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ENDOTOXIN FEVER IN THE NEW-BORN GUINEA-PIG AND THE MODULATING EFFECTS OF INDOMETHACIN AND *p*-CHLOROPHENYLALANINE

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SUMMARY

1. At 30 °C ambient temperature *E. coli* endotoxin injected into the cerebral ventricles evokes a febrile response in 0–3 day-old guinea-pigs. If the dose is sufficiently high, the fever is biphasic: two rising phases separated by a transient fall.

2. At 20 °C ambient temperature the change in body temperature after the endotoxin is still biphasic, but the transient fall is more pronounced and, finally, hypothermia develops. The relatively large surface area of the new-born cannot explain, by itself, the hypothermia.

3. The phasic changes in body temperature following endotoxin administration are unlikely to be mediated by a single central factor, and a sequence of several factors could be postulated.

4. Indomethacin prevents the first-phase febrile rise in body temperature, and also the consequent fall, but not the second-phase rise.

5. *p*-Chlorophenylalanine pre-treatment prevents the transient fall only, it slightly increases the first-phase rise and does not influence the second-phase rise.

6. Prostaglandins and/or other derivatives of endogenous arachidonic acid in the brain might be responsible for the first rising phase of the endotoxin fever, and might also initiate a central serotonergic mechanism which, in turn, could lead to the transient falling phase between the two rising phases of fever. The mechanism of the second-phase febrile rise in body temperature awaits some other explanation.

INTRODUCTION

Researches during the last decade have failed to reveal a single intermediary agent to which all the phases of fever could be attributed, although various naturally occurring substances in the central nervous system, which include monoamines, prostaglandins, and cations (for review see Hellon, 1975), have been implicated. It is possible that the different phases of fever, particularly in those species in which there is a biphasic rise in temperature, relate to the involvement of more than one substance. The identity of these substances and the relations or interactions between them has not, however, been adequately studied.

The new-born guinea-pig responds to endotoxin with a strongly biphasic fever (Székely & Komáromi, 1977). In the adult guinea-pig (Blatteis, 1974) the biphasic

fever-course is usually less spectacular, possibly because of the thermal inertia of the greater body mass. The new-born animal's response to endotoxin therefore offered an opportunity to study the factors responsible for the biphasic character of the endotoxin fever. We have investigated the characteristics of the endotoxin fever in the new-born guinea-pig and examined the possible roles that prostaglandins (or similar substances) and 5-hydroxytryptamine (5-HT, serotonin) might have in it.

METHODS

The ninety-seven guinea-pigs used were from the Department's colony, and were up to 3 days old. Body weight ranged between 69 and 132 g; mean body weight was 96 g.

The animals were taken from the nest immediately before the experiment. First, the skin over the skull was incised under local anaesthesia with 0·1 ml. procaine HCl (Richter). A fine rectal probe containing a copper-constantan thermocouple was then introduced into the rectum to a depth of 50–60 mm. The probe was fixed in position with adhesive tape or with a stitch to the skin. Next, the animals were placed singly into a small open-circuit metabolic chamber, in which there was a certain freedom of movement but the animal was unable to turn around. The bottom of the chamber was lined with layers of filter paper to absorb urine. The whole chamber was immersed in a thermostatically controlled water-bath to maintain chamber temperature at near to thermoneutrality (usually 30 °C, but 1 or 2 °C warmer for very small animals; nominal value: T_a 30 °C) or at a standard low temperature (20 °C T_a). Air was pulled through the chamber with a rate of 90–100 l./hr, and in some instances the air leaving the chamber was analysed by a modified Kipp Noyons diaferometer (Donhoffer, Szegvári, Varga-Nagy, Járai & Haug-László, 1958). Colonic temperature (T_c) was continuously recorded by a Kipp micrograph (sensitivity: 1 °C = 40 mm). Recordings were begun after the animal had become settled in the chamber and colonic temperature (T_c) had stabilized; this took usually 30–60 min.

30 min after the recordings began the animals were taken out and injected either into the peritoneum (I.P.) or into a lateral cerebral ventricle (I.C.V.). They were then returned to the original environment within about 30–60 sec. For I.C.V. injections the head of the animal was held firmly in one hand between the thumb and forefinger and bolstered by a wooden holder whilst, with the other hand, a 5·5–6·5 mm long (length varied with body size) 20-gauge needle was inserted at an angle of 90° through the soft skull, at a point 1·0–1·5 mm behind and 1·0 mm lateral to the coronary and sagittal sutures, respectively, into one or other of the lateral cerebral ventricles. From the attached syringe, substances were injected in a volume of 10–20 μl. This technique had been developed during a preliminary technical study, in which the Evans-blue solution similarly injected appeared, with very few exceptions, in the third ventricle. Nevertheless, the position of the injector needle was regularly checked post mortem; the few cases in which the localization of the injection was uncertain or where bleeding or obviously serious tissue damage had occurred, were excluded from the statistical analysis.

All glassware, needles and syringes were cleaned with strong acids and detergents, carefully rinsed with pyrogen-free distilled water and then autoclaved (135 °C for 30–60 min) before use.

Materials used. (1) Pyrogen-free 0·9% NaCl (Biogal) was used as solvent and was also used for the control I.C.V. injections. (2) *E. coli* endotoxin (O 111, 1838 S_4, Max-Planck-Institut für Immunbiologie, Freiburg) dissolved in 0·9% (w/v) NaCl. (3) Indomethacin (Chinoin) was dissolved in absolute alcohol plus Tween 80, and diluted with 0·9% NaCl to get a solution of 2 mg indomethacin and 20% alcohol per ml. The Figures and text relate to the effects of an I.P. injection of indomethacin (10 mg/kg) but every indomethacin treated animal had also received a similar I.P. injection of indomethacin 4–8 hr before removal from the nest, since one single dose did not ensure consistent blocking effects. (4) A suspension of PCPA (D-L-*p*-chlorophenylalanine, Sigma) (30 mg/ml.) was made in 1% carboxymethylcellulose vehicle. PCPA (300 mg/kg) was injected I.P. 48 and also 24 hr before experiments. In a few instances 30 μl. of this suspension was injected I.C.V. 48 hr before experiment.

Any group treated with either of these materials or with various combinations of them consisted of six animals, excepting those groups that were used to clarify the basic characteristics of the endotoxin response at T_a 30 °C (n = 11) and at T_a 20 °C (n = 14). Student's t test was used for statistical analysis.

RESULTS

The pooled data for T_c at the start of recordings at -30 or -60 min (as indicated in the Figures), irrespective of the forthcoming treatment, are given in Table 1.

TABLE 1. Influence of the ambient temperature (T_a) and of various pre-treatments on the colonic temperature (T_c) in new-born guinea-pigs.

Treatment	T_a (°C)	Mean $T_c \pm$ S.E. (°C)	n
Controls	30	39·34 ± 0·07	35
(no pre-treatment)	20	39·10 ± 0·09	20
PCPA pre-treated	20	39·20 ± 0·11	12
Indomethacin pre-treated	30	39·27 ± 0·11	18
	20	38·66 ± 0·14	12
		Total n =	97

Within the control group there was a slight but statistically significant ($P < 0·05$) difference in T_c at the two environments. Indomethacin pre-treated animals in the cold had significantly lower T_c than the corresponding controls ($P < 0·01$) or those receiving similar treatment and kept at T_a 30 °C ($P < 0·001$). No other comparison between the groups showed a significant difference in T_c. Guinea-pigs treated with indomethacin 4–8 hr beforehand were not hypothermic at T_a 30 °C, and Fig. 3 demonstrates that in these animals the start of the endotoxin fever response was almost the same as that of the controls. Fig. 2 shows that at T_a 30 °C further treatment with indomethacin during the recordings resulted in a T_c fall which developed slowly and reached a maximum of about 0·3–0·5 °C about 130–160 minutes after this I.P. treatment; whereas at T_a 20 °C the extent of the fall was similar from a lower initial T_c, but it developed sooner and persisted throughout the experimental period.

Intracerebroventricular injections of 0·9 % NaCl had no influence on the T_c of control or PCPA-treated animals at T_a of either 30 or 20 °C, nor did they modify the effect of indomethacin. Control and PCPA treated animals maintained homoeothermy at T_a 30 °C as well as at T_a 20 °C, throughout the experiments.

Fig. 1 shows the relation of the T_c response to endotoxin dose at T_a 30 °C: the larger the dose the sooner a rise started. Smaller doses resulted in monophasic fevers, whereas larger doses elicited biphasic fevers. Due to variations in the individual fever time courses the biphasic character was less evident in plots of the average T_c changes. The individual variations were greater with very large doses, hence the biphasic course could be best studied after a dose of 0·2 μg endotoxin I.C.V.

The results observed upon injecting 0·2 μg endotoxin I.C.V. to control and indomethacin treated animals are shown in Fig. 2. At T_a 30 °C T_c started to rise after a latency of about 15 min and reached a peak about 50 min and another one about 120 min after the injection, the two peaks having been separated by a transient decline between about the 50th and 85th min. At T_a 20 °C the T_c changes were still biphasic; the thermal inertia of the body might, in part, explain slight differences in timing and in peak values. At T_a 20 °C the rising phases, considered alone, were similar to those at 30 °C T_a, i.e. the first rise in T_c at T_a 20 °C was almost the same as

that at T_a 30 °C, and the extent of the second rise in T_c was also similar at the two environmental temperatures. The main T_a-dependent difference was in the extent of the transient fall: at T_a 20 °C this was much greater than at 30 °C. A result of this was that the second rise in T_c did not elevate it to the initial level so a state of hypothermia persisted.

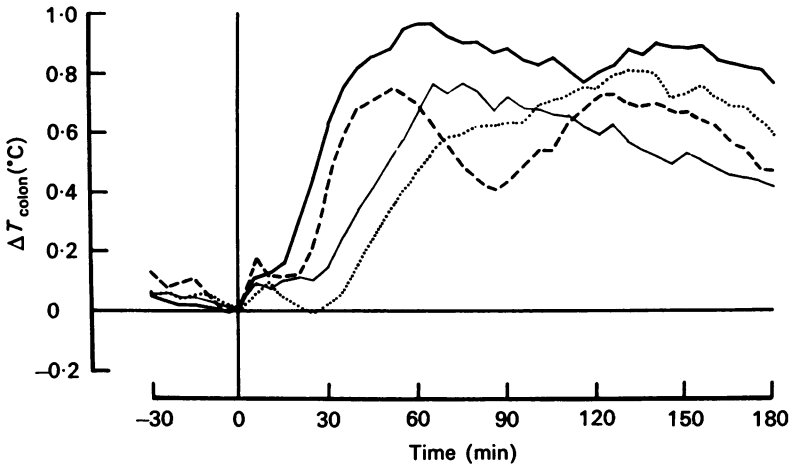

Fig. 1. Colonic temperature (T_c) changes in new-born guinea-pigs after an I.C.V. injection of 2·0 μg (——), 0·2 μg (– – –), 0·02 μg (——) or 0·002 μg (.....) *E. coli* endotoxin at T_a 30 °C. Each line represents the mean of six measurements (in case of 0·2 μg dose, the line refers to the first six experiments out of the total of eleven shown in Fig. 2). Base line represents 39·14 ± 0·11, 39·30 ± 0·13, 39·06 ± 0·06 and 39·16 ± 0·12 °C, respectively.

In guinea-pigs treated with indomethacin 4–8 hr before experiment, and again 30 min before the endotoxin (i.e. about 45 min before the expected onset of fever), the early T_c rise from the endotoxin response was prevented, and the ensuing transient fall was also absent. A late rise in T_c, coincident in time with the second rise which generally occurred in response to the pyrogenic agent, still occurred. Indomethacin had these effects at both 20 and 30 °C.

In other experiments the indomethacin injection was repeated 40 min after the endotoxin injection (instead of preceding it by 30 min), i.e. about 45 min before the expected onset of the second-phase T_c rise. As in the previous experiments, T_c fell after indomethacin, but the fall was reversed within about 50 min. After subtracting from the actual T_c change the fall that would have followed the I.P. injection of indomethacin on its own (see in Fig. 2) at the same T_a, the resultant T_c course, which is shown in Fig. 3, revealed that there was still a rise in T_c at the time when the second febrile rise normally occurred.

The effects of PCPA on fever are shown in Fig. 4. At T_a 20 °C the very pronounced transient fall in T_c between the two rising phases of endotoxin-induced fever was much smaller in PCPA-treated animals than in controls: instead of the hypothermia observed in the controls, T_c of the PCPA-treated guinea-pigs was significantly elevated even 180 min after the endotoxin injection. The first-phase rise in T_c was

greater in the PCPA-treated group than in the controls. The second-phase rise, however, although starting at a higher T_c, was in the same order of magnitude as that of controls. Similar results were obtained in the few cases when PCPA was administered I.C.V. in a minute dose.

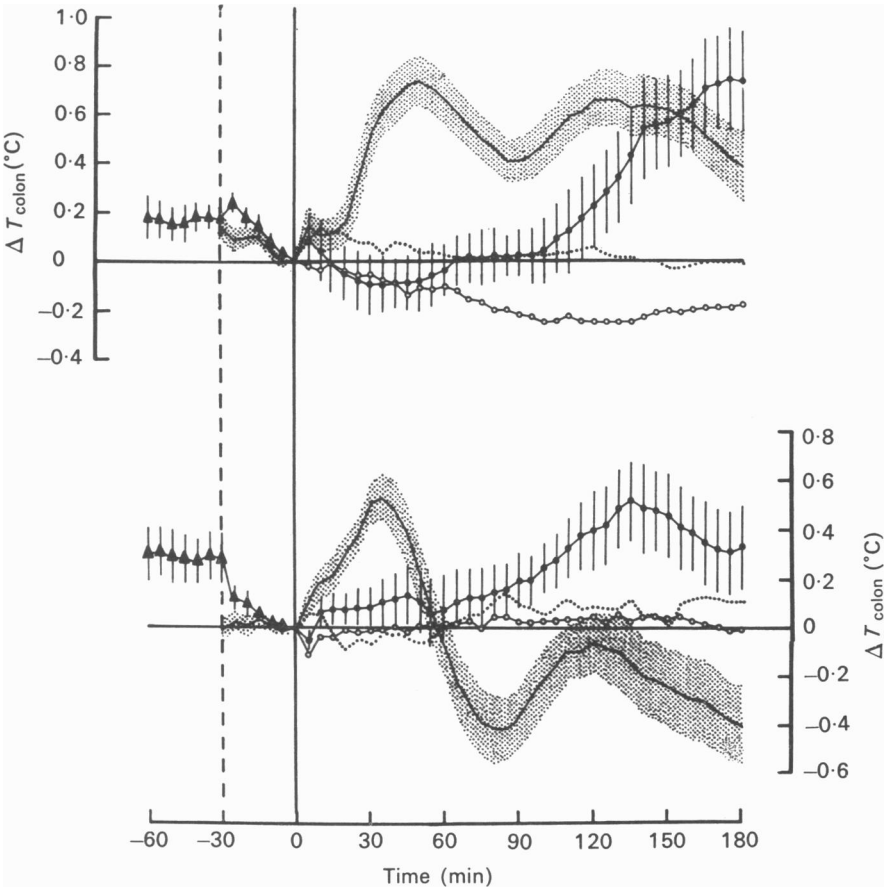

Fig. 2. Mean changes in T_c in control animals after an I.C.V. injection of 0·9% NaCl (.....) or 0·2 μg endotoxin (——) at the continuous vertical line. Indomethacin pretreated guinea-pigs were regarded as one group (▲—▲), they were injected again with indomethacin at the interrupted vertical line, and after the I.C.V. injection they were divided to two equal groups receiving 0·9% NaCl (○—○) or 0·2 μg endotoxin (●—●) I.C.V. Shaded areas (normal fever response) and vertical bars (indomethacin treated animals) represent S.E. of mean. *Above:* experiments at T_a 30 °C. Base line represents 39·27 ± 0·16 °C (n = 6), 39·38 ± 0·15 °C (n = 11), 39·31 ± 0·20 °C (n = 6), and 39·09 ± 0·15 °C (n = 6), respectively. *Below:* experiments at T_a 20 °C. Base line represents 39·24 ± 0·11 °C (n = 6), 39·16 ± 0·07 °C (n = 14), 38·48 ± 0·19 °C (n = 6), and 38·25 ± 0·24 °C (n = 6), respectively.

DISCUSSION

In agreement with the experiments of Pittman, Cooper, Veale & Van Petten (1973) on lambs, Blatteis (1975, 1976) reported that endotoxin had no effect on body temperature in the new-born guinea-pig: at thermoneutrality febrile responses were

seen only at or beyond the age of 32 days. He concluded that the lack of fever was due to the immaturity of some central febrigenic mechanism, supposedly quite independent of general thermoregulation, since new-born guinea-pigs can maintain homoeothermy even on exposure to severe cold (Alexander, 1975). In a more recent publication Blatteis (1977) demonstrated that the insensitivity of the new-born guinea-pig to endotoxin was relative, but even with the highest doses he could not observe biphasic fever before the age of 8 days, whereas the biphasic response is characteristic for the adult guinea-pig.

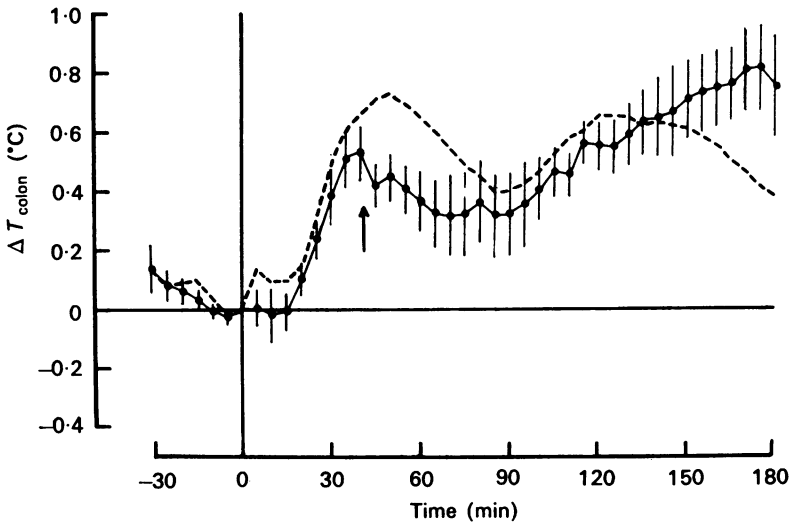

Fig. 3. Changes in T_c at T_a 30 °C in indomethacin pre-treated guinea-pigs (mean of six ± S.E. of mean, ●—●) given I.C.V. 0·2 μg endotoxin at the vertical line plus I.P. indomethacin at the arrow. Base line represents 39·29 ± 0·20 °C. After the arrow the values were calculated by subtracting the mean change caused by indomethacin *per se* from the temperatures that were actually measured. For comparison the mean endotoxin response of control animals (– – –) is also shown.

The present results confirm our earlier data obtained with I.P. endotoxin administration (Székely & Szelényi, 1977), and show that at thermoneutrality guinea-pigs are able to develop endotoxin-induced fever immediately after birth. If the dose of endotoxin is sufficiently high, the fever is biphasic. In fact, we applied relatively high doses, but the fever response in these new-born guinea-pigs was qualitatively similar to that reported for the adults of the same (Blatteis, 1974), and some other (Bennett & Cluff, 1957) species. The discrepancy between the fever responses obtained in our present experiments and those of Blatteis may be due largely to methodical differences, since we used I.C.V. route, a different pyrogen, and no general anaesthesia.

At 3 days of age, or less, endotoxin also evoked a change in T_c at T_a 20 °C, but the net response was hypothermia. This hypothermia also has some other implications. Independently of age, small-sized mammals have been reported to respond to endotoxin with hypothermia or no change in T_c when T_a is below thermoneutrality (Van Miert & Frens, 1968). The explanation most generally given for this effect on T_c is that with a large surface area relative to mass the endotoxin-induced rise in

heat production was exceeded by a concurrent increase in heat loss resulting from whole body movements due to concomitant shivering. The available data do not seem to support this explanation. First, because the same reasoning should apply to almost any hyperthermic agent, but both in adult rats (Feldberg & Saxena, 1971) and in new-born guinea-pigs (Székely & Komáromi, 1977) a rise in T_c has been shown to occur in response to prostaglandin E_1 and to other substances at the same ambient temperatures at which endotoxin resulted in hypothermia or was without effect on T_c. Secondly, because in the present experiments the hypothermia developed in a particular way indicative of a physiological rather than a purely physical explanation: the changes still resembled those seen at T_a 30 °C, both in the biphasic

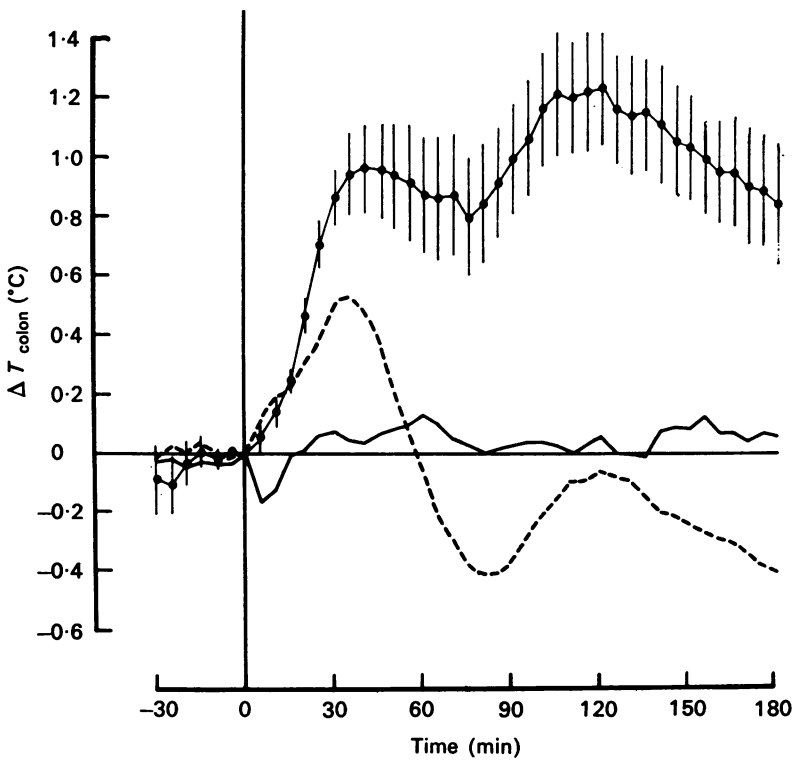

Fig. 4. Mean T_c changes at T_a 20 °C after an I.C.V. injection of 0·9 % NaCl (——) or 0·2 μg endotoxin (●—●) to PCPA pre-treated guinea-pigs at the vertical line. Vertical bars show S.E. of mean. Base line represents 39·16 ± 0·19 °C (n = 6) and 39·34 ± 0·09 °C (n = 6), respectively. For comparison, the mean endotoxin-response of control animals is also demonstrated (– – –).

pattern and in the time courses of the rising and falling phases; the extent of the fall between the two rising phases, however, was more pronounced, and this was responsible for the sustained hypothermia. Simultaneous measurements of oxygen consumption revealed that at T_a 20 °C oxygen consumption increased in the periods of T_c rise, but it fell much below the pre-injection level during the period of T_c fall. This clearly indicated that the hypothermia was due to a physiological effect and not simply to an excessive heat loss at the lower T_a. Although this co-ordinated hypo-

thermic reaction is dominant in the cold, it is still restricted to a certain period of the endotoxin response, while in other periods other co-ordinated reactions elevated T_c both at T_a 30 °C and at T_a 20 °C.

The essentially similar, biphasic courses of endotoxin-induced fever at 20 and 30 °C T_a, with the only ambient-temperature-dependent difference being the greater fall in T_c between the two rising phases, suggest that a single central factor is unlikely to be directly responsible for the complex multiphasic changes in T_c in response to the endotoxin. A series of distinct events within the central nervous system, involving several factors, would seem more likely.

A great body of circumstantial evidence suggests that central prostaglandins might be a factor or factors in the genesis of fever (Milton & Wendlandt, 1971; Feldberg, 1975; Hellon, 1975). In the new-born guinea-pig, I.C.V. injections of prostaglandin E_1 resulted in monophasic rises in T_c both at 30 and at 20 °C T_a (Székely and Komáromi, 1977), thus a prostaglandin could not alone be the cause of the whole multiphasic endotoxin response or for the T_a-dependent variations of the response, although prostaglandins or other products of arachidonic acid (Cranston, Duff, Hellon, Mitchell & Townsend, 1976, Laburn, Mitchell & Rosendorff, 1977) probably do play a part in one of the rising phases.

Indomethacin, which prevents the catabolism of arachidonic acid into more than one pyrogenic derivative including the prostaglandins (Laburn *et al.* 1977), also prevented the first-phase rise in T_c in response to endotoxins, but a late rise which probably corresponded to the second-phase rise of the normal endotoxin-induced fever, still occurred. This indicated that an increased synthesis of prostaglandins, or of other arachidonic acid derivatives, had a decisive role in only the first-phase rise in T_c. It is arguable that the late rise in T_c could be due to the wearing off of the effect of the single injection of indomethacin, thus permitting a delayed production and release of prostaglandin-like pyrogenic substances. In new-born kittens and guinea-pigs, however, similar indomethacin treatment prevents the hyperthermia which occurs 80–90 min after an I.C.V. injection of 5-HT, but does not interfere with more immediate effects of the drug on T_c (Székely, 1978). This observation indicates that indomethacin was probably still effective at the time of the secondary rise in T_c. Indeed, Fig. 3 shows that indomethacin did not prevent the second-phase T_c rise even when it was given only 45–60 min before the expected occurrence of the second phase. This interval was the same as that which elapsed between the indomethacin injection and the expected first-phase rise in Fig. 2.

5-Hydroxytryptamine has been also implicated in the central mediation of fever (Feldberg & Myers, 1964; Myers, 1971) although it now seems more likely that the long lasting rise in T_c following central injections of 5-HT was due to an incidental release of prostaglandins. The immediate effects of I.C.V. or intrahypothalamic injection of 5-HT on T_c have been found to vary between species and in one species in different studies (for reviews see Bligh, 1973; Feldberg, 1975; Hellon, 1975). Various influences of serotonin synthesis blocker PCPA (Koe & Weissman, 1966) on experimentally induced fever have been observed in different studies (e.g. Des Prez & Oates, 1968; Giarman, Tanaka, Mooney & Atkins, 1968; Carruba & Bächtold, 1976). Thus, there is no unequivocal evidence of a role of endogenous 5-HT in the genesis of fever.

In rats, mice and dogs 48 hr after the administration of PCPA (300 mg/kg) brain levels of 5-HT were decreased to about 10 % of control (Koe & Weissman, 1966). The effect of a similar dose of PCPA in the study now being discussed was to diminish the fall in T_c which normally occurs between the two rising phases of the endotoxin fever of new-born guinea-pigs. This can be interpreted as evidence of the involvement of a serotonergic mechanism in the transient fall. This proposition fits with the finding of Székely (1978) that centrally applied 5-HT resulted in a primary hypothermia in the guinea pig, and reconciles the hypothermic effect of centrally administered 5-HT in the guinea-pig with the apparent involvement of endogenous 5-HT in the hypothermic phase of endotoxin induced fever. Apart from its involvement in this hypothermic phase, 5-HT may not be a factor in the genesis of fever. The extent of the first-phase rise was somewhat greater in the PCPA treated group. A possible explanation for this could be that through the release of endogenous 5-HT the course of hypothermia was already slightly active during the first-phase rise in T_c. The second-phase rise, however, was not affected by PCPA treatment.

Since the secondary hyperthermia which is induced by centrally applied 5-HT can be attenuated with indomethacin (Székely, 1978), it could be supposed that prostaglandins or similar substances are responsible for the second-phase rise in T_c during endotoxin-induced fever. If this were so, both indomethacin and, perhaps, PCPA should prevent the second-phase rise in T_c, but in the present experiments neither of these substances had that effect. Thus, the secondary rise in T_c of endotoxin-induced fever may be unrelated to the second rise in T_c following centrally administered 5-HT.

As well as preventing the first of the rises in T_c in endotoxin-induced fever, indomethacin also prevented the transient fall which follows the rise, at both 20 and 30 °C T_a. A possible explanation for this is that indomethacin blocked the synthesis of some derivative of arachidonic acid which has a hypothermic effect. So far, however, no such substances have been demonstrated. A more likely explanation is that the presence of those arachidonic acid breakdown products which induce the first-phase rise in T_c, or the presence of this rise itself, is necessary to activate the 5-HT-mediated mechanism which causes the transient fall in T_c after the first-phase rise. In other words, the blocking of arachidonic acid breakdown with indomethacin, may only indirectly inhibit the transient fall.

The experiments suggest that products of arachidonic acid breakdown are essential to induce the first-phase rise of T_c in endotoxin fever, and may play a role in the initiation of a central serotonergic process which leads to the transient fall in T_c. They are, however, not essential for the second-phase rise in T_c.

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