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REVIEW

# LEPTIN 21 YEARS LATER: FROM FAT'S BIG BANG TO CENTRAL STAGE NEVER BEFORE HAS ADIPOSE TISSUE BEEN SO ACTIVE

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## Abstract

Here we focus on Fat's Big Bang exploring officially by the discovery of leptin by Jeffrey Friedman and colleagues on 1 December 1994 in *Nature*. We recall their journey of discovery and discuss perspective on the further research in adipobiology and adipopharmacology of cardiometabolic, neuropsychiatric and cancer diseases. Friedman's seminal discovery makes a paradigm shift in our knowledge of adipose tissue biology - from merely a fat storage and metabolizer to a major endocrine and paracrine organ of the human body, producing more than 600 signaling proteins collectively termed adipokines. Leptin thus became the fundament in the obesity research and related diseases.

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**Key words:** adipose tissue, adipokines, adipobiology, Jeffrey M. Friedman, leptin, disease, therapy

*The new paradigm should always  
be better, not just different.*  
**Thomas Kuhn**, *The Structure  
of Scientific Revolutions*, 1962

More than 20 centuries ago in his poem *De rerum natura* (On the Nature of Things, or On the Nature of the Universe) Titus Lucretius (c. 99 BC – c. 55 BC), a Roman poet and philosopher, described “Universum” as operating according to physical principles, guided by *fortuna*, “chance”. The latter supposedly managed a scenario of the Big Bang that explored about 14 billion years ago with a superhot universal dance of quarks, protons, neutrons. And leptons (light particles; Greek *leptos* – thin, slim), the dance leading to the formation of all galaxies composed of stars, planets, comets, meteors, asteroids, quasars, black holes, all “rotating as one.” And “the universe suddenly became boundless as hope” as in Jorge Luis Borges' *Library of Babel*.

**Four** billion years ago Cell's Big Bang has occurred - the birth of a single cell compartmentalized by phospholipid bilayer. *Natura non facit saltus* (Nature does not make leaps) – a saying attributed to Carl Linnaeus (1707 – 1778),

Swedish botanist and physician, “father of modern taxonomy” who introduced the system of naming organisms in his book *Systema Naturae*, the first edition being published in 1735.

Gradually, about 800 million years ago, the first multicellular organisms arose, fish, reptiles, birds, monkeys, man - *Homo habilis* (the skilled person) left Africa, migrated to Europe, became *Homo sapiens recens*.

Forty-fifty thousand years ago occurs Brain's Big Bang - increases gray matter of the brain, appear smart genes that help people to remember, to think logically and abstractly, to understand other people - his thinking, feelings, behavior. “We are not thinking beings, we are emotional creatures who think” - summed up in 1994 Antonio Damazio in his book *Descartes' Error* and by Danilo Mainardi in his text *The Cultural Animal*.

### Fat's Big Bang: the discovery of leptin

The descriptions of *ob/ob* (obese) mice in 1950 and *db/db* (diabetic) mice in 1966 have established that the *ob/ob* mouse lacked a circulating factor to which the *db/db* mouse was resistant. It was Douglas Coleman who presented the hypothesis of “satiety hormone” in the 1970s when working in Jackson Laboratory, Bar Harbor, Maine, the largest reserve of obese and diabetic mice (see 4). Hundreds of them were transferred to the Laboratory of Jeffrey Friedman at Rockefeller University. For their work leading to the discovery of leptin, an adipocyte-secreted hormone, Jeffrey Friedman and Douglas Coleman received the 2009 Shaw Prize in Life Science and Medicine, known as Nobel Prize of the Far East. And the Albert Lasker Prize, a Nobel Prize of America.

Jeffrey M. Friedman was born in Orlando, Florida, USA on July 20, 1954, and received his MD at the age of 22. “As a doctor, you're trained to absorb the facts you're given and accept them. Science is almost the opposite. It's a frontier of discovery that's always moving. And I decided I wanted to do research” - says Friedman. He started his affiliation with the Rockefeller University in 1980, where he was awarded a PhD degree in 1986. His research curiosity led him to pursue a field related to the *ob* gene in mice, a search that took 8 years. And in 1994 resulting in the discovery of a very talented cytokine/hormone secreted by adipocytes, now known as leptin (1) (Box 1).

Leptin functions as an afferent signal in a negative feedback loop that regulates food intake and energy homeostasis to maintain control of adipose tissue mass. From the adipocytes leptin is exported into the blood circulation, enters the brain and stimulates anorexogenic and inhibits orexogenic neurons (Table 1), the arcuate nucleus, paraventricular nucleus, dorsomedial nucleus, ventromedial nucleus and lateral hypothalamic area being the brain leptin sensitive hub. The net effect of these actions is satiety, stop eating. When mice leptin gene is deleted, knockout mice (*ob/ob* mice), or the gene for leptin receptor (*db/*

*db* mice) is deleted, the mice eat without filling of satiety, thus becoming obese and diabetic respectively (1-7).

Since the Fat's Big Bang explored officially on 1 December 1994, onwards until December 5, 2015 leptin appeared in 29 032 scientific articles (according to PubMed, National Library of Medicine, USA) and participated in more than 50 international symposia, including four International Symposia on Adipobiology and Adipopharmacology (ISAA), the 4th ISAA being held on 28 - 31 October 2015 in Bucharest, Romania (see selected abstracts in this volume of *Adipobiology*). The 5<sup>th</sup> ISAA will be held in Mexico City, Mexico in 2018 organized by Marcia Hiriart, Head, Instituto de Fisiologia Celular, Universidad Nacional Autonoma de Mexico, Mexico D.F., Mexico.

The discovery of leptin shifts the adipose tissue paradigm from merely a fat storage, the tissue is now known as a major endocrine and paracrine organ of the human body, producing more than 600 signaling proteins (adipokines) (8). Bulgarian and Italian scientists also actively participate in the action of Fat's Big Bang conceptualizing two new fields of research designated adipobiology and adipopharmacology (9, 10; Box 2).

Onward, it is demonstrated that adipose tissue is able to send and receive different types of protein and non-protein signals, thus communicating with many organs in the body. And, in effect, contributing to the control of lipid and glucose metabolism, inflammation, immunity, reproduction, hemostasis, vascular smooth muscle contraction-relaxation, learning, memory, emotions among many other biological functions. Thus in the last 21 years, that is, the time after Friedman's discovery of leptin, the adipose tissue horizon rises to take center stage in so many diseases that it leaves most scientists and medical doctors astonished. Associated with leptin discovery/ “rediscovery” of adipose tissue, the studies of cardiometabolic, neuropsychiatric, liver and lung diseases have increasingly emerged (11-42; Table 2). For diabetes-Alzheimer link, see Aloe *et al* in this volume of *Adipobiology*.

In a 2012 interview with Jeffrey Friedman (7), to the questions “More recently, you have been studying how leptin affects neuronal plasticity. Can you tell us about this? Your lab is working on several projects. What are you most excited about at the moment?”, Friedman replies: “Leptin changes the types and patterns of connections among neurons... One of the main projects in the lab is delineating the neural circuitry that regulates food intake and body weight. I think that understanding the molecular and cellular basis of making behavioural decisions is going to be a very important and exciting area for future research. To develop drugs that normalize weight will be a more difficult task moving forward, but I am optimistic that safe molecules that reduce weight enough to improve diabetes, hypertension and other complications associated with obesity will be developed.”

**Box 1.** Curriculum Vitae of Leptin

<b>Name:</b> Leptin, 16 kD, 167 amino acids
<b>Gene:</b> Obese ( <i>ob</i> , <i>Lep</i> ), Chromosome 7q31.3
<b>Receptors:</b> Ob-R (LEP-R, CD295), <i>db</i> gene splicing products LEP-R <sub>L</sub> (LEP-Rb, long form of the leptin receptor, containing a 302-amino acid cytoplasmic domain) LEP-R <sub>S</sub> (LEP-Ra, c, d, e, and f, OB-R short forms, containing a 34-amino acid cytoplasmic domain) Megalin (gp600/LRP2)
<b>Born officially:</b> 1 December 1994 in <i>Nature</i> 1994; 372: 425-432.
<b>Official birth place:</b> Laboratory of Molecular Genetics, The Rockefeller University York Avenue, between 63 <sup>rd</sup> and 68 <sup>th</sup> Streets, the Upper East Side of Manhattan, New York City, NY, USA
<b>Natural birth place:</b> adipocytes
<b>Other birth places:</b> gastric epithelial cells, cardiomyocytes, interstitial lung perialveolar fibroblasts, ovaries, bone marrow, placenta, lymphocytes, mast cells, macrophages, liver perisinusoidal lipid storage cells (Ito cells, hepatic stellate cells)...
<b>Functions:</b> food intake, energy balance, cell growth, reproduction, immunity, hemostasis, angiogenesis, collagen fibrogenesis, osteogenesis, neuroprotection, neuronal plasticity, mood...

**Box 2.** Lingua Adipobiologica – definition of terms

<b>Adipobiology</b> – study of molecular and cell biology of adipose tissue in health and disease
<b>Adipokines</b> – adipose cells-secreted signaling proteins
<b>Adipokinome</b> – proteome of adipokines
<b>Adipopharmacology</b> – adipose tissue-targeted studies for drug discovery
<b>Adipocrinology</b> - a component of endocrinology - <b>Adipoendocrinology</b> - <b>Adipoparacrinology</b>
<b>Neuroadipocrinology</b> – a component of neuroendocrinology
<b>Adipimmunology</b> – study of the role of adipose tissue-associated immune cells
<b>Adipotoxicology</b> – study the accumulation and metabolism of xenobiotics in adipose tissue
<b>Tunica adiposa</b> – the outermost coat of the wall of blood vessels
<b>Homo obesus</b> – man obese
<b>Homo diabetes</b> – man with diabetes and obesity
<b>Triactome</b> – neuro-immune-adipose interactions

**Table 1.** Examples of neuromediators in leptin signaling in the brain, controlling food intake\*

Anorexigenic pathway ↑	Orexigenic pathway ↓
Proopiomelanocortins	Neuropeptide tyrosine (NPY)
Melanocortin 4	<i>Agouti</i> -related protein
α-melanocyte stimulating hormone	Endocannabinoids
Brain-derived neurotrophic factor	

\* For brain dopaminergic circuit in the motivational behavior in “how do we decide to eat or do not eat?”, see (3, 4, 7). Also (6) for amylin-leptin interaction in controlling food intake.

**Table 2.** A selected list of leptin-related diseases and symptoms

Obesity, Anorexia nervosa, Bulimia nervosa
Atherosclerosis, Hypertension, Metabolic syndrome, Type 2 diabetes mellitus
Obstructive sleep apnea, Polycystic ovary syndrome
Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Liver cirrhosis
Osteoporosis, Rheumatoid arthritis, Cancers, Cachexia
Bronchial asthma, Chronic obstructive pulmonary disease
Alzheimer’s disease, Depression, Schizophrenia
Leptin deficiency syndromes
Congenital generalized, acquired generalized lipodystrophy*
Hypothalamic amenorrhea, delayed onset of puberty
Immune abnormalities leading to an increased susceptibility to infectious disease
Type 1 diabetes mellitus

\*On 24 February, 2014, the USA Food and Drug Administration approved Myalept (metreleptin for injection) as replacement therapy to treat the complications of leptin deficiency in patients with these lipodystrophies (see 4).

## Post scriptum

Dear Dr Chaldakov and Colleagues,

Thanks to you for what I believe to be the only birthday party celebrating the anniversary of the cloning of the *ob* gene. I had forgotten entirely that this milestone was about to pass and am grateful to you all for bringing this to my attention. I will now have to organize a party here as well. It is hard to believe so much time has passed. I hope you have a productive and illuminating meeting and wish you the joy of discovery.

Regards,  
Jeffrey Friedman  
Professor, Rockefeller University  
Investigator, HHMI

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