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The role of the renin-angiotensin system in obesity and insulin resistance

Oliveira-Junior SA, Martinez PF, Guizoni DM, Campos DHS, Fernandes T, Oliveira EM, Marina P, et al. AT1 receptor blockade attenuates insulin resistance and myocardial remodeling in rats with diet-induced obesity. **PlosOne 2014;9(1):e86447**

Cardiac remodeling consists of a series of adaptive changes to maintain cardiac function during pressure or volume overload. This process is common in different diseases, including obesity. Experimental evidence shows that an obesity-induced diet is associated with cardiac remodeling, contractile disturbances, hypertrophy, interstitial fibrosis and changes in the expression of some proteins as of myosin heavy chain β isoform. Moreover, this type of diet generally produces insulin resistance and glucose metabolism disorders.

On the other hand, different studies have demonstrated the interaction between signaling pathways that mediate the effect of insulin and angiotensin on the heart. It has been shown that activation of angiotensin AT-1 receptors modifies the metabolic effects of insulin. Therefore, in conditions or diseases which activate the renin-angiotensin system, and consequently, the AT-1 receptors, there is a certain degree of cardiac insulin resistance. As obesity is a metabolic condition characterized by the chronic activation of the renin-angiotensin system, the aim of this study was to evaluate whether angiotensin AT-1 receptor activation has an inhibitory effect on the intracellular cardiac insulin receptor signaling cascade in an obesity and insulin resistance rat model.

A group of control (C) rats and another group treated with hypercaloric diet (OB) were studied during 30 days. The experiments were repeated in a second lot of animals treated with losartan (CL and OBL).

The OB animals had higher body weight and adiposity than their corresponding controls. Obesity also exhibited elevated cholesterol and insulin levels. Another characteristic in these animals was increased triglycerides, free fatty acids, angiotensin-converting enzyme activity and glucose intolerance. Losartan treatment reduced these alterations and decreased insulin and HOMA index levels.

In addition, losartan treatment, as expected, reduced blood pressure, and it also attenuated the diastolic dysfunction observed in obese animals.

Postmortem analysis revealed increased myocyte cross-sectional area (a hypertrophy index) as well as greater interstitial collagen volume, without changes in myosin β heavy chain expression. All these changes reversed with losartan.

As the MAP kinase pathway is an important signaling pathway associated with angiotensin AT-1 receptor activation, the study evaluated the expression of these enzymes (ERK and JNK). Obesity increased ERK expression, which might be showing the relationship between hyperinsulinemia and angiotensin AT-1 receptor activation. It also increased the expression of PI3K, a key enzyme in the insulin receptor signaling cascade which is able to activate the MAP kinase pathway. Thus, angiotensin AT-1 receptor blockade attenuates different metabolic disorders produced by an obesity-induced diet, as dyslipidemia, altered glucose metabolism and insulin resistance. In addition, losartan normalizes blood pressure and some signals participating in ventricular remodeling.

The study from Oliveira-Junior et al. shows the relationship between intracellular angiotensin and insulin receptor signaling pathways at the cardiac level in an obesity and insulin resistance model. It is known that angiotensin AT-1 receptor activation has different peripheral effects as vasoconstriction, aldosterone secretion, sodium reabsorption and development of hypertension. Blocking these receptors improves peripheral resistance, increased blood flow to the skeletal muscle and blood glucose levels. However, it is interesting that some of these effects and others on cardiac remodeling occur through the cross-talk between insulin and angiotensin mechanisms using MAP kinases as a common pathway.