Leptin and the control of body weight

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Summary

Mutations in the mouse *ob* and *db* genes result in obesity and diabetes in a syndrome resembling morbid human obesity (1,2). Coleman predicted that the *ob* gene encoded a novel hormone and that the *db* gene encoded its receptor (1). Recent data from this laboratory are consistent with this hypothesis. The *ob* gene was identified by positional cloning and found to encode a 4.5 kB RNA expressed exclusively in adipocytes (3-6). The *ob* gene product, known as leptin, circulates as a 16 kilodalton protein in mouse and human plasma but is undetectable in plasma from C57BL/6J *ob/ob* mice (7). Plasma levels of this protein are increased in diabetic (*db*) mice, a mutant thought to be resistant to the effects of *ob* (7). The levels of leptin are also increased in several other genetic and environmentally induced forms of rodent obesity including mice with lesions in the hypothalamus (6,8).

Daily intraperitoneal injections of recombinant mouse leptin reduced body weight of *ob/ob* mice by 30% at two weeks and by 40% after four weeks but had no effect on *db/db* mice (7). The protein reduced food intake and increased energy expenditure in *ob/ob* mice. In wild type mice, twice daily injections with the mouse protein resulted in a sustained 12% weight loss, decreased food intake and a reduction of body fat from 12.2 to 0.7%. Recombinant human leptin reduced body weight with equivalent potency to mouse leptin when injected into *ob* mice (7). In humans, the plasma level of leptin correlated with body mass index (BMI) and % body fat (8). However at a given BMI, there was significant variability in the leptin level. Weight loss in humans was associated with a decrease in plasma leptin concentration in all cases (8). These data suggest that leptin serves an endocrine function to regulate body fat stores. In most instances, obesity is associated with an apparent decrease in sensitivity to endogenous leptin resulting in a compensatory increase in adipocyte mass. However, in a subset of cases human obesity appears to result from subnormal leptin secretion (8).

The complete insensitivity of *db* mice to leptin and the identical phenotype of *ob* and *db* mice suggested that the *db* locus encodes the leptin receptor (1,7). The *db* gene was localized to a 300 kb interval on mouse chromosome 4 (9-11). Exon trapping and cDNA selection identified a candidate gene in this region. This candidate was found to be identical to a receptor (*ob-R*) which was functionally cloned from choroid plexus (11,12). However, because this receptor was normal in *db* mice, the possibility was raised that the *db* mutation affected an alternatively spliced form (11). The Ob-R gene was found to encode at least five alternatively spliced forms. One of the splice variants is expressed at a high level in the hypothalamus and at a lower level in other tissues. This transcript is mutant in C57BL/Ks *db/db* mice (11). The mutation is the result of abnormal splicing leading to a 106 bp insertion into the 3' end of its RNA. The mutant protein is missing the cytoplasmic region and is likely to be defective in signal transduction. A nonsense mutation in fa^{fa} rats, a rat equivalent of *db*, leads to premature termination NH2-terminal of the transmembrane domain (unpublished data). These data suggest that the weight-reducing effects of leptin are mediated by signal transduction through a receptor in the hypothalamus and elsewhere.

Further studies have revealed that Stat3 (involved in signal transduction) is activated specifically in the hypothalamus within 15 minutes of a single injection of leptin in *ob* and wild type but not in *db* mice (unpublished data). In situ hybridization indicates that *ob-Rb* is expressed in three different hypothalamic regions: the arcuate, ventromedial and lateral hypothalamic nuclei. Lesions of each of these nuclei affects body weight regulation. Further characterization of the

neurons in these brain regions and their connections will have important implications for our understanding of leptin's actions and the molecular mechanisms regulating body weight.

References

1. Coleman DL. Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. Diabetologia 1978;14:141-8.
2. Friedman JM, Leibel RL. Tackling a weighty problem. Cell 1992;69:217-20.
3. Friedman JM, Leibel RL, Siegel DA, Walsh J, Bahary N. Molecular mapping of the mouse ob gene. Genomics 1991;11:1054-62.
4. Bahary N, Siegel DA, Walsh J, Zhang Y, Leopold L, Leibel R, Proenca P, Friedman JM. Microdissection of proximal mouse chromosome 6: identification of RFLPs tightly linked to the *ob* mutation. Mammalian Genome 1993;4:511-5.
5. Zhang Y, Proenca P, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425-32.
6. Maffei M, Fei H, Lee GW, Dani C, Leroy P, Zhang Y, Proenca R, Negrel R, Ailhaud G, Friedman JM. Increased expression in adipocytes of *ob* RNA in mice with lesions of the hypothalamus and with mutations at the *db* locus. Proc Nat Acad Sci USA 1995;92:6957-60.
7. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543-6.
8. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, Feiu H, Kim S, Lallone R, Ranganathan S, Kern PA, Friedman JM. Leptin levels in human and rodent: measurement of plasma leptin and *ob* RNA in obese and weight-reduced subjects. Nature Medicine 1995;1:1155-61.
9. Bahary N, Leibel RL, Joseph L, Friedman JM. Molecular mapping of the mouse *db* mutation. Proc Nat Acad Sci USA 1990;87:8642-6.
10. Bahary N, McGraw DE, Shilling R, Friedman JM. Microdissection and microcloning of mid-chromosome 4: genetic mapping of 41 microdissection clones. Genomics 1993;16:113-22.
11. Lee GH, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI, Friedman JM. Abnormal splicing of the leptin receptor in diabetic mice. Nature 1996;379:632-5.
12. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J, Muir C, Sanker S, Moriarty A, Moore KJ, Smutko JS, Mays GG, Woolf EA, Monroe CA, Tepper RI. Identification and expression cloning of a leptin receptor, *OB-R*. Cell 1995;83:1263-71.