Molecular insights into the regulation of energy intake and expenditure

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The maintenance of a precise caloric equilibrium is one of the most closely regulated parameters, as illustrated by the calculation that a positive energy balance of only +0.3% over 30 years would lead to an increase in body weight of over 20 kg. Hence, the caloric input (i.e. appetite) and energy expenditure must be tightly regulated processes. The recent elucidation of the role of the melanocortin-4 receptor (MC4-R) and the cloning of the uncoupling protein 2 (UCP-2) gene have broadened our molecular understanding of the regulation of energy intake and dissipation respectively.

I. The role of the melanocortin-4 receptor in regulating food intake

The list of peptides involved in the hypothalamic regulation of food intake comprises leptin, neuropeptide Y (NPY), corticotropin-releasing hormone, urocortin, and melanin-concentrating hormone. Melanocortinergic peptides (such as a-melanocyte-stimulating hormone, a-MSH), and their hypothalamic MC4-R in particular, have now to be added to this list. The concept of a potential link between the melanocortinergic system and body weight is derived from the agouti model mouse of genetic obesity. The agouti allele results in the ectopic expression of agouti, a 131 amino acid peptide, which is normally only expressed in the hair follicle where it acts in a paracrine manner. These mutant agouti animals are not only of yellow fur color, but they also develop hyperphagia and maturity-onset obesity due to adipocyte hyperplasia. While the absence of black hair color could be attributed to the antagonistic effect of agouti on a-MSH at the level of the melanocortin-1 receptor (MC1-R) controlling melanin synthesis in hair follicles, the obesity phenotype remained unexplained. Notably, lack of functional MC1-R does not result in obesity, suggesting that the ectopically expressed agouti protein must have other sites of action. In vitro studies have demonstrated that agouti can act as an a-MSH antagonist not only on the MC1-R, but also on the MC4-R, a G-protein coupled receptor primarily expressed in the brain, and particularly in the hypothalamic nuclei implicated in the regulation of food intake (1). In order to test whether the MC4-R is involved in the pathophysiology of the agouti phenotype, and hence in the regulation of appetite, Huszar et al. created a mouse knock-out model for the MC4-R gene (2). Interestingly, these mice lacking MC4-R exhibit maturity-onset obesity with hyperphagia, hyperinsulinemia and hyperglycemia, closely resembling the agouti phenotype. While it is formally possible that the observed phenotype results from abnormal brain development rather than from a role of the MC4-R in regulating feeding, the results of Fan et al. strongly argue against this possibility (3). These investigators identified pharmacological agonistic (MTII) and antagonistic (SHU9119) analogs of a-MSH. In keeping with the hypothesis that melanocortinergic neurons are involved in the inhibition of feeding behavior, the MTII analog not only decreased normal nocturnal food intake in mice, but it also acutely reduced food consumption in several models of hyperphagic obesity, such as the leptin-deficient ob/ob mouse, the obese yellow agouti mouse, and NPY-induced hyperphagia. Conversely, the a-MSH antagonist (and agouti-nimetic) SHU9119 not only blocked the effects of MTII, but it also enhanced nocturnal feeding when given alone. In summary, these observations suggest that the MC4-R and its agonist(s) are involved in the regulation of body weight and that the obesity phenotype in the agouti mice results from the inhibition of this pathway. At a clinical level, a phase II clinical study with MC4-R agonists is currently being conducted in obese type II diabetics, but no data regarding their efficiency are yet available.

II. Regulation of energy expenditure: a role for UCP-2?

Uncoupling protein (UCP-1) is expressed in the mitochondria of brown adipose tissue and it allows increased heat production in response to cold temperature and food intake in rodents. Its physiological role in adult humans, however, is not well defined. In addition, the role of UCP-1 in maintaining body weight is controversial, since genetically UCP-1-deficient mice are not obese, suggesting that a previously reported transgenic animal model in which brown adipose tissue was ablated through the expression of diphtheria toxin may not be representative (4, 5). However, it was generally felt that
the strong genetic component influencing the basal metabolic rate in humans, and hence their propensity to develop obesity, cannot be explained by alterations in UCP-1. Fleury et al have now cloned a human and mouse homolog of UCP-1, termed UCP-2 (6). This 309 amino acid protein has 59% structural homology to UCP-1 and the known functionally relevant motifs are conserved. In addition, UCP-2 was able to alter the mitochondrial membrane potential and growth rate in yeast similarly to UCP-1, indicating that this protein is likely to have an uncoupling, and hence an energy-dissipating, activity in vivo. Intriguingly, the mRNA for this protein was found in skeletal muscle, lung, heart, adipose tissue, kidney and placenta. While UCP-1 can be induced in brown adipocytes by cold exposure, sympathetic stimulation, and by pharmacological $\beta_3$-adrenoceptor agonists, these stimuli do not alter UCP-2 mRNA levels. In contrast, a high fat diet strongly induced UCP-2 levels, suggesting an adaptive response to a caloric excess. The degree of induction appears, however, to depend on other genetic factors, since obesity-resistant C57BL/A/J mice expressed markedly more UCP-2 in the basal and fat-stimulated states than their obesity-prone C57BL/B6 colleagues. The hypothesis that genetic variations in either the expression or activity of UCP-2 might contribute to the variation in body weight in the general population is supported by these researchers’ finding that the UCP-2 locus maps to a region on chromosome 11 which has previously been associated with several quantitative trait loci for obesity and hyperinsulinemia. Given the pace at which obesity research is currently progressing, more direct information regarding a potential link between the UCP-2 gene and human obesity will certainly be rapidly forthcoming.

References