The Role of Prostaglandins in Pyrexia

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Milton & Wendlandt (1970) first suggested that prostaglandins could affect body temperature. They found that minute amounts of prostaglandin E₁ when injected into the third cerebral ventricle of the conscious cat produced vigorous shivering and ear vasoconstriction, and the animals appeared sedated and curled up in a ball with the fur erect. These effects were accompanied by a rapid rise in deep-body temperature. The threshold dose of prostaglandin E₁ to produce a rise in temperature was of the order of 30 pmol and the duration of the response was short (see Fig. 1). Prostaglandins A₁, F₁₂, and F₂₁ did not produce any significant changes in temperature when administered in similar doses. Milton & Wendlandt (1971b) showed that prostaglandin E₁ had similar hyperthermic effects in the rabbit and that prostaglandin E₂ produced the same effects as prostaglandin E₁. Milton & Wendlandt (1971a) reported on the hyperthermic effects of prostaglandin E₁ in the rat. More recently, Ewen et al. (1976) have found that prostaglandin D₂, an isomer of prostaglandin E₂, is without effect on body temperature and that prostaglandin F₂₁ in larger doses than previously suggested does produce a rise in temperature in the cat. However, the effects are different from those produced by prostaglandin E₂ in that shivering is not observed.

Feldberg & Saxena (1971a,b) confirmed the original observations of Milton &

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![Figure 1](https://example.com/figure1.png)

**Fig. 1.** Rectal temperature of an unanaesthetized cat after prostaglandin E₁ injection

Prostaglandin E₁ was injected at the doses indicated at times shown by the arrows. [This Figure is from Milton & Wendlandt (1971b) with permission of The Journal of Physiology (London).]
Wendlandt (1971b) that prostaglandin \( E_1 \) was hyperthermic in the cat, and they also showed that it produced a rise in temperature in the rabbit and rat. Of particular importance they located the site of action of prostaglandin \( E_1 \) to the preoptic area of the hypothalamus, and in addition they observed that when prostaglandin \( E_1 \) was infused into the cerebroventricular system the hyperthermia was sustained for only as long as the infusion was continued; thereafter the temperature rapidly returned to the pre-infusion value.

**Thermoregulatory responses to prostaglandins**

To investigate the physiological and autonomic responses to prostaglandin \( E_1 \) responsible for the increase in deep-body temperature, Bligh & Milton (1973) infused prostaglandin \( E_1 \) into the cerebroventricular system of the Welsh mountain sheep. The animals were maintained at different ambient temperatures and the effects of prostaglandin \( E_1 \) on respiratory rate, shivering, ear-skin temperature and deep-body temperature were measured. It was found that when the animals were at low ambient temperature (10°C) the respiratory rate was low (approx. 35 min\(^{-1}\)) indicating minimum evaporative heat loss, the ear skin temperature approached ambient temperature indicating vasoconstriction and therefore minimal heat loss from the extremities, and occasional bursts of activity were observed on the electromyograph recording from a thigh muscle indicating shivering and therefore production of metabolic heat. These measurements showed that the animals were maintaining deep-body temperature by minimizing heat loss and by a slightly increasing heat production. When prostaglandin \( E_1 \) was infused into the ventricles at a rate of 2.5 \( \mu \)g/min the respiratory rate dropped slightly to 30 min\(^{-1}\), there was no change in ear skin temperature, but violent shivering was recorded and the deep-body temperature increased. On stopping the infusion, shivering ceased completely and the respiratory rate increased until the deep-body temperature had returned to normal.

At an ambient air temperature of 45°C, that is above the animals' deep-body temperature of approx. 39°C, the animals panted vigorously with respiratory rates about 200 min\(^{-1}\), the ear vessels were dilated and no shivering was recorded. These measurements indicated that the animals were actively preventing body temperature from rising primarily by evaporative heat loss. The infusion of prostaglandin \( E_1 \) produced a dramatic fall in respiratory rate to about 30 min\(^{-1}\), but did not produce shivering and was without effect on ear-skin temperature. Deep-body temperature rose rapidly due to the inhibition of evaporative heat loss. When the prostaglandin \( E_1 \) infusion was stopped panting returned and the rate rose well above pre-infusion value to over 300 min\(^{-1}\) and remained increased until the extra heat gained had been lost and the deep-body temperature had returned to normal.

If the animals were maintained at 18°C (which is above the thermoneutral temperature for the unshorn sheep) respiratory rate was about 150 min\(^{-1}\), ear skin temperature was between ambient temperature and deep-body temperature and no shivering was seen. Under these conditions the animals were maintaining body temperature by evaporative heat loss and by changes in vasomotor tone. At 18°C the prostaglandin \( E_1 \) infusion decreased respiratory rate to about 30 min\(^{-1}\), ear skin temperature fell indicating vasoconstriction and bursts of shivering were recorded. The prostaglandin \( E_1 \) was therefore both increasing heat production and decreasing heat loss. As in the other experiments, after the infusion was stopped respiratory rate rose and shivering stopped; in addition ear skin temperature increased indicating vasodilatation.

These experiments on the Welsh mountain sheep showed that prostaglandin \( E_1 \) increases deep-body temperature by both inhibiting heat-loss mechanisms including surface heat loss and evaporative heat loss and by stimulating heat-gain mechanisms such as shivering that represents metabolic heat production. Of particular interest was the observation that as soon as the prostaglandin \( E_1 \) infusion was stopped the animals actively lost the extra heat which had been gained and deep-body temperature was quickly restored to normal. This response is very reminiscent of the effects of antipyretic drugs in reducing fever produced by bacterial pyrogen.
Prostaglandins and pyrogen fever

In their very first paper on the hyperthermic effects of prostaglandin E₁, Milton & Wendlandt (1970) reported that the increase in body temperature was not affected by the intraperitoneal injection of the antipyretic drug 4-acetamidophenol (paracetamol). This was in complete contrast with the effect of paracetamol on the increase in body temperature produced by intraventricular injection of pyrogen, where it completely inhibited or suppressed the fever (Milton & Wendlandt, 1968). It was as a result of these two observations that Milton & Wendlandt (1968) put forward the theory that bacterial pyrogens produced fever by releasing a prostaglandin in the central nervous system and that antipyretic drugs acted by preventing this release. At that time they had no idea on how prostaglandin release could be prevented by antipyretic drugs. The answer was to come in 1971 when Vane in his now classical paper showed that the synthesis of prostaglandins E₂ and F₂α from arachidonic acid by guinea-pig lung homogenate was inhibited by aspirin-like drugs. Vane (1971) suggested that not only the analgesic and anti-inflammatory actions of these chemicals, but also their antipyretic action, could be explained by an inhibition of prostaglandin synthesis, a view that is now widely accepted. Piper & Vane (1971) had indicated that since there is little pre-formed prostaglandin in body tissue, prostaglandin synthesis could be equated with prostaglandin release, therefore the proposal put forward by Milton & Wendlandt (1970) that antipyretic drugs acted by preventing prostaglandin release could be explained by the action of these drugs in inhibiting prostaglandin synthesis.

A prostaglandin-like substance was first reported to be present in the cerebrospinal fluid of a cat during pyrogen fever by Milton & Wendlandt (1970). In 1973 Feldberg & Gupta obtained cerebrospinal fluid from the third ventricle of the conscious cat and assayed it for contractile activity using the rat fundus strip preparation. They found that in afebrile animals the activity was very low or absent, whereas during fever produced by injecting pyrogen directly into the third ventricle the activity was considerably increased. When they administered the antipyretic drug 4-acetamidophenol the fever abated and the contractile activity of the cerebrospinal fluid was again low. From their results Feldberg & Gupta (1973) concluded that the contractile substance present in the cerebrospinal fluid was a prostaglandin. Subsequently, Feldberg et al. (1973) collected cerebrospinal fluid from the cisterna magna of the conscious cat and assayed it for prostaglandin E-like activity. They found that the bacterial pyrogen produced a fever when given intravenously, and during the febrile response the prostaglandin E-like activity of the cerebrospinal fluid increased and the three antipyretic drugs, acetylsalicylic acid (aspirin), 4-acetamidophenol (paracetamol) and indomethacin all abolished fever and at the same time the cerebrospinal fluid content of prostaglandin E was decreased (Fig. 2). T.1.c. of the cerebrospinal fluid samples followed by bioassay and radioimmunoassay indicated that the prostaglandin present in the cerebrospinal fluid of the cat during fever was prostaglandin E₂. Similar results were obtained by Harvey et al. (1975) in the rabbit.

Harvey & Milton (1975) prepared endogenous pyrogens from cat peritoneal exudate and found that when this material was infused intravenously into a conscious cat it produced a fever that was associated with an increase in prostaglandin E content of the cisternal cerebrospinal fluid, and that this fever and the increase in prostaglandin E were inhibited by antipyretic drugs (Fig. 3). Harvey & Milton (1975) also found that if plasma obtained from a donor cat in which fever had been produced by intravenous pyrogen was injected into a recipient cat that had been made refractory to the pyrogen, then this recipient cat also developed a fever accompanied by an increase in cisternal cerebrospinal fluid and prostaglandin E concentrations. It was concluded that the circulating pyrogen in the donor cat was endogenous pyrogen. In the early experiments in which cerebrospinal fluid was assayed for prostaglandins using either bioassay or radioimmunoassay a prostaglandin of the E series, most likely E₂, was the only prostaglandin to be found. Radioimmunoassay techniques for the prostaglandins are now considerably more sensitive and Milton et al. (1977) reported the presence of a prostaglandin F in the cerebrospinal fluid, the concentrations of which
Fig. 2. Rectal temperature from two unanaesthetized cats (a and b)

The height of the columns and the values above refer to prostaglandin E₁-like activity in ng/ml of cisternal cerebrospinal fluid; the position of the columns refers to the time, but not to the duration, of the cerebrospinal-fluid collection. The first arrow in (a) and (b) indicates an intravenous injection of 250μg of pyrogen, the second arrow in (b) indicates an intraperitoneal injection of indomethacin 2mg/kg. [This Figure is from Feldberg et al. (1973) with permission of The Journal of Physiology (London)].

Fig. 3. Rectal temperature of an unanaesthetized cat

The height of the columns and the values above the columns refer to the prostaglandin-\(E_2\)-like activity in ng/ml of cisternal cerebrospinal fluid. The position of the columns refers to the time, but not to the duration, of the cerebrospinal-fluid collection. Between the arrows endogenous pyrogen (\(2 \times 10^6\) cell equivalents/min for 5 min, then \(2 \times 10^8\) cell equivalents/min) was infused into a saphenous vein. Paracetamol (50mg/kg) was injected intraperitoneally at the time marked by the single arrow (C. A. Harvey & A. S. Milton, unpublished work).
were increased during fever. However, further research is needed before the involvement of a prostaglandin F in fever can be considered.

Summary

It is now just 8 years since Milton & Wendlandt (1970) first proposed that a prostaglandin E was a mediator of pyrogen fever and that antipyretic drugs exerted their action by inhibiting the release of this prostaglandin. The evidence is now fairly convincing; when injected directly into the thermoregulatory area of the anterior hypothalamus both prostaglandins E₁ and E₂ activate heat-gain and inhibit heat-loss mechanisms in a manner very similar to that produced by bacterial and endogenous pyrogens. The E-type prostaglandins are among the most potent substances known that increase the deep-body temperature when injected directly into the central nervous system. They produce a rise in deep-body temperature in all the placental animals in which they have so far been studied.

Bacterial pyrogen and endogenous pyrogen both produce fever and increase the concentration of the prostaglandin found in the cerebrospinal fluid. During bacterial pyrogen fever a circulating pyrogenic material that is not the bacterial pyrogen and is of endogenous origin is found in the plasma and this when transferred to a recipient animal produces both a fever and a rise in the prostaglandin E concentrations of the cerebrospinal fluid.

The antipyretic drugs such as aspirin, paracetamol and indomethacin, all of which have been shown to inhibit the enzyme systems concerned with prostaglandin synthesis, inhibit the rise in prostaglandin E concentrations of the cerebrospinal fluid when administered during pyrogen fever at the same time as they produce antipyresis.