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Chapter 34

Fever and hypothermia in systemic inflammation

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Abstract

Systemic inflammation-associated syndromes (e.g., sepsis and septic shock) often have high mortality and remain a challenge in emergency medicine. Systemic inflammation is usually accompanied by changes in body temperature: fever or hypothermia. In animal studies, systemic inflammation is often modeled by administering bacterial lipopolysaccharide, which triggers autonomic and behavioral thermoeffector responses and causes either fever or hypothermia, depending on the dose and ambient temperature. Fever and hypothermia are regulated changes of body temperature, which correspond to mild and severe forms of systemic inflammation, respectively. Mediators of fever and hypothermia are called endogenous pyrogens and cryogens; they are produced when the innate immune system recognizes an infectious pathogen. Upon an inflammatory challenge, hepatic and pulmonary macrophages (and later brain endothelial cells) start to release lipid mediators, of which prostaglandin (PG) E_2 plays the key role, and cytokines. Blood PGE_2 enters the brain and triggers fever. At later stages of fever, PGE_2 synthesized within the blood-brain barrier maintains fever. In both cases, PGE_2 is synthesized by cyclooxygenase-2 and microsomal PGE_2-synthase-1. Mediators of hypothermia are not well established. Both fever and hypothermia are beneficial host defense responses. Based on evidence from studies in laboratory animals and clinical trials in humans, fever is beneficial for fighting mild infection. Based mainly on animal studies, hypothermia is beneficial in severe systemic inflammation and infection.

INTRODUCTION[1]

Systemic inflammation is a generalized pathologic process, which can be clinically manifested in various forms, including systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple-organ dysfunction and failure (Bone et al., 1992). The inflammatory response is a series of complex pathophysiologic events that can result from infections, as well as from non-infectious causes, such as trauma or burns (Balk, 2014). When the underlying cause of the systemic inflammatory response is infection, it is termed sepsis.

The exact definitions and clinical criteria of sepsis and related syndromes have changed over the past three decades (Bone et al., 1992; Levy et al., 2003; Singer et al., 2016). According to the latest consensus (Singer et al., 2016), sepsis is defined as evidence of infection plus life-threatening organ dysfunction. Even nowadays, it constitutes a global burden for healthcare, with an estimated 31 million cases and 5.3 million deaths worldwide annually (Fleischmann et al., 2016) and an incidence rate of ~30% in patients admitted to the intensive care unit (Vincent et al., 2014). Of note,

[1]Abbreviations used in the chapter are listed at the end of the chapter before References section.

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not only can sepsis lead to death acutely, but it also increases the risk of death for 5–8 years after the septic event (Quartin et al., 1997; Dreiher et al., 2012). In the United States, the incidence of hospitalizations with sepsis increased by ~50% between 2003 and 2009 (Walkey et al., 2015), with estimated annual healthcare costs exceeding $17 billion nationally (Angus et al., 2001).

The importance of a change (elevation) in body temperature (T_b) in inflammation was recognized a long time ago. This is also reflected in the word inflammation, as it originates from the Latin *inflammare* (to set on fire). Fever was recognized as a disease symptom already in the time of Hippocrates (5th–4th century BC) (Atkins, 1982). Heat (*calor*) is also one of the four cardinal symptoms of inflammation, along with redness, swelling, and pain, which were originally described by Celsus in the first century AD (Scott et al., 2004). The inflammatory response is also accompanied by changes in vital functions, including heart rate, respiratory rate, white blood cell count, and T_b, the same parameters that serve as bases for the clinical diagnosis of SIRS (Bone et al., 1992; Singer et al., 2016). Among the criteria for SIRS (first established in 1991), a deep T_b above 38°C or below 36°C was considered to be positive (Bone et al., 1992). The inclusion of T_b alterations in the SIRS criteria also indicates that the systemic inflammatory response is commonly accompanied by changes in T_b (either fever or hypothermia). This chapter focuses on T_b changes in systemic inflammation caused mainly by infectious agents, while the thermoregulatory disorders in non-infectious diseases, which may also involve inflammatory processes, are covered in other chapters; for example, obesity (see Chapter 26), brain injury (see Chapter 49), and spinal cord injury (see Chapter 50).

THERMOREGULATORY MANIFESTATIONS OF CLINICAL SYSTEMIC INFLAMMATION

Systemic inflammation can be induced by a variety of microbial and nonmicrobial stimuli (Bone et al., 1992; Robertson and Coopersmith, 2006; Lenz et al., 2007). The microbial agents include viruses, bacteria, fungi, and parasites, which may infect different bodily compartments (for example, the upper respiratory, urinary, or gastrointestinal system). As a result, a complex inflammatory response is initiated to fight the intruding pathogen. In severe cases, however, the host's deleterious, non-resolving inflammatory response to the infection can lead to organ dysfunction, which is defined as sepsis (Vincent et al., 2013; Singer et al., 2016). A more severe variant of sepsis is septic shock, which is associated with hypotension (defined as mean arterial pressure of less than 65 mmHg) and has a higher mortality (Singer et al., 2016). Despite its diverse etiology, systemic inflammation is usually accompanied by one of the two prototypic changes in the regulation of T_b: fever or hypothermia (Romanovsky et al., 2005). Fever is the most frequent thermal manifestation in infections of different severities ranging from minor viral illnesses to bacterial sepsis, while hypothermia characteristically develops in severe cases of sepsis, e.g., septic shock. At the time of the diagnosis of sepsis, the majority of the patients are febrile, while hypothermia occurs in 9–16% of septic patients (Clemmer et al., 1992; Arons et al., 1999; Kushimoto et al., 2013; Drewry et al., 2015) and in 13–21% of patients with septic shock (Marik and Zaloga, 2000; Peres Bota et al., 2004). A retrospective study, which looked at the T_b of septic patients during their entire stay at the intensive care unit, found that the prevalence of hypothermia may be closer to 50% (Fonseca et al., 2016).

In accordance with the frequent thermoregulatory disorders that accompany systemic inflammation, many clinical scoring systems include the change of T_b. Among them, the SIRS criteria are used for diagnosis (Bone et al., 1992; Levy et al., 2003), while other scores are calculated to assess the prognosis of critically ill patients. The latter group of scores includes the Simplified Acute Physiology Score (Le Gall et al., 1993), the Acute Physiology and Chronic Health Evaluation (Knaus et al., 1985), and the Predisposition, Insult, Response, Organ Dysfunction system (Opal, 2005). A common setback of these scoring systems is that reduced and elevated T_bs are considered to be equal-level concerns (Beverly et al., 2016), which contradicts the prevailing view in the field that fever is associated with lower, and hypothermia with higher, severity of a disease (Romanovsky and Szekely, 1998; Romanovsky et al., 2005). A recent meta-analysis, including data from over 10,000 septic patients, also revealed that fever is associated with reduced mortality, while hypothermia with increased mortality, in sepsis (Rumbus et al., 2017). It has to be noted that the prognostic value of hypothermia in sepsis does not automatically imply a detrimental effect of T_b itself. Instead, the association between hypothermia and mortality can merely reflect the higher prevalence of hypothermia in severe cases of sepsis; without hypothermia, the outcomes of severe sepsis could have been even worse (Romanovsky and Szekely, 1998; Steiner et al., 2017).

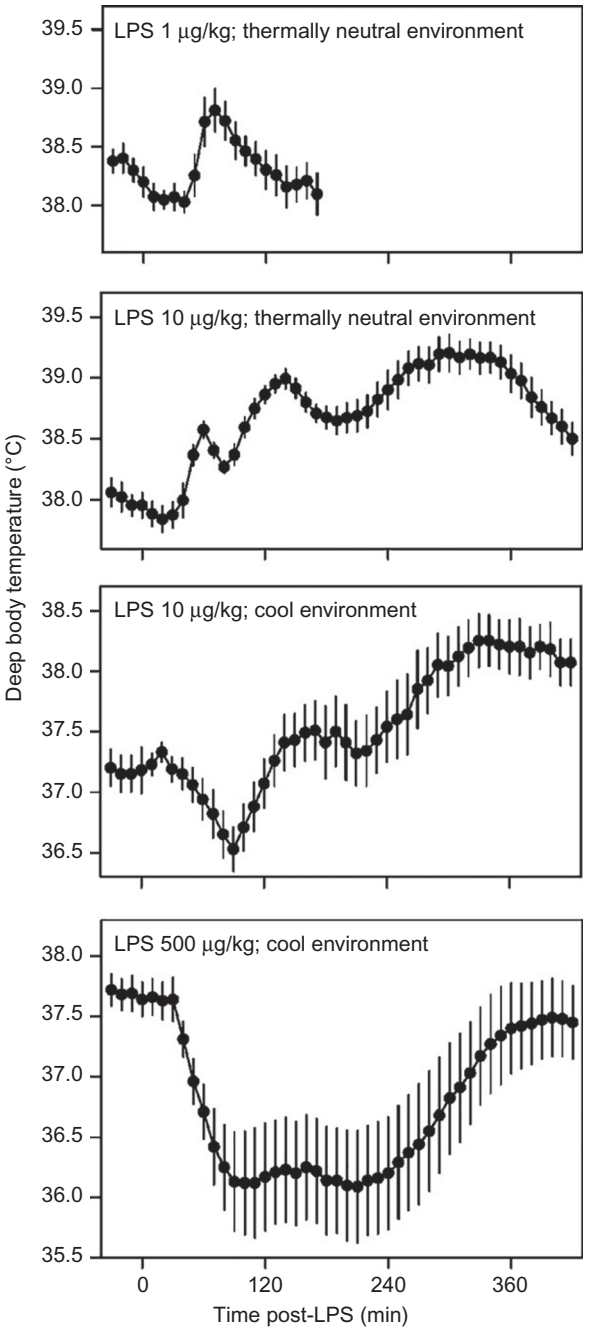

Fig. 34.1. Thermoregulatory responses of rats to intravenous injection of lipopolysaccharide (LPS; doses indicated) in thermally neutral and cool environments. From top to bottom: monophasic fever, polyphasic fever, hypothermia followed by fever, and long-lasting hypothermia. Note that fever prevails when the LPS dose is lower or the environment is warmer, or both, whereas hypothermia prevails when the LPS dose is higher or the environment is cooler, or both. Data are presented as mean ± SE. (Reproduced from Steiner AA, Romanovsky AA (2007) Leptin: at the crossroads of energy balance and systemic inflammation. Prog Lipid Res 46: 89–107.)

PHENOMENOLOGY OF THERMOREGULATORY MANIFESTATIONS OF SYSTEMIC INFLAMMATION IN EXPERIMENTAL MODELS

Body temperature responses to bacterial lipopolysaccharide

In experimental models, systemic inflammation is commonly induced by the administration of bacterial lipopolysaccharide (LPS, endotoxin). Experimental animals respond to intravenous (i.v.) administration of LPS with fever or hypothermia (Romanovsky et al., 2005; Steiner and Romanovsky, 2007). The direction and pattern of T_b change depend on the ambient temperature (T_a) and LPS dose. In a thermally neutral or supraneutral (warm) environment, fever is the prevalent response. It is monophasic when the dose of LPS is low (just above subpyrogenic), but becomes polyphasic as the dose increases (Romanovsky et al., 1996a, 1997b; Rudaya et al., 2005; Steiner et al., 2005a) (Fig. 34.1). As part of the febrile response, three phases have been identified in rats (Romanovsky et al., 1998a, b; Steiner et al., 2004a, b, 2005a) and mice (Oka et al., 2003; Rudaya et al., 2005; Steiner et al., 2006a). In a cool environment, when LPS is administered at doses that cause polyphasic fevers at a neutral T_a, rats develop hypothermia, which is often followed by fever (Romanovsky et al., 1996b, 1997b; Steiner et al., 2004a, b) (Fig. 34.1). The magnitude of hypothermia increases along with the LPS dose. The T_a- and dose-dependence of LPS-induced T_b responses reflect different thermoeffector activity patterns.

Autonomic and behavioral thermoeffectors of fever and hypothermia

The febrile response of rats to LPS (10–1000 μg/kg, i.v.) is characterized by a short latency (~10 minutes), followed by three T_b rises, with peaks occurring at ~1, 2.5, and 5 hours postinjection (Romanovsky et al., 1998b). Several methodologic factors (viz., the length of observation period, level of stress, dose of LPS, and T_a) can interfere with the detection of the febrile phases; for example, the first phase is often masked by stress hyperthermia if LPS is administered in a stressful manner, involving a needle prick (Romanovsky et al., 1998a).

In the rat, the hypothermia in response to higher doses of LPS occurs very early at subneutral T_as (latency of ~20 minutes) and has a consistent nadir at ~90 minutes postinjection. This relatively short-lasting first hypothermic phase can be followed by a long-lasting decrease in

T_b, occurring at approximately the same time as the third febrile phase (Romanovsky et al., 1996b; Almeida et al., 2006a; Liu et al., 2012).

Fever

During fever, T_b typically rises as the result of coordinated behavioral (e.g., seeking a warmer environment) and autonomic responses; the autonomic responses involved are aimed at decreasing heat loss (e.g., skin vasoconstriction) and increasing heat production (e.g., activation of thermogenesis) (Romanovsky, 2004a). The contribution of the various thermoeffectors depends on the T_a: in a supraneutral environment, inhibition of heat loss is mainly responsible for the rise in T_b, while in a subneutral environment, the increase in heat production is of greater importance. Under thermoneutral conditions, skin vasoconstriction can occur simultaneously with the activation of thermogenesis, but they can still have different thresholds and can defend different values of T_b.

In the first (early) phase of fever, the threshold T_b for cold thermogenesis and that for skin vasodilation are shifted upwards equally (Jansky and Vybiral, 2004). As a result of this shift, T_b is maintained at a new, elevated level. The later (second, and presumably third) phases of fever are often, though not always, characterized by an elevation in T_b as well. However, these phases involve the so-called threshold dissociation, meaning that the T_b threshold for vasodilation remains elevated, while the threshold T_b for cold thermogenesis decreases by several degrees (Vybiral et al., 1987). As a consequence, T_b regulation changes to poikilothermic: autonomic effectors are not activated in a wide T_b range, and deep T_b is determined solely by the passive heat exchange between the body and the environment. Under such conditions, behavioral thermoregulation (selection of thermal environment) plays a crucial role, as in poikilothermic animals. In other words, T_b becomes highly dependent on T_a, and hypothermia occurs easily at subneutral T_as (see section on hypothermia, below).

The principal physiologic (autonomic) thermoregulatory effectors are discussed in detail in other chapters (see Chapters 9–14). In small animals, the main autonomic effectors of fever are cutaneous vasoconstriction (particularly in the glabrous skin), the principal means by which small animals elevate deep T_b in a warm environment, and brown adipose tissue (BAT) thermogenesis, which mammals recruit to elevate T_b in a cool environment. A representative example for endotoxin-induced changes in the activity of different autonomic effectors in a rabbit is shown in Figure 34.2 (Szelenyi and Szekely, 1979). When the rabbit was able to utilize all of its physiologic thermoeffectors in response to LPS,

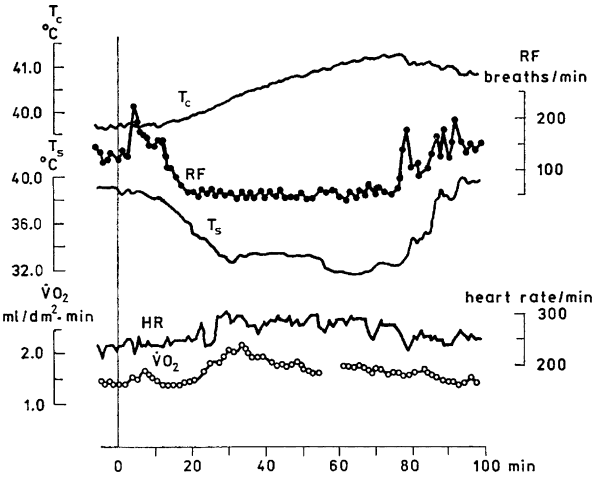

Fig. 34.2. The effects of *Escherichia coli* endotoxin (1.0 μg/kg, intravenously) on colonic temperature (T_c, a form of deep body temperature) and on the activity of autonomic thermoregulatory effector mechanisms in a rabbit in a thermoneutral environment (ambient temperature of 23°C). Thermoeffector mechanisms were assessed: polypnea – by respiratory frequency (RF); ear-skin vasoconstriction – by ear-skin temperature (T_s); thermogenesis – by rate of oxygen consumption ($\dot{V}O_2$). *HR*, heart rate. (From Szelenyi Z, Szekely M (1979) Comparison of the effector mechanisms during endotoxin fever in the adult rabbit. Acta Physiol Acad Sci Hung 54: 33–41, with permission from Akadémiai Kiadó.)

a complete inhibition of thermal polypnea (i.e., an increase in the pulmonary ventilation rate due to an increased rate of breathing; for details, see Chapter 14) developed first, with no marked changes in ear-skin temperature (T_{sk}, an indicator of cutaneous vasomotor tone) or oxygen consumption ($\dot{V}O_2$, an indicator of thermogenesis). A marked fall in T_{sk} occurred only after the respiratory rate had already reached its nadir. The rise in $\dot{V}O_2$ started even later, only after the respiratory rate and T_{sk} reached their low steady-state values (Fig. 34.2). The deactivation of effectors occurred in the opposite order: a decline in $\dot{V}O_2$ occurred first, followed by cutaneous vasodilation and thermal polypnea (Szelenyi and Szekely, 1979). As noted above, heat conservation and heat production are not always activated simultaneously; in different thermal environments, they usually operate over distinct ranges of T_a.

The afferent and efferent neural pathways controlling BAT and skin vasculature are described in other chapters (see Chapters 16–19). For triggering the fever response, two populations of γ-aminobutyric acid (GABA)-ergic neurons in the medial preoptic area (MPO) of the hypothalamus are important: those that control BAT and those that control skin vasculature (for details, see Chapters 17 and 18). These GABAergic neurons are warmth-sensitive and tonically suppress BAT

thermogenesis and skin vasoconstriction (Osaka, 2004). In rodents, LPS induces the synthesis of prostaglandin (PG) E_2 (see section on prostaglandin E_2 as a mediator of fever, below), which, in turn, triggers autonomic heat conservation and heat production by acting on EP3 receptors to reduce the activity of preoptic GABAergic neurons, thus, disinhibiting sympathetic activation of tail-skin vasoconstriction and BAT thermogenesis (Saper et al., 2012). The preoptic hypothalamic area (POA) has a principal, but non-essential, role in fever, as evidenced by the finding that POA-lesioned rats can also develop a normal febrile response to LPS when they use warmth-seeking behavior (Fig. 34.3) (Almeida et al., 2006b). Squirrel monkeys (Lipton and Trzcinka, 1976) and rabbits (Korneva et al., 1992) have also been shown to develop normal fever in response to LPS and PGE_1 when the POA is electrolytically ablated. These studies suggest that POA neurons are not the sole targets of pyrogenic mediators. Neurons in the locus ceruleus (Almeida et al., 2004) and the paraventricular nucleus (Horn et al., 1994; Lu et al., 2001) seem to mediate a thermogenic response to febrigenic stimuli (bacterial LPS or PGE_2), but not to cold-induced thermogenesis or a nocturnal T_b rise in rodents.

Behavioral thermoregulatory responses range from simple (e.g., postural extension) to complex (e.g., pressing a lever to trigger warming or cooling of the environment). In experimental animals, behavioral responses are usually studied in a thermogradient apparatus, where the animals are allowed to select their preferred T_a, and warmth- and cold-seeking behaviors can be observed. In fever, the changes in preferred T_a have been studied in rats (Sugimoto et al., 1996; Bodurka et al., 1997; Briese, 1997; Florez-Duquet et al., 2001; Turek et al., 2005; Almeida et al., 2006a, b), mice (Akins et al., 1991), and rabbits (Satinoff et al., 1976). In all of these studies, the animals responded to LPS with warmth-seeking behavior. In carefully conducted experiments, Almeida et al. (2006a) observed that the warmth-seeking behavior was present during the entire polyphasic fever response to LPS (Fig. 34.4). The same study has also demonstrated that the switch from warmth- to cold-seeking behavior in systemic inflammation depends on the dose of LPS: while lower (fever-inducing) doses cause warmth seeking, higher (hypothermia-inducing) doses cause cold seeking (Almeida et al., 2006a). The brain structures that mediate the warmth-seeking behavior in fever are largely unknown. Neurons in the POA are unlikely to be involved in this response, as large bilateral preoptic lesions (including the entire MPO) did not change the warmth-seeking responses of rats to low doses of bacterial LPS (Fig. 34.3) (Almeida et al., 2006b).

Hypothermia

Hypothermia in systemic inflammation is a regulated response. The fall in T_b can be achieved by recruitment of coordinated behavioral (e.g., seeking a cooler environment) and autonomic thermoeffectors. The autonomic effectors recruited are aimed at increasing heat loss (e.g., skin vasodilation) and decreasing heat production (e.g., inhibition of thermogenesis) (Romanovsky, 2004a).

A principal mechanism of the response to high (shock-inducing) doses of LPS is a decrease in the

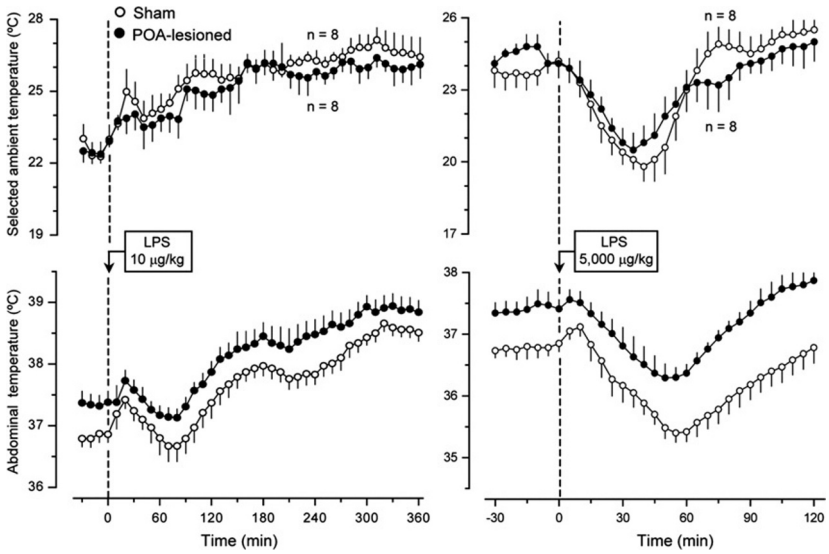

Fig. 34.3. The effects of intravenously administered lipopolysaccharide (LPS; doses indicated) on the preferred ambient temperature (top panels) and deep (abdominal) body temperature (bottom panels) in sham-lesioned and preoptic area (POA)-lesioned rats. Data are presented as mean ± SE. (Reproduced from Almeida MC, Steiner AA, Branco LG, et al. (2006b) Neural substrate of cold-seeking behavior in endotoxin shock. PLoS One 1: e1.)

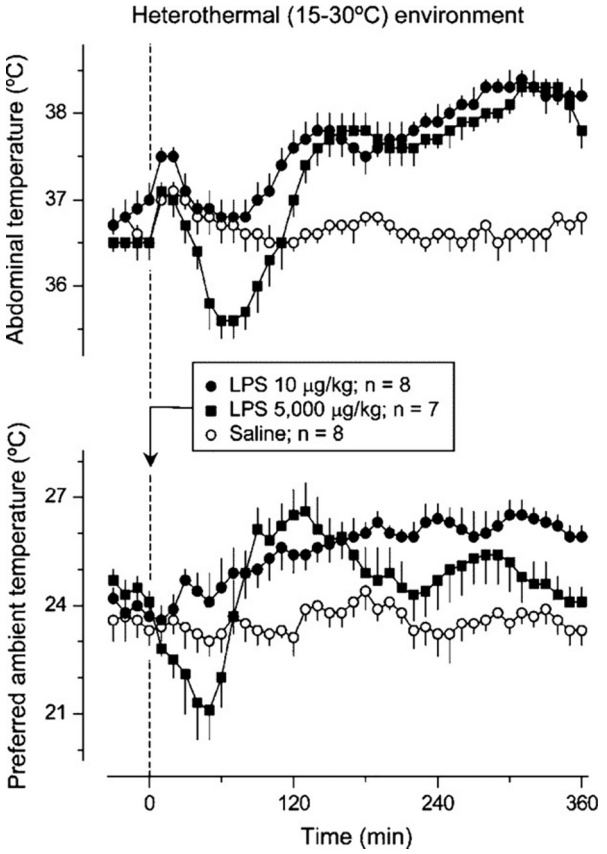

Fig. 34.4. The effects of lipopolysaccharide (LPS; 10 or 5000 μg/kg, intravenously) or saline on body temperature (top panel) and preferred ambient temperature (bottom panel) of the rats allowed to move freely in a heterothermal environment (ambient temperature gradient from 15 to 30°C). Data are presented as mean ± SE. (From Almeida MC, Steiner AA, Branco LG, et al. (2006a) Cold-seeking behavior as a thermoregulatory strategy in systemic inflammation. Eur J Neurosci 23: 3359–3367, with permission from John Wiley and Sons.)

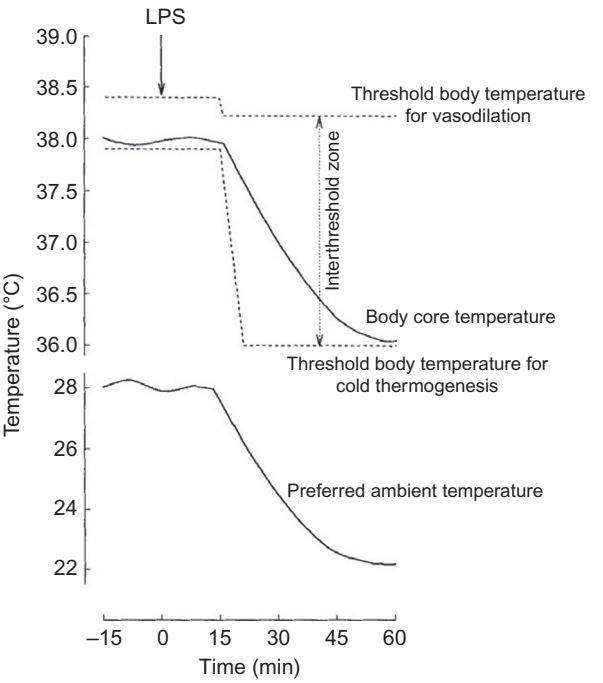

Fig. 34.5. Schematic representation (based on experimental data) of the mechanism of rats' thermoregulatory response to a shock-inducing dose of lipopolysaccharide (LPS). (From Romanovsky AA, Shido O, Sakurada S, et al. (1997a) Endotoxin shock-associated hypothermia. How and why does it occur? Ann N Y Acad Sci 813: 733–737, with permission from John Wiley and Sons.)

threshold T_b for activation of metabolic heat production (Romanovsky et al., 1996b, 1997a). The inhibition of thermogenesis is so drastic that it can lead to a substantial drop of T_b, even if the animal does not exhibit skin vasodilation and cannot utilize behavioral effectors (i.e., cold seeking). The inhibition of metabolic heat production in endotoxin shock is a regulated suppression, and not the result of impaired thermogenic capacity due to a fall in oxygen delivery, as evident from the preserved hypermetabolic effect of CL316,243, a β_3-adrenergic agonist known to activate BAT thermogenesis, in rats injected with shock-inducing doses of LPS (Corrigan et al., 2014). Cutaneous vasodilation can also accompany the onset of endotoxin shock, but since the dilation of skin vessels is quite sensitive to T_a, it rarely occurs in a cool environment. At a higher T_a, shock-inducing doses of LPS consistently cause transient tail-skin vasodilation in rats (Romanovsky et al., 1996b), which is in agreement with the clinical manifestation of the initial phase of distributive (septic) shock, also known as the "warm phase" because of the warm (vasodilated) skin. This vasodilation is mediated by several inflammatory mediators released into the circulation in response to LPS (e.g., histamine, kinins, nitric oxide, and prostanoids).

Under normal circumstances, the T_b thresholds for activating heat and cold defense mechanisms are relatively close to each other (for details, see Romanovsky (2004a) and Chapter 1, this volume). Due to the rapid downward shift of the threshold T_b for activation of thermogenesis during LPS shock, the thresholds for cold and heat defense mechanisms become separated by a wide (sometimes 2°C) zone (Fig. 34.5). Within this new, wide interthreshold zone, T_b becomes dependent exclusively on passive heat transfer between the body and the environment (Vybiral et al., 1987; Romanovsky et al., 1996b). If T_a is low enough (the difference between T_b and T_a is large enough), the body cools rapidly until the threshold for thermogenesis is reached.

Only a few studies have been published about behavioral thermoregulation in hypothermia with

systemic inflammation (Romanovsky et al., 1996b, 1997a; Almeida et al., 2006a, b; Wanner et al., 2017). These studies have shown that cold-seeking behavior is an important response in severe systemic inflammation, such as endotoxin-induced shock. The hypothermic response and the associated cold-seeking behavior are often followed by fever and warmth-seeking behavior (Almeida et al., 2006a) (Fig. 34.4). Similarly to fever, LPS-induced hypothermia can also occur in POA-lesioned rats, provided that the animals are allowed to use behavioral thermoregulation (Fig. 34.3). In contrast to POA lesions, electrolytic ablation of either the paraventricular hypothalamus (PVH) or the entire dorsomedial hypothalamus (DMH) strongly attenuated LPS-induced hypothermia in the study by Almeida et al. (2006b), indicating a crucial role for these brain structures in severe forms of systemic inflammation. When the authors lesioned the neuronal bodies in the DMH with ibotenic acid, these lesions also attenuated the hypothermic response to LPS (Fig. 34.6), while excitotoxic lesion of the PVH did not affect LPS hypothermia. These findings indicate that neuronal bodies located in the DMH and axons passing through the PVH play an important role in the mediation of LPS-induced hypothermia (Almeida et al., 2006b; Wanner et al., 2017). These structures are the first two landmarks to have been identified in mapping the cold-seeking behavior associated with endotoxin shock. Further supporting the role of the PVH and DMH in LPS hypothermia, both structures had much stronger c-Fos expression during LPS hypothermia than fever (Wanner et al., 2013). In the more recent study by Wanner et al. (2017), the functional topography of the DMH was further expanded. By placing small bilateral lesions at different DMH sites in a large number of rats, the authors showed that LPS-induced cold seeking was represented by a site at the ventral border of the dorsomedial nucleus (Fig. 34.7). With three-dimensional functional topography, Wanner et al. (2017) discovered that the shape of this site is a hemisphere of ~1 mm in diameter, which sits on top of the caudal aspect of the ventromedial hypothalamic nucleus like a bowl and supports (contains) the central aspect of the dorsomedial hypothalamic nucleus. This neuronal group is situated at the following stereotaxic coordinates (Paxinos and Watson, 2007): anteroposterior, 2.90–3.80 mm caudal to bregma; mediolateral, 0.10–0.90 mm from the midline; and dorsoventral, 8.90–9.50 mm below bregma (Wanner et al., 2017).

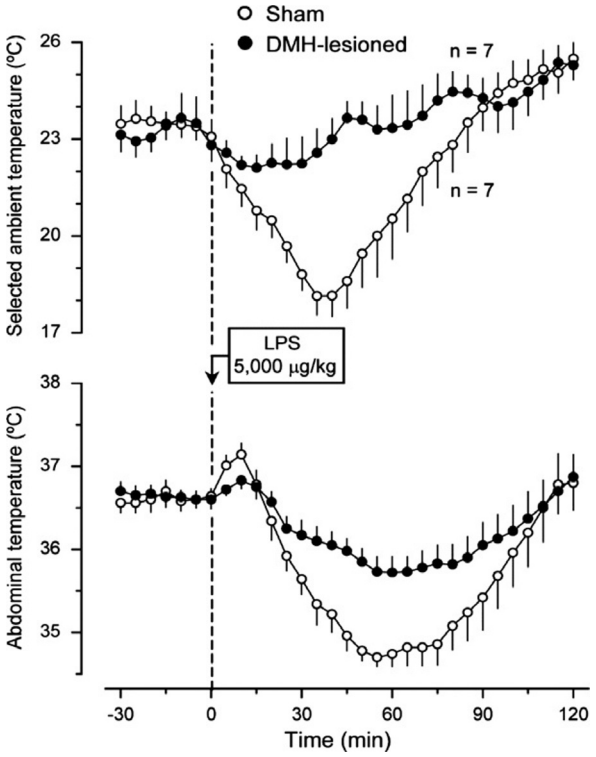

Fig. 34.6. The effects of lipopolysaccharide (LPS; 5000 µg/kg, intravenously) on the preferred ambient temperature (top panel) and deep body temperature (bottom panel) of sham-lesioned rats and rats with bilateral ibotenic acid-induced lesions of the dorsomedial hypothalamus (DMH). Data are presented as mean ± SE. (Reproduced from Almeida MC, Steiner AA, Branco LG, et al. (2006b) Neural substrate of cold-seeking behavior in endotoxin shock. PLoS One 1: e1.)

PATHOGENESIS OF FEVER AND HYPOTHERMIA IN SYSTEMIC INFLAMMATION

Innate immune response

Pathogen recognition

Natural barriers of the body represent the first line of defense against microbial infection. If pathogens penetrate the body's barriers (e.g., in the gastrointestinal, respiratory, or urinary tract, or in the skin), they encounter the immune system, and the immune responses are initiated. Traditionally, the immune system has been divided into the innate and acquired components, each with a distinct function. This section briefly summarizes the activation of the innate immune system in systemic inflammation, while details about the interactions between acquired immunity and thermoregulation can be found in Chapter 24.

The innate immune response is mediated mainly by phagocytic cells and antigen-representing cells, including macrophages and granulocytes (Mogensen, 2009). Immune sensing of infection is initiated with the binding of pathogen-associated molecular patterns (PAMPs), such as LPS, viral RNA, and fungal sugars, to pattern

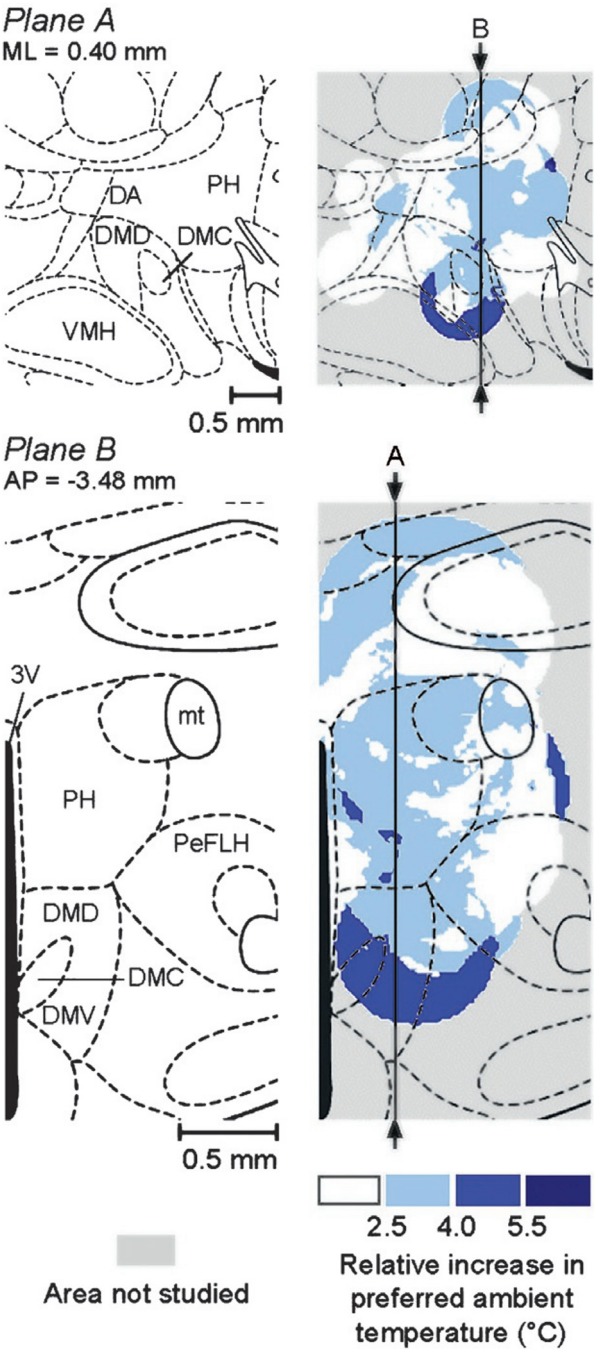

Fig. 34.7. Representation maps of lipopolysaccharide (LPS)-induced cold-seeking behavior in the rat. The left panels show a sagittal section (top row, plane A) and a coronal section (bottom row, plane B) at the specified mediolateral (ML) and anteroposterior (AP) coordinates, respectively (modified from Paxinos and Watson, 2007). The right column shows the corresponding representation maps for the LPS-induced cold-seeking behavior. In each map, arrows and letters indicate the lines at which the plane of this map is crossed by the other plane shown. The magnitude of the behavioral impairment used for constructing these maps is coded by color. All abbreviations of the names of brain structures are according to Paxinos and Watson (2007). *3V*, third ventricle; *DA*, dorsal hypothalamic area; *DMC*, compact part of the dorsomedial hypothalamic nucleus; *DMD*, dorsal part of the dorsomedial hypothalamic nucleus; *DMV*, ventral part of the dorsomedial hypothalamic nucleus; *mt*, mammillothalamic tract; *PeFLH*, perifornical part of lateral hypothalamus; *PH*, posterior hypothalamic nucleus; *VMH*, ventromedial hypothalamic nucleus. (Adapted from Wanner SP, Almeida MC, Shimansky YP, et al. (2017) Cold-induced thermogenesis and inflammation-associated cold-seeking behavior are represented by different dorsomedial hypothalamic sites: a three-dimensional functional topography study in conscious rats. J Neurosci 37: 6956–6971.)

recognition receptors (PRRs, see below for details) expressed by these immune cell populations (Fig. 34.8) (Evans et al., 2015). This results in the activation of gene expression and synthesis of a broad range of molecules, including enzymes, lipid mediators, proinflammatory cytokines, chemokines, cell adhesion molecules, and immunoreceptors (Mogensen, 2009). The cellular (e.g., autophagy, phagocytosis) and soluble (e.g., antimicrobial peptides, complement pathway) components of the innate immune system constitute the early host response to infection, which is important for rapidly limiting the spread of the invading pathogen and for facilitating the resolution of the infection (Medzhitov and Janeway, 2000). In addition, the innate immune system interacts with and controls acquired immune responses (see Chapter 24).

The role of mononuclear phagocytes in the initiation of the fever response deserves special attention. Occurring within 30 minutes after LPS administration, the first phase of polyphasic fever is one of the earliest manifestations of systemic inflammation (Fig. 34.1). The early onset of fever suggests a role of innate immunity in triggering the response. Indeed, the depletion of peripheral macrophages by liposome-mediated suicide resulted in attenuated pyrogenic and thermogenic responses to LPS in rats (Derijk et al., 1994). The early febrile and hypothermic responses to LPS were also absent in animals subjected to selective elimination of hepatic macrophages with gadolinium chloride (Derijk et al., 1994; Sehic et al., 1998). In the study by Steiner et al. (2006b), lung and liver tissues were double-stained for cyclooxygenase (COX)-2 and the macrophage marker, ED2. At the onset of LPS fever, nearly 90% of COX-2-positive cells in the lungs and more than 80% in the liver were identified as macrophages. These results suggest that peripheral macrophages contribute to the induction of the thermoregulatory manifestations in systemic inflammation.

The innate immune system recognizes microorganisms via a variety of receptors, commonly referred to as PRRs. These receptors can detect components of pathogens (PAMPs) that are essential for the survival of the

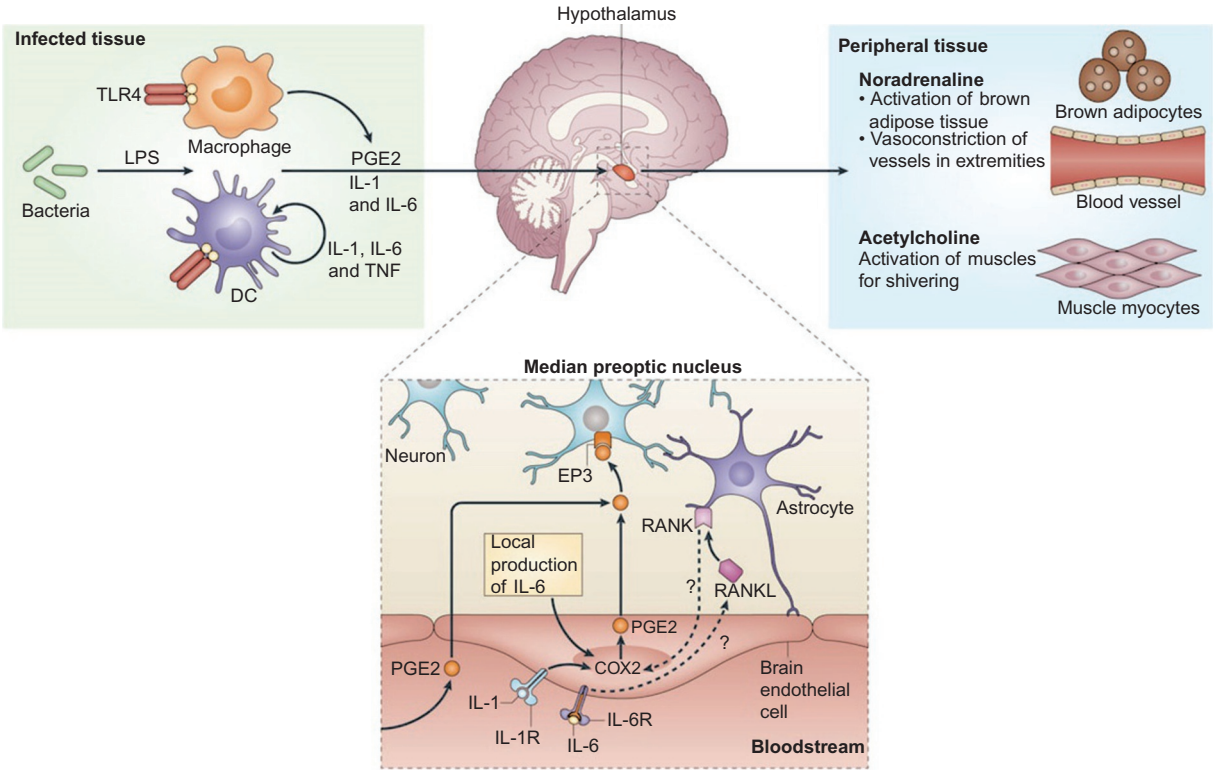

Fig. 34.8. Induction of fever during infection. The recognition of pathogen-associated molecular patterns (such as lipopolysaccharide (LPS)) by Toll-like receptors (TLRs) and other pattern recognition receptors drives the activation of immune cells, including macrophages. These innate immune cells release prostaglandin E_2(PGE_2) and pyrogenic cytokines (namely, interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α)) which act systemically to induce fever. IL-6 operates downstream of IL-1 in the median preoptic nucleus within the hypothalamus to induce the synthesis of cyclooxygenase-2 (COX-2), the enzyme responsible for production of additional PGE_2. PGE_2 is considered the major pyrogenic mediator of fever. Receptor activator of NF-κB (RANK) expressed by astrocytes also acts via the COX-2 PGE_2 pathway to induce fever. However, it is not known whether this pathway parallels the IL-6 response, or if the IL-6 and RANK ligand (RANKL) pathways converge, potentially via IL-6 regulation of RANKL expression in vascular endothelial cells in the hypothalamus. Neurons expressing PGE_2 receptor 3 (EP3) trigger the sympathetic nervous system to release norepinephrine, which elevates body temperature by increasing thermogenesis in brown adipose tissue, as well as by inducing vasoconstriction to decrease heat loss. Additionally, acetylcholine contributes to fever by stimulating muscle myocytes to induce shivering. *DC*, dendritic cell; *IL-1R* and *IL-6R*, receptor of IL-1 and IL-6, respectively. (From Evans SS, Repasky EA, Fisher DT (2015) Fever and the thermal regulation of immunity: the immune system feels the heat. Nat Rev Immunol 15: 335–349, with permission from Nature Publishing Group.)

microorganism and are therefore difficult for the microorganism to alter. The first discovered PRRs belonged to the Toll-like receptor (TLR) family, which consists of 12 identified members in mammals (O'Neill et al., 2013). TLRs can be divided into subgroups based on whether they are located on the cell surface and recognize mainly microbial membrane components (TLR1, 2, 4–6, and 11) or whether they are expressed only in intracellular vesicles and detect microbial nucleic acids (TLR3, and 7–9) (Akira et al., 2006; Kawai and Akira, 2010). After the discovery of TLRs, further PRR families have also been identified. The retinoic acid-inducible gene I-like receptor family consists of three members, RIG-I, Mda5, and LGP2, that detect RNA viruses (Franchi et al., 2009). Within the cytoplasm, the family of nucleotide-binding oligomerization domain-like receptors (NLRs) consists of more than 20 members, and several respond to the various PAMPs, non-PAMP particles, and cellular stresses (Ishii et al., 2006; Martinon et al., 2009). Mutations in the genes of NLR proteins 3 and 12 lead to hereditary periodic fever syndromes (Zhong et al., 2013). Cytosolic PRRs, like NLRs, can facilitate the activation of the proinflammatory caspase-1 within large macromolecular protein complexes in macrophages, which are also referred to as inflammasomes. It has been shown that inhibition of the inflammasomes ameliorates symptoms of the inflammatory response to shock-inducing doses of LPS, including hypothermia (de Almeida et al., 2015). The roles of PRRs and the associated intracellular signaling pathways in innate immunity

are reviewed in detail elsewhere (Akira et al., 2006; Kawai and Akira, 2010).

Among the PRRs, cellular TLR4 is of special interest for the current chapter as it recognizes LPS (Fig. 34.8) (Poltorak et al., 1998). On the cell surface, the TLR4 forms a complex with myeloid differentiation protein-2, which binds LPS (Kim et al., 2007; Park et al., 2009). In order to be recognized by the complex, LPS first requires interaction with the CD14 and the LPS-binding protein (Schumann et al., 1990; Haziot et al., 1996). Stimulation of TLR4 with LPS triggers the activation of intracellular signaling cascades, resulting in the translocation of NF-κB into the nucleus, which, in turn, initiates the expression of numerous genes involved in inflammatory processes (Akira et al., 2006; Kawai and Akira, 2010). These genes encode proinflammatory cytokines, chemokines, adhesion molecules, receptors, and inducible forms of inflammatory enzymes such as COX-2, and microsomal (m) PGE_2 synthase (PGES)-1 (Barnes and Karin, 1997).

The essential role of TLR4 in fever was demonstrated in direct experiments (Steiner et al., 2006a). The authors generated four mouse chimeras: functional TLR4 in all cells, no functional TLR4 in any cells, no functional TLR4 in bone marrow-derived cells only, and functional TLR4 in bone marrow-derived cells only. By studying the thermoregulatory responses of these mice to LPS, the authors found that the first phase of LPS fever was triggered via the TLR4 on bone marrow-derived cells, while the second and third phases involved TLR4 signaling in cells derived from both the bone marrow and elsewhere (Fig. 34.9) (Steiner et al., 2006a). Among the bone marrow-derived cells, monocytes express high levels of TLR4, whereas neutrophils express low levels of TLR4 (Sabroe et al., 2002). The role of granulocytes in the initiation of fever is of lesser importance, as evident from the fact that fever can develop in neutropenic patients (White and Ybarra, 2014) and rats (Tavares et al., 2006). Neutrophil granulocytes are suggested to limit the responsiveness of macrophages to LPS (Tavares et al., 2006). Considering that hepatic and alveolar macrophages can effectively detoxify LPS, while neutrophils cannot (Filkins, 1980), the findings of Steiner et al. (2006a) suggest that pulmonary and hepatic macrophages that recognize LPS via TLR4 are likely the cells that trigger fever (Romanovsky et al., 2006).

TLR2 is also known to recognize LPS (Yang et al., 1998) and was proposed to contribute to the mediation of fever (Dinarello et al., 1999), but it was demonstrated later that activation of TLR2 was not caused by LPS itself, but rather by highly bioactive lipoprotein contaminants of LPS preparations, the so-called endotoxin proteins (Hirschfeld et al., 2000; Lee et al., 2002). Lipoprotein-free LPS preparations cause normal fevers (with all three phases present) and normal hypothermic responses (Steiner et al., 2005a). In agreement, TLR2-deficient mice were also shown to respond to LPS with normal fever and cytokine production (Welsch et al., 2012). The same study suggested a role for TLR2 in the mediation of cytokine and fever responses to macrophage-activating lipopeptide-2, as both responses were abolished in the TLR2-deficient mice (Welsch et al., 2012). Several more examples of proteins that interact with LPS are reviewed elsewhere (Gioannini et al., 2003). It is possible that different thermoregulatory responses to LPS are mediated by different receptors at different cells. For example, it has been shown that fever can be triggered by LPS recognition inside and outside the blood-brain barrier (BBB), while hypothermia depends exclusively on LPS recognition outside the brain (Al-Saffar et al., 2013).

Pyrogenic and cryogenic cytokines

Activation of the innate immune cells by LPS leads to the production of inflammatory cytokines (Fig. 34.8), most importantly, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6, in the order of their appearance in the bloodstream (Conti et al., 2004; Dinarello, 2004; Leon, 2004). Other cytokines that may be involved in LPS fever and hypothermia are ciliary neurotrophic factor (Shapiro et al., 1993; Kelly et al., 2004), macrophage migration inhibitory factor (Bernhagen et al., 1993; Bozza et al., 1999, 2004), and interferons (Kluger, 1991; Dinarello, 2004).

Because of its early surge in the blood in systemic inflammation, TNF-α is a good candidate for mediating the onset of LPS fever and hypothermia (Blatteis et al., 2004; Jansky and Vybiral, 2004). TNF-α is considered to be the most important cryogenic cytokine, but it can also act as a pyrogenic molecule. Indeed, TNF-α has been shown to induce relatively rapid fever-like responses in guinea pigs (Roth and Zeisberger, 1995), rabbits (Dinarello et al., 1986), and humans (Michie et al., 1988). However, neutralization of TNF-α with antibodies or by its type 1 soluble receptor had no influence on the first phase of LPS fever, though it attenuated the second phase (Nagai et al., 1988; Roth et al., 1998), which indicates that TNF-α contributes to the maintenance rather than to the induction of the febrile response. Further supporting the role of cytokines in the maintenance (rather than initiation) of fever, the onset of the T_b response was shown to precede the surge in plasma cytokine levels, even that of TNF-α, which is the first to appear in blood in LPS-treated animals (Li et al., 2006). TNF-α and its receptors are also involved in the suppression of T_b in systemic inflammation, as rats treated with antiserum against TNF-α, as well as the mice

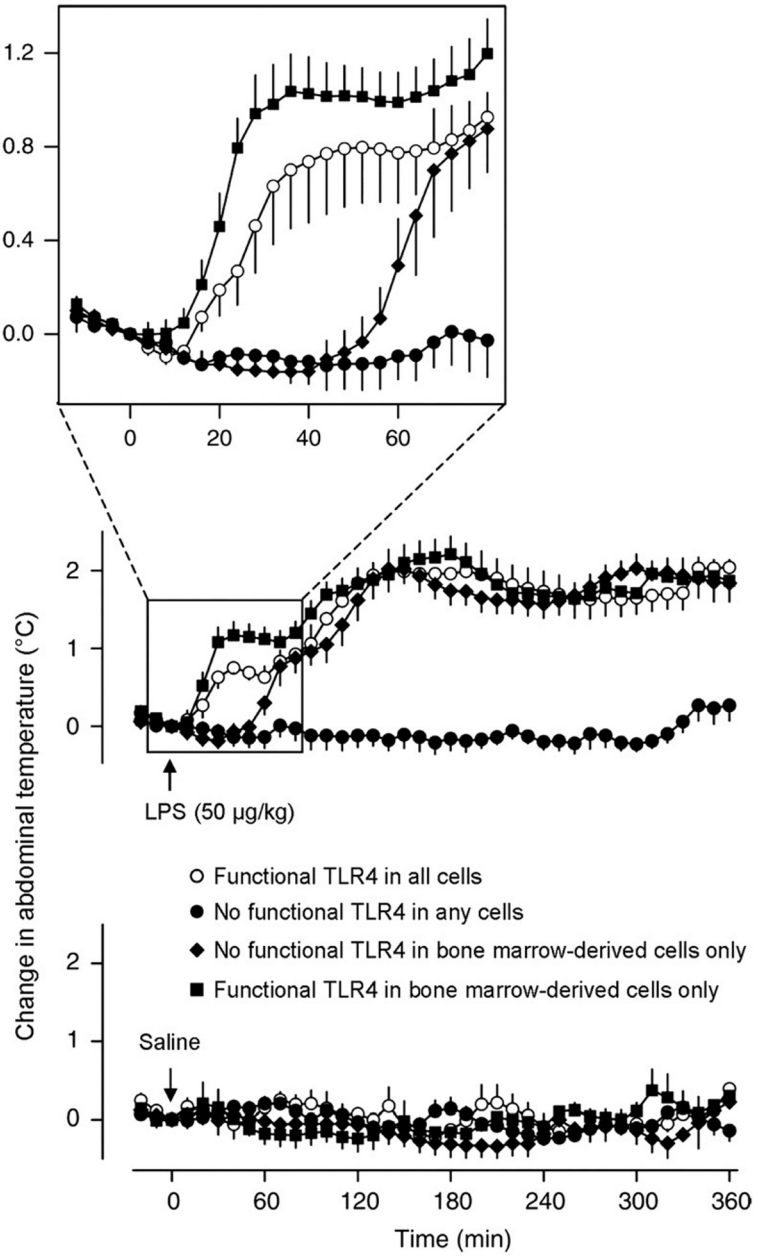

Fig. 34.9. Fever responses of four mouse chimeras: HeOuJ mice with HeOuJ bone marrow (functional Toll-like receptor 4 (TLR4) in all cells), HeOuJ mice with HeJ bone marrow (nonfunctional TLR4 in bone marrow-derived cells only), HeJ mice with HeOuJ bone marrow (functional TLR4 in bone marrow-derived cells only), and HeJ mice with HeJ bone marrow (nonfunctional TLR4 in all cells). Deep (abdominal) body temperature (mean ± SE) responses of the four indicated types of chimeric mice to lipopolysaccharide (LPS; 50 µg/kg, intravenously) or saline (1 mL/kg, intravenously) are shown. At the time of the injection, the values of abdominal temperature of LPS- and saline-treated mice were, respectively, 35.7 ± 0.2°C ($n = 7$) and 35.9 ± 0.2°C ($n = 6$) for the HeOuJ mice with HeOuJ bone marrow, 36.0 ± 0.2°C ($n = 7$) and 36.2 ± 0.4°C ($n = 7$) for the HeJ mice with HeJ bone marrow, 35.9 ± 0.2°C ($n = 9$) and 35.9 ± 0.2°C ($n = 7$) for the HeOuJ mice with HeJ bone marrow, and 36.2 ± 0.3°C ($n = 7$) and 35.9 ± 0.2°C ($n = 5$) for the HeJ mice with HeOuJ bone marrow. These values did not differ statistically from each other. (From Steiner AA, Chakravarty S, Rudaya AY, et al. (2006a) Bacterial lipopolysaccharide fever is initiated via Toll-like receptor 4 on hematopoietic cells. Blood 107: 4000–4002, with permission from the American Society of Hematology.)

genetically lacking its receptors, developed exaggerated fever responses to LPS (Long et al., 1990; Leon et al., 1997). The cryogenic property of TNF-α may be modulated by nutritional status, since TNF-α induced a brief hypothermia in lean rats, but a pronounced hypothermia in obese rats (Steiner et al., 2004a). The contradiction regarding the pyrogenic versus the cryogenic role of TNF-α deserves separate discussion. It has been proposed that TNF-α is febrigenic at low concentrations, but cryogenic at moderate-to-high concentrations (Bibby and Grimble, 1989). It has also been suggested that increasing production of TNF-α promotes a shift from fever to hypothermia (Kozak et al., 1995a; Leon et al., 1998; Tollner et al., 2000). The term "cryogenic" refers to those inflammatory mediators that can lower T_b, whereas the term "antipyretic" refers to those inflammatory mediators that block febrigenic signaling. Cryogenic substances are often proinflammatory, like TNF-α. In contrast, anti-inflammatory substances often block both LPS fever and hypothermia, like glucocorticoids (Coelho et al., 1992, 1993; Alexander and Fewell, 2011).

IL-1 has also been shown to induce a relatively rapid fever in mice, rats, guinea pigs, rabbits, and humans (Kluger, 1991; Dinarello, 2004). In human patients, the administration of IL-1β caused fever and chills in a dose-dependent manner (Tewari et al., 1990; Nemunaitis et al., 1994; Ogilvie et al., 1996). Of note, the higher doses (above 100 ng/kg) of IL-1β markedly decreased the blood pressure in the patients, which suggests that IL-1β can also play a role in shock. When the IL-1β signaling pathway is inhibited by genetic deletion of IL-1β (Kozak et al., 1995b), antiserum against IL-1β (Long et al., 1990), or antagonists of the IL-1 receptor (Long et al., 1990; Smith and Kluger, 1992), the fever response is attenuated in experimental animals. Similarly to the blockade of TNF-α, antagonism of IL-1β also reduced the late phases of fever. These data indicate that, like TNF-α, IL-1β is involved in the maintenance, but not the induction, of fever.

Both TNF-α and IL-1β stimulate the production of IL-6 (van Damme et al., 1986), which, arguably, is the most important pyrogenic cytokine (followed by IL-1). The pyrogenic activity of IL-6 has been demonstrated in a variety of species (Blatteis et al., 1990; Cartmell et al., 2000; Harre et al., 2002; Rummel et al., 2006; Nilsberth et al., 2009). The neutralization of IL-6 with antibodies attenuates LPS fever in guinea pigs and rats (Cartmell et al., 2000; Harden et al., 2006, 2011; Rummel et al., 2006). Unresponsiveness to LPS has been also demonstrated in IL-6-deficient mice (Chai et al., 1996), suggesting that IL-6 also contributes to the induction of fever. In turpentine- and LPS-induced inflammation models, the upregulation of COX-2 was abolished in the brain of the animals when IL-6 was blocked with gene ablation in mice or with neutralizing antiserum in rats (Turnbull et al., 2003; Rummel et al., 2006), suggesting a direct link between IL-6 and PGE_2 synthesis. In contrast, LPS-induced PGE_2 production was not affected in IL-6 knockout mice despite their reduced fever response in a later study (Nilsberth et al., 2009), raising the possibility that PGE_2-independent mechanisms, such as the IL-6-induced suppression of some cryogenic factor, are involved in the interaction between IL-6 and LPS fever (Nilsberth et al., 2009). Deletion of the membrane-boundIL-6 receptor α on brain endothelial cells strongly attenuated the febrile response of conditional knockout mice to LPS, which indicates that IL-6 induces PG synthesis by acting on these cells (Eskilsson et al., 2014). The involvement of other cytokines was proposed by Hanada et al. (2009), who showed that receptor activator of NF-κB ligand (RANKL) activates brain regions involved in thermoregulation (e.g., POA) and induces fever via the COX-2 pathway. In mice genetically lacking the receptor of RANKL, fever responses to LPS, TNF-α, and IL-1β were all absent (Fig. 34.10). It was also shown that RANKL induces PGE_2 production and mediates fever via the EP3 receptor (Hanada et al., 2009). On the basis of evidence that IL-6 directly stimulates RANKL

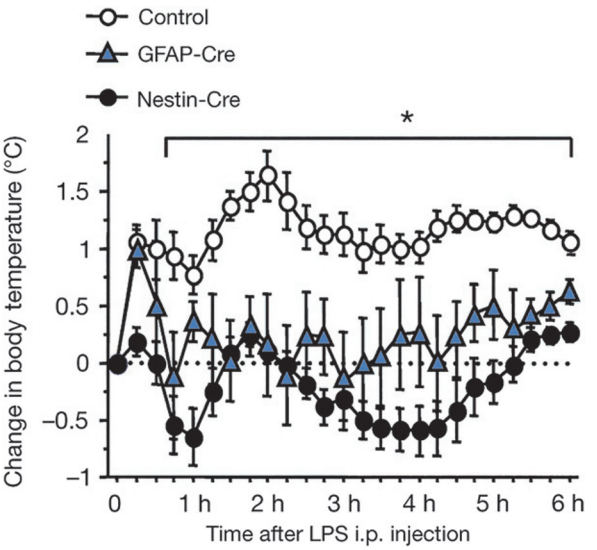

Fig. 34.10. Abdominal temperature (mean ± SE) responses of $rank^{floxed/\Delta}$ (control, $n = 4$), Nestin-Cre $rank^{floxed/\Delta}$ (receptor activator of NF-κB (RANK) deleted in brain neurons and astrocytes, $n = 5$) and glial fibrillary acidic protein (GFAP)-Cre $rank^{floxed/\Delta}$ (RANK deleted specifically in astrocytes, $n = 5$) mice to lipopolysaccharide (LPS; 10 μg per mouse, intraperitoneally). $^*p < 0.05$ (analysis of variance with a post-hoc Fisher's test). (Adapted from Hanada R, Leibbrandt A, Hanada T, et al. (2009) Central control of fever and female body temperature by RANKL/RANK. Nature 462: 505–509, with permission from Nature Publishing Group.)

synthesis by synovial fibroblasts in a mouse model of rheumatoid arthritis (Hashizume and Mihara, 2011), it can be speculated that RANKL is a downstream mediator of IL-6-induced pyrogenesis (Fig. 34.8) (Evans et al., 2015).

Periphery-to-brain communication in systemic inflammation

Four main mechanisms have been sought to transmit the peripheral proinflammatory signals to brain: (1) transport of circulating cytokines across the BBB; (2) cytokine entry to brain tissue at the sites lacking the BBB such as the circumventricular organs (primarily the organum vasculosum of the lamina terminalis); (3) neural signaling via the sensory fibers of the hepatic vagus; and (4) active signal transduction by the BBB itself (Romanovsky et al., 2005; Roth and Blatteis, 2014). The physiologic relevance of peripheral cytokines directly penetrating the brain is doubtful (Romanovsky et al., 2005; Roth and Blatteis, 2014), whereas the involvement of the vagus is likely to be limited to triggering the febrile response to very low doses of LPS (Romanovsky et al., 1997b) or cytokines (Hansen et al., 2001); for critical reviews, see Romanovsky (2012) and Saper et al. (2012). Afferent vagal signaling is also not required for the febrile response to circulating PGE_2 (Ootsuka et al., 2008); circulating PGE_2 is the principal trigger of fever (see below). The circumventricular organs may be crucial for fever genesis, but their role is likely to be related to local production of fever mediators rather than to serving as points of entry of cytokines into brain tissue (Romanovsky et al., 2005).

The remaining (fourth) mechanism is probably the most important one. Peripheral administration of LPS, IL-1β, or TNF-α has been shown to rapidly induce the expression of PGE_2-synthesizing enzymes in the BBB (Ek et al., 2001; Yamagata et al., 2001), most importantly in endothelial cells (Cao et al., 1996; Matsumura et al., 1998; Yamagata et al., 2001) and perivascular macrophages in the brain (Elmquist et al., 1997a). Brain endothelial cells can be activated by LPS administered centrally (Cao et al., 1999) or peripherally (Inoue et al., 2002; Engblom et al., 2003; Engstrom et al., 2012). Administration of LPS intracerebroventricularly (i.c.v.) can also activate microglia (Zhou et al., 2006) and astrocytes (Guerra et al., 2011). However, no cell population activated by i.c.v. LPS is the trigger of hypothermia, as the hypothermic response to inflammation can be triggered only by LPS acting outside the brain (Al-Saffar et al., 2013).

Lipid mediators of the thermoregulatory responses to systemic inflammation

Biochemistry of lipid-derived mediators

Besides secreting cytokines, activated leukocytes and endotheliocytes also release considerable amounts of lipid-derived mediators. In animal models of acute systemic inflammation, the release of such products is rather quick, preceding the surge in circulating cytokines by at least 30 minutes (Han et al., 2002; Perlik et al., 2005; Li et al., 2006). The most prominent lipid-derived mediators identified to date are platelet-activating factor (PAF), derivatives of arachidonic acid (AA), and endocannabinoids. The production of these mediators begins with the mobilization of membrane lipids, and involves constitutive and inducible enzymes that are arranged in sets of spatiotemporally-coupled reactions. These pathways, described briefly below, are depicted in Figure 34.11.

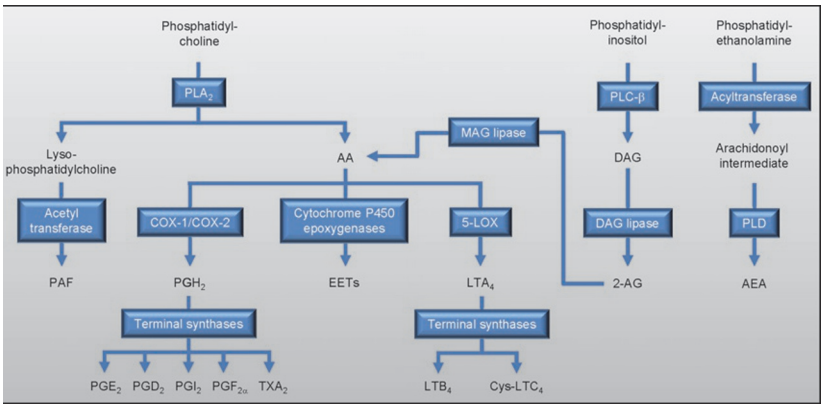

Fig. 34.11. The biosynthesis of lipid-derived mediators. For further details, see section on biochemistry of lipid-derived mediators. *2-AG*, 2-arachidonoyl-glycerol; *AA*, arachidonic acid; *AEA*, arachydonoyl *N*-ethanolamide; *COX*, cyclooxygenase; *DAG*, diacylglycerol; *EETs*, epoxyeicosatrienoic acids; *LOX*, lipoxygenase; *LT*, leukotriene; *MAG*, monoacylglycerol; *PAF*, platelet-activating factor; *PG*, prostaglandin; *PL*, phospholipase; *TXA_2*, thromboxane A_2.

Of the two known pathways for PAF biosynthesis, the so-called remodeling pathway seems to be the most relevant in inflammatory states (Montrucchio et al., 2000; Prescott et al., 2000). The first step in this pathway is the removal of arachidonoyl residues from phosphatidylcholine by phospholipase (PL) A_2, a superfamily of enzymes with more than 20 members, which represent three classes: secretory PLA_2, cytosolic PLA_2, and calcium-independent PLA_2 (Schaloske and Dennis, 2006; Burke and Dennis, 2009). The PLA_2 reaction yields lysophosphatidylcholine, which can be converted to PAF by enzymatic acetylation. PAF is inactivated by the reverse reaction (i.e., deacetylation), which is catalyzed by a distinct enzyme known as PAF acetylhydrolase. PAF appears in the circulation within minutes after i.v. LPS administration (Han et al., 2002) and has been shown to have high pyrogenic activity (Ivanov et al., 2003a, 2005; Steiner and Romanovsky, 2015).

Indicating a role for PAF in systemic inflammation, at least one PAF antagonist, BN52021, has been shown to attenuate LPS fever (Ivanov et al., 2003a). However, this Ginkgo biloba-derived PAF antagonist is nonselective and can activate PAF acetylhydrolases (Bonin et al., 2004), which are catabolic enzymes that metabolize PAF and other substrates, e.g., oxidized phospholipids (Stafforini et al., 1997; Karasawa et al., 2003). LPS fevers were only slightly affected by a PAF antagonist in horses (Carrick et al., 1993) and were unaffected by another PAF antagonist in humans (Thompson et al., 1994). An involvement of PAF in the development of LPS hypothermia was also suggested (Libert et al., 1996; Ephgrave et al., 1997). This suggestion was supported by the finding that, similar to LPS, PAF (at higher doses) causes hypothermia in a subthermoneutral environment (Steiner and Romanovsky, 2015). However, by using two highly potent, structurally distinct antagonists of the PAF receptor, CV6209 and WEB2086, the latter study also revealed that the pyrogenic and cryogenic effects of PAF are independent of PGs, and that the PAF receptor does not mediate LPS-induced fever or hypothermia, which challenges the dogma that PAF is an upstream mediator of the thermal responses to LPS (Steiner and Romanovsky, 2015).

The PLA_2 reaction also yields AA, and is thought to account for the main pool of this substrate in mammalian cells. However, recent efforts have led to the discovery of an alternative biosynthetic pathway for AA in the brain, which involves the hydrolysis and inactivation of a member from the endocannabinoid family (see below). Once produced, AA is oxygenated via reactions catalyzed by COX, 5-lipoxygenase (LOX), or cytochrome P450 epoxygenases. The COX reaction yields a hydroperoxy compound, PGG_2, which is unstable and spontaneously transformed into PGH_2. The latter compound is, in turn, converted by terminal synthases to the primary group of biologically active prostanoids: PGE_2, PGD_2, PGI_2, $PGF_{2\alpha}$, and thromboxane A_2(TXA_2) (Murakami and Kudo, 2004; Ueno et al., 2005). The 5-LOX reaction yields leukotriene (LT) A_4 via the hydroperoxy intermediate, 5(*S*)-hydroperoxyeicosatetraenoic acid. LTA_2 is then metabolized by downstream enzymes to give origin to LTB_4 and its cysteine-bound counterparts, namely LTC_4, LTD_4, and LTE_4 (Haeggstrom and Funk, 2011; Radmark et al., 2015). Finally, the cytochrome P450 epoxygenase reaction yields four regioisomers of the epoxyeicosatrienoic acid (5,6-EET,8,9-EET, 11,12-EET, and 14,15-EET), which do not require any other metabolic step to gain biologic activity (Spector, 2009).

Since COX (also known as PGH synthase) has received the most attention in connection with inflammation and its thermal manifestations, we will describe it in more detail. Two isoforms of COX, encoded by different genes, are known to exist: COX-1 and COX-2. As a general rule, COX-1 is constitutively expressed in various tissues, and its expression is not affected by inflammatory stimuli. On the other hand, the expression of COX-2 is negligible in most tissues under healthy conditions, but is strongly induced by inflammatory stimuli (Smith et al., 2000; Simmons et al., 2004). However, as with any rule, there are exceptions. More specifically, there are reports of COX-2 being constitutively expressed in the brain cortex (Yamagata et al., 1993) and in the renal macula densa (Harris et al., 1994), as there are reports of COX-1 being activated post-transcriptionally during endotoxin shock (Steiner et al., 2009) and transcriptionally in some tumors (Hwang et al., 1998).

A third COX isoform has been identified in canine tissue (Chandrasekharan et al., 2002). Originally named COX-3, this isoform is now most commonly referred to as COX-1b, for being a splice variant of the COX-1 mRNA. However, the biologic significance of this most recently identified isoform remains a matter of skepticism, since it has been difficult to identify functional COX-1b protein in other species. No functional protein has been identified in the rat (Snipes et al., 2005), and the functional protein identified in humans differed from the canine protein in that it was insensitive to inhibition by acetaminophen (Qin et al., 2005). The contribution of the COX isoforms to the thermoregulatory manifestations of systemic inflammation has been investigated in a number of studies (see following sections for details).

The endocannabinoid class of lipid-derived mediators receives this name because its members act as endogenous ligands for receptors originally described in connection with the pharmacology of tetrahydrocannabinol. The best-understood endocannabinoids are 2-arachidonoyl-glycerol (2-AG) and *N*-arachidonoyl-ethanolamine (AEA; also

known as anandamide). These substances are not derived directly from AA, despite the presence of arachidonoyl in their core structures. The biosynthesis of 2-AG occurs in two steps: (1) PLC-β converts phosphatidylinositol into the corresponding diacylglycerol (DAG); and (2) a DAG lipase removes the non-arachidonoyl fatty acid from the intermediate (Piomelli, 2003; Ligresti et al., 2016). The biosynthesis of AEA is less understood. Although it has been known that the first step in AEA biosynthesis is the *N*-arachidonoylation of phosphatidylethanolamine, the acyltransferase involved has been identified only later (Ogura et al., 2016). Additionally, the subsequent transformation of the arachidonoyl intermediate into AEA can occur via several pathways, the most investigated of which is the direct conversion, catalyzed by a subtype of PLD (Leung et al., 2006). Both 2-AG and AEA have biologic actions of their own. However, 2-AG also represents a relevant source of AA for the biosynthesis of PGs in the brain (Nomura et al., 2011). Such a role involves the enzyme monoacylglycerol (MAG) lipase, which catalyzes the breakdown of 2-AG into AA and glycerol. Two studies from independent groups demonstrated that either genetic or pharmacologic ablation of MAG lipase significantly reduces fever responses to LPS in mice (Kita et al., 2015; Sanchez-Alavez et al., 2015). The involvement of other AA pools could not be excluded, because MAG lipase inhibitors did not completely suppress fever (Sanchez-Alavez et al., 2015), and MAG lipase inhibition in LPS-stimulated $cPLA_2$-deficient mice additively reduced brain PGE_2 levels beyond MAG lipase or $cPLA_2$ ablation alone (Nomura et al., 2011). AEA acts mainly on cannabinoid (CB) 1 receptors (Vogel et al., 1993) and, to a lesser extent, on CB2 receptors (Gonsiorek et al., 2000). It also acts as a full agonist of the transient receptor potential vanilloid-1(TRPV1) channel (Smart et al., 2000). The role of AEA and its receptors in systemic inflammation has been investigated in a study by Steiner et al. (2011). The authors used a variety of pharmacologic tools to probe whether three different receptors are involved in LPS-induced hypothermia in rats. They found that the selective antagonism of the CB1 receptor with rimobanant blocked the hypothermic response to LPS, while inhibition of CB2 receptors with the selective antagonist, SR144528, was without effect (Fig. 34.12). The blockade of TRPV1 did not influence LPS hypothermia either (not shown in Fig. 34.12) (Steiner et al., 2011). The blockade of CB1 receptors with i.c.v. administration of rimonabant attenuated the LPS-induced rise in plasma TNF-α in rats (Villanueva et al., 2009; Johnson et al., 2015), hence these results cumulatively suggest that CB1 receptors in the brain are permissive for the LPS-induced rise in circulating TNF-α, thus for the development of hypothermia.

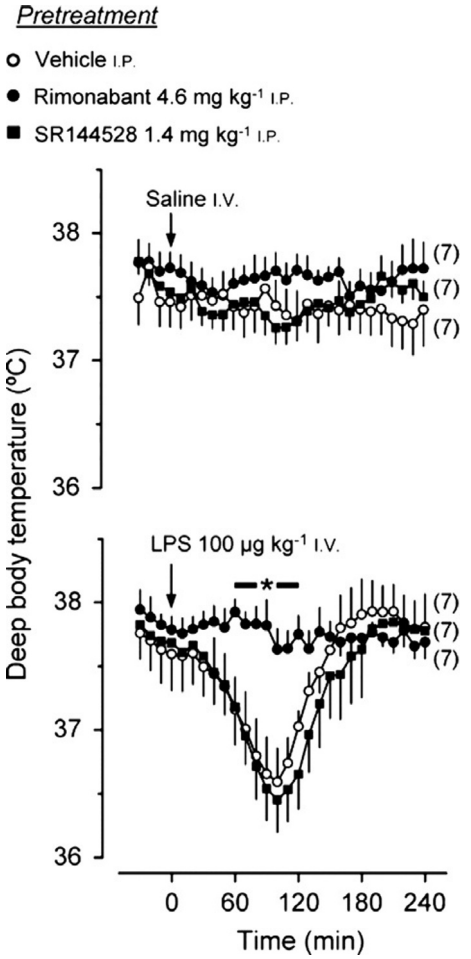

Fig. 34.12. Lipopolysaccharide (LPS) hypothermia is blocked by a cannabinoid (CB) 1 receptor antagonist (rimonabant), but is unaffected by a CB2 receptor antagonist (SR144528). Effects of intraperitoneal (i.p.) pretreatment with rimonabant, SR144528, or their vehicle on the body temperature responses to LPS (100 µg/kg, intravenously (i.v.)) or saline in rats exposed to an ambient temperature of 22°C. The number of animals in each group is shown in parentheses. $*p < 0.05$ compared to vehicle pretreatment. Data are represented as mean ± SE. (From Steiner AA, Molchanova AY, Dogan MD, et al. (2011) The hypothermic response to bacterial lipopolysaccharide critically depends on brain CB1, but not CB2 or TRPV1, receptors. J Physiol 589: 2415–2431, with permission from John Wiley and Sons.)

Prostaglandin E_2 as a mediator of fever

Originally, the involvement of PGs of the E series in fever was established by Milton and Wendlandt (1970, 1971), who showed that PGE_1 and E_2 have pyrogenic activity, and by Vane (1971), who demonstrated that aspirin-like drugs exert their antipyretic effects through inhibition of PG synthesis from AA. Further supporting the role of PGE_2 in fever, the elevation of T_b in response

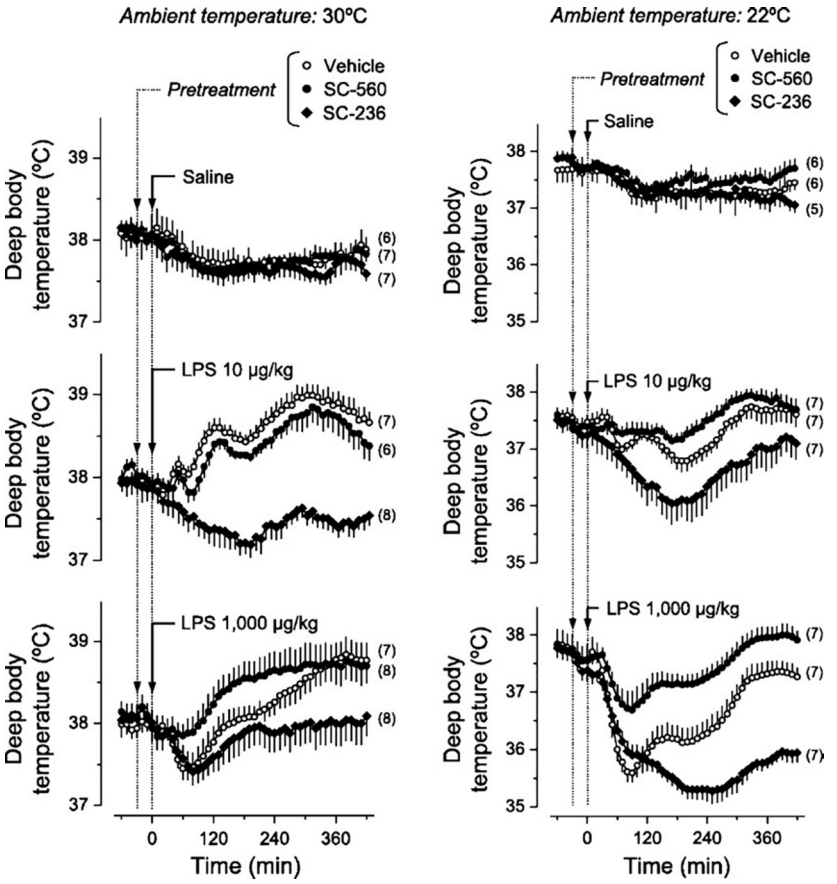

Fig. 34.13. Effects of cyclooxygenase (COX)-1 and COX-2 inhibitors on the thermal responses to lipopolysaccharide (LPS) at a neutral ambient temperature (T_a) of 30°C (left column) and a subneutral T_a of 22°C (right column). Rats were pretreated intravenously with a COX-1 inhibitor (SC-560; 5 mg/kg), a COX-2 inhibitor (SC-236; 2.5 mg/kg), or their vehicle before the intravenous administration of LPS (doses indicated) or saline. Arrowheads indicate the time at which pretreatment (10-minute infusion) started; arrows indicate the time of LPS injection. The number of animals in each group (n) is indicated. Data are presented as mean ± SE. (Adapted from Steiner AA, Hunter JC, Phipps SM, et al. (2009) Cyclooxygenase-1 or -2 – which one mediates lipopolysaccharide-induced hypothermia? Am J Physiol Regul Integr Comp Physiol 297: R485-R494.)

to pyrogens was paralleled by rises in the levels of PGE_2 in the cerebrospinal fluid (Coceani et al., 1988) and blood (Rotondo et al., 1988; Steiner et al., 2006b). In later studies, targeted disruption of the genes of either PGE_2-synthesizing enzymes (Li et al., 1999; Engblom et al., 2003; Steiner et al., 2005b) or the EP3 receptor (Ushikubi et al., 1998; Oka et al., 2003) provided evidence for the indispensable role of PGE_2 signaling in the mediation of fever.

Clinical fevers (Aronoff and Neilson, 2001), and all phases of LPS-induced experimental fevers (Cao et al., 1997; Li et al., 1999; Steiner et al., 2001, 2005b, 2009; Zhang et al., 2003), are mediated by the inducible COX isoform, COX-2, and not by COX-1, the predominantly constitutive isoform. In one of the studies (Steiner et al., 2009), the authors conducted a differential analysis of the effects of two highly selective COX inhibitors, SC-560 (COX-1 inhibitor) and SC-236 (COX-2 inhibitor), on several models of LPS fever and hypothermia. They found that SC-236 blocked all phases of LPS-induced fever, but none of the phases were affected by SC-560 (Fig. 34.13). In line with this observation, COX-2 knockout mice failed to develop fever in response to LPS (Li et al., 1999; Steiner et al., 2005b), thus also demonstrating the indispensable role of COX-2 in LPS fever. Because PGE_2 plays a principal role in mediating the febrile response (Ivanov and Romanovsky, 2004; Saper et al., 2012), we focus here on the PGE_2-synthesizing cascade.

Once formed via the action of COX-2, PGH_2 is isomerized to PGE_2 by terminal PGES, which can be mPGES-1,mPGES-2, and cytosolic PGES (Urade et al., 1995; Murakami et al., 2002). Fever responses are absent in mice with deletion of the *Ptges* gene, encoding mPGES-1 (Engblom et al., 2003), indicating that these responses are mediated by PGE_2 produced by mPGES-1. It has been shown that mPGES-1 is functionally coupled with COX-2; the COX-2-mPGES-1 couple is crucial for

the synthesis of PGE_2 during the febrile response (Dieter et al., 2000; Murakami et al., 2000). In LPS-processing organs (e.g., the liver and lungs), robust upregulation of mRNA and protein for COX-2 and mPGES-1 occurs, thus leading to an increase in PGE_2 in both venous and arterial blood following LPS administration already at the onset of the first phase of fever (Ivanov et al., 2002; Steiner et al., 2006b). As discussed above, hepatic and pulmonary macrophages were identified as the cellular sources of the LPS-induced PGE_2 synthesized by COX-2 (Steiner et al., 2006b), and as the triggers of the fever response. The PGE_2 rise in the blood is reproducible, massive, and occurs before the T_b starts increasing (Skarnes et al., 1981; Rotondo et al., 1988; Morimoto et al., 1992; Steiner et al., 2006b; Engstrom et al., 2012), and blood PGE_2 readily crosses the BBB and causes fever (Dascombe and Milton, 1979; Skarnes et al., 1981; Siren, 1982b; Eguchi et al., 1988; Jones et al., 1993; Coceani et al., 1995; Parrott et al., 1995; Abul et al., 1997; Romanovsky et al., 1999; Ootsuka et al., 2008).

In the bloodstream, PGE_2 is bound to albumin, which transports it and likely protects from enzymatic inactivation (Ivanov and Romanovsky, 2004). Blood-borne PGE_2 may dissociate from albumin and then be carried across the BBB to its site of action by specialized transporters that are expressed in the hypothalamus (Ivanov and Romanovsky, 2004; Hosotani et al., 2015; Schuster, 2015).

The study by Engstrom et al. (2012) seemingly contradicts the critical role of peripheral PGE_2 in fever. The authors used chimeric mice, in which mPGES-1 was knocked-out in all cells, except for bone marrow-derived cells, and showed that these mice responded to LPS with a normal rise of PGE_2 in the blood, but no PGE_2 rise in the brain, and developed no fever. The authors, however, did not look at the blood-to-brain transport of PGE_2 in these mice. In the absence of mPGES-1, PG synthesis is shifted towards other terminal synthases; e.g., the synthesis of $PGF_{2\alpha}$ increases 1.6 times (Trebino et al., 2005). If PG transporter is responsible for transport of PGE_2 across the BBB endothelium, then this acute rise in $PGF_{2\alpha}$ from LPS would cause acute internalization of PG transporter from the plasma membrane (Vezza et al., 2001). In such a case, peripheral PGE_2 would not reach the brain in mPGES-1 knockout mice due to inadequate transport across the BBB. Such a scenario is fully compatible with the data presented by Engstrom et al. (2012). More importantly, no experiment in genetically modified animals (which often have multiple genetic and functional compensations) can dismiss the facts that PGE_2 is rapidly and massively released in the blood at the onset of fever, and that blood PGE_2 readily crosses the BBB in normal circumstances and causes fever, as repeatedly shown in many laboratories and discussed above.

The more prominent later phases of fever, which start at about 1 hour after LPS administration and last for several hours (Romanovsky et al., 1998b), are characterized by further upregulation of PGE_2-synthesizing enzymes both in the periphery and in the brain (Ivanov and Romanovsky, 2004). For LPS fever in rats, the second phase involves the robust upregulation of PLA_2, COX-2, and mPGES-1, whereas the third phase involves the upregulation of PLA_2 and mPGES-1 (Ivanov et al., 2002). These phases are also accompanied by transcriptional downregulation of principal PGE_2-catabolizing enzymes (Ivanov et al., 2003b).

In the brain, PGE_2 is produced by COX-2 in perivascular and endothelial cells (Breder and Saper, 1996; Elmquist et al., 1997b; Matsumura et al., 1998; Schiltz and Sawchenko, 2002). Low doses of LPS upregulate COX-2 expression in perivascular cells, whereas higher doses of LPS also increase COX-2 in endothelial cells, but mainly along venules (Schiltz and Sawchenko, 2002; Serrats et al., 2010). However, only endothelial cells have been found to produce mPGES-1 in the adult brain (Yamagata et al., 2001), indicating that they are the source of PGE_2 in the later phases of fever. The selective deletion of COX-2 or mPGES-1 in brain endothelial cells strongly attenuated the febrile response to peripheral immune challenges in a genetically engineered mouse model (Wilhelms et al., 2014), which supports the critical role of PGE_2 synthesis in brain endothelial cells in fever. In a recent study by Eskilsson et al. (2017) it was shown that the deletion of COX-2 in hypothalamic endothelial cells, preferentially in small- and medium-sized vessels, attenuates the fever response. The authors also found that local augmentation of mPGES-1 expression in the median preoptic nucleus (MnPO) of mPGES-1 knockout mice by the injection of a vector virus resulted in a temperature elevation in response to LPS (Eskilsson et al., 2017).

PGE_2 can act on four different subtypes of PGE_2 receptors (EP1–EP4), which have different distribution patterns in the brain (Inoue et al., 2002). In fever, the EP3 receptor plays the principal role (Ushikubi et al., 1998; Oka et al., 2003; Lazarus et al., 2007), but the EP1 receptor can also be involved (Oka et al., 2003). The EP3 receptor is highly expressed in the MnPO (Nakamura et al., 2000; Oka et al., 2003; Lazarus et al., 2007), which is also the most responsive part of the brain to the pyrogenic action of PGE_2 (Scammell et al., 1998). Signal transduction through the EP3 receptor results in reduced cAMP levels and, thus, is associated with inhibition of the adenylate cyclase activity (Toh et al., 1995). The study by Steiner et al. (2002) also confirms that reduction of cAMP levels could be

responsible for fever genesis. The authors used pharmacologic modulation of the cAMP pathway and found that the levels of cAMP and cGMP in the POA are decreased during fever. It has also been shown that the genetic deletion of EP3 receptors limited to the MnPO and possibly adjacent preoptic structures abrogates the fever responses to LPS (injected intraperitoneally, i.p.) and PGE_2 (administered into the brain) (Lazarus et al., 2007). The EP3-expressing preoptic neurons are mostly GABAergic (Nakamura et al., 2002) and are thought to inhibit the downstream neurons that drive autonomic cold-defense responses. Suppression of the activity of these neurons by PGE_2 disinhibits the downstream targets, which enhances cutaneous vasoconstriction and elevates BAT thermogenesis, thus leading to the development of fever (see section on fever, above).

Eicosanoids in the mediation of hypothermia

In LPS hypothermia, an involvement of COX was also suggested (Ueno et al., 1982; Derijk and Berkenbosch, 1994; Azab and Kaplanski, 2004), but it is rather COX-1 that mediates this response. In support, the T_b drop during LPS hypothermia was attenuated by administration of the preferential COX-1 inhibitor, valerylsalycilate (Dogan et al., 2002; Akarsu and Mamuk, 2007), or by the selective COX-1 inhibitor, SC-560 (Akarsu and Mamuk, 2007). In the study by Steiner et al. (2009), the administration of SC-560 to rats also blocked LPS hypothermia (but not fever) under all experimental conditions tested (Fig. 34.13). The authors also showed that the functional activity of the COX-1 pathway (COX-1-mediated PGE_2 synthesis) was increased in the spleen at the onset of LPS-induced hypothermia. In contrast with induction of COX-2 in LPS fever, the increase in the activity of the COX-1 pathway during hypothermia did not involve the upregulation of COX-1 mRNA or protein (Steiner et al., 2009). It was speculated that COX-1 activation results from the post-translational modification due to an increased production of hydroperoxide and peroxynitrate in severe forms of systemic inflammation (Steiner et al., 2009).

The terminal synthases involved in the hypothermia associated with systemic inflammation remain to be identified, but considering that PGD_2 can cause hypothermia (Ueno et al., 1982; Kandasamy and Hunt, 1990; Krall et al., 2010), PGD synthase (PGDS) is a good candidate. PGDS has two isoforms: lipocalin and hematopoietic PGDS (H-PGDS) (Murakami and Kudo, 2004). The former is involved in LPS-induced production of PGD_2 in neural tissues in a COX-2-dependent manner (Grill et al., 2006), while H-PGDS and COX-1 mediate the early production of PGD_2 by activated macrophages (Murakami et al., 1995; Naraba et al., 1998). H-PGDS is present in large amounts in the spleen (Jowsey et al., 2001), where the activation of the COX-1 pathway was also found (Steiner et al., 2009). It has to be mentioned that the hypothermic activity of PGD_2 contradicts multiple reports in rats, rabbits, and cats, showing that PGD_2 either does not affect T_b or causes hyperthermia (Table 34.1; also see Romanovsky and Garami, 2010). Another candidate for mediating LPS hypothermia is 15-deoxy-$\Delta^{12,14}$-PGJ_2, a PGD_2 metabolite, which is antipyretic in rats (Mouihate et al., 2004). The question of whether LPS-induced hypothermia is triggered by the activation of the COX-1 H-PGDS pathway and consequent production of PGD_2 in the spleen awaits a definitive answer. As an alternative, some products of the AA-metabolizing LOX and epoxygenase pathways also possess antipyretic and cryogenic activities and, thus, may contribute to the limitation of fever and induction of hypothermia in systemic inflammation (Kozak and Fraifeld, 2004).

THE BIOLOGIC VALUE OF FEVER AND HYPOTHERMIA

Thermoregulatory manifestations as a part of the sickness syndrome

Mild to moderate forms of systemic inflammation are typically characterized by an elevated level of T_b, hyperalgesia, and motor hyperexcitability (Romanovsky et al., 1996a). These three symptoms form a relatively stable syndrome, which we termed "the early phase syndrome" (Romanovsky et al., 1996a; Romanovsky, 2004b). The early phase syndrome also includes the precise type of T_b regulation (Vybiral et al., 1987) and, possibly, arterial hypertension (Shido and Nagasaka, 1986) and an increase in vigilance (Shoham and Krueger, 1988; Romanovsky et al., 1993). In contrast, severe forms of systemic inflammation (e.g., septic shock), as well as the response to a pyrogen (e.g., LPS) at its later stages, can be manifested with either fever or hypothermia. In addition to fever or hypothermia, the late phase is accompanied by low motor activity, hypoalgesia (Romanovsky et al., 1996a), low or normal arterial blood pressure (Shido and Nagasaka, 1986), and possibly sleepiness (Romanovsky et al., 1993). We termed this constellation of symptoms "the late phase syndrome" (Romanovsky et al., 1996a).

As we have pointed out (Romanovsky et al., 1996a), the early phase syndrome occurring at the onset of mild infection constitutes a response of a healthy organism to the forthcoming disease. Its biologic significance is the signaling of the pathogenic challenge (hyperalgesia), recruiting active defense mechanisms (fever), and securing the means (wakefulness, hypertension, generalized motor agitation) for the active search for an optimal

Table 34.1

Effect of prostaglandin D_2 on deep body temperature

Species	Site of administration	Dose (μg)	Effect	References
Rat	Preoptic area	~0.9[a]	↓	Ueno et al. (1982)
	Third ventricle	~0.02–0.8[a]	↓	Ueno et al. (1982)
	Lateral ventricle	0.001–10	↑	Siren (1982a)
		0.01–0.03	↓	Kandasamy and Hunt (1990)
		0.1	↓	Krall et al. (2010)
		~1–3[a]	↓	Ueno et al. (1982)
		1–50	↔	Brus et al. (1980)
		2	↓	Forstermann et al. (1983)
		20	↑	Forstermann et al. (1983)
	Cisterna magna	0.05–0.5	↑	Gao et al. (2009)
	Subarachnoid space	13[b]	↑/↓	Matsumura et al. (1994)
	Femoral vein	0.1–10	↔	Siren (1982a)
	Vena cava	16–102	↓	Unpublished[c]
		85	↓	Unpublished[d]
Rabbit	Lateral ventricle	0.09–18	↔	Krueger et al. (1992)
		176	↑	Krueger et al. (1992)
Monkey	Lateral ventricle	2–285[b]	↔	Onoe et al. (1988)
		190[b]	↑	Onoe et al. (1988)
Cat	Third ventricle	0.4-64	↔	Ewen et al. (1976)

Adapted from Romanovsky AA, Garami A (2010) Prostaglandin riddles in energy metabolism: E is for excess, D is for depletion. Focus on "Food deprivation alters thermoregulatory responses to lipopolysaccharide by enhancing cryogenic inflammatory signaling via prostaglandin D_2". Am J Physiol Regul Integr Comp Physiol 298: R1509–1511.

[a]The dose was recalculated based on the body mass reported.

[b]The total amount administered over a 6-hour infusion.

[c]A. Garami, E. Pakai, A. A. Romanovsky; unpublished; cited from Steiner et al. (2009).

[d]A. A. Steiner, A. S. Dragic, J. Pan, A. A. Romanovsky; unpublished; cited from Steiner et al. (2009).

Effects on deep body temperature are marked as: ↓, decrease; ↑, increase; ↔, no change; ↑/↓, inconsistent.

environment for fighting the beginning malady. For wild animals such an environment would include adequate conditions for behavioral thermoregulation, sufficient water supply, and protection from predators. A sick person would make appropriate arrangements at work or at home and seek medical assistance, etc. This type of adaptation to infection develops through the active (fight/flight (energy expenditure)) coping pattern (Henry, 1992), at a high energetic cost. It is a disease-fighting strategy (see section on fever: a friend or a foe?). Clinically, the early phase syndrome is readily recognizable in a febrile patient at the onset of an acute infection: such a patient is usually restless and often complains that light is too bright, sounds are too loud, and no position is comfortable.

In contrast, the late phase syndrome represents the systemic response to infection at a stage when the disease has further progressed or when it was severe to start with: this is a response of the already sick organism to a continuing, severe pathologic challenge. Compared with the onset of a mild disease, manifestations of sickness change drastically and become more severe. The pain loses its signaling function and becomes handicapping, thus contributing substantially to morbidity (Levine et al., 1987); consequently, hyperalgesia changes to hypoalgesia. Energy resources become reduced by the costly early phase syndrome and by pathologic energy expenditure (inefficient functioning of damaged tissues), while energy supply decreases or even becomes completely broken, e.g., due to the development of adaptive anorexia (for references, see Hart (1988)). Hence, energy-intensive responses are no longer affordable or advisable: wakefulness, motor agitation, and arterial hypertension change into sleep, motor depression, and normo- or hypotension, respectively. An elevated T_b remains potentially beneficial, but its benefits can now be easily offset by the harmfully high energetic cost. Responding to this delicate balance, hypothermia often occurs. In summary, the late phase syndrome is an example of adaptation occurring through a passive (depression/withdrawal (energy conservation)) coping pattern (Henry, 1992). This is a disease resistance strategy (see section on hypothermia: friend or foe?). It is characteristic for this type of adaptation that, to withstand a severe homeostatic

challenge, parameters of the internal environment are regulated with a drastically decreased precision and often at a different, "pathologic" level. The primary significance of the late phase syndrome is conservation of energy; several of its energy-saving symptoms have been either proposed (motor depression (Hart, 1988)) or directly shown (sleep (Krueger and Majde, 1994)) to be beneficial during infection. Clinically, the late phase syndrome can be recognized in a patient with a severe infectious disease when decreased responsiveness to stimuli, depression, sleepiness, and arterial hypotension (or even shock) is present, together with either hypothermia or fever.

Fever: a friend or a foe?

Despite the fact that fever is generally perceived as a disorder in itself, there are reasons to believe that it bears a biologic value in infectious diseases. Fever is highly conserved in animal taxa, having its first appearance estimated at ~600 millions of years ago (Kluger, 1991; Hasday et al., 2014). The most primitive form of fever consists of warmth-seeking behavior in ectothermic animals ranging from invertebrates to lower vertebrates, a feature that was preserved in endothermic mammals and birds (Bicego et al., 2007). It is hard to imagine that fever would have been so conserved in evolution if it were disadvantageous.

In 1975, Kluger et al. published the first study demonstrating in a direct experiment that fever can be beneficial to an infected animal. In that study, an elevation in the T_b of bacteria-infected lizards from 36 to 40°C augmented their survival rate from ~25% to 65%. Similar results were subsequently obtained in other ectothermic species (Covert and Reynolds, 1977; Louis et al., 1986), as well as in some endothermic species (Vaughn et al., 1980; Kurosawa et al., 1987; Jiang et al., 2000). Presently, the beneficial value of fever is thought to result from enhancement of innate and acquired immune mechanisms, which include: neutrophil migration to the site of infection; phagocytic activity and microbial killing; antigen presentation by dendritic cells; lymphocyte trafficking through lymphoid organs; and lymphocyte proliferation and antibody production – see Chapter 24, as well as recent review articles (Hasday et al., 2014; Evans et al., 2015). At the same time, an elevation in T_b is expected to take several pathogenic microorganisms out of their optimal growth temperature (Kluger et al., 1975; Small et al., 1986). There are, however, certain microorganisms that have developed strategies to take advantage of fever (Freitas Lione et al., 2010; Loh et al., 2013). This may be a case in which an exception reinforces the rule, since an effective immune strategy is expected to impose evolutionary pressure on pathogenic microorganisms.

Unfortunately, the picture is not as straightforward in the clinical setting. Observational studies on the relationship between antipyresis and outcomes in life-threatening infections (sepsis) have yielded contradictory results (Kuikka et al., 1997; Kuikka and Valtonen, 1998; Plaisance et al., 2000; Lee et al., 2012; Mohr et al., 2012). This should not come as a surprise, though, since confounding factors are unavoidable limitations of observational studies, which often render such studies inadequate to infer a cause-effect relationship. For example, patients who display the highest fevers are likely to be given more antipyretics, in which case it is impossible to distinguish whether an altered outcome in this group reflects the height of the fever or its blockade by antipyretic drugs.

More compelling clinical evidence on the value of fever can be found in randomized, placebo-controlled trials. Plaisance et al. (2000) have shown that rhinovirus-infected volunteers who receive aspirin or acetaminophen present an attenuated antibody response, heightened nasal symptoms, and a tendency to increased viral shedding. The effect of aspirin on viral shedding was also found in another study with a similar design (Stanley et al., 1975). In a vaccination study, Prymula et al. (2009) have shown that children who receive acetaminophen prophylactically mount a weaker antibody response after primary vaccination for pneumococcus, diphtheria, tetanus, and other infections. Similar results have been obtained for hepatitis B vaccination in adults (Doedee et al., 2014). With regard to life-threatening infections (sepsis), Schulman et al. (2005) have found that non-neurologic critical care patients subjected to aggressive antipyresis displayed strong trends towards a higher risk of infection and increased mortality. On the other hand, Schortgen et al. (2012) have observed the opposite outcome (reduced mortality) when fever was ablated by external cooling in patients with a very severe form of sepsis (septic shock). These seemingly contradictory reports on sepsis may be reconciled based on experimental evidence indicating that the costs of fever may exceed its benefits when the immune response becomes severe to the point of seriously impairing cardiorespiratory function (Rice et al., 2005; Liu et al., 2012; Tulapurkar et al., 2012; Corrigan et al., 2014). Therefore, we have proposed that fever might be a friend in the early, less severe stages of sepsis, but may turn into a foe in the later, more severe stages (Romanovsky et al., 1996a; Romanovsky and Szekely, 1998). Another situation in which fever is known to be detrimental is neurologic injury, like in stroke patients (Jauch et al., 2013; Ntaios et al., 2015).

In assessing the cost-benefit relationship of fever, febrile seizures have also to be taken into account, as this is the number-one concern of caregivers about fever

in children (Crocetti et al., 2001). A febrile seizure is defined as a seizure occurring in association with a febrile illness, in the absence of a central nervous system infection or acute electrolyte imbalance, in children older than 1 month of age without prior afebrile seizures. Its incidence is 2–4% in children under 3 years of age in the United States and Europe (Hauser, 1994). Antipyretic drugs have been recommended to prevent the recurrence of febrile seizures, but, surprisingly, the available data indicate that this therapeutic approach is inefficacious (Rosenbloom et al., 2013). This raises a question as to whether the elevated T_b is actually the cause of the associated seizure. In fact, it is possible that mediators of fever such as IL-1β can act as the causal agents of seizures and fever independently (Heida et al., 2009). Interestingly, there is no consensus as to whether febrile seizures should be a serious concern (Reid et al., 2009). The prevailing view is probably that febrile seizures are relatively benign. First, there is the fact that febrile seizures are usually short-lasting (10–15 minutes) and not life-threatening. Second, febrile seizures seem to depend on genetic predisposition (Saghazadeh et al., 2014), so only a small fraction of children are at a high risk of febrile seizures. Third, the predisposition to febrile seizures spontaneously fades away as the susceptible individuals reach the age of 5 years. Fourth, there is no evidence that the typical febrile seizure can result in long-term sequelae (Lewis, 1999; Shinnar, 2003). It should be pointed out, however, that atypical febrile seizures that are focal or prolonged (>30 minutes) may be associated with negative long-term consequences (Lewis, 1999; Shinnar, 2003).

Hypothermia: friend or foe?

Based on the evidence indicating that hypothermia is an active, regulated response in rats injected with LPS at high doses, it has been proposed that hypothermia might have an adaptive value when the energy cost of fever exceeds its benefits (Romanovsky et al., 1996a; Romanovsky and Szekely, 1998). Experimental support of this hypothesis has been produced in rats with aseptic systemic inflammation caused by LPS (Romanovsky et al., 1997a; Liu et al., 2012) or with *Escherichia coli* infection (Liu et al., 2012). In these studies, rats challenged with high doses of LPS or live *E. coli* bacteria were either allowed to develop hypothermia in a mildly cool environment (which they prefer) or were "forced" to develop fever in a warm environment. Development of hypothermia instead of fever in these cases resulted in a drastic reduction in mortality and diminished organ damage (Fig. 34.14). Similar results have been obtained in mice injected with LPS at a high dose (Li et al., 2015). Importantly, the protection aided by hypothermia in the rat model of *E. coli* sepsis appears to be independent of the host's ability to fight or tolerate the infection, as bacterial burden was actually elevated in the liver of the hypothermic rats (Liu et al., 2012). The latter finding fits into the emerging concept that the host's ability to tolerate the presence of a pathogen (disease tolerance) is sometimes more important to its fitness and survival than its ability to clear the pathogen (disease-fighting); for review, see Medzhitov et al. (2012). From this perspective, it is reasonable to propose that, while fever represents a disease-fighting strategy, hypothermia represents a disease tolerance strategy.

The mechanisms behind the protection aided by hypothermia in severe forms of systemic inflammation are still poorly understood, but two possibilities deserve comment. First, it has been shown that the metabolic suppression that drives hypothermia occurs concurrently with the earliest decrease in cardiac output in endotoxic shock, to the extent that the balance between oxygen delivery and consumption is maintained and tissue hypoxia does not ensue (Corrigan et al., 2014). Tissue hypoxia in this model only becomes evident when the hypometabolic, hypothermic response is prevented (Corrigan et al., 2014). Second, there is the possibility that hypothermia lessens lung dysfunction by limiting the infiltration of this organ by neutrophils (Liu et al., 2012). Such an effect appears to occur independently of changes in inflammatory cytokines and prostaglandins (Liu et al., 2012), and might reflect an influence of temperature on adhesion and cytoskeleton molecules.

In sharp contrast with these experimental studies in animals, the prevailing clinical perception is that hypothermia is a dysregulated, detrimental phenomenon in sepsis (Cunha, 2012; Beverly et al., 2016). Such a perception arises from observational studies that identified hypothermia as a poor prognostic factor in septic patients (Clemmer et al., 1992; Arons et al., 1999; Marik and Zaloga, 2000; Peres Bota et al., 2004; Kushimoto et al., 2013; Drewry et al., 2015). More recently, however, it has been increasingly recognized that the prognostic value of hypothermia does not imply that it is the hypothermia itself that worsens outcome, the main reason being that those septic patients who develop hypothermia are usually sicker than those who do not (Jiang et al., 2015; Rumbus et al., 2017; Steiner et al., 2017).

By evaluating the dynamics of hypothermia in septic patients not subjected to active rewarming, Fonseca et al. (2016) have concluded that spontaneous hypothermia in sepsis is a transient, self-limiting response, with nadir at 34.0°C and median duration of 6 hours. Bidirectional fluctuations in T_b similar to those seen during fever were present during the episodes of hypothermia in the records of patients observed. Moreover, hypothermia was rarely present in the moments that preceded death, when

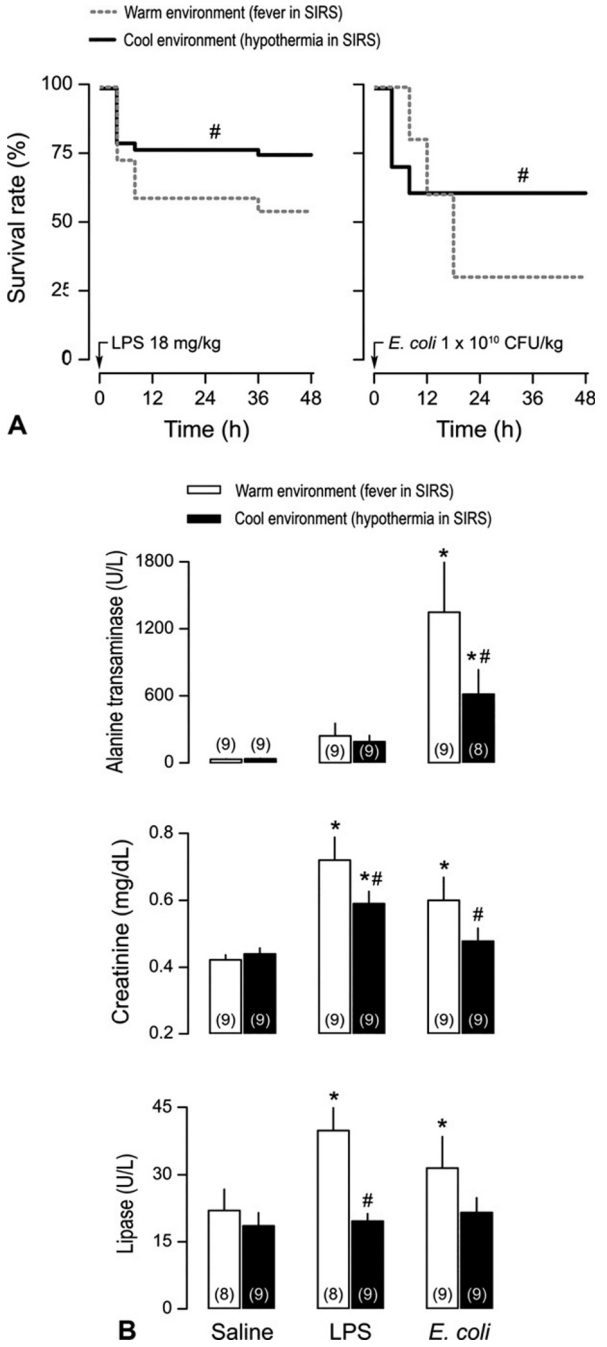

Fig. 34.14. Impacts of hypothermia versus fever on mortality and organ dysfunction. (**A**) Survival rates were assessed in lipopolysaccharide (LPS)- or *Escherichia coli*-injected rats (doses indicated) that developed hypothermia in a cool environment or fever in a warm environment. The number of rats per group was 29 for the LPS-injected rats in a warm environment, 42 for the LPS-injected rats in a cool environment, 10 for the *E. coli*-infected rats in a warm environment, and 10 for the *E. coli*-infected rats in a cool environment. #Hypothermic group differs statistically ($p < 0.05$) from the febrile group. (**B**) Markers of organ dysfunction in the blood of LPS- or *E. coli*-injected rats that developed hypothermia (ambient temperature (T_a) of 22°C) or fever (T_a of 28°C). Blood samples were collected at 360 minutes post-LPS, 240 minutes post *E. coli*, and 240–360 minutes after saline injection. Data are presented as mean ± SE. The number of animals in each group is shown in parentheses. *Statistically significant difference ($p < 0.05$) from the saline control group. #Hypothermic group differs ($p < 0.05$) from the corresponding febrile group. *SIRS*, systemic inflammatory response syndrome. (Adapted from Liu E, Lewis K, Al-Saffar H, et al. (2012) Naturally occurring hypothermia is more advantageous than fever in severe forms of lipopolysaccharide- and *Escherichia coli*-induced systemic inflammation. Am J Physiol Regul Integr Comp Physiol 302: R1372–R1383.)

multiple organ failure is presumably maximal. Hence, it is plausible that an early, regulated form of hypothermia exists in human sepsis. Prospective studies are warranted to assess whether spontaneous hypothermia may be of value in this patient population.

Another important consideration is that spontaneous hypothermia is quite distinct from forced hypothermia in terms of physiology and potential value. In forced hypothermia (usually referred to as "therapeutic" hypothermia), the T_b of a patient is lowered artificially by surface cooling devices under sedation. The body normally tries to compensate for this "unwanted" cooling by increasing metabolic heat production, a response that limits the desired hypometabolic effect of therapeutic hypothermia (Gordon, 2001). Although sedatives may attenuate the compensatory metabolic response, they certainly do not eliminate it (Villar and Slutsky, 1993). Spontaneous and forced hypothermia also differ from each other in terms of magnitude, with the former being less pronounced than the latter. Perhaps because of these factors, the use of forced hypothermia in animal models of sepsis has resulted in contradictory observations (Torossian et al., 2003, 2004; Chu et al., 2005; L'Her et al., 2006; Lindenblatt et al., 2006; Huet et al., 2007; Kanakura and Taniguchi, 2007). In spite of that, forced hypothermia of 32–34°C for 24 hours has been shown to lessen coagulopathy in a single prospective study in septic patients (Johansen et al., 2015), but it remains to be seen if this translates into reduced mortality.

SUMMARY

Systemic inflammation, a major significant challenge in critical care medicine, is often accompanied by changes in T_b, which manifest themselves as either fever or hypothermia, or some combination of both. In experimental animals, systemic inflammation is often modeled by administering bacterial LPS, which can cause either fever or hypothermia (or both) depending on dose and T_a.

Both fever and hypothermia are regulated thermoregulatory responses brought about by behavioral and autonomic effectors. Fever is brought about by warmth seeking in combination with skin vasoconstriction, sometimes with the help of increased thermogenesis. Hypothermia, on the other hand, is brought about by cold seeking in combination with inhibition of thermogenesis, with minimal contribution of skin vasodilation.

Fever is mediated by the COX-2 PGE_2 pathway, with substantial contribution of IL-6. The first phase of fever precedes cytokine production, and likely depends on PGE_2 originated from liver and lung macrophages. PGE_2 circulates in the blood in an albumin-bound form and can cross the BBB by facilitated transport. The later phases of fever are mediated by PGE_2 produced at the level of the BBB, in the preoptic hypothalamus, by endothelial cells or perivascular macrophages. IL-6 can be a major inducer of COX-2 in the later phases, although there is also evidence that IL-6 can act via COX-2-independent mechanisms.

The neural substrate of fever includes EP3-expressing preoptic neurons, at least some of which are located in the MnPO, and which are likely to be warmth-sensitive and GABAergic. These neurons—through descending connections to cells in the sympathetic ganglia and in the ventral horn—tonically inhibit cutaneous vasoconstriction and nonshivering and shivering thermogenesis. By acting on these neurons, PGE_2 disinhibits these cold-defense effectors. In contrast, the neural pathways driving thermoregulatory behaviors involved in fever are currently unknown, but it has been firmly established that these pathways do not go through the preoptic hypothalamus.

The mechanisms of hypothermia in systemic inflammation are poorly understood, but it is known that hypothermia is not the result of endogenous antipyretic mechanisms. On the contrary, hypothermia seems to have its own set of proinflammatory mediators, which may include TNF-α and a COX-1 product that remains to be identified.

Afferent signaling through the vagus nerve is unlikely to play any substantial role in either fever or hypothermia in systemic inflammation.

The neural substrate of the hypothermic response to systemic inflammation has not been delineated, but it involves a small group of neurons located at the ventral border of the dorsomedial hypothalamic nucleus, as well as neuronal fibers of passage within the PVH. These neural elements are necessary for the cold-seeking behavior seen in severe systemic inflammation.

The existence of distinct mechanisms for fever and hypothermia is consistent with the notion that they have evolved independently of each other to deal with different evolutionary pressures. The available evidence indicates that fever is the response of choice when systemic inflammation is of mild-to-moderate severity; it assists the immune system to clear pathogens at the cost of consuming the host's energy reserves (disease-fighting strategy). On the other hand, hypothermia is the response of choice in the most severe cases of systemic inflammation; it seems to aid the host in lessening tissue hypoxia and damage while lowering the ability of the immune system to clear the pathogens (disease tolerance strategy).

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ABBREVIATIONS

2-AG, 2-arachidonoyl-glycerol; AA, arachidonic acid; AEA, *N*-arachydonoyl-ethanolamine; BAT, brown adipose tissue; BBB, blood-brain barrier; CB, cannabinoid; COX, cyclooxygenase; DAG, diacylglycerol; DMH, dorsomedial hypothalamus; EET, epoxyeicosatrienoic acid; GABA, γ-aminobutyric acid; H-PGDS, hematopoietic PGD_2 synthase; i.c.v., intracerebroventricular(ly); IL, interleukin; i.p., intraperitoneal(ly); i.v., intravenous(ly); LOX, lipoxygenase; LPS, lipopolysaccharide; LT, leukotriene; m, microsomal; MAG, monoacylglcerol; MnPO, median preoptic nucleus; MPO, medial preoptic area; NLR, nucleotide-binding oligomerization domain-like receptor; PAF, platelet-activating factor; PAMP, pathogen-associated molecular patterns; PG, prostaglandin (e.g., in PGE_2); PGDS, PGD_2 synthase; PGES, PGE_2 synthase; PL, phospholipase (e.g., in PLA_2); POA, preoptic area; PRR, pattern recognition receptor; PVH, paraventricular hypothalamus; RANKL, receptor activator of NF-κB ligand; SIRS, systemic inflammatory response syndrome; T_a, T_b, and T_{sk}, ambient, body, and skin temperatures; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; TRPV1, transient receptor potential vanilloid-1 (channel); TXA_2, thromboxane A_2; $\dot{V}O_2$, rate of oxygen consumption.

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