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The regulation of the biological furnace of warm blooded animals

Introduction

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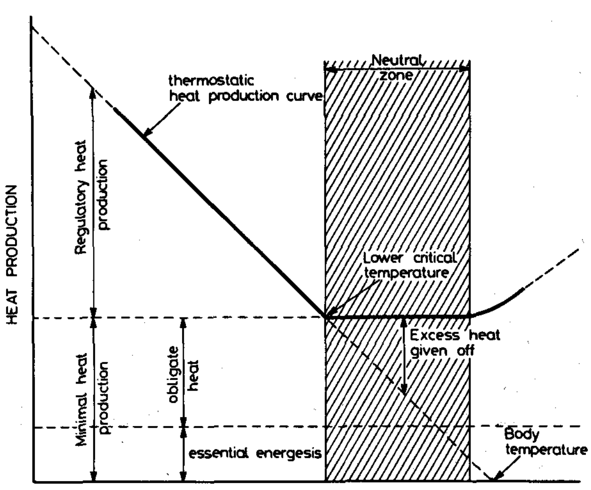
Mammals are described as warm-blooded animals because of their ability to maintain a blood temperature higher than that of their normal environment. One of their most striking attributes is the capacity to regulate temperature so that it remains relatively constant under a great variety of conditions. Except for marsupials and monotremes, the temperature of mammals, whether they weigh 10 g or 10 t, lies within the narrow range of 36–38 °C[1]. The development of this capacity was a crucial step in the evolving emancipation of higher organisms from the effects of changes in their environment.

Homeothermy, i.e. the maintenance of a stable blood temperature, obviously involves a delicate balance between heat production and heat loss. The latter varies within a very wide range depending upon physical conditions and the former must therefore vary accordingly to meet the changing demands.

The heat production curve

In general the graph obtained by plotting heat production of a resting homeotherm as a function of ambiant temperature has certain characteristics that are schematized in the figure. If resistance to heat flow were independent of temperature, the thermostatic heat requirement would follow an approximately straight line decreasing to zero for an effective environmental temperature equal to the body temperature. The fact is, however, that when the effective environmental temperature increases above a certain level (lower critical temperature) there is no further decrease in heat production which then remains constant within a range called the neutral zone. Beyond this zone, the environmental temperature is so high that the animal is unable to get rid of the heat which it produces. The slope of the thermostatic heat requirement and therefore the critical temperature as well, depend on the integumental insulation of the animals. The total heat production of a homeotherm can be schematically divided into 2 fractions, minimal and thermoregulatory. The minimal heat production fraction can, in turn, be subdivided into essential energesis and obligate heat.



This diagram illustrates the heat production of a fasted, resting homeotherm as a function of the ambiant temperature.

Essential energesis

Because of the dynamic state of their constituents, all cells, even those seemingly at rest, produce entropy. By means of isotopic tracers, it has been found that the concentration of most biomolecules remain constant due to a perfect balance of the building up (anabolism) and breaking down (catabolism) processes. Since catabolic reactions are generally exergonic with the energy dissipated as heat, the corresponding anabolic reactions cannot proceed spontaneously and must use different pathways requiring energy. It can be seen, therefore, that the cell maintains its structure by means of specific cycles of orderly and well regulated reactions which necessarily produce entropy. This cyclic process is the core of the dynamic state and an essential

1 R. Morrison and F. A. Ryser, Science *116*, 231 (1952).

distinguishing characteristic of the living organism[2]. Another characteristic is active transport, i.e. transport of solutes across membranes against the direction in which they would normally diffuse. This is the mechanism by which the cell is able to maintain its solute and ion concentrations at different levels from those in the milieu. Large differences in solute and ion concentrations are thus constantly being built up and result in spontaneous back-flow through the membrane, which, at steady state, compensates for the active transport. Since this cyclic process, like the dynamic maintenance of cell structure, requires constant work, it is evident that a certain energy exchange is necessary for the life of every cell and therefore of every animal. In addition to this energy requirement, the animal must also expend energy for nerve, digestive, renal, circulatory and pulmonary function for integration and for supply of food to the cells. The total sum of these three energy expenditures is what Swan[3] has termed 'essential energesis'.

Obligate heat

This essential energesis, however, could not have produced sufficient heat to maintain the body temperature at a level above that of the environment for any except the largest of the homeotherms. For smaller animals, including man, another form of continuous metabolism designed especially to produce heat was clearly necessary and comparative studies of metabolism show, in fact, that the evolutionary appearance of homeothermy is associated with a sharp rise in metabolic activity. The rate of heat production of a 200-g-rat for example, is 5 times higher than that of a reptile of the same body weight corrected for the same temperature[4].

Assuming that heat dissipation of the resting reptile represents the essential energesis of any animal of the same weight, it can be estimated that $^4/_5$ of the heat production of the rat is used for maintaining its temperature at 38°C. This fraction of the minimal heat production is termed obligate heat[3]. The use of this obligate heat, however, would be feasible only for animals that had already evolved a thermally insulative integument, since without one an exorbitant increase in heat production would be necessary to maintain the body temperature at a level distinctly higher than that of the environment[5]. This higher level is a necessary condition for autonomous temperature regulation since it allows for the adjustment of heat dissipation by controlling the supply of blood to, and evaporation of moisture from, the surface of the body, thus altering the effective insulation. It is possible that obligate heat is a product of normal metabolism under continuous stimulation. If so, this stimulation would have a long time constant since minimal heat production of a homeotherm in vivo has been found to be approximately equal to the sum of heat production of each of the body tissues, as measured in vitro[6], indicating that obligate heat is controlled by factors still present in the tissue, and no longer under the direct influence of the central regulator. Some of these factors are controlled by the thyroid hormone whose calorigenic action has been observed to peak after 48 h. The mechanism by which the thyroid hormone could control the thermogenic factors of the tissue might be related to an evolutionary increase in sodium permeability of cell membrane which may have occurred in the late tertiary period and a consequent increase in the requirements for osmotic work performed by the thyroxine-stimulated sodium pump[7]. This mechanism, however, cannot account for all of the obligate heat since the minimal heat production of the thyroidectomized rat is greater than that of a reptile of the same weight.

Regulatory heat

The range of temperature within which homeothermy can be maintained is considerably extended by the ability of the animal to produce the extra heat known as regulatory heat. The distinguishing characteristics of regulatory heat are its short time constant and its continuous regulation by the central nervous system. Our knowledge of this fraction of the animal's total heat production has grown considerably in recent years and some of the interesting findings will be presented in the following papers. Skeletal muscle as a major effector of regulatory heat is discussed by L. Jansky. Brown adipose tissue, a specialized effector organ of regulatory heat is described by T. Barnard. The short time constant of brown adipose tissue heat production following sympathetic nerve stimulation is demonstrated by J. Seydoux and L. Girardier, whereas B. Horwitz and J. Horowitz discuss brown adipose tissue as a model for the study of the intracellular recording of the nerve signal and D. Nicholls proposes a unique mechanism of controlled mitochondrial coupling in brown adipose tissue which may be the crux of its thermogenesis.

Although only 2 effectors of regulatory heat have been discussed in this series of papers, it is certain that other organs also play some role which remains to be evaluated.

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