MINI REVIEW

Role of the Sarcoplasmic Reticulum Ca\(^{2+}\)-ATPase on Heat Production and Thermogenesis

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The sarcoplasmic reticulum of skeletal muscle retains a membrane bound Ca\(^{2+}\)-ATPase which is able to interconvert different forms of energy. A part of the chemical energy released during ATP hydrolysis is converted into heat and in the bibliography it is assumed that the amount of heat produced during the hydrolysis of an ATP molecule is always the same, as if the energy released during ATP cleavage were divided in two non-interchangeable parts: one would be converted into heat, and the other used for Ca\(^{2+}\) transport. Data obtained in our laboratory during the past three years indicate that the amount of heat released during the hydrolysis of ATP may vary between 7 and 32 kcal/mol depending on whether or not a transmembrane Ca\(^{2+}\) gradient is formed across the sarcoplasmic reticulum membrane. Drugs such as heparin and dimethyl sulfoxide are able to modify the fraction of the chemical energy released during ATP hydrolysis which is used for Ca\(^{2+}\) transport and the fraction which is dissipated in the surrounding medium as heat.

KEY WORDS: Ca\(^{2+}\)-ATPase; Ca\(^{2+}\) transport; energy interconversion; ATP hydrolysis; heat production; sarcoplasmic reticulum

THERMOGENESIS

Heat generation and burning calories are implicated in the regulation of several physiological processes including body temperature, metabolism, body weight, energy balance and cold acclimation. At least two different systems are known to be involved in the process of nonshivering thermogenesis and these are the uncoupling proteins (UCP) and the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase of skeletal muscle. In both systems the process of heat dissipation is initiated by the leakage of ions through the membrane, protons in the case of the UCPs and Ca\(^{2+}\) in the case of the Ca\(^{2+}\)-ATPase [1–7].

Different uncoupling protein (UCP) isoforms have already been identified [4–7]. These include UCP1 specific for brown adipose tissue, UCP2 found in most tissues and UCP3 which is highly expressed in skeletal muscle. From the three isoforms, only UCP1 is clearly involved in heat production. The physiological role of UCP2 and UCP3 is still controversial [4–7]. The different UCP isoforms promote

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the dissipation of the proton electrochemical gradient formed across the inner mitochondrial membrane during respiration. In order to restore the gradient and to prevent the decrease of the cytosolic ATP concentration, the proton leakage promoted by the UCP leads to increased mitochondrial respiration, increase fatty acid oxidation and heat production.

Skeletal muscle is by far the most abundant tissue of the human body and accounts for over 50% of the total oxygen consumption in a resting human and up to 90% during very active muscular work. Calorimetric measurements of rat soleus muscle indicate that 25–45% of heat produced in resting muscle is related to Ca\(^{2+}\) recirculation between sarcoplasm and sarcoplasmic reticulum [8]. Ca\(^{2+}\) leakage from the reticulum is accompanied by an increase of the Ca\(^{2+}\)-ATPase activity needed to pump back Ca\(^{2+}\) into the reticulum. In steady state conditions the Ca\(^{2+}\)-ATPase is able to synthesize ATP from ADP and P\(_i\) using the energy derived from the Ca\(^{2+}\) gradient [9–11] but the amount of ATP synthesized is much smaller than the amount of ATP cleaved and therefore an increase of Ca\(^{2+}\) leakage from the reticulum ultimately leads to increased mitochondrial respiration to maintain the cytosolic ATP concentration [3, 4].

Conditions that promote a change of the rate of heat production in animals are usually associated with changes of expression of both, the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase and UCP proteins. Thus, during cold adaptation, UCP1, and UCP2, but not UCP3 are overexpressed [6, 7, 12–14]. Similarly, in cold-acclimated ducklings, there is a 30–50% increase of both sarcoplasmic reticulum Ca\(^{2+}\)-ATPase and ryanodine-sensitive Ca\(^{2+}\) release channels. In cold-acclimated ducklings 70% of the total heat production is derived from muscle [15, 16]. The expression of both sarcoplasmic reticulum Ca\(^{2+}\)-ATPase and UCP1 are decreased in hypothyroid rats. In these animals, the injection of the thyroid hormone 3,5,3′-triiodo L-thyronine (T\(_3\)) increases the expression of both Ca\(^{2+}\)-ATPase and UCP1 [12, 17–20].

A curious system that highlights the importance of the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase in heat production is the heater tissues of billfishes. In marlin and swordfish, ocular muscles are transformed into specialized heater tissues [3]. During the daily fluctuations in temperature, the swordfish reduces the temperature changes experienced by the brain and retina by warming these tissues with the heater organ. The heater tissues are composed of modified muscle cells in which the contractile filament is virtually absent and the cell volume is packed with mitochondria and a highly developed sarcoplasmic reticulum. Activation of thermogenesis seems to be associated with the ATP-dependent cycling of Ca\(^{2+}\) at the sarcoplasmic reticulum. Mitochondrial respiration is then stimulated by cytosolic ADP generated by the Ca\(^{2+}\)-ATPase, the result being increased heat production.

Altered thermogenesis is observed in different pathological conditions as for instance obesity and the hypothermia noted during ischemia. Obesity results from a chronic imbalance between energy intake (feeding) and energy expenditure. Ischemia and hypoxia elicits hypothermia as a compensatory mechanism to oxygen deprivation. Obesity affects more than one-third of the U.S. population and is a major public health concern because it is associated with diabetes, hypertension and cardiovascular disease. In different studies it was shown that some humans resist fat gain with overeating, whereas others readily store excess fat [21–23]. The resistance