Life, Death, Food

and the Disease of Aging

Ron Rosedale M.D.
know thy enemy...

Aging
Otherwise, We Know Just Enough To Be Dangerous

Examples; Sulfonylureas PPARγ agonists
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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Another Example in the Making As We Speak;

DPP₄ inhibitors
Dipeptidyl Peptidase Inhibits Malignant Phenotype of Prostate Cancer Cells by Blocking Basic Fibroblast Growth Factor Signaling Pathway

Umadevi V. Wesley, Michelle McGroarty, and Asal Homoyouni

Department of Microbiology and Molecular Genetics, Vermont Cancer Center, University of Vermont, Burlington, Vermont

Abstract

Dipeptidyl peptidase IV (DPPIV) is a serine protease with tumor suppressor function. It regulates the activities of mitogenic peptides implied in cancer development. Progression of benign prostate cancer to malignant metastasis is linked to increased production of basic fibroblast growth factor (bFGF), a powerful mitogen. In this study, using in vitro model system we show that DPPIV loss is associated with increased bFGF production in metastatic prostate cancer cells. DPPIV reexpression in prostate cancer cells blocks nuclear localization of bFGF, reduces bFGF levels, inhibits mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK)1/2 activation, and decreases levels of urokinase-type plasminogen activator, known downstream effectors of bFGF signaling pathway. These molecular changes were accompanied by induction of apoptosis, cell cycle arrest, inhibition of in vitro cell migration, and invasion. Silencing of DPPIV by small interfering RNA results in increased bFGF levels and restoration of mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK)1/2 activation. These results indicate that DPPIV inhibits the malignant phenotype of prostate cancer cells by blocking bFGF signaling pathway. (Cancer Res 2005; 65(4): 1325-34)

Introduction

Prostate cancer is the second leading cause of cancer deaths among men. Recent evidence suggest that the development of androgen-independent, metastatic prostate cancer is associated with increased activities of basic fibroblast growth factor (bFGF), a powerful mitogen and an angiogenic inducer (1–6). Although, the role of bFGF in cancer progression is fairly well understood, very little is known about the mechanisms that regulate bFGF signaling during the transition from benign to highly malignant prostate cancer.

Dipeptidyl peptidase IV (DPPIV), a membrane glycoprotein, regulates the activities of mitogenic growth factors and neuropeptides. Its proteolytic activity leads to inactivation or degradation of these peptides (7, 8). DPPIV is involved in diverse biological processes, including differentiation, cell adhesion, cell survival, cell motility, and cell migration. It is highly expressed in a number of tumors and is consistently linked to increased production of basic fibroblast growth factor (bFGF) leading to inhibition of MAPK-ERK1/2 activation and uPA production, known downstream effectors of bFGF signaling pathway. We also show that DPPIV expression is associated with increased production, known downstream effectors of bFGF signaling pathway.
Dipeptidyl Peptidase Inhibits Malignant Phenotype of Prostate Cancer Cells by Blocking Basic Fibroblast Growth Factor Signaling Pathway

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DPPIV is involved in diverse biological processes, including cell differentiation, adhesion, immunomodulation, and apoptosis, functions that are critical for controlling neoplastic transformation. pathway. We also show that DPPIV expression is associated with inhibition of in vitro cell migration, invasion, induction of apoptosis, and cell cycle arrest.

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Materials and Methods

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Antibodies and Reagents

The antibodies to bFGF, uPA, p27, and actin were used. The antibodies were purchased from Cell Signaling Technologies, Inc.

Results

In vitro cell migration, invasion, induction of apoptosis, and cell cycle arrest.

Conclusion

In conclusion, DPPIV loss is associated with increased bFGF production, and malignant phenotype of prostate cancer cells. These data identify a novel mechanism by which DPPIV inhibits the malignant phenotype of prostate cancer cells.
In other words, DPP4 is necessary to keep cancer at bay. Conversely, inhibition of DPP4 may do the opposite; promote the progression and metastasis of cancers...
New Study Says Januvia Could Pose Problems
By Norm Schneider
A drug manufactured by Merck & Co. for use by those who have Type 2 Diabetes may instead cause cancer, according to just published research. The research on the popular drug Januvia (stagliptin) is published in the most recent issue of the journal "Diabetes."

Type 2 diabetes is the most common form of diabetes and affects around 90 percent of the approximately 21 million people who have diabetes. Anyone can get Type 2 diabetes. People at particular risk are those who are overweight, people with a family history of diabetes, people with a combination of health issues that include high cholesterol and high blood pressure. The elderly are more susceptible to diabetes because aging makes the body less able to properly handle sugars.

In the new study, researchers found that Januvia could lead to a form of low-grade pancreatitis in some patients and a higher risk of pancreatic cancer in people who use the drug over a long period of time. They found that Januvia created abnormalities in the pancreas. Those abnormalities were found to be indicators for pancreatitis and, over time, pancreatic cancer. Although Januvia has been proven to be effective in lowering blood sugar in people with Type 2 diabetes, caution is now being urged. Moreover, since the effect of the drug may not be evident for years, there is added reason for concern.

In their study, the researchers used rats to test both Januvia and another drug, Glucophage (metformin), an older diabetes drug that has been in use for more than 50 years to treat Type 2 diabetes. The latter drug has recently been found to have an "antitumor" effect. Therefore the researchers wanted to find out how the two drugs affected "beta cells" responsible for releasing insulin in people without diabetes, but don't produce adequate amounts of insulin in people who do have diabetes. The researchers tested the drugs on 40 rats over a 12-week period. What they found was that the two drugs used together were helpful in preserving the beta cells, how they functioned, and improved the rats' sensitivity to insulin. When used alone on the rats, Januvia had had too high a rate of cell production in their pancreas and some of them developed abnormalities associated with pancreatitis.
Type 1 Diabetics Can Get 'Double Diabetes' From Insulin Resistance, Says University Of Pittsburgh

PITTSBURGH, April 21 – Insulin resistance, a condition commonly associated with the development of type 2 diabetes, is likely a major cause of heart disease in people with type 1 diabetes, according to study results published by University of Pittsburgh Graduate School of Public Health (GSPH) researchers in the *May 2003 issue of Diabetes Care*, a journal of the American Diabetes Association.

"Heart disease is a major complication for people with diabetes, including those with type 1 diabetes, and until now there has been no clear explanation for its cause," said principal investigator Trevor Orchard, M.D., professor and acting chair, department of epidemiology, GSPH. "We now suspect that insulin resistance occurs in those with type 1 diabetes in the same way as it does in those with type 2, essentially giving these individuals double diabetes and greatly increasing their risk of heart disease."

Insulin resistance, long associated with type 2 diabetes and a known risk factor for heart disease, occurs when the body does not properly use insulin to metabolize blood glucose, or sugar. The condition results when insulin fails to enable cells to admit glucose, necessary for cells' energy production. Glucose then builds up in the blood, and additional insulin is required. The new study suggests that this condition can occur in people who have type 1 diabetes as well.

"The good news is that not all people with type 1 diabetes are insulin resistant, and for them the risk of heart disease may not be as high," Dr. Orchard said. "Clearly, reducing or preventing insulin resistance through exercise, weight loss and possibly medication may help people with type 1 diabetes avoid heart disease."

The study analyzed data from the Pittsburgh Epidemiology of Diabetes Complication Study (PEDCS), a 10-year prospective investigation based on a cohort of adults with type 1, or childhood-onset, diabetes. Of the 658 subjects in PEDCS, 603 did not have heart disease at baseline and were followed for the current study.

Over the 10-year period there were 108 cardiovascular events such as angina, heart attack or death among the participants. Risk factors were lowest among those who experienced no cardiovascular events, moderate among those with angina and highest among those who died.

Insulin resistance was a risk factor that predicted all adverse events, and it was the most severe among those participants who experienced the most serious events.

To measure insulin resistance, investigators used the estimated glucose disposal rate (eGDR), a novel calculation based on waist-to-hip ratio, hypertension status and long-term blood sugar levels. Study participants with no cardiovascular events had a normal eGDR; those who experienced angina, considered a moderate event, had a lower eGDR; and those with the most severe events had the lowest eGDR.

High blood sugar itself was the only potential risk factor that did not appear to predict cardiovascular events.
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Effects of Intensive Glucose Lowering in Type 2 Diabetes
The Action to Control Cardiovascular Risk in Diabetes Study Group
June 12, 2008

Abstract

BACKGROUND
Epidemiologic studies have shown a relationship between glycated hemoglobin levels and cardiovascular events in patients with type 2 diabetes. We investigated whether intensive therapy to target normal glycated hemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors.

METHODS
In this randomized study, 10,251 patients (mean age, 62.2 years) with a median glycated hemoglobin level of 8.1% were assigned to receive intensive therapy (targeting a glycated hemoglobin level below 6.0%) or standard therapy (targeting a level from 7.0 to 7.9%). Of these patients, 38% were women, and 35% had had a previous cardiovascular event. The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The finding of higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up.

RESULTS
At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04). Hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P<0.001).

CONCLUSIONS
As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)
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Diabetes Health Goes Beyond Blood Sugar

By Tara-Parker Pope

The startling findings of a major federal study on the effects of lowering blood sugar are unlikely to change the way most people with Type 2 diabetes manage their illness, doctors said Thursday.

The study, announced Wednesday, showed that an intensive program to lower blood sugar actually increased risk of death. The findings were so surprising that the study was stopped early, and they seemed to undercut the accepted wisdom that people with diabetes should do everything possible to get their blood sugar down to normal.

But the methods used in the study, called Accord (for Action to Control Cardiovascular Risk in Diabetes), bear little resemblance to the techniques most doctors and patients use to manage blood sugar levels. And the patients in the study were typically far sicker than many people with diabetes today.

“The intensity of what we did is done virtually nowhere on the planet,” said Dr. John Buse, vice chairman of the study’s steering committee and the president of medicine and science at the American Diabetes Association. “It’s far beyond what’s common in clinical practice.” Dr. Buse called the study’s regimen to lower blood sugar a “brutal program.”

Still, doctors are likely to reconsider their emphasis on lowering blood sugar at all costs, because it is becoming clear that other factors influence the overall health of patients with diabetes.

The New England Journal of Medicine published a study this week showing that a three-pronged approach of managing sugar, blood pressure and cholesterol — combined with low doses of aspirin — prolonged the lives of people with diabetes. The patients who did best in that study did not reach the nearly normal sugar levels that were the aim of the Accord study. Instead, their levels were just slightly higher than normal.

In the Accord study, the group of patients who were randomly assigned to lower their blood sugar levels to nearly normal had 54 more deaths than the group whose levels were less rigidly controlled. The patients were in the study for an average of four years when investigators stopped the intense regimen and put all of them on the less intense one.
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February 13, 2008

LETTERS; A Diabetes Study

To the Editor:

Re "Study Undercuts Diabetes Theory" (front page, Feb. 7):

While the interim results of the Accord trial may be disappointing to patients with Type 2 diabetes, it is important to remember that there is incontrovertible evidence from the 20-year Diabetes Control and Complications Trial that controlling high blood glucose levels does indeed prevent vascular complications.

The most recent data from this trial even demonstrated a benefit of intensive treatment of blood glucose on cardiovascular disease, an effect that persisted many years after the formal study ended.

Of course, patients with Type 2 diabetes have many other risk factors for heart disease in addition to high blood glucose, including older age, overweight or obesity, high blood pressure and abnormal lipids. The interplay between all these risk factors and glucose is likely the reason that people with diabetes are at such high risk for heart attacks.

Finally, it is clear that people with Type 2 diabetes are at the same risk for developing eye, kidney and nerve problems from high blood glucose levels as patients with Type 1 and therefore will benefit from proper control of blood glucose.

Also, since the level of blood glucose control being tested in the Accord trial was significantly lower than that ordinarily achieved in medical practice, their results should not be taken as evidence that current standards should be abandoned. For all these reasons, most diabetes experts will continue to tell their patients to keep their blood glucose levels as near to normal as feasible.

Jill P. Crandall
Harry Shamoon
Bronx, Feb. 7, 2008

The writer are medical doctors at the Diabetes Research Center, Albert Einstein College of Medicine.

To the Editor:

The results of the Accord study are not surprising. Diabetes is not a disease of blood sugar; it is a disease of faulty hormonal signaling, particularly insulin and leptin.

The increased mortality seen in the diabetics in this study is not from lowering the sugar, but from the treatment that neglects and often worsens the underlying cause of insulin resistance.

Until medical "science" begins to recognize the difference between symptoms and disease we will continue to see results such as this and the recent Vytorin (Enhance) cholesterol-lowering study, where the treatment itself becomes the disease.

Ron Rosedale
Denver, Feb. 9, 2008

The writer is a medical doctor.
February 13, 2008

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**daf-2, an Insulin Receptor-Like Gene That Regulates Longevity and Diapause in Caenorhabditis elegans**

Koutarou D. Kimura, Heidi A. Tissenbaum, Yanxia Liu, Gary Ruvkun


**Abstract**

A C. elegans neurosecretory signaling system regulates whether animals enter the reproductive life cycle or arrest development at the long-lived dauer diapause stage. daf-2, a key gene in the genetic pathway that mediates this endocrine signaling, encodes an insulin receptor family member. Decreases in DAF-2 signaling induce metabolic and developmental changes, as in mammalian metabolic control by the insulin receptor. Decreased DAF-2 signaling also causes an increase in life-span. Life-span regulation by insulin-like metabolic control is analogous to mammalian longevity enhancement induced by caloric restriction, suggesting a general link between metabolism, diapause, and longevity.
**daf-2**, an Insulin Receptor-Like Gene That Regulates Longevity and Diapause in *Caenorhabditis elegans*  
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The role of insulin and IGF-1 signaling in longevity

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Abstract. There are many theories of aging and parameters 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.

Key words. Aging; lifespan; genetic instability; telomerase; oxidative stress; superoxide dismutase; oxidants; antioxidants; reactive oxygen species; glutathione; thioredoxin metabolism; calorie restriction; insulin; IGF-1; growth hormone; signaling; Sir; FOXO; p66; klotho; animal models; S. cerevisiae; C. elegans; D. melanogaster; mouse; knockout; human; syndrome; Ames Dwarf; Snell Dwarf; FIRKO.

Introduction

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 increasing longevity good for survival of the species, since natural/energy resources (water, food etc.) are limited? Will artificially prolonged lifespan alter natural evolutionary processes? How do we balance quality of life with quantity of life?

These two perspectives of aging and longevity are certainly connected, but are also distinct. One is the biology of aging and lifespan and the other is the social and evolutionary 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 focus especially on the role of metabolism and insulin and insulin-like growth factor-1 (IGF-1) signaling in this process.

What is aging?

Aging is a progressive loss of physiological functions that increases the probability of death. This decline in function occurs both within individual cells and within the organism as a whole. Life expectancy (or average lifespan) depends highly on both the biology of aging and the life circumstances of the organism. Evolutionarily speaking, very few organisms or animals were allowed to age, since mortality from starvation, predators, infection, diseases or environmental stresses often resulted in death before the biology of aging could play a role. Even human aging has become common in only the past few centuries. Two hundred years ago average lifespan was about 24 years due to high infant mortality, poor hygiene and inability to treat infectious disease [1, 2]. Now, with the development of good principles of hygiene, a wide range of effective
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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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 increasing longevity good for survival of the species, since natural/energy resources (water, food etc.) are limited? Will artificially prolonged lifespan alter natural evolutionary processes? How do we balance quality of life with quantity of life?

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What is insulin signaling?
The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn*

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Abstract. There are many theories of aging and parameters 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.

Key words. Aging; lifespan; genetic instability; telomerase; oxidative stress; superoxide dismutase; oxidants; antioxidants; reactive oxygen species; glutathione; thioredoxin metabolism; calorie restriction; insulin; IGF-1; growth hormone; signaling; 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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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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Mutation of these genes has revealed the important role of insulin/IGF-1 signal transduction as a central regulator of aging in *C. elegans*. Mutations of *daf-2* can double the lifespan of *C. elegans*. When coupled with removal of germline precursor cells, which independently extends lifespan by ~60%, *daf-2* mutant worms can live four times longer than controls... Mutation of the downstream gene *age-1* also leads to a 65% increase in mean lifespan.

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The role of insulin and IGF-1 signaling in longevity

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Mutation of these genes has revealed the important role of insulin/IGF-1 signal transduction as a central regulator of aging in C. elegans... mutations of daf-2 can double the lifespan of C. elegans. When coupled with removal of germline precursor cells, which independently extends lifespan by ~60%, daf-2 mutant worms can live four times longer than controls...Mutation of the downstream gene age-1 also leads to a 65% increase in mean lifespan.

Insulin and IGF-1 initiate their action via highly homologous signaling systems...Grb2 adaptor proteins that links insulin action to the Ras-MAP kinase pathway, and plays a role in the ability of insulin to stimulate cell growth and differentiation.
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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, dIPL-2, that is synthesized in neurons, and represses endogenous insulin-dependent signaling in the peripheral fat. 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 the liver of Ames Dwarf mice insulin sensitivity is increased with lower levels of insulin. 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 [and/or leptin] signaling pathway in fat in the longevity process. Thus, in some ways, the FIRKO mouse mimics some of the effects of calorie restriction without caloric restriction.

The role of insulin and IGF-1 signaling in longevity
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Abstract
There are many theories of aging and parameters 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 a subject of considerable interest. These two perspectives of aging and longevity are certainly connected, but are also distinct. One is the biology of aging and lifespan and the other is the social and evolutionary 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 focus especially on the role of metabolism and insulin and IGF-1 signaling in this process.

Introduction
What is aging? Evolutionarily speaking, very few organisms or animals were allowed to age, since mortality from starvation, predators, infection, diseases or environmental stresses. A hundred years ago average lifespan was about 24 years due to high infant mortality, poor hygiene and inability to treat infectious disease. Now, with the development of good principles of hygiene, a wide range of effective treatments and advance in understanding of biology, life expectancy is generally increased.

Theories of Aging
There are many theories of aging and parameters that influence lifespan, including genetic instability, telomerase activity and oxidative stress. The key to understanding the role of insulin and IGF-1 signaling in longevity is to understand the role of these genes in the biology of aging and lifespan. This is a very complex interaction to influence lifespan.

Aging; lifespan; genetic instability; telomerase; oxidative stress; superoxide dismutase; oxidants; antioxidants; reactive oxygen species; glutathione; S. cerevisiae; C. elegans; D. melanogaster; mouse; knockout; human; syndrome; Ames Dwarf; Snell Dwarf; FIRKO.
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 was previously proposed nearly a century ago by Augusto O. Larque (1905) and more recently by John Harman (1981). 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...It has been found that individuals bearing at least one A allele at the IGF-1R locus have lower plasma IGF-1 levels, and this variant is found at an increased proportion in long-lived individuals.
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 connection between calorie restriction, metabolism and insulin and IGF-1 signaling in longevity is a function of the central role of insulin signaling in the stress response.

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The most recent results have shown that activation of dFOXO in the adult pericerebral fat body of D. melanogaster is sufficient to increase the length of the fly's life. In other words, one of the findings is likely to control aging...a moderate decrease in insulin and IGF-1 signaling has been shown to extend longevity in C. elegans.

These findings suggest that, as in C. elegans, autonomous and non-autonomous roles of insulin signaling combine to control aging...Insulin and IGF-1 initiate their action via highly homologous signaling systems...Grb2 pathway links insulin action to the Ras-MAP kinase pathway, and plays a role in the ability of C. elegans to control aging...Insulin sensitivity is increased with lower levels of insulin...[Possibly allowing for increased fat metabolism.]

The connection between calorie restriction, metabolism and chromatin structure in yeast has pointed to a role of a group of proteins called sirtuins (Sir).
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 insulin is a master regulator of cell-controlled processes regulated by chromatin structure and activity decreases lifespan 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-γ (peroxisome proliferator-activated receptor-γ), including genes that mediate fat storage...upregulation of SIRT1 in differentiated fat cells triggers lipolysis and loss of fat 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...It has been found that individuals bearing at least one A allele at the IGF-1R locus have lower plasma IGF-1 levels, and this variant is found at an increased proportion in long-lived individuals. 

Increasing the level of Sir-2 in yeast and C. elegans prolongs lifespan, while decreasing Sir activity decreases lifespan in yeast...In C. elegans, dFOXO is essential for long-lived mutants, including the daf-2 and age-1 mutations. When coupled with removal of germline precursor cells, which also leads to a 65% increase in mean lifespan.

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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.
On the importance of fatty acid composition of membranes for aging

A.J. Hulbert

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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.

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 years and for elephants ~80 years. Although elephants are much larger than humans, they are shorter-living than Homo sapiens with a maximum lifespan of ~115 years (Carey and Judge, 2000).

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). Theories of 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 as an extension of the oxidative stress theories of aging.
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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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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.

...insulin stimulates the desaturase enzymes responsible for increased polyunsaturation of fatty acids.

It suggests that reduced insulin/IGF signalling might extend lifespan via modification of membrane fatty acid composition.

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). Theories of 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 as an extension of the oxidative stress theories of aging.

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On the importance of fatty acid composition of membranes for aging

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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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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 years and for elephants ~80 years. Although elephants are much larger than humans, they are shorter-living than Homo sapiens with a maximum lifespan of ~115 years (Carey and Judge, 2000).

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).

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The potential role of insulin is highlighted by the finding that mitochondrial changes following calorie-restriction in rats are reversed by insulin treatment (Lambert and Merry, 2004).
Leptin
Obesity in middle-aged humans is a risk factor for many age-related diseases and decreases life expectancy by about 7 years, which is roughly comparable to the combined effect of all cardiovascular disease and cancer on life span. The prevalence of obesity increases up until late middle age and decreases thereafter. Mechanisms that lead to increased obesity with age are not yet well understood, but current evidence implicates impairments in hypothalamic function, especially impairments in the ability of hypothalamic pro-opiomelanocortin neurons to sense nutritional signals. The rapid increase in the prevalence of obesity 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 developed 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, conversely, 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.
Obesity Over the Life Course
Tooru Mizuno, I-Wei Shu, Hideo Makimura, Charles Mobbs
Sage KE, Science, (Published 16 June 2004)

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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 agouti-related 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
The Fat-Brain Axis Enters a New Dimension
Joel K. Elmquist and Jeffrey S. Flier
SCIENCE VOL 304 2 APRIL 2004

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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 experimental 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 \textit{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.

Michael Rosenbaum and Rudolph L. Leibel are at the Department of Pediatrics, Division of Molecular Genetics, Columbia University, College of Physicians and Surgeons, 650 West 168th Street, New York, NY 10032, USA.

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 \textit{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 \textit{et al.} 1980, Hale 1983, Meyer \textit{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 (directly and/or indirectly) affects gonads or gonadotrophs (fertility) and/or systems of energy homeostasis (body weight regulation) (Leibel 1977, Rosenbaum \textit{et al.} 1997a).

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Leptin: a review of its peripheral actions and interactions
S Margetic, CGazzola, GG Pegg and RA Hills
2002 Nature Publishing Group

Following the discovery of leptin in 1994, the scientific and clinical communities have held great hope that manipulation of the leptin axis may lead to the successful treatment of obesity. This hope is not yet dashed; however the role of the leptin axis is now being shown to be ever more complex than was first envisaged. It is now well established that leptin interacts with pathways in the central nervous system and through direct peripheral mechanisms. In this review, we consider the tissues in which leptin is synthesized and the mechanisms which mediate leptin synthesis, the structure of leptin and the knowledge gained from cloning leptin genes in aiding our understanding of the role of leptin in the periphery. The discoveries of expression of leptin receptor isotypes in a wide range of tissues in the body have encouraged investigation of leptin interactions in the periphery. Many of these interactions appear to be direct, however many are also centrally mediated. Discovery of the relative importance of the centrally mediated and peripheral interactions of leptin under different physiological states and the variations between species is beginning to show the complexity of the leptin axis. Leptin appears to have a range of roles as a growth factor in a range of cell types: as be a mediator of energy expenditure; as a permissive factor for puberty; as a signal of metabolic status and modulation between the foetus and the maternal metabolism; and perhaps importantly in all of these interactions, to also interact with other hormonal mediators and regulators of energy status and metabolism such as insulin, glucagon, the insulin-like growth factors, growth hormone and glucocorticoids. Surely, more interactions are yet to be discovered. Leptin appears to act as an endocrine and a paracrine factor and perhaps also as an autocrine factor. Although the complexity of the leptin axis indicates that it is unlikely that effective treatments for obesity will be simply derived, our improving knowledge and understanding of these complex interactions may point the way to the underlying physiology which predisposes some individuals to apparently unregulated weight gain.

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In females of most mammalian species, high leptin levels may signal the attainment of the sufficient long-term energy stores that are crucial for successful reproduction...leptin is a factor permissive to the onset of puberty.

Leptin is also expressed in skeletal muscle tissue. Thus, leptin may act as an indicator of general well-being: that sufficient muscle mass has developed and that a commensurate level of body fat has been deposited, such that it is favourable for puberty (and its consequences, such as pregnancy) to proceed.
The hypothalamic-pituitary-thyroid axis is down-regulated during starvation, and falling levels of leptin are a critical signal for this adaptation, acting to suppress preprothyrotropin-releasing hormone (prepro-TRH) mRNA expression in the paraventricular nucleus of the hypothalamus. This study addresses the mechanism for this regulation, using primary cultures of fetal rat hypothalamic neurons as a model system. Leptin dose-dependently stimulated a 10-fold increase in pro-TRH biosynthesis, with a maximum response at 10 nM. TRH release was quantified using immunoprecipitation, followed by isoelectric focusing gel electrophoresis and specific TRH radioimmunoassay. Leptin stimulated TRH release by 7-fold. Immunocytochemistry revealed that a substantial population of cells expressed TRH or leptin receptors and that 8–13% of those expressing leptin receptors coexpressed TRH. Leptin produced a 5-fold induction of luciferase activity in CV-1 cells transfected with a TRH promoter and the long form of the leptin receptor cDNA. Although the above data are consistent with a direct ability of leptin to promote TRH biosynthesis through actions on TRH neurons, addition of α-melanocyte-stimulating hormone produced a 3.5-fold increase in TRH biosynthesis and release, whereas neuropeptide Y treatment suppressed pro-TRH biosynthesis 3-fold. Furthermore, the melanocortin-4 receptor antagonist SHU9119 partially inhibited leptin-stimulated TRH release from the neuronal culture. Consequently, our data suggest that leptin regulates the TRH neurons through both direct and indirect pathways.
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.

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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 non-adipocytes. The facts that when leptin receptors are dysfunctional, TG content in nonadipocytes such as islets can increase 100-fold, and that constitutively expressed ectopic hyperleptinemia depletes TG, suggest that leptin controls the homeostatic 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 fa/fa Zucker diabetic fatty rats is the only proven lipodegenerative disease, but the possibility of lipotoxic disease of skeletal and/or cardiac muscle may require investigation, as does the possible influence of the intracellular TG content on autoimmune and neoplastic processes.

Leptin was discovered by positional cloning of a single gene mutation in the ob/ob 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 credentials 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 triglycerides (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
Regulation of fatty acid homeostasis in cells: Novel role of leptin

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The fact that when leptin receptors are dysfunctional TG content in nonadipocytes such as islets can increase 100-fold.. suggests that leptin controls the homeostatic system for intracellular TG.
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 obesity 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.

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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

Cases JA; Barzilai N
Division of Endocrinology and the Diabetes Research and Training Center, Albert Einstein College of Medicine, New York 10461, USA.

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 and its own secretion suggest that 'leptin resistance' may be a pathologic feature in obesity.
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Leptin directly stimulates aromatase activity in human luteinized granulosa cells.


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.
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,"...
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 \pm 2.04 ng/mL versus 5.04 \pm 2.09 ng/mL, \(P \leq 0.001\)). 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; \(P \leq 0.001\)). There was minimal change in this RR with correction for body mass index (RR, 1.24; 95% CI, 1.06 to 1.45; \(P \leq 0.006\)) 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; \(P \leq 0.03\)). Leptin correlated with C-reactive protein (\(r = 0.24, P \leq 0.001\)) 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; \(P \leq 0.05\)) 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
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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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.
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§*

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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.

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.

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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.

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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.

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

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

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Leptin and Inflammation
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*,†

*Departments of Medicine, †Molecular Microbiology and Immunology, ‡Surgery, and §Biological Chemistry, Johns Hopkins University, Baltimore, Maryland 21205, USA

ABSTRACT: Obesity is associated with an increased incidence of infection, diabetes, and cardiovascular disease, which together account for most obesity-related 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 leptin-dependent signal transduction directly promotes any of the conditions that frequently complicate obesity. Abnormalities in tumor necrosis factor a expression have been noted in each of the above comorbid conditions, so leptin deficiency could promote these complications if leptin had immunoregulatory 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-regulated both phagocytosis and the production of proinflammatory cytokines. These results identify an important and novel function for leptin: up-regulation of inflammatory immune responses, which may provide a common pathogenetic mechanism that contributes to several of the major complications of obesity.—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 immune responses. FASEBJ. 12, 57–65 (1998)

Key Words: obesity macrophage cytokine phagocytic function TNF lipopolysaccharide

LEPTIN, THE PROTEIN ENCODED by the ob gene, is known to regulate appetite and energy expenditure. Obese/obese (ob/ob) mice, homozygous for a spontaneous mutation in the ob gene, fail to produce lep-tin and exhibit hyperphagia and obesity. Treatment of such mice with recombinant leptin results in decreased food intake and weight loss (1–5). It is not known whether leptin deficiency per se explains other aspects of the ob/ob phenotype, such as diabetes and hyperlipidemia. Recently, ectopic expression 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
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Leptin Activates a Novel CNS Mechanism for Insulin-Independent Normalization of Severe Diabetic Hyperglycemia

Jonathan P. German, Joshua P. Thaler, Brent E. Wisse, Shinsuke Oh-I, David A. Sarruf, Miles E. Matsen, Jonathan D. Fischer, Gerald J. Taborsky, Jr, Michael W. Schwartz and Gregory J. Morton

Diabetes and Obesity Center of Excellence Department of Medicine, University of Washington, Seattle, Washington 98109; and Veterans Affairs Puget Sound Health Care System Department of Veterans Affairs Medical Center, Seattle, Washington 98108

The brain has emerged as a target for the insulin-sensitizing effects of several hormonal and nutrient-related signals. The current studies were undertaken to investigate mechanisms whereby leptin lowers circulating blood glucose levels independently of insulin. After extending previous evidence that leptin infusion directly into the lateral cerebral ventricle ameliorates hyperglycemia in rats with streptozotocin-induced uncontrolled diabetes mellitus, we showed that the underlying mechanism is independent of changes of food intake, urinary glucose excretion, or recovery of pancreatic B-cells. Instead, leptin action in the brain potently suppresses hepatic glucose production while increasing tissue glucose uptake despite persistent, severe insulin deficiency. This leptin action is distinct from its previously reported effect to increase insulin sensitivity in the liver and offers compelling evidence that the brain has the capacity to normalize diabetic hyperglycemia in the presence of sufficient amounts of central nervous system leptin.
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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

William Mair, Matthew D. W. Piper, Linda Partridge

Centre for Research on Ageing, University College London, Department of Biology, London, United Kingdom

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.


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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Anti-Aging Effects of Caloric Restriction: Involvement of Neuroendocrine Adaptation by Peripheral Signaling

TAKUYA CHIBA,* HARUYOSHI YAMAZA, YOSHIKAZU HIGAMI, AND ISAO SHIMOKAWA Division of Experimental Medicine: Pathology and Gerontology, Department of Respiratory and Digestive Medicine, Nagasaki University School of Medicine, Nagasaki City 852-8523, Japan

KEY WORDS: leptin; insulin; ghrelin; adipocytokine; IGF-I

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 implicated in life span extension (Guarente and Kenyon, 2000). Here we discuss the anti-aging effects of CR focused on the mechanisms of hypothalamic neuroendocrine 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 shortage periods (Holliday, 1989). The molecular mechanisms 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 secreted by adipocyte (Zhang et al., 1994), and it is an important factor controlling the balance of energy consumption and food intake. Subsequent studies have revealed the role of leptin as a neuroendocrine modulator 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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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.
In C. elegans, the transcription factor DAF-16 promotes 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 lifespan 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(e1611) germ-line-deficient animals, and increases the lifespans of daf-16(0) insulin/IGF-1 -pathway mutants substantially. Our findings indicate that DAF-16 may control two types of downstream signals: DAF-16 activity in signaling cells upregulates DAF-16 in specific responding tissues, possibly via regulation of insulin-like peptides, and also evokes DAF-16-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.

**Summary**

How signaling between tissues coordinates the physiology of an animal is a fundamental problem in endocrinology. The aging of C. elegans is controlled by an endocrine system that also regulates the lifespans of flies and mammals (Tatar et al., 2003). Reduction-of-function mutations affecting the insulin/IGF-1-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 expression 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 animal's rate of aging. First, the C. elegans genome 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 hormones, because daf-2 acts cell-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).

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DAF-2 (and by extension, DAF-16) has been thought to function primarily in the nervous system to influence lifespan. Mosaics lacking daf-2 in AB, a lineage producing mainly ectodermal cell types (neurons and epidermis) 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 promoters has been reported to shorten the lifespan of daf-2 mutants to control levels (Wolkow et al., 2000). It seemed possible that DAF-16 might function in a different 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-16 activity (Hsin and Kenyon, 1999). Curiously, whereas DAF-16 accumulates in the nuclei of many cell types in daf-2 mutants, in germline-deficient animals DAF-16 accumulates primarily 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.

In this study, we have investigated the tissue-specificity of DAF-16 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(0) animals. However, we find that DAF-16 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(0) germline-defective mutants. We also find that DAF-16 activity in signaling cells elicits two types of responses, one that requires DAF-16 activity in responding cells, and thus may involve feedback from fat regulates lifespan. In other words, signals from fat regulate the genetic expression of aging.
In *C. elegans*, the transcription factor DAF-16 promotes 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.

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

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The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men

Jean L. Chan,1 Kathleen Heist,1 Alex M. DePaoli,2 Johannes 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.

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Thus, in normal men, the fall in leptin with fasting may be both necessary and sufficient for the physiologic adaptations of these [hypothalamic-pituitary-gonadal axis and, in part, the hypothalamic-pituitary-thyroid axis and IGF-1 binding capacity] axes.

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-iolologic 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...
Fat Metabolism Links Germline Stem Cells and Longevity in *C. elegans*

Meng C. Wang, Eyleen J. O’Rourke, and Gary Ruvkun*

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**Summary**

Fat metabolism, reproduction, and aging are intertwined regulatory axes; however, the mechanism by which they are coupled remains poorly understood. We found that germline stem cells (GSCs) actively modulate lipid hydrolysis in *Caenorhabditis elegans*, which in turn regulates longevity. GSC arrest promotes systemic lipolysis via induction of a specific fat lipase. Subsequently, fat mobilization is promoted and life span is prolonged. Constitutive expression of this lipase in fat storage tissue generates lean and long-lived animals. This lipase is a key factor in the lipid hydrolysis and increased longevity that are induced by decreased insulin signaling. These results suggest a link between *C. elegans* fat metabolism and longevity.

A balance of fat storage and mobilization is a universal feature of animal physiology (1). Reproduction is an energy-intensive process, which is modulated by the availability of nutrients and in turn influences lipid metabolism (2). Reproductive ability declines with age, and many organisms undergo reproductive senescence (3). Obesity increases with age and is also associated with the transition to menopause in women (4). Genetic studies have suggested endocrine roles of adipose tissue and the reproductive system in regulation of life span (5–8). Thus, understanding the mechanisms by which fat metabolism is coupled to reproductive cues may reveal systemic regulation of fat metabolism and provide insights into the control of aging.
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Burn Fat, Live Longer

Ting Xie*

Endocrine signals from germline stem cells control fat metabolism in the worm, thus affecting the animal's life span.
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.

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

IABG 10th Congress

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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 β-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-JB, 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.

... the cellular damage in aging is, at least in part, the result of FA excess secondary to leptin resistance. So, we may come to a conclusion that youth is a leptin-sensitive state, and that resistance to leptin occurs with aging.
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.

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Hormone levels and cataract scores as sex-specific, mid-life predictors of longevity in genetically heterogeneous mice.

Mech Ageing Dev 2003 Jul;124(7):801-10 (ISSN: 0047-6374)
Harper JM; Wolf N; Galecki AT; Pinkosky SL; Miller RA

Department of Pathology, School of Medicine, University of Michigan, Ann 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 longer life span. Additional work is needed to evaluate the role of these hormones as potential modulators of the aging process, and to resolve the conflicting data obtained for cataract severity as a predictor of life span.

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The winners;
Centenarians

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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

Diabetes/metabolism research and reviews 2001, vol. 17, pp. 19-26 (89 ref.)

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 dehydroepiandrosterone 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. Copyright © 2001 John Wiley & Sons, Ltd.
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The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn*

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

Abstract. There are many theories of aging and parameters 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.

Key words. Aging; lifespan; genetic instability; telomerase; oxidative stress; superoxide dismutase; oxidants; antioxidants; reactive oxygen species; glutathione; thioredoxin metabolism; calorie restriction; insulin; IGF-1; growth hormone; signaling; Sir; FOXO; p66; klotho; animal models; S. cerevisiae; C. elegans; D. melanogaster; mouse; knockout; human; syndrome; Ames Dwarf; Snell Dwarf; FIRKO.

Introduction

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 increasing longevity good for survival of the species, since natural/energy resources (water, food etc.) are limited? Will artificially prolonged lifespan alter natural evolutionary processes? How do we balance quality of life with quantity of life?

These two perspectives of aging and longevity are certainly connected, but are also distinct. One is the biology of aging and lifespan and the other is the social and evolutionary 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 focus especially on the role of metabolism and insulin and insulin-like growth factor-1 (IGF-1) signaling in this process.

What is aging?

Aging is a progressive loss of physiological functions that increases the probability of death. This decline in function occurs both within individual cells and within the organism as a whole. Life expectancy (or average lifespan) depends highly on both the biology of aging and the life circumstances of the organism. Evolutionarily speaking, very few organisms or animals were allowed to age, since mortality from starvation, predators, infection, diseases or environmental stresses often resulted in death before the biology of aging could play a role. Even human aging has become common in only the past few centuries. Two hundred years ago average lifespan was about 24 years due to high infant mortality, poor hygiene and inability to treat infectious disease [1, 2]. Now, with the development of good principles of hygiene, a wide range of effective
The role of insulin and IGF-1 signaling in longevity

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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 (FT3), free thyroxine (FT4), reverseT3 (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, FT3 and FT4 fell within the normal range in both groups. However, by comparison to old controls, in centenarian subjects, TSH levels were significantly lower, whereas rT3 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 rT3 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.

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Clinical Application of the Biology of Aging: A Diet To Control Aging

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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
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.

Keywords: glycolytic substrates, citric acid cycle intermediates, metabolism, energy
Short-term, high-fat diets lower circulating leptin concentrations in rats

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

Original Research Communications

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 animals 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 leptin 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 secretion in adipose tissue.

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 proportion to adipose tissue mass (2) that can act on the brain to increase satiety (3). Therefore, a persistent reduction in either the secretion 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 hyperleptinemia (4), yet are hyperphagic (5) and expend less. However, higher body weight is correlated with high leptin, not low.
Short-term, high-fat diets lower circulating leptin concentrations in rats

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

Original Research Communications

ABSTRACT

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High-Fat Meals Reduce 24-h Circulating Leptin Concentrations in Women

Diabetes 48:334–341, 1999

Peter J. Havel, Raymond Townsend, Leslie Chaump, and Karen Teff

Leptin induces weight loss in rodents via its effects on food intake and energy expenditure. High-fat diets induce weight gain, but the mechanism is not well understood. Previous studies have not found an effect of dietary fat content on fasting leptin. There is a nocturnal increase of leptin, however, which is related to insulin responses to meals.

Accordingly, high-fat, low-carbohydrate (HF/LC) meals, which induce smaller insulin and glucose responses, would produce lower leptin concentrations than low-fat, high-carbohydrate (LF/HC) meals. Blood samples were collected every 30–60 min for 24 h from 19 normal-weight (BMI, 24.2 ± 0.7 kg/m²; percent body fat = 31 ± 1%) women on 2 days (10 days apart) during which the subjects were randomized to consume three isocaloric 730-kcal meals containing either 60/20 or 20/60% of energy as fat/carbohydrate. Overall insulin and glycemic responses (24-h area under the curve [AUC]) were reduced by 55 and 61%, respectively, on the HF/LC day (P < 0.0001). During LF/HC feeding, there were larger increases of leptin 4–6 h after breakfast (38 ± 7%, P < 0.001) and lunch (78 ± 14%, P < 0.001) than after HF/LC meals (both P < 0.02). During LF/HC feeding, leptin increased from a morning baseline of 10.7 ± 1.6 ng/ml to a nocturnal peak of 21.3 ± 1.3 ng/ml (change, 10.6 ± 1.3 ng/ml; percent change, 123 ± 16%; P < 0.0001). The amplitudes of the nocturnal rise of leptin and the 24-h leptin AUC were 21 ± 8% (P < 0.005) and 38 ± 12% (P < 0.0025) larger, respectively, on the LF/HC day. In summary, consumption of HF/LC meals results in lowered 24-h circulating leptin concentrations. This result may be a consequence of decreased adipocyte glucose metabolism. Decreases of 24-h circulating leptin could contribute to the weight gain during consumption of high-fat diets.

In summary, consumption of HF/LC meals results in lowered 24-h circulating leptin concentrations in women.
Huang XF, Xin X, McLennan P, Storlien L.

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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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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Fish-Rich Diet May Reduce Levels of Fat Hormone

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Clinical Experience of a Diet Designed to Reduce Aging

Ron Rosedale MD, Eric C. Westman MD MHS, John Konhilas PhD

The Rosedale Center, Denver CO, Department of Medicine, Duke University Medical Center, Durham NC

The Journal of Applied Research Vol.9 No.4 2009

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% (p<0.001), while TSH did not change significantly.

We conclude that a high-fat, adequate-protein, low-carbohydrate diet with nutritional supplementation led to improvements in serum factors related to the aging process in adherent patients. Further research regarding this nutritional approach and its relationship to aging is in order.

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Interestingly, this study cohort exhibited a reduction in circulating free T3... Paralleling this reduction in insulin and leptin levels were strongly correlated with the reduction in weight and centenarians.

Reduction in insulin and leptin levels were strongly correlated with the reduction in weight. The percent reduction in leptin was [far] greater than the percent weight (fat) loss.

The impact of this dietary approach on aging mechanisms can only be implied from comparisons with longevity studies that have examined the same metabolic parameters. Many aging studies have used calorie restriction as the means to impact aging. These types of studies become difficult in humans for obvious reasons.
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Interestingly, this study cohort exhibited a reduction in circulating free T3... Paralleling this reduction in body temperature... Similar findings were reported in caloric restricted rodents, monkeys, humans, and centenarians.

For this reason, investigators have examined the effectiveness of weight loss as a surrogate for caloric restriction on human mortality rates (25) but have found an increased mortality rate and reduced lifespan (26)... It is now speculated that fat loss as opposed to weight loss decreases all-cause mortality in humans be implied from comparisons with longevity studies that have examined the same metabolic parameters. Many aging studies have used calorie restriction as the means to impact aging. These types of studies become difficult in humans for obvious reasons.

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Clinical Experience of a Diet Designed to Reduce Aging

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...although patients were not told to restrict calories, there may have been a reduction in caloric intake secondary to reduced hunger, with the decrease in circulating leptin reflecting an increase in leptin sensitivity.

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Conclusion
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Conclusion

A high-fat, adequate protein, low carbohydrate diet with nutritional supplements reduced correlates of aging in an outpatient setting.
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A high-fat, adequate protein, low carbohydrate diet with nutritional supplements reduced correlates of aging in an outpatient setting.

From the beginning to the end of the diet program there were reductions in body weight, insulin, glucose, leptin, triglycerides, and

Reductions in free T₃.
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Further research into the effects of this program on aging and its symptoms appear to be indicated.

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Back to the Future...
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Your brain, via leptin, is a servant of your fat... and is what your fat uses to do its bidding
BURNING FAT...OR NOT... DETERMINES YOUR HEALTH AND LIFESPAN

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...and that will be determined by specific hormones (insulin and leptin)...

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...and they will be controlled by what you eat
Health and Happiness

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