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News and Reviews

Dorsomedial hypothalamic NPY and energy balance control

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ABSTRACT

Neuropeptide Y (NPY) is a potent hypothalamic orexigenic peptide. Within the hypothalamus, *Npy* is primarily expressed in the arcuate nucleus (ARC) and the dorsomedial hypothalamus (DMH). While the actions of ARC NPY in energy balance control have been well studied, a role for DMH NPY is still being unraveled. In contrast to ARC NPY that serves as one of downstream mediators of actions of leptin in maintaining energy homeostasis, DMH NPY is not under the control of leptin. *Npy* gene expression in the DMH is regulated by brain cholecystokinin (CCK) and other yet to be identified molecules. The findings of DMH NPY overexpression or induction in animals with increased energy demands and in certain rodent models of obesity implicate a role for DMH NPY in maintaining energy homeostasis. In support of this view, adeno-associated virus (AAV)-mediated overexpression of NPY in the DMH causes increases in food intake and body weight and exacerbates high-fat diet-induced hyperphagia and obesity. Knockdown of NPY in the DMH via AAV-mediated RNAi ameliorates hyperphagia, obesity and glucose intolerance of Otsuka Long-Evans Tokushima Fatty rats in which DMH NPY overexpression has been proposed to play a causal role. NPY knockdown in the DMH also prevents high-fat diet-induced hyperphagia, obesity and impaired glucose homeostasis. A detailed examination of actions of DMH NPY reveals that DMH NPY specifically affects nocturnal meal size and produces an inhibitory action on within meal satiety signals. In addition, DMH NPY modulates energy expenditure likely through affecting brown adipocyte formation and thermogenic activity. Overall, the recent findings provide clear evidence demonstrating critical roles for DMH NPY in energy balance control, and also imply a potential role for DMH NPY in maintaining glucose homeostasis.

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1. Introduction

The dorsomedial hypothalamic nucleus (DMH) plays an important role in maintaining energy homeostasis. Beginning with the work of Bernardis et al. (1963), we have appreciated that electrolytic or excitotoxic lesions of the DMH result in hypophagia, hypodipsia, reduced body weight and decreased linear growth (Bellinger and Bernardis, 2002). Chemical stimulation or disinhibition of neurons in the DMH provokes nonshivering thermogenesis and elevates core body temperature (Dimicco and Zaretsky, 2007; Morrison and Nakamura, 2011). These data indicate the importance of the DMH in the control of energy balance through affecting both aspects of food intake and energy expenditure. Within the

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DMH, a number of neuropeptides such as neuropeptide Y (NPY), cholecystokinin (CCK), corticotrophin-releasing factor (CRF), and receptors such as CCK-1, melanocortin (MC) 4, Y1, Y5, and leptin receptors (LepRb) have been found, and their roles in controlling energy balance have been investigated (Bellinger and Bernardis, 2002; Bi, 2007). Relevant to this review, we have recently established a critical role for DMH NPY in the control of energy balance (Chao et al., 2011; Yang et al., 2009).

NPY is a 36-amino acid neuropeptide that was discovered by Tatemoto et al. (1982) and belongs to the pancreatic polypeptide family that includes peptide tyrosine–tyrosine (PYY) and pancreatic polypeptide (PP) (Tatemoto et al., 1982; Tatemoto, 1982). NPY is ubiquitously distributed in both central and peripheral nervous systems. Central NPY is most prevalent in cortical, limbic, and hypothalamic regions (Adrian et al., 1983; Allen et al., 1983) and peripheral NPY is produced in the sympathetic nervous system (SNS) and co-operates with norepinephrine to affect sympathetic functions (Lundberg et al., 1982). NPY exhibits a variety of biological and physiological actions including modulation of feeding, thermoregulation, locomotor activity, cardiovascular function, cognition and memory, and stress-related behaviors (Bi, 2007; Colmers and Wahlestedt, 1993; Gray and Morley, 1986). This review will outline our present understanding of the actions of DMH NPY in the control of energy balance and underscore DMH NPY as a potential target for combating obesity and related metabolic disorders.

2. Arcuate NPY in energy balance control

Within the hypothalamus, NPY plays a pivotal role in the regulation of food intake and body weight. Central administration of NPY via intracerebroventricular (Clark et al., 1984; Levine and Morley, 1984) or intrahypothalamic injection (Stanley and Leibowitz, 1985; Stanley et al., 1986) causes robust increases in food intake and body weight and, with chronic administration, can eventually produce obesity (Zarjevski et al., 1993). Hypothalamic NPY-expressing neurons are primarily identified in the arcuate nucleus (ARC) and the DMH (Bi et al., 2003; White and Kershaw, 1990). A role for ARC NPY in the control of energy balance has been well studied. The ARC contains two distinct populations of neurons: orexigenic neuropeptide NPY/agouti-related protein (AgRP) neurons and anorexigenic proopiomelanocortin (POMC) neurons. Both types of neurons contain LepRbs. Leptin, a hormone produced by adipose tissue (Friedman and Halaas, 1998), acts on these neurons to down-regulate *Npy*/*Agrp* gene expression and up-regulates *Pomc* gene expression (Schwartz et al., 2000). We now appreciate that these two neural systems integrate adiposity signals (such as leptin) and nutrient signals as well as other hormonal signals (such as ghrelin) to modulate food intake and energy balance (Cone, 2006; Elmquist et al., 1999; Friedman and Halaas, 1998; Nakazato et al., 2001; Schwartz et al., 2000; Spiegelman and Flier, 2001). Anatomically, these ARC peptide containing neurons project to the paraventricular nucleus (PVN) and the lateral hypothalamus (LH), to act on local neurons to affect food intake and energy homeostasis (Elmquist et al., 1999). Although data from mouse models with targeted disruption of NPY [either knock-out (Erickson et al., 1996a) or transcriptional alterations through doxycycline-regulated system (Ste Marie et al., 2005)] have failed to demonstrate significant effects on food intake or body weight, the deletion of NPY does attenuate a hyperphagic and obese phenotype of leptin-deficient *ob*/*ob* mice (Erickson et al., 1996b) and modulation of ARC NPY signaling in adult animals also significantly impacts energy balance. Genetic ablation of neurons expressing NPY/AgRP in adult mice results in a lean and hypophagic phenotype (Bewick et al., 2005; Gropp et al., 2005). In addition, NPY/AgRP neurons co-release GABA (γ-amino butyric acid) (Horvath et al., 1997) that also contributes to the actions of NPY/AgRP neurons in feeding control through affecting hypothalamic and extrahypothalamic neuronal signaling (Pu et al., 1999; Wu and Palmiter, 2011). Furthermore, adeno-associated virus (AAV)-mediated expression of antisense *Npy* cRNA in the ARC of adult rats decreases NPY expression and results in decreased food intake and body weight (Gardiner et al., 2005). Consistent with ARC NPY mediation of food deprivation-induced feeding, knockdown of NPY in the ARC via AAV-mediated RNA interference (RNAi) attenuates the feeding response to food deprivation (Yang et al., 2009). Together, these data identify ARC NPY serves as an important neuromodulator in the controls of food intake and energy balance.

3. Regulation of DMH NPY expression

Although NPY-expressing neurons in the DMH have long been noted (White and Kershaw, 1990) and alterations in *Npy* gene expression in the DMH have been reported in various rodent models of obesity, the study of the importance of DMH NPY in the control of energy balance is just beginning. Evidence has indicated that the regulation or control of *Npy* gene expression in the ARC and the DMH differs. While ARC NPY is under the control of circulating leptin, the controls of DMH NPY are leptin-independent (Bi et al., 2003). DMH NPY neurons do not contain LepRbs although LepRbs are abundant in the DMH (Bi et al., 2003). Dual in situ hybridization histochemistry revealed that while *Npy* and *LepRbs* are co-expressed in ARC neurons, DMH *Npy*-expressing neurons do not co-express *LepRbs* (Bi et al., 2003). Gene expression determination further revealed that *Npy* gene expression is increased in the ARC in response to acute food deprivation, a time when circulating leptin levels are significantly decreased, whereas DMH *Npy* expression is only significantly increased in rats with chronic food restriction (Bi et al., 2003). Moreover, *Npy* gene expression is elevated or induced in the DMH of certain rodent models of obesity including the lethal yellow agouti (A^y) (Kesterson et al., 1997), MC4R knockout (Kesterson et al., 1997), diet-induced obese (Guan et al., 1998a), tubby (Guan et al., 1998b), and brown adipose tissue-deficient obese mice (Tritos et al., 1998) and Otsuka Long-Evans Tokushima Fatty (OLETF) rats (Bi et al., 2001), but such elevation or induction is not evident in leptin deficient *ob*/*ob* mice (Kesterson et al., 1997). In fact, while *Npy* gene expression is significantly increased in the ARC of obese animals with leptin signaling deficiency (Beck, 2006; Sanacora et al., 1990; Wilding et al., 1993), obese animals with DMH NPY overexpression generally have significantly decreased *Npy* expression in the ARC (Bi et al., 2001; Guan et al., 1998a; Kesterson et al., 1997).

To investigate the potential molecules that regulate *Npy* expression in the DMH, we have examined hypothalamic gene expression in OLETF rats, an obesity model with a congenital deletion of CCK1Rs (Takiguchi et al., 1997). We found that *Npy* gene expression is significantly elevated in the DMH in both adult pair-fed and pre-obese young OLETF rats (Bi et al., 2001). Based on these observations, we hypothesized that DMH NPY overexpression in OLETF rats is resulted from CCK1R deficiency. To test this hypothesis, we conducted dual immunohistochemistry in DMH areas with anti-NPY and anti-CCK1R antibodies. We found that while NPY and CCK1R are co-localized in DMH neurons in lean control rats, DMH NPY neurons are not co-stained with CCK1Rs in OLETF rats (Bi et al., 2004). These data suggest that brain CCK directly acts on DMH NPY neurons to regulate DMH *Npy* expression and that a lack of CCK1Rs results in a deficit in the control of DMH NPY signaling, such that the resultant increased *Npy* expression in the DMH causes the hyperphagia and obesity of OLETF rats. In support of this view, parenchymal administration of CCK into the DMH decreases *Npy* mRNA levels in the DMH and inhibits food intake in intact rats