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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.

Keywords

glucocorticoids; glucocorticoid receptor; mineralocorticoid receptor; cardiomyocytes; transgenic mice

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

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the hypothalamus to release corticotropin-releasing hormone (CRH). CRH then acts on the anterior pituitary to stimulate the synthesis and secretion of adrenocorticotrophic 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 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 adrenal ectomized 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.

2.0 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.

Unliganded GR resides predominantly in the cytoplasm of cells as part of a large multiprotein complex (Fig. 1) (44, 45). Upon binding glucocorticoids, GR dissociates from the associated proteins and translocates into the nucleus. Nuclear GR binds directly to GREs and induces or represses the expression of target genes (46–48), which can comprise up to 10–20% of the human genome (29, 49, 50). Only a small fraction of GREs across the genome are actually occupied by the receptor, and these sites of GR binding vary in a tissue-specific manner due to differences in chromatin landscape that regulate the accessibility of the GRE (51). Genome-wide analyses have also found that the majority of GR binding sites

do not reside in the promoter of glucocorticoid responsive genes but rather in intergenic or intragenic regions that can be great distances away from the transcription start site (52). The GRE-bound receptor undergoes conformational changes that lead to the recruitment of coregulators and chromatin remodeling complexes that regulate RNA polymerase II activity and thereby alter the transcription rates of target genes (53–55). Many factors appear to influence the polarity and magnitude of the transcriptional response, including the specific GRE sequence, epigenetic regulators and chromatin context, the specific cofactors assembled, and the nature and concentration of the bound glucocorticoid ligand (56–59). Nuclear GR can also regulate transcription of target genes by physically interacting with other transcription factors, such as NF- κ B and AP-1, either apart from or in conjunction with GRE binding (60).

The GR is derived from a single gene; however, a large cohort of functionally distinct isoforms exist because of alternative splicing and alternative translation initiation mechanisms (1, 61). Alternative splicing in exon 9 of the GR primary transcript generates 2 receptor isoforms, termed GR α and GR β , which differ at their carboxyl termini. In contrast to the classic hormone-binding GR α isoform, the GR β splice variant does not bind glucocorticoids and resides constitutively in the nucleus of cells. GR β antagonizes the activity of GR α on many glucocorticoid-responsive genes, and elevated expression of GR β has been associated with glucocorticoid resistance. The A3669G polymorphism discussed above leads to increased GR β expression and relative glucocorticoid resistance by prolonging the half-life of the GR β mRNA (62, 63). Alternative translation initiation from conserved AUG start codons in exon 2 of the GR gene produces 8 additional receptor subtypes with progressively shorter NTDs (64, 65). These translational isoforms of GR have a similar affinity for glucocorticoids and a similar capacity to bind GREs; however they differ in their subcellular distribution and gene regulatory profiles. The relative levels of these GR subtypes vary across tissues and even in the same tissue in response to differentiation, aging, and certain pathological conditions. Differences in the expressed complement of the individual GR isoforms are thought to be a major factor contributing to the tissue-specific actions of glucocorticoids.

An additional complexity to the study of glucocorticoid signaling is that the endogenous glucocorticoids can also bind with high affinity to the mineralocorticoid receptor (MR) (66). Among the members of the nuclear receptor superfamily, MR is most closely related to GR. In contrast to the ubiquitously expressed GR, MR exhibits a more restricted pattern of tissue expression. MR is abundant in epithelial cells of the kidney, colon, and salivary glands and is also found in certain non-epithelial tissues, such as the heart. The primary hormone for MR is aldosterone which circulates at levels 100- to 1000-fold lower than glucocorticoids. In epithelial tissues, MR is “protected” from occupancy by glucocorticoids by the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) (67). This enzyme converts endogenous glucocorticoids to their inactive metabolite (cortisol to cortisone; corticosterone to 11-dehydrocorticosterone) and thereby permits MR to bind aldosterone and regulate sodium and water reabsorption. The expression of 11 β -HSD2 is virtually undetectable in cardiomyocytes, suggesting that endogenous glucocorticoids may be the predominant ligand for MR in the heart (Fig. 1) (68). It has been proposed that the glucocorticoid occupied MR in cardiomyocytes may have limited transcriptional activity under normal conditions but

become more active under pathological conditions that result in the accumulation of reactive oxygen species (69, 70). Indeed, the ability of glucocorticoids to increase myocardial infarct size in isolated rat hearts and enhance the rate of spontaneous contractions of isolated rat ventricular cardiomyocytes has been shown to occur through MR only in the presence of oxidant stress (71, 72). Therefore, an understanding of both GR and MR signaling pathways in cardiomyocytes is necessary for a full appreciation of the direct role played by glucocorticoids in cardiac physiology and pathology.

3.0 Transgenic Mouse Models Targeting Cardiomyocyte GR

The first demonstration in vivo that GR signaling in cardiomyocytes can have direct and specific effects on the heart came from a transgenic mouse model in which human GR (hGR) was conditionally overexpressed in mouse cardiomyocytes (73). An elegant feature of this mouse model is that a tetracycline inducible hGR construct was utilized, permitting transgene expression to be shut off by doxycycline treatment. Overexpression of hGR in cardiomyocytes at 3 times the level of endogenous GR did not lead to any major alterations in cardiac function. Echocardiography revealed only a minor reduction in ejection fraction, and tissue Doppler showed no difference in myocardial contractility between control and hGR overexpressing hearts. In addition, hearts with increased expression of hGR did not undergo adverse remodeling as no significant cardiac hypertrophy, fibrosis, apoptosis, necrosis, or inflammation was observed. The most overt phenotype to emerge in the mice overexpressing hGR in cardiomyocytes was bradycardia and atrio-ventricular block (AVB). Electrocardiogram (ECG) abnormalities associated with the AVB included an extended PQ interval, long QRS duration, and increased QTc dispersion. The conduction defects were dependent upon hGR overexpression as they could be reversed following doxycycline administration. Electrophysiology performed on isolated cardiomyocytes overexpressing hGR revealed decreases in sodium and potassium currents and increases in L-type calcium currents, calcium transient amplitudes, and sarcoplasmic reticulum (SR) calcium content. These findings suggest that elevated levels of cardiomyocyte GR (and the presumed increase in glucocorticoid signaling) lead to abnormal conduction properties and sinus node function which occurs in the absence of cardiac dysfunction or remodeling processes.

Mice with global and tissue-specific inactivation of the GR gene were generated by Rog-Zielinska et al. to investigate the role of glucocorticoid signaling in fetal heart maturation (74). Glucocorticoids rise dramatically shortly before birth and are known to promote the maturation of the lung and other organs to prepare the fetus for post-natal life but their direct actions on the fetal heart are poorly understood (75, 76). Clinically, this is an important question because glucocorticoids are routinely used for improving neonatal survival of preterm babies and fetuses at risk of premature birth and excessive fetal exposure to glucocorticoids can negatively impact adult cardiovascular health (35, 77–79). Fetal hearts from the global GR knockout mice appeared to develop correctly but were reduced in size and exhibited impaired performance, with diastolic function being the most significantly affected parameter. The Myocardial Performance Index (MPI), in which higher values correspond to more pathology and overall cardiac dysfunction, was markedly increased due to increased contraction and relaxation times of the left ventricle. Both ejection fraction and heart rate, however, were normal in the late gestation hearts from global GR knockout mice.

Structurally, cardiomyocytes from these hearts were irregularly shaped, failed to align properly in the compact myocardium, and contained short, disorganized myofibrils. At a molecular level, the late gestation hearts from the global GR knockout mice failed to show the normal maturational increase in alpha myosin heavy chain (Myh6), the major contractile protein in adult hearts, and in critical calcium handling proteins such as the cardiac ryanodine receptor (Ryr2), sodium calcium exchanger (NCX1), and the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2a). The deficiency in the expression of these genes suggests that immature excitation-contraction coupling may underlie the functional defects observed in the fetal hearts devoid of GR. A maturational increase was also not observed for the cardiac hormone atrial natriuretic peptide (Nppa) and for peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Ppargc1a) that plays a critical role in postnatal heart metabolism. All of these genes were upregulated in vitro by glucocorticoid treatment of fetal cardiomyocytes isolated from wild-type mice; however, many of them appear to be secondary targets of GR signaling as their induction required new protein synthesis (80).

A limitation to the studies performed on the fetal hearts from mice with global knockout of GR is that the observed effects could arise directly from the absence of glucocorticoid signaling in cardiomyocytes or indirectly from pathologies originating in other GR deficient cells. To distinguish between these two possibilities, Rog-Zielinska et al. inactivated the GR gene specifically in cardiomyocytes and vascular smooth muscle cells (VSMC) using the Cre-loxP technology (74). Mice with loxP sites inserted into the GR gene to flank exon 3 (which encodes the first zinc finger of the DBD of GR) were crossed with mice expressing Cre recombinase driven by the smooth muscle 22 promoter which is active only in cardiomyocytes and VSMC. The resulting conditional GR knockout mice were shown to have a ~65% reduction in GR levels in late gestation hearts, with the residual level of GR likely reflecting its expression in other cell types of the heart. Many of the phenotypes observed in the fetal hearts from the global GR knockout mice were also found in the fetal hearts from the conditional GR knockout mice, but important differences were also noted between the two models. For example, while cardiac function was impaired in the fetal hearts lacking GR in cardiomyocytes and VSMC, the increase in MPI was due only to a prolonged contraction time of the left ventricle. In addition, diastolic function was unaltered in these hearts and there was no reduction in heart size. As observed in the fetal hearts from the global GR knockout mice, cardiomyocytes from the conditional GR knockout hearts showed aberrant alignment in the compact myocardium and the myofibrils were short and disorganized. Subsequent in vitro studies on isolated fetal cardiomyocytes confirmed a direct role for GR in promoting maturation of myofibrillar content and organization (80). Finally, many of the genes dysregulated in the hearts from global GR knockouts, such as SERCA2a and Ryr2, were also similarly dysregulated in the conditional GR knockouts. Notable exceptions were Myh6 and Nppa, as the expression level of these genes underwent the normal maturational increase in the fetal hearts lacking GR in cardiomyocytes and VSMC. Together, these studies indicate that GR signaling in cardiomyocytes and VSMC plays a major role in the structural and functional maturation of the fetal heart. An important goal for future work will be to delineate the contributions made by cardiomyocyte GR from those made by VSMC GR to this maturation process.

Because global inactivation of the GR gene leads to perinatal lethality due to lung immaturity (42), our laboratory used the conditional knockout approach to study the role of glucocorticoid signaling in the adult heart (81). Mice with loxP sites inserted in the GR gene to flank exons 3 and 4 (which encode the entire DBD of GR) were crossed with mice expressing Cre recombinase under the control of the alpha myosin heavy chain (α MHC) promoter. In contrast to the SM22 promoter which drives Cre expression in both cardiomyocytes and VSMC, the α MHC promoter is active only in cardiomyocytes (82). Mice lacking GR specifically in the cardiomyocytes were generated on a mixed C57BL/6 and FVB/N background and were born at the expected Mendelian ratio. GR mRNA and protein were significantly reduced in whole heart extracts by approximately 70%, and immunohistochemistry confirmed that the reduction was specific to cardiomyocytes. Residual levels of GR reflected its expression in other cell types of the heart, such as fibroblasts, VSMC, and endothelial cells. Accompanying the reduction in GR was diminished glucocorticoid responsiveness. In mice treated with the synthetic glucocorticoid dexamethasone, the GR dependent regulation of classic target genes was greatly impaired in GR deficient hearts.

Mice lacking cardiomyocyte GR appeared normal early in life but died prematurely (median survival age ~7 months) from heart failure (Fig. 2A). Hearts from 6 month old mice were enlarged and showed marked dilation of the left ventricle (Fig. 2, B and C). Atrial thrombosis with lamellated fibrin was frequently observed, consistent with atrial blood stasis and chronic heart failure (Fig. 2C). Echocardiography was performed to investigate the cardiac pathology underlying the spontaneous death. Whereas GR-deficient hearts from 1 month old mice had normal function, knockout hearts from older 3–6 month old mice exhibited left ventricular systolic dysfunction (Fig. 2D), as both ejection fraction and fractional shortening were significantly reduced. The deficiency in cardiomyocyte GR led to cardiac hypertrophy, but no increase in fibrosis was observed in the knockout hearts. A hallmark of pathological cardiac hypertrophy and heart failure is the re-expression of certain fetal genes in the adult heart. Significant increases were measured for beta-myosin heavy chain (Myh7), skeletal muscle alpha actin (Acta1), smooth muscle alpha actin (Acta2), and brain natriuretic peptide (Nppb) indicating that the observed cardiac hypertrophy in the GR deficient hearts was mechanistically pathological. Interestingly, in contrast to the conduction abnormalities found in hearts overexpressing GR (73), ECGs were normal in mice with cardiomyocyte inactivation of the GR gene.

To elucidate the molecular events and biological pathways underlying the cardiac pathology, genome wide microarray analyses were performed on hearts from control mice and mice with cardiomyocyte-specific inactivation of the GR gene that were 2 days, 1 month, 2 months, or 3 months of age (81). Analysis of the differentially regulated genes at each time point by Ingenuity Pathway Analysis software identified “cardiovascular disease” as one of the top biological functions most significantly affected by the altered gene expression pattern in the GR knockout hearts. A total of 130 genes known to be associated with cardiovascular disease and over 1,000 genes not previously associated with heart dysfunction had altered expression profiles in the GR deficient hearts. Genes important for cardiac contractility (Ryr2; dystrophin, Dmd), repressing cardiac hypertrophy (Kruppel like factor 15, Klf15), promoting cardiomyocyte survival (prostaglandin D2 synthase, Ptgsd) and

inhibiting inflammation (lipocalin 2, Lcn2; tristetraprolin, Zfp36) had diminished expression in hearts lacking GR. Klf15, Ptgs, Lcn2, and Zfp36 are bona fide glucocorticoid responsive target genes known to be upregulated by activated GR. Accordingly, the expression of these genes was reduced in hearts lacking an intact GR signaling pathway. Consistent with the reduced expression of Ryr2, adult cardiomyocytes isolated from the GR deficient hearts had altered calcium responses, suggesting defects in calcium handling may contribute to the observed cardiac pathology. In summary, our studies on mice with cardiomyocyte specific deletion of GR reveal an obligate role for GR in maintaining normal cardiovascular function.

4.0 Transgenic Mouse Models Targeting Cardiomyocyte MR

In addition to GR, cardiomyocytes also express MR. Much interest has focused on the function of MR signaling in the heart since treatment with the specific MR antagonists eplerenone or spironolactone leads to a reduction in morbidity and mortality in patients with heart failure (83). The contribution of renal, vascular, and/or cardiac MR to the improved cardiac outcome following blockade of this receptor, however, is poorly understood. Also not clear is the identity of the ligand that is responsible for activation of cardiac MR in heart failure patients. Patients participating in the clinical trials that demonstrated the efficacy of MR antagonists for treating heart failure had plasma aldosterone levels in the lower range of normal (69, 70). This suggests that cardiomyocyte MR is predominantly occupied and activated by endogenous glucocorticoids in these diseased hearts, given the high concentration of glucocorticoids (relative to aldosterone) and the deficiency in 11 β -HSD2 expression in cardiomyocytes (68). Insight into the direct role MR signaling plays in both healthy and diseased hearts has come from several new mouse models targeting MR in cardiomyocytes.

The first mouse model developed for exploring the function of cardiomyocyte MR was a transgenic mouse with cardiac-specific overexpression of the human MR (hMR) (84). Since a tetracycline-inducible hMR construct was employed, hMR expression could be shut off with doxycycline administration. Hearts from the transgenic mice expressed 4 times more hMR mRNA than endogenous MR mRNA. Unfortunately, the extent to which the hMR protein was overexpressed in these hearts was not determined. Mice overexpressing hMR exhibited early lethality, and this sudden death was prevented by shutting off hMR overexpression with doxycycline or by antagonizing MR activity with spironolactone. Hearts overexpressing hMR had no structural alterations and the majority of mice had normal cardiac function. In addition, no increase in fibrosis, inflammation, or apoptosis was observed in the myocardium of these mice. However, major ECG abnormalities were measured in surviving mice overexpressing hMR in the heart. Increases were measured both in the PQ, QRS, and QT intervals and in the occurrence of severe ventricular arrhythmias such as premature ventricular beats and ventricular tachycardia. Mechanistically, ion channel remodeling leading to alterations in potassium transient outward current and L-type calcium current appeared to underlie the prolonged ventricular repolarization and the corresponding risk of arrhythmias. Results from these hMR overexpressing transgenic mice not only revealed a pro-arrhythmic role for cardiomyocyte MR signaling but also suggested that blockade of this effect may underlie the clinical benefit of MR antagonists.

Three subsequent studies investigating the function of MR in the heart employed the Cre-loxP technology to conditionally knock out MR from cardiomyocytes. Fraccarollo et al. crossed floxed MR mice containing loxP sites in the MR gene flanking exon 3 (which encodes the first zinc finger of the DBD of MR) with mice expressing Cre recombinase under control of the atrial myosin light chain promoter (85). The resulting mice with cardiomyocyte-specific inactivation of the MR gene had reduced levels of MR in isolated cardiomyocytes. Interestingly, the absence of MR had no detectable effect on cardiac morphology and function at baseline, suggesting MR is dispensable for normal function of the heart. To investigate whether MR played a role in ischemic heart disease, mice were subjected to left coronary artery ligation. The progressive left ventricular dilation and dysfunction observed in infarcted control mice were significantly attenuated in mice lacking MR in cardiomyocytes. Cardiac hypertrophy and the accumulation of extracellular matrix proteins were also reduced in the infarcted mice lacking MR in the heart, and the diminished remodeling was accompanied by decreased expression of genes associated with pathological hypertrophy (Myh7; angiotensin I converting enzyme, ACE) and fibrosis (ACE; connective tissue growth factor, CTGF; collagen; periostin; fibronectin; vimentin). In addition, the increases in myocardial oxidative stress and superoxide anion production in mitochondria observed in control infarcted mice were prevented in the MR deficient hearts. Finally, ischemic cardiomyocytes from hearts lacking MR were protected from apoptosis in a pathway possibly involving enhanced activation of NF- κ B. These studies suggest that cardiomyocyte MR is not necessary for the normal function of the heart but its signaling under disease conditions contributes to the development and progression of heart failure. They also suggest that the clinical benefit of MR blockade in patients with acute or chronic heart failure stems primarily from the antagonism of MR signaling in cardiomyocytes.

Hein and colleagues also generated mice with cardiomyocyte-specific deletion of MR (86). Using the same strategy as Fraccarollo et al., they bred mice containing loxP sites flanking exon 3 of the MR gene with mice expressing Cre recombinase from the atrial myosin light chain promoter. MR mRNA was reduced by approximately 90% in cardiomyocytes isolated from the knockout mice. Untreated mice deficient in cardiomyocyte MR displayed normal cardiac function. Compared to controls, no differences were observed in heart rate, left ventricular contractility and relaxation properties, ejection fraction, fractional shortening, and left ventricular chamber dimensions. These mice also did not exhibit any significant fibrosis. The loss of cardiomyocyte MR was accompanied, however, by mild cardiac hypertrophy and by distinct changes in gene expression. Microarray analysis revealed that 82 genes were significantly altered in untreated MR deficient hearts, including increased expression of atrial natriuretic peptide (Nppa), brain natriuretic peptide (Nppb), and skeletal muscle alpha actin (Acta1) and decreased expression of cardiac ryanodine receptor (Ryr2) and prostaglandin D2 synthase (Ptgds). To explore whether the loss of MR was cardioprotective after chronic pressure overload, mice were subjected to transverse aortic constriction (TAC). Mice deficient in cardiomyocyte MR were protected from the left ventricular dilatation and dysfunction that developed in the control mice. Levels of phosphorylated ERK1/2 were elevated in the MR deficient hearts after TAC, suggesting that ERK1/2 signaling may contribute to the observed cardioprotection. Loss of cardiomyocyte MR did not, however, prevent cardiac hypertrophy, fibrosis, apoptosis, and inflammation

from developing in the myocardium after pressure overload. These studies suggest that MR signaling in cardiomyocytes is not required for normal heart function, though it may modestly impact cardiac wall thickness. Instead, cardiomyocyte MR plays a major role mediating the ventricular dilatation and dysfunction that accompanies chronic pressure overload.

A third cardiomyocyte-specific MR knockout mouse was recently generated by Rickard et al. by breeding floxed MR mice with mice expressing Cre recombinase under control of the ventricular isoform of the myosin light chain promoter (87). The location of the loxP sites in the MR gene was not described, but Cre-mediated recombination resulted in decreased MR protein expression in cardiomyocytes. At baseline, the function of the MR deficient hearts was normal and the loss of MR in cardiomyocytes did not lead to cardiac hypertrophy. Distinct gene expression profiles, however, were observed in the untreated mice as the MR deficient hearts had reduced levels of markers for oxidative stress, inflammation, and fibrosis. The role of cardiomyocyte MR in the development of cardiac inflammation and fibrosis induced by deoxycorticosterone (DOC)/salt treatment was then evaluated. In mice treated with DOC/salt, the MR-deficient hearts showed no increase in recruitment of inflammatory cells or induction in proinflammatory gene expression. Moreover, cardiac fibrosis was prevented in the hearts lacking MR. Several markers of fibrosis and remodeling, such as plasminogen activation inhibitor 1 (Serpine1) and transforming growth factor β 1 (TGF β 1), were reduced in the hearts from the knockout mice treated with DOC/salt. These findings suggest that cardiomyocyte MR signaling is not critical for normal cardiac development and function but plays a direct role in the heart inflammation and remodeling triggered by a model of hypertensive heart disease.

5.0 Conclusion

The development of transgenic mouse models targeting GR and MR for inactivation or overexpression in cardiomyocytes has provided valuable new tools for elucidating the direct role of glucocorticoid signaling in the heart (Fig. 3). These studies have revealed a critical role for cardiomyocyte GR in preparing the late gestation heart for birth and for maintaining normal cardiac function in the adult, suggesting cardiac abnormalities reported in humans with deficits in glucocorticoid signaling may arise directly from insufficient GR signaling in cardiomyocytes. The mouse models have also revealed that cardiomyocyte MR, while apparently not necessary for normal heart function, can be deleterious to the hearts challenged in various models of disease, suggesting that blockade of cardiomyocyte MR signaling is critical to the therapeutic efficacy of MR antagonists currently used for treating heart failure patients. An important goal for future research is to determine the precise molecular pathways and genes by which glucocorticoid signaling in cardiomyocytes can either promote or protect against heart pathology.

Heart failure remains a leading cause of death in man, and stress is increasingly recognized as a contributing factor to the onset and progression of cardiac pathologies. The rise in glucocorticoids in response to acute stress may benefit the heart by direct actions on cardiomyocytes that improve contractility and promote survival. However, sustained increases in glucocorticoids due to chronic stress or therapeutic intervention may negatively

impact the heart through systemic effects that lead to hypertension and metabolic syndrome and local effects involving maladaptive responses to both prolonged activation of cardiomyocyte GR and increased activation of cardiomyocyte MR as tissue damage ensues. Understanding how glucocorticoid signaling in cardiomyocytes influences the heart holds promise for the development of new therapies for combatting cardiac disease. Results from transgenic mice targeting GR and MR in cardiomyocytes suggest that combining a selective GR agonist with a selective MR antagonist may represent an improved approach for treating a failing heart.

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Highlights

- We discuss new transgenic mouse models targeting GR or MR in cardiomyocytes
- Cardiomyocyte GR is important for fetal heart development
- Cardiomyocyte GR is critical for normal adult heart function
- Cardiomyocyte MR appears unnecessary for normal heart development and function

Figure 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).

Figure 2.

Heart pathology and dysfunction in mice lacking GR specifically in cardiomyocytes (cardio GRKO mice). A. GR deficiency in cardiomyocytes leads to premature death. B. GR deficient hearts from 6 month old mice are larger than their control counterparts. C. Hemotoxylin-eosin stained section of a GR deficient heart from a 6 month old mouse. Note the dilated left ventricle and the left atrial thrombus with lamellated fibrin (asterisk). D. Echocardiography on conscious 3 month old mice reveals left ventricular systolic dysfunction in GR deficient hearts. [Data in this figure originally published in *Proc Natl Acad Sci U S A* (2013), 110 (42):17035–17040.]

Figure 3.

Phenotypes of transgenic mice targeting GR or MR in cardiomyocytes. Shown are the major mouse phenotypes associated with GR overexpression (GR+), GR inactivation (GR-), MR overexpression (MR+), and MR inactivation (MR-) specifically in cardiomyocytes.

Cardioprotection was observed in response to transverse aortic constriction (TAC), myocardial infarction (MI), and deoxycorticosterone/salt (DOC/salt).