cies. Some of the surprises might, in principle, have been foreseen through better linkages with the research community of plant physiologists and ecologists. But several visiting ecologists doubted that a viable closed habitat to support human life could have been assured, even had the best ecological knowledge of the time been brought to bear.

The major retrospective conclusion that can be drawn is simple. At present there is no demonstrated alternative to maintaining the viability of Earth. No one yet knows how to engineer systems that provide humans with the life-supporting services that natural ecosystems produce for free (5). Dismembering major biomes into small pieces, a consequence of widespread human activities, must be regarded with caution. Despite its mysteries and hazards, Earth remains the only known home that can sustain life.

There may be a partial analogy between the initial problems of Biosphere 2 and the early, well-publicized flaws of the Hubble Space Telescope. Just as the Hubble telescope's initial images, although fuzzy, produced insights for astronomers, the initial work in Biosphere 2 has already provided insights for ecologists—and perhaps an important lesson for humanity. Now that the Hubble telescope has been improved, it is a major instrument with the potential for observations never possible before. Similarly, research in a retooled Biosphere 2 may well contribute exciting insights into the task of maintaining the viability of Biosphere 1—the Earth.

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BIOMEDICINE

Does Leptin Contribute to Diabetes Caused by Obesity?

Simeon I. Taylor, Valarie Barr, Marc Reitman

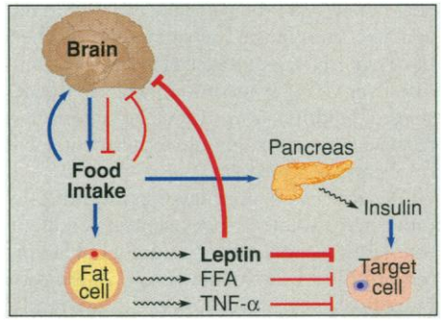
Obesity—an all-too-common public health problem—increases the chances of developing several other diseases including non–insulin-dependent diabetes mellitus (NIDDM) and hypertension. In a report on page 1185 of this issue, Cohen *et al.* (*1*) suggest that secretion of the satiety-inducing peptide leptin may be one way that obesity causes insulin resistance and thus NIDDM.

In 1994, Friedman and his colleagues (*2*) achieved a major breakthrough when they identified and characterized the *obese* gene, mutated in the obese mouse strain *ob/ob*. The *obese* gene encodes leptin, a 16-kD peptide that is secreted by fat cells (adipocytes). (*Leptin* is also the new name assigned to the *obese* gene.) Treatment of *ob/ob* mice with leptin reversed all the manifestations of the *ob/ob* phenotype and also caused weight loss in wild-type mice (*3*, *4*). This dramatic success raised the hope that leptin would be therapeutically useful for human obesity; it is now in the early phases of clinical testing in humans. Despite this enthusiasm, there remain many unanswered questions about leptin action: Which cells and tissues respond to leptin? What are the molecular mechanisms of leptin action? What is the role of leptin in the pathophysiology of human disease?

Mice with the *ob/ob* phenotype are very similar to animals with lesions in the ventromedial hypothalamus, leading to the prediction that leptin acts in the central nervous system to suppress appetite. This hypothesis was supported by the demonstration that intraventricular infusion of leptin is more effective than is intraperitoneal injection in causing weight loss in mice (*4*). However, leptin does more than decrease food intake. Without leptin, animals show decreased physical activity, hypothermia, and infertility. Indeed, leptin and its receptor probably evolved to trigger an array of adaptations to starvation, rather than as a "satiety hormone" to prevent overeating when food is abundant (*5*). Scarcity of food and starvation was a common problem throughout evolution; abundance of food is a relatively recent development.

At least two defects characterize NIDDM: insulin resistance and insulin deficiency. Genetic defects have been identified in patients with quite rare forms of NIDDM (for example, mutations in the insulin receptor gene that cause insulin resistance and mutations in the glucokinase gene that impair insulin secretion). But in most patients with NIDDM, the primary causes of the disease are unknown. Nevertheless, there is a strong association of NIDDM with obesity. In addition, obesity at least in part causes insulin resistance because weight reduction ameliorates insulin resistance. Circumstantial evidence suggests a role for the adipocyte in the genesis of insulin resistance (see figure). One hypothesis is that adipocytes secrete factors that cause insulin resistance. Free fatty acids, produced by hydrolysis of triglycerides stored in adipose tissue, can inhibit glucose utilization by peripheral tissues. Therefore, free fatty acids were among the first candidates proposed to explain the association between increased adiposity and insulin resistance (*6*). More recently, increased tumor necrosis factor–α (TNF-α), also produced by adipocytes, has been invoked as a cause of insulin resistance (*7*).

The new work by Cohen *et al.* (*1*) suggests that secretion of leptin by adipose tissue may be another mechanism whereby increased adiposity causes insulin resistance. Their data suggest the existence of "cross talk" between the signaling pathways downstream from insulin and leptin receptors. According to the usual model of insulin action, insulin binding stimulates phosphorylation of multiple tyrosine residues in the cytoplasmic domain of its receptor; this, in turn, activates the receptor to phosphorylate other substrates such as insulin receptor substrate–1 (IRS-1). Tyrosine phosphorylation of IRS-1 (and other substrates) is required to activate downstream effector pathways. When phosphotyrosines in YXXM motifs in IRS-1 bind the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI 3-kinase), PI 3-kinase is activated—a necessary step for the triggering



Now there are three. Leptin joins free fatty acids (FFAs) and TNF-α as possible mediators of the insulin resistance (and NIDDM) caused by obesity.

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of many of the metabolic actions of insulin (such as stimulation of glucose transport). Similarly, another phosphotyrosine in IRS-1 binds to GRB2 (growth factor receptor binding protein–2), which activates the Ras/Raf/MAP (mitogen-activated protein) kinase pathway. Cohen *et al.* (*1*) now report that leptin antagonizes insulin signaling, consistent with their finding that it decreases insulin-induced tyrosine phosphorylation of IRS-1. As expected, decreased phosphorylation of IRS-1 was associated with decreased binding of GRB-2.

However, other observations are harder to rationalize with current models of insulin action. For example, why was decreased tyrosine phosphorylation of IRS-1 associated with an increase in binding of p85? In addition, leptin was observed to potentiate insulin-induced tyrosine phosphorylation of the insulin receptor. Ordinarily, tyrosine phosphorylation of the receptor results in activation of the receptor tyrosine kinase. Why, then, did leptin inhibit phosphorylation of IRS-1? Finally, Cohen *et al.* showed that leptin antagonizes insulin's ability to decrease mRNA encoding phosphoenolpyruvate carboxykinase (PEPCK), the enzyme catalyzing the rate-limiting step in gluconeogenesis. Previous work showed that insulin's effect on PEPCK requires activation of PI 3-kinase, but not the MAP kinase pathway (*8*). Why did leptin and insulin have antagonistic effects on expression of PEPCK mRNA although both activate PI 3-kinase? Providing answers to these provocative questions has the potential to expand our understanding of the mechanisms of insulin action.

How does leptin act on hepatoma cells? All of the variably spliced isoforms of leptin receptor mRNA encode proteins that bind leptin, but they differ in their cytoplasmic domains (*9*). The longest form (isoform b) is the only one known to activate the Jak-Stat pathway. In fact, mice with a mutant allele of the murine leptin receptor gene [originally named the *diabetes* (*db*) locus] do not express isoform b yet have the same phenotype as mice completely lacking leptin. This observation led to the hypothesis that isoform b mediates all of the biological actions of leptin. However, Cohen *et al.* (*1*) detected only isoform a (a short form that does not activate the Jak-Stat pathway) in human liver and cultured hepatoma cells. [Others have reported the presence of isoform b in murine liver (*10*).] If isoform a mediates the actions of leptin in liver, the molecular mechanism whereby it antagonizes insulin action will be of particular interest.

Because *ob*/*ob* mice develop insulin resistance in the total absence of leptin, it is likely that leptin is only one of a number of factors responsible for the induction of insulin resistance in obesity. Nevertheless, the new results (*1*) will generate renewed interest in the possible role of leptin in NIDDM in humans. It would be both disappointing and ironic if a peptide with the potential to cause people to lose weight exacerbated insulin resistance, thereby predisposing them to NIDDM. We hope that clinical trials will demonstrate that leptin does not have this unfortunate toxicity.

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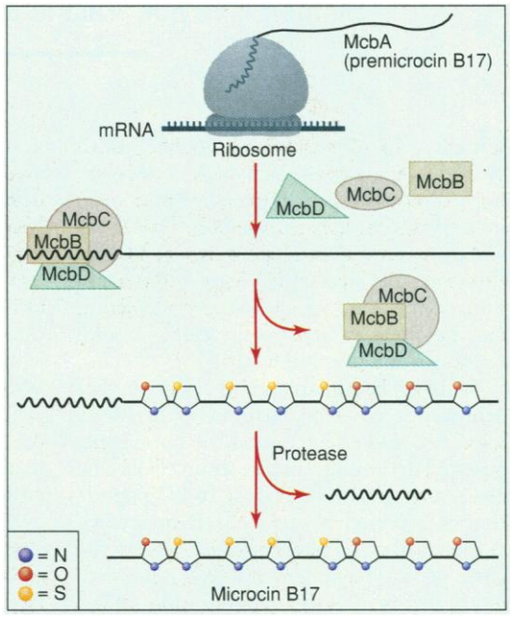
NATURAL PRODUCTS

One of Nature's Macromolecular Machines Demystified

JoAnne Stubbe

Enzyme-based macromolecular machines inside bacteria synthesize, with amazing efficiency, a diverse array of medicinally interesting polypeptides and polyketides with unusual ring structures (*1*–*3*). Polypeptides such as cyclosporin are made nonribosomally from pantetheinylated modular protein components and monomeric building blocks such as amino acids. Alternatively polypeptides such as microcins (*4*, *5*) and lantibiotics (*26*) are made by ribosomes from mRNA and then extensively posttranslationally modified by macromolecular machines. On page 1188 of this issue, Li *et al.* report the first purification of the enzymes required to synthesize microcin B17 (see figure). The purification of the essential components of this process lays the groundwork for understanding the chemical basis for these interesting conversions, which may lead to the development of novel compounds with unprecedented properties (*7*).



Making microcin. Biochemical reaction steps in the synthesis of microcin B17 in *Escherichia coli*. The precursor peptide is modified after ribosomal translation to form the microcin product with oxazole and thiazole rings.

Peptide antibiotics with five-member heterocyclic rings are prevalent and varied in structure. They function as antibacterial, antiviral, and antitumor agents and act on diverse targets (*4*, *5*, *8*). The peptide antibiotics made by ribosomes have a number of features in common (see figure). In each case, several gene products are required for their biosynthesis and they are usually part of a single operon. In the case of the lantibiotics and microcins, one gene from the operon codes for the prepeptide. Additional gene products within the operon then convert the natural amino acids within the prepeptide into the novel heterocyclic ring structures. Subsequent to this posttranslational modification, in many cases, the resulting modified peptide is cleaved proteolytically to generate the active natural product (see figure). In addition, the operons usually contain genes that code for proteins that are involved in transport of these peptides out of the host cell, as a defense mechanism when a

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