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SOME EFFECTS OF PROSTAGLANDINS E_1 AND E_2 AND OF ENDOTOXIN INJECTED INTO THE HYPOTHALAMUS OF YOUNG CHICKS: DISSOCIATION BETWEEN ENDOTOXIN FEVER AND THE EFFECTS OF PROSTAGLANDINS

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1 Prostaglandins E_1 and E_2 elevated body temperature of young chicks when injected into the hypothalamus at thermoneutrality (31°C). In contrast, they lowered body temperature when so injected below thermoneutrality (16°C): the relation of the fall in body temperature to increased heat loss and decreased heat production was examined.

2 The above effects below thermoneutrality were potentiated by pretreatment with inhibitors of prostaglandin synthetase and possible reasons for this potentiation are given.

3 The 'O'-somatic antigen of *Shigella dysenteriae* consistently evoked hyperthermia when injected into the hypothalamus, irrespective of whether the chicks were within or below thermoneutrality.

4 Pretreatment with prostaglandin synthetase inhibitors failed to prevent the onset of endotoxin fever; however, duration of the fever, induced by intrahypothalamic injection of the O-somatic antigen of *Shigella dysenteriae* was reduced.

5 The intrahypothalamic injection, below thermoneutrality of prostaglandins E_1, E_2, noradrenaline, 5-hydroxytryptamine or carbachol reversed endotoxin fever, inducing even substantial falls in body temperature.

6 While the results cast some doubts on the role of prostaglandins of the E series as mediators of endotoxin fever in chicks, they cannot be eliminated as mediators until the significance of the reduction in duration of the pyrexic response by indomethacin and 5,8,11,14-eicosatetraynoic acid, and the degree of synthesis inhibition attained, are known.

Introduction

Prostaglandins are present in mammalian and avian tissues, their concentrations in those of chickens, including the brain, mostly exceeding those in mammals (Horton & Main, 1967; Karim, Hillier & Devlin, 1968). Prostaglandins of the E series are generally thought to be mediators of endotoxin fever because, for example, they raise body temperature when injected intraventricularly, they appear in cerebrospinal fluid during endotoxin and lipid A fever in mammals, but disappear from it when fever is controlled by antipyretic drugs which inhibit prostaglandin synthesis (for references see Feldberg, 1975). However, there are significant exceptions to this relation. For example, hypothermic effects of intraventricular prostaglandin E_1 and E_2 injection have been demonstrated over a wide range of ambient temperatures in Echidna, *Tachyglossus aculeatus* (Baird, Hales & Lang, 1974). Prostaglandin E_1 injected into the hypothalamus of young chicks below thermoneutrality also lowered body temperature (Artunkal & Marley, 1974) and indeed, suppressed fever produced by the 'O'-somatic antigen of *Shigella dysenteriae* (Artunkal, Marley & Stephenson, 1975).

The present paper extends these preliminary findings and includes an investigation into the mechanism whereby prostaglandins lower body temperature in young chicks and the interactions between the 'O'-somatic antigen of *Shigella dysenteriae*, E prostaglandins, inhibitors of prostaglandin synthesis and putative transmitters within the hypothalamus.

Method

Animals

Rhode Island Red pullets of 80–90 g were used

(11–17 days old). They were housed under thermoneutral conditions i.e. at 33–34°C for the first week after hatching and for the following 2 weeks at 29–31°C.

Operative procedures

All operative procedures were performed under halothane anaesthesia. Methods for implanting an intrahypothalamic cannula, an intravenous jugular cannula, a carotid arterial cannula and a thermistor placed subcutaneously between the scapulae have been described (Dewhurst & Marley, 1965; Allen & Marley, 1967; Marley & Stephenson, 1970): leg temperature was recorded from a thermistor taped to the tarsometatarsal region of a hind limb.

Experimental procedure

Chicks were tested when recovery was complete, at least 24 h after the operative procedures; only those chicks which had fed since the operation, as indicated by the presence of food in the crop, were tested. About 1 h before the control period, each chick was placed in a soundproof, environment-controlled experimental box with a one-way screen and facilities for external monitoring of physiological temperatures. Ambient temperature was maintained at 16 ± 0.5°C or 30–31°C i.e. below or within the thermoneutral range for chicks of this age (Freeman, 1963; Allen & Marley, 1967); relative humidity was maintained at approximately 60%.

Intracerebral injections were given via a length of polyethylene tubing which passed through the roof of the box and was connected externally to a 10 µl Hamilton syringe; drug injections (1 µl) were given over a period of 1 minute. Cannulae positions were subsequently located histologically. Body and leg temperatures were monitored continuously on Grant miniature temperature recorders. In experiments in which leg temperature was recorded, the chick was supported in a rubber cradle through which the legs protruded so that it was not able to squat to prevent heat loss.

For recording carbon dioxide elimination the chick was placed in a 1 litre chamber, maintained at 16°C through which CO_2-free air, also at 16°C, was passed at a rate of 1 l/minute. Percentage CO_2 in the expired air, measured with an infra-red analyser (Hartmann & Braun) was recorded continuously. Oxygen consumption was measured as described by Allen & Marley (1967). Mean arterial blood pressure was monitored on a Devices polygraph.

Drugs

These were: prostaglandins E_1 and E_2 (Upjohn Co. Ltd.), indomethacin (Merck, Sharp & Dohme, Ltd.), 'O'-somatic antigen of *Shigella dysenteriae* (W.H.O.), 5,8,11,14-eicosatetraynoic acid (ETA, Roche Ltd.), carbamylcholine chloride, 5-hydroxytryptamine maleinate, (–)-noradrenaline. (–)-Noradrenaline base was dissolved in equimolar HCl immediately before use, prostaglandins E_1 and E_2 were dissolved in ethanol and sodium carbonate (1 mg prostaglandin E_1 in 0.1 ml 95% ethanol and 0.9 ml of a 0.02% w/v Na_2CO_3 solution) and prepared freshly for each experiment, indomethacin was dissolved in 0.8% w/v $NaHCO_3$ solution. Other drugs were dissolved in 0.9% w/v NaCl solution (saline).

Results

Effects of prostaglandins E_1 and E_2

At a thermoneutral ambient temperature (31°C), prostaglandin E_1(14.3 nmol) injected into the hypothalamus of young chicks elevated body temperature (Figure 1a), the increase in body temperature commencing approximately 10 min after injection with a mean maximum increase (1.1°C) occurring after 140 minutes. Injection of saline or prostaglandin vehicle (each 1 µl) did not change body temperature by more than ± 0.1°C (6 chicks). Four hours after prostaglandin E_1 injection, the mean elevation was 0.7°C, the duration of the pyrexic response ranging in individual chickens from 5 to 6 hours. After injection, chicks slept either erect or squatting with the wings applied closely to the trunk. Respiratory rate was elevated to about 60/min but not to the extent that gular flutter occurred. Prostaglandin E_2 (14.3 nmol) injected into the hypothalamus elevated body temperature a mean maximum of 1.05°C (3 chickens).

Below thermoneutrality (16°C), injections of prostaglandin E_1 (14.3 nmol) into the hypothalamus lowered body temperature (Figure 1b). The fall in body temperature commenced immediately after the injection with a mean maximum decline in 6 chicks of $2.45°C \pm 0.9°C$ being obtained between 70 and 120 min (mean 90 min); recovery occurred within 110–170 min (mean 140 min) of infusion. Sleep was much less marked than in tests at thermoneutrality and chicks squatted (hindering heat loss) rather than stood. The hypothermic effect of an equimolar dose of prostaglandin E_2 (14.3 nmol) was greater than that of prostaglandin E_1, body temperature falling a mean maximum of 3.85°C (2 chicks) at 60 minutes. In one chick, body temperature recovered within 3 h of the injection, whereas in the other, recovery occurred after 5 h but was then followed by an 'overshoot' of 1.5°C lasting a further 5 h before body temperature returned to normal.

The cause of this unexpected hypothermia was investigated by determining the actions of prosta-

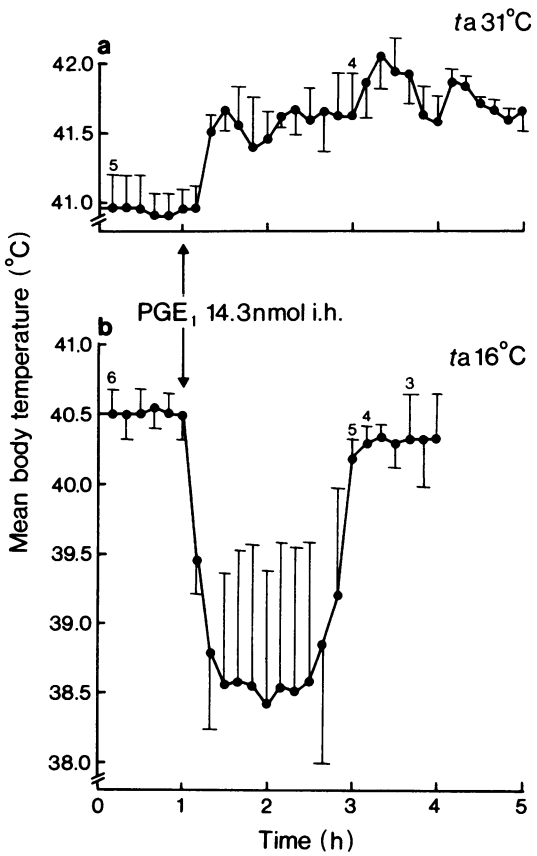

Figure 1 Mean effects of intrahypothalamic injection (i.h.) of prostaglandin E_1 (PGE_1, 14.3 nmol) at ambient temperatures (t_a) of (a) 31° and (b) 16°C. In this and Figures 3 and 4, points connected with continuous line indicate means; vertical bars indicate s.e. mean and the number of chicks used is shown by the numerals; where no numeral is shown, the last number appertains.

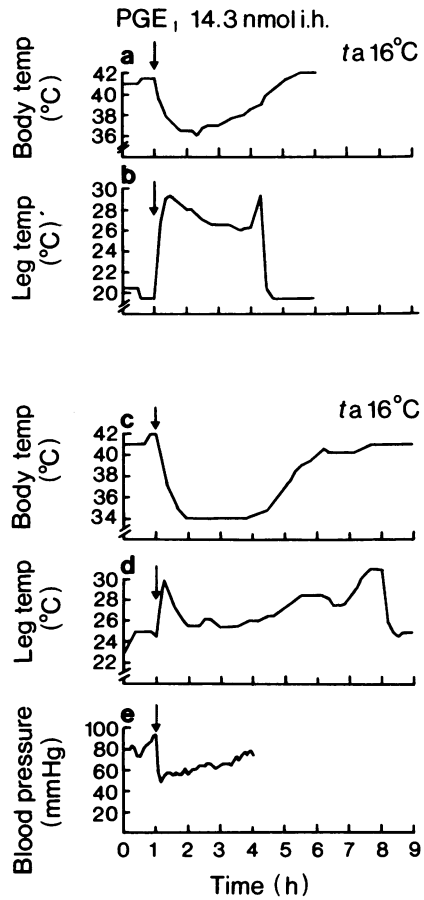

Figure 2 Effects of intrahypothalamic injection (i.h.) of prostaglandin (PGE_1, 14.3 nmol) on body temperature, leg temperature and mean arterial blood pressure at an ambient temperature (*ta*) of 16°C. In both chicks, the fall in body temperature (a,c) was associated with a related increase in leg temperature (b,d) more conspicuous in (b) and indicative of vasodilatation. The increased leg temperature (d) after prostaglandin E_1 was associated with a decline in arterial blood pressure (e).

glandin E_1 on heat loss and heat production mechanisms.

Heat loss. An increase in heat loss was inferred from the increase in temperature of the unfeathered lower limbs (hereafter, leg temperature) following injections of prostaglandin E_1 into the hypothalamus. It should be noted that covering the exposed lower limbs by squatting, reduces heat loss of adult fowls by one-third, (Deighton & Hutchinson, 1940). Since squatting alone elevated leg temperature by 3.0.°C, the experiments were performed with the chick suspended from a cradle (see Methods). Prostaglandin E_1 (14.3 nmol) injected into the hypothalamus caused a mean maximum increase in leg temperature of 6.5°C together with a mean maximum fall in body temperature of 5.5°C (4 chicks). The time-courses of the reciprocal responses were roughly similar although the rise in leg temperature was invariably more rapid than the fall in body temperature (Figure 2); the recovery of body temperature was preceded by that of leg temperature (Figures 2a,b) or *vice versa* (Figure 2c). The greater fall in mean body temperature that occurred in these experiments than is shown by chicks that were allowed to squat (5.5°C compared with 2.1°C) is presumably due to the inability of these chicks to reduce heat loss from the lower limbs.

The elevation in leg temperature was assumed to be secondary to general vasodilatation and was reflected

in a reduced blood pressure. Thus prostaglandin E_1 (14.3 nmol) injected into the hypothalamus lowered mean blood pressure from 93 to 48 mmHg, while at the same time, leg temperature increased from 25° to 30°C (Figure 2e); body temperature began to fall during this period. Blood pressure gradually recovered over the ensuing 3 h whereas restoration of body temperature and leg temperature took considerably longer. These results, confirmed in 3 other chicks, support the suggestion that prostaglandin E_1 injected into the hypothalamus produced vasodilatation.

Heat production. Prostaglandin E_1 (14.3 nmol) injected into the hypothalamus of 8 chicks lowered CO_2 elimination within 5 min of injection from 56.43 ± 3.38 ml kg^{-1} min^{-1} to 33 ± 2.49 ml kg^{-1} min^{-1} ($P < 0.005$); the mean maximum decrease in temperature was 3.2°C. Oxygen consumption, measured at 100% humidity, was reduced in 6 chicks from 56.4 ml kg^{-1} min^{-1} to means of between 46.5 and 47.0 ml kg^{-1} min^{-1} over the ensuing 40 min; mean body temperature fell 2.2°C.

Effects of prostaglandin E_1 after indomethacin

Within thermoneutrality (31°C), indomethacin (1.4 μmol/100 g i.v. 30 min previously) delayed onset of the mean rise in body temperature to intrahypothalamic injection of prostaglandin E_1 (14.3 nmol) by approximately 70 min (compare Figure 3 with Figure 1a); the mean increase in body temperature of 1.05°C (4 chicks) was not significantly different from that elicited by prostaglandin E_1 alone. Despite considerable variations in the effects of prostaglandin E_1 after indomethacin, it appeared to attenuate the duration of the pyrexic response. Thus, following indomethacin, the mean duration of the pyrexic response was 4 h, at which time, body temperature after prostaglandin E_1 alone was still 0.7°C above the control values.

In contrast, the effects of indomethacin (1.4 μmol/100 g i.v. 30 min previously) below thermoneutrality (16°C) were clear-cut, the hypothermic effects of prostaglandin E_1 (14.3 nmol) being intensified and prolonged (Figure 3b). Thus the mean maximum fall in body temperature after intrahypothalamic injection of prostaglandin E_1 in 6 chicks was 5.4°C, significantly greater than after prostaglandin E_1 alone ($P < 0.025$); body temperature returned to pre-injection values approximately 4 h (225 ± 30 min, mean ± s.e. mean) after the injection compared to just under 2 h (108 ± 20 min) after prostaglandin E_1 alone ($P < 0.01$). Similar effects were obtained by pretreatment with a ten-fold greater dose of indomethacin (14 μmol/100 g i.v.), an amount likely to inhibit prostaglandin dehydrogenase as well as prostaglandin synthetase (R.J. Flower, personal communication).

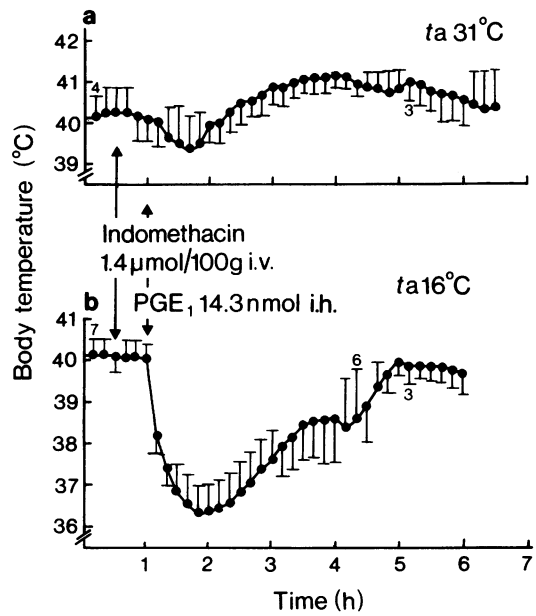

Figure 3 Mean effects (± s.e. mean) of intrahypothalamic injection (i.h.) of prostaglandin E_1 (PGE_1, 14.3 nmol) given 30 min after indomethacin (1.4 μmol/100 g i.v.) at an ambient temperature (t_a) of (a) 31° and (b) 16°C. Compare with Figure 1.

Effects of prostaglandin E_1 after 5,8,11,14-eicosatetraynoic acid (ETA)

The effects of prostaglandin E_1 were also intensified and prolonged after pretreatment with ETA (1 mg/100 g i.v. 30 min previously), a more selective inhibitor of prostaglandin synthetase than indomethacin. Thus at thermoneutrality (31°C) and after ETA pretreatment, body temperature of one chick rose 1.5°C after intrahypothalamic injection of prostaglandin E_1 (14.8 nmol), recovery not occurring until 8 h later. Similarly below thermoneutrality (16°C), the mean duration of the hypothermic effects of prostaglandin E_1 (14.3 nmol) in 4 chicks was significantly increased by ETA ($P < 0.05$) from 108 ± 20 min with prostaglandin E_1 alone to 312 ± 92 min (mean ± s.e. mean); the mean fall in temperature was 5.6°C, significantly greater ($P < 0.05$) than that after prostaglandin E_1 alone (2.45°C).

Effects of the 'O'-somatic antigen of Shigella dysenteriae

Within thermoneutrality (31°C) injections of the 'O'-somatic antigen of *Shigella dysenteriae* (0.1 and 1 μg) into the hypothalamus rapidly evoked pyrexia, that after 1 μg being the longer-lasting: effects of 10 ng

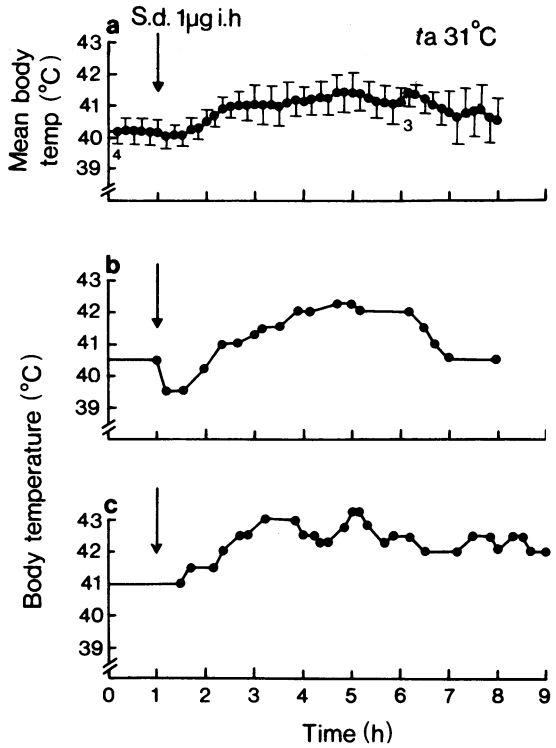

Figure 4 Mean effects (± s.e. mean) of *Shigella dysenteriae* (S.d.) on body temperature of four chicks at an ambient temperature (*ta*) of 31°C (a); (b) and (c) illustrate two types of effect observed in individual chicks.

were inconsistent. The mean pyrexic effect (4 chicks) of the 1 μg dose is illustrated in Figure 4a; body temperature was unaffected by intrahypothalamic injection of the control vehicle, it remaining within the limits observed during the control period. After a small reduction, mean body temperature began to increase after 60 min attaining a maximum increase of 1.2°C after the infusion, and was still 0.6°C above pre-infusion values 3 h later. This mean temperature response probably conceals two different forms of response to the endotoxin, one (2 chicks) in which a fall in body temperature preceded a sustained rise in body temperature (Figure 4b) and another, (2 chicks) in which body temperature increased within 30 min of infusion without a prior fall in body temperature (Figure 4c).

Below thermoneutrality (16°C), mean body temperature initially rose 0.95°C with the injection of 'O'-somatic antigen of *Shigella dysenteriae* (1 μg) then declined again to pre-injection values followed by a more sustained temperature increase of 1.2°C and returned to control values 12–13 h after injection. Again the mean pattern concealed apparently different

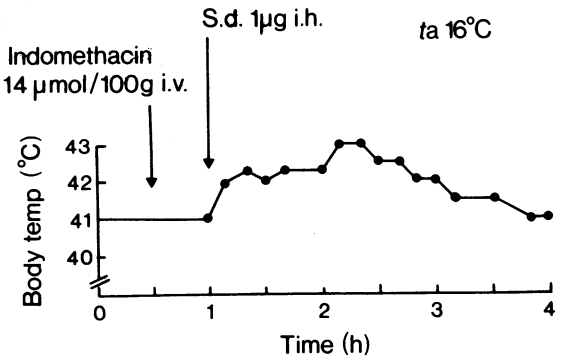

Figure 5 Effect of indomethacin (14 μmol/100 g i.v.) on the pyrexic response to *Shigella dysenteriae* (S.d., 1 μg injected into the hypothalamus, i.h., 30 min later). Ambient temperature (t_a), 16°C.

types of body temperature response to bacterial pyrogen. In 3 chicks the pattern conformed to that for the mean body temperature change, in 2 chicks there was a delay of up to 2 h before body temperature began to increase and in 1 chick, increase in body temperature commenced immediately after injection.

Effects of the 'O'-somatic antigen of Shigella dysenteriae *after indomethacin*

In each of three chicks tested within thermoneutrality (31°C), intrahypothalamic injection of the 'O'-somatic antigen of *Shigella dysenteriae* (1 μg) 30 min after injection of indomethacin (1.4 μmol/100 g i.v.) evoked hyperthermia. The mean increase in body temperature was the same as that seen after endotoxin alone (1.2°C). However, the duration of the response was reduced from more than 7 h to between 5 and 6.5 hours.

In 5 chicks tested below thermoneutrality (16°C), the 'O'-somatic antigen of *Shigella dysenteriae* (1 μg) elevated body temperature a mean of 1.5°C when given 30 min after indomethacin (1.4 μmol/100 g i.v.). Again the duration of response was attenuated, recovery occurring within 3.5 hours. Figure 5 illustrates persistence of the hyperthermic response to endotoxin even after a large dose of indomethacin (14 μmol/100 g, 30 min previously).

Antagonism of endotoxin pyrexia by prostaglandins E_1 and E_2 at 16°C

Injected into the hypothalamus at varying times after *Shigella dysenteriae*, prostaglandins E_1 and E_2 either prevented the onset of hyperthermia or reversed it. Thus in Figure 6a, prostaglandin E_1 (14.3 nmol) was injected 1.75 h after endotoxin (1 μg) when a rise in body temperature would be expected to occur; body temperature rapidly fell by 8.5°C within 1.5 h of infusion. Recovery approximately 6 h later was

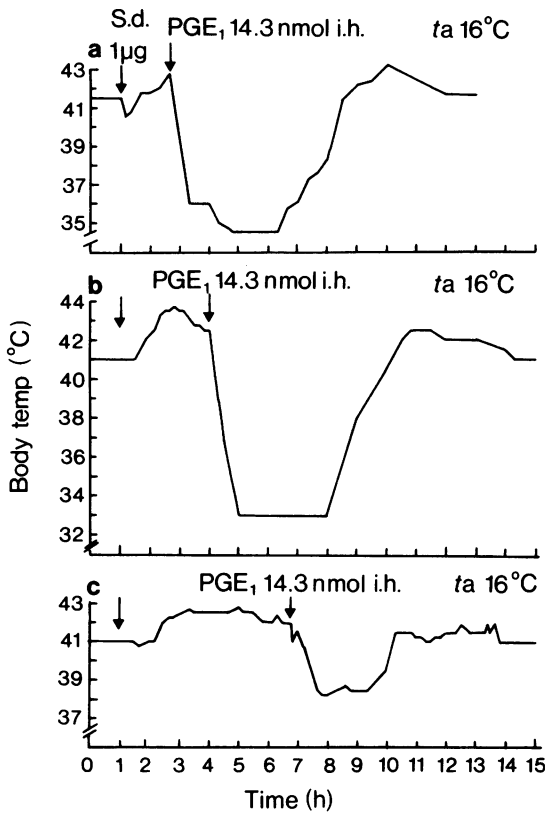

Figure 6 Effects of intrahypothalamic injection (i.h.) of prostaglandin E_1 (PGE_1, 14.3 nmol) at different intervals after intrahypothalamic injection of *Shigella dysenteriae* (S.d., 1 µg). Prostaglandin E_1 was given at the start (a), during (b), and towards the end (c) of the induced pyrexia. Ambient temperature (t_a), 16°C.

followed by an overshoot of 1.5°C before body temperature fiinally returned to normal. The hypothermic response to prostaglandin E_1 was apparently potentiated since the temperature fall of 8.5°C compares with a mean fall of 2.1°C after prostaglandin E_1 alone (Figure 1b). A similar potentiation was seen when prostaglandin E_1 was given shortly after onset of hyperthermia (Figure 6b). In this experiment, prostaglandin E_1 (14.3 nmol) was injected 3 h after the endotoxin at which time body temperature was elevated 1.5°C; prostaglandin E_1 lowered body temperature some 9.5°C, recovery again being followed by the characteristic overshoot. This enhanced response to prostaglandin E_1 was not seen when it was given in the later stages of endotoxin fever, 6 h after the pyrogen (Figure 6c). The hypothermic effects of prostaglandin E_2after the 'O'-somatic antigen of *Shigella dysenteriae* were similar to those of prostaglandin E_1.

Suppression of endotoxin pyrexia by noradrenaline, 5-hydroxytryptamine and carbachol at 16°C

Noradrenaline, 5-hydroxytryptamine and carbachol each produced hypothermia when given alone into the hypothalamus of chicks maintained at 16°C and each counteracted endotoxin pyrexia produced by intrahypothalamic infusion of the 'O'-somatic antigen of *Shigella dysenteriae* (1 µg).

Noradrenaline. When given during the early stages of endotoxin fever at a time when body temperature was elevated 0.75–1°C (2 chicks), noradrenaline (0.05 µmol) abolished the pyrexia and lowered body temperature, although its effects were considerably attenuated. In one chick, maximum fall in body temperature was 8.25°C with recovery after 4 h and in the other, 5.5°C with recovery 2.5 h later; these compare with a mean maximum fall of 15.7°C and recovery in 6–14 h after noradrenaline alone (Marley & Stephenson, 1975).

5-Hydroxytryptamine. 5-Hydroxytryptamine (0.05 µmol) injected into the hypothalamus (3 chicks) lowered body temperature irrespective of whether it was given at the onset or during endotoxin fever. Thus in one chick in which body temperature was elevated 1.25°C, 1.5 h after giving *Shigella dysenteriae*, 5-hydroxytryptamine lowered body temperature 4.25°C with recovery, followed by an overshoot of 0.8°C min later.

Carbachol. Carbachol lacked effect on body temperature when given alone at thermoneutrality (Marley & Seller, 1974) but when given below thermoneutrality it was found to be a potent hypothermic agent. Figure 7 illustrates reversal of

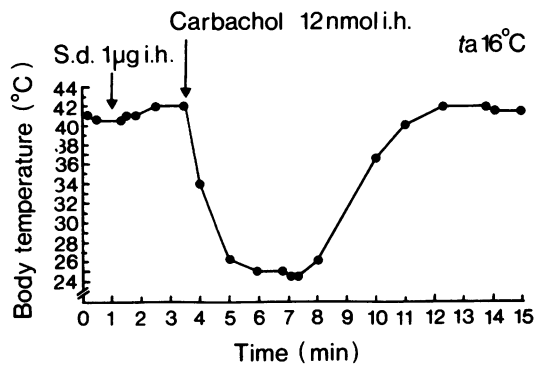

Figure 7 Reversal of endotoxin fever, induced by intrahypothalamic infusion of *Shigella dysenteriae* (S.d., 1 µg), by intrahypothalamic injection (i.h.) of carbachol (12 nmol). Ambient temperature (t_a), 16°C.

established endotoxin hyperthermia by carbachol (12 nmol) injected into the hypothalamus.

Discussion

In young chicks at thermoneutrality, prostaglandin E_1 and E_2 injected into the hypothalamus elevated body temperature, an effect similar to that seen after their intraventricular or intrahypothalamic injection in adult fowls (Nisticò & Marley, 1973; Kane & Peterson, 1975). However, in chicks maintained at an ambient temperature below thermoneutrality (16°C), intrahypothalamic injections of prostaglandin E_1 and E_2 lowered body temperature. The potencies of E_1 and E_2 prostaglandins were similar, E_1 possibly being slightly more active than E_2 at thermoneutrality, whereas below thermoneutrality the converse was true. It is unlikely that the hypothermic responses to prostaglandin E_1 could be attributed to a general proclivity of compounds affecting thermoregulation to depress the body temperature in young chicks when administered below thermoneutrality, since under these circumstances it might be expected that the 'O'-somatic antigen of *Shigella dysenteriae* would also be hypothermic. An ambient temperature of 16°C is not a severe cold stress for young chicks of this age, since plasma non-esterified fatty acids were not significantly elevated and the chicks were able to maintain normal body temperature for over 48 h without shivering (Marley & Stephenson, 1975).

Pretreatment with indomethacin potentiated the hypothermic responses to prostaglandin E_1. Assuming indomethacin to be an effective inhibitor of prostaglandin synthetase then the results could be explained by the presence of two prostaglandins with opposite effects on body temperature, an increased effect of one being counterbalanced by increased release of the other. When the synthesis of both prostaglandins is inhibited, the injected prostaglandin will exert its effect unopposed by the endogenous prostaglandin with the opposite effect. A similar explanation for potentiation of the opposing effects on bronchial tone of prostaglandin E_1 and prostaglandin $F_{2\alpha}$ after indomethacin has been advanced by Frey & Schafer (1974). A simpler alternative explanation, that indomethacin was also inhibiting prostaglandin 15-dehydrogenase, is less likely, since the effects of prostaglandin E_1 were also potentiated by pretreatment with ETA, a more selective inhibitor of prostaglandin synthetase. Should the above explanation be correct then the other prostaglandin is not prostaglandin $F_{2\alpha}$ since this is hypothermic at all ambient temperatures studied, both above and below thermoneutrality (Whelan, 1976).

The opposite effects on body temperature of E series prostaglandins, depending on ambient temperature, and indeed the antagonism below thermoneutrality of endotoxin fever by prostaglandins E_1 and E_2, do not necessarily preclude these as mediators of endotoxin fever in chicks. There remains the possibility that hypothalamic prostaglandins, in addition to their role in the genesis of fever, are also involved in the regulation of peripheral vasomotor tone, the actions of prostaglandin E_1 and E_2 being to cause vasodilatation. Such an action, while not preventing hyperthermia induced by intrahypothalmic infusion of prostaglandins E_1 and E_2 at thermoneutrality, may reverse their hyperthermic action when given below thermoneutrality (not unreasonable considering the large surface/volume ratio of young chicks) and be sufficient to overcome pyrogen fever evoked by a more localized release of endogenous prostaglandin E_1 in response to administration of the 'O'-somatic antigen of *Shigella dysenteria*. However, hypothermic responses to prostaglandins of the E series have also been reported in the adult spiny anteater, *Tachyglossus aculeatus* (Baird *et al.*, 1974). In this non-placental mammal, intraventricular prostaglandins E_1 and E_2 lowered body temperature in both warm and cool environments and, as in the chick, hypothermia was associated with peripheral vasodilatation. The reduction in metabolic rate observed in both species may have been secondary to behavioural sedation in young chicks and to the 'general relaxation' observed in the anteater. It would be of considerable interest to know whether or not prostaglandins E_1 and E_2 were also hypothermic after injection into the preoptic/anterior hypothalamic area of the anteater since this species (a monotrematous mammal) has, unlike birds, evolved from the same reptilian stock as the placental mammals. Below thermoneutrality (16°C), endotoxin fever was also antagonized by intrahypothalamic infusions of noradrenaline, 5-hydroxytryptamine and carbachol, compounds which produce hypothermia when given alone. Interestingly, carbachol lacked effect on body temperature when given at thermoneutrality (Marley & Seller, 1974).

Failure of indomethacin and ETA to prevent onset of endotoxin fever and to abolish established fever make it uncertain that prostaglandins mediate endotoxin fever in chicks. However such a conclusion can only be tentative until the significance of the moderate reduction in the duration of the hyperthermic response to endotoxin after indomethacin and ETA is known and also the degree to which indomethacin and ETA inhibited prostaglandin synthesis. Experiments are in progress to answer these questions.

In summary, the present experiments demonstrate that below thermoneutrality, prostaglandins of the E series produce hypothermia when infused into the hypothalamus of young chicks and that the hypothermia is sufficient to antagonize endotoxin fever. Endotoxin fever is not prevented or abolished by two inhibitors of prostaglandin synthetase,

indomethacin and ETA. Doses of prostaglandin and endotoxin are larger than those used in many mammalian studies but this probably relates to the known resistance of birds to pyrexic agents (Sollman, 1957) and to endotoxin (Jordan & Hinshaw, 1964). Experiments are now in progress to determine whether or not prostaglandins of the E series can be excluded as mediators of endotoxin fever in chicks.

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