HYPERTHERMIC EFFECT OF TRYPSIN INHIBITOR IN RATS AND RABBITS

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Limited proteolysis is an important stage in the formation of many highly active regulatory peptides and, in particular, of neuropeptides concerned in body temperature regulation, in the brain [5, 7, 8]. Activity of proteolytic enzymes has been shown to change in the rat brain during hypo- and hyperthermia [3, 4], and inhibitors of intracellular proteinases as well as trypsin and chymotrypsin, can be isolated from subcellular fractions of animal brain [6, 10]. However, there are no data on changes in body temperature as a result of the central action of inhibitors of proteolytic enzymes.

This paper describes a study of the effect of trypsin inhibitor on body temperature, when administered centrally and systematically.

EXPERIMENTAL METHOD

Unanesthetized albino rats of both sexes weighing 160-180 g and unanesthetized adult rabbits weighing 2.5-3 kg were used. An aqueous solution of soy trypsin inhibitor (from Reanal, Hungary) was injected in a single dose: into rats, under local anesthesia (5% procaine, subcutaneously), into the right lateral ventricle in a volume not exceeding 20 µl, or into the lateral caudal vein in a volume of 0.2 ml; into rabbits into the third ventricle

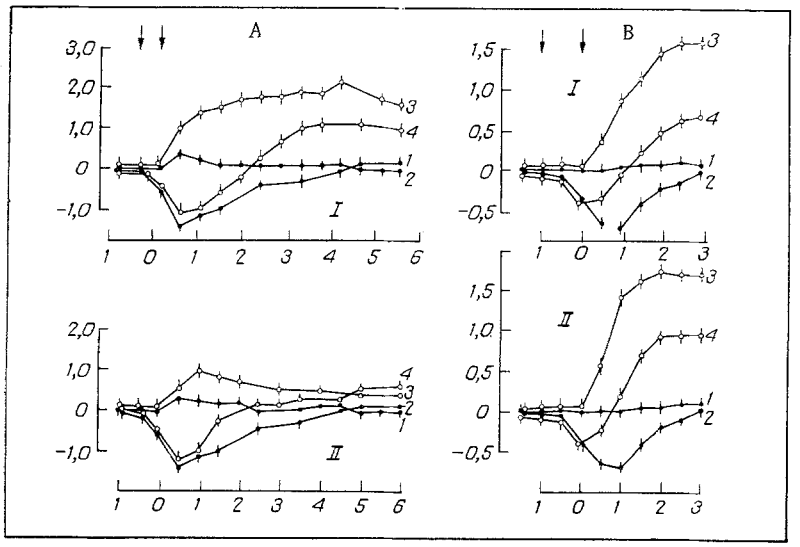

Fig. 1. Effect of trypsin inhibitor on body temperature of rats (A) and rabbits (B). Abscissa, time (in h); ordinate, changes in body temperature (in °C). I) Injection of inhibitor into system of cerebral ventricles; II) injection of inhibitor into blood stream. 1) Control: H_2O + H_2O (n = 10); 2) sodium salicylate + H_2O (n = 12); 3) H_2O + trypsin inhibitor (n = 16); 4) sodium salicylate + trypsin inhibitor (n = 16). Number of experiments given in parentheses. First arrow indicates time of injection of sodium salicylate or H_2O (control); second arrow indicates time of injection of trypsin inhibitor or H_2O.

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through implanted chemical electrodes [1] in a volume of 50 µl or into the marginal vein of the ear in a volume of 1 ml. All observations were made under thermoneutral conditions (20-22°C). Sodium salicylate was used (intramuscular or intraperitoneal injections) in the experiments on both rats and rabbits. Tissue prostaglandin (PG) levels in the rat hypothalamus were determined by a radiocompetitive method, using kits from "Clinical Assays" (USA). The serum free fatty acid (FFA) level was determined by a colorimetric method [9]. The body temperature (rectal) was measured in the rats by a TPÉM-1 electrothermometer. In the experiments on rabbits changes in heat emission were judged on the basis of changes in skin temperature on the outer surface of the ear. This parameter was recorded by means of thermistors, and synchronized with measurement of the rectal temperature on an ÉPP-09-M3 electronic potentiometer.

EXPERIMENTAL RESULTS

Injection of trypsin inhibitor (100 µg per animal) into the cerebral ventricles caused a marked rise of body temperature (Fig. 1A). The duration of hyperthermia was 7-8 h. This response was weakened by preliminary (30 min before injection of the trypsin inhibitor) injection of sodium salicylate (300 mg/kg). Injection of trypsin inhibitor (0.3 mg/kg) into the blood stream was followed by weak and transient hyperthermia.

Central and systemic administration of trypsin inhibitor to rabbits led to the development of stable and prolonged hyperthermia (Fig. 1B). The hyperthermia effect of trypsin inhibitor in rabbits also was weakened by sodium salicylate (300 mg/kg).

The rise of the animals' body temperature after central and systemic administration of trypsin inhibitor took place because of an increase in heat production (the oxygen consumption of the animals was increased and the blood FFA level rose) and on inhibition of heat loss (the skin temperature of the rabbits' ear or of the base of the rats' tail fell). For instance, the serum FFA level of rats, which was 456 ± 31.9 meq/liter in the control (n = 12), rose by 23% ($P < 0.05$) 3 h after injection of trypsin inhibitor into the cerebral ventricles. The animals' oxygen consumption increased under these circumstances from 42.5 ± 2.68 to 53.1 ± 3.71 ml O_2/kg/min. The central action of trypsin inhibitor (100 µg per animal) was accompanied under conditions of increasing hyperthermia by a marked fall in the PGE_2 concentration in the hypothalamus (by 61% 3 h after injection; $P < 0.001$), whereas the $PGE_{2\alpha}$ level was unchanged. PGE_2 and $PGE_{2\alpha}$ concentrations in the control were 428.0 ± 60.49 and 31.8 ± 2.46 ng/g tissue respectively.

The experimental results suggest that hyperthermia arising after administration of trypsin inhibitor to animals is the result of the central action of this substance, and that PGE_2 in the hypothalamus are not mediators of the response observed. The reason for its development is evidently inhibition of activity of trypsin-like brain proteinases. In view of information in the literature that acid brain proteinases are inhibited by certain substances of bacterial origin [10], it can be tentatively suggested that inhibition of activity of certain trypsin-like serine proteinases in temperature regulating centers may be one factor in the development of febrile states.

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