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Perspective on fever: The basic science and conventional medicine

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Summary This review describes how fever is generated as a regulated increase in body temperature. It results from an upward shift in the thermoregulatory set point, mediated by pyrogenic cytokines released from monocytes/macrophages in response to infection or trauma. Evidence will be presented that fever is part of an integrated host defense system, and that failure to generate a fever in response to infection is generally associated with a poorer prognosis.

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''Normal'' body temperature

Maintaining a constant, stable body temperature is a critical aspect of homeostasis since the biochemical reactions involved in metabolism are exponentially dependent upon temperature.[1] This relationship is often expressed as the change in reaction rate over a 10 °C change in temperature, called the Q_{10}. Most reaction rates double or triple over such a range, resulting in a Q_{10} of 2 or 3. Nevertheless, temperature is not uniform throughout the body. Deep tissue (core) temperature is higher than peripheral temperatures in the extremities and the skin. Core temperature varies in a diurnal manner, approximately 0.8—1.0 °C higher during the day than at night. In women, menstrual cycle variations exist, with ~0.5 °C higher average temperatures in the luteal phase than in the follicular phase.[2] ''Normal'' core temperature also varies among individuals. Rather than the nominal 37 °C (98.6 °F), ''normal'' oral temperature may range from 35.6 °C (96.1 °F) to 38.2 °C (100.8 °F).[3] A discussion of various body temperature measurement methods can be found in Avner.[4]

Physiological mechanisms for temperature regulation

Fever is a regulated increase in body temperature above ''normal''. It is mechanistically distinct from the hyperthermia that occurs during exercise or exposure to a hot environment. The mechanisms for each are described:

Hyperthermia

During exercise, increased metabolic heat production causes an increase in body core temperature that exceeds the thermoregulatory reference temperature. This reference or ''set-point'' temperature is established by the firing rate of thermoregulatory neurons in the hypothalamus.[5] In response to the mismatch between actual and set-point temperatures (the ''load error''), effector mechanisms for heat dissipation, such as sweating and cutaneous vasodilation, are called into action. This negative-feedback loop for thermoregulation is depicted in Fig. 1. During hyperthermia, cooling the skin by convection or application of cool water will aid in heat removal, bringing body temperature closer to set-point, reducing the load error, and thus providing an improved sense of comfort.

Fever

In contrast, fever is initiated by an increase in set point. Body temperature is now below this reference temperature and as a result, a person may begin to shiver to generate heat, and will feel ''chills'', which will promote behavioral responses to conserve heat such as wrapping in a blanket or moving to a warmer environment. Cutaneous vasoconstriction will also ensue in order to conserve heat by reducing heat loss to the environment. Since the body is actively generating additional heat and recruiting mechanisms to retain heat, attempts to bring down body temperature by cutaneous cooling imparts additional metabolic stress and discomfort. A fever ''breaks'' when the set-point reverts back to ''normal''. As a result, body temperature is now greater than set-point, so heat dissipation mechanisms such as cutaneous vasodilation and sweating are engaged. In addition, a person will feel hot and respond behaviorally by shedding heavy clothing and seeking a cooler environmental temperature. This sequence of events is illustrated in Fig. 2.

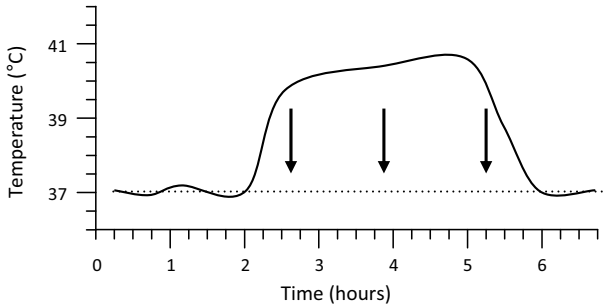

Figure 1 Thermoregulatory mechanisms during hyperthermia. A subject begins to exercise at the 2-hour time point. Metabolic heat production increases, temporarily produced at a greater rate than it is dissipated, causing core temperature to increase. Effector mechanisms (cutaneous vasodilation, sweating) are recruited to increase the rate of heat loss. At steady state (hours 2.5—5), the rates of heat generation and heat loss are approximately equal, with core body temperature displaced above set point temperature. It is this displacement, called the load error, which is the continued stimulus for vasodilation and sweating. When the subject stops exercising at hour 5, heat dissipation mechanisms continue to operate at increased levels until body temperature once more matches set point temperature (load error = 0). (Arrows indicate the direction effector mechanisms are trying to drive body temperature.)

Altering the set point

As just described, the initiation and resolution of a fever are set into motion by changes in the thermoregulatory set point. These set-point changes are induced by cytokines secreted primarily by monocytes and macrophages. When these cells encounter infectious microorganisms or toxins (exogenous pyrogens) or cellular products of trauma, they produce multifunctional cytokines such as interleukin-1, interleukin-6, tumor necrosis factor and others known collectively as ''endogenous pyrogens'' because of their influence on the thermoregulatory set point.[6] For the sake of simplicity, this review will focus on a single cytokine — interleukin-1 (IL-1). Once released from cells at the site of infection, IL-1 travels through the bloodstream and can either cross the blood—brain—barrier via specific transporters or interact with cells of the organum vasculosum of the lamina terminalis, stimulating increased synthesis of prostaglandin E_2 (PGE_2) in the anterior hypothalamus.[7] PGE_2, in turn, alters the firing rates of thermoregulatory neurons, which causes an increase in set-point. Meanwhile, IL-1 stimulates a wide range of host defense responses in other tissues: several of these defense responses are