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Stress Response Signaling Pathways May Lead to Mitochondrial Biogenesis

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Diabetes, a worldwide epidemic, represents a major public health problem and the vast majority of the patients with diabetes presents with insulin resistance, a fundamental manifestation of this disease. Insulin resistance impairs glucose uptake into skeletal muscle, which takes up about 80% of postprandial glucose in healthy individuals (1). Thus, skeletal muscle plays an indispensable role in maintaining glucose homeostasis. However, the mechanisms underlying the development of insulin resistance remains poorly understood, which perhaps accounts for the lack of effective therapies.

Mitochondria, where low levels of superoxide radicals are constitutively generated as a by-product of electron transport, serve as the powerhouse and are also considered a main source for overproduction of reactive oxygen species (ROS) triggered by diabetes (2,3). Oxidative stress is a key pathological signal leading to diabetes complications (4,5). It has been disappointing that broad-spectrum antioxidant therapies have not been effective in improving outcomes in high-risk patients, including patients with diabetes (6), when used as primary prevention, suggesting that detailed knowledge of oxidative injury mechanisms is necessary to develop effective antioxidant therapies that target specific pathogenic mechanisms while sparing physiologically important ROS-dependent pathways. Oxidative stress causes mitochondrial dysfunction and contributes to mitochondrial uncoupling and impaired energetics in the diabetic heart (7–9). Overexpression of ROS-detoxifying proteins, including superoxide dismutase, metallothionein, and catalase, reverses mitochondrial dysfunction induced by diabetes (10–12). These results suggest that mitochondria are a key source of oxidative stress in patients with diabetes and an important target for ROS-mediated damage.

In this issue, Jain et al. (13) reveal a role of mitochondrial-generated ROS in causing mitochondrial biogenesis via a mechanism dependent on calcium/calmodulin protein kinase II (CaMKII). They use an obesity model of high-fat feeding in both rats and mice to demonstrate that the increase in fat intake triggers signaling cascades, ultimately activating CaMKII and AMP-activated protein kinase (AMPK) and stimulating mitochondrial biogenesis. The increase in mitochondria was measured at both the mitochondrial DNA and protein levels (specifically, electron transport chain constituents were measured) following high-fat feeding. CaMKII can be activated by modification of a number of residues in the activation domain (14), and two of these amino acid sites were tested (13). CaMKII activation by phosphorylation occurred following high-fat feeding and was reversed by inhibiting mitochondrial ROS emissions. Surprisingly, CaMKII was not activated via oxidation, indicating a different mode of CaMKII activation than reported for the streptozotocin diabetic model of CaMKII activation (15). In the streptozotocin diabetic mouse model, activation of CaMKII occurs by both phosphorylation (16) and oxidation (15) (Fig. 1). Uncovering the different mechanisms of CaMKII activation under various pathologic conditions is paramount for a thorough understanding of mitochondrial function.

AMPK, a main regulator of cellular energy, preserves an optimal AMP/ATP ratio and is activated by mitochondrial ROS. However, the AMPK activation that is found with high-fat feeding likely occurs by a signaling pathway other than ROS because, unlike CaMKII activation, inhibition of mitochondrial ROS further increased AMPK activation (13). This is consistent with the possible alternate modes of activation for this energy regulator (17). An increase in cytosolic calcium from the ryanodine receptor (RyR) can activate CaMKII (18). Jain et al. (13) report that an increase in S-nitrosylation by ROS activates the RyR but did not test this in the presence of an antioxidant; however, the authors do show that CaMKII phosphorylation depends on opening of the RyR. High-fat feeding conceivably activates several signaling pathways,

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COMMENTARY

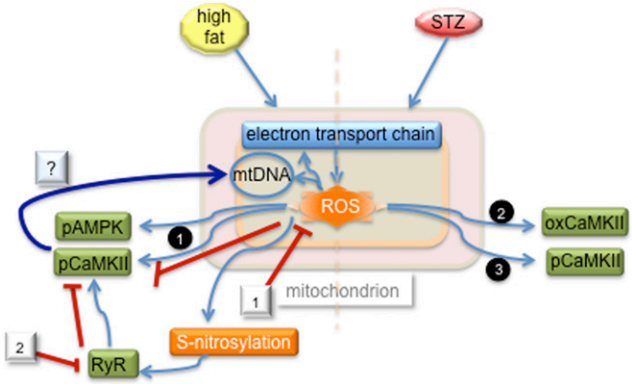

Figure 1—Consequences of chronic high-fat feeding. High-fat feeding (*left* side of mitochondrion) leads to increased mitochondrial ROS production causing a number of signaling changes, including increased phosphorylated (p)CaMKII (black circle 1 [13]) and pAMPK and S-nitrosylation of the RyR. These changes either directly or indirectly result in mitochondrial biogenesis, as measured by increased mitochondrial DNA (mtDNA) and protein complexes. Streptozotocin (STZ) treatment (*right* side of mitochondrion) leads to increased CaMKII activation by both oxidation (ox) (black circle 2 [15]) and phosphorylation (black circle 3 [16]) with downstream outcomes not shown. Blocking excess mitochondrial ROS generation reduces CaMKII activation, but not AMPK activation (red line 1), and blocking RyR calcium current will reduce CaMKII activation (red line 2). The key to this signaling cascade will be to show whether inhibiting CaMKII activity under these conditions prevents mitochondrial biogenesis (blue arrow ?).

as components of one signal transduction pathway may affect another because of shared constituents.

Jain et al. (13) suggest that the function of mitochondrial biogenesis under the stress of high fat may be to promote fatty acid oxidative phosphorylation and to decrease mitochondrial ROS production. However, mitochondrial ROS production did not decrease in the time frame of this study. Interestingly, a considerably longer-term study of a high-fat diet showed increase in ROS per unit respiration for liver and heart tissue mitochondria (19). In a study to identify whether activated CaMKII is upstream of mitochondrial biogenesis following high-fat feeding, it would be useful to show whether inhibiting CaMKII activity reverses the mitochondrial biogenesis observed in Jain et al., as has been suggested by others (20). Furthermore, it remains to be determined whether mitochondrial biogenesis or dysfunction is a cause or consequence of insulin resistance.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Thiebaud D, Jacot E, DeFronzo RA, Maeder E, Jequier E, Felber JP. The effect of graded doses of insulin on total glucose uptake, glucose oxidation, and glucose storage in man. Diabetes 1982;31:957–963
2. Yu T, Robotham JL, Yoon Y. Increased production of reactive oxygen species in hyperglycemic conditions requires dynamic change of mitochondrial morphology. Proc Natl Acad Sci U S A 2006;103:2653–2658
3. Nishikawa T, Edelstein D, Du XL, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 2000;404:787–790
4. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 2010;107:1058–1070
5. Di Filippo C, Cuzzocrea S, Rossi F, Marfella R, D'Amico M. Oxidative stress as the leading cause of acute myocardial infarction in diabetics. Cardiovasc Drug Rev 2006;24:77–87
6. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P; The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. N Engl J Med 2000;342:154–160
7. Boudina S, Sena S, Theobald H, et al. Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. Diabetes 2007;56:2457–2466
8. Shen X, Zheng S, Thongboonkerd V, et al. Cardiac mitochondrial damage and biogenesis in a chronic model of type 1 diabetes. Am J Physiol Endocrinol Metab 2004;287:E896–E905
9. Pierce GN, Dhalla NS. Heart mitochondrial function in chronic experimental diabetes in rats. Can J Cardiol 1985;1:48–54
10. Cai L, Wang Y, Zhou G, et al. Attenuation by metallothionein of early cardiac cell death via suppression of mitochondrial oxidative stress results in a prevention of diabetic cardiomyopathy. J Am Coll Cardiol 2006;48:1688–1697
11. Shen X, Zheng S, Metreveli NS, Epstein PN. Protection of cardiac mitochondria by overexpression of MnSOD reduces diabetic cardiomyopathy. Diabetes 2006;55:798–805
12. Ye G, Metreveli NS, Donthi RV, et al. Catalase protects cardiomyocyte function in models of type 1 and type 2 diabetes. Diabetes 2004;53:1336–1343
13. Jain SS, Paglialunga S, Vigna C, et al. High-fat diet–induced mitochondrial biogenesis is regulated by mitochondrial-derived reactive oxygen species activation of CaMKII. Diabetes 2014;63:1907–1913
14. Joiner ML. NO generation by β-AR stimulation to activate CaMKII. Cardiovasc Res 2013;100:352–353
15. Luo M, Guan X, Luczak ED, et al. Diabetes increases mortality after myocardial infarction by oxidizing CaMKII. J Clin Invest 2013;123:1262–1274
16. Nishio S, Teshima Y, Takahashi N, et al. Activation of CaMKII as a key regulator of reactive oxygen species production in diabetic rat heart. J Mol Cell Cardiol 2012;52:1103–1111
17. Towler MC, Hardie DG. AMP-activated protein kinase in metabolic control and insulin signaling. Circ Res 2007;100:328–341
18. Niggli E, Ullrich ND, Gutierrez D, Kyrychenko S, Poleáková E, Shirokova N. Posttranslational modifications of cardiac ryanodine receptors: Ca(2+) signaling and EC-coupling. Biochim Biophys Acta 2013;1833:866–875
19. Yu L, Fink BD, Herlein JA, Oltman CL, Lamping KG, Sivitz WI. Dietary fat, fatty acid saturation and mitochondrial bioenergetics. J Bioenerg Biomembr 2014;46:33–44
20. Ojuka EO, Jones TE, Han D-H, Chen M, Holloszy JO. Raising Ca2+ in L6 myotubes mimics effects of exercise on mitochondrial biogenesis in muscle. FASEB J 2003;17:675–681