MINIREVIEW

Fever and Fever Syndrome—Current Problems

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Exogenous pyrogen is “a substance which, when injected in the “milieu intérieur,” will cause the release of endogenous pyrogen and in turn fever” [1]. As the endotoxin of gram-negative bacteria, such as *E. coli*, is the most potent exogenous pyrogen, the humoral and neurophysiological events connecting endotoxin with the febrile response of the organism have most often been investigated. The effective component of endotoxin as a pyrogen is lipopolysaccharide (LPS).

The generation of fever by endotoxin typically involves the following steps: a) endotoxin stimulates immune active phagocytes, such as leucocytes, macrophages, and reticuloendothelial cells, to produce and release endogenous pyrogen (EP); b) EP is transported by the blood stream into the brain and acts, via mediator (s), upon specific target sites mainly at the hypothalamic levels; c) the resulting hyperthermia, i.e. fever in the strict sense of the word, is induced by the attenuation of heat loss and/or the augmentation of heat production, depending on the thermal conditions of the organism.

While the chain of events characterizing endotoxin fever may be considered as paradigmatic, fever as a natural pathophysiological response has turned out to be more diverse. This applies to the chain of events leading to the hyperthermic response, as well as to accompanying humoral and neuronal changes in bodily functions.

Firstly, generation of febrile hyperthermia may involve endogenous compounds not identical with the endogenous pyrogen that is typically released in response to LPS.

Secondly, the significance of the mediators involved at the central nervous level is disputed and their actions have been shown to be subject to modifications.

Thirdly, discrepancies remain to be settled when considering the molecular properties of the various mediators in the febrile response and the mechanisms by which they are assumed to get to and act upon their target sites.

Among the complex set of events which have been evaluated in connection with the hyperthermic response, interest has increasingly been focused on the systemic changes in bodily functions, due to humorally and neuronally induced alterations.

These effects have been shown to originate, in principle, independently from the leading symptom of fever, the hyperthermic response. However, the extent to which these non-thermal components of the host-defence response are effective independently from the febrile hyperthermia and, correspondingly, whether and to which degree they interact, has not been fully elucidated. Fever as a syndrome needs to be further defined with respect to the significance of its thermal and non-thermal components from the viewpoint of the host-defence response.

I. ENDOGENOUS MEDIATORS OF FEVER AND SITES OF ACTION

A. Systemic endogenous pyrogens

As mentioned above, exogenous pyrogens act on the immune active phagocytes, to stimulate the release of EP as the primary mediator at the systemic level. EP was reported to be a heat-labile protein with a molecular weight ranging between 38,000 and 12,000 daltons [13]. Experimental application of EP induces a febrile response which is, in many respects, similar to that produced, for example, by endotoxin or LPS. The detailed analysis of endogenous, pyrogenic agents has revealed their close relationship to, or identity with mediators known to be involved in the non-specific or immunological defence of bodily integrity. EP produced in response to bacterial infections, or at least a part of it, is now believed to be identical with the leucocytic endogenous mediator (LEM) and the lymphocyte activating factor (LAF) and its preferred genetic name is now interleukin 1 (IL1). Pyrogenic actions have also been demonstrated for interferon (IFN) and tumor necrosis factor (TNF).

1. *Interleukin 1.* When endotoxin acts on immune active phagocytes, such as macrophages, IL1 will be produced as an endogenous pyrogen. While EP produced *in vitro* was frequently reported to produce fever with shorter latency and duration in comparison to exogenous pyrogen, this does not seem to be a consistent difference. Fever induced in rabbits by i.v. injection of recombinant human IL1 showed two peaks, with the first occurring 1.5–2 h and the second peak 2–4 h after IL1 administration [22]. IL1 has been shown to stimulate the formation of prostaglandin E (PGE) in the course of its action on the hypothalamic thermoregulatory center [48].

According to the recent analysis of the molecular properties of IL1, it represents a family of polypeptides which can be separated into two subgroups, IL1 α and IL1 β [33]. IL1 β acts on fibroblasts and produces interferon β (IFN β), and exerts antiviral activity of these cells [52]. However, there is no evidence that fever induced by IL1 β is mediated by IFN β . The time courses of fevers induced by IL1 β and IFN are different, i.e., the IL1 β fever is fast, while the IFN fever is slow [52]. When comparing the pyrogenic actions of IL1 α and IL1 β in rabbits, we found that fever produced by IL1 β was more intense in comparison to the fever produced by IL1 α . However, there were no differences in the time course of fever induced by IL1 α and IL1 β (Hashimoto and Iriki, unpublished data).

2. *Interferon*. IFN is represented by highly specific types of protein, or substances with protein as the main constituent, with antiviral activity as their most significant property. IFN can be produced by normal diplocytes, lymphoblasts and normal (sensitized) lymphocytes, when stimulated, e.g. by viruses. Besides its antiviral activity IFN has manifold effects, including antitumor activity, augmentation of differentiated cell functions, effects on immune system, effects on cell surface structures, etc.

IFN, especially IFN α , produces fever. Its pyrogenic effect was first reported as a side effect of IFN therapy by Bocci in 1980 [9]. Recombinant human IFN, free of extraneous human proteins, was shown to produce fever in nearly all recipients [44]. Following single intramuscular injections of a human IFN α , all of the volunteers had febrile reactions with influenza-like symptoms. Fever produced by IFN progresses slowly and is monophasic, the peaks of which are reported to be 2–3 h [2] or 6–8 h [44] after administrations.

Recently it was shown that IFN α produces fever by its direct action on the thermoregulatory center [15]. IFN stimulated PGE₂ release from rabbit hypothalamic tissue *in vivo*. Intracerebroventricular (icv.) injection of human IFN into the awake cat also produced fever and a rise in PGE₂ levels in the cerebrospinal fluids.

Because there is a possibility that IFN can be produced in response to infection, its contribution to fever in inflammatory diseases has to be taken into consideration. In accordance with this notion, IFN β has been ascertained to be produced after administration of endotoxin/IL1.

3. *Tumor necrosis factor*. TNF has been associated with *in vitro* and *in vivo* killing of tumor cells. Macrophages activated by endotoxin, etc., may constitute the major cellular origin of TNF, providing an important criterion for distinguishing these factors from the lymphoid cell-derived cytotoxin, lymphotoxin [4]. Human TNF has about 30% homology in its amino acid sequence with lymphotoxin. While the significance of TNF is seen in its ability to induce tumor necrosis, it is also intrinsically pyrogenic and, like IL1 and IFN, directly stimulates hypothalamic PGE₂ formation [16].

Recombinant TNF (rTNF) can be obtained by expression of its complementary DNA in *E. coli* and was shown to induce hemorrhagic necrosis of transplanted sarcomas in syngeneic mice [37]. A monophasic fever response is produced by rTNF, with a peak at about 1.5 h after administration. After administration of larger doses the fever becomes biphasic, with the second peak occurring about 3–4 h after administration [16]. Considering that TNF—different from IFN α —also acts as an endogenous inducer of IL1 formation, the first fever phase induced by TNF is ascribed to its direct action on the thermoregulatory center, whereas the second phase is produced indirectly by IL1, stimulated by TNF [16]. Using TNF antibodies to differentiate between direct and indirect effects [36], we did not see a suppression of the first phase of TNF fever, but the second phase was significantly diminished. This observation suggests effective blockade of IL1 production by the TNF antibody, but this assumption requires further experimental

support.

In summary, currently available evidence attributes the ability to act as an endogenous pyrogen (EP) not only to IL1 but also to IFN and TNF. So far, the possibility cannot be excluded that additional pyrogenic factors exist among the various humoral factors which are produced by phagocytes in response to stimulation by endotoxins or other exogenous or endogenous agents.

B. Central mediators of fever, with special consideration of prostaglandin E

EP acts on the thermoregulatory center via mediators. Various amines, peptides and/or electrolytes are known to act on the thermoregulatory center and to change the core temperature. Among these various humoral factors, PGE is currently considered to possibly be the most important central mediator of the fever response.

The reports supporting this view are summarized in the review of STITT in 1986 [49]. The important points can be summarized as follows:

1) Febrile responses to injections of PGE into the cerebral ventricles or preoptic/anterior hypothalamus: the febrile response is observed in nearly every homeothermic species (with the notable exception of the goat) and equally in cold, hot, and neutral environments (in poikilothermic vertebrates and invertebrate animals, PGE may enhance behavioral body warming).

2) The changes of discharge frequencies of thermosensitive neurons of preoptic/anterior hypothalamus following PGE administration: a tendency exists for stimulatory effects on cold responsive and inhibitory effects on warm responsive neurons; compared to the effects observed *in vivo* the results of studies on slice preparations *in vitro* seem to yield more consistent results.

3) Release of PGE during fever: *in vivo*, PGE concentration in cerebrospinal fluid increases during endotoxin fever; *in vitro*, releases of PGE from brain tissue is augmented by administration of EP. These results and others indicate enhanced PGE production in the CNS as an obligatory effect of EP.

4) Prevention of the production and release of PGE and antipyresis: aspirin and indomethacin are established antipyretics and have been shown to block the synthesis of PG's from arachidonic acids.

Despite this wealth of experimental support for PGE as one important or even the only relevant central mediator of fever, this view still faces evidence to the contrary which has been summarized by COCEANI *et al.* in 1986 [10] as follows.

1) Reported PGE₂ levels in CSF are variable and the range of concentrations measured in afebrile and febrile conditions overlap.

2) Following intravenous (i.v.) endotoxin administration, the rate of PGE₂ release in the rostral hypothalamus does not correlate with the height of fever.

3) Salicylate at an appropriate dose prevents PGE₂ elevation in the CSF but not the fever response to intravenous IL1.

4) Inhibition of protein synthesis attenuates the fever in response to systemic pyrogens without causing a concomitant fall in PGE₂ levels in the CSF.

5) Prostaglandin antagonists interfere with the hyperthermic response to intraventricular PGE₂ while leaving the pyrogenic action unaffected.

6) Animals with extensive lesions of the rostral hypothalamus develop fever to intravenous pyrogen but not to intrathecal PGE₂.

7) Newborns may respond to pyrogens but not centrally applied PGE₂.

8) Systemic pyrogens, bacterial and leucocytic, promote PGE₂ synthesis in brain despite their apparent inability to cross the blood-brain barrier.

One of the most powerful critical arguments follows from the observation that endotoxin fever cannot be suppressed completely by, and may even be produced after, the administration of cyclooxygenase inhibitors, such as aspirin or indomethacin [11]. Figure 1 schematically illustrates the metabolic pathways leading to the formation of prostaglandins from arachidonic acid derived from phospholipids. When fatty acid mobilization was inhibited by the administration of a phospholipase A₂ blocker, endotoxin fever was completely suppressed [12]. This indicates the participation of arachidonic products in endotoxin fever. If enhanced PGE synthesis should not be essential, other products, e.g. thromboxanes, would have to be considered as alternative pyrogenic mediators. However, evidence in support of this view of the problem is still controversial. Mediators different from the metabolites of polyunsaturated fatty acids are certainly involved in the molecular chain of events leading to fever at the central nervous level; at least, this follows from the suppression of fever by inhibitors of protein synthesis. The nature of these mediators and their position in the chain of events, especially whether they act in sequence with or independent of the PG's, needs to be further elucidated. Accepting additional mediators in the central mediation of the fever response is, however, not meant to exclude contributions of PGE.

Several lines of evidence suggest that PGE, while not responsible for the entire course of the fever episode, may contribute to one of its phases. In view of the

Fig. 1. Simplified diagram of enzymes and metabolites in the biosynthetic pathway of 2-series prostanoids from phospholipids [35].

biphasic course of the fever induced by LPS/EP—an early phase with a first peak 1.5 to 2 h after its onset, and a second or plateau phase with a further peak after 1.5–2 h—differences between the mechanisms responsible for the two phases would not appear improbable.

According to concentration measurements of PGE or of PG metabolites in plasma after i.v. injection of endotoxin, plasma PGE metabolites rose from an undetectable level to an average of $2 \text{ nmol} \cdot \text{l}^{-1}$ during the early phase of fever, but fell during the second phase [29]. Endotoxin administration was followed by a surge of PGE in blood from the carotid artery and jugular vein which was coincident with the pressor response during the early phase of fever but was no longer detectable in plasma samples collected throughout the second phase [46]. The changes in concentration were more significant in the samples taken from the jugular vein than in those from the carotid artery. All these results are compatible with the view that PGE may mediate the early thermal events of the fever episode but does not account for entire thermal responses to endotoxin. This view can be reconciled with the notion that PGE is not a mediator in normal thermoregulation [38, 47].

Evaluation of the threshold temperatures for activation of thermoregulatory responses of rabbits has revealed differences between the adjustments induced by icv. injections of LPS and PGE_2 [23, 28]. This comparison was based on the threshold core temperatures for ear cutaneous vasoconstriction (Thcv) and shivering (Thsh), as determined by means of internal whole body cooling at different times during the hyperthermic episodes. Core temperature was lowered by whole body cooling with an intestinal thermode before LPS or PGE_2 injection and during the second phase of fever, 1.5–2 h after LPS or PGE_2 injection. In the case of LPS injected icv., Thsh was not changed at this time while Thcv was significantly elevated in comparison to the threshold determined before LPS injection. In the case of PGE_2 icv., however, both Thsh and Thcv were increased significantly at this time. Blockade of PGE synthesis by aspirin administration did not change the relationship between Thsh and Thcv established after LPS injection during the plateau phase of fever.

Recently this observation of threshold dissociation in pyrogen-induced fever was confirmed by studies on rabbits in which the stimulus response relationships between core temperature and various thermoregulatory effectors were determined before and during the course of endotoxin fever [53]. Both Thcv and Thsh increased during the early phase of LPS fever; however, during the second phase, Thcv remained elevated whereas Thsh decreased even below its normal value, resulting in the expansion of the inter-threshold zone between heat and cold defence activation from about 0.5 to 3.0°C. The sensitivities of the responses during both the first and second phases of fever were not different from those before LPS injection.

The pattern of the regional differentiation of sympathetic efferents, especially the thermoregulatory, cutaneo-visceral antagonism of vasoconstrictor innervation, has been shown to be modified differently during fevers evoked by either LPS or PG administered icv. [43]. During the early phase of fever after both LPS and PGE icv.

injection, ear cutaneous symphthetic activity increased and simultaneously renal sympathetic activity decreased. This antagonistic response corresponded to the typical pattern of autonomic cold defence. However, during the second phase of fever after icv. PGE₂ injection, renal sympathetic activity returned to its control level, whereas this activity was significantly enhanced above the control level during the late phase of LPS fever. This observation corresponds to the notion that, while the effects of PGE and LPS are indiscernible during the early phase of fever, they deviate during the later phases and thus the importance of PG's as the essential mediator for the entire course of the febrile response is in question.

In summary, if the analysis of thermal effects of pyrogens and PG's is extended to the evaluation of stimulus response relationships, differences become apparent between the actions of these hyperthermic agents. The results are compatible with the view that stimulation of PGE formation by pyrogens may be essential for the generation of hyperthermia during the early phase of the fever episode. However, other humoral factors seem to be responsible for the later phases of elevated body temperature.

C. The site of pyrogen action

It is generally accepted that EP, after having been produced by reticuloendothelial elements in response to exogenous pyrogens, acts upon central nervous structures, presumably of the hypothalamic region, to initiate the chain of events leading to fever. As a precondition, EP carried with the blood to the cerebral circulation would have to penetrate the blood-brain barrier (BBB) to reach its targets.

It has also been demonstrated repeatedly that exogenous pyrogens, LPS for instance, when administered into the CSF or into the brain, are capable of producing fever. If the possibility of direct febrile actions of exogenous pyrogens at the central nervous level is considered unlikely, i.e., if formation of EP is obligatory

Fig. 2. Hypothetical schema for the effect of endotoxin injected in the periphery or in the brain. EP denotes endogenous pyrogen; IL1, interleukin 1; PGE, prostaglandin E; BBB, blood-brain barrier; OVLT, organum vasculosum laminae terminalis.

in the sequence of steps leading to fever, phagocytic elements capable of producing EP/IL1 must be accessible to exogenous pyrogen from the brain side of the BBB. Whether this can be accomplished by certain glial elements[19] or whether such elements incorporate exogenous pyrogen to transfer it to cerebral, perivascular reticuloendothelial elements capable of producing EP/IL1, has to be further elucidated. The latter alternative would imply the possibility of local, perivascular EP/IL1 formation in the brain in response to both centrally and systemically applied exogenous pyrogen.

According to the report of STITT and BERNHEIM[50], fevers induced with endogenous pyrogens by the icv. route have a longer latency to onset, a less steep rise in body temperature, and need a longer time to reach the peak of body temperature elevation than do fevers induced by the i.v. route. Furthermore, a dose of i.v. administered indomethacin which effectively attenuates EP fever produced by the i.v. route, is completely ineffective in suppressing EP fever induced by the icv. route. Conversely, pretreatment with indomethacin given icv. effectively reduces EP fever induced by the icv. route, but has little effect on EP fever induced by the i.v. route. These results strongly suggest that the sites of action which mediate the febrile responses to EP given i.v. and icv., must be different or, at least, exhibit large differences in their accessibility to indomethacin and EP from the blood and brain side.

The above and other experimental observations, as well as theoretical considerations, point to the BBB as a structural entity whose function is of critical importance in the mediation of fever. This follows from the nature of the main candidates for generation and mediation of fever. Exogenous pyrogens are usually large molecules—for instance, LPS is a relatively large glycoprotein—and, thus, unlikely to permeate the BBB effectively. Compounds acting as endogenous pyrogens, such as IL1, INF, and TNF are large peptides for which the BBB should be difficult to penetrate. Even for PG's, the presumptive secondary messengers, the BBB should be a significant barrier at low concentration gradients, considering that these polyhydroxy compounds are less lipophilic than their long chain fatty acid precursors.

Recent experiments have drawn particular attention to the circumventricular organs (CVO's) which are usually described as lacking a BBB [49]. The capillaries of these brain structures, while anatomically "outside" the BBB, are endowed with a fenestrated endothelial layer which differs from the "tight" endothelium that is otherwise typical for brain capillaries. The parenchyma of CVO's and their interstitial compartment respectively, are continuous with the adjacent brain tissue; hence, the CVO's establish circumscribed interfaces which permit even large molecules to diffuse into the brain. On the other hand, the ependymal surfaces of the CVO's are "tight," quite in contrast to the usual ventricular ependyma, and direct transfer from the blood to the CSF is thereby prevented.

Due to its location the organum vasculosum laminae terminalis (OVLT) is an obvious candidate to serve as the main route for systemic mediators of fever to

reach the thermoregulatory centers at the hypothalamic level. The OVLT is located within the rostral wall of the third ventricle, immediately dorsal to the optic chiasma above the supraoptic recess and, thus, in close connection on either side with the median septal and preoptic area [48]. Studies aiming at the elucidation of OVLT function in the mediation of fever have shown that fever induced by i.v. injection of EP was markedly enhanced after OVLT lesions. This may be due to a facilitated passage of EP through the lesion into the brain, or even directly into the CSF, or to an augmented sensitivity or density of pyrogen receptor sites within the OVLT [48]. Furthermore, the lesions within the anteroventral portion of the third ventricle, adjacent to the OVLT, which are usually accessible only via the circumscribed, fenestrated capillary sections of this CVO, resulted in the suppression of fever produced by systemically applied endotoxin[7].

Recently, STITT [49] postulated that a reticuloendothelial cell type, possibly located within the confinements of the OVLT, could be the source of PGE that mediates the febrile response to EP. EP enters the perivascular spaces of the OVLT from the circulation through the fenestrated capillary walls and stimulates these cells of mesenchymal origin to produce PGE. The PGE produced within the OVLT is thought either to diffuse into the adjacent preoptic/anterior hypothalamic (POAH) region to cause fever, or to act upon neurons within the OVLT as the organ involved in the mediation of fever in response to endotoxin acting from both inside and outside the BBB.

Our own studies concerning the significance of the blood-brain interface for the generation of fever by EP proceeded from the comparative analysis of icv. and i.v. applications of EP and antipyretics. Fever induced by icv. administered IL1 α was significantly suppressed by pretreatment with indomethacin given either icv. or systemically. The same pretreatment with indomethacin, however, did not completely suppress fever induced by i.v. application of IL1 α . Studies with IL1 β produced similar results, except that the febrile responses to this EP were more strongly expressed (unpublished observations). Taken together, these data suggest a greater effectiveness of target sites outside, as compared to inside, the BBB in mediating the febrile response to IL1. Since the BBB is rather permeable to indomethacin and other antipyretics, no safe conclusions can be drawn from the more efficient antipyresis exerted by both icv. and systemically applied indomethacin upon fever stimulated by icv. application of IL1.

In summary, the OVLT has emerged as a site whose function as an interface between the systemic circulation and the brain may be paradigmatic for the mediation of fever. Current hypotheses consider the passage of EP directly into the brain through this interface and even its formation in local reticuloendothelial elements. PGE formation in elements of the OVLT is considered as providing the local messenger to the brain, and would explain the differences in action observed with regard to fever generation and antipyresis, respectively, of pyrogens and antipyretic drugs administered inside and outside of the BBB. However, this explanation has to consider that the role of PGE as the essential mediator of fever is

not yet definitely established.

II. FEVER SYNDROME—HOST-DEFENCE RESPONSE INVOLVING FEVER

IL1 has emerged as a key substance linking the hyperthermic response with the multitude of systemic humoral changes which characterize fever as a complex host-defence response. Figure 3 summarizes the responses evoked by IL1. The identity of EP with a number of mediators in cellular and immunological adjustments which was revealed only recently, has provided the basis for an analytical approach to the ancient problem of the benefits vs. the drawbacks of the febrile response. This question is most appropriately assessed by considering fever as a concerted response, with hyperthermia as only one aspect, and by analyzing the relevance of the single response components, as well as the interactions between certain responses, with regard to the goal of an effective host defence. The choice of the title of this chapter, "fever syndrome," derives from this consideration.

A. Response components of the fever syndrome

The fever syndrome is defined as the set of concerted responses evoked by the actions of EP on a multitude of central and systemic target sites. The fever syndrome produced by exogenous pyrogens, for instance, endotoxins, is held to be elicited indirectly by enhancing EP formation and release and, thus, should produce the same syndrome, apart from those effects of the primary agent which characterize it as detrimental or as a "toxin." The congruent aspects of the fever syndrome in endotoxin and EP fever are summarized in Fig. 4.

Fig. 3. The multiple biologic activities of interleukin 1 (IL1). AG denotes antigen; AB, antibody; and IL2, interleukin 2 [14].

Fig. 4. Manifold responses evoked by endotoxins/EP.

1. *Neurohormonal responses.* Arginine vasopressin (AVP) release is generally enhanced during febrile response; its release as a central mediator (perhaps in the lateral septal area of the brain) is assumed to correspond to its intrinsic function as an endogenous antipyretic limiting the height of fever [14].

Also endogenous central melanocyte-stimulating hormone (MSH), the 1–13 amino acids fragment of ACTH, is assumed to contribute to the physiological limitation of the rise in body temperature during fever [45]. The concentration of MSH within the septal area of the brain increases during fever [25]. Further, MSH injected into the septal area acts as an antipyretic. ACTH (the 1–24 amino acids sequence) has, as does its fragment MSH (the 1–13 amino acids sequence), antipyretic effects and is considered to act also as an endogenous antipyretic [31].

During fever, release of endorphin at the hypothalamic level has been observed. Its intracerebral microinjection into the preoptic/anterior hypothalamic region was shown to cause a prolonged elevation of body temperature [19]. However, evidence against the involvement of endorphin in the generation of fever has also been reported. For example, naloxone does not prevent the febrile response to endotoxin and IL1, suggesting that the induction of fever is not modulated through naloxone-reversible opioid receptors [24].

Corticotropin-releasing hormone (CRH) injected icv. has been shown to act as an antipyretic. CRH is a potent stimulator of the release of ACTH, MSH, and endorphin from the anterior and intermediate lobes of the pituitary; thus its action might be a primary one, as well as secondary to its stimulatory effects on hormone release.

Thyrotropin releasing hormone (TRH) seems to be consistently released within the CNS and to modulate thermoregulatory effector systems in “cold defence” conditions [39, 42]. Stimulation of its release during fever has been concluded from the changes in systemic thyroid hormone levels [42].

2. *Acute phase reaction.* In the “Glossary of terms for thermal physiology” (second edition) [1], acute phase reaction is defined as follows: “Typically the multifactorial humoral response of a multicellular organism (host) to bacterial

infection. In homeotherms this reaction comprises changes in the plasma concentrations of trace metals and fibrinogen and the appearance in the blood plasma of various peptides; several have been identified as mediators which alter the functions of the leucocytic and lymphatic systems (leucocytic endogenous mediators (LEM), lymphocyte activating factor (LAF), etc.) and act as endogenous pyrogen. The acute phase reaction is considered as an early host-defence response to infection." The preferred name of LEM and LAF is now IL1.

The acute phase reaction includes changes in the plasma levels of certain trace metals and glycoproteins (acute phase glycoprotein reaction), which are induced by the effect of endotoxin/EP/IL1 on the liver[33]. For example, the plasma concentrations of iron and zinc decrease substantially, while those of copper (hence, of ceruloplasmin, to which it is bounded) and protein-bound N-acetylneuraminic acid (NANA, the terminal residue of most glycoproteins) increase. Further, endotoxin/EP/IL1 stimulates hepatic synthesis of various acute phase proteins such as C-reactive protein, fibrinogen, ceruloplasmin, serum amyloid, and others[14]. All components of the acute phase reaction are assumed to contribute to host defence; at least for the drop of plasma iron, especially in combination with elevated temperature, an inhibitory effect on the growth of certain pathogenic organisms has been demonstrated.

3. *Immune responses.* One of the actions of IL1, after having been produced by macrophages under the influence of exogenous pyrogens, is the stimulation of IL2 production in certain lymphocytic T cells. This action has formerly been ascribed to a lymphocyte activating factor (LAF) whose identity or close relationship with IL1 was discovered only later. IL2, in turn, acts upon certain responsive T cells to promote T cell proliferation and a series of other immune responses[17].

4. *Behavioral responses.* Behavior can be altered during fever. For example, the sleep pattern is influenced by fever[54]. IL1 was shown to induce increased slow wave sleep (SWS) and inhibit rapid-eye-movement (REM) sleep[54]. TNF also is an endogenous somnogen[5]. Anorexia, depression, inactivity, and other behavioral responses can be observed during fever[21]. These changes could be part of a highly organized adaptive strategy which is, however, currently not yet understood.

5. *Others.* Alterations of bodily functions during fever which derive from effects of endotoxin/EP/IL1 are far from being completely recognized and elucidated. For instance, PG's is synthesized in synovial cells, and collagenase is synthesized in synovial cells and fibroblasts[26]. These responses can be related to local inflammatory responses which are induced by mononuclear cell factor (MCF). The elevation of circulating PG's and enhanced renal excretion of PG metabolites, especially during the early phase of fever, might further bear some relationship with altered organ functions during fever, e.g., the sequence of antidiuresis and diuresis observed in goats during endotoxin fever[30] or the dissociation of renal blood flow and local sympathetic activity[41].

In summary, the question of whether the fever syndrome is advantageous or disadvantageous for the infected host involves very controversial judgements. The

progress in knowledge, especially with regard to the non-thermal components of the fever syndrome, indicates activation of cellular and immunological defence as consistent effects of endogenous pyrogen which were formerly ascribed to separate humoral principles. Some aspects of the acute phase response, such as the drop in plasma iron, are also considered as potentially inhibitory for microbial intruders. Most difficult to decide is the question about the significance of the hyperthermic component of the fever syndrome. With respect to cellular and immunological defence, a higher temperature appears to stimulate nonspecific leucocytic activities, while lymphocytic, natural killer activity is decreased. On the other hand, more specific cytotoxic activity of some T cells and antibody formation may become enhanced at elevated temperatures.

B. The regulation of fever syndrome

As summarized above, endotoxin/EP/IL1 induces a series of host-defence responses including fever. It is important to analyze how these responses are regulated to form an integrative defence response of the host as a whole.

Fever is induced by the stimulation of endotoxin/EP acting via mediator (PGE) on the thermoregulatory center in the preoptic/anterior hypothalamic region. This effect is generally described as a change in the set-point of temperature regulation and, as such, implies the more or less undisturbed function of the biological thermostat in controlling body temperature, although at an elevated level. The control of other responses which are induced concomitantly with the hyperthermic response, is less obvious.

For example, when considering anorexia as a side effect of fever after endotoxin administration, food intake was found to remain suppressed after alleviation of fever by means of antipyretics and, thus, indicates a dissociation of the chain of events leading to each of these effects [34]. Behavioral responses induced by endotoxin such as anorexia, depression, and inactivity, were found to be linked with the onset of the acute phase reaction, rather than with the course of febrile hyperthermia [20].

The regulatory mechanisms controlling the acute phase reaction and fever are different, because both responses can occur separately [6, 32]. The decrease of plasma Fe and Zn evoked by EP can be observed even after suppression of fever by administration of PG blockers, such as sodium salicylate or indomethacin, indicating that PG's are probably not involved in this decrease [51]. This corresponds to the observation that a decrease of the plasma Fe and Zn could be induced by intraperitoneal injection of EP but not by intrapreoptic (iPO.) injection. While fever is obviously mediated by structures in the preoptic area, the decrease of plasma Fe and Zn are direct peripheral effects of EP [8].

Because the plasma levels of Cu or NANA were found to be elevated by iPO. injected IL1, this response is thought to be mediated also by the preoptic region [8]; however, PG's do not seem to be involved. This follows from the observation that hyperthermia induced by iPO. injections of PGE₂ was not accompanied by changes

in the plasma levels of Cu or NANA [34]. Selective thermal stimulation of the hypothalamus also did not evoke the acute phase reactions [27].

While PG's do not seem to be systematically involved in the generation of the acute phase response, in contrast to the fever response in the strict sense of the word, these mediators are nevertheless involved in the variety of humoral events associated in a less consistent fashion with the fever syndrome. For example, in association with the fever syndrome, nociception at a site of bacterial inflammation will depend on the formation of PG's [18]. The breakdown of muscle proteins due to PGE is supposed to be one of the causes of myalgia during various infectious diseases [3]. As mentioned before, PG's produced systemically during a fever episode may be responsible for the modulation of the effects exerted by the sympathetic outflow upon some vascular beds. Circumstantial evidence further points to PG's as mediators responsible for the temporary suppression of the thermoregulatory drive for panting observed in rabbits during the late phase of fever [40].

SUMMARY

Research into the complex humoral and neurophysiological events of pyrogen-induced fever has proceeded rapidly to establish the thermal and non-thermal components of the fever syndrome. The major breakthroughs derive from the elucidation of the identity of the endogenous pyrogen interleukin 1 with the humoral factors responsible for the acute phase reaction and for the activation of lymphocytic, cellular, and immunological defence as host responses to infections. As a consequence, fever research is no longer concerned primarily with the changes in temperature regulation responsible for the febrile alteration of temperature regulation, but aims at the elucidation of the contributions that are made by both the thermal and non-thermal components of the fever syndrome to the defence of the host against the microbial intruder responsible for this syndrome.

In order to account for this development in these introductory remarks to the current issues of fever research, this review has tried to pay particular attention to the following points:

- 1) The role of humoral factors in the generation of febrile hyperthermia, including endogenous pyrogens as well as mediators acting on the thermoregulatory center.
- 2) The "fever syndrome" with special consideration of its regulation and of the significance of its components from the viewpoint of fever as a host-defence reaction.
- 3) The assessment of the role of PG's in the generation of the fever syndrome, both as putative central mediators and as systemically released agents, with special consideration of the inhibitory action of the established antipyretic drugs on PG synthesis.

Key words: fever, fever syndrome, endogenous pyrogen, interleukin 1, prostaglandin E.

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