can be made, however, that in muscles the control of thermogenesis by increasing the ATP breakdown (during shivering) and by obstructing the ATP synthesis (during NST) might occur at the same time.
It can be stated that muscles contribute to a great extent not only to shivering, but also to NST. While during shivering muscles are the principle source of heat, during NST some other organs also contribute to the total thermogenesis. The organismic control of each of these heat production mechanisms is different; it is realized by somatic nerves during shivering and by sympathetic nervous system and hormones during NST. The most striking feature of muscles, in respect to heat production is that they can produce heat evidently by 2 different cellular mechanisms simultaneously.

Brown adipose tissue as an effector of nonshivering thermogenesis

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Occurrence

Brown adipose tissue (BAT) is the only organ whose main function is considered to be thermogenesis. The tissue is found only in homeotherms, although not in primitive mammals having imperfect thermoregulation (edentates and monotremes)[1]. Until recently believed to be absent from larger animals, BAT is now recognized as abundant in newborn lambs, calves and harp-seal pups and is also present in chronically cold-exposed primates, e.g. Macaca, Homo.
BAT occurs as discrete masses within the body core. The cervical, interscapular, axillary, para-aortic, mediastinal and perirenal deposits are the most common. In small animals the thoraco-cervical masses predominate, while in larger animals the abdominal deposits are more abundant.

Structure

About 80% of the tissue volume consists of multilocular adipocytes (MLA). Fully differentiated BAT is thus a rather homogeneous tissue. The average volume of the MLA is highly dependent upon the level of triglycerides stored. In the hamster, under the normal range of physiological conditions, the tissue triglyceride content will be 15–80%; the average cell volumes will then be, respectively, $4\text{–}30 \times 10^3$ μm^3 and there will be $\gg 5 \times 10^3$ and $\ll 0.4 \times 10^3$ triglyceride droplets per cell. The inverse relationship between triglyceride content and the number of triglyceride droplets results in a remarkably constant value (range 0.4–0.8 m^2 cm^{-3}) for the area of the triglyceride/aqueous phase interface, at which lipolysis is considered to occur[2].
A predominant ultrastructural feature of MLA is the abundance of mitochondria (volume fraction up to 0.3 in the rat). They are generally elongate or pleiomorphic with numerous, parallel-oriented cristae. The high respiration of the tissue is matched by a high amount of inner membrane (~ 10 m^2 cm^{-3}, compared to ~ 4 m^2 cm^{-3} in rat liver) and, correspondingly, high concentrations of respiratory enzymes[3,4]. The endoplasmic reticulum is considered to be sparse; however, smooth elements are found closely apposed to a major portion of the triglyceride droplet interface, as well as scattered throughout the cytoplasm, so the true abundance is likely to have been underestimated. A loose basketwork of fine, naked axon terminals studded with small varicosities surrounds each MLA. These nerves, as well as those innervating the capillaries, contain norepinephrine, so they can be revealed by the Falck-Hillarp fluorescence-histochemical technique. The presence of a direct innervation onto the adipocytes is considered to be one of the most reliable criteria of brown, as opposed to white, adipose tissue[5]. MLA are surrounded by capillaries; in the human, up to $^1/_3$ of the adipocyte surface may be in contact with endothelial cells[6]. This rich vascularization permits a high blood flow through the tissue upon stimulation by cold; the response is mediated by norepinephrine.

Ontogenic and seasonal changes

In the neonate, BAT is present at an advanced state of differentiation, except in the hamster. In the nonhibernator, the tissue later involutes, as expressed by a decreased respiratory capacity and an increased content of triglycerides per g tissue. These parameters are restored, entirely in the rat, and partially in the guinea-pig, to the typical postnatal condition by

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chronic exposure of the adult to cold[7,8]. In hibernators, a marked involution does not occur; instead, species-specific seasonal variations of blood flow, triglyceride content and composition, enzyme activities and norepinephrine content have been reported[9–12]. An increased triglyceride lipolysis in brown, but not in white, adipose tissue is characteristic of the cold-exposed state; indeed, this response is sometimes a more reliable way to distinguish between the 2 sorts of tissue than by their histological appearance[13]. These alterations are under hormonal, as well as nervous, control.

Function

The only hypothesis regarding the function of BAT currently receiving widespread support is that it participates in regulatory nonshivering thermogenesis (NST). Operationally, NST may be estimated from the maximal in vivo increase in oxygen consumption elicited by an appropriate dose of norepinephrine, when the animal is maintained within its thermoneutral zone.

Thermogenesis

Qualitative evidence that BAT is actively thermogenic has been obtained from experiments with implanted thermocouples. Upon exposure of the organism to cold, the BAT temperature increased, whereas the rectal temperature fell[14]; the same response in the BAT could be initiated by an injection of norepinephrine[15]. Thermography of babies exposed to cold has also shown the skin over the dorsal region is the warmest part of the surface[16]. As the blood flow through BAT is also increased by cold[17,18], it is obvious that there must be an appreciable production of heat by BAT. However, agreement has not been reached as to the precise physiological significance of this thermogenesis. The most convincing demonstration of BAT as a major source of NST has been obtained in experiments on the newborn rabbit, in which several conditions combine to favour the experimenter. These are: the relatively large size of the pup and the relatively large amount of BAT in the cervical region, as well as the usual attributes of the mammalian young; lack of insulation, high surface-to-volume ratio and poorly developed muscular activity. By cannulation, the arterio-venous difference of oxygen tension and an approximate measure of blood-flow through the tissue could be measured. By comparing the oxygen consumption of the BAT to the total increase of oxygen consumption elicited by norepinephrine, BAT was estimated to be responsible for about $^2/_3$ of total NST[19]. This corresponded well with the decreased oxygen consumption of pups from which the dorso-cervical BAT masses had been removed, when compared with sham-operated littermates[20].

The relative contributions of shivering and nonshivering thermogenesis have been assessed in the guinea-pig at different postnatal ages by the use of drugs to block these responses. The relative contribution of NST to total thermogenesis fell rapidly during the first weeks of postnatal life, in parallel with biochemical and morphological alterations of the tissue towards a white adipose tissue-like state. According to Huttunen, Vapaatalo and Hirvonen[21], the innervation to the adipocytes also disappears during this process. The maximal contribution of BAT to NST was estimated to be 50%, occurring during the immediate postnatal period[22].

In the cold-exposed lamb, NST provided about 40% of the increased heat requirement, the remainder being supplied by shivering[23]. BAT might account entirely for NST in the newborn[24].

The essential argument against the concept that BAT should have quantitative importance in the adult rat is the small contribution ($< 1\%$) of the tissue to total body weight. From estimates of tissue blood flow and oxygen consumption, BAT has been calculated to supply 6–13% of NST, which itself has been reported to range between 70 and 225% of resting metabolism (for details see Foster[25]). Thus, even after cold acclimations, BAT seems able to support only a small fraction of total thermogenesis in the adult rat.

Local warming

Two hypotheses have been proposed to reconcile the relatively small total heat production of BAT with its apparent physiological importance in the cold-exposed rat. Firstly, the venous drainage of the major

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deposits (interscapular and dorso-cervical) flows almost directly to the heart. The tissue may therefore have importance as local warming elements[26]. In the guinea-pig, thermosensitive elements have been discovered in the cervical CNS that suppress shivering thermogenesis, if kept above a (variable) threshold temperature[27]. Local warming is also of importance during arousal from hibernation, as the thoracic region warms first and only then is warm blood shunted peripherally[28-30]. It should be noted that conclusive evidence is now available that in the cold acclimated rat, the hamster and the human neonate, BAT exports free fatty acids in amounts that can cause plasma free fatty acid levels to rise[31-34]. In the hibernating hamster, BAT may export acetate[35]. These substrates will be delivered along with the heated blood to local target organs. The possible importance of substrate export from BAT for NST in the whole organism is as yet uninvestigated.

In conclusion, BAT is now known to be widely distributed in mammalian neonates, cold-stressed adults and in hibernators. This indicates a physiologically important role of the tissue for the efficient functioning of the organism in a cold environment. During the neonatal period, BAT can contribute half or more of nonshivering thermogenesis, but the tissue involutes as other thermoregulatory mechanisms (insulation, muscular activity) become effective. In adult animals in the cold, BAT is attributed a local warming function on the CNS and heart, and it also exports free fatty acids in the heated blood. Just as white fat produces a certain amount of heat in addition to free fatty acids, so brown fat produces free fatty acids as well as heat. The most important qualitative differences between the 2 tissues, apart from the ratio in which each releases its products, might then reside in their control systems, which cause an activation of BAT by cold and of white adipose tissue by starvation. BAT has also been hypothesized to have an endocrine function, but the evidence for this is conflicting. An important source of technical difficulties, and hence ambiguities in the interpretation of results, can be traced to the diffuse distribution of BAT within the small rodents generally used for research. The appreciation that neonates of larger animals also have brown adipose tissue, which is largely concentrated to the abdominal cavity, may aid future attempts to define more precisely the ways by which this tissue affects thermogenesis.

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Role of the plasma membrane in brown fat thermogenesis

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The plasma membrane is the site of several mechanisms involved in the cold-induced heat generation by brown adipocytes. On the one hand, membrane receptors recognize an extracellular signal that arrives at the brown adipocyte in the form of graded amounts of norepinephrine (NE) as released from nerve terminals near the cell. This incoming signal originates in a complex neural network involving thermoreceptors strategically situated to provide the central nervous system with inputs that are integrated and channelled over efferent sympathetic pathways. Following recognition by the membrane, the extracellular signal is converted to an intracellular message capable of activating the metabolic pathways that result in elevated rates of brown fat heat production. Finally, the plasma membrane appears to function, to a certain extent, as part of the thermogenic effector mechanism itself. Thus, there are at least 3 aspects of brown fat thermogenesis with which the cell membrane is directly associated – recognition of the extracellular signal, transduction of this signal to an intracellular message, and conversion of chemical and potential energy to heat. These 3 aspects are the focus of the following discussion.

Recognition of the extracellular signal

The brown adipocyte membrane has both α-and β-adrenergic receptors for detection of the extracellular information. The evidence that activation of brown fat thermogenesis involves β-adrenergic receptors and