

EFFECT OF β -LIPOTROPIN DERIVATIVES ON DRINKING AND FOOD
BEHAVIOR OF RATS

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Opioid peptides (α -, β -, and γ -endorphins, met-enkephalin) and β -melanocyte-stimulating hormone (β -MSH) are derivatives of pituitary β -lipotropic hormone [9, 11, 12] and have certain common physiological properties. The lipolytic [5, 13] and analgesic [6, 10, 15] action of this group of peptides (β -lipotropin, α - and β -MSH, β -endorphin, enkephalins) and also their effect on memory and learning processes [1, 7] have been discovered. The degree to which structural features of oligopeptides determine common and specific features of their physiological action is an interesting problem.

This paper describes a comparative analysis of the effect of some hitherto unstudied derivatives of β -lipotropin (fragments MSH₄₋₇ and MSH₅₋₈, corresponding to β -lipotropin fragments 40-43 and 41-44, and also a modified met-enkephalin analog — enkephalin-like tetrapeptide) on drinking and food behavior of rats.

EXPERIMENTAL METHOD

Experiments were carried out on 69 noninbred male rats weighing 200-250 g. Body weight and quantity of water consumed daily in the presence of food and water ad lib. were determined in all animals at intervals. The effect of the substances tested on drinking behavior of rats was assessed by the change in quantity of water consumed by the animals after injection of the peptides. The action of β -lipotropin derivatives on food behavior was studied in previously fed rats and in animals deprived of food for 12 h, in the course of 1 h after administration of physiological saline and of 1 h after injections of physiologically active peptides. The quantity of food consumed by the rats was determined from the gain in weight during 1 h of observation. Enkephalin-like tetrapeptide (Tyr-D-Ala-Gly-Phe-NH₂), synthesized in the Laboratory of Peptide Synthesis of the All-Union Cardilogic Scientific Center, Academy of Medical Sciences of the USSR (Director, Dr. Chem. Sci. M. I. Titov), was injected intraperitoneally and subcutaneously in doses of 50 μ g/kg and into the lateral ventricles in a dose of 0.9 μ g in 3 μ l. β -Lipotropin fragments β -MSH₄₋₇ (Lys-Asp-Glu-Gly-OH) and β -MSH₅₋₈ (Asp-Glu-Gly-Pro-OH), synthesized in the Department of Chemistry of Natural Compounds, A. A. Zhdanov Leningrad University (Head, Dr. Chem. Sci. Prof. V. F. Martynov) were injected into the lateral ventricles in a dose of 3 μ g in 3 μ l. The volume of physiological saline injected in systemic controls was 0.15-0.2 ml, and in the case of intraventricular microinjections 3 μ l. The effects of the test substances were recorded over a long period of time, in some cases as long as 4-4.5 months. The location of the cannulas in the lateral ventricles of the brain was determined by a rapid photographic method. The experimental results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Enkephalin-like tetrapeptide and β -MSH₄₋₇ caused no significant changes in water intake. Meanwhile injection of β -MSH₅₋₈ caused an increase (on average by 4.5 times) in the total daily water intake (Fig. 1). This increase in water intake persisted for 14-16 days of observation.

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TABLE 1. Effect of Enkephalin-like Tetrapeptide, β -MSH₄₋₇, and β -MSH₅₋₈ on Food Behavior of Rats after Starvation for 36 h (1) and in the Fed State (2) after Injection of Physiological Saline (A) and of the Test Substances (B)

Test substance	Mode of injection	Dose	Number of rats	Increase in body weight during 1 h				Mean daily increase in weight over 2-3 weeks		Duration of effect of peptides on	
				A		B		A	B	food intake	body weight
				1	2	1	2				
Enkephalin-like tetrapeptide	Subcutaneous	50 μ g/kg	6	32,8 \pm 1,9	—	19,7 \pm 1,7*	—	4,9 \pm 1,3	16,6 \pm 2,7*	8—10 days	2 1/2—4 months
	Intraperitoneal	50 μ g/kg	23	212,9 \pm 2,1	—	7,5 \pm 1,1*	—	5,8 \pm 2,3	19,0 \pm 3,2*	7—9 days	4—4 1/2 months
	Intraventricular	0,9 μ g in 3 μ l	12	12,0 \pm 1,8	2,1 \pm 0,9	8,8 \pm 1,6*	10,2 \pm 3,7*	4,7 \pm 1,2	8,2 \pm 3,4	4—4 1/2 months	4—4 1/2 months
β -MSH ₄₋₇	Intraventricular	5 μ g in 5 μ l	10	27,3 \pm 2,4	1,7 \pm 0,8	4,3 \pm 1,2*	14,2 \pm 2,2*	4,9 \pm 1,1	2,6 \pm 0,7*	2—3 days	20—25 days
β -MSH ₅₋₈	Intraventricular	5 μ g in 5 μ l	18	19,7 \pm 3,1	3,8 \pm 1,2	20,4 \pm 3,9	2,9 \pm 1,2	4,7 \pm 1,9	5,0 \pm 2,1	—	—

Legend. Asterisk indicates statistically significant changes ($P < 0.05$).

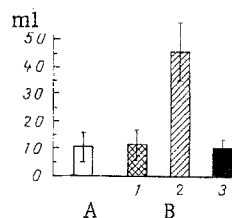


Fig. 1. Daily water consumption before (A) and after (B) injection of various β -lipotropin derivatives. 1) Enkephalin-like tetrapeptide; 2) β -MSH₅₋₈; 3) β -MSH₄₋₇.

Enkephalin-like tetrapeptide and β -MSH₄₋₇ were found to have a marked effect on food intake; the character of this effect largely depended on the original state of the animals' motivation. By whatever method the enkephalin-like tetrapeptide was given, and after intraventricular microinjections of β -MSH₄₋₇, a significant decrease in the quantity of food consumed was observed in rats deprived of food for 36 h, and in the case of β -MSH₄₋₇, the mean decrease was 84.2%. Intraventricular microinjections of these substances into fed animals, on the other hand, activated food behavior. Despite the similar character of action of enkephalin-like tetrapeptide and MSH₄₋₇ on food behavior, the changes in body weight after the injection differed. For instance, after injection of enkephalin-like tetrapeptide the mean daily gain in body weight increased significantly, but during the first 2 weeks after injection of β -MSH₄₋₇ this parameter decreased and returned to its initial values.

It was an interesting fact that β -MSH₅₋₈, which had a dipsogenic action, caused no significant changes in food intake either of hungry or of fed animals and did not affect the dynamics of the rats' body weight.

It must be specially emphasized that the changes in food behavior and body weight described above in response to single intraventricular microinjections of enkephalin-like tetrapeptide and β -MSH₄₋₇, like the dipsogenic effect of β -MSH₅₋₈, continued for a long time. Data on the effect of enkephalin-like tetrapeptide, β -MSH₄₋₇, and β -MSH₅₋₈ on behavior of the rats are given in Table 1.

All the peptides tested, irrespective of the character of their effect on food and drinking behavior of the rats, caused similar changes in the animals' motor activity, manifested as the appearance of stereotyped movements (obsessive chewing, biting, rotary movements, intensive grooming), but after injection of enkephalin-like tetrapeptide specific disturbances of gait and muscle tone also were observed.

It can be tentatively suggested that structural similarity of peptides does not always imply that they have common physiological effects, in agreement with experimental results of workers [8] who demonstrated differences in the effects of structurally similar ACTH analogs on self-stimulation behavior in rats. It has also been found that the character of action of some of the tested peptides (enkephalin-like tetrapeptide and β -MSH₄₋₇) on food behavior is not only connected with their structural features, but, like the effects of β -lipotropin investigated previously [4], it depends on the initial state of the animals' motivations.

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