CREATION OF A GENERATOR OF PATHOLOGICALLY ENHANCED EXCITATION IN A SEPTAL NUCLEUS AS A MODEL OF PSYCHOSIS IN CATS

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Investigations associated with the theory of generator mechanisms of neuropathological syndromes [4] have shown that the creation of a generator of pathologically enhanced excitation (GPEE) in certain parts of the CNS, by local disturbance of inhibitory mechanisms with the aid of various drugs, may result in the production of corresponding neuropathological syndromes. The CNS formations in which these GPEE are created play the role of hyperactive determinant structures, forming pathological systems (PS), whose activity is manifested clinically as corresponding neuropathological syndromes [4].

Continuing our investigations in this direction, we created GPEE by means of penicillin in various formations in the septal region. Particular attention was directed toward disturbances of behavior in cats arising after injection of penicillin into the pars interna (PI) of the bed nucleus of the stria terminalis (BNST), according to the atlas of Andy and Stephan [6]. In one atlas [11] this formation is described as the nucleus prothalamicus, in another [13] as the nucleus interstitialis striae terminalis, included in the system of the septal nuclei [3].

Electrical stimulation of parts of the septum, including the nucleus of the stria terminalis and the anterior commissure, has been shown to induce behavioral and emotional disturbances in rabbits [3]. Injection of bicuculline into the ventral tegmental field, connected by dopaminergic pathways with nuclei of the septal region, is known to induce biphasic changes in behavior in cats with alternation of motor stereotypes and epileptic paroxysms [14]. The results of the present investigation are evidence that consecutively changing neuropathological syndromes may arise when a GPEE is created with the aid of penicillin in PI of BNST.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 21 cats. A GPEE was created with penicillin, which disturbs GABA-ergic inhibitory mechanisms [8, 9] and induces depolarization of neurons [12]. For this purpose a cannula-electrode was introduced unilaterally into this structure stereotaxically, under pentobarbital anesthesia (30-40 mg/kg) at coordinates (Fr = 14.5, L = 2.0, H = +0) taken from the atlas [11]. Simultaneously with the cannula, electrodes were inserted into the head of the caudate nucleus (CN) and the sensomotor cortex of 17 cats. Penicillin was injected as a 20% aqueous solution into 12 cats 3-4 days after the operation, by means of a microinjector, at the rate of 0.006×10^{-3} ml/sec, in a volume of 10^{-3}–2×10^{-3} ml (340-680 IU). Animals (six cats) into which the corresponding volumes of isotonic NaCl solution were injected served as the control. Three cats, undergoing electrocoagulation of PI of BNST 5-10 min after the formation of a GPEE in them, constituted a separate group.

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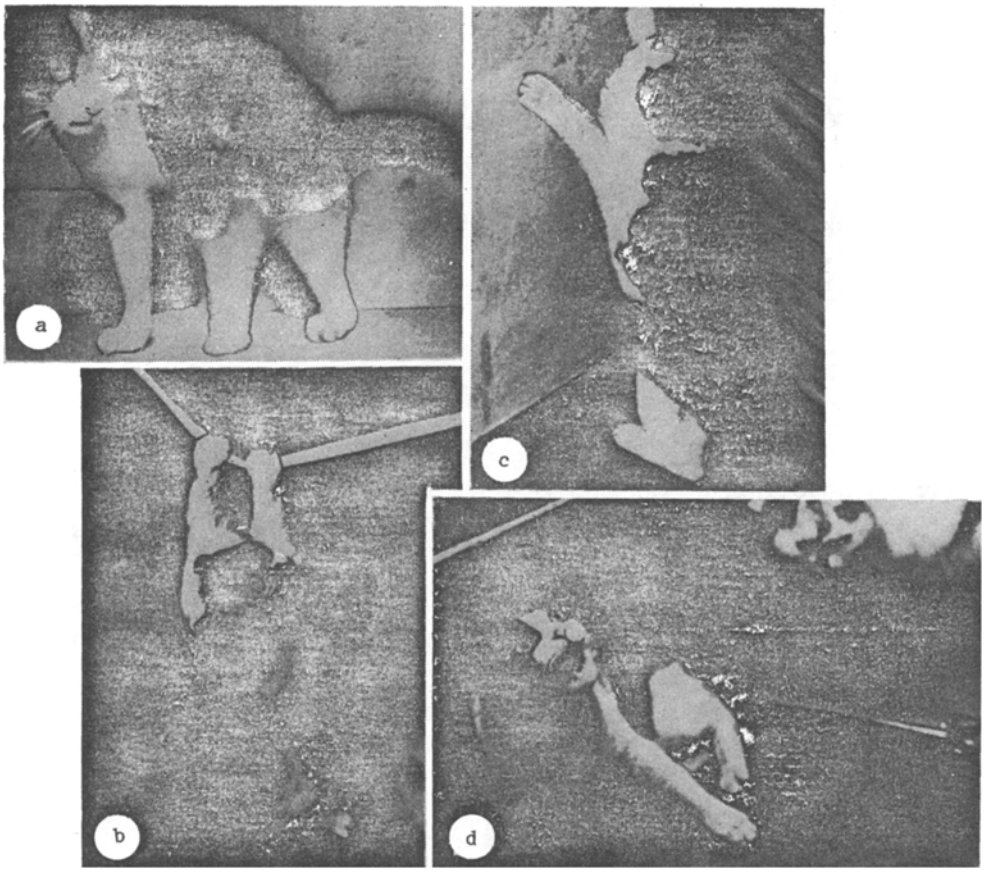

Fig. 1. Behavioral manifestations in cats after injection of penicillin into PI of BNST. a) Affective defensive response, b) catalepsy, c) cataleptic test, d) aimless aggression in response to nociceptive stimulation.

The experimental animals were kept in a spacious room, so that their individual and group behavior could be assessed. Attention was paid to motor, feeding, sexual, and orienting behavior, and to catatonic and epileptic phenomena, using the criteria of these behavioral reactions described in the literature [1, 4]. The severity of the catatonic, affective, and other symptoms was determined on a 3-point scale. Absence of manifestations of catatonia (having seized a rope with its forelimbs, the cat did not hang on it) was assessed as a negative test, if the cat hung for up to 2 sec the test was considered to be weakly positive (1 point), if the cat hung for 2 to 30 sec it was positive (2 points), and if it hung for over 30 sec, strongly positive (3 points).

The localization of the tip of the electrode–cannula and of the subcortical electrodes was verified after the end of the experiments by examination of serial frontal sections of the fixed brain, in accordance with maps of the atlases [6, 11].

EXPERIMENTAL RESULTS

All the experimental animals developed behavioral disturbances 10-15 min after the injection of penicillin. Initially, emotional changes were observed for 5-10 min in the form of an affective defensive reaction with postural–mimic (fixation of the gaze, pressing in of the ears, staying motionless, etc.) and with vocal components (Fig. 1a) and in this period, single spikes with an amplitude of 180-200 μV were generated in PI of BNST (Fig. 2b). After the affective manifestations motor stereotypy developed: monotonous movements, replaced by the animals remaining in one fixed position, most frequently in a corner of the room. When the cats were forcibly moved, they returned to the same spot, even if they were repeatedly exposed to the action of a painful stimulus when there. During the period of stereotypy hypersynchronous activity was recorded (2 waves/sec with an amplitude of up to 400 μV) in PI of BNST, CN, and the sensomotor cortex (Fig. 2c). Nociceptive stimulation (squeezing the tail) caused an increase in the frequency and amplitude of the activity in PI of BNST and CN,

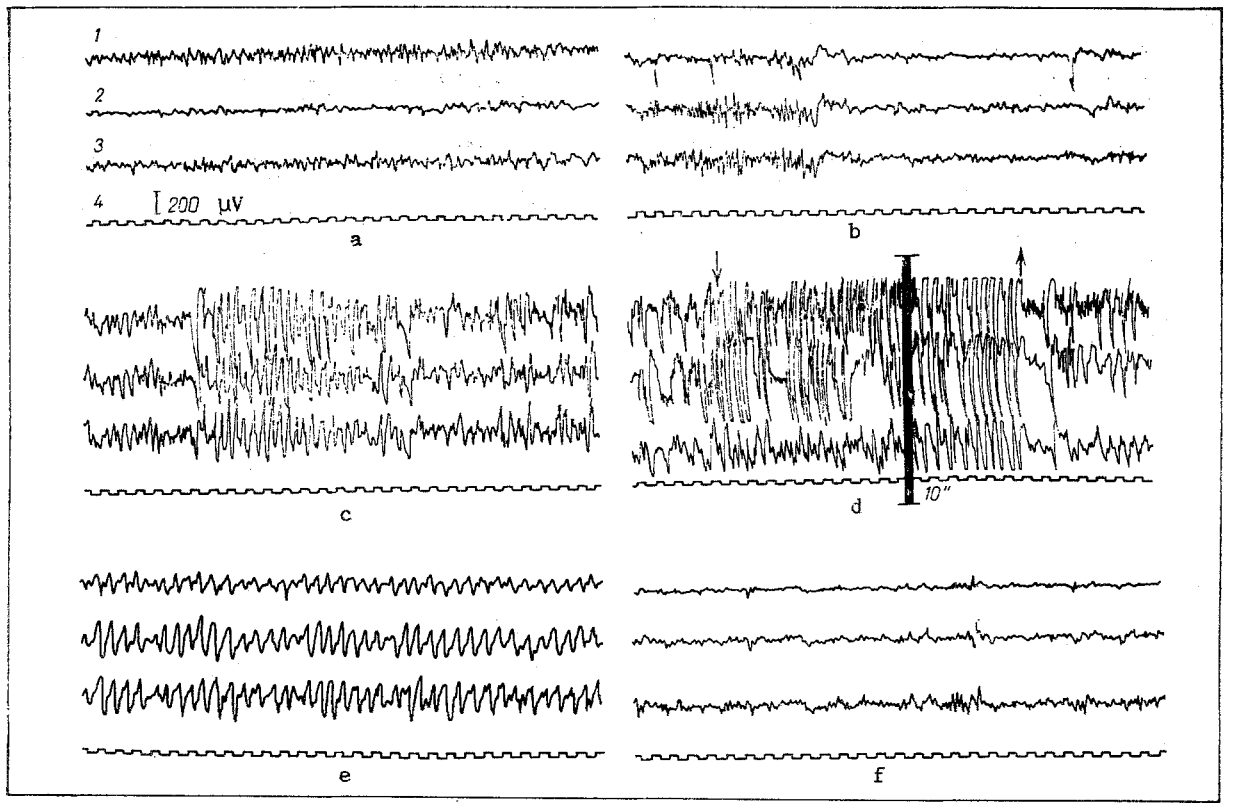

Fig. 2. Electrical activity in PI of BNST (zone of injection of penicillin), head of CN, and sensomotor cortex before and after injection of penicillin into PI of BNST. 1) PI of BNST, 2) head of CN, 3) sensomotor cortex, 4) time marker (1 sec). a) Electrical activity before injection of penicillin; b) spike activity in PI of BNST (recorded during an affective defense response); c) spontaneous hypersynchronous activity in PI of BNST, CN, and sensomotor cortex (recorded during period of stereotyped standstills); d) intensification of hypersynchronous activity in PI of BNST, CN, and sensomotor cortex during aimless aggression, evoked by nociceptive stimulation (pinching the tail — the beginning and end of stimulation are indicated by arrows; a 10-sec fragment of similar electrical activity is cut out of the trace; e) synchronized generalized slow activity during catatonic stupor; f) electrical activity of control animal after injection of isotonic NaCl solution.

whereas in the sensomotor cortex high-frequency discharges appeared, after a longer (by 8-10 sec) latent period (Fig. 2d). Cessation of the painful stimulation caused the animals to remain motionless. In this state the cats could assume various unnatural postures, which they maintained for a long time (Fig. 1b). Under conditions of interspecific interaction (cat—mouse), no aggressive actions were observed. The cataleptic test was positive (Fig. 1c). Responses to pain were inhibited (hypoalgesia) and reversed. If a clamp was placed on the tail, aimless aggression was observed without any attempt to localize and remove the painful stimulus (Fig. 1d). Often an aggressive response of this kind was replaced by distorted food behavior, in the form of eating inedible objects placed near to them.

For 5-15 days, besides the paroxysmal manifestations of stereotypy and the catatonic—cataleptic syndrome described above, a gradual reduction of motor activity (hypokinesis) was observed in the majority of cats, and in some of them, this progressed into a stuporose state. During this period constant and regular slow-wave activity was recorded in all structures tested, in the form of 1.5 waves/sec with an amplitude of up to 300 μV (Fig. 2e). Orienting reflexes were seriously impaired, interest in the surroundings and zoosocial interaction disappeared, and food-getting activity was considerably reduced, so that at first the animals ate less food, and later completely refused to eat and drink. Negativism toward food was active: in an attempt to feed the animals, they pressed their jaws together even more tightly.

Absence of response to nociceptive stimulation (pinching the paw or tail) was conspicuous. Instead of it, nociceptive stimulation induced lengthening of the duration of the cataleptic test by 5-6 times, or (with unrestrained animals) led to the appearance of stereotyped chewing and indeterminate searching movements, which did not lead to any concrete result, for example, eating food, etc. The final stage of the process in nine animals, after 5-15 days, was characterized by affective indifference, passiveness, akinesia, depression of instinctive behavior, zoosocial isolation, and catatonia. This stage continued for 3-6 days and ended in death. In three animals, after the manifestations described above, on the 5th-6th day as the final stage generalized convulsions developed, followed by death.

Injection of isotonic NaCl solution into PI of BNST of the control animals gave rise to no pathological electrophysiological (Fig. 2f) or clinical phenomena.

Electrocoagulation of PI of BNST, which was done on three cats during the transition from affective symptoms to catatonic, when single spikes of 180-200 μV were recorded in this structure, abolished the pathological behavioral changes in the animals. During the first day, only drowsiness was observed in them, but later, against the background of natural behavior, a very slight depression of the responses to pain was observed. These phenomena disappeared by the 6th-7th day of observation.

The results of these investigations are evidence that the formation of a GPEE in PI of BNST is the essential pathogenetic mechanism of onset of progressively changing behavioral disturbances. This part of the nucleus becomes hyperactive and plays the role of initial pathological determinant, which involves other brain formations in the process and forms a multicomponent PS. As electrographic investigations show, this system includes CN and the sensomotor cortex. It will be evident, however, that other brain structures are also included in PS, each of them making its own contribution to the general clinical picture of this form of pathology. Affective disturbances observed in the early stage of the process are evidence of involvement of the limbic system, and catatonic manifestations arising immediately thereafter are evidently connected with activation of CN and of mesencephalic structures. The symptom-complex of pathological phenomena includes regression of behavior with suppression of inclinations, complex instinctive reactions, zoosocial behavior, etc. It is a noteworthy fact that the response to nociceptive stimulation was depressed in all the animals, especially in the late stages of the process. Systemic administration of naloxone in a dose of 1 mg/kg reduced the degree of hypoalgesia in the stage of affective and catatonic manifestations. This state of affairs suggests activation of the endogenous opioid system [7, 15]. Reduction of nociceptive sensitivity is known to occur in patients with schizophrenia [2], and it is evidently connected with an increase in the concentration of endorphine and enkephalins in acute and chronic schizophrenia [10].

When the form of pathology described above is analyzed, the definite order of appearance of the symptoms must be noted. It can be compared with the feature known in clinical psychiatry as "processionalism" [5]. It is an interesting fact that in eight animals of the experimental group the pathological process was continuous, whereas in four it was episodic in character, with "lucid" intervals (1-3 days), during which no pathological behavioral or electrographic manifestations were present. It must be emphasized that the pathological process developed after a single injection of penicillin, and in the absence of any additional pathogenic influences, suggesting that it is progressive in nature. Both these factors may be connected with the properties of the PS, and its ability to develop under the influence of a pathological determinant and to include new brain formations in its structure [4].

LITERATURE CITED

1. A. V. Val'dman, É. É. Évartau, and M. M. Kozlovskaya, The Psychopharmacology of Emotions [in Russian], Moscow (1976).
2. M. O. Gurevich, Psychiatry [in Russian], Moscow (1949).
3. M. M. Kozlovskaya and A. V. Val'dman, Zh. Vyssh. Nerv. Deyat., 20, No. 5, 1022 (1970).
4. G. N. Kryzhanovskii, Determinant Structures in Pathology of the Nervous System [in Russian], Moscow (1980).
5. A. V. Snezhnevskii, Textbook of Psychiatry, ed. by A. V. Snezhnevskii [in Russian], Vol. 1, Moscow (1983), pp. 16-96.
6. O. J. Andy and H. Stephan, The Septum of the Cat, Springfield (1964).
7. V. Clement-Jones, S. Tomlin, L. H. Ress, et al., Lancet, 2, 946 (1980).
8. D. R. Curtis, C. J. A. Game, G. A. R. Johnston, et al., Brain Res., 43, 242 (1972).

9. R. A. Davidoff, Brain Res., 45, 638 (1972).
10. J. J. Hoo, D. P. Agarwal, and H. W. Goedde, N. Engl. J. Med., 301, 946 (1980).
11. H. H. Jasper and C. Ajmone-Marsan, A Stereotaxic Atlas of the Diencephalon of the Cat, Ottawa (1954).
12. D. Prince, Annu. Rev. Neurosci., 1, 395 (1978).
13. R. S. Snider and W. T. Niemer, Stereotaxic Atlas of the Cat Brain, Chicago (1961).
14. J. R. Stevens and A. Livermore, Neurology (Minneapolis), 28, 36 (1978).
15. L. Terenius, J. Psychosom. Med., 24, 220 (1980).

REGULATION OF THE HEART AFTER ISCHEMIC DAMAGE TO THE VENTRICULAR MYOCARDIUM

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KEY WORDS: sinus node of the heart; afferentation; cerebral cortex; ischemia.

The characteristics of responses of the afferent systems of the heart during ischemia and changes in the functional state of the organ accompanying potentiation of descending influences [4, 5, 7, 8] has been inadequately studied.

Previously [1, 2] it was shown that impulsation from certain formations of the myocardium to the cerebral cortex (CC) is conducted mainly along spinal afferent systems.

The aim of this investigation was to study the conduction of afferent impulsation from the zone of the sinus node of the heart (ZSN), one of the myocardial formations of the greatest importance from the point of view of regulation, to CC during ischemia of the right and left ventricles of varied duration. In addition, a model of disturbed coronary blood flow was used to study responses of the heart during potentiation of efferent influences of the vagus nerve.

EXPERIMENTAL METHOD

Altogether four series of experiments were carried out on 19 cats and 14 rabbits. In the first three series, experiments were carried out on cats weighing 2.5-3 kg, anesthetized with chloralose (40-50 mg/kg) and curarized. In these experiments bipolar stimulating electrodes were fixed to ZSN and the heart was subjected to square pulses 0.3 msec in duration, 10-15 mA in amplitude, and with a frequency of not more than 0.3 Hz. Evoked potentials (EP), recorded from the exposed surface of CC at the focus of maximal activity, were analyzed by the coherent cumulation method on a Neuroaverager (Biomedica, Italy), with 10-15 presentations of the discrete signal. The ECG also was recorded in standard lead II. In the experiments of series IV, potentiation of descending influences of the parasympathetic system was induced in rabbits weighing 2-2.5 kg, anesthetized with hexobarbital (0.01-0.02 g/kg), by electrical stimulation of the right vagus nerve at the level of the thyroid cartilage, by series of square pulses of current 1 msec in duration, with a frequency of 50 Hz, and the strength of 1-3 mA. In this series of experiments both the undivided vagus nerve and its peripheral end after bilateral vagotomy were stimulated. Stimulation of ZSN and of the nerve trunks was carried out by means of an ÉSU-2 stimulator. Disturbances of the coronary blood flow were induced by compressing the second-order arteries on the left or right side by means of a silk ligature, placed inside a rigid plastic tube, by means of which the development of myocardial ischemia could be induced for a varied period of time. In the experiments of series I triple reversible ischemia of the left ventricular myocardium was induced by the following scheme: the first period of ischemia lasted 5 min, the second 10 min, and the third 15 min; the interval between periods of ischemia was 10 min. In the experiments of series II reversible ischemia of the right ventricular myocardium was induced by the same scheme. In the experiments of series III the coronary blood flow in the territory of the right coronary artery was

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