Circadian Rhythms and Energy Metabolism Reprogramming in Parkinson's Disease

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Abstract
Entropy rate is increased by several metabolic and thermodynamic abnormalities in neurodegenerative diseases (NDs). Changes in Gibbs energy, heat production, ionic conductance or intracellular acidity are irreversible processes impelling modifications of the entropy rate. The present review focuses on the thermodynamic implications in the reprogramming of cellular energy metabolism enabling in Parkinson's disease (PD) through the contrasting interplay of the molecular signaling pathways WNT/β-catenin and PPARγ. In PD, WNT/β-catenin pathway is downregulated while PPARγ is upregulated. Thermodynamic behaviors of metabolic enzymes are modified by dysregulation of the canonical WNT/β-catenin pathway. Downregulation of WNT/β-catenin pathway leads to hypometabolism, oxidative stress and cell death through inactivation of glycolytic enzymes such as Glut, PKM2, PDK1, MCT-1, LDH-A but also to activation of PDH. In addition, in NDs, PPARγ is dysregulated even though it contributes to the regulation of several key circadian genes. PD processes may be considered as dissipative structures that exchange energy or matter with their environment far-from the thermodynamic equilibrium. Far-from-equilibrium thermodynamics are notions driven by circadian rhythms, which directly contribute to regulation of the molecular pathways WNT/β-catenin and PPARγ involved in the reprogramming of cellular energy metabolism enabling in Parkinson's disease.

Introduction
Parkinson's disease (PD) is a major neurodegenerative disease with a progressive degeneration of neurons containing dopamine in the substantia nigra pars compacta. PD is triggered in brainstem or in the spinal cord of subjects who remain asymptomatic for a long time (Braak, Ghebremedhin, Rüb, Bratzke, and Del Tredici, 2004; Grinberg, Rueb, Alho, and Heinsen, 2010). While the primary etiology remains unknown, the presence of Lewy bodies (clumps of a-synuclein and ubiquitin proteins in neurons which are detectable in post-mortem brain histology) has observed from the earlier stages. PD is characterized by tremor symptom, rigidity, bradykinesia and postural instability. These symptoms occur only when the majority of dopaminergic cells is lost in the substantia nigra pars compacta, which means that the smooth, coordinated regulation of striatal motor circuits is also lost (Maguire-Zeiss and Federoff, 2010). Depression or rapid eye movement (REM)-associated sleep behavior disorder (RBD) are non-motor symptoms that could precede the onset of disease.

In most cases PD is an idiopathic form, but familial PD genes are often referred to as PARK genes. Indeed, mutations in PARK8, codifying for Leucine-rich repeat kinase 2 (LRRK2), have been identified as a cause of familial Parkinson's (Häbig, Walter, Poths, Riess, and Bonin, 2008). No treatment can currently delay or stop the progression of PD, and the medications currently available are mostly symptomatic.

Age is a major risk factor for neurodegenerative diseases (NDs). The aging process can perturb

molecular pathways regulating cellular homeostatic mechanisms. Neurodegenerative cells are the sites of numerous energy abnormalities (Yin, Boveris, and Cadenas, 2014). The altered cells are derived from exergonic processes and emit heat that flows to the surrounding environment. Many irreversible processes can occur once the entropy rate has been modified. This rate represents a thermodynamic quantity that measures irreversible processes such as Gibbs energy, heat production, or ionic conductance (Kondepudi and Prigogine, 1999; Prigogine, 1986; Prigogine, Nicolis, and Babloyantz, 1974; Sandler, 2006). Several energy cellular mechanisms can induce and develop neurodegenerative processes. PD presents an energy and metabolic remodeling entailing increased oxidative stress and neuroinflammation (Kim, Kim, Rhie, and Yoon, 2015). This energy metabolism remodeling increase the entropy production rate in NDs (Riggs, 1998).

WNT/β-catenin signaling is a crucial factor in the development of many NDs (Libro, Bramanti, and Mazzon, 2016). Overexpression of GSK3 increases neurotoxicity via inactivation of WNT/β-catenin signaling, and activation of GSK3 is involved in neurodegeneration (Dun et al., 2012; Wiedau-Pazos, Wong, Solomon, Alarcon, and Geschwind, 2009). Parkinson's disease (PD) presents downregulation of the canonical WNT/β-catenin pathway (Libro et al., 2016). Inactivation of WNT/β-catenin pathway leads to oxidative stress in mitochondria (Harris, Tindale, and Cumming, 2014). In parallel, peroxisome proliferator-activated γ (PPARγ) is modified in neurodegenerative diseases. Targeting PPARγ expression appears as an interesting therapeutic perspective against neurodegeneration (Esmaeili et al., 2016), and neuroinflammation, especially in PD (Pinto et al., 2016).

Some of the processes involved during NDs, such as WNT proteins (Goldbeter and Pourquié, 2008) and (PPARγ) (Yves Lecarpentier, Claes, and Hébert, 2010), are considered as dissipative structures that exchange energy or matter with their environment. Dissipative structures are open systems which operate far-from a thermodynamic equilibrium and driven by circadian rhythms (CRs) (Goldbeter, 2017; Prigogine, 1986; Prigogine et al., 1974). Indeed, CRs are directly involved in regulation of the molecular open-system pathways found in NDs processes (Videnovic and Zee, 2015).

In numerous tissues, inhibition of the canonical WNT/β-catenin pathway is induced by the activation of PPARγ, while activation of the canonical WNT/β-catenin pathway induces inactivation of PPARγ (Yves Lecarpentier, Claes, Duthoit, and Hébert, 2014; Siersbæk et al., 2012; N. Wang et al., 2008; K. Zhang, Zhang, Han, Pu, and Kang, 2012). PD is characterized by downregulation of the canonical WNT/β-catenin while PPARγ is upregulated (Berwick and Harvey, 2012; J. Clark, Reddy, Zheng, Betensky, and Simon, 2011).

PPARγ can regulate CRs through some key circadian genes, such as Bmal1 (brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1) (N. Wang et al., 2008). Dysfunction of PPARγ can influence statistical mechanics by modifying thermodynamic force, thermodynamic flow, and rate of entropy production (Kondepudi and Prigogine, 1999; Y. Lecarpentier et al., 2008).

The opposite interplay between WNT/β-catenin pathway and PPARγ in PD plays a major role in both energy metabolism dysregulation and disruption of CRs. Thermodynamic dysregulation observed in PD is the consequence of an energy metabolism reprogramming induced by the dysfunction of the contrasting interplay between WNT/β-catenin pathway and PPARγ. We focused this review on the opposed interactions observed in PD between the canonical WNT/β-catenin pathway and PPARγ and their circadian rhythms and energy metabolism implications.

Interplay between canonical WNT/β-catenin pathway and PPARγ

Canonical WNT/β-catenin pathway

During embryogenesis, the Wingless/Int (WNT) pathway is involved in neural development and in adulthood in the maintenance of neuronal homeostasis (Harrison-Uy and Pleasure, 2012; Ille and Sommer, 2005; Oliva, Vargas, and Inestrosa, 2013; Salinas, 2012). It regulates synaptogenesis and synaptic function (Salinas, 2012).

WNT proteins belong to the family of secreted lipid-modified glycoproteins, present in different species (Al-Harthi, 2012). WNT ligands are activators of the WNT signaling stimulating intracellular WNT signaling. WNT ligands are secreted by both neurons and immune cells in the central nervous system (Marchetti and Pluchino, 2013). WNT family genes comprises 19 members which are classified as canonical WNTs and non-canonical WNTs.

Canonical WNT ligands (WNT1, WNT2, WNT3, WNT8a, WNT8b, WNT10a, WNT10b) are activators of the WNT signaling which stimulate the intracellular WNT signaling (such as the beta-catenin nuclear translocation), and secreted by both neurons and immune cells in the central nervous system (Marchetti and Pluchino, 2013). WNT ligands are cysteine rich proteins of approximately 350-400 amino acids that contain an N-terminal signal peptide for secretion since they are lipid modified secreted proteins (MacDonald, Tamai, and He, 2009).

Metabolism, embryonic development, cell fate, and epithelial-mesenchymal transition (EMT) are involved by the regulation of the WNT/β-catenin pathway. Immunohistochemical staining and Western blotting can detect elevated levels of β-catenin in the nucleus and/or cytosol after WNT signaling activation. WNT pathway dysfunction is involved in numerous diseases, particularly in neurodegenerative diseases (Yves Lecarpentier et al., 2014; Yves Lecarpentier and Vallée, 2016; Vallée and Lecarpentier, 2016). The major key of the canonical WNT pathway is the β-catenin/T-cell factor/lymphoid enhancer factor (TCF/LEF) complex. After entered the nucleus, β-catenin engages DNA-bound TCF/LEF complex transcription factor. This association with β-catenin transiently converts TCF/LEF complex from a transcriptional repressor into an activator of specific target genes involved throughout development, cell survival and proliferation. In the absence of WNT ligands, TCF/LEF complex interacts with Groucho transcriptional repressors preventing genes transcription (Clevers and Nusse, 2012).

β-catenin accumulation is controlled by the destruction complex AXIN, tumor suppressor adenomatous polyposis coli (APC), and glycogen synthase kinase-3 (GSK3). In the absence of WNT ligands, the destruction complex provides a scaffold to allow GSK3 and CK1 (casein kinase 1) to phosphorylate β-catenin and then to generate its degradation into the proteasome. In the presence of WNT ligands, the latter interact with Frizzled (FZL) and LDL receptor-related protein 5/6 (LRP 5/6). This interaction disturbs the destruction complex and prevents β-catenin degradation into the proteasome by translocating it to the nucleus for interaction with TCF/LEF. This leads to the activation of β-catenin target genes (PDK1, MCT-1, c-Myc, cyclin D1, COX2, AXIN2) (Angers and Moon, 2009; He et al., 1998; Shtutman et al., 1999).

GSK3 and Dikkopf-1 (DKK1) are two major inhibitors of WNT/β-catenin pathway signaling (Clevers and Nusse, 2012; Inestrosa, Montecinos-Oliva, and Fuenzalida, 2012; Rosi et al., 2010; Sharma, Pradeep, Wong, Rana, and Rana, 2004). DKK1, an antagonist of the WNT signaling (Semënov, Zhang, and He, 2008), binds to LRP5/6 co-receptors and then inhibits WNT signaling (Kawano and Kypta, 2003). Through a negative feedback loop, the β-catenin/TCF complex can regulate DKK1 transcription (Niida et al., 2004). GSK3 is a main negative regulator of the WNT pathway (Aberle, Bauer, Stappert, Kispert, and Kemler, 1997). As an intracellular serin-threonin kinase, GSK3 is involved in the regulation of several forms of pathophysiological signaling, including cell membrane signaling, neuronal polarity, and inflammation (Ambacher et al., 2012; Hur and Zhou, 2010; D. Wu and Pan, 2010). GSK3 acts through inhibition of β-catenin cytosolic stabilization and nuclear migration. Neuroinflammation is an age-related process with increased GSK3 and decreased Akt and WNT/β-catenin pathways in the hippocampus of older rats (Orellana et al., 2015). Akt regulates GSK3 activity by a direct phosphorylation S21 for GSK3-α and S9 for GSK3-β (H. H. Zhang, Lipovsky, Dibble, Sahin, and Manning, 2006). Dysregulation of WNT/β-catenin pathway is observed in NDs, with downregulation of WNT signaling appearing in PD (Libro et al., 2016).

PPARγ

The ligand-activated transcriptional factor peroxisome proliferator receptor γ (PPARγ) is a member of the nuclear hormone receptor super family. It forms a heterodimer with retinoid X receptor (RXR), generating a PPARγ-RXR complex for binding to specific peroxisome proliferator response element (PPRE) regions in the DNA and activating several target genes involved in fatty acid transport (FABP3), cholesterol metabolism (CYP7A1, LXRα, CYP27), glucose homeostasis (PEPCK, GyK) and lipid catabolism (SCD-1). This dimer interacts with other coactivators proteins such as PGC-1α, and induces specific genes expression (Ahmadian et al., 2013). Few endogenous ligands of PPAR gamma are known, these include fatty acids, phytanic acid, oxidized metabolites of linoleic acid, such as 9-hydroxy and 13-hydroxy octadecadienoic acids (9-HODE and 13-HODE); polyunsaturated fatty acids (arachidonic acid), and eicosanoids (Behl, Kaur, Goel, and Kotwani, 2016; Grygiel-Górniak, 2014). Anandamide, an endogenous cannabinoid receptor ligand binds PPAR gamma and induces differentiation of 3T3-L1 fibroblast cell

of mice into adipocytes (Schild et al., 2002). However, the major endogenous ligand of PPAR gamma is 15-deoxy-delta 12, 14-prostaglandin J2 (15d-PGJ2) (Behl et al., 2016).

Glucose homeostasis, insulin sensitivity, lipid metabolism, immune responses, cell fate and inflammation are regulated by PPARγ activation (Elbrecht et al., 1996; Fajas et al., 1997). PPARγ is abundantly expressed in adipose tissue, whereas in heart, skeletal muscle and in liver PPARγ is lower expressed (Bright, Kanakasabai, Chearwae, and Chakraborty, 2008). PPARγ is little expressed in central nervous system (CNS) but present in several cell types such as neurons, astrocytes, oligodendrocytes and microglia (Braissant, Foufelle, Scotto, Dauça, and Wahli, 1996; Y.-C. Chen et al., 2012; Chiang et al., 2010, 2015). PPARγ expression is localized mainly in the microglia and astrocytes and plays a major role in the inflammatory response of the CNS (Kapadia, Yi, and Vemuganti, 2008). In neurons, PPARγ immunoreactivity appears mainly as a nuclear labeling, even though at times, cytoplasmic staining is detectable in cortical neurons (Chiang et al., 2015). Circadian variations of blood pressure and heart rate are regulated by PPARγ through its action on Bmal1 (Yves Lecarpentier et al., 2010; N. Wang et al., 2008). PPARγ modulates the expression of several genes involved in inflammation, and it decreases the activity of inflammation-related transcription factors such as NF-kappaB (Ricote and Glass, 2007).

PPARγ expression and activity may be dysregulated during aging and be associated with loss of function (Haramizu, Ota, Hase, and Murase, 2011). PPARγ agonists can prevent the metabolic effects of aging-induced neuroinflammation and neurodegeneration (Esmaeili et al., 2016). PPARγ agonists induce neuroprotective effects in PD (Carta et al., 2011).

Opposing effects between the canonical WNT/β-catenin pathway and PPARγ

WNT/β-catenin pathway and PPARγ act in an opposite manner. Functional interaction between β-catenin and PPARγ involves a TCF/LEF domain of β-catenin and a catenin-binding domain within PPARγ (Liu, Wang, Zuo, and Farmer, 2006; Lu and Carson, 2010; Sharma et al., 2004; Takada, Kouzmenko, and Kato, 2009). A previous study has shown that mutation of K312 and K435 in the TCF/LEF binding domain of oncogenic S37 β-catenin decreases its ability to interact with and inhibit PPARγ activity. Furthermore, these mutations render S37A β-catenin susceptible to proteasomal degradation in response to activation of PPARγ. Mutation of F372 within the catenin-binding domain (helices 7 and 8) of PPARγ disrupts its binding to β-catenin and reduces PPARγ ability to induce the proteasomal degradation of β-catenin (Liu et al., 2006).

In several diseases when the WNT/β-catenin pathway is downregulated, PPARγ appears to be upregulated whereas when the WNT/β-catenin is upregulated, PPARγ appears to be downregulated (Yves Lecarpentier et al., 2014). This observation is also observed in arrthymogenic right ventricular cardiomyopathy (ARVC) (Djouadi et al., 2009; Garcia-Gras et al., 2006), hypertension (Vallée, Lévy, and Blacher, 2018), osteoporosis (Korvala et al., 2012), bipolar disorder (Valvezan and Klein, 2012), schizophrenia (Panaccione et al., 2013) and certain neurodegenerative diseases (NDs) such as Alzheimer's disease (Vallée and Lecarpentier, 2016; Vallée, Lecarpentier, Guillevin, and Vallée, 2017b, 2018c). Conversely, in other diseases, WNT/β-catenin signaling is upregulated whereas PPARγ is downregulated. This is the case in cancers (Yves Lecarpentier, Claes, Vallée, and Hébert, 2017b, 2017a; Vallée, Guillevin, and Vallée, 2017; Vallée, Lecarpentier, Guillevin, and Vallée, 2017e), lymphomas (Vallée, Lecarpentier, and Vallée, 2019), type 2 diabetes (Yves Lecarpentier et al., 2017a), and certain NDs, such as amyotrophic lateral sclerosis (Yves Lecarpentier and Vallée, 2016; Vallée, Lecarpentier, Guillevin, and Vallée, 2018a), Huntington's disease (Godin, Poizat, Hickey, Maschat, and Humbert, 2010; Vallée, Lecarpentier, et al., 2018a), exudative AMD (Vallée, Lecarpentier, Guillevin, and Vallée, 2017d, 2017a), multiple sclerosis (Vallée, Lecarpentier, Guillevin, and Vallée, 2018b; Vallée, Vallée, Guillevin, and Lecarpentier, 2017), fibrosis processes (Vallée, Lecarpentier, Guillevin, and Vallée, 2017c; Vallée, Lecarpentier, and Vallée, 2017), autism (Vallée, Vallée, and Lecarpentier, 2018) and Friedreich's ataxia (Coppola et al., 2009). The activation of PPARγ can be induced by inhibition of the WNT/β-catenin pathway (Garcia-Gras et al., 2006) while PPARγ agonists can inhibit β-catenin in several cellular systems (Elbrecht et al., 1996; Fajas et al., 1997; Moldes et al., 2003). PPARγ agonists could act through WNT/β-catenin/PI3K/Akt pathway as neuroprotective agents and promote synaptic plasticity (Farshbaf, Ghaedi, Shirani, and Nasr-Esfahani, 2014). The WNT pathway increases methyl-CpG binding protein 2, which represses PPARγ and activates hepatic stellate cells. Crosstalk between PPARγ and WNT signaling is

also observed in the regulation of mesenchymal stem cell differentiation (Xu et al., 2016).

Downregulation of the canonical WNT/β-catenin pathway and upregulation of PPARγ in PD.

Downregulation of the canonical WNT/β-catenin pathway (Table 1)

Abnormalities of WNT signaling are implicated in PD (Parish et al., 2008; Rawal et al., 2009). Dysregulation of WNT signaling is considered as an initiating event in the development of PD (Berwick and Harvey, 2012). Several cell biological functions affected in PD are controlled by the WNT signaling pathway, such as microtubule stability, axonal function and membrane trafficking (Berwick and Harvey, 2011; Inestrosa and Arenas, 2010). The mesencephalic dopaminergic neuron-astrocyte crosstalk is controlled by WNT1 regulated Frizzled-1/β-catenin signaling pathway (L'episcopo et al., 2011). DKK1 and GSK3, two inhibitors of the WNT pathway, increase in PD (Zhou et al., 2016). PD mouse model show a crosstalk between inflammatory and WNT/β-catenin signaling pathway (L'Episcopo et al., 2012). In normal circumstances, LRRK2 interacts with WNT family with the Disheveled (DSH) proteins. This interaction inhibits the β-catenin destruction complex to promote the activation of the canonical WNT pathway (Berwick and Harvey, 2012). In family forms of PD, LRRK2 mutations can reduce the LRRK2-LRP5/6 binding affinity and are associated with reduced activation of canonical WNT pathway (Libro et al., 2016). PARKIN is an E3 ubiquitin ligase encoded by the PARK2 gene. PARKIN genetic alterations are implicated in family PD development and act as β-catenin repressors promoting β-catenin ubiquitination and degradation (Rawal et al., 2009).

Upregulation of PPARγ (Table1)

Chronic inflammation is one of the hallmarks of PD with increased pro-inflammatory factor levels in substantia nigra (Hirsch, Vyas, and Hunot, 2012; Q. Wang, Liu, and Zhou, 2015). The PPARγ ligand 15-deoxy-ProstaglandinJ2 production is enhanced by stress, which increases expression of PPARγ in cerebral cortex to counteract inflammation and oxidative stress (García-Bueno et al., 2005). Inflammation and oxidative consequences of stress exposure may be prevent by PPAR ligands (García-Bueno et al., 2005) through an action of neuroprotection mediator (Galea, Heneka, Dello Russo, and Feinstein, 2003). The main neuroprotection action of PPARγ agonists consists in their anti-inflammatory activity (Carta et al., 2011). In rat nigro-striatal system, the degeneration of dopaminergic neurons is induced by non-physiological overexpression of PGC-1α (Ciron, Lengacher, Dusonchet, Aebischer, and Schneider, 2012).

Brain energy metabolism

Energy is the main determinant of neuronal viability. Under normal physiological conditions, adult brain uses exclusively glucose for energy metabolism (S.-H. Yang et al., 2015). Glucose is almost metabolized to CO2 and water through glycolysis, tricarboxylic acid (TCA) cycle, and mitochondrial oxidative

Table 1. Role of the WNT and PPARγ in PD.

WNT pathway in PD	**Reference**
PARKIN inhibits WNT	Rawal et al., 2009
Inhibited WNT enhances hypometabolism and mitochondrial dysfunction	Mosconi et al., 2008
Inhibited WNT reduces activity of PI3K/Akt pathway	Yu et al., 2010
Reduced PI3K/Akt participates to PD progression	Heras-Sandoval et al. 2014
Inhibited WNT stimulates ROS production	Blesa et al., 2015
Dysregulation of CRs inhibits WNT pathway	Sahar and Sassone-Corsi, 2009
PPARγ in PD	**References**
PPARγ controls oxidative phosphorylation	Tsunemi et al., 2012
PPARγ represses neuroinflammation	Corona and Duchen, 2015
PPARγ inhibits oxidative stress	Pinto et al.,2016
Pioglitazone increases neuronal glucose uptake	Rong et al., 2011
PPAR agonist can regulate CRs genes	Yang et al., 2012

phosphorylation (Bélanger, Allaman, and Magistretti, 2011). In the presence of oxygen, glycolysis is coupled with TCA cycle and mitochondrial oxidative phosphorylation. Cytosolic lactate is shuttled out of the cell through monocarboxylate transporter (MCT) for oxidation to obtain pyruvate. Pyruvate is converted into many organic acids through TCA cycle (Schurr, 2014). TCA cycle reduces NDA+ to NADH into mitochondrial oxidative phosphorylation to generate ATP, the ultimate biochemical energy. Dysfunction of mitochondrial dynamics has been observed in NDs and cancers (H. Chen and Chan, 2009; Grandemange, Herzig, and Martinou, 2009). Mitochondrial oxidative phosphorylation is considered as the major metabolic pathway in brain. Aerobic glycolysis predominates in the developing brain during embryogenesis (Bauernfeind et al., 2014), while there is progressively a shift from aerobic glycolysis to oxidative phosphorylation from embryogenesis to late adulthood within the human brain (Barros, 2013; Harris et al., 2014). Mitochondrial oxidative phosphorylation allows brain glucose to fuel neuronal activity (Simpson, Carruthers, and Vannucci, 2007). The single largest glucose reserve glycogenesis predominately localizes in astrocyte end-feet, bodies and processes (DiNuzzo, Maraviglia, and Giove, 2011; Oz et al., 2007). Astrocytes can mobilize glycogen for neuronal metabolism under normal circumstances, and under increased energy demand or failure of neurons (S.-H. Yang et al., 2015). But, due to low content of glycogen in brain as compared to liver and skeletal muscles, astrocytic glycogen is unlikely to serve as an alternative energy supply during hypoglycemia. Thus brain metabolism under normal conditions uses astrocytic glycogen as an integral source of energy (DiNuzzo et al., 2011; Obel et al., 2012). Astrocytes may play a major role in bioenergetics and biosynthetic metabolism in the brain while pyruvate derived from neuronal glucose is considered as the main fuel for neurons (Patel et al., 2014). NDs show dysfunctions of astrocyte metabolism (Stobart and Anderson, 2013). The causal role of mitochondrial dysfunctions in aging and age-related NDs has been shown by abundant evidence (Bratic and Larsson, 2013; H. Chen and Chan, 2009; S.-H. Yang et al., 2015).

Energy metabolism disorders in Parkinson's disease

Cerebral hypometabolism in PD

PD brain shows reduction in its glucose metabolism (Borghammer, 2012; Borghammer et al., 2010; Dunn et al., 2014). Glucose hypo-metabolism has been found in cerebral cortex in PD patients with and without dementia (Edison et al., 2013). Symptom severity is temporally correlated with cerebral hypo-metabolism, which can be considered as a predictive value for onset of dementia (Mosconi, Pupi, and De Leon, 2008). Mitochondrial dysfunctions have also been observed in PD brains by increasing production and releasing reactive oxygen species (ROS) (Franco-Iborra, Vila, and Perier, 2016). Such mitochondrial defects cause cell damage and death by energy depletion due to the disruption of oxidative phosphorylation (Luque-Contreras, Carvajal, Toral-Rios, Franco-Bocanegra, and Campos-Peña, 2014). Oxidative stress and mitochondrial dysfunction increase cell death and dementia (Benilova, Karran, and De Strooper, 2012; Islam, 2017; Sochocka, Koutsouraki, Gasiorowski, and Leszek, 2013).

Donwregulation of WNT pathway involves cerebral hypometabolism in PD (Figure 1)

Downregulation of the canonical WNT/β-catenin pathway inhibits β-catenin target genes (PDK1, MCT-1, c-Myc, cyclin D1, LDH-A) which contribute to regulation of glucose metabolism (Angers and Moon, 2009; He et al., 1998; Shtutman et al., 1999). PARKIN deficiency leads to mitochondrial dysfunctions in neuronal cells, and contribute to progression of family forms of PD (Palacino et al., 2004; Pesah et al., 2004) by inhibiting the WNT/β-catenin pathway (Rawal et al., 2009).

Downregulation of β-catenin also reduces the activity of PI3K/Akt pathway (Park et al., 2004; Yue et al., 2010). PI3K/Akt pathway is downregulated in PD humans brain (Heras-Sandoval, Pérez-Rojas, Hernández-Damián, and Pedraza-Chaverri, 2014). HIF-1α, a downstream target of PI3K/Akt pathway (Sun et al., 2011), is responsible for the expression of enzymatic enzymes such as Glut, LDH-A, PDK1 and PKM2 (Semenza, 2010; Sun et al., 2011). Inactivation of HIF-1α induces PKM2 non-translocation to the nucleus, which induces PKM2 inhibition on PEP cascade and the formation of pyruvate. β-catenin is not binding by PKM2, and glycolytic enzymes (Glut, LDH-A, PDK1) are not activated because of non-formation of c-Myc/PKM2 complex. In conclusion, downregulation of WNT/β-catenin decreases PI3K/Akt activity and its downstream targets such as HIF-1α, Glut, PKM2, PDK1, and LDH-A. This phenomenon leads to glucose hypometabolism and mitochondrial dysfunction increasing symptom severity and may

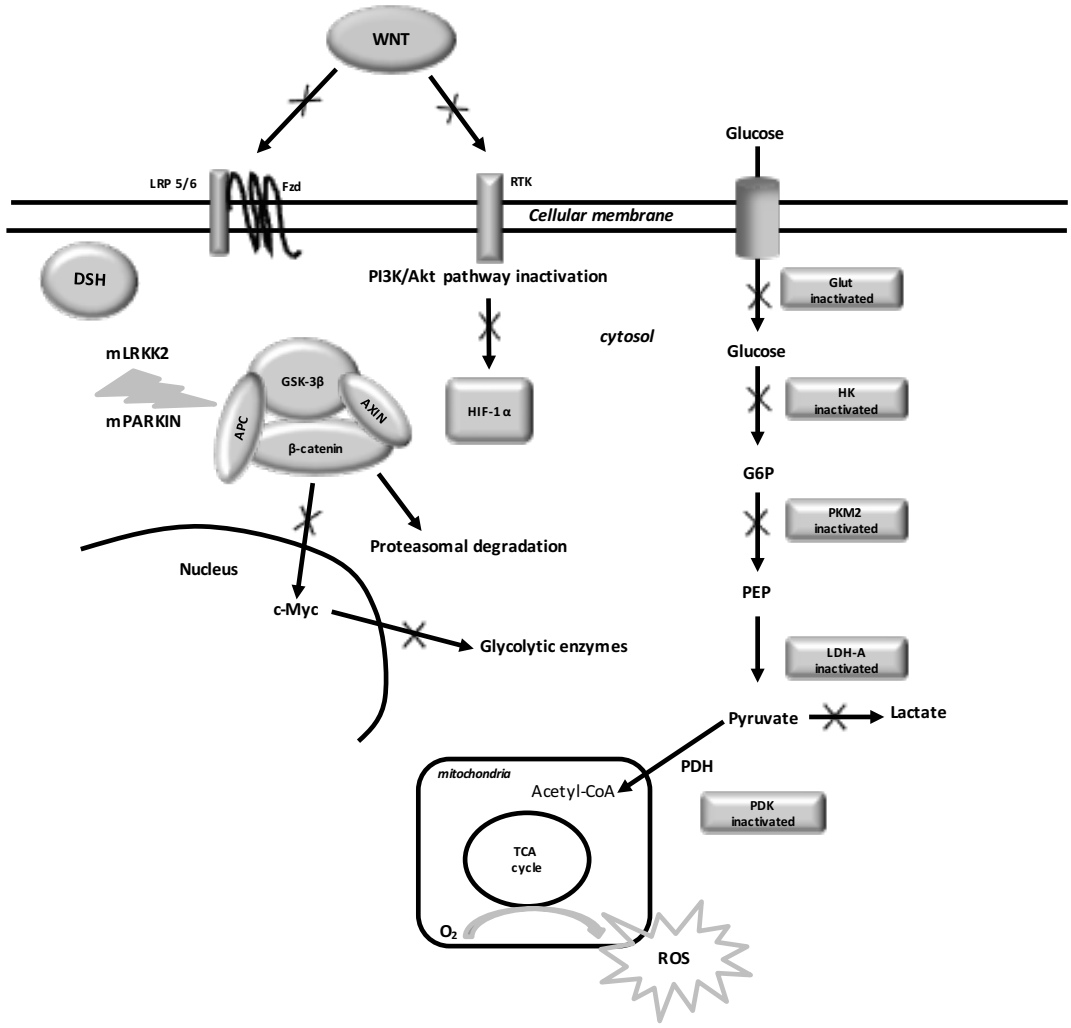

Figure 1. Cerebral hypometabolism and downregulation of the WNT/β-catenin pathway in PD. In PD, mutant PARKIN and mutant LRRK2 activate β-catenin destruction complex. AD and PD lead to WNT "off state". DSH dissociates from FZD and AXIN. APC and AXIN complex with GSK3. B-catenin is phosphorylated, dissociates from GSK3, migrates to the cytosol and is destroyed in the proteasome. Natural decline in glycolysis is associated with old age. Inhibition of WNT/β-catenin decreases PI3/Akt pathway and inhibits levels of HIF-1α. Decreased HIF-1α activity reduces expression of glycolytic enzymes (GLUT, HK, PKM2, LDH-A, PDK) and increases metabolic flux through mitochondrial respiration. Decreased activity of PKM2 reduces its translocation to the nucleus and its activation of glycolytic genes. Cellular respiration produces large amounts of ROS and thereby induces apoptosis. Downregulation of WNT pathway leads to decreased glucose metabolism and to the increased of oxidative stress associated with ROS.

appear as a predictive value for onset of dementia (Mosconi et al., 2008).

Oxidative stress in PD

Development of PD is associated with the initiation of oxidative stress (Kim et al., 2015). Reduction of the respiratory chain activity in substantia nigra pars compacta of PD patients generates excessive ROS and induces apoptosis (Blesa, Trigo-Damas, Quiroga-Varela, and Jackson-Lewis, 2015; Franco-Iborra et al., 2016; Schapira, 2008). In family forms of PD, mitochondrial dysfunction and oxidative stress are caused by mutations in PARKIN and PINK1 (Blesa et al., 2015). PINK1 mutations lead to mitochondrial defects and respiratory chain abnormalities (Hoepken et al., 2007), while PINK1 knockout increases ROS generation (Wood-Kaczmar et al., 2008). PINK1 and PARKIN can regulate mitochondrial function and cell survival in which PINK1 seems to be functioning upstream of

PARKIN in Drosophilia disease models (I. E. Clark et al., 2006). To conclude, PARKIN and PINK1 both influence the risk of certain forms of mutated PD (Schapira, 2008; Thomas and Beal, 2007).

Oxidative stress and PPARγ in PD

PPARγ and PGC-1α control oxidative phosphorylation, antioxidant defense, and autophagy (St-Pierre et al., 2003; Tsunemi et al., 2012). PPARγ agonists repress microglial activation and reduce neuroinflammation by inhibiting the expression of TNF-α, COX2 and iNOS. PPARγ agonists increase PGC-1α, which induces the downstream target genes involved in mitochondrial biogenesis, and then inhibit mitochondrial dysfunction, oxidative stress, neuroinflammation, apoptosis and increase expression of mitochondrial proteins and oxidative phosphorylation capacity (Corona and Duchen, 2015; Pinto et al., 2016; Wenz, Diaz, Spiegelman, and Moraes, 2008). In PD mouse brain, the PPARγ agonist rosiglitazone, induces mitochondrial biogenesis and glucose utilization (Strum et al., 2007). Also in PD, pioglitazone, a PPARγ agonist, increases neuronal glucose uptake, restores brain ATP levels, oxygen consumption, and increases PGC-1α expression (García-Bueno, Caso, Pérez-Nievas, Lorenzo, and Leza, 2007; Ghosh et al., 2007; Rong et al., 2011).

Circadian rhythms (CRs) and circadian clock genes (*Figure 2*)

Several biologic processes in the body are controlled by the circadian "clock" (circadian locomotors output cycles kaput). The circadian clock is in the hypothalamic suprachiasmatic nucleus (SCN). CRs are endogenous and entrainable free-running periods that last approximately 24 hours. Several transcription factors are responsible for the regulation of CRs. They are named circadian locomotors 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) (Gekakis et al., 1998; Hogenesch, Gu, Jain, and Bradfield, 1998). These transcription factors are subject to positive and negative self-regulation mediated by CRs (Reppert and Weaver, 2002; Schibler and Sassone-Corsi, 2002). Clock and Bmal1 heterodimerize and then initiate transcription of Per1, Per2, Cry1 and Cry2 (Ko and Takahashi, 2006). The Per/Cry heterodimer can inhibit its activation through negative feedback. Its translocates back to the nucleus to directly repress the Clock/Bmal1 complex and then inhibits its own transcription (Ko and Takahashi, 2006).

Clock/Bmal1 heterodimer also activates the transcription of retinoic acid-related orphan nuclear receptors, Rev-Erbs and retinoid-related orphan receptors (RORs). Through positive feedback RORs can activate the transcription of Bmal1, whereas Rev-Erbs can repress their transcription through negative feedback (Ko and Takahashi, 2006).

CRs, dissipative structures

Changes in the balance of CRs is directly due to negative feedback produced by a protein on the expression of its own gene (Goodwin, 1965; Hardin, Hall, and Rosbash, 1990). In addition, CRs are dissipative structures and operate in far-from-equilibrium manner. They spontaneously exchange energy with their external environment and thereby change the entropy rate production of cells (Goldbeter, 2002; Prigogine et al., 1974). Several physiological and metabolic functions, such as heart rate, blood pressure, body temperature, sleep-awake, and feeding patterns, are regulated by CRs (Sahar and Sassone-Corsi, 2009). Similarly, energy metabolism is also governed by CRs. The free-energy dissipation per period has a regulated role on the phase diffusion constant and is proportional to the number of phase coherent periods. ATP is hydrolyzed by multiple irreversible cycles driven by oscillation (Cao, Wang, Ouyang, and Tu, 2015).

CRs and aging

Several studies have shown that the core clock machinery is obviously present not only in the SCN, but also in neurons and astrocytes (Abe et al., 2002; Marpegan et al., 2011). Circadian dysfunction occurs in the pathogenesis of aging and several diseases, such as cancers and chronic diseases (Anea et al., 2009; Bass and Takahashi, 2010; Evans and Davidson, 2013). Aging is marked by changes in the circadian system (Videnovic and Zee, 2015). Aging is characterized by changes in circadian rhythmicity with reduced amplitude, increased intra-daily variability, and decreased inter-daily stability of circadian rhythms (Czeisler et al., 1992; Duffy et al., 2002; Hofman, 2000).

Circadian rhythms, WNT/β-catenin pathway and PPARγ (Figure 3)

CRs and WNT/β-catenin pathway

WNT/β-catenin pathway is downstream of the RORs regulation factors and possesses divers putative Bmal1 clock-binding sites within its promoter (T. L. Chen, 2004). Through these interactions, circadian genes can control cell cycle progression via the

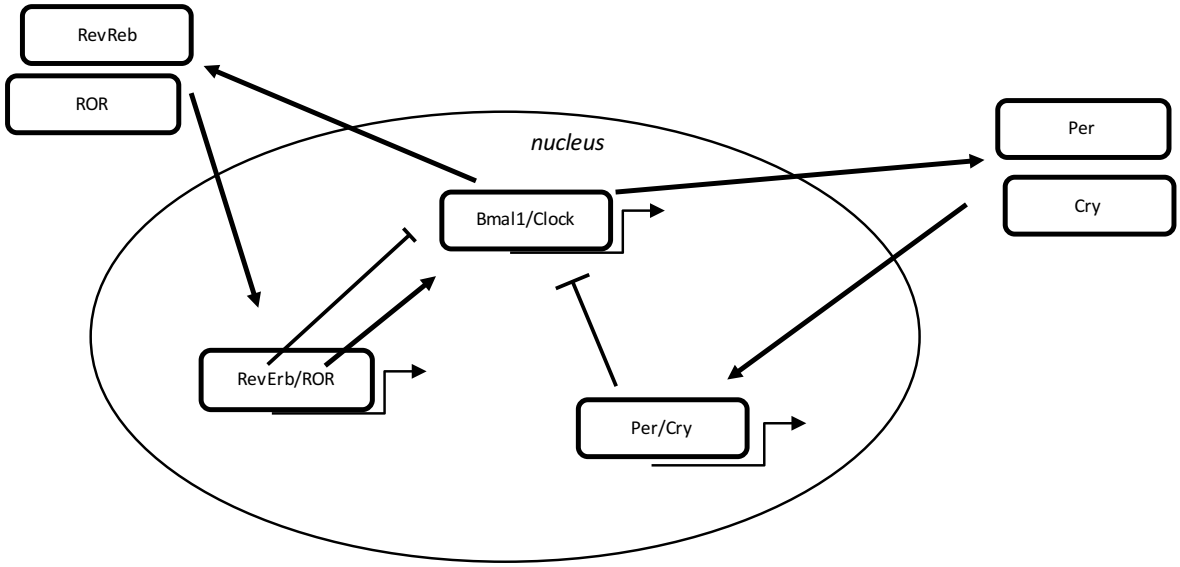

Figure 2. Circadian clock genes mechanism. The clock consists of a stimulatory loop, with the Bmal1/Clock heterodimer stimulating the transcription of Per and Cry genes, and an inhibitory feedback loop with the Per/Cry heterodimer translocating to the nucleus and repressing the transcription of the Clock and Bmal1 genes. An additional loop involves the RORs and RevErbs factors with a positive feedback by ROR and a negative feedback by RevErbs.

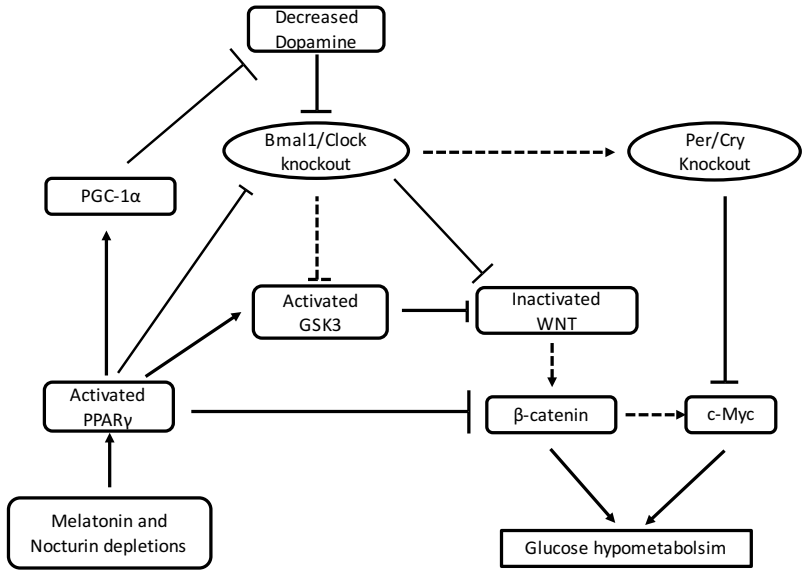

Figure 3. Interactions between PPARγ, WNT pathway and circadian rhythms in PD. Depletions of melatonin and nocturin increase the expression of PPARγ in PD. Increased PPARγ stimulates the expression of PGC-1α to decrease the expression of Dopamine leading to Bmal1/Clock heterodimer knockout. Increased PPARγ expression directly inhibits the formation of the heterodimer Bmal1/Clock and β-catenin cytosolic accumulation but increases the activity of GSK3, the main inhibitor of the WNT/β-catenin pathway. Bmal1/Clock knockout also increases GSK3 activity and inhibits the WNT/β-catenin pathway and its downstream gene c-Myc through the knockout of the heterodimer Per/Cry. The inhibition of the WNT/β-catenin pathway by the degradation of the cytosolic β-catenin and the inactivation of c-Myc leads to glucose hypometabolism in PD.

WNT pathway (Soták, Sumová, and Pácha, 2014). Expression and activity of the WNT signaling pathway can be inhibited by a Bmal1 knockdown (Guo et al., 2012). Expression levels of WNT-related genes in wild-type mice is higher than levels of WNT-related genes with Bmal1 knockdown mice (Janich et al., 2011; Yasuniwa et al., 2010). Cell proliferation and cell cycle progression are regulated by Bmal1 via the stimulation of the canonical WNT/β-catenin pathway (Lin, Chen, Li, Zhao, and Tan, 2013). Bmal1 can enhance β-catenin transcription, reduce β-catenin degradation and repress GSK3 expression (Sahar and Sassone-Corsi, 2009). Per2 degradation induced by β-catenin involves circadian dysregulation in intestinal mucosa of ApcMin/+ mice (Xiaoming Yang et al., 2009). Per1 and Per2 maintain cells circadian rhythm and regulate cell-related genes expression such as c-Myc (Duffield et al., 2002; Sancar, Lindsey-Boltz, Unsal-Kaçmaz, and Linn, 2004).

CRs and PPARγ

PPARγ interacts with the mammalian clock and energy metabolism (L. Chen and Yang, 2014). PPARγ directly interacts with the core clock genes and presents diurnal variations in liver and blood vessels (N. Wang et al., 2008; Xiaoyong Yang et al., 2006). In mice, impaired diurnal rhythms are caused by a deletion of PPARγ (G. Yang et al., 2012). Circadian metabolism is directly regulated by PPARγ (G. Yang et al., 2012). PPARγ agonists can control Bmal1 expression and formation of the heterodimer Clock/Bmal1 (H.-M. Wang et al., 2010; N. Wang et al., 2008) and can target Rev-Erb (Fontaine et al., 2003). Diminution of the clock controlled gene Nocturin decreases PPARγ oscillations in the liver of mice fed on high-fat diet. Under normal conditions, Nocturin binds PPARγ to improve its transcriptional activity (Green et al., 2007). PPARγ deletion impacts circadian function of 15-Deoxy-D 12,14-prostaglandin J2 (15-PGJ2) (G. Yang et al., 2012). The partner of PPARγ, RXR, acts on Clock protein in a ligand-dependent manner and then inhibits Clock/Bmal1 heterodimer formation and transcriptional activity (L. Chen and Yang, 2014).

CRs and oxidative stress

In Drosophila, disruption of Per involves a dysregulation of oxidative stress marker levels with circadian oscillations (Beaver et al., 2012). Per deletion exacerbates oxidative injury and shortens lifespan (Krishnan, Davis, and Giebultowicz, 2008; Krishnan, Kretzschmar, Rakshit, Chow, and Giebultowicz, 2009). Flies bearing a carbonyl reductase mutation show Per deletion, which accelerates neurodegeneration and causes oxidative injury to neurons (Krishnan et al., 2008). High levels of oxidative damage in the cortex and neurodegeneration are associated with Bmal1 knockout (Musiek, 2015). Bmal1 directly regulates the transcription of several important redox defense genes in the brain, including Nqo1 and Aldh2 (Musiek, 2015).

Melatonin and neurodegeneration

Melatonin (also named 5-methoxy-N-acetyl-tryptamine) is a natural secreted by the pineal gland (Csernus and Mess, 2003). Melatonin synthesis regulates the modulation of sleep (Dubocovich, 2007; Pevet and Challet, 2011). Its released is observed during darkness and thereby contributes to the circadian regulation of sleep (Crowley and Eastman, 2013; Mauriz, Collado, Veneroso, Reiter, and González-Gallego, 2013). Reduction of the amplitude of melatonin rhythms is associated with aging (Duffy et al., 2002; Y.-H. Wu and Swaab, 2005), and its dysregulation has been observed in several neurodegenerative diseases (Cardinali, Pagano, Scacchi Bernasconi, Reynoso, and Scacchi, 2013).

Melatonin has anti-inflammatory, anti-oxidant and neuroprotective effects (Calvo, González-Yanes, and Maldonado, 2013; Galano, Tan, and Reiter, 2013; Mauriz et al., 2013; Rosales-Corral et al., 2012, p.; X. Wang et al., 2011; H.-M. Zhang and Zhang, 2014). Melatonin decreases phosphorylation of GSK3 (Giese, 2009; Hoppe et al., 2010). Melatonin controls PPARγ expression, restores mitochondrial membrane potential, stimulates the biogenesis of mitochondria (Guven, Taskin, and Akcakaya, 2016) and enhances mitochondrial function (Kato et al., 2015).

Parkinson's disease and circadian rhythms

Several studies have underlined a relationship between circadian rhythms and PD development (Abbott et al., 2005; Gao et al., 2011; Weishaupt et al., 2006). Low peak activity levels and low amplitude of the rest-activity cycle are observed in PD patients (Videnovic and Zee, 2015). In PD, increase of physical activity levels and shorter periods of immobility during the night, result in a diurnal motor activity without oscillations (Videnovic and Zee, 2015).

Dopamine, by activation of the DR22 receptors, regulates the rhythm of clock protein Per2 expression (Hood et al., 2010; Videnovic and

Golombek, 2013). Striatal dopamine regulates Bmal1/Clock heterodimer activity (Yujnovsky, Hirayama, Doi, Borrelli, and Sassone-Corsi, 2006) in a receptor dependent manner (Imbesi et al., 2009). Dopaminergic receptors and TH (Tyrosine hydroxylase),the enzyme responsible for the synthesis of dopamine (Parekh, Ozburn, and McClung, 2015), exhibit daily fluctuations.

Circadian disorders can accelerate the neuropathology of PD (Lauretti, Di Meco, Merali, and Praticò, 2017), although PD reveals progressive deterioration in motor function with day-to-day progression (Bonuccelli et al., 2000; Piccini et al., 1991) insomuch as PD circadian fluctuations underline dysregulations in motor performance and visual performance (Struck, Rodnitzky, and Dobson, 1990). Blood pressure and heart rate alterations are common in PD. Elevations of blood pressure and heart rate occur during the light phase and decrease during the dark phase of the light/dark cycle (L. Chen and Yang, 2014). Sympathetic activity during the day decreases with a loss of circadian heart rate variability and a decrease of the sympathetic morning peak in melatonin in PD (Devos et al., 2003). PD patients show an elevation of cortisol levels, reduction of melatonin levels, and alteration of Bmal1 expression (Breen et al., 2014). Levels of Per1 and Cry1 diminish in Rotenone model of PD (Mattam and Jagota, 2015), whereas administration of melatonin results in restoration of Per1 levels but not on Cry and Bmal1 (Mattam and Jagota, 2015). The hypothalamic-pituitary-adrenal (HPA) axis is modulated by the circadian system and can be restored by promotion of normal dopamine function (Mizobuchi, Hineno, Kakimoto, and Hiratani, 1993).

Dopamine regulates circadian rhythmicity at molecular and behavioral levels (Videnovic and Willis, 2016). Depletion of dopamine by 6-hydroxydopamine (6-OHDA) injection into medial forebrain results in decreased dorsal striatum Per2 level in rats (Hood et al., 2010). Per2 rhythms are restored by the activation of D2 receptors in the DA-depleted striatum (Gravotta, Gavrila, Hood, and Amir, 2011). Bmal1 is reduced during dark span in PD, and Bmal1 levels are positively correlated with PD severity (Cai, Liu, Sothern, Xu, and Chan, 2010). Altered Bmal1 levels in PD are associated with dopamine depletion may be due to its capacity to regulate Bmal1/Clock heterodimer activity (Breen et al., 2014; Yujnovsky et al., 2006). This mean that dopamine depletion may directly affect the central component of the molecular clock and circadian disruption, which can accelerate PD progression (Kondratova and Kondratov, 2012).

Conclusion

Changes in entropy production rates are associated with metabolic and thermodynamic alterations and abnormal circadian rhythms in NDs. In PD, the canonical WNT/β-catenin pathway is down-regulated, while PPARγ is upregulated. These two systems act in an opposed and reverse manner. From a thermodynamic point of view, ND processes are like many irreversible processes which can occur by changing the entropy production rate. Thermodynamic behaviors of metabolic enzymes in PD are modified by the dysregulation of both the canonical WNT/β-catenin pathway and PPARγ expression. Downregulation of WNT/β-catenin pathway results in inhibition of c-Myc, HIF-1α, PDK, LDH-A, and MCT-1. This explains the glucose hypometabolism and the stimulation of oxidative stress observed in PD cells. In parallel, PPARγ interfere with the mammalian clock and energy metabolism and could be a promising therapeutic way in PD due to these interactions. PD processes may be considered as dissipative structures, which exchanges energy or matter with their environment. WNT pathway and PPARγ are open systems, far-from the thermodynamic equilibrium that operate under non-linear regime evolving to non-stationary states. Far-from-equilibrium thermodynamics are notions driven by circadian rhythms. Indeed, CRs directly contribute to regulation of the molecular pathways WNT/β-catenin pathway and PPARγ involved in the reprogramming of cellular energy metabolism enabling Parkinson's disease.

Author contributions

All authors listed have contributed to the work, and approved it for submitting to publication.

Conflict of Interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Abbreviations

Acetyl-coA: Acetyl-coenzyme; APC: Adenomatous polyposis coli; ARVC: Arrthymogenic right ventricular dysplasia/cardiomyopathy; Bmal1: Brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1; Clock: Circadian locomotor output cycles kaput; COX-2: Cyclooxygenase-2; Cry: Cryptochrome; DSH: Disheveled; EMT: Epithelial-mesenchymal transition; FZD: Frizzled;

GK: Glucokinase; GLUT: Glucose transporter; GSK3: Glycogen synthase kinase-3; HD: Huntington's disease; LDH: Lactate dehydrogenase; LRP 5/6: Low-density lipoprotein receptor-related protein 5/6; MCT-1: Monocarboxylate lactate transporter-1; NDs: Neurodegenerative diseases; PD: Parkinson's disease; Per: Period; PPARγ: Peroxisome proliferator-activated receptor γ; PGC-1α: Peroxisome proliferator-activated receptor-γ coactivator-1 α; PI3K-Akt: Phosphatidylinositol 3-kinase-protein kinase B; PFK-1: Phosphofructo-kinase-1; PDH: Pyruvate dehydrogenase complex; PDK: Pyruvate dehydrogenase kinase; RORs: retinoid-related orphan receptors; TCF/LEF: T-cell factor/lymphoid enhancer factor; TZD: Thiazolidinedione; TCA: Tricarboxylic acid.

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