Hyperthermic states and syndromes

Normothermia, fever and hyperthermia

The term 'hyperthermia' is used without definition in the general ST, and much other, literature. The term 'fever' is often used imprecisely instead of hyperthermia. What constitutes a normal temperature is not usually considered in much depth.

The range is up to 37.7, noting the time of day variability (6 AM min, 6 PM max), so the upper limit of normal is AM 37.2°C, and PM 37.7°C [1-3]. But in reality temperature varies more than is often supposed for various reasons, see below. 'Core' temperature is taken as being best represented by pulmonary artery blood temperature. Core temperature is thought to vary ~1°C as a result of the circadian rhythm, the influence of the menstrual cycle, and body temperature distribution [4]. Furthermore, 'normal' body temperature varies with activity, and with the site, and method, of measurement: such variations will become more relevant as temperature measuring technology allows more precise and site-specific measurements to be made, e.g. deep brain temperature, muscle mass, etc. Not surprisingly, Human temperatures seem to extend over the usual temperature range for other mammals, and that varies from 36-40°C [5] (from Table 1, p.111).

Fever (pyrexia is used synonymously) is defined as a pyrogen mediated temperature above the normal range (a single oral temperature of 38.5 °C, or 38.0°C for 1 hour, Infectious Diseases Society of America (IDSA) [2] and it is triggered by pyrogenic cytokines which mediate the **acute phase response (APR)**, the APR involves a change in the **thermal set point (TSP)** to a higher level and a variety of systemic responses, including: somnolence, anorexia, and changes in plasma protein and hormone synthesis, gluconeogenesis and erythropoiesis (**white cell count, WCC**).

Hyperthermia is used to indicate an elevated temperature not involving pyrogenic cytokines in which antipyretics are ineffective. However, physiologists, like clinicians, use the term loosely for smaller changes within the physiological range (e.g. see stress-induced hyperthermia [6]), as well as for pathological elevations. In hyperthermia the thermoregulatory control mechanisms are impaired, disabled or overwhelmed [7], unlike in fever where they are intact. Clinicians use hyperthermia in a different sense, often to mean problematic or dangerous temperature elevation, but again, the term is used loosely and with improper definition. The use of the term hyperthermia would best be confined to temperatures considered clinically and physiologically abnormal, and thus, by implication, benefiting from, or requiring, intervention.

Thermoregulation

The **thermal or thermoregulatory set point (TSP)** that alters during fever is probably a composite set point of several thermo-sensitive brain areas and several different thermoregulatory responses. Pyrogenic cytokines, released by phagocytic leukocytes, raise the thermal set point, but it is not known if cytokines cross the blood-brain barrier, or if they act by releasing prostaglandin E2, which then interacts with the **Circumventricular organs (CVOs)**, and is the final mediator responsible for the thermoregulatory set point. Circumventricular organs (CVOs) have cells in contact with the cerebroventricular system that have a dense vascularization and lack a blood-brain barrier. NB The role of NO is uncertain: some febrigenic models implicate it, others do not [8-10]: however methylene blue (an NO synthase inhibitor) does seem to block

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lipopolysaccharide (LPS) induced fever [11] and NO may lower the thermoregulatory set point.

The most important control center for thermoregulation is the preoptic anterior hypothalamic area. The key difference between fever and hyperthermia is that in hyperthermia the body is trying to loose heat, there is increased skin blood flow and sweating (except in drug induced hyperthermia due specifically to anti-muscarinic drugs); whereas in fever it is conserving heat to meet the higher TSP, thus there is reduced skin blood flow and shivering. Sessler states, 'A simple way to distinguish the etiologies is that patients with fever and increasing core temperature will have constricted, cold fingertips, whereas those with other types of hyperthermia will be vasodilated and have warm fingertips [12, 13].

Fever, resulting from the APR, is also a response to injury (surgery, trauma) chemicals, burns, endogenous autoimmune processes and tumours. Gurrera also points out the mutli-level nature of thermal responses, reflecting their phylogenetic evolution [14], going from local, spinal, brain stem to hypothalamus and cortical (i.e., behavioural responses).

A further key observation is that there are interactions between these processes of thermal set point (TSP) via pyrogens, and hyperthermia, such that an existing acute phase response (APR) alters the threshold at which heat loss mechanisms due to other stimuli are triggered, thus leading to increased heat accumulation [15-17]. A documented case illustrating this was reported by Carter of a soldier whose temperature increased much more rapidly when an inchoate infection was present [18, 19]. Although a single instance, this case report shows abnormal hyperthermia, in a laboratory setting, from low intensity exercise and was thoroughly documented with serial rectal temperatures, before, during and after the episode. This strongly supports this model and the likely causal association of infection with hyperthermia in heat stroke, in Parkinson disease, and in NMS too, which may be examples where the consequences of this possible TSP/APR interaction may play a part.

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