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ACTH FRAGMENTS IN MECHANISMS OF COMPENSATION OF SELF-STIMULATION BEHAVIOR AFTER SEPTAL DESTRUCTION IN RABBITS

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The septal region of the brain, connecting phylogenetically older and newer brain formations by means of numerous afferent and efferent connections passing through it, plays a leading role in the organization of self-stimulation (SS) behavior [4, 9]. The role of the septum in mechanisms of SS is particularly interesting because, by virtue of 2-way functional connections with the paraventricular and supraoptic nuclei of the hypothalamus [8], it participates in regulation of the hypothalamo-hypophyseo-adrenocortical system. Many ACTH-sensitive neurons are found in the septal region [11]. Injections of ACTH 4-10 lowered the threshold for evocation of SS behavior from the medial septum in rats and increased the number of times the animals pressed the lever in response to low-intensity stimulation [10]. In experiments on rats [6] fragments ACTH 4-9 and 5-8 potentiated SS behavior evoked from the medial forebrain bundle, whereas intraperitoneal injection of ACTH 5-10 [1] reduced the intensity of SS from the lateral hypothalamus in rabbits. In our previous investigations cyclic analogs of ACTH/MSH fragments, depending on the dose, increased or reduced the frequency of SS of the lateral hypothalamus [2], whereas fragment ACTH 4-10 restored SS in rabbits in which protein synthesis was blocked by cycloheximide and actinomycin [3].

The aim of this investigation was to study the effects of fragments ACTH 1-24 and ACTH 4-10 in the mechanisms of SS behavior in rabbits after destruction of the septal region of the brain.

EXPERIMENTAL METHOD

Experiments were carried out on 32 male chinchilla rabbits weighing 3-3.5 kg. Bipolar nichrome stimulating electrodes were implanted 24 h after the animals were scalped into the region of the lateral hypothalamus (P = 2, L = 2, H = 15-16 mm). Electrodes also were implanted unilaterally into the rabbits in the region of the septum (A = 3, L = 1, H = 9-10 mm). To inject the ACTH fragments into the animals, steel cannulas 14 mm long and 0.8 mm in diameter were implanted into the lateral ventricles. During the experiments the rabbits were kept in a chamber with a fixed metal ring, and had free access to water and food. By touching the metal ring with their nose and lips, the unrestrained animals quickly learned to close the electric circuit in

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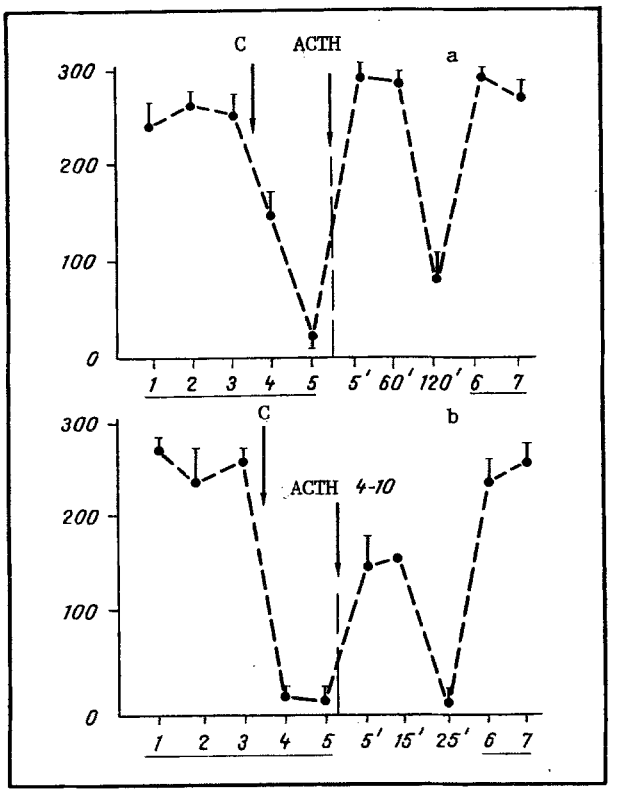

Fig. 1. Changes in frequency of SS after coagulation of septal region and intraventricular injections of fragments of ACTH 1-24 (a) and 4-10 (b). Abscissa, time of experiment (days); ordinate, frequency of SS during 5-min time intervals. C) coagulation.

order to obtain electrical stimulation of the lateral hypothalamus. The parameters of the stimulating current were: bundles of square pulses with frequency of 100 Hz and duration 0.3 sec, current strength 200-600 μA, single pulse 1.4 msec in duration. Sessions of SS were given daily for 7-10 days. The frequency of SS during a period of 5 min was studied every 10 min for 2 h of the experiment, in the background period 3 days before coagulation and again 4-7 days after coagulation of the septal region. Coagulation was carried out unilaterally, ipsilaterally relative to the stimulating electrode in the lateral hypothalamus, for 60 sec with a direct current of 2 mA. The peptides were dissolved in 10 μl of sterile physiological saline and injected into the lateral ventricles in the following doses: ACTH 1-24 in a dose of 0.5-1.0 μg, ACTH 4-10 in a dose of 0.5-10 and 20 μg. After the end of the experiments the animals' brain was fixed for 5-7 days in 10% formalin solution, frozen, and frontal sections were cut to a thickness of 30 μm. The sites of the lesions were identified against maps from stereotaxic atlases. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The action of ACTH fragments of SS behavior was studied after stimulation of the septal region. The morphological investigations showed that the lesions in these animals were unilateral and extended to the lower parts of the anterior commissure, the anterior commissural nucleus and fornix, the upper parts of the medial and lateral preoptic (7 rabbits, group 1) and anterior hypothalamic (2 rabbits, group 2) regions. After these lesions had been produced, no change was observed in the feeding, drinking, or motor behavior of the rabbits of both groups. The frequency of SS on the second day after coagulation was reduced by half in all the animals and it had virtually disappeared by the 3rd day. On the 3rd day, immediately after being placed in the experimental chamber, the rabbits went up to the ring, closed the circuit by touching it with their nose 6-8 times, then went away, returned again and received 5-8 stimulations, after which they stopped the stimulation. The animals were not stimulated, even if the strength of the current was increased by 50-80 μA. Injection of ACTH 1-24 into 5 rabbits at this time in a dose of 0.5-1.0 μg caused intensive SS as early as 1-2 min after the injections. The frequency of SS was actually higher than ini-

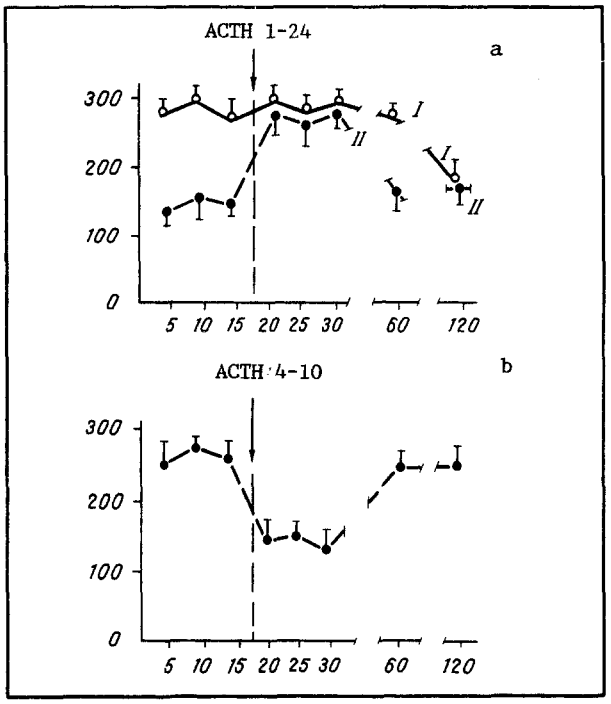

Fig. 2. Change in frequency of SS after intraventricular injections of ACTH fragments 1-24 (a) and 4-10 (b). Abscissa, time of experiment; ordinate, frequency of SS during 5-min time intervals. I) injection of ACTH 1-24 into rabbits with high, and II) with low original frequency of SS.

tially, before coagulation, by 10-12% (Fig. 1a). The animals showed grooming and orienting-investigative behavior (OIB) 15-20 min after the ACTH 1-24 injections. After the 25th-30th minutes grooming was intensified and the rabbits developed a stretching-yawning syndrome (SYS). By the 120th minute of the experiment the frequency of SS was reduced to 70-90 pulses during 5-min intervals. Next day, the animals demonstrated intensive SS only if the threshold of SS was increased by 100-150 μA. Injections of ACTH 4-10 in doses of 0.5-10 μg did not restore SS, when disturbed by destruction of the septal region, in 4 rabbits. When the dose of ACTH 4-10 was increased to 20 μg, the animal began SS. The frequency of SS increased from 7.6-2.4 to 126-21.5 pulses/min ($p < 0.005$; Fig. 1b). It must be emphasized that the effects of ACTH 4-10 were of short duration — under 25 min. On the following days SS was observed only when the threshold of stimulation was increased.

In special control experiments ACTH 1-24 was injected into 11 intact rabbits. In these experiments, in 6 rabbits with a low initial SS level (Fig. 2a), ACTH 1-24 caused a statistically significant increase in the intensity of SS by 85.6-6.6%. The potentiating action of ACTH 1-24 on SS appeared 1-2 min after its injection and continued for 50-60 min, after which the frequency of SS fell by 48.5-10.2%, and the rabbits exhibited intensive and prolonged grooming, OIB, increased arousal, and also the SYS syndrome. These effects lasted on average 40-50 min, after which the animals became quiet. In 5 rabbits with a high initial level of SS injections of ACTH 1-24 did not cause any appreciable changes in the frequency of SS during the first 50-60 min. The frequency of SS was then reduced 54.2-11.4% (Fig. 2a). The animals exhibited intensive grooming, OIB, and SYS. On the second day after injection of ACTH 1-24 the frequency of SS in these animals returned to its original level. Injections of ACTH 4-10 in a dose of 20 μg led in 6 rabbits to reduction of the frequency of SS by 56.6-8.4% after 5-10 min and to a change in the pattern of SS: the rabbits received 5-7 stimulations, they stopped, went away from the ring, returned after 8-10 sec, and again applied the stimulation (Fig. 2b). After 40-50 min SS was restored to its original level. ACTH 4-10, in the above doses, did not affect the food and water consumption of the rabbits and did not potentiate OIB and grooming. Injections of 10 μl of physiological saline into 6 rabbits in the control experiments caused no significant changes in SS.

In a previous study [4] we showed that unilateral destruction of only the medial and lateral septal nuclei led to a very slight decrease in SS from the septum ipsilateral, and to an increase in SS from the septum contralateral to the electrode stimulating the lateral hypothalamus. In the present investigation we accordingly produced more extensive destruction of the region of the septum ipsilateral relative to the electrode stimulating the lateral hypothalamus, extending to the inferior parts of the anterior commissure, the commissural nucleus, and the fornix, as well as to the superior parts of the medial and lateral pre-

optic region. It was found that lesions of this extent led to a marked decrease in SS or even its complete disappearance. The experiments showed that ACTH 1-24 and 4-10 restored SS after destruction of the septal region as described above. ACTH 1-24 was found to increase SS in rabbits with an initially low frequency of SS. It can be tentatively suggested on the basis of these results that ACTH-like substances necessary for organization of SS behavior are produced and/or accumulate in the septal region. After destruction of this region receptors for ACTH fragments are preserved in other parts of the brain, and SS is therefore restored after injection of these substances into the cerebral ventricles. It has been shown [10, 12] that labeled analogs of ACTH, on intraventricular injection, do in fact appear initially in the septal neurons and in adjacent structures. Compensatory effects of oligopeptides relative to SS behavior have been found after destruction of the ventromedial hypothalamus [7] and also relative to active avoidance after destruction of the fornix and of the stria terminalis [10, 12]. Compensatory effects have been described for other fragments of pro-opiomelanocortin also. For instance, in experiments on rats [5] β-LPH and β-endorphin restored food and drinking motivation after unilateral destruction of the lateral and arcuate hypothalamic nuclei. All these facts offer encouraging prospects for the use of oligopeptides to compensate disturbed brain functions. Our own results indicate that ACTH 1-24 and 4-10 have an unambiguous action on SS in intact rabbits and after destruction of the septal region, and also that the effects of these peptides depend on the initial level of SS.

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