Editorial Comment

The Role of Tumor Necrosis Factor- α in Inducing Insulin Resistance in the Renin-Angiotensin System

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Recent evidences suggest that insulin resistance is one of the most important factors in cardiovascular diseases. Insulin resistance is also involved in metabolic syndrome, a clustering of atherosclerotic metabolic abnormalities. In the therapeutic strategies for metabolic syndrome, the relation between the action of insulin and the renin-angiotensin system (RAS) appears to be clinically important.

Skeletal muscle and adipose tissue are known as insulin-sensitive organs. Adipose tissue not only plays an important role in lipid metabolism, but also functions as an endocrine organ that produces bioactive molecules called adipokines, such as leptin, adiponectin and tumor necrosis factor- α (TNF- α). On the other hand, skeletal muscle is known as a major cause of energy expenditure. Insulin resistance in skeletal muscle is observed in diabetic patients and animal models (1–3). TNF- α induces insulin resistance by inhibiting insulin-mediated intracellular signaling (3). Moreover, recent reports have indicated that TNF- α is produced in skeletal muscle (4–6). Angiotensin II (Ang II) type 1 (AT₁) receptor blocker (ARB) has been shown to inhibit TNF- α production as well as insulin resistance (5–7). However, the mechanism of action of Ang II on regulation of TNF- α production has not been clear. In an article appearing in this issue of *Hypertension Research* (pp. 773–778), Yamaguchi *et al.* provide new evidence on the mechanism of action of RAS in TNF- α production in skeletal muscle using fructose-fed rats (8). They show that the tissue level of TNF- α in rat skeletal muscle was elevated by fructose-rich chow, and that this increase was

inversely related with the level of cAMP. An ARB, olmesartan, inhibited the increase in TNF- α level as well as the change in cAMP level caused by fructose-rich chow. Their results suggest that TNF- α production is negatively regulated through cAMP in skeletal muscle. Moreover, they found that a blockade of AT₁ receptor decreased TNF- α production by increasing the level of cAMP.

The possible involvement of AT₁ receptor signaling in the regulation of cAMP production is also an interesting subject. Most physiological actions of Ang II are mediated through AT₁ receptor. Ang II stimulation is often linked with phospholipase C activation, resulting in generation of diacylglycerol and inositol trisphosphate (IP₃), activation of protein kinase C and intracellular Ca²⁺-mobilization through AT₁ receptor in the cardiovascular system and sympathetic neurons. However, as Yamaguchi *et al.* report (8), Ang II also inhibits adenylyl cyclase/cAMP in rat heart myocytes, aorta and hepatocytes. On the other hand, Ang II stimulates cAMP production in some tissue (9), and may enhance cAMP production *via* Ca²⁺/calmodulin (10). An increase in adenylyl cyclase/cAMP by a rise in available Ca²⁺ has also been suggested (11). These findings suggest a complex and variable intracellular signaling of Ang II depending on cell types.

To study the relation between RAS and TNF- α as well as other adipokines and its mechanism may provide a fresh perspective on the role of RAS in metabolic syndrome and a therapeutic strategy for insulin resistance with ARB.

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