EFFECT OF SYNAPTICALLY ACTIVE SUBSTANCES ON THE HYPERTHERMIC EFFECT OF PROSTAGLANDIN E_2 IN RATS

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KEY WORDS: prostagladin hyperthermia; synaptically active substances; monoamines; cholinomimetics; acetylcholine blocking agents.

Injection of prostaglandins (PG) of the E group into the cerebral ventricles of homoiothermic animals causes a rapid and considerable rise of body temperatures [4, 7, 9, 14]. The opposite effect, i.e., a fall of body temperature, is observed in many animals, especially in rats, during excitation of central cholinergic and monoaminergic systems [1, 2, 9]. The development of hyperthermia under the influence of PG is not prevented by antipyretics [3, 6, 13] but it is weakened by certain monoamines, their antagonists, cholinomimetics, and Ca^{++} [1, 3, 6, 10, 11]. To test the hypothesis that the hyperthermic effect of PG may be modulated by synaptically active substances, further experimental studies were necessary.

The object of this investigation was to study the effect of α- and β-adrenomimetics, α- and β-adrenoblockers, serotonin and deseryl, M- and N-cholinomimetics, M- and N-acetylcholine blocking agents, and also hemicholinium-3 on the hyperthermic effect of PG-E_2 in rats by injection of the drugs into the lateral cerebral ventricles.

EXPERIMENTAL METHOD

Experiments were carried out on 145 unanesthetized noninbred albino rats weighing 160-180 g. Aqueous solutions of the drugs were injected into the right lateral cerebral ventricle in a volume not exceeding 20 µl, under local anesthesia (5% procaine, subcutaneously). The PG-E_2 used was from the Upjohn Company, USA, clofelin and isoproterenol bitartrate dihydrate were from Winthrop, USA, noradrenalin bitartrate monohydrate, phenoxybenzamine, and propranolol were from Ayerst Zul, USA, serotonincreatinine sulfate was from Reanal, Hungary, and deseryl (methysergide), oxotremorine, nicotine, metamizil (methyldiazine), and IÉM-506) (β-ethyldiphacil) were of USSR origin, and the hemicholinium-3 was from the Aldrich Chemical Company, USA. All mimetics were injected in some experiments 5 min before, in the others 15 min after injection of PG-E_2, when the animals' body temperature was raised by more than 1.5°C. The blockers were injected 15 min before injection of PG-E_2. The body temperature was measured rectally with the TPÉM-1 electrothermometer.

EXPERIMENTAL RESULTS

Injection of PG-E_2 (2 µg) into rats caused the body temperature of the animals to rise within 15 min by 1.5°C, and after 30 min by 2.5°C. This reaction was weakened by the central action of the α-adrenomimetic clofelin (1 µg) in experiments in which this drug was injected both before and after injection of PG-E_2, but it was unchanged when the β-adrenomimetic isoproterenol was given in a dose of 10 µg (Fig. 1).

Injection of noradrenalin (10 µg), serotonin (25 µg), the β-adrenoblocker propanolol (100 µg) and the serotoninolytic deseryl (40 µg) 15 min before injection of PG-E_2 did not prevent the rise of temperature, but the action of the α-adrenoblocker phenoxybenzamine (100 µg), injected previously, potentiated this response (Fig. 2). In animals receiving a preliminary injection of the M-cholinomimetic oxotremorine (4 µg), the hyperthermic effect of PG-E_2 did not develop, but under the influence of nicotine (10 µg) this effect was substantially unchanged (Fig. 3). These same experiments revealed that neither the M-acetylcholine blocking

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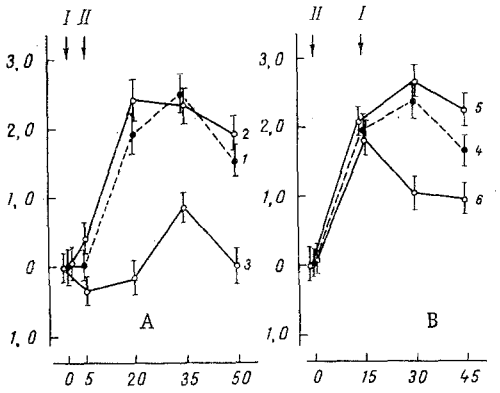

Fig. 1

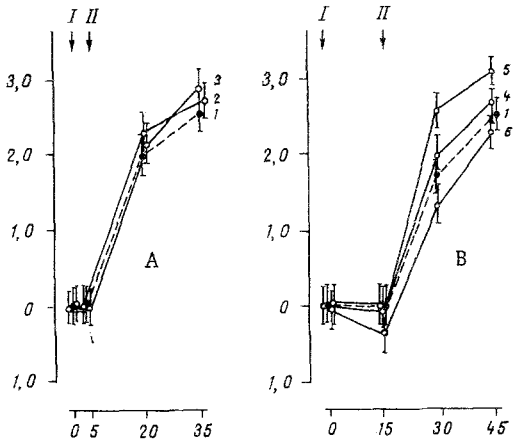

Fig. 2

Fig. 1. Effect of adrenomimetics on development of PG-E_2 hyperthermia in rats. A) Adrenomimetics + PG-E_2, B) PG-E_2 + adrenomimetics. 1) Control (distilled water + PG-E_2; n = 10); 2) isoproterenol + PG-E_2 (n=6); 3) chofelin + PG-E_2 (n = 7); 4) control (PG-E_2 + distilled water; n = 10); 5) PG-E_2 + isoproterenol (n = 12); 6) PG-E_2 + clofelin (n = 7). I (arrow) — time of injection of adrenomimetics; II (arrow) — time of injection of PG-E_2. Abscissa, time (in min): ordinate, change in body temperature (in °C).

Fig. 2. Effect of monoamines and their antagonists on development of PG-E_2 hyperthermia in rats. A) Monoamines + PG-E_2; B_o) blockers + PG-E_2. 1) Control (distilled water + PG-E_2; n = 10); 2) noradrenalin + PG-E_2 (n = 7); 3) serotonin + PG-E_2 (n = 7); 4) deseryl + PG-E_2 (n = 6); 5) phenoxybenzamine + PG-E_2 (n = 8); 6) propranolol + PG-E_2 (n = 8). I (arrow): in A — time of injection of monoamines; in B — time of injection of adrenoblockers and deseryl; II (arrow) — time of injection of PG-E_2. Remainder of legend as to Fig. 1.

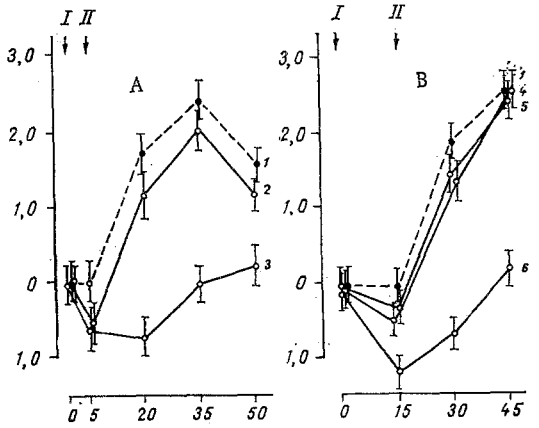

Fig. 3. Effect of cholinomimetics, acetylcholine blocking agents, and hemicholinium-3 on development of PG-E_2-induced hyperthermia in rats. A) Cholinomimetics + PG-E_2; B) acetylcholine blocking agents, hemicholinium-3 + PG-E_2. 1) Control (distilled water + PG-E_2; n = 10); 2) nicotine + PG-E_2 (n = 7); 3) oxotremorine + PG-E_2 (n = 7); 4) IEM-506 + PG-E_2 (n = 7); 5) metamizil + PG-E_2 (n = 7); 6) hemicholinium-3 + PG-E_2 (n = 7). I (arrow): in A — time of injection of cholinomimetics; in B — time of injection of PG-E_2. Remainder of legend as to Fig. 1.

agent metamizil (100 μg) nor the N-acetylcholine blocking agent IEM-506 (100 μg) prevented PG-E_2-induced hyperthermia, although it did not develop under the influence of hemicholinium-3 (30 μg) on subcortical structures (Fig. 3).

The results of the present experiments in which synaptically active substances were injected into the cerebral ventricles confirm the previous hypothesis [3] that hyperthermia may be weakened through activation of central mediator-ergic mechanisms, Since PG-E_2-induced hyperthermia can be weakened by injection of the α-adrenomimetic clofelin (but not the β-adrenomimetic isoproterenol), the action of noradrenalin is evidently due to its effect on α-adrenoreceptors.

These results are in agreement with other observations [12], from which it follows that hyperthermia, induced by pyrogenic substances, is not affected by the action of reserpine and

6-hydroxydopamine. Meanwhile there are reports in the literature that the hyperthermic effect of PG can be weakened by injection of α-adrenoblockers [10, 11], atropine [5], and serotonin antagonists [10] into the ventricles or into hypothalamic structures.

According to the results of the present experiments PG-hyperthermia is effectively prevented by hemicholinium-3. However, this substance is reported to have a marked action on membranes and, for that reason, the effect observed evidently cannot be explained purely in terms of the anticholinergic action of the drug.

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EFFECT OF ETHIMIZOLE ON RNA-SYNTHESIZING ACTIVITY OF RAT BRAIN CELL NUCLEI DURING LEARNING

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KEY WORDS: ethimizole; RNA synthesis; cerebral cortex; hippocampus; rats; irradiation.

Activation of the genetic apparatus of nerve cells may be the trigger factor in induction of synthesis of macromolecules (RNA and polypeptides) which participate in learning and memory processes [2, 6]. One of the most important indicators of activity of the genetic apparatus of cells is the RNA-polymerase activity of the nuclei, characterizing the level of chromatin transcription.

The object of this investigation was to study the effect of ethimizole (bis-1-ethylimidazole-4,5-dicarboxylic acid bis-methylamide), which increases the intensity of memory processes in man and animals [1, 4, 5], on RNA synthesis in isolated nuclei of the cerebral cortex and hippocampus during the formation and consolidation of conditioned reflexes in rats.

EXPERIMENTAL METHOD

Experiments were carried out on 155 male Wistar rats weighing 180-200 g. In the experiments of series I the animals were taught to solve a problem of conditioned active avoidance

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