A STABLE SYNDROME OF ENHANCED FOOD MOTIVATION IN RABBITS

O. A. Timofeeva

UDC 616.89-008.441.12-092.9

KEY WORDS: food motivation; excitation generator; electrical stimulation; hypothalamus.

The study of the neurophysiological mechanisms of goal-directed food behavior is an urgent problem in modern neurophysiology and experimental medicine. This accounts for the interest in the creation of models reflecting the state of chronically enhanced food motivational excitation, which would provide a means of studying the mechanisms of its organization and manifestation. In the writer's previous investigations [6] a state of stable enhanced food excitation was obtained by the formation of a generator of pathologically enhanced excitation [4, 5] in the "pacemaker" of food motivation [1, 7], by microinjections of tetanus toxin into the lateral hypothalamus (LH). The syndrome thus induced was characterized by well-defined symptoms of hyperphagia, by its rapid development, and by its severe course.

A qualitatively new attempt was undertaken to create a long-term excitation generator [4] in the initiating centers of food motivation by application of chronic measured electrical stimulation to structures of LH.

EXPERIMENTAL METHOD

Experiments were carried out on 11 adult rabbits of both sexes weighing 2.5-3.7 kg. The rabbits were taught a food-getting instrumental skill, namely tugging on a ring with their teeth, after which they were given food (2 g of carrot). After stabilization of the reflex, bipolar stimulating electrodes were implanted in the "hunger center" of LH by Lilly's method [2]. The investigation began 7-10 days after implantation of the electrode. Small autonomous electrical stimulators [8], secured in special jackets which the animals wore, and which did not embarrass their movements, were used for chronic electrical stimulation (CES). CES of the hypothalamic structures of the rabbits' brain was carried out by square pulses 0.5 msec in duration, with an amplitude of 1 V, frequency 100 Hz, and total duration of stimulation 0.1 sec, applied at intervals of 5 min round the clock, for 2-4 weeks, while the animals lived a natural life in the animal house, and also during the experiment. In the course of CES (2-4 weeks) and after its end (2-4 weeks) observations were made on the animal's instrumental activity and on changes in their body weight and blood glucose concentration. The blood glucose level of the rabbits was determined twice a week at the same time of day by the anthrone method [11]. In the animal house the rabbits were given access to food ad lib. The localization of the electrodes in the rabbit's brain was determined by a rapid photographic method.

EXPERIMENTAL RESULTS

The first external signs of electrical stimulation of LH (histological control) were found in the rabbits only 24 h after the beginning of stimulation, and took the form of an increase in the animals' body weight, but changes in their behavior were not observed until after 5-6 days. On average one week after the beginning of CES, the number of instrumental food-getting reactions began to increase in all the animals and their motor activity and orienting and investigative behavior were intensified, to reach a considerable level on average after two weeks. In the second or third week after the beginning of CES the general motor activity and number of instrumental responses of the rabbits reached a stable, high level, on average five times higher than initially. In this period the rabbits, if placed in the experimental chamber, examined it continuously, sniffed at the walls and floor, and behaved as if listening for something. Most frequently they remained near the food-supplying

P. K. Anokhin Institute of Normal Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR N. P. Bekhtereva.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 289-91, September, 1980. Original article submitted October 31, 1979.

0007-4888/80/9009-1201$07.50

mechanism: They licked and chewed the ring and feeding bowl, sometimes held onto the ring with sufficient force, but as a rule they did not eat the food which was delivered into the feeding bowl. This type of behavior was maintained by the animals even after the end of electrical stimulation, throughout the period of observation (2-4 weeks) with no sign of extinction.

In the course of electrical stimulation the increase in the rabbits' body weight was greatest in the first five days, when it amounted to 37.6 g/day ($P < 0.05$), a rate of increase 11.4 times faster than initially (3.3 g/day; $P < 0.05$). In the second week of stimulation the mean increase in body weight of the animals *per diem* was 13.8 g, and in the 3rd week it was 17 g. After the end of electrical stimulation the body weight of the rabbits continued to increase, at a mean rate of 5.2 g/day in the first week, and 6 g/day in the second week, which was 1.7 times higher than the initial rate ($P < 0.05$). After three weeks of stimulation the rabbits' body weight was increased by 14%, and after 5 weeks of observation (stimulation and poststimulation periods) it increased by 20%. The blood glucose concentration of the animals remained within normal limits, and relative to the initial level it actually showed a moderate fall.

As a result of continuous subthreshold electrical stimulation of LH for several days the rabbits' motor activity was thus sharply intensified, their food-getting activity (operant level of behavior) was enhanced, and at the same time their body weight increased significantly. It is important to note that all these changes develop gradually in the animals and were observed immediately; later a stable high level was established, which was completely maintained after cessation of CES, and showed no sign of reduction for a long time.

The conditions of stimulation of LH chosen in these experiments thus led to the formation of a phenomenon of stable food hypermotivation in the rabbits. This phenomenon was characterized by a number of special features of its development and manifestation, distinguishing it considerably from the syndrome of hyperphagia and adiposity obtained by other workers by chronic electrical stimulation of LH.

Steffens [12], for instance, who stimulated LH of rats for 30 min three times a day for three weeks, and also Steinbaum and Miller [13], who stimulated LH of animals twice a day for 1 h each time, observed well-marked hyperphagia in the animals only during electrical stimulation. For the rest of the 24-h period the rats were immobile and completely refused to eat. During electrical stimulation of LH a sharp increase was observed [12] in the blood glucose level (up to 200 mg%). It is very striking that in these experiments the body weight of the rats rose very rapidly — by 50% during three weeks of stimulation. After cessation of electrical stimulation for several days their body weight also fell sharply to reach the normal level after a time interval equal to the period of stimulation and if the animals regained their initial level of motor activity by the same time.

In the present experiments intensified food-getting activity of the rabbits was not found during the first hours or days of electrical stimulation of LH, but it was formed gradually and it persisted for a long time without extinction after discontinuation of electrical stimulation. These observations show that the evoked behavior of the animals was connected with the formation of certain novel and relatively stable intracentral relationships in their brain [2, 3].

In a special series of investigations the writer demonstrated a marked increase in excitability of the stimulated region of the hypothalamus after CES, as well as the appearance of epileptiform activity on the EEG of the rabbits during the period of electrical stimulation; this activity appeared in the hypothalamus (on the 1st-3rd days) and spread (on the 5th-8th days) to the cerebral cortex of the rabbits (to the sensomotor area first, later to the occipital region). Subsequently during CES the epileptiform activity weakened considerably but did not disappear completely, for it could be detected even after the end of electrical stimulation, chiefly in the hypothalamus, for a considerable time (2-4 weeks). These results indicate that a long-term excitation generator was formed in the stimulated region of the brain [4, 5]. This result could not be obtained by other conditions of stimulation [12, 13]. Although maintenance of hyperphagic activity in cats during the 24 h after electrical stimulation of LH for 1 h has been described [9], this phenomenon gradually became extinguished after the end of stimulation. In the present experiment, however, subthreshold electrical stimulation was used, and its total duration during the 24-h period was only 30 sec, or only 10 min in the course of three weeks. To some degree the conditions of stimulation chosen were similar to those of stimulation of "kindling" type [10]. However, by contrast with the kindling effect, the rabbits in the present experiment did not develop convulsions, and the epileptiform activity on the EEG was limited in character. It can be tentatively suggested that the conditions of CES used in the present experiments led not only to the formation of a long-term excitation generator, but also to the development of certain restraining, antiepileptic mechanisms, preventing excessive generalization of the excitation process.

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MECHANISM OF ACTION OF BLOOD PLASMA IN POSTRESUSCITATION STATES

I. S. Novoderzhkina, L. V. Molchanova, I. E. Trubina, and A. N. Sundukov

UDC 616-036.882-08-06-085,382

KEY WORDS: postresuscitation syndrome; defibrinated plasma; peripheral circulation; low cardiac output syndrome; thrombohemorrhagic syndrome.

Unfavorable consequences of the terminal state in the form of disturbances of blood rheology and the development of a thrombohemorrhagic syndrome [4, 8, 12] are the immediate cause or an aggravating factor of postresuscitation circulatory disorders [6]. To combat these complications, solutions of low-molecular-weight dextrans and anticoagulants have been used with success [1, 2]. It has been shown in recent years that native plasma possesses antithrombin properties [13, 14].

In this connection it was interesting to study the effect of plasma on some indices of the clotting system and viscosity of the blood, and also the state of the central and peripheral hemodynamics after prolonged circulatory arrest.

EXPERIMENTAL METHOD

Experiments were carried out on 28 dogs anesthetized with trimeperidine (8-10 mg/kg) and pentobarbital (10-15 mg/kg); circulatory arrest was induced for 17 min in the animals by electric shock. The dogs were revived by the method of Negovskii et al. In 11 experiments

Research Laboratory of General Resuscitation, Academy of Medical Sciences of the USSR, Moscow. Physicotechnical Institute, Gor'kii. (Presented by Academician of the Academy of Medical Sciences of the USSR V. A. Negovskii.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 291-293, September, 1980. Original article submitted September 11, 1979.

0007-4888/80/9009-1203$07.50