

2nd International Conference on **Endocrinology**

October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore, USA

Disrupted melanocortin signaling may cause erectile dysfunction and loss of libido accompanying metabolic syndrome

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Melanocortins are a family of peptides that are derived from proteolytic cleavage of pro-opiomelanocortin (POMC) by prohormone convertases. POMC products, like α -melanocyte-stimulating hormone (MSH) dramatically improve hepatic insulin sensitivity and regulate glucose production. Reduced melanocortin activity may contribute to hyperglycemia in type 2 diabetes (T2D); indeed, melanocortin pathways have recently been implicated in mediating the reversal of T2D following gastric bypass surgery. Erectile Dysfunction (ED) is highly prevalent in men with both T2D and obesity. While the primary therapy for men with ED is phosphodiesterase type 5 (PDE5) inhibitors like Viagra, half of male patients with T2D are unresponsive to this treatment. Melanocortineric agents are currently being investigated for a possible therapeutic role in male and female sexual dysfunction. These investigations were initially sparked by findings that systemic administration of a synthetic analog of α -MSH, MT-II, causes penile erection in humans. Subsequent studies demonstrated neuronal α -MSH signaling promotes erectile activity and copulatory behavior in male mice. We have previously shown that male rodents lacking both insulin and leptin receptors in POMC neurons (LepR/IR^{POMC} mice) exhibit metabolic syndrome, including increased in body weight, hyperglycemia, hyperinsulinemia, and systemic insulin resistance. Here we show that LepR/IR^{POMC} males are sub-fertile due to dramatic alterations in sexual behavior and erectile function. Remarkably, these reproductive changes were accompanied by a dramatic decrease in POMC gene expression and α MSH production by POMC neurons. These results are compatible with reduced endogenous α -MSH production driving both T2D and erectile dysfunction. Thus, the melanocortineric system may prove a particularly effective pharmacological target for the treatment of ED in patients with T2D.

Biography

Jennifer W Hill earned her PhD in 2003 from Northwestern University and completed her postdoctoral training at Harvard and the University of Texas Southwestern. She is currently an Assistant Professor at the University of Toledo Medical Center where she chairs the steering committee for the Center for Diabetes and Endocrine Research. She received the Endocrine Society Young Investigator Award in 2013 for her work investigating the interactions between the neuroendocrine reproductive system and neural pathways regulating energy and glucose homeostasis.

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