EXPERIMENTAL SIMULATION OF NEUROPATHOLOGICAL SYNDROMES BY CREATING PATHOLOGICALLY ENHANCED EXCITATION GENERATORS IN THE RABBIT HYPOTHALAMUS

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Experiments on rabbits under free behavior conditions showed that injection of tetanus toxin into motivation-emotiogenic pacemaker regions of the hypothalamus, with the object of producing generators of pathologically enhanced excitation in those regions gives rise to stable and prolonged disturbances of the animals' motivational-emotional behavior. These changes were expressed as a marked increase in food-getting activity by the animals, including an increase in "secondary motivational" responses, increased motor activity, the appearance of an excessive number of automated chewing movements, aggressiveness, a fear reaction, and the corresponding autonomic changes. The character of these responses depended on the region into which the toxin was injected and on its dose. Investigations showed that the formation of long-acting generators of pathologically enhanced excitation in motivation-emotiogenic pacemaker centers of the hypothalamus with the aid of tetanus toxin can be used to simulate psychopathological states in animals. The results confirm, by the use of this new model, the theory of generator mechanisms of neuropathological syndromes characterized by hyperactivity of systems.

KEY WORDS: *hypothalamus; motivation-emotiogenic centers; generator of pathologically enhanced excitation; determinant structure; tetanus toxin; neuropathological syndromes.*

An urgent problem in contemporary clinical and experimental medicine is the elucidation of the mechanisms and creation of models of neuropathological syndromes. Previous investigations have shown that, by creating generators of pathologically enhanced excitation [8, 10, 11], playing the role of determinant structures ("determinant dispatch stations") [7, 8], in certain regions of the CNS the corresponding sensory and motor neuropathological syndromes can be reproduced [8]. Although these syndromes have already included certain changes in the emotional sphere and higher nervous activity, it was considered to be important to attempt to create models of stable motivation-emotional excitation, by using this same technique for the formation of hyperactive determinant structures (excitation generators) in the emotiogenic centers of the hypothalamus. Many forms of brain pathology are known to consist of combinations of cerebral and somatic, autonomic and psychopathological components, including lasting disturbances in the emotional and motivational sphere [2-4, 16], which are manifested particularly clearly in the case of pathological foci in the hypothalamus. Some regions and nuclei of the hypothalamus have been shown to have the properties of unique pacemakers of biological motivaiton [1, 13]. It might be expected that if such pacemakers were converted into generators of pathologically enhanced excitation, the activity of the corresponding functional system would be endowed with a pathological character and, in that way, a lasting neuropathological syndrome would be produced.

Just as previously, to create the generator of pathologically enhanced excitation (GPEE), it was decided to use tetanus toxin (TT), which disturbs various types of inhibition [6, 9, 12, 14, 15], as a result of which the neuron population into which the TT is injected is converted into a GPEE [8, 10, 11].

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EXPERIMENTAL METHOD

Experiments were carried out on 23 rabbits of both sexes into the lateral hypothalamus of which a cannula-electrode was inserted, for combined electrical stimulation and microinjection of biologically active substances. The cannula-electrode was inserted into points of the lateral hypothalamus, electrical stimulation of which (square pulses, 50 Hz, 2.5 msec, 3-5 V) evoked a distinct food response (searching, sniffing, consumption of extra food) in previously fed animals. After fixation of the cannula-electrode in the "food" zone of the hypothalamus, a single microinjection of tetanus toxin was given by means of a specially designed microinjector. The location of the cannula-electrode tip was determined histologically in all the animals (rapid photographic method, brain sections stained by Nissl's method).

Depending on the doses of TT injected, the animals were divided into two groups: the rabbits of group 1 (10) received 2.5-3.0 MLD for rabbits in a volume of $1.0\text{-}1.5 \cdot 10^{-4}$ ml, the rabbits of group 2 (7) an injection of 0.2-0.5 MLD for rabbits in a volume of $1.0\text{-}5.0 \cdot 10^{-4}$ ml. For the next 14-20 days observations were made on behavior of the animals and fluctuations in weight, the quantity of food consumed, changes in the rectal temperature, and the dynamics of certain autonomic indices were recorded.

In a special series of experiments (group 3, 6 rabbits) changes in instrumental food responses were studied after injection of TT (0.5-1.0 MLD for rabbits in a volume of $1.0 \cdot 10^{-4}$ ml) into the lateral hypothalamus. In the experimental chamber these animals were taught a special food-getting skill: pulling on a ring with their teeth, after which they were given food. Before and after microinjection, the number of "true" food instrumental responses (pulling on the ring and taking food) and the number of so-called secondary motivational responses (pulling on the ring without subsequently taking food) were compared.

The animals of all groups received antitoxin intramuscularly before the injection of TT in specially chosen doses (corresponding to the dose of TT) in order to neutralize the TT should it be absorbed into the blood stream.

EXPERIMENTAL RESULTS

In the animals of group 1, on the first day after injection of TT into the lateral hypothalamus sharp changes were observed in the state of the animal's motivations and emotions, and these changes persisted. Mixed behavioral responses of the "aggression–fear" appeared, with considerable predominance of the latter. The general inhibitedness of the rabbits was frequently replaced by sudden motor activity of the "panic running" type, readily provoked by neutral stimuli (clicks, stroking, movement of the experimenter's hand, and so on). In some cases the animals developed aggressive responses, in the form of threatening tapping with the hind limbs. In five animals of this group spontaneous chewing movements were observed, and these frequently changed into a general seizure. Changes were found in several autonomic indices: dyspnea, an increase of 0.5-1.0°C in the rectal temperature, frequent micturition, diarrhea, and a loss of weight of up to 400 g during 2-3 days. All the ten rabbits included in this group died on the fourth to seventh day after injection of the toxin with general seizures.

In the animals of group 2, on the 1st or 2nd day after microinjection of tetanus toxin lasting disturbances in the emotional sphere also were observed but, unlike in the rabbits of group 1, their behavioral responses were chiefly aggressive in type. Motor activity was sharply increased, and this was accompanied by threatening tapping with the hind limbs, attacking the experimenter's hand, biting and scratching the floor with the forelimbs, threatening sounds, etc. Food activity also was increased, but this was manifested only as an excessive number of "automatized" chewing movements and search responses. Throughout the period of observation (until 20 days) the weight of the animals of this group did not change significantly. Two rabbits developed general seizures on the seventh to eighth day. Just as in group 1, in the rabbits of this group dyspnea was present, the rectal temperature was increased by 0.5°C, and in some cases frequent micturition and diarrhea were present. The changes in behavior and in the autonomic indices described above were lasting in character and were still observed after 14-20 days of observation.

In the animals of group 3 instrumental food reflexes were studied after injection of TT. In 4 of the 6 rabbits in this group electrical stimulation of the lateral hypothalamus through the cannula-electrode in preliminary experiments did not produce any instrumental food-get-

ting skills or subsequent taking of food. In these four animals a sharp decrease in food-getting activity was observed on the second day after microinjection of TT. As a rule the rabbits kept in the corner of the experimental chamber showing no interest in their surroundings, they were inhibited and listless and they frequently slept. Instrumental food reflexes were virtually absent, but the animals did not refuse food when it was offered. The autonomic indices showed no significant changes. This picture was observed for 10-14 days after injection of TT. Histological examination of the brain of these animals showed that the tip of the cannula-electrode was situated 1.0-1.5 mm laterally and frontally to the central part of the lateral hypothalamic region.

In two rabbits distinct instrumental food reflexes were manifested in the experimental chamber during electrical stimulation of the lateral hypothalamus. On the second day after microinjection of the toxin into the lateral hypothalamus of these animals a marked increase was observed in their feeding and food-getting activity. The number of instrumental food and "secondary" motivational responses increased on average by 300%, the latter most frequently predominating. Meanwhile increased motor activity and investigative activity of the animals were observed. The autonomic indices showed no significant changes except body weight, which increased by 400-500 g in the course of 8-10 days. The same picture was observed for 10-14 days after microinjection of tetanus toxin into the brain. Histological examination of the brain of these animals showed that the tip of the cannula-electrode was situated in the central part of the lateral hypothalamic region.

In the control series of experiments (3 rabbits) TT was injected into the region of the lateral geniculate bodies. Changes in the behavior of the animals similar to those described above were not found, and only slight variations of the autonomic indices occurred.

The results of the investigations thus demonstrate that injection of TT into the motivational centers of the hypothalamus induces the formation of long-lasting disturbances of the motivational and emotional behavior of animals. Since injection of TT into the structures of the spinal cord and brain causes the formation of a GPEE in them [8, 10, 11], this mechanism may be presumed to exist also when TT is injected into the lateral hypothalamus. The conclusion that the disturbances described above are based on generator mechanisms is also supported by the gradual onset and long preservation of these disturbances, and also by the paroxysmal character of their manifestation and the role of trigger stimulation in their provocation, characteristic features of generator activity. In the late stages of the process, when excitability of the generator neurons is greatly increased [8], neutral stimuli of different biological modalities can "trigger" the generator and thus provoke the appearance of the syndrome. It is a striking fact that injection of TT precisely into the central part of the lateral hypothalamus should cause the appearance of a syndrome characterized by specific features of hyperactivation of the system responsible for feeding, food-getting, and "secondary motivational" responses. Differences in the character of the emotional disturbances in animals receiving comparatively larger (group 1) and smaller (group 2) doses of the toxin can be explained on the grounds that, when larger doses are given the toxin spreads also to other structures of the hypothalamus, and may perhaps reach the ventromedial nucleus. Electrical stimulation of the latter is known to induce a fear response, a passive defensive reflex, and inhibition of food-getting behavior [3, 5, 13, 16], features which were observed in the present experiments also.

The creation of long-acting GPEE in the hypothalamic nuclei by means of tetanus toxin can thus be used to simulate psychopathological states in animals.

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DYNAMICS OF TRANSCALLOSAL POTENTIALS DURING LOCAL ACTION OF A HIGH TEMPERATURE ON THE CEREBRAL CORTEX

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The effect of local heating of an area of the sensomotor cortex on transcallosal responses was studied in acute experiments on cats anesthetized with pentobarbital. Short and prolonged heating of localized areas of the cortex of both hemispheres, starting from temperatures above 44°C, was found to cause initial depression of the negative component of the transcallosal response, followed by irreversible blocking of both phases of the response within the range 47-49°C. It is concluded that the direct inhibitory effect of high temperatures on cortical neurons is manifested only within the range of extremal temperatures, incompatible with vital activity of the whole animal. Experiments with heat blocking of an area of the cortex of one hemisphere provide evidence that transcallosal responses may arise chiefly through direct stimulation of callosal fibers beneath the stimulating electrodes and may entirely reflect postsynaptic potentials.

KEY WORDS: *high temperature; cerebral cortex; evoked potentials.*

Previous investigations showed that the effect of a high degree of hyperthermia on the intact organism is to inhibit dendritic and transcallosal potentials [3]. However, the role of the temperature factor itself in the mechanism of the change in excitability of the cortical neurons remained obscure, for the changes recorded could have been caused by changes in the functional state of other systems of the body in general hyperthermia. To investigate this problem, local heating of a localized area of the brain surface, whereby the direct effect of the high temperature on cortical function can be assessed under normothermic conditions of the rest of the body, can be used as an adequate model. Meanwhile this technique has certain possibilities also for the study of the genesis of cortical potentials [2, 8, 11].

The object of this investigation was to analyze changes in the transcallosal response (TCR) during a local increase in temperature of the cerebral cortex and after restoration of temperature homeostasis.

EXPERIMENTAL METHOD

Acute experiments were carried out on 15 cats anesthetized with pentobarbital (40 mg/kg). Burr-holes 10 mm in diameter were drilled above the sensomotor cortical areas, the dura was removed, and a transparent plastic plate of corresponding diameter, into which stimulating

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