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The role of transcriptional regulators in central control of appetite and body weight

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SUMMARY

Individuals who live in industrialized countries often eat a calorie-rich diet and perform little physical activity. These habits are thought to be critical contributors to the rapidly rising incidence of obesity, a condition that affects hundreds of millions of people worldwide. High-calorie intake alters metabolic-sensing pathways in central nervous system neurons, and these changes have pathogenic roles in the development of obesity. This review aims to summarize our current knowledge about the neuronal populations (the central melanocortin system in particular) and transcriptional regulators, including STAT3 and FOXO1, that are involved in the maintenance of normal body weight. We describe the interactions between these transcriptional factors and their target genes, which encode the main appetite-regulating neuropeptides (agouti-related peptide and α -melanocyte-stimulating hormone). We discuss the transcriptional co-activator PGC-1- α and the supposed metabolic-sensor protein SIRT1, and their potential roles as targets for novel antiobesity medications.

Keywords

body-weight homeostasis; feeding; melanocortin system; obesity; transcription factors

INTRODUCTION

Obesity develops when energy intake surpasses energy expenditure over time. The rapid increase in the incidence of obesity and the deleterious disorders associated with it, such as type 2 diabetes mellitus, cardiovascular disease, and cancer, pose a huge threat to public health. Obesity is attributable to single-gene mutations in only a small percentage of obese individuals; the rapid surge in obesity levels in developed countries is thought to be caused by genetic susceptibility and changes in environmental factors, including a sedentary lifestyle and high intake of calories. Nevertheless, the primary defects that cause this metabolic imbalance are still largely unknown.

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Competing interests

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To develop effective treatments for obesity, an improved understanding of the molecules and neuronal circuits that regulate body-weight homeostasis is urgently needed. Several studies have demonstrated that peripheral hormones (e.g. leptin and insulin) and nutrients (e.g. glucose and free fatty acids) function as key signals that regulate energy balance by directly acting on hypothalamic neurons. However, the downstream, molecular mechanisms that mediate these effects are yet to be fully determined. Here, we discuss the contributions of potential molecular mediators, including SIRT1 and PGC-1- α , in the development of obesity.

NEURAL CONTROL OF BODY-WEIGHT HOMEOSTASIS

Hypothalamic and caudal hindbrain neurons sample peripheral hormonal, neural and nutrient signals that reflect the energy status of the whole body. The aforementioned neurons integrate these signals and provide coordinated outputs to downstream sites (e.g. the pituitary gland, neocortex, and autonomic, preganglionic, and mesolimbic reward neurons, etc.) that are involved in the maintenance of normal body weight. These neuro-circuits are highly complex (reviewed by Morton *et al.*¹), so in this article we will only focus on the well-characterized melanocortin system within the central nervous system (CNS).

The melanocortin system comprises nerve cells that express melanocortin receptor 3 (MC3-R) and melanocortin receptor 4 (MC4-R) and neurons that secrete the ligands of these receptors, namely agouti-related peptide (AGRP) and α -melanocyte stimulating hormone (α -MSH).² AGRP is an orexigenic (i.e. appetite-stimulating) neuropeptide that is secreted by neurons within the arcuate nucleus of the hypothalamus,³ and α -MSH is an anorectic (i.e. appetite-suppressing) neuropeptide that is an endoproteolytic product of the pro-opiomelanocortin peptide. This peptide is secreted by neurons within the arcuate nucleus and the nucleus of the solitary tract in the hindbrain.^{2,4-7} Thus, the central melanocortin system includes an endogenous agonist, α -MSH, as well as an endogenous antagonist, AGRP, which act at MC3-R and MC4-R.⁸⁻¹⁰

The physiological role of the CNS melanocortin system is well established in mammals, including humans. Mutations that disrupt MC4-R signaling cause increased food intake (hyperphagia), reduced energy expenditure, hyperinsulinemia and obesity.¹¹⁻¹⁵ MC4-R-expressing neurons in the paraventricular, hypothalamic nucleus are likely to mediate the appetite-suppressing effects of upstream melanocortin neurons, as reported in a study that used genetically engineered mouse models.¹⁶ However, the identity of the MC4-R-expressing neurons that regulate energy expenditure has yet to be established. Candidates include MC4-R-expressing neurons in the raphe pallidus¹⁷ and autonomic preganglionic nerve cells, some of which have direct contact with hypothalamic pro-opiomelanocortin-expressing neurons.¹⁸ Furthermore, neuron-specific gene-deletion studies in mice revealed that leptin, which is known to regulate adiposity, prevents weight gain, partially through its action on AGRP-expressing and/or pro-opiomelanocortin-expressing neurons.^{6,19} Together, these findings suggest that AGRP-expressing and pro-opiomelanocortin-expressing neurons are ideal candidates through which to study the role of intracellular neuronal pathways that regulate food intake and body weight.

Whereas the role of neuropeptides and their receptors in regulation of energy balance have received considerable attention, the roles of specific transcription factors, coactivators and other proteins that affect gene expression are only partially understood. Below, we provide an overview of what is currently known about the functions of these transcriptional regulators with regard to coordinated body–energy homeostasis.

TRANSCRIPTIONAL REGULATORS OF BODY-WEIGHT HOMEOSTASIS

In the past decade, tremendous advances have been made in understanding the peripheral and central neural networks that control body weight. We will only briefly mention these pathways, as they have been reviewed in depth by Morton and colleagues.¹ These circuits include peripheral hormonal signals and their receptors, which are expressed by hypothalamic and hindbrain neurons. For example, leptin and insulin convey signals to the brain about adiposity i.e. the amount of energy stored as fat in the body. Increased signaling via leptin receptors or insulin receptors in CNS neurons leads to reduced food intake; a lack of signaling through either pathway leads to obesity.¹

Signaling mechanisms mediated by leptin and insulin include changes in neuronal membrane potential, firing rate and gene expression. The appetite-suppressing effect of leptin is in part mediated by its ability to directly activate anorectic, pro-opiomelanocortin-expressing neurons and directly inhibit orexigenic, AGRP-expressing neurons.¹ Moreover, the binding of leptin to its receptors activates the JAK2–STAT3 signal-transduction pathway. Leptin-induced autophosphorylation of JAK2 causes a phosphorylation cascade that targets STAT3, a transcription factor. Phosphorylated STAT3 quickly moves into the cell nucleus, where it binds to regulatory elements of *POMC* and *AGRP* promoters. In combination with other transcription factors that are discussed below, phosphorylated STAT3 activates transcription of *POMC* and suppresses the expression of the *AGRP* gene.^{20,21}

Another transcription factor that acts downstream of leptin-receptor signaling and insulin-receptor signaling in brain neurons is FOXO1. Depending on the neuron type, the binding of both insulin and leptin to their receptors activates the PI3K–AKT1 pathway.¹ FOXO1 is a direct target of AKT1²², and AKT1-mediated phosphorylation of FOXO1 leads to its nuclear exclusion and protein degradation.²³

Of note, the anorectic effects of leptin and insulin are in part attributable to AKT1-mediated suppression of FOXO1 transcriptional activity. The CNS melanocortin system is probably involved in this pathway, as FOXO1 is specifically recruited to bind to the *AGRP* promoter and enhances its expression. On the other hand, FOXO1 antagonizes STAT3-induced activation of the *POMC* promoter.^{21,24} The molecular signaling mechanisms that coordinate the expression of these neuropeptides are, therefore, interconnected and are downstream of at least two pathways: the JAK2–STAT3 and the PI3K–AKT1 pathways. Because leptin receptors and insulin receptors share some of their downstream signaling molecules, these hormones are very likely to work together to orchestrate the activity and gene-expression profile of neurons that are involved in the control of food intake and energy expenditure.

Potential role of PGC-1- α in regulation of energy balance

PGC-1- α (also known as PRGC1) was first described in 1998 by Puigserver and colleagues²⁵ as a cold-inducible co-activator of PPAR- γ , a transcription factor that is expressed in brown fat tissue. The discovery of PGC-1- α spurred intense research that aimed to elucidate its physiological roles. A decade later, investigations have revealed that PGC-1- α is a critical co-activator in not only adipose tissue, but also in the liver, skeletal muscle, heart, and brain.^{26–30}

PGC-1- α coordinates various transcriptional pathways in a cell-specific and transcription-factor-selective fashion. For example, this protein has a critical role in regulation of hepatic glucose production; indicated by the fact that mice with no Pgc-1- α expression in the liver have decreased fasting-induced expression of gluconeogenic genes.³¹ Conversely, adenovirus-mediated overexpression of PGC-1- α in hepatocytes leads to activation of the entire gluconeogenic pathway.³² PGC-1- α regulates this process by co-activating the promoters of genes that encode the enzymes that catalyze the first and last steps of the gluconeogenic pathway, namely phosphoenolpyruvate carboxykinase 1 and glucose-6-phosphatase.³¹ These co-activations occur through selective interactions of PGC-1- α with various transcription factors, such as HNF-4- α , FOXO1, and a liganded glucocorticoid receptor.^{30,32,33}

PGC-1- α expression and activity is not only fine-tuned to the body's nutritional status, but also to environmental stimuli, including ambient temperature and exercise. The ability of mammals to survive prolonged exposure to external temperatures a long way below their core body temperature might be, at least in part, due to the activity of PGC-1- α and the biological processes it triggers in thermogenic tissues, in particular brown fat.²⁸ Indeed, Pgc-1- α -deficient mutant mice are unable to cope with cold environments and die a few hours after exposure to 4 °C.²⁸ The plasticity of skeletal muscle is also greatly influenced by PGC-1- α . In addition to its effect on overall health, regular exercise has been shown to influence the relative abundance of different muscle-fiber types in response to different types of physical activity. For example, endurance training increases the number of type 1 and type 2A muscle fibers, because these types are relatively resistant to fatigue (although they have a low peak force).³⁴ Strength training, by contrast, increases the number of type 2B and type 2X muscle fibers, which can generate high force (but fatigue quickly).³⁵

Interestingly, PGC-1- α expression in skeletal muscle correlates closely with the type and frequency of the exercise that an individual performs. For example, a single bout of endurance exercise transiently induces PGC-1- α mRNA expression. Additionally, chronic exercise leads to constitutively higher levels of PGC-1- α mRNA compared with those in untrained muscle.^{36,37} These changes in PGC-1- α expression are pivotal for skeletal muscle to properly adapt to training. In fact, skeletal-muscle-specific PGC-1- α overexpression increases the proportion of type 1 and type 2A muscle fibers, which leads to improved endurance in mice.^{27,38} Conversely, skeletal muscle-specific PGC-1- α deletion increases the percentage of type 2B and type 2X muscle fibers, which leads to reduced endurance in mice.³⁹

Although the role of PGC-1- α in peripheral metabolic tissues has been established, its role in CNS neurons and the regulation of feeding and body weight remains to be clarified. Pgc-1- α -deficient mice have reduced body weight, but this phenotype is thought to result from hyperactivity-induced increases in energy expenditure secondary to primary defects in the striatum.²⁸ However, PGC-1- α could potentially have a unique function in body-weight regulation that is different from that of other members of the PGC super-family, as deletion of its close homolog, PGC-1- β , does not result in altered body weight.⁴⁰ The role of PGC-1- α in the central regulation of appetite and body weight, therefore, might have been underestimated. Our research group has found that PGC-1- α is expressed in the hypothalamus, where its level increases during fasting (G Ramadori and R Coppari, unpublished data). These results suggest that in hypothalamic neurons, PGC-1- α coordinates transcriptional changes that are required to cope with fluctuations in body-energy content. As mentioned earlier, a well-characterized partner of PGC-1- α is FOXO1,³⁰ a transcription factor that is expressed in pro-opiomelanocortin-expressing and AGRP-expressing neurons, where, together with other factors, it inhibits or enhances the expression of *POMC* and *AGRP*, respectively.²¹

On the basis of these results, a plausible hypothesis is that PGC-1- α could also interact mechanistically with *FOXO1* in melanocortin-expressing neurons. This interaction could boost the effects that FOXO1 has on *POMC* and *AGRP* promoters, and thus promote food intake and weight gain. This hypothesis is supported by our unpublished data, which suggest that PGC-1- α protein content increases in the hypothalamus during fasting. If PGC-1- α is instrumental in the appropriate expression of neuropeptides that stimulate a positive energy balance, we would expect a characteristic change in the body weight of mice that lack this cofactor. Indeed, Pgc-1- α -deficient mice are leaner than wild-type mice, but (as we discussed above) this phenotype is considered to be caused by primary defects in the striatum rather than in brain centers that regulate food intake. Nevertheless, ubiquitous deletion of PGC-1- α leads to a notably long array of dysfunctions in multiple tissues.^{28,41} These regulatory defects might overshadow the selective effects of PGC-1- α deletion in neurons that are known to control feeding and energy expenditure. As a result, the interpretation of body-weight results obtained from Pgc-1- α knockout-mice is inherently difficult. The role of PGC-1- α in the hypothalamic and extrahypothalamic neurons that control body-energy balance, can only be clarified by animal studies in which PGC-1- α is selectively manipulated by genetic engineering in single neuronal populations.

Another way in which PGC-1- α might control feeding behavior is by determining the amount of cytokines that are secreted from skeletal muscle into the bloodstream. Among these cytokine is interleukin 6 (IL6), which is known to exert body-weight-reducing effects. Indeed, mice that are unable to synthesize IL6 become obese, whereas mice that overproduce IL6 have reduced body weight.^{42,43} The fact that mice that lack Pgc-1- α only in skeletal muscles have increased levels of IL6 is of particular interest.⁴⁴ Thus, circulating levels of this cytokine might affect the function of neurons in neural centers that control feeding, which would explain the hypophagia and reduced body weight found in mice with skeletal-muscle-specific knockout of Pgc-1- α .⁴⁴

Potential role of SIRT1 in the regulation of energy balance

SIRT1 is a NAD-dependent deacetylase⁴⁵ whose targets include histones, transcription factors, and cofactors, such as PGC-1- α and *FOXO1*.⁴⁶ Because SIRT1 depends on NAD⁺ to function, it is thought to be a metabolic-sensor protein that links the body's energy status with cellular function. Similarly to PGC-1- α , SIRT1 regulates a variety of biological pathways, including apoptosis,^{47,48} metabolism,^{49–51} circadian clock,^{52,53} and neuroprotection,^{46,54–56} depending on the cellular context and its target molecules.

Plentiful data support the idea that SIRT1 is a critical component of the molecular mechanisms that underlie metabolic adaptations to reduced energy status. For example, adipocytes store energy in the form of triglycerides to allow the body to survive periods of fasting. A reduced supply of energy triggers lipolysis of triglycerides in adipocytes, which results in the release of free fatty acids into the bloodstream to provide fuel to other tissues. SIRT1 orchestrates this physiological adaptation by inhibiting PPAR- γ , and, therefore, increasing lipolysis and the release of free fatty acids from adipocytes.⁴⁹

As mentioned above, another target of SIRT1 is PGC-1- α .⁵⁰ SIRT1-dependent activation of PGC-1- α is critical to induce gluconeogenesis program in the liver during fasting.⁵⁰ The physiological relevance of this effect is demonstrated by the fact that mice with reduced SIRT1 levels in the liver alone are hypoglycemic.⁵⁷ In skeletal muscle, interactions of SIRT1 and PGC-1- α coordinate the physiological switch from glucose oxidation to lipid oxidation under conditions of nutrient deprivation.⁵¹ Whether SIRT1 influences PGC-1- α to suppress IL6 secretion from skeletal muscle tissue has not yet been established.

SIRT1 has been proposed to have several functions in the brain: a protective role against neurodegenerative diseases, including Alzheimer disease and amyotrophic lateral sclerosis;^{54,55} mediation of the protective effects of NAD⁺ against axonal degeneration;⁵⁶ and an influence on the differentiation of neuronal progenitor cells.^{58,59} SIRT1 is not thought to be important for the regulation of feeding and body weight homeostasis in CNS neurons. However, its role in CNS neurons that control appetite and body weight in CNS neurons has not been systematically investigated. For example, Sirt1-deficient mice have reduced body weight (along with other defects).^{47,60–63} Furthermore, our research group has reported that SIRT1 is expressed in hypothalamic melanocortin neurons and that its expression and activity in the hypothalamus is influenced by the availability of energy.⁶⁴ Finally, we found that Sirt1 regulation by the availability of energy is aberrant in the hypothalamus of obese animals.⁶⁴ These findings suggest that SIRT1 could have a critical role in regulation of normal energy balance.

Of note, other metabolic-sensor proteins that are expressed in the hypothalamus have been established as important for coordinated feeding and body-weight homeostasis. For example, the hypothalamic activation of FRAP (also known as mammalian target of rapamycin or mTOR), an ATP-sensor kinase, leads to reduced food intake, whereas its pharmacological inhibition in the same brain area induces increased food intake.⁶⁵ Also, a decrease in the hypothalamic activity of AMP-activated protein kinase (AAKB1) results in reduced food intake and weight loss, whereas constitutive AAKB1 activation within this area leads to hyperphagia and obesity.⁶⁶ Interestingly, the effect of AAKB1 in different classes of

hypothalamic neurons seems dependent on the function of these neurons in the regulation of energy balance. Neuron-specific gene-deletion studies revealed that ablation of AAKB1 in orexigenic *AGRP*-expressing neurons leads to weight loss, whereas deletion of AAKB1 in anorectic proopiomelanocortin-expressing neurons results in weight gain and increased adiposity.⁶⁷

SIRT1 activates both PGC-1- α and FOXO1, which indicates a possible scenario for transcriptional regulation in melanocortin neurons that control body–energy balance: by removing acetyl groups from PGC-1- α and FOXO1, SIRT1 could increase the probability that these two factors physically interact with each other when the energy balance is low (Figure 1). These SIRT1-dependent, post-translational modifications are expected to enhance the recruitment of PGC-1- α and FOXO1 to DNA binding sites, where they regulate gene expression. Determination of whether SIRT1, PGC-1- α and FOXO1 physically interact in the hypothalamus, and whether these interactions are important for normal body-weight regulation requires very sophisticated future studies.

Are PGC-1- α and SIRT1 potential targets for antiobesity drugs?

Given the pleiotropic effects of both PGC-1- α and SIRT1, systemic activation or inhibition of either of them seems unlikely to result in a single outcome. To date, activators have been identified for SIRT1, but not for PGC1 α . For example, resveratrol (a small polyphenol produced by a variety of plants, including grapes) has potent antidiabetic activity when given to genetically engineered diabetic rodents that are fed on a high-fat diet—a dietary regimen that is known to induce obesity and diabetes mellitus.^{68,69} The results that have been published about the effects of resveratrol on body weight are controversial: one study reported that oral administration of resveratrol causes weight loss in mice that are fed on a high-fat diet,⁶⁹ whereas another group reported that oral delivery of resveratrol does not result in changes in body weight in mouse models of diet-induced obesity.⁶⁸ Similarly, no changes were observed in a study where more potent SIRT1 activators than resveratrol were used.⁷⁰ However, whether the metabolic effects of SIRT1 activators in wild-type animals are specifically mediated by SIRT1, or whether they might act through alternative pathways, remains unclear. Future work in animal models with tissue-specific SIRT1 deficiency is clearly needed to provide answers to the aforementioned question.

CONCLUSIONS

Neuroanatomical, electrophysiological and physiological studies have unraveled many of the factors that regulate body-weight homeostasis. Previous studies have established that hormonal inputs are deciphered by CNS neurons and that these signals are translated into coordinated feeding and energy expenditure. However, little is known about the transcriptional regulation of these neurons and the mechanisms that render these cells ready to be engaged by peripheral, metabolic cues. We have just begun to understand the roles of these transcriptional regulators in CNS neurons. Further work in this field might help to identify new targets for highly effective antiobesity medications.

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REVIEW CRITERIA

A search for original articles published between 1950 and 2008 that focused on obesity and food intake was performed in MEDLINE and PubMed. The search terms used were “obesity”, “feeding”, “energy expenditure” and “transcription factors”. All papers identified were English-language, full-text papers. We also searched the reference lists of identified articles for further papers.

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KEY POINTS

- High-calorie intake alters metabolic-sensing pathways in central nervous system neurons; these alterations contribute to the development of obesity
- A key center of the neural control of energy balance is the melanocortin system
- Peripheral hormones, including insulin and leptin, function as key signals that regulate energy balance by direct effects on their cognate receptors on hypothalamic neurons
- Hypothalamic receptors activate intracellular signaling molecules, including the transcription factors STAT3 and FOXO1, which translate hormonal signals into coordinated body-weight regulation
- The transcriptional co-activator PGC-1- α and the supposed metabolic-sensor protein SIRT1 are potential molecular mediators of weight regulation, and might represent targets for novel antiobesity medications

Figure 1.

A proposed model of gene-expression regulation by SIRT1, PGC-1- α , and FOXO1 in central melanocortin neurons. Note the SIRT1-mediated, post-translational modification (i.e. deacetylation) of PGC-1- α and FOXO1, which occurs when the energy balance is low. Deacetylated PGC-1- α -FOXO1 complexes are recruited to promoter regions of *AGRP* or *POMC* and alter their expression level, which leads to changes in appetite. Abbreviation: Ac, acetyl group.