




Review

Demyelination in Multiple Sclerosis: Reprogramming Energy Metabolism and Potential PPAR γ Agonist Treatment Approaches

Alexandre Vallée ^{1,*} , Yves Lecarpentier ², Rémy Guillevin ³ and Jean-Noël Vallée ^{4,5}

¹ Délégation à la Recherche Clinique et à l'Innovation (DRCI), Hôpital Foch, 92150 Suresnes, France

² Centre de Recherche Clinique, Grand Hôpital de l'Est Francilien (GHEF), 77100 Meaux, France; yves.c.lecarpentier@gmail.com

³ Data Analysis and Computations Through Imaging Modeling-Mathématiques (DACTIM), Unité mixte de recherche (UMR), Centre National de la Recherche Scientifique (CNRS) 7348 (Laboratoire de Mathématiques et Application), University of Poitiers, Centre Hospitalier Universitaire (CHU) de Poitiers, 86000 Poitiers, France; remy.guillevin@chu-poitiers.fr

⁴ Centre Hospitalier Universitaire (CHU) Amiens Picardie, University of Picardie Jules Verne (UPJV), 80000 Amiens, France; valleejn@gmail.com

⁵ LMA (Laboratoire de Mathématiques et Applications), Unité mixte de recherche (UMR), Centre National de la Recherche Scientifique (CNRS) 7348, Université de Poitiers, 86000 Poitiers, France

* Correspondence: alexandre.g.vallee@gmail.com; Tel.: +33-629-303-240

Received: 21 March 2018; Accepted: 11 April 2018; Published: 16 April 2018



Abstract: Demyelination in multiple sclerosis (MS) cells is the site of several energy metabolic abnormalities driven by dysregulation between the opposed interplay of peroxisome proliferator-activated receptor γ (PPAR γ) and WNT/ β -catenin pathways. We focus our review on the opposing interactions observed in demyelinating processes in MS between the canonical WNT/ β -catenin pathway and PPAR γ and their reprogramming energy metabolism implications. Demyelination in MS is associated with chronic inflammation, which is itself associated with the release of cytokines by CD4⁺ Th17 cells, and downregulation of PPAR γ expression leading to the upregulation of the WNT/ β -catenin pathway. Upregulation of WNT/ β -catenin signaling induces activation of glycolytic enzymes that modify their energy metabolic behavior. Then, in MS cells, a large portion of cytosolic pyruvate is converted into lactate. This phenomenon is called the Warburg effect, despite the availability of oxygen. The Warburg effect is the shift of an energy transfer production from mitochondrial oxidative phosphorylation to aerobic glycolysis. Lactate production is correlated with increased WNT/ β -catenin signaling and demyelinating processes by inducing dysfunction of CD4⁺ T cells leading to axonal and neuronal damage. In MS, downregulation of PPAR γ decreases insulin sensitivity and increases neuroinflammation. PPAR γ agonists inhibit Th17 differentiation in CD4⁺ T cells and then diminish release of cytokines. In MS, abnormalities in the regulation of circadian rhythms stimulate the WNT pathway to initiate the demyelination process. Moreover, PPAR γ contributes to the regulation of some key circadian genes. Thus, PPAR γ agonists interfere with reprogramming energy metabolism by directly inhibiting the WNT/ β -catenin pathway and circadian rhythms and could appear as promising treatments in MS due to these interactions.

Keywords: WNT/ β -catenin pathway; PPAR γ ; multiple sclerosis; energy metabolism; aerobic glycolysis; demyelination; Warburg effect; circadian rhythms; clock genes

1. Introduction

Multiple sclerosis (MS) presents chronic inflammation, immune responses, blood–brain barrier (BBB) breakdown, and demyelination in the white matter of the central nervous system (CNS) [1,2].

In brain and spinal cord areas, chronic inflammation leads to axonal myelin sheath destruction and the progressive loss of neurological functions with neuronal death. The inflammatory process in MS is initiated by the microglia in association with the release of players CD4⁺ helper (Th) (Th1 and Th17), the markers of the chronic inflammation [3]. Pro-inflammatory mediators, such as cytokines (interleukin (IL-6, IL-17, IL-22), tumor necrosis factor α (TNF- α)), are synthesized by Th17 cells, which are the main immune actors in the pathogenesis of MS [4]. MS can be considered as an autoimmune disease which presents neurological disability and many genetic and environmental determinant etiologies [5].

Glial cells, called oligodendrocytes (OLs), synthesize myelin sheaths in CNS by wrapping axons with multi-lamellar sheets of plasma membrane which are composed of specific lipids and proteins. Loss of myelinating OLs is considered as the origin of MS pathogenesis [6–9]. In white matter lesions of MS, oligodendrocyte precursor cells (OPC) present a stop state and a non-differentiation into myelinating OLs [6,10–14].

Altered cells in MS are derived from exergonic processes and emit heat that flows to the surrounding environment. Several irreversible processes occur by changing reprogramming energy metabolism [15,16].

Peroxisome proliferator-activated receptor γ (PPAR γ) and the WNT/ β -catenin pathway act in an opposite manner in many diseases, including MS [17,18]. Numerous autoimmune disorders present this opposed interplay, such as type 1 diabetes [19,20], thyroid autoimmunity [21,22] and rheumatoid arthritis [23,24].

In MS, the dysregulation of both PPAR γ [25] and the WNT/ β -catenin pathway [26] influence several statistical mechanisms by modifying energy metabolism leading to aerobic glycolysis, called the Warburg effect [27,28].

PPAR γ is a member of the nuclear superfamily of ligand-activated transcription factors which regulates glucose metabolism and cellular homeostasis. WNT ligands belong to the family of glycoproteins participating in the control of cell cycle, cell life and embryogenesis.

The Warburg effect is the shift of an energy transfer production from mitochondrial oxidative phosphorylation to aerobic glycolysis. The Warburg effect was discovered by Otto Warburg in 1930 in cancer processes [28]. This energy shift is partly due to injury of mitochondrial respiration, leading to an increase of adenosine triphosphate (ATP) production by glycolysis. Indeed, although aerobic glycolysis is less efficient in producing ATP molecules than oxidative phosphorylation, its production cycles are much faster than those of oxidation phosphorylation [29], which results in higher ATP molecule production than oxidative phosphorylation [30]. Recent studies have shown that this phenomenon is not specific to cancers but is also observed in non-tumor diseases, such as MS [31].

In parallel, dysregulation of circadian rhythms (CRs) has been observed in MS [32]. This dysfunction leads to upregulation of the canonical WNT/ β -catenin pathway that contributes to MS pathogenesis. PPAR γ can control CRs by regulating some key circadian genes, like Bmal1 (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1) [33] and can directly target the WNT pathway [34] and energy balance in CNS [35]. By acting on these systems, PPAR γ appears as an interesting therapeutic pathway. In MS, the opposed interplay between PPAR γ and the WNT/ β -catenin pathway has a major role in the dysregulation of energy metabolism and the disruption of CRs. Several energy balance abnormalities found in MS are induced by several cellular processes involved in both of these. We focus this review on the opposing interactions observed in MS between PPAR γ and the canonical WNT/ β -catenin pathway and their reprogramming energy metabolism implications.

2. PPAR γ

Peroxisome proliferator-activated receptor γ (PPAR γ) is an orphan nuclear receptor which is a member of the nuclear superfamily of ligand-activated transcription factors [36,37]. PPAR γ is composed of a ligand binding domain which is hydrophobic and a type II zinc finger DNA-binding domain [38].

PPAR γ ligands form a heterodimer with the retinoic X receptor (RXR). RXR is a 9-*cis* retinoic acid receptor. The heterodimer binds to peroxisome proliferator response element (PPRE) to activate several target genes [39]. PPAR γ is highly expressed in adipose tissues [40] and in cardiac and skeletal muscle, pancreatic β -cells, kidney, macrophages [41], and other vascular cells, like endothelial cells [42,43].

PPAR γ expression is implicated in numerous homeostasis pathways such as glucose and lipid metabolism. Likewise, PPAR γ expression is implicated in migration, apoptosis, cell growth, antioxidant and inflammatory responses [39,44,45]. PPAR γ is normally little expressed in CNS [46], but its expression is found in neurons, OLs, astrocytes, microglia/macrophages [47], T and B lymphocytes, dendritic cells [48] and brain endothelial cells [49]. PPAR γ can repress inflammation by decreasing nuclear factor- κ B (NF- κ B) activity [50].

Synthetic ligands of PPAR γ are prostaglandins like 15-deoxy- Δ , 14 prostaglandin J2 [51], hydroxyl octadecadienoic acid with derivatives of fatty acid oxidation [52] and lysophosphatidic acid (LPA) [53]. Pioglitazone and rosiglitazone are thiazolidinediones (TZD) which are synthetic PPAR γ ligands [52].

3. Canonical WNT/ β -Catenin Pathway (Figure 1)

Canonical WNT/ β -catenin pathway is named as the discovery of the cascade gene “W”ingless in *Drosophila* and its homologue in mice “INT”(Integration site) [54] (Figure 1). The WNT/ β -catenin pathway is involved in numerous life cycles, such as embryogenesis in migration, proliferation, differentiation, apoptosis and cell polarity [55]. Deregulation of the WNT/ β -catenin pathway is observed in several pathologies, such as cancers, fibrosis, neurodegenerative diseases, and atherosclerosis, and its targeting appears as an emerging therapeutic pathway [56].

WNT ligands are glycoproteins, which activate the canonical WNT/ β -catenin pathway [57]. Extracellular WNT ligands bind the receptor Frizzled (FZD) and then stimulate the co-receptor Low-Density Lipoprotein (LDL) receptor-related proteins 5 and 6 (LRP 5/6) [58].

β -catenin is considered as the main molecule of the canonical WNT pathway. Its major function is transcriptional activity. In physiologic conditions, cytoplasmic β -catenin is in constant turnover between synthesized and destroyed intracellular cycles.

Cytosolic β -catenin is maintained at a minimal level through the activation of the β -catenin destruction complex, which is formed by a combination of AXIN (a cytoplasmic protein regulating G-protein signaling), glycogen synthase kinase-3 β (GSK-3 β , a serine-threonine kinase), adenomatous polyposis coli (APC, a tumor suppressor gene), and casein kinase 1 (CK-1, a serine/threonine-selective enzyme) [59]. CK-1 and GSK-3 β target β -catenin by phosphorylating the serine and threonine residues located in the amino acid terminus [60–62]. CK-1 phosphorylates an N-terminus of β -catenin and GSK-3 β phosphorylates a threonine 41 (Th41), Ser33 and Ser37 sites of β -catenin [55,63]. These phosphorylations result in the recruiting of APC in the destruction complex. APC modulates the degradation of the cytosolic β -catenin into the proteasome through its tumor suppressor properties [59,64].

Activation of the WNT/ β -catenin pathway is characterized by the initiation of WNT ligands and their interactions with FZD and LRP 5/6 co-receptors [65]. This binding stimulates Dishevelled (DSH) to inhibit the destruction complex and to permit cytosolic β -catenin accumulation. Nuclear β -catenin binds T-cell factor/lymphoid enhancer factor (TCF/LEF) to activate several WNT target genes, such as c-Myc and cyclin D1 [66,67].

Demyelinating events present an upregulation of the WNT/ β -catenin pathway correlated with a release of pro-inflammatory cytokines [68]. Moreover, PPAR γ stimulation has a beneficial role in MS [69,70] through the decrease of neuroinflammation [71] and the downregulation

of the WNT/ β -catenin pathway in MS [17,18]. PPAR γ agonists are considered as potential therapeutic perspectives against neuroinflammation and neurodegeneration [72]. In MS, these two pathways operate in an opposed interplay [18] and their dysregulations lead to energy metabolism reprogramming. The objectives of this review are to describe this opposed crosstalk with circadian rhythms regulation, and to better understand the energy remodeling aspect, called the Warburg effect, observed in MS and the potential therapeutic benefits of targeting these two pathways to improve MS-related symptoms.

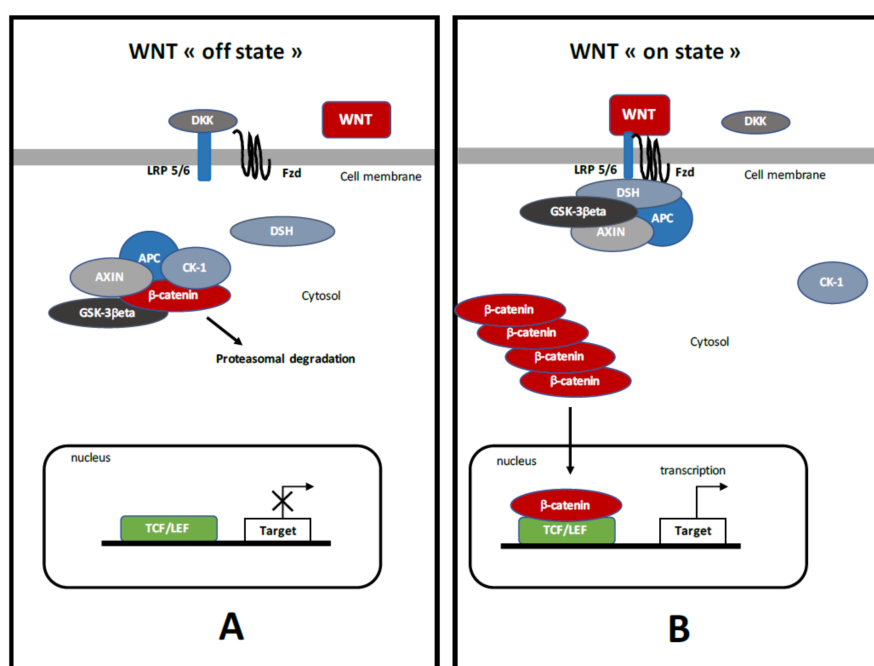


Figure 1. The canonical WNT/ β -catenin pathway. (A) Under physiological circumstances, the WNT “off state”, the cytosolic β -catenin is bound to its destruction complex, consisting of adenomatous polyposis coli (APC), AXIN and glycogen synthase kinase-3 β (GSK-3 β). After CK-1 phosphorylates on Ser45 residue, β -catenin is further phosphorylated on Thr41, Ser37, and Ser33 residues by GSK-3 β . Then, phosphorylated β -catenin is degraded into the proteasome. Therefore, the cytosolic level of β -catenin is kept low in the absence of WNT ligands. If β -catenin is not present in the nucleus, the T-cell factor/lymphoid enhancer factor (TCF/LEF) complex cannot activate the target genes. Dickkopf (DKK) can inhibit the WNT/ β -catenin pathway by binding to WNT ligands or low-density lipoprotein receptor-related protein 5/6 (LRP 5/6). (B) When WNT ligands bind to both Frizzled (FZD) and LRP 5/6, the WNT “on state”, Disheveled (DSH) is recruited and phosphorylated by FZD. Phosphorylated DSH in turn recruits AXIN, which dissociates the β -catenin destruction complex. Therefore, β -catenin escapes from phosphorylation and subsequently accumulates in the cytosol. The accumulated cytosolic β -catenin goes into the nucleus, where it binds to TCF/LEF and activates the transcription of target genes.

4. Crosstalk between PPAR γ and Canonical WNT/ β -Catenin Pathway in Diseases

The opposed interplay between the canonical WNT/ β -catenin pathway and PPAR γ has been observed in numerous pathologies. Cancers, such as gliomas [73–75] and colon cancer [76], present an upregulation of the canonical WNT/ β -catenin pathway associated with a decrease of PPAR γ expression [77]. The process of fibrosis exhibits the same mechanism [78–80]. Neurodegenerative diseases are classified in two categories [34], i.e., diseases that present a downregulation of the canonical WNT/ β -catenin pathway and an upregulation of PPAR γ , such as Alzheimer’s disease [81–83], and diseases with an upregulation of the canonical WNT/ β -catenin pathway whereas PPAR γ

is decreased, such as exudative age related macular degeneration [84,85], amyotrophic lateral sclerosis [86], and multiple sclerosis [18].

Numerous studies have suggested that PPAR γ may be considered as a negative β -catenin target [87,88]. The β -catenin pathway can decrease PPAR γ expression [89–98]. Indeed, PPAR γ and WNT/ β -catenin pathway interact via a catenin-binding domain within PPAR γ and a TCF/LEF β -catenin domain [99–102].

The decrease of the WNT/ β -catenin pathway stimulates the expression of PPAR γ [103], while the increase of PPAR γ expression inhibits β -catenin levels in numerous cellular systems [104–106]. Troglitazone, a PPAR γ agonist, can downregulate c-Myc expression, a WNT target gene [107]. PPAR γ agonists, can activate WNT inhibitors, such as Dickkopf-1 (DKK1) [108] and GSK-3 β [109] to decrease β -catenin levels. In parallel, the WNT target COUP II can decrease PPAR γ [110]. Inflammatory cytokines and cellular pathways, such as WNT/ β -catenin pathway, interleukin 1 (IL-1) and TNF- α , can inhibit PPAR γ expression [111–113].

5. PPAR γ and the Canonical WNT/ β -Catenin Pathway in MS

5.1. PPAR γ in MS

Several studies have shown that PPAR γ agonists can reduce the clinical expression of experimental autoimmune encephalomyelitis (EAE) models of MS (Table 1). In EAE models, the PPAR γ agonist 15-deoxy- Δ (12,14)-prostaglandin acts by inhibiting NF- κ B activity [114–116]. In addition, PPAR γ deficiency has been shown to exacerbate the clinical symptoms of EAE models [117]. The downregulation of PPAR γ during demyelination in MS is well-described in previous studies [18]. However, the stimulation of PPAR γ [118,119] leads to decreased inflammation and permits the remyelination in oligodendrocytes (OLs) models of MS [120]. The overexpression of PPAR γ is correlated with neuroprotection in both OLs and neurons [121–128]. Th17 differentiation is decreased by PPAR γ agonists in both murine CD4⁺ T cells and in human models [129]. In CNS-infiltrating CD4⁺ T cells, IL-17 expression is diminished by PPAR γ overexpression [130]. The anti-inflammatory role of PPAR γ is responsible for both the decreased release of inflammatory cytokines [41,131,132], and the expansion of encephalitogenic Th1 [117], Th17 cells [129] and B lymphocytes [133]. Lovastatin induces the expression of PPAR γ in the central nervous system (CNS) of EAE models [134]. However, simvastatin impedes the remyelination mechanism in cuprizone-CNS demyelinating models (non-EAE-models) [135,136].

5.2. Demyelination and Activation of WNT/ β -Catenin Pathway

Several studies have shown that the WNT/ β -catenin pathway is overexpressed during the demyelination process (for review, see [18]) (Table 1). The expression of WNT/ β -catenin pathway is overexpressed in the spinal cord dorsal horn (SCDH) in EAE models of mice [68]. The increase of the β -catenin inhibitor indomethacin is known to decrease mechanical allodynia in EAE mice [68]. In EAE models, over-activation of the WNT/ β -catenin pathway impairs and delays OPC differentiation [137]. The WNT/ β -catenin pathway, by stimulating pro-inflammatory cytokines, has a major role in neuropathic pain pathogenesis [138]. β -catenin accumulation and nuclear transcription are associated with alteration of endothelial adherens in experimental models [139,140] and in MS brain tissue [141].

5.3. Opposed Interaction between PPAR γ and WNT Pathway in MS

In MS models, moringin (4-[α -L-rhamnopyranosyloxy]-benzyl isothiocyanate) can modulate neuroinflammation through both decreased β -catenin signaling and increased PPAR γ expression [142]. Moringin can also repress inflammatory factors, such as IL-1, IL-6 and cyclo-oxygenase-2 (COX2) in EAE mice by increasing PPAR γ levels [142]. In MS, moringin is known to protect against neurodegenerative disorders [143,144].

6. Reprogramming Energy Metabolism in Demyelination

6.1. Aerobic Glycolysis

Aerobic glycolysis, called the Warburg effect, is the conversion of glucose to lactate in the presence of oxygen sufficient to support glucose catabolism via the tricarboxylic acid (TCA) cycle with oxidative phosphorylation [28] (Figure 2). Numerous studies have shown that the canonical WNT/ β -catenin pathway stimulates aerobic glycolysis and glycolytic enzymes such as glucose transporter (Glut), hexokinase (HK), pyruvate kinase M2 (PKM2), lactate dehydrogenase A (LDH-A), monocarboxylate transporter 1 (MCT-1) [27,73,77,85,145,146]. An increased rate of glucose metabolism is correlated with activation of the PI3K/Akt pathway [147]. The WNT/ β -catenin pathway directly stimulates PI3K/Akt signaling [148,149]. Activation of the PI3K/Akt pathway leads to HIF-1 α stimulation (hypoxia-inducible factor 1- α) [150] to induce overexpression of glycolytic enzymes such as Glut, LDH-A, pyruvate dehydrogenase kinase 1 (PDK1) and PKM2 [150,151]. The allosteric enzyme Phosphofruktokinase (PFK) catalyzes the conversion between β -D-fructose-6-phosphate and β -D-fructose-1,6-biphosphate. This reaction, by using ATP, leads to glycolytic oscillations and can be organized in time and space driven by PFK with a positive feedback responsible for periodic behavior [152].

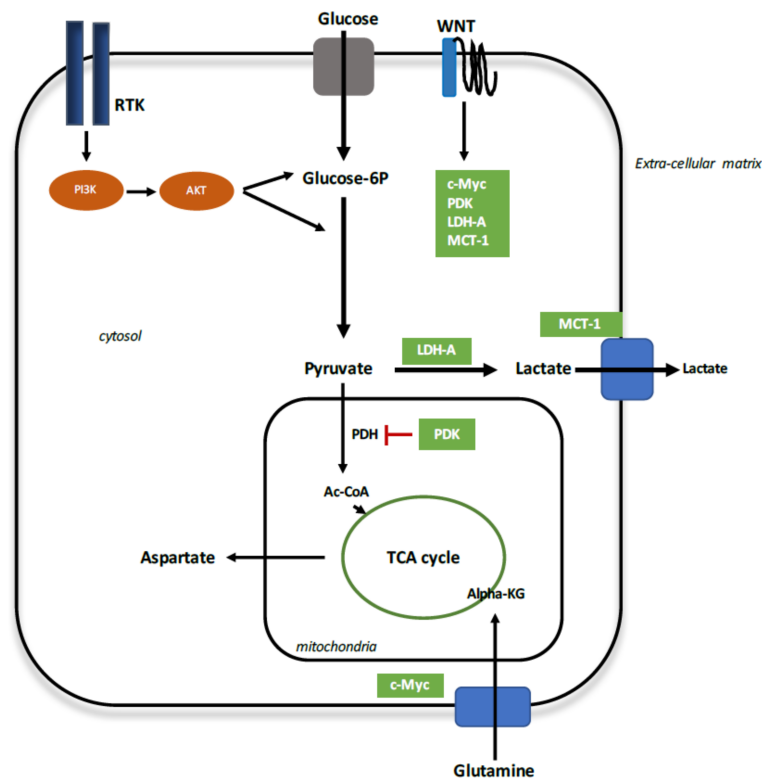


Figure 2. Aerobic glycolysis stimulation by activated canonical WNT/ β -catenin pathway. Activation of the receptor tyrosine kinase (RTK) is required to take up enough glucose to cell survival. PI3K/Akt pathway is stimulated to maintain a sufficient ATP production through the metabolism of glucose. Glucose is transformed into pyruvate into the mitochondria for the oxidative phosphorylation process. However, during WNT activation, WNT signal transduction results in activation of c-Myc, lactate dehydrogenase A (LDH-A), pyruvate dehydrogenase kinase (PDK) and monocarboxylate transporter 1 (MCT-1). The WNT target genes cooperate to divert glycolytically derived pyruvate into lactate which is expelled out the cell by MCT-1. Moreover, c-Myc induces glutamine uptake and glutaminolysis to support mitochondrial integrity and aspartate production. Accumulation of cytosolic lactate involves several pathways such as nucleotide synthesis, lipid synthesis and cell division.

6.2. Aerobic Glycolysis in MS

An imbalance between energy production and consumption has been observed in MS [153–155]. Decrease of oxidative phosphorylation and mRNA deletions observed in MS neuronal cell bodies indicate a mitochondrial dysregulation [156,157]. Indeed, alteration of energy metabolism is observed in urine [158] and in serum of MS patients [159]. Activation of aerobic glycolysis and decrease of oxidative phosphorylation aggravate MS pathogenesis by inducing dysfunction of CD4⁺ T cell [160]. CD4⁺ T cell dysregulation has a major role in MS pathogenesis by aggravating axonal and neuronal damage [1,161].

Inhibition of aerobic glycolysis in MS by copaxone restores mitochondrial activity and then diminish CD4⁺ T cell dysregulation [162]. Glycolytic metabolism reduces ROS (reactive oxygen species) production, oxidative damage and promotes the production of lipids and fatty acid required by OLs for myelin production [163–165].

Neuronal cell death and astrocytic inflammation processes are associated with the increase of glycolytic activity [166,167]. Shunt of TCA cycle by decrease of pyruvate dehydrogenase (PDH) activity is associated with neurodegeneration [168,169]. Lactate metabolism is upregulated upon the increase of aerobic glycolysis in MS [170,171]. The increase in lactate levels is correlated with the progression of MS [172,173]. Reduction of oxidative phosphorylation, shunt of the TCA cycle and activation of aerobic glycolysis inducing lactate production are observed in MS lesions [31,159]. Recently, magnetic resonance spectroscopy and positron emission tomography (PET) have shown that lactate levels are increased in MS lesions [170,174] and that lactate concentration in the cerebral spinal fluid is associated with the number of inflammatory plaques and mitochondrial dysregulation in MS [175–177]. Modulation of aerobic glycolysis appears as a potential treatment for myelin maintenance in MS lesions [26].

Table 1. WNT pathway, peroxisome proliferator-activated receptor γ (PPAR γ) and aerobic glycolysis in multiple sclerosis (MS) models.

Pathway	Expression	Actions	Model	References
PPAR γ	Agonists	Inhibition of NF- κ B	EAE models	[114–116]
		Decrease inflammation, permits remyelination	OLs models	[118,119]
		Neuroprotection	EAE models	[121–128]
		Th17 differentiation	Murine CD4 ⁺ T cells	[129]
		Decrease IL-17 expression	EAE models	[130]
		Decrease IL-1, IL-6 and COX2	EAE models	[142]
WNT	Overexpression	Decrease β -catenin	EAE models	[142]
		Chronic pain	EAE models	[68]
		Impairs OPC differentiation	EAE models	[137]
		Alteration of endothelial adherens	EAE models	[139,140]
Aerobic Glycolysis	Activation	Alteration of endothelial adherens	MS brain tissue	[141]
		Neuronal cell death and astrocytic inflammation	EAE models	[166,167]
		MS progression	Human models	[172,173]
		Increased lactate production	Human models	[31,159]
		Mitochondrial dysregulation	Human models	[175–177]

NF- κ B: nuclear factor- κ B; EAE: experimental autoimmune encephalomyelitis; OLs: oligodendrocytes; OPC: oligodendrocyte precursor cells; MS: multiple sclerosis.

7. Circadian Rhythms in MS

7.1. Circadian Rhythms, Definition

Several biologic mechanisms in the body are controlled by the circadian “clock” (circadian locomotor output cycles kaput). The circadian clock is located in the hypothalamic suprachiasmatic nucleus (SCN). CRs are endogenous and entrainable free-running periods that last approximately

24 h. Numerous transcription determinants are responsible for the regulation of CRs. They are called circadian locomotor output cycles kaput (Clock), brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1 (Bmal1), Period 1 (Per1), Period 2 (Per2), Period 3 (Per3), and Cryptochrome (Cry 1 and Cry 2) [178,179] (Figure 3). These transcription factors are controlled by positive and negative feedbacks mediated by CRs [180,181]. Clock and Bmal1 heterodimerize and then initiate transcription of Per1, Per2, Cry1 and Cry2 [182]. The Per/Cry heterodimer can inhibit its activation through negative feedback. It translocates back to the nucleus to directly inhibit the Clock/Bmal1 complex and then inhibits its own transcription [182].

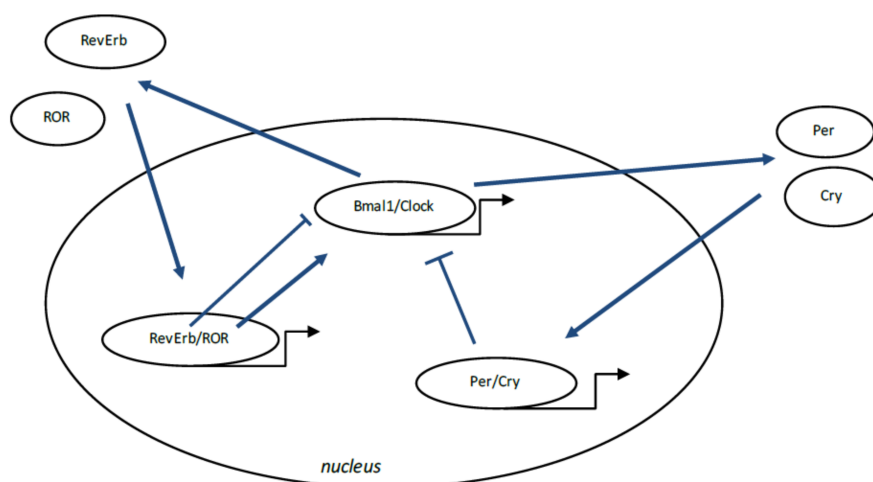


Figure 3. Circadian clock genes process. The clock is considered as a stimulatory loop, with the Bmal1/Clock heterodimer activating the transcription of Period (Per) and Cryptochrome (Cry) genes, and then a negative feedback loop with the Per/Cry heterodimer which translocates to the nucleus and then represses the transcription of the Clock and Bmal1 genes. An additional loop implicates the RORs and Rev Erbs factors with a positive feedback by retinoid-related orphan receptors (ROR) and a negative feedback by Rev Erbs. Arrows: activation; T bar: inhibition.

The Clock/Bmal1 heterodimer activates the transcription of retinoic acid-related orphan nuclear receptors, Rev-Erbs and retinoid-related orphan receptors (RORs). By a positive self-regulation RORs can activate Bmal1 transcription, whereas Rev-Erbs can repress their transcription through negative feedback [182].

7.2. Circadian Rhythm Disruption in MS

Several studies have shown that circadian rhythms have a main role in MS [183]. Late-night shift work in MS patients is associated with disruption of circadian rhythms and sleep [184,185]. Indeed, sleep dysregulation worsens EAE symptoms [186] by increasing the infiltration of inflammatory cells in the CNS, such as CD4⁺ T cells [186]. EAE severity is associated with both sleep disruption and degree of sleep fragmentation [187]. Few studies have examined CRs dysregulation in MS. However, MS is associated with many symptoms such as hypertension, heart disease, anxiety, depression and sleep disturbances [188,189]. Sleep disorders observed in MS patients [190] are characterized by prolonged sleep latency and frequent nocturnal awakening [191]. In MS, fatigue symptom is associated with CRs abnormalities [192,193], such as sleep phase syndrome and irregular sleep wake pattern. In MS, dorsolateral hypothalamic neurons secrete less neuropeptide hypocretin-1/orexin-A [194]. The Orexin-A system is responsible for the modulation of sleep-wake cycle [195]. Decreased orexin-A levels lead to the promotion of consolidated night sleep [196].

Hypersomnia observed in MS patients is associated with low cerebrospinal fluid (CSF) orexin-A and hypothalamic lesions [197]. Inflammation may suppress the orexin-A system [198] through the

overexpression of cytokines, TNF- α and interferon γ (IFN- γ) leading to fatigue syndrome in MS patients [199].

The orexin-A system is influenced by seasonal fluctuations and day length [200]. Demyelination process may put MS patients at risk for CR disorders [201]. Seasonal fluctuations observed in MS may be due to variations of melatonin levels which increase in winter and decrease in summer [202]. Moreover, this seasonal variation could also act through the birth month in susceptibility to developing MS [203,204]. Cytokine and chemokine expression in lymphoid tissues present some seasonal variation in EAE mice [204,205].

By inducing Rev-Erbs, CRs can regulate the balance of Th17/Th1/Treg in EAE mice [206]. The number of Th17 cells decreases during the acute phase of MS and is associated with melatonin levels [206].

7.3. Interaction between WNT/ β -Catenin Pathway and Circadian Rhythms

The WNT/ β -catenin pathway is downstream of the RORs regulation factors and contains diverse putative Bmal1 clock-binding sites within its promoter [207]. By these interactions, circadian genes can regulate cell cycle progression through the WNT pathway [208] (Figure 4). Expression of WNT pathway can be downregulated by Bmal1 knockdown [209]. Expression levels of WNT-related genes in wild-type mice are higher than levels of WNT-related genes with Bmal1 knockdown mice [210,211]. Bmal1 appears to be upregulated in MS [212]. Cell proliferation and cell cycle progression are regulated by Bmal1 via stimulation of the canonical WNT/ β -catenin pathway [213]. Bmal1 activation increases β -catenin transcription and decreases both β -catenin degradation and GSK-3 β activation [214]. Per2 degradation induced by β -catenin involves the dysregulation of circadian genes in intestinal mucosa of ApcMin/+ mice [215].

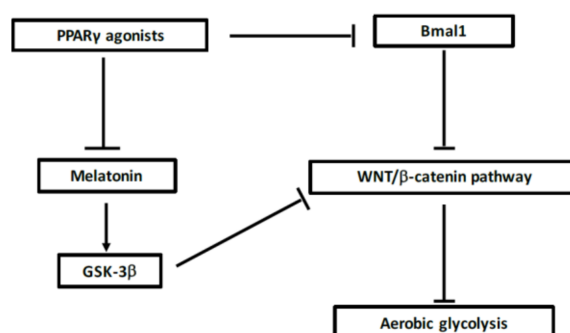


Figure 4. Schematic interaction between WNT, peroxisome proliferator-activated receptor γ (PPAR γ) and circadian rhythms. PPAR γ agonists can decrease Bmal1 expression. The knockout of Bmal1 leads to decrease WNT/ β -catenin pathway activity and then in absence of initiation of aerobic glycolysis. In parallel, PPAR γ agonists can decrease melatonin levels leading to activate GSK-3 β activity, the main inhibitor of WNT pathway.

In normal circumstances, the core circadian genes work in accurate feedback loops and keep the molecular clockworks in the SCN. They permit regulation of peripheral clocks [180,181].

Per1 and Per2 control CRs cells and modulate cell-related genes expression, such as c-Myc, to sustain the normal cell cycle [216,217]. mRNAs and proteins levels of circadian genes oscillate throughout the 24-hour period [180].

7.4. Action of PPAR γ on Circadian Rhythms

PPAR γ directly acts with the core clock genes and presents diurnal fluctuations in liver and blood vessels [33,218]. In mice, impaired diurnal rhythms are induced by a knockdown of PPAR γ [219]. PPAR γ agonists can regulate Bmal1 and the constitution of the heterodimer Clock/Bmal1 [33,220] and can then target Rev-Erb [221] (Figure 4). Decrease of the clock-controlled gene Nocturnin inhibits

PPAR γ oscillations in the liver of mice fed on high-fat diet. In normal circumstances, nocturin binds to PPAR γ to enhance its transcriptional activity [222]. The inhibition of PPAR γ expression prevents circadian function of 15-Deoxy-D 12,14-prostaglandin J2 (15-PGJ2) [219]. The partner of PPAR γ , RXR, interacts with Clock protein in a ligand-dependent manner and then decreases the formation and transcriptional activity of the Clock/Bmal1 heterodimer [223]. PPAR γ acts on the mammalian clock and energy metabolism [223]. Circadian metabolism is directly regulated by PPAR γ [219]. Retinoic acid receptor-related orphan receptor γ t (ROR γ t) is considered as a key transcriptional factor for Th17 differentiation [224,225]. PPAR γ can influence the function of Th cell clones [226]. PPAR γ agonists inhibit Th17 differentiation through the inhibition of ROR γ t induction [129,227,228]. CD4⁺ T cells fail to express ROR γ t under the action of PPAR γ agonists [129].

7.5. Interest of Cortisol in MS

Cortisol production by the HPA axis (hypothalamic-pituitary-adrenal axis) during the acute phase of MS leads to suppression of T cell secretion of inflammatory factors, such as cytokines [229]. The peak of inflammatory factor production occurs in association with low levels of cortisol. TNF- α and IL-6 production during active phases is consistent with reduction of night-time cortisol production [230]. Cortisol production is regulated by circadian rhythms that present an elevated morning level, but normalizes by the evening in MS patients [231]. However, the role of cortisol in MS remains unclear [183]. HPA axis seems to be activated in relapsing-remitting MS patients but this phenomenon has not been shown in all studies [232,233]. Nevertheless, a normal cortisol level is associated with a more severe disease course [234]. Rat strains with low HPA axis activity present worse EAE in comparison to rat strains with high HPA axis activity [235]. These results suggest that elevated levels of cortisol suppress inflammation in MS even if other studies have shown that over-active HPA axis in association with high serum cortisol contributed to worse forms of MS [236]. Cortisol seems not to act alone, and corticosteroids present in the CNS and blood may have an impact on the immune response. Corticosteroid concentration in cerebrospinal fluid present high levels in MS patients with stable disease and low levels with worse forms despite similar serum cortisol level [237]. High serum cortisol level can inhibit inflammation process through an over-active HPA axis leading to protection in MS whereas disruption of HPA axis is associated with worse forms of the disease. Cortisol is known to have immunosuppressive effects by affecting cytokine secretion and T cell activation [238]. Glucocorticoids are not limited to the inhibition of T cell response but also affect the decrease of macrophages, B cells and dendritic cells [239]. Glucocorticoids in MS present many beneficial effects but the resistance observed in humans may complicate its use [240]. Nevertheless, cortisol can affect CRs by glucocorticoid receptors [by activating the transcription of Per1 and Per2 [241,242]. In MS, the circadian oscillations of cortisol levels show that cortisol may have a key role in the regulation of peripheral clocks. In MS, no study has shown a link between PPAR γ expression and cortisol level. Few studies have observed that high PPAR γ agonists can increase cortisol levels in cancers [243].

7.6. Interest of Melatonin in MS

Melatonin (also named 5-methoxy-*N*-acetyltryptamine) is secreted by the pineal gland [244]. Melatonin is released during darkness and thereby regulates the circadian regulation of sleep [245,246]. An inverse correlation is observed between melatonin levels and MS progression [247,248]. Melatonin has anti-inflammatory, anti-oxidant and neuroprotective effects [245,249–253]. Administration of melatonin reduces EAE severity through the suppression of Th17 cell number [202,254]. Moreover, CRs could be related to inflammation by affecting immunization [255]. TNF- α and IL-1 β overexpression can inhibit the melatonin synthesis pathway [256–258]. TNF- α directly inhibits melatonin expression [259]. Melatonin ameliorates EAE development by suppressing Th17 cells generation [202,254,260–262]. Melatonin also ameliorates symptoms in EAE mouse models [202,254,260–262] through the inhibition of Rev-Erb and ROR expressions, and by limiting Th17 cell differentiation and function [206,260]. Melatonin decreases phosphorylation of GSK-3 β [263,264]. PPAR γ agonists can upregulate melatonin

levels to restore mitochondrial membrane potential, stimulate the biogenesis of mitochondria [265] and enhance mitochondrial function [266].

8. Conclusions

Demyelination during MS lesions is associated with reprogramming energy metabolism through the dysregulation of the opposed interplay of PPAR γ and the WNT/ β -catenin pathway (Table 1). The canonical WNT/ β -catenin pathway is upregulated by chronic neuroinflammation, whereas PPAR γ is downregulated during demyelinating processes. These two systems act in an opposed and reverse manner. Demyelinating processes are associated with the increase of the WNT/ β -catenin pathway and dysregulation of the circadian clock genes. In MS, over-activation of Bmal1 leads to stimulation of the canonical WNT/ β -catenin pathway. Then, activation of the WNT/ β -catenin pathway results in stimulation of glycolytic enzymes leading to activation of aerobic glycolysis. Lactate production induces dysfunction of CD4⁺ T cells leading to axonal and neuronal damage during the MS demyelinating processes. PPAR γ agonists can inhibit Th17 differentiation in CD4⁺ T cells and can diminish cytokine release. In parallel, PPAR γ agonists can interfere with reprogramming energy metabolism by directly inhibiting the WNT/ β -catenin pathway and interacting with clock genes and thus, could be a promising therapeutic pathway in MS due to their interactions (Figure 5). These findings support the possibility of targeting these pathways with the goal of improving the symptoms of MS. Clinical trials and studies are needed to confirm this hypothesis in MS pathogenesis.

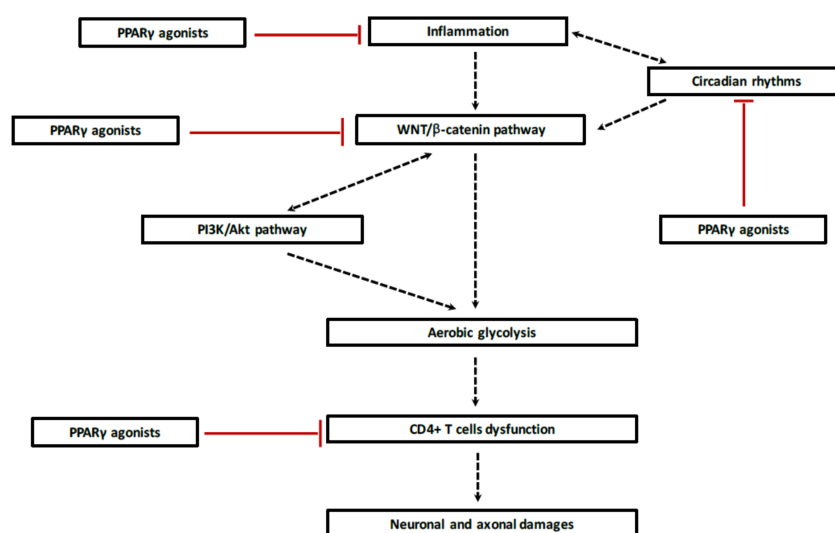


Figure 5. Potential PPAR γ agonists treatment approach in demyelination. During acute phase, inflammation processes, activated by disruption of circadian rhythms, lead to release of several cytokines and pro-inflammatory factors which stimulate the canonical WNT/ β -catenin pathway. Activation of the WNT ligands involves WNT target genes that are responsible for the initiation of the shunt of the tricarboxylic acid (TCA) resulting in aerobic glycolysis instead of oxidative phosphorylation. Lactate production, the main factor of energy metabolism alteration, and its release out the cells enhance CD4⁺ T cells dysfunction which aggravates MS pathogenesis, neuronal and axonal damages. Using PPAR γ agonists could be interesting because of their four interactions in the demyelination cascade. First, PPAR γ agonists directly inhibits neuroinflammation by inhibiting cytokines and inflammatory factors release. Secondly, PPAR γ agonists can regulate circadian clocks, such as Bmal1, to decrease inflammatory factors release and to target WNT ligands. Third, their opposed interaction with the canonical WNT/ β -catenin pathway can prevent the initiation of aerobic glycolysis process and then the energy metabolism reprogramming enable MS. At last, PPAR γ agonists have neuroprotective effects by targeting CD4⁺ T cells to prevent neuronal and axonal damages. Arrow: activation; T bar: inhibition.

Author Contributions: Alexandre Vallée, Yves Lecarpentier, Rémy Guillevin and Jean-Noël Vallée have contributed to this review. Alexandre Vallée, Yves Lecarpentier, Rémy Guillevin and Jean-Noël Vallée read and approved the final manuscript.

Conflicts of Interest: The authors declare that they have no competing interests.

Abbreviations

Acetyl-coA	Acetyl-coenzyme A
APC	Adenomatous polyposis coli
Bmal1	Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1
Clock	Circadian locomotor output cycles kaput
Cry	Cryptochrome
CRs	Circadian rhythms
DSH	Disheveled
FZD	Frizzled
Glut	Glucose transporter
GSK-3 β	Glycogen synthase kinase-3 β
LDH	Lactate dehydrogenase
LRP 5/6	Low-density lipoprotein receptor-related protein 5/6
MCT-1	Monocarboxylate lactate transporter-1
Per	Period
PPAR γ	Peroxisome proliferator-activated receptor γ
PI3K-Akt	Phosphatidylinositol 3-kinase-protein kinase B
PDH	Pyruvate dehydrogenase complex
PDK	Pyruvate dehydrogenase kinase
RORs	Retinoid-related orphan receptors
TCF/LEF	T-cell factor/lymphoid enhancer factor
TCA	Tricarboxylic acid

References

1. Goverman, J. Autoimmune T cell responses in the central nervous system. *Nat. Rev. Immunol.* **2009**, *9*, 393–407. [[CrossRef](#)] [[PubMed](#)]
2. Trapp, B.D.; Nave, K.-A. Multiple sclerosis: An immune or neurodegenerative disorder? *Annu. Rev. Neurosci.* **2008**, *31*, 247–269. [[CrossRef](#)] [[PubMed](#)]
3. Rasmussen, S.; Wang, Y.; Kivisäkk, P.; Bronson, R.T.; Meyer, M.; Imitola, J.; Khoury, S.J. Persistent activation of microglia is associated with neuronal dysfunction of callosal projecting pathways and multiple sclerosis-like lesions in relapsing—Remitting experimental autoimmune encephalomyelitis. *Brain J. Neurol.* **2007**, *130*, 2816–2829. [[CrossRef](#)] [[PubMed](#)]
4. Jadidi-Niaragh, F.; Mirshafiey, A. Th17 cell, the new player of neuroinflammatory process in multiple sclerosis. *Scand. J. Immunol.* **2011**, *74*, 1–13. [[CrossRef](#)] [[PubMed](#)]
5. Didonna, A.; Oksenberg, J.R. Genetic determinants of risk and progression in multiple sclerosis. *Clin. Chim. Acta Int. J. Clin. Chem.* **2015**, *449*, 16–22. [[CrossRef](#)] [[PubMed](#)]
6. Chang, A.; Tourtellotte, W.W.; Rudick, R.; Trapp, B.D. Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *N. Engl. J. Med.* **2002**, *346*, 165–173. [[CrossRef](#)] [[PubMed](#)]
7. Franklin, R.J.M. Why does remyelination fail in multiple sclerosis? *Nat. Rev. Neurosci.* **2002**, *3*, 705–714. [[CrossRef](#)] [[PubMed](#)]
8. Khwaja, O.; Volpe, J.J. Pathogenesis of cerebral white matter injury of prematurity. *Arch. Dis. Child. Fetal Neonatal Ed.* **2008**, *93*, F153–F161. [[CrossRef](#)] [[PubMed](#)]
9. Woodward, L.J.; Anderson, P.J.; Austin, N.C.; Howard, K.; Inder, T.E. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N. Engl. J. Med.* **2006**, *355*, 685–694. [[CrossRef](#)] [[PubMed](#)]
10. Back, S.A.; Rosenberg, P.A. Pathophysiology of glia in perinatal white matter injury. *Glia* **2014**, *62*, 1790–1815. [[CrossRef](#)] [[PubMed](#)]

11. Billiards, S.S.; Haynes, R.L.; Folkert, R.D.; Borenstein, N.S.; Trachtenberg, F.L.; Rowitch, D.H.; Ligon, K.L.; Volpe, J.J.; Kinney, H.C. Myelin abnormalities without oligodendrocyte loss in periventricular leukomalacia. *Brain Pathol.* **2008**, *18*, 153–163. [[CrossRef](#)] [[PubMed](#)]
12. Buser, J.R.; Maire, J.; Riddle, A.; Gong, X.; Nguyen, T.; Nelson, K.; Luo, N.L.; Ren, J.; Struve, J.; Sherman, L.S.; et al. Arrested preoligodendrocyte maturation contributes to myelination failure in premature infants. *Ann. Neurol.* **2012**, *71*, 93–109. [[CrossRef](#)] [[PubMed](#)]
13. Fancy, S.P.J.; Kotter, M.R.; Harrington, E.P.; Huang, J.K.; Zhao, C.; Rowitch, D.H.; Franklin, R.J.M. Overcoming remyelination failure in multiple sclerosis and other myelin disorders. *Exp. Neurol.* **2010**, *225*, 18–23. [[CrossRef](#)] [[PubMed](#)]
14. Kuhlmann, T.; Miron, V.; Cui, Q.; Cuo, Q.; Wegner, C.; Antel, J.; Brück, W. Differentiation block of oligodendroglial progenitor cells as a cause for remyelination failure in chronic multiple sclerosis. *Brain J. Neurol.* **2008**, *131*, 1749–1758. [[CrossRef](#)] [[PubMed](#)]
15. Sandler, S. *Chemical and Engineering Thermodynamics*, 4th ed.; Wiley: New York, NY, USA, 2006.
16. Garcia, H.G.; Kondev, J.; Orme, N.; Theriot, J.A.; Phillips, R. Thermodynamics of biological processes. *Methods Enzymol.* **2011**, *492*, 27–59. [[CrossRef](#)] [[PubMed](#)]
17. Lecarpentier, Y.; Claes, V.; Duthoit, G.; Hébert, J.-L. Circadian rhythms, Wnt/beta-catenin pathway and PPAR alpha/gamma profiles in diseases with primary or secondary cardiac dysfunction. *Front. Physiol.* **2014**, *5*, 429. [[CrossRef](#)] [[PubMed](#)]
18. Vallée, A.; Vallée, J.-N.; Guillemin, R.; Lecarpentier, Y. Interactions between the Canonical WNT/Beta-Catenin Pathway and PPAR Gamma on Neuroinflammation, Demyelination, and Remyelination in Multiple Sclerosis. *Cell. Mol. Neurobiol.* **2017**, *38*, 783–795. [[CrossRef](#)] [[PubMed](#)]
19. Tsentidis, C.; Gourgiotis, D.; Kossiva, L.; Marmarinos, A.; Doulgeraki, A.; Karavanaki, K. Increased levels of Dickkopf-1 are indicative of Wnt/ β -catenin downregulation and lower osteoblast signaling in children and adolescents with type 1 diabetes mellitus, contributing to lower bone mineral density. *Osteoporos. Int.* **2017**, *28*, 945–953. [[CrossRef](#)] [[PubMed](#)]
20. Pörksen, S.; Nielsen, L.B.; Mortensen, H.B.; Danne, T.; Kocova, M.; Castaño, L.; Pociot, F.; Hougaard, P.; Ekstrøm, C.T.; Gammeltoft, S.; et al. Hvidøre Study Group on Childhood Diabetes Variation within the PPARG gene is associated with residual beta-cell function and glycemic control in children and adolescents during the first year of clinical type 1 diabetes. *Pediatr. Diabetes* **2008**, *9*, 297–302. [[CrossRef](#)] [[PubMed](#)]
21. Ferrari, S.M.; Fallahi, P.; Vita, R.; Antonelli, A.; Benvenga, S. Peroxisome Proliferator-Activated Receptor- γ in Thyroid Autoimmunity. *PPAR Res.* **2015**, *2015*, 232818. [[CrossRef](#)] [[PubMed](#)]
22. Tao, W.; Ayala-Haedo, J.A.; Field, M.G.; Pelaez, D.; Wester, S.T. RNA-Sequencing Gene Expression Profiling of Orbital Adipose-Derived Stem Cell Population Implicate HOX Genes and WNT Signaling Dysregulation in the Pathogenesis of Thyroid-Associated Orbitopathy. *Investig. Ophthalmol. Vis. Sci.* **2017**, *58*, 6146–6158. [[CrossRef](#)] [[PubMed](#)]
23. Xiao, C.Y.; Pan, Y.F.; Guo, X.H.; Wu, Y.Q.; Gu, J.R.; Cai, D.Z. Expression of β -catenin in rheumatoid arthritis fibroblast-like synoviocytes. *Scand. J. Rheumatol.* **2011**, *40*, 26–33. [[CrossRef](#)] [[PubMed](#)]
24. Marder, W.; Khalatbari, S.; Myles, J.D.; Hench, R.; Lustig, S.; Yalavarthi, S.; Parameswaran, A.; Brook, R.D.; Kaplan, M.J. The peroxisome proliferator activated receptor- γ pioglitazone improves vascular function and decreases disease activity in patients with rheumatoid arthritis. *J. Am. Heart Assoc.* **2013**, *2*, e000441. [[CrossRef](#)] [[PubMed](#)]
25. Lecarpentier, Y.; Krokidis, X.; Martin, P.; Pineau, T.; Hébert, J.-L.; Quillard, J.; Cortes-Morichetti, M.; Coirault, C. Increased entropy production in diaphragm muscle of PPAR alpha knockout mice. *J. Theor. Biol.* **2008**, *250*, 92–102. [[CrossRef](#)] [[PubMed](#)]
26. Rone, M.B.; Cui, Q.-L.; Fang, J.; Wang, L.-C.; Zhang, J.; Khan, D.; Bedard, M.; Almazan, G.; Ludwin, S.K.; Jones, R.; et al. Oligodendroglial pathology in Multiple Sclerosis: Low Glycolytic Metabolic Rate Promotes Oligodendrocyte Survival. *J. Neurosci. Off. J. Soc. Neurosci.* **2016**, *36*, 4698–4707. [[CrossRef](#)] [[PubMed](#)]
27. Thompson, C.B. Wnt meets Warburg: Another piece in the puzzle? *EMBO J.* **2014**, *33*, 1420–1422. [[CrossRef](#)] [[PubMed](#)]
28. Warburg, O. On the origin of cancer cells. *Science* **1956**, *123*, 309–314. [[CrossRef](#)] [[PubMed](#)]
29. Yang, D.; Wang, M.-T.; Tang, Y.; Chen, Y.; Jiang, H.; Jones, T.T.; Rao, K.; Brewer, G.J.; Singh, K.K.; Nie, D. Impairment of mitochondrial respiration in mouse fibroblasts by oncogenic H-RAS(Q61L). *Cancer Biol. Ther.* **2010**, *9*, 122–133. [[CrossRef](#)] [[PubMed](#)]

30. Pfeiffer, T.; Schuster, S.; Bonhoeffer, S. Cooperation and competition in the evolution of ATP-producing pathways. *Science* **2001**, *292*, 504–507. [[CrossRef](#)] [[PubMed](#)]
31. Chen, Z.; Liu, M.; Li, L.; Chen, L. Involvement of the Warburg effect in non-tumor diseases processes. *J. Cell. Physiol.* **2018**, *233*, 2839–2849. [[CrossRef](#)] [[PubMed](#)]
32. Newland, P.; Starkweather, A.; Sorenson, M. Central fatigue in multiple sclerosis: A review of the literature. *J. Spinal Cord Med.* **2016**, *39*, 386–399. [[CrossRef](#)] [[PubMed](#)]
33. Wang, N.; Yang, G.; Jia, Z.; Zhang, H.; Aoyagi, T.; Soodvilai, S.; Symons, J.D.; Schnermann, J.B.; Gonzalez, F.J.; Litwin, S.E.; et al. Vascular PPARgamma controls circadian variation in blood pressure and heart rate through Bmal1. *Cell Metab.* **2008**, *8*, 482–491. [[CrossRef](#)] [[PubMed](#)]
34. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Thermodynamics in Neurodegenerative Diseases: Interplay between Canonical WNT/Beta-Catenin Pathway-PPAR Gamma, Energy Metabolism and Circadian Rhythms. *Neuromolecular Med.* **2018**. [[CrossRef](#)] [[PubMed](#)]
35. Ryan, K.K.; Li, B.; Grayson, B.E.; Matter, E.K.; Woods, S.C.; Seeley, R.J. A role for central nervous system PPAR- γ in the regulation of energy balance. *Nat. Med.* **2011**, *17*, 623–626. [[CrossRef](#)] [[PubMed](#)]
36. Bookout, A.L.; Jeong, Y.; Downes, M.; Yu, R.T.; Evans, R.M.; Mangelsdorf, D.J. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* **2006**, *126*, 789–799. [[CrossRef](#)] [[PubMed](#)]
37. Michalik, L.; Auwerx, J.; Berger, J.P.; Chatterjee, V.K.; Glass, C.K.; Gonzalez, F.J.; Grimaldi, P.A.; Kadowaki, T.; Lazar, M.A.; O’Rahilly, S.; et al. International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. *Pharmacol. Rev.* **2006**, *58*, 726–741. [[CrossRef](#)] [[PubMed](#)]
38. Abbas, A.; Blandon, J.; Rude, J.; Elfar, A.; Mukherjee, D. PPAR- γ agonist in treatment of diabetes: Cardiovascular safety considerations. *Cardiovasc. Hematol. Agents Med. Chem.* **2012**, *10*, 124–134. [[CrossRef](#)] [[PubMed](#)]
39. Oyekan, A. PPARs and their effects on the cardiovascular system. *Clin. Exp. Hypertens.* **2011**, *33*, 287–293. [[CrossRef](#)] [[PubMed](#)]
40. Adams, M.; Montague, C.T.; Prins, J.B.; Holder, J.C.; Smith, S.A.; Sanders, L.; Digby, J.E.; Sewter, C.P.; Lazar, M.A.; Chatterjee, V.K.; et al. Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. *J. Clin. Investig.* **1997**, *100*, 3149–3153. [[CrossRef](#)] [[PubMed](#)]
41. Ricote, M.; Li, A.C.; Willson, T.M.; Kelly, C.J.; Glass, C.K. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. *Nature* **1998**, *391*, 79–82. [[CrossRef](#)] [[PubMed](#)]
42. Asakawa, M.; Takano, H.; Nagai, T.; Uozumi, H.; Hasegawa, H.; Kubota, N.; Saito, T.; Masuda, Y.; Kadowaki, T.; Komuro, I. Peroxisome proliferator-activated receptor gamma plays a critical role in inhibition of cardiac hypertrophy in vitro and in vivo. *Circulation* **2002**, *105*, 1240–1246. [[CrossRef](#)] [[PubMed](#)]
43. Chandra, M.; Miriyala, S.; Panchatcharam, M. PPAR γ and Its Role in Cardiovascular Diseases. *PPAR Res.* **2017**, *2017*, 6404638. [[CrossRef](#)] [[PubMed](#)]
44. Chen, R.; Liang, F.; Moriya, J.; Yamakawa, J.; Takahashi, T.; Shen, L.; Kanda, T. Peroxisome proliferator-activated receptors (PPARs) and their agonists for hypertension and heart failure: Are the reagents beneficial or harmful? *Int. J. Cardiol.* **2008**, *130*, 131–139. [[CrossRef](#)] [[PubMed](#)]
45. Polvani, S.; Tarocchi, M.; Galli, A. PPAR γ and Oxidative Stress: Con(β) Catenating NRF2 and FOXO. *PPAR Res.* **2012**, *2012*, 641087. [[CrossRef](#)] [[PubMed](#)]
46. Braissant, O.; Fougère, F.; Scotto, C.; Dauça, M.; Wahli, W. Differential expression of peroxisome proliferator-activated receptors (PPARs): Tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. *Endocrinology* **1996**, *137*, 354–366. [[CrossRef](#)] [[PubMed](#)]
47. Bernardo, A.; Minghetti, L. Regulation of Glial Cell Functions by PPAR-gamma Natural and Synthetic Agonists. *PPAR Res.* **2008**, *2008*, 864140. [[CrossRef](#)] [[PubMed](#)]
48. Yang, Y.; Lovett-Racke, A.E.; Racke, M.K. Regulation of Immune Responses and Autoimmune Encephalomyelitis by PPARs. *PPAR Res.* **2010**, *2010*, 104705. [[CrossRef](#)] [[PubMed](#)]
49. Klotz, L.; Diehl, L.; Dani, I.; Neumann, H.; von Oppen, N.; Dolf, A.; Endl, E.; Klockgether, T.; Engelhardt, B.; Knolle, P. Brain endothelial PPARgamma controls inflammation-induced CD4⁺ T cell adhesion and transmigration in vitro. *J. Neuroimmunol.* **2007**, *190*, 34–43. [[CrossRef](#)] [[PubMed](#)]

50. Ricote, M.; Glass, C.K. PPARs and molecular mechanisms of transrepression. *Biochim. Biophys. Acta* **2007**, *1771*, 926–935. [[CrossRef](#)] [[PubMed](#)]
51. Touyz, R.M.; Schiffrin, E.L. Ang II-stimulated superoxide production is mediated via phospholipase D in human vascular smooth muscle cells. *Hypertens.* **1999**, *34*, 976–982. [[CrossRef](#)]
52. Széles, L.; Töröcsik, D.; Nagy, L. PPARgamma in immunity and inflammation: Cell types and diseases. *Biochim. Biophys. Acta* **2007**, *1771*, 1014–1030. [[CrossRef](#)] [[PubMed](#)]
53. McIntyre, T.M.; Pontsler, A.V.; Silva, A.R.; St Hilaire, A.; Xu, Y.; Hinshaw, J.C.; Zimmerman, G.A.; Hama, K.; Aoki, J.; Arai, H.; et al. Identification of an intracellular receptor for lysophosphatidic acid (LPA): LPA is a transcellular PPARgamma agonist. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 131–136. [[CrossRef](#)] [[PubMed](#)]
54. Nusse, R.; Brown, A.; Papkoff, J.; Scambler, P.; Shackleford, G.; McMahon, A.; Moon, R.; Varmus, H. A new nomenclature for int-1 and related genes: The Wnt gene family. *Cell* **1991**, *64*, 231. [[CrossRef](#)]
55. MacDonald, B.T.; Tamai, K.; He, X. Wnt/beta-catenin signaling: Components, mechanisms, and diseases. *Dev. Cell* **2009**, *17*, 9–26. [[CrossRef](#)] [[PubMed](#)]
56. Nusse, R.; Clevers, H. Wnt/ β -Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell* **2017**, *169*, 985–999. [[CrossRef](#)] [[PubMed](#)]
57. Nusse, R. Wnt signaling. *Cold Spring Harb. Perspect. Biol.* **2012**, *4*. [[CrossRef](#)] [[PubMed](#)]
58. He, X.; Semenov, M.; Tamai, K.; Zeng, X. LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: Arrows point the way. *Dev. Camb. Engl.* **2004**, *131*, 1663–1677. [[CrossRef](#)]
59. Miller, J.R.; Hocking, A.M.; Brown, J.D.; Moon, R.T. Mechanism and function of signal transduction by the Wnt/beta-catenin and Wnt/ Ca^{2+} pathways. *Oncogene* **1999**, *18*, 7860–7872. [[CrossRef](#)] [[PubMed](#)]
60. Reya, T.; Clevers, H. Wnt signalling in stem cells and cancer. *Nature* **2005**, *434*, 843–850. [[CrossRef](#)] [[PubMed](#)]
61. Anastas, J.N.; Moon, R.T. WNT signalling pathways as therapeutic targets in cancer. *Nat. Rev. Cancer* **2013**, *13*, 11–26. [[CrossRef](#)] [[PubMed](#)]
62. Kim, W.; Kim, M.; Jho, E. Wnt/ β -catenin signalling: From plasma membrane to nucleus. *Biochem. J.* **2013**, *450*, 9–21. [[CrossRef](#)] [[PubMed](#)]
63. Rao, T.P.; Kühl, M. An updated overview on Wnt signaling pathways: A prelude for more. *Circ. Res.* **2010**, *106*, 1798–1806. [[CrossRef](#)] [[PubMed](#)]
64. Aoki, K.; Taketo, M.M. Adenomatous polyposis coli (APC): A multi-functional tumor suppressor gene. *J. Cell Sci.* **2007**, *120*, 3327–3335. [[CrossRef](#)] [[PubMed](#)]
65. Komiya, Y.; Habas, R. Wnt signal transduction pathways. *Organogenesis* **2008**, *4*, 68–75. [[CrossRef](#)] [[PubMed](#)]
66. Singh, R.; De Aguiar, R.B.; Naik, S.; Mani, S.; Ostadsharif, K.; Wencker, D.; Sotoudeh, M.; Malekzadeh, R.; Sherwin, R.S.; Mani, A. LRP6 enhances glucose metabolism by promoting TCF7L2-dependent insulin receptor expression and IGF receptor stabilization in humans. *Cell Metab.* **2013**, *17*, 197–209. [[CrossRef](#)] [[PubMed](#)]
67. Wang, S.; Song, K.; Srivastava, R.; Dong, C.; Go, G.-W.; Li, N.; Iwakiri, Y.; Mani, A. Nonalcoholic fatty liver disease induced by noncanonical Wnt and its rescue by Wnt3a. *FASEB J.* **2015**, *29*, 3436–3445. [[CrossRef](#)] [[PubMed](#)]
68. Yuan, S.; Shi, Y.; Tang, S.-J. Wnt signaling in the pathogenesis of multiple sclerosis-associated chronic pain. *J. Neuroimmune Pharmacol.* **2012**, *7*, 904–913. [[CrossRef](#)] [[PubMed](#)]
69. Kaiser, C.C.; Shukla, D.K.; Stebbins, G.T.; Skias, D.D.; Jeffery, D.R.; Stefoski, D.; Katsamakis, G.; Feinstein, D.L. A pilot test of pioglitazone as an add-on in patients with relapsing remitting multiple sclerosis. *J. Neuroimmunol.* **2009**, *211*, 124–130. [[CrossRef](#)] [[PubMed](#)]
70. Shukla, D.K.; Kaiser, C.C.; Stebbins, G.T.; Feinstein, D.L. Effects of pioglitazone on diffusion tensor imaging indices in multiple sclerosis patients. *Neurosci. Lett.* **2010**, *472*, 153–156. [[CrossRef](#)] [[PubMed](#)]
71. Klotz, L.; Schmidt, M.; Giese, T.; Sastre, M.; Knolle, P.; Klockgether, T.; Heneka, M.T. Proinflammatory stimulation and pioglitazone treatment regulate peroxisome proliferator-activated receptor gamma levels in peripheral blood mononuclear cells from healthy controls and multiple sclerosis patients. *J. Immunol.* **2005**, *175*, 4948–4955. [[CrossRef](#)]
72. Esmaeili, M.A.; Yadav, S.; Gupta, R.K.; Waggoner, G.R.; Deloach, A.; Calingasan, N.Y.; Beal, M.F.; Kiaei, M. Preferential PPAR- α activation reduces neuroinflammation, and blocks neurodegeneration in vivo. *Hum. Mol. Genet.* **2016**, *25*, 317–327. [[CrossRef](#)] [[PubMed](#)]
73. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Thermodynamics in Gliomas: Interactions between the Canonical WNT/ β -Catenin Pathway and PPAR Gamma. *Front. Physiol.* **2017**, *8*, 352. [[CrossRef](#)] [[PubMed](#)]

74. Vallée, A.; Guillevin, R.; Vallée, J.-N. Vasculogenesis and angiogenesis initiation under normoxic conditions through Wnt/ β -catenin pathway in gliomas. *Rev. Neurosci.* **2018**, *29*, 71–91. [[CrossRef](#)] [[PubMed](#)]
75. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Opposite Interplay between the Canonical WNT/ β -Catenin Pathway and PPAR Gamma: A Potential Therapeutic Target in Gliomas. *Neurosci. Bull.* **2018**. [[CrossRef](#)] [[PubMed](#)]
76. Lecarpentier, Y.; Claes, V.; Vallée, A.; Hébert, J.-L. Interactions between PPAR Gamma and the Canonical Wnt/Beta-Catenin Pathway in Type 2 Diabetes and Colon Cancer. *PPAR Res.* **2017**, *2017*, 5879090. [[CrossRef](#)] [[PubMed](#)]
77. Lecarpentier, Y.; Claes, V.; Vallée, A.; Hébert, J.-L. Thermodynamics in cancers: Opposing interactions between PPAR gamma and the canonical WNT/beta-catenin pathway. *Clin. Transl. Med.* **2017**, *6*, 14. [[CrossRef](#)] [[PubMed](#)]
78. Vallée, A.; Lecarpentier, Y.; Vallée, J.-N. Thermodynamic Aspects and Reprogramming Cellular Energy Metabolism during the Fibrosis Process. *Int. J. Mol. Sci.* **2017**, *18*, 2537. [[CrossRef](#)] [[PubMed](#)]
79. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Interactions between TGF- β 1, canonical WNT/ β -catenin pathway and PPAR γ in radiation-induced fibrosis. *Oncotarget* **2017**, *8*, 90579–90604. [[CrossRef](#)] [[PubMed](#)]
80. Lecarpentier, Y.; Schussler, O.; Claes, V.; Vallée, A. The Myofibroblast: TGF β -1, A Conductor which Plays a Key Role in Fibrosis by Regulating the Balance between PPAR γ and the Canonical WNT Pathway. *Nucl. Recept. Res.* **2017**, *23*. [[CrossRef](#)] [[PubMed](#)]
81. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Effects of cannabidiol interactions with Wnt/ β -catenin pathway and PPAR γ on oxidative stress and neuroinflammation in Alzheimer's disease. *Acta Biochim. Biophys. Sin.* **2017**, *49*, 853–866. [[CrossRef](#)] [[PubMed](#)]
82. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Reprogramming energetic metabolism in Alzheimer's disease. *Life Sci.* **2018**, *193*, 141–152. [[CrossRef](#)] [[PubMed](#)]
83. Vallée, A.; Lecarpentier, Y. Alzheimer Disease: Crosstalk between the Canonical Wnt/Beta-Catenin Pathway and PPARs Alpha and Gamma. *Front. Neurosci.* **2016**, *10*, 459. [[CrossRef](#)] [[PubMed](#)]
84. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. Aerobic Glycolysis Hypothesis Through WNT/Beta-Catenin Pathway in Exudative Age-Related Macular Degeneration. *J. Mol. Neurosci.* **2017**, *62*, 368–379. [[CrossRef](#)] [[PubMed](#)]
85. Vallée, A.; Lecarpentier, Y.; Guillevin, R.; Vallée, J.-N. PPAR γ agonists: Potential treatments for exudative age-related macular degeneration. *Life Sci.* **2017**, *188*, 123–130. [[CrossRef](#)] [[PubMed](#)]
86. Lecarpentier, Y.; Vallée, A. Opposite Interplay between PPAR Gamma and Canonical Wnt/Beta-Catenin Pathway in Amyotrophic Lateral Sclerosis. *Front. Neurol.* **2016**, *7*, 100. [[CrossRef](#)] [[PubMed](#)]
87. Ajmone-Cat, M.A.; D'Urso, M.C.; di Blasio, G.; Brignone, M.S.; De Simone, R.; Minghetti, L. Glycogen synthase kinase 3 is part of the molecular machinery regulating the adaptive response to LPS stimulation in microglial cells. *Brain Behav. Immun.* **2016**, *55*, 225–235. [[CrossRef](#)] [[PubMed](#)]
88. Jansson, E.A.; Are, A.; Greicius, G.; Kuo, I.-C.; Kelly, D.; Arulampalam, V.; Pettersson, S. The Wnt/beta-catenin signaling pathway targets PPARgamma activity in colon cancer cells. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 1460–1465. [[CrossRef](#)] [[PubMed](#)]
89. Drygiannakis, I.; Valatas, V.; Sfakianaki, O.; Bourikas, L.; Manousou, P.; Kambas, K.; Ritis, K.; Kolios, G.; Kouroumalis, E. Proinflammatory cytokines induce crosstalk between colonic epithelial cells and subepithelial myofibroblasts: Implication in intestinal fibrosis. *J. Crohns Colitis* **2013**, *7*, 286–300. [[CrossRef](#)] [[PubMed](#)]
90. Farmer, S.R. Regulation of PPARgamma activity during adipogenesis. *Int. J. Obes.* **2005**, *29* (Suppl. 1), S13–S16. [[CrossRef](#)] [[PubMed](#)]
91. Jeon, K.-I.; Kulkarni, A.; Woeller, C.F.; Phipps, R.P.; Sime, P.J.; Hindman, H.B.; Huxlin, K.R. Inhibitory effects of PPAR γ ligands on TGF- β 1-induced corneal myofibroblast transformation. *Am. J. Pathol.* **2014**, *184*, 1429–1445. [[CrossRef](#)] [[PubMed](#)]
92. Kumar, V.; Mundra, V.; Mahato, R.I. Nanomedicines of Hedgehog inhibitor and PPAR- γ agonist for treating liver fibrosis. *Pharm. Res.* **2014**, *31*, 1158–1169. [[CrossRef](#)] [[PubMed](#)]
93. Lee, Y.; Kim, S.H.; Lee, Y.J.; Kang, E.S.; Lee, B.-W.; Cha, B.S.; Kim, J.W.; Song, D.H.; Lee, H.C. Transcription factor Snail is a novel regulator of adipocyte differentiation via inhibiting the expression of peroxisome proliferator-activated receptor γ . *Cell. Mol. Life Sci.* **2013**, *70*, 3959–3971. [[CrossRef](#)] [[PubMed](#)]

94. Li, Q.; Yan, Z.; Li, F.; Lu, W.; Wang, J.; Guo, C. The improving effects on hepatic fibrosis of interferon- γ liposomes targeted to hepatic stellate cells. *Nanotechnology* **2012**, *23*, 265101. [[CrossRef](#)] [[PubMed](#)]
95. Liu, J.; Farmer, S.R. Regulating the balance between peroxisome proliferator-activated receptor gamma and beta-catenin signaling during adipogenesis. A glycogen synthase kinase 3beta phosphorylation-defective mutant of beta-catenin inhibits expression of a subset of adipogenic genes. *J. Biol. Chem.* **2004**, *279*, 45020–45027. [[CrossRef](#)] [[PubMed](#)]
96. Qian, J.; Niu, M.; Zhai, X.; Zhou, Q.; Zhou, Y. β -Catenin pathway is required for TGF- β 1 inhibition of PPAR γ expression in cultured hepatic stellate cells. *Pharmacol. Res.* **2012**, *66*, 219–225. [[CrossRef](#)] [[PubMed](#)]
97. Segel, M.J.; Izbicki, G.; Cohen, P.Y.; Or, R.; Christensen, T.G.; Wallach-Dayana, S.B.; Breuer, R. Role of interferon-gamma in the evolution of murine bleomycin lung fibrosis. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2003**, *285*, L1255–L1262. [[CrossRef](#)] [[PubMed](#)]
98. Shim, C.Y.; Song, B.-W.; Cha, M.-J.; Hwang, K.-C.; Park, S.; Hong, G.-R.; Kang, S.-M.; Lee, J.E.; Ha, J.-W.; Chung, N. Combination of a peroxisome proliferator-activated receptor-gamma agonist and an angiotensin II receptor blocker attenuates myocardial fibrosis and dysfunction in type 2 diabetic rats. *J. Diabetes Investig.* **2014**, *5*, 362–371. [[CrossRef](#)] [[PubMed](#)]
99. Sharma, C.; Pradeep, A.; Wong, L.; Rana, A.; Rana, B. Peroxisome proliferator-activated receptor gamma activation can regulate beta-catenin levels via a proteasome-mediated and adenomatous polyposis coli-independent pathway. *J. Biol. Chem.* **2004**, *279*, 35583–35594. [[CrossRef](#)] [[PubMed](#)]
100. Li, X.-F.; Sun, Y.-Y.; Bao, J.; Chen, X.; Li, Y.-H.; Yang, Y.; Zhang, L.; Huang, C.; Wu, B.-M.; Meng, X.-M.; et al. Functional role of PPAR- γ on the proliferation and migration of fibroblast-like synoviocytes in rheumatoid arthritis. *Sci. Rep.* **2017**, *7*, 12671. [[CrossRef](#)] [[PubMed](#)]
101. Lu, D.; Carson, D.A. Repression of beta-catenin signaling by PPAR gamma ligands. *Eur. J. Pharmacol.* **2010**, *636*, 198–202. [[CrossRef](#)] [[PubMed](#)]
102. Takada, I.; Kouzmenko, A.P.; Kato, S. Wnt and PPARgamma signaling in osteoblastogenesis and adipogenesis. *Nat. Rev. Rheumatol.* **2009**, *5*, 442–447. [[CrossRef](#)] [[PubMed](#)]
103. Garcia-Gras, E.; Lombardi, R.; Giocondo, M.J.; Willerson, J.T.; Schneider, M.D.; Khoury, D.S.; Marian, A.J. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. *J. Clin. Investig.* **2006**, *116*, 2012–2021. [[CrossRef](#)] [[PubMed](#)]
104. Elbrecht, A.; Chen, Y.; Cullinan, C.A.; Hayes, N.; Leibowitz, M.D.; Moller, D.E.; Berger, J. Molecular cloning, expression and characterization of human peroxisome proliferator activated receptors gamma 1 and gamma 2. *Biochem. Biophys. Res. Commun.* **1996**, *224*, 431–437. [[CrossRef](#)] [[PubMed](#)]
105. Fajas, L.; Auboeuf, D.; Raspé, E.; Schoonjans, K.; Lefebvre, A.M.; Saladin, R.; Najib, J.; Laville, M.; Fruchart, J.C.; Deeb, S.; et al. The organization, promoter analysis, and expression of the human PPARgamma gene. *J. Biol. Chem.* **1997**, *272*, 18779–18789. [[CrossRef](#)] [[PubMed](#)]
106. Moldes, M.; Zuo, Y.; Morrison, R.F.; Silva, D.; Park, B.-H.; Liu, J.; Farmer, S.R. Peroxisome-proliferator-activated receptor gamma suppresses Wnt/beta-catenin signalling during adipogenesis. *Biochem. J.* **2003**, *376*, 607–613. [[CrossRef](#)] [[PubMed](#)]
107. Akinyeke, T.O.; Stewart, L.V. Troglitazone suppresses c-Myc levels in human prostate cancer cells via a PPAR γ -independent mechanism. *Cancer Biol. Ther.* **2011**, *11*, 1046–1058. [[CrossRef](#)] [[PubMed](#)]
108. Gustafson, B.; Eliasson, B.; Smith, U. Thiazolidinediones increase the wingless-type MMTV integration site family (WNT) inhibitor Dickkopf-1 in adipocytes: A link with osteogenesis. *Diabetologia* **2010**, *53*, 536–540. [[CrossRef](#)] [[PubMed](#)]
109. Jeon, M.; Rahman, N.; Kim, Y.-S. Wnt/ β -catenin signaling plays a distinct role in methyl gallate-mediated inhibition of adipogenesis. *Biochem. Biophys. Res. Commun.* **2016**, *479*, 22–27. [[CrossRef](#)] [[PubMed](#)]
110. Okamura, M.; Kudo, H.; Wakabayashi, K.; Tanaka, T.; Nonaka, A.; Uchida, A.; Tsutsumi, S.; Sakakibara, I.; Naito, M.; Osborne, T.F.; et al. COUP-TFII acts downstream of Wnt/beta-catenin signal to silence PPARgamma gene expression and repress adipogenesis. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5819–5824. [[CrossRef](#)] [[PubMed](#)]
111. Simon, M.F.; Daviaud, D.; Pradère, J.P.; Grès, S.; Guigné, C.; Wabitsch, M.; Chun, J.; Valet, P.; Saulnier-Blache, J.S. Lysophosphatidic acid inhibits adipocyte differentiation via lysophosphatidic acid 1 receptor-dependent down-regulation of peroxisome proliferator-activated receptor gamma2. *J. Biol. Chem.* **2005**, *280*, 14656–14662. [[CrossRef](#)] [[PubMed](#)]

112. Tan, J.T.M.; McLennan, S.V.; Song, W.W.; Lo, L.W.-Y.; Bonner, J.G.; Williams, P.F.; Twigg, S.M. Connective tissue growth factor inhibits adipocyte differentiation. *Am. J. Physiol. Cell Physiol.* **2008**, *295*, C740–C751. [[CrossRef](#)] [[PubMed](#)]
113. Yamasaki, S.; Nakashima, T.; Kawakami, A.; Miyashita, T.; Tanaka, F.; Ida, H.; Migita, K.; Origuchi, T.; Eguchi, K. Cytokines regulate fibroblast-like synovial cell differentiation to adipocyte-like cells. *Rheumatology* **2004**, *43*, 448–452. [[CrossRef](#)] [[PubMed](#)]
114. Niino, M.; Iwabuchi, K.; Kikuchi, S.; Ato, M.; Morohashi, T.; Ogata, A.; Tashiro, K.; Onoé, K. Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by an agonist of peroxisome proliferator-activated receptor-gamma. *J. Neuroimmunol.* **2001**, *116*, 40–48. [[CrossRef](#)]
115. Diab, A.; Deng, C.; Smith, J.D.; Hussain, R.Z.; Phanavanh, B.; Lovett-Racke, A.E.; Drew, P.D.; Racke, M.K. Peroxisome proliferator-activated receptor-gamma agonist 15-deoxy-Delta(12,14)-prostaglandin J(2) ameliorates experimental autoimmune encephalomyelitis. *J. Immunol.* **2002**, *168*, 2508–2515. [[CrossRef](#)] [[PubMed](#)]
116. Feinstein, D.L.; Galea, E.; Gavrilyuk, V.; Brosnan, C.F.; Whitacre, C.C.; Dumitrescu-Ozimek, L.; Landreth, G.E.; Pershadsingh, H.A.; Weinberg, G.; Heneka, M.T. Peroxisome proliferator-activated receptor-gamma agonists prevent experimental autoimmune encephalomyelitis. *Ann. Neurol.* **2002**, *51*, 694–702. [[CrossRef](#)] [[PubMed](#)]
117. Natarajan, C.; Bright, J.J. Peroxisome proliferator-activated receptor-gamma agonists inhibit experimental allergic encephalomyelitis by blocking IL-12 production, IL-12 signaling and Th1 differentiation. *Genes Immun.* **2002**, *3*, 59–70. [[CrossRef](#)] [[PubMed](#)]
118. Schulman, I.G.; Shao, G.; Heyman, R.A. Transactivation by retinoid X receptor-peroxisome proliferator-activated receptor gamma (PPARgamma) heterodimers: Intermolecular synergy requires only the PPARgamma hormone-dependent activation function. *Mol. Cell. Biol.* **1998**, *18*, 3483–3494. [[CrossRef](#)] [[PubMed](#)]
119. Westin, S.; Kurokawa, R.; Nolte, R.T.; Wisely, G.B.; McInerney, E.M.; Rose, D.W.; Milburn, M.V.; Rosenfeld, M.G.; Glass, C.K. Interactions controlling the assembly of nuclear-receptor heterodimers and co-activators. *Nature* **1998**, *395*, 199–202. [[CrossRef](#)] [[PubMed](#)]
120. Huang, J.K.; Jarjour, A.A.; Oumesmar, B.N.; Kerninon, C.; Williams, A.; Krezel, W.; Kagechika, H.; Bauer, J.; Zhao, C.; Baron-Van Evercooren, A.; et al. Retinoid X receptor gamma signaling accelerates CNS remyelination. *Nat. Neurosci.* **2011**, *14*, 45–53. [[CrossRef](#)] [[PubMed](#)]
121. Benedusi, V.; Martorana, F.; Brambilla, L.; Maggi, A.; Rossi, D. The peroxisome proliferator-activated receptor γ (PPAR γ) controls natural protective mechanisms against lipid peroxidation in amyotrophic lateral sclerosis. *J. Biol. Chem.* **2012**, *287*, 35899–35911. [[CrossRef](#)] [[PubMed](#)]
122. Drew, P.D.; Storer, P.D.; Xu, J.; Chavis, J.A. Hormone regulation of microglial cell activation: Relevance to multiple sclerosis. *Brain Res. Brain Res. Rev.* **2005**, *48*, 322–327. [[CrossRef](#)] [[PubMed](#)]
123. Drew, P.D.; Xu, J.; Racke, M.K. PPAR-gamma: Therapeutic Potential for Multiple Sclerosis. *PPAR Res.* **2008**, *2008*, 627463. [[CrossRef](#)] [[PubMed](#)]
124. Duvanel, C.B.; Honegger, P.; Pershadsingh, H.; Feinstein, D.; Matthieu, J.-M. Inhibition of glial cell proinflammatory activities by peroxisome proliferator-activated receptor gamma agonist confers partial protection during antimyelin oligodendrocyte glycoprotein demyelination in vitro. *J. Neurosci. Res.* **2003**, *71*, 246–255. [[CrossRef](#)] [[PubMed](#)]
125. Luna-Medina, R.; Cortes-Canteli, M.; Alonso, M.; Santos, A.; Martínez, A.; Perez-Castillo, A. Regulation of inflammatory response in neural cells in vitro by thiazolidinones derivatives through peroxisome proliferator-activated receptor gamma activation. *J. Biol. Chem.* **2005**, *280*, 21453–21462. [[CrossRef](#)] [[PubMed](#)]
126. Paintlia, A.S.; Paintlia, M.K.; Singh, I.; Singh, A.K. IL-4-induced peroxisome proliferator-activated receptor gamma activation inhibits NF-kappaB trans activation in central nervous system (CNS) glial cells and protects oligodendrocyte progenitors under neuroinflammatory disease conditions: Implication for CNS-demyelinating diseases. *J. Immunol.* **2006**, *176*, 4385–4398. [[PubMed](#)]
127. Swanson, C.R.; Joers, V.; Bondarenko, V.; Brunner, K.; Simmons, H.A.; Ziegler, T.E.; Kemnitz, J.W.; Johnson, J.A.; Emborg, M.E. The PPAR- γ agonist pioglitazone modulates inflammation and induces neuroprotection in parkinsonian monkeys. *J. Neuroinflamm.* **2011**, *8*, 91. [[CrossRef](#)] [[PubMed](#)]
128. Xing, B.; Xin, T.; Hunter, R.L.; Bing, G. Pioglitazone inhibition of lipopolysaccharide-induced nitric oxide synthase is associated with altered activity of p38 MAP kinase and PI3K/Akt. *J. Neuroinflamm.* **2008**, *5*, 4. [[CrossRef](#)] [[PubMed](#)]

129. Klotz, L.; Burgdorf, S.; Dani, I.; Saijo, K.; Flossdorf, J.; Hucke, S.; Alferink, J.; Nowak, N.; Novak, N.; Beyer, M.; et al. The nuclear receptor PPAR gamma selectively inhibits Th17 differentiation in a T cell-intrinsic fashion and suppresses CNS autoimmunity. *J. Exp. Med.* **2009**, *206*, 2079–2089. [[CrossRef](#)] [[PubMed](#)]
130. Unoda, K.; Doi, Y.; Nakajima, H.; Yamane, K.; Hosokawa, T.; Ishida, S.; Kimura, F.; Hanafusa, T. Eicosapentaenoic acid (EPA) induces peroxisome proliferator-activated receptors and ameliorates experimental autoimmune encephalomyelitis. *J. Neuroimmunol.* **2013**, *256*, 7–12. [[CrossRef](#)] [[PubMed](#)]
131. Storer, P.D.; Xu, J.; Chavis, J.; Drew, P.D. Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: Implications for multiple sclerosis. *J. Neuroimmunol.* **2005**, *161*, 113–122. [[CrossRef](#)] [[PubMed](#)]
132. Xu, J.; Drew, P.D. Peroxisome proliferator-activated receptor-gamma agonists suppress the production of IL-12 family cytokines by activated glia. *J. Immunol.* **2007**, *178*, 1904–1913. [[CrossRef](#)] [[PubMed](#)]
133. Padilla, J.; Leung, E.; Phipps, R.P. Human B lymphocytes and B lymphomas express PPAR-gamma and are killed by PPAR-gamma agonists. *Clin. Immunol.* **2002**, *103*, 22–33. [[CrossRef](#)] [[PubMed](#)]
134. Paintlia, A.S.; Paintlia, M.K.; Singh, A.K.; Stanislaus, R.; Gilg, A.G.; Barbosa, E.; Singh, I. Regulation of gene expression associated with acute experimental autoimmune encephalomyelitis by Lovastatin. *J. Neurosci. Res.* **2004**, *77*, 63–81. [[CrossRef](#)] [[PubMed](#)]
135. Klopffleisch, S.; Merkler, D.; Schmitz, M.; Klöppner, S.; Schedensack, M.; Jeserich, G.; Althaus, H.H.; Brück, W. Negative impact of statins on oligodendrocytes and myelin formation in vitro and in vivo. *J. Neurosci.* **2008**, *28*, 13609–13614. [[CrossRef](#)] [[PubMed](#)]
136. Miron, V.E.; Zehntner, S.P.; Kuhlmann, T.; Ludwin, S.K.; Owens, T.; Kennedy, T.E.; Bedell, B.J.; Antel, J.P. Statin therapy inhibits remyelination in the central nervous system. *Am. J. Pathol.* **2009**, *174*, 1880–1890. [[CrossRef](#)] [[PubMed](#)]
137. Fancy, S.P.J.; Baranzini, S.E.; Zhao, C.; Yuk, D.-I.; Irvine, K.-A.; Kaing, S.; Sanai, N.; Franklin, R.J.M.; Rowitch, D.H. Dysregulation of the Wnt pathway inhibits timely myelination and remyelination in the mammalian CNS. *Genes Dev.* **2009**, *23*, 1571–1585. [[CrossRef](#)] [[PubMed](#)]
138. Kiguchi, N.; Kobayashi, Y.; Kishioka, S. Chemokines and cytokines in neuroinflammation leading to neuropathic pain. *Curr. Opin. Pharmacol.* **2012**, *12*, 55–61. [[CrossRef](#)] [[PubMed](#)]
139. Kam, Y.; Quaranta, V. Cadherin-bound beta-catenin feeds into the Wnt pathway upon adherens junctions dissociation: Evidence for an intersection between beta-catenin pools. *PLoS ONE* **2009**, *4*, e4580. [[CrossRef](#)] [[PubMed](#)]
140. Lock, C.; Hermans, G.; Pedotti, R.; Brendolan, A.; Schadt, E.; Garren, H.; Langer-Gould, A.; Strober, S.; Cannella, B.; Allard, J.; et al. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat. Med.* **2002**, *8*, 500–508. [[CrossRef](#)] [[PubMed](#)]
141. Padden, M.; Leech, S.; Craig, B.; Kirk, J.; Brankin, B.; McQuaid, S. Differences in expression of junctional adhesion molecule-A and beta-catenin in multiple sclerosis brain tissue: Increasing evidence for the role of tight junction pathology. *Acta Neuropathol.* **2007**, *113*, 177–186. [[CrossRef](#)] [[PubMed](#)]
142. Giacoppo, S.; Soundara Rajan, T.; De Nicola, G.R.; Iori, R.; Bramanti, P.; Mazzon, E. Moringin activates Wnt canonical pathway by inhibiting GSK3 β in a mouse model of experimental autoimmune encephalomyelitis. *Drug Des. Dev. Ther.* **2016**, *10*, 3291–3304. [[CrossRef](#)] [[PubMed](#)]
143. Galuppo, M.; Giacoppo, S.; De Nicola, G.R.; Iori, R.; Navarra, M.; Lombardo, G.E.; Bramanti, P.; Mazzon, E. Antiinflammatory activity of glucomoringin isothiocyanate in a mouse model of experimental autoimmune encephalomyelitis. *Fitoterapia* **2014**, *95*, 160–174. [[CrossRef](#)] [[PubMed](#)]
144. Giacoppo, S.; Galuppo, M.; Montaut, S.; Iori, R.; Rollin, P.; Bramanti, P.; Mazzon, E. An overview on neuroprotective effects of isothiocyanates for the treatment of neurodegenerative diseases. *Fitoterapia* **2015**, *106*, 12–21. [[CrossRef](#)] [[PubMed](#)]
145. Pate, K.T.; Stringari, C.; Sprowl-Tanio, S.; Wang, K.; TeSlaa, T.; Hoverter, N.P.; McQuade, M.M.; Garner, C.; Digman, M.A.; Teitell, M.A.; et al. Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. *EMBO J.* **2014**, *33*, 1454–1473. [[CrossRef](#)] [[PubMed](#)]
146. Vallée, A.; Vallée, J.-N. Warburg effect hypothesis in autism Spectrum disorders. *Mol. Brain* **2018**, *11*, 1. [[CrossRef](#)] [[PubMed](#)]
147. Reuter, S.; Gupta, S.C.; Chaturvedi, M.M.; Aggarwal, B.B. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radic. Biol. Med.* **2010**, *49*, 1603–1616. [[CrossRef](#)] [[PubMed](#)]

148. Park, K.S.; Lee, R.D.; Kang, S.-K.; Han, S.Y.; Park, K.L.; Yang, K.H.; Song, Y.S.; Park, H.J.; Lee, Y.M.; Yun, Y.P.; et al. Neuronal differentiation of embryonic midbrain cells by upregulation of peroxisome proliferator-activated receptor-gamma via the JNK-dependent pathway. *Exp. Cell Res.* **2004**, *297*, 424–433. [[CrossRef](#)] [[PubMed](#)]
149. Yue, X.; Lan, F.; Yang, W.; Yang, Y.; Han, L.; Zhang, A.; Liu, J.; Zeng, H.; Jiang, T.; Pu, P.; et al. Interruption of β -catenin suppresses the EGFR pathway by blocking multiple oncogenic targets in human glioma cells. *Brain Res.* **2010**, *1366*, 27–37. [[CrossRef](#)] [[PubMed](#)]
150. Sun, Q.; Chen, X.; Ma, J.; Peng, H.; Wang, F.; Zha, X.; Wang, Y.; Jing, Y.; Yang, H.; Chen, R.; et al. Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 4129–4134. [[CrossRef](#)] [[PubMed](#)]
151. Semenza, G.L. HIF-1: Upstream and downstream of cancer metabolism. *Curr. Opin. Genet. Dev.* **2010**, *20*, 51–56. [[CrossRef](#)] [[PubMed](#)]
152. Goldbeter, A. Patterns of spatiotemporal organization in an allosteric enzyme model. *Proc. Natl. Acad. Sci. USA* **1973**, *70*, 3255–3259. [[CrossRef](#)] [[PubMed](#)]
153. Cambron, M.; D'Haeseleer, M.; Laureys, G.; Clinckers, R.; Debruyne, J.; De Keyser, J. White-matter astrocytes, axonal energy metabolism, and axonal degeneration in multiple sclerosis. *J. Cereb. Blood Flow Metab.* **2012**, *32*, 413–424. [[CrossRef](#)] [[PubMed](#)]
154. Hattingen, E.; Magerkurth, J.; Pilatus, U.; Hübers, A.; Wahl, M.; Ziemann, U. Combined (1)H and (31)P spectroscopy provides new insights into the pathobiochemistry of brain damage in multiple sclerosis. *NMR Biomed.* **2011**, *24*, 536–546. [[CrossRef](#)] [[PubMed](#)]
155. Trapp, B.D.; Stys, P.K. Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. *Lancet Neurol.* **2009**, *8*, 280–291. [[CrossRef](#)]
156. Campbell, G.R.; Ziabreva, I.; Reeve, A.K.; Krishnan, K.J.; Reynolds, R.; Howell, O.; Lassmann, H.; Turnbull, D.M.; Mahad, D.J. Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis. *Ann. Neurol.* **2011**, *69*, 481–492. [[CrossRef](#)] [[PubMed](#)]
157. Witte, M.E.; Bø, L.; Rodenburg, R.J.; Belien, J.A.; Musters, R.; Hazes, T.; Wintjes, L.T.; Smeitink, J.A.; Geurts, J.J.G.; De Vries, H.E.; et al. Enhanced number and activity of mitochondria in multiple sclerosis lesions. *J. Pathol.* **2009**, *219*, 193–204. [[CrossRef](#)] [[PubMed](#)]
158. Gebregiworgis, T.; Nielsen, H.H.; Massilamany, C.; Gangaplara, A.; Reddy, J.; Illes, Z.; Powers, R. A Urinary Metabolic Signature for Multiple Sclerosis and Neuromyelitis Optica. *J. Proteome Res.* **2016**, *15*, 659–666. [[CrossRef](#)] [[PubMed](#)]
159. Nijland, P.G.; Molenaar, R.J.; van der Pol, S.M.A.; van der Valk, P.; van Noorden, C.J.F.; de Vries, H.E.; van Horssen, J. Differential expression of glucose-metabolizing enzymes in multiple sclerosis lesions. *Acta Neuropathol. Commun.* **2015**, *3*, 79. [[CrossRef](#)] [[PubMed](#)]
160. De Riccardis, L.; Rizzello, A.; Ferramosca, A.; Urso, E.; De Robertis, F.; Danieli, A.; Giudetti, A.M.; Trianni, G.; Zara, V.; Maffia, M. Bioenergetics profile of CD4(+) T cells in relapsing remitting multiple sclerosis subjects. *J. Biotechnol.* **2015**, *202*, 31–39. [[CrossRef](#)] [[PubMed](#)]
161. Kebir, H.; Kreymborg, K.; Ifergan, I.; Dodelet-Devillers, A.; Cayrol, R.; Bernard, M.; Giuliani, F.; Arbour, N.; Becher, B.; Prat, A. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat. Med.* **2007**, *13*, 1173–1175. [[CrossRef](#)] [[PubMed](#)]
162. De Riccardis, L.; Ferramosca, A.; Danieli, A.; Trianni, G.; Zara, V.; De Robertis, F.; Maffia, M. Metabolic response to glatiramer acetate therapy in multiple sclerosis patients. *BBA Clin.* **2016**, *6*, 131–137. [[CrossRef](#)] [[PubMed](#)]
163. Bauernfeind, A.L.; Barks, S.K.; Duka, T.; Grossman, L.I.; Hof, P.R.; Sherwood, C.C. Aerobic glycolysis in the primate brain: Reconsidering the implications for growth and maintenance. *Brain Struct. Funct.* **2014**, *219*, 1149–1167. [[CrossRef](#)] [[PubMed](#)]
164. Bongarzone, E.R.; Pasquini, J.M.; Soto, E.F. Oxidative damage to proteins and lipids of CNS myelin produced by in vitro generated reactive oxygen species. *J. Neurosci. Res.* **1995**, *41*, 213–221. [[CrossRef](#)] [[PubMed](#)]
165. Brand, K.A.; Hermfisse, U. Aerobic glycolysis by proliferating cells: A protective strategy against reactive oxygen species. *FASEB J.* **1997**, *11*, 388–395. [[CrossRef](#)] [[PubMed](#)]
166. Rodriguez-Rodriguez, P.; Fernandez, E.; Almeida, A.; Bolaños, J.P. Excitotoxic stimulus stabilizes PFKFB3 causing pentose-phosphate pathway to glycolysis switch and neurodegeneration. *Cell Death Differ.* **2012**, *19*, 1582–1589. [[CrossRef](#)] [[PubMed](#)]

167. Wang, J.; Li, G.; Wang, Z.; Zhang, X.; Yao, L.; Wang, F.; Liu, S.; Yin, J.; Ling, E.-A.; Wang, L.; et al. High glucose-induced expression of inflammatory cytokines and reactive oxygen species in cultured astrocytes. *Neuroscience* **2012**, *202*, 58–68. [[CrossRef](#)] [[PubMed](#)]
168. Patel, K.P.; O'Brien, T.W.; Subramony, S.H.; Shuster, J.; Stacpoole, P.W. The spectrum of pyruvate dehydrogenase complex deficiency: Clinical, biochemical and genetic features in 371 patients. *Mol. Genet. Metab.* **2012**, *106*, 385–394. [[CrossRef](#)] [[PubMed](#)]
169. Trofimova, L.K.; Araújo, W.L.; Strokina, A.A.; Fernie, A.R.; Bettendorff, L.; Bunik, V.I. Consequences of the α -ketoglutarate dehydrogenase inhibition for neuronal metabolism and survival: Implications for neurodegenerative diseases. *Curr. Med. Chem.* **2012**, *19*, 5895–5906. [[CrossRef](#)] [[PubMed](#)]
170. Schiepers, C.; Van Hecke, P.; Vandenberghe, R.; Van Oostende, S.; Dupont, P.; Demaerel, P.; Bormans, G.; Carton, H. Positron emission tomography, magnetic resonance imaging and proton NMR spectroscopy of white matter in multiple sclerosis. *Mult. Scler. J.* **1997**, *3*, 8–17. [[CrossRef](#)] [[PubMed](#)]
171. Simone, I.L.; Tortorella, C.; Federico, F.; Liguori, M.; Lucivero, V.; Giannini, P.; Carrara, D.; Bellacosa, A.; Livrea, P. Axonal damage in multiple sclerosis plaques: A combined magnetic resonance imaging and 1H-magnetic resonance spectroscopy study. *J. Neurol. Sci.* **2001**, *182*, 143–150. [[CrossRef](#)]
172. Amorini, A.M.; Nociti, V.; Petzold, A.; Gasperini, C.; Quartuccio, E.; Lazzarino, G.; Di Pietro, V.; Belli, A.; Signoretti, S.; Vagnozzi, R.; et al. Serum lactate as a novel potential biomarker in multiple sclerosis. *Biochim. Biophys. Acta* **2014**, *1842*, 1137–1143. [[CrossRef](#)] [[PubMed](#)]
173. Petzold, A.; Nijland, P.G.; Balk, L.J.; Amorini, A.M.; Lazzarino, G.; Wattjes, M.P.; Gasperini, C.; van der Valk, P.; Tavazzi, B.; Lazzarino, G.; et al. Visual pathway neurodegeneration winged by mitochondrial dysfunction. *Ann. Clin. Transl. Neurol.* **2015**, *2*, 140–150. [[CrossRef](#)] [[PubMed](#)]
174. Schocke, M.F.H.; Berger, T.; Felber, S.R.; Wolf, C.; Deisenhammer, F.; Kremser, C.; Seppi, K.; Aichner, F.T. Serial contrast-enhanced magnetic resonance imaging and spectroscopic imaging of acute multiple sclerosis lesions under high-dose methylprednisolone therapy. *NeuroImage* **2003**, *20*, 1253–1263. [[CrossRef](#)]
175. Lutz, N.W.; Viola, A.; Malikova, I.; Confort-Gouny, S.; Audoin, B.; Ranjeva, J.-P.; Pelletier, J.; Cozzone, P.J. Inflammatory multiple-sclerosis plaques generate characteristic metabolic profiles in cerebrospinal fluid. *PLoS ONE* **2007**, *2*, e595. [[CrossRef](#)] [[PubMed](#)]
176. Regenold, W.T.; Phatak, P.; Makley, M.J.; Stone, R.D.; Kling, M.A. Cerebrospinal fluid evidence of increased extra-mitochondrial glucose metabolism implicates mitochondrial dysfunction in multiple sclerosis disease progression. *J. Neurol. Sci.* **2008**, *275*, 106–112. [[CrossRef](#)] [[PubMed](#)]
177. Simone, I.L.; Federico, F.; Trojano, M.; Tortorella, C.; Liguori, M.; Giannini, P.; Picciola, E.; Natile, G.; Livrea, P. High resolution proton MR spectroscopy of cerebrospinal fluid in MS patients. Comparison with biochemical changes in demyelinating plaques. *J. Neurol. Sci.* **1996**, *144*, 182–190. [[CrossRef](#)]
178. Hogenesch, J.B.; Gu, Y.Z.; Jain, S.; Bradfield, C.A. The basic-helix-loop-helix-PAS orphan MOP3 forms transcriptionally active complexes with circadian and hypoxia factors. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 5474–5479. [[CrossRef](#)] [[PubMed](#)]
179. Gekakis, N.; Staknis, D.; Nguyen, H.B.; Davis, F.C.; Wilsbacher, L.D.; King, D.P.; Takahashi, J.S.; Weitz, C.J. Role of the CLOCK protein in the mammalian circadian mechanism. *Science* **1998**, *280*, 1564–1569. [[CrossRef](#)] [[PubMed](#)]
180. Reppert, S.M.; Weaver, D.R. Coordination of circadian timing in mammals. *Nature* **2002**, *418*, 935–941. [[CrossRef](#)] [[PubMed](#)]
181. Schibler, U.; Sassone-Corsi, P. A web of circadian pacemakers. *Cell* **2002**, *111*, 919–922. [[CrossRef](#)]
182. Ko, C.H.; Takahashi, J.S. Molecular components of the mammalian circadian clock. *Hum. Mol. Genet.* **2006**, *15*, R271–R277. [[CrossRef](#)] [[PubMed](#)]
183. De Somma, E.; Jain, R.W.; Poon, K.W.C.; Tresidder, K.A.; Segal, J.P.; Ghasemlou, N. Chronobiological regulation of psychosocial and physiological outcomes in multiple sclerosis. *Neurosci. Biobehav. Rev.* **2018**. [[CrossRef](#)] [[PubMed](#)]
184. Hedström, A.K.; Åkerstedt, T.; Hillert, J.; Olsson, T.; Alfredsson, L. Shift work at young age is associated with increased risk for multiple sclerosis. *Ann. Neurol.* **2011**, *70*, 733–741. [[CrossRef](#)] [[PubMed](#)]
185. Hedström, A.K.; Åkerstedt, T.; Olsson, T.; Alfredsson, L. Shift work influences multiple sclerosis risk. *Mult. Scler. J.* **2015**, *21*, 1195–1199. [[CrossRef](#)] [[PubMed](#)]

186. Haspel, J.A.; Chettimada, S.; Shaik, R.S.; Chu, J.-H.; Raby, B.A.; Cernadas, M.; Carey, V.; Process, V.; Hunninghake, G.M.; Ifedigbo, E.; et al. Circadian rhythm reprogramming during lung inflammation. *Nat. Commun.* **2014**, *5*, 4753. [[CrossRef](#)] [[PubMed](#)]
187. He, J.; Hsuchou, H.; He, Y.; Kastin, A.J.; Wang, Y.; Pan, W. Sleep restriction impairs blood-brain barrier function. *J. Neurosci.* **2014**, *34*, 14697–14706. [[CrossRef](#)] [[PubMed](#)]
188. Akpınar, Z.; Tokgöz, S.; Gökbel, H.; Okudan, N.; Uğuz, F.; Yılmaz, G. The association of nocturnal serum melatonin levels with major depression in patients with acute multiple sclerosis. *Psychiatry Res.* **2008**, *161*, 253–257. [[CrossRef](#)] [[PubMed](#)]
189. Marck, C.H.; Neate, S.L.; Taylor, K.L.; Weiland, T.J.; Jelinek, G.A. Prevalence of Comorbidities, Overweight and Obesity in an International Sample of People with Multiple Sclerosis and Associations with Modifiable Lifestyle Factors. *PLoS ONE* **2016**, *11*, e0148573. [[CrossRef](#)] [[PubMed](#)]
190. Lunde, H.M.B.; Bjorvatn, B.; Myhr, K.-M.; Bø, L. Clinical assessment and management of sleep disorders in multiple sclerosis: A literature review. *Acta Neurol. Scand.* **2013**, *127*, 24–30. [[CrossRef](#)] [[PubMed](#)]
191. Turek, F.W.; Dugovic, C.; Zee, P.C. Current understanding of the circadian clock and the clinical implications for neurological disorders. *Arch. Neurol.* **2001**, *58*, 1781–1787. [[CrossRef](#)] [[PubMed](#)]
192. Attarian, H.P.; Brown, K.M.; Duntley, S.P.; Carter, J.D.; Cross, A.H. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch. Neurol.* **2004**, *61*, 525–528. [[CrossRef](#)] [[PubMed](#)]
193. Najafi, M.R.; Toghianifar, N.; Etemadifar, M.; Haghghi, S.; Maghzi, A.H.; Akbari, M. Circadian rhythm sleep disorders in patients with multiple sclerosis and its association with fatigue: A case-control study. *J. Res. Med. Sci.* **2013**, *18*, S71–S73. [[PubMed](#)]
194. Ayache, S.S.; Chalah, M.A. Fatigue in multiple sclerosis—Insights into evaluation and management. *Neurophysiol. Clin. Clin. Neurophysiol.* **2017**, *47*, 139–171. [[CrossRef](#)] [[PubMed](#)]
195. Tsujino, N.; Sakurai, T. Role of orexin in modulating arousal, feeding, and motivation. *Front. Behav. Neurosci.* **2013**, *7*, 28. [[CrossRef](#)] [[PubMed](#)]
196. Kiyashchenko, L.I.; Mileyskiy, B.Y.; Maidment, N.; Lam, H.A.; Wu, M.-F.; John, J.; Peever, J.; Siegel, J.M. Release of hypocretin (orexin) during waking and sleep states. *J. Neurosci.* **2002**, *22*, 5282–5286. [[CrossRef](#)] [[PubMed](#)]
197. Oka, Y.; Kanbayashi, T.; Mezaki, T.; Iseki, K.; Matsubayashi, J.; Murakami, G.; Matsui, M.; Shimizu, T.; Shibasaki, H. Low CSF hypocretin-1/orexin-A associated with hypersomnia secondary to hypothalamic lesion in a case of multiple sclerosis. *J. Neurol.* **2004**, *251*, 885–886. [[CrossRef](#)] [[PubMed](#)]
198. Grossberg, A.J.; Zhu, X.; Leininger, G.M.; Lavoie, P.R.; Braun, T.P.; Myers, M.G.; Marks, D.L. Inflammation-induced lethargy is mediated by suppression of orexin neuron activity. *J. Neurosci.* **2011**, *31*, 11376–11386. [[CrossRef](#)] [[PubMed](#)]
199. Pokryszko-Dragan, A.; Frydecka, I.; Kosmaczewska, A.; Ciszak, L.; Bilińska, M.; Gruszka, E.; Podemski, R.; Frydecka, D. Stimulated peripheral production of interferon-gamma is related to fatigue and depression in multiple sclerosis. *Clin. Neurol. Neurosurg.* **2012**, *114*, 1153–1158. [[CrossRef](#)] [[PubMed](#)]
200. Boddum, K.; Hansen, M.H.; Jennum, P.J.; Kornum, B.R. Cerebrospinal Fluid Hypocretin-1 (Orexin-A) Level Fluctuates with Season and Correlates with Day Length. *PLoS ONE* **2016**, *11*, e0151288. [[CrossRef](#)] [[PubMed](#)]
201. Taphoorn, M.J.; van Someren, E.; Snoek, F.J.; Strijers, R.L.; Swaab, D.F.; Visscher, F.; de Waal, L.P.; Polman, C.H. Fatigue, sleep disturbances and circadian rhythm in multiple sclerosis. *J. Neurol.* **1993**, *240*, 446–448. [[CrossRef](#)] [[PubMed](#)]
202. Farez, M.F.; Mascanfroni, I.D.; Méndez-Huergo, S.P.; Yeste, A.; Murugaiyan, G.; Garo, L.P.; Balbuena Aguirre, M.E.; Patel, B.; Ysraelit, M.C.; Zhu, C.; et al. Melatonin Contributes to the Seasonality of Multiple Sclerosis Relapses. *Cell* **2015**, *162*, 1338–1352. [[CrossRef](#)] [[PubMed](#)]
203. Torkildsen, O.; Aarseth, J.; Benjaminsen, E.; Celius, E.; Holmøy, T.; Kampman, M.T.; Løken-Amsrud, K.; Midgard, R.; Myhr, K.-M.; Riise, T.; et al. Month of birth and risk of multiple sclerosis: Confounding and adjustments. *Ann. Clin. Transl. Neurol.* **2014**, *1*, 141–144. [[CrossRef](#)] [[PubMed](#)]
204. Reynolds, J.D.; Case, L.K.; Kremontsov, D.N.; Raza, A.; Bartiss, R.; Teuscher, C. Modeling month-season of birth as a risk factor in mouse models of chronic disease: From multiple sclerosis to autoimmune encephalomyelitis. *FASEB J.* **2017**, *31*, 2709–2719. [[CrossRef](#)] [[PubMed](#)]
205. Dang, A.K.; Tesfagiorgis, Y.; Jain, R.W.; Craig, H.C.; Kerfoot, S.M. Meningeal Infiltration of the Spinal Cord by Non-Classically Activated B Cells is Associated with Chronic Disease Course in a Spontaneous B Cell-Dependent Model of CNS Autoimmune Disease. *Front. Immunol.* **2015**, *6*, 470. [[CrossRef](#)] [[PubMed](#)]

206. Yu, X.; Rollins, D.; Ruhn, K.A.; Stubblefield, J.J.; Green, C.B.; Kashiwada, M.; Rothman, P.B.; Takahashi, J.S.; Hooper, L.V. TH17 cell differentiation is regulated by the circadian clock. *Science* **2013**, *342*, 727–730. [[CrossRef](#)] [[PubMed](#)]
207. Chen, T.L. Inhibition of growth and differentiation of osteoprogenitors in mouse bone marrow stromal cell cultures by increased donor age and glucocorticoid treatment. *Bone* **2004**, *35*, 83–95. [[CrossRef](#)] [[PubMed](#)]
208. Soták, M.; Sumová, A.; Pácha, J. Cross-talk between the circadian clock and the cell cycle in cancer. *Ann. Med.* **2014**, *46*, 221–232. [[CrossRef](#)] [[PubMed](#)]
209. Guo, F.; He, D.; Zhang, W.; Walton, R.G. Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010. *J. Am. Coll. Cardiol.* **2012**, *60*, 599–606. [[CrossRef](#)] [[PubMed](#)]
210. Yasuniwa, Y.; Izumi, H.; Wang, K.-Y.; Shimajiri, S.; Sasaguri, Y.; Kawai, K.; Kasai, H.; Shimada, T.; Miyake, K.; Kashiwagi, E.; et al. Circadian disruption accelerates tumor growth and angio/stromagenesis through a Wnt signaling pathway. *PLoS ONE* **2010**, *5*, e15330. [[CrossRef](#)] [[PubMed](#)]
211. Janich, P.; Pascual, G.; Merlos-Suárez, A.; Batlle, E.; Ripperger, J.; Albrecht, U.; Cheng, H.-Y.M.; Obrietan, K.; Di Croce, L.; Benitah, S.A. The circadian molecular clock creates epidermal stem cell heterogeneity. *Nature* **2011**, *480*, 209–214. [[CrossRef](#)] [[PubMed](#)]
212. Lavtar, P.; Rudolf, G.; Maver, A.; Hodžić, A.; Starčević Čizmarević, N.; Živković, M.; Šega Jazbec, S.; Klemenc Ketiš, Z.; Kapović, M.; Dinčić, E.; et al. Association of circadian rhythm genes ARNTL/BMAL1 and CLOCK with multiple sclerosis. *PLoS ONE* **2018**, *13*, e0190601. [[CrossRef](#)] [[PubMed](#)]
213. Lin, F.; Chen, Y.; Li, X.; Zhao, Q.; Tan, Z. Over-expression of circadian clock gene Bmal1 affects proliferation and the canonical Wnt pathway in NIH-3T3 cells. *Cell Biochem. Funct.* **2013**, *31*, 166–172. [[CrossRef](#)] [[PubMed](#)]
214. Sahar, S.; Sassone-Corsi, P. Metabolism and cancer: The circadian clock connection. *Nat. Rev. Cancer* **2009**, *9*, 886–896. [[CrossRef](#)] [[PubMed](#)]
215. Yang, X.; Wood, P.A.; Ansell, C.M.; Ohmori, M.; Oh, E.-Y.; Xiong, Y.; Berger, F.G.; Peña, M.M.O.; Hrushesky, W.J.M. Beta-catenin induces beta-TrCP-mediated PER2 degradation altering circadian clock gene expression in intestinal mucosa of ApcMin/+ mice. *J. Biochem.* **2009**, *145*, 289–297. [[CrossRef](#)] [[PubMed](#)]
216. Duffield, G.E.; Best, J.D.; Meurers, B.H.; Bittner, A.; Loros, J.J.; Dunlap, J.C. Circadian programs of transcriptional activation, signaling, and protein turnover revealed by microarray analysis of mammalian cells. *Curr. Biol.* **2002**, *12*, 551–557. [[CrossRef](#)]
217. Sancar, A.; Lindsey-Boltz, L.A.; Unsal-Kaçmaz, K.; Linn, S. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annu. Rev. Biochem.* **2004**, *73*, 39–85. [[CrossRef](#)] [[PubMed](#)]
218. Yang, X.; Downes, M.; Yu, R.T.; Bookout, A.L.; He, W.; Straume, M.; Mangelsdorf, D.J.; Evans, R.M. Nuclear receptor expression links the circadian clock to metabolism. *Cell* **2006**, *126*, 801–810. [[CrossRef](#)] [[PubMed](#)]
219. Yang, G.; Jia, Z.; Aoyagi, T.; McClain, D.; Mortensen, R.M.; Yang, T. Systemic PPAR γ deletion impairs circadian rhythms of behavior and metabolism. *PLoS ONE* **2012**, *7*, e38117. [[CrossRef](#)] [[PubMed](#)]
220. Wang, H.-M.; Zhao, Y.-X.; Zhang, S.; Liu, G.-D.; Kang, W.-Y.; Tang, H.-D.; Ding, J.-Q.; Chen, S.-D. PPAR γ agonist curcumin reduces the amyloid-beta-stimulated inflammatory responses in primary astrocytes. *J. Alzheimers Dis.* **2010**, *20*, 1189–1199. [[CrossRef](#)] [[PubMed](#)]
221. Fontaine, C.; Dubois, G.; Duguay, Y.; Helledie, T.; Vu-Dac, N.; Gervois, P.; Soncin, F.; Mandrup, S.; Fruchart, J.-C.; Fruchart-Najib, J.; et al. The orphan nuclear receptor Rev-Erb α is a peroxisome proliferator-activated receptor (PPAR) γ target gene and promotes PPAR γ -induced adipocyte differentiation. *J. Biol. Chem.* **2003**, *278*, 37672–37680. [[CrossRef](#)] [[PubMed](#)]
222. Green, C.B.; Douris, N.; Kojima, S.; Strayer, C.A.; Fogerty, J.; Lourim, D.; Keller, S.R.; Besharse, J.C. Loss of Nocturnin, a circadian deadenylase, confers resistance to hepatic steatosis and diet-induced obesity. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 9888–9893. [[CrossRef](#)] [[PubMed](#)]
223. Chen, L.; Yang, G. PPARs Integrate the Mammalian Clock and Energy Metabolism. *PPAR Res.* **2014**, *2014*, 653017. [[CrossRef](#)] [[PubMed](#)]
224. Ivanov, I.I.; McKenzie, B.S.; Zhou, L.; Tadokoro, C.E.; Lepelley, A.; Lafaille, J.J.; Cua, D.J.; Littman, D.R. The orphan nuclear receptor ROR γ directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell* **2006**, *126*, 1121–1133. [[CrossRef](#)] [[PubMed](#)]

225. Manel, N.; Unutmaz, D.; Littman, D.R. The differentiation of human T(H)-17 cells requires transforming growth factor-beta and induction of the nuclear receptor RORgamma. *Nat. Immunol.* **2008**, *9*, 641–649. [[CrossRef](#)] [[PubMed](#)]
226. Clark, R.B.; Bishop-Bailey, D.; Estrada-Hernandez, T.; Hla, T.; Puddington, L.; Padula, S.J. The nuclear receptor PPAR gamma and immunoregulation: PPAR gamma mediates inhibition of helper T cell responses. *J. Immunol.* **2000**, *164*, 1364–1371. [[CrossRef](#)] [[PubMed](#)]
227. Li, W.; Zhang, Z.; Zhang, K.; Xue, Z.; Li, Y.; Zhang, Z.; Zhang, L.; Gu, C.; Zhang, Q.; Hao, J.; et al. Arctigenin Suppress Th17 Cells and Ameliorates Experimental Autoimmune Encephalomyelitis Through AMPK and PPAR- γ /ROR- γ t Signaling. *Mol. Neurobiol.* **2016**, *53*, 5356–5366. [[CrossRef](#)] [[PubMed](#)]
228. Lochner, M.; Peduto, L.; Cherrier, M.; Sawa, S.; Langa, F.; Varona, R.; Riethmacher, D.; Si-Tahar, M.; Di Santo, J.P.; Eberl, G. In vivo equilibrium of proinflammatory IL-17+ and regulatory IL-10+ Foxp3+ RORgamma t+ T cells. *J. Exp. Med.* **2008**, *205*, 1381–1393. [[CrossRef](#)] [[PubMed](#)]
229. Cermakian, N.; Lange, T.; Golombek, D.; Sarkar, D.; Nakao, A.; Shibata, S.; Mazzocchi, G. Crosstalk between the circadian clock circuitry and the immune system. *Chronobiol. Int.* **2013**, *30*, 870–888. [[CrossRef](#)] [[PubMed](#)]
230. Cutolo, M.; Sulli, A.; Pincus, T. Circadian use of glucocorticoids in rheumatoid arthritis. *Neuroimmunomodulation* **2015**, *22*, 33–39. [[CrossRef](#)] [[PubMed](#)]
231. Kern, S.; Schultheiss, T.; Schneider, H.; Schrempf, W.; Reichmann, H.; Ziemssen, T. Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis. *Psychoneuroendocrinology* **2011**, *36*, 1505–1512. [[CrossRef](#)] [[PubMed](#)]
232. Wipfler, P.; Heikkinen, A.; Harrer, A.; Pilz, G.; Kunz, A.; Golaszewski, S.M.; Reuss, R.; Oschmann, P.; Kraus, J. Circadian rhythmicity of inflammatory serum parameters: A neglected issue in the search of biomarkers in multiple sclerosis. *J. Neurol.* **2013**, *260*, 221–227. [[CrossRef](#)] [[PubMed](#)]
233. Powell, D.J.H.; Moss-Morris, R.; Lioffi, C.; Schlotz, W. Circadian cortisol and fatigue severity in relapsing-remitting multiple sclerosis. *Psychoneuroendocrinology* **2015**, *56*, 120–131. [[CrossRef](#)] [[PubMed](#)]
234. Melief, J.; de Wit, S.J.; van Eden, C.G.; Teunissen, C.; Hamann, J.; Uitdehaag, B.M.; Swaab, D.; Huitinga, I. HPA axis activity in multiple sclerosis correlates with disease severity, lesion type and gene expression in normal-appearing white matter. *Acta Neuropathol.* **2013**, *126*, 237–249. [[CrossRef](#)] [[PubMed](#)]
235. Mason, D.; MacPhee, I.; Antoni, F. The role of the neuroendocrine system in determining genetic susceptibility to experimental allergic encephalomyelitis in the rat. *Immunology* **1990**, *70*, 1–5. [[PubMed](#)]
236. Gold, S.M.; Raji, A.; Huitinga, I.; Wiedemann, K.; Schulz, K.-H.; Heesen, C. Hypothalamo-pituitary-adrenal axis activity predicts disease progression in multiple sclerosis. *J. Neuroimmunol.* **2005**, *165*, 186–191. [[CrossRef](#)] [[PubMed](#)]
237. Heidbrink, C.; Häusler, S.F.M.; Buttmann, M.; Ossadnik, M.; Strik, H.M.; Keller, A.; Buck, D.; Verbraak, E.; van Meurs, M.; Krockenberger, M.; et al. Reduced cortisol levels in cerebrospinal fluid and differential distribution of 11beta-hydroxysteroid dehydrogenases in multiple sclerosis: Implications for lesion pathogenesis. *Brain Behav. Immun.* **2010**, *24*, 975–984. [[CrossRef](#)] [[PubMed](#)]
238. Van den Brandt, J.; Lühder, F.; McPherson, K.G.; de Graaf, K.L.; Tischner, D.; Wiehr, S.; Herrmann, T.; Weissert, R.; Gold, R.; Reichardt, H.M. Enhanced glucocorticoid receptor signaling in T cells impacts thymocyte apoptosis and adaptive immune responses. *Am. J. Pathol.* **2007**, *170*, 1041–1053. [[CrossRef](#)] [[PubMed](#)]
239. Bellavance, M.-A.; Rivest, S. The HPA—Immune Axis and the Immunomodulatory Actions of Glucocorticoids in the Brain. *Front. Immunol.* **2014**, *5*, 136. [[CrossRef](#)] [[PubMed](#)]
240. Van Winsen, L.M.L.; Muris, D.F.R.; Polman, C.H.; Dijkstra, C.D.; van den Berg, T.K.; Uitdehaag, B.M.J. Sensitivity to glucocorticoids is decreased in relapsing remitting multiple sclerosis. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 734–740. [[CrossRef](#)] [[PubMed](#)]
241. Cheon, S.; Park, N.; Cho, S.; Kim, K. Glucocorticoid-mediated Period2 induction delays the phase of circadian rhythm. *Nucleic Acids Res.* **2013**, *41*, 6161–6174. [[CrossRef](#)] [[PubMed](#)]
242. So, A.Y.-L.; Bernal, T.U.; Pillsbury, M.L.; Yamamoto, K.R.; Feldman, B.J. Glucocorticoid regulation of the circadian clock modulates glucose homeostasis. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 17582–17587. [[CrossRef](#)] [[PubMed](#)]
243. Pan, Z.; Xie, D.; Choudhary, V.; Seremwe, M.; Tsai, Y.-Y.; Olala, L.; Chen, X.; Bollag, W.B. The effect of pioglitazone on aldosterone and cortisol production in HAC15 human adrenocortical carcinoma cells. *Mol. Cell. Endocrinol.* **2014**, *394*, 119–128. [[CrossRef](#)] [[PubMed](#)]

244. Csernus, V.; Mess, B. Biorhythms and pineal gland. *Neuro Endocrinol. Lett.* **2003**, *24*, 404–411. [[PubMed](#)]
245. Mauriz, J.L.; Collado, P.S.; Veneroso, C.; Reiter, R.J.; González-Gallego, J. A review of the molecular aspects of melatonin's anti-inflammatory actions: Recent insights and new perspectives. *J. Pineal Res.* **2013**, *54*, 1–14. [[CrossRef](#)] [[PubMed](#)]
246. Crowley, S.J.; Eastman, C.I. Melatonin in the afternoons of a gradually advancing sleep schedule enhances the circadian rhythm phase advance. *Psychopharmacology* **2013**, *225*, 825–837. [[CrossRef](#)] [[PubMed](#)]
247. Farez, M.F.; Calandri, I.L.; Correale, J.; Quintana, F.J. Anti-inflammatory effects of melatonin in multiple sclerosis. *BioEssays* **2016**, *38*, 1016–1026. [[CrossRef](#)] [[PubMed](#)]
248. Sandyk, R.; Awerbuch, G.I. Nocturnal plasma melatonin and alpha-melanocyte stimulating hormone levels during exacerbation of multiple sclerosis. *Int. J. Neurosci.* **1992**, *67*, 173–186. [[CrossRef](#)] [[PubMed](#)]
249. Wang, X.; Sirianni, A.; Pei, Z.; Cormier, K.; Smith, K.; Jiang, J.; Zhou, S.; Wang, H.; Zhao, R.; Yano, H.; et al. The melatonin MT1 receptor axis modulates mutant Huntingtin-mediated toxicity. *J. Neurosci.* **2011**, *31*, 14496–14507. [[CrossRef](#)] [[PubMed](#)]
250. Rosales-Corral, S.A.; Acuña-Castroviejo, D.; Coto-Montes, A.; Boga, J.A.; Manchester, L.C.; Fuentes-Broto, L.; Korkmaz, A.; Ma, S.; Tan, D.-X.; Reiter, R.J. Alzheimer's disease: Pathological mechanisms and the beneficial role of melatonin. *J. Pineal Res.* **2012**, *52*, 167–202. [[CrossRef](#)] [[PubMed](#)]
251. Galano, A.; Tan, D.X.; Reiter, R.J. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. *J. Pineal Res.* **2013**, *54*, 245–257. [[CrossRef](#)] [[PubMed](#)]
252. Calvo, J.R.; González-Yanes, C.; Maldonado, M.D. The role of melatonin in the cells of the innate immunity: A review. *J. Pineal Res.* **2013**, *55*, 103–120. [[CrossRef](#)] [[PubMed](#)]
253. Zhang, H.-M.; Zhang, Y. Melatonin: A well-documented antioxidant with conditional pro-oxidant actions. *J. Pineal Res.* **2014**, *57*, 131–146. [[CrossRef](#)] [[PubMed](#)]
254. Chen, S.-J.; Huang, S.-H.; Chen, J.-W.; Wang, K.-C.; Yang, Y.-R.; Liu, P.-F.; Lin, G.-J.; Sytwu, H.-K. Melatonin enhances interleukin-10 expression and suppresses chemotaxis to inhibit inflammation in situ and reduce the severity of experimental autoimmune encephalomyelitis. *Int. Immunopharmacol.* **2016**, *31*, 169–177. [[CrossRef](#)] [[PubMed](#)]
255. Markowska, M.; Bialecka, B.; Ciechanowska, M.; Koter, Z.; Laskowska, H.; Karkucinska-Wieckowska, A.; Skwarlo-Sonta, K. Effect of immunization on nocturnal NAT activity in chicken pineal gland. *Neuro Endocrinol. Lett.* **2000**, *21*, 367–373. [[PubMed](#)]
256. Fernandes, P.A.C.M.; Cecon, E.; Markus, R.P.; Ferreira, Z.S. Effect of TNF-alpha on the melatonin synthetic pathway in the rat pineal gland: Basis for a "feedback" of the immune response on circadian timing. *J. Pineal Res.* **2006**, *41*, 344–350. [[CrossRef](#)] [[PubMed](#)]
257. Herman, A.P.; Bochenek, J.; Król, K.; Krawczyńska, A.; Antushevich, H.; Pawlina, B.; Herman, A.; Romanowicz, K.; Tomaszewska-Zaremba, D. Central Interleukin-1 β Suppresses the Nocturnal Secretion of Melatonin. *Mediators Inflamm.* **2016**, *2016*, 2589483. [[CrossRef](#)] [[PubMed](#)]
258. Pontes, G.N.; Cardoso, E.C.; Carneiro-Sampaio, M.M.S.; Markus, R.P. Pineal melatonin and the innate immune response: The TNF-alpha increase after cesarean section suppresses nocturnal melatonin production. *J. Pineal Res.* **2007**, *43*, 365–371. [[CrossRef](#)] [[PubMed](#)]
259. Kallaur, A.P.; Oliveira, S.R.; Simão, A.N.C.; Alfieri, D.F.; Flauzino, T.; Lopes, J.; de Carvalho Jennings Pereira, W.L.; de Meleck Proença, C.; Borelli, S.D.; Kaimen-Maciél, D.R.; et al. Cytokine Profile in Patients with Progressive Multiple Sclerosis and Its Association with Disease Progression and Disability. *Mol. Neurobiol.* **2017**, *54*, 2950–2960. [[CrossRef](#)] [[PubMed](#)]
260. Álvarez-Sánchez, N.; Cruz-Chamorro, I.; López-González, A.; Utrilla, J.C.; Fernández-Santos, J.M.; Martínez-López, A.; Lardone, P.J.; Guerrero, J.M.; Carrillo-Vico, A. Melatonin controls experimental autoimmune encephalomyelitis by altering the T effector/regulatory balance. *Brain Behav. Immun.* **2015**, *50*, 101–114. [[CrossRef](#)] [[PubMed](#)]
261. Constantinescu, C.S.; Hilliard, B.; Ventura, E.; Rostami, A. Luzindole, a melatonin receptor antagonist, suppresses experimental autoimmune encephalomyelitis. *Pathobiology* **1997**, *65*, 190–194. [[CrossRef](#)] [[PubMed](#)]
262. Kang, J.C.; Ahn, M.; Kim, Y.S.; Moon, C.; Lee, Y.; Wie, M.B.; Lee, Y.J.; Shin, T. Melatonin ameliorates autoimmune encephalomyelitis through suppression of intercellular adhesion molecule-1. *J. Vet. Sci.* **2001**, *2*, 85–89. [[PubMed](#)]

263. Giese, K.P. GSK-3: A key player in neurodegeneration and memory. *IUBMB Life* **2009**, *61*, 516–521. [[CrossRef](#)] [[PubMed](#)]
264. Hoppe, J.B.; Frozza, R.L.; Horn, A.P.; Comiran, R.A.; Bernardi, A.; Campos, M.M.; Battastini, A.M.O.; Salbego, C. Amyloid-beta neurotoxicity in organotypic culture is attenuated by melatonin: Involvement of GSK-3beta, tau and neuroinflammation. *J. Pineal Res.* **2010**, *48*, 230–238. [[CrossRef](#)] [[PubMed](#)]
265. Guven, C.; Taskin, E.; Akcakaya, H. Melatonin Prevents Mitochondrial Damage Induced by Doxorubicin in Mouse Fibroblasts Through Ampk-Ppar Gamma-Dependent Mechanisms. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2016**, *22*, 438–446. [[CrossRef](#)]
266. Kato, H.; Tanaka, G.; Masuda, S.; Ogasawara, J.; Sakurai, T.; Kizaki, T.; Ohno, H.; Izawa, T. Melatonin promotes adipogenesis and mitochondrial biogenesis in 3T3-L1 preadipocytes. *J. Pineal Res.* **2015**, *59*, 267–275. [[CrossRef](#)] [[PubMed](#)]



© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).