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Is Prostaglandin E the Neural Mediator of the Febrile Response? The Case Against a Proven Obligatory Role

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We have reviewed the evidence in favor of a prostaglandin mediator of the thermal responses in fever and found that PGE injected into the hypothalamus does not always cause fever, that cerebrospinal fluid concentrations of PGE are not reliable reflections of hypothalamic events, and that antipyretic drugs may act in ways other than inhibiting PGE synthesis. Fever is not blocked by prostaglandin antagonists, nor by ablation of PGE-sensitive areas of the brain. There is poor correlation between the effects of pyrogens and of PGE on cerebral neurons. There is evidence that at least one prostanoid other than prostaglandin is a mediator of fever, but the prostanoid has not been identified yet. We conclude that PGE may contribute to the neural responses in fever but is not essential.

Whatever the origin of the fever, many of the physiological and biochemical events which constitute the host response are mediated by interleukin-1 (IL-1) [1]. The thermal consequences of fever result from an interaction between IL-1 and cerebral neurons [2]. Circulating IL-1 does not appear to enter brain tissue, so there has been a search for mediators of the interaction. The initial step of the interaction involves protein synthesis in the brain [3,4]. Our paper concerns the hypothesis that there is a second step in the interaction, one which involves prostanoid synthesis.

It is fifteen years since Milton and Wendlandt [5] injected prostaglandin E (PGE) into the cerebral ventricles of cats and observed prompt and potent hyperthermia. Soon afterward, Feldberg and Gupta [6] demonstrated increased concentration of PGE in ventricular cerebrospinal fluid (CSF) following injections of pyrogens in cats, and Philipp-Dormston [7] reported increased PGE concentrations in the lumbar CSF of febrile patients. At the same time, Vane [8] discovered that aspirin and other well-known antipyretic drugs share the property of inhibiting prostaglandin synthesis. Since then further evidence, along similar lines, has accrued relating to PGE involvement during fever, and this evidence has been reviewed recently by Milton [9].

Elsewhere in this symposium the case will be argued that the accumulation of circumstantial evidence justifies the proposition that PGE is an essential neural

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mediator of the febrile response. We take a different view; namely, that the case for PGE is unproven. Though we concede that PGE is released in the brain during fever and is highly pyrogenic, we and others have evidence that PGE release is not an essential stage of the development of fever. This evidence has been reviewed briefly before [10,11,12]. Here we consolidate and extend our case.

IS THE EVIDENCE IN FAVOR OF PROSTAGLANDIN INVOLVEMENT VALID?

Does PGE Injection Always Cause Hyperthermia?

In many animal species, microinjection of PGE into the anterior hypothalamic/pre-optic (AH/PO) area, or into the cerebral ventricles, causes a prompt rise of body temperature, which is sustained for several hours [9]. PGE_1 and PGE_2 have similar, but not necessarily equipotent, effects. The thermoregulatory mechanisms by which the rise in temperature is achieved are similar to those evident following intravenous injections of pyrogens [13]. If, however, brain PGE synthesis is an essential component of the elevation of body temperature in fever, then PGE injection should cause the appropriate rise in body temperature, in the same species and circumstances in which pyrogens do so. Pittman, Veale, and Cooper [14,15] showed that lambs and sheep often did not respond to intrahypothalamic PGE injection, at a time when fever developed following intravenous injection of bacterial pyrogen. Other workers indeed demonstrated both elevated body temperature and appropriate thermoregulatory reactions in sheep in response to intracerebroventricular (ICV), rather than intrahypothalamic, PGE [16,17]. ICV infusion of PGE in adult goats, on the other hand, had no effect on body temperature [18].

Thus, although injection of PGE in or near the AH/PO area of many species causes a fever-like change in body temperature, it does not do so in all circumstances.

What Do Changes in CSF PGE Concentration Mean?

One of the traditional arguments supporting a role for PGE as the neural mediator of the febrile response was the increase in the CSF concentration of PGE which follows injection of pyrogen [6,19] and the fact that this increase is abolished by antipyretic drugs [20]. The situation changed when sodium salicylate was shown to abolish the increase in CSF PGE concentrations which otherwise occurred following intravenous injection of endogenous pyrogen[1] (EP) in rabbits, but did not affect the fever [21]. Later, indomethacin was shown to effect a similar dissociation [22].

The experiments demonstrating dissociation between fever and PGE concentration prompted a re-evaluation of the meaning of CSF PGE concentrations. Bernheim, Gilbert, and Stitt [23] criticized the methodology of Cranston et al. [21], who used CSF tapped from the cisterna magna, which is relatively distant from the AH/PO area. The lumbar spinal column is even more remote, of course, so that, according to that argument, one certainly should not accept that the increase in PGE concentration which occurs in human lumbar CSF during fever [7,24] is evidence supporting PGE as the neural mediator of fever.

Bernheim and his colleagues [23] analyzed CSF from the third ventricle of febrile rabbits; the concentration of PGE showed a significant positive correlation with body

[1] Pure endogenous pyrogen (EP) subsequently has been shown to be identical to IL-1; we shall use "endogenous pyrogen" to denote the crude preparation of IL-1 we and others used at the time.

temperature elevation. Using a similar procedure, Crawford and colleagues [25] also collected rabbit third ventricular PGE during fever, and their data can be analyzed in the same way: these data exhibit no significant correlation between PGE concentration and body temperature.

In view of the contradictory results, it is worth discussing what CSF PGE concentration represents. If PGE appears in the AH/PO area as a consequence of IL-1 action, it must be synthesized locally or enter from the blood. It is unlikely to enter from the CSF. Rapid washout of the ventricular system of rabbits did not affect EP fever [26]. Also, filling the ventricular space with inert oil exaggerated, rather than diminished, the febrile response to EP [27]. Thus any PGE in the CSF must be en route from the brain tissue. Veale and Cooper [28] demonstrated that PGE from the hypothalamus indeed enters the CSF by perfusing the hypothalamus with radioactive PGE and sampling CSF washed from lateral ventricle to cisterna magna.

The hypothalamus is not the only site of origin of PGE entering CSF during fever: the PGE probably originates from widespread areas of the brain [29]. Thus CSF concentrations of PGE do not necessarily reflect recent events in the AH/PO area.

There are other problems that confound the interpretation of CSF PGE concentrations. During fever, the CSF contains leucocytes which elaborate prostaglandins and may continue to do so after the sample is taken, and it contains protein which binds prostaglandin [30]. Coceani and his colleagues [30] believe that many measurements of CSF prostaglandin concentration, and especially those of Bernheim et al. [23], have been erroneously high.

Thus, current measurements of CSF PGE concentration may be wrong, for technical reasons and, even if correctly measured, may not reflect what is happening in the AH/PO area. We doubt whether any of the current studies of CSF prostaglandin concentration are valid evidence either for or against the involvement of PGE as the neural mediator of fever.

Do Intracerebral Injections of Realistic Doses of PGE Cause Fever?

In many of the investigations of the possible hyperthermic activity of PGE, microinjections have been made into the lateral or third ventricles, in the expectation that the prostaglandin will reach the AH/PO area. For the reasons given above, administering PGE from ventricle to hypothalamus is against the normal diffusion direction. Moreover, prostaglandin does not diffuse easily through brain tissue: microinjections into brain tissue at sites a few millimeters away from the AH/PO region, even in sensitive species, have no effect on body temperature [31]. Consequently, ICV injections of PGE have to be made at relatively high doses, and whether the effects they cause are physiological may be questioned.

Even when injections are made directly into the hypothalamus, the doses necessary to produce significant hyperthermia seem high to us. According to Stitt [13], a dose of 20 ng or more of PGE_1 is necessary in rabbits. This dose will be distributed over a few cubic millimeters of tissue, so the peak local concentration may exceed 1,000 ng/ml. The CSF concentration of PGE in afebrile rabbits is less than 0.5 ng/ml [30]. During fever, CSF PGE concentration may increase tenfold, according to Bernheim et al. [23], though other authors report only a doubling or tripling of concentration [19,20,30]. The tissue concentrations necessary to produce a CSF concentration of a few ng/ml will be somewhat higher but are likely to be orders of magnitude lower than 1,000 ng/ml.

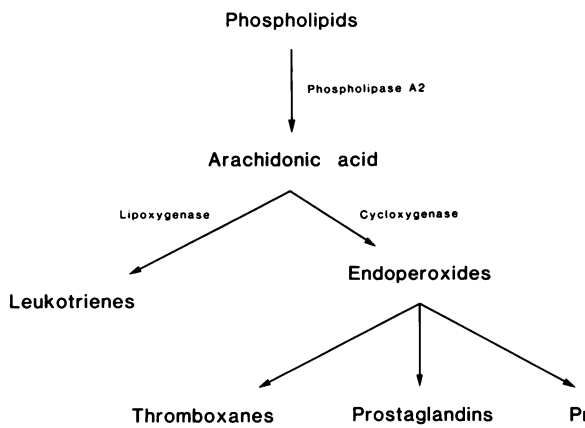

FIG. 1. Simplified diagram of enzymes and metabolites in the biosynthetic pathway of 2-series prostanoids from phospholipids.

Is Inhibition of Prostaglandin Synthesis the Mechanism of Action of Antipyretic Drugs?

Many antipyretic drugs are able to inhibit prostaglandin synthesis in brain tissue [32,33]. They do so by inhibiting the activity of cyclooxygenase enzymes (Fig. 1). However, the drugs have other actions too [34], and the possibility that these other actions may account for the antipyretic properties has not been investigated extensively. The potent antipyretic indomethacin, for example, inhibits cyclic AMP-dependent protein kinase at concentrations orders of magnitude lower than those at which it inhibits cyclooxygenase [35]. Clark and Cumby [36] indeed concluded that neither indomethacin nor paracetamol exert their antipyretic action by inhibiting prostaglandin synthesis.

Apart from those already mentioned [21,22] there are other reports dissociating the inhibition of prostaglandin synthesis by aspirin-like drugs from antipyresis. Floctafenine is reported to be as potent as indomethacin in inhibiting prostaglandin synthesis but has far lower antipyretic action when injected directly into the cerebral ventricles of rabbits [37]. Abdel-Halim and co-workers [38] found that the common antipyretics aspirin and paracetamol do not inhibit prostaglandin synthesis in rat brain homogenates at concentrations at which they are certainly antipyretic *in vivo*.

Until possible mechanisms of action other than inhibition of prostaglandin synthesis have been eliminated properly, it is unjustified to claim that the antipyretic action of aspirin-like drugs is proof that prostaglandin is the neural mediator of the febrile response. Even if cyclooxygenase inhibition is shown to be the relevant mechanism, any of the multiple products of cyclooxygenase activity (Fig.1) may be a mediator of fever.

THE EVIDENCE AGAINST AN ESSENTIAL ROLE FOR PGE

Prostaglandin Antagonists

Perhaps the strongest evidence that any brain prostaglandin synthesized during pyrogen fever does not play an essential role in the genesis of the fever derives from experiments using prostaglandin antagonists. Sanner [39] was the first to notice that the PGE antagonist SC 19220, injected intraperitoneally in rabbits, did not diminish fever. Systemic injection of the antagonist produces severe side effects, making interpretation of the results difficult [40]. However, ICV injections of two PGE antagonists SC 19220 and HR 546 have less severe side effects, and such injections

abolished the hyperthermia which followed ICV injection of PGE_2 but had no effect on the fever which followed an equipotent dose of EP [41].

Milton [9] criticized the experiments of Cranston et al. [41] on the grounds of the high doses of antagonists used and recommended that any conclusion be held in abeyance until a more potent, more specific, centrally active prostaglandin antagonist became available. In the ten years since the work was done, no better antagonist has become available, as far as we are aware.

Hypothalamic Ablation

Further evidence inconsistent with an essential role for PGE has been provided by Veale and Cooper [42], who observed the consequence of bilateral ablation of the AH/PO area. In some rabbits, following the ablation, PGE_1 had no effect on body temperature, whether administered into the AH/PO region or ICV. EP, however, injected either ICV or intravenously produced a fever of normal height, though slower onset. The EP must have acted at a site other than the AH/PO to produce the fever, perhaps the midbrain site of Rosendorff and Mooney [43]. Unless this site is peculiarly inaccessible to ICV PGE, it appears not to be sensitive to PGE, and the thermal responses generated at it consequently are not dependent on PGE.

Neuronal Responses to Pyrogens and Prostaglandins

If PGE is the neural mediator of fever, then one would expect that it would affect neurons in the AH/PO area of the brain in a way consistent with the way in which pyrogens affect these neurons. The temperature-sensitive neurons in the hypothalamus behave in a rather consistent way following intravascular injection of bacterial pyrogen or EP. Eisenman [44] recently has consolidated the results of various authors: 95 percent of all warm-sensitive neurons had been inhibited by pyrogens, and 95 percent of all cold-sensitive neurons facilitated. Thermosensitive neurons in the brain stem [45,46] show similar responses to intravenous pyrogens, and the same pattern of responses, with more rapid onset, is evident when EP is microinjected directly into the AH/PO area [47] or the brain stem [48].

Reports on the action of PGE administered locally on temperature-sensitive neurons are not nearly so consistent [44]. Some authors report a pattern of responses very similar to the pyrogen pattern [49], but others [50] found no association between temperature and PGE sensitivity. In his consolidation of the results of various authors, Eisenman [44] found that three-quarters of all warm-sensitive neurons investigated had not been affected by PGE, nor had almost half the cold-sensitive neurons. Thus the action of PGE on temperature-sensitive neurons is not at all like the action of pyrogens on the neurons, so it is difficult to accept that PGE mediates the action of the pyrogens on the neurons.

It is possible that the neurons responsible for the upward shift of body temperature regulation during fever are neurons insensitive to changes in their own temperature [44]. If this were the case, one would expect pyrogens and PGE to have a consistent effect on the thermally insensitive neurons of the AH/PO area. It turns out that almost none of the insensitive neurons are affected by either pyrogens or PGE [44].

IS THERE AN ESSENTIAL PROSTANOID MEDIATOR OF THE FEBRILE RESPONSE?

The appearance of prostaglandin implies that phospholipase A_2 is activated during fever, and consequently all of the associated prostanoids will be present too, provided

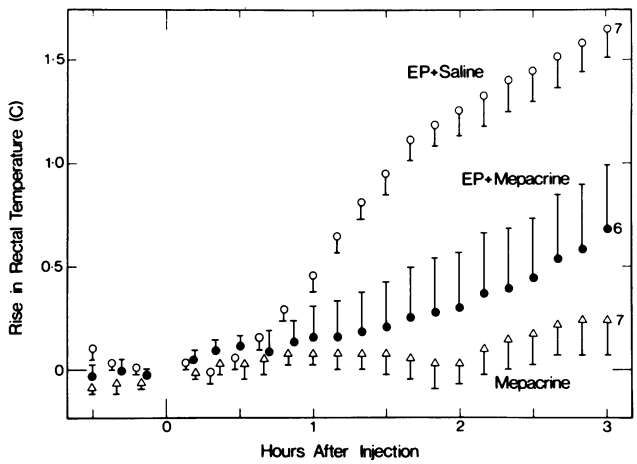

FIG. 2. Rise in rectal temperature (mean ± SE) in rabbits (number shown at the end of each curve) after injection of endogenous pyrogen (EP) with and without the phospholipase A_2 inhibitor mepacrine, or mepacrine alone. From Cranston et al. [51], by copyright permission of The Physiological Society.

that subsequent enzymes in the pathways are available (Fig. 1). Cranston et al. [51] investigated whether any of the prostanoids or leukotrienes are essential mediators of fever by using drugs which inhibit the activity of phospholipase A_2, and which therefore block the biosynthetic pathway at its origin (Fig. 2). Two disparate drugs, mepacrine and parabromophenacylbromide, injected ICV rather than given orally [52], abolished EP fever for at least an hour after injection and attenuated it thereafter [51]. They concluded that at least one of the metabolites is an essential mediator, at least in the initial stages of fever.

The metabolite is not arachidonic acid itself. ICV injection of arachidonic acid elevates body temperature, but the hyperthermia is abolished, at least initially, by cyclooxygenase inhibitors [36,53,54], so the active metabolite is downstream of arachidonic acid. It is not a product of lipoxygenase activity [55], but may be a non-prostaglandin product of cyclooxygenase activity (Fig. 1). Laburn and her colleagues injected arachidonic acid together with the prostaglandin antagonists SC 19220 and HR 546 ICV into rabbits [54]. Although the antagonists abolished the hyperthermic effects of PGE administered by the same route, they inhibited only transiently the hyperthermia of arachidonic acid (Fig. 3), confirming again that prostaglandin is not an essential intermediate in the process. However, we can conclude that either the endoperoxides, or the thromboxanes, or prostacyclin, or possibly other metabolites not shown in Fig. 1, are involved in the febrile process.

Investigation of the action of the endoperoxides is difficult, because they are unstable and short-lived. Stable analogs of the endoperoxides are available, however, and Harrisberg et al. [56] have shown that ICV injections of one such analog in rabbits resulted in dose-dependent hyperthermia. Unfortunately, in the hands of the others, endoperoxide analogs have proven hyperthermic, hypothermic, inactive, or toxic [57,58] so the evidence for or against their involvement in fever remains equivocal.

Another candidate mediator is prostacyclin. ICV injections of prostacyclin in cats and rabbits produce long-lasting elevations of body temperature, at doses higher than those necessary in the case of PGE [58,59]. However, ICV prostacyclin is hypothermic in guinea pigs [60], so that, even if it is involved in the febrile process in some species, it cannot be an essential mediator of fever.

The final candidate prostanoids in the cyclooxygenase pathways are the thromboxanes. Again, they are unstable and difficult to investigate. Coceani and his colleagues

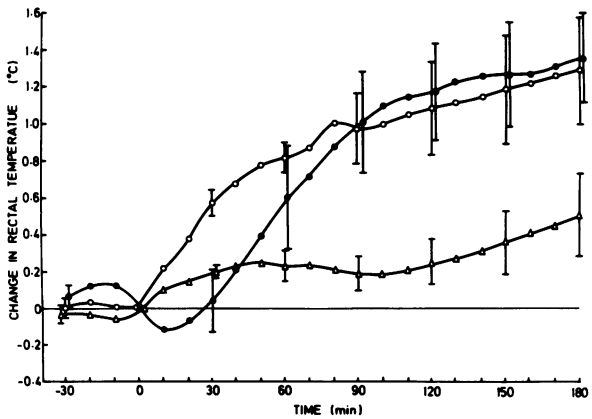

FIG. 3. Change in rectal temperature (mean ± SE) of six rabbits following ICV injection of sodium arachidonate (*open circles*), sodium arachidonate plus SC 19220 (*closed circles*), or SC 19220 alone (*triangles*). Based on Laburn et al. [54].

have detected elevated levels of thromboxane B_2, the stable metabolite of thromboxane synthesis from arachidonic acid, in the CSF of cats in the rising phase of fever [30]. They also found that imidazole, which inhibits synthesis of thromboxanes from endoperoxides, suppressed both the fever and the thromboxane B_2 synthesis. Milton and his colleagues [58], on the other hand, were unable to detect any effect of imidazole on the hyperthermia which followed arachidonic acid injection in rabbits. Too little work has been done on thromboxanes to allow any firm conclusions about their involvement in fever, but it remains possible that they contribute to the process in some way.

In summary, therefore, we believe that synthesis of one or more of the prostanoids is an essential stage of at least the initial phases of fever, and more than one prostanoid may contribute to the overall process. We do not know what the essential prostanoid is yet, and it may not be the same one in different species. We cannot exclude the possibility of a non-prostanoid mediator, nor of a direct action of IL-1 on neurons, after the first few hours of fever.

WHAT IS THE ROLE OF PGE?

Our contention is the PGE synthesis is not essential in fever; we do not deny that PGE synthesis may contribute to the thermal component of fever. We conceive of at least two roles that PGE may play.

The first role that could be assigned to PGE is mediation of the very early thermal events in fever. When arachidonic acid was injected into rabbits, together with prostaglandin antagonists, fever indeed was suppressed for about 30 minutes or so following the injection [54]. The breakdown of arachidonic acid may produce at least two pyrogenic derivatives, the faster-acting of which is PGE. That PGE is responsible for the initial stages of fever is supported by the work of Székely [61,62], who believes that PGE cannot account for all the thermal responses to endotoxin but may well account for the first phase. Further support comes from Skarnes and his colleagues [63], who showed that PGE was present in the jugular venous plasma of sheep only in the first 1½ hours of an endotoxin fever which lasted at least six hours, and peaked at four hours (Fig. 4).

The second role of PGE derives from a consideration of the role PGE plays in an entirely different physiological mechanism, nociception. PGE is released in peripheral tissues during inflammation or trauma and contributes to the associated hyperalgesia.

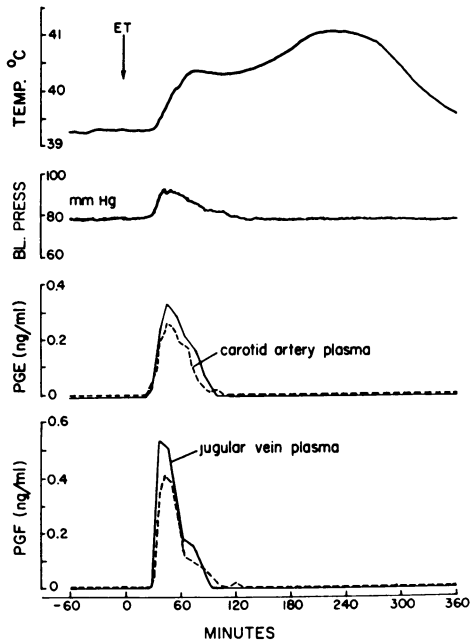

FIG. 4. Vaginal temperature, mean blood pressure, and concentration of PGE and PGF in carotid artery and jugular vein plasma of a sheep, following intracarotid injection of endotoxin (ET). From Skarnes et al. [63], by copyright permission of the Rockefeller University Press.

It does so, not by exciting the neuronal receptors directly, but by sensitizing them to other forms of noxious stimulation [64]. The cyclooxygenase inhibitors, which are analgesics as well as antipyretics, function by preventing this sensitization. By analogy, PGE may sensitize the neurons involved in fever to IL-1, endogenous neurotransmitters, or some other intermediate as yet unidentified [51].

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