EFFECT OF ARECOLINE ON POSTERIOR HYPOTHALAMIC UNIT ACTIVITY IN RABBITS WITH EXPERIMENTAL FEVER

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In fever caused by endogenous (leukocytic) pyrogen hypothalamic unit activity is modified, mainly in its preoptic region [1, 11]. The hyperthermic effect of prostaglandins (PG) of the E group also is connected with changes in activity of certain neurons in this region [10]. The development of hyperthermia under the influence of PG and pyrogen is inhibited by cholinomimetics [3-5]. However, the problem of relations between synaptically active substances and pyrogens has received little study. In particular, the hypothesis on antagonistic effects of cholinomimetics and pyrogenic substances on unit activity in the posterior hypothalamus, which performs integrative functions in the formation of a controlling signal to effectors of the temperature regulating system, requires experimental verification.

The object of the investigation described below was to study the effect of the muscarinic cholinomimetic arecoline on unit activity in the posterior hypothalamus and on the body temperature during fever induced by leukocytic pyrogen and during hyperthermia induced by PG.

EXPERIMENTAL METHOD

Experiments were carried out on 18 unanesthetized rabbits weighing 2.8-3.5 kg at neutral temperatures (20-24°C). Under hexobarbital anesthesia (50 mg/kg, intravenously) a platform for securing the microelectrode manipulator and two chemotrodes (bilaterally) for injecting substances into the lateral ventricles was mounted on the animal's skull 4-5 days before the experiments. Unit activity in the posterior hypothalamus (coordinates $P_1L_1H_{14-15}$ according to Sawyer's atlas) was recorded extracellularly with tungsten microelectrodes. Action potentials were amplified by the UBP1-01 amplifier and displayed on an oscilloscope screen for visual monitoring, then converted into standard square pulses 2.5 msec in duration and recorded on an N-327 automatic writer. The results were processed simultaneously by AMG-1 pulse analyzer (the mean momentary frequency was calculated every 4 sec during the period of observation). In some experiments, simultaneously with unit activity, the rectal temperature and temperature of the concha auriculae were recorded. Temperature curves were recorded on tape by a KSP-4 electronic automatic writer. Aqueous solutions of the substances were injected successively into the lateral ventricles in a volume not exceeding 30 µl. Arecoline, PGE_2 (from the Upjohn Company, USA), and leukocytic pyrogen, prepared by a modified method [9] from endotoxin of *Klebsiella scleromatis* (strain 170/64) were used. The effects of the substances were assessed by comparing the mean firing rate before and after injection of the preparations. Differences in firing rate were considered to be significant in the case of a change from the original value by ±25%. The significance of differences was estimated by nonparametric methods [2]. The use of a morphological express photographic technique showed that the neurons studied lay in the dorsomedial nuclei of the hypothalamus and also in the dorsal hypothalamic region.

EXPERIMENTAL RESULTS

Injection of arecoline (50 µg) into intact rabbits caused the body temperature of the animals to fall by more than 0.4°C within 30 min, and modified unit activity in the posterior hypothalamus variously. Of 12 neurons studied seven increased and three decreased their fir-

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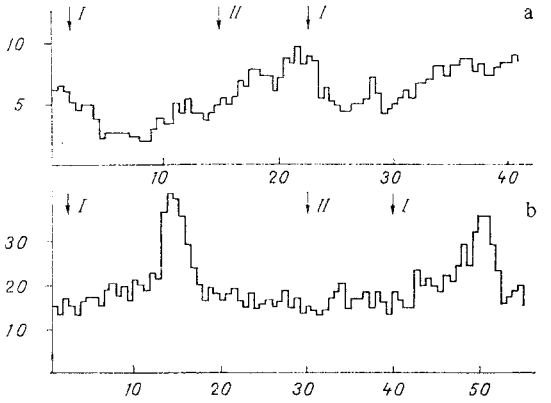

Fig. 1. Frequency histograms of single unit activity in posterior hypothalamus during action of arecoline under conditions of fever induced by leukocytic pyrogen (a) and hyperthermia induced by PG (b). I (Arrow) — time of injection of arecoline (50 μg) into cerebral ventricles; II (arrow) — time of injection of leukocytic pyrogen (50 μl) or PGE_2 (0.5 μg) into cerebral ventricles. Abscissa, time (in min); ordinate, firing rate of neuron (spikes/sec).

ing rate, and in two it was unchanged, in agreement with other observations [7] in which both a decrease an an increase in posterior hypothalamic unit activity was observed under the influence of acetylcholine.

Injection of leukocytic pyrogen (50 μl) caused the body temperature to rise by more than 0.5°C within 30 min, and this was accompanied by excitation of the activity of seven and inhibition of activity of one of eight neurons tested. Subsequent injection of arecoline (50 μg after 15 min) caused inhibition of activity of the neurons that were excited by leukocytic pyrogen, and gave a distinct hypothermic effect. The only neuron whose activity was inhibited by leukocytic pyrogen responded to the cholinomimetic by an increase in firing rate. A typical response of a nerve cell of this series is shown in Fig. 1a. Three other neurons whose activity was inhibited by arecoline during experimental fever also were found in the posterior hypothalamus. The experiments showed that an increase in unit activity evoked by injection of leukocytic pyrogen immediately preceded a fall in ear temperature, whereas inhibition of the activity of these neurons observed during subsequent injection of arecoline was accompanied by elevation of the ear temperature.

Injection of PGE_2 (0.5 μg) caused the body temperature to rise by more than 0.6°C within 30 min, but it was not accompanied by any change in activity of the nine neurons tested. Subsequent injection of 50 μg arecoline (50 μg after 15 min) was accompanied by an increase in the activity of these neurons (Fig. 1b) and gave a hypothermic effect, associated with intensification of heat loss processes, as was shown previously [4]. Evidence of this was given by elevation of the ear temperature by more than 10°C after 15 min.

It follows from the experimental results thus obtained that the central action of pyrogens and of arecoline differs in its effect on the activity of certain posterior hypothalamic neurons. This part of the hypothalamus has been shown [6] to contain neurons which participate in temperature regulation. Our observations agree with reports [11] of antagonism in the action of leukocytic pyrogen and the antipyretic sulpyrin on single unit activity in the hypothalamus.

The results of the present investigation suggest that arecoline can effectively counteract the effect of leukocytic pyrogen on certain hypothalamic neurons, leading to enhancement of their activity, and that changes observed in the firing rate of these neurons are connected with changes in activity of neuronal groups which send controlling signals to effectors of the temperature regulating system. It can also be postulated that leukocytic pyrogen and PGE_2 do not act on the same neurons in the hypothalamus but have different points of application. PGE_2, for example, may affect predominantly adrenergic synapses [8]. This last hypothesis is

supported by the fact that neurons responding to injection of arecoline by an increase of activity were found in the experiments with hyperthermia induced by PGE_2, whereas in animals with experimental fever neurons were found which responded to the cholinomimetic by a decrease in firing rate.

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