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Prostaglandin E as the Neural Mediator of the Febrile Response

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The evidence favoring a role for prostaglandin E (PGE) as the neural mediator of the febrile response is reviewed and considered under five different essential criteria which would need to be satisfied, if such a role is to be accepted. These criteria are: *(1)* the ability of intracerebrally microinjected exogenous PGE to cause fever; *(2)* the detection of increased levels of endogenous PGE in the brain during the normal production of fever; *(3)* the ability of substances that inhibit the production and release of PGE to block normal fevers; *(4)* the ability of substances that are specific PGE antagonists to inhibit normal fevers; and *(5)* the identification of a specific site and cell type for the release of PGE in response to the action of pyrogens. Evidence from the literature that supports these criteria is reviewed and presented in this format, and the conclusion is drawn that the evidence available is more than sufficient to support the initial hypothesis.

Before reviewing the evidence favoring a role for PGE as the neural mediator in the febrile response, I believe it is important to define specifically what is meant by the febrile response. This is important, because I believe that much of the conflicting data that have confused this issue in the recent literature stems from inappropriate comparisons of different fever models. By this statement, I mean that the debate should be confined to the role that PGE may or may not play in the normal pathogenesis of fever. The normal pathogenesis of fever is defined as the progression of steps that occur between the infection of the host by a foreign pathogen and the manifestation of the febrile sign of hyperthermia [1,2]. A current, widely accepted hypothesis of these events is illustrated in Fig. 1.

It is now generally acknowledged that the first step in the pathogenesis of fever is the interaction of a variety of pathogens with bone marrow-derived mononuclear cells, such as blood monocytes, and fixed tissue macrophages, such as the Kupffer cells in the liver [3]. That interaction results in the elaboration and release of an endogenous pyrogen (EP) into the circulation. This monokine, whose major active component is believed to be the polypeptide interleukin-1 (IL-1), reaches the brain via the cerebral circulation, where it acts at or near the preoptic anterior hypothalamic (PO/AH) neuropile to produce changes in the thermoregulatory pathways that result in fever. Thus, for the purposes of this debate, I am defining the stimulus as *circulating* endogenous pyrogen (produced experimentally by intravenous injection) and the febrile response as the short-latency, monophasic increase in body temperature that reaches its peak at 50–60 minutes after the injection of EP, and which gradually declines thereafter. I believe that the use of the strict, almost oxymoronic, term of a "normal pathogenesis" of the febrile response is important at the outset, because there are other ways in which fever can be produced experimentally; these are artificial and

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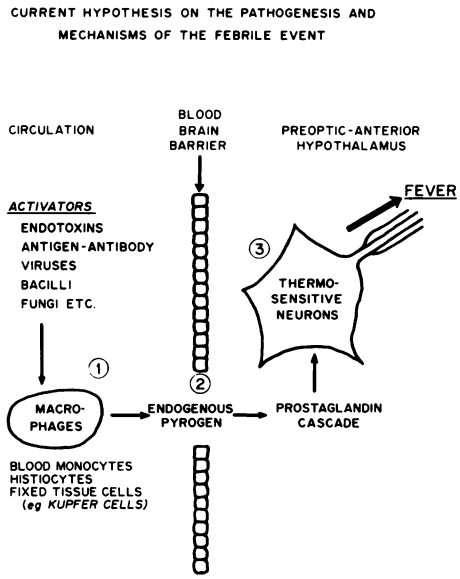


FIG. 1. A current hypothesis on the pathogenesis and mechanisms of the febrile event. A variety of pathogens (activators) stimulate bone marrow-derived cells to elaborate and release EP into the circulation (1). This polypeptide travels via the cerebral circulation to the blood-brain barrier, where it is believed to somehow enter the PO/AH neuropile (2). The EP is then thought to stimulate the production of prostaglandin from an unknown cell type. The prostaglandins are then thought to alter the thermosensitivity of temperature-sensitive neurons in the PO/AH area in such a manner as to cause fever (3).

are unrelated to the normal progression of disease-initiated fevers. One such method that is commonly employed is the intracerebroventricular (ICV) injection of EP. The fever that results from using this technique is fundamentally different from that produced by intravenously injected EP in a number of ways [4], as is illustrated in Fig. 2. It can be seen that the latency of onset for the febrile response in the rabbit after ICV injection of EP is almost twice that which results from the intravenous injection (IV) of EP. Furthermore, the rate of rise of body temperature is much slower and the duration of the febrile response is greatly extended when the intracerebral route of EP

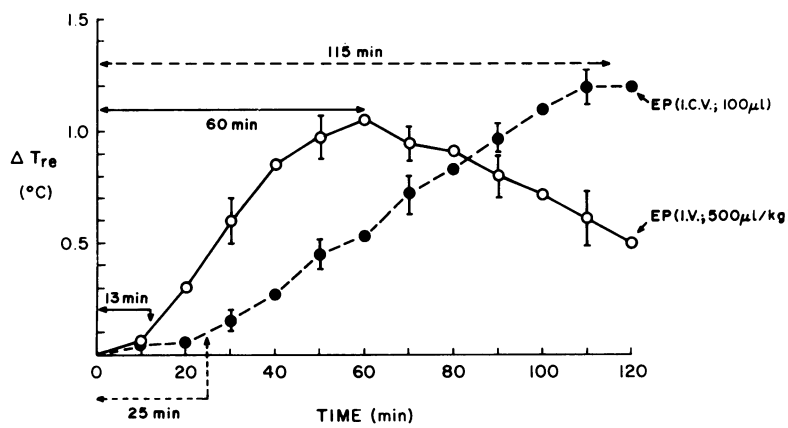


FIG. 2. A comparison of fevers produced by intravenous and intracerebroventricular administration of EP into a group of six rabbits. Three distinct differences are apparent. The latency to the onset of fever is much shorter (13 minutes) after IV injection than after ICV injection (25 minutes). The rate of rise of T_{re} (fever intensity) after IV injection is greater (0.022° C/minute) than in response to ICV injection (0.014° C/minute). The time taken to reach peak rise in T_{re} after IV injection (60 minutes) is about half that taken after ICV injection (115 minutes).

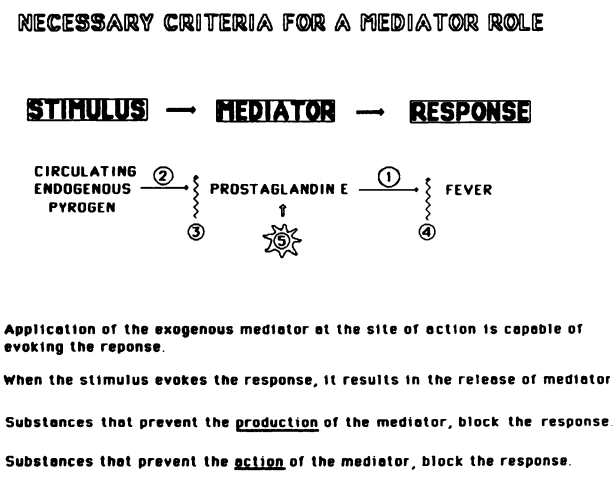


FIG. 3. A set of five criteria that would need to be satisfied, before the proposition that PGE is the neural mediator of the febrile response could be accepted by an objective observer. Each criterion is based on a step in the pathway from the arrival of the circulating EP stimulus at the putative site of action, to the release and action of the putative mediator in producing the febrile response.

administration is used. These differences in the latency of fever onset and its duration are commonly observed by other investigators and in other species of mammal [5,6]. Finally, there is absolutely no evidence that, in normal fevers, EP ever enters the cerebral ventricles of the brain [7]. For these reasons, there seems no compelling reason to believe that this type of fever is produced by the same biochemical steps that occur when fever is elicited intravenously. I believe that this distinction is an important one, because I think that much of the conflicting data appearing in the recent literature that have confused the issue of the role of PGE in fever stems from inappropriate comparisons made between these two different types of febrile responses [5].

In order to provide a framework around which to build the evidence for the role of PGE as the neural mediator of the febrile response, I have proposed a set of criteria that would need to be satisfied before such a proposition could be acceptable to an objective observer. They are illustrated in Fig. 3.

I intend to concentrate primarily upon those criteria which are related to the fever-producing actions of PGE and to the production of PGE within the brain in response to the intravenous injection of EP. My colleague Dr. Bernheim will concentrate on the biochemistry of the release of PGE in response to the EP stimulus [8].

FEBRILE RESPONSES TO INTRACEREBRAL INJECTIONS OF EXOGENOUS PGE

Clearly, there is little disagreement in the literature that intracerebral injection of PGE produces fever [9,10]. While some might still hedge at the term "PGE fever," preferring to call it "PGE hyperthermia," I believe that the important criteria for fever are met by PGE, and it can be regarded as a true pyrogen [11]. Nearly every homeothermic species that has been injected with PGE intracerebrally exhibits a febrile response, as well as several other vertebrate and invertebrate classes [9,10]. The first report that implicated PGE in a fever-producing role was that of Sabine Wendlandt and Tony Milton in 1970 [12]. They showed that when PGE was injected into the lateral cerebral ventricle of cats, it caused prompt and large increases in rectal temperature. While they initially postulated a role for PGE in the normal regulation of

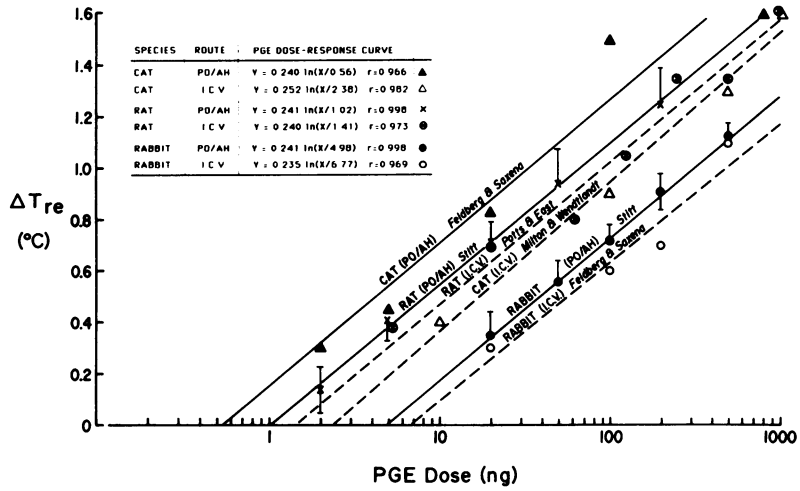


FIG. 4. A compilation of the available PGE dose-response curves of three species of mammals, the cat, the rabbit, and the rat, to both ICV and PO/AH microinjection of at least four different doses of PGE. The data are plotted semilogarithmically, and the equations of these curves have been determined by the method of least squares. Note the similarity of the slopes in all six curves.

body temperature, it soon became obvious that a more likely role for PGE was that of producing fever [13]. Shortly thereafter, Feldberg and Saxena [14] reported that injections of PGE directly into the tissue of the PO/AH region produced fever in cats, and they also showed that injections into the tissue of the posterior region of the hypothalamus were without effect on body temperature. These observations seemed to replicate the earlier findings of Cooper et al. [15] and of Jackson [16], using endogenous pyrogen, and reinforced the idea that the PO/AH was the site at which pyrogens acted to produce fever. In 1973, our laboratory [11] reported the first direct evidence that PGE acts as a pyrogen, rather than as a nonspecific hyperthermic agent, and we also produced a systematic fever dose-response curve for the intrahypothalamic injection of PGE in rabbits. A recent survey of the literature has yielded only six reports in which the febrile responses of one or more animals have been tested by at least four different dose levels of PGE, either by the intracerebroventricular or the intrahypothalamic route [11,14,17,18,19]. These reports also encompass three different species, the cat, the rabbit, and the rat, and for each species the febrile responses to body ICV and PO/AH injections of PGE were compared. These data are compiled in Fig. 4. The first striking feature about these data is the similarity in the slopes of all six dose-response curves. While there is a tenfold difference in the dose-response thresholds, the dose-response sensitivities vary by less than 8 percent. This fact is quite remarkable considering the varied sources of the data, and it suggests that a similar fever-producing mechanism is being activated in all three species of animals. More puzzling, however, is the fact that there is little or no difference between the fever dose-response curves obtained by ICV and by PO/AH injection of PGE in each species. In both the cases of the rat and the rabbit, there are no significant differences between either the thresholds or the slopes of the dose-response curves produced by the two different routes of PGE administration. If the site of action of PGE were to reside within the tissue of the PO/AH region, then one would expect that this route of

injection should have a much higher sensitivity to PGE than the intracerebroventricular route, because the dilution occurring when PGE is injected into the cerebrospinal fluid (CSF) of the lateral cerebral ventricle would reduce the final concentration of the PGE by the time it diffused into the tissues of the PO/AH region. Such a dilution would then be reflected in a difference between the two fever dose-response curves. This is not the case, and it calls into doubt the premise that the site of action of PGE resides within the PO/AH tissue. Furthermore, as long ago as 1973, we had made the observation that double bilateral injections of PGE into the PO/AH region were no more potent in producing fever in rabbits than single unilateral injection [11]. This, too, seems incompatible with the idea that the specific site of action of PGE is the PO/AH region. Thus, at this time I have serious reservations that the PO/AH is the actual site of action of PGE in producing fever; this will be discussed later, when the source of the release of PGE in response to endogenous pyrogen stimulation is considered.

However, on the basis of the data that has been presented here, I submit that there is clear support for the fulfillment of the first criterion for a mediator role for PGE in fever.

RELEASE OF PGE DURING THE FEBRILE RESPONSE

The second criterion requires that PGE must be shown to be released when fever is produced by normal pyrogenic stimuli. There have been several such demonstrations over the past dozen years, both in response to endotoxin and endogenous pyrogens, administered by both the intravenous and the intracerebroventricular routes [20,21,22,23,24]. In every case the presence or absence of PGE in CSF was used as an index of PGE release in response to fever production.

The first studies of this nature were reported by Feldberg and Gupta [20] before immunoassay techniques for prostaglandins were widely available, and the presence of PGE in CSF, withdrawn from the cisterna magna of the cat, was demonstrated using a rat stomach strip bioassay that was sensitive to PGE. Two important observations were made using this technique. It was shown that the PGE-like activity in the CSF more than doubled when animals were made febrile by an intravenous injection of shigella endotoxin and, just as important, that this level of PGE-like activity in CSF was decreased after antipyresis had been brought about by intravenous paracetamol treatment.

While these data fulfilled, in some respects, the requirements of the second criterion, they were however challenged on several grounds. It was pointed out that the bioassay used was not specific for PGE and that the experiments in no way demonstrated any causality between the presence of PGE in the CSF and the production of fever. Indeed, Cranston et al. [22] reported a series of experiments in rabbits where they showed that treatment with the weak antipyretic, sodium salicylate, could suppress the appearance of PGE activity in the CSF, while the animals still exhibited febrile responses. Some of these objections were resolved by more specific immunoassay techniques for identifying and quantifying PGE in a series of reports from several different laboratories such as our own [23] and that of Dinarello and Coceani [24]. Furthermore, since the CSF samples used in both Feldberg's and Cranston's studies were withdrawn from the cisterna magna, a site distant from the hypothalamus, it is doubtful that Cranston's ability to depress PGE levels in these CSF samples using weak antipyretics [22] compromises the theory to any significant extent. In 1980, our laboratory reported a

series of experiments in which the PGE content of third ventricular CSF was measured under a variety of conditions that induced hyperthermia and thermogenesis in rabbits, and it was shown that the only condition where PGE content rose significantly was during fever produced by the intravenous injections of endogenous pyrogen [23]. These studies indicated that the increase in PGE concentrations in the CSF were not the nonspecific result of hyperthermia per se, but were only associated with the febrile response. Furthermore, the criticism that these experiments demonstrate no causality in the relation between PGE and fever must also be rejected purely on logical grounds, since the fulfillment of the first criterion (see the previous section) dictates that the mere presence of PGE in CSF must be regarded as a cause of fever. At best, critics can only protest that PGE may not be the *sole* cause of fever.

In summary, I would submit that the second criterion for the role of PGE as a mediator in the febrile response has been completely fulfilled.

PREVENTION OF THE PRODUCTION AND RELEASE OF PGE AND ANTIPYRESIS

It has long been known that aspirin-like drugs, along with a number of other drugs such as the steroidal anti-inflammatories, have the capacity to inhibit the febrile response. It was not until the detailed biochemistry of the prostinoid compounds was investigated by Vane and his colleagues [13], however, that the relationship between these antipyretic drugs and the enzymes that produce the prostaglandins became apparent. The details of the biochemistry of prostanoids will not be reviewed here, since they are discussed in Dr. Bernheim's presentation [8]. It should be noted, however, that in at least two places in the prostaglandin production pathway two different types of antipyretic compounds, aspirin-like drugs and the steroidal anti-inflammatories, have been shown to inhibit the function of specific enzymatic steps that are essential in the production of PGE [8]. Furthermore, we have recently demonstrated that calcium channel antagonists such as verapamil and nifedipene have the capacity to inhibit the febrile response of both rats and rabbits to endogenous pyrogen [25]. We believe that this inhibition is related to the ability of these substances to block one of the early steps in the PGE production pathway, since they do not inhibit the action of exogenous PGE. Specifically, we believe that the calcium channel antagonists act as antipyretics by blocking the EP receptor mechanism on the EP "target cell" that is thought to release PGE in response to EP stimulation. Their most likely mechanism of action is the prevention of the early rise in the intracellular level of unbound calcium that is necessary for the activation of the enzyme phospholipase A_2 [26]. The action of this enzyme is the first step in the production of arachidonic acid from the phospholipids which are the precursors of all the prostinoid compounds. A diagram, showing three probable sites of action of inhibitors of the production and release of PGE, appears as Fig. 5.

In summary, there is overwhelming evidence that many substances which specifically inhibit the production of PGE also inhibit the normal febrile response, and therefore the third criterion for the role of PGE as a mediator in the febrile response appears adequately fulfilled.

THE ACTION OF PROSTAGLANDIN ANTAGONISTS AND FEVER INHIBITION

Perhaps the most perplexing aspect of the debate about the role of PGE in the pathogenesis of fever are the reports by Cranston et al. [5,27] and by Mitchell et al.

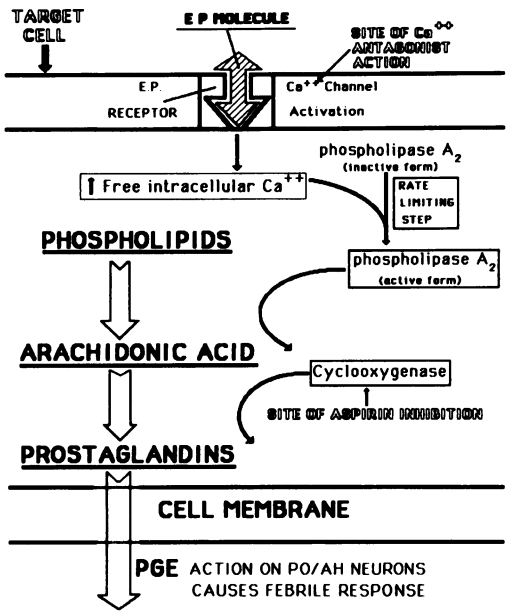


FIG. 5. A diagram illustrating the events occurring when EP stimulates the putative target cell that is thought to release PGE and the steps at which three different substances that inhibit fever are believed to act to prevent the production of PGE. The EP molecule attaches to the cell EP receptor site, activating the calcium channel, which causes unbound intracellular [Ca^{++}] to rise inside the cell. Ca^{++} channel antagonists such as verapamil and nifedipene block this step, thereby preventing the activation of the enzyme phospholipase A_2, which converts phospholipids into arachidonic acid. The steroidal anti-inflammatory drugs are also thought to block the action of phospholipase A_2 by impairing calmodulin activity. Finally, aspirin-like drugs are thought to block the activity of the enzyme cyclooxygenase which converts arachidonic acid to prostaglandins.

[26] on the inability of PGE antagonists to block fever. These reports have claimed that while the supposedly specific PGE antagonists SC 19220 and HR 546, administered intracerebroventricularly, are effective in blocking the fever-producing effects of PGE, they are unable to prevent the fevers produced by intracerebroventricular injections of either endogenous pyrogen or the PGE precursor, sodium arachidonate. This has been cited as evidence to repudiate the idea that PGE is a mediator of fever, and, on the face of it, the evidence can not be dismissed lightly. These results should be viewed sceptically, however, because of the manner in which the EP fevers were produced. As was stated earlier, at the outset of this paper, in any discussion of the pathogenesis of fever production, it is important to distinguish the method by which fever is being produced. During fever, EP normally reaches the brain via the cerebral circulation. There is no reason to believe that EP enters the cerebrospinal fluid from the circulation, and indeed there is absolutely no evidence that EP ever enters the brain during the production of fever [7]. Figure 6 shows a comparison of the febrile responses produced by PGE (ICV), EP (IV), and EP (ICV) taken from the work of Cranston et al. [22,5].

It can be seen that the dynamics of the febrile response to intravenously injected EP approximate more closely those of an intracerebroventricular injection of PGE, rather than those of an intracerebroventricular injection of EP. I believe that this fact demonstrates that the action of EP on the target cell that is thought to release PGE must occur at a site that is diffusionally closer to the circulation than to the brain neuropile. It is likely that those more slowly developing, longer-lasting fevers that result from injection of EP into the cerebral ventricles are due to a direct, nonspecific action of EP on the neural tissue, rather than on the target cell that releases PGE [28]. Indeed, it may well be that this intracerebroventricular action of EP is *not* mediated by PGE. However, the mere fact that PGE antagonists, introduced into the cerebral ventricles, do not block fevers produced by the intracerebroventricular injection of EP, cannot be used to repudiate the hypothesis that PGE is the mediator of the normal

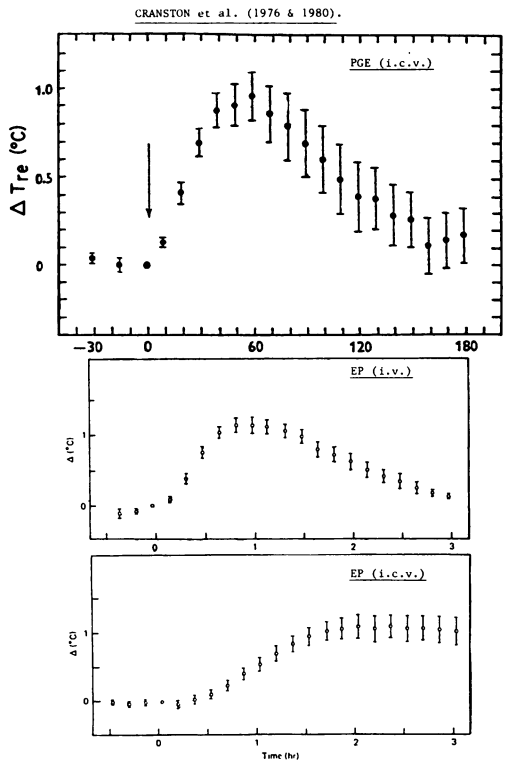


FIG. 6. A comparison of the dynamics of the febrile responses induced in the rabbit by the intracerebroventricular injection of PGE (*upper panel*), the intravenous injection of EP (*middle panel*), and the intracerebroventricular injection of EP (*lower panel*). It can be seen that the dynamics of the upper two panels are identical and are very different from that of the lower panel. Data taken and plotted in a modified form from Cranston et al. [5,27].

febrile response, since, under normal circumstances, EP reaches the brain via the cerebral circulation rather than through the cerebral ventricles. For these reasons, I would submit that the criterion regarding the action of prostaglandin antagonists on fever production has neither been proved nor disproved, at least to my satisfaction, although others may disagree.

THE SITE AND CELL TYPE RESPONSIBLE FOR THE RELEASE OF PGE IN FEVER

Current thinking on the pathogenesis of fever seems to favor the idea that EP, which is carried to the brain in the cerebral circulation, crosses the blood-brain barrier to enter the neuropile. There, it is believed to induce the production of PGE, which, in turn, acts upon thermosensitive neurons in the PO/AH region to induce fever (see Fig. 1). Therefore, one would expect that the site and cell type responsible for the release of PGE would be located within the neuropile of the PO/AH region of the brain. Indeed, there are several studies reported in which minced whole brain tissue [28] or cultured brain astrocytes [29] have been shown to respond to *in vitro* incubation with EP by releasing PGE. Glial cells have also been suggested as possible sites of PGE release. Caution is warranted when interpreting these results, however, since there is increasing evidence that many cell types will release PGE in response to EP or IL-1 incubation *in vitro*. In truth, when one is attempting to identify the source of PGE in response to EP stimulation, there seems to be no paucity of cell types from which to choose [2,8,28,29,30]. The real problem is identifying the *correct* source among *many* diverse possibilities. Dr. Bernheim's paper reviews in some detail the PGE-releasing responses

of several different cell types to stimulation by EP and IL-1 [8]. However, it should be noted that several mesenchymally derived cells possess this property in response to EP and/or IL-1 stimulation.

Furthermore, for the reasons stated earlier, I believe that the site of action of EP in causing the release of PGE is closer to the circulation side of the blood-brain barrier than it is to the brain neuropile. I base this opinion on the fact that fevers that result from the intravenous injection of EP are faster in developing and shorter in duration than those that result from either the intrahypothalamic or intracerebroventricular injection of EP [4]. As was pointed out earlier, there is no evidence to support the idea that EP even crosses the blood-brain barrier to reach the neuropile [7]. Clearly, the site of PGE release must be somewhere at or near the brain neuropile, but, given the facts that the EP molecule is a large polypeptide of >15,000 daltons and that the cerebral vasculature is predominantly composed of capillaries with tight-junctioned, non-fenestrated endothelial cells [7], entry of EP into the brain neuropile is doubtful.

I would prefer to approach the discussion of this problem in a slightly unorthodox manner. Some time ago, we investigated the possibility that EP reached the blood-brain interface via the peculiar vasculature of the circumventricular organs. These organs are close to the brain parenchyma, outside the blood-brain barrier, and accessible to larger protein molecules that cannot cross the blood-brain barrier. We were particularly interested in the organum vasculosum lamina terminalis (OVLT), which resides in the rostral wall of the third ventricle (lamina terminalis), adjacent to the PO/AH region [31], and we obtained evidence that this region was, indeed, involved in the mediation of the febrile response. In particular, we found that small lesions placed in this region augmented and enhanced the sensitivity of both rats and rabbits to intravenously injected EP [32]. Shortly thereafter, we also observed that the fever sensitivity of rats to EP was also enhanced by the intravenous injection of substances that possessed immuno-adjuvant properties and which stimulated the phagocytic activity of cells of the reticuloendothelial system [33,34]. Naturally, we then investigated whether there was any relationship between these two observations on fever enhancement. We found that microinjection of very small amounts of immuno-adjuvants directly into the OVLT region of rats was equally effective in enhancing their responses to intravenously injected EP, as was the injection of much larger quantities of the immuno-adjuvants intravenously [35]. Since the OVLT was accessible to intravenously injected immuno-adjuvants and to EP, these observations led us to postulate that the site of action of EP in the production of fever was located within the OVLT itself and that the target cell for the action of EP was some kind of immuno-adjuvant-sensitive reticuloendothelial cell, residing within the perivascular space of the OVLT. Histological evidence for the presence of a mesenchymally derived phagocytic cell type within the perivascular space of the OVLT has been provided by Murabe et al. [36]. We postulated that this cell was the source of PGE that is released in response to EP stimulation, and that the lipophilic PGE molecule then diffused across the blood-brain barrier into the adjacent PO/AH neuropile and produced fever. The increased sensitivity of animals to EP after immuno-adjuvant treatment could then be explained by an increase in the sensitivity of the target cells' EP receptors and/or the amount of PGE released by these cells in response to the EP stimulus [35].

In reviewing the reported responses of animals to intracerebrally injected PGE, I have noted some puzzling aspects that are not entirely consistent with our current

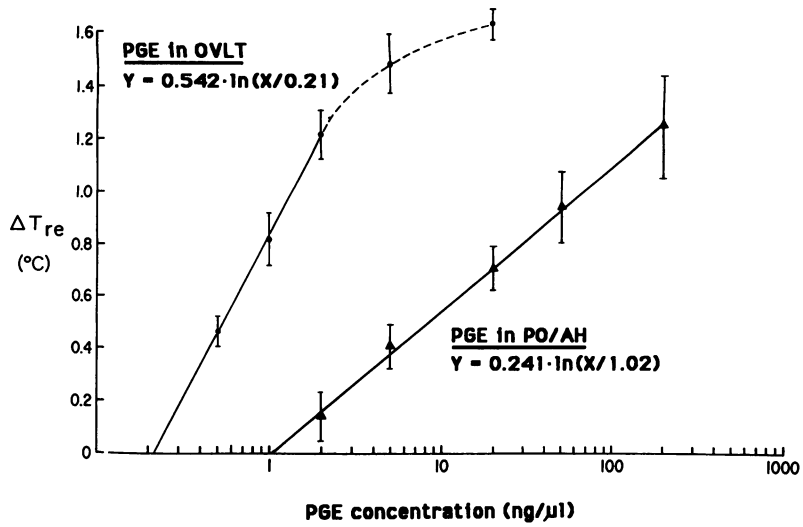
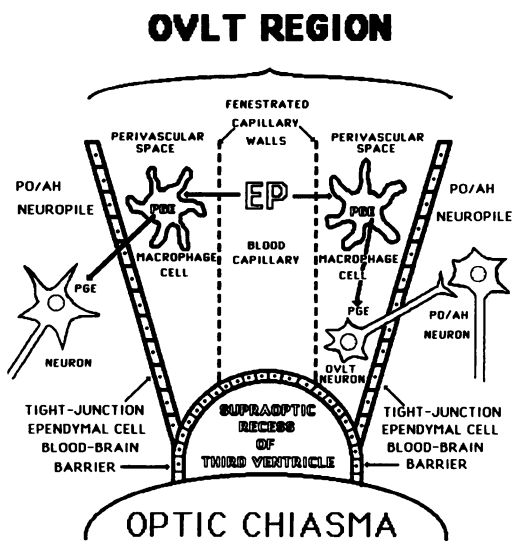


FIG. 7. A comparison of the fever dose-response curves to PGE in rats when the PGE is microinjected into either the PO/AH area or the OVLT region. Each curve is composed from the data derived from groups of eight rats, and the slope and intercept of the linear portion of each curve was derived by regression analysis. A comparison of both the slope and the dose threshold of the two equations indicates that the OVLT region is much more sensitive than the PO/AH area in the production of fever by PGE.

concepts of the pathogenesis of fever. For example, if PGE were to act within the PO/AH neuropile to produce fever, then one would expect that fevers produced in response to intrahypothalamic injection of PGE would be greater than those produced in response to intracerebroventricular injection of PGE, yet, as was stated earlier and is illustrated in Fig. 4, there is no evidence that PO/AH tissue is any more sensitive to the microinjection of PGE than are the cerebral ventricles. This fact seems to indicate that neither region is the site of action of PGE in the production of fever, but that both regions are equally accessible to PGE. The location of the OVLT, adjacent to the PO/AH region and protruding into the supraoptic recess of the third ventricle, seemed to fulfill this requirement [31]. Therefore, we compared the sensitivity of the OVLT region and the PO/AH region to microinjection of PGE in the production of fever. The results are shown in Fig. 7, where it can be seen that the slope of the dose-response curve for PGE in the OVLT is more than twice that obtained when PGE is injected into the PO/AH region and the dose-response threshold for OVLT-induced fever has been reduced by a factor of five.

We interpret these results as indicating that not only is the source of the release of PGE located in the OVLT, but that the locus of the site of action of PGE also lies within the confines of the OVLT.

In summary, considerable evidence now exists that EP or IL-1 can cause the release of PGE from a variety of mesenchymal cells within the body [8] and we have presented evidence that a reticuloendothelial cell type, possibly located within the confines of the OVLT, could be the source of PGE that mediates the febrile response to EP. Thus, there are substantial grounds to believe that the fifth criterion for the role of PGE as the mediator of the febrile response has been satisfied.



HYPOTHESIS ON THE ROLE OF THE OVLT IN THE PATHOGENESIS OF FEVER

FIG. 8. A hypothesis on the role of the OVLT in the pathogenesis of fever. The diagram represents a coronal section of the PO/AH at the level of the supraoptic recess of the third ventricle, showing the organum vasculosum in the lamina terminalis, bounded on either side by the neuropile of the PO/AH. EP enters the perivascular spaces of the OVLT from the circulation through the fenestrated capillary walls and stimulates the mesenchymally derived cells (stellate-shaped cells) in the parenchyma to produce PGE. The PGE thus released into the OVLT is thought either to diffuse into the adjacent PO/AH region to cause fever (*left-hand side*), or to act upon neurons within the OVLT region to cause fever (*right-hand side*).

A MODIFIED MODEL OF THE ROLE OF PGE IN THE PATHOGENESIS OF FEVER

In completing this review of the evidence for a role for PGE as a mediator of fever, I would like to suggest some modifications to the schema, presented in Fig. 1 at the outset of this review, that might account for the apparent discrepancies and disagreements that have been mentioned in the course of this review. These modifications are shown in Fig. 8, which depicts a coronal section through the rostral portion of the PO/AH, showing the OVLT region that is situated medially within the rostral anterior wall of the third ventricle of brain.

It also shows the fenestrated capillaries of the cerebral vasculature which supply the parenchyma and perivascular spaces of the OVLT, and the PO/AH neuropile which abuts the OVLT region bilaterally. It is known that the perivascular spaces of the OVLT contain phagocytic reticuloendothelial-like cells that are capable of taking up a variety of large molecular weight substances such as horseradish peroxidase and trypan blue-bound albumen which are excluded by the blood-brain barrier [36]. We hypothesize that these mesenchymal cells are the target cells for circulating EP. When EP arrives at the brain via the cerebral circulation, it is excluded from the neuropile proper due to its large molecular size (>15,000 daltons) and because of the typical non-fenestrated, tight-junctioned endothelial cells that invest all cerebral capillaries. However, the OVLT is an exception to this rule, in that its capillaries are fenestrated, which allow large molecules into its perivascular spaces [31]. Here, the EP is postulated to stimulate the phagocytic mesenchymal cell, which like all macrophages has the capacity to release PGE, if appropriately stimulated [29]. We postulate that these cells possess specific receptors for EP. Once PGE is released from these cells in response to the EP stimulus, two possibilities exist. The first is that the PGE crosses the tight-junctioned ependymal cells that form the blood-brain barrier and separate the

OVLT region from the PO/AH neuropile proper [37]. PGE, due to its small molecular size and its lipophilic character, has no difficulty in crossing the blood-brain barrier, and it has been shown to be extremely pyrogenic when it is deposited within the PO/AH region [11]. It is then presumed that fever production is due to a direct action of the PGE on the PO/AH neurons controlling temperature regulation (Fig. 7, left-hand side). The second possibility is that of a direct action of PGE on neural elements known to reside within the OVLT [38,39]. This must be considered because of the fact that in the rat we have shown that any given dose of PGE, microinjected directly into the OVLT region, is more effective in producing fever than when it is injected into the PO/AH area (see Fig. 7). This possibility is depicted by the configuration of neurons that are illustrated on the right-hand side of the model in Fig. 8.

In summary, the evidence favoring a role for PGE as the neural mediator of fever has been reviewed under five essential criteria that must be satisfied in order to support such a hypothesis. Exogenous PGE, delivered intracerebrally, has been shown to cause fevers in all mammalian species studied thus far. Fever production caused by the natural pyrogenic stimulus, EP, has been shown to be accompanied by the release of endogenous PGE into the CSF. A variety of substances that are known to block the production of PGE all exhibit antipyretic activity. An anatomical site and cell type, close to the brain and the cerebral circulation, has been identified as a possible source of release and the possible site of action of PGE in response to stimulation by circulating EP. The only criterion for which the evidence is still equivocal is whether PGE antagonists can block normal fever production. Therefore, on the balance of evidence presented, it is submitted that a strong case exists for believing that PGE is, indeed, the neural mediator of fever.

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