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]. PGE₁ and PGE₂ 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 pyrogen¹ (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 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.
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 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 PGE₂ 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 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 A₂ is activated during fever, and consequently all of the associated prostanoids will be present too, provided
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
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 $1\frac{1}{2}$ 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.
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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REFERENCES

1. Dinarello CA: Interleukin-1 and the pathogenesis of the acute-phase response. New Eng J Med 311:1413–1418, 1984
2. Mitchell D, Laburn HP: The pathophysiology of temperature regulation. Physiologist 28:507–517, 1985
3. Cranston WI, Hellon RF, Townsend Y: Suppression of fever in rabbits by a protein synthesis inhibitor, anisomycin. J Physiol (Lond) 305:337–344, 1980
4. Ruwe WD, Myers RD: The role of protein synthesis in the hypothalamic mechanism mediating pyrogen fever. Brain Res Bull 5:735–743, 1980
5. Milton AS, Wendlandt S: Effect on body temperature of prostaglandins of the A, E and F series on injection into the third ventricle of unanaesthetized cats and rabbits. J Physiol (Lond) 218:325–336, 1971
6. Feldberg WS, Gupta KP: Pyrogen fever and prostaglandin activity in cerebrospinal fluid. J Physiol (Lond) 228:41–53, 1973
7. Philipp-Dormston WK: Prostaglandins as possible mediators of fever genesis in man. Zentralbl Bakteriol Mikrobiol (A) 236:415–421, 1976
8. Vane JR: Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol 231:232–235, 1971
9. Milton AS: Prostaglandins in fever and the mode of action of antipyretic drugs. In Pyretics and Antipyretics. Edited by AS Milton. Berlin, Springer-Verlag, 1982, pp 257–303
10. Cranston WI, Duff GW, Hellon RF, Mitchell D, Townsend Y: Is brain prostaglandin synthesis essential in fever? In Drugs, Biogenic Amines and Body Temperature. Edited by KE Cooper, P Lomax, E Schönbaum. Basel, Karger, 1977, pp 140–141
11. Hellon RF, Cranston WI, Townsend Y, Mitchell D, Dawson NJ, Duff GW: Some tests of the prostaglandin hypothesis of fever. In Fever. Edited by JM Lipton. New York, Raven Press, 1980, pp 159–164
12. Myers RD: Hypothalamic control of thermoregulation. In Handbook of the Hypothalamus. Volume 3. Edited By PJ Morgane, J Panksepp. New York, Dekker, 1980, pp 83–210
13. Stitt JT: Prostaglandin E1 fever induced in rabbits. J Physiol (Lond) 232:163–179, 1973
14. Pittman QJ, Veale WL, Cooper KE: Temperature responses of lambs after centrally injected prostaglandins and pyrogens. Am J Physiol 228:1034–1038, 1975
15. Pittman QJ, Veale WL, Cooper KE: Absence of fever following intrahypothalamic injections of prostaglandins in sheep. Neuropharmacology 16:743–749, 1977
16. Bligh J, Milton AS: The thermoregulatory effects of prostaglandin E1, when infused into the lateral cerebral ventricle of the Welsh Mountain sheep at different ambient temperatures. J Physiol (Lond) 229:30–31 P, 1973
17. Hales JRS, Bennett JW, Baird JA, Fawcett AA: Thermoregulatory effects of prostaglandins E1, E2, F1α, F2α in the sheep. Pfugers Arch 339:125–133, 1973
18. Leksell LG: Effects on fluid balance induced by non-febrile intracerebroventricular infusions of PGE2, PGF2α, and arachidonic acid in the goat. Acta Physiol Scand 104:231–255, 1978
19. Philipp-Dormston WK, Siegent R: Prostaglandins of the E and F series in rabbit cerebrospinal fluid during fever induced by Newcombe disease virus, E. coli endotoxin, or endogenous pyrogen. Med Microbiol Immunol (Berl) 159:279–284, 1974
20. Feldberg W, Gupta KP, Milton AS, Wendlandt S: Effect of pyrogen and antipyretics on prostaglandin activity in cisternal c.s.f. of unanaesthetized cats. J Physiol (Lond) 234:279–303, 1973
21. Cranston WI, Hellon RF, Mitchell D: A dissociation between fever and prostaglandin concentration in cerebrospinal fluid. J Physiol (Lond) 253:583–592, 1975
22. Saxena PN: Role of prostaglandins in mediation of pyrogen fever. Indian J Med Res 70:499–503, 1979
23. Bernheim HA, Gilbert TM, Stitt JT: Prostaglandin E levels in the third ventricular cerebrospinal fluid of rabbits during fever and changes in body temperature. J Physiol (Lond) 301:69–78, 1980
24. Saxena PN, Beg MMA, Singhal KC, Ahmad M: Prostaglandin-like activity in the cerebrospinal fluid of febrile patients. Indian J Med Res 70:495–498, 1979
25. Crawford IL, Kennedy JI, Lipton JM, Ojeda SR: Effects of central administration of probencid on fever produced by leukocytic pyrogen and PGE2 in the rabbit. J Physiol (Lond) 287:519–533, 1979
26. Veale WL, Cooper KE: Evidence for the involvement of prostaglandins in fever. In Recent Studies of Hypothalamic Function. Edited by K Lederis, WL Veale. Basel, Karger, 1974, pp 359–370
27. Cooper KE, Veale WL: The effect of an inert oil in the cerebral ventricular system upon fever produced by intravenous pyrogen. Can J Physiol Pharmacol 50:1066–1071, 1972
28. Veale WL, Cooper KE: Prostaglandin in cerebrospinal fluid following perfusion of hypothalamic tissue. J Appl Physiol 37:942–945, 1974
29. Dinarello CA, Bernheim HA: Ability of human leukocytic pyrogen to stimulate brain prostaglandin synthesis in vitro. J Neurochem 37:702–708, 1981
30. Coccoani F, Bishai I, Dinarello CA, Fitzpatrick FA: Prostaglandin E2 and thromboxane B2 in cerebrospinal fluid of afebrile and febrile cat. Am J Physiol 244:R785–793, 1983
31. Williams JW, Rudy TA, Yaksh TL, Viswanathan CT: An extensive exploration of the rat brain for sites mediating prostaglandin–induced hyperthermia. Brain Res 120:251–262, 1977
32. Clark WG: Mechanisms of antipyretic action. Gen Pharmacol 10:71–77, 1979
33. Flower RJ: Drugs which inhibit prostaglandin biosynthesis. Pharmacol Rev 46:33–67, 1974
34. Splawinski JA, Wojtaszek B, Swies J: Endotoxin fever in rats: is it triggered by a decrease in breakdown of prostaglandin E2? Neuropharmacology 18:111–115, 1979
35. Cantor HS, Hampton M: Indomethacin in submicromolar concentrations inhibits cyclic AMP–dependent protein kinase. Nature 276:841–842, 1978
36. Clark WG, Cumby HR: Antagonism by antipyretics of the hyperthermic effect of a prostaglandin precursor, sodium arachidonate in the cat. J Physiol (Lond) 257:581–595, 1976
37. Laburn H, Mitchell D, Stephen J: Effects of intracerebroventricular flotafenine and indomethacin on body temperature in febrile rabbits. Br J Pharmacol 71:525–528, 1980
38. Abdel-Halim MS, Sjöquist B, Anggard E: Inhibition of prostaglandin synthesis in rat brain. Acta Pharmacol Toxicol (Copenh) 43:266–272, 1978
39. Sanner JH: Substances that inhibit the actions of prostaglandins. Arch Intern Med 133:133–146, 1974
40. Clark WG, Cumby HR: Effects of prostaglandin antagonist SC 19220 on body temperature and on hyperthermic responses to prostaglandin E1 and leukocyte pyrogen in the cat. Prostaglandins 9:361–368, 1975
41. Cranston WI, Duff GW, Hellon RF, Mitchell D, Townsend Y: Evidence that brain prostaglandin synthesis is not essential in fever. J Physiol (Lond) 259:239–249, 1976
42. Veale WL, Cooper KE: Comparison of sites of action of prostaglandin and leukocyte pyrogen in brain. In Temperature Regulation and Drug Action. Edited by P Lomax, E Schönbaum, J Jacob. Basel, Karger, 1975, pp 218–226
43. Rosendorff C, Mooney JJ: Central nervous sites of action of a purified leukocyte pyrogen. Am J Physiol 220:597–603, 1971
44. Eisenman JS: Electrophysiology of the hypothalamus: thermoregulation and fever. In Pyretics and Antipyretics. Edited by AS Milton. Berlin, Springer-Verlag, 1982, pp 187–217
45. Nakayama T, Hori T: Effects of anesthetic and pyrogen on thermally sensitive neurons in the brainstem. J Appl Physiol 34:351–355, 1973
46. Sakata Y: Effects of pyrogen on the medullary temperature-responsive neurone of the rabbit. Jpn J Physiol 29:585–596, 1979
47. Schoener EP, Wang SC: Leucocyte pyrogen and sodium acetylsalicylate on hypothalamic neurons in the cat. Am J Physiol 229:185–190, 1975
48. Sakata Y, Morimoto A, Takase Y, Murakami N: Direct effects of endogenous pyrogen on medullary temperature-responsive neurons in rabbits. Jpn J Physiol 31:247–257, 1981
49. Jell RM, Sweatman P: Prostaglandin-sensitive neurons in cat hypothalamus: relation to thermoregulation and to biogenic amines. Can J Physiol Pharmacol 55:560–567, 1977
50. Stitt JT, Hardy JD: Microelectrophoresis of PGE1 onto single units in the rabbit hypothalamus. Am J Physiol 229:240–245, 1975
51. Cranston WI, Hellon RF, Mitchell D, Townsend Y: Intraventricular injections of drugs which inhibit phospholipase A2 suppress fever in rabbits. J Physiol (Lond) 339:97–105, 1983
52. Spagnuolo C, Galli C, Omini C, Folco GC: Antipyretic action of mepracine without blockade of prostaglandin (PG) synthesis in the C.N.S. Pharmacol Res Commun 10:779–786, 1978
53. Splawinski JA, Reichenberg K, Vetulani J, Marchaj J, Kaluza J: Hyperthermic effect of intraventricular injections of arachidonic acid and prostaglandin E2 in the rat. Pol J Pharmacol Pharm 26:101–107, 1974
54. Laburn H, Mitchell D, Rosendorff C: Effects of prostaglandin antagonism on sodium arachidonate fever in rabbits. J Physiol (Lond) 267:559–570, 1977
55. Cranston WI, Hellon RF, Townsend Y: Evidence that leukotrienes do not act as central mediators of fever in rabbits. J Physiol (Lond) 355:29P, 1984
56. Harrisberg CJ, Laburn H, Mitchell D: Intraventricular microinjections of a stable analogue of prostaglandin endoperoxide cause fever in rabbits. J Physiol (Lond) 291:25–29, 1979
57. Hawkins M, Lipton JM: Analogs of endoperoxide precursors of prostaglandins: failure to affect body temperature when injected into the primary and secondary central temperature controls. Prostaglandins 13:209–218, 1977
58. Milton AS, Cremades-Campos A, Sawhney VK, Bichard A: Effects of prostacyclin, 6-oxo- PGE1a and endoperoxide analogues on the body temperature of cats and rabbits. In Thermoregulatory Mechanisms and Their Therapeutic Implications. Edited by B Cox, P Lomax, AS Milton, E Schönbaum. Basel, Karger, 1980, pp 87–92
59. Clark WG, Lipton JM: Hyperthermic effect of prostacyclin injected into the third ventricle of the cat. Brain Res Bull 4:15–16, 1979
60. Kandasamy SB, Kirlin WG, Kaul PN: Prostacyclin-induced hypothermia: involvement of central histamine H1 receptors. Life Sci 28:2553–2560, 1981
61. Székely M, Komáromi I: Endotoxin and prostaglandin fever of newborn guinea pigs at different ambient temperatures. Acta Physiol Acad Sci Hung 51:293–298, 1978
62. Székely M: Endotoxin fever in the newborn kitten. The role of prostaglandins and monoamines. Acta Physiol Acad Sci Hung 54:265–276, 1979
63. Skarnes RC, Brown SK, Hull SS, McCracken JA: Role of prostaglandin E in the biphasic fever response to endotoxin. J Exp Med 154:1212–1224, 1981
64. Ferreira SH: Inflammatory pain, prostaglandin hyperalgesia and the development of peripheral analgesics. Trends Pharmacol Sci 2:183–186, 1981