Brown adipose tissue in man: a review[1]

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Brown adipose tissue has recently attracted considerable attention. It differs from white adipose tissue in both structure and function, the major similarity being the presence of fat. Whereas white adipose tissue typically has one large fat vacuole, a round nucleus and few mitochondria, brown adipose tissue is multilocular, has a crescent-shaped nucleus and many large mitochondria (Hull 1966). White adipose tissue is primarily a storage site, brown adipose tissue a site of heat production or thermogenesis. It is this capacity for thermogenesis which makes it of special interest. Recent work has demonstrated that brown adipose tissue is a major site of cold-induced thermogenesis in cold-adapted rats (Foster & Frydman 1978). There is also some evidence that it is involved in the metabolic response to overfeeding (dietary-induced thermogenesis) in rats fed a variety of palatable foods (Rothwell & Stock 1979).

It has been shown that genetically-obese rats and mice have a reduced capacity for cold-induced thermogenesis (Davis & Mayer 1954, Kaplan & Leveille 1974, Thurlby *et al.* 1976) which leads to reduced energy expenditure and hence to obesity. As some theories of human obesity have postulated a thermogenic defect as a primary factor (James & Trayhurn 1976), these findings have given rise to the speculation that a defect in brown adipose tissue may be an important cause of obesity in man (James & Trayhurn 1981). Such speculation makes the assumption that small rodents make satisfactory models for man, and while this may be true for many aspects of physiology it is less likely to be so for thermoregulation. The difficulties of temperature maintenance of the rat, a small mammal with a relatively large surface area, are not those experienced by much larger mammals. While it is not unreasonable that small mammals should retain specialized heat-producing tissues, it does not follow that large animals would require such a mechanism.

This review sets out to examine the evidence for a significant contribution by brown adipose tissue to the energy expenditure of man. The level of current knowledge differs in the case of the neonate and the adult, and these will be considered separately.

The human neonate

As long ago as 1902, Hatai recognized that the dorsal and cervical 'embryonal fat' of the human neonate was similar to the interscapular or hibernating gland of hibernating mammals, which is now known to be a site of heat production in arousal from hibernation (Smalley & Dryer 1963). More recently Hull and his coworkers (Aherne & Hull 1964, Dawkins & Hull 1964) carried out necropsies on large numbers of infants and found brown adipose tissue at several sites. These were chiefly abdominal but some of this tissue was also found in the interscapular region and in the posterior triangle of the neck. Many of these sites were common to those described for the neonates of other species.

This anatomical evidence supported the observation that newborn babies were capable of large increases in oxygen consumption apparently without shivering or other muscular activity. This has been observed in many species and is called non-shivering thermogenesis.

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In the newborn of other species, brown adipose tissue has been shown to be the site of heat production. For example, in a series of very elegant experiments in newborn rabbits, Dawkins & Hull (1964) placed thermocouples over brown adipose tissue sites and observed that at an ambient temperature of 25°C the temperature over these sites was greater than the deep body temperature. Hypoxia reduced the metabolic response, with a concomitant fall in the temperature over the brown adipose tissue. This then increased more rapidly than deep body temperature when the oxygen supply was restored. These results suggest that brown adipose tissue is the site of the additional heat production.

Hull & Segall (1964) showed that surgical excision of three-quarters of the brown adipose tissue also reduced the response to cold compared with sham operated animals. They also found that after depletion of the brown adipose tissue fat (by 48-hour exposure to 30°C) the rabbits were only capable of a reduced metabolic response (Hull & Segall 1965). The link between the human and rabbit neonate is that both show an increase in plasma glycerol when exposed to cold (Dawkins & Hull 1964, Dawkins & Scopes 1965). The brown adipose tissue of the newborn rabbit lacks the enzyme glycerol kinase (Dawkins & Hull 1964): hydrolysis of triglyceride therefore leads to an increase in plasma glycerol, and this coincides with local heat production in brown adipose tissue.

Some of the most interesting evidence is circumstantial and derived from post-mortem data. Aherne & Hull (1966) took tissue from 394 infants dying before the age of 4 weeks. Brown adipose tissue was found in all these infants but in 42 the brown adipose tissue was depleted of fat. This may indicate either starvation or activity of the tissue; however, in 36 cases starvation was the obvious cause. The other six had suffered from 'cold syndrome' and their white adipose tissue still contained fat. This eliminates starvation, and makes it likely that the tissue had become depleted through activity.

The weight of the evidence, therefore, suggests that brown adipose tissue is present and functional in the human neonate, as in many other mammalian species. In the modern centrally-heated environment this mechanism may not often be called into play, although perhaps in rare cases it is important. Premature babies are particularly at risk as they lack sufficient insulation from white adipose tissue and have brown adipose tissue which is less well developed (Aherne & Hull 1966).

Adult man

The study of brown adipose tissue in adult man is a much more recent and controversial field. A thermogenic defect in brown adipose tissue has been shown to be the cause of obesity in some genetically-obese rodents, but the situation in human obesity is much less clear. The idea of a thermogenic defect has gained momentum in recent years as the solution to the development of obesity in individuals whose resting metabolic rate appears to be normal, and whose energy intake is not abnormally high in comparison with their peers (James & Trayhurn 1976).

However, before brown adipose tissue can be postulated as a major site of thermogenesis in man, it is necessary to examine the evidence that adult man is capable of thermogenesis. In the late 1950s a great deal of research was carried out on the response of man to exposure to cold conditions ($< 10°C$), and it was shown that energy expenditure did increase in response to the cold. However, even after several weeks exposure, basal metabolic rate (measured in warm conditions) was unchanged (Iampietro *et al.* 1957, Keatinge 1961), implying that the response is quickly switched on and off as the stimulus is applied. It was suggested that this response could be accounted for by the muscular activity of shivering rather than by any metabolic heat production (non-shivering thermogenesis). Keatinge (1961) and Rochelle & Horvath (1969) related the degree of the response to the intensity of shivering, although Girling (1964) divided subjects into 'shiverers' and 'non-shiverers'. The magnitude of response was similar in both groups but the onset of the shiverers' response was delayed by 15 minutes. Neilsen (1975) found that cold-induced thermogenesis and the response to exercise were additive, suggesting that these were independent and that shivering

was not the source of the cold response. It is quite likely that both shivering and non-shivering thermogenesis exist in man and overlap at certain ambient temperatures.

It is also possible that man can increase energy expenditure when energy intake is increased, thereby opposing any change in body weight. Much of the information supporting this is anecdotal (Neumann 1902, Gulick 1922). However, one long-term study has been reported in which prisoners were overfed a high-fat diet for several months (Sims & Horton 1968): some individuals appeared to be resistant to weight gain whereas others gained weight easily.

It appears then that man has some capacity for thermogenesis, at least in conditions of extreme cold or prolonged overfeeding. However, if obesity is the result of a thermogenic defect, thermogenesis must make a significant contribution to energy expenditure in everyday life. Further, it should be possible to demonstrate that obese people have a reduced capacity for thermogenesis.

Pittet *et al.* (1976) found differences between lean and obese women in the size of response to a small meal (50 g glucose), but this was not confirmed by other workers (Kaplan & Leveille 1976, Clough & Durnin 1970). Blaza (1980) found no differences in the response of five lean and five obese women to a 1000 kcal (4.2 MJ) meal and moderate exercise although there were some differences in response to warm and cool environmental temperatures (all within 20–30°C and described by the subjects as 'comfortable'). However, in all cases the obese subjects had much greater total daily energy expenditure than the lean. This was also true of the subjects of Jung *et al.* (1979) although these obese subjects did show a reduced response to noradrenaline infusion. It is possible, of course, that the obese subjects were already above the threshold for the stimulation of thermogenesis and therefore had smaller capacity remaining. This emphasizes the fundamental problem with the assessment of obese subjects, in that many of the differences may be secondary characteristics of obesity rather than a primary cause. The case for a thermogenic defect as a primary cause is as yet unproven, and since obesity is likely to be a multifactorial disturbance of energy balance, studies of a few individuals may not show up those with thermogenic defects.

The evidence for the presence and function of brown adipose tissue in adult man is similarly incomplete. Identification is often difficult even with modern histological techniques. Heaton (1972) studied 52 subjects at post-mortem, taking fat from 18 sites and grading them according to fat content (as an indication of activity). She concluded that brown adipose tissue was found in the greatest quantity during the first decade and that during this period it was also most active. Peripheral sites were depleted first, but some brown adipose tissue was retained in the deep sites into old age. Huttunen *et al.* (1981) looked at the incidence and activity of brown adipose tissue in outdoor and indoor workers at post-mortem. Tissue was excised from the neck and pericardium within 5 days of death and assessed for proportion of multilocular cells and mitochondrial enzyme presence and activity. There were no mitochondrial enzyme reactions seen in the tissue taken from indoor workers, whereas both multilocular cells and increased enzyme activities were found in some of the outdoor workers. There was also a suggestion that the presence of brown adipose tissue was related to the most recent exposure to cold; thus an outdoor worker dying in the winter had more brown adipose tissue than one who died in August.

There is also additional circumstantial evidence. Aherne & Hull (1966) described two elderly patients who had suffered from hypothermia. These people had brown adipose tissue which was severely depleted of fat, indicating that the tissue had been active. Infrared thermography (a technique which gives a colour map of surface temperature of any object) has produced mixed results; Rothwell & Stock (1979) gave the thermogenic drug ephedrine and identified 'hot spots' which might have correlated with brown adipose tissue sites, but in studies by the author (unpublished) only a generalized heating was observed.

In summary, the case for the presence and activity of brown adipose tissue in adult man is far from complete. Although there is now some evidence for its presence in the adult, there is little to show that it has an active role in thermogenesis in man, nor that a defect in its thermogenic capacity might predispose to obesity.

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