NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION
NCBI Coffee Break

27 October 2000

Article reference: CB16.271000
Coffee Break archives

nature REVIEWS Story contributed by Jane Alfred, Nature Reviews Genetics

The mouse that eats less but gains weight

Mc3r+/+ *Mc3r*-/-

Mice that possess a defective melanocortin 3-receptor (*Mc3r*$^{-/-}$) are unable to respond to the neuropeptide α-MSH. Weight gain in *Mc3r*$^{-/-}$ mice is apparent after 26 weeks of age. Littermates that express functional Mc3r do not exhibit increased adiposity, even though the level of food intake is equivalent between the two groups.

Image courtesy of the Department of Obesity Research, Merck & Co., Inc. © Merck & Co., Inc. (2000).

Obesity contributes to poor public health in many western populations, underlying illnesses that range from cardiovascular disease to hypertension and stroke. Over the past years, research into animal models of obesity has teased apart some of the endocrinological pathways that mammals have evolved to regulate the body's fat content in times of feast and famine. Now, new insight into the subtle workings of these pathways comes from a paper in the September issue of *Nature Genetics* , which reports the phenotypic effects of inactivating the gene that encodes the mouse melanocortin receptor 3 (Mc3r).

Mc3r functions in a feedback loop that lies downstream of leptin, an adipocyte-derived hormone that circulates in the blood in proportion to body adiposity. In the brain, leptin elicits neuropeptide responses that stabilize the body's fat content by decreasing food intake and increasing energy expenditure. One such neuropeptide is alpha-melanocyte stimulating hormone (alpha-Msh), which acts on several melanocortin receptors, including Mc3r and Mc4r. Until now, the relative importance of each receptor in this feedback loop has been unknown, but the study by Chen *et al.* shows that inactivating Mc3r has different effects on food intake and adiposity to inactivating Mc4r.

Mc3r-/- mice appear to grow normally up to 26 weeks of age but, although at this age they are not overtly obese, their fat mass is almost double that of wild type and heterozygote littermates. This is because their increased fat mass is initially obscured by a compensatory decrease in lean muscle mass. It is only after 26 weeks that their increased weight gain becomes more obvious (see picture). Unexpectedly, this increased adiposity is not caused by increased food intake. Instead, *Mc3r-/-* mice gain more fat per calorie of food consumed, apparently at the expense of their lean body mass. This so-called increased feed efficiency means that the mutant mice store more fat despite eating less than normal mice do, and they become obese if fed a high-fat diet. The mechanism behind these responses is unclear because the *Mc3r-/-* mice have normal metabolic rates, body temperatures and thyroid function. However, they are less active than wild-type mice, which might contribute to their tendency to obesity, and they also show a transient reduction in neuropeptide Y levels. As this hypothalamic neuropeptide has been implicated in feeding-control mechanisms, Chen *et al.* suggest that its reduction in *Mc3r-/-* mice may contribute to their reduced food intake.

So how do *Mc3r-/-* mice differ from *Mc4r-/-* mice, and what does this tell us about the different functions of the two receptors in the control of food intake and energy expenditure? *Mc4r-/-* mice eat more than normal mice and are obese. They also have altered metabolic rates and a normal lean body mass. When Chen *et al.* treated *Mc3r-/-* mice with a non-selective melanocortin agonist, it reduced food consumption in both mutant and normal mice to a similar degree, indicating that alpha-Msh probably inhibits food intake by acting through Mc4r. Further evidence supporting distinct functions for these two receptors came when Chen and colleagues crossed the two knockout mice to produce double homozygote mutants, which were more obese than mice lacking just Mc4r. In an accompanying News and Views article, David Cummings and Michael Schwartz speculate that this phenotype occurs because the double mutants eat

Live PubMed searches

|| Melanocortin receptor 3 || The role of melanocortin and leptin in obesity || REVIEWS ||

Cn3D tutorial

|| Search for proteins with tertiary structure similar to leptin || VIEW ANALYSIS ||

Further NCBI resources

|| Mc3r in OMIM || Mc4r in OMIM || Mc3r in LocusLink ||

excessively, owing to the loss of Mc4r signalling, and store consumed calories more efficiently, owing to the absence of both receptors.

These new insights into the functions of Mc3r could contribute to the development of new diagnostic and therapeutic approaches to treating obesity disorders in humans, and further research should clarify whether drugs that act through Mc3r and Mc4r could be used therapeutically to reduce food intake and its storage as fat.

NCBI

Tutorial Coffee Break

PubMed | Nucleotide | Protein | Genome | Structure | PopSet | Taxonomy | OMIM

Search Structure for leptin Go Clear

Limits | Preview/Index | History | Clipboard

About Entrez

Entrez PubMed
Overview
Help | FAQ
New/Noteworthy

PubMed Services
Journal Browser
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Cubby

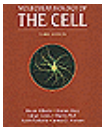
Related Resources
Order Documents
Grateful Med
Consumer Health
Clinical Alerts
ClinicalTrials.gov

Privacy Policy

To search for structures, type search terms in the textbox above, as shown, and click 'Go'. For this tutorial, note that the search database selection menu (to the immediate left of the textbox) has been set to 'Structure'. This menu allows one to search any of the databases from different locations within the Entrez system.

PubMed is the National Library of Medicine's search service that provides access to over 10 million citations in MEDLINE, PreMEDLINE, and other related databases, with links to participating online journals.

Books linked to PubMed



In collaboration with book publishers, NCBI is adapting books for the web and linking them to PubMed. The first book, Molecular Biology of the Cell by Alberts et al., is now available.

New Cubby feature!

The Cubby provides you with a Stored Search feature to store and update searches. It also allows you to customize your LinkOut display to include or exclude links to providers. See Help and FAQ for additional information.

About Entrez

Entrez Structure
Help | FAQ

Structure Research
The NCBI Structure group

MMDB
About Entrez's structure database

PDBeast
Taxonomy in MMDB

Cn3D
3D-structure viewer

VAST
Structure comparisons

VAST Search
Submit structure database searches

Research
Structure Group research projects

Display Summary Save Text Details Add to Clipboard

The search for leptin structures has resulted in one match: '1AX8'. (This is the Protein Data Bank identification number for leptin.) Click on this link below to view the summary page for this record.

1: 1AX8 PubMed, Protein, Related Structures, Taxonomy
Human Obesity Protein, Leptin
[9153]

Revised: November 2, 1999.

NCBI *MMDB* STRUCTURE SUMMARY Entrez ?

MMDB Id: 9153 PDB Id: 1AX8

This is the MMDB (Molecular Modelling DataBase) summary page for the human leptin protein (PDB Id='1AX8'). Note that the databases use different identification numbers.

Protein Chains: (single chain)
MEDLINE: PubMed
Taxonomy: Homo sapiens

PDB Authors: F.Zhang, J.M.Beals, S.L.Briggs, D.K.Clawson, J.-P.Wery & R.W.Schevitz
PDB Deposition: 31-Oct-97
PDB Class: Cytokine
PDB Title: Human Obesity Protein, Leptin

Sequence Neighbors: (single chain)
Structure Neighbors: (single chain)

For this demonstration, we are interested in viewing the 3D model of leptin superimposed with other proteins possessing similar structures. To view a list from which to select structural neighbors of leptin, click on the '**Structure Neighbors:** (single chain)' link above (identified by the arrow).

View / Save Structure NEW *Get Cn3D 3.0!*

Options:
- (•) Launch Viewer
- ( ) See File
- ( ) Save File

Viewer:
- (•) Cn3D (asn.1)
- ( ) Cn3D v1.0 (asn.1)
- ( ) Mage
- ( ) RasMol (PDB)

Complexity:
- (•) Cn3D Subset
- ( ) Virtual Bond Model
- ( ) All Atom Model
- ( ) Up to 5 Models
- ( ) Up to 10 Models
- ( ) All Models

Help MMDB, Cn3D, Viewing Options, VAST, PDB, NCBI Structure

NCBI VAST STRUCTURE NEIGHBORS Entrez ?

This page list proteins whose 3D structure is similar to leptin as determined by VAST (Vector Alignment Search Tool) analysis.

Structures similar to MMDB 9153, 1AX8

Human Obesity Protein, Leptin

View / Save Alignments NEW *Get Cn3D 3.0!*

Options:
- (•) Launch Viewer
- ( ) See File
- ( ) Save File

Viewer:
- (•) Cn3D (asn.1)
- ( ) Mage (Kinemage)
- ( ) (PDB)

Complexity:
- (•) Aligned Chains only
- ( ) All Chains
- (•) Alpha Carbons only
- ( ) All Atoms

Structure neighbors 1-12 out of 12 displayed. Page 1 of 1.

Items may be selected for 3D alignment by checking the box that is to the left of the PDB Id. 'Human Granulocyte Macrophage Colony Stimulating Factor' and 'Human IL4' have been marked for selection (see below). Click on the 'View/Save Alignments' button above to see the two selected structures aligned with leptin using the Cn3D viewer.

	PDB C D	RMSD	NRES	%Id	Description
☐	1HUW	2.1	88	7.9	Human Growth Hormone Mutant With Phe 10 Replaced By Ala, Met 14 Replaced By Trp, His 18 Replaced By Asp, His 21 Replaced By Asn, Lys 41 Replaced By Ile, Tyr 42 Replaced By His, Leu 45 Replaced By Trp, Gln 46 Replaced By Trp, Phe 54 Replaced By Pro, Arg 64 Replaced By Lys, Arg 167 Replaced Asn, Asp 171 Replaced By Ser, Glu 174 Replaced By Ser, Phe 176 Replaced By Tyr, Ile 179 Replaced By Thr (F10a, M14w,H18d,H21n,K41i,Y42h,L45w,Q46w,F54p,R64k,R167n,D171s, E174s,F176y,I179t)
☐	1CNT 1	1.5	104	9.6	Ciliary Neurotrophic Factor
☑	2GMF A	1.7	68	14.7	Human Granulocyte Macrophage Colony Stimulating Factor
☐	1BGE A	1.4	95	13.7	Granulocyte Colony-Stimulating Factor (Form Ii Rcg-Csfii)
☐	1BUY A	1.7	76	15.8	Human Erythropoietin, Nmr Minimized Average Structure
☐	1JLI	1.7	69	14.5	Human Interleukin 3 (Il-3) Mutant With Truncation At Both N- And C-Termini And 14 Residue Changes, Nmr, Minimized Average Structure
☐	1AU1 A	2.1	93	5.4	Human Interferon-Beta Crystal Structure
☐	1A7M	2.1	83	7.2	Leukaemia Inhibitory Factor Chimera (Mh35-Lif), Nmr, 20 Structures
☑	1RCB	1.6	76	13.2	Interleukin 4
☐	1IL6	2.0	88	18.2	Human Interleukin-6, Nmr, Minimized Average Structure
☐	3INK C	2.1	72	16.7	Interleukin 2 Mutant With Cys 125 Replaced By Ala (C125a)
	1HMC A	3.2	84	9.5	Human Macrophage Colony Stimulating Factor (Alpha Form, Soluble)

Analysis Coffee Break

The mouse that eats less but gains weight

Structural alignment of leptin with two cytokines using the Cn3D viewer

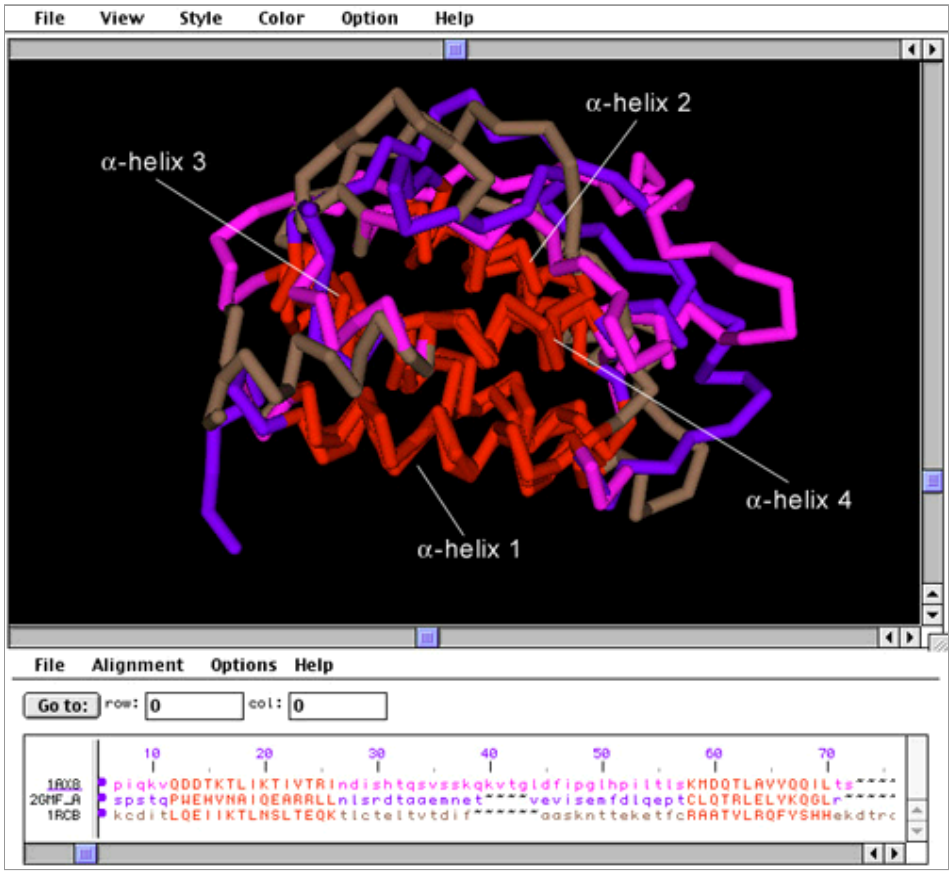


Figure 1

Figure 1 shows the 3-dimensional ribbon structure of human leptin aligned with two cytokine proteins: human IL4 and human Granulocyte Macrophage Colony Stimulating Factor (GM-CSF). The primary amino acid sequences are displayed in the lower panel and each protein is assigned a unique color. This color designation is conserved in the primary amino acid window and in the 3D structure display, making it easy to distinguish between proteins. Peptide domains that are structurally similar among the separate sequences are highlighted in red. To download this structure alignment in Cn3D format, click on the Figure 1 image or click here.

Leptin is mainly produced by white adipose tissue, although it is also found to be expressed in certain non-adipose tissues. Previous studies have shown that leptin is similar in structure to cytokines [1, 2], which is demonstrated in this Cn3D example. It is believed that leptin plays an important role in mediating metabolism and indicating to the body the current level of energy stores. Leptin levels in the bloodstream rise within hours after eating, and fall within hours after the initiation of fasting [3-5]. Mutation of the gene that codes for leptin, *ob,* leads to the development of juevenile obesity in mice [6-8].

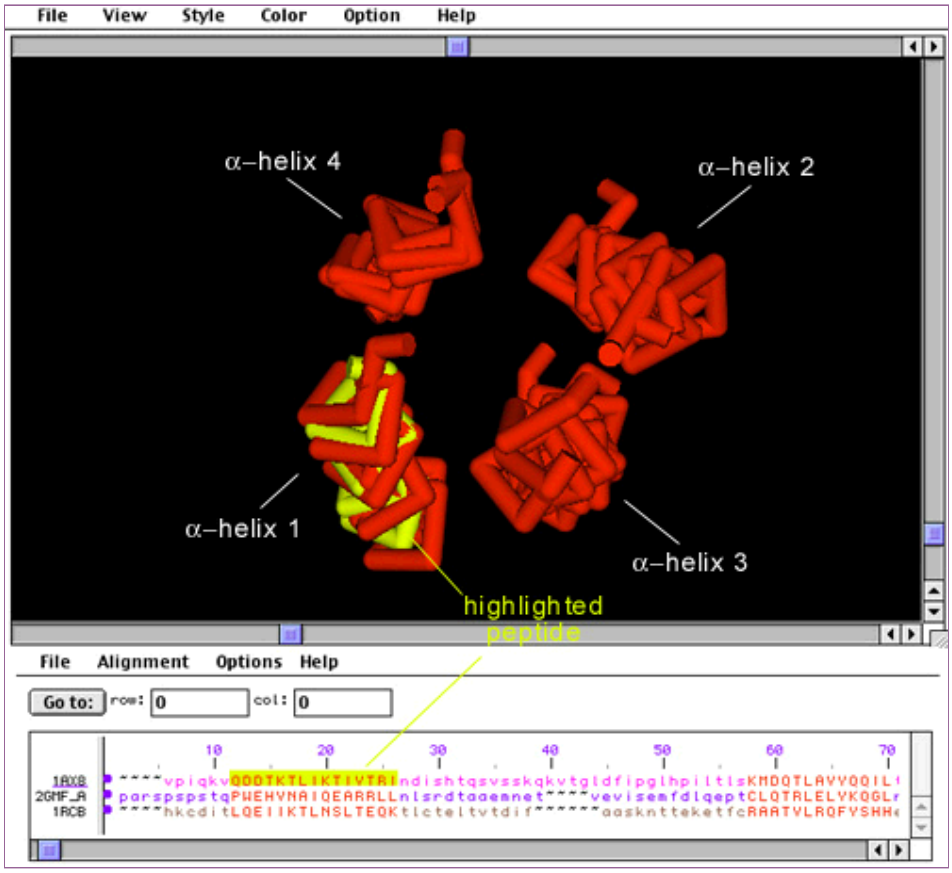


Figure 2

Figure 2 demonstrates the ability of Cn3D to display only the aligned regions of the proteins. To acheive this effect, navigate through the "View" menu and select "Drawing Settings..." From the "Drawing Settings..." menu, select the "Show/Hide" tab and deselect the "unaligned" option by clicking on the box next to it. Finally, click on the "Apply!" button to update the display with the desired settings. In addition to this feature, Figure 2 also demonstrates the ability to highlight specific amino acids through cursor selection in the primary sequence window. To download this structure alignment in Cn3D format, click on the Figure 2 image or click here.

Human leptin was used to search the MMDB/PDB database using the VAST program [9] with standard parameters. Sequences included in the multiple alignment of the leptin protein were selected from the output of the first iteration. The multiple sequence alignment was constructed using Cn3D 3.0 [10].

[1] Madej T, Boguski MS, Bryant SH (1995) Threading analysis suggests that the obese gene product may be a helical cytokine. *FEBS Lett* 1, 13-18.

[2] Zhang F, et al. (1997) Crystal structure of the obese protein leptin-E100. *Nature* 6629, 206-209.

[3] Saladin R, et al. (1995) Transient increase in obese gene expression after food intake or insulin administration. *Nature* 377, 527-529.

[4] Harris RB, et al. (1996) Early and late stimulation of ob mRNA expression in meal-fed and overfed rats. *J Clin Invest* 97, 2020-2026.

[5] Kolaczynski JW, et al. (1996) Responses of leptin to short-term fasting and refeeding in humans: a link with ketogenesis but not ketones themselves.*Diabetes* 45, 1511-1515.

[6] Zhang Y, et al. (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* 372, 425-432.

[7] Pelleymounter M, et al. (1995) Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 269, 540-543.

[8] Halaas RBS, et al. (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 269, 543-546.

[9] Madej T, et al. (1995) Threading a database of protein cores. *Proteins* 23, 356-369.

[10] Wang Y, et al. (2000) Cn3D: sequence and structure views for Entrez. *Trends Biochem Sci* 25, 300-302.