JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 8, NO. 6, 2023

EDITORIAL COMMENT

At the Crossroads of Cardiac Beta-Adrenergic Receptor Signaling and Myocardial Glucose Metabolism*

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Heart failure remains a leading cause of global mortality. Despite recent advances in clinical therapy, long-term prognosis is poor. Beta-adrenergic receptors (βARs) are members of the G protein-coupled receptor (GPCR) family and play a central role in the progression of heart failure. In the heart, β2AR is a predominant isoform. Under pathological conditions, including myocardial ischemia and injury, βARs undergo GPCR kinase (GRK)-mediated desensitization and downregulation. Chronic desensitization of βARs leads to activation of the sympathetic nervous system, which in turn causes catecholamine toxicity resulting in ventricular dysfunction.[1]

Cardiac energy metabolism is the process by which the heart produces the necessary amount of adenosine triphosphate (ATP) required to sustain contractile function.[2] Under normal physiological conditions, the adult heart generates most of its ATP from fatty acid oxidation[2]; however, glucose is also necessary for cardiac function in response to various physiological and pathological stimuli.[2,3] It is well understood that adrenergic stimulation increases cardiac function, necessitating an increase for fuel and energy, but there is limited knowledge in how βAR signaling controls glucose uptake metabolism in the heart.

At the crossroads of cardiac βAR signaling and myocardial glucose metabolism is the recent study conducted by Jovanovic et al,[4] published in this issue of *JACC: Basic to Translational Science,* in which the investigators aimed to determine how β2AR controls cardiac glucose metabolism. Jovanovic et al[4] showed that the cardiac β2AR is required to stimulate glucose transporter type 4 (GLUT4)-mediated glucose uptake in 2 ex vivo model systems, isolated ventricular myocytes and isolated working hearts. Myocytes and hearts were isolated from mice with a cardiac-specific deletion of β2AR (β2AR cardiac knockout mice) and mice developed using Clustered Regularly Interspaced Short Palindromic Repeats knock-in technology, expressing endogenous β2AR but lacking the GRK2 phosphorylation site at Ser355/356 (β2AR GRK mutant mice). In the study, all mice exhibited normal and relatively similar cardiac function at baseline and after adrenergic stimulation with isoproterenol.[4] Using these models, Jovanovic et al[4] first demonstrated that deletion of β2AR inhibited adrenergic stimulation of GLUT4-mediated glucose uptake in myocytes and glucose oxidation in working hearts. In the working heart model, glucose oxidation was measured at baseline and after infusion of isoproterenol, and deletion of β2AR prevented isoproterenol induced increases in glucose oxidation.[4] Additionally, membrane insertion of GLUT4 was blocked in the β2AR cardiac knockout mice working hearts. Jovanovic et al[4] then showed that stimulation of β2AR resulted in G_i-Akt-mediated GLUT4 translocation and glucose uptake in isolated myocytes from rat hearts. Adult myocytes were first pretreated with a β1AR or β2AR selective blocker and subsequently stimulated with isoproterenol, where pretreatment with the β2AR selective blocker prevented isoproterenol induced phosphorylation of Akt and completely blocked GLUT4 membrane insertion.[4] The

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2023.02.016

investigators further demonstrated that activation of cardiac β2AR was necessary to promote Akt-mediated (but not AMP activated protein kinase [AMPK]-mediated) phosphorylation of AS160 for GLUT4 membrane insertion and glucose uptake in hearts, as inhibition of Akt blocked GLUT4 membrane insertion induced by isoproterenol but AMPK inhibition did not. Further, Jovanovic et al[4] showed that inhibition of G_i with pertussis toxin prevented isoproterenol induced increases in Akt and AS160 phosphorylation, GLUT4 membrane insertion, and glucose uptake in adult myocytes. Taken together, Jovanovic et al[4] showed that stimulation of β2AR results in G_i-Akt-mediated GLUT4 translocation and glucose uptake in isolated myocytes. They also isolated adult myocytes from β2AR cardiac knockout mice and demonstrated that β2AR deletion resulted in inhibition of GLUT4 translocation and prevention of glucose uptake. This was observed concomitantly with abolishment of isoproterenol-induced phosphorylation of Akt and AS160 in the hearts. Therefore, Jovanovic et al[4] demonstrated that cardiac β2AR is necessary to stimulate Akt and AS160 for GLUT4 translocation and glucose uptake in hearts.

Jovanovic et al[4] then showed that when GRK2 was inhibited using paroxetine (a commonly prescribed selective serotonin reuptake inhibitor and pharmacological inhibitor of GRK2[1]), isoproterenol induced translocation of GLUT4 and glucose uptake in rat ventricular myocytes was prevented. Jovanovic et al[4] then reintroduced wild-type β2AR and mutant β2AR (lacking the GRK phosphorylation site at Ser355/356) in the β2AR cardiac knockout mice. As demonstrated in the study, isoproterenol induced GLUT4 translocation and glucose uptake was restored when wild-type β2AR was introduced, but not when the β2AR mutant was introduced.[4] Furthermore, in working hearts isolated from β2AR GRK2 mutant mice, adrenergic stimulation of glucose oxidation was prevented, showing that GRK2 phosphorylated β2AR is needed to stimulate glucose uptake and use in hearts. Therefore, the results presented by Jovanovic et al[4] outline the molecular mechanism by which cardiac glucose uptake and use is under β2 adrenergic stimulation in isolated myocytes and working hearts.

Although the experiments by Jovanovic et al[4] were performed using ex vivo ventricular myocytes and isolated working heart models with the addition of isoproterenol to initiate acute stress, future work should aim to investigate adrenergic regulation of glucose uptake and use under conditions of in vivo cardiac stress, such as myocardial ischemia. Under conditions of cardiac stress, alterations in myocardial glucose oxidation occur and glucose metabolism is needed to generate ATP to sustain contractile function as well as protect the heart from ischemic damage.[2,3] The study also does not address the important role that cardiac contractility has on glucose uptake, and future experiments interrogating this signaling pathway while assessing calcium flux and myocardial contractility should be conducted. Furthermore, it is unknown whether there are differences in adrenergic regulation of glucose uptake between male and female mice and whether any sex-specific effects are observed in the isolated cardiomyocyte or working heart models.

Understanding the role of β2AR signaling on glucose uptake and metabolism in the context of cardiac disease is an important next step. Additionally, with the exponential increases in the rates of diabetes and obesity, the effect of adrenergic signaling on glucose uptake by the heart under conditions of comorbid cardiac and metabolic stress should also be considered. The work by Jovanovic et al[4] is positioned to lead to future development of new approaches that regulate cardiac glucose metabolism.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Koch is supported by R01 HC061690, P01 HL174841, R01 HL071818, R01 HL15715, P01 HL134608, and AHA18MERIT33900036. Dr Kereliuk has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS adrenergic receptor, Akt substrate, G protein receptor kinase 2, glucose transporter 4, glucose uptake