

COMPARATIVE LIPID-MOBILIZING ACTIVITY OF SOME PITUITARY HORMONES AND ADIPOSIN

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Adiposin and pituitary hormones, when injected into rabbits, increase the concentration of nonesterified fatty acids in the blood. ACTH is the most active of these substances, followed by adiposin, and thyrotropic and somatotropic hormones. Simultaneous administration of adiposin and these hormones potentiates the effect.

Adiposin, a substance isolated from the anterior lobe of the bovine pituitary [7], is a sterile lyophilized protein powder soluble in water. It possesses a lipid-mobilizing action: under experimental conditions it stimulates lipolysis of fatty tissue and correspondingly increases the concentration of nonesterified fatty acids (NEFA) in the blood [10]. Clinical data indicate that if this substance is injected intramuscularly it also activates the lipolytic activity of the fatty tissue of obese persons [12] and has a beneficial effect in the treatment of patients with various forms of obesity [1, 4, 11]. The substance has been approved by the Pharmacological Committee of the Ministry of Health of the USSR for extensive use in medicine.

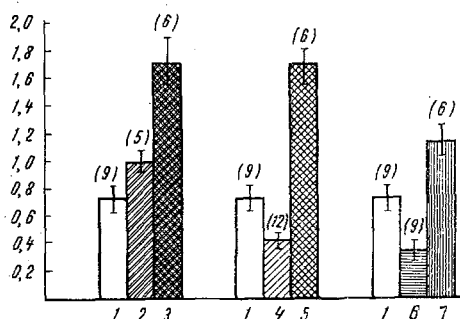


Fig. 1. Increase in NEFA concentration in rabbits' blood serum (number of animals in parentheses) under the influence of combined administration of adiposin and pituitary hormones. Abscissa: 1) adiposin (0.05 mg/kg); 2) ACTH (0.025 mg/kg); 3) adiposin + ACTH (0.05 + 0.025 mg/kg); 4) TTH (0.1 mg/kg); 5) adiposin + TTH (0.05 + 0.1 mg/kg); 6) STH (0.2 mg/kg); 7) adiposin + STH (0.05 + 0.2 mg/kg). Ordinate: increase in NEFA level (μeq/ml).

During recent years investigators have reported the discovery of polypeptides possessing lipid-mobilizing activity [16, 18, 20]. Certain adenohypophyseal hormones—adrenocorticotrophic (ACTH), thyrotropic (TTH), and somatotrophic hormones (STH)—also exhibit marked adipokinetic activity [8, 9, 17, 19]. Keda [6] produced conformational changes in the bovine STH molecule which deprived it of its somatotrophic activity but considerably increased its lipid-mobilizing activity.

To continue the study of the nature of the lipid-mobilizing action of adiposin and of the pituitary tropic hormones, the effect of adiposin, ACTH, TTH, and STH was studied on the NEFA concentration in the blood serum of rabbits. Changes in the NEFA level reflect to some extent the intensity of lipid mobilization from the fat depots [13, 15].

EXPERIMENTAL METHOD

Male rabbits weighing 2.7–4.2 kg, which were starved for 18–20 h before the experiment, served as experimental animals. The substances were injected subcutaneously in different doses at logarithmic intervals of 0.3 ($\log 2 = 0.3$), calculated per kg body weight. The serum NEFA concentra-

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TABLE 1. Lipid-Mobilizing Activity (as change in NEFA concentration in rabbits' blood serum) of ACTH, Adiposin, TTH, and STH ($M \pm m$)

Substance tested	No. of animals	Dose (mg/kg)	NEFA ($\mu\text{eq/ml}$)		P
			before injection	2 h after injection	
ACTH, batch No. 53	6	0.006	0.41 ± 0.13	0.55 ± 0.14	<0.1
The same	7	0.0125	0.21 ± 0.06	0.41 ± 0.11	<0.01
"	5	0.025	0.33 ± 0.09	1.36 ± 0.12	<0.001
"	6	0.05	0.31 ± 0.04	2.31 ± 0.31	<0.001
"	6	0.1	0.26 ± 0.04	2.27 ± 0.27	<0.001
"	6	0.2	0.39 ± 0.09	2.12 ± 0.26	0.01
Adiposin, batch No. 1	6	0.0125	0.25 ± 0.04	0.20 ± 0.03	>0.1
The same	6	0.025	0.23 ± 0.05	0.41 ± 0.07	<0.1
"	9	0.05	0.17 ± 0.03	0.9 ± 0.16	<0.01
"	9	0.1	0.14 ± 0.03	1.68 ± 0.27	<0.001
"	6	0.2	0.10 ± 0.02	1.5 ± 0.23	<0.01
TTH, batch No. 3	6	0.5	0.17 ± 0.02	0.26 ± 0.07	>0.1
The same	12	0.1	0.21 ± 0.03	0.64 ± 0.13	<0.01
"	6	0.2	0.21 ± 0.03	1.66 ± 0.11	<0.001
"	6	0.4	0.25 ± 0.06	2.11 ± 0.25	<0.01
"	6	0.8	0.36 ± 0.07	1.68 ± 0.17	<0.01
STH, batch No. 1-2	6	0.1	0.19 ± 0.02	0.38 ± 0.05	<0.02
The same	9	0.2	0.16 ± 0.02	0.51 ± 0.14	<0.05
"	6	0.4	0.17 ± 0.02	1.15 ± 0.18	<0.01
"	6	0.8	0.22 ± 0.03	1.28 ± 0.15	<0.01

tion was determined by Duncombe's method [15]. Blood for NEFA investigation was collected from the marginal vein of the rabbits' ear. Adiposin (batch No. 1), STH (batch No. 1-2), and TTH (batch No. 3), obtained from the Research Laboratory of the Department of Technology of Endocrine Preparations, All-Union Research Institute of Antibiotics, from bovine pituitary glands by a combined method were used in the experiments. The specific activity of STH by the tibial test [2] was 0.5 unit/mg, and TTH activity assessed by the increase in weight of the thyroid glands in chickens [5] was 0.3-0.4 unit/mg. ACTH (batch No. 53) was obtained from the Medical Preparations Factory of the Leningrad Meat Combine from the pituitary glands of pigs. ACTH activity, after comparison with the Third International Standard [3], was 9 units/mg.

In the experiments of series I, changes in the NEFA level under the influence of adiposin, ACTH, TTH, and STH were investigated 2 h after their administration. In the experiments of series II the same tests were carried out following the combined administration of adiposin and each of these hormones. Adiposin and the hormones were injected into different parts of the body in the minimal dose producing a statistically significant increase in the NEFA level.

EXPERIMENTAL RESULTS

The original serum NEFA level of the experimental rabbits in these investigations was 0.24 ± 0.04 $\mu\text{eq/ml}$ (mean of 20 determinations on 135 animals). As a rule, following the administration of all these substances, the NEFA level showed a definite increase, the degree of which depended on the dose of the preparation (Table 1). It is clear from Table 1 that the largest increase in blood NEFA concentration was observed after injection of ACTH in a dose of 0.05 mg/kg, adiposin in a dose of 0.1 mg/kg, TTH in a dose of 0.4 mg/kg, and STH in a dose of 0.4 mg/kg. A further increase in the dose of ACTH, adiposin, and STH caused no further increase in the NEFA level, while an increase in the dose of TTH actually reduced the degree of the reaction.

A definite linear relationship between the degree of increase in the blood NEFA level and the size of the dose of the tested substances was obtained within the following dose range: for ACTH 0.0125-0.05 mg/kg, for adiposin 0.05-0.1 mg/kg, for TTH 0.1-0.2 mg/kg, and for STH 0.2-0.4 mg/kg.

Simultaneous administration of adiposin (0.05 mg/kg) and STH (0.2 mg/kg) or ACTH (0.025 mg/kg) caused a greater increase in the NEFA level (Fig. 1) than injection of each substance separately.

Following the simultaneous administration of adiposin in the same dose (0.05 mg/kg) and TTH (0.1 mg/kg) potentiation of the lipid-mobilizing effect was observed: the effect of this combined administration exceeded the sum of the effects of each preparation separately (Fig. 1).

The results of these experiments show that the smallest active doses of ACTH and adiposin to produce a definite (statistically significant) increase in the NEFA level in the blood serum are 0.006-0.025 mg/

kg body weight. The smallest active doses of TTH and STH were from 4 to 8 times higher (Table 1). By the degree of their lipid-mobilizing activity, the investigated substances can be arranged in the following order: ACTH, adiposin, TTH, and STH.

Following simultaneous administration of adiposin and the pituitary tropic hormones, as a rule potentiation of their lipid-mobilizing activity was observed. The phenomenon of well-marked potentiation of the action of adiposin in combination with TTH is apparently of particular interest. This is a matter for further investigation.

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