Molecular Aspects of Fever and Hyperthermia

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Hyperthermia and fever defined

When heat production or heat gain exceeds heat dissipation or heat loss, this imbalance leads to a rise in body core temperature above its range specified for the normal active state of the species [1,2]. Such a disequilibrium of thermal balance leads to a state of hyperthermia and can occur for several reasons: an increase in metabolic heat production, an impairment of heat-dissipating effector mechanisms, a decrease in heat-absorbing mechanisms by the environment under hot external conditions, or a response to a drug. The resulting hyperthermia is caused most frequently by an overwhelming of the mechanisms for temperature control.

Fever is a state that also is characterized by an elevation of body temperature, but there is no overwhelming of thermoregulatory control mechanisms. In contrast, the thermoregulatory control system is adjusted to increase body temperature to match a higher set point (ie, the higher body temperature actively is established and defended by the operation of heat-producing and heat-conserving thermoeffectors) [1].

Persons who are hyperthermic have increased skin blood flow to improve convective heat loss and sweat to dissipate heat by evaporation of water. In contrast, at least during the rising phase of fever, skin blood flow is reduced and persons who are febrile do not sweat but rather shiver to increase
metabolic heat production. These thermoregulatory effector mechanisms are supported by appropriate behavior. Although a hyperthermic organism seeks a cool environment, the state of fever is characterized by huddling or by the search for warm environmental conditions [3,4]. The strategy to establish fever seems to depend on ambient temperature. In the cold, increased heat production is activated to achieve the febrile state, whereas a suppression of heat loss mechanisms is observed predominantly in a warm environment [5].

In summary, the rise in core temperature during fever usually is designated as a result of change in the thermocontroller characteristics resulting in an elevation of the set point of body temperature. Time course and extent of natural fevers are variable, but an upper limit (41°C in humans), at which core temperature is maintained for some time and reduced when the set point of body temperature returns to its normal level, rarely is exceeded. Although any rise in body temperature may result from fever, those rises that are not accompanied by supportive changes in thermoeffector activities are termed hyperthermia [1].

Fever as a part of the acute-phase response to infection or systemic inflammation

A strong association between fever and infection has been recognized for a long time; fever, therefore, frequently is called a “hallmark of infection” [6]. The manifestation of fever, however, is not restricted to infectious diseases of bacterial, viral, protozoal, fungal, or other origin. Fever also is observed in response to injury, such as surgery, trauma, chemicals, or thermal insults. In addition, there are endogenous mechanisms that frequently are accompanied by fever. Such mechanisms include autoimmune responses, for example rheumatoid arthritis, or tumors. The question arises, therefore, of what is common in all these situations that elicits fever.

Inflammation is the general term for changes that may occur in vascularized tissues as part of the response to tissue damage, infection, or immunologic reactions. The aforementioned stimuli, which can cause fever, are identical to those capable of eliciting inflammatory responses (ie, infection, injury, and endogenous mechanisms). The functions of the inflammatory response include destruction or inactivation of the initiating irritant or agent and then the clearance of the area of debris so that healing can occur. Various cell types activated in the damaged or infected tissue release many soluble mediators, including growth factors, cytokines, chemokines, eicosanoids, kinins, biogenic amines, neuropeptides, and others. At the site of inflammation, these mediators exert vascular effects (vasodilation, vascular stasis, and increased capillary permeability), promote leukocyte migration from the circulation into the inflamed tissue, and coordinate the still-localized array of defense responses. Some of these mediators have the capacity to stimulate local sensory nerves (discussed later). In cases...
where the inflammatory response exceeds a certain strength, significant amounts of endogenous mediators and, in case of infection, microbes or microbial products enter the systemic circulation and are disseminated by blood flow to different organs. This results in a complex array of systemic reactions, collectively termed the acute-phase response (APR), which is defined as the multifactorial stereotyped response of an organism to infection, injury, or trauma. The APR comprises changes in plasma concentrations of trace metals, liver proteins (acute-phase proteins), hormones, intermediary metabolism, neutrophilia, and a characteristic set of brain-controlled signs of illness, collectively termed sickness behavior [1,7]. Sickness behavior includes development of fever, loss of appetite, increased slow wave sleep, decreased motor activity, reduced libido, and decreased alertness [8].

The APR is considered an early, nonspecific host defense response and is triggered by the release of cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, interferons, and others. These cytokines and other inflammatory mediators, which may appear in the blood during infection, injury, or endogenous pathophysiologic reactions (discussed previously), therefore are implicated in fever and frequently called endogenous pyrogens [3,6,9–12].

Experimental fever

Depending on the disease that causes clinical fever, febrile patterns are categorized into diagnostically valuable groups. A published report of a symposium summarizes clinical fever patterns [13]. There are sustained fevers of several days with only slight remissions (pneumonia, typhoid fever, or malaria), intermittent fevers with large fluctuations (sepsis), biphasic fevers with two phases lasting several days (many viral infections), weekly periods of fever with equally long afebrile periods and with repetition of this cycle (Hodgkin’s disease), and several other fever patterns [13].

Current knowledge of molecular mechanisms of fever derive almost exclusively from experimental fever research performed in animals or, in rare cases, human volunteers. Experimental fever is induced by injection of an exogenous pyrogen, a fever-inducing microbial component or product. Bolus injections of a given exogenous pyrogen usually result in a generalized inflammatory response. In the majority of experimental fever studies, lipopolysaccharide (LPS), also known as bacterial endotoxin, from gram-negative bacteria is used to induce a febrile response. Depending on dosage, ambient temperature, and route of administration, LPS evokes a stereotypic and reproducible fever that consists of several phases and has a duration of 6 to 8 hours [14–17]. The typical thermal responses of rats to intraperitoneal injections of a moderate or a high LPS dose compared with sterile saline at an ambient temperature of 24°C are shown in Fig. 1.

In rats, the injection procedure causes a transient stress-induced increase of abdominal temperature, which is measured continuously by means of an
intra-abdominally implanted telemetry transmitter. In rats treated with 100 mg/kg LPS, this rise of body temperature is followed by a fever, which is absent in control animals injected with sterile saline. Administration of 5 mg/kg LPS causes a septic shock-like state, characterized by the development of hypothermia rather than fever.

Because most knowledge of molecular aspects of fever derives from studies in which LPS is used as exogenous pyrogen, the majority of the findings presented in this article derive from the experimental model of LPS fever. It should be noted, however, that there are many other products from various microorganisms (gram-positive bacteria, mycoplasmas, viruses, fungi, and parasites) that are capable of inducing a pronounced febrile response. The question of whether or not there are common, or rather distinct, molecular mechanisms for the generation of experimental fever in response to all of these exogenous pyrogens is under current investigation [18,19]. In addition to microbial products, experimental fever also can be induced by some nonmicrobial agents (different antigens, inflammatory agents, plant lectins, and alkaloids), synthetic products (polynucleotides, antitumor agents, and immunoadjuvants), or even some host-derived substances (destroyed tissue, antigen-antibody complexes, activated complement fragments, certain metabolites, and lymphocyte products). Because most of these fever-inducing pathogenic stimuli are derived from the body’s external environment, they generally are termed exogenous pyrogens [11,20].
Exogenous pyrogens cause the production of endogenous pyrogens

The hypothesis that fever is not caused directly by exogenous pyrogens derives from the historical discovery of the “endogenous pyrogen” in 1948 [21]. This substance was obtained from isolated peritoneal macrophages and capable of inducing fever in noninfected rabbits. The substance was heat labile and was suggested, therefore, to be a protein. In later studies, it was demonstrated that after injection of an exogenous pyrogen, such as LPS, endogenous pyrogen appeared in the circulation of the LPS-stimulated animals [20].

Intensive research has focused on the molecular identification and cloning of putative endogenous pyrogens. These molecules are members of the growing family of cytokines. The term, cytokine, is used as a generic name for a diverse group of soluble proteins acting as humoral regulators that modulate the functional activities of individual cells and tissues. In the context of this article, those cytokines are of particular interest that are associated with the inflammatory response. With regard to experimentally induced LPS fever (see Fig. 1), there are four sets of observations supporting a role for inflammatory cytokines in the manifestation of the observed febrile response.

The first set of observations relates to the appearance of several cytokines in the systemic circulation more or less in parallel to the development of fever. In response to injections of LPS, TNF-α is the first cytokine that appears in the bloodstream [22–24], followed by traces of IL-1 [24] and high amounts of IL-6 [23,25,26]. From these three cytokines, considered the most important endogenous mediators of LPS fever, only IL-6 can be measured in significant quantities in the blood during the time course of fever, and circulating levels of IL-6 show the best correlation with the febrile changes of body temperature [23,25,27].

The second body of evidence relates to the repeated observations that systemic injections or infusions of single proinflammatory cytokines can induce fever, as shown for IL-1 [28,29], TNF-α [30,31], and IL-6 [32,33]. In this context, the pyrogenic effects of peripherally administered IL-6 are moderate compared with those of IL-1 or TNF-α. It is a matter of debate whether or not the pyrogenic effects of systemic injections of these cytokines reflect the physiologic conditions induced by administration of LPS [3].

The third set of observations derives from experimental procedures, in which single LPS-induced cytokines were neutralized or antagonized in their biologic activity and a concomitant reduction of LPS fever observed. Thus, treatments with IL-1 receptor antagonist [12,26], a TNF-α-neutralizing synthetic form of the P55 soluble TNF-α-receptor [12,34], or IL-6-neutralizing IL-6-antibodies [35] resulted in a significant attenuation of the febrile response to LPS, indicating a role for these cytokines in the manifestation of LPS fever. Predominantly the late phases of LPS fever, however, were inhibited by such anticytokine strategies and there seemed to be some
species-specific differences in the role of TNF-α in the LPS-induced febrile response [3,12,22,34].

Finally, the fourth set of observations derives from studies in cytokine-deficient knockout (KO) mice [36]. In IL-1 KO mice, LPS fever is reduced although not abolished [37,38]. The investigators in these studies conclude that IL-1 contributes to, but is not essential for, the manifestation of a febrile response to LPS. Alternatively, fever in response to a moderate fever-inducing LPS-dose is abolished in IL-6 KO mice [38,39], suggesting that IL-6 gene expression is essential for fever caused by a moderate LPS-challenge.

Thus, there is a large body of evidence supporting the view that the appearance of an exogenous pyrogen (LPS or others) in a host causes fever via the formation of endogenous pyrogens (cytokines). Within recent years, knowledge of how predominantly immune cells are stimulated by foreign molecules to produce a cascade of pyrogenic cytokines has improved substantially. The innate immune system, predominantly associated with neutrophils, monocytes, and macrophages, represents the first defense line against a variety of pathogens. The presence of a given pathogen within an infected host is recognized by endogenous receptors for so-called “pathogen-associated molecular patterns” (PAMP). Members of the Toll-like receptor (TLR) family are identified as key receptors for the recognition of PAMP. TLR signal transduction mechanisms in myeloid and possibly other cells finally leads to the production of inflammatory cytokines in the infected host [19,40,41]. LPS from gram-negative bacteria, the best-studied activator of the innate immune system, acts via the TLR4 receptor [42]. Meanwhile, several distinct microbe-associated PAMP and several specific TLR subtypes recognizing those PAMP are identified [40,41]. It seems that the activation of various TLRs finally results in similar circulating cascades of proinflammatory cytokines and, thereby, the manifestation of a febrile response [18,19,34].

How may circulating cytokines convey a pyrogenic message to the brain?

There is agreement that the febrile shift of the thermoregulatory set point to a higher body temperature occurs within the preoptic-anterior hypothalamic area, the most important control center of thermoregulation. Accepting that circulating cytokines are important humoral mediators of fever, the question arises of how these large hydrophilic peptides with a molecular weight of 15 to 25 kd pass the relatively impermeable blood-brain barrier to stimulate the relevant hypothalamic thermoregulatory structures. Three mechanisms for immune-to-brain signaling by circulating pyrogenic cytokines are proposed. Cytokines that are transported by the bloodstream could act at sites lacking a tight blood-brain barrier, the so-called “circumventricular organs” (CVOs) [43]. Alternatively, circulating cytokines could interact with their specific receptors on brain endothelial cells [44] or perivascular cells [45]. Finally, it is proposed that fever-promoting cytokines
can pass the blood-brain barrier by active and saturable transport systems that are specific for individual cytokines [46]. An assumed manifestation of a febrile response by these mechanisms collectively is termed, humoral hypothesis of fever induction. The mechanisms of how endogenous pyrogens are transported from the blood to the brain are discussed elsewhere in this issue in the article by Banks and colleagues. Here, a brief look is directed to both of the other humoral fever induction pathways.

Interactions of endogenous pyrogens with sensory circumventricular organs

CVOs are brain structures that have cells in contact with the cerebroventricular system, have a dense vascularization, and lack a blood-brain barrier. A subgroup of the CVOs is called sensory CVOs and includes the vascular organ of the laminae terminalis (OVLT), the subfornical organ (SFO), and the area postrema (AP). These brain structures have capillaries with fenestrated endothelia surrounded by perivascular spaces. Because of the lack of a blood-brain barrier, the cells within the sensory CVOs are exposed directly to circulating signal molecules, which they might be able to sense via specific receptors [43]. The OVLT and the SFO are located within the anterior wall of the third ventricle, the lamina terminalis. The AP is a component of the dorsal vagal motor complex, a major viscerosensory and autonomic center of the medulla oblongata. The locations of the sensory (and other) CVOs are illustrated schematically in Fig. 2.

Each of the three sensory CVOs is suggested as participating in the manifestation of brain-controlled sickness responses because of their properties as target structures for circulating inflammatory molecules. With regard to fever, the OVLT has special importance because of its location in close

![Fig. 2. Schematic diagram of a midsagittal section through the rat brain; areas that lack a tight blood-brain barrier are indicated by red color. ME, median eminence; NL, neural lobe of the pituitary; PIN, pineal organ; SCO, subcomissural organ.](image-url)
vicinity to the preoptic area. This part of the anterior-preoptic hypothalamic structures, where fever is induced, is activated strongly after intravenous injection of LPS, as demonstrated by a high level of FOS immunoreactivity, which is a neuroanatomic marker for physiologically activated neurons [47] (Fig. 3). Because of its high sensitivity to pyrogenic stimulation, this part of the preoptic area is suggested as representing a pyrogenic zone of the brain [48].

The first evidence for a role of the OVLT in the manifestation of fever was in lesion studies. Large lesions of the lamina terminalis that completely included the OVLT prevented fever after systemic injections of bacterial LPS [49,50]. At the cellular and molecular levels, more prerequisites are fulfilled for the OVLT to act as a sensor of circulating pyrogenic cytokines: (1) cellular elements within the OVLT possess receptors for IL-1 [51], IL-6 [52], and TNF-α [53]; (2) neurons located in the OVLT change their firing rate under the influence of pyrogenic cytokines [54]—such electrical activity changes might affect adjacent thermosensitive neurons transsynaptically and, thereby, contribute to the generation of fever; and (3) a direct genomic activation of cellular elements within the OVLT occurs in response to circulating cytokines as revealed by the expression of the c-fos gene [43] or by the nuclear translocation of cytokine-specific transcription factors into the nuclei of cytokine-stimulated cells, such as the acute phase response factor,
Signal-transducer and activator of transcription 3 (STAT3) [17,33]. Thus, there is much evidence that the OVLT has the possibility of acting as a sensor for circulating endogenous pyrogens and, thus, might be able to transfer febrile signals to the preoptic-hypothalamic structures situated in closest vicinity.

**Interactions of endogenous pyrogens with brain endothelial cells and perivascular cells**

Several lines of arguments support the view that not only sensory CVOs but also the entire brain endothelium is a major target for circulating cytokines, which are implicated in fever. Thus, there is clear evidence that brain endothelial cells constitutively express receptors for TNF-α [53] and IL-1 [55]. Namely, the IL-1 receptor type 1 seems to be predominantly expressed in endothelial cells of brain venules but not in those of arterioles [55]. The accessory signal transduction molecule for the IL-6 receptor, named glycoprotein (gp)130, also is expressed constitutively in brain endothelial cells, whereas the expression of the IL-6 receptor itself is induced in these cells under inflammatory conditions [52]. An IL-6–activated signal transduction in the brain endothelium also can be achieved by circulating soluble IL-6 receptors in connection with their ligand (IL-6) and the gp130 signal transducer located in the membranes of endothelial cells within the brain.

A genomic activation of the brain endothelium by IL-1 [56] or IL-6 [57] recently has been demonstrated. IL-1 and IL-6 induce a pronounced nuclear translocation of the transcription factors, nuclear factor (NF)-κB (activated by IL-1) or STAT3 (activated by IL-6), in endothelial cells all over the brain [56,57]. An example from the authors’ experiments for IL-6–stimulated brain endothelial cells showing nuclear STAT3 activation is shown in Fig. 4.

At least the IL-1 receptor type 1 and its stimulation under inflammatory stimulation also is demonstrated in perivascular cells [55], a subset of bone marrow–derived brain macrophages. The final response of such a genomic activation of brain endothelial and perivascular cells is the expression of enzymes, which are responsible for the formation of prostaglandin E2 (PGE2). PGE2 is regarded as a key mediator of fever. In this context, there seems to be a critical role for perivascular and endothelial cells in monitoring circulating cytokines. With regard to the capacity of both cell types to respond to such signals with the production of prostaglandins, perivascular cells seem to exhibit an even greater sensitivity to inflammatory stimuli [45].

**A crucial role for prostaglandin E2 within the central nervous system**

Whether or not pyrogenic cytokines are interacting with cells in sensory CVOs or with brain endothelial/perivascular cells or whether or not they are transported into the brain, they have to cause production or release of the final mediators of fever within the preoptic-anterior hypothalamus. For
the following reasons, PGE\(_2\) traditionally is regarded as the key fever mediator in the brain and as the biologic agent finally responsible for the febrile upward shift of the thermoregulatory set point: (1) prostaglandins evoke fever when injected into cerebral ventricles [58], even in very small amounts into the most PGE\(_2\)-sensitive site within the preoptic-anterior hypothalamic area [48]; (2) the levels of PGE\(_2\) in the blood [59] and in the brain [60] rise parallel to the febrile changes of body temperature; and (3) drugs that block prostaglandin synthesis also inhibit fever effectively [11,12,59]. An example from the authors’ experiments on the effects of inhibitors of PGE\(_2\) synthesis on LPS-induced fever in rats is shown in Fig. 5. Systemic treatments with a nonselective cyclooxygenase (COX) inhibitor (diclofenac) or with a preferential COX-2 inhibitor (meloxicam), which blocks formation of PGE\(_2\), result in significant and similar attenuations of LPS-induced fever in rats.

PGE\(_2\) is a derivative of arachidonic acid, which is cleaved from membrane phospholipids by phospholipase A\(_2\). In a second step, arachidonic acid is converted to prostaglandin H\(_2\) (PGH\(_2\)) by enzymes named COX. Finally, PGH\(_2\) is isomerized to PGE\(_2\) by prostaglandin E synthase (PGES) [44,61]. Several isoenzymes exist for each of these catalytic steps. COX-2 and microsomal PGES-1 (mPGES-1) are inducible enzymes that are regulated transcriptionally by NF-\(\kappa B\), a transcription factor that is activated by LPS, IL-1, or TNF-\(\alpha\) (ie, under inflammatory conditions) [62]. During LPS fever, the expressions of COX-2 and mPGES-1 are upregulated.
strongly by pyrogenic cytokines [63], and the colocalized expressions of COX-2 and mPGES-1 are suggested as the major source for PGE₂ biosynthesis in the brain during fever [44,62,63]. Predominantly brain endothelial cells and perivascular cells express COX-2 under the influence of inflammatory cytokines [44,45]. A strong expression of COX-2 in response to a fever-inducing systemic treatment with LPS occurs in the OVLT and the SFO. This is demonstrated for the SFO, by an example from the authors’ experiments (see Fig. 3). In contrast, systemic treatment with LPS does not cause a pronounced induction of COX-2 in the hypothalamic paraventricular nucleus, which is known to activate during fever [47], as shown by the pronounced LPS-induced expression of the c-fos gene (see Fig. 3).

The fact that an upregulation of COX-2/mPGES-1 is observed during LPS fever alone is not proof of a critical role of these inducible enzymes in the manifestation of the febrile response. There is, however, more experimental support for such a hypothesis. Selective COX-2–specific inhibitors repeatedly are reported to block LPS-induced fever [63–65]. Further evidence derives from studies in KO mice deficient in either COX-2 [66,67] or mPGES-1 [68,69]. In both cases, the febrile response is depressed. It seems, therefore, that the synthesis of COX-2/mPGES-1 in the brain, which is induced by pyrogenic cytokines, is critical for the brain-intrinsic formation of PGE₂ during fever.
PGE\textsubscript{2} seems to evoke fever via activation of the prostaglandin receptor subtype EP3, as suggested from studies in KO mice deficient in this receptor, in which fever in response to LPS is strongly impaired \cite{70,71}. It is suggested that an efferent fever-inducing pathway arises from activated EP3 receptors located in the preoptic-anterior hypothalamic area in close vicinity to the OVLT \cite{72}. Using the viral tracing technique combined with immunocytochemical detection of the EP3 receptor, a complete efferent fever pathway starting from the medial preoptic area and ending finally in the thermogenic brown adipose tissue of the rat is demonstrated neuroanatomically \cite{73}. A colocalization of virus protein with the EP3 receptor also is found in some neurons of the OVLT itself \cite{73}. This neuronal chain thus might be regarded as the efferent part of the thermoregulatory reflexes, which are activated by interactions of circulating endogenous pyrogens with cells located within the OVLT and the adjacent medial preoptic area.

An alternative and rapid mechanism of pyrogenic signal transmission from the periphery to the brain

A complete chain of events leading to the genesis of fever, starting with the LPS-induced formation of endogenous pyrogens (cytokines), their interactions with relevant targets in the brain (CVOs and brain endothelial cells), the induction of enzymes responsible for the formation of PGE\textsubscript{2} (COX-2 and mPGES-1), the activation of descending neuronal pathways via the EP3 receptor, and the stimulation of thermogenesis via this pathway to support the febrile shift of the thermoregulatory set point, has been introduced. Is this the end of the story? This conclusive hypothesis has been challenged recently, regarding the initial or “early” phase of LPS-induced fever (see Figs. 1 and 5) \cite{74}. The objections to the prevailing view are based mainly on the observation that, at least under some specific experimental conditions, the first phase of LPS-induced fever seems to be initiated before the appearance of cytokines in the blood. Therefore, an alternative and rapid signal pathway for the induction of the early phase of LPS fever is suggested \cite{75}.

Within the past 10 years, several published studies indicate that the humoral hypothesis (described previously) does not represent the only and exclusive pathway by which inflammatory signals from the periphery are transported to the brain. There is some evidence that the stimulation of afferent nerves, namely afferents from the vagus nerve but also possibly cutaneous afferent sensory nerves \cite{76}, might participate in the manifestation of brain-controlled sickness responses under specific experimental conditions. Initially, this evidence derived from the observation that such signs of illness, which are regulated by the brain, can be attenuated or even abrogated by surgical section of the abdominal trunks of the vagus nerve \cite{8,11,12,77,78}. In addition to these effects of subdiaphragmatic vagotomy, there are additional arguments that support a role of the vagus nerve as
a pathway for transmission of immune signals to those parts of the brain where fever, anorexia, or sickness behavior are induced. Injection of IL-1 into the portal vein is shown to increase the firing rate of the vagal hepatic afferent nerve branch [79] and, in primary afferent neurons of the vagus nerve, immediate early genes seem to be activated by cytokines [80]. The role of the vagus nerve in the manifestation of fever is discussed controversially, especially because the results from studies of vagotomized animals lead, in part, to conflicting results [81].

Based on several experimental studies, Blatteis [74,75,78] suggests a novel hypothesis, including afferent parts of the vagus nerve, which could account for a rapid induction of the early phase of LPS-induced fever before the release of larger amounts of cytokines into the bloodstream, which then might be involved in the maintenance rather than in the initiation of fever under some conditions. According to this hypothesis, the febrigenic process is initiated by the arrival of LPS in the liver and its uptake by Kupffer’s cells, causing an immediate activation of complement. The complement component C5a, in turn, seems to stimulate the Kupffer’s cells to a rapid release of PGE2, which is suggested as activating local sensory vagal terminals that project to the medulla oblongata of the brainstem. From the medulla, this vagally transmitted excitation is believed to be transmitted to the pre-optic-anterior hypothalamic area via the ventral noradrenergic bundle. An intrahypothalamic release of norepinephrine might cause immediate neuronal activity changes via stimulation of α-adrenoreceptors, which are capable of activating efferent fever-promoting pathways. The aforementioned role for intrahypothalamic COX-2/mPGES-1–dependent release of PGE2 in the manifestation of fever thus might operate only for the longer second phase (see Figs. 1 and 5) of the LPS-induced febrile response [74,75].

In summary, it seems possible that the brain is informed by inflammatory processes in the periphery by rapid neuronal and with some delay by humoral signals. The combination of both types of signals might allow the brain to improve the recognition of the nature of the inflammatory challenge and, thereby, help activate an appropriate defense strategy. Fever, as a part of many successful defense strategies, thus may be a beneficial component of the APR, which helps to optimize the responses of the immune system against an infectious insult.

**Molecular aspects of hyperthermia**

As discussed previously, hyperthermia occurs when temperature regulation against overheating is active as a consequence of the temporary or permanent imbalance between heat load and the capacity to dissipate heat. Molecular aspects of hyperthermia include the description of molecular changes, which occur in the heat-stressed brain and, in some cases, the molecular mechanisms, which are the specific causes for a developing hyperthermia.
**Malignant hyperthermia**

Malignant hyperthermia is caused by a rare, genetically fixed mutation of the ryanodine receptor, or calcium release channel, in the sarcoplasmatic reticulum of the striated muscles. Some inhalation anesthetics, such as halothane or isofluorane, cause excessive release of calcium from the sarcoplasmatic reticulum in genetically susceptible subjects. Also, the muscle relaxant, succinylcholine, or high circulating levels of stress hormones can act as triggering agents. As a consequence, uncoordinated muscle contractions with a tremendous rise in oxygen consumption and metabolic rate induce a severe hyperthermia that is accompanied by acidosis, tachycardia, or cardiac arrhythmias. The often-fatal hyperthermia is supported by the limitations of active heat dissipation during anesthesia [1,2].

**Drug-induced hyperthermia**

The use of amphetamine-type stimulants can induce a pronounced and sometimes lethal increase in body temperature. Intoxication with 3,4-methylenedioxyamphetamine (ecstasy), as a consequence of its worldwide recreational use, results in increasing numbers of hospital cases and deaths [82]. In most cases, lethality results from persistent hyperthermia, which leads to a breakdown of skeletal muscles (rhabdomyolysis) and renal failure. Ecstasy-induced hyperthermia seems to result from a strong activation of the sympathetic nervous system and the hypothalamic-pituitary thyroid/adrenal axes [83]. The excessive release of norepinephrine causes pronounced heat generation via β3-adrenergic activation of uncoupling protein type 3 and α1-adrenergic suppression of heat dissipation resulting from sympathetically mediated vasoconstriction [83]. Ecstasy thus represents an impressive example of a drug-induced manifestation of hyperthermia.

**The heat stroke syndrome**

During prolonged hyperthermia, with a body temperature of 41°C or higher, the brain suffers severe damage, which frequently leads to death. Alterations in microvascular permeability cause the development of cerebral edema. Postmortem findings show microhemorrhages, tissue softening, and destruction of neurons. Victims exhibit disorientation, delirium, and convulsions. This syndrome is referred to popularly as heat stroke. The precise mechanisms that account for the manifestation of heat stroke are under current investigation [84,85]. Several molecular changes that occur in the heat-stressed brain already are identified [86]. The expression of several molecules is upregulated in the brain under conditions of severe hyperthermia. Thus, the induction of a specific set of proteins, the so-called “heat-shock proteins,” is related closely to damaged brain areas and thus can be used as markers of cell injury. There is some evidence that heat-shock proteins have neuroprotective properties [86]. Hyperthermic brain injury is accompanied further
by an activation of glial cells (ie, astrocytes), as indicated by the expression of the cell marker protein, glial fibrillary acidic protein. Under pathologic conditions, such as brain hyperthermia, induction of this protein is associated with a breakdown of the blood-brain barrier and vasogenic edema.

Activation of the immune system during infection or inflammation is characterized not only by a systemic formation of cytokines but also by the expression of cytokines in the brain [8,87]. There is evidence that an increased expression of IL-1 within the central nervous system is associated with brain injury. Heat stroke–induced cerebral ischemia and neuronal damage are accompanied by an increased production of IL-1 in the damaged brain. Because the survival time of rats can be prolonged by treatment with an IL-1 receptor antagonist, a role for IL-1 and possibly other cytokines in the manifestation of the heat stroke syndrome is indicated [88]. In this context, it recently has been reported that elevated cytokine concentrations occur in human heat stroke and in experimental animal heat stroke models [84,85]. As opposed to fever, the precise role of the stimulated formation of cytokines in heat stroke still has to be elucidated. It is anticipated that a more detailed understanding of the putative roles of cytokines in the modifications of body core temperature in experimental heat stroke models will provide important insight into the role of these substances in the complex etiology of the long-term consequences of this syndrome [85].

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