a hallmark in the pathogenesis of MS. Thus, metformin, through activation of FGF21, may inhibit early pathogenic mechanism involved in the pathogenesis of MS.

6.5 | Homeostatic Pathway

Of not, disruption of the BBB integrity in MS facilitates the entry of clotting factors, such as fibrinogen, into the CNS with subsequent induction of neuroinflammation (Yates et al. 2017). A cohort study, involved 47 postmortem brains of MS patients and 10 healthy controls, revealed significantly a higher fibrinogen deposition in the motor cortex of MS patients compared with controls (Yates et al. 2017). This pathological feature arises from deregulation of fibrinolysis and increased fibrinogen-induced neurotoxicity in MS (Yates et al. 2017). In addition, fibrinogen is implicated in MS neuropathology through the activation of microglia (Adams et al. 2007). Perivascular microglia activation is a hallmark of inflammatory demyelination in MS, but the mechanisms underlying microglia activation and specific strategies to attenuate their activation remain elusive. It has been reported that fibrinogen as a novel regulator of microglia activation and targeting of the interaction of fibrinogen with the microglia integrin receptor Mac-1 is adequate to suppress EAE in mice. Fibrinogen, which is deposited in MS plaques, signals through Mac-1 can induces the differentiation of microglia to phagocytes via activation of Akt and Rho. Genetic disruption of fibrinogen-Mac-1 interaction in fibrinogen-gamma (390-396A) knock-in mice or pharmacologically impeding fibrinogen-Mac-1 interaction through intranasal delivery of a fibrinogen-derived inhibitory peptide attenuates microglia activation and suppresses relapsing paralysis (Adams et al. 2007). Therefore, targeting fibrinogen or the fibrinolysis pathway could reduce MS neuropathology. Interestingly, FGF21 has been reported to inhibit thrombus formation without increasing the risk of bleeding (Li et al. 2022). This finding indicates that FGF21 has antithrombotic effects by inhibiting the expression of fibrinogen and platelet aggregation while it enhancing fibrinolysis by activating the expression of tissue plasminogen activator (tPA) and inhibition of plasminogen activator inhibitor 1(tPA-1) (Li et al. 2022). As well, FGF21 inhibits thrombosis-induced inflammation by blocking the NF-κB signaling pathway (Li et al. 2022). Recently, tPA and tPA-1 are dysregulated in MS patients (Abbadessa et al. 2022). Therefore, activation of FGF21 signaling may mitigate MS neuropathology by regulating the homeostatic pathway. Besides, metformin, regarded as a potent activator of FGF21, plays a critical role in the regulation of blood homeostasis. Several studies have reported the fibrinolytic effects of metformin (Krysiak and Okopien 2012; Serdyńska-Szuster et al. 2011). In vivo and ex vivo studies illustrated that metformin reduces circulating fibrinogen and PAI-1, interferes with fibrin polymerization, and promotes clot-lysis effect (Standeven et al. 2002; Grant 2003).

Moreover, endothelial dysfunction and platelet dysfunction contribute to the progression and development of

TABLE 1 | Roles of metformin and FGF21in MS.

Study type	Findings	Ref.
Preclinical	FGF21 mRNA and protein expression are reduced in both rat and human hepatocytes treated with AMPK inhibitor.	(Nygaard et al. 2012).
Preclinical	FGF21 and metformin accelerate the expression of AMPK, a critical factor in the remyelination process in MS.	(Largani et al. 2019).
Preclinical	Metformin promotes the expression of neuroprotective PGC-1α and SIRT1 signaling.	(Aatsinki et al. 2014; Ren et al. 2020).
Preclinical	Metformin protects dopaminergic neurons and improved dopamine-sensitive motor performance in an MPTP-induced PD animal model via ATF2/CREB-PGC-1α pathway.	(Kang et al. 2017).
Preclinical	Metformin protects oligodendrocytes via activation of AMPK/ PGC-1α signaling pathway in mixed glial cultures.	(Paintlia et al. 2013).
Preclinical	Metformin improves mitophagy in neurodegenerative diseases by activating neuronal SIRT1 signaling.	(Chen et al. 2021).
Preclinical	FGF-21 protects mesenchymal stem cells from apoptosis induced by oxidative stress and inflammation.	(Linares et al. 2020).
Preclinical	Metformin attenuates LPS-induced oxidative stress and inflammation by increasing the expression of FGF21.	(Xu et al. 2021).
Preclinical	Metformin attenuates glutamate-induced excitotoxicity in experimental stroke model by inhibiting glutamate-induced excitotoxicity and neurotoxicity.	(Zhou et al. 2016).
Preclinical	Metformin increases β-Klotho and its downstream effectors, SIRT1 and ERK, thereby improving FGF21 sensitivity.	(Majeed et al. 2016).
Preclinical	FGF21 by protecting of the BBB attenuates the progression of MS neuropathology.	(Chen et al. 2018).
Preclinical	Metformin also inhibits T cell-mediated immune responses by inducing the expression of FGF21 mRNA in the brain of EAE model.	(Nath et al. 2009).

neurodegenerative diseases, including MS (Ahmad et al. 2020). The interaction between platelets and immune cells triggers neurovascular inflammation (Ahmad et al. 2020). Notably, platelet granules and mediators such as β thromboglobulin (βTG) and platelet factor 4 (PF-4) are activated in MS (Dziedzic and Bijak 2019; Wachowicz et al. 2016). The interaction between platelets and leukocytes promotes neuroinflammation in MS (Dziedzic and Bijak 2019). Similarly, the interaction between platelets and immune cells, along with the release of platelet microparticles, is involved in the development of autoimmune encephalomyelitis (Wachowicz et al. 2016). PF-4 enhances the differentiation of monocytes into macrophages, causing inflammation and oxidative stress (Y. Zhang et al. 2013). FGF21 has been shown to effectively reduce thromboembolic disorders by inhibiting platelet activation (Takeda et al. 2015). The increase of FGF21 in ischemic stroke could be a compensatory mechanism to inhibit platelet aggregation (Maglinger et al. 2021). Besides, metformin and its derivatives have a potential antiplatelet effect and help maintain platelet homeostasis (Wijnen et al. 2014; Markowicz-Piasecka et al. 2019). Moreover, metformin reduces the expression of platelet receptors and activators like αIIbβ3 and P-selectin (Xin et al. 2016). Likewise, metformin decreases the risk of thrombosis by inhibiting oxidative stress and release of extracellular mitochondrial DNA (Nijland et al. 2014). Metformin prevents the development of platelet mitochondrial dysfunction by regulating Ca^{2+} homeostasis (Markowicz-Piasecka et al. 2019; Xin et al. 2016). Therefore, modulation of platelet function and coagulation cascades by FGF21 and its activators like metformin may mitigate thrombotic-induced MS neuropathology. Taken together, metformin, through activation of FGF21, and related signaling pathways can mitigate different neuropathological processes in MS (Table 1).

The present review has several limitations, including that most of findings were from preclinical studies that does not specifically addressing the role of FGF21 in MS patients. In addition, biomarkers of metformin and FGF21 effects in MS have not been assessed in clinical studies. A key strength of this review is the suggestion of metformin's potential impact on MS neuropathology through the augmentation of the neuroprotective FGF21. Therefore, this review highlights the need for future clinical trials and pilot studies to confirm the potential role of metformin in the development and progression of MS through FGF21 signaling.

7 | Conclusions

MS is a progressive demyelinating disease of the CNS characterized by immune-mediated injury of the myelin sheath. The MS neuropathology involves the formation of CNS plaques, inflammation, and damage to the neuronal myelin sheath that induced by both genetic and environmental factors. MS is classified as an immune-mediated disease triggered by the hyperactivation of peripheral autoreactive T lymphocytes, which induce inflammatory changes within the CNS. FGF21, a growth factor involved in different metabolic disorders and neurodegenerative disorders, exhibits neuroprotective effects against neurodegenerative diseases through inhibition of mitochondrial dysfunction, cerebrovascular aging,

and associated inflammatory and oxidative stress disorders. FGF21 promotes the differentiation and proliferation of oligodendrocyte precursor cells, which are essential for the remyelination process in MS. FGF21 and its co-receptor β-Kloth play crucial roles in the remyelination of MS.

Activation of FGF21 by metformin can mitigates the pathogenesis of MS. Metformin in virtue of its anti-inflammatory could be effective against MS neuropathology. Metformin also influences the expression of FGF21 and attenuates the inflammatory reactions in MS. It increases the expression of PGC-1α and SIRTI signaling, either directly or indirectly, through the activation of FGF21. Metformin enhances β-Klotho expression, modulates oxidative stress, reduces glutamate-induced excitotoxicity, and regulates platelet function and coagulation cascades.

These observations suggest that metformin can improve the functional activity of FGF21 in counteracting the development and progression of MS. Preclinical and clinical studies are warranted to investigate these effects further and confirm the potential therapeutic role of metformin in MS through FGF21 signaling.

Author Contributions

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The authors have nothing to report.

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The authors have nothing to report.

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