Editorial Comment

The Vascular Renin-Angiotensin System as a Possible Source of Vascular Inflammation in Fructose-Fed Rats

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Increased consumption of carbohydrates underlies the pandemic increase in the number of people with obesity in the industrialized world. Obesity is frequently associated with other metabolic derangements, thereby leading to more morbid cardiovascular diseases. Hypertension is one of the key derangements clustered in obesity and/or insulin resistance (*1*). Why is that increased consumption of carbohydrates, rather than salt, raises blood pressure? This question has puzzled researchers for some time. Fortunately, we can use fructose-fed rats (FFR) (*2*), which develop hypertension, dyslipidemia and insulin resistance, as an ideal model to address this question. Pharmacological studies suggest that activation of the sympathetic nervous system (*2*, *3*) as well as the renin-angiotensin system (RAS) is involved in the development of hypertension in this model. In particular, the angiotensin II (Ang II) type 1 (AT1) receptor in the cardiovascular system has emerged as a central player of this link (*4*).

In an article appearing in this issue of *Hypertension Research* (*5*), Nyby *et al*. provide a fresh look at the role of the vascular AT1 receptor in vascular dysfunction, oxidative stress and inflammation in FFR. They show that the increased oxidative stress and inflammation in the aorta of FFR are associated with the increased expression of tissue AT1 receptor. Captopril, an angiotensin-converting enzyme (ACE) inhibitor, reversed hypertension and all of these vascular abnormalities. These results suggest that vascular dysfunction and vascular oxidative stress in FFR are mediated by vascular RAS.

It is widely accepted that inflammation underlies both insulin resistance and accelerated atherosclerosis in obesity and type 2 diabetes (*6*). From this point of view, it is noteworthy that the treatment with captopril did not alleviate hyperinsulinemia or glucose intolerance, which is in keeping with a previous study (*7*). Although insulin sensitivity was not directly measured by more sophisticated techniques such as glucose clamp, these findings have several implications. First, the anti-inflammatory effects of captopril seem more prominent in vascular tissues than in adipose tissues and skeletal muscles, since the drug did not affect systemic insulin resistance, which conceivably correlates RAS signaling in the latter two tissues. Second, neither hyperinsulinemia nor hyperglycemia *per se* mediate vascular inflammation in this model. This notion appears to contradict the hypothesis that hyperinsulinemia selectively stimulates MAP kinase signaling in vascular tissues in Zucker fatty rats (*8*), thereby aggravating cell proliferation and atherosclerosis. As suggested by Nyby *et al*. (*5*), vascular inflammation may be directly determined by the activity of vascular RAS. However, some investigators have reported that other ACE inhibitors such as enalapril (*9*, *10*), quinapril (*11*) and temocapril (*12*), and AT1 receptor antagonists such as losartan (*4*, *13*) and olmesartan (*12*, *14*), reverse insulin resistance as well as hypertension. Therefore, further studies may be warranted to clarify the differential effects of various RAS-blocking agents on insulin resistance.

In addition to antihypertensive agents, fish oil (*15*), troglitazone (*16*), and pioglitazone (*17*) have been reported to alleviate hypertension in FFR, suggesting that oxidative stress

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and insulin resistance *per se* are involved in the development of hypertension in FFR. Deciphering the precise relationship between RAS and each of these other targets for unconventional blood pressure–lowering therapy should provide us with further insight into the pathophysiology of metabolic syndrome, and ultimately lead to an ideal strategy for alleviating aortic blood pressure in patients with metabolic syndrome.

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