The Role of Brown Adipose Tissue in Metabolic Efficiency [1]

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Maintaining ideal body weight appears to be a battle that is waged all over the world. In many Western societies an overabundance of food combined with a sedentary lifestyle lead to substantial problems of corpulence. The opposite occurs in Asia, Africa, and the Indian Subcontinent where the struggle is to acquire sufficient body fat to provide life-sustaining energy reserves.

It is a simple problem at first glance, a matter of balancing energy input with energy output. Yet decades of research have failed to provide a rationale capable of yielding effective therapies for altering body weight. As the complexities of energy balance mount, the evidence leads us to entirely new avenues of investigation. Past efforts, which emphasized the energy intake side of the balance equation, have given way to new questions concerning energy expenditure, metabolic efficiency and traditional energy values for carbohydrates, proteins and fat.

It seems clear that individuals differ in their efficiency of weight gain and exhibit a variety of adaptive responses to either a positive or negative caloric state. Rose and Williams (I) studied large and small eaters whose caloric intakes ranged from 1600 to 7400 kcal/day and whose weight remained constant over a period of weeks. Several studies of overfeeding have reported weight gain to fall shorter than would be predicted from the amount consumed (2, 3). Perhaps the most famous of these studies was that conducted by Sims et. al. on the Vermont Prisoners (4). With normally lean subjects fed an additional 1, 500 kcal/day, they found some individuals extremely resistant to weight gain.

Individual variation in response to a nutritional stimulus has also been reported by Miller and Parsonage (5) who observed large differences in weight loss responses of obese women submitted to a 1, 500 kcal diet. The reverse situation was examined by Poehlman et. al. (6) who found that some individuals when presented with a nutritional stress of a 22, 000 kcal surplus manifest relatively little change in regard to body weight, skinfolds, fat cell diameter, percent body fat, or fat mass. The ability to adapt to varying degrees of caloric intake has given rise to the term "diet-induced thermogenesis," indicating the apparent ability of humans to maintain weight on varying intakes.

Genetic Versus Environment Determinants of Body Weight

The nature versus nurture argument for the determination of body weight was fueled by Mayer's data (7) showing the strongest determinant of body weight to be parents' body weight. Accordingly, if one parent is obese, there is a 40%

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chance the child will be obese. If both parents are obese, the chances are 80%. If neither parent is obese, the chance of obesity is only 7% for the child. These data, of course, didn't address the cause of the relationship. Was it genetic or environmental ?

Numerous studies have attempted to discern the contribution of heredity versus environment to the determination of body weight (assuming at-least adequate caloric intake is available). The most conclusive data have been provided by Stunkard et. al. (8) who performed a large adoption study (N = 540) of human body weight. The virtue of the study was that it included information on both the biologic and adoptive parents. This was accomplished by use of the Danish Adoption Register, which contained official records of every nonfamilial adoption granted in Denmark between 1924 and 1947. As a measure of fatness, the investigators determined the body mass index (weight in kg divided by height in meters squared) and categorized the adoptees as thin, median weight, overweight and obese. A major genetic contribution was clearly indicated; they found that the mean body mass index of the biologic parents increased with the increase in weight class of the adoptees. In contrast, there was no apparent relationship between the body mass index of the adoptive parents and the weight class of the adoptees.

No one is denying a role for food intake in the determination of body weight. Rather, it appears that, as summarized by Miller, there are two necessary conditions for significant weight gain: an ample food supply plus a genetic predisposition (9).

The studies described above raise the challenge of defining the basis of a genetic difference in food utilization efficiency. If this challenge can be met, the next goal would be to put that knowledge to use. The ultimate results might benefit both those in need of more energy and those suffering from excess energy reserves. Understanding the basis for metabolic efficiency could provide the means to improve food utilization for those suffering from malnutrition and decrease food utilization for those disposed to obesity.

What follows is an explanation of one hypothesis regarding individual variations in efficiency of energy metabolism. It is based on recent evidence regarding heat production by brown adipose tissue.

Brown Adipose Tissue--Mechanism of Heat Production

Brown fat can best be explained by contrasting it with its more abundant and well-known relative, white fat. Differences in both appearance and function distinguish the two forms of adipose tissue. White fat cells, which serve as an energy repository, consist primarily of a large droplet of triglyceride and are thus considered unilocular (10). Brown fat cells are multilocular; triglycerides are localized in smaller droplets surrounding numerous mitochonidria (II). Extensive vascularization and densely striated mitochondria give the tissue its brown appearance, and the impressive oxidative capacity allows for its basic function--heat production (12).

The means by which brown fat produces heat is the major cause for the excitement the tissue generates for those interested in bioenergetics. In other tissues the dissipation of chemical energy as heat by mitochondria is classically minimized by tight coupling of respiration to ATP production. Respiration is, therefore, limited not by substrate supply or oxidative capacity but by the rate of utilization of the ATP located outside the mitochondria.

The unique feature of brown fat is that fatty acid oxidation can be uncoupled from ATP synthesis and the oxidative energy directly released as heat. The electrochemical proton gradient generated by respiration is dissipated under certain conditions by a conductance pathway which allows protons to leak back across the inner mitochondrial membrane without the usual coupling reaction to ATP synthesis. This proton channel can be attributed to the presence of a unique 32, 000 molecular weight protein, referred to as the uncoupling protein, in the inner membrane of brown fat mitochondria (12).

When ADP, ATP or GDP are present in the medium, brown fat mitochondria behave conventionally with regard to respiratory control. This is believed to be due to an affinity of these compounds for the uncoupling protein which results in blockage of the pathway which allows for re-entry of protons into the mitochondrial matrix (13).

Norepinephrine-induced activation of adenylate cyclase on the brown adipocyte plasma membrane results in the increase of cyclic-AMP which stimulates triglyceride lipolysis. The production of free fatty acids and fatty acyl-GoA provides substrate for mitochondrial oxidation and appears to stimulate the proton conductance pathway

The addition of GDP is used as one means of assessing the functional capacity of the proton leakage pathway in vitro by measuring the amount of bound purine nucleotide. An increase in GDP binding indicates an increase in functional uncoupling protein. Several studies have shown that the total amount of uncoupling protein present in brown fat mitochondria correlates well with the thermogenic status of the animal (12).

Colored DNAs corresponding to the mitochondrial uncoupling protein of rat brown adipose tissue have been sequenced and the complete amino acid sequence of this unique membranous component has been determined by Bouillaud et. al (14). They found a significant sequence homology between the uncoupling protein and the ADP/ATP carrier and proposed that the nucleotide binding site of the uncoupling protein is localized at the C-terminal end.

Diet--Induced and Nonshivering Thermogenests

Brown fat has been proposed to provide heat to the body via two forms of thermogenesis. One form, diet-induced thermogenesis, was described above as a phenomenon by which the energy cost of weight gain and maintenance is altered by manipulating the amount or composition of the diet. An animal model was necessary to test this hypothesis to allow for the removal and examination of brown adipose tissue in the overfed condition. Because normal animals fed standard laboratory chow will not eat beyond their needs, Rothwell and Stock (15) exploited a dietary regimen more closely related to human eating habits. In what they describe as the "cafeteria diet" rates were offered additional tasty items, such as chololate, cheese, and fruit. Although the cafeteriafed rats consumed on the average 80% more kcal than controls, they gained only 27% more weight. They concluded that diet-induced thermogenesis indeed took place because measurement of metabolic rate indicated that the overfed rats increased their energy expenditure more than their weight gain alone would dictate.

The second form of heat production proposed to be mediated by brown fat is referred to as nonshivering thermogenesis. Nonshivering theremogenesis is a mechanism for maintaining body temperature when exposed to a cold environment. Opposed to this is shivering, which is a response to sudden cold exposure and relies on muscle contraction to produce heat. Based on cold adaptation studies with laboratory rodents, nonshivering thermogenesis mediated by brown fat has been shown to account for a substantial portion of energy expenditure (16, 17).

In normal rodents both diet-induced and nonshivering thermogenesis are adaptive mechanisms that result in hypertrophy and increased heat-producing capacity of brown fat. While brown fat constitutes approximately O. 5% to 1.0% of the body weight of non-cold-acclimated rats, the trophic response is characterized by a several-fold increase in tissue weight and proliferation of inner mitochondrial membrane (18, 19). The enhanced thermogenic capacity is associated with a corresponding increase in the concentration of uncoupling protein (20).

Brown Adipose Tissue in Humans

What role does brown fat-mediated thermogenesis ply in humans? In humans it is of primary significance in newborns, where its role in heat regulation is especially important for survival at a time when the surface area of the body is proportionately greater. Brown fat was believed to be nonexistent in the human adult until Heaton (21) reported results of autopsy studies describing its extent and localization as a function of age.

The principal criterion Heaton adopted for differentiating white from brown adipose tissue was the number of triglyceride droplets per cell; unilocular cells were classified as white adipocytes, whereas multilocular cells were considered brown adipocytes. She found brown adipocytes in nearly all adipose depots obtained from children 0 to 10 years old. Regression of the tissue occurs to the point where it accounts for only 1% of adult body weight and is localized in small deposits in the neck region and around the heart and kidney. Its continued role in thermogenesis is suggested, however, by data demonstrating a larger accumulation of brown fat in the cervical region of outdoor workers in Finland (22).

Brown Adipose Tissue and Energy Balance

The hypotesis that obesity may be the result of malfunctioning brown fat had its origin in an earlier observation of the inability of genetically obese mice to survive cold temperatures (23). Investigators at Cambridge University (24) tested this hypothesis by placing genetically obses and lean mice in a cool environment with equal amounts of food. Oxygen consumption and core body temperature measurements indicated that the genetically obese mice gained more weight because they devoted less energy to nonshivering thermogenesis. The difference in weight gain could be accounted for by the difference in energy applied to maintaining body temperature. By injecting norepinephrine, to mimic stimulation by the sympathetic nervous system, it was determined that lean mice have twice the capacity for nonshivering thermogenesis. Impaired head production in genetically obese mice has been traced to compositional and functional alternations in brown fat (25-28).

Increased metabolic efficiency in animal models of obesity has also been attributed to failure of diet-induced thermogenesis. In some strains of obese mice, the ability to adapt to alternations in food intake by a change in energy expenditure is poor, despite normal activation of their sympathetic nervous system by food intake (29, 30). Genetically obese rats have also shown impaired thermogenesis in response to a cafeteria diet, and brown adipose tissue does not increase in size as expected (31).

If brown adipose tissue and uncoupling protein increase with overfeeding in an attempt to waste excess kcalories, we would expect the reverse to be true in the underfed animal. Indeed, Trayhurn et. al (32) have shown this to be the case. They examined the effects of fasting and refeeding on the concentration of uncoupling protein in brown adipose tissue mitochondria in mice. Fasting appeared to induce a selective loss of uncoupling protein from brown adipose tissue mitochondria, which was rapidly reversible on refeeding.

In general, the ability of brown adipose tissue to waster or conserve kcalories parallels the physiological condition of the animal. While cold and overfeeding cause an increase in heat production, conditions in which metabolic efficiency is paramount lead to a decrease in brown fat and uncoupling protein. In addition to fasting, lactation, which is known as a state of formidable metabolic efficiency, causes the expected reduction in brown fat activity (33).

Although it is tempting to assign a role for brown adipose tissue in metabolic efficiency in humans, the evidence is tenuous. Presently, the contribution of brown fat to metabolic rate in adults has been estimated as minor (34). However, newer techniques might force a reappraisal of this conclusion. Lean et. al. (35) have described a solid-phase radioimmunoassay for estimation of uncoupling protein content of human brown adipose tissue mitochondria, as an index of thermogenic capacity. Variations in brown adipose tissue uncoupling protein content, which would be consistent with changing thermogenic requirements and capacity, were observed in different groups of subjects. As expected, significantly lower concentrations were found in adults and in pre-term and stillborn infants than in older infants and children. However, these investigators also provided evidence that brown adipose tissue function may be modifiable by norepinephrine in adults. Therefore, it is potentially accessible for pharmacological manipulations of body weight.

In conclusion, a current hypothesis is that differences in metabolic efficiency between humans is related to the state of uncoupling of brown adipose tissue mitochondria. The uniqueness of the physiological uncoupling of oxidative phosphorylation provides a wealth of possibilities for investigators involved in bioenergetics. The potential of these

findings is vast, bringing forth the possibility of manipulating body weight by changes in metabolic efficiency. Hopefully, these discoveries will have far-reaching effects for the achievement and maintenance of ideal body weight.

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