ROLE OF CYCLIC AMP IN THE MECHANISM OF THE FEBRILE REACTION

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Evidence of the exceptionally important role of cyclic nucleotides in the regulation of functional activity of cells and systems and of homeostasis as a whole has been obtained recently [1, 3, 13]. There are also data on the role of cyclic AMP in the mechanism of the febrile reaction. In fever induced by endogenous and bacterial pyrogens, for instance, the concentration of cyclic AMP in the CSF is raised [10, 11], and injection of exogenous dibutyryl-cyclic AMP into the lateral ventricles of the brain or anterior hypothalamus causes an increase in the body temperature [12, 14]. One approach to the study of the role of cyclic AMP in the mechanism of the febrile reaction is by the use of agents blocking phosphodiesterase (an enzyme converting cyclic AMP into inactive AMP), which leads to an increase in the cyclic AMP concentration in cells.

One such blocking agent, in particular, is theophylline [5], which was used in the present investigation to study the reactions to endogenous and bacterial pyrogens under comparable conditions, and also reactions to prostaglandin E_1 (PGE_1), to which great importance is attached in the mechanism of the febrile reaction [7, 9].

EXPERIMENTAL METHOD

Experiments were carried out on 37 chinchilla rabbits of both sexes weighing 2-3 kg. PGE_1 (from Upjohn) was injected into the lateral ventricles of the rabbits in a dose of 1.0 μg in a volume of 0.1 ml of 0.85% NaCl solution through implanted cannulas. To verify readiness of the rabbit for the experiment, on the day before injection of PGE_1 0.1 ml of pyrogen-free 0.85% NaCl solution was injected into the lateral ventricles. PGE_1 was injected intravenously in a dose of 2.5 μg. A standard preparation of rabbit leukocytic pyrogen (LP), produced in the Department of General Pathology, Research Institute of Experimental Medicine, was used [2]. The threshold pyrogenic dose, obtained with the standard LP preparation diluted 7 times, was specially determined.

The bacterial pyrogen pyrogenal was used in doses of 1 minimal pyrogenic dose (MPD)/kg body weight and of 0.2 MPD/kg. Theophylline was injected intravenously 1 h before or simultaneously with the pyrogenic preparations in a dose of 10 mg/kg. In the doses used, theophylline caused no change in the animals' body temperature. The rectal temperature was measured with an electrothermometer at intervals of 30-60 min for 3-5 h. Conditions preventing possible contamination with bacterial pyrogens were observed throughout the work: The glassware was sterilized for 2 h at 170°C, absence of pyrogenicity of all solutions was verified, and so on. The experimental results were subjected to statistical analysis by Student's t-test.

EXPERIMENTAL RESULTS

Intravenous injection of PGE_1 in a dose of 2.5 μg caused no change in body temperature, and for that reason PGE_1 was injected into the lateral cerebral ventricle. Injection of PGE_1 into the lateral ventricle in a dose of 1 μg caused a rapid rise of body temperature with a maximum after 30-60 min, and the reaction ended after 3 h. After preliminary intravenous injection of theophylline, the temperature reaction to PGE_1 was enhanced (Fig. 1).

A considerable increase in the temperature reaction to intravenous injection of a threshold dose of LP also was observed after preliminary injection of theophylline. Similar results were obtained with pyrogenal. Theophylline considerably enhanced the rise of temperature to subthreshold doses of pyrogenal (Fig. 2). After injection of both types of pyro-

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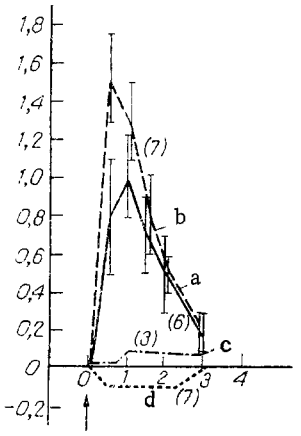

Fig. 1

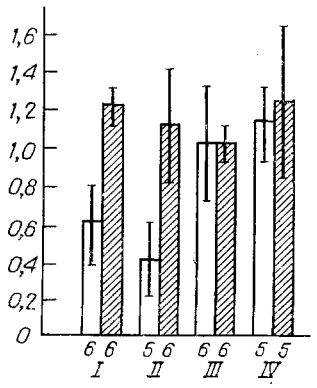

Fig. 2

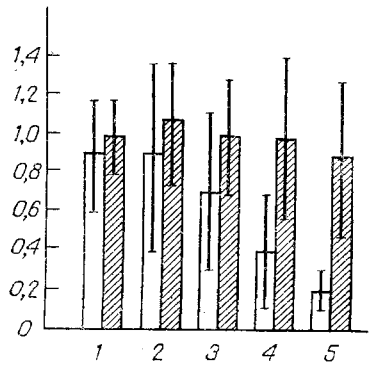

Fig. 3

Fig. 1. Effect of theophylline on pyrogenic activity of PGE_1. PGE_1 was injected into a lateral cerebral ventricle (LV) in a dose of 1 μg, intravenously in a dose of 2.5 μg; theophylline was injected intravenously 1 h before injection of PGE_1 into LV. a) PGE_1 into LV; b) theophylline i.v. + PGE_1 into LV; c) PGE_1 i.v.; d) pyrogen-free 0.85% NaCl solution into LV. Abscissa, time (in h); ordinate, rise of body temperature (in °C). Arrow indicates time of injection. Vertical lines show confidence limits; number of animals given in parentheses.

Fig. 2. Effect of theophylline on pyrogenic activity of LP and pyrogenal. Pyrogens injected intravenously: LP in a volume of 1 ml/kg of standard preparation (working dose) and sevenfold dilution (threshold dose); pyrogenal in doses of 1 and 0.2 MPD/kg. Theophylline in a dose of 10 mg/kg injected i.v. simultaneously with pyrogens. I) LP; II) pyrogenal — threshold doses; III) LP; IV) pyrogenal — working doses. Columns represent maximal rise of animals' body temperature (unshaded — control, shaded — animals receiving theophylline). Ordinate, rise of body temperature (in °C). Vertical lines represent confidence limits; numbers below columns indicate number of animals.

Fig. 3. Effect of theophylline on development of state of tolerance. Mean results of five observations in each group. Pyrogenal injected daily in a dose of 1 MPD/kg, theophylline in dose of 10 mg/kg. Abscissa, time (in days). Remainder of legend as in Fig. 2.

gens in higher doses, no differences were observed in the reaction after preliminary injection of theophylline.

With an increase in the cyclic AMP concentration induced by theophylline, sensitivity to minimal concentrations of pyrogens was thus increased. The pyrogenic stimuli in higher doses evidently also induced changes in the temperature regulation system so that the potentiating effect of theophylline was not exhibited. This was confirmed by further experiments with repeated daily injections of pyrogenal for 5 days, in which no decrease in temperture reaction was found in animals treated with theophylline (Fig. 3). A state of tolerance is known to develop during repeated injections of bacterial pyrogens, and under these circumstances the pyrogens rapidly disappear from the circulation. In the present experiments, against the background of increased cyclic AMP concentrations, very small quantities of pyrogenal were probably sufficient to induce the ordinary temperature reaction when injected repeatedly.

In fever evoked by endogenous pyrogen and PGE_1 the cyclic AMP concentration in the CSF is approximately doubled [10]. Since cyclic AMP does not pass through the blood–brain barrier [10], the increase in the concentration of this nucleotide in the CSF must evidently be due to its biosynthesis in regions of the brain in contact with the ventricular system. Enhancement of the temperature reaction against the background of theophylline, after injection of endogenous pyrogen which can penetrate into the brain, and of PGE_1 which was injected into the CSF, can probably be explained by an increase in the cyclic AMP concentration in the corresponding zones of the CNS and, in particular, in the anterior hypothalamus, where the central temperature-sensitive zone is located [6, 8]. In fever induced by bacterial pyrogen an

increase in the cyclic AMP concentration in the CSF also is observed [10]. Bacterial pyrogens are known to have an indirect action, through the formation of endogenous pyrogens [4]. In the present experiments with pyrogenal, therefore, theophylline could enhance the pyrogenic action of endogenous pyrogen formed under the influence of pyrogenal, and able to penetrate into the brain. Theophylline also raises the cyclic AMP concentration not only in the brain, but also in other organs and tissues. Since cyclic nucleotides are universal biological regulators of cell metabolism [3], it is perfectly possible that when the cyclic AMP level is raised, endogenous pyrogen formation is increased under the influence of pyrogenal.

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BLOOD ANTIDIURETIC ACTIVITY AND PHARMACOLOGICAL CORRECTION OF THE HYPOTHALAMIC-NEUROHYPOPHYSEAL SYSTEM AFTER THERMAL TRAUMA

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An essential role in the pathogenesis of burns is played by the neurohypophyseal hormone vasopressin [10]. Some workers largely attribute the development of the oliguria and anuria which follow burns to the release of large quantities of antidiuretic hormone (ADH) from the neurohypophysis into the blood stream as a result of nociceptive stimulation induced by burn trauma. Meanwhile the view has been expressed [9] that a key place in the mechanisms of disturbance of the excretory function of the kidneys is occupied by circulatory disorders due primarily to a reduction in the circulating blood volume because of extensive plasma loss and the escape of fluid from the blood vessels into the tissues of burned subjects. However, as Kochetygov [4] points out, the fact must be borne in mind that the reduction in the circulating fluid volume during the development of burns is in turn a powerful stimulus to the increase in ADH secretion. This, in the writers' view, creates the conditions for a prolonged rise in the blood vasopressin concentration in burned subjects. Morphological investigations of the hypothalamic-neurohypophyseal system [6] have shown that its response to thermal trauma is phasic in character; however, the changes in antidiuretic activity (ADA) of the blood in the course of burns have so far received little study.

KEY WORDS: thermal trauma; hypothalamic-neurohypophyseal system.

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