Hypothesis

DIABETES, OBESITY AND HEAT PRODUCTION – POSSIBLE LINKS

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1. Introduction

Animal models have proved useful in the study of obesity and diabetes, and the genetically obese (ob/ob) mouse has been suggested as the counterpart of maturity onset diabetes in humans [1].

The adult obese mouse is hyperglycaemic, hyperinsulinaemic and is grossly obese [2]. Ketosis is not present, and obese mice are resistant to the hypoglycaemic effect of exogenous insulin [3]. When subjected to restricted food intake, obese mice show a reduction in blood glucose to the level observed in lean controls and a significant fall in plasma insulin levels [4], but remain obese (since the percentage of body weight accounted for by lipid is above that of lean controls, despite weight loss), indicating that hyperglycaemia and hyperinsulinaemia are secondary to the genetic lesion.

The sequence of events regarding the development and manifestation of the obese–hyperglycaemic syndrome in the ob/ob mouse is not fully understood. Increased fat cell size occurs at a very early age [5] prior to an elevation in serum insulin levels. This appears to rule out the possibility that a pancreatic defect causes the obesity through a lipogenic effect of increased insulin secretion. Recent work indicates that in preweanling mice serum insulin levels are the same in obese mice and lean controls, but the obese mice have lower blood glucose levels [6]. After weaning, hyperglycaemia, hyperinsulinaemia and insulin resistance develop rapidly.

However, the genetic lesion in obese mice is not apparently associated with white adipose tissue since the size of fat cells diminishes when adipose tissue is transplanted from obese to lean mice, and increases when transplanted from lean to obese mice [7].

Where human maturity onset diabetes is associated with obesity, ketosis is rarely present; hyperinsulinaemia, hyperglycaemia and insulin resistance are usually observed – the total profile in fact closely resembles that seen in the obese hyperglycaemic mouse. This contrasts with the lowered or non-existent insulin production in juvenile onset diabetes where ketosis is present if exogenous insulin is not supplied.

2. Failure to adapt to cold stress

A pointer for the understanding of the primary lesion in ob/ob mice may lie in another special feature: their failure to survive cold exposure [8] due to their inability to increase their heat production [9]. This susceptibility to cold has been demonstrated in preweanling mice aged 17 days, before obvious signs of obesity appear at an age of about 4 weeks [10]. Normal mice rendered obese by feeding a high fat diet have normal serum insulin and glucose levels [11], and it would be interesting to determine their susceptibility to cold.

During short term cold exposure, serum fatty acids are the major source of heat production in normal mice [12]. Since short exposure to cold produces an elevation in serum fatty acids in obese mice similar to that obtained with normal mice, it is unlikely that fatty acid mobilisation is impaired in obese mice [12]. It appears that the failure of obese mice to survive cold stress may be due to a defective utilization of mobilised fatty acids.

Two tissues, brown adipose tissue and skeletal muscle have been implicated in supplying the increased heat production required during cold stress [13]. The role of brown adipose tissue in the adult animal is a matter of dispute [13] and in view of the rise in serum fatty acids on cold exposure it seems likely that fatty acid oxidation in muscle during non-

shivering thermogenesis plays an important part in the regulation of heat production. Since fatty acids produced by lipolysis in brown adipose tissue are oxidized in situ [13], a rise in serum fatty acids would not be expected if this tissue has a major role in the increased heat production required during cold stress. It would seem likely, therefore, that the catabolism of fatty acids by muscle is impaired in the ob/ob mouse.

3. Hypothesis – an impairment in the utilization of fatty acids by muscle in obese mice

Trayhurn and James [9] have measured the resting metabolic rates (RMR) of lean and obese mice at various temperatures. Below the thermoneutral temperature of 31°C, the RMR of both lean and obese mice increases with decreasing ambient temperature but is consistently about 20% higher in lean mice at any given temperature. This reduced capacity for heat production results in death on cold exposure due to a rapid fall in body temperature. The decrease in RMR coupled with a 20–25% increase in food intake explains the obesity at normal environmental temperatures. The increased food intake may be a response to the lowered body temperature of obese mice. However, this hyperphagia is insufficient in itself to account for their obesity [14]. Moreover, obese mice accumulate excess fat even when given a lower food intake than lean mice fed ad libitum [15].

Non-shivering thermogenesis constitutes part of the RMR at all temperatures below thermoneutrality and the 20% reduction in RMR in obese mice may correspond to a reduced capacity for non-shivering thermogenesis due to impaired fatty acid oxidation in muscle.

The lesion in obese mice could be due to any of the following:

(i) Fatty acids are not taken up by muscle cells.
(ii) Fatty acids are not transported across the mitochondrial membrane.
(iii) An enzyme of the β-oxidation sequence for fatty acid oxidation is missing.
(iv) A futile cycle catalysing rapid ATP utilisation (in effect a thermogenic ATPase stimulating fatty acid oxidation in muscle) is missing.
(v) Oxidative phosphorylation cannot be uncoupled from respiration with fatty acid substrates.
(vi) A failure of catecholamines to affect thermogenesis from fatty acids. Although catecholamines stimulate lipolysis in obese mice, in normal mice they may also stimulate thermogenesis by acting more directly at some as yet undetermined site. A lesion at this point of action in the obese mouse is also a possibility.

The turnover of triglycerides in adipose tissue of obese mice is increased compared with lean controls [16,17], and at first sight this appears to be entirely inconsistent with their obesity. However, a high rate of fat turnover may represent an unsuccessful attempt to generate heat and raise RMR through ATP utilisation during the breakdown and resynthesis of triglyceride; it may indicate a re-use of mobilised fatty acids which cannot be metabolised by other tissues such as muscle. Moreover, there is a net synthesis of triglyceride.

4. Blood sugar and insulin levels

In connexion with the hypothesis outlined above, it is interesting to note that the insulin-stimulated uptake of glucose into muscle is impaired in obese mice [18]. This impairment may account for the observed insulin resistance in vivo and is consistent with a reduced degree of fatty acid oxidation by muscle, since it is known that accumulated levels of fatty acids inhibit glucose uptake [19].

The insulin resistance of obese mice contrasts with their obesity since insulin normally stimulates lipogenesis and inhibits lipolysis. However, in isolated adipocytes from obese mice lipogenesis and lipolysis respond to insulin at the high insulin concentrations found in these animals [20]. The lack of ketosis in association with the insulin resistance observed in vivo is therefore explained and the anomaly of obesity associated with resistance to a hormone which stimulates lipogenesis is therefore apparent rather than real. Hyperinsulinaemia and hyperglycaemia are therefore seen as secondary effects to the obesity and may be necessary to sustain high fat biosynthesis and turnover. Hyperglycaemia in obese mice is related to their increased food intake; dietary restriction results in a return to normal blood glucose levels [4]. Hyperinsulinaemia is reduced by dietary restriction but insulin levels remain higher than in lean controls [4]. Hyperactivity accompanies dietary restriction and this may provide extra heat from muscular contraction, but the animals remain obese in the absolute sense, since

a higher proportion of their body weight is fat compared with lean controls.

On the above hypothesis, although obesity appears to precede the development of diabetic symptoms, obesity due simply to overeating is not per se the primary cause of maturity onset diabetes in humans. Maturity onset diabetes is due rather to an inborn error of metabolism but the lesion is only expressed in individuals with an above normal food intake, and is controlled by dietary restriction.

The hyperglycaemic obese mouse is a good model for maturity onset diabetes in humans but it is clear that human obesity has several causes. In the obese mouse fed a high carbohydrate diet, fat is synthesised from carbohydrate in adipose tissue [21]. In the Zucker fatty rat (fa/fa) [22], and in humans [23], fed a high carbohydrate diet, fat is synthesised from carbohydrate in the liver and transported to adipose tissue. Obese humans and Zucker rats are therefore hyperlipaemic whilst the obese mouse is not, and the Zucker rat may be a better model than the obese mouse for certain types of human obesity.

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