WEAKENING OF THE HYPERTHERMIC EFFECT OF PROSTAGLANDIN E_2 BY CHOLINOMIMETICS, MONOAMINES, AND CALCIUM IONS

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Experiments on unanesthetized rats showed that the hyperthermic effect of prostaglandin E_2 ($PG-E_2$) is not prevented by aspirin, but can be considerably weakened by injection of arecoline, noradrenalin, serotonin, histamine, and $CaCl_2$ into the lateral ventricles of the brain or by intraperitoneal injection of eserine. Experiments on unanesthetized rabbits showed that arecoline and nicotine have a similar action on $PG-E_2$-induced hyperthermia if injected into the 3rd ventricle. Effects of serotonin and arecoline also were found when reinjected into the cerebral ventricles. In the center for heat loss there are evidently mechanisms which incorporate cholinergic neurons whose activity is not totally inhibited by prostaglandins.

KEY WORDS: prostaglandin hyperthermia; cholinomimetics; monoamines; calcium chloride; aspirin.

Injection of prostaglandins (PG) of the E group, which perform the function of "mediators" of fever in the hypothalamic centers, into the cerebral ventricles of homoiothermic animals leads to a rapid and considerable rise in the body temperature [6, 7, 9, 15]. This effect is not prevented by antipyretics [8, 13] but is weakened by antagonists of monoamines [10, 11] and Ca^{++} [8]. An opposite, i.e., hypothermic, effect is observed in many animals in response to excitation of central cholinergic systems, and in rats it occurs not only after injection of cholinomimetics, but also as a result of injections of monoamines [3-5, 9] and also of solutions with a high Ca^{++} concentration [9, 14] into the cerebral ventricles. However, the question of relations between neuromediators, ions, and prostaglandins has not yet been adequately studied and, in particular, the hypothesis that the hyperthermic effect of prostaglandins may be modulated by activation of certain neuromediator mechanisms of the brain requires experimental confirmation.

The object of the present investigation was to study the effect of M- and N-cholinomimetics, noradrenalin, serotonin, and histamine, and also of an excess of Ca^{++} on the hyperthermic effect of $PG-E_2$ after injection of the substances into the cerebral ventricles.

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized male rats weighing 160-180 g (the substances were injected into the right lateral ventricle) and on adult unanesthetized male rabbits weighing 2.5-3 kg (the substances were injected into the third ventricle through implanted chemical electrodes) [1, 2]. The $PG-E_2$ used was from the Upjohn Company, arecoline, nicotine, and serotonin-creatinine sulfate from Reanal, and noradrenalin hydrotartrate and histamine dihydrochloride from Gee Lawson Chemicals; $CaCl_2$ also was used. Aqueous solutions of the substances for the experiments on rats were injected in a volume of not more than 20 μl, and in experiments on rabbits, not more than 50 μl. Intraventricular injections of monoamines and cholinomimetics were given at various time intervals after the injection of $PG-E_2$ but, as a rule, when the rectal temperature of the rats was raised by more than 1.5°C and of the rabbits by more than 0.5 °C. Aspirin (injected as an aqueous suspension by gastric tube) and eserine (intraperitoneal injections) were used in the experiments on rats. The body temperature of the animals was measured per rectum by means of a TPÉM-1 electrothermometer. In the experiments on rabbits, changes in heat loss were estimated from changes in the ear temperature, which was recorded throughout the experiment by means of a thermistor on an ÉPP-09 electronic potentiometer, and also from the changes in respiration rate, which were measured by studying the electrical activity of the intercostal muscles.

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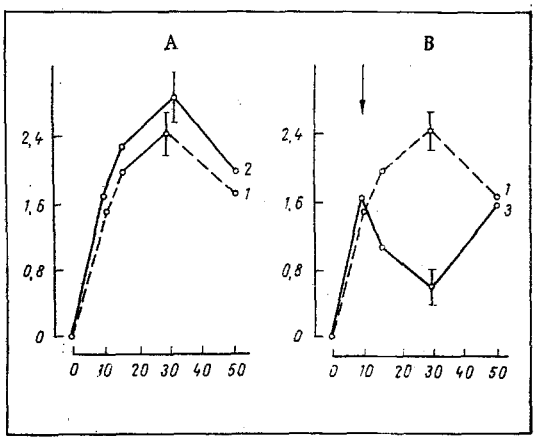

Fig. 1. Effect of aspirin (A) and eserine (B) on development of PG-E_2-hyperthermia in rats. 1) Control (PG-E_2; n = 10); 2) aspirin + PG-E_2 (n = 6); 3) PG-E_2 + eserine (n = 6). Number of experiments in parentheses. Arrow marks time of injection of eserine or distilled water (control). Abscissa, time (in min); ordinate, change in body temperature (in °C).

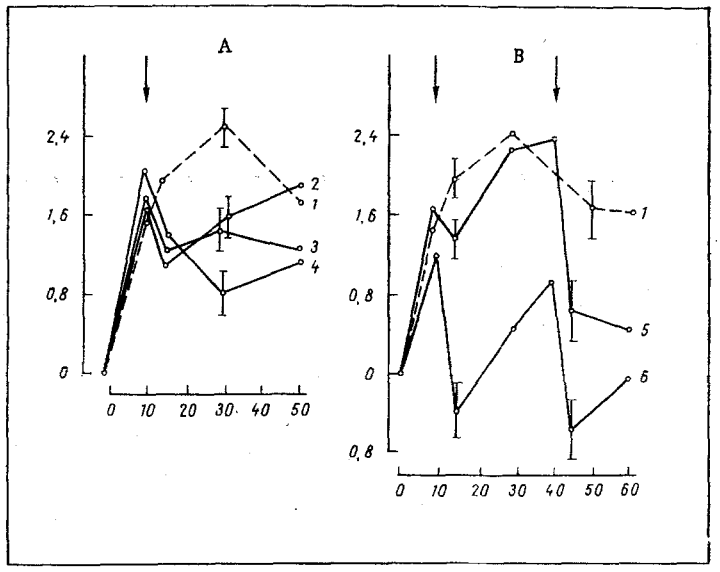

Fig. 2. Effect of cholinomimetics, monoamines, and Ca^{++} on development of PG-E_2-hyperthermia in rats. A) Single injection of substance; B) two injections of substances. 1) Control (PG-E_2 + distilled water; n = 10); 2) PG-E_2 + noradrenalin (n = 6); 3) PG-E_2 + $CaCl_2$ (n = 8); 4) PG-E_2 + histamine (n = 8); 5) PG-E_2 + arecoline (n = 6); 6) PG-E_2 + serotonin (n = 6). Remainder of legend as in Fig. 1.

EXPERIMENTAL RESULTS

Injection of PG-E_2 (2 μg) into rats caused their body temperature to rise by more than 1.5°C after only 10 min, and after 20 min the increase was more than 2.0°C. This reaction was not prevented by preliminary administration of aspirin in a dose of 300 mg/kg (Fig. 1A) but it was appreciably weakened by eserine (0.3 mg/kg), if injected 10 min after the PG-E_2 (Fig. 1B). Injection of noradrenalin (4 μg), serotonin (25 μg), histamine (30 μg), and $CaCl_2$ (20 μl of an 80 mM solution) into the ventricles 10 min after injection of PG-E_2 not only prevented a further increase in the body temperature, but actually reduced it appreciably, and sometimes considerably (Fig. 2A), i.e., these substances had the same effect on these animals as was observed in the writers' previous experiments [3-5]. The present experiments showed that the effect of serotonin (25 μg) and also of

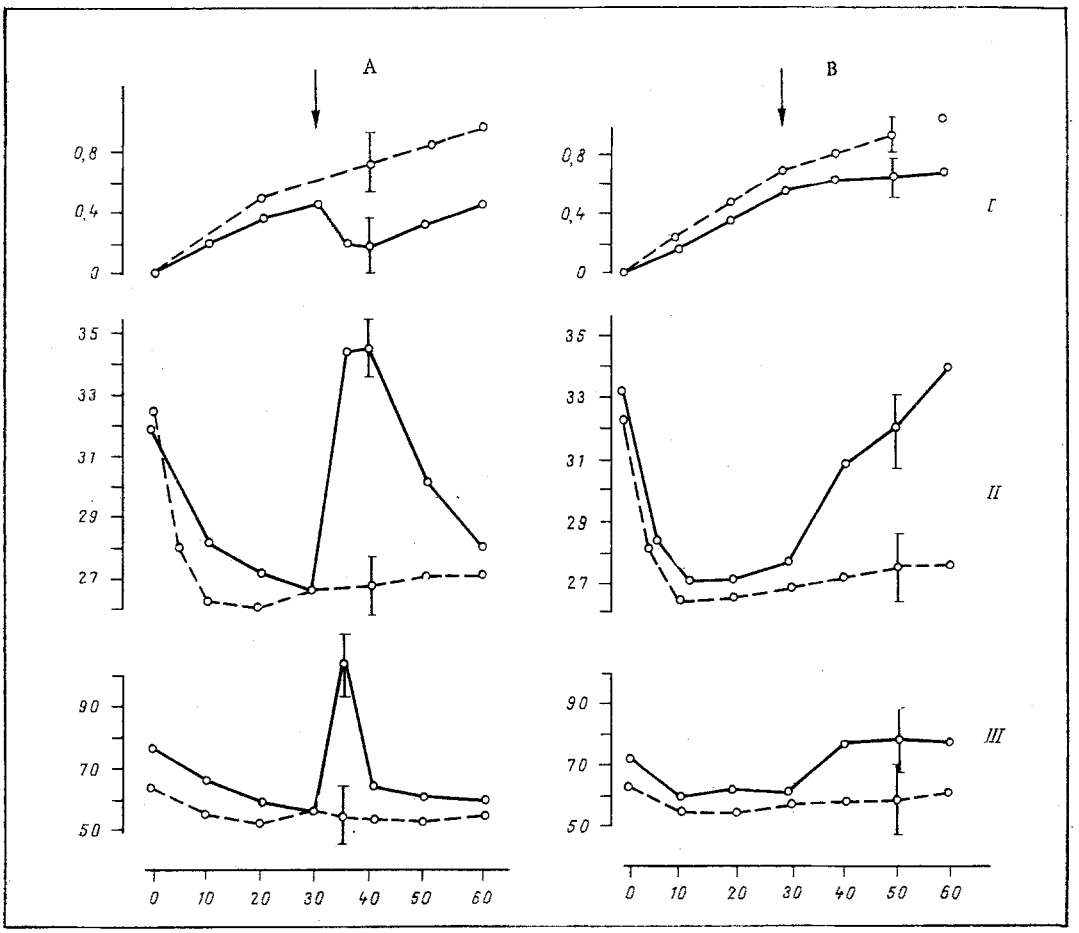

Fig. 3. Effect of arecoline (A) and nicotine (B) on development of changes induced by PG-E_2 in body temperature, ear temperature, and respiration rate in rabbits. I) Changes in body temperature (in °C); II) changes in ear temperature; III) changes in respiration rate per minute). Broken line — control (PG-E_2, n = 6); continuous line — PG-E_2 + arecoline or nicotine. Arrows mark time of injection of cholinomimetics.

the muscarinic cholinomimetic arecoline (10 μg) can be produced over and over again in the same animals. It will be clear from Fig. 2B that under the influence of serotonin the rectal temperature of the rats fell twice to its initial values.

In rabbits PG-E_2 (200 ng) caused a rise of body temperature by more than 0.5°C after 30 min. The temperature was raised by more than 1°C 60 min after injection. Injection of arecoline (50 μg) 30 min after PG-E_2 gave a distinct hypothermic effect (Fig. 3A), such as was always observed in these animals under the influence of muscarinic cholinomimetics [9]. Nicotine (50 μg) was less effective (Fig. 3B). The effect of arecoline was evidently largely due to stimulation of heat loss in the animals. Evidence of this was given by elevation of the ear temperature (through dilatation of the superficial vessels) and an increase in the respiration rate.

The results of the present experiments on rats in which $CaCl_2$ solutions were injected into the cerebral ventricles agreed with other observations [8], which showed that PG-fever can be reduced by increasing the Ca^{++} concentration in the solutions used for ventricular perfusion in the animals. According to reports in the literature the hyperthermic effect of PG can also be appreciably weakened by preliminary injection of α-adrenoblockers [10,11], 6-hydroxydopamine [11], and serotonin antagonists [10] into the ventricles or into structures of the hypothalamus. However, according to other investigators [12], fever induced by pyrogenic agents is resistant to the action of reserpine and 6-hydroxydopamine.

It follows from the results of the present experiments that PG-hyperthermia in various animals can be reduced by activation of central neuronal mechanisms utilizing acetylcholine and certain monoamines. These results are of definite interest for they show that it is possible, in principle, to lower the body temperature considerably under conditions simulating fever in diseases when antipyretics are ineffective.

The results of this investigation indicate that the heat loss center in different animals contains mechanisms which incorporate cholinergic neurons whose activity is not significantly inhibited by PG. There is also reason to suppose that the development of febrile reactions is modulated to a considerable degree by the functional activity of central cholinergic and monoaminergic systems.

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ABOLITION OF THE PRESYNAPTIC ACTION OF CARBACHOL BY TUBOCURARINE

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The presynaptic action of carbachol (C) was studied in experiments on a neuromuscular preparation of the sartorius muscle of Rana ridibunda. C was shown to significantly reduce the quantum composition of the endplate potentials (mEPP) as a result of the direct action of C on motor nerve endings. D-Tubocurarine caused a marked decrease in the sensitivity of motor nerve endings to C. Relations between C and tubocurarine as regards their action on the quantum composition of mEPP were of the competitive antagonism type. Atropine, in low concentrations, had no effect on the presynaptic action of C. The results of these experiments indicate that the decrease in mEPP under the influence of C is mediated through specific nicotinic cholinergic structures of motor nerve endings.

KEY WORDS: nerve ending; carbachol; presynaptic action; tubocurarine; competitive relations.

Many cholinomimetic drugs are known to possess a presynaptic action, manifested as changes in the process of mediator liberation in response to motor nerve stimulation [2, 9, 10, 12]. In particular, acetylcholine

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