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MINIREVIEWS

Adrenal G protein-coupled receptor kinase-2 in regulation of sympathetic nervous system activity in heart failure

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Abstract

Heart failure (HF), the number one cause of death in the western world, is caused by the insufficient performance of the heart leading to tissue underperfusion in response to an injury or insult. It comprises complex interactions between important neurohormonal mechanisms that try but ultimately fail to sustain cardiac output. The most prominent such mechanism is the sympathetic (adrenergic) nervous system (SNS), whose activity and outflow are greatly elevated in HF. SNS hyperactivity confers significant toxicity to the failing heart and markedly increases HF morbidity and mortality *via* excessive activation of adrenergic receptors, which are G protein-coupled receptors. Thus, ligand binding induces their coupling to heterotrimeric G proteins that transduce intracellular signals. G protein signaling is turned-off by the agonist-bound receptor phosphorylation courtesy of G protein-coupled receptor kinases (GRKs), followed by βarrestin binding, which prevents the GRK-phosphorylated receptor from further interaction with the G proteins and simultaneously leads it inside the cell (receptor sequestration). Recent evidence indicates that adrenal GRK2 and βarrestins can regulate adrenal catecholamine secretion, thereby modulating SNS activity in HF. The present review gives an account of all these studies on adrenal GRKs and βarrestins in HF and discusses the exciting new therapeutic possibilities for chronic HF offered by targeting these proteins pharmacologically.

Key words: G protein-coupled receptor; G protein-coupled receptor kinase; Heart failure; Sympathetic nervous system; Adrenergic receptor; Adrenal medulla

Core tip: The present manuscript is a mini-review describing the current knowledge in the field of adrenal GRKs and βarrestins, both of which are protein families that regulate adrenergic receptor function throughout the cardiovascular system. We specifically discuss the roles of these proteins in the adrenal medulla, as they pertain to regulation of catecholamine secretion and of

sympathetic activity in chronic heart failure (HF). We also outline the exciting new possibilities of targeting these molecules in the adrenal glands for HF therapy.

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INTRODUCTION

The sympathetic (adrenergic) nervous system (SNS) induces in the heart positive chronotropy, inotropy, lusitropy, dromotropy, accompanied by a decrease in venous capacitance, and constriction of resistance and cutaneous vessels[1,2]. All of these effects aim to prepare the body for "fight or flight response" and are mediated by the two catecholamines (CAs) norepinephrine (NE) and epinephrine (Epi)[3,4]. These are synthesized and released *via* the following mechanisms: (1) cardiac sympathetic nerve terminals release NE directly into the heart; (2) the adrenal medulla releases Epi and NE into the circulation; and (3) peripheral, local adrenergic nervous systems[5-7].

The actions of NE and Epi are mediated by the ARs, which are all G protein-coupled receptors (GPCRs) and consist of three α_1AR subtypes, three α_2AR subtypes (α_{2A}, α_{2B}, α_{2C}), and three βAR subtypes[8]. The main role of βARs in the heart is positive inotropy and chronotropy in response to CAs[9]. Agonist activation of GPCRs compels the cognate heterotrimeric G protein to dissociate from guanosine triphosphate and instead bind guanosine diphosphate on its Gα subunit; this results in splitting of the heterotrimer into two active functional components, Gα and $G_{\beta\gamma}$ subunits, both of which mediate signaling[9,10]. With specific regards to the α_2ARs, the α_{2B}AR is expressed in vascular smooth muscle causing vasoconstriction, while centrally located α_2ARs lower sympathetic outflow and systemic blood pressure[11,12]. NE release is controlled by presynaptic α_2ARs[13], since genetic deletion of α_2ARs leads to cardiac hypertrophy and HF, thanks to increased cardiac NE release and adrenal CA secretion[14,15].

Most GPCRs are subject to agonist-promoted desensitization and/or downregulation[16-18]. This process occurs courtesy of the GPCR kinases (GRKs) and the βarrestins[19]. The βarrestins uncouple the receptor from the G proteins, subsequently internalizing it[20]. GRK2 and GRK5 are the prominent GRKs in the heart and in most other tissues, including the adrenals[20,21]. Receptor internalization *via* the βarrestins results in either its resensitization or its degradation (downregulation)[20,21]. The receptor-bound βarrestins can also tranduce their own, G protein-independent intracellular signals[20,21]. Herein, we review the current literature regarding the roles of adrenal GRK2 and βarrestins in regulation of SNS activity in HF, with a focus on the therapeutic targeting of adrenal GRK2 as a sympatholytic strategy in chronic heart failure (HF).

ADRENAL GRK2 AND SNS ACTIVITY IN HF

A salient pathophysiological feature of chronic HF is SNS hyperactivity, reflected by increased levels of circulating Epi and NE[3,4,22]. Although it normally serves as a mechanism to re-adjust the heart from underperforming, it ultimately becomes cardiotoxic, contributing to HF progression, morbidity and mortality[3,4,22]. Adrenal CA secretion is stimulated by nicotinic cholinergic receptors and is refined by presynaptic inhibitory α_2ARs[5,23,24]. α_2ARs, similarly to cardiac βARs, also undergo GRK-dependent desensitization[10]. Of note, increased GRK2 expression and activity occur in the adrenal medulla during HF, which critically influence CA secretion from this source[25]. In particular, as we and others have documented, adrenal GRK2 overexpression is responsible for severe adrenal α_2AR dysfunction in chronic HF, leading to a loss of the sympatho-inhibitory function of these receptors in the adrenal medulla (and possibly also in sympathetic neurons); thus, CA secretion is chronically elevated[25-29]. The importance of the role of adrenal GRK2 in HF is evidenced by that its inhibition leads to a significant reduction in CA circulating levels, restoring not only adrenal, but also cardiac function[25]. In fact, HF rats treated with adrenal-specific βARKct (a GRK2 inhibitory mini-gene[30]) gene delivery show improved cardiac function and cardiac βAR number and signaling[25]. Therefore, an important crosstalk at the level of entire organs seems to exist in chronic HF and adrenal GRK2 is a crucial regulator of the circulating CA levels that affect HF progression. Consequently, adrenal GRK2 targeting to restore α_2AR function and reduce CA secretion from the adrenal medulla may provide a novel sympatholytic strategy for chronic HF treatment[25-29].

Another study demonstrating the advantages of therapeutic targeting of adrenal GRK2 is a study performed in transgenic mice having GRK2 genetically deleted only in cells expressing the phenylethanolamine-N-methyl-transferase enzyme. These mice lack GRK2 in their adrenal medullae[26]. These mice exhibit significantly reduced SNS activity during progression to chronic HF secondary to myocardial infarction (MI), as reflected by their circulating CA levels measured at 4 wk post-MI. In addition, their cardiac contractility, structure/morphology (dilatation), and βAR signaling/function, all show marked improvement at the same time-point (4 wk) post-MI[26]. Thus, prevention of the sympathetic "rush" that attacks the myocardium shortly after an MI thanks to adrenal GRK2 inhibition can help the heart work close to normal and limit its tissue damage, which normally occurs in the period directly following a heart attack. Therefore, adrenal GRK2 inhibition applied as early as possible after an MI may provide significant

survival and quality of life benefits in human HF. Of note, this is exactly the same rationale behind start of β-blocker therapy immediately after the heart attack in MI patients.

Adrenal GRK2 regulates CA secretion also under normal conditions, as adrenal βARKct transduction resulted in lowering of circulating CA levels in normal, otherwise healthy rats, and adrenal GRK2 overexpression increased their CA levels[27]. In addition, exercise training, beneficial for the cardiovascular system as it reduces HF-related SNS overactivation, can also normalize adrenal GRK2 expression and α_2AR function in HF rats[28].

It is also very likely that, in chronic HF, GRK2-mediated α_2AR deregulation also occurs in the cardiac adrenergic terminals, thus contributing to excessive NE release. Thus, global GRK2 blockade will decrease systemic circulating CA's, and perhaps a small molecule GRK2 inhibitor is best-suited for that therapeutic purpose. In that vein, it is interesting to point out that the known antidepressant drug (selective serotonin reuptake inhibitor, SSRI) paroxetine was recently shown to inhibit myocardial GRK2, thereby improving experimental HF in post-MI mice[29]. However, the results of this study must be treated with extreme caution, given that paroxetine exerts a variety of pharmacological effects, which may have contributed to its amelioration of cardiac function post-MI. For instance, it can also inhibit the other major cardiac GRK isoform, GRK5 (albeit to a lesser extent than it inhibits GRK2)[30], and it also activates glycogen synthase kinase (GSK)3-beta[31], which is known to have beneficial actions in cardiac fibrosis, hypertrophy and adverse remodeling[32]. In fact, exactly because it activates pancreatic GSK3β, paroxetine can precipitate insulin resistance/diabetes mellitus[31], a significant adverse effect that can potentially limit the drug's usefulness in HF therapy. Nevertheless, paroxetine may aid in the development of more specific (and potent) pharmacological GRK2 inhibitors by serving as a lead drug compound[30].

In summary, GRK2 inhibition is a novel sympatholytic strategy in HF, curbing CA release from SNS nerve terminals and the adrenal glands. In addition, it can be safely combined with β-blockers, as this combination cuts SNS overactivity and blocks adrenal GRK2 in HF[33]. However, while β-blockers improve inotropy of the failing heart indirectly, by protecting it from the catecholaminergic overstimulation[34,35], adrenal GRK2 inhibition can block also the non-cardiac adverse effects of the SNS (activation of endothelin, renin-angiotensin-aldosterone axis, *etc.*). Additionally, β-blockers acutely lower cardiac contractility and thus, are contraindicated in the acute setting of HF[36]. Adrenal GRK2 blockade, by diminishing global SNS activity in a cardiac-independent manner, may thus be much safer than β-blockers, as a sympatholytic approach, for acute HF. Finally, adrenal GRK2 inhibition would allow for reduction of dose and propensity for adverse effects of β-blocker therapy.

ADRENAL βARRESTINS AND SNS ACTIVITY IN HF

Aldosterone is another elevated hormone in HF and produces various detrimental effects on the failing heart, including adverse cardiac remodeling and HF progression post-MI[37-40]. It can also stimulate sympathetic neurons in the central nervous system to enhance NE release[37-40]. Aldosterone is produced by the adrenocortical zona glomerulosa cells in response to AT_1 receptor activation by angiotensin Ⅱ (Ang Ⅱ)[41,42]. A crucial role for βarrestin1 in mediating AT_1 receptor-induced aldosterone synthesis and secretion in the adrenal cortex has been documented[43]. Specifically, βarrestin1 causes upregulation of steroidogenic acute regulatory protein (StAR), the most critical enzyme in its biosynthesis[43]. Moreover, βarrestin1 does so independently of G proteins[43]. *In vivo*, adrenal βarrestin1 appears to be a major regulator of normal circulating aldosterone levels, since its upregulation, specifically in the adrenal gland, can cause hyperaldosteronism in normal healthy animals[43]. Importantly, in chronic HF, which is also characterized by hyperaldosteronism, adrenal βarrestin1 overexpression/overactivity promotes aldosterone elevation, resulting in accelerated cardiac adverse remodeling and deterioration of heart function[44]. Moreover, the cardio-toxic effects of aldosterone in post-MI HF are prevented by adrenal βarrestin1 inhibition *in vivo*[44] and βarrestin1-knockout mice progressing to HF after experimental MI fail to show any elevation in their circulating aldosterone levels, remaining essentially normal even as late as 4 wk post-MI[45]. CA levels are also significantly reduced in post-MI βarrestin1-knockouts, contributing to the overall better survival and cardiac function of these animals in post-MI HF[45]. Thus, adrenal βarrestin1 is a major driving force behind the cardio-toxic hyperaldosteronism and SNS hyperactivity, both of which accompany and aggaravate chronic HF. Thus, adrenal βarrestin1 inhibition might also be of therapeutic value in post-MI HF therapy. In fact, considering that it also participates in the adrenal GRK2-dependent α_2AR desensitization/downregulation, which chronically elevates CA secretion in HF[25,45], it becomes apparent that adrenal βarrestin1 inhibition could be an attractive therapeutic strategy for countering neurohormonal cardiotoxicity in HF.

CONCLUSION

Preclinical studies on cardiac GRK2 inhibition have established it as a promising therapeutic modality for HF. However, recent studies have brought GRK2 targeting in another organ, the adrenal medulla, to the limelight of potential HF therapies. Adrenal GRK2 inhibition appears to directly lower the neurohormonal (*i.e.*, sympathetic) burden of the failing post-MI heart, without affecting the heart muscle *per se*. As better, safer, and more effective vectors for gene therapy and/

or small molecule inhibitors get developed, the potential for GRK2 inhibition, in both the heart and adrenals, to find its place in the HF therapeutic armamentarium will continue to rise exponentially in the years to come.

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