

The roles of α_{1A} - and α_{1B} -adrenergic receptors in heart: insights from studies of genetically modified mice

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Summary

1. A number of mouse strains have been prepared in which different subtypes of the α_1 -adrenergic receptor (α_1 -AR) are overexpressed or deleted. The phenotypes of the animals generated vary depending on whether the receptors are expressed specifically in heart or generally throughout the animal, but some overall conclusions can be drawn.

2. Heightened activity of α_{1B} -ARs by overexpressing the receptors leads to depressed contractile responses to β -AR activation, which may be related to activation of the inhibitory G protein, Gi. In contrast, α_{1A} -AR cause substantially heightened contractility when overexpressed in heart.

3. Overexpressed α_{1B} -ARs predispose hearts to hypertrophy and worsen heart failure caused by pressure overload, whereas increased α_{1A} -AR expression does not influence hypertrophic responses, and furthermore improves outcomes after pressure overload or myocardial infarction.

4. α_{1A} -ARs mediate a preconditioning action to improve functional recovery after acute ischaemic insult, whilst α_{1B} -ARs are ineffective. Both subtypes appear to protect from inositol(1,4,5)trisphosphate (Ins(1,4,5)P₃) generation and arrhythmogenesis in early post-ischaemic reperfusion.

5. Whilst some of the protective effect of heightened α_{1A} -AR drive may be related to their enhanced contractility, it is also possible that α_{1A} -ARs protect from cardiomyocyte apoptotic responses.

Introduction

The heart's most obvious function is to contract rhythmically and in a controlled manner, but it must also be able to increase in size to accommodate changes during development, chronic exercise or when faced with a pathological stimulus. Both contractility and growth are influenced by the sympathetic nervous system that modifies heart function through activation of adrenergic receptors (ARs). All AR family members are seven transmembrane receptors that signal *via* interaction with heterotrimeric G proteins. ARs have been classified into 2 major isoforms, α and β initially on pharmacological criteria, but more recently the genes for the different receptor subtypes have been cloned. Both of these isoforms are further classified into subtypes as shown in Figure 1. Under physiological conditions, the heart responds most importantly through β -AR mediated pathways that acutely increase rate and force of contraction and can also influence cardiac size

through hypertrophic growth in the longer term.¹ Cardiomyocytes express α_1 -ARs but not α_2 -ARs. Whilst α_1 -ARs are not generally considered major regulators of cardiac function under physiological conditions, they have been thought to exert more influence under some pathological circumstances. Hearts of most species studied express both α_{1A} - and α_{1B} -ARs at the protein level. The α_{1B} -AR subtype predominates in rodents, whereas α_{1A} -ARs are the major subtype in human heart.²⁻⁴ Both of these subtypes couple *via* the heterotrimeric G protein Gq to phospholipase C (PLC) β isoforms⁵ and thus both would be expected to cause activation of protein kinase C (PKC) isoforms and possibly to perturb localized Ca²⁺ signalling *via* generation of Ins(1,4,5)P₃.⁶ To date, major differences in downstream signalling have not been reported, although the lack of sufficiently selective drugs may have made such experiments difficult. On this basis, α_{1A} - and α_{1B} -ARs would have been expected to induce similar effects in the myocardium. However, this view has been substantially challenged by recent studies where the two receptor subtypes were overexpressed in different transgenic models.

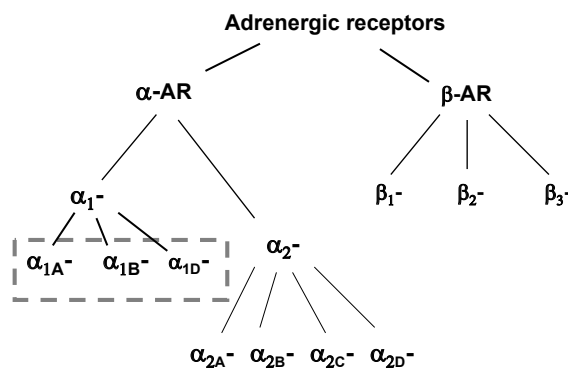


Figure 1. The adrenergic receptor family of G protein coupled receptors. The boxed area shows the α_1 -adrenergic receptor subtypes that are the focus of this review.

The transgenic mouse models

Two different transgenic mouse lines were prepared with wild type (WT) α_{1B} -ARs overexpressed under an α -myosin heavy chain (α -MHC) promoter to ensure expression in ventricle in the post-natal heart. The hearts overexpressed the α_{1B} -AR by 20-40 fold above the endogenous content of total α_1 -ARs (i.e. both α_{1A} - and

α_{1B} -).⁷ The higher overexpressing strain was shown to have somewhat heightened basal PLC activity, but PLC responses to α_1 -AR agonists were not evaluated. Mice were also generated to express a constitutively active (CA) α_{1B} -AR in heart (CA α_{1B} -AR). Constitutive activity was achieved by making three point mutations in the third intracellular loop of the hamster receptor (R²⁸⁸/K, K²⁹⁰/H, A²⁹³/L) and the mutant receptor was again expressed under an α -MHC promoter.⁸ Hearts from these animals showed only 2-3 fold increases in total α_1 -AR content, but had substantially heightened basal PLC activity as well as enhanced responses to α_1 -AR agonists.⁹ In addition to these lines with the α_1 -ARs overexpressed selectively in heart, transgenic lines have also been prepared with the wild type and constitutively active mutant α_{1A} - and α_{1B} -ARs overexpressed under their own promoters.¹⁰⁻¹²

As well as mice with increased α_1 -AR expression, knockout mice have also been prepared for all three α_1 -AR subtypes and these mice have been cross bred to generate double knockouts.¹³⁻¹⁵ To date, these have been general knockouts, rather than cardiac-specific knock-outs, and so receptor depletion would be expected to alter cardiac function both directly and indirectly by central and vascular actions.

Contractile responses

Under physiological conditions, increases in contractile rate and force in response to sympathetic activation are mediated primarily by β -ARs and any influence of α_1 -ARs on these responses is generally minor. So it was not surprising when studies using hearts overexpressing α_{1B} -ARs did not show enhanced contractility. Hearts overexpressing the WT α_{1B} -ARs actually showed a depression of the contractile response to β -AR stimulation, possibly because the highly overexpressed α_{1B} -ARs activate Gi sufficiently to limit β -AR signalling.^{7,16} Hearts expressing the CA α_{1B} -ARs under the α -MHC promoter did not show this inhibitory action, presumably because their expression level is lower and so interference from activated Gi would be expected to be minimal. However overexpression of CA α_{1B} -ARs under their own promoter did result in depressed contractile responses to β -AR stimulation and substantially reduced β_1 -AR density. The different phenotypes observed when α_{1B} -ARs were expressed under an α -MHC or the endogenous promoter may reflect developmental effects, as the mice with generalised overexpression show evidence of autonomic failure and neurodegeneration.¹⁰

In marked contrast to hearts expressing α_{1B} -ARs, hearts overexpressing α_{1A} -ARs have substantially heightened contractile responses.¹⁷ Characteristically this involves increases in systolic function without heightened diastolic function. In the very highly expressing strains (180 fold overexpression) the heightened contractility decreased by 6 months of age, but no such loss was observed in lower expressing strains.¹⁸ To date, the signalling pathways responsible for the heightened contractility remain unidentified, but clearly the critical

factors must be selectively regulated by α_{1A} - but not α_{1B} -ARs.

In apparent contradiction to these findings, hearts from the α_{1A} - , α_{1B} -AR double knock out mice (ABKO) showed heightened ventricular function in Langendorff preparations as well as in isolated right ventricular trabeculae.¹⁹ However, the enhanced pressure response could not be mimicked by α_1 -AR antagonists in WT heart preparations, showing that the endogenous α_1 -ARs do not exert an acute negative inotropic action. The data suggest rather that the endogenous α_1 -ARs mediate chronic trophic effects on the heart that negatively modulate contractile performance, possibly *via* receptors other than those expressed on cardiomyocytes. This might explain why α_{1A} -ARs overexpressed under their own promoter reduce contractile responses, whereas cardiac-targeted overexpression results in heightened contractility.

Hypertrophic growth responses

Activation of α_1 -ARs in neonatal rat cardiomyocytes is a classic model of cardiac hypertrophy that has provided much of the available information about cardiac growth signalling pathways. Studies from our laboratory, as well as others, demonstrated increased expression of α_{1A} -ARs in hypertrophied rat heart²⁰ and in the isolated myocyte model²¹ leading to the idea that hypertrophy was most likely mediated primarily by the α_{1A} -AR subtype. However, heightened activity of α_{1B} -ARs, by expressing a CA- α_{1B} -AR in heart, was shown to exacerbate hypertrophic responses to pressure overload, leading to heart failure and premature death.²² In the absence of a hypertrophic stimulus, hearts from these animals were not larger than WT in our laboratory,^{9,22} although others have reported a very slight hypertrophy (~10%).⁸ Mice overexpressing either WT or CA α_{1B} -ARs under the endogenous promoter showed clear cardiac hypertrophy. As the mice showed reduced, rather than heightened, blood pressure, this was most likely a direct cardiac action of the α_{1B} -AR.¹⁰

In marked contrast, overexpression of α_{1A} -ARs did not increase heart size, did not enhance pressure overload hypertrophy and did not hasten the development of heart failure.^{17,23} In fact, heightened α_{1A} -ARs activity improved survival.²³ These results were surprising for several reasons. First, downstream signalling pathways have generally been considered to be similar for the two receptor subtypes. Second, as mentioned above, previous data from experiments in rat had pointed to an important role for the α_{1A} -AR subtype in hypertrophy. Third, both α_{1A} - and α_{1B} -ARs activate Gq, and Gq is a well established initiator of cardiac growth *in vivo* and in cardiomyocyte models.²⁴

The marked selectivity of cardiac growth responses for the α_{1B} -AR over the α_{1A} -AR subtype indicates either that some critical factor is selectively regulated by the α_{1B} -AR, or alternatively that α_{1A} -ARs activate growth inhibitory pathways. This latter explanation seems unlikely because the degree of hypertrophy seen in the α_{1A} -AR overexpressing animals was identical to, not lower than, that in WT after pressure overload.²³ Identifying signalling

intermediates differentially regulated by α_{1A} - and α_{1B} -ARs may thus help in identifying factors that are truly critical to the growth response.

Interestingly, hearts from animals in which both α_{1A} - and α_{1B} -ARs had been knocked out were smaller than WT hearts, implying a permissive role for one or both of these subtypes in postnatal physiological hypertrophy.¹⁵ These animals also have exercise intolerance, further supporting this view. However, pathological hypertrophy induced by pressure overload was similar in the two strains, providing further evidence for differences in signalling pathways responsible for physiological and pathological hypertrophy as has been suggested from other studies.^{25,26}

Thus, we can conclude that pathological hypertrophy associated with pressure overload is influenced by α_{1B} -ARs, whereas the physiological hypertrophy associated with postnatal growth may involve both receptor subtypes.

Myocardial ischaemic injury

In the case of recovery from ischaemic injury, studies using transgenic mice with α_{1A} - and α_{1B} -ARs overexpression under either their endogenous promoters or the α -MHC promoter have provided essentially similar insights. Heightened activity of α_{1B} -ARs, achieved by overexpressing the constitutively active mutant did not alter myocardial ischaemic injury as determined by infarct size or functional recovery.^{11,27} This might imply a failure of the α_{1B} -ARs to precondition the hearts. Increased α_{1A} -AR activity, in contrast, improved functional recovery in the short term and provided longer term protection of the myocardium from the progression to heart failure.^{11,28} Hearts used in the studies of Du *et al.* overexpressed the wild type α_{1A} -AR under an α -MHC promoter.²⁸ These hearts have substantially enhanced contractility and this may have improved functional recovery after ischaemic insult. However, the hearts used in the study of Rorabaugh *et al.* where CA α_{1A} -ARs were expressed under an α_{1A} -AR promoter, actually had depressed contractile function under basal and β -AR stimulated conditions, and therefore any post-ischaemic protection may reflect a preconditioning mechanism.¹¹

Ischaemia/reperfusion arrhythmias

Our previous studies have shown that reperfusion of rat or mouse hearts after brief periods of ischaemia causes the generation of large amounts of $\text{Ins}(1,4,5)\text{P}_3$ that appear to be essential for the development of arrhythmias in early reperfusion.^{29,30} Overexpression of either α_{1A} -ARs or α_{1B} -ARs increases PLC responses to α_1 -AR agonists, although the α_{1A} -AR overexpressing strains show much stronger enhancement (Figure 2). Neither strain appears to produce large amounts of $\text{Ins}(1,4,5)\text{P}_3$ in response to stimulation under physiological, normoxic, conditions.⁹ WT mice subjected to brief periods of ischaemia and reperfusion generate large amounts of $\text{Ins}(1,4,5)\text{P}_3$ transiently, and this $\text{Ins}(1,4,5)\text{P}_3$ appears to be essential for the development of reperfusion arrhythmias in these mice. Expression of CA α_{1B} -ARs while increasing PLC responses

in normoxia, actually prevented PLC activation by noradrenaline during post-ischaemic reperfusion.⁹ These receptors also protected against reperfusion arrhythmias, ventricular tachycardia and ectopic beats in this mouse strain. Thus we concluded that the α_{1B} -ARs had protected the myocardium against reperfusion arrhythmias, presumably by a preconditioning mechanism. In this case preconditioning appears to be selective for arrhythmogenic responses because the α_{1B} -ARs did not reduce infarct size or improve functional recovery after brief ischaemia.^{11,27}

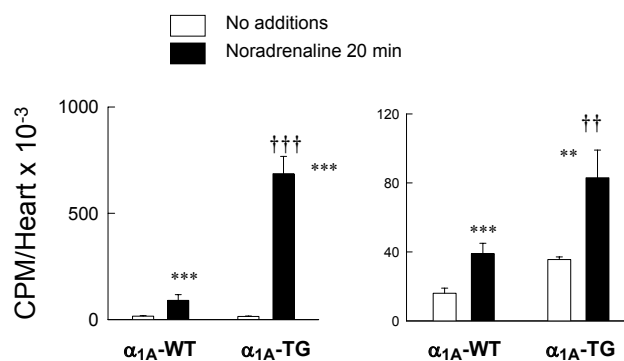


Figure 2. Phospholipase C responses in hearts from α_{1A} - and α_{1B} -AR overexpressing transgenic mice. Isolated perfused [³H]inositol-labelled mouse hearts were stimulated with 100 μM noradrenaline (plus 1 μM propranolol) for 20 min in the presence of 10 mM LiCl to block [³H]inositol phosphate metabolism. [³H]inositol phosphates were extracted and quantified by anion-exchange HPLC. Values shown are total [³H]inositol phosphates, mean \pm SEM, $n=6$.

** $p < 0.01$

*** $p < 0.001$ relative to no additions

†† $p < 0.01$

††† $p < 0.001$ relative to WT animals

Interestingly, overexpression of α_{1A} -ARs also prevented $\text{Ins}(1,4,5)\text{P}_3$ generation in early post-ischaemic reperfusion. However, in this case overall PLC activity was actually heightened by the overexpressed α_{1A} -ARs but, despite this, $\text{Ins}(1,4,5)\text{P}_3$ generation was prevented. These findings imply that both α_1 -AR subtypes can provide protection under ischaemia/reperfusion conditions but that this involves different mechanisms.

Cardioprotection and apoptotic responses

Mice with cardiac-targeted overexpression of α_{1B} -ARs develop premature heart failure either after pressure overload or with ageing. Thus the α_{1B} -AR does not appear to provide protection from cardiomyocyte death.^{16,22} The α_{1A} -AR overexpressing strains, in contrast, show functional improvement after myocardial infarction or following pressure overload.²³ In the case of the cardiac targeted- α_{1A} -AR transgenics, this may in part reflect heightened contractility. However, the hearts from animals

Table 1. Phenotypes of mice with genetic alterations in α_1 -adrenergic receptor expression.

| Receptor subtype | Promoter | Contractility | Hypertrophy | Ischaemic injury | Reperfusion arrhythmias | References |
|-------------------------|---------------|-----------------------------|-------------|------------------|-------------------------|------------|
| α_{1A} -AR OX | α -MHC | Increased | No effect | Decreased | Decreased | 1-3 |
| CA α_{1A} -AR OX | Endogenous | Inh. β -AR | No effect | Decreased | Decreased | 3 |
| α_{1B} -AR OX | α -MHC | Depressed, Inh. β -AR | Increased | Not reported | Not reported | 4 |
| α_{1B} -AR OX | Endogenous | Depressed, Inh. β -AR | Increased | No effect | Not reported | 3,5 |
| CA α_{1B} -AR OX | α -MHC | No effect | Increased | No effect | Not reported | 6,7 |
| CA α_{1B} -AR OX | Endogenous | Inh. β -AR | Increased | No effect | Not reported | 3 |

Available data from several transgenic lines that overexpress α_1 -ARs under either the α -MHC (cardiac-specific) promoter or their endogenous promoters. CA is constitutively active. OX is overexpression, Inh is inhibition.

expressing CA α_{1A} -ARs under their own promoter showed no enhanced contractility and these also were protected. Thus, it seems possible that the α_{1A} -AR directly opposes cell death responses. In agreement with this suggestion, mice with double knockout of α_{1A} - and α_{1B} -ARs had high mortality after pressure overload even though they have increased, rather than decreased, contractility.³¹

Conclusions and future directions

Studies using transgenic animals have demonstrated that the two α_1 -AR subtypes expressed in heart are functionally distinct (Table 1). To date, the data imply that α_{1B} -ARs are associated with growth and α_{1A} -ARs with contractility, and possibly with cardio-protection. The knock-out strains currently available involve total knock-out of the AR subtypes and thus many of the cardiac changes observed in these animals may relate to loss of vascular or central α_1 -ARs. Similar problems exist with the strains where the receptors are overexpressed under their own promoters. Strains where the receptors are overexpressed under an α -MHC promoter avoid these particular problems. The problem, however, remains that the receptors are expressed in ventricle continually from birth and in the atria before birth. Thus, some of the phenotypes observed in the adult animals may relate to developmental effects of the chronically heightened receptor expression. These reservations can be addressed by the development of cardiac-specific knock-out strains and strains in which the α_1 -AR is overexpressed under a inducible promoter allowing acute turning on or off of the transgene in adult animals.

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