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The cardioprotective effects of mineralocorticoid receptor antagonists

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ABSTRACT

Despite state-of-the-art reperfusion therapy, morbidity and mortality remain significant in patients with an acute myocardial infarction. Therefore, novel strategies to limit myocardial ischemia–reperfusion injury are urgently needed. Mineralocorticoid receptor (MR) antagonists are attractive candidates for this purpose, since several clinical trials in patients with heart failure have reported a survival benefit with MR antagonist treatment. MRs are expressed by several cells of the cardiovascular system, including cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cells, and endothelial cells. Experiments in animal models of myocardial infarction have demonstrated that acute administration of MR antagonists, either before ischemia or immediately at the moment of coronary reperfusion, limits infarct size. This action appears to be independent of the presence of aldosterone and cortisol, which are the endogenous ligands for the MR. The cardioprotective effect is mediated by a nongenomic intracellular signaling pathway, including adenosine receptor stimulation, and activation of several components of the Reperfusion Injury Salvage Kinase (RISK) pathway. In addition to limiting infarct size, MR antagonists can improve scar healing when administered shortly after reperfusion and can reduce cardiac remodeling post myocardial infarction. Clinical trials are currently being performed studying whether early administration of MR antagonists can indeed improve prognosis in patients with an acute myocardial infarction, independent of the presence of heart failure.

Contents

1. Introduction

In 2008, more than 17 million people died of cardiovascular diseases worldwide, according to summary tables of the World Health Organisation. In low-, middle- and high-income countries, ischemic heart disease and cerebrovascular disease are the leading cause of death. Percutaneous coronary intervention and thrombolysis are the main strategies to restore perfusion in patients with an acute myocardial infarction. Despite state-of-the-art reperfusion strategies, mortality and morbidity in patients with an acute myocardial infarction remain significant. This is caused, at least in part, by the fact that reperfusion itself also

Abbreviations: 11βHSD1, 11-β-hydroxysteroid dehydrogenase type 1; 11βHSD2, 11-β-hydroxysteroid dehydrogenase type 2; ACS, acute coronary syndrome; IL, interleukin; IR, ischemia–reperfusion; IS, infarct size; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mineralocorticoid receptor; NAD^+, nicotinamide adenine dinucleotide; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NYHA, New York Heart Association; PKC, protein kinase c; RISK, reperfusion injury salvage kinase; RR, relative risk; VSMC, vascular smooth muscle cell.

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contributes to tissue injury, a phenomenon which has been termed "lethal reperfusion injury" (Yellon & Hausenloy, 2007). Therefore, novel therapeutic options to limit ischemia–reperfusion (IR) injury are urgently needed to improve outcome in these patients.

It has been suggested that the mineralocorticoid receptor (MR) antagonists spironolactone and eplerenone could potentially serve this goal, because these drugs reduce mortality in patients with heart failure (Pitt et al., 1999; Zannad et al., 2011; Pitt et al., 2003). These reported effects of MR antagonists are consistent with the observations that the most important endogenous ligand for the MR, aldosterone, can have detrimental cardiovascular effects. Patients with autonomous adrenal overproduction of aldosterone (primary hyperaldosteronism; PHA) have an increased risk of cardiovascular and cerebrovascular events, and cardiac remodeling, independent of blood pressure levels (Rossi et al., 1997; Milliez et al., 2005b; Stowasser et al., 2005). Also, in patients without PHA, a high aldosterone level or high aldosterone-to-renin ratio is associated with an increased risk of cardiovascular events (Kisaka et al., 2012). In the setting of an acute myocardial infarction, aldosterone levels, even within the normal range, are associated with cardiovascular death and heart failure (Beygui et al., 2006).

Preclinical studies have now provided convincing evidence that MR antagonists have beneficial effects on various pathophysiological processes that contribute to cardiovascular morbidity and mortality (Fig. 1). MR antagonists attenuate the process of atherosclerosis (Rajagopalan et al., 2002; Keidar et al., 2003; Takai et al., 2005; Suzuki et al., 2006; Deuchar et al., 2011; Raz-Pasteur et al., 2012), modulate endothelial function and blood flow in animal studies (Kobayashi et al., 2005; Sanz-Rosa et al., 2005; Sartorio et al., 2007; Schafer et al., 2010) and in various patient groups (Farquharson & Struthers, 2000; Abiose et al., 2004; Macdonald et al., 2004; Joffe et al., 2007; Syngle et al., 2009; Rossi et al., 2011; Studen et al., 2011; Fujimura et al., 2012), limit myocardial IR-injury, prevent IR-induced arrhythmias (Barr et al., 1995; Ramires et al., 2000; Perrier et al., 2004; Gao et al., 2007; Laszlo et al., 2010; Dabrowski & Szwed, 2012; Lammers et al., 2012; Swedberg et al., 2012), and beneficially modulate cardiac remodeling. Protective effects against IR-injury have not only been reported in the heart, but also in the kidney (Mejia-Vilet et al., 2007; Sanchez-Pozos et al., 2012), the brain (Dorrance et al., 2001; Iwanami et al., 2007), and the retina (Liu et al., 2012).

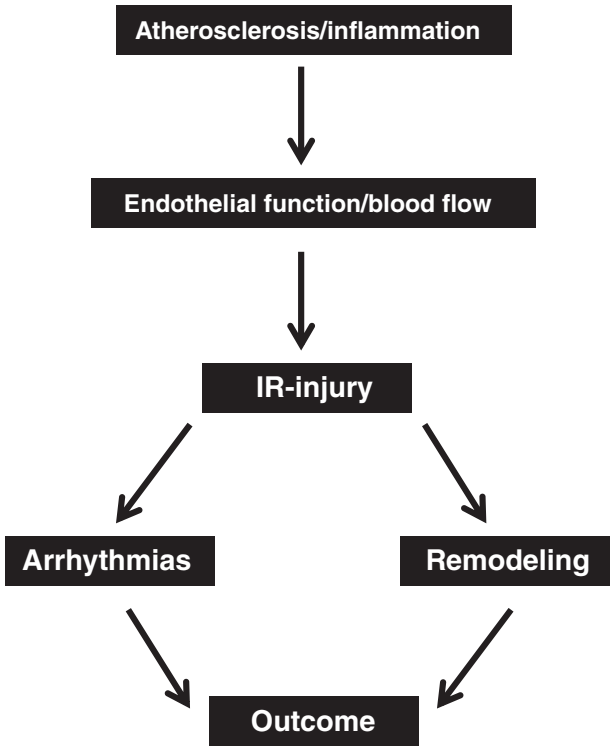

Fig. 1. Overview of the various pathophysiological processes that ultimately lead to cardiovascular morbidity and mortality which can be affected by MR antagonists (please see text for references).

In this review paper, we will summarize current knowledge on the effects of MR antagonists on myocardial IR-injury and post-infarction remodeling. To appreciate the molecular mechanisms underlying these beneficial effects, detailed knowledge about the distribution and function of the MR throughout the body is essential. Therefore, we will discuss the expression of the MR receptor in cardiovascular tissues, the effects of MR antagonists on IR-injury and the underlying mechanisms, and the effects of MR antagonists on post-infarction remodeling.

2. Expression and function of the mineralocorticoid receptor in the cardiovascular system

2.1. Characteristics of the mineralocorticoid receptor

From the classical physiological perspective the MR is expressed in the distal tubular cells of the kidney. The most important endogenous ligand is aldosterone, which is synthesized in the zona glomerulosa of the adrenal cortex. In this paradigm the role of this major mineralocorticoid is to regulate blood pressure and water balance by promoting the reabsorption of sodium and the excretion of potassium. The MR displays similar affinity for aldosterone and glucocorticoid hormones. Despite a 100- to 1000-fold higher concentration of these latter hormones than aldosterone, the MR in aldosterone target cells is not stimulated by glucocorticoids under normal physiological conditions. The enzyme 11-β-hydroxysteroid dehydrogenase type 2 (11βHSD2), co-expressed with the MR, converts cortisol into the inactive metabolite cortisone (Fig. 2). In rodents, where corticosterone instead of cortisol is the major glucocorticoid, corticosterone is metabolized to 11-deoxycorticosterone by 11βHSD2. Cortisone and 11-deoxycorticosterone have a much lower affinity for the MR (Funder, 2005; Odermatt & Atanasov, 2009). In this way 11βHSD2 protects the MR from stimulation by cortisol and confers specificity to aldosterone binding. The isozyme 11βHSD type 1 (11βHSD1), in vitro catalyzes interconversion of cortisol and cortisone (Tomlinson et al., 2004), but in vivo the enzyme converts cortisone into cortisol only. Taken together, this suggests that MR stimulation by aldosterone only takes place in cells that express 11βHSD2, but not in cells expressing 11βHSD1, both types, or none of these enzymes.

Alternative mechanisms of mineralocorticoid selectivity for aldosterone, including intrinsic discriminating properties of the MR itself, and distinct molecular ligand–MR interactions, have been described. Kinetic studies have shown that aldosterone has a 5-times lower off-rate from the human MR than cortisol, pointing to an intrinsic discriminating property of the receptor, which leads to an increase in transcriptional activity by aldosterone (Lombes et al., 1994). In addition, there are indications that the expression of co-activators of the MR can increase aldosterone-mediated transactivation (Pascual-Le Tallec et al., 2005). These mechanisms have been reviewed elsewhere (Farman & Bocchi, 2000; Funder, 2005; Skott et al., 2006; Fuller et al., 2012; Odermatt & Kratschmar, 2012) and we will not further discuss them here since they do not seem to bear relevance to cardioprotection by MR antagonists.

2.2. Expression of the mineralocorticoid receptor and 11βHSD in cells of the cardiovascular system

From the above it follows that the role of MR stimulation by aldosterone or by glucocorticoids can only be understood if it is known whether 11βHSD2 and perhaps 11βHSD1 are co-expressed with the MR. This is important, because the MR is expressed not only in the distal tubular cells of the kidney, but also in other cell types that are relevant to the cardiovascular system, including cardiomyocytes, cardiac fibroblasts,