ENDOGENOUS FACTORS OF HUMAN OBESITY

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Abstract: The cause of obesity is well recognised to be multifactorial, encompassing genetics, nutrition, and physical activity. Any attempt to link obesity to a single cause or a particular food without consideration of the complexity, is inherently simplistic. Although the major factors that contribute to the increased prevalence of obesity are inappropriate dietary intake and low physical activity, it is clear that endogenous factors influence such effects of this modern environment. Both exogenous and endogenous factors are involved in the onset and progression of weight gain. This review paper identifies endogenous factors of human obesity: genetic factors, endocrine factors, and congenital factors. The review discusses the significance of each of these factors, and briefly reviews prior research in each area.

1. GENETIC FACTORS

The research interest has been focused on the genetics of obesity because of the high prevalence of this disease. It is likely that the genes involved in weight gain increase the susceptibility of an individual to the development of obesity when exposed to environmental conditions. For example, the Pima Indians in the Arizona appear to have a genetic predisposition to develop obesity at alarmingly high rates in a modern Western environment. It is of a major interest that a genetically very similar group of Pima Indians in Mexico have very low rates of obesity and exhibit none of the comorbidities and alterations in metabolism that are seen in the Arizona Pimas. The Mexican Pimas live in relatively underdeveloped conditions, consume a low-fat diet and have to undertake moderate to high levels of physical activity to carry out the tasks of daily living.

In most humans, body fatness is a continuous, quantitative trait that reflects the interactions of development and environment with genotype. Studies in twins, adopted, and families indicate that as much as 80 percent of the variance in the body-mass index is attributable to genetic factors. Twin, adoption, and family studies have now established that an individual’s risk of
obesity is increased when he or she has relatives who are obese (Comuzzie, 1998). In 30% of the cases, both parents of obese children are obese, with a range in frequency of 5-45%. It has also been estimated that 25-35% of the obese cases occur in families with normal weight parents despite the fact that the risk of becoming obese is higher if the person had obese parents. The risk of obesity is about two to three times higher for an individual with a family history of obesity and it increases with the severity of obesity. Heritability is estimated to be as high as 30 to 40 percent for factors such as adipose-tissue distribution (the ratio of upper-body fat to lower body fat), physical activity, resting metabolic rate, changes in energy expenditure in response to overeating, certain aspects of eating behaviour, food preferences, lipoprotein lipase activity, maximal insulin-stimulated glyceride synthesis, and basal rates of lipolysis.

Given the importance of energy stores to individual survival and reproductive capacity, the ability to conserve energy in the form of adipose tissue would at one time to confer a survival advantage (Rosenbaum, 1997). For this reason, humans are presumably enriched with genes that favour energy intake and storage and diminish energy expenditure. However, the combination of easy access to calorically dense foods and a sedentary lifestyle has made the metabolic consequences of these genes maladaptive (Rosenbaum, 1997). The increasing prevalence of obesity, the inverse relation between obesity and social class, and the secular trend toward increasing obesity provide clear evidence of potent environmental influences on adiposity. Although numerous environmental factors, such as television watching and low family income have been implicated, no single factor is causative. Nevertheless, the increasing prevalence of obesity clearly indicates that environmental manipulation (e.g., changes in diet and physical activity) may alter or prevent some aspects of obesity.

Thus, aside from several single-gene disorders resulting in obesity (e.g., the Prader-Willi, Bardet-Biedl, Alström, and Cohen syndromes), each of which is associated with other striking dysmorphic features, obesity is probably due in most cases to subtle alterations in interactions between genetic and environmental factors that favour the net depositions of calories of fat. Segregations analyses in which the familial transmissions of obesity were examined have provided evidence of the segregations of major genes that influence the body-mass index (accounting for 20 to 35 percent of variation). The heritability of early-onset obesity may be considerably higher than that of adult-onset obesity (Barlow et al., 1998). What is likely to be most
strongly inherited is the rank order of the amount of body fat per unit of lean body mass among persons in a given environment.

Obesity is an example of a phenotype that is not likely to be attributable to a single gene unless it is extreme (body-mass index, >60) or present in an isolated population group. Because obesity can develop only from an excess of energy intake over expenditure, the search for candidate obesity genes has focused on those that have a role in energy metabolism. Extended families, sibling pairs, and subjects within distinct ethnic or geographic populations are examined for links between obesity and molecular markers for candidate genes on the basis of metabolic factors (e.g., the \( \beta_2 \)-adrenergic receptor, the glucocorticoid receptor, and \( \text{Na}^+/{\text{K}}^+\)-ATPase), obesity syndromes in humans, (Caterson et al., 2002) and obesity genes in rodents (e.g., the genes for leptin and the leptin receptor).

Mice and rats with single-gene mutations resulting in obesity have been studied extensively in an effort to understand the physiologic and biochemical basis of the most salient aspects of their phenotype: increased food intake, reduced energy expenditure, preferential storage of calories as fat, and susceptibility to non-insulin-dependent diabetes mellitus. All the extend rodent genes in which mutations cause obesity have been cloned (Table no.1) and have counterparts in humans.

Obesity (Whitaker et al., 1997) and non-insulin-dependent diabetes mellitus have been linked to a region (chromosome 1p22-p31) that contains the leptin receptor (Yanovski et al., 2002). Although sequence variation has been reported in some exons of the leptin-receptor gene, none of these variations have yet been linked to body fat mass (Macdonald, 2002). Thus, the linkage detected in these regions is presumably due to genetic differences in regulatory elements of the genes or to other genes located nearby.

Isolated cases of obesity in humans have recently been identified that result from single-gene mutations in metabolic pathways that are abnormal in genetically obese rodents. Members of a single family have been reported to have a mutation in the leptin coding sequence, with hypoleptinemia and obesity, as in ob/ob mice (Treuth et al., 2000). Another mouse mutation (fat) is characterized by defective carboxypeptidase E, hyperproinsulinemia, infertility, hypoadrenalism, and moderate late-onset obesity (West et al., 1998). Carboxypeptidase E is an enzyme that is expressed at high levels in neuroendocrine secretory cells and that removes exposed basic C-terminal residues from a number of prohormones (including proinsulin) and proneuropeptides (including proneuropeptide Y, proopiromelanocortin, proglucagon-like peptide 1, promelanocyte-concentrating hormone, and
procholocystokinin – that is, peptides that both stimulate and inhibit energy conservation and food intake). Although no mutation in the coding sequence for carboxypeptidase E has yet been identified in humans, one person has recently been described who has a phenotype remarkably similar to that of the fat mouse and a mutation in prohormone convertase, an endoprotease that cleaves pairs of basic amino acid residues in these same prohormones just before carboxypeptidase E exerts its action (Rosenbaum, 1997). Some investigators have examined genes that may regulate responses to an obesity-promoting environment. Inbred strains of rats and mice differ widely in their susceptibility to spontaneous and diet-induced obesity. Several groups have mapped some of the relevant genes to specific regions in the rodent genome, using crosses between strains at the extremes of the phenotype of interest (e.g., high and low body fat or high and low susceptibility to obesity with a high-fat diet (Vickers et al., 2000). Some of the quantitative trait loci that have been indentified are in regions of single genes known to cause obesity syndromes (Table no.1), raising the possibility that allelic variations at these loci accounts for some portion of the heritable variation in body fat stores in rodents.

2. ENDOCRINE FACTORS

Less than 1% of obese patients have an underlying endocrine dysfunction: cortisol excess (Cushing’s syndrome), hypothyroidism, and Polycystic Ovarian syndrome (Gonzales, 2000).

CUSHING’S SYNDROME

Excess cortisol, which induces adipocyte expansion and truncal obesity, may be caused by an adrenal tumour or ectopic adrenocorticotropin hormone (ACTH) production. Additionally, excess ACTH may be produced by either a nonpituitary or a pituitary tumor (Cushing’s disease). The clinical manifestations include purple abdominal striae, a buffalo hump, moon facies, osteoporosis, and hypertension. Hirsutism, acne, facial plethora, and oligomenorrhea result from increased adrenal androgen secretion. Increased insulin resistance leading to frank diabetes mellitus, hypokalemia, or hypochloremia may also be seen.
Table 1. Mutations in obese rodents

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Gene Product</th>
<th>Rodent Chromosome</th>
<th>Human Homologue</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lep</td>
<td>ob</td>
<td>Leptin</td>
<td>6 (mouse)</td>
<td>7q31.3</td>
<td>Central effects resulting in decreased food intake and increased energy expenditure</td>
</tr>
<tr>
<td>Lepr</td>
<td>db fa</td>
<td>Leptin receptor</td>
<td>4 (mouse) 5 (rat)</td>
<td>1p32</td>
<td>Leptin signal processing, transport or clearance</td>
</tr>
<tr>
<td>Cpe</td>
<td>fat</td>
<td>Carboxypeptidase E</td>
<td>8 (mouse)</td>
<td>11p15</td>
<td>Prohormone (including neuropeptide) processing</td>
</tr>
<tr>
<td>Tub</td>
<td>tub</td>
<td>Phosphodiesterase</td>
<td>7 (mouse)</td>
<td>4q32</td>
<td>Hypothalamic cellular apoptosis</td>
</tr>
<tr>
<td>Agouti</td>
<td>Ay</td>
<td>Agouti signaling protein</td>
<td>2 (mouse)</td>
<td>20q11.2</td>
<td>Blocking of melanocortin-4 receptor</td>
</tr>
</tbody>
</table>
HYPOTHYROIDISM

Hypothyroidism seldom causes true obesity but is more often associated with edema, which usually resolves with thyroid hormone replacement. Symptoms include the non-specific and insidious onset of lethargy, depression, fatigue, constipation, cold intolerance, and muscle cramping. Menorrhagia, dry coarse skin, brittle hair, alopecia, and weight gain are also common complaints. Confirmatory tests include an elevated thyroid stimulating hormone (TSH) level and/or a low serum free thyroxine level (Breier et al., 2001).

POLYCYSTIC OVARIAN SYNDROME

Polycystic Ovarian syndrome, or Stein-Leventhal syndrome, is characterized by obesity, secondary amenorrhea, hirsutism, insulin resistance, acanthosis nigricans, and infertility. The ovaries, consisting of numerous small follicles, produce excess androgens. The basal body temperature chart and endometrial sampling confirm anovulation. An elevated luteinizing hormone: follicle-stimulating hormone ratio and a mildly elevated serum testosterone level are frequently noted. In some women, the adrenal glands play a role in hyperandrogenism, as manifested by increased dehydroepiandrosterone sulphate levels.

CONGENITAL FACTORS

Foetal life seems to be a critical period for the development of obesity. Although Barker’s work infers that low birth weight is associated with obesity, several sources of data suggest that increased rather than decreased birth weight is associated with later obesity, whereas low birth weight is associated with reduced subsequent growth and possibly leanness (Dietz et al., 1997).

The Dutch famine was a natural experiment that occurred near the end of World War II, beginning in October 1944, as retribution for subversive activities, as the Germans put it. The Germans began to restrict food for most of the population in Northern Holland; over about a 6-month period, food intake declined from 1500 kcal to 1000 kcal in January 1945, to 500 kcal per person in April 1945, until the famine ended promptly with the liberation of Holland by the allies in May 1945. This exposure to famine was thus quite defined, and caloric intake could at least be estimated.
On the basis of the timing of their intrauterine exposure to famine, a number of cohorts were constituted. The cohort exposed to famine in the last trimester was found to have a reduced prevalence of obesity at age 18 years. Because the last trimester of foetal life represents a period of adipocyte replication and rapid increases in body fat, these results suggest that reduced foetal fat deposition late in pregnancy may lead to subsequent leanness.

In contrast, an increased prevalence of obesity was observed among individuals exposed to famine in the first two trimesters of pregnancy who were examined at age 18 years. The first two trimesters of pregnancy are when the hypothalamus begins to organize. Therefore, responsiveness to caloric clue or caloric intake might well be set by the responsiveness of the hypothalamus and sympathetic nervous system to intrauterine substrate availability on the famine cohort.

A study by Whitaker et al., examined the prevalence of obesity at age 7 years among infants of mothers with gestational diabetes. Infants of mothers who required insulin had an increased prevalence of obesity, whereas there was no significant increase in obesity among 7-years-old children whose mothers had glucose intolerance or gestational diabetes by common criteria, but did not require insulin. These data suggest that either the severity of glucose intolerance or the use of insulin during pregnancy may represent the more important risk factors for subsequent adiposity.

REFERENCES