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Mini-Review

A discussion of heat generation during a fever

Weidong Zhou*, Lance A. Liotta and Emanuel F. Petricoin

Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, Virginia 20110, USA.

ABSTRACT

Fever can be caused by pathogen infection. We analyze the thermogenesis mechanism and reveal that heat is naturally generated during the immune system's fight against pathogen infection. Particularly, the heat production by reactive oxygen species that originates in the respiratory burst significantly contributes to the fever development. This analysis can help address mechanisms of SARS-CoV-2 pathogenesis or provide a foundation for future mechanistic inquiries.

KEYWORDS: fever, thermogenesis, reactive oxygen species, respiratory burst, SARS-CoV-2.

Introduction

It is a well-accepted concept that the normal range of human body's temperature is 36.5 °C-37.5 °C and the temperature is regulated in the preoptic area in the hypothalamus [1]. Bacterial and viral infections (such as influenza and SARS-CoV-2) can trigger the release of prostaglandin E2 (PGE2) that acts on the hypothalamus to reset the body temperature to a higher degree, achieved by increased heat generation and decreased heat loss (such as peripheral vasoconstriction). Fever is characterized by an elevated temperature that is above the normal range, though fever is defined by some scholars as the point in which the core temperature is above 38.3 °C [2]. Fever phobia is not rare among people who believe that fever is a disease [3]; however, some physicians view fever as a host defense mechanism, a beneficial response to infections that taking a fever reducer is not needed if the body temperature is not greater than 38.5 °C [4]. Here we attempt to dissect the fever-related heat production mechanism from a biochemical point of view.

*Corresponding author: wzhou@gmu.edu

Thermogenesis

In mammalian cells, heat can be generated by the hydrolysis of adenosine triphosphate (ATP), proton (H^+) decoupling, and reactive oxygen species (ROS) annihilation [5]. Firstly, ATP, referred to as the 'molecular unit of currency' of intracellular energy transfer, provides energy to drive many processes in living cells, such as muscle contraction, ion transport, and synthesis of proteins, DNA, and RNA [6]. One method to raise temperature is through shivering, in which the increased muscular activity results in the generation of heat as a byproduct [7]. In addition, heat will be produced in the ATP-dependent biosynthesis of cytokines and antibodies that are utilized for immunological defense. The duplication of immune cells and the proliferation of pathogens inside the host require energy and consequently release heat as well (Figure 1). Secondly, the oxidative phosphorylation in mitochondria normally allows the synthesis of ATP from ADP using H^+ gradient; however, energy is dissipated as heat when the H^+ movement is decoupled from this pathway. It is reported that brown adipose tissue has such a unique uncoupling protein that allows the heat to be generated in febrile response [7-9]. Thirdly, heat can be generated from ROS. ROS can be

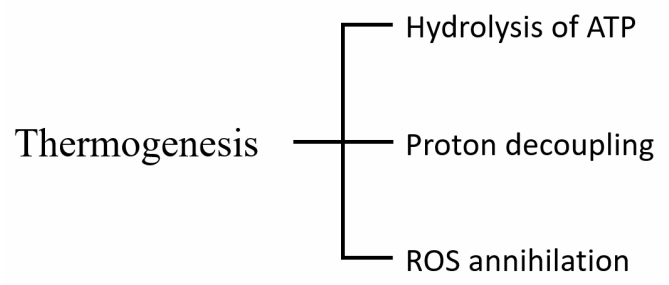

Figure 1. Mechanism of thermogenesis in human cells. The chemical energy from glucose is stored in synthesized ATP by a series of biochemical reactions including glycolysis, Krebs cycle, and oxidative phosphorylation. Heat is produced while ATP is consumed in biosynthesis and in the transportation of molecules. The hydrolysis of ATP into ADP and inorganic phosphate releases 20.5 kJ/mol of enthalpy [15]. The proton gradient used for ATP synthesis can be decoupled by the uncoupling protein (UCP) located in mitochondrial inner membrane. The energy lost in dissipating the proton gradient is not used to do biochemical work and heat is generated instead. This type of thermogenesis plays a role in cold exposure or hibernation [16, 17]. In addition, high energy reactive oxygen species (ROS) can be generated due to electron uncoupling in the oxidative phosphorylation pathway. Heat is spontaneously generated when the ROS is destroyed to form water through chemical reactions [5]. ROS, superoxide anion and hydrogen peroxide can be rapidly released from phagocytic leukocytes by the respiratory burst. The formation of these oxidizing molecules is catalyzed by the NADPH oxidase which transfers electrons from cytosolic NADPH (produced via pentose phosphate pathway) to oxygen in the phagosome [11]. This mechanism is unappreciated in previous research.

formed in mitochondria when electron movement is decoupled in the oxidative phosphorylation pathway. ROS are high-energy-containing particles and heat will be released when they are destructed. Previous studies of ROS were focused on roles in protein/DNA damage and signal transduction, particularly in the cellular immune response and cancer research [10]; however, its involvement in thermogenesis is a neglected topic. It has been reported that phagocytic leukocytes (such as macrophages and neutrophils) employ 'respiratory burst', a phenomenon of rapid release of ROS to destroy the engulfed pathogens [11]. The main products of the respiratory burst are strong oxidizing agents including hydrogen peroxide, free oxygen radicals, and hypochlorite, which are vital for the host's innate immune response [12, 13]. Heat production is a natural consequence when these oxidizing agents are finally annihilated. In mammalian cells, oxygen is the final electron acceptor and oxygen consumption is proportional to the heat production. Since the respiratory burst requires a 10 to 20-fold increase in oxygen consumption, a large amount of heat will be produced while the internalized pathogens are degraded. On the one hand, it is possible that the body temperature can temporarily reach up to a degree over the desired point set by hypothalamus, namely hyperthermia [14]; on the other hand, an abrupt excessive oxygen consumption from the respiratory burst may result in hypoxia in the surrounding area (Figure 2).

Conclusion

In conclusion, understanding the thermogenesis mechanism is essential for drug development and the treatment of fever. The heat production by ROS that arises in the respiratory burst stands out as noteworthy. The notion that the immune system's fight against pathogen infection is accompanied by spontaneous heat generation may help lessen people's fear of body temperature elevation. If the fever-reducing medicine works by down-regulating the crucial respiratory burst, recovery could be delayed since the pathogen is still proliferating even though body temperature is back to normal. Unsurprisingly, many physicians believe that mild fever does not necessarily need to be treated based on previous clinical observations. Certainly, body temperature should be closely monitored and medication can be considered to bring the body temperature down to the safe range to avoid a high fever's deleterious effects on organ and cellular function.

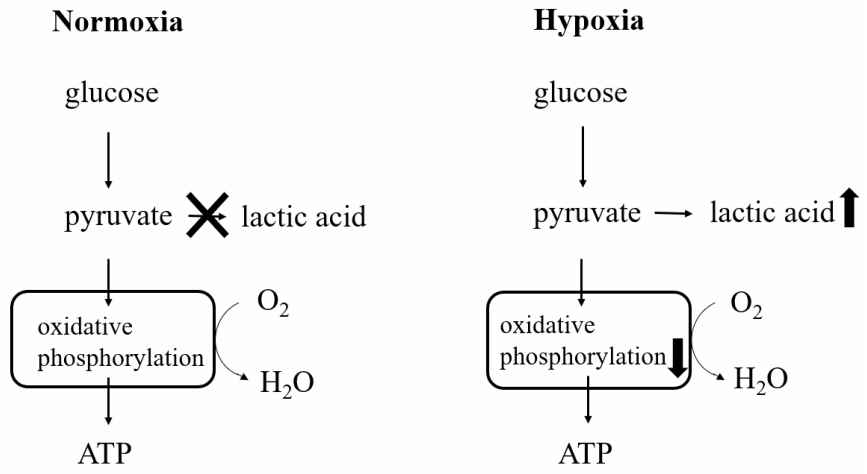

Figure 2. Cellular respiration in humans. Human cells use aerobic respiration to synthesize ATP, a process in which electrons are shuttled to an electron transport chain and oxygen is the final electron acceptor [18]. Under normoxia condition, the pyruvate molecules produced by glycolysis are actively transported into mitochondria for subsequent chemical reactions to produce ATP; under hypoxia condition, a hybrid approach is adopted — a portion of pyruvate molecules can be converted to lactic acid, known as fermentation. Fermentation is an oxygen-independent metabolic pathway, and it is a respiration mechanism that normally occurs in an anaerobic environment. Since it does not use an electrochemical gradient but instead uses only substrate-level phosphorylation to produce ATP, fermentation is less efficient at using the energy from glucose: only 2 ATP are produced per glucose, compared to the 38 ATP per glucose produced by aerobic respiration under normoxia condition. Generalized hypoxia occurs in healthy people during strenuous physical exercise or when they ascend to a high altitude [19]. The speedy and extensive oxygen consumption by the respiratory burst in macrophages and neutrophils can cause hypoxia to happen during inflammation. We have proposed that the long-term-inflammation-induced-hypoxia promotes gene mutations in epithelial cells and selects the cell that is adapted to a low-oxygen environment, resulting in carcinoma initiation. Indeed, cancer cells utilize this hybrid respiration mechanism (aerobic respiration and fermentation coexist with each other) with up-regulated lactic acid fermentation and down-regulated oxidative phosphorylation capacity in order to minimize oxygen consumption in the hypoxia environment [5].

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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