Sex Differences in Obesity Mediated Cardiovascular Disease

The current obesity epidemic that affects more women than men worldwide is a leading cause to hypertension. While it has been shown that leptin contributes to obesity-induced hypertension by increasing sympathetic activity in males, it is unknown whether similar mechanisms trigger hypertension in obese females. Females secrete 3 to 4 times more leptin than males, but do not exhibit high sympathetic tone with obesity. They however show inappropriately high aldosterone levels that positively correlate with adiposity and blood pressure (BP). Here we hypothesized that leptin induces hypertension by increasing aldosterone production in obese females. Hyper-sensitivity to leptin, in lean mice or high leptin levels, in obese Agouti (Ay/a) mice induced hypertension but did not increase sympathetic control of BP. However, leptin sensitization and obesity elevated plasma aldosterone levels and adrenal aldosterone synthase (CYP11B2) expression, in females. Chronic leptin or mineralocorticoid receptors inhibition restored BP to baseline levels in leptin sensitized and obese agouti female mice. Leptin or leptin receptor deficiency in female ob/ob and db/db mice, respectively, abolished obesity-induced increases in adrenal CYP11B2 and plasma aldosterone while chronic leptin infusion in female mice triggered a dose-dependent increase in adrenal CYP11B2 and plasma aldosterone levels. Leptin-mediated aldosterone secretion was independent of changes in plasma angiotensin II, potassium and corticosterone and preserved in the presence of losartan or α and β-adrenergic receptors antagonists. Stimulation of human adrenocortical cells with leptin dose-dependently increased CYP11B2 expression and aldosterone production. While investigating the interaction between percentage of body fat, leptin and aldosterone levels in young healthy adult Caucasians we reported a positive correlation between adiposity and aldosterone, and between leptin and aldosterone in adult women only. Together these data suggest that leptin directly regulates aldosterone secretion and demonstrated that leptin induces HTN via aldosterone dependent mechanisms in obese females.