

## SIGNALING THE BRAIN IN THE EARLY SICKNESS SYNDROME: ARE SENSORY NERVES INVOLVED?

Andrej A. Romanovsky

Systemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

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### 1. ABSTRACT

Nonspecific manifestations (sickness symptoms) of inflammation and infection occur as two sequential syndromes, the early and late. This review deals with the early sickness syndrome, which occurs at the onset of the inflammatory process and manifests itself with a high deep body temperature, hyperalgesia/allodynia, arousal, motor agitation, and arterial hypertension. Two rat models of intravenous lipopolysaccharide (LPS)-induced fever are used to study the early syndrome: 1) a monophasic response to low, just suprathreshold doses of LPS and 2) the first rise in body temperature (*Phase I*) of the polyphasic response to higher doses. Experiments in the first model reveal a blockade of monophasic fever by total subdiaphragmatic or selective hepatic vagotomy, thus suggesting mediation of this response by the hepatic vagal fibers, presumably afferent. Experiments in the second model show that *Phase I* of polyphasic fever is insensitive to surgical vagotomy but does not occur in animals desensitized with low intraperitoneal doses of capsaicin (an agonist of the vanilloid receptor VR1). These findings suggest that *Phase I* is mediated by intra-abdominal, VR1-receptor-bearing afferents, either splanchnic or possibly splanchnic and vagal. The involvement of the splanchnic nerve and VR1 receptor in *Phase I* of LPS fever is currently under investigation in our laboratory. Based on studies completed so far, neural signaling mechanisms are involved in both monophasic fever and *Phase I* of polyphasic fever. We speculate that these mechanisms are triggered by peripherally originated, blood-borne prostaglandin E<sub>2</sub>.

### 2. INTRODUCTION

There is little doubt that the febrile response and other nonspecific manifestations (sickness symptoms) of inflammation and infection are mediated by the central

nervous system, but the mechanisms by which peripherally originated inflammatory signals reach the brain remain unclear. At least four possibilities have been proposed. The first possibility is that the peripheral immune signals enter the brain through the *organum vasculosum laminae terminalis* (1) and possibly other periventricular organs, in which capillaries are fenestrated resulting in a "leaky" blood-brain barrier (BBB) (2). For a long time, this route has been considered the most important. However, the significance of this route has been questioned in several recent studies (3-5) and reviews (6). The second theory holds that pyrogenic cytokines, such as interleukin (IL)-1, can access the brain by carrier-mediated transport across the BBB (7). The third possibility is that circulating pyrogens bind to cells in or adjacent to the wall of cerebral microvessels (endotheliocytes, perivascular cells, and brain macrophages) and stimulate production of fever mediators [most importantly prostaglandin (PG) E<sub>2</sub>] by these cells; these cells then release PG E<sub>2</sub> into the brain tissue (8, 9). Lastly, inflammatory agents could act on neural terminals in peripheral tissues and convey febrile signals to the brain via sensory nerve fibers (10-14). In this review, we analyze our own data and data from the literature dealing with the involvement of sensory nerves (primarily the vagus) in fever (specifically the early febrile phase) as one of the symptoms of the early sickness syndrome. The review consists of four major parts (Sections 3-6). In Section 3, we describe the phenomenology of the febrile response and of the so-called sickness response. We emphasize that the sickness syndrome is a dynamic entity, and that sickness symptoms at the onset of systemic inflammation/infection differ drastically from those of an infectious process at its culmination. We further conjecture that neural signaling is likely to be of greater importance for the early than for the late sickness syndrome. In Section 4, we briefly overview the history of the research

**Table 1.** The thermoregulatory responses to LPS and their correspondence to the early and late sickness symptoms <sup>1</sup>

Sickness Syndrome	Thermal Response	Thermoregulatory Features	Other Sickness Symptoms
The early sickness syndrome	<ul style="list-style-type: none"> <li>• The early febrile phase (either monophasic fever or <i>Phase I</i> of polyphasic fever)</li> </ul>	<ul style="list-style-type: none"> <li>• High body temperature</li> <li>• Narrow-dead-band (homeothermic) type of body temperature regulation</li> <li>• Weak dependence on ambient temperature</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperalgesia and/or allodynia</li> <li>• Arterial hypertension</li> <li>• Increased vigilance</li> <li>• Motor agitation</li> </ul>
The late sickness syndrome	<ul style="list-style-type: none"> <li>• The late febrile phase (<i>Phase II</i> or <i>Phase III</i> of polyphasic fever) or</li> <li>• Hypothermia</li> </ul>	<ul style="list-style-type: none"> <li>• High or low body temperature</li> <li>• Wide-dead-band (poikilothermic) type of body temperature regulation</li> <li>• Strong dependence on ambient temperature</li> </ul>	<ul style="list-style-type: none"> <li>• Hypoalgesia</li> <li>• Arterial hypotension</li> <li>• Sleepiness</li> <li>• Anorexia</li> <li>• Motor depression</li> </ul>

<sup>1</sup> See Ref. 22 for review.

on neural signaling in the early sickness syndrome and fever. In Section 5, we analyze the results of recent experiments involving vagotomy and related techniques. In the concluding Section 6, we propose a signaling mechanism that entails peripherally originated PG E<sub>2</sub> and sensory nerve fibers. We also outline the topics for future studies.

### 3. THE SICKNESS SYNDROME: A DYNAMIC ENTITY

Bacterial lipopolysaccharide (LPS, endotoxin) is used widely to model in experimental animals the thermoregulatory and other innate defense responses to gram-negative infection. Over the last decade, it has become clear that the thermoregulatory response to LPS is much more complex than previously thought. In fact, an intravenous (i.v.) injection of LPS causes several different thermoregulatory responses in experimental animals, depending on the dose, ambient temperature, and other factors (14). When a small, near-threshold dose (1 microgram/kg, in the case of the rat) is administered at a neutral or near-neutral (27-32°C) ambient temperature (for more information on thermal neutrality, see Ref. 15), a so-called monophasic fever typically occurs: it consists of a single burst of thermoeffector activity and a single rise of deep body temperature peaking at 1-1.5 h postinjection. If the ambient temperature remains near-neutral, but the dose increases, the response changes in an intriguing way: a single, bolus injection of LPS now produces several sequential bursts in the activity of thermoregulatory effectors and, consequently, several rises in body temperature. These rises are called febrile phases. They are characterized by remarkably precise timing (16), which remains the same for different preparations of LPS and different rat strains (17). For the very narrow dose range (from slightly below to slightly above 5 microgram/kg), the febrile response of rats to LPS consists of two body temperature rises: *Phase I* (peaks ~1 h postinjection) and *Phase II* (peaks at 2-2.5 h). If the dose increases further (from 10 microgram/kg to lethal), the response becomes at least triphasic with *Phase III* peaking at 5-6 h postinjection (17).

The thermoregulatory mechanism of *Phase I* (and possibly of monophasic fever) is a parallel upward shift of the threshold body temperatures for activation of different thermoregulatory effectors (18). Such a shift leads to precise regulation of body temperature but at a new, elevated level; it is often described as an increase in the "set point". The thermoregulatory mechanism of *Phase II* (and

possibly *Phase III*) involves a so-called threshold dissociation: the threshold body temperature for activation of heat-defense effectors remains elevated (as it was during *Phase I*), but the threshold body temperature for activation of cold-defense effectors decreases by several degrees (18). [This clearly shows that any model with a single "set point" is grossly inadequate to describe the thermoregulatory system (19).] The development of threshold dissociation means that body temperature regulation switches to the poikilothermic type. When this happens, autonomic effectors are no longer used for thermoregulation in a wide range of body temperatures (wide dead band regulation), and the thermoregulatory behavior becomes the only thermoregulatory tool available, like in poikilothermic animals. This also means that the animal's body temperature becomes more sensitive to the ambient temperature, and that hypothermia readily occurs at subneutral ambient temperatures. Therefore, it is not surprising that i.v. LPS causes hypothermia rather than a fever in a cold environment (16, 20, 21); this hypothermia is more pronounced with lower ambient temperature and higher LPS dose.

Monophasic fever and *Phase I* of polyphasic fever, which are characterized by an increased level of body temperature and the precise (i.e., with a narrow dead band) type of body temperature regulation, are accompanied by hyperalgesia/allodynia, motor hyperexcitability, and possibly arterial hypertension and an increase in vigilance. These symptoms form a relatively stable syndrome, which we have termed "the early sickness syndrome" (22). In contrast, the thermoregulatory response to larger doses of LPS at later times postinjection can be manifested either as the late *Phases II* and *III* of polyphasic fever or as hypothermia. These thermoregulatory manifestations are accompanied by motor depression, hypoalgesia, and possibly hypotension and sleepiness (22). We have termed these symptoms "the late sickness syndrome". With increase in LPS dose and/or the time elapsed after the injection of LPS, the early phase sickness syndrome diminishes, and the late phase syndrome prevails. Further justification of the ideas that the sickness response is a dynamic entity, that it occurs in two stages, and that each stage represents a different sickness syndrome can be found in the original report by Romanovsky *et al.* (22). How different thermoregulatory responses to LPS correspond to different (the early and late) sickness syndromes is shown in Table 1.

From the clinical point of view, it is important that the two syndromes represent two different strategies of fighting infection (22, 23). Occurring at the onset of infection, the early sickness syndrome constitutes a response of the healthy organism to the forthcoming disease. Its biological 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 of the optimal environment (conditions for behavioral thermoregulation, sufficient water supply, protection from predators, *etc.*) for fighting the beginning malady. This type of adaptation to infection develops through the active (fight/flight — energy expenditure) coping pattern (24), at a high energetic cost. The early sickness syndrome can be readily recognized in a febrile patient: it occurs at the onset of an acute infection, when the patient is usually restless and often complains that lights are too bright, sounds are too loud, and no position is comfortable.

The late sickness syndrome represents the systemic response to infection at a stage when the disease has already progressed: this is a response of the sick, damaged, and weakened organism to the continuing pathologic challenge. Compared to the onset of the disease, manifestations of sickness change drastically. The pain associated with damage has lost its signaling function and started to substantially contribute to morbidity; consequently, hyperalgesia changes to hypoalgesia. Energy resources have been reduced by the costly early phase syndrome and pathological energy expenditure (inefficient functioning of damaged tissues); energy supply has been decreased or even completely broken off due to the compromised ability of getting food and the development of adaptive anorexia (see Ref. 25). Even if energy deficiency has not already occurred, its threat becomes obvious. Energy-intensive responses are, therefore, no longer advisable and/or affordable: wakefulness, motor agitation, and arterial hypertension change into sleep, motor depression, and normo- or hypotension, respectively. An elevated body temperature remains potentially beneficial, but its benefits could now be easily offset by the harmfully high energetic cost. Responding to this delicate balance, threshold dissociation develops, thus allowing body temperature to be maintained (by using thermoregulatory behavior) at either an elevated level or, if the benefits-cost ratio is especially unfavorable (*e.g.*, in a cold environment), at a lowered level. The late sickness syndrome is an example of adaptation occurring through a passive (depression/withdrawal — energy conservation) coping pattern (24). Clinically, the late sickness syndrome can be recognized in a patient with an infectious disease exhibiting a decreased responsiveness to stimuli, either hypothermia or fever, generalized depression, sleepiness, and low blood pressure (or even shock) together with specific symptoms of damage caused by the pathogen; such a patient is usually viewed as a "severe patient."

#### 4. SENSORY NERVES IN THE SICKNESS SYNDROME: A BRIEF HISTORICAL EXCURSUS

The early and the late sickness syndromes (and the early and late febrile phases) have been thought to be

mediated differently (26, 27). As a response to forthcoming inflammation or infection, the early sickness syndrome should involve rapid signaling to the brain, possibly via sensory nerve fibers. "Messages, by means of nerve fibers, would have the advantage of much greater speed of transmission, and would not be subject to impedance by the BBB" (Ref. 28, p. 444). The late sickness syndrome, a response to the continuing pathologic challenge, is a slow process *a priori*, and circulating mediators of the ongoing inflammation or infection provide plentiful humoral signals to the brain. First experimental hints suggesting that neural signaling via unidentified sensory nerves may be involved in the early, but not late, stages of the febrile/inflammatory response were obtained by Morimoto *et al.* (29) fifteen years ago and by Cooper and Rothwell (30) a few years later. Several studies published in 1992-1993 suggested that at least some sensory nerve fibers conveying febrigenic signals to the brain travel within the vagus nerve. For example, Nijima (31) described an activation of vagal afferent neurons by a pyrogenic cytokine, IL-1, whereas Ericsson *et al.* (32) and Wan *et al.* (33) showed that systemic administration of both exogenous (LPS) and endogenous (IL-1) pyrogens leads to expression of the early response genes in the nucleus of the solitary tract, the major collector of vagal sensory inputs.

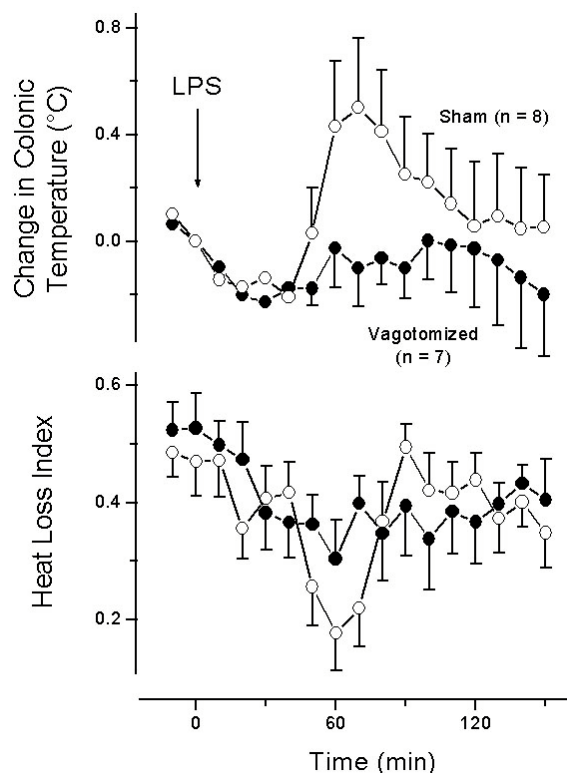
A "breakthrough" happened in 1994, when Watkins *et al.* (34) demonstrated that subdiaphragmatic vagotomy leads to an attenuation of an early phase symptom, hyperalgesia, thus suggesting an important role for the abdominal vagus in its genesis. In 1995, the same group (35) found that subdiaphragmatically vagotomized rats do not develop fever in response to intraperitoneal (*i.p.*) administration of IL-1. The same year, Székely *et al.* (36) reported that desensitization of intra-abdominal chemosensitive afferents with small *i.p.* doses of the vanilloid receptor VR1 agonist capsaicin (sometimes, this procedure is referred to as "chemical vagotomy") greatly decreases the febrile response of rats to *i.v.* LPS, mostly its Phase I. These initial demonstrations of the ability of both surgical vagotomy and capsaicin desensitization to attenuate the febrile response have now been confirmed by several laboratories in two animal species: the rat and guinea pig, as reviewed elsewhere (14). The same review contains a much more complete list of articles dealing with neural signaling in fever and sickness.

While trying to understand the reason for decreased febrile responsiveness of vagotomized animals, it should be remembered that both surgical vagotomy and capsaicin desensitization can lead to severe "side effects", including malnutrition, thermoeffector deficiency, and other thermoregulatory impairments (37). Although these side effects may be responsible for some cases of fever attenuation in vagotomized animals, they clearly cannot explain all such cases (for detailed analysis, see Ref. 14). It is reasonable, therefore, to suggest that vagally transmitted signals are intimately involved in the thermoregulatory response to systemic inflammation. However, such intimate involvement seems limited to only the early phase sickness syndrome (13, 14).

**Table 2.** Effects of vagotomies and related procedures on the monophasic febrile response and *Phase I* of the polyphasic febrile response to intravenous lipopolysaccharide (LPS)<sup>1</sup>

Procedure	Response	LPS Dose, microgram/kg	Effect	Species	References
Bilateral truncal subdiaphragmatic vagotomy	Monophasic fever	1	↓↓	Rat	37, 38
Selective hepatic vagotomy	Monophasic fever	1	↓↓	Rat	39
Bilateral selective gastric vagotomy	Monophasic fever	1	↔	Rat	39
Bilateral selective celiac vagotomy	Monophasic fever	1	↔	Rat	39
Bilateral truncal subdiaphragmatic vagotomy	<i>Phase I</i> of polyphasic fever	10	↔	Rat	38, 58
Bilateral truncal subdiaphragmatic vagotomy	<i>Phase I</i> of polyphasic fever	100	↔	Rat	38
Bilateral truncal subdiaphragmatic vagotomy	<i>Phase I</i> of polyphasic fever	1000	↔	Rat	38
Bilateral truncal subdiaphragmatic vagotomy	<i>Phase I</i> of polyphasic fever	2	↓↓	Guinea pig	68
Desensitization of intra-abdominal nerves by intraperitoneal capsaicin	<i>Phase I</i> of polyphasic fever	10	↓↓	Rat	36, 58
Inherent deficiency of the cholecystokinin-A receptor	<i>Phase I</i> of polyphasic fever	10	↔	Rat	56

<sup>1</sup> The effects are marked: ↓↓, complete blockade or strong attenuation; ↔, no effect.



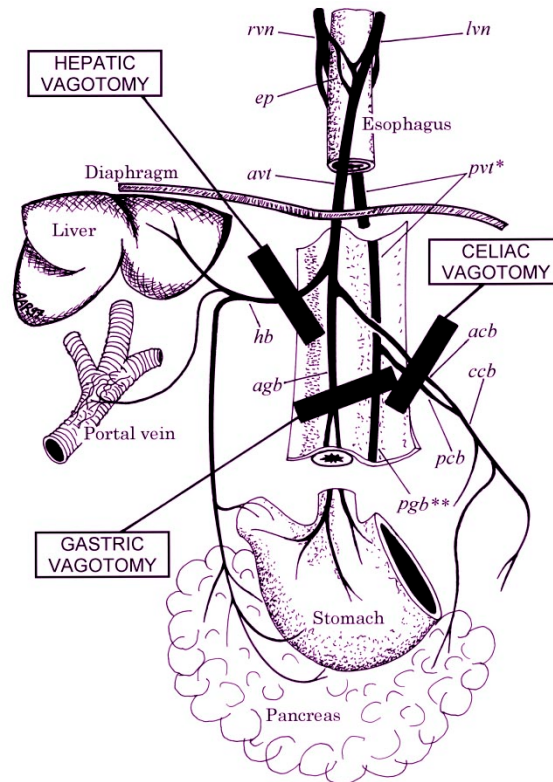
**Figure 1.** Thermoregulatory effects of the intravenous injection (arrow) of lipopolysaccharide (LPS; 1 microgram/kg) in vagotomized and sham-operated rats. The heat loss index is used to assess thermoeffector responses of the tail skin vasculature (see Ref. 15). It is calculated as a ratio between two temperature gradients: skin-ambient and deep body-ambient; it changes from 0 (full vasoconstriction) to 1 (full vasodilation). (Modified from Ref. 37, published with permission of the American Physiological Society.)

## 5. EFFECTS OF VAGOTOMY AND RELATED PROCEDURES ON THE EARLY FEBRILE PHASE

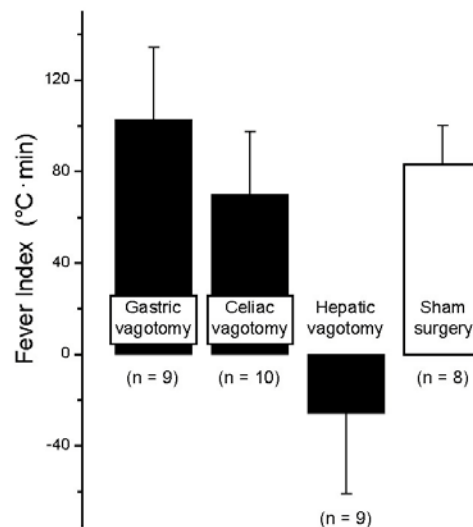
Below, we will review recent data suggesting an involvement of sensory nerves in the thermoregulatory manifestations of the early sickness syndrome. Specifically, we will analyze the effects of different types of vagotomy on the LPS-induced monophasic fever and *Phase I* of the polyphasic fever (Table 2). Whether monophasic fever and *Phase I* of polyphasic fever are identical is unclear. One similarity between the two is that they are accompanied by the same sickness symptoms (22). Furthermore, the time dynamics of a monophasic fever is almost identical to that of *Phase I* of a polyphasic fever in several animal species, including the rabbit, guinea pig, dog, and mouse (personal observations). In the rat, however, monophasic fevers often have longer latency and duration than *Phase I* of polyphasic febrile responses (22), thus suggesting that the two phenomena may be different.

### 5.1. Monophasic fever

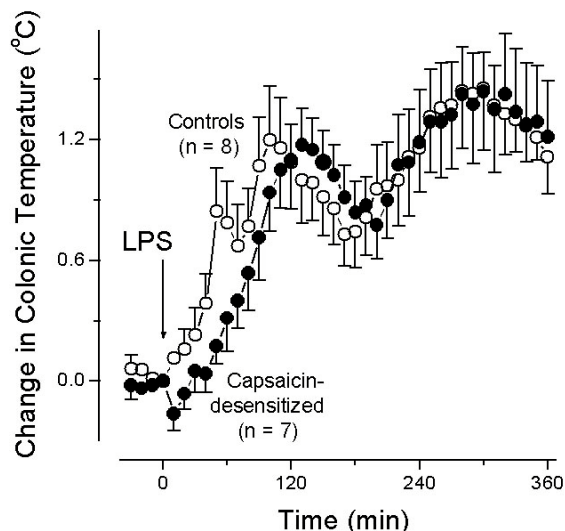
We have found that the integrity of the subdiaphragmatic vagus is required for the development of the monophasic febrile response to LPS (37, 38). Indeed, whereas sham-operated rats respond to a small dose of LPS (1 microgram/kg, i.v.) with a typical monophasic fever, subdiaphragmatically vagotomized rats show no increase in body temperature (Figure 1). We also questioned which abdominal vagal branch is involved in the genesis of monophasic fever (39). In the rat, the anterior and posterior vagal trunks divide just below the diaphragm into five primary branches: the anterior (ventral) gastric, posterior (dorsal) gastric, anterior (accessory) celiac, posterior celiac, and hepatic (Figure 2; for a detailed description, see Ref. 40). In rats with selective abdominal vagotomies (celiac, gastric, hepatic, or sham), integrity of only the hepatic branch is critical for the development of a monophasic fever (Figure 3). The hepatic branch is the second smallest of the primary branches of the abdominal vagus and has the



**Figure 2.** Three types of selective subdiaphragmatic vagotomy, viz., celiac, gastric, and hepatic, are shown on a schematic representation of the typical distribution of the rat abdominal vagal branches. Abbreviations used: *acb*, anterior celiac branch; *agb*, anterior gastric branch; *avt*, anterior vagal trunk; *ccb*, common celiac branch; *ep*, esophageal plexus; *hb*, hepatic branch; *lvn*, left vagus nerve; *pcb*, posterior celiac branch; *pgb*, posterior gastric branch; *pvt*, posterior vagal trunk; and *rvn*, right vagus nerve. For the sake of clarity, two simplifications are made. First (\*), the dorsal esophageal surface is shown as if the serosa was cut along the right side of the esophagus, partially separated from its underlying tissues, and laid in a frontal plane; the posterior vagal trunk was transected immediately below the diaphragm. Second (\*\*), the posterior gastric branch is shown only to the level of the lesser gastric curvature, with the distal portion being entirely omitted. (Reprinted from Ref. 39 with permission of the American Physiological Society.)



**Figure 3.** The febrile response to intravenous lipopolysaccharide (1 microgram/kg) compared among rats subjected to four different types of surgery (indicated). The fever index, an integral of the deviation of body temperature from its preinjection level, was calculated over 0-4 h postinjection and used as a response measure. (Modified from Ref. 39, published with permission of the American Physiological Society.)



**Figure 4.** The febrile response of rats pretreated with a small intraperitoneal dose of capsaicin (5 mg/kg) and of control rats to an intravenous injection (arrow) of lipopolysaccharide (LPS, 10 microgram/kg). (Modified from Ref. 58, published with permission of Elsevier.)

lowest content of efferent fibers (41). Arguably, selective hepatic vagotomy is the least traumatic method of vagal deafferentation that has been demonstrated to successfully alter febrile responsiveness. Hence, it is reasonable to suggest that the effect observed in the rats with selective hepatic vagotomy was not due to surgical complications or side effects. Rather, it reflected the missing of afferentation from the anatomic region (the liver and its portal vein) serviced by the hepatic branch, a predominantly sensory nerve.

The liver with its Kupffer cells has long been suspected of having a role in the pathogenesis of fever (42). This suspicion has been reinforced by reports of hepatic clearance of peripherally injected pyrogens (43, 44) and, more recently, on the early induction by LPS of hepatic synthesis of the ultimate downstream mediator of fever, PG E<sub>2</sub> (27). Studies with gadolinium chloride (in certain experimental paradigms, this drug is thought to selectively inactivate Kupffer cells) further confirmed the involvement of Kupffer cells in the pathogenesis of both LPS-induced fever (45) and hyperalgesia (46). Most convincingly, experiments in the rabbit, a species that is more sensitive to LPS than the rat, have shown that an infusion of a small dose of LPS (100 ng/kg) in the portal vein produces a greater monophasic fever than ear vein infusion (47). It has also been shown that intraportal infusion of IL-1 increases the discharge rate of hepatic vagal afferents (31, 48), and that IL-1 receptors (49) and PG receptors (50) are present on vagal paraganglia associated with the hepatic branch. In agreement with the authors of earlier reviews (10-13), we conclude that febrigenic chemical signals (possibly including IL-1, other pyrogenic cytokines, and PG E<sub>2</sub>) originate in the Kupffer cells and bind to appropriate receptors on the hepatic vagus. The proposed mechanism seems important for triggering the monophasic febrile

response to i.v. LPS at low doses (38), as well as the febrile response to low (100 ng/kg), but not high (1 microgram/kg), i.p. doses of IL-1 (51). More recently, our laboratory has also demonstrated that sensory vagal fibers originating in the liver are required for the induction of LPS tolerance by low doses of i.v. LPS (52).

## 5.2. Phase I of Polyphasic Fever

To assess the potential role of sensory vagal fibers in *Phase I* of the polyphasic febrile response to LPS, we have used three approaches: 1) “genetic vagotomy”, 2) “chemical vagotomy”, and 3) surgical vagotomy. These approaches produced somewhat contradictory results (Table 2).

“*Genetic vagotomy*”. For a limited purpose, mutant Otsuka Long-Evans Tokushima Fatty rats can be considered “genetically vagotomized”, because they lack the cholecystinin (CCK)-A receptor (53), one of the functionally important receptors on vagal afferents (54, 55). In our experiments (56), the mutant rats exhibited a normal *Phase I* of i.v. LPS-induced fever, thus suggesting that CCK-A receptor-bearing vagal afferents are uninvolved in this phase. A pharmacological study by Martin *et al.* (57) has similarly shown that the CCK-A receptor is uninvolved in i.p. LPS- or IL-1-induced fever.

“*Chemical vagotomy*”. What is often referred to as “chemical vagotomy” is achieved by i.p. application of low doses (1-5 mg/kg) of capsaicin (58), which desensitizes afferent C and thin (delta) A fibers, both vagal and nonvagal (splanchnic) (59). This treatment causes transient (3-5 weeks) neural damage that is limited primarily to the abdominal cavity and does not lead to the known systemic effects of desensitization with high doses (60). As we have repeatedly shown (36, 58), the desensitization of intra-abdominal afferent fibers in rats by low doses of capsaicin abolishes *Phase I* of the polyphasic febrile response to LPS (Figure 4). These data suggest an involvement of intra-abdominal, VR1-receptor-bearing afferents, either vagal, splanchnic, or both. The fibers involved may include the same fibers that trigger the development of monophasic fever, *i.e.*, hepatic vagal fibers originating in the liver and its portal vein. Interestingly, the liver is innervated by capsaicin-sensitive vagal afferents (61), and *Phase I* of LPS fever is absent in rats with hepatic pathology, including congestive hepatomegaly (62). However, there are also data arguing that hepatic mechanisms are important not for *Phase I*, but rather for *Phase II*, at least in the rabbit (47).

Recently (27), we have shown that *Phase I* of the polyphasic febrile response to LPS is accompanied by robust overexpression of hepatic mRNA encoding PG E<sub>2</sub>-synthesizing enzymes, *viz.*, secretory phospholipase A<sub>2</sub>-IIA, cyclooxygenase-2, and microsomal PG E synthase. Moreover, such an overexpression in the liver occurs earlier and reaches a higher magnitude than in the brain. These data agree with the proposed involvement of blood-borne PG E<sub>2</sub> in fever, especially in its *Phase I* (66-69). Of note are the facts that vagal sensory neurons express PG receptors of the EP3 type (38), and that *Phase I* of LPS fever does not occur in EP3 or EP1 receptor knockout mice

(70, 71). Furthermore, peripheral PG E<sub>2</sub> exhibits multifaceted regulatory actions by modifying vagal afferent transmission (for review, see Ref. 50). It has also been shown that activation of vagal afferents by cytokines is at least partially PG-mediated (48, 50). Based on this information, we suggest that neural mechanisms of monophasic fever and *Phase I* of the polyphasic febrile response may be triggered by circulating PGs.

*Surgical vagotomy.* In contrast to capsaicin desensitization, surgical (total truncal subdiaphragmatic) vagotomy had no effect on *Phase I* of the response to moderate-to-high (10-1000 microgram/kg) i.v. doses of LPS in our studies (38, 58). Yet, monophasic fever, another manifestation of the early phase syndrome, has been repeatedly blocked by surgical vagotomy (*vide supra*). Furthermore, Sehic and Blatteis (72), observed a complete blockade of *Phase I* of i.v. LPS-induced fever by subdiaphragmatic vagotomy in a different species, the guinea pig. Although nonspecific complications of vagotomy (14) may explain the difference between our results and those of Sehic and Blatteis, the involvement of vagal fibers in the genesis of *Phase I* cannot be ruled out completely. Moreover, the extent of vagal involvement may differ in different species, which is in agreement with the fact that parenchymal vagal innervation of the liver is denser in the guinea pig than in the rat (40, 73). Unfortunately, several other studies that could have tested the sensitivity of *Phase I* of the febrile response of rats to LPS or IL-1 (for review, see Ref. 14) failed to do so. *Phase I* is easily masked by stress hyperthermia, if several methodological conditions (including extensive habituation of the animals to the experimental setup and a painless injection of the pyrogen through a preimplanted catheter) are not observed (74). Notwithstanding the results of Sehic and Blatteis (72), *Phase I* of the polyphasic febrile response to LPS is insensitive to vagotomy, but sensitive to capsaicin desensitization. This implies that the involvement of nonvagal (splanchnic) fibers may be more important for this febrile phase. It further suggests that *Phase I* of the polyphasic response to moderate-to-large doses of LPS is different from the monophasic response to small doses.

## 6. CONCLUDING REMARKS AND PERSPECTIVES

In conclusion, the monophasic febrile response to low doses of LPS requires the integrity of the hepatic vagal fibers, presumably afferent, whereas *Phase I* of the polyphasic febrile response is likely mediated by capsaicin-sensitive (VR1-receptor-bearing) fibers traveling within either the splanchnic nerve or both the splanchnic and vagus nerves. These capsaicin-sensitive fibers initiate the febrile response via a CCK-A receptor-independent mechanism; peripheral PGs are likely involved in this mechanism. Interestingly, Ross *et al.* (75, 76) have recently reported that the induction of the febrile response to localized LPS (administered into the subcutaneous chamber) requires the participation of the same players: afferent nerve fibers (in this case, cutaneous) and PGs. The neurons involved are speculated to be cold-sensitive receptors, which are selectively activated by PG E<sub>2</sub> (77).

Hence, PGs acting on sensory nerves, whether visceral or somatic, may be a triggering mechanism for fever and other early sickness symptoms. It is intriguing that this recently emerged and still speculative idea might have been unknowingly exploited by patients and physicians for decades, if not centuries or even millennia. From willow leaves used by the ancient Egyptians to the latest selective inhibitors of cyclooxygenase-2, the vast majority of anti-inflammatory/antipyretic drugs have the same principal mechanism of action, inhibition of the synthesis of the major downstream mediator of fever, PG E<sub>2</sub>. One of the COX inhibitors, indomethacin, has been shown to block *Phase I* of LPS fever when administered peripherally but not centrally (29). Several other PG synthesis inhibitors are known to possess a robust antipyretic activity when administered peripherally, and yet they are believed (whether justifiably or not) to be unable to cross the BBB. The recently identified PG receptors on sensory nerves driving the early phase sickness syndrome (50) may, thus, constitute one of the oldest therapeutic targets.

It should be emphasized, however, that the model of the early sickness syndrome as a phenomenon involving sensory nerves and blood-borne PGs is still “under construction”. Several laboratories, including the author’s, are currently conducting multiple studies on the topic of this review. Specifically, the effects on the febrile response of the following experimental procedures are being studied: topical, perivagal application of the relatively weak VR1 receptor agonist capsaicin; localized and general desensitization with the highly potent and selective VR1 agonist resiniferatoxin; acute systemic administration of the VR1 antagonist capsazepine; transection of the major splanchnic nerve, a principal nonvagal conductor of sensory information from the abdominal viscera; and peripheral administration of antibodies to PG E<sub>2</sub> (as large, hydrophilic proteins, these antibodies do not cross the BBB). It is, therefore, possible that the picture outlined in the present article based on the currently available data will have to be changed when the abovementioned experiments are finished.

It should also be noted that investigations of the role of the vagus nerve in immune-to-brain signaling opened several new territories (see Ref. 14 for review). It appeared that vagal involvement in infection and inflammation is not limited to triggering the early sickness syndrome. The vagal afferents, presumably from the upper gastrointestinal tract, modulate the brain circuitry involved in the control of inflammation and pain (78, 79). The vagal efferent fibers, possibly those innervating the liver, form the so-called cholinergic antiinflammatory pathway, which is thought to inhibit the production of tumor necrosis factor by Kupffer cells and/or other macrophages (80, 81). Interruption of this latter pathway can potentially explain the exaggeration of hypothermic and other responses to shock-inducing doses of LPS in rats subjected to total subdiaphragmatic (38) or selective hepatoceliac (52) vagotomy. The efferent vagal fibers innervating the gut have been proposed to participate in the late sickness syndrome, because their selective lesion attenuates i.p. LPS-induced fever at its later stages via an unknown



mechanism (82). These newly discovered territories are open for exploration.

## 7. ACKNOWLEDGEMENTS

Important contributions to the research of the author's laboratory reviewed in this paper have been made by Drs. Miklós Székely (the author's mentor), Vladimir A. Kulchitsky (collaborator), Andrei I. Ivanov (former fellow), and Christopher T. Simons (former student). The reviewed research has been supported by grants and generous donations from the National Institutes of Health (NINDS grant R01 NS-41233), Arizona Disease Control Research Commission (category II grant 8-061), Collins Medical Trust, Good Samaritan Foundation, Oregon Health Sciences Foundation (Medical Research Foundation of Oregon), Bayer AG (Germany), Women's Board of the Barrow Neurological Institute, and Dr. Temple Fay's Memorial Account. Drs. Allison N. B. Phayre, Miklós Székely and Victoria F. Turek read a draft of the manuscript and provided important feedback. Dr. Alexandre A. Steiner acted as a Reviewing Editor for this article.

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**Key Words:** Body temperature, thermoregulation, fever, lipopolysaccharide, afferent nerve fibers, vagus, vagotomy, hepatic branch, capsaicin, vanilloid receptor VR1, cholecystokinin A receptor, splanchnic nerve, prostaglandins, Review

**Send correspondence to:** Andrej A. Romanovsky, M.D., Ph.D., Director, Systemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital and Medical Center, 350 West Thomas Road, Phoenix, Arizona 85013, USA, Tel: 602 406-5059, Fax: 602 406-4113, E-mail: [aromano@chw.edu](mailto:aromano@chw.edu)