FOOD HYPERMOTIVATION SYNDROMES IN RABBITS WITH HYPERACTIVITY OF LATERAL HYPOTHALAMIC STRUCTURES

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A focus of hyperactivity in the initiating centers for food motivation was created in experiments on unrestrained rabbits by blocking inhibitory mechanisms in the lateral hypothalamus (LH) by injection of tetanus toxin (group 1) or by chronic electrical stimulation of the same region of the brain (group 2). The syndromes thus evoked differed in the intensity of food hypermotivation. The syndrome evoked by injection of tetanus toxin was characterized by very rapid development, clear symptoms of hyperphagia, and a severe course. Marked epileptiform activity was recorded in LH, evidence of the formation of a generator of pathologically enhanced excitation in the "pacemaker" of food motivation. Mechanisms of adequate correction of behavior depending on the result obtained were completely disturbed in the animals. The syndrome evoked by chronic electrical stimulation of LH was characterized by slower formation and a more favorable course. Relatively weak epileptiform activity was recorded in LH. Enhanced food-getting activity of the rabbits also was observed in the late periods after the beginning of electrical stimulation, but the animals' behavior did not lose its adaptive character in this case. The formation of the two syndromes of food hypermotivation described above was connected with the formation of two excitation generators, differing in the intensity of excitation produced by them.

KEY WORDS: lateral hypothalamus; food motivation; tetanus toxin; generator of pathologically enhanced excitation.

Motivational excitation is an essential and very important component of any behavioral act [1, 8], and its study under normal and pathological conditions is an urgent task in modern neurophysiology and neuropathology. In this context it is interesting to have a model of states of prolonged hyperactivity of those parts of the CNS with whose activity the formation and realization of motivations of a particular type are connected. It was shown previously that the formation of generators of pathologically enhanced excitation in certain regions of the CNS makes the corresponding physiological systems hyperactive and gives their activity a pathological character [4, 5]. Such generators can be created by long-term disturbance of inhibitory mechanisms in a neuron population with the aid of tetanus toxin (TT) [6, 7]. Another method of creating excitation generators is by chronic electrical stimulation (CES) of particular brain structures. These methods were used in the investigation described below to create hyperactivity of structures of the lateral hypothalamus, which is regarded as the "pacemaker" of food motivation [1, 8].

EXPERIMENTAL METHOD

Experiments were carried out on 25 rabbits of both sexes. All the animals were trained in a food-getting instrumental skill. A stimulating electrode or cannula-electrode was then

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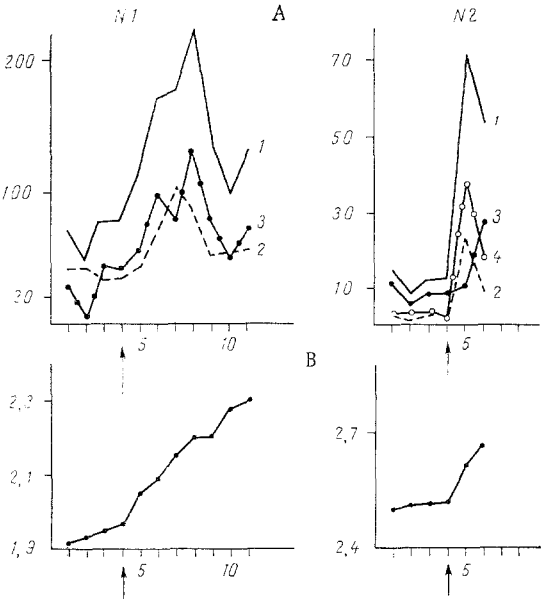

Fig. 1. Character of food behavior (A) and changes in body weight (B) of two rabbits (Nos. 1 and 2) after microinjection of TT into lateral hypothalamus. A: 1) Total number of instrumental responses; 2) instrumental responses ending with the taking of food; 3) instrumental responses not ending with the taking of food; 4) licking and biting the ring. Abscissa, days of experiment; ordinate, number of instrumental responses. B: Abscissa, days of experiment; ordinate, body weight (in kg). Arrow indicates time of injection of TT.

implanted into the "food" zone of the hypothalamus of these rabbits by the "wandering" method [2], under the control of food behavior. To create generators of enhanced excitation in the food motivation centers of the hypothalamus, TT (1 µl, 0.5-0.8 MLD) was injected through a cannula into the rabbits (eight animals — group 1). In the animals of the other group (17 rabbits — group 2) the same regions of the hypothalamus were subjected to CES (duration of series 0.1 sec, 20 square pulses, interval between series 5 min; CES carried out day and night for 2-4 weeks on unrestrained animals). Small electrical stimulators [9], fixed to the animals' body in special jackets, not interfering with the rabbits' movements, were used for CES. Changes in food-getting instrumental activity, changes in body weight, and EEG indices were recorded in the rabbits. Food instrumental activity of the rabbits was studied strictly at the same time of day in a special chamber, in one wall of which there was a food-delivering mechanism, operating when a ring was pulled out by 2.5 cm. In the animal house the rabbits had free access to food *ad lib*. The body weight of the rabbits was measured daily. The EEG was recorded on unrestrained animals. The locations of the electrode and cannula tips in the rabbits' brains were determined by a rapid photographic method.

EXPERIMENTAL RESULTS

During the formation of an excitation generator in the lateral hypothalamus by blocking inhibitory processes with TT the whole syndrome of food hypermotivation developed very quickly, in the course of 24 h, and it reached its maximal level of development on the 2nd or 3rd day. The number of instrumental responses by this time was 3-7 times greater than initially. The considerable increase in the number of "completed" instrumental responses (ending with the taking of food) must be noted, despite the fact that these rabbits consumed food to excess in the animal house also, and they gained weight rapidly (Fig. 1). Well-marked hyper-

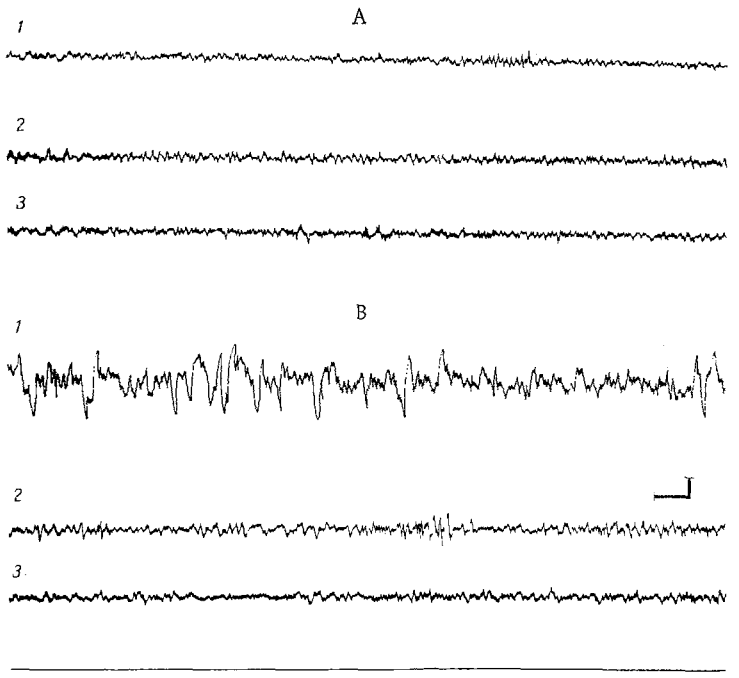

Fig. 2. EEG of rabbit before (A) and after (B) creation of generator of pathologically enhanced excitation in lateral hypothalamus after injection of TT. 1) Lateral hypothalamus; 2) sensomotor cortex; 3) occipital cortex. Calibration: 100 μV, 1 sec.

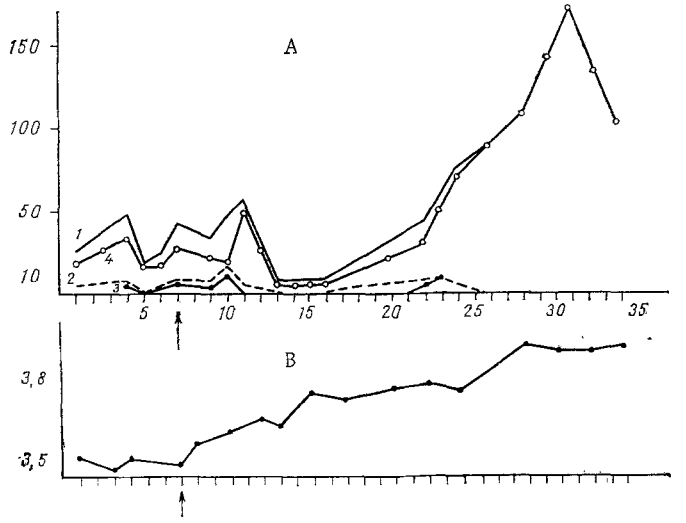

Fig. 3. Character of food behavior (A) and changes in body weight (B) of rabbits after CES of lateral hypothalamus. Legend as in Fig. 1. Arrow indicates beginning of CES.

phagia was present in the animals of this group. Epileptiform discharges were recorded in the hypothalamus (Fig. 2). In some cases this activity could be generalized and evoke general convulsions. These data show that after injection of TT a generator of pathologically enhanced excitation was formed in the lateral hypothalamus. The latent period of the syndrome thus arising was short, but its manifestations were severe. The whole syndrome was characterized by a very severe course.

Hyperactivity of the lateral hypothalamus induced by CES was characterized by the slower formation of the food hypermotivation syndrome. Enhanced food instrumental activity of the rabbits was observed on average 1 week after the beginning of CES, and a significant ex-

TABLE 1. Characteristics of Syndromes Evoked by Creation of Excitation Generator in Lateral Hypothalamus by Microinjections of TT (group 1) and CES (group 2)

Group 1	Group 2
1. Sharp increase in number of instrumental responses, increased motor activity and orienting reaction	1. Sharp increase in number of instrumental responses, strengthening of motor activity and orienting reaction
2. Increase in number of instrumental responses observed 24 h after injection of TT	2. Increase in number of instrumental responses observed 5.5 days after beginning of CES
3. Most marked changes in instrumental activity during first 3 days after injection of TT	3. Most marked changes in instrumental activity 15 days after beginning of CES
4. Considerable increase in number of "completed" instrumental responses	4. Increase mainly in number of "uncompleted" instrumental responses
5. Changes in body weight appear 24 h after injection of TT	5. Changes in body weight appear 24 h after beginning of CES
6. Increase in body weight rapid and stepwise	6. Increase in body weight uniform and gradual, with plateau formation
7. Development of dyspeptic phenomena and death after 3-7 days*	7. State of animals good, with no external signs of pathology
8. Prolonged series of epileptiform discharges in hypothalamus on EEG	8. Single epileptiform spikes on EEG

*The causes of death are not clear: presumably besides the syndrome itself, tetanus poisoning may also be implicated.

cess over the background level (on average, fivefold) was reached at the end of the 2nd or during the 3rd week (Fig. 3). It is striking that in the rabbits of group 2, compared with those of group 1, mainly the number of "uncompleted" instrumental responses (without the taking of food) was increased. The whole syndrome in group 2 was characterized by a favorable course and by relative preservation of the animals' adaptive behavior. The gradual intensification of food-getting instrumental activity indicated gradual strengthening of food motivation in these animals. The excitation generator in this case was formed comparatively slowly. The above-mentioned syndrome was not found in rabbits in which the electrode or cannula tip was located in the region of the dorsomedial hypothalamus.

The fact should be specially noted that the syndrome lasted for a long time (2-4 weeks) after the end of CES. During this period the animals continued to gain weight, their food-getting behavior was the same as during CES, and isolated epileptiform spikes were recorded in the lateral hypothalamus. All these facts are evidence that CES caused the formation of a long-term excitation generator in the lateral hypothalamus, which determined the hyperactivity of this part of the brain.

As the above description shows, syndromes evoked by hyperactivation of the lateral hypothalamus following injection of TT or during CES are basically similar: In both cases food hypermotivation was present and the rabbits' analyses showed that significant differences were present between these effects, due to differences in the formation of the excitation generator in the initiating centers of food motivation (Table 1).

In the first case, in the presence of excessive excitation of the "pacemaker" as a result of the formation of a generator of pathologically enhanced excitation, the rabbits' behavior was clearly pathological in character; the animals ate or were constantly engaged in food getting, despite the fact that their stomach was overfilled. In this case, the mechanisms of adequate correction of behavior depending on the result achieved were completely disturbed. The result achieved by the activity of such a system with excessively enhanced excitation of the "pacemaker" of food activation is of no adaptive importance and cannot suppress its activity, for this determinant component has escaped from inhibitory control.

In the second case the generator produces a weaker volley and inhibition in it is still sufficiently well preserved. The activity of such a generator can be corrected. The syndrome associated with it is not so pathological in character, and its manifestations can be suppressed by physiological mechanisms. In the rabbits of group 2 most instrumental responses were "uncompleted," i.e., motivation was suppressed in the intermediate stage of the re-

sponse. This effect can be explained on the grounds that the instrumental response itself acquired the properties of a reinforcing stage [3, 10] and led to a unique type of "sensory satiation" of the fed animals. In other words, the intermediate result achieved at the stage of the instrumental response, against the background of true satiation of the animals, was effective for suppression of the subsequent course of the response. In this case, inhibitory control of the response was thus preserved, so that the animal's behavior did not lose its adaptive character.

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ENDOGENOUS PYROGEN FORMATION BY MONONUCLEAR PHAGOCYTES

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Incubation of alveolar macrophages from rabbits and of peritoneal macrophages from peritoneal washings of albino mice did not lead to liberation of endogenous pyrogen. Peritoneal macrophages obtained after intraperitoneal injection of thioglycollate, glycogen, or heterologous blood cells into mice likewise did not secrete pyrogen on incubation without additional stimulation. Macrophages isolated after intraperitoneal injection of heterologous blood cells did not possess pyrogenic activity, probably because of the long time after phagocytosis of foreign agents. The process of pyrogen formation by macrophages in these experiments may have been triggered by phagocytosis of corpuscular particles — staphylococci or heterologous blood cells — *in vitro*.

KEY WORDS: fever; endogenous pyrogen; macrophages.

In the modern view the development of a febrile reaction in various pathological processes is due to the formation of endogenous pyrogens (EP) in the body by cells of the professional phagocyte system [2, 5, 15]. There is evidence that, besides neutrophilic granulocytes, EP may also be formed by mononuclear phagocytes: blood monocytes [6, 9, 10], alveolar [4] and peritoneal [7, 8, 13] macrophages, and the Kupffer cells of the liver [12].

The object of this investigation was to study some conditions of activation and formation of pyrogen by mononuclear phagocytes.

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