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ANTIPYROGENIC PROPERTIES OF OXYTOCIN

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Several humoral factors of endogenous origin are known which can influence the development of the febrile reaction and, in particular, can weaken it. These include interleukin 1 inhibitor, found in the brain of patients with fever, and which is also considered to block the action of endogenous pyrogen [9], a mediator of fever, and vasopressin [8]. Ability to depress the body temperature of normal animals has been shown to be a property of steroids [7], ACTH, and melanocyte-stimulating hormone [5]. Despite progress in the study of the antipyrogenic properties of hormones, the effect of other substances with hormonal activity on the origin and development of fever is not yet clear.

The aim of this investigation was to study the effect of oxytocin on the course of experimental fever.

EXPERIMENTAL METHOD

Noninbred rabbits weighing 2.5-3.0 kg were used. Fever was induced by intravenous injection of pyrogenal, a lipopolysaccharide from Salmonella typhi (N. F. Gamaleya Research Institute of Epidemiology and Microbiology) in a dose of 5 MPD†/kg or endogenous pyrogen (EP) in a dose of 1.2 ml/kg. EP was obtained in a culture of human peripheral blood monoclears isolated in a ficoll-verigrafin solution [4]. The cells were incubated in a concentration of 5 million/ml for 2 h at 37°C with heat-inactivated Staph. epidermidis microbial particles (in a 1:40 ratio). After incubation, the cells were washed twice and cultured in in a concentration of 5 million/ml in RPMI-1640 medium (Serva), supplemented with L-glutamine (2 mM), penicillin (100 units/ml), and streptomycin (100 μg/ml), for 18 h at 37°C in an atmosphere containing 7.5% CO_2 in air. The cells were precipitated by centrifuging (400 g, 15 min), and the supernatant liquid was used as the source of EP. Oxytocin (Serva, Gedeon Richter) was introduced by intravenous drip in an apyrogenic solution of 0.87% sodium chloride at a rate of 10-12 ml/h in a dose of 0.4 or 4 μg/kg in 1h, or intramuscularly in a dose of 0.2 μg/kg at 0.5 h intervals. The animals of the control group were infused with 0.87% saline solution. The influence of oxytocin on EP formation was studied in a culture of

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†Maximal permissible dose.

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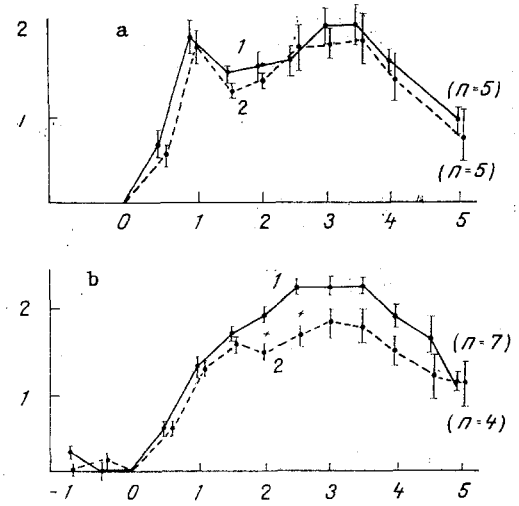

Fig. 1

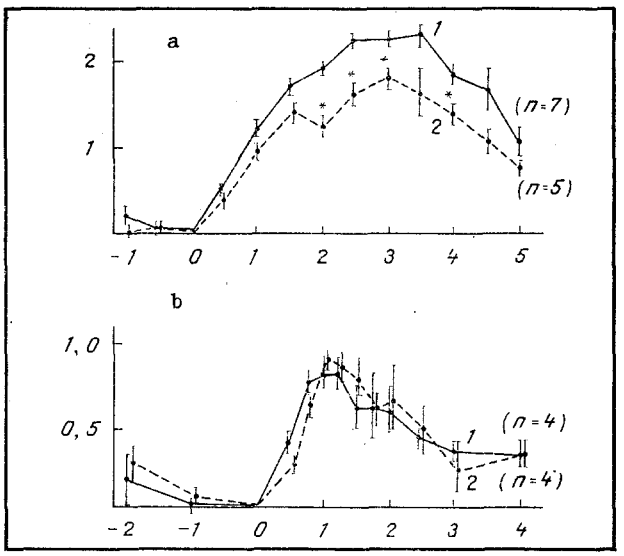

Fig. 2

Fig. 1. Effect of intramuscular (a) or intravenous (b) injection of oxytocin (0.4 μg/kg/h) on fever induced by pyrogenal. Abscissa, time (in h); ordinate, change in rectal temperature (ΔT, in °C). 1) Control, 2) injection of oxytocin. Pyrogen injected at time 0. Number of animals given in parentheses. *$p < 0.05$.

Fig. 2. Effect of intravenous injection of oxytocin (4 μg/kg/h) on fever induced by pyrogenal (a) or by endogenous pyrogen (b). Endogenous pyrogen injected at time 0. Remainder of legend as to Fig. 1.

human peripheral blood mononuclears (2 million/ml), stimulated by lipopolysaccharide from E. coli (Sigma, 0.2 μg/ml). Oxytocin was introduced in a 10^{-10} M concentration. The culture conditions were analogous to those indicated above in the description of EP production. Oxytocin was removed from the supernatant liquid by gel filtration on Sephadex G-25 (Pharmacia). A concentrate of RPMI-1640 nutrient medium was introduced into desalted samples to restore the single content of nutrients in them [1]. The pyrogenic activity of the samples obtained was determined on C57Bl/6 mice by injection of 0.2 ml into the caudal vein. The mice were kept in individual boxes in a thermochamber at 33°C [3]. The rectal temperature of the rabbits was measured with a TPEM-1 electrothermometer, and that of the mice using thermocouples and an F116/1 microvoltameter.

RESULTS OF THE INVESTIGATION

The action of the intravenously infused pyrogen was manifested in rabbits by a typical biphasic body temperature rise (Fig. 1a). Intramuscular injections of oxytocin while the pyrogen was exerting its effect did not lead to any substantial change in the temperature curve. Considering that the half-decay time of oxytocin injected into the blood stream does not exceed 3 min [6], in the next series of experiments oxytocin was injected by continuous intravenous drift in the same doses (0.4 μg/kg/h) beginning 1 h before the injection of pyrogenal. In these experiments a significant fall of the second peak of the temperature curve and weakening of the hyperthermia within the interval from 2 to 4.5 h by 0.45°C on average, or by 24%, were observed (Fig. 1b). The use of oxytocin in a dose of 4 μg/kg/h gave a more marked effect: weakening of the response on average by 0.6°C, or by 31% (Fig. 2a). As the control experiments showed, oxytocin in this case does not change the temperature of intact animals. Thus the febrile reaction was weakened while the oxytocin concentration remained constant. It will be noted that oxytocin lowered the second peak of the temperature curve. Some workers consider that the second phase of the temperature response was connected with the formation and action of EP [2].

To study the possible mechanisms of action of oxytocin, its effect was examined on fever induced by EP. As will be clear from Fig. 2b, oxytocin does not change the hyperthermic effect of EP. To explain the influence of oxytocin on EP formation experiments were carried out in vitro. Oxytocin was added to cultures of human peripheral blood mononuclears producing EP in a concentration of 10^{-10} M which, according to our calculations (based on the half-decay period of oxytocin and the circulating blood volume), corresponded to that reached by

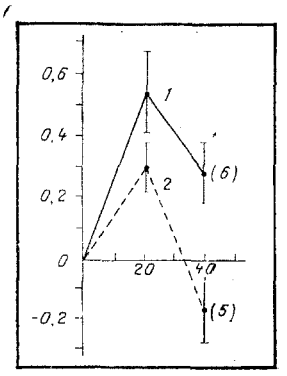

Fig. 3. Effect of oxytocin on endogenous pyrogen formation in culture of human peripheral blood mononuclears. Abscissa, time (in min). Remainder of legend as to Fig. 1.

intravenous drip administration of oxytocin at the rate of 0.4 μg/kg/h. One of eight typical experiments in which the inhibitor action of oxytocin on EP production was observed, is illustrated in Fig. 3. The mean rise of the rectal temperature of the mice 20 min after injection of the control EP, according to the results of these experiments, was 0.58 ± 0.05°C, but after injection of EP obtained in culture in the presence of oxytocin, it was 0.39 ± 0.04°C ($p < 0.01$).

The present investigation thus showed for the first time that oxytocin has antipyrogenic properties. Its action is unconnected with the blockage of receptors for EP, as was shown recently for vasopressin [10], for oxytocin did not diminish fever induced by EP. Its effect is evidently connected with inhibition of EP production. This is shown by the decrease of the second peak of the temperature curve after injection of pyrogenal and the decrease in EP production in vitro. The mechanism of action of oxytocin on cells producing EP is not clear. It can be tentatively suggested that it induces activation of mechanisms of negative regulation of EP synthesis or inhibiton of EP secretion. Calcium ions are probably involved in the realization of the inhibitory action of oxytocin. It has been shown [12] that oxytocin causes an increase in their concentration in the cytoplasm of epithelial cells. The effects of oxytocin may perhaps be due to changes in the electrophysiological properties of the cell membrane [11].

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