Contribution of striated muscles to regulatory heat production

by L. Janský

Department of Comparative Physiology, Faculty of Sciences, Charles University, 128 44 Praha, ČSSR

All homeotherms, including man, when exposed to lowered temperatures, tend to loose heat and thus, tend to become hypothermic. Therefore, the heat loss must be compensated by the increased heat production within their bodies, in order to maintain the heat balance.

Shivering thermogenesis

The most obvious mechanism producing heat during defence to cold is muscular tremor (shivering)[1]. Shivering appears as fine rhythmic movements of muscles or even limbs, which do not induce any substantial changes in body position. It is realized by randomly appearing contractions, occurring simultaneously in both flexor and extensor muscles. Shivering is involuntary, but it is very sensibly regulated by centers located in the hypothalamus. The effector pathways involve somatic nerves.

Shivering can be observed in almost all muscles of the body, the greatest intensity being recorded in neck and the smallest in leg muscles. Shivering has a complex behaviour; it is discontinuous and fluctuates between different areas of the body. In man, it appears after 2 min of cold exposure and becomes generalized within 24 min.

From the thermoregulatory point of view shivering is an effective process, since it increases the resting heat production by a factor of 2 or 3. In muscle cells, the energy is generated from ATP[2]. Contractile proteins in the muscle break ATP to ADP, anorganic phosphate and energy. The availability of ADP becomes thus a crucial factor responsible for the intensity of oxidative phosphorylation. It can be stated that the intensity of heat production in muscles is related to the rate of ATP breakdown.

Nonshivering thermogenesis

Already 100 years ago, it was realized, however, that in addition to shivering, there exists another source of heat, able to maintain the heat balance in some cold exposed animals, because the transection of the spinal cord or curarisation did not influence the body temperature substantially.

Since 1950's an extensive work has been done on this subject and the term 'nonshivering thermogenesis' was suggested for this additional mechanism of heat production. Regulatory nonshivering thermogenesis (NST) has been defined as a heat production mechanism occurring in cold exposed homeotherms, which liberates chemical energy due to processes not involving muscular contractions[3].

Nonshivering thermogenesis is also under the control of hypothalamic thermoregulatory centers, but, contrary to shivering, the effector pathways involve the sympathetic nervous system. A substantial activation of all hormonal glands also occurs during NST. In target cells the NST is based on calorigenic action of some hormones, namely noradrenaline.

Nonshivering thermogenesis is additional to shivering and takes place at mildly lowered temperatures, while for induction of shivering a heavier cooling load is necessary, in animals possessing both components of heat production. It appears predominantly in small mammals and in newborns and can increase heat production to the same extent as shivering.

Great attention was paid to the problem of localization of heat production during NST[4]. Originally, visceral organs were considered as the main source of heat under these conditions, since it was found that the liver temperatures increased in cold exposed animals. However, since temperature changes of body organs are affected by organ blood flow and do not give any quantitative data on heat production, an additional method was sought to solve this problem.

Substantial progress in this field was made possible when the technique of cannulation of small vessels was elaborated and when the oxygen extraction from the blood could be measured under physiological conditions. It was shown that oxygen consumption of skeletal muscle increases considerably in curarized animals exposed to cold, as well as in those infused by noradrenaline. The direct method, together with the indirect ones, based on measurements of total cytochrome oxidase activity in the carcass and on measurements of the maximum oxygen delivery by blood to body organs, indicated that the skeletal muscles are the main heat producing organ, contributing to the total NST by about 50% in adult rats. These findings, however, do not exclude a participation of other organs during NST, namely of the brown adipose tissue and of abdominal organs.

Cellular mechanisms which produce heat during NST are far from being clear. In the brown adipose tissue it was found that the metabolism is controlled by mechanisms obstructing the ATP synthesis (loosening of phosphorylation from oxidation), which induces a relative surplus of ADP[2]. Whether or not this mechanism occurs also in muscles is not known. Conclusion

1 A. Hemingway, Physiol. Rev. *43*, 397 (1963).
2 J. Himms-Hagen, Ann. Rev. Physiol. *38*, 315 (1976).
3 L. Janský, Biol. Rev. *48*, 85 (1973).
4 L. Janský, in: Nonshivering Thermogenesis, p. 159. Ed. L. Janský. Academia, Prague 1971.

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

by T. Barnard

The Wenner-Gren Institute, University of Stockholm, Stockholm, Sweden

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, $4\text{–}30\times10^3$ μm^3 and there will be $\geqslant 5\times10^3$ and $\leqslant 0.4\times10^3$ 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 ($\sim$ 10 $m^2\ cm^{-3}$, compared to $\sim$ 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

1 U. Rowlatt, N. Mrosovsky and A. English, Biologia Neonat. *17*, 53 (1971).
2 I. Ahlabo and T. Barnard, J. Ultrastruct. Res. *48*, 361 (1974).
3 T. Barnard, J. Skala and O. Lindberg, Comp. Biochem. Physiol. *33*, *499* (1970).
4 S. Prusiner, B. Cannon and O. Lindberg, in: Brown Adipose Tissue, p. 283. Ed. O. Lindberg. American Elsevier, New York 1970.
5 H. Daniel and D. M. Derry, Can. J. Physiol. Pharmac. *47*, 941 (1969).
6 W. Ahearne and D. Hull, J. Path. Bact. *91*, *223* (1966).