EDITORIAL

Korean J Intern Med 2017;32:439-441
https://doi.org/10.3904/kjim.2017.153

Oxidative stress: link between hypertension and diabetes

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Redox homeostasis is essential for maintaining cellular structure and function, and is tightly regulated by exogenous and endogenous stimuli. When this homeostasis is disrupted, however, oxidative stress may lead to aberrant cell dysfunction and death and also contribute to disease development. In particular, the role of oxidative stress in the pathogenesis of type 2 diabetes and hypertension is well-established [1].

The renin angiotensin system (RAS) plays a major role in mitochondrial dysfunction in obesity and insulin resistance [2]. Angiotensin II (Ang II) is an inflammatory adipokine that has been implicated in oxidative stress and the pathogenesis of insulin resistance. Aberrant Ang II secretion promotes the production of reactive oxygen species (ROS) in the mitochondria via mitochondrial respiratory chain complexes I and III and a protein kinase C-dependent pathway, which leads to mitochondrial dysfunction [3]. Thus, understanding the role of RAS in oxidative stress is crucial for elucidating the pathogenesis and treatment of metabolic disorders such as obesity, hypertension, and diabetes.

The excessive ROS production induced by RAS activation affects several organs that have major roles in glucose metabolism, such as the pancreas, liver, muscle, and adipose tissue. In pancreatic β-cells, chronic hyperglycemia and hyperlipidemia upregulate the RAS pathway, which results in oxidative stress and subsequent β-cell dysfunction and apoptosis [4]. Moreover, β-cells are more vulnerable to oxidative stress than other cells because their antioxidant capacity is weaker than that of other organs [5,6]. In this context, blocking the RAS system using angiotensin receptor blockers (ARB) could help preserve β-cell function [7]. For example, the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study showed that long-term treatment (5 years) with valsartan (160 mg) reduced the onset of type 2 diabetes by 14% in individuals with impaired glucose metabolism [8]. Another study demonstrated that treatment with valsartan (320 mg) for 26 weeks increased glucose-stimulated insulin secretion in subjects with prediabetes compared with the placebo group [9]. In addition, insulin sensitivity, as assessed in a clamp study, was significantly improved with valsartan treatment, even though body mass index remained unchanged in both groups [9].

Numerous studies have shown that the upregulation of components of the RAS and oxidative stress contribute to insulin resistance and that ARBs can

Received: April 7, 2017
Accepted: April 26, 2017

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pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

help improve insulin resistance in muscle, adipose tissues, and the liver via a variety of mechanisms [2]. In diet-induced obese mice, olmesartan treatment inhibited ROS production and ameliorated dysregulated adipocytokines in adipose tissues [10]. Losartan [11] and valsartan [12] improved insulin-dependent glucose uptake into muscles with deteriorated insulin sensitivity. Collectively, dysregulation of the RAS is closely related to oxidative stress in the development and progression of type 2 diabetes. Furthermore, the role of RAS and oxidative stress in the development and progression of diabetic complications is most important in patients with both diabetes and hypertension.

Although the benefits of ARB have been established, only a few studies have investigated the effects of amlodipine on oxidative stress, and the results tend to be conflicting. Amlodipine had strong antioxidant actions in vitro, independent of calcium channel modulation [13]. It also attenuated oxidative stress and high blood pressure (BP) in an oxidative stress-induced hypertensive animal model, which appeared to be mediated by prostanoid endothelium-derived factors and nitric oxide [14]. However, another study reported that amlodipine had only an additive role with ARB for reducing oxidative stress in metabolic syndrome rats. Hirooka et al. showed that valsartan, but not amlodipine, treatment for 1 year reduced oxidative stress markers and improved endothelial functions in patients with essential hypertension [15]. Conversely, amlodipine and valsartan equally decreased oxidative stress markers in patients with chronic kidney disease on hemodialysis [16]. Although further studies are needed, the overall results suggest that amlodipine can effectively ameliorate oxidative stress and exert hypotensive effects.

In the current issue, Kim et al. [17] assessed the effects of two kinds of antihypertensive drug (amlodipine and valsartan) on oxidative stress in patients with type 2 diabetes. BP drug-naïve subjects were randomly assigned to each group, and the authors found that both agents were beneficial for reducing the levels of oxidative stress markers and BP, even though there were no changes in glucose and lipid levels. However, it is unknown whether these are "BP-lowering" or "class" effects. Recent studies demonstrated that oxidative stress is the consequence, not the cause, of hypertension and that adequate BP control improves oxidative stress regardless of the type of drug [18]. Similarly, the findings of Kim et al. [17] are thought to be a result of BP control rather than the characteristics of each drug. Additionally, does reducing oxidative stress improve the clinical outcomes, such as decreasing the incidence of cardiovascular events or diabetic complications? Interestingly, studies using antioxidants to reduce oxidative stress have failed to change the natural course of diabetes and/or hypertension [19]. The authors also did not determine whether reducing oxidative stress would affect clinical outcomes in this study, but this could be easily inferred from previous large clinical trials. As fundamental trials have suggested, proper BP control and reducing oxidative stress could delay the progress of complications in patients with diabetes and hypertension. Thus, preventing the oxidative stress, the link between diabetes and hypertension, is a novel treatment strategy in clinical practice.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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