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ÉDITIONS DE L'ACADÉMIE DE LA RÉPUBLIQUE SOCIALISTE DE ROUMANIE

INFLUENCE OF INSULIN ON THE METABOLISM OF S^{35}-METHIONINE IN CUSHING'S SYNDROME*

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The influence of exogenous insulin on the S^{35}-methionine metabolism in 10 patients with Cushing's syndrome was studied.

The initial values of the circulating half-lives and urinary excretions of S^{35}-methionine were altered comparatively to the normal ones.

The concomitant injection of 1 U/10 kg b.w. of crystalline insulin with the second dose of S^{35}-methionine improved the initial results, reaching thus the upper limit of the normal.

The exogenous insulin seems to correct the protein metabolism balance, as proved by the S^{35}-methionine turnover.

The protein anabolic effect of insulin in spite of its decreased hypoglycaemic effect in the Cushing's syndrome is discussed.

Previously we have shown that S^{35}-methionine can be used to appreciate various steps of protein metabolism in endocrine diseases [5] [13].

Methionine belongs to the amino acid group, essential for the synthesis of proteins, its rate of metabolization depending on cortisol [13] and insulin level [15].

Many researches have confirmed the protein catabolic effect of corticosteroids [2] [9] and the protein anabolic effect of insulin independently of its action on carbohydrate metabolism [10] [14]. Thus, the antagonism between cortisol and insulin could be extended to the protein metabolism. We have considered the Cushing's syndrome to be a peculiar clinical opportunity in which cortisol excess, leading to reduction or blocking of insulin action in carbohydrate metabolism, could contribute to a differential study of the effect of insulin on protein metabolism.

METHODS

The study was carried out on 10 patients with Cushing's syndrome, selected to form a homogeneous group, according to criteria of age, duration and severity of the illness and the close values of urinary excretion

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of the corticosteroids. The tumoral cases of Cushing's syndrome were omitted.

Initially, the circulating half-life and urinary excretion in the following 24 and 48 hours of S^{35}-methionine was controlled in all the patients. The same investigations were repeated with a new tracer dose of S^{35}-methionine associated with 1 U/10 kg b.w. of crystalline insulin, five days after the first determinations.

The circulating half-life of S^{35}-methionine was expressed by computing its half-time from blood specimens obtained at regular time intervals, 50 min. after the i.v. injection of the tracer dose [7] [12]. The S^{35}-methionine doses were of 2 μC/kg body at each charge.

The percentage of urinary excretion of S^{35} metabolites was determined 24 and 48 hours after the injection of the S^{35}-methionine and it was expressed in impulses given by the totally measured radiosulphur [11].

All the patients fasted for 12 hours before the tests.

During the studies the patients were maintained on a normo-caloric diet with a protein content of about 100 g/24 h.

RESULTS

Table 1 shows all the data obtained in the 10 patients studied.

Table 1

Individual values of the metabolism of S^{35}-methionine before and with insulin association and steroid excretions determined in the course of investigations

No	Name	Age	Sex	before insulin				with insulin			
				Methionine half-life (minutes)	Urinary S^{35}-excretion (% of the dose injected)	17 CS	17 CG	Methionine half-life (minutes)	urinary S^{35}-excretion (% of the dose injected)	17 CS	17 CG
1	M. L.	31	f	51	24	13.1	15.2	27	17	10	11.4
2	B. E.	44	f	37	66	10.1	11.7	24	24	10.8	11.2
3	L. N.	48	f	85	31	13.9	14.7	22	22,1	—	—
4	G. V.	34	m	46	22	14	15.5	34	17	13.4	14
5	T. G.	49	m	53	22	14	15.1	29	15	14.4	15.2
6	R. A.	54	m	36	22	15.2	16.2	25	27	13.6	13.6
7	M. V.		f	42	38	14.7	14.7	25	19	14.4	14.7
8	B. I.		f	50	33	14.2	15	35	23	14.3	14.3
9	P. M.	38	f	47	19	12	14.6	18	25	12.5	15
10	F. S.	36	f	42	22	12.4	12.8	29	25	12	12.6
Averages				49±14	30±14			27±4	21±4		

It appears that the circulating half-life of the S^{35}-methionine was prolonged with all the patients. The average time was 49 ± 13 min., a value significantly increased as compared to the normal (24 ± 4 min.) [4] [7]. The urinary excretion of organic S^{35}/24 h (30 ± 14) also exceeded the percentage of normal output (14 ± 4) [13].

There were no significant differences from the normal in the 48-hour excretions.

Insulin decreased the circulating half-life of S^{35}-methionine to $27 \pm \pm 4$ min., reaching thus the upper limit of the normal.

This fall was present in all the individual values.

The percentage of urinary output of S^{35} at 24 hours decreased to $21 \pm 4\%$. This value is statistically significant as compared to the initial one (Table 2).

Table 2

Averages and statistical significance of the mean circulating half-lives and the urinary excretion in patients with Cushing's syndrome, as compared to the values obtained after insulin and in normals

	S^{35}-methionine half-life			Urinary excretion		
	averages	±	p	averages	±	p
Normal (28)	24.4	4	< 0.01	14	4	< 0.01
Cushing	49	13	< 0.01	30	14	≅ 0.05
Cushing with insulin	27	4	> 0.05	21	4	< 0.01
Normal	24.4	4		14	4	

No differences before and after insulin were found in the period of 48 h.

After insulin the excretion of controlled urinary steroids was not significantly changed.

DISCUSSIONS

The altered circulating half-life of S^{35}-methionine, concomitantly with the increase of the excretion of S^{35} metabolites, points out a deficient methionine metabolism in Cushing's syndrome.

The cortisol excess acts differently upon various circulating amino acids [6].

Whereas this cortisol excess stimulates the tyrosine-transaminase in the liver, with the concomitant increase in the concentration of glutamic acid, aspartic acid and alanine, at the same time it diminishes the other amino acids, including methionine. The lack of the necessary liver energetical substratum transfers the S^{35}-methionine on another metabolic way.

Subsequently, a rise in the excretion of the S^{35}-methionine metabolites appears.

This phenomenon was previously mentioned by Kinsell [8] in one patient with Cushing's syndrome.

Data in the literature assert that corticosteroids have not only a catabolic action, but an anabolic one as well, depending on the different target tissues [1]. Doses of cortisol close to physiologic ones exert an anabolic action on the hepatic cell, proved by some clinical studies [3]. Large doses modify the hepatic metabolism, producing disturbances of the carbohydrate and lipid metabolism with a marked protein catabolism [3].

This means that the corticosteroids are anabolic or catabolic, according to the target tissues, but their action could be different even within the same tissue, depending on the dose.

Exogenous insulin seems to restore the metabolic balance of the amino acids, a fact proved by the tendency to normalize the S^{35}-methionine metabolism.

The protein anabolic effect of insulin in Cushing's syndrome is preserved, even if its hypoglycemic effect is reduced [6].

In clinical conditions the protein anabolic effect of insulin does not seem independent, but it is validated only in the presence of a threshold level of corticosteroids.

In patients with panhypopytuitarism even if their blood insulin levels were high, the methionine metabolism was altered. The improvement was obtained only after substitution treatment with physiological doses of cortisol [13].

These results and those obtained in the Cushing's syndrome prove the necessity of an optimum of insulin and cortisol ratio, so that the protein metabolism would take place under normal conditions.

To conclude, the exogenous insulin in doses without hypoglycaemic effect improves the S^{35}-methionine metabolism in Cushing's syndrome.

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