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Opinion

A Biochemical Point of View of Fever

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Introduction

Living organisms are able to carry out a highly integrated network of biochemical reactions, known as metabolism, in order to convert nutrients into energy and building blocks for growth and repair. Many biochemical reactions in cells are enthalpy-favoured exothermic reactions, which release heat. Among these reactions, some can release enough energy to drive the synthesis of NADH ($NAD^+ + 2e^- + H^+ \rightarrow NADH$, entropically unfavoured). The energy preserved in NADH subsequently can be utilized to generate ATP through oxidative phosphorylation, ultimately reducing oxygen to water [1]. For an entropically unfavoured biochemical reaction, such as protein synthesis, a decrease in disorder or randomness occurs. However, the reaction can proceed by utilizing the heat released from ATP hydrolysis to compensate for this entropy decrease, since the overall change in Gibbs free energy (ΔG) determines the spontaneity of a reaction, and ΔG is influenced by both enthalpy and entropy [2]. In addition to hydrolysis of ATP, heat generation can be achieved by proton decoupling and Reactive Oxygen Species (ROS) annihilation [3].

It is an established concept that the normal human temperature is around 37°C and temperature is sensed by the peripheral and central thermoreceptors. The preoptic area in the hypothalamus is involved in temperature regulation, and the physiological core body temperature can be maintained by balancing heat generation with heat loss [4]. If a person is exposed to a cold environment for a prolonged period, hypothermia (body temperature below 35°C) occurs, because the body loses heat faster than it can produce it or preserve it by vasoconstriction [5]. On the contrary, if a person engages in strenuous exercise or has prolonged exposure to high temperature, hyperthermia (body temperature greater than 38.3°C) occurs because the body produces or absorbs more heat than it dissipates by vasodilation and sweating [6,7]. Another type of abnormal body temperature increment is fever, a well-known phenomenon due to bacterial and viral infections. It is a widely held belief that the infections trigger the synthesis of prostaglandin E2 (PGE2), which acts on the hypothalamus to reset the body temperature to a higher degree, achieved by increased heat generation and decreased heat loss [8]. As such, hyperthermia is an increase in body temperature over the temperature set point, due to either too much heat production or not enough heat loss [9].

Opinion

Milton and Wendlandt reported that injection of prostaglandin into the cerebral ventricles of a cat produced a rise in body temperature, accompanied by shivering, in 1971 [10]. The report prompted follow-up studies, in which many researchers postulate that infections reset the body temperature by hypothalamus and PGE2 is a mediator of fever [11,12]. It is assumed that the currently measured core body temperature is the new setpoint. The setpoint can be adjusted to a safe range (below 39°C), or it can be inappropriately adjusted to a dangerous range (above 39°C) for some adult patients. Since some patients display shivering (a method of heat generation by muscle contraction and hydrolysis of ATP) during a fever, this proposition provides a popular explanation that patients feel cold after the body temperature is adjusted to a higher setpoint. However, since shivering can occur when people are excited, nervous, or afraid with normal body temperature, it is possible that shivering is one of many complications due to pathogenic infections. Noticeably, the role of PGE in the pathogenesis of fever was questioned by some researchers who argued that PGE antagonists were unable to block fever [13]. We also think that the current adjustable setpoint theory is unsound for several reasons. Firstly, PGE2 is commonly used for labour induction. It has been reported that half of the recipients displayed elevated temperatures while the other half did not [14]. Secondly, there is no report that the PGE2 level measured in the body closely correlates with body temperature and vice versa. Thirdly, it

has been suggested that some commercial antipyretic drugs work by inhibiting cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes into various prostaglandins. Thus, the synthesis of PGE2 is inhibited by the drugs and the setpoint is readjusted to a lower range [15]. However, we seldom hear complaints that the body temperature will be readjusted to a subnormal range, such as 35 °C, if one or two extra doses are taken.

Some researchers suggest that fever contributes to host defence by hindering reproduction of pathogens and increases the rates of some important immunological reactions [8,16-18]. However, many biochemical reactions in human cells are catalysed by enzymes that have optimum activity at 37°C after numerous years of adaptation. There is no report that fever can kill bacteria and viruses, and it is certain that the enzymes involved in cytokine synthesis and immune cell duplication do not have optimum activity in elevated body temperature. Heat will be produced in the ATP-dependent biosynthesis of cytokines and antibodies that are utilized for immunological defence. Additionally, the duplication of immune cells requires energy and consequently releases heat. For instance, a high neutrophil count (neutrophilia or neutrophilic leucocytosis) can be caused by most bacterial infections [19]. More strikingly, high-energy-containing ROS molecules are abundantly produced in phagocytic leukocytes (such as macrophages and neutrophils), by a mechanism named "respiratory burst", to destroy the engulfed pathogens [20-24]. When the oxidizing agents are finally scavenged or destroyed, heat will be released as a byproduct. Since it has been reported that a 10 to 20-fold increase in oxygen consumption occurs in this process and oxygen consumption is generally proportional to the heat production, a large amount of heat will be spontaneously produced by the immune cells to elevate body temperature [25]. It is possible that some immune cells also are damaged or killed by ROS, since it is known that pus is formed by dead pathogens and immune cells [26]. In conclusion, we think that the development of the theory that body temperature can be reset upon infections is largely attributed to previously limited knowledge of thermogenesis in immune cells. We propose that the human body temperature is evolutionarily maintained at around 37°C and the resetting of body temperature by the hypothalamus upon pathogen infection does not happen. It is likely that pyrogens, such as lipopolysaccharides (LPS) and cytokines, can cause elevated body temperature by metabolic regulation or involvement in heat-generating immune response such as in respiratory burst. Thus, we support a concept that the traditionally defined "fever" can be viewed as infection-induced hyperthermia.

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Conflicts of Interest

None.

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