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PRECLINICAL RESEARCH

An Oral Selective Alpha-1A Adrenergic Receptor Agonist Prevents Doxorubicin Cardiotoxicity

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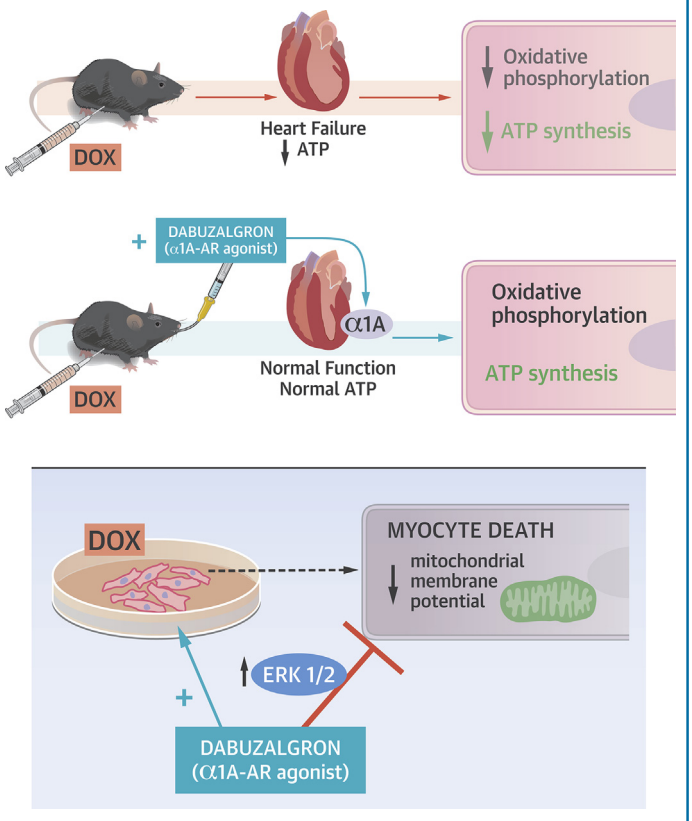
VISUAL ABSTRACT



Beak, J.Y. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(1):39–53.

HIGHLIGHTS

- There are 2 α1-ARs on cardiac myocytes: α1A and α1B. α1A adrenergic receptors serve important cardioprotective roles and do not mediate cardiac hypertrophy.
- Dabuzalgron, an oral α1A-AR agonist developed for the treatment of urinary incontinence and tolerated well in Phase 2 clinical trials, protects against doxorubicin-induced cardiotoxicity in vivo. Dabuzalgron enhances contractile function, regulates transcription of genes related to energy production and mitochondrial function, and preserves myocardial ATP content after doxorubicin.
- Activation of α1A-ARs on cardiomyocytes protects against doxorubicin cytotoxicity and enhances mitochondrial function in vitro. These cytoprotective effects likely are mediated by activation of ERK 1/2.
- Future studies will explore whether dabuzalgron, a well-tolerated oral α1A-AR agonist, might be repurposed to treat heart failure.

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ABBREVIATIONS AND ACRONYMS

α1-AR = alpha-1 adrenergic receptor

AKO = alpha-1A adrenergic receptor knockout

ATP = adenosine triphosphate

BP = blood pressure

DOX = doxorubicin

EC50 = half-maximal effective concentration

ERK = extracellular signal-regulated kinase

HF = heart failure

HR = heart rate

IP = intraperitoneal

NRVM = neonatal rat ventricular myocyte

PGC1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha

qRT-PCR = quantitative reverse transcription polymerase chain reaction

TBARS = thiobarbituric acid reactive substances

WT = wild type

SUMMARY

Alpha-1 adrenergic receptors (α1-ARs) play adaptive and protective roles in the heart. Dabuzalgron is an oral selective α1A-AR agonist that was well tolerated in multiple clinical trials of treatment for urinary incontinence, but has never been used to treat heart disease in humans or animal models. In this study, the authors administered dabuzalgron to mice treated with doxorubicin (DOX), a widely used chemotherapeutic agent with dose-limiting cardiotoxicity that can lead to heart failure (HF). Dabuzalgron protected against DOX-induced cardiotoxicity, likely by preserving mitochondrial function. These results suggest that activating cardiac α1A-ARs with dabuzalgron, a well-tolerated oral agent, might represent a novel approach to treating HF. (J Am Coll Cardiol Basic Trans Science 2017;2:39–53)

Evidence from studies in cells and animals indicates that alpha-1 adrenergic receptors (α1-ARs) play numerous protective roles in the heart (reviewed in O'Connell et al. [1]). There are 3 α1-AR subtypes: α1A, α1B, and α1D. In rodent and human myocardium, the α1A and α1B predominate, and there is no measurable α1D. The α1D is the major α1-AR subtype in human and mouse coronary arteries, where its activation promotes vasoconstriction (2,3). The role of the myocardial α1B remains unclear, but multiple lines of evidence suggest that the cardioprotective effects of nonselective α1-AR agonists are mediated by the α1A. Mice overexpressing the α1A have increased contractility (4) and are protected from ischemia-reperfusion injury (5), myocardial infarction (6,7), and transverse aortic constriction (8). Abrogation of these adaptive processes may also account for the 2-fold increase in incident heart failure (HF) in hypertensive patients treated with the non-selective α1-AR antagonist, doxazosin, in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (9). These findings and other evidence from animal and human studies suggest that activating myocardial α1A-ARs could be therapeutically effective in HF.

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In this study, we used the oral selective α1A agonist dabuzalgron (Ro 115-1240) to test our hypothesis that stimulation of myocardial α1As could confer cardioprotection without increasing blood pressure (BP) through vascular α1-AR activation. Roche developed dabuzalgron for the treatment of urinary incontinence. It showed excellent α1A selectivity in preclinical testing (10) and was well tolerated by a total of 1,223 women in a Phase 1 trial (11); 2 Phase 2 randomized multicenter trials (Roche NN16378 and NN16691); and a subsequent open-label study (Roche NN16586). Importantly, there were no significant changes in BP in the subjects who received dabuzalgron in any of these trials, suggesting that the chosen dose did not affect vascular tone. When interim analysis of the Phase 2 trials revealed no clinically meaningful difference in urinary incontinence between the dabuzalgron and placebo groups, Roche decided to close trial enrollment and halt further development of dabuzalgron. The drug never has been used either clinically or experimentally to treat heart disease.

We chose to test the therapeutic efficacy of dabuzalgron in preventing heart injury using an anthracycline cardiotoxicity model, given previous evidence demonstrating α1A-mediated cytoprotection after doxorubicin (DOX) treatment (12–14). Anthracyclines, including DOX, are highly effective and commonly used chemotherapeutic agents, but have dose-limiting cardiotoxicity. Although the incidence of anthracycline-induced cardiomyopathy has declined with contemporary dosing regimens, left ventricular dysfunction still occurs in 20% to 30% of anthracycline recipients (15,16) and remains an important cause of systolic HF. Numerous mechanisms contribute to cardiomyocyte injury after anthracycline administration, but mitochondrial dysfunction and broad deficits in cardiomyocyte energy production

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