EFFECT OF ENKEPHALIN-LIKE TETRAPEPTIDE ON FOOD INSTRUMENTAL BEHAVIOR OF RATS

L. F. Kelesheva

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The biochemical structure of the various analogs of opiate-like neuropeptides [2, 14] and their distribution in various brain structures [5, 7, 11] have now been investigated in adequate detail. Much attention has also been paid to the study of behavioral effects of the endorphins, enkephalins, and other opiate derivatives. In particular, when opiate-like peptides are injected systemically and into the brain, marked motor disturbances are observed, with the appearance of deep immobility, muscular rigidity, sedation, catatonia and, in some cases, myoclonic convulsions or stereotyped motor activity [3, 12]. Besides motor disturbances, many workers have found other behavioral effects of opiate derivatives also. It has been shown that endorphins and enkephalins affect the mechanisms of memory and learning, have an analgesic effect [1, 6, 9], reduce the food intake of animals [10], have an antidipsogenic action [4], inhibit sexual behavior [13], and so on. Changes in the concentration of opiate-like peptides have been observed in the CSF of patients with various mental diseases [8, 15]. Yet there are virtually no data on the role of these peptides in the organization of goal-directed behavioral acts.

This paper describes a study of the effect of enkephalin-like tetrapeptide on food instrumental behavior in rats.

EXPERIMENTAL METHODS

Experiments were carried out on 23 noninbrd male rats weighing initially 180-250 g, and trained in instrumental behavior (pressing a lever to obtain a portion of food), and also on 19 untrained control animals. Food behavior and the motor activity of the rats was observed in every case for 1 h after presentation of food to the animals after deprivation for 36 h. Every day the rats' weight and the amount of water consumed (by nine animals) were recorded. Food behavioral responses in trained and untrained rats deprived of food for 36 h were described first. Immediately after, in the experiments of series I (19 untrained and 23 trained animals) the effect of a single subcutaneous (50 μg/kg), intraperitoneal (50 μg/kg), and intraventricular (0.9 μg in 3 μl) injection of enkephalin-like tetrapeptide Tyr-O-Ala-Gly-

TABLE 1. Statistical Data on Short-Term Effects (during 1 h) of Injection of Tetrapeptide on Food Instrumental Activity of Trained Rats after Deprivation of Food for 36 h

Time of determining parameters	Gain in weight of animals, g	Number of completed food instrumental behavioral acts	Number of uncompleted food instrumental behavioral acts	
			intraperitoneal and subcutaneous injection	intraventricular injection
Before injection of tetrapeptide	16,3±2,15	85,6±13,26	24,4±4,09	19,4±3,45
After injection of tetrapeptide	11,1±2,90*	53,9±11,46*	12,3±4,35*	27,8±8,21

*P = 0.05.

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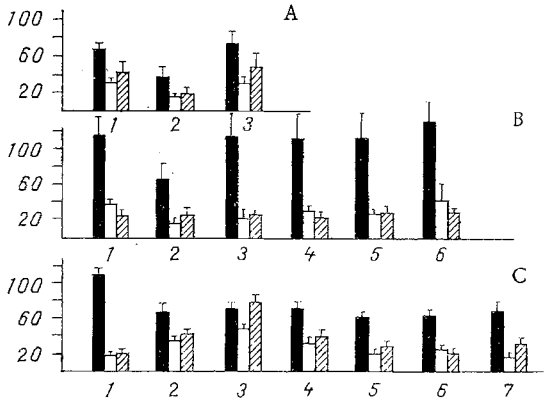

Fig. 1

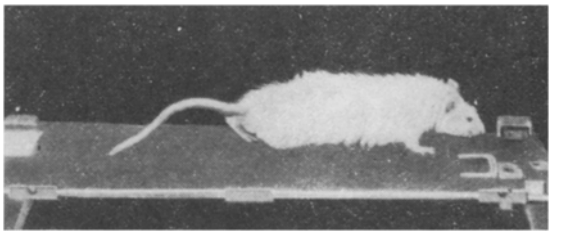

Fig. 2

Fig. 1. Statistical data on effect of enkephalin-like tetrapeptide on outcome of food getting instrumental behavior of rats. A) Intraperitoneal injection; B) subcutaneous injection; C) intraventricular injection. Black columns denote number of completed instrumental acts, unshaded columns — number of uncompleted instrumental acts, obliquely shaded columns — number of repeated pressings on lever. 1) Background, 2) injection of tetrapeptide, 3) 4th-6th day after injection, 4) 1 month after injection, 5) 1.5 months, 6) 2 months, and 7) 5 months after injection of tetrapeptide. Ordinate, number of instrumental acts.

Fig. 2. Characteristic change in rat's motor activity.

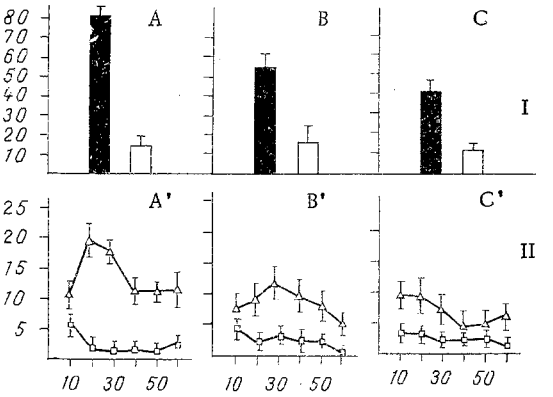

Fig. 3. Effect of Narcan on food getting instrumental activity of rats. I) Mean statistical data on effects of tetrapeptide and Narcan on food getting behavior of rats; II) time course of instrumental activity of rats after injection of tetrapeptide and Narcan. A) Background, B) injection of tetrapeptide, C) injection of Narcan on 4th day after injection of tetrapeptide. Black columns and curves drawn through triangles represent completed instrumental acts, unshaded columns and curves drawn through squares represent uncompleted instrumental responses.

Phe-NH_2, obtained in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR (Director, Dr. Chem. Sci. M. I. Titov) on food instrumental behavior and motor activity of the animals was investigated. The observations usually lasted 2-3 months, but sometimes 5 months. In the experiments of series II (7 trained and 6 untrained rats) the effect of the opiate antagonist naloxone hydrochloride (intraperitoneal injection of 2 mg/kg of Narcan, from Dupont) on the behavioral effects of the tetrapeptide was studied. Narcan was injected on the 4th day after intraperitoneal injection of the tetrapeptide.

EXPERIMENTAL RESULTS

A marked decrease in food intake (on average by 40.3%) was found in the control animals after injection of the enkephalin-like tetrapeptide by all routes. Besides a decrease in the quantity of food eaten (on average by 33.5%), in response to injection of the tetrapeptide the normal instrumental activity of the trained rats was depressed (on average by 37%) (Table 1). This decrease in the number of normal (or completed) instrumental responses after intraventricular injection of the tetrapeptide subsequently continued during five months of observation. When the compound was injected subcutaneously the rats' instrumental activity recovered, but after intraperitoneal injection, it was actually activated a little on the 6th day after injection (Fig. 1). Injection of the enkephalin-like tetrapeptide, incidentally, was accompanied by changes not only in the completed, but also in the so-called incomplete instrumental behavioral acts, not ending with the taking of food. After systemic (intraperitoneal and subcutaneous) injections of the tetrapeptide the number of incomplete instrumental behavioral responses was reduced on average by 49.6% (Table 1). After subcutaneous injection this decrease persisted for 1-1.5 months (Fig. 1). By contrast with systemic injections, injection of microdoses of the enkephalin-like tetrapeptide into the lateral cerebral ventricles (6 rats) caused, on the contrary, an increase in the number of incomplete instrumental behavioral acts with a tendency for them to increase during the first two weeks after microinjections.

It will be noted that the increase in the number of uncompleted instrumental behavioral acts made by rats after intraventricular injection of the tetrapeptide was accompanied by a two- to threefold increase in the number of repeated, outwardly purposeless pressings on the lever, by an increase in the duration of pressing in some cases up to 7-10 min, by the appearance of stereotyped circular movements near the feeding bowl, and also by the total disappearance of instrumental activity. In the last case the animals were either in a state of catatonia or they frequently assumed a vertical posture, moved their head, and attempted to escape from the case. When hungry rats in this state were offered food, they did not respond adequately.

Besides changes in the character of performance of the instrumental behavioral responses, specific disturbances of motor activity were observed in all trained and control rats in response to injection of the tetrapeptide. They were expressed as the appearance of a "duck-like gait," stretching movements, motor stereotypes, flexion of the tail, changes in tone of the abdominal muscles, and so on. Disturbances of the rats' motor activity of this kind appeared during the first 10-20 min after injection of the tetrapeptide, increased in severity until the 5th-20th day after injection, and persisted for up to 3-5 months. The motor disturbances were particularly severe in the trained rats and they were exhibited more strongly during performance of instrumental food getting reflexes (Fig. 2).

The body weight of all the experimental animals showed a tendency to increase during the 1-1.5 months after injection of the tetrapeptide. Meanwhile no significant changes could be found in the quantity of water consumed by the rats daily, either immediately after injections of the tetrapeptide (intraperitoneal injection in 4 rats, intraventricular in 5) or on the following days of observation.

The general features of the effect of the enkephalin-like tetrapeptide on food getting instrumental activity of the rats after injection of the compound by different routes thus were a diminution of the effectiveness of the animal's behavior, a decrease in the quantity of food eaten, a change in the number of uncompleted instrumental responses, and disturbances of the rats' motor activity.

The use of Narcan as a possible blocker of the effects of the enkephalin-like tetrapeptide in the experiments of series II showed that intraperitoneal injection of the antagonist of the opiate receptors on the 4th day after injection of the tetrapeptide (intravenously – 7 days) not only did not depress, but sometimes enhanced the effects of the latter (Fig. 3). After injection of Narcan, moreover, all the animals showed marked stereotyped chewing behavior.

The results are evidence that the effect of enkephalin-like tetrapeptide on goal-directed food instrumental behavior and on motor activity of rats is evidently not mediated through activation of the μ-receptors of the opiate system of the brain but is connected with disturbances of the central-peripheral organization of the behavioral act. The appearance of distinctive behavior, manifested as various types of motor disorders, against the background

of a lowered level of food motivation (and, after intraventricular injection, sometimes its total absence) can be regarded as a biological model of cytopathological states.

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