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Progress of G Protein-Coupled Estrogen Receptor in Cardiovascular System Diseases

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ABSTRACT

Cardiovascular disease is one of the leading causes of death worldwide, and estrogen is thought to play a protective role in cardiovascular health. The mechanism of action and clinical significance of GPER, as an emerging class of estrogen receptors, in the cardiovascular system is being extensively studied. This elucidation of the signaling pathways and specific roles of GPER in cardiovascular diseases, i.e., the multiple roles of GPER in cardiovascular protection through the activation of multiple signaling pathways, provides new hopes and strategies for the prevention and treatment of cardiovascular diseases. The purpose of this article is to summarize the progress of research on GPER in the field of cardiovascular disease.

KEYWORDS

Estrogen; GPER; Signal transduction; Cardiovascular and cerebrovascular systems/diseases; Cardiovascular and cerebrovascular diseases

1. INTRODUCTION

Cardiovascular diseases (CVDs)constitute a serious challenge to human health and are a major chronic disease. ranking first among the causes of human deaths and causing an increasing socioeconomic burden. It has been found that the prevalence of cardiovascular and cerebrovascular diseases is low in premenopausal women [1] and rises rapidly to the level of men of the same age in postmenopausal women [2] suggesting that there is a correlation between oestrogens and the development of cardiovascular diseases.

Estrogen is a steroid hormone mainly produced by the ovary, it plays a key role in the female reproductive system, bone health, cardiovascular system, as well as neurological, immune, endocrine and other aspects, estrogen plays its biological effects through the action of estrogen receptor (ER), Initial studies generally concluded that estrogen regulates gene expression and exerts its effects by acting on the traditional nuclear receptors ERα and ERβ. The recent discovery of GPER has provided a new perspective on the pathway of estrogen action.

The G protein-coupled estrogen receptor (GPER) was first discovered in the 1990s, and its designation was formally revised by the International Union of Pharmacology in 2007 [3, 4]. The study reveals that GPER is prevalent in numerous tissues, and that it can bind to estrogen and mediate rapid nongenomic effects, and with the gradual deepening of the research, its potential role in cardiovascular disease has been widely concerned.

2. ESTROGEN RECEPTOR

2.1. Classification of Estrogen Receptors

Estrogen receptors (ERs) fall into two main categories: the traditional nuclear receptors, which include ERα and ERβ; and the membrane receptors, which cover the counterparts of the nuclear receptors on the cell membrane, which were found to be distributed on cell membranes in addition to intracellular expression in CHO cells by Razandi [5] et al. in 1995. and GPER, which belongs to the G protein-coupled receptor family.

2.2. Classical Nuclear Receptors

ERα and ERβ are part of the nuclear receptor superfamily, include the A/B, C, D, and E/F regions and regulate target gene transcription mainly through the classical transcriptional regulatory pathway of genomic effects: i.e., When the ER is activated, it migrates into the nucleus and binds to the estrogen response element (ERE), which in turn forms a complex that triggers the transcription process of a gene.

Other modes of genomic action include ERE-independent transcriptional pathways that regulate downstream gene expression via transcription factor response elements and ligand-independent genomic actions [6].

2.3. The Membrane Receptor GPER

The history of the discovery and study of the GPER has been a gradual process. Initially, GPER was discovered as an orphan receptor GPR30 in 1997 by Carmeci [4] et al. and then in 2005, Revankar [3] et al. and Thomas [7] et al. demonstrated almost consecutively that oestrogen can bind to GPR30.GPER is a heptameric transmembrane G-protein and is widely distributed in the cardiovascular system, with expression in several cardiac myocyte cell types expressed in several cardiomyocyte types, including cardiomyocytes, cardiac fibroblasts, cardiovascular endothelial cells, and mast cells [8], which is particularly important for the study of GPER in the cardiovascular system

Another important study of GPER is its potential role in cerebral ischemic stroke. GPER is expressed predominantly In key areas of the brain, localized neurons as well as different types of glial cells [9]. activation of GPER can positively affect cardiovascular health through a variety of mechanisms.

3. SIGNAL TRANSDUCTION

GPER-mediated signal transduction: When activated by estrogen or ligands such as G-1, GPER first activates the G proteins associated with it and dissociates the Gαβγ heterotrimer into Gα and Gβγ. The dissociated G proteins activate or inhibit the activation of downstream signalling molecules that Regulate a wide range of biological activities such as cell proliferation, apoptosis and migration [10, 11]. In the GPER-EGFR-MAPK pathway, after GPER activation, dissociated Gβγ activates src family tyrosine kinases and MMPs one by one, leading to the release of HB-EGF and transactivation of EGFR, followed by activation of Ras-Raf-1-MEK- ERK, which leads to MAPK activation. this pathway can promote the proliferation and differentiation of different types of tumor cells through ERK up-regulation of proto-oncogenes and cell cycle proteins, but also through the mobilisation of calcium pools to promote cell proliferation ② PI3K-AKT pathway: similar to the MAPK pathway, the trans-activation of Gβγ activates the EGFR, which then activates the PI3K leading to the localisation and aggregation of PIP3 on the cell membrane, and then the recruitment of PIP3, which then activates PIP3. The activation of PI3K leads to the localisation and aggregation of PIP3 at the cell membrane, which then recruits protein kinase B (Akt) to the cell membrane and activates it. Activation of these two pathways can also activate another GC-cAMP-PKG pathway through NO

production by NOS [12] (iii) The PLC-IP3-Ga2+ pathway regulates contraction mainly by increasing intracellular calcium ion concentration. In addition, PKC can also be directly activated by calcium mobilisation, causing activation of membrane calcium channels ④ cAMP-PKA pathway: after GPER is activated, dissociated Gα activates AC, catalysing ATP to generate the intracellular second letter cAMP. cAMP activates PKA, which contributes to the inactivation of Raf-1 and reduces the activity of Erk1/2, antagonising the MAPK pathway, and acting as a regulator of homeostasis. In addition, PKA can also induce the transcriptional expression of bcl2 gene and inhibit apoptosis ⑤ NF-κB pathway

4. ESTROGEN RECEPTOR AND CARDIOVASCULAR DISEASE

4.1. GPER and Vascular Function

Activated GPER in vascular smooth muscle can mediate non-endothelial-dependent or endothelial-dependent vasodilation in vascular endothelium. Also GPER expression is upregulated in aldosterone-induced hypertension models and its activation significantly reduces blood pressure levels [13]. This suggests that GPER can act on ECs, VSMC and the renin-angiotensin system to produce vasoprotective effects such as vasodilatation [14],lowering blood pressure [15] and anti-inflammation[16].

4.2. GPER and Atherosclerosis (AS)

Increased low-density lipoprotein (LDL), inflammatory damage to the coronary vasculature, and damage to the endothelium are important factors that contribute to AS, specifically in five ways.

4.2.1. Endothelial cell protection and function

Feng Z et al. (2021) showed that the natural compound Kaempferol kaempferol up-regulates GPER expression, activates the downstream PI3K/Akt signalling pathway [17], attenuates oxidized LDL (ox-LDL), and reduces endothelial cell damage; it can also alter apoptosis-associated protein levels to inhibit vascular endothelial cell damage through PI3K/Akt signalling. protein levels to inhibit apoptosis of vascular endothelial cells [18]; activation of GPER also inhibits phagocytosis of LDL by endothelial cells, i.e., GPER improves the function of the vascular endothelium and reduces the risk of atherosclerosis.

4.2.2. Anti-inflammatory antioxidant and vasodilator effects

Atherosclerosis itself is also an inflammatory process [19], In a mouse model of AS, a lack of GPER expression was found to lead to a significant increasing, for the number of inflammatory cells . and a significant decrease in the activity of nitric oxide, which promotes vasodilatation, and that the use of the GPER-selective agonist G1 resulted in an improvement in the degree of inflammation in vivo, and the activation of nitric oxide synthase (NOS), which resulted in the modulation of vascular tone of the coronary arteries [20]. GPER attenuates the inflammatory response by inhibiting the NF-κB signalling pathway in order to reduce intercellular adhesion and markedly reduces the number of inflammatory cells such as CD68-positive cells and CD3-positive cells in the AS lesion area. Studies have also shown that inhibition or silencing of GPER in VSMCs reduces the production and secretion of oxidative coenzyme II oxidase 1 (Nox1), which leads to a reduction in the generation of reactive oxygen species (ROS) [21], which can attenuate oxidative stress, but this mechanism needs to be clarified by further studies.

4.2.3. Regulation of lipid metabolism

Selective agonists of GPER can reduce LDL levels by elevating the production of LDLR and enhance the uptake of LDL by liver cells, thereby reducing LDL levels in the blood. have also shown that

GPER can down-regulate preprotein converting enzyme (chymotrypsin converting enzyme 9), which can inhibit LDL receptor catabolism to improve LDL clearance.

4.2.4. VSMCs proliferation and migration

VSMCs can induce their own release of nitric oxide through direct activation of GC by GPER and indirectly mediate intracellular calcium mobilisation, activate ERK1/2 or AKT downstream signalling pathways, and induce increased NO release. Ultimately, it inhibits the activation, migration and apoptosis of VSMCs [22].GPER also inhibits smooth muscle cell proliferation by suppressing the expression of cell cycle-related proteins. In addition GPER appears to play an important role in regulating the vascular smooth cell phenotype, which is critical for atherogenesis.

The activation of GPER could ameliorate atherosclerosis through mechanisms such as lowering LDL levels, improving the degree of inflammation, and activating NOS, thereby positively affecting coronary heart disease.

4.3. GPER and Cardioprotection

4.3.1. Myocardial ischaemia-reperfusion (IR) injury

After myocardial ischemia, the restoration of myocardial blood flow during treatment makes the original ischemic myocardial injury worse, which is called myocardial ischemia/reperfusion injury (I/R). GPER activation can reduce myocardial infarction area and mitigate myocardial IR by inhibiting the apoptotic pathway of mitochondrial cells. Myocardial IR can lead to the disruption of the structural function of mitochondria, causing the release of proteins, such as cytochrome C, to the cytoplasm, activating Caspase-9, and causing the release of Caspases-9 to the cytoplasm. The activation of GPER activates Caspase-9, which causes a cascade reaction of downstream caspases, leading to apoptosis. The activation of GPER was found to protect the myocardium by inhibiting apoptosis caused by the release of cytochrome C [23]. In addition, Feng et al. demonstrated that GPER increased mitochondrial Ca2+ tolerance and decreased mitochondrial autophagy levels in an in vivo myocardial IR model in female OVX rats, thus improving mitochondrial dysfunction, which further demonstrated the anti-myocardial IR injury effect of GPER. substances release to ameliorate mitochondrial dysfunction [24].

4.3.2. Cardiac hypertrophy

Activation of GPER can inhibit pathological hypertrophy of cardiomyocytes, and is expected to be a novel therapeutic target against ventricular remodelling. mRNA levels of ANP and BNP, important cardiac neuroendocrine hormones, are important indicators of cardiac hypertrophy, and studies have shown that mRNA levels of ANP and BNP basically decrease in a gradient with the increase in G1 concentration, indicating that activation of GPER can effectively alleviate myocardial hypertrophy. activation of GPER can effectively alleviate cardiomyocyte hypertrophy. In addition, the present study also showed that GPER receptors may play an antihypertrophic role in cardiomyocytes by mediating cellular autophagy through the PI3K-AKT-mTOR signalling pathway.

5. SUMMARY AND OUTLOOK

Future studies need to delve into the mechanisms of GPER action in different cardiovascular diseases and how to treat cardiovascular diseases by modulating GPER activity. and develop GPERGPER agonists and antagonists with high selectivity and affinity may help to develop new therapeutic drugs for cardiovascular diseases and to study the dose-effect relationship and the optimal timing of dosing. In addition, GPER plays a role in multiple physiological systems, and thus an interdisciplinary research approach may also be useful for a comprehensive understanding of the function of GPER within the cardiovascular system and its interactions with other systems through an interdisciplinary research approach. However, more basic and clinical studies are needed to elucidate the specific

mechanism of action of GPER and the optimal therapeutic application of GPER in order to translate these findings into clinical applications.

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