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Research Summary:  
Neuroendocrine control of pituitary function. Hypothalamic regulation of energy homeostasis.

Dr. Wardlaw’s Neuroendocrine Program encompasses basic, translational, and clinical research. Clinical neuroendocrine research has ranged from studies of normal pituitary physiology to the diagnosis and treatment of pituitary diseases. A major clinical and basic research interest has been the stress response and the regulation of the hypothalamic-pituitary-adrenal axis and of the ACTH precursor, proopiomelanocortin (POMC). An important research focus has been the regulation of POMC gene expression and peptide processing in the hypothalamus and on the physiology of the brain POMC-derived peptides, β-endorphin and α-MSH. Studies have shown that POMC is regulated in the hypothalamus by sex steroids in rodents and primates and that this is important in regulating the pituitary–gonadal axis. Related studies have demonstrated that POMC is regulated in the hypothalamus by glucocorticoids, opioids, dopamine and leptin. More recently, research has focused on the neuroendocrinology of obesity. Studies have centered on understanding how the brain senses levels of peripheral energy stores and integrates these signals to maintain energy balance. An exciting focus has been on the hypothalamic melanocortin system which plays a critical role in maintaining energy balance in humans and animals. The melanocortin neuropeptide system regulates appetite, body weight and adiposity and is an important target for leptin and insulin in the hypothalamus. Studies center on the regulation of POMC and the POMC-derived peptides, LEP, together with agouti related protein (AgRP) which is synthesized in arcuate hypothalamic neurons. α-MSH inhibits feeding and AgRP is an orexigenic peptide that antagonizes the actions of α-MSH at specific melanocortin receptors. Recent studies have examined the regulation of POMC and AgRP gene expression, peptide processing and peptide release in the rodent hypothalamus by both leptin and insulin as well as interactions between the POMC and AgRP neurons themselves which both express melanocortin receptors. Transgenic and knockout mouse models have been used to study role of the melanocortin system in modulating metabolic responses to energy excess on a high fat diet and to food restriction and to characterize underlying mechanisms with respect to changes in body weight/composition and glucose and fat metabolism. An important focus is on the regulation of POMC peptide processing with respect to energy balance. The role of leptin and the melanocortin system in the regulation of the hypothalamic-pituitary-adrenal and gonadal responses to food restriction is also being studied. Human translational studies are evaluating cerebrospinal fluid (CSF) POMC and AgRP measurements as a surrogate for hypothalamic melanocortin activity, as related to CSF leptin, insulin and
nutrient levels. The intact POMC prohormone is being measured in CSF as this has been shown to reflect hypothalamic POMC activity in rodents. We have confirmed that the POMC prohormone is the predominant POMC peptide in human CSF and demonstrate a strong relationship to BMI and adiposity. 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.

Selected Publications:


Xiao E, Xia-Zhang L, Vulliemoz N, Ferin M, Wardlaw SL: Agouti-related


More about Sharon L. Wardlaw, MD: