

BIOCHEMISTRY AND BIOPHYSICS

THE INFLUENCE OF THE ADRENOCORTICOTROPIC HORMONE OF THE PITUITARY GLAND ON CERTAIN ASPECTS OF LIPID, CARBOHYDRATE AND NITROGEN METABOLISM IN DOGS

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The adrenocorticotrophic hormone of the pituitary gland (ACTH) is known to activate mainly the formation of glucocorticoids (corticosterone and hydrocortisone) in the adrenal cortex. Reports in the literature [1, 2, 6] point out that the glucocorticoids of the adrenal cortex affect several aspects of lipid, carbohydrate and nitrogen metabolism, mainly influencing gluconeogenesis from protein and causing deposition of glycogen in the liver [3, 4, 5]. Information in the literature on the effect of ACTH on metabolic processes is contradictory, evidently because of failure to take into account the varying degree of activation of the adrenal cortex by this hormone and the possible development not only of stimulation but also of depression of the functional power of the adrenal cortex during the prolonged administration of ACTH.

In the present work we aimed to explain still further the influence of administration of ACTH of Soviet origin on certain aspects of lipid, carbohydrate and nitrogen metabolism.

EXPERIMENTAL METHOD

As experimental animals we used dogs weighing 5.5 - 10 kg. The ACTH preparation was injected subcutaneously in different doses. In the first series of experiments we investigated the effect of a single injection of ACTH on the content of sugar, cholesterol, ketone bodies, residual nitrogen and amino acid nitrogen in the blood 3 and 5 hours after injection of ACTH, and also on the daily urinary excretion of total nitrogen, amino acid nitrogen, creatine, creatinine and neutral 17-ketosteroids. In a second series of experiments we studied the effect of repeated (over a period of 5-10 days) injection of ACTH and in a third series — the influence of this drug on a background of increased metabolism caused by administration of phenamine and thyroidin. In all the experiments a series L-4 preparation was used with an activity of 1 unit/mg determined by the State control laboratory of our Institute. Furthermore, in each experiment the activity of the preparation was checked by the eosinopenic reaction which it caused.

EXPERIMENTAL RESULTS

I. Experiments (46 in number), carried out on 9 dogs, show that the changes in the content of sugar, ketones, cholesterol, amino acids and nitrogen in the blood in the 3-5 hours after a single subcutaneous injection of ACTH in doses of 5-15 units per 1 kg body weight are within the normal limits of variation. Under these circumstances, in the majority of the experiments the following regular feature is observed: when the initial level of the above constituents of the blood is at the lower limit of normal the injection of ACTH increases this level to the upper limit of normal (Fig. 1, a and b, curve 1; Fig. 2, curves 1 and 2). If the initial level of these constituents is at the upper limit of normal, injection of ACTH lowers it (see Fig. 1, a and b, curve 2; Fig. 2, curves 1, a and 2, a).

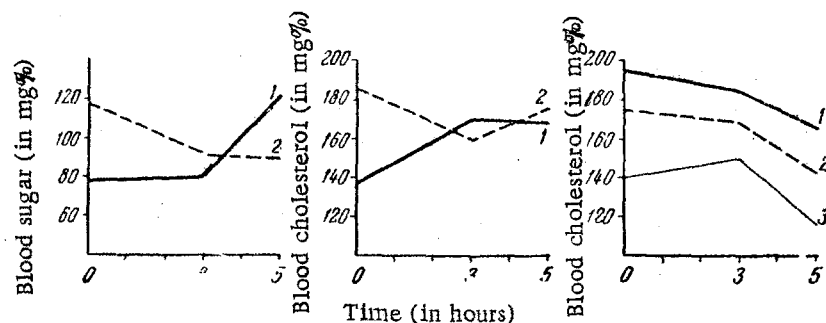


Fig. 1. Changes in the blood sugar (a) and cholesterol (b) in dogs 3 and 5 hours after injection of ACTH in a dose of 5 units per 1 kg body weight, when the initial level was high (1) and low (2); (c) blood cholesterol 3 and 5 hours after injection of ACTH in a dose of 15 units per 1 kg body weight, for various initial levels: (1) for an initial level of 194 mg%; (2) for an initial level of 175 mg%; (3) for an initial level of 140 mg%.

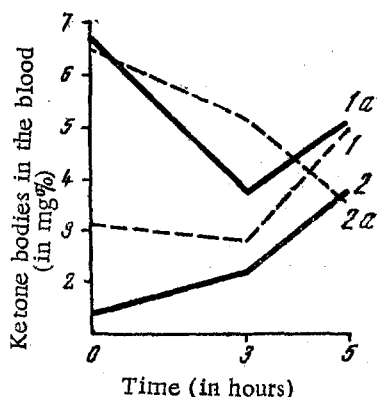


Fig. 2. Changes in the content of ketone bodies in the blood of dogs with a low (1) and high (1a) initial level, 3 and 5 hours after injection of ACTH in a dose of 5 units per 1 kg body weight; with a low (2) and high (2a) initial level, 3 and 5 hours after injection of ACTH in a dose of 15 units per 1 kg body weight.

The changes in the nitrogenous constituents of the urine after a single injection of ACTH stand out in greater relief. The nitrogen content of a 24-hour sample of urine increases as a rule after the injection of both 5 and 15 units per 1 kg body weight. If, however, in this particular dog the initial (before injection of ACTH) nitrogen excretion was above the average level, injection of ACTH in a series of experiments reduces this excretion (Table 1). The same feature is regularly observed with excretion of amino acids: when the amino acid content of the urine is low injection of ACTH usually increases the excretion of amino acids in the urine; if the amino acid nitrogen excretion is raised considerably, injection of the same dose of ACTH causes a fall in its content in a 24-hour sample of urine. However it must be emphasized that injection of relatively large doses of ACTH (15 units per 1 kg body weight) increases the excretion of amino acid nitrogen in those cases when the initial content of this in the urine is raised (see Table 1).

When relatively large doses of the preparation (15 units per 1 kg body weight) are used the changes in the blood cholesterol and the content of amino acids in the urine show a definite directional trend: the blood cholesterol falls slightly (see Fig. 1, c, curves 1, 2, 3), and the amino acid content of the urine rises (see Table 1, dogs Nos. 3, 6 and 10). The first

must be considered to be connected with utilization of cholesterol in the formation of glucocorticoids in the adrenals, and the second is evidently due to increased decomposition or to interference with the resynthesis of protein.

II. Repeated (over a period of 10 days) injection of ACTH in a dose of 5 units per 1 kg body weight daily (experiments on 7 dogs) causes changes in the content of sugar, ketone bodies, residual nitrogen and amino acid in the blood which are within normal limits of variation. At the same time it must be emphasized that when the initial level of these constituents is relatively low, during the first stage (5 days) of its injection, ACTH causes a rise and later (until the 10th day) a fall once more.

When the initial blood level of these constituents is relatively high, during prolonged administration of ACTH their content becomes closer to the average normal value.

TABLE 1

The Effect of a Single Injection of ACTH on the Total Nitrogen and Amino Acid Nitrogen Excretion in the Urine

Dog No.	Dose of ACTH in units per 1 kg body weight	Daily excretion of nitrogen in the urine (in g)		Dog No.	Dose of ACTH in units per 1 kg body weight	Daily excretion of amino acid nitrogen in the urine (in mg)	
		before injection of ACTH	after injection of ACTH			before injection of ACTH	after injection of ACTH
1	5	3.8	7.5	3	5	90	139
3	5	3.7	7.4	5	5	58	134
5	5	4.7	7.0	2	5	52	137
8	5	6.2	11.5	8	5	425	209
8	5	6.5	9.1	7	5	118	102
6	15	4.5	7.1	3	15	150	320
6	15	8.2	5.7	3	— ¹	162	169
3	15	13.2	8.5	6	15	173	281
3	— ¹	11.1	11.4	10	15	163	270
				10	15	150	212

* Control (no ACTH injected). Examined at the same times as the experimental dogs.

Under these experimental conditions cholesterol in the majority of cases shows a tendency to fall (Table 2).

The changes in the content of nitrogenous constituents of the urine are characteristic. Whereas the repeated injection of ACTH over a period of the first 5 days causes a significant increase in the total nitrogen and the amino acid nitrogen excreted in the urine, further (for the next 5 days) injection of ACTH results in a fall in their excretion. In dog No. 2, for instance, before injection of ACTH the total nitrogen content was 3.2 g in 24 hours, on the 5th day after injection of ACTH it was 8.8 g in 24 hours and on the 10th day after injection of ACTH the total nitrogen content fell to 1.3 g in 24 hours. The corresponding amino acid nitrogen content was: before the experiment 53 mg in 24 hr, on the 5th day after injection of ACTH it was 76 mg in 24 hours and on the 10th day after injection of ACTH it had fallen to 37 mg in 24 hours. The same thing was observed in dog No. 1.

In the animals in which the initial total nitrogen and amino acid nitrogen contents in the urine were high, prolonged injection of ACTH causes a fall in their excretion. Before injection of ACTH, dog No. 4, for instance, excreted in the urine in 24 hours 13.2 g of total nitrogen, on the 5th day after injection of ACTH it excreted 7.8 g in 24 hours and on the 10th day — 2.7 g in 24 hours. The amino acid nitrogen content of another dog (No. 5) was: before the experiment — 87 mg in 24 hours, on the 5th day after injection of ACTH — 79 mg in 24 hours and on the 10th day — 52 mg in 24 hours.

Thus after both single and repeated injections of ACTH, in the majority of experiments this hormone has a normalizing effect on the various indicators of lipid, carbohydrate and nitrogen metabolism which we investigated.

III. It must be mentioned that the normalizing effect of ACTH on the various aspects of nitrogen metabolism is also shown in cases when this has been deranged by suitable experimental procedures. Two examples will be given. After administration of phenamine (1 mg per 1 kg body weight daily for 5 days) there is an increase in the total nitrogen, amino acid nitrogen, creatine and creatinine excreted in the urine, and a single injection of ACTH in a dose of 5 units per 1 kg body weight given at this stage reduces the content of these constituents in the urine.

In dog No. 1, for instance, the total nitrogen content before injection of ACTH was 4.2 g in 24 hours, after injection of ACTH it became 2.4 g in 24 hours; the amino acid nitrogen content before injection of ACTH was 128 mg in 24 hours and after injection of ACTH it fell to 49 mg in 24 hours; the level of creatine was 0.50 g

TABLE 2

The Effect of Repeated Injection of ACTH (5 units per 1 kg body weight) on Constituents of the Blood (in mg %)

Dog No.	Sugar			Cholesterol			Ketone bodies			Residual nitrogen			Aminoacid nitrogen		
	0	5-h	10-h	0	5-h	10-h	0	5-h	10-h	0	5-h	10-h	0	5-h	10-h
3	75	84	77	137	95	94	—	—	—	29	46	40	—	—	—
5	—	—	—	140	93	89	7.5	6.0	4.4	32	44	37	8.4	12.0	7.6
6	—	—	—	93	110	96	5.8	7.0	1.3	43	34	35	12.3	10.2	8.7

before injection and 0.16 g in 24 hours after injection of ACTH; the creatinine content before the experiment was 0.18 g and after injection of ACTH it fell to 0.10 g in 24 hours.

In precisely the same way, when the excretion of nitrogenous constituents of the urine is increased after administration of thyroindin in the diet, injection of ACTH lowers the total nitrogen, amino acid nitrogen, creatinine and creatine contents of the urine. In dog No. 2, for instance, the total nitrogen excreted in the urine before injection of ACTH was 6.5 g, and after injection of ACTH in the above dose it was 2.3 g in 24 hours; the amino acid nitrogen excreted before injection of ACTH was 116 mg, and after injection of ACTH — 1.27 mg in 24 hours; the creative content before injection of ACTH was 1.27 and after injection — 0.40 g in 24 hours; the corresponding creatinine levels were — before injection of ACTH, 1.02 g and after injection of ACTH, 0.31 g in 24 hours.

The results given show that ACTH and consequently, the glucocorticoids of the adrenal cortex in a determined dose play an essential role in physiological regulation by normalizing abnormal metabolic processes. This adaptive effect of ACTH is evidently brought about by appropriate functional changes in the adrenal cortex, in so far as the function of this organ can be judged by the excretion of neutral 17-ketosteroids in the urine. Parallel investigations of the excretion of 17-ketosteroids in the urine gave the following results: in a series of experiments in which the level of excretion (for the particular animal) of 17-ketosteroids in the urine was low or average, injection of ACTH in a dose of 5-15 units per 1 kg body weight raised the level of excretion. If the initial level of excretion of 17-ketosteroids in the particular animal was high, injection of ACTH either did not change this level, or lowered it (Table 3, dogs Nos. 6 and 3).

TABLE 3

The Effect of a Single Injection of ACTH on the Excretion of 17-Ketosteroids in the Urine

Dog no.	Dose of ACTH, in units per 1 kg body weight	17-ketosteroids, mg./24 hr	
		before injection of ACTH	after injection of ACTH
8	5	3.7	5.2
8	5	3.3	4.4
8	5	8.4	9.1
3	5	8.6	5.0
3	5	3.0	4.0
6	15	1.3	2.8
6	15	4.4	1.6

The initial functional state of the adrenal cortex thus determines the character of its response to the injection of ACTH and hence the direction of its influence on metabolism. The action of ACTH on the function of the adrenal cortex does not consist only of stimulation, but when certain doses of ACTH are given in certain conditions, of the correction or normalization of this function.

SUMMARY

Examination of the fat-carbohydrate and nitrogen metabolism in the blood and urine of dogs demonstrated that the initial condition of the adrenal cortex may determine the character of response of adrenal cortex to the administration of ACTH. The effect of ACTH on the function of adrenal cortex, probably consists not only in its stimulation but also in normalization (in definite conditions and with certain doses of ACTH).

LITERATURE CITED

- [1] M. B. Lebedeva, Voprosy Med. Khimii 2, 4, 278-286 (1956).
- [2] T. N. Protasova, Uspekhi Sovremennoi Biol. 38, 199-215 (1954).
- [3] N. A. Yudaev, The Biochemistry of the Steroid Hormones of the Adrenal Cortex, Moscow (1956).
- [4] N. A. Yudaev, Problemy Éndokrinol. i Gormonoterap. 1, 2, 95-111 (1955).
- [5] D. J. Ingle, J. Clin. Endocrinol. 10, 1312-1354 (1950).
- [6] G. Sayers, Physiol. Rev. 30, 241-320 (1950).

*In Russian.