

# Central control of feeding

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F1000 Biology Reports 2009, 1:10 (doi: 10.3410/B1-10)

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## Abstract

The rising rate of obesity in Western countries has led to intensified efforts to understand the molecular mechanisms underlying the central control of appetite and feeding behavior. This report highlights studies published from 2006 to 2008 revealing novel centrally acting anorexigenic hormones, the continued unraveling of complex hypothalamic intracellular signaling pathways that regulate feeding, and insights into leptin resistance.

## Introduction and context

The arcuate nucleus (ARC) of the hypothalamus has been identified as a primary brain site involved in the initial sensing of an array of nutritional signals that convey the availability of fuels circulating in the plasma, ready to be absorbed from the gastrointestinal tract, or stored as glycogen or fat [1,2]. This information is integrated and passed on to other brain areas, ultimately to be integrated by the whole brain, along with external cues outside the body, into changes in feeding behavior [3]. One goal of intense recent investigation has been to define the intracellular signaling and neural circuitry occurring within the ARC that controls feeding behavior. Much of our understanding of how the ARC works to regulate feeding comes from study of the action of leptin, a hormone produced in white fat that serves as a satiety signal to reduce food intake. Within the ARC are two neuronal populations, the neuropeptide Y (NPY) neurons and the pro-opiomelanocortin (POMC) neurons, that both respond to leptin. A general consensus is that, in addition to leptin, the major circulating nutritional signals converge on these two neuronal populations and utilize overlapping intracellular signaling pathways and neural circuitry. A second effort is aimed at understanding leptin resistance, a maladaptive state in which the hormone loses its capacity to reduce appetite and increase energy expenditure when cellular energy stores are plentiful and which is believed to contribute to diet-induced obesity in rodents [4]. Research addresses how

leptin signaling becomes compromised when leptin resistance occurs and at how it may be prevented or circumvented.

## Major recent advances

The first two studies highlighted below are important because they identify yet additional hormones that regulate feeding through direct action in the ARC. In what has been a controversial area of investigation, Kubota *et al.* [5] show that adiponectin, a hormone synthesized in white fat cells, enters the central nervous system from the circulation and interacts with adiponectin receptor R1 expressed in the hypothalamus. This leads to the activation of AMP-activated protein kinase (AMPK), NPY gene induction and increased feeding. In addition, the central action of adiponectin decreases energy expenditure and promotes fat storage. In the second study, Coppola *et al.* [6] demonstrate that triiodothyronine (T3) locally produced in hypothalamic glial cells triggers uncoupling protein 2 (UCP2) production and activity in mitochondria in NPY neurons which in turn leads to mitochondrial proliferation. This is a pathway activated by fasting and the authors predict that by the time refeeding occurs after a fast, the increased mitochondria number in NPY neurons plays a critical role in sustaining increased activity of these orexigenic cells so that food intake remains elevated.

In a third study related to appetite modulating hormones, Yang *et al.* [7] identify the acyltransferase that octanoylates ghrelin, the appetite stimulating peptide hormone secreted by the stomach when energy stores are low. The octanoylation of ghrelin is required to activate its endocrine actions, and identification of the unique enzyme responsible, ghrelin O-acyltransferase (GOAT), provides a new avenue in the search for inhibitors that reduce appetite.

One of the most exciting new players in hypothalamic intracellular signaling is AMPK, which serves as a point of convergence for multiple hormone and nutrient induced signaling pathways in the ARC. AMPK is an evolutionarily conserved serine-threonine protein kinase with a well-established role as 'energy sensor' in peripheral tissues. In hypothalamus glucose, leptin and insulin each inhibit AMPK activity, and ghrelin activates it, and it is these effects on AMPK that are required for the final feeding responses elicited. Anderson *et al.* [8] demonstrate that hypothalamic  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase kinase 2 (CaMKK2) functions as an AMPK kinase to phosphorylate and activate AMPK in the ARC, thus mediating ghrelin-induced NPY gene expression and increased feeding. Inhibition or deletion of CaMKK2 in mice inhibits food intake and protects the animals from high-fat-diet-induced obesity, insulin resistance and glucose intolerance. Also involving AMPK signaling, the electrophysiological studies by Claret *et al.* [9] demonstrate that deletion of AMPK $\alpha$ 2 from POMC or agouti-related peptide (AgRP) neurons completely abrogates glucose sensing by these neurons. Mammalian target of rapamycin (mTOR) is a second exciting evolutionarily conserved energy sensor and point of converging hypothalamic signaling cascades. The study by Cota *et al.* [10] demonstrates colocalization of mTOR with NPY and POMC neurons in the ARC and shows that central administration of leucine increases hypothalamic mTOR signaling and decreases food intake and body weight. The ability of leptin to inhibit feeding appears to function through this pathway as well. A third important signaling study deals with glucose sensing by POMC neurons. The excitation of POMC neurons by glucose was predicted to involve ATP-induced closure of  $\text{K}^{\text{ATP}}$  channels in the plasma membrane, as occurs in pancreatic beta cells, although the significance of this pathway in neurons remained unknown. Parton *et al.* [11] demonstrate, using conditional knockout technology, that glucose sensing in POMC neurons does indeed have a physiological role in controlling systemic glucose homeostasis and furthermore, that the glucose sensing is lost in a UCP2-dependent manner with obesity linked to a high-fat diet. The authors suggest that loss of glucose sensing in glucose-excited neurons could be an

important pathogenic component of type 2 diabetes. The study by Hill *et al.* [12], also dealing with signaling in POMC neurons, is interesting because it demonstrates a requirement for phosphoinositide-3-kinase (PI3K) signaling for the acute action of leptin in reducing food intake, but not the long-term regulation of organismal energy balance. The study also demonstrates that both leptin-induced activation and insulin-induced inhibition of POMC neurons require PI3K signaling. That complete opposite responses require exactly the same intracellular signaling cascades raises the intriguing possibility that leptin and insulin responsive POMC neurons may comprise distinct cell populations.

The final two papers highlighted deal with the important issue of leptin resistance. Using a unique hypothalamic explant secretion assay, Enriori *et al.* [13] demonstrate that leptin modulates NPY and  $\alpha$ -melanocyte-stimulating hormone secretion from the ARC of lean mice and that this response is specifically lost in diet-induced obese animals. Despite the leptin resistance that has developed in the obese animals, the melanocortin system downstream from the ARC remains intact and capable of regulating appetite, and is, in fact, over-responsive to melanocortin agonists. Tanaka *et al.* [14] also find that centrally acting melanocortin agonists can bypass high-fat-diet-induced leptin resistance and inhibit feeding behavior. They demonstrate that the centrally acting agonists also affect the periphery, specifically restoring skeletal muscle AMPK phosphorylation that is attenuated in the leptin resistant state and that functions as master regulator of fatty acid  $\beta$ -oxidation in this tissue.

### Future directions

Incoming signals that convey whole body nutritional status to the ARC and the intracellular signaling pathways they initiate in key ARC neuronal populations is a focus of recent research where much progress has been made. A future challenge is to understand more fully how this metabolic information is integrated by the ARC, passed on to other brain regions, and ultimately translated into behavior. The later steps occurring outside the ARC are currently the least clear. Knockout mouse models have been invaluable in identifying signaling components involved in the central control of feeding, although the approach most often applied, the global, germ-line disruption of a particular gene, can result in developmental compensatory changes in neural function that may profoundly influence the phenotypes observed and produce misleading or confusing interpretations [15]. Conditional inducible gene disruption in specific neuronal cell populations in adult animals

will circumvent this issue and should be a goal, when possible, of future efforts.

### Abbreviations

AgRP, agouti-related peptide; AMPK, AMP-activated protein kinase; ARC, arcuate nucleus; CaMKK2, Ca<sup>2+</sup>/calmodulin-dependent protein kinase kinase 2; GOAT, ghrelin O-acyltransferase; mTOR, mammalian target of rapamycin; NPY, neuropeptide Y; PI3K, phosphoinositide-3-kinase; POMC, pro-opiomelanocortin; UCP2, uncoupling protein 2.

### Competing interests

The authors declare that they have no competing interests.

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