Melanocortin Regulation of Energy Balance  
Research Description American Heart Association  
Scientific Development Grant

Obesity has rapidly become one of the most urgent public health crises claiming over 300,000 people each year. Energy balance involves accurate matching of energy intake with energy expenditure. To accomplish energy balance regulation, the body senses fuel stores from the periphery from either short term meal-related signals or long term signals arising from adipose tissue and relays this information to the central nervous system to interpret. The hypothalamus is arguably the most critical site for the integration of this information. Specifically, neurons within the arcuate nucleus that make up the melanocortin system have been established as essential components of body weight regulation. The melanocortin receptors within the hypothalamus that receive secondary downstream input from the arcuate neurons are the melanocortin 3 and melanocortin 4 receptor. Agouti-related peptide (AgRP) and alpha melanocyte stimulating hormone (α-MSH; derived from pro-opiomelanocortin) are two endogenous ligands for these receptors and are synthesized within the arcuate nucleus. AgRP is a potent stimulant of hyperphagia acting upon the MC3R and the MC4R while α-MSH inhibits food intake through the same receptors. Additionally, it has been determined that a co-receptor named syndecan-3 also helps facilitate the action of AgRP on the MC4R. Our previous work described the phenotype of syndecan-3 deficient mice and identified gender specific differences in energy balance regulation. Male syn-3-/- mice are resistant to diet-induced obesity (DIO) because they consume fewer calories than female syn-3-/- mice in relation to their wild-type counterparts. In contrast, female syn-3-/- mice are resistant to DIO because they show a disproportionate increase in energy expenditure compared to male syn-3-/- and their wild type counterparts. The interesting finding from these studies is that both male and female syn-3-/- mice show reduced adiposity but achieve this through distinct physiological mechanisms. Given this finding we hypothesized that since syn-3 interacts with AgRP exogenous central administration of AgRP to rodents should yield the opposite gender specific effects seen in the syn-3-/- mice. Our preliminary data reveal gender specific effects of AgRP on food intake and energy expenditure. Males respond to AgRP with prolonged hyperphagia (5 days) compared to females (3 days). Interestingly, both male and female rats gain the same percent body weight following AgRP administration. Because the increase in body weight seen in the female rats was not due to prolonged hyperphagia we hypothesized that they disproportionately decreased their energy expenditure in response to AgRP. In fact, female rats decreased their energy expenditure in response to AgRP dramatically while male rats only slightly decreased their energy expenditure during the light phase. These findings point to very distinct physiological gender specific mechanisms of body weight regulation. Our proposed studies aim to determine the underlying mechanisms of the sex differences seen after melanocortin ligand administration. The proposal will investigate the central hypothesis that gonadal hormones modulate the activity of the melanocortin signaling system. We hypothesize that estrogen inhibits the AgRP-induced hyperphagia and increases energy expenditure in females and that differences in energy expenditure may be due to different neural substrates activated by AgRP. Lastly, by utilizing behavioral, physiological, and molecular techniques we will examine the relative contributions to feeding and energy expenditure of the melanocortin 3 and 4 receptors within the hypothalamus in male and female rats. Understanding the sex differences underlying melanocortin control on energy balance is critical for the understanding of gender specific treatment of obesity.