AANA Journal Course

Update for nurse anesthetists

1

6 CE Credits*

The neurobiology of the human febrile response

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Fever is a normal adaptation in response to a pyrogenic stimulus resulting in the generation of cytokines and prostaglandins. Fever differs from hyperpyrexia and hyperthermia associated with hot environs and pharmacological triggers. Typically, pyrogens are infectious organisms or their direct products (toxins). The body produces a wide array of pyrogenic cytokines such as interleukins (IL-1, IL-6), interferon, and tumor necrosis factor. Tissue trauma can trigger the febrile response, as can infectious organisms, certain medications, and blood products.

The circumventricular organ system (CVOS) is neuronal tissues lying outside the blood-brain barrier that has a key role in initiating the communication sequence responsible for the synthesis of febrile prostaglandins. When pyrogenic cytokines are detected by the CVOS, prostaglandin synthesis, especially cyclooxygenase-dependent prostaglandin E_2, is induced, activating the febrile response. Once the appropriate signal is received by the hypothalamus, autonomic, endocrine, and behavioral processes are activated until the hypothalamic set-point is reset downward as a consequence of a reduction in pyrogen content or antipyretic therapy, with subsequent heat loss.

There is little evidence that fever facilitates recovery from disease or assists the immune system in mounting a response. Antipyretics are used commonly to decrease the distressing manifestations associated with fever.

Key words: Circumventricular organ system, febrile response, fever, hypothalamus, pyrogenic cytokines.

Objectives

At the completion of this course, the reader should be able to:

1. Understand the processes that define and maintain thermoregulation.
2. Describe the central role of the hypothalamus in generating a febrile response.
3. Discuss the roles of the blood-brain barrier and the circumventricular organ system as they pertain to the genesis of a febrile response.
4. Discuss the value and purpose of fever and whether it should be treated routinely.
5. Recognize the major causes of postoperative fever, and develop a rationale for intervention.

Table 1. Manifestations of fever

- Shivering, chills
- Loss of appetite
- General malaise
- Anorexia
- Arthralgia, myalgia, skin sensitivity to touch
- Decreased secretion of vasopressin
- Production of acute-phase proteins
- Diversion of blood from the periphery to the central compartment
- Absence of sweating
- Blood pressure and heart rate increased

Introduction

Virtually everyone has experienced the stereotypical manifestations of fever resulting from the acute-phase response to an immunologically based challenge. The overt physical manifestations usually include anorexia, general malaise, somnolence, and alternating shivering and chills with sensations of being hot (Table 1). Fever may be seen in patients who are about to undergo anesthesia and surgery and is common in postoperative patients.

This course reviews normal temperature homeostasis, the mechanisms of the febrile response, and the rationale for target therapies. Special consideration will be given to the matter of postoperative fever. This course considers only fever, distinguishing fever from hyperthermia and hyperpyrexia, the latter having the

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potential to be rapidly fatal. Hyperthermia and hyperpyrexia usually are associated with a pharmacological instigator (eg, malignant hyperthermia, neuroleptic malignant syndrome) or occur in an environment where heat production exceeds the victim's ability to lose it (heat stroke).

Normal thermoregulation

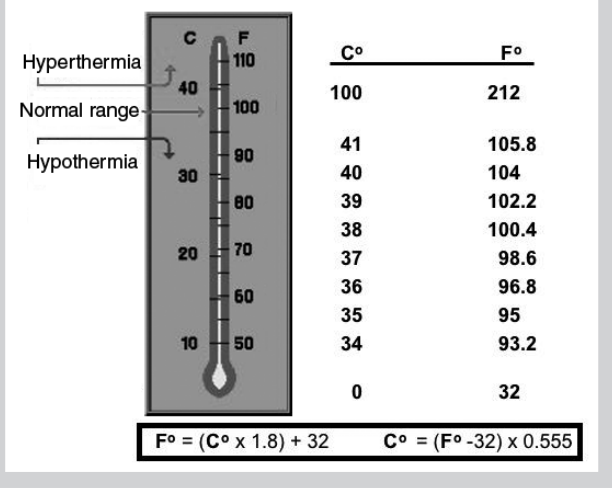
Fever is a normal physiologic adaptation occurring largely in response to circulating cytokines and prostaglandins. Under normal conditions, the average individual experiences only a slight variation in body temperature in any 24-hour period, maintaining a steady core temperature because of the exquisite, complex orchestration of the hypothalamus in the coordination and balance of heat production with heat dissipation.

Most of us respond "98.6 degrees F" when asked what "normal" body temperature is, and reference sources differ slightly on just what temperature represents normality. An authoritative, critical analysis of the issue suggests that in the average young adult (teens to 40 years), normal body temperature averages 98.2°F ± 0.7°F (36.8°C ± 0.4°C) with a nadir in the early morning and a peak in the late afternoon.[1] Ovulation results in a predictable perturbation in thermoregulation (an increase of about 1.0°F associated with ovulation) such that many women monitor body temperature as a component of birth-control strategy. Figure 1 is a brief conversion index of some representative Fahrenheit and Celsius measurements.

Reporting of body temperature must be put in the context of where the temperature measurement was obtained. This is a major conundrum in research directed at determining the efficacy of heat-conservation interventions such as convective warmers, radiant lights, and heated intravenous fluid administration devices. Measures of core temperature are thus superior to those of surface temperature whenever possible.

Our skin may be viewed as our single largest "organ" and is amazingly efficient in terms of regulating our core temperature. It acts, in effect, like a radiator due to the large and diffuse venous plexus that exists just below the skin. Enormous amounts of heat can be transferred from the body core to the skin as an effective mechanism of radiant heat loss. Likewise, heat can be conserved by decreasing blood flow to the skin, with both processes controlled by the autonomic nervous system's influence on vascular mechanics. Subcutaneous fat is a superb insulator because it conducts heat at only a fraction of the rate of other body tissues, a factor accounting for the relatively large amount of heat lost from the head, which has a large vascular plexus and minimal subcutaneous fat.

Figure 1. Representative temperature conversions from degrees Celsius (C) to degrees Fahrenheit (F)



Thermoregulation is a sophisticated balancing act between heat production (a normal consequence of the body's metabolism) and heat loss (to the ambient surroundings). Only when these are in equilibrium is a state of heat balance achieved. The major mechanisms of body heat loss are radiation, conduction, convection, and evaporation (Figure 2).

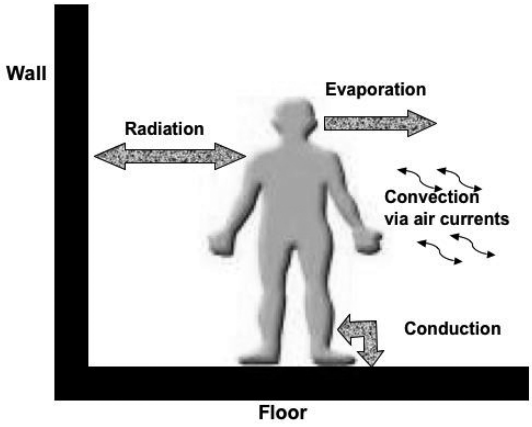
The role of the hypothalamus: The thermoregulatory "conductor"

If the integrated thermoregulatory response of the body is viewed as the symphony, then the conductor is the hypothalamus (Figure 3). The hypothalamus acts much like the thermostat located centrally in a home. The "set-point" or thermostatic setting of the hypothalamus is shifted somewhat in febrile conditions. Elevating the set-point activates neurons in the vasomotor center to initiate vasoconstriction with resultant blood shifting from the periphery to the central compartment.[2] Likewise, shivering will increase heat production from muscular activity. Reduction in activity (somnolence and malaise), loss of fluid from decreased vasopressin release (less body fluid to warm), suppression of sweating, and seeking a warm environment all contribute to heat production and conservation, allowing for blood contacting the hypothalamus to meet the new set-point.

Pyrogens

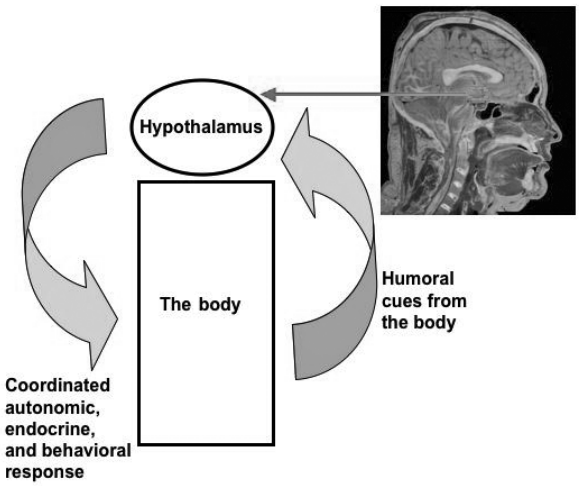
Pyrogens come in many forms and provoke a febrile response. Typically, pyrogens are infectious organisms or their direct products (toxins). The body can produce a wide array of endogenous pyrogens such as certain interleukins (IL-1, IL-6), interferon, tumor necrosis factor, and other compounds that fall under the general rubric of "pyrogenic cytokines."[2] Cytokines

Figure 2. Mechanisms of heat loss



Radiant loss via electromagnetic waves is a major form of heat loss. We radiate heat in all directions to objects in our surroundings. The gradient of heat influences the direction of heat transfer. *Conductive* loss may be high in the operating room where the patient comes into direct contact with a cold bed. *Convective* loss via air currents and *evaporation* of moisture from the skin, lungs, and open wounds also occur.

Figure 3. The integrated, autonomic febrile response



The generation of a febrile response is largely under the control of the hypothalamus, which, like a symphony conductor, coordinates a diverse set of players that marshal a complex set of autonomic, endocrine, and behavioral responses.

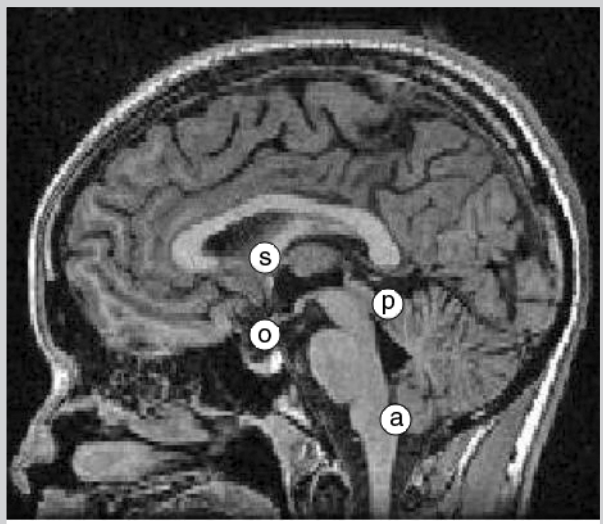
are relatively low-molecular-weight proteins that modulate immune, inflammatory, and hematopoietic processes in the body. Cytokines can be induced by viral invasion as well.

How does the brain sense the presence of a pyrogen?

The blood-brain barrier (BBB) is a specialized network of capillary endothelial cells designed to protect the brain from harmful blood-borne substances, yet allowing access to essential substrates for brain function. The BBB strictly controls transport into the brain through physical (tight junctions) and metabolic (enzymes) barriers. Pyrogenic compounds generally do not trespass the BBB, raising the question, "How then does the hypothalamus sense their presence so that a febrile response can be mounted?"

There are various structures adjacent to the central nervous system that are termed the *circumventricular organ system* (CVOS). The structures represent small clusters of neurons that are in contact with blood and have an intrinsic neuronal connection with the hypothalamus but are outside the BBB[3] (Figure 4). The CVOS has many diverse functions in the body besides informing the hypothalamus about the presence of pyrogens. For example, a component of the CVOS called the subfornical organ assesses the level of circulating angiotensin II, sending feedback information to the brainstem and subsequently participating in neurogenic regulation of blood pressure. Likewise, another component of the CVOS, the area postrema,

Figure 4. Sagittal section of brain illustrating the approximate location of the circumventricular organ system (CVOS)*



The CVOS includes midline structures bordering the third and fourth ventricles that are outside the blood-brain barrier. These are important sites of recognition of blood and cerebrospinal fluid constituents and communicating the information recognized to the brain. The CVOS consists of the pineal gland, median eminence, subfornical organ, area postrema, subcommissural organ, and organum vasculosum. The major CVOS structures involved in the febrile response are depicted.

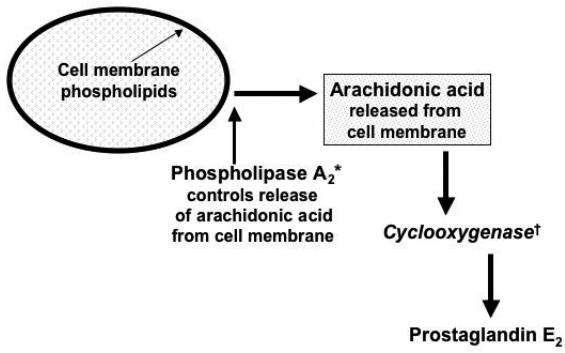
*** s indicates subfornical organ; o, organum vasculosum; p, pineal gland; a, area postrema.**

Table 2. Possible benefits of fever[6-9]*

- Enhanced immunological response
- Impairment of bacterial and viral replication
- Fall in blood glucose level, denying bacteria substrate
- Production of acute-phase reactants by the liver†
- Activation of the stress response

* "Proof" of these phenomena is not absolute; supporting evidence is largely indirect and often theoretical.
† Divalent cations (DCs) are necessary for the growth and replication of many microorganisms. During fever, the liver generates acute-phase reactants, which bind with DCs and, thus, may impede bacterial growth.

Figure 5. Cyclooxygenase (COX)-dependent pathway



A number of conditions can induce the formation of prostaglandins. The synthesis of prostaglandins and, in this case, prostaglandin E_2, which is of special relevance to the febrile response, begins with arachidonic acid and the action of the cyclooxygenases on this substrate.

* Action blocked by corticosterioids.
† Aspirin is a prototypical nonselective COX inhibitor.

monitors blood levels of cholecystokinin, providing feedback, via the brainstem, to regulate gastrointestinal activity and appetite.[4]

The CVOS has an important role in initiating the communication sequence responsible for the synthesis of prostaglandins that are crucial to the febrile response. When circulating pyrogenic cytokines are detected by the CVOS, prostaglandin synthesis, especially prostaglandin E_2 (PGE_2) is induced, which activates the febrile response. Indirect evidence of this comes in the observation that certain drugs that are potent inhibitors of prostaglandin synthesis (eg, aspirin, indomethacin) are highly effective in blocking the febrile response. Further evidence for the critical role of prostaglandins in mounting a febrile response can be found in the location and high density of PGE_2 receptors in that part of the brain highly associated with the genesis of fever.[5]

The study of the nature and mechanics of fever is enormously complicated for many reasons, some of them nearly insurmountable. Logistic and technical issues abound, primarily due to the deep brain location and delicate nature of the relevant control structures. Ethical issues preclude exposing humans to most pyrogens and, in controlled trials, withholding therapy or subjecting people with fevers to alternative therapies when traditional interventions are highly successful. Because of these and other factors, there is a high reliance on research using animal models. The direct application of animal-based models to humans is always suspect, and this limitation must be considered as such studies are considered and their implications for practice weighed.

What is certain is that once the appropriate febrile signal is received and processed in the hypothalamus, a diverse set of autonomic, endocrine, and behavioral processes is activated. Under the control of the hypothalamus, these processes continue until the hypothalamic set-point is reset downward as a consequence of a decline in pyrogen content or as a result of antipyretic therapy. At this point, heat loss is initiated.

What is the value of fever, and should it be treated?

Despite the predictable occurrence of fever in infection, there is no clear proof that fever per se facilitates recovery from the infectious process, nor is there direct evidence that it assists the immune system in mounting a response. There is some indirect evidence that fever may improve the efficiency of the body in destroying bacteria and may inhibit replication of a variety of microorganisms.[6,7] It also has been suggested (again with indirect evidence) that a variety of metabolic processes are altered in a manner that empowers the body's immune response to infection.[8,9] Table 2 lists some of the suggested benefits of the febrile response.

Although fever usually is self-limiting, treatment targeted at reducing fever and its associated distressing effects (eg, malaise, anorexia, myalgia, skin sensitivity) is common. Because of the relative absence of direct evidence that fever enhances recovery, treating fever is generally thought to be advantageous. Depending on the condition of the patient (eg, age, level of consciousness, coexisting vomiting), oral, rectal, or parental preparations of a variety of antipyretics might be used. Aspirin and nonsteroidal anti-inflammatory drugs are the mainstays of antipyretic therapy. The potency of an antipyretic is associated directly with its ability to inhibit brain cyclooxygenase (COX).[10]

Table 3. Causes of postoperative fever

- Tissue trauma and associated cytokine release
- Bacterial endotoxins and exotoxins
- Nosocomial infection
- Meningitis
- Foreign body reaction (implanted hardware or device)
- Medications that provoke immune-mediated reactions
- Transfused blood products
- Malignant hyperthermia
- Pneumonia and ventilator-associated pneumonia
- Pulmonary aspiration
- Urinary tract infection, especially in the presence of an indwelling catheter
- Intravascular catheter–related infection
- Noninfectious causes
  - Pancreatitis, myocardial infarction, embolization
  - Acute alcohol withdrawal, acute gout
  - Hyperthyroidism, cancer, intracranial pathology

The formation of PGE_2 (see earlier text) that is important in mounting the febrile response is inextricably linked to COX (Figure 5). Arachidonic acid released from cell membranes is the substrate that COX acts on to create a number of prostaglandins, including PGE_2. (There are at least 3 types of COX, each responsible for the synthesis of different subsets of prostaglandins.) Antipyretics that owe their effect to blocking the formation of PGE_2 achieve this end by inhibiting COX.

Acetaminophen is relatively ineffective in inhibiting COX in peripheral body tissue despite its efficacy in reducing fever. Acetaminophen undergoes oxidation in the brain by cytochrome P-450 isoenzymes, where it is oxidized to a form that effectively inhibits COX activity. Also of interest is the efficacy of corticosteroids as antipyretics, an effect due to their inhibition of PGE_2 synthesis by blocking the activity of phospholipase A_2, an enzyme that controls the expression of arachidonic acid from the cell membrane (see Figure 5).

Special consideration: Postoperative fever

It is not uncommon during a postanesthetic visit for us to encounter our previously afebrile patient with a low-grade fever. The majority of fevers in postoperative patients are likely due to tissue trauma and the subsequent release of cytokines in response to that trauma.[11,12] In a systematic study of the issue, laparoscopic procedures were associated with fewer episodes of fever than open procedures when the cofactor of infection was controlled.[13]

Although tissue trauma can trigger the cytokine-mediated febrile response, it is quite apparent that bacteria can provoke postoperative fever.[14,15] Certain medications and blood product administration can trigger a postoperative fever through immune-mediated responses. Although discussion is not within the scope of this article, the onset of malignant hyperthermia has been reported hours after the inhalational agent was discontinued.[16] Table 3 lists some of the potential factors and causes that should be considered in the differential diagnosis of postoperative fever. The potential causes for postoperative fever are extensive, and Table 3 is merely representative.

Delayed postoperative fever most often is due to an infectious process. Blood product administration can provoke a delayed febrile response, most often due to cytomegalovirus or hepatitis virus exposure.

Treating postoperative fever is complicated by the many causes, so carefully excluding as many causes as possible is an essential first step. Discontinuing unnecessary interventions (eg, medications; intravenous, bladder, or gastric catheters) should be considered. Treating the fever with acetaminophen for 12 to 48 hours is not likely to complicate the patient's course and will provide comfort while the underlying cause of the fever is sought and treated. If the fever is simply due to the trauma of the surgical intervention, spontaneous resolution should occur within 2 or 3 days.

Conclusion

Fever is a normal adaptive physiologic response that does not demand treatment unless a specific underlying cause is found (eg, wound infection) or unless it provokes significant patient discomfort. Central nervous system damage can occur with temperatures that exceed 105°F (40°C), although common febrile responses are unlikely to approach this level.

Fever is a coordinated response "managed" at the level of the brain with a relatively well-described mechanism of action that is based in part on the release and detection of cytokines. It should be emphasized that randomized controlled trials showing that fever reduces the course of an illness or improves patient outcome are not available.

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