

Research Summary of Zhen Wang, PhD

Mechanisms of hypertensive diabetic nephropathy.

Diabetes mellitus and hypertension (HT) are two major risk factors for kidney disease, accounting for approximately 70% of end-stage renal disease (ESRD). Many patients with diabetes are hypertensive, which substantially increases the risk for the onset of kidney disease and progression of diabetic nephropathy. These patients are commonly treated with angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. However, these treatments only slow, rather than halt, the progression to ESRD. Therefore, there is an urgent need to understand the molecular mechanisms by which HT and diabetes interact to promote renal injury in order to identify and develop novel therapeutic targets to halt the progression of hypertensive-diabetic nephropathy.

We will use Goto-Kakizaki (GK) rats, a model of type II diabetes, to test our hypothesis that HT interacts synergistically with diabetes to promote renal injury by initiating a positive feedback loop including mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and oxidative stress. First, we will determine whether HT and diabetes interact to amplify renal injury by synergistic effects on mitochondrial dysfunction and ER stress. Then, we will examine whether treatment with specific mitochondrial targeted reactive oxygen species scavenger MitoTEMPO or ER stress inhibitor TUDCA after the onset of HT can prevent progression of renal injury induced by HT and diabetes. Our study will use a unique model in which both kidneys are exposed to the same levels of hyperglycemia, circulating hormones, and neural influences but have different blood pressures. The findings from this study will provide novel insights into the pathogenesis of hypertensive-diabetic nephropathy; more importantly, this proposal will also assess mitochondria and ER stress as potential therapeutic targets for treating hypertensive-diabetic nephropathy.

Role of negative regulators of leptin signaling (SOCS3) in modulating leptin's actions.

SOCS3 is a negative regulator of JAK-STAT3 signaling and serves as a negative feedback controller of LR signaling. Hypothalamic SOCS3 is upregulated in obese animals fed a high-fat diet and may contribute to development of resistance to leptin's anorexic and metabolic effects. Whether SOCS3 also attenuates leptin's effects to increase RSNA and BP has not been determined. Our preliminary studies indicate that selective CNS deletion of SOCS3 amplifies the BP effects of physiological increases in plasma leptin despite weight loss which would tend to reduce BP. We hypothesize that selective deficiency of SOCS3 in POMC neurons will amplify leptin's chronic effects to

increase RSNA and BP in normal mice and in mice fed a high fat diet. In current study, we will determine the impact of selectively decreasing SOCS3 expression in POMC neurons on leptin's chronic CV and metabolic effects.