α1-Adrenergic signaling mediates cardiac adaptation to development and stress

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α1-Adrenergic receptors are prototypic 7-transmembrane domain receptors that couple to the Gq class of G-proteins and activate calcium signaling in cardiac myocytes. Over-expression studies suggest that myocyte Gq-coupled receptors as a class mediate pathological hypertrophic signaling that causes cardiomyopathy and heart failure. α1-Adrenergic receptors were the first hypertrophic receptors discovered in the neonatal rat culture model of cardiac hypertrophy, and, because they activate the "fetal hypertrophic gene program", it was assumed that they also mediate pathological hypertrophic signaling. We have tested this hypothesis using mice with knockout of one or all of the three α1-adrenergic receptor subtypes (A, B, and D). Contrary to the prevailing view, we find that α1-receptors are required for normal growth of the heart during post-weaning development, the most common form of physiological hypertrophy. Furthermore, α1-receptors are required for the heart to adapt to the pathological disease stress of pressure overload, when multiple Gq-coupled and other hypertrophic agonists are also increased. These α1 functions during development and in stress appear to be mediated by different α1 subtypes. Therefore, in agreement with α1-blocker clinical trials in humans and with α1-agonist and transgenic data, α1-adrenergic receptors have an essential adaptive and protective trophic role in cardiac myocytes. These results point to receptor-specific Gq-coupled calcium signaling. They also suggest that α1-receptors are candidate targets for agonist therapy in heart failure.