Luxuskonsumption, diet-induced thermogenesis and brown fat: the case in favour

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Introduction

The idea that the body can adapt to over-nutrition, by activating energetically wasteful mechanisms to dispose of excess energy as heat, goes back to the turn of the century [1]. Originally called 'Luxuskonsumption', the phenomenon is now described as an adaptive form of thermogenesis (diet-induced thermogenesis, DIT). In spite of its early beginnings, substantial quantitative evidence for DIT has been available only in the past 3–4 years, and this recent work has also suggested that a small and relatively obscure form of adipose tissue (brown fat) is the main effector of DIT. Therefore it is not altogether surprising to find a certain reluctance to accept what is for many a major revision of their understanding of energy metabolism. Nevertheless, we believe that the experimental evidence now available leaves little doubt about the importance of DIT in the regulation of energy balance in laboratory animals and that brown fat is the principal source of this form of heat production. Apparently we are not alone in this belief, and the high level of research activity now under way in the U.S.A. and Canada provides a marked contrast with the scene in this country, where only two or three groups are trying to maintain the impetus of what has been until now a uniquely British scientific advance. The evidence supporting this advance has already been published by ourselves and other workers, and in the following review we will concentrate on discussing various points of criticism that have been raised. Before doing so, it is perhaps worthwhile summarizing the experimental work that has led to the recent flurry of interest in this area of metabolism.

Rats offered a highly palatable and varied ‘cafeteria’ diet (utilizing foods normally consumed by man) can increase their metabolizable energy intake from 40 to 120% above that of rats fed on conventional stock diets. Depending on the age and strain of rat, this hyperphagia results in anything from no change in the rate of weight gain to overt obesity. In those animals that resist obesity, energy expenditure is elevated considerably, and this is associated with many metabolic changes. These mainly involve the sympathetic nervous system and brown adipose tissue (BAT) and resemble strongly those seen in cold-adapted animals exhibiting non-shivering thermogenesis (see Table 1 for references and list of similarities). However, the most important piece of evidence linking BAT to DIT has been the demonstration that rates of BAT oxygen utilization in vivo can quantitatively account for all of the enhanced thermogenic capacity of hyperphagic rats exhibiting DIT [6].

Various arguments, ranging from the methodological to the semantic, have been raised against the experimental procedures utilized to demonstrate DIT. They are considered under the various headings listed below, even though some have been discussed previously [13].

Definition of diet-induced thermogenesis

The effect of feeding on metabolic rate was originally termed Specific Dynamic Action.
This Table was compiled from the papers quoted in references [21–12].

1. Increased energy intake and expenditure.
2. Reduced efficiency of energy utilization.
3. Improved cold tolerance and lower threshold temperature for shivering.
4. Increased sympathetic activity.
5. Activation by \( \beta \)-adrenoceptor agonists.
6. Inhibition by \( \beta \)-adrenoceptor antagonists, ganglionic blocking agents and hypoxia.
7. Raised plasma tri-iodothyronine, reduced plasma insulin and/or improved glucose homeostasis.
8. Hypertrophy and hyperplasia of brown adipose tissue.
9. Increased brown adipose tissue mitochondrial respiration and proton conductance.
10. Increased brown adipose tissue \( \text{Na}^+ \cdot \text{K}^+ \)-activated, \( \text{Mg}^{2+} \)-dependent adenosine triphosphatase activity.

Methods for producing hyperphagia

It could be argued that, compared with giving a cafeteria diet, forced feeding by stomach tube is a more accurate and better controlled method for increasing energy intake. However, there are several disadvantages associated with forced feeding, not the least of which is the considerable, and occasionally fatal, stress placed on the animal. In addition, the disruption of the normal ‘nibbling’ meal pattern of laboratory rodents inhibits DIT and produces obesity, even in animals fed at normal or subnormal levels [14–17]. Thus, force feeding by gastric intubation is entirely inappropriate for studies on adaptive thermogenesis. Cafeteria feeding, however, not only produces voluntary increases in intake that far exceed those possible by tube-feeding liquid slurries, but also achieves this without stress and with a diet very similar to that eaten by man.

Methods for measuring energy balance

The cafeteria diet involves presenting animals with a large variety of human foods, and therefore we have used food composition tables to assess metabolizable energy intake. Contrary to some people’s expectations, this is a very accurate method when used by experienced workers and gives values that agree to within 2% with those determined by bomb calorimetry [18]. This level of accuracy is clearly sufficient to discriminate differences in intake of 40–100% usually produced by cafeteria feeding.

Changes in energy retention can be assessed either by direct determination of carcass energy (bomb calorimetry) or by determining body composition and using predetermined values for the heat of combustion of protein and fat. The two methods given values that agree to within 3% and are not significantly different [18]. The gain in carcass energy is calculated as the difference in energy content between experimental animals and animals killed at the start of the experiment. This initial group is carefully matched to the experimental groups for age, weight and body composition.

Heat production over the entire experiment is calculated as the difference between metabolizable energy intake and carcass energy gain (i.e. what goes in must either stay in or leave as heat, having allowed for faecal and urinary energy losses). The difference between energy consumed and energy retained will obviously be influenced by errors in the measurements, but these are usually of a different order of magnitude and not necessarily biased. This carcass balance method has been used successfully for over 50 years by most workers in animal energetics, and we have recently confirmed (although at this stage it hardly seems necessary) that heat production determined in this way gives values identical with those determined by 24-h measurements by indirect calorimetry, i.e. oxygen consumption [19].
Variations in any physiological parameter that relate to age, genetic strain, species etc. are to be expected and, rather than detracting from its biological significance, in fact strengthen the arguments for DIT playing a role in adjusting the individual to meet a variety of metabolic and environmental challenges. Thus the facts that thermogenic responses to overnutrition depend on age [18], genetic strain [20] and even the subtle genetic or early environmental influences on rats of the same strain raised in different colonies [21] suggest that DIT is an important and sensitive mechanism in homeostasis. DIT has been also confirmed in the pig [22, 23], and very recently Trayhurn and co-workers [24] demonstrated the large capacity for DIT of cafeteria-fed lean mice. They simultaneously compared the response of lean mice with their genetically obese (ob/ob) littermates and found that the latter became massively obese owing to a failure to raise heat production in response to hyperphagia. This mouse experiment used similar protocols and methods to those used by ourselves with rats and, apart from confirming our conclusions regarding the importance of DIT, also demonstrates the profound influence of genotype on the metabolic fate of ingested energy.

Conflicting evidence

To date, we have carried out full energy-balance studies on over 200 cafeteria-fed rats of different ages and strains, and housed and fed under a variety of conditions. In every study there has been evidence for DIT, and other workers [24–26] have been able to produce similar evidence for this effect of cafeteria feeding. A study of cafeteria-fed rats carried out at thermoneutrality (29°C) has failed to show DIT [27], but this may be due to thermoregulatory inhibition of thermogenesis.

Apart from this, the only other conflicting reports are those of Hervey and Rolls and their co-workers [28, 29]. In spite of the limited information available, there are sufficient data in these two abstracts seriously to question the validity of these experiments and their interpretation. The strain of rat used (WAG/C × PVG/C) appears to be unique and not generally available to other workers. Furthermore, there would appear to be something seriously wrong with this colony, since young female control rats [29] were reported to be eating 164 kJ/day (after correction for the stated systematic error) and expending 155 kJ/day (indirect calorimetry measurements). These rats were therefore gaining 9 kJ/day, which is considerably less than the 20–40 kJ/day one would expect in rats of this age and is almost identical with the energy retention reported by Trayhurn et al. [24] for control mice weighing only 20 g. With this in mind, the very small increases in energy intake (24%) produced by this group's attempts to cafeteria-feed could be considered more as an experiment in nutritional rehabilitation than in overnutrition. Calculation of the gross efficiency of energy gain indicates values of 5–8% for controls, which has to be compared with normal values of 20–30% obtained in other laboratories. These abnormally low values are sufficient cause for concern, but what is more worrying is that they are averages derived from a 7-week trial and obscure exceptionally high values for the first week of cafeteria feeding. Calculations based on their data indicate that the energy gain of cafeteria rats was approximately 56 kJ/day in the first week and then mysteriously dropped to 14 kJ/day over the rest of the experiment.

Apart from these difficulties, one has to question the logic of ascribing increases in heat production to the energy cost of fat synthesis from carbohydrate when lipogenesis de novo would be inhibited by the high intake of lipid supplied by the cafeteria diet. This error is compounded further by assuming that the residual excess heat production is due to the obligatory energy cost of assimilating the extra food ingested. However, the values used to estimate the cost of fat and protein synthesis are derived from empirical estimates of the metabolizable energy requirement for fat and protein gain, i.e. feeding trial estimates, and therefore include the energy cost of digestion, transport and assimilation of nutrients. Thus, by taking two bites at the same apple (and not necessarily the most appropriate apple), this group attempts to explain away any differences in heat production that could be ascribed to DIT.

Role of the sympathetic nervous system and brown adipose tissue

The evidence for sympathetic activation of BAT as the primary source of DIT is provided by the papers referred to in Table 1. Set against this body of evidence is one, apparently contradictory, short report [30] showing that propranolol (the β-adrenoceptor antagonist) failed to inhibit the postprandial rise in oxygen consump-
tion of tube-fed rats. This is not at all unexpected, since the same group had previously confirmed the work of ourselves and others showing that chronic force feeding promotes obesity instead of stimulating DIT (see Methods for producing hyperphagia, above). In other words, these workers were attempting to inhibit something that did not exist. In normally fed rats, however, one finds that the acute response to a single meal is markedly depressed by propranolol [31], leaving a small, residual postprandial rise in metabolic rate, which is presumably due to the obligatory costs of nutrient assimilation (i.e. the Heat Increment of Feeding).

Relevance to man
The evidence for adaptive DIT in man has been reviewed recently [see 32–34] and although firm quantitative evidence, comparable with that produced in animals, is still required, most authorities would now accept that man appears to possess the capacity for DIT. There is no direct evidence to implicate a brown-fat involvement in DIT, or a brown-fat defect in obesity. However, there is indirect histological [35, 36] and thermographic [2] evidence to suggest that adult man retains some functional BAT, which may also respond to seasonal changes in environmental temperature [37]. Direct confirmation of BAT activity in DIT or non-shivering thermogenesis in man will nevertheless prove exceptionally difficult. We have calculated that as little as 40–50 g of BAT could, if maximally stimulated, account for 20% of daily energy expenditure. This could make all the difference between maintaining a constant body weight or gaining at the rate of nearly 20 kg per year! Thus, even though the potential influence of BAT on the control of body weight is spectacular, we have consistently urged caution in extrapolating from indirect histological and thermographic evidence to a major role for BAT in human energy metabolism [2].

Most of the work cited in this review has been published or is about to be published. We would urge those who are concerned about the experimental evidence supporting our arguments to consult these papers. A more general description of the regulation of energy balance is contained in a small monograph on the topic [38]. The present review should therefore only be considered as an attempt to explain the background to the theoretical, methodological and semantic problems that have caused so much confusion, misunderstanding and controversy in this area of metabolism.

References
Diet-induced thermogenesis


