Types of Obesity: A Review

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Abstract

Whether obesity is the result of excess caloric intake or an inherent metabolic aberration has long been debated. In the laboratory animal, particularly the mouse, numerous studies suggest that obesity may be divided into two broad categories, regulatory and metabolic. Typical of the regulatory obesities are those induced by surgical or chemical destruction of certain areas of the hypothalamus with resultant hyperphagia and obesity. Metabolic obesity, on the other hand, is characterized by the fact that it is the result of an inborn error of metabolism and, when compared with regulatory obesity, stands in striking contrast to it.

While metabolic studies in the normal and obese human are still somewhat sparse, it is of interest to compare the results of these investigations with those obtained in the metabolic and regulatory obese laboratory animal. From this comparison it would appear that many obese humans exhibit metabolic characteristics similar to those seen in the genetically obese laboratory animal.

Introduction

OBESITY HAS LONG BEEN REGARDED as the result of an increased caloric intake; that is to say increased relative to those calories which are required for normal physical and metabolic expenditures. In the laboratory this may easily be demonstrated in a number of ways including the more obvious methods of simple over-feeding or restriction of physical activity or both of these combined. One of more popular methods, however, involves the destruction of certain areas of the hypothalamus which are responsible for the control of appetite. This has been accomplished either chemically by the injection of gold thioglucose or surgically by appropriate stereotoxic devices. There results in these animals a tremendously increased caloric intake with subsequent obesity.

Hereditary types of obesity have been described throughout the animal kingdom. An example would be the pig which has been selectively bred for the production of lard. Several types occur in the mouse, including the New Zealand variety, an obesity associated with a yellow coat color, and the obese-hyperglycemic syndrome. Extensive biochemical and metabolic studies have been conducted only in the obese hyperglycemic and gold thioglucose obesities of the mouse, and the characteristics exhibited by each form the basis of an interesting comparison originally made by Mayer (1). It is the purpose of this discussion to consider certain of the characteristics, to mention a number of pertinent studies which have been made in the obese human being, and to compare the results obtained in the human with those obtained in the mouse to see if any similarities exist.

Obesity in the Mouse

As the name implies, the obese hyperglycemic mouse has an elevated blood glucose concentration relative to his nonobese litter-mate control. A somewhat similar situation exists with the gold thioglucose mouse, but in this animal the hyperglycemia is not so marked. Of particular importance is the fact that when these two types of obese animals are challenged with a standard dose of insulin, the obese hyperglycemic mouse responds only minimally, indicating a relative insulin insensitivity, while the gold thioglucose animal responds in a normal manner. In support of this observation, it has been found that the obese hyperglycemic mouse has elevated levels of plasma insulin activity (2). In spite of this, the blood sugar remains markedly elevated. Unfortunately, similar data on the gold thioglucose mouse are not available.

Another difference with regard to these two kinds of obesity concerns the response of blood ketone levels to fasting. Predominantly a mixture of acetoacetic and β-hydroxybutyric acids and of acetone, these ketone bodies are normally present in relatively small concentrations in the blood. During periods of rapid fat mobilization, such as in starvation, the blood levels of these ketones rise, presumably because the liver is incapable of handling the large amount of fat with which it is presented. When the gold thioglucose mouse is fasted, the normal response, namely starvation ketosis, occurs, whereas the obese hyperglycemic mouse is resistant.

One method of measuring the rate of lipogenesis in the whole animal involves the administration of a radioactive precursor of fat and the subsequent determination of the amount of isotope which has been incorporated into the body fat store. When measured by this method using acetate-C^{14} as the substrate, the rate of lipogenesis, in the gold thioglucose as well as in the obese hyperglycemic mouse, was found to be elevated in the fed state. During periods of fast when stored body fat is being used for normal energy requirements these rates are markedly depressed, but in the obese hyperglycemic animal to a much smaller extent.

Adipose tissue, freshly harvested from normal animals and incubated in appropriate buffer medium containing albumin as a fatty acid acceptor, will release its stored triglyceride as fatty acid to that medium. A relatively large number of substances and conditions cause the rate or magnitude of this release to change. Epinephrine and fasting, for example, have both been shown to be potent stimulators of free fatty acid release under these conditions. Tissue from the gold thioglucose and obese hyperglycemic mice has been examined in this regard by Marshall and Engel (3). Adipose tissue from the gold thioglucose mouse, whether fed, fasted or when stimulated in vitro with epinephrine, behaves in a normal manner. On the other hand, tissue from the obese hyperglycemic mouse has a slightly elevated rate of free fatty acid release in the fed state, does not respond to fasting with an increased rate of release, and is less responsive to epinephrine when compared to tissue from its appropriate litter-mate control.

Thus, it seems clear that, when a number of metabolic parameters are compared, obvious differences exist between these two kinds of obesity. Indeed, Mayer has suggested that a general distinction can be made between them: the induced or regulatory obesity, in which the primary impairment involves the mechanism regulating food intake, and the hered-

itary or metabolic obesity involving an inborn error of metabolism. In the first case, habitual hyperphagia may lead to secondary metabolic abnormalities. In the second, peripheral metabolic dysfunction may in turn interfere with the proper function of the central nervous system.

An obvious and important extension of this idea involves the question as to whether or not a similar situation might exist in the human. While studies exactly similar to those just discussed have not necessarily been performed in the human, a number of experiments concerned with metabolic studies in human obesity have been reported, and certain of these are appropriate to this discussion.

Human Obesity

An impaired tolerance to glucose has long been recognized as being associated with the obese state (4–7). Ogilvie (8) has suggested that the degree of intolerance is dependent on the duration of the obesity, while Newburgh and Conn (9) have demonstrated a return to normal glucose tolerance upon weight reduction. In some cases an impaired response to orally administered glucose and a normal response to intravenously administered glucose has been reported (7). Similarly, Karam et al. (10) were unable to demonstrate any difference in the response to an intravenous glucose challenge but did, however, note a significant and sustained increase in plasma insulin levels after such a challenge in obese subjects. Such data are suggestive of a relative insulin insensitivity in the obese human not unlike that described for the obese hyperglycemic mouse. In line with this, Rabinowitz and Zierler (11) have performed a series of experiments in the normal and obese human in which forearm metabolism was investigated in the basal state and again after insulin administration. In the basal state, the obese patients exhibited an uptake of glucose slightly greater than, a release of lactic acid about the same as, and a release of fatty acids about one-half that of the control subjects. When insulin was administered, glucose uptake and lactic acid release in the obese group were enhanced, but to a much smaller extent than in the controls. Qualitatively, a similar pattern was also evident in regard to fatty acid metabolism. Of interest also in this study were the elevated levels of plasma insulin found in the obese subjects.

As previously discussed, restricted caloric intake or starvation normally results in a rise in the blood ketone levels. When placed on a low caloric, high fat diet, obese subjects have been reported to be resistant to the development of ketosis (12). On the other hand, contradictory results have more recently been obtained by other investigators using essentially the same experimental design (13). While the reason for this difference is not obvious, it is of interest to examine the data of MacKay and Sherrill (14), who demonstrated that, during a four-day fast, patients who were 12 to 25% overweight had an elevated rate of ketone body excretion, while those who were 50–240% overweight had excretion rates somewhat less than normal.

Previously thought to be metabolically sluggish tissue, adipose tissue has been shown to be a major site of fat synthesis and storage (15). The sole form in which this fat is mobilized from the adipose tissue is as free fatty acids which, upon release to the blood stream, display a rapid rate of turnover and utilization. In the fed state, during periods of fat synthesis, plasma free fatty acid levels are low. During periods of caloric restriction, when carbohydrate reserves are depleted, fat is mobilized for energy requirements and this is reflected in a rise in the plasma free fatty acids. As with adipose tissue in vitro, plasma free fatty acid levels have been found to be responsive to a wide variety of stimuli. Epinephrine, norepinephrine and growth hormone, for example, have been found to cause a rise in the plasma free fatty acids. Glucose and insulin, on the other hand, cause a decrease. It is therefore generally assumed that changes in plasma free fatty acids are a direct reflection of metabolic processes at the level of the adipose tissue cell. The effects of a number of these stimuli on plasma free fatty acids in cases of human obesity have been thoroughly examined.

In the fed state, plasma free fatty acid levels of obese subjects are similar to those of normal subjects (16). When fasted, however, certain differences become evident (16,17). First, obese subjects respond with elevated levels of plasma free fatty acids which are generally higher than those seen in nonobese subjects fasted for the same period of time. Second, if the fast is prolonged, obese subjects show no further increase in the free fatty acid concentration, while the nonobese subjects show a continued rise until there is essentially no difference between the two groups (16). It would then appear that obese subjects, while capable of mobilizing fat from their adipose tissue stores, do so at rates which are somewhat reduced when one considers their total adipose tissue mass.

Further evidence of a decreased free fatty acid mobilization in obesity has been provided by Bogdonoff (18), Gordon (19) and Berkowitz (20), all of whom have reported an impaired response of plasma free fatty acids to epinephrine. Gordon (19) has divided his obese subjects into two groups based on their response to epinephrine; one group (general obesity) in which the response of the plasma free fatty acids was about one-half that observed in the control subjects and a second group (metabolic obesity) in which a response to epinephrine was totally lacking.

In summary, human obesity appears to be associated with a decreased tolerance to glucose, increased levels of plasma insulin activity, a decreased sensitivity to exogenous insulin, resistance to starvation ketosis, and finally, altered blood levels of free fatty acids whose mobilization is nonresponsive, or minimally so, to known stimulators such as epinephrine and fasting.

Finally, the question of hereditary factors in human obesity should be briefly considered. Despite the difficulty one may have in separating genetic contributions from purely socioeconomic factors with regard to the development of obesity in a given population, there appears to be some evidence that hereditary factors do, in fact, play an important role (21,22). Whether such factors exert a direct causal effect or create a predisposition to the development of obesity remains to be determined.

While the existence of several types of obesity within the animal kingdom seems fairly well established, it is still somewhat hazardous to speculate on a similar classification in the human. It is of interest to note, however, that a number of the abnormal metabolic characteristics of the obese hyperglycemic mouse can be seen, to some degree at least, in the obese human. In both cases, of course, there is still the question of whether such abnormalities

are the cause or the result of the obese state. At the same time, in view of these similarities, it is tempting to speculate that certain of the obesities seen in man may, in fact, be metabolic in origin. Whether such is the case has stimulated and will continue to stimulate much valuable investigation.

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