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Review

Glucocorticoid signaling in the heart: A cardiomyocyte perspective

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ABSTRACT

Heart failure is one of the leading causes of death in the Western world. Glucocorticoids are primary stress hormones that regulate a vast array of biological processes, and synthetic derivatives of these steroids have been mainstays in the clinic for the last half century. Abnormal levels of glucocorticoids are known to negatively impact the cardiovascular system; however, surprisingly little is known about the direct role of glucocorticoid signaling in the heart. The actions of glucocorticoids are mediated classically by the glucocorticoid receptor (GR). In certain cells, such as cardiomyocytes, glucocorticoid occupancy and activation of the mineralocorticoid receptor (MR) may also contribute to the observed response. Recently, there has been a surge of reports investigating the in vivo function of glucocorticoid signaling in the heart using transgenic mice that specifically target GR or MR in cardiomyocytes. Results from these studies suggest that GR signaling in cardiomyocytes is critical for the normal development and function of the heart. In contrast, MR signaling in cardiomyocytes participates in the development and progression of cardiac disease. In the following review, we discuss these genetic mouse models and the new insights they are providing into the direct role cardiomyocyte glucocorticoid signaling plays in heart physiology and pathophysiology.

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Contents

1. Introduction

Glucocorticoids are steroid hormones necessary for life that are synthesized and released by the adrenal gland in a circadian manner and in response to stress [1]. Both physical and psychological perturbations, such as pain, fear, disease, hypoglycemia, and anxiety, trigger the hypothalamus to release corticotropin-releasing hormone (CRH). CRH then acts on the anterior pituitary to stimulate the synthesis and secretion of adrenocorticotropic hormone which, in turn, acts on the adrenal cortex to stimulate the production and secretion of glucocorticoids (cortisol in humans; corticosterone in rodents). Glucocorticoids act on nearly every tissue and organ of the body by binding the glucocorticoid receptor (GR; NR3C1), a member of the nuclear receptor superfamily of ligand-dependent transcription factors [2].

Upon glucocorticoid occupancy, GR regulates the expression of numerous genes that function to maintain homeostasis both in response to normal diurnal alterations in metabolism and in the face of stressful challenges. A host of biological processes are

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regulated by glucocorticoids, including intermediary metabolism, immune function, inflammation, skeletal growth, cognition, reproduction, and lung development [3,4]. Because of their potent anti-inflammatory and immunosuppressive actions, synthetic glucocorticoids comprise one of the most widely prescribed classes of drugs in the world today [5,6]. For more than 50 years, these steroids have been indispensable for treating inflammatory and autoimmune diseases, such as asthma, allergy, sepsis, rheumatoid arthritis, ulcerative colitis, and multiple sclerosis. In addition, they are routinely used in the clinic to prevent organ transplant rejection and to combat cancers of the lymphoid system. Unfortunately, the therapeutic benefit of glucocorticoids can be limited by severe side effects that develop in patients on long-term high-dose glucocorticoid therapy [6,7].

Despite a wealth of information regarding the tissue-specific effects of glucocorticoids and their prevalent use in the clinic, comparatively little is known about the direct role of glucocorticoid signaling in the heart. This is surprising, given that heart failure is one of the leading causes of morbidity and mortality in developed countries [8], and stress is increasingly recognized as an important factor contributing to the development and progression of heart disease [9,10]. A deficiency in glucocorticoid signaling has been linked to adverse cardiac outcomes indicating this hormone can influence heart function. Remarkably, this was first observed over 150 years ago by Dr. Thomas Addison who reported that patients with adrenal insufficiency present with a "remarkable weakness of the heart's actions [11]." This disorder, now known as Addison's disease, is characterized by decreased production of glucocorticoids by the adrenal gland and results in a variety of cardiovascular symptoms including a reduction in stroke volume [12,13]. Later studies performed nearly 50 years ago described a reduction in contractile force generation by the heart papillary muscle in adrenalectomized rats with glucocorticoid insufficiency [14]. More recent evidence that insufficient glucocorticoid signaling is detrimental to the heart has come from epidemiological studies focused on a polymorphism (A3669G) in exon 9 of the GR gene that has been associated with glucocorticoid resistance [15–17]. People with this polymorphism were found to have an increased risk of coronary artery disease, enlarged hearts, systolic dysfunction, and heart failure.

An increase in glucocorticoid signaling, due to stress or exogenous steroid treatment, has also been shown to influence cardiac function [18–20]. Some of these effects are beneficial. Glucocorticoid administration improves contractile performance of the heart [21–25], and glucocorticoids inhibit cardiomyocyte apoptosis triggered by ischemia, cytokines, and cardiotoxic drugs (doxorubicin) [26–30]. Prenatal exposure to glucocorticoids improves cardiovascular function in the newborn immediately after birth [31,32]. Conversely, elevated levels of glucocorticoids have also been linked to a variety of negative cardiac outcomes. For example, excessive in utero exposure to glucocorticoids can have a "programming" effect and lead to an increased risk of cardiovascular disease in the adult [33–35]. In addition, treatment with glucocorticoids results in a reduced heart rate in healthy human volunteers [36], and multiple studies have reported that glucocorticoids induce cardiac hypertrophy [25,29,37,38]. Patients with inappropriately high glucocorticoids for sustained periods of time (Cushing's syndrome) commonly develop hypertension and metabolic syndrome, two traditional risk factors for cardiovascular disease. Finally, epidemiological studies have revealed a significant association between supraphysiological doses of glucocorticoids and heart failure [39,40].

Clearly, glucocorticoids can exert both positive and negative effects on the heart. However, the direct role played by cardiomyocyte GR in these responses is poorly understood. Also unclear is whether the closely related mineralocorticoid receptor (MR) contributes to the actions of glucocorticoids in cardiomyocytes. To understand the role of these receptors in cardiomyocytes, genetic mouse models are needed for loss-of-function studies. Mice with global inactivation of the GR gene or MR gene die at or soon after birth precluding their use for studying glucocorticoid responses in the adult heart [41,42]. Therefore, scientists have recently developed novel mouse models that selectively target GR or MR for inactivation (and overexpression) in cardiomyocytes. In this review, we discuss these transgenic mouse models and the insights they have provided into the in vivo function of cardiomyocyte glucocorticoid signaling in both healthy and diseased hearts.

2. Glucocorticoid signaling

GR is a modular protein composed of an N-terminal transactivation domain (NTD), a central DNA binding domain (DBD), and a C-terminal ligand binding domain (LBD) [43]. The DBD is the most conserved region across the nuclear receptor superfamily. It contains 2 zinc finger motifs that recognize and bind target DNA sequences, termed glucocorticoid-responsive elements (GREs). The NTD is the most variable region among family members and contains a strong transcriptional activation function (AF1) that interacts with coregulators and the basal transcription machinery. The LBD forms a hydrophobic pocket for binding glucocorticoids and also contains a second transcriptional activation function (AF2) that interacts with coregulators in a ligand-dependent manner. Two nuclear localization signals, NL1 and NL2, have been identified in the GR protein, one located at the end of the DBD and the other residing in the LBD.

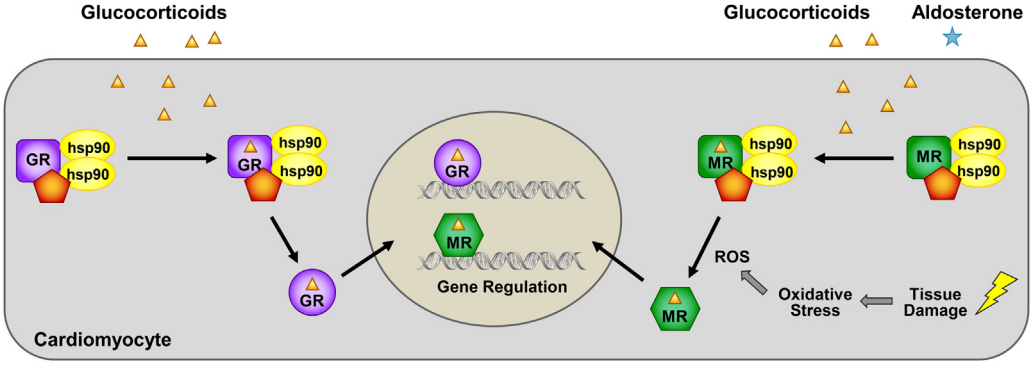

Fig. 1. Glucocorticoid signaling in cardiomyocytes. Glucocorticoid occupancy of GR results in its activation and translocation into the nucleus where it regulates gene expression. Glucocorticoids, rather than aldosterone, are also thought to be the predominant ligand for MR in cardiomyocytes. Glucocorticoid occupied MR may have limited transcriptional activity in the healthy heart but become more active in the diseased heart due to an accumulation of reactive oxygen species (ROS).

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