Elucidation of the molecular mechanism underlying insulin resistance related to salt-sensitive hypertension

Tomoichiro Asano, Hideki, Katagiri, Katsunori Tsukuda, Hiraku Ono, Midori, Fujishiro
Department of Internal Medicine, Faculty of Medicine, University of Tokyo

Summary

A high-salt diet, which is known to contribute to the pathogenesis of hypertension, is also reportedly associated with insulin resistance. We have investigated the effects of a high-salt diet on insulin sensitivity and insulin signaling in salt-sensitive (Dahl-S) and salt resistant (Dahl-R) strains of Dahl rat as well as the Sprague-Dawley rats constitutively infused with angiotensin II. Evaluation of hyperinsulinemic-euglycemic clamp studies and glucose uptake into isolated soleus muscle revealed that salt loading (8% NaCl) for 4 weeks induced hypertension and significant insulin resistance in Dahl-S rats, whereas no significant effects were observed in Dahl-R rats. Similarly, insulin resistance was observed in the AII-infused rats. Despite the presence of insulin resistance, insulin-induced tyrosine phosphorylation of the insulin receptor and insulin receptor substrates, activation of phosphatidylinositol 3-kinase, and phosphorylation of Akt were all enhanced in Dahl-S rats fed a high-salt diet and AII-infused rats. The mechanism underlying this form of insulin resistance thus differs from that previously associated with obesity and dexamethasone, and is likely due to impairment of one or more metabolic steps situated downstream of phosphatidylinositol 3-kinase and Akt activation. Interestingly, supplementation of potassium (8% KCl) ameliorated the changes in insulin sensitivity in Dahl-S rats fed a high-salt diet, associated with a slight, but significant, decrease in blood pressure. Furthermore, treatment with tempol, a membrane-permeable superoxide dismutase mimetic, reversed upregulated cholesteryl ester hydroperoxide levels in plasma of AII-infused rats and the AII-induced insulin resistance, restoring normal levels. Taken together, these results suggest that increased oxidative stress, possibly through the impaired insulin signaling located downstream from PI 3-kinase activation, is likely to be involved in AII-induced insulin resistance.