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Ron Rosedale, MD

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Review

The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn*

Joslin Diabetes Center and Department of Medicine Harvard Medical School, One Joslin Place, Boston, Massachusetts 02215 (USA), e-mail: c.ronald.kahn@joslin.harvard.edu

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Abstract. There are many theories of aging and parame-ters that influence lifespan, including genetic instability, telomerase activity and oxidative stress. The role of caloric restriction, metabolism and insulin and insulin-like growth factor-1 signaling in the process of aging is

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Metabolism and insulin-receptor and IGF 1-receptor signaling
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Studies over the last several years have revealed a central role of insulin signaling in lifespan and aging in diverse organisms, ranging from yeast to rodents. These discoveries indicate that aging is a programmed and well-controlled process regulated by the same pathways that affect growth, development and metabolism in these organisms. This supports the hypothesis that the impact of these genes on longevity of different species is an evolutionarily conserved process.

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Calorie restriction

The most striking and the most consistent model of extended lifespan, and one which dramatically demonstrates the role of metabolism in this process, is calorie restriction. Indeed, calorie restriction retards aging and extends median and maximal lifespan in yeast, worms, fish, flies, mice, rats and monkeys [145–148], and recent data suggest even in humans [148].
Some of the common and consistent effects of calorie restriction in rodents and nonhuman primates include lower fat mass, particularly visceral fat, lower circulating insulin and IGF-1 concentrations, increased insulin sensitivity, lower body temperature, lower fat-free mass, lower sedentary energy expenditure (adjusted for fat-free mass), decreased levels of thyroid hormones and decreased oxidative stress

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Review

The role of insulin and IGF-1 signaling in longevity

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Increasing the level of Sir-2 in yeast and *C. elegans* prolongs lifespan, while decreasing Sir activity decreases lifespan in yeast. … the increased Sir-2 activity is coupled with a change in yeast metabolism, due to low glucose availability, which changes from anaerobic (fermentation) to aerobic metabolism (TCA cycle), thus, producing more energy (ATP) from each glucose molecule metabolized. Sir activity is NAD^+-dependent …NAD/NADH ratio (one end product of metabolism) regulates Sir activity… calorie restriction extends yeast lifespan by lowering the level of NADH. It has been shown that Pnc1… enhances Sir-2 activity by increasing the NAD/NADH ratio in cells… The prolongation of lifespan in yeast by glucose deprivation requires Pnc1. Pnc1 levels are also elevated under other conditions known to extend yeast lifespan, including amino acid restriction, salt stress and heat stress. All these results show a strong connection between maintenance of chromatin structure/silencing, metabolism and longevity in yeast.

In mammals, it has been shown recently that SIRT1 activates a critical component of calorie restriction: fat mobilization in white adipocytes. Upon food withdrawal SIRT1 protein binds to and represses genes controlled by the fat regulator PPAR-*g* (peroxisome proliferator-activated receptor-*g*), including genes that mediate fat storage …thus increasing energy efficiency. *[Of note is the fact that oxidation of fats is an aerobic process; glucose can be used anaerobically. In times of plenty energy can be wasted with anaerobic metabolism. In times of plenty, organisms burning fuel anaerobically can burn fuel faster and thus have more babies. With low fuel availability, aerobic metabolism, though slower, affords greater fuel efficiency thereby promoting survival.]*

…upregulation of SIRT1 in differentiated fat cells triggers lipolysis and loss of fat.

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Insulin/IGF-1 signaling

Insulin and the insulin-like growth factors (IGF-1 and IGF-2) represent a family of hormones/growth factors that regulate metabolism, growth, cell differentiation and survival of most tissues in mammals.

Sir; FOXO; P66; klotho; animal models; *S. cerevisiae*; *C. elegans*; *D. melanogaster*; mouse; knockout; human; syndrome; Ames Dwarf; Snell Dwarf; FIRKO.

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While it is clear that insulin/IGF-1R signaling have important roles in metabolism and lifespan of *C. elegans,* the question remains as to what mechanisms link these pathways to aging and longevity. The answer appears to be that in nematodes the Daf-2 pathways are linked to in-creased resistance to oxidative stress… *daf-2* mutants express high levels of antioxidative enzymes…The most recent results have shown that activation of dFOXO in the adult pericerebral fat body of *D. melanogaster* is sufficient to increase both male and female lifespan... It reduces expression of the fly insulin-like peptide, *dilp-2,* that is synthesized in neurons, and represses endogenous insulin-dependent signaling in the peripheral fat*…[Possibly allowing for increased fat metabolism.]*

These findings suggest that, as in *C. elegans,* autonomous and non-autonomous roles of insulin signaling combine to control aging…

a moderate decrease in insulin and IGF-1 signaling has been shown to extend longevity in mice.

…in liver of Ames Dwarf mice insulin sensitivity is increased with concomitant insulin receptor, IRS-1 and IRS-2 upregulation and lower levels of insulin [289]. This is similar to the improved insulin sensitivity in calorie-restricted animals that have increased lifespan.

…The FIRKO mouse model clearly shows that reduced adiposity, even in the presence of normal or increased food intake, can extend lifespan. It also suggests a special role for the insulin signaling pathway in fat in the longevity process. Reduced adiposity also tends to result in lower insulin levels and protection from diabetes. Thus, in some ways, the FIRKO mouse mimics some of the effects of calorie restriction without caloric restriction.

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What is aging? Why do we age? Why do some species live longer than the others? Do genes determine lifespan? What is the role of metabolism on longevity? These are some of the questions that have intrigued biologists for ages. Social scientists have raised other considerations: Do we want to live longer? And if so, how much longer? Is in-creasing longevity good for survival of the species, since natural/energy resources (water, food etc.) are limited? Will artificially prolonged lifespan alter natural evolu-tionary processes? How do we balance quality of life with quantity of life? These two perspectives of aging and longevity are cer-tainly connected, but are also distinct. One is the biology of aging and lifespan and the other is the social and evo-lutionary forces that may interact with the biology. In this review, we will focus on the biology of aging, and try to answer some of the first group of questions. We will fo- cus especially on the role of metabolism and insulin and

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Review

The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn*

Joslin Diabetes Center and Department of Medicine Harvard Medical School, One Joslin Place, Boston, Massachusetts 02215 (USA), e-mail: c.ronald.kahn@joslin.harvard.edu

Received 8 July 2004; received after revision 25 August 2004; accepted 17 September 2004

Abstract. There are many theories of aging and parame-ters that influence lifespan, including genetic instability, telomerase activity and oxidative stress. The role of caloric restriction, metabolism and insulin and insulin-like growth factor-1 signaling in the process of aging is

especially well conserved throughout evolution. These latter factors interact with each other, the former factors and histone deacetylases of the SIR family in a complex interaction to influence lifespan.

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Interestingly, one of the striking physiological characteristics recently identified in centenarians is their greatly increased insulin sensitivity compared with younger subjects…Centenarians living in southern Italy showed that this group have a preserved glucose tolerance and insulin action and lower plasma IGF-1 levels compared with aged subjects. More recently, data from 466 healthy subjects with an age range from 28 to 110 years demonstrated a significant reduction of insulin resistance in subjects from 90 to 100 years old, even after adjustment for body mass index…

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Conclusions

In conclusion, strong similarities exist between insulin and IGF-1 signaling systems in yeast, worms, flies, mammals and humans. These may be linked to oxidative stress resistance, metabolic regulation, food utilization and lifespan in each of these organisms. Such similarities suggest that the insulin/IGF-1 system arose early in evolution and that it is a central component of an anti-aging system, which is conserved from yeast to humans.

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Ioannis Dragatsis,[3] and Domenico Accili[1,2]

[1]Department of Medicine and [2]Institute of Human Nutrition, College of Physicians and Surgeons, Columbia University, New York, New York, USA.
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The results suggest that insulin must work in the brain and liver to save mice from diabetes…We have overestimated how important insulin is in muscle and fat and underestimated its importance in other tissues.

ARTICLE

A brain-liver circuit regulates glucose homeostasis

Alessandro Pocai, Silvana Obici, Gary J. Schwartz, and Luciano Rossetti*Departments of Medicine, Neuroscience, and Molecular Pharmacology, Diabetes Research and Training Center, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461*

Cell Metabolism January 2005

Summary: Increased glucose production (GP) is the major determinant of fasting hyperglycemia in diabetes mellitus. Previous studies suggested that lipid metabolism within specific hypothalamic nuclei is a biochemical sensor for nutrient availability that exerts negative feedback on GP. Here we show that central inhibition of fat oxidation leads to selective activation of brainstem neurons within the nucleus of the solitary tract and the dorsal motor nucleus of the vagus and markedly decreases liver gluconeogenesis, expression of gluconeogenic enzymes, and GP. These effects require central activation of ATP-dependent potassium channels $_{(KATP)}$ and descending fibers within the hepatic branch of the vagus nerve. that requires the activation of ^{K}ATP and selective brainstem neurons and intact vagal input to the liver.

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Diabetes 53:347–353, 2004

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Leptin is a hormone, mainly produced by the adipose tissue, involved in the regulation of en-ergy balance (1–3). Compelling evidence indi-cates that leptin serves as a mediator in the cross-talk between the peripheral and central nervous system to adapt metabolic and neuroendocrine function to changes in the nutritional state of the organism (4).

Considerable experimental data indicate that leptin modulates glucose homeostasis (5). In most cases (6–8),

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Further evidence for the role of leptin on glucose homeostasis was obtained in *ob/ob* and in lipodystrophic mice, which lack detectable amounts of circulating leptin. In both cases, peripheral treatment with leptin alone (11–13) or in combination with the adipocyte-derived hormone adiponectin (14) reversed the characteristic dia-betic phenotype and insulin resistance of these animals, and the same has been observed in lipodystrophic patients under chronic leptin treatment (15). In contrast, in hyper-leptinemic *db/db* mice and *fa/fa* rats, which have muta-tions in the leptin receptor, and in obese rats and humans with hyperleptinemia, leptin administration does not im-prove glucose tolerance and insulin sensitivity, probably due to the existence of leptin resistance (5).

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In nonadipose insulin-target tissues, leptin prevents triglyceride accumulation, thus contributing to the maintenance of insulin sensitivity

leptin receptor has been observed in peripheral tissues, including pancreatic ~-cells, liver, fat, and muscle, suggesting direct effects of leptin that are independent of central pathways.

Roles for leptin receptor/STAT3-dependent and -independent signals in the regulation of glucose homeostasis

Cell Metabolism March 2005

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Summary

Leptin activates the long form of the leptin receptor (LRb) to control feeding and neuroendocrine function and thus regu-late adiposity. While adiposity influences insulin sensitivity, leptin also regulates glucose homeostasis independently of energy balance. Disruption of the LRb/STAT3 signal in *s/s* mice results in hyperphagia, neuroendocrine dysfunction, and obesity similar to LRb null *db/db* mice. Insulin resistance and glucose intolerance are improved in *s/s* compared to *db/db* animals, however, suggesting that LRb/STAT3-independent signals may contribute to the regulation of glucose homeosta-sis by leptin. Indeed, caloric restriction normalized glycemic control in *s/s* animals, but *db/db* mice of similar weight and adiposity remained hyperglycemic. These differences in glucose homeostasis were not attributable to differences in insulin production between *s/s* and *db/db* animals but rather to decreased insulin resistance in *s/s* mice. Thus, in addition to LRb/STAT3-mediated adiposity signals, non-LRb/STAT3 leptin signals mediate an important adiposity-independent role in promoting glycemic control.

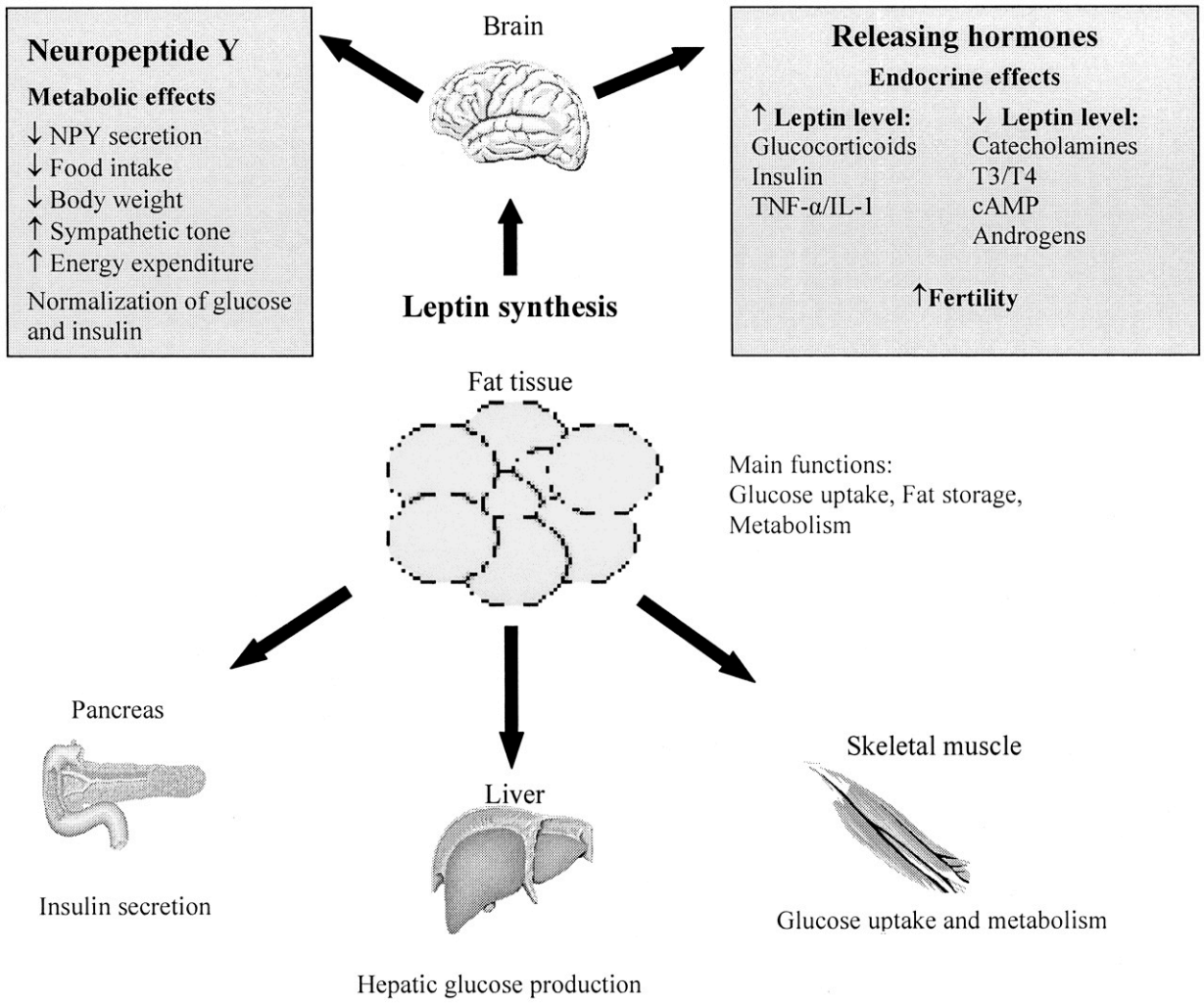
Introduction

The incidence of type 2 diabetes in industrialized nations has increased dramatically over the past several decades and con-tinues to increase; much of this increase is attributable to the burgeoning incidence of obesity in these populations (Green, 1997; Hubert et al., 1983). Leptin, the product of the *obese (ob)* gene (Friedman and Halaas, 1998; Zhang et al., 1994), is a hormone that is secreted by adipose tissue to signal the status of body energy stores to the central nervous system (CNS; Halaas et al., 1995). As a signal of energy sufficiency, adequate leptin levels suppress feeding and regulate neuroen-docrine function (Friedman and Halaas, 1998; Ahima et al., 1996, 1997; Heiman et al., 1997; Yu et al., 1997). Disrupted leptin action in *ob/ob* (devoid of leptin) and *db/db* mice (devoid of the signaling, or LRb, leptin receptor) results in hyperphagia and obesity, endocrine dysfunction, and predisposition to dia-betes.In addition to its role in regulating glucose homeostasis by controlling energy balance and thus adiposity, numerous lines of evidence suggest a direct role for CNS leptin action in regu-lating glucose homeostasis. Not only is the impaired glycemic control in animals with disruption in leptin or LRb action not reversed by pair feeding or fasting, but glycemic control is rea-sonably normal in other similarly obese rodents, such as the Ay mouse (Kahn and Rossetti, 1998). Furthermore, exogenously administered leptin acutely enhances glycemic control in *ob/ob* mice prior to noticeable effects upon feeding or adiposity, and leptin administration regulates hepatic glucose flux in wild-type as well as *ob/ob* mice (Liu et al., 1998; Burcelin et al., 1999; Kamohara et al., 1997; Barzilai et al., 1999). Furthermore, both in human patients and in animal models of lipodystrophic dia-betes, leptin administration improves insulin sensitivity and dia-betes, while food restriction does not (Petersen et al., 2002; Oral et al., 2002; Shimomura et al., 1999; Colombo et al., 2002; Ebihara et al., 2001). These leptin actions on glucose homeo-stasis appear to be mediated via the CNS, as similar effects are observed upon intracerebroventricular (ICV) as well as pe-ripheral administration of leptin in rodents (Liu et al., 1998), and brain-restricted transgenic expression of LRb predominantly rescues the obesity/diabetes phenotype of *db/db* mice (Kowal-ski et al., 2001; Chua et al., 2004; Cohen et al., 2001). It has also been suggested that leptin may directly regulate insulin production by the pancreatic Â cell, as incubation of primary islet cultures with leptin results in a suppression of insulin secretion (Kulkarni et al., 1997).Leptin binding to LRb activates the associated Jak2 tyrosine kinase to initiate downstream signaling (Ihle and Kerr, 1995; Taniguchi, 1995; Kloek et al., 2002). LRb signaling can be con-ceived of as originating from three major sites within the acti-vated receptor complex: from each of two tyrosine phosphory-lation sites on LRb itself (Tyr985 and Tyr1138) and from signaling motifs on the LRb-associated Jak2 molecule (Kloek et al., 2002; Bjorbaek et al., 2001; Banks et al., 2000). While signals mediated

Roles for leptin receptor/STAT3-dependent and -independent signals

Leptin activates the long form of the leptin receptor (LRb) to control feeding and neuroendocrine function and thus regulate adiposity. While adiposity influences insulin sensitivity, leptin also regulates glucose homeostasis independently of energy balance… Leptin signals mediate an important adiposity-independent role in promoting glycemic control. Leptin actions on glucose homeostasis appear to be mediated via the CNS…Leptin may directly regulate insulin production by the pancreatic B cell, as incubation of primary islet cultures with leptin results in a suppression of insulin secretion

Action of leptin on the hypothalamus and peripheral organs (pancreas, liver. and skeletal muscle)



Meier, U. et al. Clin Chem 2004;50:1511-1525

FAT RULES

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Your health and likely your lifespan will be determined by the proportion of fat versus sugar you burn over a lifetime

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….and that will be determined by the communication of hormones; primarily insulin and leptin

Cell Metabolism, Vol 1, 63-72, January 2005

The hypothalamic arcuate nucleus: A key site for mediating leptin's effects on glucose homeostasis and locomotor activity

Roberto Coppari,[1,6] Masumi Ichinose,[1,5,6] Charlotte E. Lee,[1] Abigail E. Pullen,[1] Christopher D. Kenny,[1] Robert A. McGovern,[1] Vinsee Tang,[1] Shun M. Liu,[3] Thomas Ludwig,[4] Streamson C. Chua Jr.,[3,7] Bradford B. Lowell,[1,7,*] and Joel K. Elmquist[1,2,7,*]

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Summary

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Leptin is required for normal energy and glucose homeostasis. The hypothalamic arcuate nucleus (ARH) has been proposed as an important site of leptin action. To assess the physiological significance of leptin signaling in the ARH, we used mice homozygous for a FLPe-reactivatable, leptin receptor null allele (*Lepr*$^{neo/neo}$ mice). Similar to *Lepr*$^{db/db}$ mice, these mice are obese, hyperglycemic, hyperinsulinemic, infertile, and hypoactive. To selectively restore leptin signaling in the ARH, we generated an adeno-associated virus expressing FLPe-recombinase, which was delivered unilaterally into the hypothalamus using stereotaxic injections. We found that unilateral restoration of leptin signaling in the ARH of *Lepr*$^{neo/neo}$ mice leads to a modest decrease in body weight and food intake. In contrast, unilateral reactivation markedly improved hyperinsulinemia and normalized blood glucose levels and locomotor activity. These data demonstrate that leptin signaling in the ARH is sufficient for mediating leptin's effects on glucose homeostasis and locomotor activity.

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LEP … CUATE … N … THE … PHY … FOR A … FL … MICE, … T … TO … SEL … VIRUS … EXPRE … S USING STEREOTAXIC INJECTIONS. WE FOUND THAT UNILATERAL RESTORATION OF LEPTIN SIGNALING IN THE ARH OF *Lepr*$^{neo/neo}$ MICE LEADS TO A MODEST DECREASE IN BODY WEIGHT AND FOOD INTAKE. IN CONTRAST, UNILATERAL REACTIVATION MARKEDLY IMPROVED HYPERINSULINEMIA AND NORMALIZED BLOOD GLUCOSE LEVELS AND LOCOMOTOR ACTIVITY. THESE DATA DEMONSTRATE THAT LEPTIN SIGNALING IN THE ARH IS SUFFICIENT FOR MEDIATING LEPTIN'S EFFECTS ON GLUCOSE HOMEOSTASIS AND LOCOMOTOR ACTIVITY.

*Source:*Cell Press*Date:*2005-01-27

Fat Hormone Acts On Brain Circuit To Curb Obesity, Diabetes

New research published in the premier issue of Cell Metabolism finds that a single brain region is sufficient for normal control of blood sugar and activity level by the fat hormone leptin. The same region also exerts significant, though more modest, control over leptin's effects on body weight. The findings in mice provide insight into potential mechanisms underlying type II diabetes and suggest new avenues for treatment, according to the researchers.

Secreted by fat cells, leptin signals the status of the body's energy content to the brain and is required for normal body weight and glucose balance. Mice lacking leptin develop obesity, diabetes, and inactivity, among other symptoms. The new results suggest that leptin signaling acts directly on the brain region known as the hypothalamic arcuate nucleus (ARH) to control insulin and glucose levels in the bloodstream, report Joel Elmquist and Bradford Lowell, both of Beth Israel Deaconess Medical Center and Harvard Medical School, and their colleagues. ARH neurons also mediate the majority, if not all, of the hormone's action on locomotor activity, they found.

Leptin receptors in the ARH accounted for approximately 22 percent of the hormone's effects on body weight, the group reports, suggesting that other brain regions are also important to this hormonal function.

"As the incidence of obesity and diabetes continues to rise in industrialized countries, a clear understanding of the cellular and neuroanatomic pathways that control energy and glucose balance is critical to the discovery of new methods to prevent or treat these conditions," Elmquist said. "The current findings definitively demonstrate that the hypothalamic arcuate nucleus is required for normal body weight homeostasis and is sufficient to control leptin's anti-diabetic actions."

Using a novel technique, the researchers unilaterally re-activated leptin receptors in the ARH of mice in which they had otherwise blocked all leptin receptor activity. The ARH had been proposed as an important site of leptin action.

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The fat-derived hormone leptin regulates energy balance in part by modulating the activity of neuropeptide Y and proopiomelanocortin neurons in the hypothalamic arcuate nucleus. To study the intrinsic activity of these neurons and their responses to leptin, we generated mice that express distinct green fluorescent proteins in these two neuronal types. Leptin-deficient *(ob/ob)* mice differed from wild-type mice in the numbers of excitatory and inhibitory synapses and postsynaptic cur-rents onto neuropeptide Y and proopiomelanocortin neurons. When leptin was delivered systemically to

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The New York Times
April 2, 2004
Studies on a Mouse Hormone Bear on Fatness in Humans
By GINA KOLATA

Published today in the journal Science: New studies in mice suggest that the hormone leptin can fundamentally change the brain's circuitry in areas that control appetite. Leptin acts during a critical period early in life, possibly influencing how much animals eat as adults. And later in life, responding to how much fat is on an animal's body, it can again alter brain circuitry that controls how much is eaten.

The Fat-Brain Axis Enters a New Dimension

Joel K. Elmquist and Jeffrey S. Flier Science April 2004

The dawn of 2004 marks the end of the first decade of leptin *(1)*. The discovery of the hormone leptin, which is produced by fat cells (adipocytes) and suppresses appetite, dramatically accelerated the pace of research on obesity, the neurobiology of feeding, and diabetes. The ensuing research produced a preliminary roadmap of the central nervous system (CNS) circuitry through which key metabolic signals like leptin exert their effects *(2–4)*. Remarkably, new actions for this hormone continue to be identified. Two papers in this issue, by Pinto *et al.* on page 110 *(5)* and Bouret *et al.* on page 108 *(6),* extend substantially the breadth of leptin's neurobiological actions within the CNS. The two reports suggest that leptin is a crucial regulator of both synaptic plasticity and axon guidance within the hypothalamus. Although much remains to be learned, these studies reveal fresh links between nutrition and neurodevelopment mediated by this adipocyte-derived hormone, with potentially important implications for the physiology of energy balance and body weight homeostasis.

Pinto and colleagues *(5)* assessed the acute effects of leptin on synaptic plasticity in the arcuate nucleus of the hypothalamus. The arcuate nucleus is one of the key targets of circulating hormones such as leptin. At least two distinct populations of neurons with opposing actions on food intake reside in the arcuate nucleus (see the figure). The first population produces the "orexigenic" (appetite-stimulating) neuropeptides NPY and AgRP (neuropeptide Y and agoutirelated protein). The second population produces the "anorexigenic" (appetite-suppressing) neuropeptides POMC and CART (proopiomelanocortin and cocaine- and amphetamine-regulated transcript). Both populations of neurons express leptin receptors, and are regulated by leptin in opposite ways. Leptin activates the POMC/CART neurons directly but blocks the activity of the NPY/AgRP neurons *(2–4)*. To add to the complexity, NPY/AgRP neurons produce the inhibitory neurotransmitter GABA and send collateral inputs to the POMC/CART neurons that may chronically inhibit these neurons *(7)*.

Pinto *et al.* add to the complexity of this state, the excitatory and inhibitory synaptic inputs to the POMC and NPY neurons are markedly altered. Using leptin-deficient (ob/ob) mice expressing variants of green fluorescent protein in POMC and NPY neurons, they assessed the electrophysiological properties of both cell groups. They found that a leptin deficiency in the ob/ob mice caused an increase in the excitatory inputs (EPSCs) to the orexigenic NPY/AgRP neurons and a parallel increase in the inhibitory inputs to the anorexigenic POMC/CART neurons. These changes in electrophysiological activity were accompanied by altered numbers of excitatory and inhibitory synapses observed at the ultrastructural level. Thus, lack of leptin increased excitatory inputs (presumably glutamatergic synapses) on NPY/AgRP neurons and decreased excitatory synaptic inputs to POMC neurons. Importantly, leptin repletion in ob/ob mice reversed these effects, both at the electro-physiological and ultrastructural levels. This reversal was very rapid, occurring within hours of leptin administration. Thus, these studies suggest that, in addition to regulating neuronal activity and neuropeptide release and expression, leptin also affects neuronal plasticity in the hypothalamic neurons that are critical to the regulation of body weight homeostasis. The results suggest that the mechanisms underlying leptin's neurobiological role in the CNS are similar to those that link learning and memory to the phenomenon of long-term potentiation in the hippocampus *(8)*. This type of synaptic plasticity might underlie, at least in part, "hypo thalamic memory" and the concept of a **a** body weight "set point," until now a nebulous concept in search of a mechanism. Future studies will need to determine the source of the synaptic inputs to these arcuate neurons, the mechanisms by which leptin signaling brings these changes about, and whether synaptic plasticity in the arcuate nucleus underlies a particular, unique dimension of the physiology of energy balance.

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NEURO SCIENCE

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Science April 2004

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Regulation of fatty acid homeostasis in cells: Novel role of leptin

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 2327–2332, March 1999 Medical Sciences

ABSTRACT It is proposed that an important function of leptin is to confine the storage of triglycerides (TG) to the adipocytes, while limiting TG storage in nonadipocytes, thus protecting them from lipotoxicity. The fact that TG content in nonadipocytes normally remains within a narrow range, while that of adipocytes varies enormously with food intake, is consistent with a system of TG homeostasis in normal nona-dipocytes. The facts that when leptin receptors are dysfunc-tional, TG content in nonadipocytes such as islets can increase 100-fold, and that constitutively expressed ectopic hyperlep-tinemia depletes TG, suggest that leptin controls the homeo-static system for intracellular TG. The fact that the function and viability of nonadipocytes is compromised when their TG content rises above or falls below the normal range suggests that normal homeostasis of their intracellular TG is critical for optimal function and to prevent lipoapoptosis. Thus far, lipotoxic diabetes of *fayfa* Zucker diabetic fatty rats is the only proven lipodegenerative disease, but the possibility of lipo-toxic disease of skeletal andyor cardiac muscle may require investigation, as does the possible influence of the intracel-lular TG content on autoimmune and neoplastic processes.

Leptin was discovered by positional cloning of a single gene mutation in the *obyob* mouse (1), a well-characterized model of obesity and diabetes with endocrine and immunologic abnormalities (2). Because the obesity is caused by deficiency of the *ob* gene product, leptin, and can be corrected by replacement of the peptide (3–5), leptin generally is regarded as an antiobesity hormone. Yet, there are theoretical and factual reasons for doubt that this is its primary function. First, there is little evidence of evolutionary pressure to prevent obesity; on the contrary, obesity can be a survival asset, a defense against famine, as proposed in the "thrifty gene" theory of Neel (6). Second, more than half of the population in the United States is overweight despite higher plasma leptin levels than the nonobese minority (7, 8)—hardly the creden-tials of a hormone that prevents obesity. Consequently, while leptin deficiency certainly causes obesity, it seems unlikely that prevention of obesity is its primary physiologic role.

A Novel Physiologic Role for Leptin

Regulating Fatty Acid Metabolism in Nonadipocytes. If prevention of obesity is not the primary function of leptin, what is its physiologic mission? Here, we propose that an important physiologic function of leptin is to regulate in nonadipocytes the intracellular homeostasis of fatty acids (FA) and triglyc-erides (TG) so as to maintain a sufficient supply of FA for essential cell functions while avoiding TG overload.

Long-chain fatty acids provide the building blocks for biologic membranes, the anchors for membrane proteins, and the source of lipid-containing messengers. Those tissues thus

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it was critical that the surplus TG be stored primarily in adipocytes and not be distributed equally to all cells. It therefore was essential that, during periods of TG deposition, adipocytes secrete a signal that would block the overaccumulation of TG in nonadipocytes and thus confine fat storage to fat cells. We propose that the signal is leptin, and that its function is to create for adipocytes a monopoly on fat storage, so as to maintain the constancy of intracellular TG in nonadipocytes

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As fat content in islets increases, b cells at first become hyperplastic and insulin production rises (20, 21). But once the fat content exceeds 50 times normal, the hyperplastic b cells undergo lipoapoptosis (22) and diabetes appears. This finding implies that lack of leptin action in these nonadipocytes tissue caused the fat

Source: **Mayo Clinic**

Date: 2004-06-25

How Fat Poisons Livers Of Obese Children And Adults

ROCHESTER, Minn. -- Obesity is the number one cause of chronic liver disease in the United States. Mayo Clinic researchers have discovered the mechanism that causes liver damage in many obese children and adults: excess fatty acids cause a protein reaction that kills liver cells, causing scarring and liver damage.

Known as Non-Alcoholic Fatty Liver Disease - NAFLD - the condition was first identified and named by a Mayo Clinic research team in 1980. It affects up to a quarter of the population in western countries. The latest Mayo Clinic discovery on NAFLD appears in today's version of the journal Hepatology online.

"As a pediatrician, I feel we are dealing with a big epidemic — NAFLD is certainly surpassing Hepatitis C, in terms of potential damage to the liver," says Ariel Feldstein, M.D., Mayo Clinic pediatric gastroenterologist and principal investigator. "NAFLD is a growing worldwide problem related to affluence and the diet and lifestyle associated with it. It's as true in the U.S. as it is in Europe, Japan, and my native country Argentina." See how NAFLD occurs here.

Early signs of NAFLD consist of accumulation of fat in the liver, which can be found in almost two-thirds of obese people. Another indication is inflammation of the liver, sometimes with scarring. While simple fatty liver is usually a benign condition, about 10 percent of individuals can develop other liver abnormalities including inflammation and scarring that can lead to impaired function in a condition known as Nonalcoholic Steatohepatitis, or NASH. Both NAFLD and NASH are strongly associated with other components of the metabolic syndrome including diabetes, elevated cholesterol and triglyceride levels, and hypertension.

Significance of the Mayo Clinic Research

The discovery of how excess fatty acids poison livers is important because currently there is no treatment for obesity-associated liver disease. Knowing the cellular mechanisms behind NAFLD is the necessary first step to developing treatments for it. And while most cases of NAFLD do not progress to cirrhosis or require a liver transplant, physicians are nonetheless worried that this could change because they are seeing more symptoms of pediatric NAFLD earlier.

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Source: **Mayo Clinic**

Date: 2004-06-25

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Obesity, regional body fat distribution, and the metabolic syndrome in older men and women.

Arch Intern Med. 2005 Apr 11;165(7):777-83

Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A, Kritchevsky SB, Simonsick EM, Nevitt M, Holvoet P, Newman AB.

Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA. bgood@pitt.edu

BACKGROUND: The metabolic syndrome is a disorder that includes dyslipidemia, insulin resistance, and hypertension and is associated with an increased risk of diabetes and cardiovascular disease. We determined whether patterns of regional fat deposition are associated with metabolic syndrome in older adults. METHODS: A cross-sectional study was performed that included a random, population-based, volunteer sample of Medicare-eligible adults within the general communities of Pittsburgh, Pa, and Memphis, Tenn. The subjects consisted of 3035 men and women aged 70 to 79 years, of whom 41.7% were black. Metabolic syndrome was defined by Adult Treatment Panel III criteria, including serum triglyceride level, high-density lipoprotein cholesterol level, glucose level, blood pressure, and waist circumference. Visceral, subcutaneous abdominal, intermuscular, and subcutaneous thigh adipose tissue was measured by computed tomography. RESULTS: Visceral adipose tissue was associated with the metabolic syndrome in men who were of normal weight (odds ratio, 95% confidence interval: 2.1, 1.6-2.9), overweight (1.8, 1.5-2.1), and obese (1.2, 1.0-1.5), and in women who were of normal weight (3.3, 2.4-4.6), overweight (2.4, 2.0-3.0), and obese (1.7, 1.4-2.1), adjusting for race. Subcutaneous abdominal adipose tissue was associated with the metabolic syndrome only in normal-weight men (1.3, 1.1-1.7). Intermuscular adipose tissue was associated with the metabolic syndrome in normal-weight (2.3, 1.6-3.5) and overweight (1.2, 1.1-1.4) men. In contrast, subcutaneous thigh adipose tissue was inversely associated with the metabolic syndrome in obese men (0.9, 0.8-1.0) and women (0.9, 0.9-1.0). CONCLUSION: In addition to general obesity, the distribution of body fat is independently associated with the metabolic syndrome in older men and women, particularly among those of normal body weight.

PMID: 15824297 [PubMed - indexed for MEDLINE]

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The regulation of body fat distribution and the modulation of insulin action.

Int J Obes Relat Metab Disord 2000 Nov;24 Suppl 4:S63-6 (ISSN: 0307-0565)

Cases JA; Barzilai N
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Body fat distribution may determine insulin resistance and its metabolic syndrome in humans, independent of obesity. Surgical removal of visceral fat (VF) in obese rats was associated with decreased leptin plasma levels and its gene expression in subcutaneous fat (SC). Chronic leptin treatment to rats decreased VF specifically supporting the role of leptin in determining fat distribution. Surgical removal of selected VF provided direct evidence of improved in vivo insulin action on hepatic glucose production (HGP) by over 2-fold vs sham-operated control. The impact of decreased VF on improved in vivo insulin action was further supported by obtaining similar decreases in VF by treating rats with leptin (Lep), beta3-aderenoreceptor agonist, or by severe caloric restriction (CR). All these three interventions improved insulin action on the modulation of HGP and were mostly attributed to preservation of hepatic glycogen stores. Because free fatty acids (FFA) plasma levels were unchanged, this effect may not be mediated portally by substrates. Improved peripheral insulin sensitivity and glycogen synthesis was demonstrated only in Lep. These data suggest that VF is a major determinant of hepatic insulin action. In obese rats, the ability of leptin to prevent visceral adiposity and its own expression is attenuated. Thus, the failure of leptin to regulate fat distribution

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Removal of Visceral Fat Prevents Insulin Resistance and Glucose Intolerance of Aging

An Adipokine-Mediated Process?

Ilan Gabriely Nir Barzilai *Diabetes* 51:2951–2958, 2002

Age-dependent changes in insulin action and body fat distribution are risk factors for the development of type 2 diabetes. To examine whether the accumulation of visceral fat (VF) could play a direct role in the patho-physiology of insulin resistance and type 2 diabetes, we monitored insulin action, glucose tolerance, and the expression of adipo-derived peptides after surgical re-moval of VF in aging (20-month-old) F344/Brown Nor-way (FBN) and in Zucker Diabetic Fatty (ZDF) rats. As expected, peripheral and hepatic insulin action were markedly impaired in aging FBN rats, and extraction of VF (accounting for ~18% of their total body fat) was sufficient to restore peripheral and hepatic insulin ac-tion to the levels of young rats. When examined at the mechanistic level, removal of VF in ZDF rats prevented the progressive decrease in insulin action and delayed the onset of diabetes, but VF extraction did not alter plasma free fatty acid levels. However, the expression of tumor necrosis factor-~ and leptin in subcutaneous (SC) adipose tissue were markedly decreased after VF removal (by approximately three- and twofold, respec-tively). Finally, extracted VF retained ~15-fold higher resistin mRNA compared with SC fat. Our data suggest that insulin resistance and the development of diabetes can be significantly reduced in aging rats by preventing the age-dependent accumulation of VF. This study doc-uments a cause-and-effect relationship between VF and major components of the metabolic syndrome.

VF removal was also associated with decreased plasma concentrations of both insulin and leptin. Leptin mRNA in SC adipose tissue was also decreased. The decline in circulating levels of these hormones may simply reflect their improved biological action. However, it is also likely that a decrease in plasma insulin concentrations and perhaps decreased carbon flux into the hexosamine pathway may account for the decreased expression of leptin in SC adipose tissue after VF removal (19).

Diabetes 51:2951–2958, 2002

A progressive increase in visceral adiposity is a common feature of aging, and epidemiological evidence supports its role as a prominent risk factor for insulin resistance, diabetes, and mor-tality from atherosclerotic cardiovascular disease (1–5). Among various body fat depots, the amount of visceral fat

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Received for publication 15 April 2002 and accepted in revised form 2 July 2002.

CR, caloric restriction; dsDNA, double-stranded DNA; EGP, endogenous glucose production; FFA, free fatty acid; SC, subcutaneous; TNF-~, tumor necrosis factor-~; VF, visceral fat.

(VF) best correlates with insulin sensitivity in animal models and in humans. Insulin action is markedly im-paired in individuals with visceral obesity (6,7), and epi-demiological studies have shown that VF can account for most of the variability in insulin sensitivity in heteroge-neous populations (2,4,6,7). However, these studies are associational in nature, and VF may be simply a "marker" of more complex endocrine and metabolic changes rather than playing a "causative" role in the pathogenesis of insulin resistance and its metabolic consequences. Puta-tive mechanisms responsible for the modulation of insulin action by VF include increased portal release of free fatty acids (FFAs) (8,9) and/or abnormal expression and secre-tion of fat-derived peptides, such as resistin (10), leptin, ACRP30, and tumor necrosis factor-~ (TNF-~) (11).

A consistent observation in the biology of aging is that chronic restriction of caloric intake in rodents markedly improves survival and prevents the onset of insulin resis-tance. We and others have hypothesized that the beneficial effects of caloric restriction (CR) on the metabolic alter-ations of aging are largely accounted for by its prevention of VF accumulation (12,13). To directly examine the contribution of VF to the insulin resistance of aging, it is important to separate the potential effects of a decrease in VF per se from other nutritional, anthropometric, and metabolic consequences of CR. Having demonstrated that surgical removal of VF rapidly improves hepatic insulin action in young rats (14), we made use of this novel animal model to investigate the following two main questions: *1)* Does VF play a causative role in the peripheral and hepatic insulin resistance of aging? and *2)* Can VF removal alter the natural history of developing diabetes in a rodent model of obesity and diabetes?

RESEARCH DESIGN AND METHODS

Animals. A total of 34 F1 hybrids of F344/Brown Norway rats obtained from the National Institutes of Aging were housed in individual cages and subjected to a standard light (6:00 A.M. to 6:00 P.M.)/dark (6:00 P.M. to 6:00A.M.) cycle. Rats were assigned into five experimental groups: *1)* VF~ (*n* ~ 6): 15-month-old ad libitum–fed rats that were anesthetized (pentobarbital 50 mg/kg body wt i.p.), and their epididymal and the perinephric fat pads were removed, weighed, and

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Internal fat's role in type 2 diabetes probed

The Reporter of Vanderbilt University March 18, 2005

Naji Abumrad, M.D.
by Lisa Peper

A multi-disciplinary research team at Vanderbilt University Medical Center is looking past waistlines and deeper into the role visceral fat plays in type 2 diabetes.

A new study - made possible by the seamless collaboration of no less than nine distinct operating units - will test how patients' insulin sensitivity is affected by removal of the omentum, a blanket of internal abdominal fat that rests on top of the intestines and is attached to both the stomach and the small bowel.

The study, led by Naji Abumrad, M.D., professor and chair of General Surgery, will combine the removal of the omentum with gastric bypass surgery.

The investigation is a novel approach to treating type 2 diabetes, but has its basis in years of obesity and diabetes-related research, Abumrad said.

"The world community has spent a tremendous amount of time looking at the relationship of weight and type 2 diabetes. It's known that the higher the weight, the higher the chance of developing type 2 diabetes," Abumrad said. "We have also shown the reversal of this through gastric bypass surgery. We know that this surgery leads to significant weight loss and a significant resolution of diabetes. We wanted to know how the reversal occurred - what were the predictive variables that led to resolution of diabetes."

With Alfonso Torquati, M.D., assistant professor of Surgery, Abumrad learned that the only weight-loss variable of sufficient determining power in the reduction of type 2 diabetes is waist circumference.

"The larger the waist circumference, the higher the incidence of type 2 diabetes," Abumrad said. "So we started asking - what is it about waist circumference that is so predictive?"

The answer could be the internal or visceral fat padding the waistline. Studies have shown that removing large amounts of abdominal fat on the periphery through liposuction does not affect insulin sensitivity. Therefore, Abumrad said, they are looking at the fat inside the belly, most of which is located in the omentum.

"We decided to take the concept to the lab first," he said. In animal studies, they tested insulin sensitivity and how the liver and muscle metabolize sugar both before and after removing the visceral fat. They found after removing the omentum, the liver cuts down production of sugar by nearly 40 percent.

"The effect of the omentum on the liver is quite powerful," Abumrad said. "This is as effective in shutting down the liver production of insulin as many of the drugs being used to treat type 2 diabetes. We also observed one additional surprising finding: Removing the omentum also increased the consumption of sugar by the peripheral tissues, primarily skeletal muscle."

The team will test omentum removal in morbidly obese adults. Participants will be randomized to either a Roux-en-Y gastric bypass surgery with omentum removal or a Roux-en-Y gastric bypass surgery alone. The researchers will compare the participants' insulin sensitivity before and after the surgery, as well as comparing the participants to one another to understand what variables might affect the speed of response to the surgery and to a reversal in type 2 diabetes.

The collaboration of a large team of VUMC physicians and researchers will expand the focus of the investigation to include metabolic implications, genetic aspects of obesity and diabetes such as racial differences, pharmacological concerns including chronic inflammation, and cardiovascular elements.

"We have put an incredible team together - something I could only do at Vanderbilt and nowhere else," Abumrad said.

Collaborators include

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The Reporter of Vanderbilt University March 18, 2005

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Leptin directly stimulates aromatase activity in human luteinized granulosa cells.

Mol Hum Reprod 1999 Aug;5(8):708-13 (ISSN: 1360-9947)

Kitawaki J; Kusuki I; Koshiba H; Tsukamoto K; Honjo H
Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan.

Leptin, the obese (ob) gene product, is secreted by adipocytes and regulates appetite through interaction with hypothalamic leptin receptors. Leptin may also have a stimulatory effect on reproductive function. Furthermore, leptin receptor mRNA is expressed in the ovary, suggesting a direct effect on its function. The present study examines the direct role of leptin on the oestrogen-producing activity in human luteinized granulosa cells. The cells were obtained from in-vitro fertilization pre-ovulatory follicles, precultured for 24 h in the presence of 5% charcoal-treated serum, and incubated for 48-96 h in a serum-free medium containing recombinant human leptin, follicle stimulating hormone (FSH), and/or insulin-like growth factor-I (IGF-I). A single addition of leptin (0. 5-10 ng/ml) stimulated aromatase activity with the incubation time of up to 96 h. The addition of leptin (1 ng/ml) further augmented the stimulation by a single addition of FSH (100 ng/ml) or IGF-I (100 ng/ml), or a combination of both. A single addition of leptin (1 ng/ml) or a combination of leptin (1 ng/ml), FSH (100 ng/ml), and IGF-I (100 ng/ml) gave rise to an increase in each parameter of oestrogen-producing activity measured, i.e. P450arom mRNA level, P450arom protein level, aromatase specific activity, and the oestradiol concentration in the culture supernatant. However, the production of progesterone did not change. These results indicate that leptin stimulates oestrogen production by increasing P450arom mRNA and P450arom protein expression and, consequently, aromatase activity by its direct action on the human luteinized granulosa cells.

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Ann Rheum Dis. 2004 Jul;63(7):809-16.

Possible role of leptin in hypoandrogenicity in patients with systemic lupus erythematosus and rheumatoid arthritis.

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Laboratory of Neuro/endocrino/immunology, Department of Internal Medicine I, University Hospital Regensburg, D-93042 Regensburg, Germany.

BACKGROUND: Hypoandrogenicity is common in obesity and in chronic inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Adrenal androgens such as androstenedione (ASD) and dehydroepiandrosterone (DHEA) sulphate are low, which partly depends on the influence of TNF in chronic inflammatory diseases. Leptin is stimulated by TNF and is associated with hypoandrogenicity in non-inflammatory conditions. OBJECTIVE: To study the interrelation between serum levels of leptin and adrenal steroids in SLE and RA. METHODS: In a retrospective study, serum levels of leptin, ASD, DHEA, and 17-hydroxyprogesterone (17OHP) were measured by ELISA, and serum levels of cortisol by radioimmunoassay in 30 patients with RA, 32 with SLE, and 54 healthy control subjects (HS). RESULTS: In SLE and RA but not HS, serum levels of ASD correlated negatively with serum levels of leptin ($p<0.01$) independently of prior prednisolone treatment in patients with SLE ($p = 0.013$) and tended to be independent of prednisolone in patients with RA ($p = 0.067$). In a partial correlation analysis, this interrelation remained significant after controlling for daily prednisolone dose in both patient groups. In both patient groups, serum leptin levels correlated negatively with the molar ratio of serum ASD/serum cortisol and serum ASD/serum 17OHP, and positively with the molar ratio of serum DHEA/serum ASD. CONCLUSIONS: The negative correlation of serum leptin and ASD or, particularly, ASD/17OHP, together with its known anti-androgenic effects indicate that leptin is also involved in hypoandrogenicity in patients with SLE and RA. Leptin may be an important link between chronic inflammation and the hypoandrogenic state.

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Obesity Linked To Aggressive Prostate Cancer

American Society Of Clinical Oncology :2003-12-24 Alexandria, VA –

Obese men with prostate cancer are more likely to have aggressive tumors and to experience cancer recurrence after surgery compared to men of normal weight or those who are overweight but not obese, according to two new studies. Although more research is needed, the findings suggest that men may be able to modify their risk of aggressive prostate cancer by maintaining a healthy weight. The results of both studies will be reported December 22 online in the Journal of Clinical Oncology (JCO).

"The primary role of obesity in prostate cancer is still unclear, but it appears to induce the development of more aggressive tumors," said Christopher L. Amling, MD, of the Naval Medical Center's Department of Urology in San Diego and lead author of one of the studies. "I would advise patients to maintain a normal body weight to limit the possibility that they would develop clinically significant, more aggressive prostate tumors."

Both Drs. Amling and Freedland suggest that proteins and hormones stored in body fat – such as leptin and insulin-like growth factor-1 – may promote prostate tumor growth in obese men. Also, obese men typically have lower testosterone levels and higher estrogen levels, which may encourage the growth of cancer.

Both studies examined the relationship between obesity and prostate cancer recurrence in large samples of men with localized prostate cancer who had undergone surgery to remove the prostate – a procedure called radical prostatectomy.

While obesity rates in the general adult population are similar between African-American and Caucasian men, both studies found that obese patients in the study groups were more likely to be African American. This finding may help explain why African-American men with prostate cancer generally have more aggressive tumors and worse outcomes compared to Caucasians.

"We suspect that worse outcomes among African-American men with prostate cancer are related to obesity rather than race. If we can target obesity in the African-American community, we may be able to reduce the burden of prostate cancer among black men,"

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Source: **American Heart Association**
Date: 2005-04-22
URL: http://www.sciencedaily.com/releases/2005/04/050419104936.htm

Enlarged Waist + Elevated Triglycerides = Heart, Stroke Risks For Women

Women who had an enlarged waist and elevated levels of blood fats known as triglycerides had almost a fivefold increased risk of fatal cardiovascular events compared to women without those traits.
…"This type of obesity is prone to an array of metabolic alterations that increases markedly the relative risk of adverse outcomes."

Plasma Leptin and the Risk of Cardiovascular Disease in the West of Scotland Coronary Prevention Study (WOSCOPS)

A. Michael Wallace, PhD; Alex D. McMahon, PhD; Chris J. Packard, DSc; Anne Kelly, MIBiol; James Shepherd, PhD; Allan Gaw, MD; Naveed Sattar, MD, PhD; on behalf of the WOSCOPS Executive Committee

(*Circulation*. 2001;104:3052-3056.)

Background—Leptin plays a role in fat metabolism and correlates with insulin resistance and other markers of the metabolic syndrome, independent of total adiposity. Therefore, we hypothesized that raised leptin levels may identify men at increased risk of a coronary event in the West of Scotland Coronary Prevention Study (WOSCOPS).

Methods and Results—Plasma leptin levels were measured at baseline in 377 men (cases) who subsequently experienced a coronary event and in 783 men (controls) who remained free of an event during the 5-year follow-up period of the study. Controls were matched to cases on the basis of age and smoking history and were representative of the entire WOSCOPS cohort. Leptin levels were significantly higher in cases than controls (5.87_2.04 ng/mL versus 5.04_2.09 ng/mL, *P*_0.001). In univariate analysis, for each 1 SD increase in leptin, the relative risk (RR) of an event increased by 1.25 (95% confidence interval [CI], 1.10 to 1.43; *P*_0.001). There was minimal change in this RR with correction for body mass index (RR, 1.24; 95% CI, 1.06 to 1.45; *P*_0.006) or with further correction for classic risk factors, including age, lipids, and systolic blood pressure (RR, 1.20; 95% CI, 1.02 to 1.42; *P*_0.03). Leptin correlated with C-reactive protein (*r*_0.24, *P*_0.001) and, even with this variable added to the model, leptin retained significance as a predictor of coronary events (RR, 1.18; 95% CI, 1.00 to 1.39; *P*_0.05) at the expense of C-reactive protein.

Conclusions—We show, for the first time, in a large prospective study that leptin is a novel, independent risk factor for coronary heart disease.

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Leptin enhances the calcification of vascular cells: artery wall as a target of leptin.

Circ Res 2001 May 11;88(9):954-60 (ISSN: 1524-4571)

Parhami F; Tintut Y; Ballard A; Fogelman AM; Demer LL
Departments of Medicine, University of California, Los Angeles, USA.

Leptin, the product of the ob gene, regulates food intake, energy expenditure, and other physiological functions of the peripheral tissues. **Leptin** receptors have been identified in the hypothalamus and in extrahypothalamic tissues. Increased circulating **leptin** levels have been correlated with cardiovascular disease, obesity, aging, infection with bacterial lipopolysaccharide, and high-fat diets. All these conditions have also been correlated with increased vascular calcification, a hallmark of atherosclerotic and age-related vascular disease. In addition, the differentiation of marrow osteoprogenitor cells is regulated by **leptin**. Thus, we hypothesized that **leptin** may regulate the calcification of vascular cells. In this report, we tested the effects of **leptin** on a previously characterized subpopulation of vascular cells that undergo osteoblastic differentiation and calcification in vitro. When treated with **leptin**, these calcifying vascular cells had a significant 5- to 10-fold increase in alkaline phosphatase activity, a marker of osteogenic differentiation of osteoblastic cells. Prolonged treatment with **leptin** enhanced the calcification of these cells, further supporting the pro-osteogenic differentiation effects of **leptin**. Furthermore, the presence of the **leptin** receptor on calcifying vascular cells was demonstrated using reverse transcriptase polymerase chain reaction, immunocytochemistry, and Western blot analysis. We also identified the presence of **leptin** receptor in the mouse artery wall, localized to subpopulations of medial and adventitial cells, and the expression of **leptin** by artery wall cells and atherosclerotic lesions in mice. Taken together, these results suggest that **leptin** regulates the osteoblastic differentiation and calcification of vascular cells and that the artery wall may be an important peripheral tissue target of **leptin** action.

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Leptin Inhibits Bone Formation through a Hypothalamic Relay: A Central Control of Bone Mass

Cell, Vol 100, 197-207, 21 January 2000

Patricia Ducy [1], Michael Amling [2], Shu Takeda [1], Matthias Priemel [2], Arndt F. Schilling [2], Frank T. Beil [2], Jianhe Shen [1], Charles Vinson [3], Johannes M. Rueger [2], and Gerard Karsenty [1§*]

[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030, USA
[2]Department of Trauma Surgery, University of Hamburg, Hamburg, 20246, Germany
[3]Laboratory of Biochemistry, National Cancer Institute, Bethesda, Maryland 20892, USA

Gonadal failure induces bone loss while obesity prevents it. This raises the possibility that bone mass, body weight, and gonadal function are regulated by common pathways. To test this hypothesis, we studied leptin-deficient and leptin receptor–deficient mice that are obese and hypogonadic. Both mutant mice have an increased bone formation leading to high bone mass despite hypogonadism and hypercortisolism. This phenotype is dominant, independent of the presence of fat, and specific for the absence of leptin signaling. There is no leptin signaling in osteoblasts but intracerebroventricular infusion of leptin causes bone loss in leptin-deficient and wild-type mice. This study identifies leptin as a potent inhibitor of bone formation acting through the central nervous system and therefore describes the central nature of bone mass control and its disorders.

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Life is not in the parts…we are all made of the same stuff…it is what you, or more accurately your hormones, do with the parts that determines health and life….

Obesity Over the Life Course

Tooru Mizuno, I-Wei Shu, Hideo Makimura, Charles Mobbs

Sage ke, Science, (Published 16 June 2004)

Obesity in middle-aged humans is a risk factor for many age-related diseases and decreases life ex-pectancy by about 7 years, which is roughly compara-ble to the combined effect of all cardiovascular dis-ease and cancer on life span. The prevalence of obesi-ty increases up until late middle age and decreases thereafter. Mechanisms that lead to increased obesity with age are not yet well understood, but current evi-dence implicates impairments in hypothalamic func-tion, especially impairments in the ability of hypothala-mic pro-opiomelanocortin neurons to sense nutritional signals. The rapid increase in the prevalence of obesi-ty at all ages in the past decade suggests that, in the next two or three decades, diseases associated with obesity, especially diabetes, will begin to rise rapidly. Indeed, these trends suggest that for the first time in modern history, the life expectancy of people in devel-oped societies will begin to decrease, unless the rapid increase in the prevalence of obesity can be reversed.

Introduction

The relation between obesity and aging is of great concern for several reasons. First, obesity decreases life span *(1)* and, con-versely, caloric restriction increases life span *(2)*. Furthermore, obesity is a risk factor for age-correlated diseases *(3-6)*. Finally, the prevalence of obesity increases with age but, most alarmingly, in the past decade the prevalence of obesity in the United States has increased dramatically in all age groups (Fig. 1). Despite the compelling relation between obesity and aging, however, little is known about why obesity increases with age or why obesity is a risk factor for age-related diseases. However, as described herein, it is clear that the relation between obesity and aging is complex.

On the whole, available data suggest that the hypothalamic "set point" for adiposity changes with age, so that incrementally higher body weights are defended at least through late middle age. Why is the higher adiposity defended? Recent studies have focused on the possible role of the protein leptin

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On the whole, available data suggest that the hypothalamic "set point" for adiposity changes with age, so that incrementally higher body weights are defended at least through late middle age. Why is the higher adiposity defended? Recent studies have focused on the possible role of the protein leptin

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Resistance to Leptin Contributes to Obesity

Aug. 5, 1997 *Proceedings of the National Academy of Sciences*

Insensitivity to the protein leptin, which helps the body regulate its fat stores, contributes to obesity in mice according to the first formal study of leptin intolerance, report scientists at The Rockefeller University. The findings also provide clues about leptin's action in the nervous system and may help to explain some forms of obesity that affect humans, including more than 50 million overweight adult Americans, the researchers note.

"We knew obese mice and humans generally have high levels of leptin in their blood, which suggested that the protein was not fully active. Our new research directly shows that resistance to leptin can cause obesity," explains senior author Jeffrey Friedman, M.D., Ph.D., professor at The Rockefeller University and an investigator with Howard Hughes Medical Institute (HHMI).

Some investigators have suggested that leptin's principal role is to suppress the body's response to starvation. The new study also suggests that receiving extra leptin adjusts a mouse's `set point' for the body weight to a lower-- but stable level --by reducing food intake without an accompanying decrease in energy use.

"These data confirm that leptin plays an important role in the body's response to weight gain. This result suggests that lean animals increase their production of leptin to return their weight to the set point," explains first author Jeffrey L. Halaas, B.S., biomedical fellow at Rockefeller. "Also, leptin acts to blunt the reduction in energy use that typically follows a reduction in the number of calories eaten."

In previous studies, Friedman and his colleagues discovered leptin and documented weight loss in genetically obese and normal mice given daily injections of the protein for two weeks. These early studies required high dose injections of leptin. In the current study, much lower doses were effective in reducing weight when the hormone was delivered as a constant infusion. While receiving leptin, the mice ate less and had a relative increase in their energy use compared to fasted mice. Leptin, a product of the *obese* gene, is made in fat and then is released into the blood stream, by which it travels to the brain.

Obesity, defined as being more than 20 percent above a healthy weight, affects one in

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Role of premature leptin surge in obesity resulting from intrauterine undernutrition

Cell Metabolism June 2005

Shigeo Yura,1,6 Hiroaki Itoh,1,6 Norimasa Sagawa,1 ,* Hiroshi Yamamoto,3 Hiroaki Masuzaki,2 Kazuwa Nakao,2 Makoto Kawamura,1 Maki Takemura,1 Kazuyo Kakui,1 Yoshihiro Ogawa,4,5 and Shingo Fujii1

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Summary

Intrauterine undernutrition is closely associated with obesity related to detrimental metabolic sequelae in adulthood. We report a mouse model in which offspring with fetal undernutrition (UN offspring), when fed a high-fat diet (HFD), develop pronounced weight gain and adiposity. In the neonatal period, UN offspring exhibited a premature onset of neonatal leptin surge compared to offspring with intrauterine normal nutrition (NN offspring). Unexpectedly, premature leptin surge generated in NN offspring by exogenous leptin administration led to accelerated weight gain with an HFD. Both UN offspring and neonatally leptin-treated NN offspring exhibited an impaired response to acute peripheral leptin administra-tion on a regular chow diet (RCD) with impaired leptin transport to the brain as well as an increased density of hypothala-mic nerve terminals. The present study suggests that the premature leptin surge alters energy regulation by the hypothala-mus and contributes to "developmental origins of health and disease."

IntroductionObesity has increased at an alarming rate in Western countries and is now a world-wide public health problem (Flier, 2004). Obesity is often associated with insulin resistance, dyslipide-mia, and hypertension, thus a concept of metabolic syndrome has been proposed (Masuzaki et al., 2001; Wajchenberg, 2000). Genetic factors and/or environmental factors, such as high-calorie diet in Western life style, have been considered to attribute to the prevalence of obesity (Flier, 2004). More re-cently, epidemiological and experimental evidence suggest that intrauterine undernutrition is closely associated with adult-hood obesity related to detrimental metabolic sequelae (Breier et al., 2001; Godfrey and Barker, 2000; Ravelli et al., 1976), giving rise to the concept of "developmental origins of health and disease" (Breier et al., 2001; Gluckman and Hanson, 2004). Involvement of perinatal exposure to glucocorticoids or pan-creatic maldifferentiation in the development of impaired glu-cose metabolism has been demonstrated (Breier et al., 2001; Gluckman and Hanson, 2004). However, the mechanism of de-velopmental origins of obesity is yet to be clarified.Leptin is an adipocyte-derived satiety factor that decreases food intake and increases energy expenditure, thereby stabiliz-ing body adiposity in many species (Friedman and Halaas, 1998). Leptin deficient *ob/ob* mice show marked obesity that is restored by exogenous leptin treatment (Campfield et al., 1995; Halaas et al., 1995; Pelleymounter et al., 1995; Trayhurn et al., 1977). Leptin exerts its biological activities through long-form leptin receptors, expressed abundantly in the hypothalamus(Flier, 2004). However, resistance to the satiety effect of leptin is a trait of obese subjects, as circulating leptin levels are well correlated with body fat mass (Ahren and Scheurink, 1998). It remains to be elucidated whether leptin resistance at the hypo-thalamus is associated with the onset of obesity or metabolic disorders in offspring with intrauterine growth restriction.In mice, plasma leptin levels rise transiently during neonatal period, termed as "neonatal leptin surge" (Ahima et al., 1998). In neonatal period, leptin alters hypothalamic neuropeptide ex-pression and metabolic rate before exerting its anorectic effect (Ahima and Hileman, 2000; Mistry et al., 1999; Proulx et al., 2002). Moreover, neurotrophic action of leptin was recently demonstrated, which is operative only in early developmental stage, but not in adult individuals (Bouret et al., 2004a; Bouret et al., 2004b). Therefore, it is suggested that leptin surge is involved in the formation of energy-regulation circuits in the hypothalamus. However, long-term effects of physiological or pathophysiological leptin surge on hypothalamic neuronal cir-cuits are yet to be fully clarified. Here, we demonstrate a mouse model of intrauterine undernutrition in which premature leptin surge contributes to developmental origins of obesity.**Results and discussionDevelopment of obesity and related metabolic disorders in offspring with intrauterine undernutrition**Maternal body weight gain during pregnancy was significantly suppressed by 30% restriction of maternal food supply (Figure

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How Sweet It Isn't: Hormone Dampens Taste for Sugary Foods

By Neil Osterweil
WebMD Medical News Archive
Reviewed By Charlotte Grayson, MD

Sept. 18, 2000 -- That fat little mouse nibbling on cookies in your pantry may not be able to help himself: Japanese researchers have discovered that mice whose bodies lack the ability to use a naturally occurring fat-fighting hormone have a real sweet tooth. The finding, published in the journal *Proceedings of the National Academy of Sciences*, could help explain why some obese people can't resist sugary foods.

On the other hand, the researchers found that normal mice lose their fondness for sugar when injected with this so-called obesity hormone, called leptin. The shot did not appear to change their abilities to taste the other basic tastes of sour, salty, and bitter.

This finding suggests that the hormone may act on taste-sensitive cells in the tongue to suppress cravings for sweet stuff. The finding also may shed more light on the causes of obesity, the study's authors propose.

Leptin, a protein produced by fat cells in the body, has been shown to both reduce food intake and increase energy use by acting on a part of the brain known as the hypothalamus. Earlier studies have shown that extremely obese mice that have been bred to have diabetes appear to be particularly sensitive to sweet tastes such as sugar and saccharin, and they show a marked preference for sugary foods when compared with their normal-sized cousins. These obese mice also have fewer receptors, or docking sites, for leptin on their cells and thus are less susceptible to its effects than normal mice.

The Japanese researchers suspected that the gene that makes leptin could somehow be related to leptin receptors, which could explain why the mice seemed to prefer sweets. To test this idea, they measured how the nervous systems of both diabetic and normal mice responded to various tastes, both before and after injections of leptin.

They found that the skinny mice appeared to lose their sensitivity to sugar or saccharin after a leptin injection, while the diabetic mice seemed to have no change in taste sensitivity.

But whether what's true in mice will be true in men is another question, two leptin researchers tell WebMD.

"I think it's interesting in that it's another demonstration that leptin may have actions outside of the hypothalamus," says Joel Keith Elmquist PhD, DVM. Elmquist is in the division of endocrinology at Beth Israel-Deaconess Medical Center and is an assistant professor of neurology at Harvard Medical School in Boston.

He adds that a true abnormality in the receptors for leptin is rare in humans, but it's thought that we can have what's called leptin resistance. This phenomenon can be compared with memory loss -- the object is still there, but you don't recognize it. In this case, the body has normal, or even elevated, amounts of leptin, but the cells that need leptin to control food intake or increase energy use no longer recognize it.

"So a lack of response to leptin is thought to very strongly contribute to obesity. Perhaps [that] resistance [occurs] at the level of the taste system as well, [and that] may contribute to ... obesity," Elmquist tells WebMD.

Another Boston-based researcher is less sure.

"Many people [have] ... high leptin levels already, and in human studies of the effect of leptin on weight loss, some people lose weight but many people don't," says Andrew Greenberg, MD, director of the program in obesity and metabolism at the Jean Mayer USDA Human Nutrition Research Center at Tufts University.

Greenberg suggests that although the study's findings are interesting, the exact role of leptin in causing obesity is still unclear. " "Leptin has so many effects; humans who have no leptin, for example, eat lots and lots of food. This may be one piece of the puzzle, but it's probably not a major piece," he tells WebMD.

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Endocrinology Vol. 145, No. 2 839-847

Leptin Modulates Behavioral Responses to Sweet Substances by Influencing Peripheral Taste Structures

Noriatsu Shigemura, Rie Ohta, Yuko Kusakabe, Hirohito Miura, Akihiro Hino, Kiyoshi Koyano, Kiyohito Nakashima and Yuzo Ninomiya

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Address all correspondence and requests for reprints to: Yuzo Ninomiya, Section of Oral Neuroscience, Graduate School of Dental Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

Leptin is a hormone that regulates body weight homeostasis mainly via the hypothalamic functional leptin receptor Ob-Rb. Recently, we proposed that the taste organ is a new peripheral target for leptin. Leptin selectively inhibits mouse taste cell responses to sweet substances and thereby may act as a sweet taste modulator. The present study further investigated leptin action on the taste system by examining expression of Ob-Rb in taste cells and behavioral responses to sweet substances in leptin-deficient ***ob***/***ob***, and Ob-Rb-deficient ***db***/***db*** mice and their normal litter mates. RT-PCR analysis showed that Ob-Rb was expressed in taste cells in all strains tested. The ***db***/***db*** mice, however, had a RT-PCR product containing an abnormal ***db*** insertion that leads to an impaired shorter intracellular domain. ***In situ*** hybridization analysis showed that the hybridization signals for normal Ob-Rb mRNA were detected in taste cells in lean and ***ob***/***ob*** mice but not in ***db***/***db*** mice. Two different behavioral tests, one using sweet-bitter mixtures as taste stimuli and the other a conditioned taste aversion paradigm, demonstrated that responses to sucrose and saccharin were significantly decreased after ip injection of leptin in ***ob***/***ob*** and normal littermates, but not in ***db***/***db*** mice. These results suggest that leptin suppresses behavioral responses to sweet substances through its action on Ob-Rb in taste cells. Such taste modulation by leptin may be involved in regulation for food intake.

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Leptin regulates proinflammatory immune responses

FASEB 12 January 98

S. LOFFREDA,* S. Q. YANG,* H. Z. LIN,* C. L. KARP,*,† M. L. BRENGMAN,‡ D. J. WANG,‡ A. S. KLEIN,‡ G. B. BULKLEY,‡ C. BAO,* P. W. NOBLE,* M. D. LANE,§ AND A. M. DIEHL*,1

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ABSTRACT Obesity is associated with an increased incidence of infection, diabetes, and cardiovascular disease, which together account for most obesity-re-lated morbidity and mortality. Decreased expression of leptin or of functional leptin receptors results in hyperphagia, decreased energy expenditure, and obesity. It is unclear, however, whether defective lep-tin-dependent signal transduction directly promotes any of the conditions that frequently complicate obe-sity. Abnormalities in tumor necrosis factor a ex-pression have been noted in each of the above comorbid conditions, so leptin deficiency could pro-mote these complications if leptin had immunore-gulatory activity. Studies of rodents with genetic abnormalities in leptin or leptin receptors revealed obesity-related deficits in macrophage phagocytosis and the expression of proinflammatory cytokines both in vivo and in vitro. Exogenous leptin up-regu-lated both phagocytosis and the production of proin-flammatory cytokines. These results identify an important and novel function for leptin: up-regula-tion of inflammatory immune responses, which may provide a common pathogenetic mechanism that con-tributes to several of the major complications of obe-sity.—Loffreda, S., Yang, S. Q., Lin, H. Z., Karp, C. L., Brengman, M. L., Wang, D. J., Klein, A. S., Bulkley, G. B., Bao, C., Noble, P. W., Lane, M. D., Diehl, A. M. Leptin regulates proinflammatory im-mune responses. *FASEBJ.* 12, 57–65 (1998)

Key Words: obesitymacrophagecytokine phagocyticfunc-tionTNFlipopolysaccharide

LEPTIN, THE PROTEIN ENCODED BY THE OB GENE, IS KNOWN TO REGULATE APPETITE AND ENERGY EXPENDITURE. OBESE/OBESE (OB/OB) MICE, HOMOZYGOUS FOR A SPON-TANEOUS MUTATION IN THE OB GENE, FAIL TO PRODUCE LEP-TIN AND EXHIBIT HYPERPHAGIA AND OBESITY. TREATMENT OF SUCH MICE WITH RECOMBINANT LEPTIN RESULTS IN DE-CREASED FOOD INTAKE AND WEIGHT LOSS (1–3). IT IS NOT KNOWN WHETHER LEPTIN DEFICIENCY PER SE EXPLAINS OTHER ASPECTS OF THE OB/OB PHENOTYPE, SUCH AS DIA-BETES AND HYPERLIPIDEMIA. RECENTLY, ECTOPIC EXPRES-SION OF TUMOR NECROSIS FACTOR ALPHA (TNF-A)2 WAS DOCUMENTED IN ADIPOSE TISSUES OF OBESE RODENTS AND HUMANS (4, 5) AND IMPLICATED IN THE PATHOGENESIS OF

Leptin regulates proinflammatory immune responses

FASEB 12 January 98

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Reduced leptin concentrations are permissive for display of torpor in Siberian hamsters

Am J Physiol Regul Integr Comp Physiol 287: R97–R103, 2004

David A. Freeman,1 Daniel A. Lewis,1 Alexander S. Kauffman,2 Robert M. Blum,3 and John Dark1 *Departments of 1Psychology and 2Integrative Biology, University of California, Berkeley, California 94720-1650; and 3Department of Biological Sciences, Lehigh University, Bethlehem, Pennsylvania 18015*

Submitted 16 December 2003; accepted in final form 16 March 2004

Freeman, David A., Daniel A. Lewis, Alexander S. Kauffman, Robert M. Blum, and John Dark. Reduced leptin concentrations are permissive for display of torpor in Siberian hamsters. *Am J Physiol Regul Integr Comp Physiol* 287: R97–R103, 2004; 10.1 152/ajpregu. 00716.2003.—A photoperiod with a short photophase induces a winterlike phenotype in Siberian hamsters that includes a progressive decrease in food intake and body mass and reproductive organ regression, as well as reversible hypothermia in the form of short-duration torpor. Torpor substantially reduces energy utilization and is not initiated until body mass, fat stores, and serum leptin concentra-tions are at their nadir. Because photoperiod-dependent torpor is delayed until fat reserves are lowest, leptin concentrations may be a permissive factor for torpor onset. This conjecture was tested by implanting osmotic minipumps into Siberian hamsters manifesting spontaneous torpor; the animals received a constant release of leptin or vehicle for 14 days. Exogenous leptin treatment eliminated torpor in a significant proportion of treated hamsters, whereas treatment with the vehicle did not. Similarly, endogenous serum leptin concentrations were markedly reduced in all animals undergoing daily torpor. Although simply reducing leptin concentrations below a threshold value is not sufficient for torpor initiation, reduced leptin concentrations nevertheless appear necessary for its occurrence. It is proposed that drastically reduced leptin concentrations provide a "starvation signal" to an as yet unidentified central mechanism mediating torpor initia-tion.

thermoregulation; hypothermia; energy balance; adipose tissue; pho-toperiod

ENERGY BALANCE is accomplished through a delicate equating of energy intake (food consumption) and energy expenditure (calorie-fueled cellular oxidation). In mammals, a majority of the energy budget is committed to maintaining homeothermia [i.e., body temperature (Tb) ~ ~37°C]. This is particularly true for small mammals living in temperate or boreal or austral environments, including the Siberian hamster *(Phodopus sun-gorus).* During the cold winter months, the increased demand for energy intake due to higher thermogenic costs occurs when food availability and/or quality also are likely to be lowest (see Ref. 53). To contend with this circumstance, some endothermic mammals periodically abandon homeothermia in favor of het-erothermia, spending several hours with a Tb as low as 15°C (shallow, daily torpor) or up to several weeks with a Tb as low as 0°C (hibernation) (29). Heterothermia in the Siberian ham-ster is of the former type (17) and provides a considerable energetic savings, reducing daily energy utilization by as much as 24% with a single bout of torpor (43). The reduction in energy expenditure, in turn, reduces energy intake require

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Calories Do Not Explain Extension of Life Span by Dietary Restriction in Drosophila

PLOS Biology July 2005 | Volume 3 | Issue 7

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Dietary restriction (DR) extends life span in diverse organisms, including mammals, and common mechanisms may be at work. DR is often known as calorie restriction, because it has been suggested that reduction of calories, rather than of particular nutrients in the diet, mediates extension of life span in rodents. We here demonstrate that extension of life span by DR in Drosophila is not attributable to the reduction in calorie intake. Reduction of either dietary yeast or sugar can reduce mortality and extend life span, but by an amount that is unrelated to the calorie content of the food, and with yeast having a much greater effect per calorie than does sugar. Calorie intake is therefore not the key factor in the reduction of mortality rate by DR in this species.

Citation: Mair W, Piper MDW, Partridge L (2005) Calories do not explain extension of life span by dietary restriction in Drosophila. PLoS Biol 3(7): e223.

Introduction

Dietary restriction (DR), the extension of life span by reduction of nutrient intake without malnutrition, is often used as a benchmark comparison for interventions that extend life span [1–3]. Since McCay's pioneering experiments in rats 70 years ago [4], some form of food restriction has been shown to increase life span in commonly used model organisms such as yeast [5,6], nematodes [7], fruit flies [8,9], and mice [10], along with many species less often used for laboratory research such as water fleas, spiders, fish (see [3] for review), and dogs [11]. Preliminary data also suggest that DR may extend life span in nonhuman primates [12,13] and potentially give health benefits in humans [14]. Despite the finding that restricting diet increases longevity in such a diversity of species, the mechanisms responsible remain to be fully elucidated in any of them. It is therefore as yet unclear whether these mechanisms are evolutionarily conserved across taxa or if instead life extension during DR is an example of convergent evolution.

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CONVERGENT EVOLUTION.

neuroendocrine and metabolic adaptation to short-term starvation in healthy men

Jean L. Chan,1 Kathleen Heist,1 Alex M. DePaoli,2Johannes D. Veldhuis,3 and Christos S. Mantzoros1
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To elucidate the role of leptin in regulating neuroendocrine and metabolic function during an acute fast, six to eight healthy, lean men were studied under four separate conditions: a baseline fed state and three 72-hour fasting studies with administration of either placebo, low-dose recombinant-methionyl human leptin (r-metHuLeptin), or replacement-dose r-metHuLeptin designed to main-tain serum leptin at levels similar to those in the fed state. Replacement-dose r-metHuLeptin admin-istered during fasting prevents the starvation-induced changes in the hypothalamic-pituitary-gonadal axis and, in part, the hypothalamic-pituitary-thyroid axis and IGF-1 binding capacity in serum. Thus, in normal men, the fall in leptin with fasting may be both necessary and sufficient for the physiologic adaptations of these axes, which require leptin levels above a certain threshold for activation. In con-trast to findings in mice, fasting-induced changes in the hypothalamic-pituitary-adrenal, renin-aldos-terone, and growth hormone–IGF-1 axes as well as fuel utilization may be independent of leptin in humans. The role of leptin in normalizing several starvation-induced neuroendocrine changes may have important implications for the pathophysiology and treatment of eating disorders and obesity.

J. Clin. Invest. **111**:1409–1421 (2003)..

Introduction

Leptin is an adipocyte-derived hormone whose absence in mice (1) and humans (2–4) causes abnor-mal energy homeostasis and profound obesity that is ameliorated by leptin treatment (5, 6). Leptin is secret-ed into the circulation in a highly organized and pul-satile fashion (7). By activating specific leptin receptors in the hypothalamus, leptin alters the expression of

Received for publication November 27, 2002, and accepted in revised form March 6, 2003.

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Fax: (617) 667-2927; E-mail: cmantzor@caregroup.harvard.edu. **Conflict of interest:** Christos S. Mantzoros has received research support and consulting fees from Amgen Inc.

Nonstandard abbreviations used: recombinant-methionyl human leptin (r-metHuLeptin); General Clinical Research Center (GCRC); triiodothyronine (T3); sex hormone–binding globulin (SHBG); thyroxine (T4); free thyroxine (FT4); reverse T3 (rT3); thyroxine-binding globulin (TBG); IGF-binding proteins (IGFBPs); plasma renin activity (PRA); luteinizing hormone (LH); thyrotropin-stimulating hormone (TSH); gonadotrophin-releasing hormone (GnRH); thyrotropin-releasing hormone (TRH); dual energy X-ray absorptiometry (DEXA); area under the curve (AUC); hypothalamic-pituitary-adrenal (HPA); sympathetic nervous system (SNS); resting metabolic rate (RMR); hypothalamic-pituitary-gonadal (HPG); hypothalamic-pituitary-thyroid (HPT); leptin receptor (ObR); signal transducer and activator of transcription-3 (STAT3); extracellular signal-regulated kinase (ERK); neuropeptide Y (NPY).

several hypothalamic neuropeptides and thereby reg-ulates energy intake and expenditure (8–10). Although leptin was originally thought to function primarily as an antiobesity hormone in leptin-deficient states, sub-sequent research has suggested an additional and sig-nificant role for leptin in signaling changes in energy balance (especially nutritional deprivation) and in reg-ulating the neuroendocrine and metabolic responses to starvation in rodents (8–10).

Short-term fasting results in a rapid and marked decline in leptin levels out of proportion to the loss of fat mass (11, 12), and it has been proposed that this most likely serves as an adaptive mechanism to promote survival and limit procreation during starvation (8). In mice, the exogenous administration of leptin in physi-ologic replacement doses prevents the fasting-induced changes of several neuroendocrine axes (8), but this has not yet been directly studied in humans. Understanding the role of leptin in regulating neuroendocrine function during fasting in humans is a matter of profound phys-iologic interest. Moreover, this may have important therapeutic implications for low-leptin states, such as anorexia nervosa, hypothalamic amenorrhea, and lipoa-trophy and may also elucidate the compensatory neu-roendocrine mechanisms responsible for the plateauing effect of caloric restriction in the treatment of obesity. To evaluate the role of leptin in regulating neuroen-docrine and metabolic function during an acute fasting period, we studied eight healthy lean men under four

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MICROSCOPY RESEARCH AND TECHNIQUE
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Anti-Aging Effects of Caloric Restriction: Involvement of Neuroendocrine Adaptation by Peripheral Signaling

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ABSTRACT Many hormonal signals from peripheral tissues contribute to the regulation of energy homeostasis and food intake. These regulators including leptin, insulin, and ghrelin, modulate the orexigenic and anorexigenic neuropeptide expression in hypothalamic nuclei.

INTRODUCTION

The molecular mechanisms of caloric restriction (CR), which extends the life span of many species, remain unclear. Some specific signals such as insulin-like growth factors in lower organisms have been im-plicated in life span extension (Guarente and Kenyon, 2000). Here we discuss the anti-aging effects of CR focused on the mechanisms of hypothalamic neuroen-docrine adaptation by peripheral signals. In most cases, neuroendocrine alterations may not be the primary causative factors of aging, but rather mediate or modify the biological aging processes. Consequently, it is a convincing hypothesis that CR is associated with the aging processes through its action on the endocrine and/or neural regulatory systems (Masoro, 1988). From an evolutionary viewpoint, the effect of CR seems to be explained by organisms having evolved adaptation mechanisms of their neuroendocrine and metabolic systems to maximize survival rates during food short-age periods (Holliday, 1989). The molecular mecha-nisms that regulate the neuroendocrine system by CR have not yet clearly elucidated. However, leptin has been proposed as a potential candidate for the adaptive response to CR (Barzilai and Gupta, 1999; Shimokawa and Higami, 1999, 2001a,b). Leptin is a hormone se-creted by adipocyte (Zhang et al., 1994), and it is an important factor controlling the balance of energy con-sumption and food intake. Subsequent studies have revealed the role of leptin as a neuroendocrine modu-lator under fasting (Ahima et al., 1996; Ahima, 2000). It is thought that adipocytes evolved to store energy as triglycerides for survival during food shortage periods (Friedman and Halaas, 1998). When

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Adipose tissue has recently been recognized as an endocrine organ, and leptin, as secreted by adipocyte, seems to be an especially important factor for the adaptive response to fasting and neuroendocrine alterations under caloric restriction.

These leptin-sensitive ARH neurons also regulate the gonadal, growth, thyroidal, and adrenal glucocorticoid systems. It has been suggested that the dominant physiological role of leptin is as a signal for the switch between fed and fasted states. Life-threatening conditions, like starvation, reduce the plasma leptin level and suppress the gonadal, GH, and thyroidal axes, while enhancing the adrenal glucocorticoid system. Exogenous leptin administration during fasting restores those hormonal changes. There is a dual regulation of circulating plasma leptin levels; under steady-state conditions of energy balance, leptin acts as a long-term static regulator of the energy stored in the adipose tissue, whereas during acute perturbations in energy balance, leptin levels change independently of the available adipose tissue triglyceride stores

Leptin: A Molecule Integrating Somatic Energy Stores, Energy Expenditure and Fertility

Michael Rosenbaum and Rudolph L. Leibel

TEM, Vol 9 No.3 1998

The signaling of fat mass to central nervous system (CNS) regulators of food intake, energy expenditure and fertility has been inferred by experi-mental physiologists for over 75 years. The ability to modify such phenotypes based upon the status of body energy stores (fat) has critical survival value and, therefore, has been the object of potent selection pressure in evolution. The recent molecular cloning of the mouse ob mutation and the subsequent elucidation of the fundamentals of its regulatory physiology has identified a protein secreted by adipocytes, leptin, as a plausible candidate for a humoral signal with the requisite endocrinology and neurobiology.

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In 1953, Kennedy proposed that body fat content was regulated to defend a specific level of energy storage in the form of calorically dense tri-glycerides (Kennedy 1953). In the 1970s, Frisch suggested that it was necessary for women to maintain a specific percentage of body fat in order to achieve menarche (17%) and fertility (22%) (Frisch and Revelle 1970, Frisch *et al.* 1973, Frisch and McArthur 1974). Amenorrhea and infertility are observed frequently in individuals who maintain a reduced body weight through vigorous exercise and/or caloric restriction (Frisch *et al.* 1980, Hale 1983, Meyer *et al.* 1990, Stewart 1992). These hypotheses are consistent with a 'lipostatic' model of weight regulation in which adipose tissue functions as an endocrine organ by releasing an afferent signal that (di-rectly and/or indirectly) affects gonads or gonadotrophs (fertility) and/or systems of energy homeostasis (body weight regulation) (Leibel 1977, Rosenbaum *et al.* 1997a).

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Reproductive switch and aging- the case of leptin change in dietary restriction

IABG 10th Congress

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Dietary restriction experiments provide a model for exploring the phenomenon of aging. Plasma levels of several biomolecules are known to change as a result of dietary restriction and these biomolecules have been considered for their possible role in aging. We have proposed a hypothesis for interpreting extension of life by dietary restriction. It posits that normal food intake is geared toward optimizing the internal milieu for reproduction, even though some components of this milieu may be detrimental to health in the long term. In dietary restricted state, this particular milieu, with its detrimental effects on health, does not materialize and life extension occurs as a by-product. This hypothesis can provide a conceptual framework for exploring biomolecular changes seen in dietary restriction and their relevance to aging. Leptin is a case in point: Leptin, a biomolecule secreted from adipose tissue, has receptors in hypothalamus and is involved in suppressing appetite and activating hypothalamic-pituitary-gonadal axis. A picture has emerged for the role of leptin in the centrally integrated system monitoring body fat reserve, regulating appetite, and signalling reproductive competence. Plasma levels of leptin decrease in dietary restriction and this has led to considerations about its possible role in aging. We think that decrease in leptin level observed in dietary restricted animals can be explored in the light of leptins role in this complex and integrated signalling system, the reproductive switch. Does this decrease simply reflect the insufficiency of bodys fat reserve for reproduction, and is the observed extension in life attributable to the fact that reproductive competence is not signalled and downstream events with their possible detrimental effects on health do not occur? Or does leptin have some specific effect on the process of aging by itself? And if so, does this effect appear only in the context of integrated changes associated with reproductive switch or independent of them? Experiments aimed at uncoupling components of reproductive switch and downstream events should help in resolving these issues. These questions find parallels in the study of the role of insulin-like growth factor 1 in transgenic models of aging.

Reproductive switch and aging- the case of leptin change in dietary restriction

IABG 10th Congress
J. Koochmeshgi

A HYPOTHESIS FOR INTERPRETING EXTENSION OF LIFE BY DIETARY RESTRICTION...POSITS THAT NORMAL FOOD INTAKE IS GEARED TOWARD OPTIMIZING THE INTERNAL MILIEU FOR REPRODUCTION.

EXPLORING BIOMOLECULAR CHANGES SEEN IN DIETARY RESTRICTION AND THEIR RELEVANCE TO AGING. LEPTIN IS A CASE IN POINT: LEPTIN, A BIOMOLECULE SECRETED FROM ADIPOSE TISSUE, HAS RECEPTORS IN HYPOTHALAMUS AND IS INVOLVED IN SUPPRESSING APPETITE AND ACTIVATING HYPOTHALAMIC-PITUITARY-GONADAL AXIS. A PICTURE HAS EMERGED FOR THE ROLE OF LEPTIN IN THE CENTRALLY INTEGRATED SYSTEM MONITORING BODY FAT RESERVE, REGULATING APPETITE, AND SIGNALLING REPRODUCTIVE COMPETENCE. PLASMA LEVELS OF LEPTIN DECREASE IN DIETARY RESTRICTION AND THIS HAS LED TO CONSIDERATIONS ABOUT ITS POSSIBLE ROLE IN AGING. WE THINK THAT DECREASE IN LEPTIN LEVEL OBSERVED IN DIETARY RESTRICTED ANIMALS CAN BE EXPLORED IN THE LIGHT OF LEPTINS ROLE IN THIS COMPLEX AND INTEGRATED SIGNALLING SYSTEM, THE REPRODUCTIVE SWITCH. DOES THIS DECREASE SIMPLY REFLECT THE INSUFFICIENCY OF BODYS FAT RESERVE FOR REPRODUCTION, AND IS THE OBSERVED EXTENSION IN LIFE ATTRIBUTABLE TO THE FACT THAT REPRODUCTIVE COMPETENCE IS NOT SIGNALLED AND DOWNSTREAM EVENTS WITH THEIR POSSIBLE DETRIMENTAL EFFECTS ON HEALTH DO NOT OCCUR? OR DOES LEPTIN HAVE SOME SPECIFIC EFFECT ON THE PROCESS OF AGING BY ITSELF? AND IF SO, DOES THIS EFFECT APPEAR ONLY IN THE CONTEXT OF INTEGRATED CHANGES ASSOCIATED WITH REPRODUCTIVE SWITCH OR INDEPENDENT OF THEM? EXPERIMENTS AIMED AT UNCOUPLING COMPONENTS OF REPRODUCTIVE SWITCH AND DOWNSTREAM EVENTS SHOULD HELP IN RESOLVING THESE ISSUES. THESE QUESTIONS FIND PARALLELS IN THE STUDY OF THE ROLE OF INSULIN-LIKE GROWTH FACTOR 1 IN TRANSGENIC MODELS OF AGING.

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Appetite hormone restores fertility May also reduce bone loss

By William J. Cromie
Harvard News Office
September 17, 2004

A hormone that regulates appetite has been used to restore fertility in a small number of women. In an experiment conducted by researchers from Harvard Medical School, three women who had not had a period for as long as 14 years began menstruating. All were happy with the result. The hormone, called leptin, has been trumpeted as an appetite suppressor and a possible treatment for obesity. This new research shows that "a clear connection also exists between fat, or energy storage, and the ability to reproduce," says Corrine Welt, an assistant professor of medicine who works at Massachusetts General Hospital, a Harvard affiliate. Taking the results a giant step further, the leader of the research team suggests that leptin may be necessary to turn on puberty in adolescent girls. "It appears that normal, healthy girls gain weight immediately prior to puberty," notes Christos Mantzoros, a Harvard associate professor who works at the affiliated Beth Israel Deaconess Medical Center in Boston. "This suggests that leptin levels, which rise in response to an increase in body fat, are letting the body know that there's enough energy available to sustain a pregnancy." The women whose fertility was boosted by leptin injections had stopped menstruating as a result of losing an abnormal amount of fat, mainly by overexercising. In their 20s and early 30s, they pared themselves down to carrying about 40 percent less fat than is average for women their age. Such loss of menses, or amenorrhea, is also associated with abnormal levels of thyroid hormones and a loss of bone mass, which can lead to brittle, easily fractured bones. The findings thus raise the possibilities of new treatments for exercise-induced bone loss and for eating disorders, as well as for certain cases of infertility. Previous experiments by the Mantzoros group also show that low testosterone levels in men can be raised by leptin under certain conditions.

Too thin to conceive

Leptin was discovered in 1994 by Jeffery Friedman, a scientist at Rockefeller University in New York City. For a time, it looked like the solution to the obesity epidemic in the United States. But that didn't work out. "Normally, if you eat too much, leptin will give you a full feeling that makes you stop," Welt explains. "But there seems to be a threshold, a leptin level, that, once crossed, doesn't help control your weight anymore." Mantzoros, Welt, and their colleagues, however, became intrigued with the reproductive effects of leptin on mice. Laboratory experiments revealed that female mice deficient in the hormone never reach puberty. But give them leptin and they quickly get pregnant. Some women with rare mutations that turn off leptin receptors in the brain also fail to reach puberty. And decades ago, Rose Frisch of the Harvard School of Public Health showed that it's possible for women to be too thin to conceive. The Mantzoros team decided to put it all together by giving leptin injections to eight women who had not menstruated for years. "All of them were heavy exercisers who had no children and very little body fat," Welt explains. Twice a day, they received leptin injections that raised the levels of that hormone to those of normal women. The results were dramatic, according to Mantzoros and Welt. "Six of the eight women experienced bleeding. Three had full restoration of their menstrual cycles," Welt notes. All started growing follicles, the sacs that contain eggs. In addition, tests indicate that their bones started to grow rather than losing mass. Their levels of thyroid and growth hormones rose. Even vaginal dryness was mitigated. All of them were pleased with the result. "Those who began menstruating again felt very happy to have their first cycle in five or more years, despite the irritability, aches, and other physical and emotional symptoms of premenstrual syndrome," Welt says. "One subject who had not menstruated for 14 years was thrilled to feel like a normal woman again." The effects are not lasting, however. When the leptin injections stop, so do the periods.

Help on the way?

The research results are important for three groups of women. The largest, notes Mantzoros, "is made up of extremely thin women who are infertile. The second group consists of competitive athletes and dancers whose thin frames put them at a risk for developing osteoporosis and suffering bone fractures. The smallest, but most extreme group is composed of women who are battling eating disorders, such as anorexia nervosa." In the largest group, leptin does not signal the brain to begin the sequence of hormonal secretions needed for menstruation. "These women account for more than 30 percent of cases of amenorrhea in women of reproductive age," Welt notes. Infertility can be treated by injections of hormones that boost follicle and egg growth.

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Summary

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Several findings suggest that interactions between tissues play an important role in establishing the ani-mal's rate of aging. First, the *C. elegans* genome

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DAF-2 (and by extension, DAF-1 6), has been thought to function primarily in the nervous system to influence lifespan. Mosaics lacking *daf-2* in AB, a lineage produc-ing mainly ectodermal cell types (neurons and epider-mis) are quite long lived, as was one mosaic lacking *daf-2* in a small group of neurons (Apfeld and Kenyon, 1998). In addition, expression of *daf-2* using neural pro-moters has been reported to shorten the lifespan of *daf-2* mutants to control levels (Wolkow et al., 2000). It seemed possible that DAF-1 6 might function in a differ-ent tissue to promote longevity in another situation: The lifespan of *C. elegans* is increased by removing the germline, and this lifespan extension, like that of DAF-2 pathway mutants, requires DAF-1 6 activity (Hsin and Kenyon, 1999). Curiously, whereas DAF-1 6 accumulates in the nuclei of many cell types in *daf-2* mutants, in germline-deficient animals DAF-1 6 accumulates primar-ily in intestinal nuclei (Lin et al., 2001). This finding has suggested that DAF-16 might function primarily in the intestine to promote longevity in these animals.

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In this study, we have investigated the tissue-specific-ity of DAF-1 6 function. Surprisingly, we find that DAF-16 activity in neurons is sufficient to produce only a modest, 5%–20%, extension of lifespan in *daf-16(~); daf-2(~)* animals. However, we find that DAF-1 6 activity in the intestine is sufficient to extend the lifespans of these animals by 50%–60%, and can completely rescue the longevity of *daf-16(~)* germline-defective mutants. [MSOFFICE2] We also find that DAF-1 6 activity in signaling cells elicits two types of responses, one that requires DAF-1 6 activ-ity in responding cells, and thus may involve feedback MSOffice2] Signals from fat regulates lifespan. In other words, signals from fat regulate the genetic expression of aging. [MSOffice1]

Cell, Vol. 115, 489–502, November14, 2003,

Tissue-Specific Activities of *C. elegans* DAF-16 in the Regulation of Lifespan

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Summary

In *C. elegans,* the transcription factor DAF-16 pro-motes longevity in response to reduced insulin/IGF-1 signaling or germline ablation. In this study, we have asked how different tissues interact to specify the life-span of the animal. We find that several tissues act as signaling centers. In particular, DAF-16 activity in the intestine, which is also the animal's adipose tissue, completely restores the longevity of *daf-16(~)* germ-line-deficient animals, and increases the lifespans of *daf-16(~)* insulin/IGF-1 -pathway mutants substantially. Our findings indicate that DAF-16 may control two types of downstream signals: DAF-16 activity in signal-ing cells upregulates DAF-16 in specific responding tissues, possibly via regulation of insulin-like peptides, and also evokes DAF-1 6-independent responses. We suggest that this network of tissue interactions and feedback regulation allows the tissues to equilibrate and fine-tune their expression of downstream genes, which, in turn, coordinates their rates of aging within the animal.[MSOFFICE1]

Introduction

How signaling between tissues coordinates the physiol-ogy of an animal is a fundamental problem in endocrinol-ogy. The aging of *C. elegans* is controlled by an endo-crine system that also regulates the lifespans of flies and mammals (Tatar et al., 2003). Reduction-of-function mutations affecting the insulin/IGF-1 -like receptor DAF-2, or components of a downstream PI 3-kinase/PDK/AKT pathway, double the animal's lifespan (Kenyon et al., 1993; Kimura et al., 1997; Larsen et al., 1995; Morris et al., 1996; Paradis and Ruvkun, 1998). This lifespan extension requires DAF-16, a member of the FOXO-family of transcription factors (Kenyon et al., 1993; Larsen et al., 1995; Lin et al., 1997; Ogg et al., 1997). In the wild-type, the AKT-1 and AKT-2 proteins phosphorylate DAF-16, inhibiting its nuclear localization (Henderson and Johnson, 2001; Lee et al., 2001; Lin et al., 2001). In DAF-2 pathway mutants, DAF-16 accumulates in the nuclei of many cell types, where it leads to changes in the expres-sion of a wide variety of metabolic, stress response, antimicrobial, and novel genes, and thereby extends lifespan (Lee et al., 2003; McElwee et al., 2003; Murphy et al., 2003).

Several findings suggest that interactions between tissues play an important role in establishing the ani-mal's rate of aging. First, the *C. elegans* genome

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contains more than 35 insulin-like genes expressed in a variety of neurons and other tissues, and some of these have been implicated in lifespan regulation (Kawano et al., 2000; Li et al., 2003; Murphy et al., 2003; Pierce et al., 2001). In addition, in response to insulin-like ligands, cells that express the DAF-2 receptor are thought to produce (or stop producing) downstream signals or hor-mones, because *daf-2* acts cell non-autonomously to influence lifespan (Apfeld and Kenyon, 1998; Wolkow et al., 2000). For example, removing *daf-2* from either of the two blastomeres of the two-cell embryo lengthens the lifespan of the entire animal (Apfeld and Kenyon, 1998).

Recent studies suggest that the DAF-2 pathway may regulate multiple downstream signals. One potential sig-nal is SCL-1, a member of the CRISP family of secreted proteins. *scl-1* expression is upregulated in *daf-2* mu-tants, and contributes to their longevity (Ookuma et al., 2003). The DAF-2 pathway also regulates several insulin-like genes. For example, expression of *ins-7,* which en-codes a putative DAF-2 agonist, is upregulated by DAF-2 pathway activity (Murphy et al., 2003). In addition, a number of longevity genes encoding signaling proteins, as well as proteins that could be involved in synthesis of lipophilic hormones, are regulated in a*daf-16*-depen-dent manner (Lee et al., 2003; McElwee et al., 2003; Murakami and Johnson, 2001; Murphy et al., 2003).

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Nature \ **429**, 771 - 776 (17 June 2004); doi:10.1038/nature02583

Nature AOP, published online 2 June 2004<>

Sirt1 promotes fat mobilization in white adipocytes by repressing PPARg

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Calorie restriction extends lifespan in organisms ranging from yeast to mammals. In yeast, the *SIR2* gene mediates the life-extending effects of calorie restriction. Here we show that the mammalian *SIR2* orthologue, *Sirt1* (sirtuin 1), activates a critical component of calorie restriction in mammals; that is, fat mobilization in white adipocytes. Upon food withdrawal Sirt1 protein binds to and represses genes controlled by the fat regulator PPAR- (peroxisome proliferator-activated receptor-), including genes mediating fat storage. Sirt1 represses PPAR- by docking with its cofactors NCoR (nuclear receptor co-repressor) and SMRT (silencing mediator of retinoid and thyroid hormone receptors). Mobilization of fatty acids from white adipocytes upon fasting is compromised in *Sirt1*+/- mice. Repression of PPAR- by Sirt1 is also evident in 3T3-L1 adipocytes, where overexpression of Sirt1 attenuates adipogenesis, and RNA interference of Sirt1 enhances it. In differentiated fat cells, upregulation of Sirt1 triggers lipolysis and loss of fat. As a reduction in fat is sufficient to extend murine lifespan, our results provide a possible molecular pathway connecting calorie restriction to life extension in mammals.

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The skinny on fat: MIT researchers establish first link between eating and aging

massachusetts institute of technology

Denise Brehm, News Office

June 2, 2004

Forget the drastic reduction in carbs and calories called for by diet dictators. The day when people can eat their favorite foods, stay thin and live to be 120 without getting age-induced diabetes or cancer may be nearer than we think.

Scientists have known for decades that controlled famine can extend the lifespan of mammals by as much as 50 percent and that those long-lived, lean mammals don't get the diseases of old age. But just how a vastly reduced caloric intake achieves that feat has been a mystery begging for a solution—until now. Researchers at MIT believe they've found the key to a long, lean, healthy life in a single protein that controls whether a mammal stores fat or sheds it.

"For the first time, this study gives us a glimpse of how calorie restriction works at the molecular level. And it will ultimately lead to health benefits in people," said MIT Professor of Biology Leonard Guarente, who has been studying the aging process in yeast, roundworms and mice for more than a decade.

In the June 2 online issue of the journal Nature, scientists in Guarente's lab, including Frédéric Picard, a research scientist in the Department of Biology who is lead author of the paper, will publish their research results about how the Sirt1 mammalian gene promotes fat mobilization in mice.

A mammal generally burns the protein and carbohydrates in its food immediately; it stores fat in special cells called white adipose tissue (WAT). When it reduces its caloric intake, the WAT stops storing fat and begins releasing it for metabolism.

The paper's authors learned that fat is released from or metabolized by the body, rather than stored, when the Sirt1 protein senses short-term famine and turns off the receptors that normally keep fat stored in fat cells. Thus fat cells shed their fat.

They write that this happens because the "Sirt1 protein activates a critical component of calorie restriction in mammals; that is, fat mobilization in white adipocytes. Upon food withdrawal the Sirt1 protein binds to and represses the genes that are controlled by PPAR-gamma, the fat regulator," preventing fat from being stored in the body.

"The ability of fat cells to sense famine [or short-term hunger] and release the fat is regulated by this gene," said Guarente. "We like to think this applies to people as well as mice, but we don't know for sure. If we could make this happen in people, it wouldn't just make them live longer; it might also help prevent diseases of aging, like cancer, diabetes and heart disease."

Because WAT also makes hormones, especially leptin which controls satiety, Guarente speculates that by putting hormones into the bloodstream, fat cells also tell the body how fast to age.

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JUST HOW A VASTLY REDUCED CALORIC INTAKE [EXTENDS LIFESPAN] HAS BEEN A MYSTERY BEGGING FOR A SOLUTION—UNTIL NOW. IN THE JUNE 2 ONLINE ISSUE OF THE JOURNAL NATURE, SCIENTISTS IN GUARENTE'S LAB... LEARNED THAT FAT IS RELEASED FROM OR METABOLIZED BY THE BODY, RATHER THAN STORED, WHEN THE SIRT1 PROTEIN SENSES SHORT-TERM FAMINE AND TURNS OFF THE RECEPTORS [PPARG] THAT NORMALLY KEEP FAT STORED IN FAT CELLS. THUS FAT CELLS SHED THEIR FAT... *Because WAT also makes hormones, especially leptin which controls satiety, Guarente speculates that by putting hormones into the bloodstream, fat cells also tell the body how fast to age.*

Medical Hypotheses (2005) x, xxx–xxx

PPARa activators may be good candidates as antiaging agents

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Received 26 January 2005; accepted 27 January 2005

Summary

Aging is associated with a metabolic decline characterized by the development of changes in fat distribution, obesity, and insulin resistance. Dysfunctional humoral and cell-mediated immune responses occur with age, and these aberrations have been implicated in the increased incidence of infectious diseases, hyporesponsiveness to vaccination, and the etiology of numerous chronic degenerative diseases. All these metabolic and immune alterations are associated with a variety of age-related diseases that subsequently result in increased mortality. Leptin can modulate many of the metabolic alterations characteristic of aging. Leptin resistance has been implicated in the pathogenesis of obesity-related complications involving abnormalities of lipid metabolism that resemble those of old age. Increased plasma leptin levels with aging suggest resistance to leptin action and may explain why elderly subjects have abdominal obesity and insulin resistance. Leptin's failure may be considered for the metabolic decline seen with aging. Peroxisome proliferator-activated receptor (PPAR)-a, the transcription factor for the mitochondrial and peroxisomal enzymes of b-oxidation, and its target enzymes, are upregulated by hyperleptinemia. PPARa has been shown to mediate the action of the hypolipidemic drugs of the fibrate class on lipid and lipoprotein metabolism. PPARa activators furthermore improve glucose homeostasis and influence body weight and energy homeostasis. The administration of agents capable of activating the PPARa was found to restore the cellular redox balance, evidenced by a lowering of tissue lipid peroxidation, an elimination of constitutively active NF-*j*B, loss in spontaneous inflammatory cytokine production, and ailing in the aging immunity.

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The failure of leptin to regulate food intake, body fat and its distribution, and insulin action suggests that leptin resistance plays a major role in the metabolic syndrome that is typical of aging.

Leptin resistance during aging is independent of fat mass.
Diabetes 2002;51:1016–21 Gabriely I, Ma XH, Barzilai N et al.

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Obesity may accelerate the ageing process

00:01 14 June 2005

NewScientist.com news service **FROM The Lancet**

Rowan Hooper

Obesity accelerates the ageing process even more than smoking, according to the largest ever study of the "chromosomal clock" in human cells.

Tim Spector of St Thomas' Hospital in London, UK, measured the length of the ends of chromosomes, called telomeres, in the white blood cells of 1122 women aged 18 to 76. Each time a cell divides, its telomere loses a small chunk of DNA. When it becomes too short, cells can no longer divide. In effect, telomere shortening acts as a kind of chromosomal clock, counting down the cellular generations.

Spector found that the white blood cells of the youngest women had telomeres that were around 7500 base pairs long. Their length declined with age at an average rate of 27 base pairs per year.

When lifestyle factors were taken into account, however, dramatic differences emerged. The difference between being obese and being lean corresponds to 8.8 years of extra ageing, Spector told a press conference in London.

Intriguingly, the link between high leptin concentrations and telomere shortening was even stronger than the link with obesity, as measured by the body mass index. Leptin is an appetite-inhibiting hormone, but obese people are resistant to it and have higher than normal levels.

Fat smokers

Smoking was the other big factor. "Smokers were on average biologically older than lifetime non-smokers by 4.6 years," Spector says. "For a heavy smoker on 20 cigarettes a day for 40 years, that equals 7.4 years of extra biological ageing."

And there is a synergistic effect. "Fat smokers are at the highest risk of all. An obese smoker is on average at least 10 years older than a lean non-smoker," says Spector. "It's not just about heart disease or lung cancer, the whole chromosomal clock is going faster. That's the public health message."

And the effects appear to be permanent. Quitting smoking or losing weight reduces the rate of telomere loss but cannot restore them.

The damage to telomeres is probably done by free radicals. Smoking causes oxidative stress - a source of free radicals - as does obesity, says Abraham Aviv of the University of Medicine and Dentistry of New Jersey, US. Free radicals can cause mutations in DNA, and there is some evidence that mutations in telomeres cause larger chunks than normal to be lost during cell division.

"Telomere age difference"

But the findings do not necessarily prove that, say, obese people will die nearly nine years early. For one thing, Spector looked only at white blood cells, and it remains to be seen if obesity and smoking have as dramatic an effect on other tissues. For another, while the link between telomere length and cell division is well established, the effect of shortened telomeres on the overall lifespan of organisms composed of trillions of cells is less clear. Men do have shorter telomeres than women, and intriguingly the "telomere age difference" of about seven years is about the same as the length of time women live longer than men.

But animal studies have failed to reveal any simple relationship between telomere length and lifespan. Some studies suggest that the rate of loss may be the most important factor, others that the crucial factor is not telomere length per se but a protein cap found on telomeres. It could even be that shortened telomeres are merely a sign of how much free radical damage cells have suffered, rather than a direct cause of ageing.

Spector now plans to look at the effect of other lifestyle factors on telomere length, such as exercise, diet and occupation.

Journal reference: *The Lancet* (DOI: 10.1016/S0140-6736(05)66630-5)

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Review Article

Age-related insulin resistance: is it an obligatory finding? The lesson from healthy centenarians

Michelangela Barbieri, Maria Rosaria Rizzo, Daniela Manzella, Giuseppe Paolisso *
Department of Geriatric Medicine and Metabolic Diseases, II University of Naples, Naples, Italy

Abstract

It is widely known that advancing age is associated with impaired glucose handling. A unifying hypothesis explaining the relationship between aging and insulin resistance might encompass four main pathways, namely: (a) anthropometric changes (relative and absolute increase in body fat combined with a decline in fat free mass) which could be the anatomic substrate for explaining the reduction in active metabolic tissue; (b) environmental causes, mainly diet style and physical activity; (c) neuro-hormonal variations [decline in plasma dehydroepandrosterone sulphate (DHEAS) and IGF-1]; and finally (d) the rise in oxidative stress. Indeed previous studies have also investigated the occurrence and the degree of insulin resistance in healthy centenarians. Such data demonstrated that age-related insulin resistance is not an obligatory finding in the elderly and that healthy centenarians have a preserved insulin action compared to aged subjects. Why insulin action is preserved in centenarians is still not known. Nevertheless, a possible approach to the question is to outline the centenarians' anthropometric, endocrine and metabolic characteristics in order to design a clinical picture of such metabolic successful aging. According to the remodeling theory of age, the preserved insulin action in centenarians might be the net result of the continuous adaptation of the body to the deleterious changes that occur over time. Nevertheless, only future longitudinal studies specifically designed to investigate the relationship between extreme old age and degree of insulin sensitivity will provide a conclusive answer with regard to the pathophysiology of adaptive metabolic changes occurring in the elderly.

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successful aging. According to the remodeling theory of age, the preserved insulin action in centenarians might be the net result of the continuous adaptation of the body to the deleterious changes that occur over time. Nevertheless, only future longitudinal studies specifically designed to investigate the relationship between extreme old age and degree of insulin sensitivity will provide a conclusive answer with regard to the pathophysiology of adaptive metabolic changes occurring in the elderly.

Body composition, body fat distribution, and resting metabolic rate in healthy centenarians.

Am J Clin Nutr 1995 Oct;62(4):746-50 (ISSN: 0002-9165)

Paolisso G; Gambardella A; Balbi V; Ammendola S; D'Amore A; Varricchio M
Department of Geriatric Medicine and Metabolic Diseases, II University of Naples, Italy.

Our study investigated body composition and body fat distribution in healthy centenarians. Body composition, body fat distribution, and resting metabolic rate (RMR) were studied in 40 adult subjects aged < 50 y, 35 aged subjects > 75 y, and 15 healthy centenarians aged > 100 y. Body composition was determined by bioimpedance analysis, body fat distribution was calculated as waist-hip ratio (WHR), and RMR was calculated by using the Arciero-Poehlman formula. Healthy centenarians had a cognitive impairment and degree of disability greater than aged subjects. Despite such differences, fat-free mass (FFM) and RMR were not different in centenarians compared with aged subjects but were lower than in adult subjects. In contrast, healthy centenarians had a WHR lower than that of aged subjects but not different from that of the adult subjects. After the level of physical activity and degree of disability were adjusted for, FFM (44 +/- 2.7 and 40 +/- 1.1 kg; P < 0.05) and RMR (6757 +/- 761 and 5891 +/- 723 kJ/24 h; P < 0.05) were significantly higher in healthy centenarians than in aged subjects, respectively. Independent of age, sex, body weight, degree of disability, level of physical activity, and fasting plasma triiodothyronine, there was a strong correlation between RMR and FFM (r = 0.50, P < 0.05) in healthy centenarians. In conclusion, healthy centenarians had a lower FFM and higher body fat content than aged subjects. Level of physical activity and degree of disability seem to be the major determinants for explaining such differences.

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Thyroid function in physiological aging and in centenarians: possible relationships with some nutritional markers.

Metabolism 2002 Jan;51(1):105-9 (ISSN: 0026-0495)
Magri F; Muzzoni B; Cravello L; Fioravanti M; Busconi L; Camozzi D; Vignati G; Ferrari E
Department of Internal Medicine and Medical Therapy, University of Pavia, Italy.

Changes in thyroid function are often described in elderly subjects; however, their pathophysiologic significance and the possible contributory role of both malnutrition and nonthyroidal illness are still debated. The aim of this cross-sectional study was to investigate thyroid function in relationship to some markers of the nutritional status in a group of healthy old subjects and in some centenarians living in nursing homes. Patients included 24 clinically healthy elderly women (age, 71 to 93 years), 24 clinically healthy centenarian women (age, 100 to 106 years), and 20 healthy young subjects (age, 22 to 33 years). Blood samples were drawn from each subject for the evaluation of thyroid-stimulating hormone (TSH), free triiodothyronine (FT(3)), free thyroxine (FT(4),) reverseT(3) (rT3), autoantibodies against thyroglobulin (AbTg) and against thyroid peroxidase (AbTPO), and for the main humoral nutritional markers. TSH and thyroid hormones were assayed by fluoroimmunometric method; rT3 and thyroid autoantibodies by radioimmunoassay (RIA) and enzyme chemiluminescent immunometric assay, respectively. The mean values of TSH, FT(3) and FT(4) fell within the normal range in both groups. However, by comparison to old controls, in centenarian subjects, TSH levels were significantly lower, whereas rT(3) concentrations were slightly, but significantly, increased. Autoantibodies positivity was found in 4.16% of centenarians and in 10.4% and 13.6% of old and young controls. Thus, the incidence of thyroid autoantibodies was lower in centenarians than in old controls. Except for transferrin, lower than the normal range in centenarians, all of the other nutritional markers evaluated fell within the laboratory range of normality. Total cholesterol levels were significantly reduced in centenarians by comparison to old controls. Our results showed an age-related decline of the TSH levels and a significant increase of the rT(3) concentrations in centenarians by comparison to old controls. These findings may be related to an age-dependent reduction of the 5'-deiodinase activity rather than to important changes of nutritional markers. [Copyright 2002 by W.B. Saunders Company].

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Arbor, MI, USA.

Serum levels of thyroxine (T4), **leptin**, and insulin-like growth factor-I (IGF-I), as well as cataract severity, were evaluated as predictors of **life span** in a population of genetically heterogeneous mice (UM-HET3). Long **life span** was predicted by low levels of **leptin** at age 4 months in females, and by low levels of IGF-I at age 15 months and high levels of T4 at age 4 months, in males. Cataract severity at either 18 or 24 months was also a significant predictor of **life span** in females only, but in contrast to what has been reported in human studies, relatively severe cataract was correlated with

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REGULATION OF LEPTIN SECRETION FROM WHITE ADIPOCYTES BY INSULIN, GLYCOLYTIC SUBSTRATES AND AMINO ACIDS

Am J Physiol Endocrinol Metab (March 1, 2005).

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RUNNING TITLE: ENERGY SUBSTRATES IN LEPTIN SECRETION
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ABSTRACT

THE AIM OF THE PRESENT STUDY WAS TO DETERMINE THE RESPECTIVE ROLE OF ENERGY SUBSTRATES AND INSULIN ON LEPTIN SECRETION FROM WHITE ADIPOCYTES. CELLS SECRETED LEPTIN IN ABSENCE OF GLUCOSE OR OTHER SUBSTRATES AND ADDITION OF GLUCOSE (5 MM) INCREASED THIS SECRETION. INSULIN DOUBLED LEPTIN SECRETION IN THE PRESENCE OF GLUCOSE (5 MM), BUT NOT IN ITS ABSENCE. HIGH CONCENTRATIONS OF GLUCOSE (UP TO 25 MM) DID NOT SIGNIFICANTLY ENHANCE LEPTIN SECRETION OVER THAT ELICITED BY 5 MM GLUCOSE. SIMILAR RESULTS WERE OBTAINED WHEN GLUCOSE WAS REPLACED BY PYRUVATE OR FRUCTOSE (BOTH 5 MM). L-GLYCINE OR L-ALANINE MIMICKED THE EFFECT OF GLUCOSE ON BASAL LEPTIN SECRETION BUT COMPLETELY PREVENTED STIMULATION BY INSULIN. ON THE CONTRARY, INSULIN STIMULATED LEPTIN SECRETION WHEN GLUCOSE WAS REPLACED BY L-ASPARTATE, L-VALINE, L-METHIONINE OR L-PHENYLALANINE, BUT NOT BY L-LEUCINE (ALL 5 MM). INTERESTINGLY, THESE FIVE AMINO ACIDS POTENTLY INCREASED BASAL AND INSULIN-STIMULATED LEPTIN SECRETION IN THE PRESENCE OF GLUCOSE. UNEXPECTEDLY, L-GLUTAMATE ACUTELY STIMULATED LEPTIN SECRETION IN THE ABSENCE OF GLUCOSE OR INSULIN. FINALLY, NONMETABOLIZABLE ANALOGS OF GLUCOSE OR AMINO ACIDS WERE WITHOUT EFFECTS ON LEPTIN SECRETION. THESE RESULTS SUGGEST THAT 1) ENERGY SUBSTRATES ARE NECESSARY TO MAINTAIN BASAL LEPTIN SECRETION CONSTANT, 2) HIGH AVAILABILITY OF GLYCOLYSIS SUBSTRATES IS NOT SUFFICIENT TO ENHANCE LEPTIN SECRETION BUT IS NECESSARY FOR ITS STIMULATION BY INSULIN, 3) AMINO ACIDS PRECURSORS OF CITRIC ACID CYCLE INTERMEDIATES POTENTLY STIMULATE *per se* BASAL LEPTIN SECRETION, INSULIN HAVING AN ADDITIVE EFFECT, AND 4) SUBSTRATES NEED TO BE METABOLIZED IN ORDER TO INCREASE LEPTIN SECRETION.

KEYWORDS: GLYCOLYTIC SUBSTRATES, CITRIC ACID CYCLE INTERMEDIATES, METABOLISM, ENERGY

REGULATION OF LEPTIN SECRETION FROM WHITE ADIPOCYTES

Cells secreted leptin in absence of glucose or other substrates and addition of glucose (5 mM) increased this secretion.... Interestingly, these five amino acids [L-aspartate, L-valine, L-methionine or L-phenylalanine, L-leucine] potently increased basal and insulin-stimulated leptin secretion in the presence of glucose. Unexpectedly, L-glutamate acutely stimulated leptin secretion in the absence of glucose or insulin.

without effects on leptin secretion. These results suggest that 1) energy substrates are necessary to maintain basal leptin secretion constant, 2) high availability of glycolysis substrates is not sufficient to enhance leptin secretion but is necessary for its stimulation by insulin, 3) amino acids precursors of citric acid cycle intermediates potently stimulate *per se* basal leptin secretion, insulin having an additive effect, and 4) substrates need to be metabolized in order to increase leptin secretion.

Keywords: glycolytic substrates, citric acid cycle intermediates, metabolism, energy

Short-term, high-fat diets lower circulating leptin concentrations in rats[1–3]

Original Research Communications

Deborah A Ainslie, Joseph Proietto, Barbara C Fam, and Anne W Thorburn

ABSTRACT

Background: Leptin is produced in proportion to body fat mass and can act on the brain to induce satiety and regulate adipose tissue mass; factors other than adipose tissue mass may influence circulating leptin concentrations.

Objective: We explored the possibility that short-term, moderately high-fat diets induce weight gain by producing inappropriately low circulating leptin concentrations.

Design: Female Hooded Wistar rats were fed either a moderately high-fat diet or control diet. Body weight, energy intake, body composition, and fasting plasma leptin were compared after 4 and 14 wk of dietary treatment.

Results: After 4 wk, abdominal fat mass was 38% greater in rats fed the high-fat diet than in those fed the control diet ($P < 0.01$). However, plasma leptin concentrations were 24% lower in ani-mals fed the high-fat diet ($P < 0.05$), resulting in significantly lower plasma leptin concentrations per unit abdominal fat mass than in control animals ($P < 0.005$). From 4 to 14 wk, animals fed the high-fat diet gained twice as much weight and consumed 32 kJ/d more than controls (both $P < 0.05$). At 14 wk, plasma lep-tin concentrations per unit abdominal fat mass were 27% lower in rats fed the high-fat diet ($P = 0.058$) and there was a significant negative association between leptin concentrations per unit abdominal fat mass and body weight ($r = 0.44$, $P < 0.05$).

Conclusions: In the short term, a moderately high-fat diet is associated with lower than expected circulating leptin concentrations, which correlate with a higher body weight. A high-fat diet may therefore contribute to weight gain by reducing leptin secre-tion in adipose tissue. *Am J Clin Nutr* 2000;71 :438–42.

KEY WORDS: Energy intake, satiety, leptin, body weight, high-fat diet, adipose tissue, rats

INTRODUCTION

Long-term, high-fat diets can induce overconsumption and weight gain; however, the mechanism by which this occurs is unknown (1). Leptin is a circulating protein produced in propor-tion to adipose tissue mass (2) that can act on the brain to increase satiety (3). Therefore, a persistent reduction in either the secre-tion or action of leptin may cause weight gain by sending an inappropriate signal to the brain, resulting in a reduced satiety response. Mice with well-established diet-induced obesity have

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Journal of Theoretical Biology 234 (2005) 277–288

On the importance of fatty acid composition of membranes for aging

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Received 11 July 2004; received in revised form 3 November 2004; accepted 17 November 2004
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Abstract
The membrane pacemaker theory of aging is an extension of the oxidative stress theory of aging. It emphasises variation in the fatty acid composition of membranes as an important influence on lipid peroxidation and consequently on the rate of aging and determination of lifespan. The products of lipid peroxidation are reactive molecules and thus potent damagers of other cellular molecules. It is suggested that the feedback effects of these peroxidation products on the oxidative stress experienced by cells is an important part of the aging process. The large variation in the chemical susceptibility of individual fatty acids to peroxidation coupled with the known differences in membrane composition between species can explain the different lifespans of species, especially the difference between mammals and birds as well as the body-size-related variation in lifespan within mammals and birds. Lifespan extension by calorie-restriction can also be explained by changes in membrane fatty acid composition which result in membranes more resistant to peroxidation. It is suggested that lifespan extension by reduced insulin/IGF signalling may also be mediated by changes in membrane fatty acid composition.

Keywords: Membrane fatty acids; Lipid peroxidation; Maximum lifespan; Calorie-restriction; Insulin/IGF signalling; Docosahexaenoic acid

1. Introduction

Despite being a very long-living species, most of us desire more. Humankind's first literary achievement, the 4000 year old "Epic of Gilgamesh", tells the story of a search for immortality (George, 1999). The maximum lifespan of mammal species increases allometrically with body mass (Sacher, 1959), with the maximum lifespan of mice being 3–4 yearsand for elephants ~80 years. Although elephants are much larger than humans, they
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Aging is measured demographically as an increase in the "age-dependent mortality". This is a reflection that death results from a variety of causes and for many diseases the biggest risk factor is age. Undoubtedly, there is both a genetic and an environmental contribution basis to aging. In humans, studies of Danish twins suggest that the heritability of longevity is 0.26 for males and 0.23 for females(Herskind et al., 1996). Theoriesof aging are of two types; those that seek to explain "why" aging occurs (evolutionary theories) and those that seek to explain "how" aging occurs (mechanistic theories). These two types of theories are not independent of each other, in that evolutionary theories must operate within
the constraints of the mechanisms that cause aging. Most multicellular animals have a finite maximum lifespan yet we do not know the cause of this fundamental difference between species.
This contribution will describe a mechanistic theory of aging that for convenience I have called the membrane pacemaker theory of aging. It is not a completely new theory and can be regarded asan extension of the oxidative stress theories of aging.

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Of particular interest for the membrane pacemaker theory of aging is the finding that calorie-restriction is associated with substantial changes in the fatty acid composition of membranes resulting in a decreased susceptibility to lipid peroxidation

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On the importance of fatty acid composition of membranes for aging

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Received 11 July 2004; received in revised form 3 November 2004; accepted 17 November 2004
Available online 24 January 2005

Abstract
The membrane pacemaker theory of aging is an extension of the oxidative stress theory of aging. It emphasises variation in the fatty acid composition of membranes as an important influence on lipid peroxidation and consequently on the rate of aging and determination of lifespan. The products of lipid peroxidation are reactive molecules and thus potent damagers of other cellular molecules. It is suggested that the feedback effects of these peroxidation products on the oxidative stress experienced by cells is an important part of the aging process. The large variation in the chemical susceptibility of individual fatty acids to peroxidation coupled with the known differences in membrane composition between species can explain the different lifespans of species, especially the difference between mammals and birds as well as the body-size-related variation in lifespan within mammals and birds. Lifespan extension by calorie-restriction can also be explained by changes in membrane fatty acid composition which result in membranes more resistant to peroxidation. It is suggested that lifespan extension by reduced insulin/IGF signalling may also be mediated by changes in membrane fatty acid composition.

Keywords: Membrane fatty acids; Lipid peroxidation; Maximum lifespan; Calorie-restriction; Insulin/IGF signalling; Docosahexaenoic acid

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How such changes in membrane composition come about following calorie-restriction is unknown. Merry (2002) suggests there are two possible hormonal candidates; insulin and thyroid hormones. [Both of these are regulated by leptin.] Blood concentrations of insulin and triiodothyronine are significantly lowered by calorie-restriction

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An interesting perspective is that IGF-1 and insulin-signalling pathways involve membrane-bound receptors and changes in membrane fatty acid composition have been shown to influence both IGF-1 signalling (Lanson et al., 1997) and insulin-signalling (see Hulbert et al., 2004b)

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Journal of Theoretical Biology 234 (2005) 277–288

On the importance of fatty acid composition of membranes for aging

A.J. Hulbert[A,B,~]
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Received 11 July 2004; received in revised form 3 November 2004; accepted 17 November 2004
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Abstract
The membrane pacemaker theory of aging is an extension of the oxidative stress theory of aging. It emphasises variation in the fatty acid composition of membranes as an important influence on lipid peroxidation and consequently on the rate of aging and determination of lifespan. The products of lipid peroxidation are reactive molecules and thus potent damagers of other cellular molecules. It is suggested that the feedback effects of these peroxidation products on the oxidative stress experienced by cells is an important part of the aging process. The large variation in the chemical susceptibility of individual fatty acids to peroxidation coupled with the known differences in membrane composition between species can explain the different lifespans of species, especially the difference between mammals and birds as well as the body-size-related variation in lifespan within mammals and birds. Lifespan extension by calorie-restriction can also be explained by changes in membrane fatty acid composition which result in membranes more resistant to peroxidation. It is suggested that lifespan extension by reduced insulin/IGF signalling may also be mediated by changes in membrane fatty acid composition.

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Commonly, the long-living strains within a species are small and this seems to be associated with low IGF levels in these small individuals.

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Role of fat amount and type in ameliorating diet-induced obesity: insights at the level of hypothalamic arcuate nucleus leptin receptor, neuropeptide Y and pro-opiomelanocortin mRNA expression.

Diabetes Obes Metab. 2004 Jan;6(1):35-44.
PMID: 14686961 [PubMed - in process]

The dietary interventions were in twofold: (1) the obesity was induced by a 13-week obesogenic fat diet compared with a low-fat (LF) diet, and (2) the reversibility was tested by using high n-3 polyunsaturated fat (PUFA) and LF diets. Fifty-four C57Bl/6 mice were fed a high-fat (59% in kcal) diet for 13 weeks and then classified as diet-induced obese (DIO) or diet-resistant (DR) mice according to upper and lower tertiles of body weight gain. The DIO mice were then subdivided into three groups for a 6-week secondary dietary intervention. Two of the groups were switched to either a high n-3 PUFA (DIO-n3) or a low-fat (10% in kcal, DIO-LF) diet, whereas the third (controls) and DR mice continued on the initial high-fat diet.

[snip] RESULTS: After switching the DIO mice to the n-3 PUFA or LF diet, their body weights were reduced to the level of the DR and LF mice. The food efficiencies were, from the highest to lowest, in the order: DIO > LF > DR > DIO-LF > DIO-n3. Using quantitative in situ hybridization, we found that the DIO mice had higher levels of leptin receptor (LR, +290%, $p < 0.005$) and neuropeptide Y (NPY, +25%, $p < 0.05$) mRNA expression in the hypothalamic arcuate nucleus (Arc) than the DR mice, whereas the level of pro-opiomelanocortin (POMC) mRNA expression was significantly reduced (-45%, $p < 0.01$). All effects that were essentially returned to DR levels by the change to the n-3 PUFA diet and, with the exception of a failure to normalize Arc NPY mRNA levels, by the change to LF diet.

CONCLUSIONS: Taken together, the present results show that both change in level and quality of dietary fat can potently alter hypothalamic neuropeptide expression and result in effective amelioration of diet-induced obesity. Interestingly, the n-3 PUFA diet when fed to already obese mice produced a pattern of hypothalamic gene expression similar to that in obesity resistant (DR) mice. [snip]

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July 02, 2002, Scientific American

Fish-Rich Diet May Reduce Levels of Fat Hormone

A diet rich in fish may lower levels of the fat-regulating hormone leptin, scientists say. Previous findings have linked elevated levels of leptin, which is produced by fat cells in the body, to obesity and cardiovascular disease. The substance seems to tell the body when it has consumed enough food, and researchers posit that obese people somehow lose the ability to recognize these chemical cues. But exactly how the system works and what other factors influence the hormone's levels are unknown. The new work, published today in the journal *Circulation,* suggests that diet plays a key role.

Scientists have known for some time that fish or fish oil seems to provide some protection against cardiovascular disease in humans. And earlier studies in rats indicated that unsaturated fatty acids in fish may affect leptin levels. Mikolaj Winnicki of the Mayo Clinic and his colleagues thus wanted to see if a fish-rich diet has a similar effect on the hormone in humans. To do this, the team examined the body mass index (a relationship between height and weight), fat content, age, gender, diet, and leptin levels of about 600 individuals from the same tribe in Tanzania. Half of the subjects lived on a lake and ate a lot of fish; the others were vegetarians. The scientists found that for every study characteristic except diet and leptin levels the two groups were identical. The fish-eaters, however, possessed significantly lower levels of the hormone than did their inland counterparts, even though body mass index--typically an important indicator of leptin levels--was the same for both groups. Additionally, although women generally possess higher levels of the hormone than men do, the investigators found the leptin levels of women who ate fish to be less than half that of both the female and male vegetarians. "We speculate that a fish diet may change the relationship between leptin and body fat and somehow help make the body more sensitive to the leptin message," remarks team member Virend Somers, also at the Mayo Clinic.

The authors caution against extrapolating diet recommendations from these results, however. "These are African individuals living in a fairly rural environment," Somers notes. "We don't know if the findings will apply to a semi-overweight, urban-dwelling North American population." The researchers plan to further probe this relationship by looking at whether leptin levels change in people who increase their fish consumption. --*Rachael Moeller*

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Clinical Experience of a Diet Designed to Reduce Aging

Ron Rosedale MD, Eric C. Westman MD MHS
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Abstract

The neuroendocrine theory of aging is associated with elevated levels of glucose, insulin and leptin. The objective of this study is to describe the metabolic effects of a nutritional program designed to reduce these correlates of aging.

A retrospective chart review of patients attending an outpatient metabolic management program involving instruction in a high-fat, adequate-protein, low-carbohydrate diet, the use of nutritional supplements, and periodic individual visits. The general dietary recommendation was approximately 15% carbohydrate, 25% protein, and 60% fat. Recommended sources of fat included raw nuts, avocados, olives and olive oil, flax oil and cod liver oil. The intake of protein was limited to 1.0 - 1.25 grams/kg lean body mass per day (increased for exercise to 1.25 grams/day). Recommended sources of protein included sardines, fish, eggs, tofu, chicken, turkey, wild meats, non-fat cheeses (cottage, ricotta, cream), and seafood. Only non-starchy, fibrous vegetables were acceptable. Nutritional supplements recommended were: L-carnitine 2000mg, alpha-lipoic acid 400mg, coenzyme Q10 100 mg, 1 tbsp cod liver oil, magnesium 300mg, potassium 300mg, vitamin C 1000mg, vitamin E 800mg daily, and a multivitamin. Medications were adjusted if needed. The mean duration of follow-up was 91.5 days (range 36-211). Thirty-one patients were identified with baseline and follow-up body weight, and fasting laboratory tests. The mean age of patients was 57.6 years, 53% were female. Over a mean follow-up of 91.5 days, body weight decreased 8.2% ($p<0.01$), fasting serum glucose decreased 8.3% ($p=0.001$). There were 50% reductions in insulin, leptin, fasting serum triglyceride, and triglyceride/HDL ratio ($p<0.001$). Free T3 decreased 7%

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- Further research into the effects of this program on reactive oxygen species and advanced glycated end-products appears to be indicated.

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FAT…*AND* *LEPTIN*… RULES

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Your brain is what your fat uses to do its bidding