NEUROPATHOPHYSIOLOGICAL EFFECTS DURING PRIMARY HYPERACTIVATION OF THE BED NUCLEUS OF THE STRIA TERMINALIS IN RATS

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UDC 616.831.314-008.61-031.84-02:615.334]-092-092.9

KEY WORDS: bed nucleus of stria terminalis; generator of pathologically enhanced excitation; pathological system; anxiety; stereotopy; psychosis-like paroxysms.

The appearance of a pathological determinant in certain parts of the brain after the creation of a generator of pathologically enhanced excitation (GPEE) in them leads to the formation of a pathological system (PS) which is expressed clinically as a corresponding neuropathological syndrome [3].

Since an essential role in the pathogenesis of mental disorders is played by a change in reactivity of the mesolimbic system of the brain [11, 12, 15-17], in the investigation described below effects of hyperactivation of the bed nucleus of the stria terminalis (BNST) of the rat brain as a structure of the limbic striatum [2] were studied by creating a GPEE in it by injection of penicillin.

EXPERIMENTAL METHOD

Experiments were carried out on 34 male Wistar rats weighing 250-350 g. Under hexobarbital anesthesia (150 mg/kg, intraperitoneally) a chemical electrode was inserted stereotaxically [14] into BNST, and electrodes (nichrome, 200 μ, insulated) for monopolar recording of electrical activity (EA) of deep brain structures were inserted into the ventral hippocampus (area CA3, the medial amygdaloid nucleus, the rostral part of the striatum, the nucleus accumbens, and the lateral hypothalamic region). A solution of the sodium salt of penicillin (1-20% in 0.85% NaCl) was injected in the course of 1-2 min through the chemical electrodes in a volume of 1 μl, unilaterally or bilaterally. EA of the brain structures began to be recorded on the day after the operation in unrestrained animals and continued on selected days for 2-3 weeks. An RM-86M polygraph (Nihon Kohden, Japan) was used for recording. Physiological saline was injected into BNST of animals of the control group. During the investigation all the animals were kept individually under standard animal house conditions on an ordinary diet. At the end of the experiments the location of the electrode was verified histologically.

EXPERIMENTAL RESULTS

While the animal was still under general anesthesia 6-7 sec after the injection of penicillin (5-20% solution) it developed myoclonic spasms of the tail, the contralateral (in the case of unilateral injection of penicillin) hind limbs, and sometimes the contralateral forelimbs; after 10-15 sec the spasms spread to the ipsilateral limbs and were observed for 1-1.5 h. Myotonic spasms were not found after injection of a 1% solution of penicillin. On the day after the injection of penicillin (5-20% solution) EA in BNST was characterized by the presence of epileptic spikes with an amplitude of 300-750 μV and a frequency of 3-5/min, or in some cases, up to 9 spikes/min (Fig. 1a). The great variability of the amplitude and frequency of the spikes in different animals, and also in the same animal in the early periods (first 2-3 days) after injection of penicillin, will be noted. If the amplitude of the spikes was 650-750 μV, as a rule myoclonic spasms of one of the contralateral limbs or of the animal's head were observed. The amplitude of the spikes in BNST 2 days after the operation usually was reduced

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 7, pp. 10-14, July, 1988. Original article submitted March 18, 1987.

0007-4888/88/0007-0923$12.50

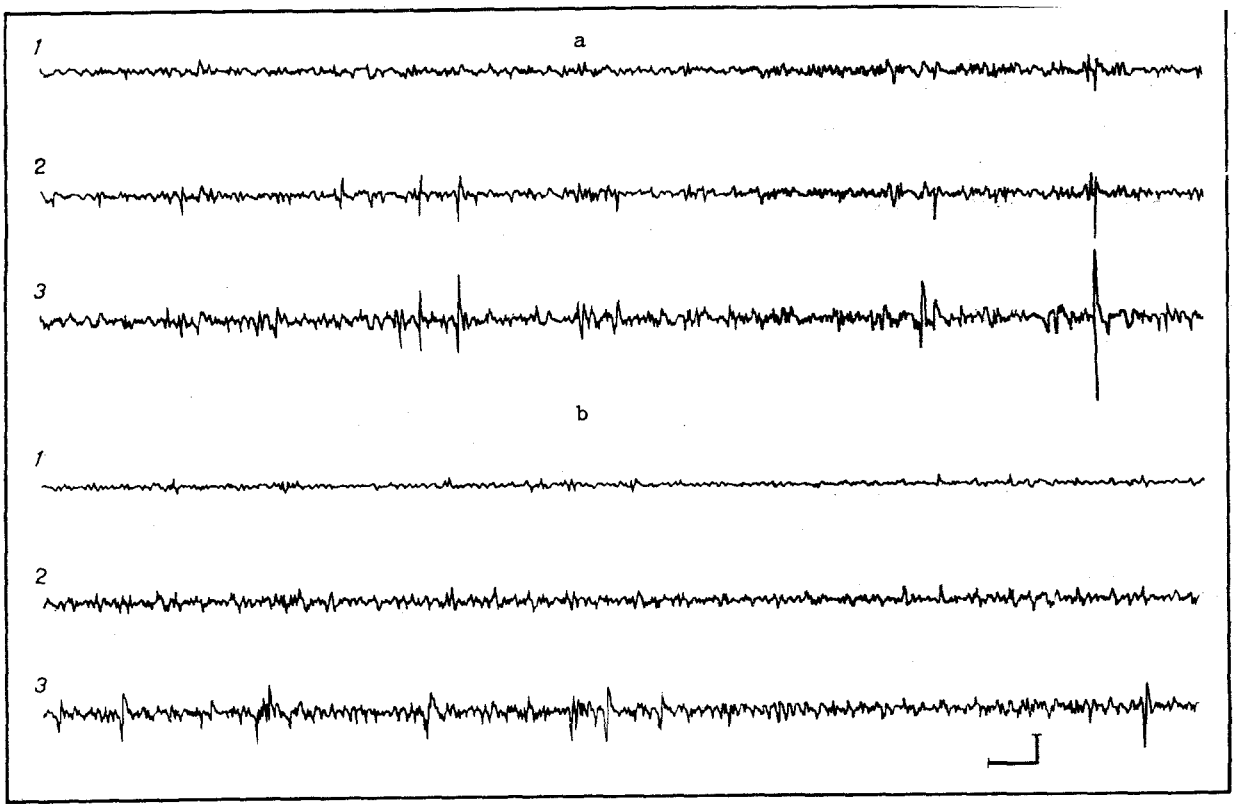

Fig. 1. EA of deep brain structures of rats in early period after injection of penicillin into BNST. a) 1 Day, b) 3 days after injection of penicillin. Derivations 1) left BNST, 2) left medial amygdaloid nucleus, 3) left ventral hippocampus (after CA3). Penicillin (5% solution) was injected into the left BNST. Here and in Figs. 2 and 3, calibration: 400 μV, 1 sec.

to 200-300 μV, and their frequency fell sharply to 1/min. After 3 days epileptic activity (EpA) was not observed in BNST (Fig. 1b). No significant changes were observed in BNST of the control animals.

In the ipsilateral amygdaloid complex and hippocampus, EpA differing in character from EpA in BNST was observed from the 1st day of recording (Fig. 1a). In the amygdala EpA continued in some cases for 5-8 days, whereas in the hippocampus EpA was observed throughout the period of recording EA in the brain (2-3 weeks).

During the first 2-3 days after unilateral injection of penicillin into BNST, epileptic spikes also were recorded bilaterally in the striatum, nucleus accumbens, and lateral hypothalamic region. On the 4th day after injection, as a rule EpA was absent in all the above structures.

Starting with the 1st day of recording EA of the brain and during the next 2-3 weeks all animals of the experimental group showed periods of generalized synchronization of EA within the range 6-8-10 spikes/sec, and in different animals their duration in the period of wakefulness varied considerably, as a rule reaching 2-3 min. The amplitude of synchronized regular activity varied with time, and this led to the appearance of bursts of spindles 0.5-2 sec long and up to 600 μV in amplitude (Fig. 2a). At the same time, in two animals of the experimental group, generalized high-amplitude (up to 1 mV) spindles (3-6/min) 3-6 sec in duration and with a frequency of 7-8 spikes/sec were recorded against the background of desynchronization of EA (Fig. 2b). In animals of the control group, the periods of synchronization of rhythmic activity did not exceed 1 min.

In the period of synchronization of EA and also during desynchronization in the absence of EpA or spindle activity in BNST and other hippocampal structures, high-amplitude pointed waves and bursts of spindle activity with a frequency of 12 spikes/sec were observed (Fig. 2).

In some animals of the experimental group, during 2-3 weeks of recording EA in the brain, a generalized intensification of high-frequency low-amplitude activity of deep brain structures was observed in the periods of psychosis-like paroxysms (see below).

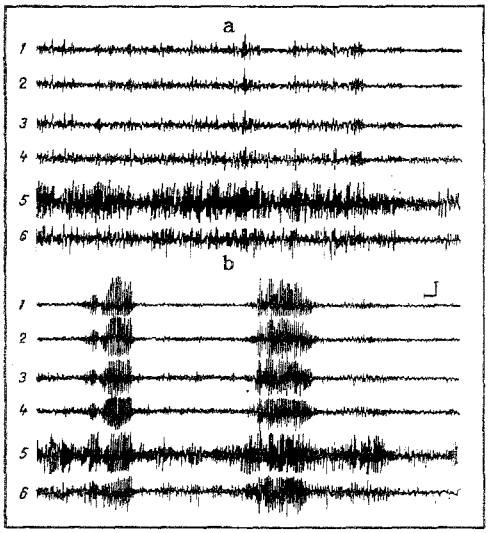

Fig. 2. Synchronized EA (6-10 spikes/sec) of deep structures of rat brain during clinical manifestation of fear. a) EA during period of locomotor immobility, in the presence of signs of fear in behavior, b) generalized high-amplitude spindle activity in the presence of intense fear. Derivations: 1) left BNST, 2) right BNST, 3) left medial amygdaloid nucleus, 4) right medial amygdaloid nucleus, 5) left ventral hippocampus (after CA3), 6) right ventral hippocampus (after CA3). Penicillin (5% solution) was injected into right BNST. Electrical activity recorded 10 days after injection.

In rats of the experimental group marked disturbances of behavior were observed to a varied degree: spontaneously and when the animal was touched, vocalization began, and if the animal was in an open, lit space, if another animal approached, it retreated, assumed a passive-defensive posture, and began to defecate. In certain cases, in the absence of any obstacle, the animal would suddenly stop dead, and this was accompanied by defecation (5-7 boluses in one place) and sometimes by vocalization. These changes in emotional behavior were observed in 50% of animals.

In animals of the experimental group during the first 1-3 days after injection of penicillin, as a rule extrapyramidal disturbances were observed: rigidity of the tail and hind limbs, lordosis, and in some cases, ptosis.

During periods of synchronized rhythmic EA, and also 1-2 sec before the onset and during recording of high-amplitude spindles (Fig. 2), animals with marked emotional behavioral disturbances stood completely still, ceased their investigative and orienting behavior, their glance was fixed at a single point, and in some cases defecation, slowing of respiration to 60 cycles/min, and vocalization were observed. In animals of the control and experimental groups, with no visible disturbances of behavior, absence of locomotor activity was noted in periods of synchronized rhythmic activity.

The state of some animals, with the emotional behavioral disturbances described above, was aggravated by the appearance of periods of unease, during which the rats made inpulsive movements, scattered the shavings, stood up frequently (15-20 times a minute), intensified their sniffing, snorting, and abortive grooming, and exhibited oral automatisms (for a long time the animals chattered their teeth and chewed the shavings and feces), resembling stereotyped behavior in character. In these periods the respiration rate quickened to 95-120 cycles/min. These psychosis-like paroxysms with stereotypy appeared both spontaneously and in response to stimulation of the animal (stroking, fixing the plug for recording EA) and lasted several minutes. They corresponded to intensification of high-frequency low-amplitude activity on the recording of EA.

The severity of the emotional–behavioral disturbances was maximal 1-2 days after injection of penicillin. After 3-5 days the severity of the symptoms was reduced and it remained at that level until 1 month. In the 2nd month of observation, in most cases a further decrease in severity of emotional–behavioral disturbances was observed, and in most cases the original behavior was restored.

The appearance of EpA in BNST after injection of penicillin into it indicated the formation of a primary GPEE in it, and the activity of the generator could be judged after the animal had completely recovered from the anesthetic. Because of hyperactivation of BNST the structures of the septo-hippocampal system (BNST, amygdala, hippocampus) acquired the properties of a pathological determinant, whose influence led to the formation of a PS, consisting of a number of limbic and extrapyramidal structures, whose activity was expressed clinically as a polymorphic neuropathological syndrome.

The appearance of extrapyramidal disorders, stereotyped behavior [13], and reduction of locomotor activity or even its complete cessation for short periods of time [10], was obviously linked with hyperactivation of the striatum. Involvement of the hypothalamus and amygdaloid complex in PS enables the onset of autonomic disturbances and changes in emotional reactivity to be explained [6]. We also know that electrical stimulation of the septal region (including BNST) may lead to the appearance of a short-term response of fear in the rats [5], and spike activity in this region and in the nucleus accumbens and bursts of spindles in the hippocampus correlate with psychotic behavior in human patients [11, 18]. The changes we observed in EA in these structures probably lie at the basis of the paroxysms of psychosis-like behavior with elements of sterotypy in rats [17]. Low-amplitude high-frequency EA corresponding to this behavior was characteristic of the EEG of patients with signs of emotional instability, anxiety, and timidity [7, 8].

The disturbances described can be regarded as a whole as a complex system of changes in which pathological enhancement of the fear reaction stands out particularly sharply.

The enhancement of EA within the 6-10-spikes/sec range in animals of the experimental group is noteworthy. In situations connected with the mental experiencing of emotionally meaningful events (including during fear) in man, a high-amplitude hypersynchronized α-rhythm is observed [7, 8]. In experiments on rabbits, during electrical stimulation of the hypothalamic emotiogenic zones, regularization of rhythms with frequencies of 4-6 or 8-10 spikes/sec was observed, without regard to the biological sign of the emotions [4]. Thus changes found in EA of the brain confirm the view that during primary hyperactivation of BNST, prolonged enhancement of emotional strain arises in some animals.

The results of the study of EA in brain structures indicate that in the process of development of the syndrome the role of hyperactive determinant structure moves to the hippocampus, which becomes a secondary pathological determinant: EpA and bursts of spindles are preserved in it throughout the period of recording of EA (14-22 days), and perhaps even longer. These data are in agreement with views on the determinant role of the hippocampus in the realization of emotional states [1, 9].

It can be concluded from the results of the investigation that on the creation of a primary GPEE in BNST, a pathological determinant arises in the septo-hippocampal system of the rat brain, under the influence of which a complex PS is formed, probably including, besides the structures investigated (septum, amygdala, hippocampus, lateral hypothalamic region, striatum, nucleus accumbens), other brain formations also, as is shown by the complex systematics of the polymorphic syndrome described above. The activity of this PS is subsequently maintained by the hyperactive hippocampus.

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CHANGES IN BIOGENIC AMINE METABOLISM IN RATS DIFFERING IN RESISTANCE TO STRESS, EXPOSED TO PRENATAL ANOXIA

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UDC 612.821.2.018:577.175.82]-06:[612.273.2+613.863

KEY WORDS: prenatal anoxia; metabolism; biogenic amines.

Cases have been described of the onset of pathology in childhood due to disturbances of the intrauterine fetal blood supply [6]. Experimental studies have shown that even transient anoxia of pregnant animals is accompanied not only by disturbances of growth and development of the progeny, but also by significant changes in orienting and conditioned-reflex behavior, and also by increased predisposition to convulsions under the influence of threshold doses of analeptics [2, 7]. The writers previously obtained data on the connection between predisposition of animals to audiogenic convulsions and brain monoamine (MA) metabolism [1, 3] and also on disturbances of investigative behavior and learning of animals due to neonatal administration of 6-hydroxydopamine (6-OHDA) [4, 9].

The aim of the present investigation was to study the effect of prenatal anoxia on biogenic amine (BA) metabolism in rats in the later period of postnatal development.

EXPERIMENTAL METHOD

Experiments were carried out on 58 rats aged 40 days, exposed to transient prenatal anoxia. On the 15th-17th days of pregnancy the rats were exposed daily for 2 h in a pressure chamber to a reduced air pressure corresponding to an altitude of 8000 m (220 mm Hg). The animals were kept in the animal house on a 12-h lightness and 12-h darkness cycle (8 a.m.-8 p.m. daylight, 8 p.m.-8 a.m. darkness) in cages and received granulated food (PK-120-7) and water and libutum. On the 30th day all the newborn animals were tested for their resistance to acoustic stimulation (electric bell, 96 db, 1.5 m). According to the results of testing, the experimental and control animals were subdivided into resistant (R) and predisposed (P) to audiogenic convulsions. The rats thus constituted four groups: groups 1 and 2 were resistant (19) and predisposed (eight) control animals and groups 3 and 4, which were R (20) and P (11) respectively, were subjected to prenatal anoxia. After 10 days the behavior of all the animals was tested in an open field measuring 1 m^2, divided into 100 squares. Observations on behavior lasted 3 min in the morning, and included determination of the latent period (LP) of the animals'

Laboratory of Neurotransmitter Systems, Institute of Biological Physics, Academy of Sciences of the USSR, Pushchino. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 7, pp. 14-17, July, 1988. Original atticle submitted April 13, 1987.

