EFFECT OF LEUKOCYTIC PYROGEN ON THERMOSENSITIVE NEURONS IN THE ANTERIOR HYPOTHALAMUS

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Unit activity in the medial preoptic and septal regions of the brain was studied in rabbits in response to changes in the local temperature and to systemic injection of leukocytic and bacterial pyrogens. A decrease in the discharge frequency of warmth receptors and activation of cold receptors were found under the influence of the pyrogens. Leukocytic pyrogen induced a faster decrease than bacterial pyrogens in the activity of warmth receptors. Temperature-neutral neurons did not respond significantly to pyrogens of either type.

KEY WORDS: temperature sensation; neurons; anterior hypothalamus; pyrogens; fever; adjusting point.

Bacterial pyrogens (BP) have been shown to depress activity of warmth neurons of the anterior hypothalamus [5, 6, 9]. No such investigations have been carried out with leukocytic pyrogen (LP).

Accordingly, in the investigation described below, the effect of systemic injection of LP on electrical activity of thermosensitive neurons in the anterior hypothalamus was studied.

EXPERIMENTAL METHOD

Single unit activity in the septal and medial preoptic regions of the brain was investigated in acute experiments on rabbits under urethane–chloralose anesthesia and with artificial ventilation.

To produce local changes in the temperature of the anterior hypothalamus (AH) and to monitor its temperature glass–water thermodes (external diameter 0.8-0.9 mm) inserted in accordance with angular coordinates with tips at the position $A_4H_{12.5}L_{2.0}$, and a thermocouple located at $A_4H_{12.5}L_0$ were used [10].

To determine the precise location of the track from the microelectrode, a needle 0.5 mm in diameter was inserted into the burr-hole by the replacement method and the site of injury was identified in brain sections.

Neurons were identified by calculating the mean firing rate and by continuously recording the function of the mean instantaneous frequency after integration of the spike train on the MN-7M analog computer. Neurons were regarded as temperature-sensitive if the mean frequency was increased by more than 24% per degree ($Q_{10} > 2.4$).

Pyrogenal (5 μg/kg) and LP obtained from $10.5 \cdot 10^7$ peritoneal exudate cells (from the Pyrogens Group, Department of General Pathology, Institute of Experimental Medicine) were used. The material for injection was sterilized by dry heat at 180°C for 3 h; solutions were made up in bidistilled water.

EXPERIMENTAL RESULTS AND DISCUSSION

In the control series of experiments (rectal temperature 38.6 ± 0.3°C) intravenous injection of 3 ml LP caused the temperature to rise on the average from the 10th minute with a maximal increase (0.8°C)

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TABLE 1. Firing Pattern of Anterior Hypothalamic Neurons (spikes/sec) Following Injection of LP and BP (mean data)

Group of neurons	Type of neurons	Number of neurons	Time after injection of pyrogen (in min)				
			0	1–5	6–10	11–15	16–20
	Leukocytic pyrogen						
1	Warmth receptors	7	11,0±3,7	10,4	4,8	0	0
2	Thermoneutral neurons	7	11,6±6,3	10,1	11,1	11,6	13,1
3	Cold receptors	4	3,2±1,3	8,3	15,5	9,4	6,5
4	Warmth interneurons	2	18,7	20,4	20,1	20,8	20,5
	Bacterial pyrogen (pyrogenal)						
1	Thermoneutral neurons	5	12,6±4,1	11,8	11,6	11,2	12,0
2	Warmth receptors	5	9,6±1,4	8,6	9,1	9,8	0,7

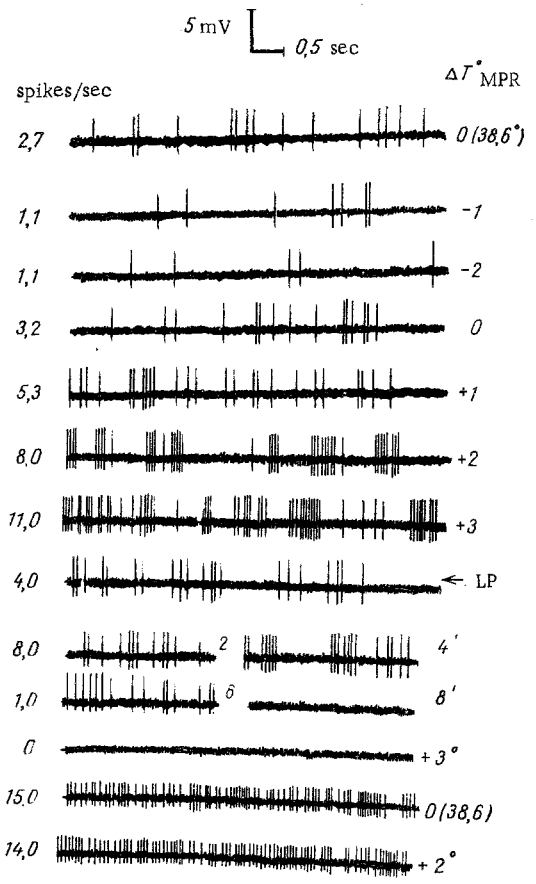

Fig. 1. Changes in firing pattern of anterior hypothalamic neurons under the influence of local temperature change and of systemic pyrogen (LP). Figures on left show mean firing rate (spikes/sec), on right changes in local temperature. Arrow indicates time of injection of LP and is followed by record of dynamics of discharge at minutes specified. Two last records show activity of a thermoneutral neuron located in the immediate vicinity of a thermosensitive neuron immediately after activity of the latter was blocked.

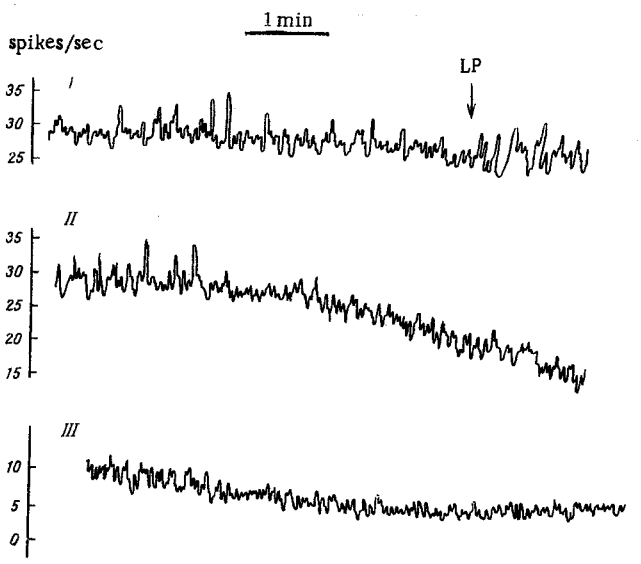

Fig. 2. Mean firing rate of thermosensitive neuron during initial period (I) and in first 15 min after injection of LP (II, III). Firing rate (in spikes/sec) shown on left; arrow indicates time of injection of LP.

after 30-40 min. Injection of 15 μg pyrogenal in 3 ml physiological saline raised the rectal temperature after 15 min, with a maximal increase (1.6°C) 1.5 h after injection.

In the main series of experiments the response of 10 neurons to BP and of 20 neurons to LP was investigated. As a first step, the character of sensitivity of these neurons to a local temperature stimulus was established [6].

In response to injection of LP activity of the warmth receptors decreased sharply or disappeared altogether (Table 1). The duration of the block to the different neurons varied from 5 to 9 min. The response lasted 25-45 min, after which the activity of three neurons was gradually restored to its initial level. A record of the response of a warmth receptor to intravenous injection of 3 ml LP is shown in Fig. 1.

The firing rate of four cold receptors rose sharply during the first 5 min after injection of LP, remained high from the 6th to the 11th minute, and then returned to its initial level (Table 1). Despite the opposite nature of changes in activity in the neurons of the first and third groups, a feature common to both was that the beginning of the response coincided and took place on the average 8 min after injection of LP. The dynamics of the response of the warmth receptor is shown in Fig. 2.

Two other groups – thermoneutral (group 2) and interneurons (group 4) – showed no substantial change in their firing pattern after injection of LP (Table 1).

All warmth receptors investigated responded to injection of BP by a sharp decrease in activity from the 16th minute after injection. Their response was thus of the same type as that to injection of LP, but the latent period was longer (almost twice). The firing pattern of the thermoneutral neurons was unchanged under these conditions (Table 1).

As a result of these experiments two regular features were discovered in the response of the various groups of anterior hypothalamic neurons to systemic injection of bacterial lipopolysaccharide (BP) and of the product of activated granulocytes (LP).

Only the temperature receptors were found to change their level of activity in response to injection of both types of pyrogens. There was a significant difference in the times of onset of the response to LP and BP, which directly confirms the view that the effect of BP on the thermoregulatory system is mediated through the liberation of endogenous leukocytic products [3, 4, 8].

The high permeability of the hypothalamus to substances of different types and the relatively rapid response of neurons in this part of the brain to injection of LP apparently confirm the penetration of LP directly to the thermosensitive cells of the anterior hypothalamus.

It is of course difficult to extrapolate the results of an acute experiment to the level of the intact organism under natural conditions. Nevertheless, the surprising coincidence in the times of onset of the response to injection of the pyrogens in acute and chronic experiments and at the macro- and microphysiological levels [1, 2] makes it possible to regard the results from the same standpoint. The change in the adjusting point for the control of body temperature during fever is thus brought about by a change in activity of the warmth and cold detector cells in opposite directions. Depending on the quantity of circulating pyrogen, presumably both the degree of activity of these neurons and the number of neurons recruited into the response can be varied.

As regards the interneurons, although they do not change their level of activity in response to the action of BP, they do raise the threshold of excitability to local temperature stimulation [6].

The difference in the times of onset of the response to injection of LP and BP discovered in these experiments is direct confirmation of the view that the effect of BP on temperature regulation is exerted indirectly through the liberation of endogenous leukocytic products and their interaction with the thermoregulatory structures of the anterior hypothalamus.

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