Materials and methods. 5–10-day-old kittens and 0–3-day-old guinea-pigs were injected by a direct puncture technique through the soft skull into the lateral cerebral ventricles (i.c.v.) with 10 µg 5-HT or solvent (0.9% NaCl) in a volume of 20–40 µl. The animals were placed in an open-circuit metabolic chamber maintained at the thermoneutral temperature (i.e. 30–33 °C for kittens and 30–32 °C for guinea-pigs), and colonic temperature was continuously measured by copper-constantan thermocouples. Indomethacin (IM; 10 mg/kg) was injected i.p. 3–6 h and 30 min prior to the i.c.v. injections of 5-HT or physiologic saline.

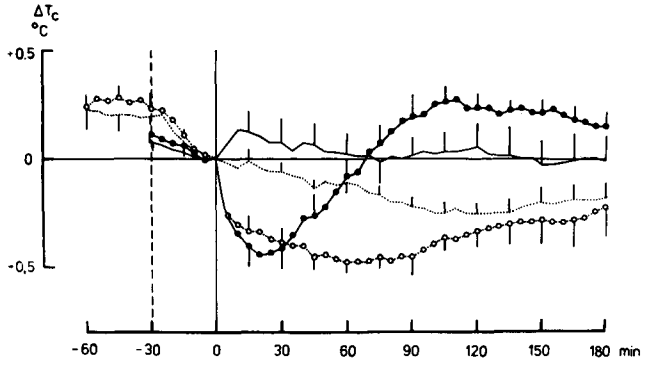

Fig. 2. Changes of Tc in 0–3-day-old guinea-pigs at 30–32 °C ambient temperature (6 animals in each group, mean ± SEM). Symbols as in figure 1. Tc at T_0 = 5-HT: 39.37 ± 0.15 °C; 0.9% NaCl: 39.27 ± 0.16 °C; IM + 5-HT: 39.09 ± 0.12 °C; IM + 0.9% NaCl: 39.14 ± 0.09 °C.

Results and discussion. In kittens (figure 1), i.c.v. 5-HT injection was followed by a marked increase in Tc as has been found by Feldberg et al.[7] in adult cats. However, in kittens the rise took place in 2 distinct steps: an early and a late one, separated by a fall to almost the initial level. IM by itself lowered Tc. In animals pretreated with IM, the early rise after 5-HT was greater, so that peak-Tc approximated that of controls, then Tc returned to the level seen before 5-HT injection and no late rise occurred.

In guinea-pigs (figure 2), i.c.v. 5-HT produced an early fall in Tc, followed by a late rise: a result resembling those of Bligh et al.[8] on adult sheep, goats and rabbits. The changes were relatively small in both directions, and confirmed the observations of Komáromi[1]. Pretreatment with IM reduced Tc by 0.2–0.4 °C, and 5-HT i.c.v. was followed by an early fall in Tc similar to that seen in guinea-pigs not treated with IM; the late increase in Tc was, however, abolished.

The experiments presented here show that 5–10-day-old kittens and 0–3-day-old guinea-pigs give thermoregulatory responses to i.c.v. 5-HT. The data suggest that:

1. In the newborn kitten hyperthermia is the primary effect of i.c.v. 5-HT in the applied dose, whereas in the newborn guinea-pig it is hypothermia.
2. In newborn kittens and guinea-pigs, the late rise in Tc after 5-HT is caused by increased PG-synthesis.

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Prostaglandin E_1-induced fever in rabbits pretreated with p-chlorophenylalanine[1]

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Summary. The prostaglandin E_1-induced fever was neither potentiated nor attenuated at all levels of the ambient temperatures (2, 22 and 32 °C) studied after pretreatment of the conscious rabbits with p-chlorophenylalanine, when compared to the untreated control.

The current evidence favors that prostaglandins of the E-series play some part in the action of pyrogens on the CNS[2,3]. Experiments which have attempted to assess the pyrogenic responses of animals with altered brain serotonin levels have produced conflicting information. Several investigators working with rabbits have found after brain depletion of serotonin by p-chlorophenylalanine (pCPA) that pyrogenic responses were enhanced[4,5]. In contrast, Des Prez and Oates[6] claim that depletion of serotonin levels in the rabbit brain to around 9% of control levels produced no alteration in the febrile responses to endotoxin injections. Milton and Harvey[7] report that cats treated with pCPA show attenuated pyrogenic responses to prostaglandin E_1(PGE_1) inoculation. In the present investigation, the febrile responses induced by intraventricular administration of the pyrogen PGE_1 were measured in rabbits pretreated with an i.p. dose of pCPA (300 mg/kg) to ascertain whether serotonin depleted animals could respond adequately to a substance which alters the level at which body temperature is regulated.

The animals treated with pCPA were studied 72 h after the injection, when serotonin depletion was maximal[5,8]. A 100 µl aliquot containing 500 ng of PGE_1 was administered into the 3rd cerebral ventricle through a ventri-

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cular cannula guide tube which had been previously implanted in the animal[2]. The responses of these pCPA-treated animals to PGE_1 were assessed at 3 different ambient temperatures (T_a: 2, 22 and 32 °C). Metabolic rate (MR), respiratory evaporative heat loss (E_{res}), ear blood flow (EBF), rectal (T_{re}) and hypothalamic (T_{hy}) temperatures were measured[2]. All drug solutions were prepared in pyrogen-free glassware which was baked at 180 °C for 4 h before use.

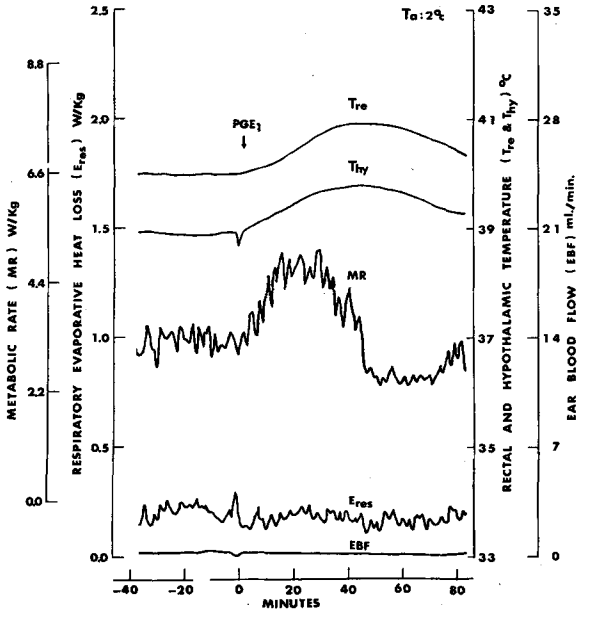

Fig. 1. Record of rectal (T_{re}) and hypothalamic (T_{hy}) temperatures, metabolic rate (MR), respiratory evaporative heat loss (E_{res}) and ear blood flow (EBF) from a pCPA-treated rabbit at an ambient temperature of 2 °C. At the arrow, injection into the 3rd cerebral ventricle of 0.1 ml with 500 ng of PGE_1.

Figures 1–3 show that in each case the pCPA-treated animals had no difficulty in maintaining their T_{re} within normal limits at all levels of T_a studied. Animals which were treated with pCPA, although showing no alterations in MR at both T_a of 22 °C and 32 °C, did show a lower MR accompanied by a lower E_{res} at T_a of 2 °C compared to the untreated control. It was found that the PGE_1-induced fever was neither potentiated nor attenuated at all levels of T_a studied after pretreatment of the conscious rabbits with pCPA, when compared to the untreated control. In the cold, the PGE_1-induced fever was brought about by an increase in MR (figure 1). At thermoneutrality, the PGE_1-induced fever was also due to an increase in MR (figure 2). In the heat, the PGE_1-induced fever caused by an inhibition of both heat loss mechanisms, both a decrease in EBF and in E_{res} (figure 3).

The present data are inconsistent with the previous results that depletion of brain serotonin by pretreatment with intraventricular administration of 5,7-dihydroxytryptamine (5,7-DHT) reduced the PGE_1-induced fever in rabbits[2]. Thus, in spite of a similarity between the pCPA-treated and 5,7-DHT-treated rabbits in brain concentrations of serotonin, the pCPA-treated animals have some more intact functioning serotonergic neurons for the development of fever. The pCPA-treated rabbits presumably have all serotonergic neurons functionally depressed but morphologically intact. Another factor which makes the 2 groups of animals not comparable is the possible development of denervated supersensitivity in 5,7-DHT-lesioned rabbits. However, it should be noted that pCPA has a number of other actions besides its action on serotonin synthesis, for example increasing uptake of amino acids through brain-blood barrier[9,10] as well as having both peripheral and central actions which may account for its action.

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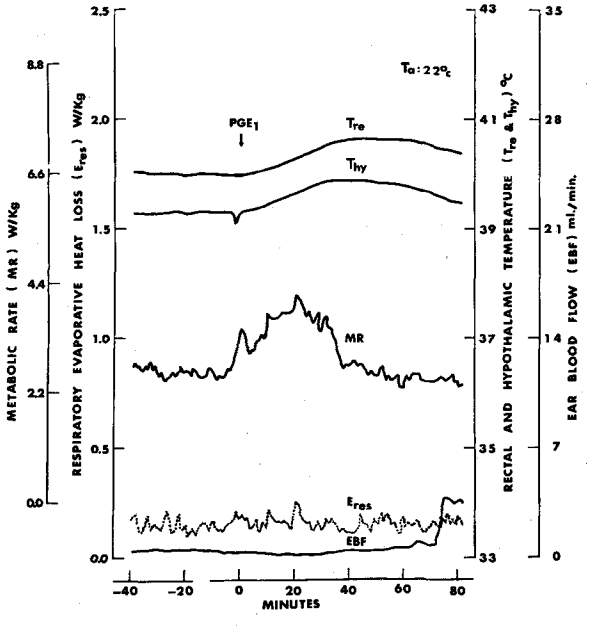

Fig. 2. Record of rectal (T_{re}) and hypothalamic (T_{hy}) temperatures, metabolic rate (MR), respiratory evaporative heat loss (E_{res}) and ear blood flow (EBF) from a pCPA-treated rabbit at an ambient temperature of 22 °C. At the arrow, injection into the 3rd cerebral ventricle of 0.1 ml with 500 ng of PGE_1.

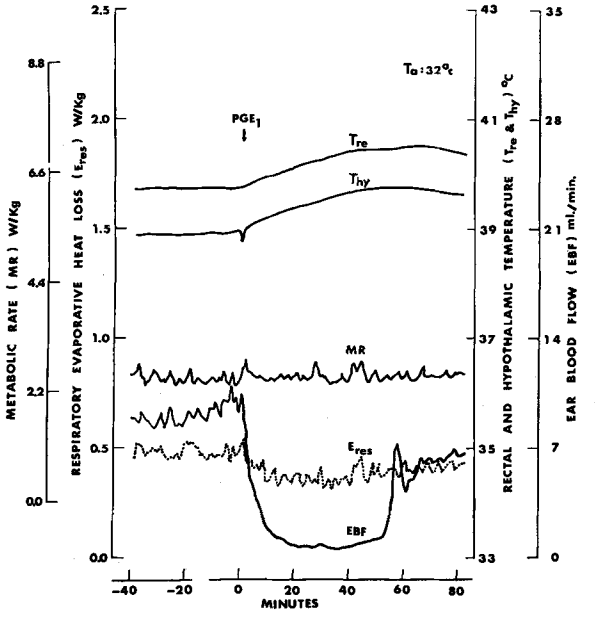

Fig. 3. Record of rectal (T_{re}) and hypothalamic (T_{hy}) temperatures, metabolic rate (MR), respiratory evaporative heat loss (E_{res}) and ear blood flow (EBF) from a pCPA treated rabbit at an ambient temperature of 32 °C. At the arrow, injection into the 3rd cerebral ventricle of 0.1 ml with 500 ng of PGE_1.