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Research Report

Interconnection between orexigenic neuropeptide Y- and anorexigenic α-melanocyte stimulating hormone-synthesizing neuronal systems of the human hypothalamus

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ABSTRACT

Peripheral feeding-related hormones such as leptin, insulin, and ghrelin exert their main central effects through neuropeptide Y- (NPY) synthesizing and α-melanocyte-stimulating hormone- (α-MSH) synthesizing neurons of the hypothalamic arcuate nucleus. In rodents, recent reports have described an asymmetric signaling between these neuron populations by showing that while NPY influences α-MSH-synthesizing neurons, the melanocortin-receptor agonist Melanotan II (MTII) does not modulate the electrophysiological properties of NPY neurons. The functional neuroanatomy of the relationship between these cell populations is unknown in humans. The aim of the current study was to analyze the putative relationship of the orexigenic NPY and anorexigenic α-MSH systems in the infundibular nucleus of the human hypothalamus, the analogue of the rodent arcuate nucleus. Double-labeling fluorescent immunocytochemistry for NPY and α-MSH was performed on postmortem sections of the human hypothalamus. The sections were analyzed by confocal laser microscopy. Both NPY- and α-MSH-immunoreactive (IR) neurons were embedded in dense, intermingling networks of NPY- and α-MSH-IR axons in the human infundibular nucleus. NPY-IR varicosities were observed in juxtaposition to all α-MSH-IR neurons. The mean number of NPY-IR axon varicosities on the surface of an α-MSH-IR neuron was approximately six. The majority of NPY-IR neurons were also contacted by α-MSH-IR varicosities, although, the number of such contacts was lower (two α-MSH-IR varicosities per NPY neuron). In summary, the present data demonstrate that these two antagonistic, feeding-related neuronal systems are interconnected in the infundibular nucleus, and the neuronal wiring possesses an asymmetric character in the human hypothalamus.

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1. Introduction

The balance of food intake and energy expenditure is tightly regulated by the brain (Friedman, 1997; Schwartz et al., 2000). The hypothalamus is a prominent constituent of this central regulatory system (Friedman, 1997; Schwartz et al., 2000). It integrates feeding-related neuronal inputs derived from multiple loci of the central nervous system (CNS), senses peripheral metabolic signals such as leptin, insulin, and ghrelin, and regulates the energy homeostasis via its efferent neuroendocrine and autonomic neuronal pathways (Schwartz et al., 2000). Peripheral hormones act as mediators between the energy stores of the body and the brain (Flier, 1998; Schwartz et al., 2000). Although leptin, insulin and ghrelin are secreted by different tissues (Kojima et al., 1999; Schwartz et al., 2000), their circulating levels are related to the amount of stored energy (Benoit et al., 2004; Cummings et al., 2005).

The hypothalamic arcuate nucleus plays a primary role in the signaling of these peripheral satiety-related hormones (Hewson et al., 2002). Chemical ablation of the arcuate nucleus results in an obese phenotype and severe leptin resistance (Dawson et al., 1997). The arcuate nucleus contains two antagonistic neuronal populations that are sensitive to all three peripheral hormones (Hewson et al., 2002; Schwartz et al., 2000). A medially located cell population expresses the potent orexigenic peptide,

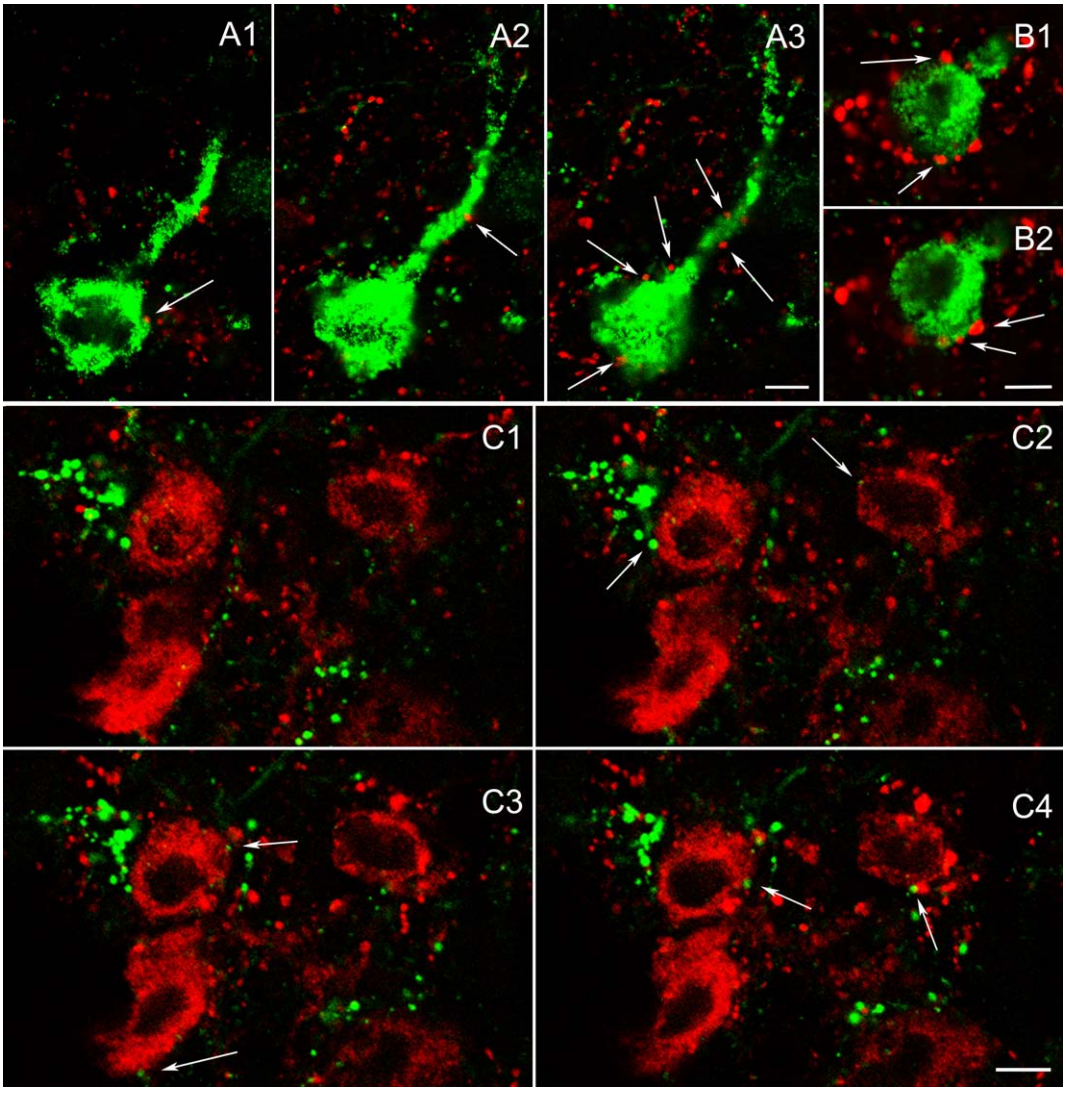

Fig. 1 – Interconnections of α-MSH- and NPY-IR neuron populations in the infundibular nucleus of the human brain. (A–B) High power magnification images show NPY-IR varicosities (red, arrows) in juxtaposition to α-MSH-IR (green) neurons. (A1–A3, B1–B2) Images of single optical slices illustrate two α-MSH-IR neurons in different focal planes. Note the high number of NPY-IR varicosities in juxtaposition to the α-MSH-IR perikarya. (C1–C4) High power magnification images of the same field in different focal planes demonstrate α-MSH-IR varicosities in contact with NPY-IR neurons (arrows). α-MSH varicosities are juxtaposed to most of the NPY cell bodies; however, only one to three α-MSH-IR varicosities are in contact with the NPY cells. The thickness of optical slices is 0.7 μm. Scale bars in panels A–C are 10 μm.