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Review article

Impact of the renin–angiotensin system on cardiac energy metabolism in heart failure

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ABSTRACT

The renin–angiotensin system (RAS) plays a key pathogenic role in heart failure. The adverse effects of angiotensin II (Ang II), a major player of the RAS, contributes to the development of heart failure. Heart failure is accompanied by significant perturbations in cardiac energy metabolism that can both decrease cardiac energy supply and decrease cardiac efficiency. Recent evidence suggests that Ang II might be involved in these perturbations in cardiac energy metabolism. Furthermore, new components of the RAS, such as angiotensin converting enzyme 2 and Ang1-7, have been reported to exert beneficial effects on cardiac energy metabolism. As a result, a further understanding of the relationship between the RAS and cardiac energy metabolism has the potential to improve the control of heart failure, and may lead to the development of new therapies to treat heart failure. This review summarizes what effects the RAS has on cardiac energy metabolism, highlighting how Ang II can induce cardiac insulin resistance and mitochondrial damage, and what role reactive oxygen species and sirtuins have on these processes.

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Abbreviations: ACC, Acetyl CoA carboxylase; ATP, adenosine triphosphate; ATGL, adipose triglyceride lipase; AMPK, AMP-activated protein kinase; Ang I, angiotensin I; Ang II, angiotensin II; ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; AT1R, Ang II type 1 receptor; AT2R, Ang II type 2 receptor; CPT-1, carnitine palmitoyl transferase-1; ERRα, estrogen related receptor α; GLUT, glucose transporter; GPCR, G-protein coupled receptor; HF-PEF, heart failure with preserved ejection fraction; HF-REF, heart failure with reduced ejection fraction; MCD, malonyl CoA decarboxylase; MCAD, medium chain acyl CoA dehydrogenase; mRNA, messenger RNA; MFN2, mitofusin 2; NADPH, nicotinamide adenine dinucleotide phosphate; NOS, nitric oxide synthase; PPARα, peroxisome proliferator activated receptor α; PKC, protein kinase C; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; ROS, reactive oxygen species; RAS, renin–angiotensin system; Sirt, Sirtuin; TNF-α, tumour necrosis factor-α; VSMC, vascular smooth muscle cell.

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1. Introduction

The involvement of the renin–angiotensin system (RAS) in contributing to the severity of heart failure has received extensive attention over the last couple of decades. Activation of RAS, especially increases in angiotensin II (Ang II) levels, has a well established pivotal contributing role to the adverse myocardial remodeling and progression of heart failure [1]. This has lead to the development of RAS suppression as an important medical therapy for heart failure, including the use of angiotensin converting enzyme (ACE) inhibitors and Ang II type 1 receptor (AT1R) antagonists [2,3].

Ang II is best known for its important role in regulating blood pressure, via vasoconstriction and renal sodium absorption. In vascular smooth muscle cells (VSMC), Ang II elicits vasoconstriction, cell proliferation and hypertrophy [4,5]. Ang II-induced elevation of blood pressure is also involved in the release and enhanced response to norepinephrine [6,7]. These actions of Ang II primarily occur via binding to G-protein coupled receptors (GPCR: Ang II receptor) found in various tissues. The Ang II receptor has two distinct receptors: the AT1R and the Ang II type 2 receptor (AT2R) [8]. Activation of the AT1R, which is highly expressed in adults, results in vasoconstriction, cell proliferation, and hypertrophy (Fig. 1). As such, overexpression of the AT1R induces cardiac hypertrophy and remodeling [9]. On the other hand, Ang II binding to AT2R counteracts the AT1R-mediated detrimental effects, resulting in vasodilation and anti-hypertrophic effects (Fig. 1). Furthermore, new components of the RAS have been discovered, with evidence indicating that their components also have significant effects on the cardiovascular system. This includes the angiotensin converting enzyme 2 (ACE2)/Ang1-7/MAS receptor axis, which has been demonstrated to be a critical negative regulator of the ACE/Ang II/AT1R axis in cardiovascular diseases (Fig. 1) [10,11]. Blockade of the AT1R results in an increase in Ang II levels, which may cause either selective stimulation of cardiac AT2R, or an accelerated conversion of Ang II to Ang1-7. Both of these effects have the potential to produce beneficial therapeutic outcomes in heart disease [12].

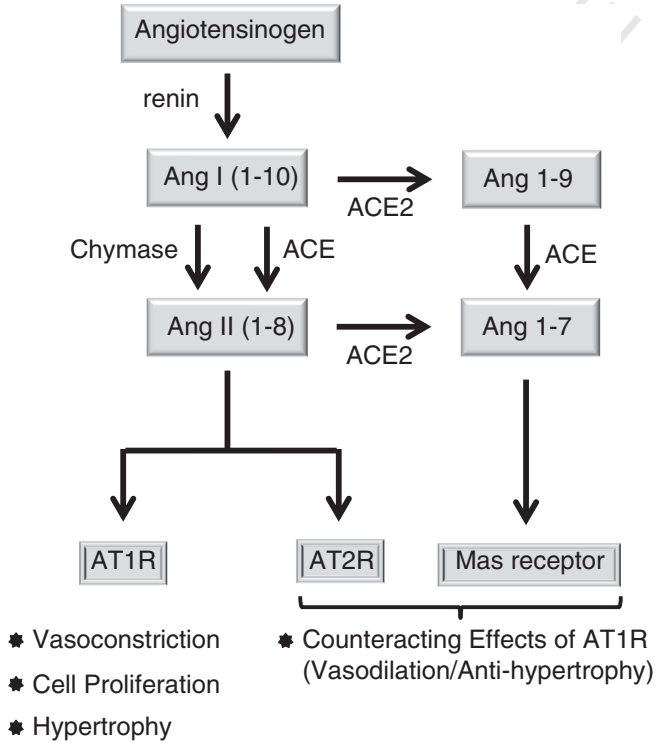

Fig. 1. Schematic representation of the renin–angiotensin system. angiotensin converting enzyme, ACE; angiotensin converting enzyme 2, ACE2; angiotensin II type1 receptor, AT1R; angiotensin II type2 receptor, AT2R.

In addition to the effects of Ang II on vasoconstriction and hypertension, cardiac hypertrophy and remodeling, recent evidence suggests that Ang II can also adversely affect cardiac energy metabolism in heart failure. Cardiac energy metabolic changes in heart failure can manifest as both a deficit in energy production by the heart, as well as a decrease in cardiac efficiency [13,14]. This impairment in cardiac energy metabolism and efficiency can contributes to the progression of left ventricular remodeling and contractile dysfunction in heart failure [13]. The energy metabolic changes that occur in the failing heart are complex, due in part to the fact that heart failure is not a uniform disease and multiple etiologies and causative factors contribute to heart failure. Also, there are different stages of heart failure development, as well different types of heart failure: heart failure with preserved ejection fraction (HF-PEF) and heart failure with reduced ejection fraction (HF-REF). For these reasons the actual alterations in cardiac energy metabolism that occur in heart failure are complicated. However, it is generally accepted that overall mitochondrial oxidative phosphorylation (glucose oxidation and fatty acid β-oxidation) decrease in heart failure [13,14]. Since mitochondrial oxidative metabolism normally contributes over 90% of the hearts energy requirements, this can create an energy deficit in the heart. Increased glycolysis can provide a source of energy (adenosine triphosphate (ATP)) in the failing heart, but cannot completely replace the deficit in mitochondrial ATP production [15]. As will be discussed, it is becoming apparent that alterations in the RAS and Ang II contribute to these changes in energy metabolism.

In addition to alterations in the amount of energy produced in the failing heart, the efficiency of producing energy can contribute to contractile dysfunction in the failing heart [13,14]. In particular, the source of energy used by the heart can have a profound impact on the efficiency of ATP production by the heart. Use of fatty acids as a source of energy (at the expense of carbohydrate oxidation) decreases cardiac efficiency (cardiac work/O_2 consumed). In heart failure, decreased cardiac efficiency can contribute to the severity of the energy deficit. As will be discussed, recent evidence has shown that chronic elevations in Ang II significantly alter the relationship between fatty acid and carbohydrate oxidation in the heart, resulting in a shift from carbohydrate oxidation towards fatty acid β-oxidation [16]. These energy metabolic alterations decrease cardiac efficiency, and contribute to the adverse effects of Ang II in heart failure.

Advances in metabolomics analysis have intensified efforts to identify cardiovascular biomarkers and disease pathways in heart failure [17,18]. Ang II can alter both mitochondrial morphology, mitochondrial respiratory chain enzyme activities, and mitochondrial biogenesis [16,19–21]. As a result, a better understanding of what effects RAS has on cardiac energy metabolism in heart failure may not only be beneficial in developing new treatments for heart failure, but may also facilitate the identification of novel energy metabolic biomarkers to identify RAS-induced heart failure. We will therefore review the effect of RAS on cardiac energy metabolism in heart failure.

1.1. Ang II effects on cardiac fatty acid β-oxidation and carbohydrate oxidation

The heart has a very high energy demand, which is derived primarily from mitochondrial oxidative phosphorylation [14]. While the heart can utilize a number of different fuels, the two main energy substrates used by the heart are fatty acids and carbohydrates (glucose and lactate). The oxidation of fatty acids is the main source of ATP production, although under certain conditions (such as after a high carbohydrate meal) glucose and lactate oxidation can become the major source of energy [14,16,22]. The metabolism of fatty acids and glucose in heart is highly regulated and closely coupled, such that an increase in fatty acid β-oxidation results in a decrease in carbohydrate oxidation, and *vice versa* (i.e. the Randle cycle) [23]. The RAS can alter this

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