# Abnormal activation of a protein may explain deadly link between high salt intake and obesity

September 19 2011

Dietary salt intake and obesity are two important risk factors in the development of high blood pressure. Each packs its own punch, but when combined, they deliver more damage to the heart and kidneys than the sum of their individual contributions. Discovering the molecular mechanisms behind this lethal synergy has presented a challenge to scientists, but research led by Toshiro Fujita, MD, professor and chairman of the Department of Internal Medicine and chief of the Department of Nephrology and Endocrinology at the University of Tokyo, suggests that high dietary salt intake and obesity work together to trigger an abnormal activation of a cellular protein called Rac1.

Dr. Fujita's team studied the effects of a high-salt diet in rats bred to have high blood pressure and different levels of blood pressure sensitivity to salt. When obese "salt-sensitive" rats were fed a high-salt diet, the team found that Rac1 activated the mineralocorticoid receptor (MR) on the rats' kidney cells. This receptor is normally activated by the hormone aldosterone. When turned on, MR leads to the expression of a protein called epithelial sodium channel (ENaC) and an enzyme called the sodium pump. Both of these substances promote the reabsorption of salt, which causes the body to retain fluid and results in high blood pressure. This is the first time scientists have seen Rac1 usurp aldosterone's role in activating MR in the regulation of blood pressure. The protein's usual duties entail regulating an array of cellular events such as cell growth.

The team made the discovery when attempting to treat the obese, hypertensive rats with drugs designed to block MR activation and inhibit Rac1. When Rac1 inhibitors were successful in lowering the rats' blood pressure, the team knew they had discovered a mechanism by which obesity and a high-salt diet team up to wreak havoc on blood pressure and the kidneys.

According to Dr. Fujita, the team's findings carry important implications for the treatment of hypertension. "Our data indicate that the Rac1-mediated pathway in the kidneys can be an alternative therapeutic target for salt-sensitive hypertension and salt-mediated kidney injury," he said. "Based upon our results, we can speculate that Rac1 in the kidneys regulates salt susceptibility of blood pressure, and that Rac1 inhibitors, as well as MR antagonists, may be effective in the treatment of salt-sensitive hypertension."

Provided by American Physiological Society