Dr. Sharon Wardlaw

The long-term objective of this proposal is to understand how peripheral metabolic signals, including leptin, insulin and ingested nutrients, interact with brain neuropeptides to maintain energy balance in the human. The Aims focus on the brain melanocortin system which plays a critical role in maintaining energy balance and is regulated by leptin, insulin and nutrients. The physiology of this system, consisting of the proopiomelanocortin (POMC)-derived MSH peptides, the MSH antagonist, agouti related protein (AgRP) and the brain melanocortin receptors, has been well studied in rodents but such studies are not possible in humans unless reliable markers of brain POMC and AgRP activity can be found. This proposal will focus on cerebrospinal fluid (CSF) POMC and AgRP measurements as a surrogate for hypothalamic melanocortin activity, as related to CSF leptin, insulin and nutrient levels. Recent studies in the rodent show that levels of the intact POMC prohormone in CSF reflect hypothalamic POMC activity. We have confirmed that the POMC prohormone is the predominant POMC peptide in human CSF and present preliminary data relating CSF POMC to BMI and adiposity. Our data support a hypothesized primary role for POMC in regulating body weight. CSF POMC, POMC-derived peptides and AgRP levels will be measured in healthy lean and obese human subjects at baseline and in response to fasting and re-feeding and diet-induced weight loss. POMC and AgRP peptide processing will be characterized in parallel, as processing can be regulated by feeding. Plasma leptin and transport into CSF will be studied in relation to soluble leptin receptor levels and as a function of adiposity and feeding; CSF insulin will be studied in parallel and correlations of CSF POMC and AgRP with plasma and CSF leptin and insulin will be determined. Since nutrients themselves interact with melanocortin neurons, CSF metabolomic analysis will be performed with an emphasis on amino acid and lipid species. Finally, there is evidence that the new weight loss drug combination of bupropion plus naltrexone stimulates the melanocortin pathway in animals. Effects of these drugs on melanocortin peptide release into human CSF will therefore be studied. This would be the first study to examine CSF leptin, insulin and nutrient levels in relation to BMI and appropriate target neuropeptides and should provide unique data about the regulation of human energy balance. An important goal is to identify biomarkers in CSF that could predict responses to dieting and to pharmacotherapy for obesity that target the melanocortin system.
