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New Insights on the Role of SERCA During Vessel Remodeling in Metabolic Syndrome

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COMMENTARY

The prevalence of metabolic syndrome in the adult population in developing countries, as it is currently conceived by the current definitions, has been estimated to range from 22 to 39% and varies depending on the definition used and on ethnicity (1–3). Metabolic syndrome is associated with future coronary heart disease events (4), and this forms the underlying basis for the study by Dineen et al. in this issue of *Diabetes* (5). Patients with metabolic syndrome have been shown to have an increased mean intimal-medial thickness (0.98 vs. 0.92 mm, $P < 0.01$) of the common carotid and an increase in the number of components of metabolic syndrome, which is associated with an increasing trend in the mean intimal-medial thickness, suggesting that metabolic syndrome can effect vessel wall modeling (6). Defining the biology of these early mural changes should allow for a better delineation of how metabolic syndrome influences the response to injury after coronary intervention.

Individuals with metabolic syndrome and a Framingham risk score greater than 20% have an increased risk of major coronary events over the next 10 years compared with people without metabolic syndrome and the same risk score (7). Metabolic syndrome is associated with an increased risk of myocardial infarction with a corresponding population-attributable risk of 14.5%. The clustering of greater than three risk factors with subthreshold values is also associated with an increased risk of myocardial infarction (odds ratio 1.50 [95% CI 1.24–1.81]) compared with component factors with values in a normal range (8). The presence of metabolic syndrome increases the risk of mortality by 1.6-fold and cardiovascular death by 2.4-fold in patients who present with an acute coronary syndrome (9). The presence of metabolic syndrome correlates with a heightened inflammatory response following elective percutaneous coronary intervention (10). Adjusting for age, sex, BMI, LDL cholesterol level, hypertension, smoking, prior coronary artery bypass graft, presentation of acute coronary syndrome, left ventricular ejection fraction, multivessel disease, and procedural success, the risk of cardiac events remains significantly elevated in patients with metabolic syndrome following percutaneous coronary intervention (11).

As a result of the impact of metabolic syndrome on cardiovascular mortality, there has been considerable interest in the cardiovascular outcomes of antidiabetes agents. Glucagon-like peptide 1 (GLP-1) is an endogenous hormone that functions in normal physiology to increase insulin sensitivity, insulin biosynthesis, and insulin secretion (12). Administration of GLP-1 receptor agonists induces weight loss, increases insulin secretion, and improves glucose tolerance in patients. Experimentally, GLP-1 receptor agonists have also been shown by several authors to reduce myocardial infarct size (13), improve cardiac function in chronic heart failure (14), and attenuate neointimal formation following vascular injury (15). GLP-1 receptor agonists selectively reduce the proliferation of vascular smooth muscle cells and the development of intimal hyperplasia in vivo without affecting the reendothelialization process that occurs after arterial injury. There is also an improvement in arterial wall elasticity. GLP-1 receptor agonists were also shown to significantly decrease the proliferation and to increase the apoptosis of vascular smooth muscle cells in vitro. These effects appeared to be mediated through cAMP signaling and endothelial nitric oxide synthase following GLP-1 receptor activation (16). GLP-1 receptor agonists have also been shown to improve sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) activity. Studies in healthy animals suggest that GLP-1 receptor agonists have cardioprotective properties, perhaps partially mediated by this improved SERCA activity.

Ossabaw swine developed more extensive and diffuse coronary artery disease and more severe restenotic responses to stenting than Yucatan swine (17). Porcine coronary

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vascular smooth muscle cells have been shown to have abnormalities of at least 10 regulatory processes, proteins, and membrane domains that influence Ca^{2+} signaling (18). Neeb et al. (17) have shown that SERCA is upregulated and sarcolemmal Ca^{2+} extrusion is increased in the coronary vascular smooth muscle cells of lean Ossabaw swine compared with lean Yucatan swine. This increased expression of SERCA decreases in metabolic syndrome (17). Neeb et al. (17) suggested that there was a propensity toward SERCA dysfunction in Ossabaw swine predisposed to metabolic syndrome. Dineen et al. (5) examined the acute effects of a GLP-1 receptor agonist on porcine coronary smooth muscle cells and found that the GLP-1 receptor agonist activated SERCA but did not alter other Ca^{2+} transporters, confirming a similar biology to that reported previously in other cell types. They followed their in vitro studies with in vivo treatment with the GLP-1 receptor agonist AC3174 in Ossabaw miniature swine fed a hypercaloric, atherogenic diet. These swine were considered to mimic metabolic syndrome without hypertension. The GLP-1 receptor agonist AC3174 attenuated weight gain, increased insulin secretion, and improved glucose tolerance. Despite these improved metabolic parameters, there was no change in the development of coronary artery disease as determined by both intravascular ultrasound and histology. The presence of metabolic syndrome abolished SERCA activation by GLP-1 receptor agonists. The authors concluded that metabolic syndrome confers vascular resistance to GLP-1 receptor agonists, partially through impaired cellular signaling steps involving SERCA.

Five isoforms of SERCA (SERCA2a, -2b, -3a, -3b, and -3c) have been detected in the murine heart and thoracic aorta. In the aorta, SERCA2a accounts for ~91% of total SERCA and SERCA2b accounts for ~5% (19). Among SERCA3 isoforms, SERCA3b is the most expressed and is mainly found in vascular smooth muscle cells, along with SERCA2a and -2b. Strong downregulation of SERCA2a is observed in atherosclerotic vessels containing mainly synthetic vascular smooth muscle cells (those with decreased contractile proteins) (Fig. 1). The proportion of both SERCA2b and SERCA3b is conversely increased to 9.5% and 8.3%, respectively (19). Hill et al. (20) demonstrated a sevenfold increase in SERCA2 in the coronary vascular smooth muscle cells of alloxan-induced diabetic swine fed a high-fat diet compared with swine fed either a low-fat diet or a high-fat/high-cholesterol diet. SERCA activity is increased in diabetic and high-fat–fed swine. In contrast, Adachi et al. (21) have shown a downregulation of SERCA function and protein in aortic vascular smooth muscle cells harvested from grossly hyperlipidemic and atherosclerotic rabbits.

It is widely accepted that endothelial dysfunction is a major feature of atherosclerosis and diabetes and is associated with decreased nitric oxide bioactivity. Modulation of L-type calcium signaling has been shown to affect the remodeling of the vessel wall in animals models or arterial injury. Transient receptor potential cation channels have been shown to be increased in metabolic syndrome before the development of coronary artery disease (22). SERCA is a major cyclic guanosine monophosphate–independent target for nitric oxide (23). Physiological

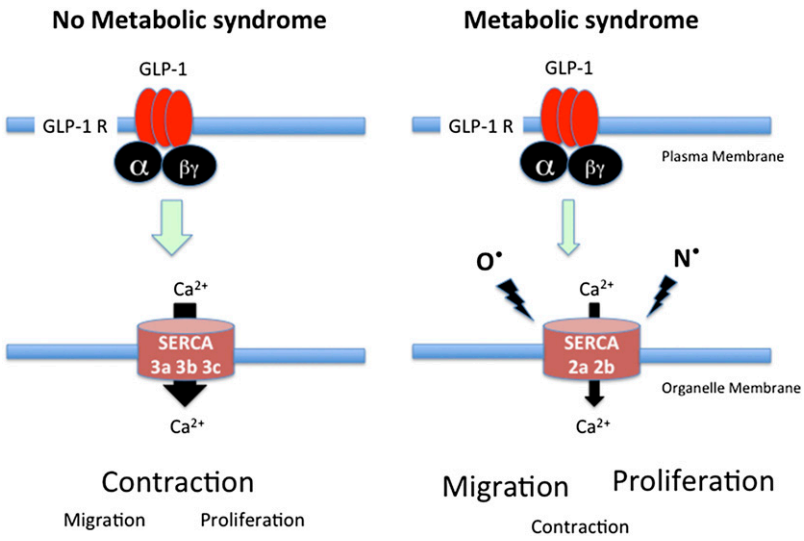

Figure 1—Proposed differences in SERCA expression and activity in metabolic syndrome. Metabolic syndrome alters the activation of SERCA and the expression of particular isoforms of SERCA in the cell membranes. There is an increase in SERCA2a and -2b compared with SERCA3a, -3b, and -3c. Furthermore, the molecule undergoes modification of its residues through activated oxygen and nitrogen species brought about by the high glucose and lipid levels in the tissue. These changes in SERCA are a component of the phenotypic change in vascular smooth muscle cells from a contractile phenotype to a synthetic phenotype that occurs during atherosclerotic remodeling of the vessel wall. The synthetic phenotype is more prone to migration and proliferation. GLP-1R, GLP-1 receptor.

levels of reactive nitrogen species have been shown to induce *S*-glutathiolation of SERCA at cysteine-674 (Cys674), resulting in an increase in SERCA activity and inhibition of Ca^{2+} influx and migration of vascular smooth muscle cells. An augmentation of reactive nitrogen species, as is seen in vascular diseases such as atherosclerosis, diabetes, and metabolic syndrome, will irreversibly oxidize Cys674 or nitrate tyrosine residues at Tyr296-Tyr297, both of which result in a loss of SERCA function. Similarly, in vascular smooth muscle cells exposed to high glucose levels in vitro, failure of nitric oxide to inhibit vascular smooth muscle cell migration is due to oxidation of the SERCA-reactive Cys674 (23). This is prevented by antioxidants and increased expression of SERCA (24).

The study of the role of multiple cardiovascular risk factors manifest in metabolic syndrome is complex. Dineen et al. (5) use a porcine model that is predisposed, compared with other breeds, to changes in calcium signaling to further the study of the effects of GLP-1 receptor agonists. In this model, GLP-1 interferes with one of the 10 known calcium-signaling SERCA but does not affect vessel wall modeling over time, which would suggest other mechanisms are more biologically relevant. Clinically, the study by Dineen et al. (5) would suggest that GLP-1 receptor agonists alone cannot mitigate the risk of atherosclerotic disease in patients with metabolic syndrome.

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

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