ROLE OF NORADRENALIN IN THE DORSAL HIPPOCAMPUS IN THE MECHANISM OF THE SELF-STIMULATION RESPONSE IN RATS

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UDC 612.833.81.06:612.825.26.018.577.175.523

KEY WORDS: noradrenalin; 6-hydroxydopamine; hippocampus; self-stimulation response; memory

The role of brain noradrenalin (NA) in the mechanism of the self-stimulation response (SSR) is well known [4]. However, the nature of the functional specificity of NA at different levels of structural organization of positive reinforcement has received little study.

In particular, there have been only isolated studies [1] of the role of hippocampal NA in SSR, although the hippocampus, which is rich in NA, and which is a component of structural organization of positive reinforcement, is known to be the principal information structure of the limbic system [2].

The aim of this investigation was to study the character of changes in SSR, arising from the lateral hypothalamus, and in the accompanying forms of behavior during the local rise and fall of the NA level in the dorsal hippocampus as a result of injection of exogenous NA and of the neurotoxin 6-hydroxydopamine (6-OHDA), which selectively destroys NA-ergic terminals.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 250-300 g (21 rats) into which directing cannulas had been introduced beforehand bilaterally into the dorsal hippocampus at coordinates (AP = 3, L = 1.2, H = 1.2) and bipolar stimulating electrodes had been introduced, also bilaterally, into the lateral hypothalamus at coordinates (AP = 2.5, L = 1.6, H = 8.5).

A stable SSR to electrical stimulation of the lateral hypothalamus was formed in the rats in a Skinner's box. Electrical stimulation was applied from an ESU-1 stimulator in the form of square pulses (duration 0.5 msec, frequency 100 Hz, duration of volley 0.2 sec, current 40-120 μA). The SSR was tested for 30 min.

Parameters such as the frequency of SSR in 30 min, the speed of single presses on the pedal, determined by the length of time the pedal was held in the depressed position, and also the number of erections on the hind limbs and of aversive responses (running away from the pedal to the oppposite side) were recorded. When a stable level of SSR had been achieved for 2-3 days, physiological saline was injected into the dorsal hippocampus of all the rats in a volume of 0.6-1 μl. The values obtained for SSR and the accompanying forms of behavior served as initial data. The SSR was then elicited in one group of animals (11 rats) against the background of the action of NA (noradrenalin bitartrate, from "Sigma," USA), applied bilaterally by microinjection into the dorsal hippocampus 10 min before the experiments, whereas in the other group (10 rat), it was elicited after destruction of the hippocampal NA-ergic pool, by preliminary injection of the neurotoxin 6-OHDA ("Sigma") 8-10 days beforehand. The NA was diluted in 0.1% ascorbic acid solution and applied by microinjection in a dose of 2 μg and a volume of 2 μl.

The data were subjected to statistical analysis by the Wilcoxon–Mann–Whitney test. After the end of the experiments the precise location of the cannula and electrodes was determined morphologically.

EXPERIMENTAL RESULTS

The results showed that NA, applied bilaterally by microinjection into the dorsal hippocampus, did not change the frequency of SSR (Fig. 1) but did change the behavioral responses

Laboratory of Neurophysiology of Reinforcement, A. I. Karaev Institute of Physiology, Academy of Sciences of the Azerbaijan SSR, Baku. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 1, pp. 5-6, January, 1990. Original article submitted July 27, 1988.

 0007-4888/90/0001-0004$12.50

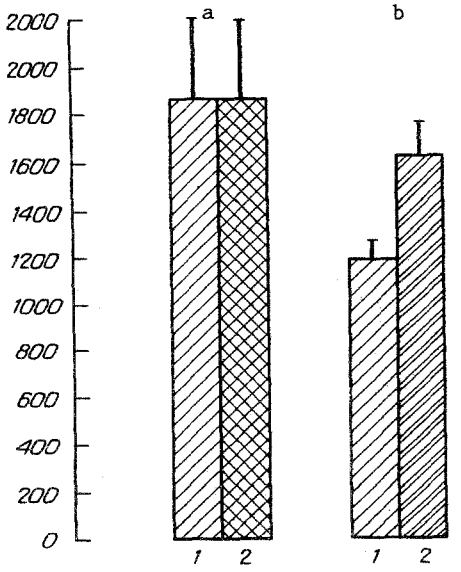

Fig. 1

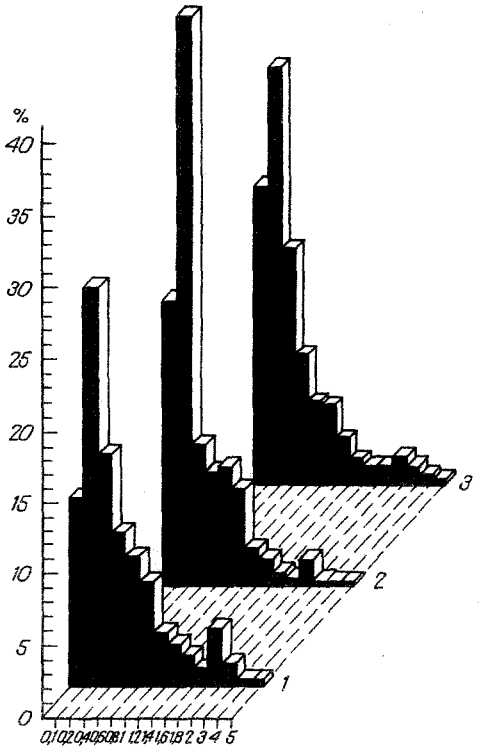

Fig. 2

Fig. 1. Changes in frequency of SSR of lateral hypothalamus in response to changes in NA level in hippocampus induced by local injection of exogenous NA and of neurotoxin 6-OHDA. Ordinate, frequency of SSR during testing for 30 min. a) Frequency of SSR after microinjection of NA into dorsal hippocampus; b) after injection of 6-OHDA. Here and in Fig. 2: 1) control; 2) action of NA; 3) action of 6-OHDA.

Fig. 2. Changes in speed of single presses on pedal during SSR preceded by microinjection of NA and 6-OHDA into doral hippocampus. Abscissa, initial time intervals of single holding of pedal in depressed position (in sec); ordinate, number of fixed time intervals of single holding of pedal in depressed position (in %).

accompanying it. The number of aversive responses was increased (84.6 ± 34, compared with the control 0.38 ± 0.3) and vertical activity was completely blocked. As Fig. 2 shows, under the influence of NA, a significant ($p < 0.01$) increase was observed in the animals' preference to keep the pedal in the depressed position for time intervals of 0.1 to 0.2 sec, i.e., in the time intervals of electrical stimulation (0.2 sec), but with significant reductions in the relative percentage of preferred time intervals of 0.4-1 sec.

Different relationships were observed in rats after destruction of the NA-ergic hippocampal pool. Lowering of the NA level in the hippocampus was accompanied by a significant increase in the frequency of SSR (Fig. 1) and vertical activity (10.7 ± 2.0 compared with 4.8 ± 4 in the control; $p < 0.01$), and a decrease in the number of aversive responses (1.8 ± 0.3, 8.4 ± 5.0 in the control). Analysis of the distribution of the rate of single presses on the pedal showed no significant changes in rats receiving 6-OHDA (Fig. 2).

It can be concluded from these results that in the structural-neurochemical organization of positive reinforcement, hippocampal NA is responsible for inhibition of retrieval and realization of memory traces relating to the reinforcing action of external stimuli, triggered by excitation of the pacemaker "reward" centers of the lateral hypothalamus [3].

This conclusion is based on the fact that NA, injected in microdoses into the hippocampus, causes an increase in the rate of single presses on the pedal, and this probably reflects the endeavor of the animals to compensate for the deficit of memory trace activity due to minimization of the intervals between volleys of hypothalamic electrical stimulation. Further confirmation of this hypothesis is given by the observed increase in the frequency of SSR and in the intensity of investigative activity in response to the positive action

of external sensory stimulation, observed when activity of the hippocampal NA-ergic pool is depressed by 6-OHDA; these events probably reflect prolongation of the retrieved memory traces relating to reinforcing stimuli, possibly through a reciprocal increase in the activity of the hippocampal serotoninergic pool [3].

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INDIRECT MECHANISM OF THE POSITIVE ACTION OF ESTROGENS ON CORTICOSTEROID-BINDING GLOBULIN LEVEL IN RATS

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UDC 612.124.577.175.53].014.46:615.256.51

KEY WORDS: corticosteroid-binding globulin; endocrine regulation; estrogens; androgens; corticosteroids

Corticosteroid-binding globulin (CBG) is a plasma protein secreted by the liver. CBG specifically binds corticosteroids and progestins circulating in the blood stream, and it is thus involved in modulation of the effect of these steroids. This function of CBG may evidently be realized differently in female and male rats, for the level of this protein differs in rats of different sexes [3, 9, 11]. The question arises of the role of sex hormones in the maintenance of sexual dimorphism for CBG concentration in rats.

The writers showed previously [3] that the lower CBG level in male rats is due to the negative programing effect of androgens in the prepubertal period and their negative regulatory action in sexually mature animals. Meanwhile, removal of the source of endogenous estrogens in the early period of ontogeny does not affect the CBG level in adult rats, and the same is true of ovariectomy in mature females or administration of physiological doses of estradiol to them.

However, the view continues to be held in the scientific literature that the CBG level in rats is an estrogen-dependent trait [10]. This view is based on data obtained by several workers [6, 9] in the 1960s, which have not subsequently been re-examined. An important role in the creation of this opinion concerning the positive action of estrogens on the CBG level in rats was evidently played by data on the stimulating effect of estrogens in respect to this trait in guinea pigs and man [4, 5, 7]. Analysis of data on estrogenic regulation of the CBG level in rats reveals their contradictory nature, for long-term administration of large doses of estradiol leads to an increase in the CBG concentration only in intact males and does not change its level in castrated males and females. Accordingly it was decided to undertake a careful study of the role of estrogens in the regulation of the CBG level in rats.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats. Gonadectomy and adrenalectomy were performed under ether anesthesia by the usual method; the animals were used 2 weeks after the operation. Estradiol was injected subcutaneously in propylene glycol in a dose of 100 μg per rat for 3 weeks. Dexamethasone, a synthetic corticosteroid, also was injected

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(Presented by Academician of the Academy of Medical Sciences of the USSR I. P. Ashmarin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 109, No. 1, pp. 6-8, January, 1990. Original article submitted April 30, 1989.

0007-4888/90/0001-0006$12.50