Fever’s Glass Ceiling

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The importance of an upper limit of the febrile response has been recognized since the time of Hippocrates. Although the precise temperature defining this limit varies according to the site at which body temperature is measured, human core temperature is almost never permitted to rise above 41°C–42°C during fever. There are compelling physiological reasons for such an upper limit of regulated body temperature. The mechanisms by which the limit is maintained are most likely complex and involve special properties of thermoregulatory neurons themselves, circulating endogenous antipyretics (such as arginine vasopressin and α-melanocyte-stimulating hormone), and soluble receptors for the (pyrogenic) cytokine mediators of the febrile response.

"Heat is the immortal substance of life endowed with intelligence... However, heat must also be refrigerated by respiration and kept within bounds if the source or principle of life is to persist; for if refrigeration is not provided, the heat will consume itself."

Hippocrates [1]

Although the importance of limiting the accumulation of body heat has been recognized since the time of Hippocrates [1], the upper limit of the febrile range has received scant attention in the clinical literature since 1949, when DuBois [2] published a provocative paper entitled “Why Are Fever Temperatures over 106°F Rare?” In fact, textbooks of physiology and medicine rarely consider the matter worthy of even a passing comment. Nevertheless, experimental data confirming the existence of an upper limit of the febrile range and stressing the importance of this limit to life have accumulated in recent years. The present review summarizes these data as they pertain to the nature of fever’s ceiling in humans, the physiological necessity for such a ceiling, and the mechanisms by which it is maintained.

Fever’s Upper Limit

Clinicians generally subscribe to the notion that the febrile range has an upper limit [3]. However, there is no agreement as to the precise temperature defining this limit. The lack of a consensus in this regard is understandable, owing to the fact that profiles of body temperature in homeotherms vary considerably. Most mammals have temperatures between 36.1°C and 38.8°C, with upper safe limits of 41.6°C to 43.3°C. Birds, however, have higher and more labile normal temperatures, with an upper safe limit of 45°C [4]. Furthermore, the upper limit of the febrile range varies according to disease, with some infections (such as malaria) inducing notoriously high fevers and others (e.g., HIV infection) eliciting little if any detectable fever (Wheeler D, Call S, Wasserman SS, Ingram J, Mackowiak PA, unpublished data). Basal temperature exhibits considerable individual variability [5], and it is likely that the same holds true for the febrile range. In addition, clinical readings vary depending on the site (oral, rectal, or tympanic membrane) at which temperature measurements are obtained [6]. Finally, no systematic study of the question of fever’s upper limit has been published since the report by DuBois [2] in 1949.

In his report, DuBois [2] placed fever’s upper limit between 41°C and 42°C (105.8°F and 107.6°F). He based this conclusion on a survey of 1,761 (axillary and rectal) temperature readings in 357 patients with diseases characterized by high fever. Only 4.3% of the readings exceeded 41.1°C (105.8°F), and none were above 42°C (106°F). As illustrated in one of the figures included in his report (figure 1), fevers rarely reach this upper limit, even when rectal temperatures are monitored in patients with especially severe febrile infections.

DuBois [2] conducted his survey before the advent of antibiotic therapy. In today’s setting one rarely sees temperature
readings of >40°C (104°F) in adults, even during the most intensely febrile infections (figure 2). This rarity is, in part, because of the fact that today effective antimicrobial therapy and antipyretic medications are given to such patients but also because oral rather than rectal temperatures are most often monitored in today's clinical setting.

In view of the many variables affecting fever's ceiling, it is not appropriate to view the upper limit of the febrile range as a single temperature applicable to all body sites of all people at all times during the day. Nevertheless, the febrile response—unlike the hyperthermia of the neuroleptic malignant syndrome, malignant hyperthermia, or heat stroke—is a regulated physiological response in which temperature is maintained within certain carefully controlled limits. The upper limit almost never exceeds 42°C [2]—unless there is failure of thermoregulatory mechanisms—regardless of the type of infection, underlying disease, or site at which temperature measurements are taken.

Physiological Necessity of Fever's Ceiling

From a physiological standpoint, at neutral ambient temperatures, it should be only slightly more difficult to raise body temperature from 40°C to 43°C than from 37°C to 40°C [8]. However, temperatures in the former range are rarely seen, even during the most severe infections. The fact that febrile temperatures rarely rise above 40°C and are almost never above 42°C suggests a fortiori that the adverse consequences of body temperatures above the upper limit of the febrile range outweigh any potential benefits to the human host.

Experimental evidence supporting this conclusion has been provided by Kluger et al. [9], Bernheim and Kluger [10], and Bernheim et al. [11]. In a model involving infection of the lizard *Dipsosaurus dorsalis* with one of its natural pathogens, *Aeromonas hydrophila*, Kluger et al. [9] demonstrated a positive correlation between temperature and survival when temperature of the experimental poikilotherm was raised by physical means from 34°C to 40°C. However, when temperature was increased to 42°C, the highest temperature studied, deaths were observed for the first time in uninfected control animals. It is interesting that, whereas the doubling time of *A. hydrophila* was constant in vitro between 34°C and 40°C, it began to decrease rapidly at incubation temperatures of ≥42°C. Thus, in the model of Kluger and associates, a body temperature of ≥42°C, while deleterious to pathogenic microorganisms, was also harmful to the host.

The specific adverse consequences of increases in body temperature above 41°C–42°C cannot be reliably ascertained by studying subjects with infections or other classical febrile disorders, because such disorders are so rarely associated with temperatures of this magnitude and because, in cases of fatal febrile conditions, it is impossible to separate the morphological and physiological effects of fever from those of the underlying disease. To ascertain such effects one must examine fatal cases of heat stroke or fever therapy. In the former instance, body temperature may exceed the upper limit of the febrile range.
because of failure of thermoregulatory systems; in the latter instance, body temperature may exceed the upper limit of the febrile range because such systems are overridden by physical means.

The cardinal features of classical heat stroke are a core temperature of $\geq 40.5^\circ\text{C} (105^\circ\text{F})$; hot, flushed, and dry skin; and CNS dysfunction [12]. In cases associated with physical exertion (exertional heat stroke), persistence of sweating may obscure the diagnosis, because cooling of the skin by vaporization masks a markedly elevated core temperature. Acid-base abnormalities are common and are due, at least in part, to the fact that simple heating of healthy subjects leads to hyperventilation and respiratory alkalosis. Hypokalemia, hypernatremia, hypophosphatemia, and hyperphosphatemia are also seen in some cases [13]. If circulatory failure and shock supervene, lactic acidosis tends to complicate the acid-base abnormalities. Disseminated intravascular coagulation with thrombocytopenia and elevated fibrinolytic split products in plasma and urine are also features of severe cases of heat stroke.

These protean biological abnormalities reflect the widespread organ dysfunction that occurs at body temperatures of $>41^\circ\text{C} - 42^\circ\text{C}$. The pathological picture is characterized by cellular swelling and degeneration and by widespread hemorrhages varying from petechiae to massive bleeding [14]. As a result, affected organs such as the brain, kidneys, and liver are congested or edematous, with increased weights and swollen cells. Not all organs are equally susceptible to this form of injury. For instance, the pancreas and adrenal glands are often spared, even when there are severe abnormalities in organs such as the brain, liver, and kidney [14].

Similar morphological abnormalities and associated physiological dysfunction are also occasionally seen in patients subjected to whole-body hyperthermia in devices such as the Kettering Hypertherm Cabinet [15]. The earliest abnormalities occurring in the course of such therapy are visceral congestion and disseminated focal hemorrhages in internal organs [16–19]. The subendocardium is especially susceptible in this regard; however, the brain, lungs, liver, and kidney are also commonly affected in fatal cases.

The precise explanation for the widespread abnormalities occurring when body temperature rises above the upper limit of the febrile range is uncertain. Thermal sensitivity of the brain, but not other vital organs, has been attributed to the unique susceptibility of its polyribosomes to thermal injury [20]. At $40^\circ\text{C} - 42^\circ\text{C}$, these polyribosomes begin to disaggregate; above $41^\circ\text{C}$, irreversible destruction of cerebral mitochondria occurs [21, 22]. However, in most animals thermal death occurs well below temperatures causing coagulation of proteins or denaturation of enzymes [23]. In experimental animals both immunization against endotoxin and administration of antibiotics before heating sharply reduce mortality due to hyperthermia, thus suggesting that pyrogens of intestinal origin mediate at least some of the deleterious effects of heat stroke [12].

In one of the earliest theories concerning mechanisms responsible for the adverse effect of hyperthermia itself on cell function, Hartman [24] proposed that anoxia was the prime
Hartman theorized that the morphological abnormalities of hyperpyrexia, which share many features in common with those of prolonged asphyxia, are due in large part to alterations in oxygen supply and delivery. Central to his theory was the observation that both the metabolic rate and oxygen utilization increase with temperature, whereas physiological mechanisms for furnishing oxygen to tissues decrease at body temperatures of >41°C-42°C [25–27]. He suggested that the respiratory alkalosis that invariably accompanies hyperpyrexia leads to increased stability of oxyhemoglobin, thereby impairing release of oxygen to tissues—the latter effect being at least partially offset by the hyperthermia itself—which decreases oxyhemoglobin stability.

Although numerous more contemporary theories have sought to explain these same abnormalities, none are generally accepted as valid. Hubbard and Armstrong [28] have proposed an “energy depletion model” to explain hyperthermia-induced cellular dysfunction. According to their model, the increased morbidity and mortality due to exercise-induced hyperthermia (as compared with equivalent heat loads in the absence of physical effort) derives from a thermally driven energy drain superimposed on the energy lost as a result of exhaustive physical work. These investigators believe that during heat-induced cellular dysfunction, a vicious cycle of increasing cellular activity, increasing energy consumption, and decreasing steady-state energy levels results in dissipative ionic fluxes, adverse metabolic cascades, and other reactions leading to irreversible cell damage. In this model, as in all of the models thus far proposed, the ultimate adverse consequences of hyperthermia on cell function depend on the duration, intensity, and rate of heating as well as on variations in regional and local circulation within the affected tissue.

Lepock and Kruuv [29], for their part, have proposed that protein denaturation is the most likely initial rate-limiting event in hyperthermia-induced cytotoxicity. They offer as support for their theory a wide array of data demonstrating protein denaturation during exposure of mammalian cells to temperatures in excess of 40°C; these investigators estimate that 5%-10% of denaturation occurs during 15- to 30-minute exposures to 45°C. However, the critical target affected by such denaturation has not been identified, nor has the target been localized to any particular organ or cellular component.

Yatvin and Cramp [30] have recently concluded from their own work and a review of the literature that, rather than protein denaturation per se, alterations in the fluidity of cell membranes that result from an increase in the content of cholesterol, phospholipids, and protein is the critical cellular derangement induced by hyperthermia. Other researchers have pointed to degradation of DNA, inhibition of DNA synthesis, induction of chromosomal aberrations [31–34], inhibition of protein synthesis [35, 36], protein denaturation [37], increased protein phosphorylation [38], increased lysosomal enzyme activity [39–41], alterations in cytoskeletal and structural proteins [42–47], and increases in intracellular free calcium in association with relocation of kinase C [48–51] as events contributing to the adverse effects of hyperthermia. More than likely, multiple adverse cellular events are triggered simultaneously by temperatures of >42°C, and together these events mediate the cellular dysfunction and death due to hyperthermia.

**Mechanisms Regulating Fever’s Upper Limit**

The foregoing evidence supporting an upper limit of the febrile range infers the existence of regulatory mechanisms involved in fever that prevent body temperature from rising above 41°C–42°C (105.8°F–107.6°F). Since body temperature and fever are controlled by neural structures near the rostral hypothalamus, it is likely that fever’s upper limit is controlled by neurons in this area. The mechanisms involved in such regulation might lie in the intrinsic properties of the neurons themselves or in the release of endogenous antipyretic substances that antagonize the effects of pyrogens on the neurons.

**Neuronal Properties**

Neurons coordinating thermoregulatory responses are located in the preoptic region and anterior hypothalamus (PO/AH) and in adjacent septal areas. As shown in figure 3, these...
structures are located near the organum vasculosum of the lamina terminalis (OVLT), a circumventricular region thought to be the site at which cytokines or other pyrogenic mediators enter the brain from the blood [52, 53]. The importance of the PO/AH in thermoregulation is best illustrated in studies of animals with implanted thermodes that induce localized hypothalamic warming and cooling (figure 3). All physiological and behavioral thermoregulatory responses can be elicited in these animals simply by changing hypothalamic temperature with the implanted thermode [54]. Each thermoregulatory response has its own hypothalamic set-point temperature, such that the response is evoked when the PO/AH is either warmed or cooled beyond this set point. PO/AH warming evokes heat loss responses, like panting [55–57] or sweating [58], whereas PO/AH cooling evokes heat production responses, such as shivering [55, 59] or nonshivering thermogenesis [60, 61]. In addition, more moderate changes in PO/AH temperature elicit changes in blood flow in the skin [62] and a variety of thermoregulatory behaviors [63, 64].

When hypothalamic temperature is changed and microelectrodes record neuronal activity, three cell types are recognized: temperature-insensitive neurons, warm-sensitive neurons, and cold-sensitive neurons. Electrophysiological studies have been conducted, both in vivo (in anesthetized and unanesthetized animals) and in vitro (in hypothalamic tissue slices and cultures); most studies find similar ratios of these neurons in the PO/AH and septum as well as throughout the diencephalon [54, 65, 66]. Approximately 60% of the neurons are classified as temperature-insensitive, since they show little or no change in their firing rates when hypothalamic temperature is changed.

Warm-sensitive neurons account for >30% of PO/AH neurons and exhibit increased firing rates during hypothalamic warming or decreased firing rates during hypothalamic cooling. By comparison, <10% of PO/AH neurons are considered cold-sensitive, with firing rates that increase during cooling or decrease during warming. Within each of these three cell populations, there are neurons that also respond to various nonthermal stimuli, such as changes in glucose concentration, osmolality, and reproductive hormones [67–69]. Since these nonthermal stimuli can alter the activity of thermoregulatory neurons, they might have a role in regulating fever’s upper limit, which would be particularly important if these nonthermal stimuli are altered by elevated temperatures or other conditions associated with fever.

In the PO/AH and septum, warm-sensitive and cold-sensitive neurons also receiveafferent input from thermoreceptors in the skin and spinal cord [70–72]. As shown in figure 3, it is likely that much of this afferent information arrives over multisynaptic pathways from the spinothalamic tract to the reticular formation in the brain stem and the hypothalamus [73]. In the PO/AH and septum, this afferent input rarely affects temperature-insensitive neurons; however, most warm-sensitive and cold-sensitive neurons respond to changes in skin or spinal cord temperature [72]. Thus, the thermosensitive neurons integrate thermal information derived from both central and peripheral sources.

Warm-sensitive neurons in the PO/AH are intrinsically thermosensitive and retain their thermosensitivity even when their synaptic input is experimentally blocked [74, 75]. Intracellular recordings from these neurons indicate that the mechanism responsible for their warm sensitivity is a temperature-dependent depolarizing prepotential that precedes each action potential [76]. In contrast to warm-sensitive neurons, cold-sensitive neurons in the PO/AH do not appear to be intrinsically thermosensitive. The activity of cold-sensitive neurons is much more dependent on excitatory and inhibitory postsynaptic potentials [76], and neuronal cold sensitivity usually disappears during synaptic blockade [74, 75].

Experimental data summarized in figure 4 suggest that neuronal cold sensitivity is due to synaptic inhibition from adjacent warm-sensitive neurons. At 37°C, populations of warm-sensitive neurons display a wide range of spontaneous firing rates, and these firing rates often correlate with the neurons’ range of thermosensitivity [54, 73, 76–78]. Warm-sensitive neurons
with low firing rates usually express their greatest thermosensitivity above 37°C, thus suggesting that such neurons participate in heat loss responses that are elicited in the hyperthermic range. By contrast, warm-sensitive neurons with high firing rates often display their maximum firing rates when the hypothalamic temperature is near 37°C.

Figure 4A shows a warm-sensitive neuron with a high firing rate under normal conditions (N) in the absence of pyrogens. Hypothalamic warming above 37°C has little effect on the firing rate of this neuron; however, cooling below 37°C causes the firing rate to decrease markedly. As shown in figure 4B, some warm-sensitive neurons synaptically inhibit adjacent spontaneously firing neurons, thereby causing the inhibited neurons to appear to be cold-sensitive. Hypothalamic cooling decreases the firing rate of warm-sensitive neurons and, therefore, decreases the synaptic inhibition of cold-sensitive neurons. This causes cold-sensitive neurons to increase their firing rate as the hypothalamus is cooled below 37°C. Thus, the firing rate of cold-sensitive neurons is a mirror image of the firing rate of warm-sensitive neurons. If some cold-sensitive neurons control shivering and nonshivering thermogenesis as shown in figure 4C, heat production should increase when the hypothalamic temperature is cooled below 37°C.

Fever develops when pyrogens alter the activity of hypothalamic neurons that control body temperature [79]. In response to exogenous pyrogens, such as bacterial lipopolysaccharides, leukocytes and macrophages produce an array of endogenous pyrogens that include IL-1, IL-6, TNF, and IFN. Some investigators believe that circulating endogenous pyrogens cause mediators, such as prostaglandin E, to be released at the OVLT (figure 3) [80, 81]. Other researchers suggest that there are fragments of endogenous pyrogens small enough to cross the blood-brain barrier or that endogenous pyrogens in the circulation trigger elevations in a separate pool of endogenous pyrogens within the brain [82–84]. Several studies have shown that fever is produced in response to PO/AH or OVLT injections of prostaglandin E and endogenous pyrogens, such as IL-1 [85, 86]. During infections, concentrations of these substances often increase within the brain [84, 87].

Some electrophysiological studies indicate that pyrogenic substances inhibit warm-sensitive neurons, excite cold-sensitive neurons, and have either mixed or little effect on temperature-insensitive neurons [88, 89]. Figure 4 shows how pyrogens might act on PO/AH neurons to generate fever through increased heat production. The predictive effects of a low concentration of pyrogen (P₁) and a high concentration of pyrogen (P₂) on the activity of hypothalamic neurons controlling shivering and nonshivering thermogenesis are illustrated. These predictive effects are based on previous studies that correlate the spontaneous firing rate at 37°C and thermosensitivity (i.e., the slope of the firing rate plotted as a function of temperature) [54, 71–73, 77, 78]. Often, in the hyperthermic range, increases in thermosensitivity occur when warm-sensitive neurons decrease their spontaneous firing rate (figure 4A) or when cold-sensitive neurons increase their spontaneous firing rate (figure 4B). As a result, thermoregulation curves of both warm-sensitive and cold-sensitive neurons tend to converge at hypothalamic temperatures near 42°C — fever’s upper limit.

Figure 4A illustrates the change in activity of a warm-sensitive neuron during inhibition by low and high concentrations of pyrogen. While low concentrations of pyrogen partially reduce the firing rate at 37°C, the neuron also becomes sensitive over a wider range of temperatures. High concentrations of pyrogen reduce the firing rate to minimal levels at 37°C so that the neuron is only sensitive to temperatures in the hyperthermic range. Since neuronal cold sensitivity is determined by synaptic inhibition from warm-sensitive neurons, the thermoregulation curves in figure 4B are the mirror images of those in figure 4A.

If cold-sensitive neurons regulate thermogenesis, then similar responses might be expected for heat production (figure 4C). In the presence of low concentrations of pyrogen, heat production should increase, even when body temperature is 37°C. This heat production eventually raises body temperature and is equivalent to the chill phase of fever. Heat production gradually diminishes as body temperature rises to a new elevated level, and regulation around the new elevated set-point temperature is equivalent to the plateau phase of fever. High concentrations of pyrogen maximally inhibit warm-sensitive neurons and, in this way, allow cold-sensitive neurons to spontaneously fire at their highest levels. As shown in figure 4C, this causes maximal heat production at 37°C; however, when body temperature rises, heat production quickly decreases as the temperature approaches the febrile set point.

As illustrated in figure 4, the plots of neuronal firing rates and heat production tend to converge as body temperature approaches 42°C. At 42°C the firing rates of warm-sensitive neurons reach their zenith and cannot be increased further in response to temperatures of >42°C. Similarly, the firing rates of cold-sensitive neurons reach their nadir at 42°C and cannot decrease further if temperatures increase above 42°C. Thus, regardless of the pyrogen concentration, thermosensitive neurons may be incapable of providing additional neural signals to finely regulate body temperature once the temperature reaches 42°C. Regulated increases in body temperature (i.e., fever) above 42°C, therefore, might not be possible because thermoregulatory neurons are incapable of responding appropriately to temperatures of >42°C.

**Endogenous Antipyretics**

As indicated above, thermosensitive neurons in the PO/AH are influenced by a variety of endogenous substances [67–69]. At least some of these substances appear to function as endogenous antipyretic agents that might have a role in regulating fever’s upper limit.

**Arginine vasopressin (AVP).** The search for endogenous antipyretics responsible for limiting the height of the febrile
response began in earnest with studies of the temporarily blunted febrile response of periparturient ewes and newborn lambs to challenges with iv endotoxin [90]. Unable to identify a thermoregulatory defect or an inability of such animals to respond began in earnest with studies of the temporarily blunted febrile response of periparturient ewes and newborn lambs to challenges with iv endotoxin [90]. Unable to identify a thermoregulatory defect or an inability of such animals to synthesize and release endogenous pyrogens, Kasting et al. [91] hypothesized the existence of an endogenous antipyretic agent responsible for the state of pyrogen unresponsiveness. AVP emerged as a likely candidate for such an endogenous antipyretic, after several groups of investigators [92–94] showed that the low-molecular-weight neuropeptide was present in increased concentrations in the circulation of pregnant ewes at the time of their diminished responsiveness to challenge with fever-inducing agents. More importantly, it was shown that if AVP is perfused into discrete areas of the brain of the nonpregnant ewe via a push-pull cannula system, application to the ventral septal area (but not other areas) reduces endotoxin-induced fever in a dose-dependent manner [95].

Subsequent studies by numerous investigators using a variety of animal models have established that AVP is present in the fibers and terminals of the ventral septal area, that it is released into the ventral septal area during fever, that it reduces fever via its action at V1 receptors when introduced into the ventral septal area, and that it prolongs fever when inhibited [96]. The means by which AVP brings about a reduction in body temperature are not yet clear [97]. Its action appears to be mediated by V1-type receptors [98]. AVP can interfere with glutamate-induced excitation of neurons [99], but the importance of this action to its antipyretic effect is not known. It apparently does not specifically impair thermogenesis [99]. Rather, it appears to prevent or reduce fever through a receptor-mediated action that has no effect on normal body temperature [100].

Evidence against the role of AVP as a physiologically important endogenous antipyretic agent comes from work involving the Brattleboro rat. This genetic variant of the Long-Evans rat possesses a recessive autosomal allele expressing AVP deficiency. Although animals homozygous for the allele are profoundly deficient in AVP, they do not exhibit an exaggerated febrile response to challenges with endogenous pyrogens or to prostaglandin E or endotoxin [101–104]. Nevertheless, it has been suggested that such conflicting evidence, rather than obviating a role for AVP in setting the upper limit of the febrile response, indicates that, like the febrile response itself, endogenous antipyresis most likely involves several peptidergic systems [20] (vide infra).

α-Melanocyte-stimulating hormone (α-MSH). Another central peptide exhibiting endogenous antipyretic activity is the neuropeptide α-MSH [105]. This relatively small molecule shares the 1–13 amino acid sequence with adrenocorticotropic hormone. Unlike some antipyretic peptides, α-MSH has not been identified in fibers projecting into the septum [106]. It does, nevertheless, reduce pyrogen-induced fever when administered (intragastrically, iv, intracerebroventricularly, or into the septal region of the brain) to experimental animals in doses below those having an effect on afebrile temperature [107–111]. When given centrally, α-MSH is >25,000 times more potent as an antipyretic than is acetaminophen [105]. Repeated central administration of α-MSH does not induce tolerance to its antipyretic effect [112]. In addition, injection of antiserum to α-MSH into the cerebral ventricles augments the febrile response of experimental animals to IL-1 [113].

The greatest increases in central concentrations of α-MSH have been shown to occur during the chill phase of fever, when the temperature is rising rapidly, rather than during the plateau or defervescence phases [114]. No such increase in septal α-MSH concentrations occurs when the core temperature is raised by physical means [105]. Whereas large iv doses of α-MSH inhibit fever, they have no demonstrable effect on other aspects of the acute-phase response [115].

The biochemical pathway through which α-MSH exerts its antipyretic effect is not yet known. In fact, little can be said currently of its specific mechanism of action other than that α-MSH does not inhibit prostaglandin synthesis [116] and does not act as a receptor antagonist of IL-1 [117]. In addition, it is not known whether α-MSH exerts its antipyretic effect in concert with AVP. Nevertheless, from the data reviewed above, it is clear that it is a potent endogenous antipyretic agent and, like AVP, might have some role in setting fever’s upper limit.

Miscellaneous antipyretic neurochemicals. Numerous neurochemicals appear to have the capacity to influence the hypothalamic control of body temperature. Depending on the environmental temperature, hypothalamic injections of these substances can often increase or decrease body temperature. Although antipyretic agents lower body temperature only when fever is present (i.e., in the presence of endogenous pyrogens), some of the agents considered below are more appropriately viewed as hypothermic agents because they have the capacity to lower body temperature even in the absence of fever. Theoretically, either type of neurochemical might be involved in setting fever’s upper limit; however, proof of such involvement remains to be established for any of these agents.

Feldberg and Myers [118], in some of the earliest work in this area, observed that intracerebroventricular injections of epinephrine and norepinephrine cause a fall in body temperature in cats, whereas injections of serotonin cause body temperature to rise. On the basis of these observations, they proposed that regulation of body temperature depends on the balance between the release of catecholamines (inducing heat loss) and serotonin (activating heat production) in the anterior hypothalamus. More recent data, including those considered in the present review, suggest that the basis of set-point determination by the thermoregulatory network is considerably more complex [119].

Glucocorticoids and their inducers (corticotropin-releasing factor and adrenocorticotropic hormone) exhibit striking antipyretic properties under certain conditions. For example, there are numerous in vitro studies showing inhibition of production of pyrogenic cytokines such as IL-6 and TNF by glucocorti-
coids [120–122]. Through such effects, glucocorticoids exert inhibitory feedback on lipopolysaccharide-induced fever [94]. Lipocortin, a proposed mediator of glucocorticoid function, has also been shown to inhibit the pyrogenic actions of IL-1 and IFN [123]. Corticotropin-releasing factor injected into the third ventricle produces similar antipyretic effects [124], which are most likely mediated by the associated rise in blood levels of glucocorticoids [20].

Thyrotropin-releasing hormone [125], gastric inhibitory peptide [126], neuropeptide Y [127], and bombesin [128] are additional neuropeptides exhibiting hypothermic properties under certain conditions. Of these neuropeptides, bombesin is probably the most potent because it constantly produces hyperthermia associated with changes of heat dissipation and heat production when injected into the PO/AH of conscious goats and rabbits [128–130]. Bombesin is believed to exert its hypothermic effect by increasing the temperature sensitivity of warm-sensitive and temperature-insensitive neurons [129].

Endogenous Pyrogens and Their Receptors

Pyrogenic cytokines, the mediators of the febrile response, might themselves play a direct role in determining fever’s upper limit. For instance, there is experimental evidence indicating that under certain conditions these cytokines act to lower, rather than raise, body temperature [113, 131]. Thus, it is possible that at certain concentrations or in the appropriate physiological milieu (e.g., at 41°C–42°C), pyrogenic cytokines might function paradoxically as endogenous antipyretic agents.

The febrile response might also peak at 41°C–42°C, because such temperatures inhibit the production of pyrogenic cytokines by inflammatory cells, inhibit the capacity of effector systems to respond to such cytokines, or might promote the elimination of pyrogenic cytokines. With regard to the first possibility, Ensor et al. [132, 133] have recently demonstrated that temperatures within the febrile range (40°C) cause degradation of TNF mRNA in macrophage-like cells in vitro, inhibit TNF-α release, and inhibit total protein synthesis by lipopolysaccharide-stimulated human macrophages but do not inhibit IL-6 expression (figure 5). Several other groups of researchers have reported similar temperature-dependent inhibition of expression of various pyrogenic cytokines [134–137]. The specific effects of temperatures at the upper end of the febrile range on responsiveness of effector cells to endogenous pyrogens or on the elimination of such cytokines are not yet known.

A growing body of literature indicates that the release of pyrogenic cytokines such as IL-1 is followed by increased shedding of soluble receptors for such cytokines that function as endogenous inhibitors of such pyrogens [138]. In the case of IL-1, a 22- to 25-kD molecule that blocks binding of IL-1 to its receptors has been identified in supernatants of human monocytes [139]. The receptor antagonist of IL-1 is structurally related to IL-1α and IL-1β [140] and binds to both type I and type II receptors on various target cells without inducing a specific biological response [141, 142]. Similar receptor antagonists of TNF-α have been described [143–147]. The precise biological function of such receptor antagonists is not known. However, it is possible that one such function is to serve as a natural braking system for the febrile response.

Conclusion

Extensive clinical experience and the above-reviewed experimental data affirm the existence of an upper limit of the febrile response. Although the precise temperature defining this limit varies according to the site at which body temperature is measured, it is clear that human core temperature is almost never permitted to rise higher than 41°C–42°C during the regulated increase in temperature that characterizes fever. Recent investigations have identified several mechanisms by which fever’s ceiling might be set. The upper limit of the febrile range might
be determined simply by the maximum and minimum firing rates of hypothalamic neurons that regulate body temperature. It is also possible that antipyretic substances that antagonize the actions of endogenous pyrogens play a pivotal role in this process. In all likelihood several different mechanisms are involved simultaneously in the process of endogenous "refrigeration" that prevents body heat from "consuming itself" during the febrile response.

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References

5. Deleted in proof.
72. Boula NT, Hardy JD. The effect of spinal and skin temperatures on the firing rate and thermosensitivity of preoptic neurons. J Physiol (Lond) 1974;240:639-60.
83. Chow et al. GHA, Saravis C, Bigatello L, Billee C. The hormonal functions of “proteolysis inducing factor” (PIF), the active circulating cleavage fragment of interleukin-1 (IL-1). In: Kluger MJ, Oppenheim JJ, Powanda MC, eds. The physiologic, metabolic, and immunologic


131. Holt SJ, Grimble RF, York DA. Tumor necrosis factor-α and lymphotoxin have opposite effects on sympathetic efferent nerves to brown adipose tissue by direct action in the central nervous system. Brain Res 1989;497:183–6.
140. Eisenberg SP, Brewer MT, Verderber E, Heimdal P, Brandhuber BJ, Thompson RC. Interleukin 1 receptor antagonist is a member of the interleukin 1 gene family; evolution of a cytokine control mechanism. Proc Natl Acad Sci USA 1991;88:5232–6.
141. Dripps DJ, Brandhuber BJ, Thompson RC, Eisenberg SP. Interleukin-1 (IL-1) receptor antagonist binds to the 80-kDa IL-1 receptor but does not initiate IL-1 signal transduction. J Biol Chem 1991;266:10331–6.