Editorial: Lords and Ladies Leapin' on Leptin*

Yond' Cassius has a lean and hungry look . . . me thinks perhaps he has want for leptin.[1]

Leptin joined our lexicon barely 2 years ago, yet there are now many scores of papers making reference to the protein product of the *obese* (*ob*) gene. Leptin plays an important role in the regulation of feeding behavior and metabolism (1–9); however, the functional significance of leptin now appears to extend well beyond this realm to include many organ systems (10–13). Endocrinologists are busy piecing together an increasingly complicated puzzle to reveal the physiological role of leptin, and, with a King's ransom paid for the patent rights to this molecule, someone, somewhere, thinks this newly discovered hormone has a future in the pharmaceutical industry.

In this issue of *Endocrinology*, the work of Willis Samson and his colleagues presents the scientific community with two tantalizing bits of new information about leptin. The first is an insight into the structure-function relationships of this 167-amino acid protein. Their results show that a 35-amino acid fragment of the molecule, near its N-terminus, is capable of mimicking the effect of the intact, whole molecule—at least with respect to the inhibition of feeding behavior. With this new information, we now have a glimpse of what could prove to be the biologically active portion of this molecule. It is worth noting, however, that further studies are required before it can be concluded that the effects of this leptin fragment are truly specific with respect to food intake and not simply aversive— the standards of proof are high, and so far, only partially satisfied (14). It also remains to be determined if this fragment of leptin can also mimic the other effects of the intact molecule, (*e.g.* effects on thermogenesis and reproductive function). The second significant contribution of this paper is the identification of a relatively small, biologically active peptide fragment that can be easily synthesized and made readily available—creating an opportunity for more scientists to explore the new frontiers of this fascinating hormone.

It's not as if we didn't see it coming. The idea that the body has an uncanny way of knowing its appropriate weight and adjusting appetite and metabolism to maintain its weight and percentage of body fat within a very narrow window is not a new one. It is now more than 40 years since Gordon Kennedy proposed that some unidentified signaling mechanism between the body's fat depots and the brain keeps most of us and other animals within a narrow range of body weight (15, 16), but precisely how this happens is only now becoming clear, with the discoveries of leptin and its receptor. Several recent papers shed light on the possible mechanism of leptin's action. First, it seems clear that one of leptin's target sites is the brain because leptin binding sites and expression of its receptor have been identified in regions of the brain implicated in the regulation of body weight—in particular, the hypothalamus (3, 7, 17–19). Leptin is a relatively large protein that would ordinarily find the brain inaccessible but may be transported through a saturable process into the central nervous system by one of several splice variants of the leptin receptor and thereby gain access to the brain (7, 20). Indeed, recent studies show that plasma levels of leptin, which are highly correlated with body mass index, are also positively correlated with levels of leptin measured in the cerebral spinal fluid; however, because of the saturable nature of the plasma-cerebrospinal fluid (CSF) transport system, the high concentration of leptin in the plasma of obese individuals is not reflected proportionately in their CSF, raising the possibility that the satiety regulating centers in the brains of these individuals are exposed to lower levels of leptin than might be expected on the basis of their plasma levels (21, 22). Following this logic, it is conceivable that pharmacological strategies to elevate levels of leptin in the CSF and interstitial fluid of the brain in people suffering from obesity might produce the desired effect of suppressing appetite.

Neuropeptide Y (NPY) is expressed in several hypothalamic nuclei and features prominently as a plausible mechanism to explain the central actions of leptin on the satiety regulating centers in the brain— but the simplest explanation may not tell the whole story. Centrally administered NPY exerts a powerful stimulatory effect on feeding, whereas NPY synthesis inhibitors and neutralizing antisera inhibit feeding (2, 23). The expression of hypothalamic NPY messenger RNA (mRNA) is elevated in the genetically obese, leptin-deficient, *ob/ob* mouse, and the peripheral administration of leptin inhibits the overexpression of NPY in these animals (18, 21). The central administration of leptin inhibits the induction of feeding behavior stimulated by NPY, suggesting a possible functional interaction between leptin and the NPY signal transduction pathway (24). These observations nicely fit the argument that NPY is a key element in the feedback circuit involved in the regulation of food intake. However, this story may require some editing. First, a recent report by Erickson *et al.* (25) has shown that mice with a knockout of the NPY gene maintain their ability to regulate body weight as well as virtually all other important physiological functions, and they retain the ability to respond to exogenously administered leptin. It's certainly conceivable that neuronal plasticity during development and the recruit-

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[1] Taking liberty with William Shakespeare (1564–1616).

ment of compensatory mechanisms account for the ability of NPY-deficient animals to maintain normal physiological regulation of metabolism and body weight. On the other hand, it's also plausible that NPY may not be central to the regulation of feeding behavior under normal physiological circumstances. However, this latter inference certainly does not rule out the possibility that altered expression of NPY plays an important role in the pathophysiology of body weight regulation in the various genetic models of obesity, such as the *ob/ob* and *db/db* mouse, and perhaps even some forms of human obesity. It will be interesting to learn, for example, the impact of a selective ablation of NPY expression in genetic models of obesity in which there is an overexpression of NPY. A second aspect of the NPY story that begs reconsideration is the possibility that the effects of leptin on hypothalamic NPY gene expression reflect the *indirect* actions of leptin on the adrenal axis. Glucocorticoids stimulate the expression of NPY, and plasma levels of glucocorticoids are elevated in virtually all circumstances in which NPY levels are elevated (*e.g.* normal animals with fasting and *ob/ob* mice (26). Leptin given and to *ob/ob* mice and to wild-type mice that are fasted reduces their elevated levels of hypothalamic NPY mRNA. However, leptin also reduces circulating levels of corticosterone in these animals, and recent observations in our laboratory suggest that leptin may alter steroid metabolism. It is possible, therefore, that the effects of leptin on hypothalamic NPY expression are mediated not only by a direct action in the brain but also through the peripheral actions of leptin on glucocorticoid metabolism. Teasing out the interactions of leptin, insulin, and NPY from the elements of the hypothalamic-pituitary-adrenal axis stands as one of the important challenges facing investigators in the field (27).

The story of leptin has all the earmarks of a Dostoyevsky novel— you know it's bound to get a lot more complicated before it ends with some great Truth, so you better get ready for some long nights before the fire. The first clue that this will be the case are the observations that leptin-deficient and leptin receptor-defective animals have a variety of hormonal and metabolic disorders, including infertility and dysfunctional adrenal and thyroid axes (28). The next clue came to light with the cloning of the leptin receptor and mapping of its distribution in the body. The leptin receptor is expressed in several hypothalamic nuclei (7, 19, 29)— this certainly makes sense for a peripherally derived ligand having putative effects on the satiety regulating centers in the brain. However, the leptin receptor mRNA is also expressed in other areas of the brain, including the cerebellum, cortex, hippocampus, choroid plexus, leptomeninges, and thalamus— regions not ordinarily regarded as having important functions with respect to feeding behavior. Although it's possible that leptin's putative action on these extrahypothalamic target sites reflects its involvement in integrative mechanisms controlling metabolism, energy balance, and possibly transport into the brain, the expression of the leptin receptor mRNA in these disparate brain regions suggests that leptin may serve more diverse functions in the central nervous system and perhaps even that a structurally similar molecule may be expressed as an endogenous ligand in the brain. Further, the array of possible target sites for leptin's action stretches well beyond the brain—the lung, kidney, liver, ovary, testis, prostate, and intestines, where the leptin receptor or its splice variants are also expressed (8, 10). It's also conceivable that circulating binding proteins for leptin will be discovered, perhaps analogous to the GH-binding protein, and at the very least, if this were the case, the interpretation of measured plasma leptin levels may be complicated (8). The recent observations that leptin exerts a powerful stimulatory effect on the reproductive system and reverses the effects of fasting on other endocrine systems suggests that when the story of leptin is all told, some greater truths are bound to emerge (11–13).

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