PERSPECTIVES: BIOMEDICINE

A Sympathetic Defense Against Obesity

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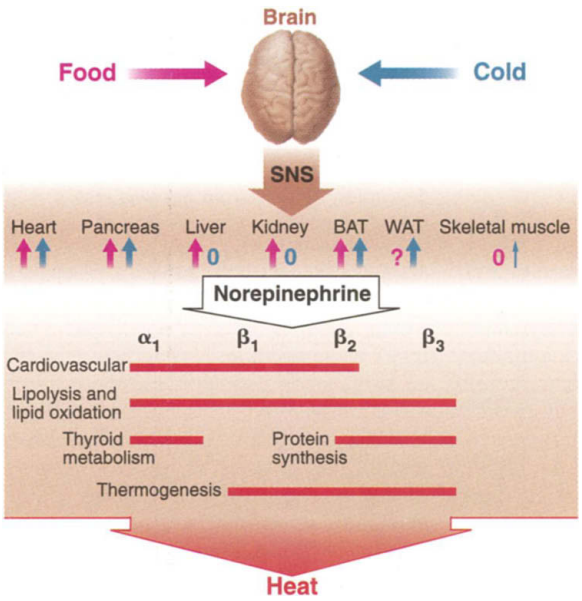
The current surge in the global prevalence of obesity reflects the failure of mechanisms that regulate body weight to cope with environments that promote overeating and discourage physical activity. Yet, within any obesity-promoting environment there is considerable variation among individuals regarding their susceptibility to weight gain. Some become obese despite a continuous struggle not to, whereas others stay lean without conscious control. Such variations in the propensity for weight gain may reflect varying susceptibilities to overeating or to a sedentary life-style. But we also know from overfeeding experiments that humans vary in their capacity to resist weight gain because of varying abilities to convert food directly into heat, a process called diet-induced thermogenesis (DIT) (*1*). The magnitude of this apparent "energy wastage" is determined by the genetic makeup of the individual (*2*) and by the composition of their diet (*3*). Identifying components of the body's autoregulatory system that induce DIT will help us to understand the genetic and metabolic basis of susceptibility to obesity, and to develop better anti-obesity therapies. With their report on page 843 of this issue, Bachman and colleagues (*4*) accelerate our understanding of obesity in mammals by showing that DIT is under the control of the sympathetic nervous system (SNS).

The SNS influences many physiological functions—ranging from body temperature homeostasis to blood pressure regulation—by releasing the neurotransmitter norepinephrine, which acts upon α- and β-adrenergic receptors. Ever since researchers began to study DIT in the 1960s, they have tried to implicate the SNS in the regulation of this process. Possible SNS involvement in thermogenesis is suggested by the ability of norepinephrine to control biochemical pathways that lead either to an increase in consumption of ATP (for example, through pumping ions across membranes or recycling substrates) or to an increased rate of mitochondrial oxidation (with poor coupling of ATP synthesis leading to increased heat production). But it was not until Landsberg *et al.* (*5*) demonstrated that SNS activity in a variety of tissues is boosted during overfeeding and decreased during starvation (a state of energy conservation) that the SNS was cast as the efferent system linking diet and thermogenesis. Finally, with their contribution in this issue, Bachman *et al.* provide direct evidence that the SNS is indeed the prime mediator of DIT (*4*). These authors reveal that mice lacking all three β-adrenergic receptors (β_1AR, β_2AR, and β_3AR) cannot increase thermogenesis and become massively obese during overfeeding. In contrast to these "β-less" mice, wild-type mice are able to resist obesity during overfeeding by activating DIT. The β-less mice are also intolerant to cold exposure, suggesting that the SNS and β-adrenergic receptor signaling pathways overlap in their control of heat production in response to both diet and cold.

It was proposed 20 years ago (*6*) that the two forms of thermogenesis (induced by diet and cold) have a common origin in brown adipose tissue. The thermogenic activity of brown adipose tissue, which is abundant in small mammals and human infants, is under SNS control. This activity is mediated primarily by a mitochondrial protein (UCP-1) that uncouples oxidative phosphorylation (that is, no ATP is synthesized during mitochondrial oxidation of food substrates, which are converted entirely into heat). Interestingly, the brown adipose tissue of β-less mice is unresponsive to physiological (cold exposure) and pharmacological (nonselective β-agonist) stimulation. The earlier discovery that norepinephrine activates thermogenesis in brown adipose tissue primarily through β_3AR signaling prompted the realization that the SNS–β_3AR–UCP-1 axis regulates thermogenesis in response to both diet and cold.



Fat feels the heat. Activation of thermogenesis by the sympathetic nervous system (SNS). In response to food (pink) or to cold (blue), SNS activity increases in a variety of tissues and organs. The thick and thin arrows depict marked and mild increases in SNS activity, respectively. SNS activity has been assessed with techniques that measure the 24-hour turnover of the SNS neurotransmitter norepinephrine (NE) in rat heart, pancreas, liver, kidney, brown adipose tissue (BAT), white adipose tissue (WAT), and skeletal muscle (*5, 8*). No change or an unknown change in SNS activity is indicated by the symbols "0" and "?", respectively. Through release of NE, which acts on some or all of the four adrenergic receptors (α, β_1, β_2, and β_3) present in these tissues, the activated SNS coordinates cardiovascular and metabolic events. These events cooperate to increase heat production: both cold-induced (nonshivering) thermogenesis and diet-induced thermogenesis (DIT).

The demonstration by Bachman *et al.* that β-less mice have major impairments in both forms of thermogenesis is something of a triumph. Previous attempts to induce obesity in mice by selectively deleting genes encoding UCP-1, β_3AR or other proteins of the SNS have ended in failure. In particular, the production of transgenic mice lacking β_3AR or UCP-1 failed to induce obesity, although varying degrees of cold sensitivity and small increases in body fat (less than twofold) were observed (*7*). These discrepancies may reflect the influence of genetic background on phenotypic outcomes of transgenic manipulations, and the existence of compensatory mechanisms that enable the transgenic mice to stay lean. Indeed, given that all three βARs possess thermogenic properties, the impairment in DIT and the development of gross obesity in β-less mice (but not in β_3AR-deficient mice) strongly suggest that the three βARs can compensate for each other. Likewise, the lack of obesity in UCP1-deficient mice may be because UCP-1 and its homologs, UCP-2 and UCP-3, can also compensate for each

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other. However, there are now doubts that UCP-2 and UCP-3 can mediate thermogenesis. An alternative explanation for why UCP-1–deficient mice are not obese is that brown adipose tissue and UCP-1 may not be quantitatively as important for DIT as is often assumed, even in small mammals.

Apart from brown adipose tissue, where else might the extra heat due to increased DIT be produced? Several other tissues and organs (such as liver, kidneys, heart, pancreas) are activated by the SNS in response to diet, but whether they contribute to DIT is unknown (see the figure). Even for skeletal muscle, the body's largest single tissue, evidence for SNS-mediated thermogenesis remains sketchy. SNS activity in the skeletal muscle of rats is unresponsive to starvation and overfeeding, and the addition of norepinephrine to mouse skeletal muscle ex vivo does not stimulate thermogenesis (*8*). In adult humans (where brown adipose tissue is scarce or quiescent), infusion of norepinephrine increases the resting metabolic rate, but there is no detectable increase in thermogenesis in forearm skeletal muscle (*9*). Nonetheless, in adult humans as in rodents, SNS activity can be modulated by short-term under- or overnutrition, as judged by measurements of norepinephrine spillover in blood and urine (*5*). Furthermore, low SNS activity has been shown to be a risk factor for weight gain in Pima Indians (*10*). But the central issue of whether subtle variations in DIT—which over months and years may lead to obesity in some humans but weight maintenance in others—reflect variations in SNS activity still remains to be firmly established in humans.

Our slow progress in understanding human variability in DIT calls into question its adaptive role in guarding against weight gain. In terms of natural selection, it may not be obvious why DIT, a process that "wastes" food energy, should have evolved. One explanation may be that DIT is poorly recruited when individuals are feeding on well-balanced diets, but readily recruited when diets are low in essential nutrients (*3*). According to the late Michael Stock, DIT probably conferred an evolutionary advantage of "homeostatic waste" because it enabled individuals to overeat relatively large quantities of poor-quality food to obtain essential nutrients without the deposition of excess, nonessential energy as fat. Excessive weight gain would be a hindrance to optimal locomotion, hunting capabilities, and the ability to fight or flee. Stock's legacy to this field lies in his proposal that DIT may have evolved as a means of regulating the metabolic supply of essential nutrients (proteins, minerals, vitamins) with only a secondary role in regulating energy balance and body weight (*3*). Indeed, in human subjects who were overfed normal and low-protein diets for 4 weeks, the relatively small individual differences in DIT that accompanied a balanced normal-protein diet were amplified on the protein-deficient diet (*11*). Consequently, short-term overfeeding on low-protein diets could provide a very sensitive method for discriminating between those who are metabolically predisposed to leanness or to fatness. Given the potent impact of protein deficiency on the activation of the SNS and thermogenesis in rodents (*3*, *5*, *11*), it remains to be seen whether low-protein diets can be used to unmask the genetic and metabolic basis of human susceptibility to obesity. Such experiments are likely to pinpoint activation of βAR signaling and SNS activity as important determinants of variations in DIT and resistance to obesity in humans.

It is almost 222 years since Lavoisier asserted that "Life is a combustion." Now, we must simulate the appropriate (unbalanced) dietary conditions under which DIT is recruited in order to understand the physiological and molecular mechanisms that enable the fire of life to "burn brighter in some than in others" (*12*).

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PERSPECTIVES: DEVELOPMENT

Riding the Crest of the Wnt Signaling Wave

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The neural crest or "fourth germ layer" of the vertebrate embryo is one of the defining characteristics of evolution and is synonymous with the transition of invertebrates to vertebrates (*1*). The neural crest—which gives rise to the peripheral nervous system, facial skeleton, and melanocytes—is generated at the interface between the surface ectoderm and neural plate of the embryo (see the figure on the next page). The interaction between the surface ectoderm (which gives rise to the epidermis) and the neural plate (which gives rise to the central nervous system) is essential for formation of the neural crest (*2*). Arising from the transition of epithelial cells to mesenchyme, neural crest cells are a pluripotent, migratory population that differentiate into an enormous array of cell types, tissues, and organs (*3*). The multistep process of neural crest development is an excellent model system with which to investigate the events of early embryogenesis, including induction, signaling, migration, differentiation, and patterning. Diverse experimental systems including those of frog and chick have helped to elucidate the complex processes that govern the formation and migration of neural crest cells [reviewed in (*2*)]. Now, on page 848 of this issue, Bronner-Fraser and colleagues (*4*) working in chick embryos disclose that Wnt signaling, and Wnt6 signaling in particular, is crucial for neural crest induction.

Given that the neural crest is highly conserved among vertebrates, why has there been so much trouble in identifying the key molecules that induce its formation? Part of the difficulty is that neural crest formation is intimately associated with the induction of neural tissue itself, and many of the same signals—such as bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), and Wnts—have been implicated in the induction of both structures (*2*, *5*). In addition, there are major differences among species regarding the timing of nervous tissue induction; for example, in the chick but not the frog, neural crest seems to be specified before the massive cell migrations that drive the formation of the three embryonic germ layers (gastrulation) (*5*). This makes it extremely difficult to distinguish between primary and secondary events in neural plate and neural crest induction and to determine the extent to which they are coupled and rely on common versus distinct signals.

Although experimental models of neural tissue induction yield controversial re-

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