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G protein-coupled receptor 91 signaling in diabetic retinopathy and hypoxic retinal diseases

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ABSTRACT

G protein-coupled receptor 91 (GPR91) is a succinate-specific receptor and activation of GPR91 could initiate a complex signal transduction cascade and upregulate inflammatory and pro-angiogenic cytokines. In the retina, GPR91 is predominately expressed in ganglion cells, a major cellular entity involved in the pathogenesis of diabetic retinopathy (DR) and other hypoxic retinal diseases. During the development of DR and retinopathy of prematurity (ROP), chronic hypoxia causes an increase in the levels of local succinate. Succinate-mediated GPR91 activation upregulates vascular endothelial growth factor (VEGF) through ERK1/2-C/EBP β (c-Fos) and/or ERK1/2-COX-2/PGE2 signaling pathways, which in turn, leads to the breakdown of blood-retina barriers in these disorders. In this review, we will have a brief introduction of GPR91 and its biological functions and a more detailed discussion about the role and mechanisms of GPR91 in DR and ROP. A better understanding of GPR91 regulation may be of great significance in identifying new biomarkers and drug targets for the prediction and treatment of DR, ROP, and hypoxic retinal diseases.

1. Introduction

The retina is the most metabolically active tissue and consumes a large amount of energy. Insufficient supplies of oxygen and nutrients in the retina may impair cellular oxygen balance and result in a hypoxic retinal environment that disturbs physiological processes and leads to pathological characteristics in the retina (Caprara & Grimm, 2012). During the progression of diabetes, hyperglycemia or high levels of retinal glucose causes hypoxia and oxygen imbalance, which is, at least partially, responsible for microaneurysms, hard exudates, hemorrhages, cotton-wool spots, and retinal neovascularization, major clinical features of diabetic retinopathy (DR) (Antonetti, Klein, & Gardner, 2012). Although not identical, the mechanisms for vascular leakage and retinal neovascularization in DR are very similar to those in retinopathy of prematurity (ROP), a disease of abnormal vascular development in infants that could lead to retinal detachment and cause vision loss (Gunay et al., 2016). DR and ROP are now considered as neurovascular diseases, since functional and structural alterations of the neurosensory retina in DR and ROP are found with electroretinography, psychophysical and retinal imaging processes (Hansen, Moskowitz, Akula, & Fulton, 2016). The mechanisms for retinal neuronal degeneration in DR may also share similarities to those in glaucoma, a disease resulted from insufficient supply of oxygen or nutrients. Extensive evidences confirm that G protein-coupled receptor 91 (GPR91), which is now widely regarded as the endogenous receptor for succinate, is involved in the development of hypoxic retinal vascular diseases (Gnana-Prakasam, Ananth, Prasad, et al., 2011; Hu, Li, Du, et al., 2015; Hu, Wu, Li, Chen, & Wang, 2013; Sapieha, Sirinyan, Hamel, et al., 2008). Under hypoxic conditions, GPR91 activation causes damages to retinal cells by upregulating cytokine expression and by inducing angiogenesis in the retina. In this review, we will have a brief introduction of GPR91 biological function and a more detailed discussion about the role and mechanisms of GPR91 in DR and ROP.

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2. GPR91 as succinate receptor

Succinate is traditionally considered as a Krebs cycle intermediate with no apparent role as a signaling molecule for a long-time until about a decade ago. In an elegant study, Ling and colleagues demonstrated that succinate was regulated by respiration, metabolism, and renal reabsorption in kidney and it was capable of serving as the ligand for GPR91, an orphan G-protein-coupled receptor (GPCR) at the time. Succinate-mediated GPR91 activation in mouse kidney causes an increase in blood pressure through renin-angiotensin system, which is abolished in GPR91-null mice (He, Miao, Lin, et al., 2004). The conclusion that succinate is the endogenous ligand for GPR91 is reached from binding affinity studies with several substances including pharmacological compounds and carboxylic acids that share structural similarities with succinate (Ariza, Deen, & Robben, 2012; Bhuniya, Umrani, Dave, et al., 2011; He et al., 2004). As a result of these studies, GPR91 is now regarded as succinate receptor 1 (SUCNR1) (He et al., 2004). The physiological concentration of succinate in the venous circulation of healthy rodents was 6–17 μM and it was lower (1–4 μM) in humans. Any increase in succinate concentration could result in GPR91 activation (Sadagopan, Li, Roberds, et al., 2007). Computational and mutational analysis of GPR91 and its possible succinate-binding sites suggest that Arg99, His103, Arg252, and Arg281 play important roles in GPR91 activation by forming a rhodopsin-like structure in which succinate is attracted to a positively charged cavity (de Castro Fonseca, Aguiar, Da, Gingold, & Leite, 2016; He et al., 2004). Apparently, it is not unusual for a Krebs cycle intermediate to function as the ligand for GPR receptors, as α-ketoglutarate is capable of stimulating GPR99, another GPCR receptor that is closely related to GPR91 (with 33% homology) (He et al., 2004).

GPRs are classified into different subfamilies based on their sequence homology and ligand diversity. GPR activation induces a conformational rearrangement involving the recruitment of heterotrimeric G protein and the dissociation of an α-subunit and a βγ dimer from the protein complex, which modulates the effector activities and mediates cellular responses by desensitization and internalization through a families of G proteins (for review see Wettschureck & Offermanns, 2005). Among them, Gi/o and Gs regulate cyclic adenosine monophosphate (cAMP) through adenylate cyclase (AC) (He et al., 2004; Robben, Fenton, Vargas, et al., 2009). GPR91 was originally described as being coupled to both Gi and Gq proteins in human embryonic kidney cells and Madin Darby canine kidney cells (He et al., 2004; Robben et al., 2009). However, the view of GPR91 being coupled to Gq has been challenged by the observation that $[Ca^{2+}]i$ mobilization was a consequence of phospholipase C-β activation by the G protein βγ dimer (Gilissen et al., 2015; Robben et al., 2009; Sundstrom, Greasley, Engberg, Wallander, & Ryberg, 2013). This discrepancy indicates the complexity of GPR91 signaling in a variety of cellular targets and tissues that are worth further investigation.

3. Biological function of GPR91

GPR91 belongs to GPCR family, the largest group of proteins involved in signal transduction across biological membranes (Fredriksson, Lagerstrom, Lundin, & Schioth, 2003). This family is the direct or indirect target for approximately 60 percent of marketing drugs and thus it is the most promising receptor family for the treatment of diseases (Davenport, Alexander, Sharman, et al., 2013). GPR91 is highly expressed in the adipocytes and it acts as a sensor for dietary energy (Regard, Sato, & Coughlin, 2008). Succinate-mediated GPR91 activation has a binary effect on body weight and metabolism. While there is no alteration in adipogenesis, GPR91-null mice appear to have increased energy expenditure, improved glucose buffering, diminished lipid accumulation, and reduced adipocyte size (McCreath, Espada, Galvez, et al., 2015). Succinate-mediated GPR91 activation has also been proposed to play a major role in regulating gonadotropin-releasing hormone expression in hypothalamus, a key mechanism to regulating energy metabolism and metabolic homeostasis (Chen, Maevsky, & Uchitel, 2015).

Since it was characterized as the receptor for succinate in 2004 (He et al., 2004), GPR91 has been found to localize to many cell-types and tissues with a large array of physiological functions. In the kidney it is localized to the renal vascular lumen (the afferent arteriole and the glomerular vasculature) and the luminal membrane of renal tubules (medullary thick ascending limb of Henle's loop and apical membrane of macula densa and collecting duct) (Robben et al., 2009; Sundstrom et al., 2013; Toma, Kang, Sipos, et al., 2008; Vargas, Toma, Kang, Meer, & Peti-Peterdi, 2009). The succinate/GPR91-mediated modulation of cAMP and calcium levels in these cellular compartments is responsible for salt sensing, blood-pressure control, and glucose-regulated renin release (He et al., 2004; Robben et al., 2009; Sundstrom et al., 2013; Toma et al., 2008; Vargas et al., 2009). The latter is the first observation that succinate/GPR91 signaling is involved in diabetic complication. Succinate is suggested to stimulate GPR91-mediated stellate cell activation in a paracrine fashion during fibrosis, a major process in liver damage (Correa et al., 2007). Succinate-induced GPR91 activation in sarcolemmal membrane and T-tubules of ventricular cardiomyocytes attributes to myocyte death and pathological hypertrophy in the heart (Aguiar, Andrade, Gomes, et al., 2010; Aguiar, Rocha-Franco, Sousa, et al., 2014). It has also been reported that succinate mediates GPR91 activation in platelets for initiating aggregation (Hogberg et al., 2011), in bone marrows for hematopoietic progenitor growth and enhancing immunity (Hakak, Lehmann-Bruinsma, Phillips, et al., 2009), in immature dendritic cells for proinflammatory cytokine production to induce rejection post-transplantation (Rubic, Lametschwandtner, Jost, et al., 2008). In addition to expression in hypothalamus (discussed above), GPR91 is also present in the central nerve system. In the brain, it is expressed in cortical neurons and astrocytes (Hamel, Sanchez, Duhamel, et al., 2014). GPR91-deficient mice increase the size of ischemia/hypoxia-induced infarction and thus succinate-mediated GPR91 activation is suggested to have a role in brain revascularization during the recovery of ischemia/hypoxia-induced stroke (Hamel et al., 2014). Succinate-mediated GPR91 activation in the retinal ganglion cells (RGCs) is also important to the regulation of retinal vascular function under ischemic/-diabetic conditions, which is the focus of this review.

4. Role of GPR91 in the retina

In the retina, GPR91 is expressed in the apical membrane of the retinal pigment epithelium (RPE). Excessive iron accumulation, ferric ammonium citrate supply and cytomegalovirus infection upregulate GPR91 (Gnana-Prakasam et al., 2011). Genetic analysis suggests that patients with an intron variant of GPR91 gene (SUCNR1) are at a higher risk for geographic atrophy, which is supported by the observation that GPR91-deficient mice have a variety of premature sub-retinal dystrophy, including abnormal thickening of Bruch's membrane and a buildup of subretinal microglia (Favret, Binet, Lapalme, et al., 2013).

GPR91 is predominantly expressed in the cell body of the RGCs under ischemic conditions, as demonstrated in rats with oxygen-induced retinopathy (OIR), a commonly accepted rodent model for retinal neovascularization in ROP and DR (Sapieha et al., 2008). In OIR-rats, the concentration of succinate was increased 3.3-fold in the ischemic retinas than that in the controls (Sapieha

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