Comparative physiology of brown adipose tissue

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It has been unequivocally established that brown adipose tissue (BAT) functions as a thermogenic organ (for review, see Trayhurn & Nicholls, 1986). In addition to functioning as an organ of thermoregulatory thermogenesis, can BAT alternatively, or additionally, act as a site of regulatory thermogenesis in energy balance regulation? Put another way, does BAT play a role in nutritional energetics?

Rothwell & Stock (1979) were the first to propose that BAT was a site of regulatory thermogenesis (diet-induced thermogenesis). Their theory has stimulated much further work on BAT form and function in general, and its putative energy regulatory role in particular. They also rekindled the long-standing controversy concerning the possibility that energy efficiency was a regulated variable. The great preponderance of work generated has been direct laboratory investigations into the role of BAT, confined mostly to small animal models of obesity (mouse and rat).

An alternative indirect approach is to use inductive reasoning from studies that have been done on the comparative physiology of those mammals that in their natural life cycle appear to, or can be demonstrated to, regulate energy efficiency and energy storage: is the time-course of changes in energy efficiency and energy storage directly related to the time-course of changes in BAT anatomy, histology, biochemistry and physiology? The purpose of the present paper is to review the available studies in the literature from this viewpoint. Unfortunately the studies available are limited. Limited because relatively little work has been done, and further limited by our new understanding of BAT function and the necessary criteria which have to be applied to be assured that the tissue under examination is indeed BAT, and if it is, to what degree it is carrying out thermogenic function. Until recently BAT could be defined histologically, now it is appreciated that uncoupling protein must be present for a tissue to be unequivocally accepted to be BAT. The full appreciation of the physiological role of BAT in any natural circumstance can only be determined using the exacting and invasive techniques pioneered by Foster & Frydman (1979) to enable determination of oxygen consumption of the tissue.

Information from animals that change energy efficiency in response to various natural requirements, and possess BAT (though the tissue has not necessarily been proven to have significant function), has been compared and contrasted with information from other animals that respond with similar changes in energy efficiency in similar circumstances but without apparently possessing functional BAT. Others, notably Trayhurn (1986) and Heldmaier *et al.* (1985), have appreciated the value of this comparative approach. Rothwell & Stock (1981) have also written about the comparative physiology of BAT, but from a different viewpoint, concerning the biological advantages that leanness might confer.

Comparative anatomy and histology of BAT

Until recently BAT was thought to be limited to mammals, and then only to certain species, and to be absent from birds (Smith & Horwitz, 1969; Afzelius, 1970). Therefore, it was presumed that the energy balance strategies of mammalian species known to be capable of using BAT functionally could be compared and contrasted with similar strategies in birds, from which BAT was absent.

This approach has become more problematic since the recent demonstration of BAT-like tissue (histological criteria only, uncoupling protein not demonstrated) in certain birds (Oliphant, 1983). Prompted by this observation we have examined two barnacle geese (*Branta leucopsis*) and observed a small amount of fat tissue in the neck, with the histological features of BAT (Andrews *et al.* 1989).

Since it is no longer possible to say categorically that functional BAT is absent in birds, the comparative contrasting of energy balance strategies between mammals and birds, arguing that the latter are occurring without the possibility of BAT involvement, is much weakened.

Seasonal changes in energy storage and energy efficiency

Intensive studies in laboratory animals have established an excellent case for an inverse causal relation between fat storage and suppression of BAT function (for reviews, see Trayhurn (1986) for the normal laboratory mouse and its *ob/ob* mutant; and Rothwell & Stock (1986*a*) for the laboratory rat). Do other species, either in the laboratory, or better still in the wild, show this relation, and may such storage occur in species where BAT is presumed absent?

Many animals undergo pre-winter, and in those animals that have the capacity, pre-hibernatory fattening. Does BAT have any role to play in this? The edible dormouse (*Glis glis*) is one of the best known of such mammals. Rothwell & Stock (1986*b*) have speculated that BAT could play a role in this energy accumulation, but have no experimental evidence to support the idea. Milner *et al.* (1989) have studied BAT of Richardson's ground squirrel (*Spermophilus richardsonii*), another species which undergoes pre-hibernatory fattening. As expected, BAT weight is much increased in hibernation, and BAT is utilized during arousal. However, during the preparatory period for hibernation, when it must be presumed that the major increase in functional BAT is occurring, this is paralleled by weight gain. Of course, BAT thermogenesis could be suppressed in this period, despite the ongoing increase in functional capacity of the tissue. Studies have been done comparing and contrasting two hamster species, the golden (*Mesocricetus auratus*) and the Djungarian (*Phodopus sungorus*). Both are clearly capable of developing the highly thermogenic BAT necessary for speedy arousal from the deep torpor of hibernation. Paradoxically, in both species the natural annual cycle of shortening day-length, or laboratory manipulation of day-length, leads to weight loss before the onset of bouts of hibernation torpor. The golden hamster needs to accumulate exogenous stores (hoarding) during the pre-hibernation preparatory phase when, amongst other physiological changes, BAT functional capacity is increasing (using histological and anatomical criteria, McKee & Andrews, 1989). Thus, in contrast to Richardson's ground squirrel, increasing thermogenic capacity is associated with weight loss, balanced by the hoarding. However, it cannot be imagined that this weight loss is due to the inability in these species to switch off BAT thermogenesis, since in the hibernation bouts, which will occur shortly after, thermogenesis is suppressed almost to zero. Yet, as biochemical (Milner *et al.* 1989) and physiological (McKee *et al.* 1983) evidence shows, BAT then possesses supreme thermogenic capacity which is unleashed during arousal. Paradoxically, given high-fat diets in environments that do not lead to adaptation for hibernation, the golden hamster (Wade & Bartness, 1985), but not the Djungarian hamster (Heldmaier *et al.* 1982) stores fat (for review, see Trayhurn, 1986). Klaus *et al.* (1988) have shown different strategies and a dissonance between BAT function and energy storage in three species of small mammal captured in the same habitat and area. Bank voles (*Clethrionomys glareolus*) and yellow-necked fieldmice (*Apodemus flaviocollis*) both suffer a loss of body mass before winter, whereas woodmice (*Apodemus sylvaticus*) maintain weight. However, in the winter, BAT mass remains constant in the vole, whereas in the two mice species it increases; yet all three species show increased whole-body non-shivering thermogenesis.

With the caveat noted above that it is possible that birds have functional BAT (Oliphant, 1983; Andrews *et al.* 1989), studies are presented which report seasonal fattening in birds. The barnacle goose, particularly the female, gains considerable weight (presumably fat) in a short period before migration and subsequent breeding (Andrews *et al.* 1985). The emperor penguin (*Aptenodytes forsteri*) exhibits a similar strategy, with quite massive pre-migratory pre-breeding fat deposition (Le Maho *et al.* 1976). Perhaps more akin to the mammalian pre-winter fattening is the example of the Svalbard rock ptarmigan (*Lagopus mutus hyperboreus*) (Stokkan *et al.* 1986). In this species body-weight increases rapidly with shortening day-length in the autumn. This occurs despite falling food intake, which the authors speculate is due to a net positive energy balance, with locomotory energy costs falling even faster than food intake.

This point of Stokkan *et al.* (1986) leads to a general analysis of energy-gain strategies. Increased food availability coupled with increased intake or reduced locomotor activity and possibly low thermoregulatory costs, or both, could separately or together account for energy storage without the need to invoke any change in energy efficiency. But certainly in any theoretical analysis, down-regulation of resting metabolic rate must be included as a potential means of energy conservation. This could be achieved in a general sense by a reduction of metabolism by all tissues of the body, or in a specific way through the reduction in metabolism of a single tissue such as BAT.

Looking at the diverse energy-balance strategies described previously, many of those which can be imagined in theory do in fact occur in practice. Thus, the barnacle goose combines additional food intake, when an improvement in climatic conditions leads to grass growth, with reduced locomotion and again, because of the improving climate, reduced thermoregulatory thermogenesis. On top of this there is reduced resting metabolism which the balance of evidence would suggest is from a whole-body suppression of metabolism. Rapid weight gain ensues: a 40% increase in body-weight in 4–6 weeks. In closely related species, the golden hamster and Djungarian hamster, and similarly in the yellow-necked fieldmouse and the woodmouse, different energy-balance strategies are demonstrated in similar circumstances

The small rodents which have been so intensively studied would seem, from the balance of evidence, to be able to use BAT as an agent of energy regulation. This I would argue can only occur in any species where there is an ongoing thermoregulatory thermogenesis in BAT. It is not generally realized that this is commonly the case in the laboratory rat and mouse. The former has a lower critical temperature of approximately 28°, the latter of 30°. Thus, at normal animal-house temperatures, in the low 20°s, mice and rats are cold acclimated and undergoing a sustained mild thermoregulatory thermogenesis in their BAT.

Reproduction: pregnancy and lactation, and egg formation

In these circumstances of changing energy demands on the body, particularly during lactation and egg formation, it is possible to imagine increases in energy efficiency. Trayhurn (1986), in particular, has taken the view that an investigation of BAT function during phases of reproduction would give information of value to our understanding of the regulatory role of the tissue. In the laboratory mouse there is little change in energy efficiency during the course of pregnancy, and except towards the very end of pregnancy little change in indices of BAT thermogenic capacity, at which time a decrease commences (Andrews *et al.* 1986). This decrease continues into lactation, when there is a considerable increase in energy efficiency paralleled by a dramatic reduction in BAT thermogenic capacity (Trayhurn & Jennings, 1987), which must result in a considerable decrease in the ongoing functional thermogenesis in BAT.

The golden hamster, in contrast to this, shows a massive suppression of BAT function very early in pregnancy (Wade *et al.* 1986). Trayhurn (1986) has argued that this does have energy regulatory significance, since most unusually the hamster responds to pregnancy by a considerable reduction in food intake, relying on maternal body stores to provide the energy needs of the growing fetus. Here again, like the mouse in lactation, suppression of the ongoing thermogenesis of BAT will result in energy conservation.

In large mammals during lactation and in birds during egg formation similar large demands for energy will occur. In the absence of functioning BAT these species are able to adopt different strategies to meet this demand.

Thus, in reproduction a number of strategies are seen to have been adopted to meet the increased energy requirements. BAT can only be involved in those small animals living at sub-thermoneutral temperatures where an ongoing thermoregulatory thermogenesis is occurring, which through its down-regulation leads to energy conservation.

Young animals

Newborn mammals range in thermoregulatory capacity from the precocious to the immature (Alexander, 1975). In the latter BAT is present and highly functional; it is absent or presumed functionally residual in the former.

The BAT of the immature animal can be argued to have value in energy conservation. The neonate will cycle between high BAT activity and, thus, homeothermic deep-body temperature and mobility, enabling feeding in the presence of the mother, to low BAT activity, leading to deep torpor and low body temperature in her absence. Thus, energy is diverted away from thermoregulatory thermogenesis and into growth. Efficiency is increased. This strategy is not, however, essential for survival in a small young homeotherm: altricial (immature) bird hatchlings thrive, it is currently presumed, without the benefit of BAT.

Thus, examining energy strategies in the young animal, it would seem that when functional BAT is present it can be utilized for energy regulatory function, but that it is not an essential component of any strategy.

Torpor and arousal

Historically, arousal from torpor is the physiological function with which BAT has been most closely associated.

Whole-body thermal and metabolic studies (golden hamster; McKee *et al.* 1983), and recently direct determination of metabolic indices of BAT function during arousal (Richardson's ground squirrel; Milner *et al.* 1989), have emphasized the importance of BAT for arousal. But even this phenomenon can occur without the benefit of BAT: hummingbirds (*Lophornis magnifica*) can arouse from torpor just as quickly as mammals of similar size using shivering thermogenesis.

Torpor is presumed to be an energy-conservation strategy. Though in arousal BAT is fulfilling an energy-consuming thermogenic role to enable rapid restoration of deep-body temperature, yet again we see that an alternative strategy, using a different mechanism, is possible to bring about arousal.

Conclusion

Energy fluxes in the body can be influenced by a number of separate physiological functions. Regulation of energy balance can be achieved by separate and combined regulation of these functions. BAT thermogenesis is only one of these regulated variables: animals can manipulate energy flux and can regulate balance without the requirement for BAT. The individual examples of energy-balance strategies I have given, with the diverse possibilities which they illustrate for achieving the same aim, long-term survival, more than amply prove this. However, when BAT is present and is functioning to produce heat, then the tissue may be used to regulate energy flux as a component of an energy-balance strategy. I emphasize that this is most likely to be the case with small animals maintained below thermoneutrality and, therefore, possessing functional BAT.

I conclude that the putative role of BAT in the regulation of energy balance and energy storage in adult man could only be established, first by showing the retention of BAT from birth, and second by unequivocally demonstrating an ongoing thermogenesis in that tissue.

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