Research Summary

Obesity is a major public health problem worldwide and increased body weight enhances the risk for hypertension, diabetes and coronary artery disease. Leptin, a peptide hormone produced by adipocytes in proportion to the degree of adiposity, plays an important role in the regulation of appetite, energy expenditure and body weight as well as sympathetic nervous system (SNS) activity and blood pressure (BP). Despite leptin levels being elevated in obesity, leptin's ability to suppress appetite is markedly attenuated, whereas its effect to increase SNS and BP are maintained, suggesting that obesity is associated with "selective" leptin resistance. The mechanisms for this differential regulation of appetite, SNS activity, and BP, however, are still unclear. We have recently found that changes in ambient temperature result in differential control of appetite. SNS activity and BP by leptin. We performed studies in lean wild-type (WT) mice to investigate the chronic metabolic and cardiovascular responses to leptin at thermoneutral zone (30oC,TNZ) and cold temperature (15oC), and we observed "selective" leptin resistance when ambient temperature was reduced from TNZ to 15oC. For instance, chronic leptin infusion for 7 days at 15^{o}C markedly raised BP and heart rate (HR) while the reduction in food intake was only modest and transient. Conversely, at TNZ leptin infusion caused pronounced and sustained suppression of food intake but failed to raise BP and HR. Thus, investigation of leptin's chronic actions at different ambient temperatures reveals divergent control of appetite and BP regulation by leptin and may provide important insights into the fundamental mechanisms by which leptin controls cardiovascular and metabolic functions independently.

Activation of leptin receptors (LR) in different areas of the brain could provide a partial explanation for differential control of appetite, energy expenditure, HR and BP regulation by leptin. In addition, each of three main intracellular signaling pathways activated by the LR (STAT3, IRS2 and SHP2) may contribute differently to the multiple actions of leptin. However, little is known about the specific areas of the brain, including the forebrain and brainstem, as well as the role of STAT3, IRS2 and SHP2 signaling in mediating the chronic effects of leptin on appetite, energy expenditure, HR and BP regulation at TNZ and during cold ambient temperature. We propose that activation of LRs in the forebrain, particularly in the hypothalamus, play a major role in controlling appetite at TZN but has only minor impact on energy expenditure, HR and BP regulation. Conversely, LRs in the brainstem are proposed to mediate important effects of leptin on energy expenditure, HR and BP, especially during cold exposure, but have minimal impact on appetite regulation.

Acute and chronic kidney diseases (CKD) are growing worldwide and in the United States the incidence of end stage renal disease (ESRD) has risen in parallel with increasing obesity and associated metabolic disorders, especially diabetes mellitus. This rise in ESRD is projected to escalate further due to increased longevity. Understanding the risks of parental obesity-induced metabolic disorders on future generations is crucial to determine potential interventions to prevent acute and CKDs and may provide insights into the mechanisms by which developmental programming influences development of cardiorenal diseases. One potential mechanism mediating the effects of parental obesity-induced developmental programming on cardiorenal function is excessive activation of the P2X purinoceptor 7 (P2X7R). Using a model of parental obesity induced by feeding chronic high fat diet (HFD), we found that P2X7R

expression is significantly greater in kidneys from offspring of obese parents, suggesting its potential role in the kidney injury observed in transgenerational obesity combined with hypertension (HT). We also found enhanced endoplasmic reticulum (ER) stress markers levels and mitochondrial dysfunction in kidneys from first generation obese parents.To determine a potential link between obesity-induced developmental programming and kidney injury, mice fed a HFD four weeks prior to mating, during gestation and lactation are used to create first and second generation models of obesity.

Further reading

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