Central Effects of 5-Hydroxytryptamine and Noradrenaline on Body Temperature and Oxygen Consumption in Infant Rats

Many mammals respond to intraventricular injections of brain monoamines by changing their body temperature[1-4]. In adult rats, 5-hydroxytryptamine (5-HT), noradrenaline (NA) and adrenaline (A) cause hypothermia, although a rise in body temperature by small doses of NA or A has also been observed[5,6]. In infant rats, it has been shown that 5-HT (30 µg) intraventricularly did not alter the oxygen consumption in animals between 9 and 16 days old but caused a decrease in older rats[7]. The aim of the present study was to investigate both temperature and thermogenetic effects of intraventricularly injected 5-HT and NA in infant rats.

Material and methods. Sprague-Dawley rats were used from birth to the age of 20 days. Injections into the lateral brain ventricles were done as described earlier[4], which method is not suitable for rats older than 20 days. The doses of 5-HT, NA or A were injected in pyrogen-free saline, the volume being 5–10 µl/animal. The control animals were injected with the solvent alone. The body temperature of rats younger than 5 days was measured in the armpit and of older rats in the rectum. The oxygen consumption was measured with a Beckman E 2 oxygen analyzer with an open circuit system. All experiments were performed at the ambient temperature of 26–27 °C.

Results. The changes in body temperature of infant rats after intraventricular injections of 5-HT or NA are presented in Figures 1 and 2. The graphs indicate that the amines lowered the body temperature. This response seems to be dependent on both the dose and the age of the rats. An injection of 5-HT had a significant effect already at the age of 2 days and on the 5th day after birth the effect was almost the same as in older animals. As compared with 5-HT the response to the injected NA obviously develops later because the animals did not show any reaction at the age of 2 days. Also smaller doses than shown in the figures were injected and then the hypothermic effect was weaker or none. A hyperthermic effect was not observed with any dose. Some experiments with A showed that the response to it was similar to the effect of NA.

The results in Figure 3 show that the intraventricularly injected 5-HT and NA reduced the oxygen consumption of 13- to 15-day-old rats significantly. The intensity of this effect correlates very well with the hypothermia caused by the same doses, but the duration of the effect seemed to be shorter, and a compensating increase in the oxygen consumption follows in many cases. Further experiments with younger age groups showed that the response in oxygen consumption always correlated with the hypothermic effect.

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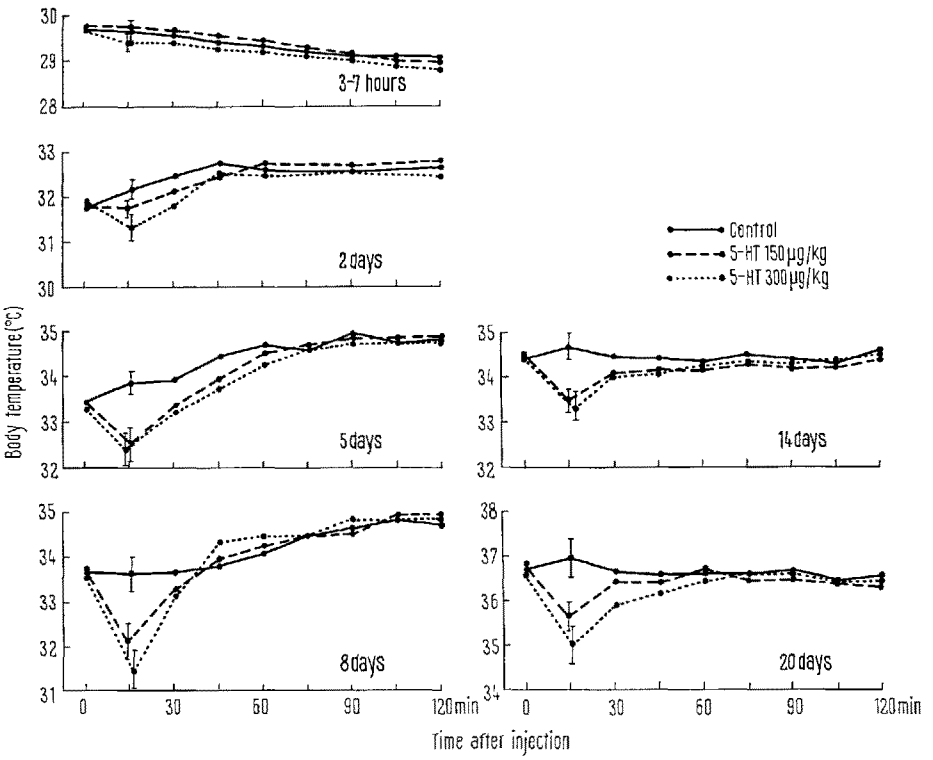

Fig. 1. The effects of intraventricular injections of 5-HT doses of 150 µg/kg (broken line) and 300 µg/kg (dotted line) on the body temperature of rats at different age after birth at 26–27 °C. The control values are indicated with continuous line. Ordinate: Body temperature in °C. Abscisse: Time after injection in min. Each curve represents the mean of 7–14 animals. Vertical bars indicate ± S.D.

Discussion. Intraventricular injections of 5-HT, NA and A caused a fall in body temperature of infant rats. This response developed already during the first days after birth, the reaction to 5-HT, however, occurring earlier than to NA or A. These results may indicate that the serotoninergic receptor systems involved in temperature control mechanisms in brain develop earlier than the adrenergic receptor systems. This difference correlates well with the amounts of 5-HT and NA found in brain; at birth the amount of 5-HT is over 50% but of NA only about 20% of the level of adult rats[8]. The greatest increase in the amount of NA occurs during the 5 first days of postnatal life[9]. These facts are probably in connection with the appearing of the first signs of thermoregulation during the first days after birth[10], although the thermoregulatory efficiency does not reach

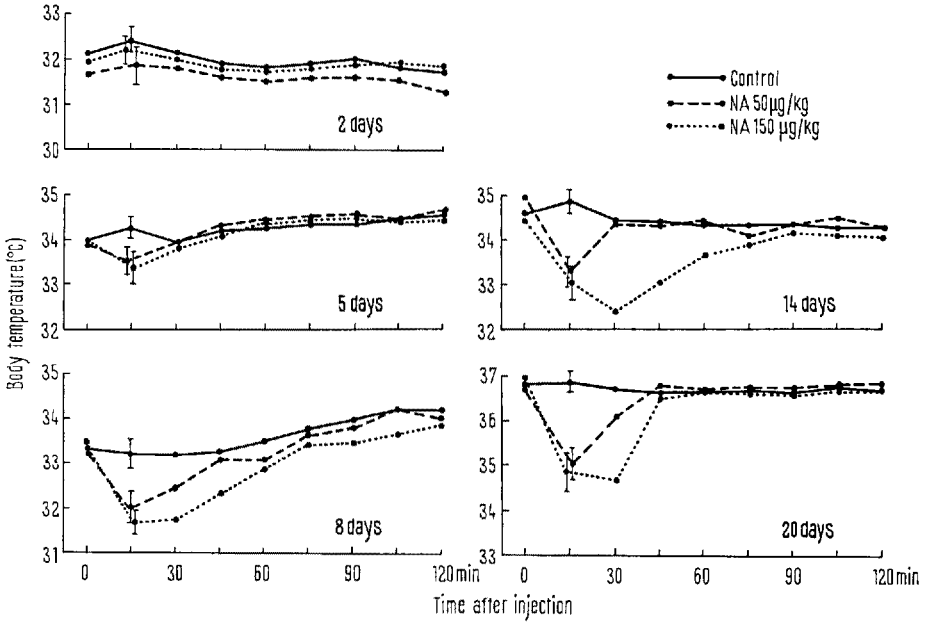

Fig. 2. The effects of intraventricular injections of NA doses of 50 µg/kg (broken line) and 150 µg/kg (dotted line) on the body temperature of infant rats. Other explanations as in Figure 1.

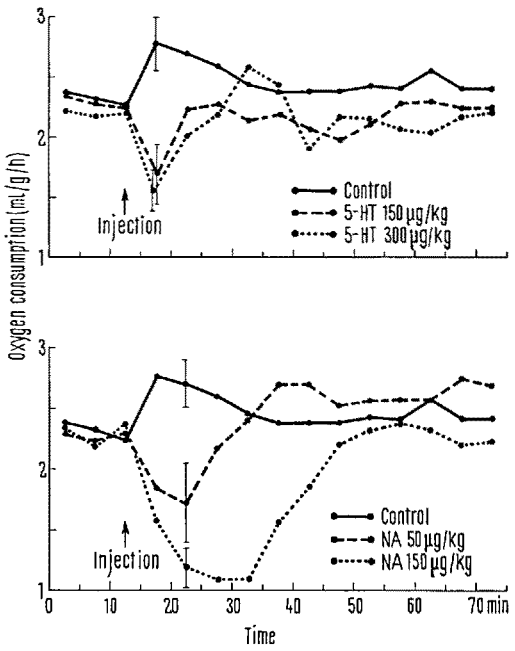

Fig. 3. The effects of intraventricular injections of 5-HT and NA on the oxygen consumption of the 13–15-day-old rats. Ordinate: Oxygen consumption as ml/g/h. Abscisse: Time in min. Each curve represents the mean of 6–8 animals. Vertical bars indicate ± S.D.

the stage of homoiothermia until the age of 2 weeks. The results from the experiments on the oxygen consumption showed that the decrease in the thermogenesis preceded the fall in body temperature. As it also was much larger than could be expected to be caused by the decrease in the body temperature, the decreased thermogenesis after injections of these amines is obviously the main cause for the hypothermia.

The effects observed may be interpreted as a response of the hypothalamic thermoregulatory center. In fact, there is ample evidence for hypothalamic serotoninergic neurones which are responsible for activating the heat loss mechanisms in rats and mice[4,11,12]. The role of NA in the thermocontrol mechanisms is less clear, although an increased activity of hypothalamic adrenergic neurones has been shown to occur in rats and mice exposed to heat[4,11,13]. However, an alternative explanation for

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these effects may be considered. The impairing effects of narcotic and sedative substances on the thermoregulatory efficiency result in the conclusion that a high arousal state is necessary for effective thermoregulation especially in small mammals. Although measurable sedative influences were difficult to find out in the present experiments, such effects have been produced in adult rats and mice by 5-HT, A and by large doses of NA[14–16]. It can be suggested that the intraventricularly injected monoamines impair the thermoregulation in infant rats by an inhibition of the brain stem reticular formation which is responsible for the maintenance of the activation level and which is, on the other hand, in interaction with the hypothalamus[17].

Zusammenfassung. Injektionen von 5-Hydroxytryptamin und Noradrenalin in die Gehirnventrikel junger Ratten verursachen einen verminderten Sauerstoffverbrauch und eine Hypothermie bereits am ersten Tag nach der Geburt Effekte, die mit dem Alter verstärkt, auftreten.

R. TIRRI

Zoophysiological Laboratory, Department of Zoology, University of Turku, Turku 2 (Finland), 31 August 1970.

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The Effects of Δ-Amino-Laevulinic Acid on Sodium and Water Movement Across Frog Skin

A high frequency of electrolyte disturbances has been noted in acute Variegate Porphyria, and in acute Intermittent Porphyria[1–3]. In addition, urinary hyperosmolality in the presence of serum hypoosmolality, marked sodium depletion, with or without excessive total body water may be present[4,5]. While a number of mechanisms may be invoked to explain these phenomena, notably the inappropriate secretion of antidiuretic hormone, one possibility is that excessive concentrations of porphyrins, or their precursors, may directly induce a renal tubular sodium-losing state[5,6]. We have endeavoured to explore this hypothesis by investigating the effect of Δ-amino-laevulinic acid (ALA) on Na transport and water movement across the skin of *Xenopus laevis*.

Frogs were prepared by injection of 0.6 mg deoxycorticosterone acetate in olive oil into the dorsal lymph sac 18 to 72 h prior to each experiment. Each frog was then pithed, and the ventral abdominal skin removed; this was divided by a midline incision, one piece of skin serving as the control for the other. Two different experimental protocols were followed; in one, the skin was mounted between Lucite chambers, bathed in normal frog Ringer's solution on either side, and the potential difference (PD) and short circuit current (SCC) measured as a function of time. In some of these experiments ^{22}Na kinetics were also studied. In the other procedure, the outer bathing solution was replaced by frog Ringer's diluted tenfold with distilled water; water movement in response to the osmotic gradient across the skin was followed by observation of movement of a meniscus in a capillary tube[7]. In both procedures the effects of ALA, with and without antidiuretic hormone (ADH)[8], were observed once equilibrium had been established.

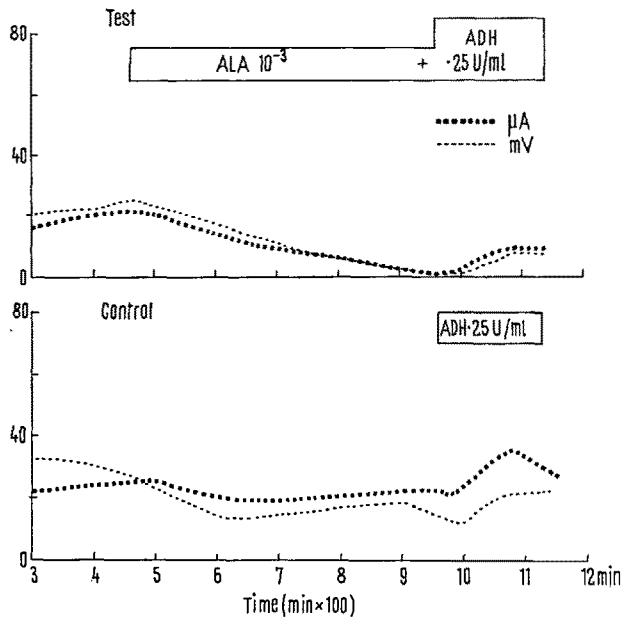

Fig. 1. The effects of ALA and ADH on short-circuit current (μA) and potential difference (mV) across paired skins. The abscissa is in hundreds of minutes.

ALA caused prolonged falls in SCC and PD, sometimes down to zero (Figure 1). These were occasionally preceded by slight and shortlived (30 min) rises. The minimal dose of ALA found to produce these effects consistently was $10^{-3}M$; this was most effective if added to the solution bathing the inside of the skin. Tracer studies (^{22}Na) have revealed a simultaneous gross reduction in the movement of Na from the outer to the inner bathing solutions; the permeability of the outer-facing barrier to Na is much reduced by ALA.

ADH, given in supramaximal doses (0.25 U/ml) always reversed the ALA effects, even in those cases where the SCC and PD had fallen to zero (Figure 1). The converse

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