

A Role for Natriuretic Peptides in the Central Control of Energy Balance?

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The natriuretic peptide (NP) family is comprised of atrial NP, brain NP, and c-type NP (CNP). These peptides play diverse physiological roles (1–5) by binding to one of two receptors: NP receptor (NPR)-A (for atrial NP and brain NP) or NPR-B (for CNP), both of which signal through the guanylyl cyclase-cyclic GMP (cGMP) pathway (6). Among the physiological systems involving NPs are those controlling circulating blood volume, vascular tone, electrolyte balance, skeletal growth, and whole-body energy expenditure (1–5). In addition to actions in peripheral tissues, NPs are present in brain (7). In the current issue of *Diabetes*, Yamada-Goto et al. (8) report that central (but not peripheral) administration of CNP reduces food intake and body weight. The underlying mechanism appears to involve activation of the hypothalamic melanocortin pathway, which is also engaged by leptin, serotonin, and several other inputs that favor weight loss. These observations raise intriguing possibilities regarding the role of NPs and, by extension, guanylyl cyclase-cGMP signaling in hypothalamic neurocircuits controlling energy balance.

The arcuate nucleus (ARC) is a key hypothalamic area for energy homeostasis. Neurons in this brain area transduce input from hormones such as leptin and insulin as well as from nutrients such as glucose. This results in adaptive changes involving both food intake and energy expenditure. Located within the ARC are pro-opiomelanocortin (POMC) and neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons that, when activated, reduce or increase food intake, respectively (Fig. 1A). In response to leptin, the simultaneous activation of POMC and inhibition of NPY/AgRP neurons reduces food intake, whereas in leptin-deficient states such as fasting, the opposite combination of responses serve to drive hyperphagia (9). However, human obesity is typically associated with increased plasma leptin levels, and hypothalamic leptin resistance is present in most rodent models of obesity (10). Consequently, strategies for bypassing leptin resistance are of interest from the standpoint of obesity treatment.

The melanocortin-4 receptor subtype (Mc4r) mediates inhibition of food intake by melanocortins such as α -melanocyte-stimulating hormone. Yamada-Goto et al. (8) report that the ability of intracerebroventricular CNP administration to reduce food intake is blunted by an Mc4r antagonist.

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DOI: 10.2337/db12-1841

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Extending this observation, the authors also found that, like leptin, intracerebroventricular CNP activates POMC cells (based on induction of c-Fos) (8). These findings imply a role for the melanocortin system in the effect of CNP on food intake and, together with evidence that both CNP and NPR-B are concentrated in the ARC (7), raise the possibility that CNP-containing ARC neurons synapse onto and activate adjacent POMC neurons (Fig. 1B). Alternatively, CNP neurons could conceivably activate POMC cells via an indirect mechanism involving an intermediary neuronal subpopulation. These untested possibilities are of interest because, although the anorectic effects of both leptin (11) and serotonin (12) involve activation of POMC cells, neither leptin receptors (which signal via Janus kinase-signal transducer and activator of transcription and phosphatidylinositol-3-kinase pathways) nor serotonin receptors [in this case, the G_{α_s} -coupled 5HT_{2C} receptor (13), which activates adenylate cyclase-cAMP] are known to activate the intracellular guanylyl cyclase-cGMP pathway used by NPR-B. These observations point to a novel, cGMP-based mechanism underlying activation of a key neuronal subset for energy homeostasis, a concept with implications for obesity drug development.

The recent approval by the Food and Drug Administration of two obesity drugs—Lorcaserin, a 5HT_{2C} receptor agonist (Arena Pharmaceuticals), and Qsymia, a combination of the anticonvulsant topiramate and the amphetamine derivative phentermine (VIVUS, Inc.)—was a significant advance in obesity treatment, but the era of effective medical therapy for obesity is still in its infancy. The melanocortin system has long been a target for obesity drug development, in part because of its potential to bypass obesity-associated leptin resistance. However, Mc4r agonists have been abandoned because of hypertension and other adverse effects.

An alternative strategy for engaging the melanocortin system in obesity treatment involves the selective activation of discrete subsets of POMC neurons. Sohn et al. (13) have found that the ARC POMC cell population is not homogenous; rather, functionally and anatomically distinct subsets exist, each being responsive to distinct neuropeptide, neurotransmitter, and/or hormonal inputs. Thus, although leptin and serotonin each reduce food intake in a melanocortin-dependent manner (11,12), POMC neuron subsets activated by leptin and serotonin are distinct from one another (13). Could yet another POMC-cell subset exist that is activated preferentially by CNP? If so, perhaps it is possible to pharmacologically target distinct POMC neuron subsets in a stepwise manner that induces weight loss while averting the untoward effects of broad-based Mc4r activation.

Hypothalamic actions of CNP (8) add to a small, but growing, body of evidence connecting hypothalamic guanylyl cyclase-cGMP signaling to the control of food intake. Like CNP, uroguanylin (a peptide liberated within

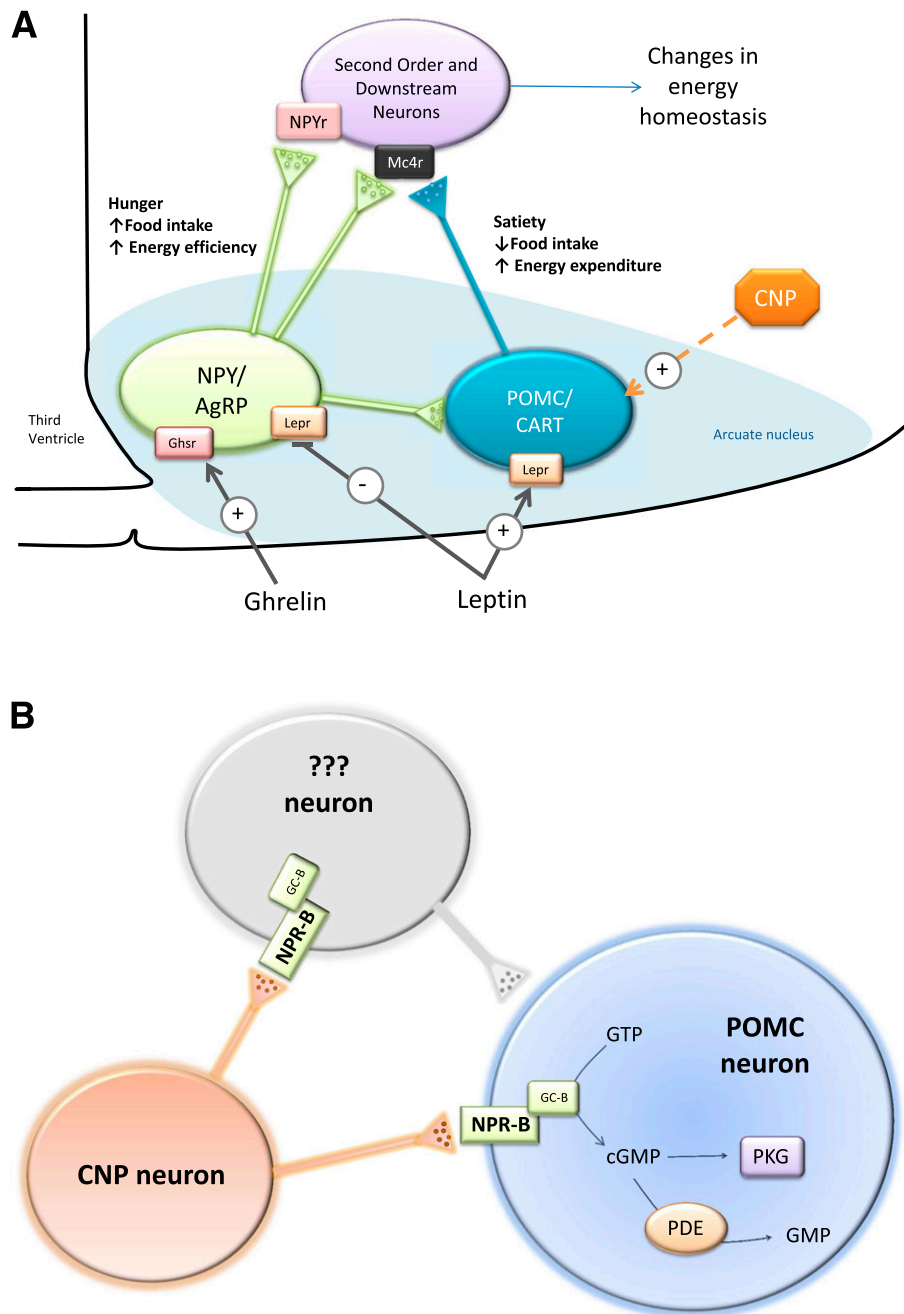


FIG. 1. A: Depiction of POMC and NPY/AgRP neurons in the hypothalamic ARC, which reduce and increase food intake, respectively, and their regulation by input from hormonal signals such as leptin and ghrelin that circulate at levels proportionate to body fat. Central administration of CNP reduces food intake via a mechanism involving activation of POMC cells. **B:** Theoretical model depicting activation of POMC neurons by either direct or indirect CNP-NPR-B signaling. CNP-containing neurons in the ARC are hypothesized to activate adjacent POMC neurons. Although untested, it is possible that this occurs via NPR-B-mediated cGMP signaling either in POMC cells or via an intermediary neuronal subset. Intracellular signaling by NPR-B involves activation of guanylyl cyclase, cGMP generation, and activation of protein kinase G (PKG). cGMP is degraded by one or more phosphodiesterases (PDE). AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; Ghsr, ghrelin receptor; Lepr, leptin receptor; NPYr, NPY receptor; GC-B, guanylyl cyclase-B.

the hypothalamus from prouroguanylin, its circulating, gut-derived precursor) reduces food intake via a central mechanism linked to activation of the melanocortin system (14), and like NPR-B, the uroguanylin receptor signals via cGMP (14). Neuronal signaling by nitric oxide (NO) activates a related guanylyl cyclase-cGMP pathway and neurons that coexpress nitric oxide synthetase and leptin receptor are concentrated in the ARC. Although a role for NO in the control of food intake remains to be investigated, Leshan et al. (15) recently demonstrated that deletion of

leptin receptors selectively from this subset of neurons induces profound hyperphagia and obesity in mice. Thus, leptin regulation of NO-producing neurons in the ARC is required for normal energy homeostasis. What relationship, if any, do these neurons have to actions of CNP and uroguanylin? Do these peptides, as well as NO, reduce food intake through actions on a common set of neuronal targets?

From a therapeutic standpoint, it is noteworthy that drugs for erectile dysfunction work by selectively blocking a cGMP-specific phosphodiesterase, thereby increasing

intracellular cGMP signaling in a tissue-specific manner. Based on the efficacy of this approach, the phosphodiesterase isoform responsible for cGMP degradation in hypothalamic neurons would seem to be a plausible target for obesity drug development. Selective inhibition of this enzyme could theoretically increase the efficacy of endogenous signals that converge on cGMP signaling in key hypothalamic neurons, thereby favoring reduced food intake and body weight.

Progress in this area will benefit from research that answers several additional questions. What are the mechanisms of CNP-mediated POMC-cell activation? Does CNP-induced weight loss occur without increasing blood pressure? Does neuron-specific deletion of either CNP or NPR-B cause obesity, a finding that would imply a physiological role for CNP in energy homeostasis? Are CNP neurons regulated by changes of nutrient status (e.g., feeding and fasting) and/or humoral inputs such as leptin? Are hypothalamic actions of CNP limited by NPR-C, a clearance receptor that competes with NPR-A and NPR-B to mitigate the biological action of NPs (6)? Lastly, translational research is needed to assess the relevance to human physiology of the action of CNP in rodent brain.

New nonsurgical approaches to achieve and sustain long-term weight loss are needed to effectively confront the obesity epidemic. This goal will likely be met only with continued advances in our understanding of energy balance neurocircuitry and its regulation. New insights into the role of CNP and neuronal cGMP signaling are a step in the right direction.

ACKNOWLEDGMENTS

This work was supported by a National Institutes of Health (NIH) Fellowship Training Program Award (T32-DK-007247), the NIH-funded University of Washington Nutrition Obesity Research Center (P30-DK-035816) and Diabetes Research Center (P30-DK-017047), and NIH Grants DK-089036 (to E.S.), DK-090320, DK-083042, and DK-052989 (to M.W.S.). M.W.S. is an advisor to Pfizer, Inc. No other potential conflicts of interest relevant to this article were reported.

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