



Association Between Pathophysiological Mechanisms of Diabetic Retinopathy and Parkinson's Disease

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Received: 29 April 2020 / Accepted: 22 August 2020 / Published online: 3 September 2020
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Abstract

Diabetic retinopathy, the most common complication of diabetes, is a neurodegenerative disease in the eye. And Parkinson's disease, affecting the health of 1–2% of people over 60 years old throughout the world, is the second largest neurodegenerative disease in the brain. As the understanding of diabetic retinopathy and Parkinson's disease deepens, the two diseases are found to show correlation in incidence, similarity in clinical presentation, and close association in pathophysiological mechanisms. To reveal the association between pathophysiological mechanisms of the two disease, in this review, the shared pathophysiological factors of diabetic retinopathy and Parkinson's disease are summarized and classified into dopaminergic system, circadian rhythm, neurotrophic factors, α -synuclein, and Wnt signaling pathways. Furthermore, similar and different mechanisms so far as the shared pathophysiological factors of the two disorders are discussed systematically. Finally, a brief summary and new perspectives are presented to provide new directions for further efforts on the association, exploration, and clinical prevention and treatment of diabetic retinopathy and Parkinson's disease.

Keywords Diabetic retinopathy · Parkinson's disease · Dopamine · Circadian rhythm · Neurotrophic factors · Wnt signaling pathways

Introduction

Diabetic retinopathy (DR), the most common chronic complication of diabetes, is a neurodegenerative disease in the eye and the leading cause of visual impairment and blindness in adults (Sivaprasad et al. 2012; Wong et al. 2016). With the increasing prevalence of diabetes globally, DR has become a disorder that seriously endangers public health (Stitt et al. 2016). The main pathophysiological mechanisms and clinical features of DR are retinal microangiopathy

and decreased visual acuity caused by retinal neuropathies (Bearse et al. 2004; Fletcher et al. 2007; Jackson and Barber 2010). Visual loss commonly results from proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME), which also occur at the advanced stages of DR (Wong et al. 2016). PDR is characteristic with abnormal growth of new blood vessels on the retina or fibrous tissue proliferation, while DME features exudation and edema in the central region of the retina. Retinal neurodegeneration is an early event in the pathogenesis of DR and is associated with the development of microvascular abnormalities, which is characterized by glial cell activation and neuronal apoptosis (Simó and Hernandez 2014; Simó et al. 2018). Current treatment for DR mainly involves blood pressure control, glycemic control, symptomatic treatment, laser photocoagulation, anti-VEGF therapy and surgery (Wong et al. 2016). Parkinson's disease (PD) is the second largest neurodegenerative disorder in the brain globally, with the incidence second only to Alzheimer's disease, and it affects the health of 1–2% of people over 60 years of age (Gasser 2009). PD is clinically characterized by muscular rigidity, resting tremor, bradykinesia and postural instability. The pathogenesis of the disorder involves the progressive loss

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of dopaminergic neurons in substantia nigra of midbrain and the aggregation of α -synuclein (α -Syn). Major therapeutic strategies for PD include symptomatic treatment, rehabilitative treatment, dopamine (DA) neurons repair, surgery and medication. Common strategy for medication involves the administration of L-3,4-dihydroxyphenylalanine (L-DOPA) (Muthuraman et al. 2018; Müller and Möhr 2018), dopamine receptor agonist (Müller et al. 2011; Seeman 2015), monoamine oxidase preparations (Mathew et al. 2020), catechol O-methyltransferase inhibitors (Müller et al. 2011) and central anticholinergics (Ory-Magne et al. 2014).

When studied carefully, DR and PD were found to show an increasing correlation in terms of pathogenesis, clinical manifestations and pathological mechanisms. Kwapon et al. reported that early PD patients suffer from the damaged retinal microvasculature and the reduced visual acuity (Kwapon et al. 2018). An epidemiological survey from Danish found that patients with diabetes are at higher risk for having PD (Hu et al. 2007; Schernhammer et al. 2011). Furthermore, another Korean epidemiological study confirmed the higher incidence of PD in DR patients, compared to patients without diabetes or diabetic patients without DR (Lee et al. 2018). These studies, therefore, suggest a potential shared pathophysiological pathway in DR and PD. Additionally, some therapeutic drugs benefiting both DR and PD, from another perspective, illustrate a close association between the two diseases. For example, Aung et al. found that the injection of L-DOPA or DA receptor agonists, common treatments for PD, into diabetic mice significantly restored retinal DA levels and ameliorated retinal dysfunction (Aung et al. 2014). Recently, Motz et al. also has reported that L-DOPA treatment can reverse retinal dysfunction in DR patients (Motz et al. 2020). Besides, exenatide, a drug used for glycemic control, significantly improved the cognitive function in PD patients (Aviles-Olmos et al. 2013). In order to further understand the association between the two diseases, in this review, their shared pathophysiological factors are reviewed and the similar and different mechanisms associated are discussed systematically.

The Dopaminergic System in Diabetic Retinopathy and Parkinson's Disease

Dopamine in Diabetic Retinopathy and Parkinson's Disease

DA, responsible for the motor, cognitive, and visual function, is a critical neurotransmitter in both the brain and retina. The accuracy of visual signal transmission is ensured by delicate networks of various retinal neurons, and DA plays an important regulatory role in this complex process (Jackson et al. 2012). The disruptions in the dopaminergic system

are related to common neurological diseases. Extensive research has established the disrupted dopaminergic system in both the DR and PD. Tian et al. found that in animal models of DR, retinal DA and tyrosine hydroxylase (TH) protein were downregulated and dopaminergic amacrine cells were degenerated (Tian et al. 2015). Gastinger et al. reported a 20% reduction in the number of cholinergic cells and a 16% reduction in dopaminergic amacrine cells in the retinas of streptozotocin (STZ)-induced diabetic mice (Gastinger et al. 2006). Damage to the dopaminergic system would affect the secretion of retinal DA, and DA levels in the retina began to decrease significantly at the third week of hyperglycemia, which might be the major cause of visual impairment in diabetic patients. The reduced DA levels exhibited in DR are similar to the most important pathological features in PD—reduced content of striatal DA (Zheng et al. 2019). Proteomic analysis performed by Sundstrom et al. showed enriched “dopamine degradation” and “Parkinson’s signaling” only in diabetic retinas with glial activation, which also indicates that the reduced DA level is a common pathological signature between DR and PD (Sundstrom et al. 2018). The DA deficiency is closely related to the tremor, rigidity, dyskinesia, apathy, impulsivity, and other behavioral complications in PD patients (Antonelli and Strafella 2014). These aforementioned facts clearly demonstrate that DA deficiency is the co-existing pathophysiological factor of DR and PD.

Dopamine Receptors in Diabetic Retinopathy and Parkinson's Disease

DA exerts its physiological functions by binding to five subtypes of DA receptors (i.e., D1, D2, D3, D4 and D5 receptors). These receptors are classified as D1-like (D1, D5) and D2-like (D2, D3, D4) receptors. Both the brain and retina reportedly show the expression of D1-like and D2-like DA receptors. The D1-like receptors contribute to the formation of heterotrimer, by coupling to G_{αs} and G_{αolf}, activate the cyclic adenosine monophosphate (cAMP), activate the protein Kinase A (PKA), and regulate various downstream ion channels (Baik 2013). While the D2-like receptors couple to G_{αi} and G_{αo}, negatively regulate the content of cAMP, reduce the activity of PKA, activate potassium channels, and regulate other ion channels (Baik 2013). D1-like receptors in the retina are mainly responsible for the light responses and regulation of spatial frequency thresholds, while in the brain they are associated with work, learning, addiction, and motor stimuli mainly. D2-like receptors in the retina are involved in light reaction, DA release, rhythmic behavior, release of neuroprotective factors and so on. In the brain these receptors behave similarly to D1-like receptors, they regulate the DA synthesis, DA release, emotion and cognition. The details about the expression and physiological functions DA receptors in retina and brain are listed in Table 1.

Table 1 Expression and physiological functions of DA receptors in retina and brain

	D1-like receptors		D1-like receptors				
	D1	D5	D2	D3	D4		
Retina Physiological functions	Express or not Express	1. Regulate the response of horizontal cells to light (Xiao 1997) 2. Responsible for the spatial frequency threshold (Jackson et al. 2012)	Unclear Express	1. Regulate the release of retinal DA (Xiao 1997) 2. Modulate the neural responses of the retina to light adaptation (Caravaggio et al. 2018) 3. Participate in the coordination of rod and cone controlled by the circadian clock during the day, and release NTFs to promote the survival of photoreceptor cells (Caravaggio et al. 2018; de Melo Reis et al. 2008; Ribelayga et al. 2008)	Unclear Express	Express 1. Promote sensitivity of photoreceptor cells to light adaptability (Jackson et al. 2012; Stepiens et al. 2007) 2. Regulate the secretion of DA (Jackson et al. 2011) 3. Responsible for the expression of Gmaz and regulation of clock rhythms (de Melo Reis et al. 2008)	Express 1. Promote sensitivity of photoreceptor cells to light adaptability (Jackson et al. 2012; Stepiens et al. 2007) 2. Regulate the secretion of DA (Jackson et al. 2011) 3. Responsible for the expression of Gmaz and regulation of clock rhythms (de Melo Reis et al. 2008)
Brain Physiological functions	Expression in DR Express or not Express	Unchanged (Aung et al. 2014) 1. Associated with the working memory, learning, drug addiction, and motor activity (Beaulieu et al. 2015),	Unclear Express	1. Associated with the drug addiction and synthesis and secretion of DA, responsible for the development of PD (Beaulieu et al. 2015) 2. Involved in memory function (Wilkerson and Levin 1999) 3. Regulate the arousal behavior (Qu et al. 2010)	Unclear Express	1. Associated with drug addiction (Beaulieu et al. 2015) 2. Involved in cognition and emotion (Missale et al. 1998) 3. Regulate the release of DA prior to protrusion (Beaulieu et al. 2015)	Unchanged (Aung et al. 2014) Express 1. Associated with the affective disorder (Manki et al. 1996)
Expression in PD	Unclear (Guigoni et al. 2007; Morin et al. 2014)	Unclear Upregulated (Mao et al. 2005)	Unclear	(Qu et al. 2010)	Unclear	Unclear	Unclear

DA receptors are well-reported targets in the pharmacology of PD clinically (Beaulieu et al. 2015). In PD patients, D1 and D2 receptors are the most studied and are found to show an increased expression. D2 receptors are highly expressed in the substantia nigra pars compacta. The degenerated dopaminergic neurons and reduced DA release have been reported in the substantia nigra at the injured side using the PD model in rats, which cause the number of D2 receptors in the striatum to increase greatly with autoregulation at this side (Mao et al. 2005). Politis et al. found the markedly higher level of D2 receptors in the striatum of PD patients than that in the striatum of healthy individuals using positron emission tomography (Politis et al. 2017). The increased expression of D2 receptors in nigrostriatal neurons of PD patients may be related to the degeneration of dopaminergic neurons. However, the alterations of D2 receptors in the early stages of PD may differ from those in the late stages of PD. In a monkey model of PD that was induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), Bezard et al. observed that D2 receptor levels, which decreased significantly before dyskinesia, showed a marked increase after dyskinesia. These findings indicated that alterations of D2 receptors may be related to the progression of PD (Bezard et al. 2001). Similarly, D1 receptors reportedly show obvious changes in PD. However, there is controversy about the changes in striatal D1 receptor content in PD. Morin et al. found that the binding level of dopamine D1 receptor antagonist ([3H]SCH-23390) in the striatum of MPTP-treated monkeys was significantly decreased when compared to that in the control group, which suggests the decreased D1 receptors in cell membrane (Morin et al. 2014). However, Guigoni et al. found unchanged number but altered distribution of D1 receptors in striatal neurons. The higher content of D1 receptors at the membrane than those in the cytoplasm indicated that D1 receptors are readily recruited to the membrane in a PD model (Guigoni et al. 2007). D1 and D2 receptors, through their activation, reportedly mediate direct and indirect pathways, respectively, in PD patients (Keeler et al. 2014). The direct pathways are responsible for habitual responses, while the indirect ones are associated with goal-directed behaviors. Effects of other DA receptors on the development of PD disease have been rarely reported so far.

Unlike in PD patients, in DR patients, unchanged expression of D1 receptors are found on the retina. D1 receptors on the retina primarily locate in the horizontal cells in the outer plexiform layer. And D2 receptors exist mainly in the inner plexiform layer and horizontal cells in the outer plexiform layer. The synapses can be formed through the contact of horizontal cells with the terminals of interplexiform cells. DA is released then to elicit effects on D1 receptors in horizontal cells, by which the responses of horizontal cells to light can be reduced. D2 receptors,

the autoreceptors of dopaminergic neurons, are reported to inhibit the DA release. The interaction between D1 and D2 receptors contributes to the physiological functions of DA (Xiao 1997). In the type 1 diabetic mice that were intervened by exogenous D1 receptor agonist (SKF38393) and D4 receptor agonist (PD168077) respectively, unchanged expression but altered distribution of D1 and D4 receptors were observed (Aung et al. 2014). Whether D2, D3 and D5 receptors could influence the formation and development of DR remains unclear.

Circadian Rhythm in Diabetic Retinopathy and Parkinson's Disease

The Dopamine-Mediated Circadian Rhythm in the Retina and Brain

Circadian rhythm refers to the behavioral and physiological changes in organisms from day to night. The changes are regulated by central circadian clock genes located at the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral circadian clock genes in surrounding tissues (Li et al. 2017). There is a wide variety of circadian clock genes in the human body, such as brain and muscle Arnt-like Protein-1 (Bmal1), circadian locomotor output cycles kaput (Clock), Period1 (Per1), Period2 (Per2) and so on. These genes form multiple transcription-translation feedback loops to regulate circadian output, and dopaminergic neurons play an important role in the process. For instance, DA and some of its metabolites have been reported to cause circadian variation (Kafka et al. 1986). The change of DA content may directly affect its ability to synthesize tyrosine hydroxylase and transporter, which is a rhythmic activity (Li et al. 2017). While the expression of TH is regulated by the Clock gene (McClung et al. 2005). Recently, striatal DA levels in mice have been confirmed to exhibit rhythmic changes that came to peak at night (Agostino et al. 2011).

In the retina, DA is mainly involved in light adaptation and the rhythmic expression of clock genes. DA modulates light that is input into the SCN from the retina (Witkovsky 2004). Circadian clock genes can regulate the synthesis of DA, and in turn the DA system can regulate the expression of clock genes (Mendoza and Challet 2014; Sleipness et al. 2007). Clock genes are reported to regulate dopaminergic transmission in the ventral specialized areas, and the dopaminergic system in turn regulates clock gene expression in the dorsal striatum (Hood et al. 2010; Roybal et al. 2007). Dopaminergic activities can also be considered to be controlled by the SCN output. In conclusion, DA exhibits bidirectional association with the circadian system from several perspectives.

Abnormal Circadian Activities in Diabetic Retinopathy and Parkinson's Disease

Abnormal circadian activities have been observed in DR and PD patients. Symptoms of abnormal circadian rhythms in PD patients include reduced amplitude of rest-activity rhythm, reduced diurnal activity, and nocturnal rest (De Lazarri et al. 2018). Especially, sleep disturbance is reported to be present in 65% to 95% of PD patients and is one of the leading causes of impaired quality of life (Hood et al. 2010). The functional impairment of retinal caused by retinal diseases reportedly affects the central circadian clock and circadian rhythms (McMahon et al. 2014; Lahouaoui et al. 2016). DR patients have been shown to exhibit the impairments in circadian activity regulated by light, such as sleep disturbance, altered blood pressure, and abnormal melatonin secretion (Obara et al. 2017).

Abnormal circadian activities in DR and PD patients are closely related to the changes in some circadian clock genes. Kudo et al. using the transgenic mouse PD models with α -Syn overexpression found the fragmented sleep and the reduced locomotor activity, a change associated with increasing age. Further studies demonstrated that neuronal firing in the SCN was significantly reduced in these mice, suggesting that abnormalities in circadian rhythms resulted from inhibited output of neural signals (Kudo et al. 2011). A study on peripheral blood showed that the expression of Bmal1 mRNA in PD patients was significantly decreased at night, and the Bmal1 level was related to the degree of exercise and quality of sleep (Li et al. 2017). Gu et al. also observed reduced Bmal expression in PD patients when testing genetic polymorphisms of circadian disruption and their susceptibility to the pathogenesis, meanwhile, the Bmal variant was associated with the tremor-dominant subtypes of PD and the Per1 subtype variant the postural instability and gait difficulty positive subtypes (Gu et al. 2015). Reduced Per2 expression in the striatum was also observed in animal models induced by 6-hydroxydopamine hydrobromide (6-OHDA) (Hood et al. 2010). Although it remains unknown whether the circadian

clock genes alter in DR, diabetes—the early stage of DR has been reported to alter the rhythmic expression of central and peripheral circadian clock genes in both humans and animal models. For example, Wang et al. reported that the expression levels of Clock and Bmal1 in diabetic rats had higher amplitudes and Per2 relatively lower amplitudes compared with normal rats (Wang et al. 2014). Loss of the clock gene Per2, through promoting β -catenin into the nucleus and activating the connective tissue growth factors, reportedly leads to the microvascular contractile dysfunction, which is the basic pathological change of DR (Jadhav et al. 2016). It has also been established that knocking out Per2 gene resulted in the increased cellular capillaries, increased capillary permeability, decreased endothelial nitric oxide enzyme, and increased transcription growth factor- β and its downstream inflammatory mediators in the retina (Bhatwadekar et al. 2013). This work suggested that disruption of clock genes may not only alter the circadian cycle and exacerbate disease progression, but also have an etiological role in the development of DR.

However, clock genes in DR and PD show different changes. Some clock genes reported in DR, such as Clock, have not been reported in PD. In addition, the Bmal1 gene is upregulated in DR while downregulated in PD (Table 2).

Neurotrophic Factors in Diabetic Retinopathy and Parkinson's Disease

Neurotrophic factors (NTFs) are secreted by brain and peripheral nerve. These factors can promote the growth, survival and regenerative repair of neurons. Besides, NTFs are reportedly involved in the pathophysiological process of DR and PD. Among these factors, brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF) are the most investigated. In this section, their roles in the process of DR and PD are discussed separately.

Table 2 Differences in the expression of clock genes between DR and PD

	Clock gene	Species	Sites	Methods	Changes	References
DR	Clock	Rats	Eye	1. Quantitative Real Time PCR	Upregulated	Wang et al. (2014)
	Bmal1	Rats	Eye	1. Quantitative Real Time PCR 2. Immunohistochemistry	Upregulated	Wang et al. (2014)
	Per2	Mice	Eye, Liver	1. Quantitative Real Time PCR 2. Knockout of gene	Downregulated	Bhatwadekar et al. (2013), Wang et al. (2014)
PD	Bmal1	Human	Peripheral Blood	1. Quantitative Real Time PCR	Downregulated	Li et al. (2017)
	Per2	Rats	Striatum	1. Quantitative Real Time PCR 2. Immunohistochemistry	Downregulated	McMahon et al. (2014)

The Brain-Derived Neurotrophic Factor in Diabetic Retinopathy and Parkinson's Disease

Extensive studies have confirmed that BDNF has a significant neuroprotective effect in both DR and PD. In STZ-induced diabetic rat retinas, it was found that the density of dopaminergic amacrine cells and expression levels of BDNF were decreased, while intraocular administration of BDNF rescued the cells from neurodegeneration, indicating the therapeutic potential of BDNF for DR (Seki et al. 2004; Yajima et al. 2005). BDNF was also confirmed to significantly alleviate the damage to dopaminergic neurons on the retina and inhibit the downregulation of TH in DR (Seki et al. 2004). In PD, the abnormality in BDNF levels is reportedly closely associated with dyskinesia (Kusters et al. 2018), cognitive disorders (Ishii et al. 2019), and cardiovascular dysfunction (Alomari et al. 2018). Furthermore, BDNF was found to affect the survival and morphology of dopaminergic neurons in the substantia nigra of the midbrain. The loss of BDNF may result in the death of dopaminergic neurons. Oral administration of the DA receptor agonist for PD, rotigotine, increased BDNF protein expression in the cortex and hippocampus, suggesting that rotigotine may exert therapeutic effects by improving the functions of BDNF (Adachi et al. 2018). Administration of endogenous or exogenous BDNF and pharmacological or genetic therapy targeting BDNF may become promising therapeutic approaches for PD patients (Tome et al. 2017).

The Nerve Growth Factor in Diabetic Retinopathy and Parkinson's Disease

NGF is another critical neurotrophic factor. Reduced NGF was observed in both the DR and PD. Marked 44% and 64% reductions in NGF levels were found in the vitreous and sera, respectively, from diabetic patients compared to non-diabetics (Mysona et al. 2015). Hammes et al. reported that NGF prevented the apoptosis of diabetic Müller cells and the pathological changes in the retinal microvasculature. Intravenous administration of NGF can ameliorate the damage to retina by diabetes via the blood-retinal barrier (Hammes et al. 1995). Besides, deficient secretion of NGF has been also reported to be associated with PD. For example, caffeoic acid derivative *N*-propargyl caffeamide was found to improve dyskinesia through increasing NGF production in the PD mice (Luo et al. 2018). It has been reported that NGF can induce the differentiation of PC12 neural cells, which are responsible for the secretion of DA (Zosen et al. 2018). NGF reportedly increased the survival of adrenal chromaffin cells transplanted into the injured striatum and the growth of fibers (Date et al. 1996).

The Gial-Derived Neurotrophic Factor in Diabetic Retinopathy and Parkinson's Disease

In addition to the BDNF and NGF, GDNF is also critical to both DR and PD. Administration of GDNF reportedly alleviated the photoreceptor cell death caused by inflammation reaction and oxidative stress in DR (Boss et al. 2017). In addition, Nami et al. found that GDNF improved the dysfunctions of blood-retinal barrier in DR (Nishikiori et al. 2007). Hyper-activation of GDNF, however, may contribute to the development of DR. Because increased mRNA levels of GDNF were observed in the retinal and vitreous fibrovascular membranes of patients with proliferative diabetic retinopathy (Klaassen et al. 2017). While in PD, GDNF can protect mesencephalic dopaminergic neurons from the toxicity of the neurotoxins, toluidine, and 6-OHDA, promote neural cell survival and regenerate dopaminergic nerve endings destroyed by toxins, increase the uptake of DA by neurons cultured in vitro, increase cellular volume, promote axonal extension, and increase the expression of phenotypic markers (Videnovic and Golombek 2017). de Araújo et al. decreased the levels of GDNF in cultured midbrain slices of rats, and observed the morphological changes at the edge of the slice and decreased TH expression, suggesting that GDNF are involved in midbrain-mediated neurodegeneration, thus revealing their role in PD (de Araújo et al. 2018). These studies suggest that GDNF may play an important role in the pathophysiological process of both DR and PD.

α -Synuclein in Diabetic Retinopathy and Parkinson's Disease

Synuclein (Syn) is a family of highly conserved proteins with small molecular weight and locates in the presynaptic membrane of nerves. α -Syn, β -Syn and γ -Syn are three homologous proteins to the Syn (Yuan et al. 2012). Syn has been found to be closely associated with the development of neurodegenerative diseases (Beyer et al. 2011). And the abnormal aggregation of α -Syn is the key involvement in the formation of Lewy bodies, which is a critical pathological feature of PD. The overexpression of α -Syn was reported to be neurotoxic (Bridi and Hirth 2018). Parihar et al. found that the α -Syn accumulation changed the mitochondrial membrane potential and increased the production of intracellular reactive oxygen species, resulting in the damage to dopaminergic neurons in PD patients (Parihar et al. 2008). The increased expression of α -Syn was also reported in DR patients. Yuan et al. observed the significantly increased mRNA expression and protein of the α -Syn in the retinal tissues of diabetic rats, when compared with those of normal rats (Yuan et al. 2012). They, therefore, inferred that the

upregulated expression of α -Syn may account for the loss of dopaminergic neurons in DR.

Interestingly, in animal models of diabetes—the early stage of DR, glucose with high concentrations reportedly promoted the expression of α -Syn in the brain (Fatima et al. 2014). Increased α -Syn expression was found to result from the alterations in glucose metabolism, which promoted protein misfolding to form α -Syn (Fatima et al. 2014). Besides, in PD patients, accumulation of phosphorylated α -Syn was found in both the retina and brain before the onset of parkinsonism or dementia in clinical practice (Ortuño-Lizarán et al. 2018). These findings indicate a shared pathophysiological mechanism behind DR and PD that the overexpression of α -Syn causes the damage or loss of dopaminergic neurons.

The Wnt Signaling Pathways in Diabetic Retinopathy and Parkinson's Disease

Wnt signaling pathways are highly conserved through biological evolution and are essential for the development of central nervous system. β -catenin is the key to the activation of Wnt signaling pathways, during the process, Wnt binds to frizzled (Fz) receptors and low-density lipoprotein receptor-related protein (LRP) 5/6 to inactivate glycogen synthase kinase (GSK)-3 β phosphorylation, dissociate the Axin/GSK-3 β complex, gradually accumulate instead of degrading β -catenin, and then translocates to the nucleus to activate the transcription of Wnt target genes (Chen and Ma 2017). Dysregulation of the canonical Wnt signaling pathways is

involved in the pathogenesis of neurodegenerative diseases. Aberrant activation of the Wnt signaling pathways has been found in the pathogenesis of both DR and PD, but the two diseases show different expression of Wnt.

Wnt Signaling Pathways Associated with Dickkopf1 (DKK 1) and β -Catenin in Diabetic Retinopathy and Parkinson's Disease

Dkk1 is an antagonist of the Wnt signaling transduction and is involved in the formation and development of DR and PD. Chen et al. found the increased levels of β -catenin in retinal sections from non-proliferative DR patients when compared to those in non-diabetic healthy patients (Chen et al. 2009). However, the levels of β -catenin were found to decrease in PD patients (Zhou et al. 2016). In human body, the levels of DKK-1 in serum of patients with DR were lower than those in patients without diabetes or without DR (Qiu et al. 2014). Intravitreal injection of DKK 1 was reported to reduce the retinal inflammation, improve the vascular leakage, and decrease neovascularization in a rat model of DR (Chen et al. 2009) (Fig. 1a). These findings suggest that aberrant activation of Wnt signaling associated with DKK-1 is critical to the development of DR. However, the expression of DKK 1 in the Wnt signaling of PD is different from that of DR. Zhou et al. confirmed that the loss of dopaminergic neurons was associated with the promoted DKK 1 levels while decreased β -catenin levels as well as increased GSK-3 β activities by analyzing the same *in vitro* model of PD (Zhou et al. 2016) (Fig. 1b).

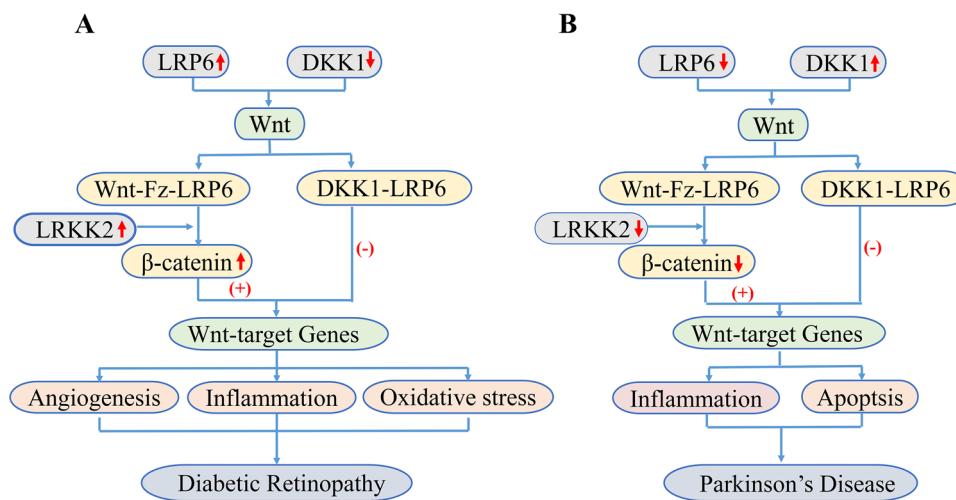


Fig. 1 Different roles of the Wnt signaling pathways in PD and DR. In DR, the levels of LRP6, Frizzled, and β -catenin are upregulated, and Wnt signaling downstream target genes are overexpressed, which result in the increased neoangiogenesis, inflammation, and oxidative stress, thus contributing to the development of DR. In PD, the lev-

els of LRP5/6 and β -catenin are downregulated, and Wnt signaling downstream inhibits the expression of target genes, which lead to increased inflammation and oxidative stress, thereby promoting the development of PD

Wnt Signaling Pathways Associated with the LRP6 Domain in Diabetic Retinopathy and Parkinson's Disease

Mutations in Leucine rich repeat kinase 2 (LRRK2), a scaffold protein of the Wnt signaling pathways, are prevalent in both PD and DR. Sancho et al. reported that LRRK2 normally interacts with members of the Wnt family, specifically binds to Disheveled family proteins (i.e., Dvl-1, Dvl-2 and Dvl-3) (Sancho et al. 2009). LRRK2 bridges the membrane and the cytosol of canonical Wnt signaling pathway. For example, its LRP6 intracellular domain binds to the Dvl proteins, which then bind to the β -catenin destruction complex, thereby activating the canonical Wnt signaling pathway. In the Wnt signaling pathway, the complex of LRRK2-LRP6 can increase activities of the Wnt signaling, however in PD, the RocCOR (Ras in Complex; C-terminal of Roc) and LRRK2 mutations in kinase domain are able to reduce the affinity of LRRK2-LRP6, thus inhibiting the activities of canonical Wnt signaling pathway and exacerbating neurodegeneration (Berwick and Harvey 2012) (Fig. 1b). Unlike the expression of LPR6 in PD, in DR, elevated expression of LPR6 was found in the retina, indicating excessive activation of the Wnt signaling pathway (Fig. 1a). In addition, Chen et al. found upregulated expression of LRP6 in animal models of DR (Chen et al. 2009). Liu et al. also found that increased retinal phosphorylation of LRP6, accompanied with increased nuclear β -catenin and activation of the Wnt/ β -catenin signaling pathway, mediated the oxidative stress-related DR lesions in the genetic type 1 diabetes model of C57BL/6J-Ins2^{Akita} mice and in ARPE-19 cells cultured with high glucose in vitro (Liu et al. 2019). The Wnt signaling pathway is overactivated in DR but repressed in PD, illustrating different effects of the Wnt signaling pathway in the DR and PD.

Conclusions and Perspectives

In summary, the major pathophysiological characteristics of PD—reduced DA and upregulated α -Syn expression—as well as important pathophysiological changes—abnormal expression of clock genes and NTFs—also play an important role in DR. The mechanisms behind all these changes are inextricably related to the abnormal DA system, which fully illustrates the close link between the two diseases. In PD and DR, however, some clock genes express differently, and the biological functions of the Wnt signaling pathways also appear to be different, which suggests that the pathophysiological mechanisms are not identical between the two. At present, there is still a lack of systematic basic research and large-sample, high-quality clinical studies on the correlation between PD and DR. Extensive mechanistic studies

and clinical experiments are needed still to further reveal the similarities and differences of co-existing pathophysiological mechanisms between the two and provide a new direction for the prevention and treatment of DR and PD in clinical practice.

Acknowledgements This work was supported by the National Natural Science Foundation of China (Nos. 81660166 and 81660146), the Yunnan Science and Technology Talents and Platform Plan (No. 2019HB050), and Yunnan Youth Talent Support Program (No. YNWR-QNBJ-2018-315).

Author Contributions ZQZ, YKZ and HYZ contributed equally to the paper. All authors read and approved of the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that there are no potential conflicts of interest.

Ethical Approval This work does not contain any studies with human participants or animals performed by any of the authors.

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