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INVITED REVIEW

Non-genomic effect of glucocorticoids on cardiovascular system

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Abstract Glucocorticoids (GCs) are essential steroid hormones for homeostasis, development, metabolism, and cognition and possess anti-inflammatory and immunosuppressive actions. Since glucocorticoid receptor II (GR) is nearly ubiquitous, chronic activation or depletion of GCs leads to dysfunction of diverse organs, including the heart and blood vessels, resulting predominantly from changes in gene expression. Most studies, therefore, have focused on the genomic effects of GC to understand its related pathophysiological manifestations. The nongenomic effects of GCs clearly differ from well-known genomic effects, with the former responding within several minutes without the need for protein synthesis. There is increasing evidence that the nongenomic actions of GCs influence various physiological functions. To develop a GC-mediated therapeutic target for the treatment of cardiovascular disease, understanding the genomic and nongenomic effects of GC on the cardiovascular system is needed. This article reviews our current understanding of the underlying mechanisms of GCs on cardiovascular diseases and stress, as well as how nongenomic GC signaling contributes to these conditions. We suggest that manipulation of GC action based on both GC and GR metabolism, mitochondrial impact, and the action of serum- and glucocorticoid-dependent kinase 1 may provide new information with which to treat cardiovascular diseases.

Keywords Glucocorticoid · Nongenomic · Cardiovascular disease · Serum- and glucocorticoid-dependent kinase · Mitochondria

Introduction

Glucocorticoids (GCs; cortisol in humans and corticosterone in rodents), named for their function in glucose metabolism, have been investigated in their metabolic roles in various biological processes, including gluconeogenesis, mobilization of amino acids, and fat breakdown, as well as in terms of their immunological function such as anti-inflammation and immunosuppression [6, 20]. As primary stress hormones, GCs released via the hypothalamic-pituitary-adrenal axis primarily recruit glucose to supply energy to organs facing stressful conditions, leading to arousal reactions and immune responses that maintain homeostasis [24, 36]. Failure to maintain ample concentrations of GCs is not acutely life threatening but widely affects metabolism and organ function adversely. Long-term stimulation of excessive or deficient GCs can result in pathophysiological manifestations, such as Cushing's disease and Addison's disease, respectively. On the other hand, the beneficial effects of GCs on immune functions (e.g., anti-inflammatory or immunosuppressive effects) have made synthetic GCs among the most frequently used drugs for the treatment of acute and chronic inflammatory diseases, autoimmune diseases, organ transplant rejection, and certain cancers. However, their widespread use has caused such

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adverse effects as steroid diabetes, osteoporosis, central obesity, delayed puberty, and glaucoma. Such effects are believed to be mediated by glucocorticoid receptor II (GR), which binds GCs, translocates into the nucleus, and alters gene expression [26]. As GR is ubiquitously expressed, consistent with the diverse effects of GCs, most researchers have looked at such genomic actions of GCs/GR to elucidate the mechanisms governing numerous systemic processes. Since the molecular mechanisms underlying GC actions on cardiovascular system are not fully understood, despite extensive study, further investigations are required to assess alternate mechanisms of GCs, such as nongenomic pathways.

The cardiovascular system is influenced by GCs in various conditions [38, 103, 112]. Therefore, GC therapy has been suggested in diverse immune- and nonimmune-mediated cardiovascular disorders, including atrioventricular conduction defects, rheumatic fever, myocarditis, dilated cardiomyopathy, Churg–Strauss syndrome, Kawasaki disease, sarcoidosis, acute myocardial infarction, angina, and postpericardiotomy syndrome and in invasive cardiology procedures, such as coronary interventions and cardiopulmonary bypass surgery [77]. However, the exact mechanisms of the GCs involved have not been clearly established. Moreover, GCs have been suggested to play roles in blood pressure maintenance and cardioprotection, such that a GC imbalance might induce cardiovascular damage, including hypertension, myocardial infarction, and arrhythmia [7, 67, 71, 77, 101, 107]. These effects are not completely explained by the genomic actions of GCs. Herein, both the genomic and nongenomic effects of GCs on the cardiovascular system should be considered to improve treatment outcomes for cardiovascular diseases. Therefore, this review will focus on the nongenomic functions of GCs on the cardiovascular system and evaluate these pathways as potential therapeutic targets for the treatment of cardiovascular diseases.

GC and GR activation

In humans, inactive cortisone and active cortisol can be metabolized by the enzymes 11β-hydroxysteroid dehydrogenases 1 and 2 (11β-HSD1 and 11β-HSD2), which exist in the endoplasmic reticulum [18, 49]. 11β-HSD1 metabolizes inactive cortisone into active cortisol, which is converted into its dormant form by 11β-HSD2 (Fig. 1). In the heart and vessel walls, there is negligible cortisol-degrading activity of 11β-HSD2 [49]; thus, the cardiovascular system can be affected by circulating GC levels directly. However, chronic, intermittent hypoxia leads to the expression of 11β-HSD2 and, in turn, augments regional sensitivity of the mineralocorticoid receptor (MR, glucocorticoid receptor I) to aldosterone [52]. The local state of 11β-HSD2, therefore, plays a role in the regulation of tissue sensitivity to GCs [54, 114]. The degradation of GC into tetrahydrocortisol or allodihydrocortisol is regulated by 5α-reductase [68]. In addition to active cortisol, 11-ketometabolites (e.g., cortisone and 11-dehydrocorticosterone), produced via degradation pathways, elicit additional effects, such as reducing responses to aldosterone [78], whereas certain products of GC metabolism potentially activate GR [68]. Circulating GC levels can be regulated by corticosteroid-binding globulin (CBG, a 50- to 60-kDa glycoprotein with a single steroid-binding site) [60]. CBG is the primary transporter for GCs in the circulation and facilitates their bioavailability [35]. However, cellular levels of GCs in target tissues can be regulated by the action of multidrug resistance (MDR) P-glycoprotein transporter, tentatively called the GC importer, which differs from the MDR P-glycoprotein transporter [56].

GCs do not typically act alone, but the actions of GCs on tissues are primarily dependent on the cellular density of functional GR (nuclear receptor subfamily 3, group C, member 1, 94 kDa). GCs can easily enter cells through the outer membrane, owing to its lipophilic nature, and bind to cytoplasmic GR [66, 90]. Alterations in plasma GC levels might be the primary component that determines GR expression; thus, GR undergoes downregulation following treatment with GCs [10]. GR structure contains a variable N-terminal domain, two hormone-independent activation function domains, a DNA-binding domain with two zinc finger motifs, a hinge region, and a C-terminal hormone-binding domain. The human GR gene consists of nine exons and expresses two alternatively spliced isoforms, GRα (classic GR) and splice variant GRβ (unbound to GC and exerts a negative effect against GRα) [16, 126]. In humans, GRα mRNA is expressed at higher levels than GRβ mRNA. Like GR splice variants, human GR gene mutations impair its actions at the molecular level and act as dominant-negative mutants, therefore altering tissue reactivity and resistance to GCs [19, 91, 117]. In addition, GR is a presumed target of various kinases and phosphatase(s); thus, posttranslational modifications of GR may modulate its transcriptional activation, receptor stability, subcellular localization, regulation of transcription, and interactions with co-regulators in response to hormones [3, 47, 55, 118]. The inactive state of GR (without bound GC) exists as a multimeric complex comprised of a receptor polypeptide and other partner proteins [13, 15, 45, 69]. GC binding to GR induces a conformational change in GR, dissociating itself from the multimeric complex (Fig. 1). GC-bound GR can exert effects in the nucleus [90] and mitochondria [51]. Together with GR, MR is found in heart tissue [32–34]. Aldosterone, the ligand for MR, regulates blood volume and pressure and circulates at 100-fold lower levels in the plasma than cortisol under physiological conditions [15]. Unlike the very low specificity of aldosterone binding to GR, cortisol and corticosterone easily bind to MR with higher affinity, which serve as antagonists to MR, possibly via

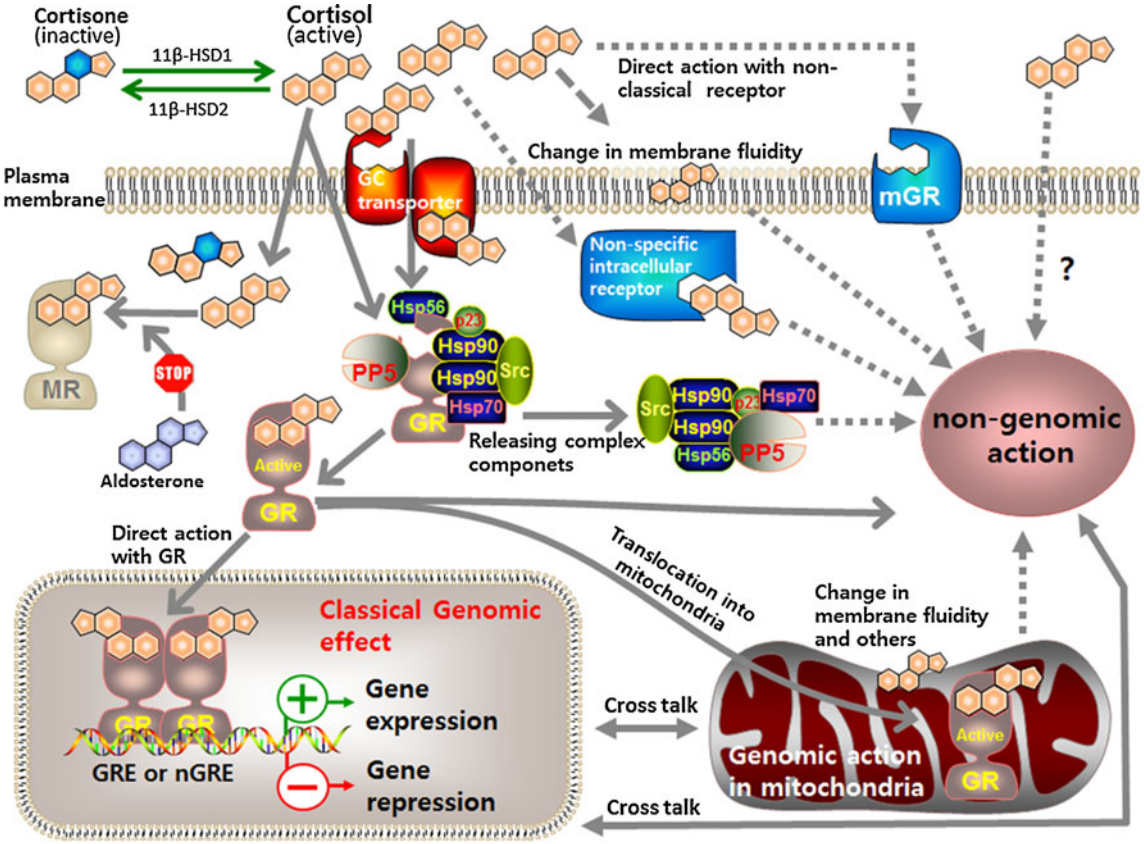

Fig. 1 Proposed genomic and nongenomic mechanisms of GCs. GC signaling results in changes in gene expression and rapid nongenomic events. In cardiomyocytes, MR is normally occupied by endogenous GCs (cortisol or corticosterone) under physiological conditions. Endogenous metabolism of GCs modulates tissue-specific sensitivity according to the status of 11β-HSD2, which metabolizes active cortisol into inactive cortisone and shields MR occupancy from GCs. The proposed criteria for nongenomic actions of GCs are rapid effects (within several minutes), resistant to simultaneous MR and GR blockade, independent of protein synthesis, reproducible in DNA-free preparations, responsive to BSA-conjugated GCs, and interactions with proteins other than MR and GR [40]. However, these criteria cannot be achieved by only nongenomic mechanisms of action. GR exists as a cytoplasmic complex with other accessory proteins in the absence of GCs. The inactive state of GR exists as a multimeric complex containing the receptor polypeptide, two molecules of HSP90, one molecule of HSP70, Src kinase, PP5 [130], and one molecule of HSP56 in the cytoplasm [13, 69]. These accessory proteins, which can be released from the GC-GR complex, participate in the nongenomic actions of GCs. GC-bound GR (active) forms a dimer and translocates into the nucleus to elicit its genomic effects, including transactivation or transuppression (or transrepression), via its interaction with other transcription factors via GREs [96]. In mitochondria, it is possible that both genomic, via mitochondrial GRE interactions, and nongenomic events will occur as in the cytoplasm. *GC* glucocorticoid (cortisol in humans and corticosterone in rodents), *GR* glucocorticoid receptor, *GRE* glucocorticoid response element, *nGRE* negative GRE, *HSP* heat shock protein, *mGR* membrane-bound GR, *PP5* ser/thr protein phosphatase type 5, *MR* mineralocorticoid receptor, *11β-HSD1* 11β-hydroxysteroid dehydrogenase 1, *11β-HSD2* 11β-hydroxysteroid dehydrogenase 2

tissue-specific co-activator/co-repressor recruitment to MR or GR complexes [75, 125].

GC and its cardiovascular functions

GCs have pleiotropic effects on the body. Changes in the GC-GR signaling pathway, due to deficits or excesses of GC, lead to pathological conditions and impair the cardiovascular stress response [95]. The functional status of the GC-GR system on the heart and other cardiovascular tissues may be influenced by circulating GC levels or locally produced GC in the heart.

GCs act on blood pressure, heart rate, and cardiac output during stress. There are huge amounts of data regarding the actions of GC on the immune system, which are important in discussions of cardiovascular disease but are beyond the scope of our review. Hypotension, hypoglycemia, and pancytopenia are indicative of cortisol insufficiency. In the heart, GCs likely contribute to normal cardiac activity, as low levels impair the cardiovascular stress response. Adrenalectomy leads to GC insufficiency and results in reduced contractile force generation in rat papillary muscle; this effect is reversed by administration of dexamethasone (DEX), possibly by the modulation of K^+ channels [59] and maintenance of membrane Ca^{2+} transport function

[81]. Plasma levels of cortisol decline with aging [63, 129], and deficits in contractile performance of the senescent heart (i.e., prolonged contraction duration and diminished contractile force) are reversible through GC-mediated improvement in Ca^{2+} pump function in the sarcoplasmic reticulum [42, 76, 87]. In cat capillary muscle, addition of GCs, such as cortisone and prednisone, does not produce marked inotropic action [111]. However, acute treatment with large doses of GCs leads to increased cardiac output, characterized as hypertension [119], as well as a decrease in total peripheral resistance in healthy humans and patients in shock [94]. In isolated perfused heart, a bell-shaped curve of myocardial inotropic stimulation by methylprednisolone was reported [99]. In the clinical setting, volume- and pressor-resistant hypotension in preterm infants was controlled by hydrocortisone administration, which rapidly restored cardiovascular stability by increasing blood pressure, possibly via the nongenomic actions of GC [100]. In contrast, brief exposure to DEX in the early neonatal period of rats leads to cardiovascular dysfunction in adulthood, which may be related to progressive deficits of cardiac adenylyl cyclase activity that is involved in the regulation of heart rate and contractility [2, 93] and the inhibition of cardiac mitosis in early life [5]. Endothelium-derived nitric oxides [21], synthesized from nitric oxide synthase [21], are physiologically important vasodilators. GCs can also affect the cardiovascular nitric oxide (NO) system, possibly via their inhibitory effects on the expression of both inducible nitric oxide synthase (NOS) [27] and endothelial NOS (eNOS) isoforms, restriction of cellular uptake of arginine, and depression of synthesis of the NO synthase cofactor tetrahydrobiopterin [86, 116]. In endothelial cells, GCs can also suppress production of vasodilators, such as prostacyclin and NO. In vascular smooth muscle cells, GCs amplify agonist-mediated pharmacomechanical coupling which modulates muscle contraction through change in intracellular free calcium or sensitivity to calcium, at several levels [122]. Therefore, chronic suppression of either the NO system or vasodilator production by GCs can lead to hypertension. GCs may induce cardiac hypertrophy via GR via α-adrenoreceptor-mediated hypertrophic signaling [22, 79]. Interestingly, the expression levels of both angiotensin II type I receptor (AT1R) and angiotensin type II receptor (AT2R) can be regulated by GCs because AT1R and AT2R contain glucocorticoid response elements (GREs) [27] in their promoter regions [67, 121]. In addition, the angiotensin II signaling pathway is critically involved in GC-induced pathophysiological changes in the myocardium [7, 67, 101]. GCs not only elevate the plasma content of catecholamines by restricting their extraneuronal uptake but also increase catecholamine sensitivity in the heart via the overexpression of various components of the β-adrenoreceptor signal transduction system [1]. Taken together, GCs have positive (e.g., maintaining cardiac contractility) and negative (e.g., enhancing vascular tone, leading to cardiac pathological changes) effects on the cardiovascular system, depending on individual conditions.

Nongenomic actions of GC

The nongenomic actions of steroid hormones, which rapidly evoke signaling pathways, including the activation of mitogen-activated protein kinase, adenylyl cyclase, protein kinase C (PKC), and G-proteins, have been widely recognized in various organ systems [64]. Although numerous reports exist, it is questionable whether the identified effects of GCs on other organ systems will have the same signaling outcomes as on the cardiovascular system. In addition, the pathophysiological actions of GCs on the cardiovascular system, which are possibly mediated by genomic effects, are widely known, but the nongenomic actions of GC-GR, which are evoked within several minutes without transcription, remain elusive. Moreover, understanding the nongenomic effects of GCs will be meaningful for future drug development or therapeutic regimens with fewer adverse effects.

As illustrated in Fig. 1, there are two different mechanisms mediated by GCs in the body [14, 62, 97, 98]. One is a classical genomic effect, which is mediated by the relatively rapid (hours) nuclear translocation of ligand-bound cytoplasmic MR and/or GR and binding to positive or negative GREs in the promoter regions of target genes [8, 40, 96]. Genomic actions of GCs are sensitive to actinomycin D (an inhibitor for transcription) or cycloheximide (an inhibitor for translation), which influences gene expression. Other rapid, nongenomic effects are mediated not by transcriptional regulation but via alternative pathways, including hormone–ligand intercommunication coupled to target nuclear receptor proteins resident in the cytoplasm [12, 102]. Such functions may be initiated at the cell surface through either membrane-bound, nonclassical GR in mitochondria [110] or cytoplasmic receptors [107] whose actions are unaffected by MR and GR [31, 40, 65]. Actually, the direct and specific effects of GCs on the heart are difficult to evaluate, as variations in plasma GC concentrations have various outcomes due to the ubiquitous expression of GR, resulting in systemic effects on cardiac function. Whereas there are many studies on aldosterone-mediated nongenomic signaling [17, 18], reports about rapid GC actions related to its nongenomic functions have been infrequent, and specific effects on the heart and cardiovascular system are more limited [9, 50, 73, 85, 108, 109, 124]. Identified nongenomic actions of GCs on the cardiovascular system are categorized as interactions of GR with other cytoplasmic signaling proteins and protein–protein interactions (Table 1). Protein function can be attributed to the transition of physiochemical properties in abutting membranes by insertion of GCs into the plasma membranes, disparity in lipophilicity, and polarity,

Table 1 Proposed nongenomic effect of GC on cardiovascular system

Site	Drug	Action (significance and reference)	Category[a] (ref)
Endothelial	DEX	Inhibition of NF-κB through direct interaction with GR (anti-inflammatory)	3 [9]
		eNOS activation by PI3K-Akt pathway (decreased vascular inflammation and reducing infarct size)	2 [39]
VSMC	Cortisol	Stimulation of the phosphoinositide system (possibly influence on vascular reactivity and blood pressure)	2 [108, 109]
	Corticosterone	Rapid activation of Src, Akt, and extracellular signal-regulated kinase 1/2 (GC-mediated MR activation)	2 [73]
CM	HC	Positive inotropism through possibly direct potentiating I_{ca} (increased contractility)	? 2 [124]
	DEX	Increase in coronary lipoprotein lipase by a AMP-activated protein kinase and p38 mitogen-activated protein kinase (whole-body insulin resistance but least effect on cardiac tissue)	2 [50]
		Reduced glucose oxidation and PDH activity (inhibit cardiac glucose oxidation)	2 [85]
Trabeculae	HC	Negative inotropic effects	? [17]
		No change in baseline contractility of coronary arteries	
Heart or vessel	DEX	NO production through GR-mediated PI3K/Akt-eNOS activation	2 [39]
		Cardioprotection through membrane stabilization	?1 [80]

CM cardiomyocyte or ventricular cell, *DEX* dexamethasone, *eNOS* endothelial nitric oxide synthase, *HC* hydrocortisone, I_{ca} L-type calcium current, *GR* glucocorticoid receptor, *MR* mineralocorticoid receptor, *NO* nitric oxide, *VSMC* vascular smooth muscle cell

[a] Categorized as follows: 1) direct membrane effect of GCs, 2) interaction of GR with other signaling proteins in the cytoplasm, 3) protein-protein interactions. Other non-genomic GC signaling through a (putative) membrane GR and mitochondrial GR translocation could be possible but there are no concrete examples. However, this classification does not reflect the exact mode of action because there is no sufficient evidence that completely excludes the other categories

which may distinguish these effects [31, 80]. As GC levels are endogenously increased in response to stress and are often applied at rather high doses, their nonspecific actions at the membrane level, including alterations of membrane fluidity and function of embedded ion channel or receptor proteins, have been suggested [65]. However, direct evidence for these actions of GCs remains elusive in the cardiovascular system.

GR was recently reported to activate the phosphoinositide 3-kinase (PI3K)-Akt pathway, possibly via the p85 subunit of PI3K in a rapid, nontranscriptional manner, whereas MR was not [51]. This and other evidences shown in Table 1 suggest that GC-GR signaling can induce rapid biological modulation in contractility, vascular reactivity and blood pressure in a nongenomic manner in the cardiovascular system. Previously, it was suggested that PKC isoforms (α or δ) may serve as receptors for steroid hormones (e.g., aldosterone or 17β-estradiol) or other interconnecting signals from the membrane [64], but further studies are required to determine whether GC mediates this type of event, and whether the physiological role of the direct activation of PKC by steroid hormones includes GC.

The GR–ligand complex undergoes a structural change after GC binding to GR, thus releasing heat shock proteins (HSPs) and other multimeric GR-bound proteins from the multimeric GR complex [13, 43, 69, 130]. Liberated components from the GR complex can also influence cellular signaling (Fig. 1). For example, Src released from the multimeric GR complex can evoke a signaling cascade in noncardiovascular systems [13, 65]. HSPs have been shown to bind Akt, resulting in decreased phosphorylation and degradation in noncardiac cells [70]. However, these actions may not be directly applicable to the cardiovascular system, because DEX rapidly increases the phosphorylation of Akt and leads to further activation of eNOS in mice [39, 113].

Apart from intact GC-GR signaling, CBGs that transport GC may play nongenomic roles in the cardiovascular system because elevated CBG levels could lead to increases in blood pressure [120]. CBG, either at very low levels due to critical illness and sepsis or absence due to genetic mutation leads to hypotension and fatigue [82]. In such cases, albumin instead of CBG can bind to cortisol, maintaining it at low normal levels. It is uncertain whether CBG is required for GC-GR function in the heart or body or has specific nongenomic actions on the cardiovascular system. Simply considering that bovine serum albumin (BSA)-bound GC can evoke nongenomic effects at the cell surface [46], there is another possibility that extracellular GC-bound CBG has hidden physiological functions. If true, this may suggest that GC-bound CBG influences the proper functioning of GCs, but there is no direct evidence.

Taken together, the nongenomic effects of GCs manifested in the immune or other systems may also be present in the cardiovascular system. Unfortunately, clear evidence or examples of these nontranscriptional effects of GCs on the cardiovascular system are lacking and require more extensive work. In addition, it is not clear whether the nongenomic effects of GCs are beneficial under physiological or pathophysiological conditions or therapeutic high doses.

GC and mitochondria

Mitochondria are immediate responders to different stresses that may affect cellular energy balance. Mitochondrial oxidative phosphorylation can be rapidly affected by GCs due to changes in membrane fluidity induced by GCs [105] or other unknown mechanisms [48, 74, 104] that are likely due to nongenomic actions. Cytoplasmic GR are translocated into mitochondria by an unknown mechanism. Mitochondrial GR can then trigger both pro- and antiapoptotic signals [51]. In HEK-293 cells, GR can interact with cytosolic thioredoxin 1 and mitochondrial thioredoxin 2, which act as antioxidants with many regulatory functions [28, 29, 83], raising the possibility for both genomic and nongenomic actions of GR in mitochondria. Although the presence of GR in noncardiovascular mitochondria has been identified [28–30, 84], the exact presence or movement of GR into cardiovascular mitochondria is not well established. The synthesis of GCs occurs in mitochondria. In addition, the presence of GR and GRE-like elements [28, 96] in mitochondria also suggests that GC-GR plays a crucial role in mitochondrial homeostasis and stress responses in a nongenomic manner. However, details of mitochondrial function involving GCs are under investigation and require more supporting results.

GC and serum- and glucocorticoid-dependent kinases 1

Serum- and glucocorticoid-dependent kinase (SGK) is a serine/threonine protein kinase (molecular weight, 49 kDa) that exists as three isoforms, is closely related to Akt [57], and is highly expressed in heart tissue [115]. SGK1 is transcriptionally upregulated by the action of GC-GR or mineralocorticoids, but neither SGK2 nor SGK3 is affected [58]. SGK1 phosphorylation on Ser422 and Thr256 intensifies the activities mediated by PI3K, phosphatidylinositol 3,4,5-trisphosphate-dependent kinase PDK1, PDK2, or other mitogen-activated protein kinases [58]. In the heart, the activity of SGK1 can be dynamically regulated via phosphorylation during hypoxia, oxidation, or serum deprivation. SGK1 inactivates glycogen synthase kinase 3β, which plays an important role in cardioprotection during ischemia/reperfusion [72]. Although SGK1 can inhibit cardiomyocyte apoptosis, prolonged activation of SGK1 induces a hypertrophic response [4].

The upregulation of SGK1 may be connected to angiotensin II-induced cardiac fibrosis through the recruitment of macrophages [123]. In cardiomyocytes, insulin-like growth factor 1 (IGF-1) or phenylephrine rapidly phosphorylates SGK1, increasing its activity [4]. The constitutive, active form of SGK1 in *Xenopus laevis* oocytes can upregulate expression levels of Na/K ATPase and increase its activity [44, 127]. In addition, numerous ion channels and transporters, including voltage-gated Na^+ channel (SCN5A) and voltage-gated K^+ channels (Kv1.3, Kv1.5, and Kv4.3), may be controlled by SGK1 [57]. SGK1 could shorten the QT interval in humans, possibly via activation of KCNE1/KCNQ1 (K^+ channel complex) or human *ether-à-go-go*-related gene (hERG) channel [11]. Considering that the heart responds to both insulin and IGF-1, and these stimuli powerfully augment PI3K-Akt signaling, rapid activation [27] of SGK1 may be possible, and thus, various kinds of ion channels, including KCNE1/KCNQ1 or hERG, may be modulated in heart tissue. It is unproven whether GC-GR can influence the activation of SGK1 [27]. Thus, more extensive studies will be valuable for understanding the more specific and nongenomic actions of GC on SGK1 in the cardiovascular system [22].

Therapeutic implications of nongenomic GC actions

In the immunological system, developing GC-mediated therapies with fewer side effects via an understanding of the nongenomic actions of GCs should be possible. GCs may not be generally used to treat cardiovascular disorders, but applications of GCs as therapies in other organ systems should lead to fewer adverse effects on the cardiovascular system. If true, we should pay more attention to both the genomic and nongenomic functions of GCs on the cardiovascular system. The impact of GCs mediated by genomic or nongenomic pathways is not sufficiently recognized and will need more extensive work, since research on GC physiology began its decline in the 1940s and is currently focused on its clinical applications [95]. In addition, relatively sparse evidence on the nongenomic actions of GCs on the cardiovascular system may be explained by their difficult identification due to their complexity, relatively lower sensitivity, or other regulatory systems that can compensate for or respond to excess GC action. The findings of beneficial or adverse effects of GCs based on nongenomic pathways will broaden our knowledge regarding their physiological/pathological roles. These findings may have further clinical implications for treating disorders of or modulating cardiovascular functions.

In contrast to its genomic transcriptional inhibitory actions on iNOS and eNOS, GCs have potential protective effects against ischemia mediated by PI3K/Akt pathway-activated eNOS [39] by stabilization of myocardial membranes [80] and reduction of myocardial infarct size [61, 106]. However, it is possible that the subsequent development of cardiac rupture related to blockade of GR genomic effects on wound recuperation or cardiac cell remodeling will arise [41]. In acute myocardial infarction, GC may be helpful; however, it may not be beneficial in the long term due to its existing genomic effects. N-terminal GR phosphorylation on serine residues or other posttranslational modifications may play important roles in the nongenomic

effects of GR [47]. When the A458T point mutation was introduced into the GR D-loop region, it caused defective DNA-binding; surprisingly, this GR alteration elicited a normal local and systemic anti-inflammatory response [88], implying that the anti-inflammatory effects of GC are not solely dependent on its genomic action. Different GCs vary in their genomic and nongenomic mechanisms of action [25], and the generation of synthetic GCs that are highly specific for GR without MR cross-reactivity is on-going [97]. Generally, side effects of GCs, such as hypertension, may be more closely related to their genomic effects because gene regulation robustly changes the physiological state of the cardiovascular system. There are no widely used drugs that specifically block the primary mode of GC action or specifically modulate hypothalamic-pituitary-adrenal axis tone [37, 53]. However, further understanding of the nongenomic actions of GC will provide insight into the development of antagonists against excess GC levels that further damage the cardiovascular system. Recent research on the development of GCs with specific nongenomic mechanisms with fewer side effects [13, 23, 26, 89, 92, 105, 128] will provide promising clinical applications, including cardiovascular interventions and suppression of inflammation.

Concluding remarks

GCs have versatile effects on the body and cardiovascular system through both genomic and nongenomic mechanisms. Despite their recognized importance on the cardiovascular system, few studies have addressed their molecular features, their regulation, and their response to disease. The majority of GC actions may be genomic, but the genomic and nongenomic actions of GCs may not be clearly distinguished, with possible cross talk. The direct, specific effects of GCs on the heart remain somewhat unclear; further clarification is warranted regarding GC sites, specific roles, and modes of interaction with the cardiovascular system. Understanding the beneficial genomic and nongenomic actions of GCs on cardiovascular functions will be promising for treatment of myocardial infarctions and malfunctions of the heart. Thus, the development of GC-mediated therapies without adverse genomic effects is necessary. To achieve this goal, we must pay closer attention to the nongenomic actions of GCs on the body, especially the cardiovascular system.

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Conflict of interest None.

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