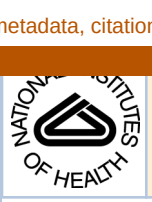

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Alpha-1-Adrenergic Receptors: Targets for Agonist Drugs to Treat Heart Failure

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Abstract

Evidence from cell, animal, and human studies demonstrates that α1-adrenergic receptors mediate adaptive and protective effects in the heart. These effects may be particularly important in chronic heart failure, when catecholamine levels are elevated and β-adrenergic receptors are down regulated and dysfunctional. This review summarizes these data and proposes that selectively activating α1-adrenergic receptors in the heart may represent a novel and effective way to treat heart failure.

Keywords

alpha-1-adrenergic receptors; cardiac myocytes; heart failure; drug development

Description of α1-ARs

The neurohormonal alterations of heart failure (HF) are characterized by marked elevations in sympathetic catecholamines, norepinephrine (NE) and epinephrine (EPI) [1]. NE and EPI activate two main classes of myocardial adrenergic receptors (ARs), alpha-1-ARs (α1-ARs) and beta-ARs (β-ARs). The most abundant cardiac AR is the β1-AR, though there are also smaller but functionally important populations of β2- and α1-ARs. All ARs are prototypical G-protein coupled receptors (GPCRs) with seven transmembrane domains, though they differentially activate Gα subunits: β-ARs couple predominantly to Gs, and α1-ARs to Gq, although β2- and α1-ARs can also couple to Gi.

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DISCLOSURES

A patent application is submitted to use α1-agonist compounds as treatment.

Acute activation of β1-ARs increases heart rate and myocardial contractility. However excessive chronic stimulation of cardiac β1-ARs, as with elevated catecholamines in HF, mediates harmful processes, including cell death, fibrosis, and adverse remodeling [2–9]. Interestingly, recent investigations suggest that myocardial β2-ARs might mitigate the harm associated with chronic β1-AR activation (article by Talan et al in this issue, and [10,11]). Nevertheless, drugs that block the activation of β-ARs (β-blockers) reduce HF morbidity and mortality and have become a cornerstone of HF therapy [12]. α1-ARs in the heart have been the subject of less intensive investigation, but multiple lines of evidence define adaptive and protective roles for cardiac α1-ARs (Tables 1–3) that contrast sharply with the toxic effects of excessive chronic β-AR activation [9].

α1-ARs exist as three distinct molecular subtypes, named α1A, α1B, and α1D (reviews in [13–19]). All three subtypes are activated by NE and EPI and blocked by the α1-antagonist prazosin. There are significant differences among subtypes in amino acid sequence, signaling, and tissue distribution. However, all α1-ARs couple to Gq to activate phospholipase Cβ1, with increases in diacylglycerol and activation of protein kinase C. In cardiac myocytes, increases in inositol trisphosphate and subsequent release of intracellular calcium are controversial. The α1B subtype might also couple to Gi [20–24]. The α1A subtype protects cardiac myocytes via ERK activation [25–27].

Further α1-AR intracellular signaling is diverse: over seventy molecules have been identified as downstream effectors of α1-AR-stimulated hypertrophy in cultured neonatal rat ventricular myocytes (NRVMs). Functionally, cardiac α1-ARs control numerous adaptive processes, including positive inotropy, gene transcription, protein synthesis, glucose metabolism, and inhibition of cell death (reviews in [16,28–32]).

This review explores the cell, animal, and human data that reveal beneficial roles for α1-AR activation in the heart, and collectively encourage a reexamination of the currently prevailing paradigm wherein chronic catecholamine elevation is felt to be wholly maladaptive in HF [33,34].

α1-AR expression and regulation in animal models and the human heart

Figure 1 summarizes expression and function of α1-ARs and β-ARs in the main cells of the animal and human heart.

α1-ARs IN HEART OF ANIMAL MODELS

α1-AR binding in the heart is similar among species, except for the rat, where binding is six-fold higher than either human or mouse [35]. In the rodent heart, cardiomyocytes express only the α1A and α1B subtypes [25], with α1B more abundant than α1A, whereas the α1D subtype is in coronary arteries [36,37].

Rodent cardiac fibroblasts (FBs) do not express α1-ARs at all [38], and thus are uninvolved in the FB proliferation that characterizes maladaptive remodeling. Indeed, α1-agonist treatment does not cause fibrosis [39], in contrast with some β-AR agonists [40,41], that stimulate cardiac FB proliferation through β2-ARs [42–45].

Numerous studies have identified functional α1-ARs in endothelial cells (ECs) of multiple systemic vascular beds in the rat [46,47], but their presence and function in cardiac ECs of animal models remains unknown.

In vitro and in vivo studies suggest that the α1A and α1B subtypes in rat cardiomyocytes might be differentially regulated by chronic stimulation [48], but total cardiac α1-ARs are not desensitized or down-regulated in hypertrophy in vitro or HF in vivo [48,49]. Strikingly,

in myocardium and arteries where the α1A is expressed, it is present in only subpopulations of vascular or cardiac myocytes [50–52], unlike the α1D, which is present in most or all vascular myocytes [53]. Another recent, unexpected finding is that the α1A and α1B subtypes in cardiac myocytes are located primarily on the nuclear membrane, not the sarcolemma [54].

α1-ARs IN HUMAN HEART

The distribution of α1-AR subtypes in the human heart mirrors the rodent heart (summarized in [55]). The α1A and α1B are the most abundant subtypes in the myocardium [56], whereas the α1D is the predominant and functional subtype in epicardial coronary arteries and smooth muscle cells [55]. Human epicardial coronary artery ECs express α1B-ARs that activate ERK and eNOS, and increase DNA synthesis [57], and could play a role in coronary vasodilation and angiogenesis.

Numerous studies show that total α1-AR expression remains stable or increases in the failing human heart [56,58–62], whereas β1-ARs reliably decrease [63,64], so that the fraction of total ARs consisting of α1-ARs increases substantially. In non-failing human myocardium, α1-ARs constitute 2–23% of total AR binding (mean of 5 studies 11%), whereas that percentage increases to 9–41% (mean 25%) in failing myocardium [56,58–62]. Levels of the α1A and α1B subtypes are undiminished in both the left ventricle (LV) and right ventricle (RV) of the failing human heart [56]. The decrease in β-ARs in HF is accompanied by an uncoupling of some beneficial pathways activated by β-ARs, including those that mediate positive inotropy [63,65]. In contrast, as in animals, α1-ARs appear to maintain their function in HF, as evidenced by the finding that the degree of positive inotropy induced by α1-AR stimulation can be equal to that induced by β-AR stimulation in failing human heart muscle [66,67].

Evidence from α1-AR gain of function in animal models

α1-AR GAIN OF FUNCTION USING PHARMACOLOGY (Table 1)

Early physiologic studies of the heart's response to α1-AR activation focused on the coronary arteries, where NE infusion causes vasoconstriction of epicardial coronary arteries, primarily or only in the setting of atherosclerosis (reviewed in [55]). Multiple studies also identify a positive inotropic response to α1-AR activation in humans [66–69], and some animals [70–73], though results vary according to species [74,75] and developmental stage [76], and are different in the normal mouse RV (negative inotropy) [76–78] and LV (positive inotropy) [73].

Subsequently, cell culture experiments using AR agonists identified a number of important functions of α1-ARs in cardiomyocytes, most notably the induction of hypertrophy and stimulation of transcription [79–87]. The initial experiments were conducted in NRVMs, though later work in cardiomyocytes from adult rat and cat confirmed the findings [88–93]. α1-AR stimulation, often with phenylephrine ("PE"), remains a standard model for assaying hypertrophic signaling, although it needs to be appreciated that PE can have substantial β-AR agonism. Further in vitro studies using AR agonists identified additional cardioprotective processes mediated by α1-AR activation, including energy production [94], preconditioning against hypoxia and calcium overload [95–98], and prevention of apoptosis and necrosis [4,27,99–102].

In vivo gain-of-function studies using pharmacology bolster the in vitro findings and demonstrate important biologic roles for cardiac α1-ARs. Chronic low-dose NE infusion in the mouse, cat, and dog stimulates adaptive hypertrophy, characterized by normal or

enhanced cardiac function, without increasing blood pressure, promoting fibrosis, or accelerating cell death [39,103–107].

α1-AR activation by NE or PE infusion in the isolated heart and in vivo also reliably ameliorates ischemia-reperfusion-induced apoptosis and necrosis in mouse, rats, dogs and rabbits [21,108–125]. Interestingly, methoxamine was ineffective in some studies [113,126], and effective in others [109,111]. α1-Agonism also protects against doxorubicin cardiotoxicity [102,127], and calcium overload [98]. Pleiotropic mechanisms implicated in these cardioprotective effects include ecto-5'-nucleotidase activation and increased adenosine release [96,108,111,128]; activation of ERK [27,129], K ATP channels [125], and protein kinase C [115,130]; increased heat shock proteins [116], β1-integrins [131], and fetal genes [130]; induction and activation of inducible nitric oxide synthase (iNOS) [124,132], superoxide dismutase (SOD) [95,97], cyclooxygenase-2 [132], and GATA-4 [102]; phosphorylation and inactivation of Bad [31,101]; and up-regulation of anti-apoptotic Bcl proteins [99,102,122].

A recent novel finding concerns α1-ARs in the RV. α1-ARs mediate a negative inotropic effect in the normal mouse RV, and a positive inotropic effect in the normal LV. However, in HF after myocardial infarction (MI), α1-AR stimulation causes positive inotropy in the RV [73]. This "switch" might be mediated partly by changes in coupling to myosin light chain kinase, though the details are under investigation. This finding might enhance the implications of α1-AR activation in chronic HF, as the development of RV failure in the setting of chronic left ventricular failure is known to be highly predictive of poor outcomes [133].

β-Blockers provide an unexpected example of α1-AR gain-of-function. NE and EPI signal predominantly through the β1-AR in the normal and failing heart, because β1-ARs are the most abundant cardiac AR, and have the highest affinity for NE and EPI [134]. In cultured adult mouse myocytes, NE or EPI *inactivate* ERK via β-ARs, whereas NE or EPI *activate* ERK via α1-ARs, in the presence of a neutral β-blocker, such as propranolol [135]. Since ERK activation by α1-ARs is cardioprotective [27], β-blockers might "work" in HF partly by unmasking beneficial α1-AR signaling, at the same time that they inhibit maladaptive β-AR pathways.

TRANSGENIC MOUSE α1-AR SUBTYPE GAIN OF FUNCTION (Table 2)

The limited number of pharmacologic agents specific for the three α1-AR subtypes prompted the creation of transgenic mouse models to explore which of the subtypes regulated these beneficial effects. Different labs used receptor cDNAs from different species, with varying activating mutations, and with MyHC or native receptor promoters to create mice with very different receptor levels. It is perhaps not surprising that the phenotypes vary.

In general, however, α1A-transgenics show enhanced contractility and cardioprotection without hypertrophy, even at extraordinarily high over-expression levels. In contrast, α1B-transgenics have variable hypertrophy without hypertension, and are predominantly maladaptive.

A constitutively active mutant (CAM) α1A causes preconditioning, when 2- to 3-fold over-expressed in heart with the endogenous mouse α1A promoter [136]. The WT α1A expressed in myocytes with the α-myosin heavy chain (α-MyHC) promoter causes increased contractility and ANF levels without hypertrophy, with 148- to 170-fold over-expression [137], and cardioprotection after coronary ligation or pressure overload, with 66-fold over-

expression [138,139]. However, long-term α1A over-expression (112- to 170-fold) causes fibrosis and early death [140].

α1B transgenic mice have less consistent results. A CAM α1B made with the α-MyHC promoter causes hypertrophy with 2- to 3-fold myocyte-specific over-expression [141,142], and worsens pathological hypertrophy after TAC [143], but reduces reperfusion arrhythmias [144]. A CAM α1B made with the endogenous mouse α1B promoter for systemic overexpression (2-fold cardiac) also causes hypertrophy, without increased blood pressure [145,146], but with decreased contractility [37]. A WT α1B with the same endogenous promoter causes variable hypertrophy and negative inotropy [145,147]. In contrast, a WT α1B 40- to 70-fold over-expressed in myocytes with the α-MyHC promoter shows no hypertrophy, but rather fetal gene induction, decreased inotropy, pathological response to PE, dilated cardiomyopathy, and early death [22,148–150].

Normal expression of the α1D subtype in heart is limited to coronary arteries and smooth muscle cells [36,37,151], and there are no formal reports of a vascular transgenic mouse [152].

Evidence from α1-AR loss of function in animal models (Table 3)

α1-Antagonists have negative effects on adaptive cardiac processes in vitro and in animal models in vivo [132,153–155] (Table 3), supporting the data from pharmacology gain of function (Table 1). However, the pharmacologic tools can have nonspecific effects, and are inadequate to distinguish α1-subtypes in vivo. The shortcomings of pharmacology and the inconsistencies of the transgenic mice prompted the creation of knockout (KO) mouse models for the three α1-AR subtypes (reviewed in [16]). Importantly, phenotypes vary markedly between mice that are on a mixed genetic background versus congenic. Furthermore, only a few studies analyze mice separately by sex, an essential precaution given sex differences in cardiovascular phenotypes [156].

Mice lacking the α1A on a mixed genetic background (FVB/N × 129SvJ) have normal heart size but low blood pressure (BP), and no vasopressor response to the α1A subtype agonist A61603 [50]. The pressor response to PE is normal [50]. In the congenic C57Bl/6J background, the α1A-KO has normal heart size and BP [157].

α1B-KOs created on a mixed background (C57Bl/6J × 129Sv) have normal heart size, and a decreased pressor response to α1-agonist infusion [107,158–160], whereas α1B-KOs on a congenic C57BL/6J background have small hearts [157]. Regardless of genetic background, α1B-KO mice have a normal blood pressure. The α1B-KO heart enlarges normally with TAC. However, a subpressor dose of PE, which causes an adaptive hypertrophy in WT mice, has no effect in α1B-KO mice [107].

α1D-KO mice in a mixed genetic background have normal hearts, but decreased blood pressure and reduced coronary vasoconstriction in response to PE infusion [37,160,161].

Mice lacking both the α1B and α1D in a mixed genetic background have a normal heart, but decreased blood pressure and a decreased pressor response to agonist infusion [160].

The double α1AB-KO has been characterized in a congenic C57BL/6J background. The double KO eliminates all cardiac α1-AR binding. A key role for ERK in the phenotype is suggested by the facts that activated ERK in the KO myocardium is reduced to 30% of WT, as assayed by phosphorylation of Elk1 in vitro by ERK immunoprecipitated from intact hearts, and PE no longer activates ERK and downstream kinases (p90RSK, p70S6K) in KO myocytes [25].

α1AB-KO mice have normal blood pressure, but males have decreased heart and myocyte hypertrophy during post-weaning development. Other organs are normal [25]. Contractility is normal by echocardiography in awake mice, but cardiac output is decreased due to lower stroke volume and bradycardia; contractility of isolated myocardium is abnormal; β-ARs are desensitized; and exercise tolerance is impaired [25,26,162].

After pressure overload by transverse aortic constriction (TAC), the α1AB-KO mice have worse dilated cardiomyopathy, HF, and increased mortality [25,26], confirming the importance of α1-ARs in cardioprotection. Mechanisms underlying this dilated cardiomyopathy include increased apoptosis, increased fibrosis, and failure to induce fetal and other genes [26]. Hypertrophy after TAC measured by heart and myocyte size is the same or greater in α1AB-KO mice as in WT mice, illustrating a dissociation between hypertrophy *per se* (unaffected) and fetal genes (not induced) [26].

Thus, the double α1AB-KO impairs the physiological hypertrophy of normal post-weaning development, and worsens pathological hypertrophy after TAC. Importantly, the double β-AR KO is opposite the double α1-AR KO. Double KO of the β1- and β2-ARs has no effect on developmental heart growth, but induces fetal genes in the basal state, and improves pathological hypertrophy after TAC [163,164].

Experiments using cultured cardiomyocytes from α1AB-KO mice provide insight into the mechanisms underlying the in vivo findings, revealing increased myocyte death with toxic stimuli, including β-AR stimulation, H2O2 and doxorubicin [25,27]. Adenoviral reconstitution of the α1A subtype in double KO myocytes rescues the phenotype, through a pathway that requires activation of ERK [27]. However, reintroduction of the α1B subtype does not rescue toxin-induced death of α1AB-KO myocytes [27]. Taken together, these data demonstrate that the α1A subtype is necessary and sufficient for myocyte protection, and that the mechanism is myocyte-autonomous and requires ERK activation.

We have made all combinations of α1-KOs congenic in C57Bl/6J, and find that heart size is smaller than WT in all genotypes lacking the B, whereas it is normal when the B is present, clearly implicating the α1B subtype in developmental hypertrophy ([157] and unpublished data).

Tentative summary of α1-AR subtype functions revealed in genetic mouse models

Although some results are conflicting, a general pattern emerges from genetically altered mouse models, wherein the α1A subtype mediates cardioprotection; the α1B stimulates developmental and α1-induced hypertrophy; and the α1D has a predominant role in vasoconstriction and maintaining blood pressure [16]. The α1A and α1B both mediate myocardial inotropic effects [78]. The α1A and α1B are not required for heart or myocyte enlargement after TAC, but are necessary for fetal gene induction.

Human α1-AR gain and loss of function

HUMAN α1-AR GAIN OF FUNCTION (Table 1)

Gain-of-function data in humans demonstrate adaptive and protective roles for cardiac α1-ARs, including positive inotropy and preconditioning. In non-failing hearts, β–ARs account for the vast majority of the catecholamine-induced increase in inotropy. However in failing hearts, α1-ARs can increase contractility equal to β̃-ARs [66,67]. As predicted by animal and cell models, α1-ARs also cause preconditioning against ischemic injury both in vitro and in vivo [165–168], and can improve cardiac performance in HF patients [169,170].

HUMAN α1-AR LOSS OF FUNCTION (Table 3)

Two large clinical trials provide loss-of-function data that support the benefit of cardiac α1-AR activation. The ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart ATtack) trial included an arm in which 24,000 hypertensive men and women received the non-selective α1-blocker doxazosin. The incidence of HF in the subjects who received the α1-blocker was twice as high as in those who received any of the other three antihypertensive agents, and the Data Safety Monitoring Board stopped the doxazosin arm of the trial prematurely [171]. Subsequent analysis confirmed that this excess harm persisted after adjustment for covariate risk factors, including blood pressure [172].

These results substantiated the findings of the earlier V-HeFT (Vasodilator-Heart Failure Trials), in which the non-selective α1-blocker prazosin was associated with a trend toward increased mortality, in contrast with the beneficial effects of other vasodilators [173]. Recently, a smaller retrospective study found evidence of increased HF hospitalizations in patients taking α1-blockers without concomitant β-blockers [174]. Phentolamine, a nonselective α-blocker, prevents ischemic preconditioning [175].

α1-Blockers might have off-target effects [176], but the maladaptive phenotype of the α1AB double KO mouse supports that the adverse results in the ALLHAT and V-HeFT trials were due to α1-AR inhibition itself, rather than some nonspecific drug effect.

Additional support for the concept that harm results from reducing α1-AR occupancy in HF arises from clinical trials evaluating the effect of sympatholysis [177]. The MOXSE and MOXCON trials (using moxonidine) [178–180] and BEST (using bucindolol) [181] all revealed harmful effects resulting from marked systemic reduction of NE levels. Given the beneficial effect of decreasing NE binding to β-ARs, these findings suggest that the observed harm might result from decreasing binding to α1-ARs below some critical threshold. Indeed, the α1AB double KO mouse indicates that the heart requires some degree of α1-AR activation by NE and/or EPI.

Translational potential of α1-AR agonists (Table 4)

As summarized above, abundant evidence from cell, animal and human studies indicates that activating cardiac α1-ARs is beneficial. α1-ARs are highly "druggable", and recruit numerous downstream adaptive and protective signaling mechanisms. Thus, α1-AR agonists could represent a novel approach to the treatment of myocardial diseases and HF. α1-AR augmentation of adaptive hypertrophy, cardioprotection, and positive inotropy might have multiple clinical applications, including acute myocardial ischemia, cardiotoxicity with cancer therapy, and chronic systolic HF. As previously mentioned, multiple studies have shown that α1-AR levels are either unchanged or increased in human HF [56,58–62]. Furthermore, myocardial α1-ARs are thought to be only 10% occupied by NE, even in HF [134], indicating the potential for additional activation by an exogenous agonist. The safety of α1-AR activation by an exogenous agonist is well established, as oral (midodrine) and intravenous (PE) agents are already in clinical use. In fact, a recent small clinical trial demonstrated a significant benefit associated with the use of midodrine in patients with advanced HF already receiving contemporary therapy [170].

Given the wealth of data in multiple models from many different labs over three-plus decades, it is important to consider reasons for possible resistance to the idea of α1-agonist therapy. Potential concerns and answers are summarized in Table 4.

First, α1B subtype over-expression in transgenic mice causes a maladaptive phenotype, or at least not adaptive, whereas the KO approach and pharmacology point to the α1A and α1B in

adaptive effects. We believe that pharmacology and the KOs provide the more reliable evidence, for reasons noted in Table 4, but the role of the α1B requires more study.

Second, α1-ARs are irrefutably linked to smooth muscle contraction, for example, in the vascular and GU systems, raising concerns of hypertension, angina, or prostatism with α1-agonist therapy. Against these possibilities is the key observation, repeated in many labs, that adaptive cardiac effects of α1-agonists occur at doses that do not increase BP, or cause myocardial ischemia. Furthermore, the α1D subtype appears to have a key role in smooth muscle contraction, but is not involved in adaptive cardiac effects, and thus could be avoided with α1A and/or α1B agonists. As with any systemic therapy, other potential extra-cardiac effects of an α1-agonist still need to be determined. Some might be favorable. For example, in the brain, there is evidence that α1-ARs might be neuroprotective [182,183]. KO of the α1B causes abnormal glucose metabolism and obesity [184], implying that an α1B agonist might have favorable metabolic effects, opposite to the view that α1-blockers have favorable metabolic profiles [185].

The proven efficacy of carvedilol in the treatment of HF [186] would also seem to argue against the therapeutic benefit of an α1-AR agonist, since carvedilol blocks both α1- and β-ARs. However, it is important to recognize that the α1-blocking properties of carvedilol extinguish shortly after initiation of therapy [187,188]. In fact, chronic carvedilol use actually increases the blood pressure response to PE infusion in HF patients [189]. Thus the benefits associated with chronic carvedilol use are likely related to β-blockade, not α1-blockade, as well as to a number of salutary effects unrelated to ARs [155,190–194].

Finally, α1-ARs are associated with "pathological" hypertrophy, because they are coupled to Gq, and induce fetal genes in rodent models. On the contrary, the studies reviewed here indicate clearly that α1-ARs stimulate adaptive and protective effects in heart, not pathological. For reasons outlined in Table 4, it is not appropriate to extrapolate from Gq over-expression to the conclusion that all cardiac Gq-coupled receptors mediate pathology. Likewise, induction of fetal genes, such as ANF, BNP, skeletal α-actin, and β-MyHC is considered a hallmark of pathological hypertrophy. However, it is not clear that induction of these genes is causal, or even maladaptive. For instance, one fetal gene, BNP is even used as therapy in HF (nesiritide, Natrecor). As another example, skeletal α-actin is increased by 5-fold in BALB/c mouse hearts, yet cardiac structure is normal and contractility is enhanced [195]. Finally, recent work suggests that the prototypical fetal gene, β-MyHC, is induced by pressure overload only in a minor population of myocytes, and that the cells with β-MyHC are smaller than those without β-MyHC, not larger [196]. The low fraction of myocytes expressing β-MyHC casts some doubt on contractile function significance, and the small cell size suggests that β-MyHC is not a marker for cell hypertrophy.

Future Directions

Given the valid concerns regarding the activation of non-cardiac α1-ARs with a putative agonist, ongoing studies will need to focus on assuring cardioselectivity. Cardioselective α1-AR activation with low doses of systemically delivered agonists appears to be feasible and beneficial, though careful investigation for previously undetected systemic effects is required.

An alternate approach to cardioselectivity would be the use of a subtype-selective agent for activation of myocardial α1A or α1B-ARs, thereby eliminating undesirable coronary vasoconstriction by activation of α1D-ARs. Indeed, our lab showed recently that a low, nonhypertensive dose of an α1A-selective agonist (A61603) prevents doxorubicin-induced cardiomyopathy and death in a mouse model of HF [127]. Future efforts should focus on further unraveling the roles of the α1A and α1B subtypes in the heart, to determine whether

both should be targeted. Importantly, the distribution of the cardiac α1-AR subtypes appears to be identical in rodents and humans, suggesting that rodent models could offer accurate platforms for assessing the cardioselectivity and safety of novel therapies, as well as for the further elucidation of mechanism.

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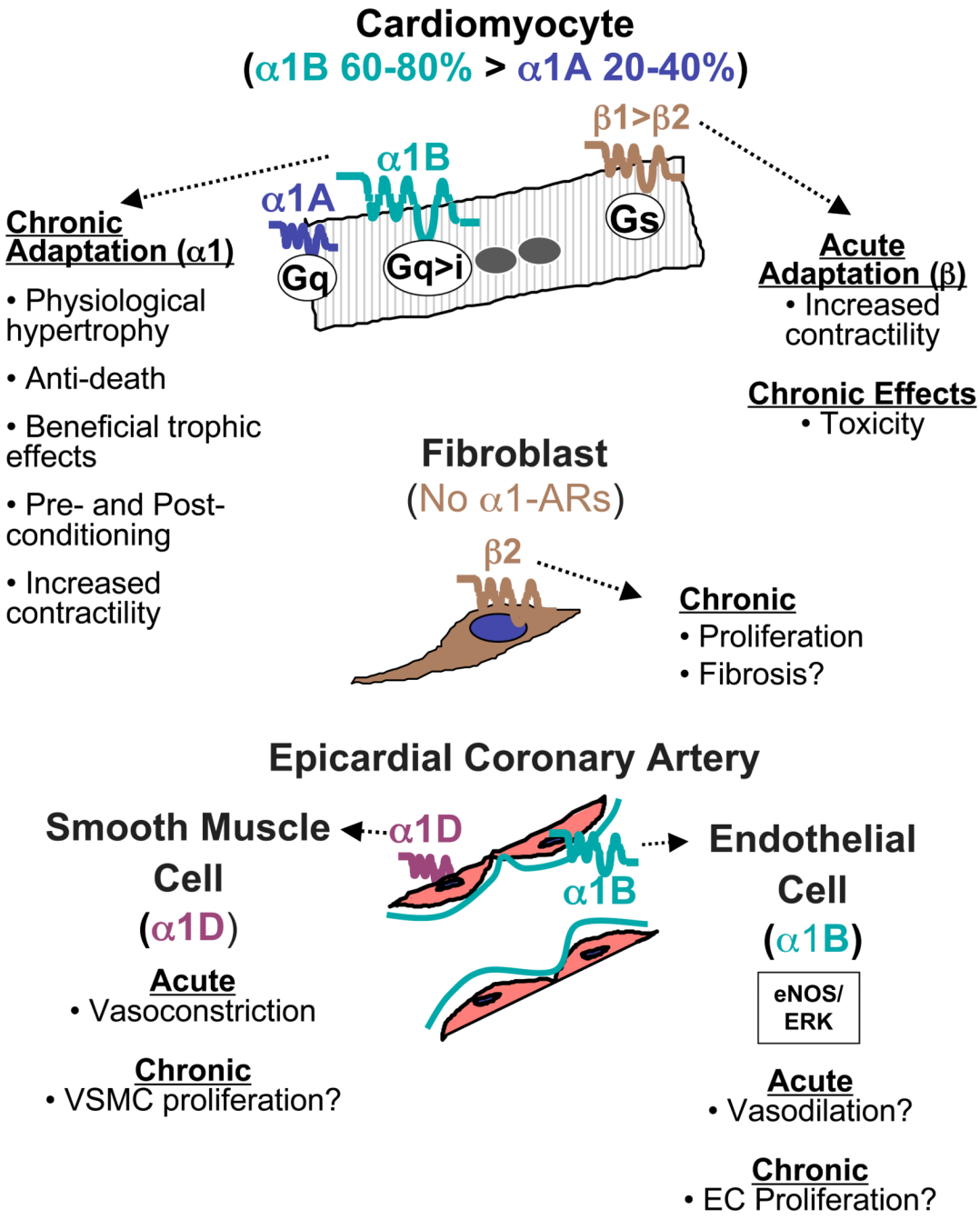

Figure 1.
Summary of α1-AR subtypes and functions in different cardiac cells.

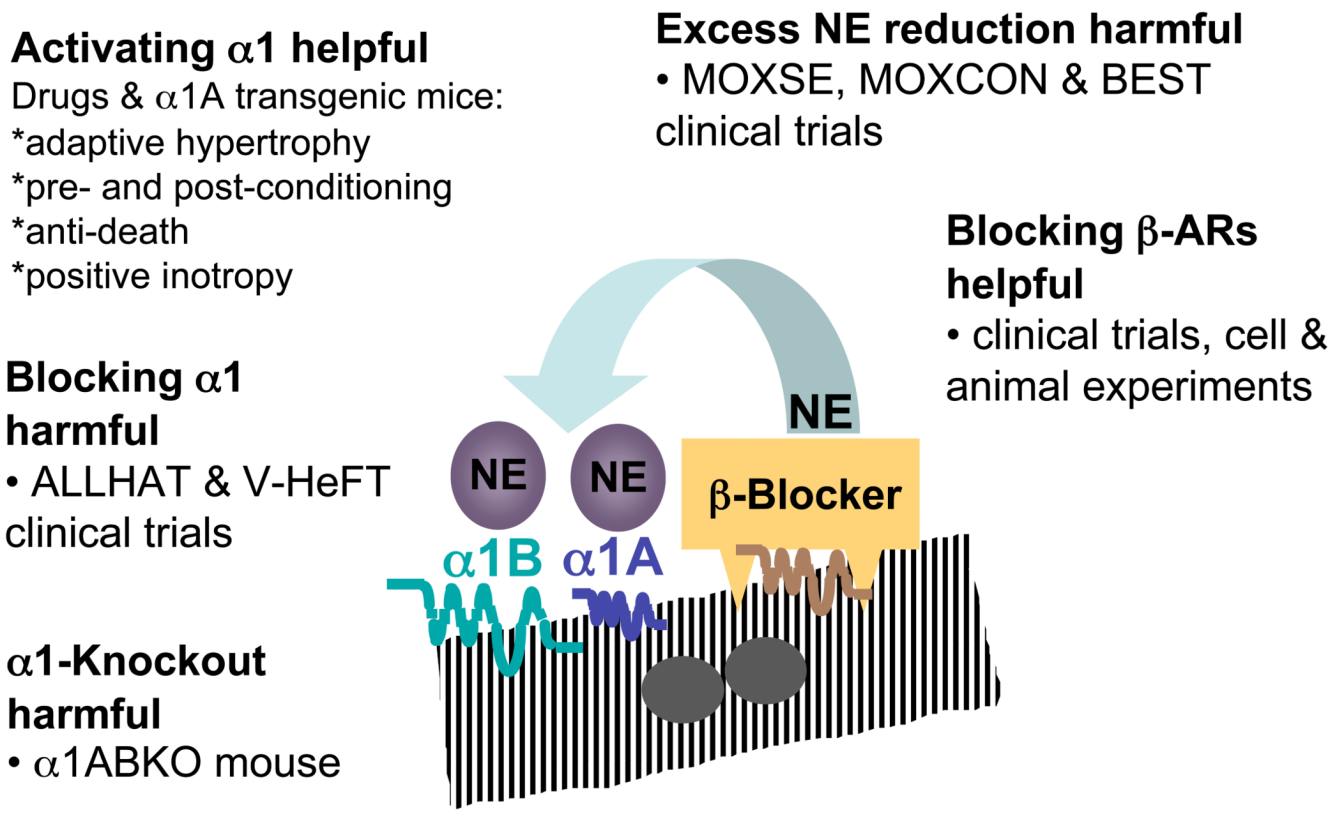

Figure 2.
Summary of α1-AR cell, animal, and clinical loss and gain of function studies.

Table 1

α1-AR Gain of Function Models: Pharmacology

IN VITRO MYOCYTES		
System	**Agonist**	**Findings & References**
NMVMs	PE	↓ Cell death with prolonged hypoxia [97]
NRVMs	NE, EPI, PE	↑ Myocyte HT, fetal gene induction [79–87]
NRVMs	PE	↓ Apoptosis [4,99–101]
NRVMs	PE	↓ Doxorubicin toxicity [102]
NRVMs & ARVMs	NE, methoxamine	↓ Cell death with hypoxia-reoxygenation [95,96]
ARVMs	NE, PE, EPI	↑ Myocyte HT, protein synthesis & cell survival [89–91]
AMVMs	PE	↓ Apoptosis & necrosis caused by β-AR agonism, H_2O_2 or doxorubicin; requires ERK signaling [27]
AMVMs	NE, EPI	↑ ERK with β-blocker, via α1-ARs [135]
ACVMs	PE	↑ Myocyte HT, fetal gene induction [88,92,93]
IN VITRO PERFUSED HEART		
Species	**Agonist**	**Findings & References**
Rat	EPI	↑ Glycolysis in heart [94]
Rat	EPI	↑ Protein synthesis in heart [89]
Rat	PE	↓ Ca^{++} injury in Ca^{++} depletion-repletion [98]
Rat	NE, PE	↓ global I-R injury [21,110,114,115,120]
Rabbit	PE	↓ regional I-R injury [113]
ANIMAL IN VIVO		
Species	**Agonist, Model**	**Findings & References**
Mouse	PE, A6 infusion	Physiologic HT without ↑ BP [107,127]
Mouse	PE in vivo & global ischemia in perfused heart	↓ I-R injury [124]
Mouse	NE & LAD ligation	↑ Right ventricular inotropy [73]
Mouse	PE, A6 infusion & Doxorubicin	Prevents CM, decreases apoptosis [102,127]
Rat	NE & regional I-R	↓ I-R injury and arrhythmia [125]
Rat	NE in vivo & global ischemia in perfused heart	↓ I-R injury (delayed cardioprotection) [116,117,130]
Rabbit	PE in vivo & global ischemia in perfused heart	↓ I-R apoptosis & necrosis [122,123]
Rabbit	PE & hypoxic cardiac arrest	PE infusion preconditions donor hearts [119]
Rabbit	NE, Tyr & LAD ligation	↓ I-R injury [112,118,128]
Cat	NE infusion	Physiologic HT without ↑ BP [39]
Dog	NE, Methoxamine & LAD ligation	↓ I-R injury [109,111,121]
Dog	NE infusion	Physiologic HT without ↑ BP [103–105] [106]
HUMAN		
System	**Agonist, Model**	**Phenotype/Findings**
Atrium in vitro	PE	↑ Ischemic preconditioning [166–168]

IN VITRO MYOCYTES		
System	**Agonist**	**Findings & References**
Ventricle in vitro	PE	↑ Ischemic preconditioning [165]
Ventricle in vitro	NE	α1-AR = β-AR inotropy in failing heart [66,67]
In vivo	Methoxamine	Improved exercise performance in HF [169]
In vivo	Midodrine	↓ Symptoms, ↑ EF, ↓ hospitalizations in HF [170]

A6 = A61603 (α1A-selective agonist); ARVM = adult rat ventricular myocytes; ACVM = adult cat ventricular myocytes; AMVM = adult mouse ventricular myocytes; CM = cardiomyopathy; EPI = epinephrine; HT = hypertrophy; I-R = ischemia-reperfusion; LAD = Left Anterior Descending coronary artery; NE = norepinephrine; NMVM = neonatal mouse ventricular myocytes; NRVM = neonatal rat ventricular myocytes; PE = phenylephrine; Tyr = tyramine (releases NE)

Table 2

α1-AR Gain of Function Models: α1 Subtype Transgenics

Subtype	α1 Receptor (fold level) with Promoter	Findings & References
A	CAM rat A (2×) with mouse α1A	Protection from ischemia [136]
A	WT rat A (148–170×) with rat αMyHC	↑ Contractility, no HT [137]
A	WT rat A (66×) with rat αMyHC	↑ Protection against myocardial infarction and transverse aortic constriction [138,139]
A	WT rat A (112–170×) with rat αMyHC	↑ Fibrosis & death in aged mice [140]
B	CAM B hamster (3×) with mouse αMyHC/	↑ HT, normal BP [141,142]; ↓ I-R arrhythmias [144]; no preconditioning [197]; ↑ cardiomyopathy after TAC [143]
B	CAM or WT hamster (2×) with mouse α1B	↑ HT, ↓ BP, ↓ HR, autonomic dysfunction [145,146]; no preconditioning [136]; ↓ inotropy [37,147]
B	WT hamster B (40–70×) with mouse αMyHC	No HT, ↑ fetal genes, ↓ β-AR response, ↑ receptor coupling to Gi, ↑ GRK2, ↓ inotropy, maladaptive HT with PE, dilated cardiomyopathy in aged mice [22,148–150]

CAM = constitutively activated mutant receptor; HT = hypertrophy; WT = wild type receptor

Table 3

α1-AR Loss of Function Models

ANIMAL PHARMACOLOGY

Species	α1-Antagonist & Model	Findings & References
Rat	Prazosin & hemorrhage	↑ I-R injury with α1-blockade [154]
Rabbit	CEC & I-R	↑ I-R injury with α1B-blockade [153]
Rabbit	Doxazosin & rapid pacing	↓ Efficacy of β-blockade with α1-blockade [155]
Pig	Prazosin & I-R	↑ I-R injury with α1-blockade (second window of preconditioning) [132]

KNOCKOUT MICE

α1 Subtype or Gene	Model	Findings & References
A	In vivo: basal & agonist infusion	Mixed genetic background: normal heart size & function, ↓ resting BP and pressor response to α1A agonist [50]
		Congenic: normal heart size and BP [157]
B	In vivo: basal, agonist infusion, TAC	Mixed background: normal heart size, normal BP, ↓ pressor response [107,158–160]; normal HT with TAC, but ↓ HT with subpressor PE [107]
		Congenic: small heart, normal BP, sinus bradycardia [157]
D	In vivo: basal, agonist infusion, salt loading	Mixed background: normal heart size, ↓ resting BP, ↓ pressor response, ↓ hypertension with salt loading [160,161]; ↓ coronary vasoconstriction with PE [37]
		Congenic: normal heart size, ↓ resting BP (unpublished data)
A & B	In vivo: basal, exercise, TAC	Congenic: small heart & myocytes (males), normal BP, bradycardia, ↓ exercise, ↓ ERK [25]; ↓ myocardial contractility [162]; normal HT with TAC, but ↓ fetal gene induction, ↑ apoptosis and fibrosis, ↑ cardiomyopathy, ↑ HF, and ↑ death [26]
A & B	In vitro	↓ ERK activation with PE, but not ET or PMA [25]; ↑ apoptosis [26]; α1A but not α1B subtype rescues ABKO myocyte survival via ERK [27]
B & D	In vivo: basal, agonist infusion	Mixed: normal heart, ↓ BP, ↓ pressor response [160]
		Congenic: small heart, normal BP (unpublished data)
A & D	In vivo: basal	Congenic: normal heart size, normal BP (unpublished data)
A, B, & D	In vivo:basal	Congenic: small heart, normal BP (unpublished data)
TH, DBH	In vivo:basal	NE required for cardiac development in utero [198–200]

HUMAN RANDOMIZED CLINICAL TRIALS

Subtype	Test Drug	Findings & References
All ARs	moxonidine or bucindolol	Sympatholysis with ↓ NE (↓ α1 occupancy) increases HF [177–181]
A, B, D	prazosin	Non-selective α1-blocker trend toward ↑ mortality [173]
A, B, D	doxazosin	Non-selective α1-blocker ↑ incident HF [171,172,201]
A, B, D	phentolamine	Non-selective α-blocker ↓ preconditioning [175]

↑ and ↓ = relative to WT mice or control treatment; BP = blood pressure; CEC = chloroethylclonidine; DBH = dopamine beta-hydroxylase; ET = endothelin; HT = hypertrophy; I-R = ischemia-reperfusion; NE = norepinephrine; PE = phenylephrine; PMA = phorbol myristate acetate; TH = tyrosine hydroxylase

Table 4

Concerns & Answers About Potential α1-Agonist Therapy

Concerns	Answers & References
Transgenics: α1B-AR over-expression can be maladaptive (Table 2).	Pharmacology and KOs are congruent on adaptive effects (Tables 1 & 3), and germline KOs are predictive of drug effects in humans [19,202]; high-level over-expression is non-physiological; over-expressed or constitutively activated α1- and β-ARs can signal differently from endogenous receptors [203–205]; over-expressed receptors can inhibit other GPCRs by "stealing" G proteins [206,207]
Hypertension: α1-receptors cause vasoconstriction, and α1-agonists will cause hypertension.	Cardiac trophic effects occur at low, cardioselective doses that do not increase blood pressure [39,103–107,127]
Angina: α1-receptors constrict coronary arteries, and an agonist will cause angina.	α1-Receptors do not constrict normal coronary arteries [208]; smooth muscle contraction occurs at higher doses than required for cardiac trophic effects [36,127]; the α1D is the subtype present in coronary smooth muscle, and could be avoided with selective agonists [36,37,55].
Prostatism: α1-receptors constrict prostate smooth muscle, and agonists will cause urinary retention or prostate symptoms.	Cardiac effects might occur at doses below those activating prostate smooth muscle, as with vascular; α1D antagonists are effective to treat prostate symptoms [209], and the α1D subtype could be avoided with α1A- and/or α1B-selective agonists.
Carvedilol: carvedilol blocks α1-receptors and is efficacious in heart failure.	Carvedilol in chronic therapy does not block α1-effects [187,188], and might even enhance them [189].
Hypertrophy: α1-receptors cause hypertrophy, which is bad.	α1-Receptor agonists stimulate an adaptive or "physiological" hypertrophy, with no fibrosis, and normal or improved cardiac function [39,103–107,127].
Fetal genes: α1-receptors increase β-MyHC and other fetal genes in rodent models, and these are hallmarks of pathological hypertrophy.	It is arguable whether fetal gene induction is maladaptive, or causative in pathological hypertrophy [195,196,210,211]
Gq: α1-receptors are coupled to Gq, and Gq over-expression in mice causes pathological hypertrophy.	Two-fold, life-long α-MyHC-driven Gq over-expression in mice has no phenotype [212,213], and 5-fold adult myocyte over-expression does not cause pathology [214]; 2-fold increases in endogenous Gq are the maximum seen in heart failure [215,216], and the Gq is shared among many cardiac cells and receptors in those cells.