Progress in Understanding the Genetics of Obesity

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ABSTRACT  Progress in understanding the genetics of obesity has moved rapidly in the past few years. The genes for all of the single gene defects that produce obesity in experimental animals have now been cloned. The new insights from these models are one spur for the examination of possible links to human obesity. In thinking about the biology of obesity produced by single gene defects, it must be kept in mind that adrenalectomy can prevent the phenotypic expression in all of the single gene models of obesity. Thus, nongenetic components can play a major role in regulating even single gene models of obesity. Transgenic mice have also expanded our understanding of obesity. Transgenic models that both increase and decrease body fat have been published. Of particular interest from the perspective of the physiological control of obesity is the destruction of the uncoupling protein in brown adipose tissue, which is followed by hyperphagia and obesity, suggesting that the sympathetic nervous system is involved in both modulation of food intake and energy storage. Gene mapping using quantitative trait loci and studies of candidate genes have been applied to experimental models of animals with differing susceptibilities to dietary fat and have been applied to the human genome in more detail. J. Nutr. 127: 940S–942S, 1997.

KEY WORDS: • obesity • gene defects • food intake

The fields of genetics and molecular biology in relation to obesity have expanded rapidly (Bouchard and Perusse 1996). In less than 4 y, all of the genes have been cloned for the forms of obesity produced by single gene defects (Bultman et al. 1992; Chen et al. 1996; Kley et al. 1996; Lee et al. 1996; Naggert et al. 1995; Tartaglia et al. 1995; Zhang et al. 1994). In addition, the use of transgenic mice, molecular biological techniques, quantitative trait loci, gene mapping, chromosomal scanning and the study of candidate genes has been widespread. This article will highlight a few issues in each of these areas.

SINGLE GENE DEFECTS IN OBESITY

Table 1 is a summary of the single gene defects in rodent models of obesity and our understanding of their molecular basis. The two most widely studied models, the obese mouse and diabetes mouse, were found to have a defect in the production of a circulating factor (Zhang et al. 1994) and in its receptor (Chen et al. 1996; Lee et al. 1996; Tartaglia et al. 1995), as had been suggested by Coleman (1978) in his prescient parabiosis studies. The identification of the gene defect that produced the ob/ob mouse was published by Zhang et al. (1994). This genetic defect resulted from a single base substitution producing a stop codon at amino acid 105 in a peptide that is normally 167 amino acids in length. This peptide has been named leptin from the Greek leptos, meaning thin. Leptin is produced entirely in adipose tissue; when leptin is injected into the ob/ob mouse, which is deficient in this peptide, it will reduce food intake, reduce body weight, increase energy expenditure and repair reproductive function (Campfield et al. 1995; Chehab et al. 1996; Halaas et al. 1995, Pelleymounter et al. 1995). When injected into the db/db mouse, which has a defect in the leptin receptor, there is no loss of weight or decrease in food intake (Campfield et al. 1995, Halaas et al. 1995, Pelleymounter et al. 1995). Leptin has also been shown to reduce the expression of neuropeptide Y (NPY) in the hypothalamus (Stephens et al. 1995).

One interpretation for the role of leptin is as a hypophagic hormone. An alternative hypothesis is related to the infertility of ob/ob mice (Bray 1996a). Female ob/ob mice are completely infertile, although their reproductive system can be induced to conceive and carry pups to parturition when appropriate hormonal support is provided. A signal to the brain about the adequacy of fat stores for reproduction has been suggested by the concept of a critical fat mass at the time when ovulation is initiated in females. For survival of the species, it is critical that pregnancy not occur when nutrient stores are insufficient. The direct relation of leptin concentrations to the quantity of adipose tissue in rodents and humans (Bray 1996a) suggests that one important function of leptin is to serve as the signal from adipose tissue to the brain about the adequacy of nutrient stores for reproduction (Bray 1996b). The hyperphagia observed in leptin-deficient ob/ob mice may in part reflect their effort to increase fat stores to “turn on” their reproductive system. If such an interpretation is correct, then one potential consequence of excess amounts of leptin in very obese women might be disruption of the reproductive system, a phenomenon that is well known in many obese people.

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The discovery of leptin has generated great excitement. It has served as a major piece of evidence that obesity is a serious subject and can be produced by genetic and molecular abnormalities. It should be kept in mind, however, that the effects of leptin are critically dependent upon adrenal glucocorticoids (Bray et al. 1990, Saito and Bray 1984). Adrenalectomy in the ob/ob mouse, the db/db mouse and all of the other animals listed in Table 1 will stop the development of obesity. Moreover, this steroid is essential for the development of insulin resistance, for the alterations in muscle function and bone growth, and for the hyperphagia that these animals manifest. The finding that a glucocorticoid produced by the adrenal can modify the phenotypic expression that results from leptin deficiency should provide useful clues to the pharmaceutical industry about potential ways of approaching this problem.

TRANSGENIC MODELS OF OBESITY

Table 2 lists several transgenic and knockout mouse models that have been shown to modify body fat (Katz et al. 1995, Kopecky et al. 1995, Levak-Frank et al. 1995, Lowell et al. 1993, Richard et al. 1993, Shepherd et al. 1993, Stenzel-Poore et al. 1992, Susulic et al. 1995).

Each of these transgenic animals provides some insight into important systems that are physiologically perceived to be involved in the regulation of food intake, fat stores and energy expenditure.

As noted above, glucocorticoids significantly block the effect of leptin deficiency as well as the defect in the leptin receptor. The finding that an anti-sense gene for the glucocorticoid receptor in the brain would lead to slowly developing obesity was of interest because this anti-sense transgene to the glucocorticoid receptor should knock out the receptor (Richard et al. 1993) and lead to overexpression of corticotropin-releasing hormone and ACTH with marked stimulation of the pituitary adrenal axis. Whether this increased food intake is simply a function of the elevated glucocorticoid secretion or whether it is in part related to the enhanced processing of pro-opiomelanocortin to produce ACTH and along with it melanocyte-stimulating hormone is unclear (Stenzel-Poore et al. 1992). The knockout of the uncoupling protein in brown adipose tissue is a second model of particular interest (Lowell et al. 1993). In males, this knockout transgene increases food intake and decreases thermic response to diet. This suggests that the ability to enhance heat production by food may play a role in the chronic setting of food intake and energy storage levels. This finding may be part of a reciprocal response of food intake and the sympathetic nervous system, which has been shown in a variety of experimental settings (Bray 1991).

QUANTITATIVE TRAIT LOCUS EVALUATION OF GENETIC SITES FOR OBESITY

Several laboratories have made substantial progress in exploring the relationship of chromosomal locations involved in the development of obesity in animals that become obese eating a high fat diet. The two major contributors have been West and his colleagues (1994) and Warden et al. (1995). One mouse strain (AKR) readily becomes fat eating a high fat diet, and a second (SWR) does not. Both laboratories used animals that were crosses to examine the relationship of the segregation of phenotypic traits in their crosses to a variety of microsatellite chromosomal markers for fatness in mice eating a high fat diet. Table 3 summarizes the current status of the findings from these two laboratories.

In this table, three chromosomal locations seem particularly interesting, because they occur in the models explored both by Fisler and her colleagues (Warden et al. 1995) and by West and his associates (1994). These are chromosomes 7, 12 and 15. In addition to the rapidly advancing work from these laboratories, several other investigators have reported chromosomal locations

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<table>
<thead>
<tr>
<th>Animal model</th>
<th>Chromosome</th>
<th>Gene defect</th>
<th>Gene product</th>
<th>Reproductive status</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant inheritance</td>
<td>2</td>
<td>Agouti signaling protein overexpressed</td>
<td>Asp (133 amino acids)</td>
<td>Impaired</td>
<td>Competes with melanocyte-stimulating hormone for receptors</td>
</tr>
<tr>
<td>Yellow Mouse (A')</td>
<td>2</td>
<td>Stop codon 105 produces truncated leptin</td>
<td>Leptin (167 amino acids)</td>
<td>Infertile</td>
<td>Leptin signal from fat to brain and other organs</td>
</tr>
<tr>
<td>Recessive inheritance</td>
<td>4</td>
<td>Splicing defect</td>
<td>Leptin receptor (505 amino acids)</td>
<td>Infertile</td>
<td>Impaired leptin receptor</td>
</tr>
<tr>
<td>Diabetes mouse (db/db)</td>
<td>4</td>
<td>Insert</td>
<td>Phosphatase (?)</td>
<td>Impaired</td>
<td>Phosphatase not cleaved</td>
</tr>
<tr>
<td>Tub mouse</td>
<td>7</td>
<td>Insert</td>
<td>Carboxypeptidase E</td>
<td>Impaired</td>
<td>Pro-peptides not cleaved</td>
</tr>
<tr>
<td>Fat mouse</td>
<td>8</td>
<td>Insert</td>
<td>Leptin receptor (505 amino acids)</td>
<td>Infertile</td>
<td>Impaired leptin receptor</td>
</tr>
</tbody>
</table>

**Table 1**

**Single gene animal models of obesity**

**Table 2**

**Transgenic models that alter body fat**

- Models that increase body fat
  1. Reduction in brain glucocorticoid receptor by antisense mRNA (Richard et al. 1993)
  2. Overexpression of corticotropin-releasing hormone (Stenzel-Poore et al. 1992)
  4. Knockout of β-3 receptor (Susulic et al. 1995)
  5. Overexpression of GLUT-4 in fat (Shepherd et al. 1993)

- Models that decrease body fat
  1. Knockout of the glut-4 gene (Katz et al. 1995)
  2. Overexpression of lipoprotein lipase (LPL) in muscle and cardiac tissue (Levak-Frank et al. 1995)
  3. Overexpression of UCP in white adipose tissue and brown adipose tissue (Kopecky et al. 1995)
  4. Overexpression of the phosphoenol pyruvate carboxykinase (PECPK) gene
STUDIES OF GENETICS IN HUMAN OBESITY

It has been clear for more than 50 y that both familial and nonfamilial factors played a role in the development of human obesity (Davenport 1923) and that a genetic basis was responsible for much of the familial components. Work in this field gathered steam rapidly from the mid 1980s onward as identical twins became the subject of work in several laboratories (Bouchard et al. 1988, Stunkard et al. 1990). In most of the studies with identical twins, the heritability has been reported to be in the range of 50–90%. Studies from nuclear families and adoption studies, on the other hand, have shown heritabilities in the range of 10–50%. In a recent paper, Vogler et al. (1995) reviewed the literature related to heritability of obesity and placed the figure for heritability at 34 ± 3%, using studies of nuclear families, adoption, twins, and a combination of all of these. The question of whether there are major genes and the relationship of potential chromosomal and candidate genes to the development of human obesity have been summarized recently by Bouchard and Perusse (1996) and will be reviewed in the next article (Bouchard and Tremblay 1997).

LITERATURE CITED


