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Review

Peroxisome proliferator-activated receptors as therapeutic targets for heart failure

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ABSTRACT

Heart failure (HF) is a common clinical syndrome that affects more than 23 million individuals worldwide. Despite the marked advances in its management, the mortality rates in HF patients have remained unacceptably high. Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription regulators, involved in the regulation of fatty acid and glucose metabolism. PPAR agonists are currently used for the treatment of type II diabetes mellitus and hyperlipidemia; however, their role as therapeutic agents for HF remains under investigation. Preclinical studies have shown that pharmacological modulation of PPARs can upregulate the expression of fatty acid oxidation genes in cardiomyocytes. Moreover, PPAR agonists were proven able to improve ventricular contractility and reduce cardiac remodelling in animal models through their anti-inflammatory, antioxidant, anti-fibrotic, and anti-apoptotic activities. Whether these effects can be replicated in humans is yet to be proven. This article reviews the interactions of PPARs with the pathophysiological mechanisms of HF and how the pharmacological modulation of these receptors can be of benefit for HF patients.

1. Introduction

Heart failure (HF) is a clinical syndrome in which the cardiac muscle cannot maintain adequate blood supply for tissue metabolism [1]. It affects approximately five-million adults in the United States and over 23 million individuals worldwide [2,3]. Its prevalence has increased recently due to the increasing number of patients surviving heart attacks [4]. Despite the substantial advances in its management, the mortality rate in HF patients has remained unacceptably elevated (50% within five years of diagnosis) [5]. It acts as an endpoint clinical state for most cardiovascular pathologies i.e. pressure overload, volume overload, and myocardial ischemia can cause cardiac damage with subsequent cardiac remodelling (the key pathophysiological process that ends in the development of pump failure) [6,7].

Pathologically, HF is characterized by impaired myocardial contractility, disruption of myocardial energy metabolism (chronic energy deficit), cardiac hypertrophy, and eventually cardiac fibrosis [7,8]. As initial compensatory mechanisms, the sympathetic nervous and the renin-angiotensin-aldosterone systems become hyperactive, creating a state of hyperadrenalism to maintain tissue perfusion [1]. However, with progression of the condition, these compensatory mechanisms turn to be a picture of maladaptation, exaggerating cardiac remodelling,

Abbreviations: DR1, direct repeat-1; ET-1, Endothelin-1; FA, fatty acid; FAO, fatty acid oxidation; HF, heart failure; NF-KB, nuclear factor kappa-B; PGC-1α, peroxisome proliferator activated receptor gamma co-activator 1 α; RXR, retinoid X receptor; SIRT1, silent information regulator 1; TNF, tumor necrosis factor; TZDs, thiazolidinediones

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dilatation, and energy deficit [9]. At the cellular level, initial compensatory growth of cardiomyocytes turns to be a maladaptive pathological hypertrophy that changes the cardiomyocyte contractile function, marking the progression towards pump failure [10–13]. Furthermore, former studies have shown that cardiac remodelling is associated with several metabolic and substrate level variations [14,15]. For example, Kagaya et al. reported that pressure overload-induced hypertrophy is associated with a marked decline in myocardial fatty acid oxidation (FAO) and altered lipid dynamics [16].

The chief goals of HF pharmacotherapy are to ameliorate symptoms, slow deterioration of cardiac function and reduce mortality. Several drugs, including diuretics [17], beta blockers (βB) [18,19], angiotensin converting enzyme (ACE) inhibitors [20] and digoxin [21] are prescribed for the management of HF symptoms. Of note, prolongation of patients' survival has been achieved by βB, ACE inhibitors, and aldosterone antagonists [21].

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor transcription factor superfamily that were discovered in 1990 [22,23]. They are involved in the regulation of fatty acid (FA) and glucose metabolism in the adipose and other metabolically active tissues, including the heart [24,25]. To date, three isoforms of PPARs [alpha (α), beta/delta (β/δ), and gamma (γ)] have been discovered in different tissues with high metabolic activity [26]. PPARα is found in the liver, kidney, heart, and muscle, while PPAR-β/δ is expressed mainly in skeletal muscles and PPAR-γ in the adipose tissue [27]. Table 1 summarizes the sites, genetic targets and functions of different PPARs.

The cardiovascular system -including the heart, endothelial cells, smooth muscle cells and macrophages- has variable amounts of the three PPAR isoforms [26]. Like other nuclear receptors, FAs (ligands) bind to PPARs in the cytoplasm and then the complex is translocated to the nucleus, where it binds to 9-cis retinoid X receptors (RXR) and the promoter regions of target genes [30]. They are further known as potential transcriptional regulators of cardiac FAO and myocardial energy balance [25,31].

This article reviews the cardiac energy metabolism in the normal and the failing heart and their relation to changes in PPARs. In addition to energy state regulation, PPARs have interactions with other pathophysiological mechanisms that are active in the failing heart and their pharmacological modulation may represent a new therapeutic target for HF.

2. Role of PPARs in HF pathogenesis

2.1. Metabolic effect

Heart failure affects cardiac energy metabolism by both systemic and cardiac-specific mechanisms [32]. Under normal physiological conditions, mitochondrial oxidative phosphorylation of FAs, glucose and lactate accounts for up to 95% of the required energy for a functioning myocardium (60–80% of which are generated by FAO) [4]. Moreover, the heart is characterized by metabolic flexibility and the ability to interchange between different substrates according to the general metabolic condition [33].

The effect of HF on FA/glucose metabolism is largely influenced by the aetiology, as well as the severity of the condition [4]. In early stages of cardiac hypertrophy, FAO is unchanged or may be increased [7]. However, with progression of the pathological process, there is a decline in the mitochondrial function including both FA and glucose oxidation with subsequent activation of the glycolytic pathway, which is not sufficient to compensate for the energy deficit (two ATP molecules are produced for each glucose molecule) [7,34]. This energy deficit exaggerates the contractile dysfunction, making the failing heart as an engine out of fuel [9].

A recent study (2015) by Roussel et al. showed an initial increase in FAO with upregulation of PPARα expression in the failed rat

Table 1
Table shows expression sites, genetic targets, and metabolic/cardiovascular functions of PPARs.

	Genetic site [28]	Tissue	Gene targets	Specific agonists	Functions [29]
PPARα	Chromosome 22q12.2–13.1	Liver, kidney, heart, and muscles	Stimulates genes involved in fatty acid (FA) oxidation (FAO) and transport (fatty acid transport protein, lipoprotein lipase, apo-lipoprotein A-I and A-II, and fatty acid-binding protein)	- Fenofibrate - Clofibrate - Gemfibrozil - GW7646	- General: Increases FA uptake and oxidation and reduces FA and triglyceride synthesis. - Cardiovascular: Increases cardiac FAO and suppresses inflammatory pathways within the heart.
PPARβ/δ	Chromosome 6p21.1–21.2	Liver, kidney, and skeletal muscles.	Stimulates genes involved in FAs uptake and suppresses those involved in FA efflux.	- L-165041 - GW0742 - GW501516	- General: Increases muscle glucose uptake and storage, as well as FA uptake and oxidation. - Cardiovascular: Increases cardiac FAO and may enhance glucose oxidative phosphorylation in late stages of heart failure.
PPARγ	Chromosome 3p25	Mainly in adipose tissue, with lower distribution in liver, kidney and heart.	Stimulates genes involved in insulin sensitivity and lipid storage.	- Pioglitazone - Rosiglitazone - Ciglitazone - Troglitazone	- General: Improves insulin sensitivity, FA uptake and maturation of adipocytes in the adipose tissue. - Cardiovascular: Decreases cardiac FA uptake and oxidation, while increasing oxidative phosphorylation of glucose and lactate.

Abbreviations: FA: Fatty acids, FAO: Fatty acid oxidation, PPAR: Peroxisome-Proliferator activated receptors.