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Alpha-1-Adrenergic Receptors in Heart Failure: The Adaptive Arm of the Cardiac Response to Chronic Catecholamine Stimulation

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Abstract

Alpha-1-adrenergic receptors are G-protein coupled receptors (GPCRs) activated by catecholamines. The alpha-1A and alpha-1B subtypes are expressed in mouse and human myocardium, whereas the alpha-1D protein is found only in coronary arteries. There are far fewer alpha-1-ARs than beta-ARs in the non-failing heart, but their abundance is maintained or increased in the setting of heart failure, which is characterized by pronounced chronic elevation of catecholamines and b□eta-AR dysfunction. Decades of evidence from gain- and loss-of-function studies in isolated cardiac myocytes and numerous animal models demonstrate important adaptive functions for cardiac alpha-1-ARs, to include physiological hypertrophy, positive inotropy, ischemic preconditioning, and protection from cell death. Clinical trial data indicate that blocking alpha-1-ARs is associated with incident heart failure in patients with hypertension. Collectively, these findings suggest that alpha-1-AR activation might mitigate the well-recognized toxic effects of beta-ARs in the hyperadrenergic setting of chronic heart failure. Thus, exogenous cardioselective activation of alpha-1-ARs might represent a novel and viable approach to the treatment of heart failure.

I. Introduction

Marked chronic elevation in the endogenous catecholamines, epinephrine and norepinephrine (NE) is one of the central neurohormonal abnormalities of heart failure. Catecholamines activate two classes of adrenergic receptors (ARs) in the myocardium: beta-ARs (β-ARs) and alpha1-ARs (α1-ARs). β-ARs are the predominant cardiac AR, and the toxic effects of chronic activation of β1-ARs on cardiac myocytes and β2-ARs on cardiac fibroblasts are central to the pathobiology of heart failure.[1,2]

α1-ARs are coupled to the $G_{q/11}$ (Gαq) family of G-proteins and activate phospholipase Cβ1 (PLCβ1), leading to intracellular calcium release though an increase in inositol trisphosphate (IP_3). Conventional wisdom views activation of myocardial Gq-coupled receptors as inherently pathological. However, this view is based in large part on a transgenic mouse model with Gq overexpression that markedly exceeds the two-fold increase found in human heart failure,[3-5] and thus cannot be considered to simulate human pathophysiology. In

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human heart failure, the maximal increase in Gq abundance is two-fold,[5] and transgenic mice with two-fold cardiomyocyte-specific Gq overexpression have no discernible cardiac phenotype.[3,4] α1-ARs also differ from other Gq-coupled receptors with respect to both cellular distribution in the heart, and intracellular localization within myocytes, as described later.

Signaling cascades downstream of α1-ARs are diverse and well-characterized, with over 70 known signaling partners.[6] The three subtypes of α1-ARs, α1A, α1B, and α1D, have differential expression in many tissues. The heart contains all three subtypes and substantial evidence demonstrates that myocardial α1-AR activation confers benefits through multiple pathways and processes.[6]

In the rodent and human heart, α1A and α1B-ARs are expressed predominantly in cardiac myocytes,[7,8] whereas the α1D is found in coronary smooth muscle cells.[9] Myocardial α1-ARs are essential for normal post-natal growth of the heart, and exert adaptive and protective effects in the setting of chronic stress, such as heart failure. Indeed, α1-AR abundance and function are maintained or increased in the setting of heart failure, in contrast to β-ARs, which are down-regulated and dysfunctional.[7,10]

In vitro and animal studies have established that α1-ARs mediate cardioprotection through numerous adaptive processes, including inhibition of cardiac myocyte death, enhanced protein synthesis, increased glucose metabolism, and positive inotropy. Human clinical trials suggest that the use of medications that antagonize the effects of α1-ARs is associated with an increased incidence of heart failure. Here we review briefly the data from cell, animal, and human studies that collectively indicate benefit from activation of α1-ARs in the heart, with a particular focus on the adaptive role of myocardial α1-ARs in the setting of heart failure, as contrasted to the maladaptive effects of β1-ARs (Figure 1).

II. There are 3 α1-AR subtypes, A, B, and D, with distinct patterns of expression in the heart

IIa. Myocardial α1-ARs: animal models

Cardiac α1-ARs were identified initially in the rat by Williams and Lefkowitz[11] and confirmed shortly thereafter in guinea pig by Karliner and colleagues.[12] α1-ARs were studied subsequently in the hearts of mice, rabbits, pigs, dogs, and cows. There is species-to-species variation in cardiac α1-AR abundance,[13,14] though the basal level of expression is uniformly lower than β-ARs. α1-AR levels are 5- to 8--fold higher in rats than in other species.[14]

The rodent heart contains mRNAs for all three α1-AR subtypes, though only the α1A and α1B are expressed as proteins (Figure 1).[8,14-17] The α1A is the most abundant transcript in the rodent heart, but competition radioligand binding identifies higher levels of α1B.[8,18] Importantly, α1-AR proteins can only be detected reliably using radioligand binding, as there are no commercially available antibodies with α1-AR specificity.[19]

Analysis of the major constituent myocardial cell types in rodents reveals that both neonatal and adult cardiac myocytes contain α1A and α1B-ARs, and cardiac fibroblasts contain no α1-ARs whatsoever (Figure 2).[17,20] Interestingly, recent data demonstrate also that the α1A subtype is expressed in only a subpopulation of myocytes.[21]

Thus, signaling events within cardiac myocytes primarily drive the cardiac effects of α1-AR activation, and α1-ARs cannot participate directly in the fibroblast proliferation and fibrosis that characterizes heart failure. Experimental chronic infusion of an α1-AR agonist causes

physiological cardiac hypertrophy without fibrosis,[22] whereas β2-AR stimulation drives proliferation of both rodent and human cardiac fibroblasts.[1,23-26]

It is axiomatic that receptor localization must determine function, and α1-, α2, and β-ARs all have distinct distributions among cardiac cells (Figures 1 and 2). These locations need to be kept in mind, when considering the roles of cardiac ARs.

Cellular distribution also distinguishes α1-ARs from the other major myocardial Gq-coupled receptors. The majority of cardiac angiotensin II receptors are found in fibroblasts, with minimal expression in cardiomyocytes,[27,28] which may account for pathological effects when angiotensin II Gq-coupled receptors are activated. ET(B) receptors are found on cardiac fibroblasts, with minimal expression on cardiomyocytes,[29] and participate in pathological fibrosis in heart failure. The effects of ET(A) stimulation are complex and not uniformly pathological,[30] with evidence to support cardioprotective effects such as positive inotropy,[31] antiapoptosis,[32] and ischemic preconditioning.[33] Thus, many of the detrimental effects of Gq-coupled receptor activation can be attributable to effects in cardiac fibroblasts, not cardiomyocytes. As a corollary, cardiac-specific, α-MHC-driven transgenic models of some other Gq-coupled receptors should be viewed with caution, given the extremely low abundance of the wild type receptors in cardiomyocytes relative to non-myocytes; transgenic over-expression in cardiac myocytes might have minimal relevance to actual pathophysiology.

α1-ARs, as most GPCRs, historically were thought to localize to the plasma membrane. However, early studies suggested that α1-ARs were present on the nucleus of neonatal rat ventricular myocytes (NRVMs),[34] and recent compelling evidence confirms nuclear localization of a substantial proportion of α1-ARs in adult mouse cardiac myocytes. Radioligand binding of fractionated adult mouse cardiac myocytes detects 80% of α1-ARs in the nuclear fraction, and this finding is substantiated using BODIPY-prazosin, a fluorescently labeled α1-AR antagonist.[35] Subsequent studies extended this finding, demonstrating that nuclear localization was required for normal α1-AR signaling and function in adult cardiac myocytes.[36] These discoveries, coupled with the identification in adult cardiac myocyte nuclei of angiotensin receptors[37] and β1-ARs[38], challenge the longstanding paradigm of ‘outside-in’ GPCR signaling in the heart. Endothelin-1 receptors also have been identified at the nucleus,[39] although endothelin receptors can function at the plasma membrane.[40] Thus nuclear compartmentalization of functional α1-ARs may also distinguish them from other Gq-coupled receptors in the heart.

IIb. Myocardial α1A- and α1B-ARs: human studies

Human and mouse cardiac α1-AR abundance and subtype distribution appear to be very similar. All three α1-AR subtype mRNAs are found in both ventricles of explanted human hearts; the α1A is the most abundant, followed by the α1B and α1D. As in the mouse, only the α1A and α1B proteins are detectable by radioligand binding, and the α1B is more abundant.[7] Collectively, these findings suggest that the mouse likely represents an accurate model for human cardiac α1-AR biology.

IIc. Coronary vascular α1D-ARs in rodents and humans

α1-ARs are well known for their effects in vascular tissue, where they typically mediate vasoconstriction. The stimulation of vascular α1-ARs by catecholamines produces little change in the diameter of normal human coronaries.[41,42] However, in coronary arteries with disrupted endothelium, α1-AR stimulation produces pronounced vasoconstriction and can lead to myocardial ischemia.[43-45] The α1D is the predominant α1-AR subtype in human epicardial coronary arteries and is pharmacologically active in primary human coronary

smooth muscle cells and ex vivo coronary rings.[9] Functional α1B-ARs are expressed in primary cultures of human epicardial coronary endothelial cells.[46] α1A mRNA represents 4% of total α1-AR mRNA in human epicardial coronary arteries and has no discernible function in either smooth muscle or endothelial cells. Of interest, the α1D also is functional in mouse coronary arteries,[47,48] further reinforcing the similarities between mouse and human cardiac α1-ARs.

III. The abundance of myocardial α1A- and α1B-ARs is maintained in heart failure

Heart failure is characterized by persistent marked elevations in catecholamines and the response of ARs to chronic stimulation is central to the pathobiology of the failing myocardium. β1-ARs are down-regulated and dysfunctional in heart failure,[10,49] and copious evidence demonstrates that excessive stimulation of cardiac β-ARs in the setting of heart failure mediates harmful processes to include cell death, fibrosis, and adverse remodeling. Many large clinical trials indicate that drugs that antagonize β-ARs (i.e. β–blockers) decrease mortality due to heart failure[50] and these medications are an essential component of contemporary heart failure therapy.[51]

In contrast, the abundance and beneficial functions of cardiac α1-ARs are maintained or augmented in the failing heart. Multiple studies indicate that α1-ARs constitute 2-23% (mean = 11%) of all AR binding in non-failing human heart tissue. However, in myocardium from failing human hearts, α1-ARs are 9-38% (mean = 25%) of all ARs.[7,52-55]

Importantly, α1-ARs also appear to maintain their function in the setting of chronic agonist exposure and heart failure. Chronic treatment of NRVMs with norepinephrine leads to upregulation of α1A-ARs without densensitization of IP_3 synthesis or cardiomyocyte growth.[56] In non-failing human myocardium, β-AR stimulation induces significantly greater inotropy than α1-AR stimulation; however in failing human heart muscle α1- and β-AR stimulation can produce equal degrees of positive inotropy.[57,58]

Analysis of α1-AR subtype profiles in failing and non-failing hearts reveals that the abundance of α1A mRNA is increased by 40% in the setting of heart failure,[7] and that α1A mRNA abundance positively correlates with left ventricular contractile function.[59] α1A and α1B binding levels are both maintained at nearly identical levels in failing human hearts, as are levels of the β2-AR, whereas the β1-AR is markedly down-regulated (Figure 3).[7] Consequently, the relative importance of α1-ARs and β2-ARs is magnified in the failing human heart.

These findings recapitulate earlier and ongoing studies in rodent hearts. Total cardiac α1-AR abundance and function are unaffected by hypertrophy or heart failure in rat models.[56,60] α1A mRNA abundance is increased in rats subjected to pressure-loading, as well as in NRVMs exposed to hypertrophic agonists,[56] similar to humans with HF.[7,59] Recent studies suggest also that α1A expression is maintained or increased in failing mouse hearts (Myagmar et al, unpublished data). Thus it appears that both the non-failing and failing mouse heart accurately model human α1-AR subtype abundance.

The mechanisms underlying the preservation of α1-AR levels and function in heart failure are partly known. β1-AR desensitization occurs through GRK2, the abundance and function of which is upregulated in human and rat heart failure, similar to upregulation of GRK5.[61,62] GRK2 and GRK5 have little if any effect on α1-ARs,[63-65] and both GRK2 and GRK5 are expressed in many myocardial cell types.[62] In contrast, GRK3 is expressed exclusively in myocytes and selectively regulates α1-ARs.[62,63] GRK3 abundance is unchanged in heart

failure,[61,62] which might partly explain the fact that heart failure does not change α1-AR levels and function. Interestingly, transgenic mice with cardiac-specific expression of a GRK3 peptide inhibitor (GRK3ct, analogous to the well-studied GRK2ct) have increased contractility without fibrosis and enhanced α1-AR signaling at baseline. After transverse aortic constriction, GRK3ct transgenic mice are protected from systolic dysfunction, despite equal induction of ventricular hypertrophy and β-myosin heavy chain induction.[66,67] These findings imply that increased α1-AR signaling can be beneficial, and collectively mirror the beneficial phenotype of mice with modest α1A-AR overexpression.[68]

IV. Blocking α1-ARs is associated with heart failure in clinical trials

α1-AR antagonists, or "α-blockers", are used widely for the treatment of benign prostatic hypertrophy (BPH) and occasionally in the treatment of hypertension. ALLHAT, the largest clinical trial of anti-hypertensive medications, included an arm in which roughly 24,000 men and women with high blood pressure received the non-selective α1-blocker, doxazosin. The incidence of heart failure in this group was twice as high as in the other arms of the trial and the Data Safety Monitoring Board discontinued the doxazosin arm prematurely due to safety concerns.[69] Of note, in 2002 13.2 million prescriptions for α-blockers were dispensed nationally, and the release of ALLHAT had little near-term effect on the use of these medications.[70,71]

Smaller studies also corroborate the association between α1-AR blockade and worsening heart failure. In the V-HeFT trial, use of the α1-blocker prazosin was associated with a trend toward increased mortality, in contrast to the beneficial effects of the other vasodilator medications tested.[72] A recent analysis also indicated an increased risk for heart failure hospitalizations in patients taking α-blockers without concomitant β-blockade.□[73]

Further loss-of-function evidence suggesting the benefit of α1-AR activation comes from multiple trials of sympatholysis for the treatment of heart failure. The Moxonidine Safety and Efficacy trial (MOXSE)[74] and the Moxonidine Congestive Heart Failure trial (MOXCON)[75] studied the efficacy of the sympatholytic agent moxonidine in the treatment of heart failure. Both trials found that moxonidine was very effective in decreasing plasma NE levels, yet both also observed an excess of mortality in the sympatholysis group. The mortality signal was strong enough to prompt premature discontinuation of enrollment in MOXCON.

The BEST trial examined the effects of bucindolol, a β-blocker with sympatholytic properties, on heart failure patients. In contrast to trials using other β-blockers for the treatment of heart failure, the bucindolol group experienced higher mortality.[76] It is controversial whether pharmacaogenetic factors play a role in this result with bucindolol.[77-82] With reference to the evidence presented in this review, we suggest that one possible explanation for sympatholytic-associated harm in heart failure is the withdrawal of adaptive pathways mediated by α1-AR activation.

The findings from these studies collectively challenge the prevailing paradigm that sympathetic activation is inherently and categorically harmful in heart failure.

V. Knockout (KO) mouse models demonstrate cardioprotective effects of α1A- and α1B-ARs

α1-Antagonists with the aforementioned adverse effects in clinical trials might have had "off-target" effects. However, α1-AR KO mice provide convincing evidence that α1-signaling is required for cardiac protection.

Va. Characterization of α1-AR KO mice

The findings from loss-of-function human trials are corroborated by studies in mice lacking cardiac α1-ARs, with evidence indicating distinct beneficial roles for both the α1A and α1B. Broadly speaking, the α1A appears to regulate α1-mediated cardioprotection, the α1B might mediate catecholamine-induced physiological hypertrophy, and the α1D contributes to regulation of blood pressure, as reviewed in detail.[83]

Mice lacking the α1A (on a mixed FVB/N-129 background) have low blood pressure and normal heart size.[18] α1B-AR knockout mice (α1B-KOs) on a mixed N-129/B6 background have normal heart size,[15,84] but a reduced cardiac hypertrophic response to subpressor infusion of an α1-agonist.[84] Furthermore, α1B-KOs on a congenic C57BL/6 background have small hearts.[85] Regardless of genetic background, α1B-KO mice have normal blood pressure, but a blunted pressor response to infusion of adrenergic agonist.[15,84-87] α1D-KO mice have normal hearts, but reduced blood pressure and decreased coronary vasoconstriction in response to phenylephrine.[47,87,88]

Systemic knockout of both the α1A and α1B (α1AB-KO) eliminates all myocardial α1-AR binding.[8] Surprisingly, the α1AB-KO mice (congenic B6 background) are normotensive, indicating that one or more of the other mechanisms controlling blood pressure can compensate for absence of α1-ARs.[8] However, cardiac growth cannot be compensated, in that adult α1ABKO male mice have small heart, indicating impaired physiological cardiac hypertrophy after weaning. This “small heart” phenotype is not seen in female mice, which have smaller hearts than do males. Overall contractility measured by echocardiography is normal in the smaller α1AB-KO hearts, but stroke volume, heart rate, and cardiac output are reduced, and the α1AB-KO mice have decreased exercise tolerance.[8]

Vb. KO models show that myocardial α1-ARs are cardioprotective

α1AB-KO mice also are more susceptible to injury, as evidenced by increased mortality and dilated cardiomyopathy leading to severe heart failure, in the setting of pressure-loading due to transverse aortic constriction.[8,89,90] Pressure-loaded α1-ABKO hearts have worse fibrosis than their wild type littermates, and increased cardiac cell death due in part to enhanced apoptosis. Cultured α1-ABKO cardiac myocytes exhibit increased necrosis and apoptosis when treated with NE, isoproterenol, doxorubicin or H_2O_2.[90-92] The enhanced susceptibility to cell death is rescued by adenoviral reintroduction of the α1A, but not the α1B, and requires activation of ERK 1/2.[92] Collectively, these in vivo and in vitro findings demonstrate an essential cardioprotective role for the α1A in cardiac myocytes, mediated through ERK signaling.

VI. Gain-of-function experiments demonstrate beneficial effects of cardiac α1-AR activation

Gain-of-function experiments, largely using well-characterized agonists, demonstrate broadly cardioprotective effects of activating myocardial α1-ARs. These adaptive processes include physiological hypertrophy, i.e. hypertrophy with preserved or increased contractile function, positive inotropy, protection from cell death, and ischemic preconditioning. In many cases, it remains unclear which α1-AR subtype regulates these cardioprotective effects, though the α1A has been implicated in a number of studies.

VIa. Pharmacologic α1-AR activation induces physiological cardiac hypertrophy

The experimental use of adrenergic agonists has been central to advancing our understanding of the function of α1-ARs in the heart. NE, epinephrine, and phenylephrine (PE) have been used in cell, animal, and human models for decades. The first report of

functional α1-ARs in cardiac myocytes described hypertrophy and an increase in beating frequency of NRVMs upon incubation with NE and the β-blocker, propranolol.[93,94] Treatment of NRVMs with α1-AR agonists remains a widely utilized model for experimental cardiac myocyte hypertrophy, and the hypertrophic response has been confirmed in adult cardiac myocytes and myocytes of multiple species.[95-100] α1-AR activation induces hypertrophy characterized by upregulation of the "fetal gene" program, to include atrial natriuretic peptide,[101,102] α-skeletal actin,[103,104] and β-myosin heavy chain.[105-107] In vitro agonist experiments have elucidated the complex signaling pathways that mediate α1-induced cellular hypertrophy, identifying over 70 downstream signaling partners to include PKC isoforms,[106,108,109] PKD,[110,111] ERK 1/2,[8], p90RSK,[112,113] and HDACs.[114,115]

Though fetal gene induction generally is considered inherently detrimental, it is unclear whether upregulation of this gene program is causative or merely a marker of pathology. In fact, numerous beneficial roles have been identified for the natriuretic peptides,[116] and any pathogenicity of α-skeletal actin and β-myosin heavy chain can be questioned.[117-119] Evidence even suggests that β-myosin heavy chain induction is not a marker for myocyte hypertrophy per se.[118]

In vivo agonist studies substantiate the biologic significance of α1-AR induction of cardiac myocyte hypertrophy. Infusion of a sub-pressor dose of NE causes cardiac hypertrophy with preserved or increased contractile function in mouse, cat, and dog models.[22,84,120-123] Importantly, the increase in cardiac mass is not accompanied by fibrosis or cell death. Collectively these findings define the in vivo response to α1-AR agonist infusion as physiological, rather than pathological, cardiac hypertrophy.

VIb. Myocardial α1-ARs cause positive inotropy, particularly in the failing heart

Though induction of hypertrophy is the most broadly studied of α1-AR effects, the first physiological response to α1-AR stimulation detected in humans was increased inotropy. In early reports, α1-AR agonists induced an inotropic response ex vivo in preparations from human atria[124] and ventricles,[125,126] as well as in vivo.[127,128] The contractile response to α1-AR activation is preserved or enhanced in failing human myocardium,[52,58,129] in contrast to the β-AR response, which is markedly diminished.[10]

Animal models generally confirm the positive inotropic response to α1-AR stimulation,[130-132] and experiments in mice reveal critical details. Ex vivo perfused hearts have a positive inotropic response to α1-AR stimulation,[48] and chronic α1-AR activation is required for normal contractile performance in perfused mouse hearts.[89] Interestingly, myocytes and ventricular trabeculae from the mouse right ventricle have a negative inotropic response to α1-AR activation, as contrasted with mostly positive responses in left ventricular myocytes and myocardium.[133-135] The overall net positive response in the intact heart is likely explained by the greater contribution of the left ventricle. A surprising finding is that heart failure switches the α1-AR inotropic response in mouse right ventricular trabeculae from negative to positive,[136] a potential adaptive response to the pulmonary hypertension of heart failure. Given the central role of impaired contractile function in the pathophysiology of heart failure, the augmentation of inotropy through α1-AR activation clearly constitutes an adaptive response.

The inotropic response to α1-AR stimulation likely arises from multiple mechanisms. Myofilament calcium sensitivity is increased,[137] as is calcium entry.[138-140] α1-AR activation also leads to phosphorylation of myosin light chain and troponin I by myosin light chain kinase and PKC.[136,141]

Vic.□ α1-AR activation promotes cardiac myocyte survival

The pathobiology of heart failure is characterized by increased cell death through both necrosis and apoptosis, mediated in part by chronic catecholamine surge.[142] Abundant evidence identifies β1-ARs as the mediators of enhanced cell death, whereas α1-ARs do not appear to participate in either necrotic or apoptotic cell death. In fact, in vitro studies offer convincing evidence that α1-ARs even counteract toxic β1-AR pathways to preserve cell viability.

In NRVMs, α1-AR agonists block apoptosis due to the β-AR specific agonist isoproterenol,[143,144] and in adult rat cardiac myocytes, NE-induced apoptosis is inhibited by a β-blocker (propranolol) but not an α-blocker (prazosin).[143] Pharmacologic α1-AR activation also protects against cell death due to numerous other experimental insults to include hypoxia,[145] serum starvation,[145] and doxorubicin.[146]

α1-AR anti-apoptotic signaling involves multiple pathways. Studies using NRVMs indicate phosphorylation of Bcl-2[145] and Bad after α1-AR activation,[147] potentially leading to stabilization of the mitochondrial membrane. ERK 1/2 is a frequent downstream partner of α1-ARs, and also regulates cytoprotective effects in the setting of agonist treatment.[92,143,144,148] Phenylephrine (PE)-mediated cytoprotection requires α1-AR regulation of the GATA-4 and NFAT transcription factors.[146,149]

In vivo models using α1-AR agonists reinforce the in vitro findings. Chronic infusion of α1-AR agonists causes physiological hypertrophy without evidence of cell death in multiple animal models.[22,84,120-123] These early studies used agonists that bind all 3 α1-AR subtypes, thus it has been unclear whether the salutary effects resulted from activation of the α1A, the α1B, or some combination thereof. However, recent evidence points toward the α1A as the primary cardioprotective AR subtype. Continuous infusion of a subpressor dose of the α1A-selective agonist A61603 prevents death and heart failure in mice injected with the chemotherapeutic agent, doxorubicin.[150,151] These results echo the findings from experiments using cardiac myocytes from α1-ABKO mice in which adenoviral reconstitution of the α1A, but not the α1B, abrogates enhanced myocyte death due to doxorubicin, β-AR stimulation, and H_2O_2.[92]

VId. α1-ARs mediate ischemic preconditioning in the heart

Abundant evidence also supports a role for α1-ARs in ischemic preconditioning. Agonist studies in multiple species including rat,[152,153] mouse,[154] dog,[155-157] pig,[158] and rabbit[159] indicate that myocardial α1-AR activation protects against ischemic injury. In particular, the α1A is implicated in the preconditioning response in a number of different models. Transgenic mice overexpressing a constitutively active α1A show complete protection from ischemic injury, whereas α1B transgenics develop injury comparable to wild type mice.[160] A novel transgenic rat model also indicates that overexpression of the α1A in the rat heart reduces infarct size after coronary ligation by mediating the second window of ischemic preconditioning.[161]

Activation of PKC is central to α1-AR mediated preconditioning,[153,162-164] and further downstream effectors include superoxide dismutase,[165,166] inducible nitric oxide synthase,[154] 5’ nucleotidase,[155] and heat shock proteins.[162]

VIe. α1-AR transgenic mouse models have variable phenotypes

Studies of mice with transgenic overexpression of α1-AR subtypes yield somewhat conflicted results, possibly resulting from disparate constructs (different promoters, different receptor cDNAs), the varying extents to which the receptors are overexpressed, whether the

transgenic mouse is systemic or cardiac-specific, the specific receptor active state conferred by the mutations in constitutively active mutants, and varied sites of transgene integration into the genome. Sex and strain of the transgenic mice studied likely contribute as well, but are not uniformly given in the various papers. Many of the details on each transgenic mouse are tabulated elsewhere.[6]

The disparate findings may also result in part from challenges inherent in the overexpression of GPCRs. In particular, transgenesis does not guarantee that the overexpressed receptor will assume the same conformation as an endogenous receptor in the setting of agonist stimulation. As such, it is conceivable that physiological responses in transgenic GPCR models are governed by aberrant signaling downstream from an overexpressed receptor in an alternate active state, rather than merely an exaggerated representation of endogenous signaling. This concept was demonstrated nicely in mouse cardiomyocytes overexpressing a constitutively active human β2-AR.[167] With reference to α1-AR transgenics, this issue is complicated further by the fact that different α1 agonists themselves induce biased signaling at wild type receptors, presumably based on receptor conformation.[168]

Two-fold systemic overexpression of a constitutively active mutant α1A enhances ischemic preconditioning.[160] In a separate transgenic model, exaggerated cardiac myocyte-specific overexpression of the wild type α1A improves contractility without hypertrophy (148-170 fold overexpression).[169] Sixty-six-fold overexpression of the wild type α1A protects against heart failure due to pressure loading and myocardial infarction, but is associated with enhanced fibrosis, apoptosis and death in aged mice.[68,170,171] The latter results are particularly surprising in light of the wealth of evidence from other gain-of-function studies indicating cardioprotection and a lack of fibrosis, and could be confounded by the grossly supraphysiological levels of α1A overexpression.

Characterization of multiple α1B transgenic mice has been even more confusing. Two-fold systemic overexpression of a constitutively active mutant α1B causes cardiac hypertrophy in the setting of normal blood pressure,[172] as does cardiac myocyte-specific 3-fold overexpression of a constitutive active mutant α1B,[173] or 70-fold overexpression of a wild type α1B.[174] However, another mouse line with 2-fold overexpression of a constitutively active α1B has normal heart size with decreased contractile function,[175] and 43-fold myocyte-specific overexpression of the α1B produces dilated cardiomyopathy and early death.[176-178]

The only clear commonality between the various α1B transgenics is the lack of a blood pressure phenotype. These apparently incompatible findings likely arise from the sources of variability mentioned above, and ultimately offer limited insight regarding the physiological role of the myocardial α1B-AR. As there is no available pharmacological compound with α1B selectivity, the best available evidence regarding the function of the α1B in the heart comes from knockout mouse models that suggest it is involved in normal post-weaning physiological developmental hypertrophy,[8,84,85] and hypertrophy induced by sub-pressor infusion of an α1-agonist.[84]

VII. Summary

Decades of studies in cells, animals, and humans describe adaptive and protective roles for α1-ARs in the heart. These functions are particularly important in the context of chronic adrenergic activation, such as heart failure, wherein β-ARs are downregulated and dysfunctional. Evidence from loss- and gain-of-function studies indicates that myocardial α1-ARs not only protect against the development of heart failure, but also maintain their beneficial functions in established heart failure. As detailed in this review, these functions include physiological hypertrophy, enhanced positive inotropy, protection against apoptotic

and necrotic cell death, and ischemic preconditioning. α1-ARs are estimated to be 90% unoccupied in chronic heart failure, suggesting that these beneficial pathways could be augmented further by activation with an exogenous agonist.[179] Indeed, this concept was affirmed in a recent small clinical trial in which advanced heart failure patients derived significant clinical benefit from the use of midodrine, a non-selective α1-AR agonist.[180]

In mice and humans, the α1A and α1B are the predominant α1-AR subtypes in the myocardium, whereas the α1D is expressed in coronary arteries. The α1A likely regulates cell survival pathways and ischemic preconditioning, and contributes to contractile function. The function of the α1B is less certain, though it appears to regulate post-natal heart size. Activation of the α1D leads to coronary vasoconstriction, particularly in the absence of a functioning endothelium. Ongoing translational work will expand upon the recent finding that selective α1A activation protects against heart failure in a mouse model,[150,151] and test the hypothesis that cardioselective α1-AR activation is a viable therapy for heart failure.

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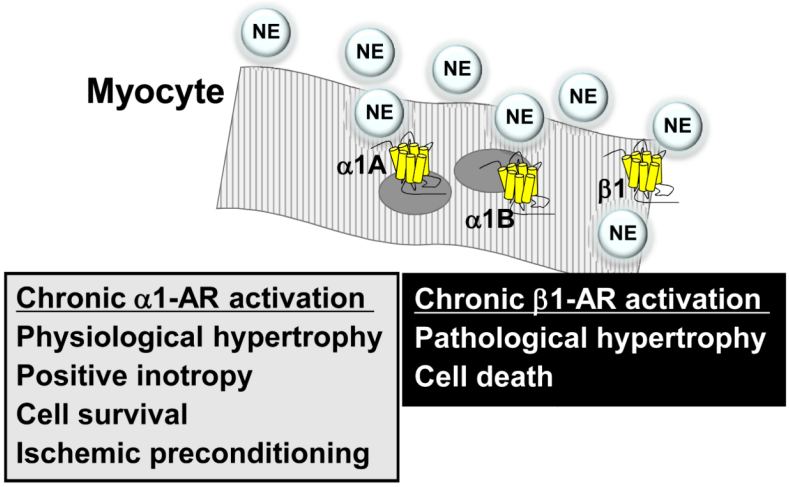

Figure 1. Adrenergic receptors in the failing cardiac myocyte

Radioligand binding levels of cardiac myocyte ARs are in the order β1 > β2 > α1B > α1A > β3. Some ventricular myocytes do not express all subtypes.[21] New data localize the α1-ARs to the myocyte nucleus.[35,36] The (patho)physiological roles of chronic activation are indicated.

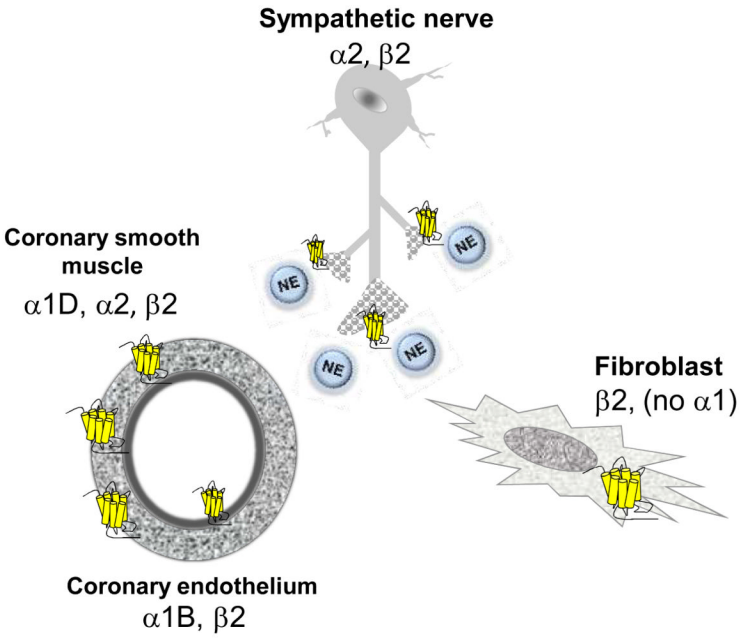

Figure 2. Adrenergic receptors in cardiac non-myocytes

Cardiac ARs are also broadly expressed on cells other than cardiac myocytes. α1D-ARs constrict coronary vascular smooth myocytes. α2-ARs constrict coronary vascular smooth muscle cells and inhibit NE release from sympathetic nerves. β2-ARs stimulate NE release from sympathetic nerves, activate fibroblasts, and relax coronary smooth muscle cells. The roles of ARs in coronary endothelium are less defined.

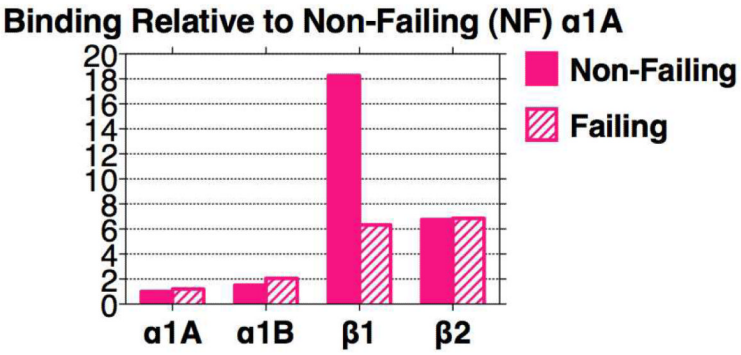

Figure 3. Adrenergic receptors in non-failing and failing human myocardium

The β1-AR is dominant in the non-failing heart, but is markedly down-regulated in the failing heart, whereas the α1A, α1B, and β2 are not. Data are taken from Jensen et al.[7] In that study, receptors in human left ventricular free wall were quantified by radioligand binding, using ^{3}H-prazosin for α1-ARs and ^{125}I-cyanopindolol for β-ARs. Specific binding at the ^{3}H-prazosin Kd was 40%. The proportion of the α1A subtype was defined by competition with 5-methyl-urapidil; the proportion of β1, with CGP 20712A; and the proportion of β2, with ICI-118,551. Non-failing hearts were unused donors, and failing were from transplant. Mean data from 4-6 patients for non-failing and failing are normalized to the value of the α1A in non-failing set at 1 (1.44 fmol/mg protein). The preparation used for binding was a complete myocardial lysate, not a "membrane" preparation, so that fmol values relative to protein are low, but no receptors are "tossed out". The rationale for this approach is that about 60% of total myocardial α1-ARs are in a typical 1000*g* pellet, and only 15% of total remain in a 40,000*g* "membrane" pellet used typically for binding.[83] Use of "membrane" preparations can cause artifacts, as documented with myocardial β-ARs.[181,182]