Results and discussion. The figure shows the effects of ischemia on the membrane potential and ATP content in the livers of ethionine-treated and untreated rats. The membrane potential and ATP content in the livers of untreated rat were −52.4 ± 3.6 mV (mean ± SD) and 2.43 ± 0.25 μmoles/g wet liver, respectively. Both of these decreased markedly during ischemia. The membrane potential and ATP content in the livers of ethionine-treated rats were −43.8 ± 4.4 mV and 0.44 ± 0.13 μmoles/g wet liver, respectively. Ethionine decreased markedly the ATP content, but did not decrease so much the membrane potential as ischemia. In addition, ischemia brought about decreases in both membrane potential and ATP content in the ethionine-treated rats; the decrease in membrane potential was statistically significant ($p < 0.01$) but the decrease in ATP content was insignificant ($0.1 < p < 0.2$). Both in ethionine-treated and untreated rats, the membrane potentials decreased by ischemia recovered to each original level when the blood flow to the liver was restored 20 min after the onset of ischemia.

Shiba et al.[4] suggested that an active ion transport mechanism contributes to the maintenance of the membrane potential of rat liver cells and that ethionine inhibits the mechanism by its ATP depleting action and, thus, brings about a decrease in the membrane potential. This is probably true in case of ethionine treatment. However, in consideration of the experimental results mentioned above, it is unlikely that the decrease in membrane potential during ischemia is brought about entirely owing to its ATP depleting effect. The energy from different source(s) other than ATP may also be utilized to maintain the membrane potential. Ischemia may cause depletions of not only ATP but also other energy source(s) and, thus, bring about a marked decrease in the membrane potential. Alternatively, ischemia might be able to cause a change in the physical membrane property of liver cell in addition to a depletion of ATP in the cell.

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5-hydroxytryptamine induced changes in body temperature of newborn kittens and guinea-pigs and the effect of indomethacin thereon

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Summary. During the first days of life 10 μg i.c.v. 5-HT evoked a primary, short-lasting hyperthermia in kittens and hypothermia in guinea-pigs. In both species, a secondary late hyperthermia occurred that could be prevented by indomethacin pretreatment.

Despite that thermoregulatory reactions of newborn mammals differ from those of adults, the effect of centrally applied 5-hydroxytryptamine (5-HT) has been studied only in newborn guinea-pigs[1], where 5-HT was found to evoke an initial fall followed by an increase in body temperature (Tc).

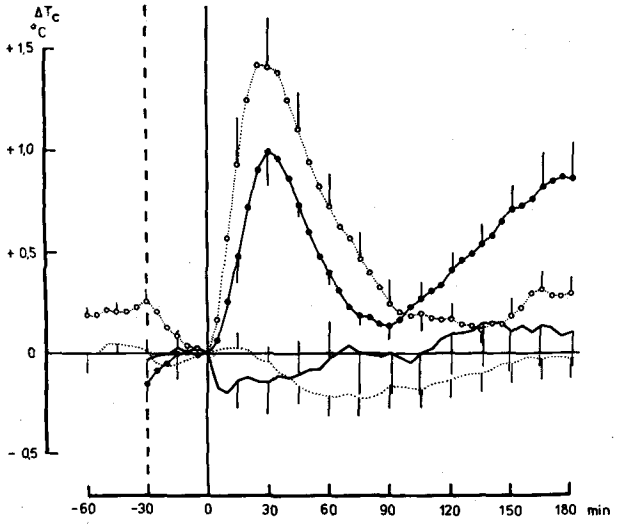

Fig. 1. Changes of Tc in 5–10-day-old kittens at 30–33 °C ambient temperature (6 animals in each group, mean ± SEM). ●—●, 10 μg 5-HT i.c.v.; ——, 0.9% NaCl i.c.v.; ○ . . . . ○, 10 μg 5-HT i.c.v. 30 min after i.p. IM; . . . . . , 0.9% NaCl i.c.v. 30 min after i.p. IM. The zero lines represents Tc at the time of i.c.v. injection of 5-HT or 0.9% NaCl (T_0). Tc at T_0 = 5-HT: 38.07 ± 0.11 °C; 0.9% NaCl: 37.96 ± 0.15 °C; IM + 5-HT: 37.33 ± 0.08 °C; IM + 0.9% NaCl: 37.29 ± 0.08 °C.

In adult mammals, as reviewed by Hellon[2], centrally applied 5-HT resulted in either hypothermia, hyperthermia, or a biphasic change in Tc, depending on species, ambient temperature, dose, etc., while prostaglandins of the E-series (PGE) produced hyperthermia in most of the species so far studied. In contrast to the striking differences in the effects of the 2 drugs, there are reports indicating an interaction between them: 5-HT was found to increase synthesis[3] and release[4] of endogenous PGE in neural tissues, and Milton and Harvey[5] have suggested that prostaglandins might be involved in the thermoregulatory effects of 5-HT in the cat, since paracetamol prevented 5-HT-hyperthermia. Indomethacin pretreatment had been used by Kandasamy et al.[6] in a study in which it was found to prevent hyperthermia following large (0.3 mg) doses of 5-HT in adult rabbits. In the present study, the thermoregulatory effects of centrally administered 5-HT were observed in newborn kittens and guinea-pigs. Also, the possible role of endogenous prostaglandins in the 5-HT induced Tc changes was tested in both species by blocking PG-synthesis with indomethacin.

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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.

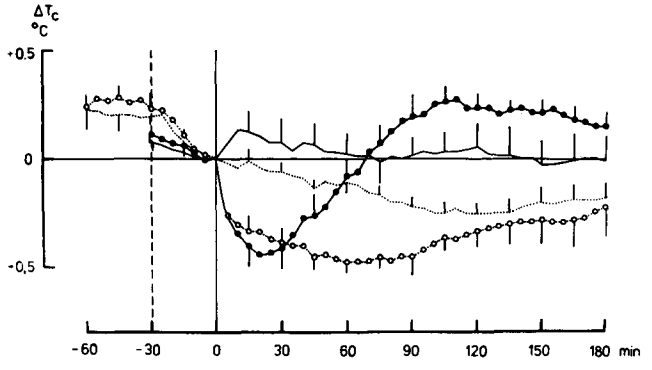

Fig. 2. Changes of Tc in 0–3-day-old guinea-pigs at 30–32 °C ambient temperature (6 animals in each group, mean ± SEM). Symbols as in figure 1. Tc at T_0 = 5-HT: 39.37 ± 0.15 °C; 0.9% NaCl: 39.27 ± 0.16 °C; IM + 5-HT: 39.09 ± 0.12 °C; IM + 0.9% NaCl: 39.14 ± 0.09 °C.

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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