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A New Road for Treating the Vascular Complications of Diabetes: So Let's Step on the Gas

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COMMENTARY

The authors van den Born et al. (1) have written a timely Perspective in this issue of *Diabetes*. Both type 1 and type 2 diabetes have reached epidemic proportions throughout the world, afflicting over 400 million people. Moreover, the number of individuals that will develop diabetes is predicted to rise (2). Both individuals with type 1 and type 2 diabetes are at a significantly greater risk for developing microvascular and macrovascular diseases. People with diabetes who cannot maintain adequate glycemic control (such as the failure to reach the recommended target level of HbA_{1c} <7%) are predisposed to develop neuropathy, retinopathy, nephropathy, cardiovascular disease, cerebrovascular disease, and premature death. In response to the enormity of this medical problem, there have been major initiatives on the part of global health organizations, national diabetes associations, and primary caregivers to educate patients about the benefits of appropriate nutrition and physical activity. For individuals with diabetes who have insufficient appropriate nutrition and physical activity, an increasing number of oral and injectable interventions are available to improve glycemic control (3,4). For many patients, however, the current forms of therapy now used for treating both types of diabetes are inadequate.

Thus, there clearly remains a large area of unmet therapeutic need for novel pharmacological interventions that target the major complications of diabetes. Such therapies need to be identified and developed with greater efficiency by exploiting innovative molecular targets. In the current Perspective, van den Born et al. (1) present interesting data suggesting that the modulation of one or more of the three major gasotransmitters (nitric oxide [NO], carbon monoxide [CO], and hydrogen sulfide [H_2S]) could eventually offer a novel therapeutic option(s) targeting the vascular complications of diabetes, as there is evidence to suggest that there is a reduced bioavailability of these gasotransmitters in people with diabetes.

In addition to other risk factors (hypertension, tobacco use, and obesity), chronic hyperglycemia can be regarded as a root cause of the vascular complications of diabetes (5,6). The basis for this assertion is that diabetes complications occur with a significantly greater frequency in hyperglycemic individuals with diabetes when compared with those with controlled diabetes. Elevated blood glucose levels cause oxidative stress due to increased production of mitochondrial reactive oxygen species (ROS), nonenzymatic glycation of proteins, and glucose autoxidation (6,7). Oxidative stress resulting from either the increased production or inadequate removal of ROS plays a key role in the pathogenesis of vascular diabetes complications (5,7).

The pathogenesis of vascular damage is multifactorial but is clearly mediated by increased concentration of ROS (8). In addition, increased concentrations of reactive nitrogen species and other inflammatory molecules (whose expression is increased by hyperglycemia and ROS) cause vascular damage (1,9). Vascular function is also dependent on NO, CO, and H_2S. Included in their myriad physiological functions (1) is vasodilatory activity. Furthermore, each gasotransmitter can reduce oxidative stress through direct interaction with ROS (1). In addition, these gasotransmitters are able to upregulate the endogenous antioxidant system via activation of nuclear factor (erythroid-derived 2)–like 2 (Nrf2) (10–12). Nrf2 is a basic leucine zipper transcription factor that controls the expression of a large number of genes including heme oxygenase-1 (HO-1), an enzyme that produces CO; antioxidant enzymes; and glutathione-related enzymes (13). Overall, Nrf2 activation is linked to reductions in both oxidative stress and inflammation (local and systemic) and has been proposed as a therapeutic approach for diabetic nephropathy (14). Depleted or even reduced levels of NO, CO, or H_2S are associated with impaired vascular function. NO is reduced in conditions of endothelial dysfunction,

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and NO-dependent vasodilation is impaired in people with type 2 diabetes (1). Similarly, HO-1 and H_2S are reduced in both people with diabetes and animal models of diabetes (1) (Fig. 1).

There is emerging evidence that the three major gasotransmitters (NO, CO, and H_2S) are associated with the microvascular and macrovascular complications of diabetes. van den Born et al. (1) provide a meticulously organized, up-to-date summary of the rodent and human studies that detail the complex roles exerted by these gasotransmitters on vascular function and pathophysiology. Due to their inherent volatility, the measurement of the gasotransmitters is challenging. Therefore, the authors discuss the methods for their analyses. Moreover, they present a brief review of the endogenous production and function of each gasotransmitter and a discussion of the interactions between them. Finally, the authors discuss the potential for the clinical use of modulators of gasotransmitters in people with diabetes. In the case of NO, approved pharmacological modulators, such as sodium nitroprusside, are available and in use. Because no CO-releasing molecules are available for clinical use, a potentially attractive alternative option might be an inducer of HO-1 (14). The authors discuss several potential approaches for modulating H_2S, although none are currently being used. While each of these gasotransmitters share the ability to promote vasodilation and reduce oxidative stress, the authors call for prudence in that elevation of these gasotransmitters above certain physiological thresholds could result in deleterious effects on vascular function.

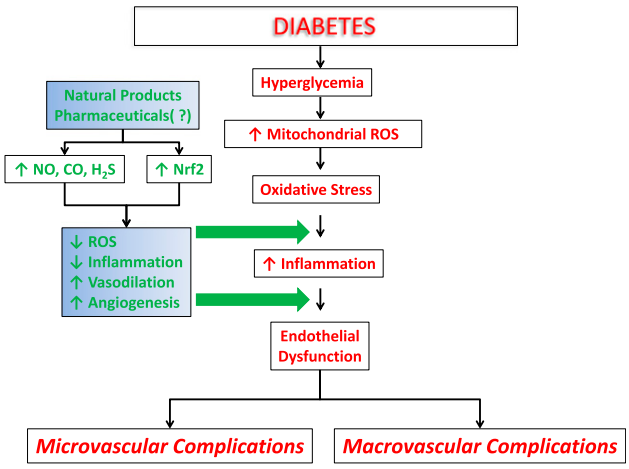

Figure 1—Potential physiological benefits of increasing gasotransmitters and/or Nrf2 to treat the micro- and macrovascular complications of diabetes. The proposed causative links between the hyperglycemia of diabetes, mitochondrial ROS generation with subsequent oxidative stress, and activation of stress-sensitive inflammatory pathways (e.g., nuclear factor-κB, p38 MAPK, and JNK) are shown (5,7). These activated pathways cause endothelial dysfunction and vascular diabetes complications. Data indicate that prevention and/or inhibition of mitochondrial ROS production will prevent the hyperglycemia-induced increase in both ROS production and activation of inflammatory pathways (8). As proposed by van den Born et al. (1), increasing the levels of one of more of the gasotransmitters and/or Nrf2 will inhibit the effects of oxidative stress and preserve vascular cells.

Beyond its cohesive and logical organization, the notable strengths of the article include *1*) a concise overview of the three major gasotransmitters implicated in the vascular complications of diabetes; *2*) consideration of the available data in the context of both microvascular and macrovascular complications of this disease; *3*) analyses of both rodent and human data, including alterations in the bioavailability of the three gasotransmitters in the context of diabetes; and *4*) examples of clinical interventions designed to modulate the levels of the gasotransmitters. The authors are to be commended for their balanced presentation and meticulous review of the subject. Elevated ROS, reactive nitrogen species, oxidative stress, and endothelial dysfunction are associated with both insulin resistance and hyperglycemia and typically precede the development of vascular diabetes complications (15). Numerous studies have reported the clinical benefits of antioxidants and other natural compounds (e.g., polyphenolics) on the improvement of vascular function. While beyond the scope of this Perspective, a targeted discussion of this area would be a useful topic in a future Perspective.

It is likely that a reduction of one or more of the gasotransmitters presented in this article plays a crucial role in the development of both the microvascular and macrovascular complications of diabetes. While there are many clinical options for improving glycemic control, there are limited pharmacological options proven to reduce the development of vascular diabetes complications. Further investigation of the modulators of the gasotransmitters should address this current unmet therapeutic need and, thus, is an intriguing area for further evaluation. However, like all emerging areas, convincing validation (i.e., proof of concept) is required, initially in relevant animal models and ultimately in humans. Importantly, initial validation could be achieved through the measurement of either biomarkers or other acceptable surrogate end points. However, any new gasotransmitter-modulating agent would have to safely reduce the risk of developing one or more of the vascular complications. Historically, the occurrence of adverse events has been and continues to be a supreme regulatory and economic challenge in clinical trials for diabetes complications. As a primary outcome measure, assessing the ability of any intervention to reduce the risk for developing one of the vascular complications requires multiple and lengthy clinical studies. However, optimism for a breakthrough on this front is warranted due to the advances in our knowledge of the pathophysiology of vascular complications, the variety of experimental therapeutic approaches available to evaluate this problem, the improved personalized characterization of

potential clinical study subjects, and a growing use of innovative clinical study designs. Thus, the Perspective by van den Born et al. (1) contributes to this optimism.

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

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