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

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

Department of Molecular Biology, Massachusetts General Hospital, and Department of Genetics, Harvard Medical School, Boston, MA 02114, USA

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.
Physiology

**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
J. Koochmesghi
National Research Center for Genetic Engineering and Biotechnology, Tehran 14155, Iran

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

IABG 10th Congress
J. Koochmeshgi
National Research Center for Genetic Engineering and Biotechnology, Tehran 14155, Iran

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

IABG 10th Congress

J. Koochmeshgi
National Research Center for Genetic Engineering and Biotechnology, Tehran 14155, Iran

A hypothesis for interpreting extension of life by dietary restriction...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 leptin's role in this complex and integrated signalling system, the reproductive switch. Does this decrease simply reflect the insufficiency of body's 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.
PPARα activators may be good candidates as antiaging agents

Adnan Erol

Silivri City Hospital, Internal medicine, Ali Cetinkaya Cad, 34930 Silivri, Istanbul, Turkey

Received 26 January 2005; accepted 27 January 2005

Summary

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

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.

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

Printed on Thu Aug 18 15:05:18 BST 2005

© Ron Rosedale M.D.
Obesity accelerates 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

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.

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.

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

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

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

Journal reference: The Lancet (DOI: 10.1016/S0140-6736(05)66630-5)
Printed on Thu Aug 18 15:05:18 BST 2005

© Ron Rosedale M.D.
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

Deparment 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.

© Ron Rosedale M.D.
The winners; Centenarians
Review Article

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

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

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.
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 dehydroepandrosterone sulphate (DHEAS) and IGF-1]; and finally (d) the rise in oxidative stress. Indeed previous studies have also investigated the occurrence and the degree of insulin resistance in healthy centenarians. Such data demonstrated that age-related insulin resistance is not an obligatory finding in the elderly and that healthy centenarians have a preserved insulin action compared to aged subjects. Why insulin action is preserved in centenarians is still not known. Nevertheless, a possible approach to the question is to outline the centenarians' anthropometric, endocrine and metabolic characteristics in order to design a clinical picture of such metabolic successful aging. According to the remodeling theory of age the preserved insulin action in centenarians might be the net result of the continuous adaptation of the body to the deleterious changes that occur over time. Nevertheless, only future longitudinal studies specifically designed to investigate the relationship between extreme old age and degree of insulin sensitivity will provide a conclusive answer with regard to the pathophysiology of adaptive metabolic changes occurring in the elderly. Copyright © 2001 John Wiley & Sons, Ltd.
The role of insulin and IGF-1 signaling in longevity

M. Katic and C. R. Kahn*

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

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

Abstract. There are many theories of aging and 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.

* Corresponding author.

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

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

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

Abstract. There are many theories of aging and 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 strategies for improving health have been developed.

Interestingly, one of the striking physiological characteristics recently identified in centenarians is their greatly increased insulin sensitivity compared with younger subjects...
Body composition, body fat distribution, and resting metabolic rate in healthy centenarians.


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

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

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

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

[Copyright 2002 by W.B. Saunders Company].

© Ron Rosedale M.D.
Our results showed an age-related decline of the TSH levels and a significant increase of the rT(3) concentrations in centenarians by comparison to old controls.

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

© Ron Rosedale M.D.
ABSTRACT

The aim of the present study was to determine the respective role of energy substrates and insulin on leptin secretion from white adipocytes. Cells secreted leptin in absence of glucose or other substrates and addition of glucose (5 mM) increased this secretion. Insulin doubled leptin secretion in the presence of glucose (5 mM), but not in its absence. High concentrations of glucose (up to 25 mM) did not significantly enhance leptin secretion over that elicited by 5 mM glucose. Similar results were obtained when glucose was replaced by pyruvate or fructose (both 5 mM). L-glycine or L-alanine mimicked the effect of glucose on basal leptin secretion but completely prevented stimulation by insulin. On the contrary, insulin stimulated leptin secretion when glucose was replaced by L-aspartate, L-valine, L-methionine or L-phenylalanine, but not by L-leucine (all 5 mM). Interestingly, these five amino acids potently increased basal and insulin-stimulated leptin secretion in the presence of glucose. Unexpectedly, L-glutamate acutely stimulated leptin secretion in the absence of glucose or insulin. Finally, nonmetabolizable analogs of glucose or amino acids were without effects on leptin secretion. These results suggest that 1) energy substrates are necessary to maintain basal leptin secretion constant, 2) high availability of glycolysis substrates is not sufficient to enhance leptin secretion but is necessary for its stimulation by insulin, 3) amino acids precursors of citric acid cycle intermediates potently stimulate per se basal leptin secretion, insulin having an additive effect, and 4) substrates need to be metabolized in order to increase leptin secretion.

Keywords: glycolytic substrates, citric acid cycle intermediates, metabolism, energy
REGULATION OF LEPTIN SECRETION FROM WHITE ADIPOCYTES BY INSULIN, GLYCOLYTIC SUBSTRATES, AND AMINO ACIDS

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

Philippe G. Cammisotto 1, Yves Gélinas2, Yves Deshaies2 and Ludwik J. Bukowiecki2
Département de Pathologie et Biologie Cellulaire, Faculté de médecine, Université de Montréal 2900 Edouard Montpetit, R-822, C.P. 6128 Succ. Centre Ville, Montréal (Qué), Canada H3C 3J7
Département d’anatomie et de physiologie, Faculté de médecine, Université Laval, Québec (Qué), CANADA, G1K7P4

Running title: energy substrates in leptin secretion
Mailing address: Dr P. G. Cammisotto, same address as above
Tel: (514) 343-6111 p3094
Fax: (514) 343-5755
Email: drphilmontreal@yahoo.ca

ABSTRACT

The aim of the present study was to determine the respective role of energy substrates and insulin on leptin secretion from white adipocytes. Cells secreted leptin in absence of glucose or other substrates and addition of glucose (5 mM) increased this secretion. Insulin doubled leptin secretion in the presence of glucose (5 mM), but not in its absence. High concentrations of glucose (up to 25 mM) did not significantly enhance leptin secretion over that elicited by 5 mM glucose. Similar results were obtained when glucose was replaced by pyruvate or fructose (both 5 mM). L-glycine or L-alanine mimicked the effect of glucose on basal leptin secretion but completely prevented stimulation by insulin. On the contrary, insulin stimulated leptin secretion when glucose was replaced by L-aspartate, L-valine, L-methionine or L-phenylalanine, but not by L-leucine (all 5 mM). Interestingly, these five amino acids potently increased basal and insulin-stimulated leptin secretion in the presence of glucose. Unexpectedly, L-glutamate acutely stimulated leptin secretion in the absence of glucose or insulin. Finally, nonmetabolizable analogs of glucose or amino acids were without effects on leptin secretion. These results suggest that 1) energy substrates are necessary to maintain basal leptin secretion constant, 2) high availability of glycolysis substrates is not sufficient to enhance leptin secretion but is necessary for its stimulation by insulin, 3) amino acids precursors of citric acid cycle intermediates potently stimulate per se basal leptin secretion, insulin having an additive effect, and 4) substrates need to be metabolized in order to increase leptin secretion.

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

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

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

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

INTRODUCTION

Long-term, high-fat diets can induce overconsumption and weight gain; however, the mechanism by which this occurs is unknown (1). Leptin is a circulating protein produced in propor-tion to adipose tissue mass (2) that can act on the brain to increase satiety (3). Therefore, a persistent reduction in either the 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

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. Am J Clin Nutr 2000;71:438–42.

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

INTRODUCTION

Long-term, high-fat diets can induce overconsumption and weight gain; however, the mechanism by which this occurs is unknown (1). Leptin is a circulating protein produced in 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.
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.

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.
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.

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 [leptin receptor activity] similar to that in obesity resistant (DR) mice.
Fish-Rich Diet May Reduce Levels of Fat Hormone

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

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

The authors caution against extrapolating diet recommendations from these results, however. "These are African individuals living in a fairly rural environment," Somers notes. "We don’t know if the findings will apply to a semi-overweight, urban-dwelling North American population." The researchers plan to further probe this relationship by looking at whether leptin levels change in people who increase their fish consumption. --Rachael Moeller
July 02, 2002, Scientific American

Fish-Rich Diet May Reduce Levels of Fat Hormone

A diet rich in fish may lower levels of the fat-regulating hormone leptin... 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.

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

© Ron Rosedale M.D.
A diet rich in fish may lower levels of the fat-regulating hormone leptin... 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.

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 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
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.
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).

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.

© Ron Rosedale M.D.
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.

© Ron Rosedale M.D.
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 8.7% (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.
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.

© Ron Rosedale M.D.
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.

© Ron Rosedale M.D.
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

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.

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.

Reduction in insulin and leptin levels were strongly correlated with the reduction in weight and centenarians.

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.

© Ron Rosedale M.D.
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

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 fasting serum triglyceride and triglyceride/HDL ratio (p<0.001). Free T3 decreased 7% (p<0.001), while TSH did not change significantly.

Interestingly, this study cohort exhibited a reduction in circulating free T3... Paralleling this reduction in 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. It is now speculated that fat loss as opposed to weight loss decreases all-cause mortality in humans.()

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.

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 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.
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

...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.

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. The percent reduction in leptin was [far] greater than the percent weight (fat) loss.

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.
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

Conclusion

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.

The 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.

Further research into the effects of this program on aging and its symptoms appear to be indicated.
Back to the Future...
Back to the Future...

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

Your brain, via leptin, is a servant of your fat... and is what your fat uses to do its bidding.

Back to the Future...
Back to the Future...

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

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

© Ron Rosedale M.D.
Back to the Future...

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

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

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