Cardiac 7-transmembrane-spanning domain receptor portfolios: diversify, diversify, diversify

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Enhanced signaling in myocytes by the G protein Gq has been implicated in cardiac hypertrophy and the transition to heart failure. α1-Adrenergic receptors (α1-ARs) are members of the 7-transmembrane-spanning domain (7-TM) receptor family and signal via interaction with Gq in the heart. The specific effects of a loss of α1-AR signaling in the heart are explored by O’Connell et al. in this issue of the JCI (see the related article beginning on page 1005). Paradoxically, gene ablation of the α1A and α1B subtypes in mice results in a maladaptive form of reactive cardiac hypertrophy from pressure overload, with a predisposition to heart failure. Thus signaling to the α1-AR (compared with signaling from other receptors such as angiotensin receptors, which also couple to Gq) appears to be specifically required for a normal hypertrophic response. This represents another example of how receptors that share common G proteins have diversified, developing unique signaling programs. These findings may have particular clinical relevance because of the widespread use of α1-AR antagonists in the treatment of hypertension and symptomatic prostate enlargement.

It is now recognized that there are 2 distinct subgroups of α1-adrenergic receptors, designated as α1A-adrenergic receptors (α1A-ARs) and α1A-ARs, all of which are members of the superfamily of 7-transmembrane-spanning domain (7-TM) receptors (also termed G protein–coupled receptors). There are 3 human α1-AR subtypes, denoted α1A, α1B, and α1D. Since α1-ARs expressed on vascular smooth muscle act to constrict and thus increase peripheral vascular resistance, there has been substantial development and widespread use of α1-AR antagonists for the treatment of hypertension. What has not been well acknowledged is the fact that α1A-ARs are also expressed on cardiomyocytes, and thus treatment of hypertension with α1-AR antagonists may also have effects on the heart that are distinct from afterload reduction. All α1-AR subtypes couple to the heterotrimeric G protein Gq. Upon agonist activation, the Gq subunit activates the effector phospholipase C, which produces at least 2 intracellular second messengers, inositol-1,4,5-triphosphate and diacylglycerol. The former increases intracellular calcium, while the latter activates several PKC isoenzymes that modify heart failure (1). Since catecholamines are elevated in heart failure, cardiac α1-AR/Gq signaling is activated to various extents in the syndrome.

The Gqαq pathway has been studied extensively as to its role in cardiac hypertrophy and heart failure (2). Cardiac overexpression of Gqαq in transgenic mice (3) results in hypertrophy, decreased ventricular function, loss of α1-adrenergic receptor inotropic responsiveness, and induction of a classic hypertrophy gene expression profile. In these mice, pressure overload by surgical transverse aortic constriction (TAC), pregnancy, or higher transgenic overexpression of Gqαq resulted in cardiomyocyte apoptosis and compensated heart failure (3, 4). Other studies showed that transgenic overexpression of a Gqαq dominant-negative minigene resulted in the lack of a hypertrophy response to TAC (5). Furthermore, cardiac overexpression of a constitutively activated α1A-AR resulted in cardiac hypertrophy (6), while a more severe cardiomyopathy developed as a result of overexpression of the Gqαq-coupled angiotensin II type 1 (AT1) receptor (7). These studies, then, began to point toward hyperactive Gqαq signaling as a key mechanism causing hypertrophy, depressed ventricular function, and failure.

A readily drawn conclusion from such studies might be that in the human heart, factors that increase Gqαq signaling predispose to cardiac hypertrophy and, potentially, the transition from hypertrophy to decompensated heart failure. In addition, approaches that decrease this signaling might be protective against the development of heart failure or be beneficial in treatment.

Ablation of α1-ARs and cardiac hypertrophy

In the report by O’Connell et al. in this issue of the JCI (8), the hypertrophic response to TAC was assessed in mice in which the genes encoding α1A-AR and α1B-AR had been ablated (α1A/B KO mice). Mice without these Gqαq-coupled receptors demonstrated rapid decompensation and heart failure after TAC. In those that survived, echocardiographic studies showed lower ejection fractions than in WT mice. Although both sets of mice exhibited hypertrophy, the α1A/B KO mice had increased apoptosis and interstitial fibrosis. Furthermore, they had an atypical hypertrophy-associated gene profile, with minimal changes in expression of β-myosin heavy chain, α-skeletal actin, and atrial natriuretic factor transcripts. These data suggest that α1-AR/Gqαq signaling is necessary for adaptation to pressure overload. This issue is of substantial clinical importance because of the extensive use of α1-AR antagonists for the treatment of hypertension and symptomatic prostate enlargement. In a large cohort of hypertensive patients, those treated with the α1-AR antagonist doxazosin had a relative risk of 2.04 (95% confidence interval = 1.79–2.32, P < 0.001) of developing heart failure compared with those receiving a diuretic (9). Other studies with smaller cohorts have also observed this relationship but indicate an attenuation of this risk after adjustment for systolic blood pressure (10). Of note, this latter study found that systolic blood pressure was lower in the diuretic group compared with the α1-AR antagonist group, particularly in women, in whom the risk of heart failure was greatest. This may

Nonstandard abbreviations used: AR, adrenergic receptor; AT1, angiotensin II type 1; TAC, transverse aortic constriction; 7-TM, 7-transmembrane-spanning domain.

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indicate that normotensive men treated with \( \alpha_1 \)-AR antagonists for symptomatic prostatic enlargement are not at significantly increased risk for developing heart failure, but this hypothesis has not been tested in adequately powered trials. Of particular concern would be the scenario in which an individual taking \( \alpha_1 \)-AR antagonists develops a stressed myocardium (e.g., new-onset hypertension, myocardial infarction). The inability to develop the appropriate hypertrophic response could predispose such individuals to cardiac failure.

**A matter of timing**

The data obtained from this study of \( \alpha_{1A/B} \) KO mice (8) provide additional support for the potential deleterious effects of \( \alpha_1 \)-AR blockade. How, though, are these results reconciled with the generally perceived notion that enhanced (as opposed to suppressed) receptor/G\( \alpha_0 \) signaling evokes hypertrophy and/or failure? There are several components to this issue. First, examination of earlier mouse studies (3) indicates that the effects observed in the \( \alpha_{1A/B} \) mouse appear to be mostly due to \( G_{\alpha_0} \) overexpression being present from birth (because of the properties of the \( \alpha \)-myosin light chain promoter that was used in the transgenic construct). When an inducible promoter was used, and \( G_{\alpha_0} \) overexpression was induced after the heart had reached normal size, no pathologic effect was noted (11). In other studies, mice lacking \( G_{\alpha_0} \) (and the similarly functioning \( G_{\alpha_1} \)) protein died in utero with underdeveloped, hypoplastic hearts (12). So, it appears that for cardiac development (one form of growth), a certain critical level of \( G_{\alpha_0} \) signaling is necessary to achieve normal morphology. \( G_{\alpha_0}/G_{\alpha_1} \) KO mice that survive the perinatal period are unable to mount a hypertrophic response to TAC as adults (13).

Thus, similarly to the requirements for normal growth during development, finely tuned \( G_{\alpha_0} \) signaling appears to be necessary for reactive growth. Taking these studies into account, then, the O’Connell report (8) does not fully define the role of \( \alpha_1 \)-AR signaling in the hypertrophic or failure response to pressure overload, because the \( \alpha_{1A/B} \) KO mice have abnormal hearts as adults. Prior to TAC, these hearts are smaller with decreased myocyte surface area and volume (14). So whether the lack of \( \alpha_1 \)-AR signaling in the normal, adult heart has an effect on hypertrophy or the transition to failure cannot be fully addressed in mice that have a lack of \( \alpha_{1A/B} \)-AR from conception. An inducible, cell type–specific knockout would be required to explore this issue in the most rigorous manner. Secondly, it is important to realize that cardiac hypertrophy per se is a form of growth whereby the heart responds to states, such as the increased afterload from hypertension, in order to maintain performance. Thus, under these circumstances hypertrophy can be considered as a compensatory and initially advantageous response of the heart. The inability to achieve the normal biochemical and anatomic hypertrophy response, such as when \( G_{\alpha_0} \) signaling is suppressed, may thus predispose to maladaptive hypertrophy and a more rapid transition to pump failure.

**7-TM receptor diversification**

It is not entirely clear why \( \alpha_1 \)-AR/G\( \alpha_0 \) signaling is specifically necessary for a normal
response to pressure overload. There are numerous other cardiac neurohumoral receptors that also couple to G_{q} and are activated in heart failure. These include the AT_{1} receptor, which is an effective pharmacologic target for angiotensin-converting enzyme inhibitors (15) and angiotensin receptor antagonists (16) in the treatment of heart failure. What is apparent, though, is that 7-TM signaling is not a simple, linear, 1-way “switch.” Indeed, in the most straightforward model, the hundreds of signaling complexes, rather than individual components, in order to ascertain critical intracellular events in myocytes that modulate the hypertrophic response and transition to failure.

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