PENTAGASTRIN AS A FACTOR OF SELECTIVE INVOLVEMENT OF DORSAL HIPPOCAMPAL NEURONS IN THE ORGANIZATION OF FOOD-MOTIVATED BEHAVIOR

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Various endogenous peptides affect the behavior of animals and men. In particular, intestinal peptide hormones, injected into the CNS, cause complex changes in food behavior. Cholecystokinin inhibits food intake by animals [1, 4, 5], whereas gastrin activates it [2]. The writers showed previously that realization of food motivation in the form of goal-directed behavior in response to electrical stimulation of the "hunger centers" in the lateral hypothalamus is impossible if peptide synthesis is blocked in the CNS [3]. Sensomotor cortical neurons of the rabbit brain cease to respond under these circumstances to motivation-inducing stimulation of the lateral hypothalamus.

The aim of this investigation was to determine the character of synthesis in dorsal hippocampal neurons of polypeptides concerned with their involvement in the organization of goal-directed food behavior, and to discover whether the endogenous peptide factor, gastrin, is the substance synthesized in the neurons without which organization of food-motivated behavior would be impossible.

EXPERIMENTAL METHOD

Experiments were carried out on four waking male chinchilla rabbits weighing 2.5 kg. Bipolar nichrome electrodes were implanted in the animals' lateral hypothalamus, electrical stimulation of which by square pulses (amplitude 1-6 V, frequency 50 Hz, pulse duration 1 msec, duration of stimulation 4 sec) evoked an orienting-investigative response, manifested as increased motor activity of the animals, sniffing the experimental chamber, and standing up on the hind limbs. An increase in the amplitude of stimulation by 1-2 V led to the appearance of food behavior in the animals: Previously fed rabbits began to eat food actively. To record single unit activity in area CA3 of the dorsal hippocampus of the rabbit and for microiontophoretic application of physiologically active substances to it, four-channel glass microelectrodes were used. The recording electrode was filled with a 3 M solution of sodium chloride, the electrode for compensating the current effect was filled with 0.5 M sodium chloride solution, the third electrode contained a 1.5×10^{-2} M solution of cycloheximide (Serva, West Germany), which blocks protein synthesis, and Tris-phosphate buffer, pH 9.4, and the fourth electrode contained an 8.6×10^{-5} M solution of pentagastrin (Serva) and Tris-phosphate buffer, pH 9.4. Unit activity of 19 hippocampal neurons was recorded in the lightly immobilized animals by means of a four-channel "Biofaz" cathode amplifier. For the microelectrode investigations the lateral hypothalamus was stimulated in lightly immobilized rabbits by square pulses of current of threshold strength, evoking food consumption in the animals, and 1.5 min later, of subthreshold strength, evoking an orienting-investigative reaction. Stimulation was repeated after application of cycloheximide 1 and 10 min after the beginning of microiontophoresis, and again during application of cycloheximide and pentagastrin, 1 and 10 min after the beginning of pentagastrin application. The traces of unit activity were analyzed by constructing frequency histograms with a controllable reset period of 2 sec.

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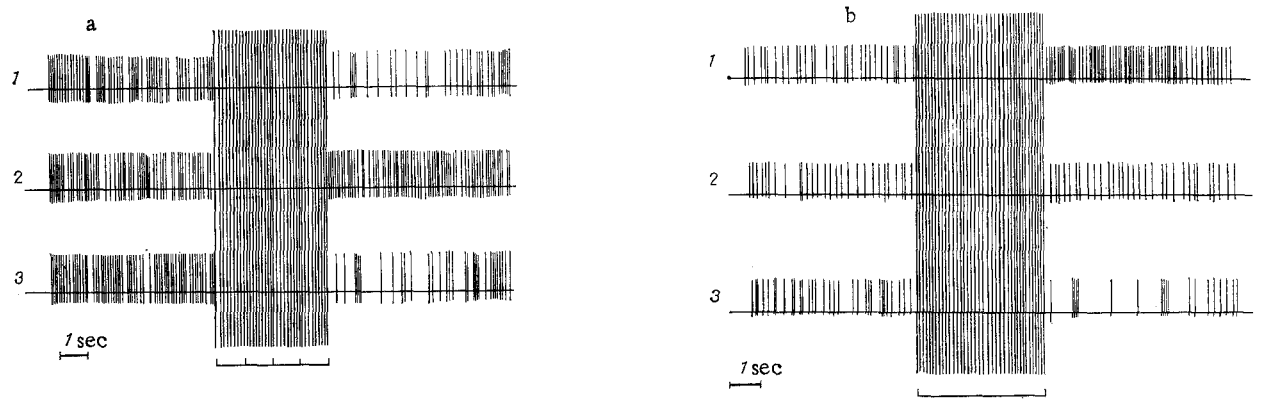

Fig. 1. Unit activity of the dorsal hippocampus: 1) threshold stimulation of lateral hypothalamus, 2) threshold stimulation of lateral hypothalamus against the background of microiontophoretic application of cycloheximide, 3) threshold stimulation of lateral hypothalamus during combined application of cycloheximide and pentagastrin. Lines denote stimulation. Remainder of legend, see in text.

EXPERIMENTAL RESULTS

Neurons of the dorsal hippocampus differ in their response to electrical stimulation of the lateral hypothalamus with different intensity. For instance, during the first 2-8 sec after subthreshold stimulation of the lateral hypothalamus, evoking an orienting-investigative reaction, nine (47%) of the 19 neurons tested responded by an increase in spontaneous discharge frequency, eight (42%) by a decrease, and two (11%) did not respond at all to stimulation.

After threshold stimulation, evoking a food reaction, 12 (63%) of the 19 neurons tested responded by an increase in discharge frequency, in five neurons (26%) the frequency decreased, and two neurons (11%) did not change their spontaneous activity.

Reactions of hippocampal neurons to stimulation of the lateral hypothalamus of different intensity were either opposite or similar in direction.

Microiontophoretic application of cycloheximide, which blocks protein synthesis, to neurons of the dorsal hippocampus caused changes in responses to threshold stimulation in 15 of 19 neurons, and to subthreshold stimulation in 10 neurons. Application of pentagastrin to these neurons led to complete recovery of the initial responses to threshold stimulation of the lateral hypothalamus in 10 of 15 neurons, but to subthreshold stimulation in only one of 10 neurons.

Recovery of the initial responses of the hippocampal neurons to stimulation of the "hunger center" in the lateral hypothalamus was observed only when the previous blocking of peptide synthesis evoked complete inhibition of the initial responses, but not their reversal (Fig. 1a). In some such neurons (3 of 13), however, microiontophoretic application of pentagastrin caused the appearance of responses to stimulation of the lateral hypothalamus, opposite in sign to the spontaneous responses (Fig. 1b).

It can thus be postulated that excitation of the "hunger center" in the lateral hypothalamus induces synthesis of certain substances of peptide nature in hippocampal neurons, which are sufficiently specific for orienting-investigative and food motivational responses. Polypeptide synthesis takes place in most neurons only in response to threshold stimulation of the lateral hypothalamus, evoking food behavior in animals. Blocking of protein synthesis by cycloheximide changes or completely inhibits the responses of dorsal hippocampal neurons to stimulation of the "hunger center" in the lateral hypothalamus. Microiontophoretic application of pentagastrin to these neurons caused recovery of their normal responses to motivation-inducing stimulation, whereas responses to subthreshold stimulation of the lateral hypothalamus, evoking an orienting-investigative response, remained changed. Consequently, for most neurons of area CA3 of the dorsal hippocampus to be involved in the organization of food behavior, the presence of a definite quantity of pentagastrin, evidently synthesized under normal conditions during food motivational excitation in the same or neighboring nerve cells, is necessary.

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POSSIBLE SEROTONINERGIC MECHANISM OF INTRACARDIAC INTERACTION BETWEEN VAGUS AND SYMPATHETIC NERVES

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The intensity of function of several internal organs is largely determined by interaction between the sympathetic and parasympathetic nervous system. Stimulation of the sympathetic ganglion reduces the inhibitory effect of the vagus on the heart [1, 8]. However, during weak stimulation of the stellate ganglion accompanied by stimulation of the vagus nerve, potentiation of vagus inhibition of the cardiac rhythm is observed [1, 7, 9]. Similar data also were obtained during an investigation of the effect of different concentrations of catecholamines and acetylcholine when applied simultaneously to the isolated frog's heart [2, 6]. The aim of this investigation was to study the mediator nature of structures involved in the realization of this effect.

EXPERIMENTAL METHOD

Experiments were carried out on chinchilla rabbits weighing 2.5-3 kg anesthetized with hexobarbital (100 mg/kg, intraperitoneally) using artificial ventilation of the lungs by the AID-3 apparatus. Altogether 40 experiments were carried out, in which separate and combined stimulation of the right stellate ganglion and the peripheral end of the divided left vagus nerve were applied (in all series of experiments). During combined stimulation of the nerves, stimulation of the sympathetic ganglion began 7-15 sec after vagus nerve stimulation began, when a stable decrease in the heart rate was established. The parameters of vagus nerve stimulation were near-threshold strength, causing slowing of the heart rate by 20-30% of the spontaneous rhythm. The duration of vagus nerve stimulation was 40-60 sec. The stellate ganglion was stimulated from 10-20 sec by means of an ÉSU-1 stimulator. The absolute arterial pressure (in mm Hg) and the pulse pressure were recorded, so that changes in heart rate and systemic arterial pressure could be judged. Arterial pressure was recorded in the right carotid artery by means of an EMT-35 pressure transducer and UBP2-03 biopotentials amplifier. To evaluate the contractile properties of the heart muscle, the impedance of the myocardium also was recorded by means of electrodes connected to an RG 4-01 rheograph. The recording was made on an N3020-5 automatic ink-writing recorder. To test the mediator nature of the chronotropic effect, trimeperidine (1-2 mg/kg), promethazine (1-2 mg/kg), and chlorpromazine (0.1-1 mg/kg) were used. All drugs were injected intravenously. The investigation comprised 10 acute experiments and 30 chronic experiments. In the latter, the right vagus nerve was divided in the neck under sterile conditions 2-3 weeks before the main part of the experiment, in order to cause its degeneration and to prevent the action of loops of current on parasympathetic fibers during stimulation of the right stellate ganglion.

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