Is β-Arrestin 2 a Magic Bullet for Heart Failure Treatment?

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Heart failure (HF) is a clinical syndrome that is the terminal stage for several cardiac conditions, such as hypertension, ischemic heart disease, and valvular heart disease. According to the National Health and Nutrition Examination Survey, ≈6.5 million Americans ≥20 years of age live with HF. The prevalence of HF is expected to increase by ≈50% by 2030, resulting in >8 million Americans with HF.[1] Mortality and morbidity rates associated with HF place a considerable burden on the healthcare system by being the second most prevalent cause of hospitalization.[2] Hemodynamically, HF is defined as a failure of the heart to pump blood in the amounts that meet the metabolic needs of the body. Several mechanisms contribute to the development of HF[2]: (1) neurohumoral activation, (2) increased myocardial fibrosis, (3) cellular hypertrophy and susceptibility to cell death, (4) vicious circle of adrenergic stimulation that raises myocardial contractility in the setting of increased afterload, (5) abnormal Ca^{2+} cycling because of Ca^{2+} leak via ryanodine receptor 2 receptors and lowered SERCa2 (sarco-endoplasmic reticulum Ca^{2+}-ATPase) activity. The article in the current issue of the journal by McCrink et al[3] provides an interesting and unexpected insight in the role of β-arrestin 2 in the last 2 mechanisms of HF (β-adrenergic stimulation and regulation of SERCa2 activity) and presents a new treatment option for HF.

β-Adrenergic Stimulation, β-Arrestins, and Ca^{2+} Cycling in Normal Heart and HF

In normal cardiomyocytes, adrenergic stimulation via β_1-adrenergic receptor (β_1-AR) and stimulatory G-protein activates protein kinase A, which acts on multiple phosphorylation targets leading to increases in Ca^{2+} influx via L-type Ca^{2+} channels, Ca^{2+} release via ryanodine receptor 2 channels, Ca^{2+} reuptake by SERCa2, and the rate of cross-bridge cycling (Figure A). Protein kinase A activity also leads to desensitization of β_1-ARs mediated by β-arrestin 1 via G-protein receptor kinase 2 (Figure A). β-Arrestins are known to facilitate recycling and degradation of GPCRs (G-protein–coupled receptors). Interaction between β-arrestins and class A GPCRs (eg, β-ARs) is weak (relatively low affinity) and transient, whereas interaction with class B GPCRs (eg, angiotensin type 1 receptor) is strong and long lasting.[4] β-Arrestins can also act as signaling molecules in their own right producing a dual modality for associated receptor (also called β-arrestin–biased signaling). Transient binding of β-arrestins to activated GPCRs triggers internalization of GPCRs via interaction with the clathrin machinery, shuts off classical GPCR signaling, and activates β-arrestins, which dissociate from GPCRs and act as an independent signaling molecule.[5] These modalities of GPCR signaling (classical and β-arrestin dependent) can lead to different physiological outcomes. For example, in neonatal ventricular myocytes, classical Gq-dependent signaling of ERK1/2 (extracellular signal-regulated kinase 1/2) promotes pathological cardiomyocyte hypertrophy, whereas β-arrestin 2–dependent ERK1/2 signaling promotes cardiomyocyte proliferation.[6]

In HF, the sympathetic nervous system and β-adrenergic signaling in cardiac myocytes undergo significant changes. Catecholamine levels increase substantially leading to desensitization of the heart to catecholaminergic stimulation. At the cellular level, HF results in (1) a reduction of β_1-AR:β_2-AR ratio from 75%:20% to ≈50%:50% (for humans,[7] whereas mice expresses primarily β_1-AR in myocytes with β_2-AR up to 20% in nonmyocyte cells[8]), (2) desensitization of β-ARs because of binding of β-arrestin 1 to G-protein receptor kinase 2–phosphorylated β-ARs leading to underphosphorylation of phospholamban inhibiting SERCa2 activity (see Figure A), (3) overall reduction of SERCa2 levels, and (4) overphosphorylation of ryanodine receptor 2 because of compartment-specific downregulation of phosphodiesterases, resulting in Ca^{2+} leak and raised diastolic Ca^{2+} concentration.[9] β-Arrestin 1 involvement is clearly responsible for broad cardiac remodeling in HF (apoptosis, fibrosis, and inflammation) because β-arrestin 1 knockout mice survive better post-myocardial infarction and exhibit considerably less of myocardial remodeling as this research group showed previously.[10]

Overexpression of β-Arrestin 2: Insight in Mechanisms of Action and Clinical Implications

The heart expresses β-arrestin 1 almost exclusively.[11] Interestingly, McCrink et al[3] showed that overexpression of β-arrestin 2 in mice restores inotropic reserves of β-adrenergic regulation. In the β-arrestin 2–overexpressing myocytes, β-arrestin 2 is activated by transiently binding to β_1-AR and shutting off regular β_1-AR signaling.[5] Activated β-arrestin 2 can act independently by promoting SUMOlation of SERCa2, as well as binding to SERCa2 and recruiting SUMO-ligase Ubc9 to the formed regulatory complex, which increase SERCa2 activity[3] (Figure B). Another possibility of beneficial β-arrestin 2 action (that was not discussed by McCrink et al[3]) is that β-arrestin 2 can potentially compete with β-arrestin 1 for

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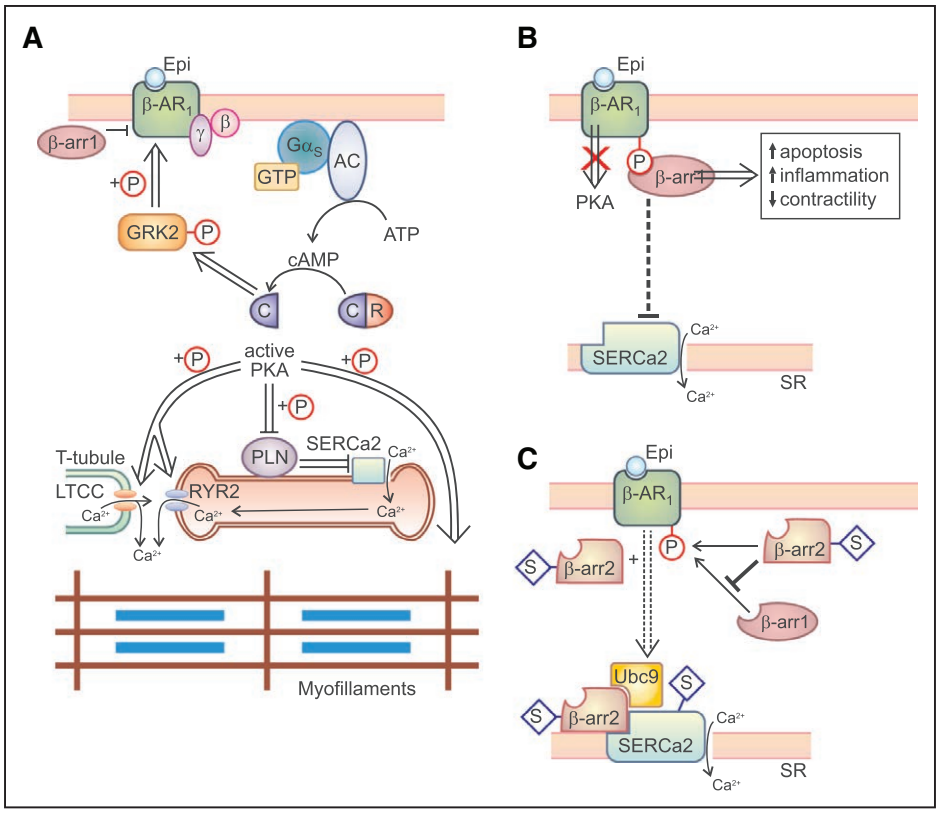

Figure. β-Adrenergic signaling via β_1-adrenergic receptor (β_1-AR) and β-arrestins. **A**, Normal β-adrenergic signaling via β_1-AR and β-arrestin 1. Binding of epinephrine (Epi) to β_1-AR activates the coupled G-protein (G-protein–bound GDP is exchanged for GTP leading to dissociation of activated $G\alpha_S$ [stimulatory], whereas βγ remains bound to the β_1-AR). $G\alpha_S$ activates adenylyl cyclase (AC) that produces cAMP. Increase in cAMP levels activate cAMP-dependent PKA (protein kinase A): inactive PKA (C.R: catalytic [C] with a bound repressor [R]) loses repressor (R). Active PKA (C) then phosphorylates L-type Ca^{2+} channels (LTCC), Ca^{2+} release channel (RYR2 [ryanodine receptor 2] channel), phospholamban (PLN; inhibitory regulator of SERCa2 [sarco-endoplasmic reticulum Ca^{2+}-ATPase]), and troponin I. In addition, PKA phosphorylates GRK2 (G-protein–coupled receptor kinase). Activated GRK2 phosphorylates β_1-AR, which enables binding of β-arrestin 1 (β-arr1). Binding of β-arrestin 1 triggers suppression β-adrenergic signaling because of internalization of β_1-AR. **B**, β-Adrenergic signaling in heart failure. β_1-AR is desensitized because of β-arr1 leading to increased apoptosis, increased inflammation, and reduced contractility. **C**, β-Adrenergic signaling after overexpression of β-arrestin 2. Activated β-arrestin 2 (β-arr2) can compete with β-arr1 preventing maladaptive signaling via β-arr1. Also, activated β-arr2 can acts independently by promoting self-SUMOlation and SUMOlation of SERCa2 and forming regulatory complex with SERCa2 and SUMO-ligase Ubc9.

binding to β_1-AR preventing activation of β-arrestin 1 and its possible GPCR-independent action (Figure B). Although both arrestins interact transiently and weakly with class A GPCRs (including β-AR), β-arrestin 2 binds with higher affinity than β-arrestin 1,[4] preventing activation and independent action of β-arrestin 1. This suggests that β-arrestin 2 overexpression acts analogous to β-arrestin 1 knockout, which was explored previously by this research group.[10] An interesting mechanistic question in this regard is whether overexpression of β-arrestin 2 in β-arrestin 1 knockout mice provides any additional protection from remodeling in HF. However, regardless of mechanistic considerations, overexpression of β-arrestin 2 is a more preferred approach to augment SERCa2 activity than blocking activity of β-arrestin 1 because pharmacological block of β-arrestin 1 can result in visual impairment. Augmenting SERCa2 activity by overexpressing SERCa2 to normalize Ca^{2+} cycling is beneficial in animal models of HF[12]; however, this approach has failed in the recently completed CUPID 2 clinical trial (Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease).[13] In this regard, work of McCrink et al[3] gives another opportunity for gene therapy to improve outcome in patients with HF by overexpressing β-arrestin 2 to improve not only SERCa2 function but also to promote reverse cardiac remodeling via beneficial GPCR-independent β-arrestin 2 signaling. However, as any gene therapies, β-arrestin 2 overexpression may potentially face challenges in gene delivery similar to SERCa2 gene therapy in the CUPID 2 clinical trial. Alternative approach to gene therapy can be a use of small molecules that promote activation of SUMO-ligase Ubc9 and SUMOlation of SERCa2 mimicking β-arrestin 2 action. Such drugs might prove to be superior in the settings of HF to other approaches of increasing myocardial contractility, such as β-AR agonists and phosphodiesterase inhibitors, because β-arrestin 2 action does not lead to increase in 3′-5′-cAMP levels and, thus, avoids the risk of raising cAMP levels in pools responsible for cardiac hypertrophy and arrthymias.[14]

Conclusions

Strategies aimed at enhancing or mimicking β-arrestin 2 function to stimulate cardiac contractility have a potential to be safer and more effective than β-AR agonists and phosphodiesterase inhibitors; therefore, development of such strategies should be considered as a viable therapeutic option for the management of HF.

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Disclosures

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