Hypotriglycemic Action of Synthetic ACTH

FUKASHI MATSUZAKI, MIKI KOMIYAMA AND KAZUO SHIZUME

*Department of Endocrinology, Toranomon Hospital, Institute for Adult Disease,
Asahi Life Foundation, The 3rd Department of Internal Medicine,
Faculty of Medicine, University of Tokyo*

Synopsis

The hypotriglycemic action of ACTH was investigated in the hyperlipemic patients of various diseases. This effect was apparent within 30 min after intravenous injection of the hormone and lasted up to 96 hr when it was administered intramuscularly. ACTH had no effect on the serum cholesterol or phospholipid concentration. As possible causes of this effect of ACTH, fatty acids mobilization and lipoprotein lipase activation were excluded and hepatic involvement was suggested.

In one hypopituitary patient associated with hypertriglycemia of carbohydrate induced type (Frederickson, Type IV), it was incidentally observed that synthetic adrenocorticotrophic hormone (β^{1-24} ACTH) markedly decreased the plasma triglyceride (TG) concentration. In the literature, Friedman, et al. have already reported the TG lowering action of ACTH in hypertriglycemic patients (Friedman *et al.*, 1964; Friedman *et al.*, 1967). However, such an effect of ACTH has not been reported elsewhere and in their report the effect of ACTH was noticed only in the moderately hypertriglycemic patients. Since this extra-adrenal action of ACTH has not widely been recognized and since its TG lowering action observed in our hypopituitary patient was so marked and rapid, we have further studied the effect of ACTH on serum TG concentration as well as on serum cholesterol and phospholipid concentration in 12 patients with various disorders.

Materials and Methods

Patients studied were chosen among those who visited the Department of Endocrinology, Toranomon Hospital. They consisted of 4 diabetics (T. I., K. T₂, K. S., S. E.), 4 hypopituitary patients postoperative to pituitary tumors (Y. I., N. O., H. A., K. K.) and one patient of acromegaly (K. T₁), essential hyperlipemia (Frederickson Type II, T. T. and Type IV, Y. S.) and Cushing's syndrome (S. M.). ACTH used in this study was cortrosyn tetracosactide (N. V. Organon), in an amount of 250 μ g intravenously or 1.0 mg intramuscularly in its long acting depot form (cortrosyn-Z). Blood samplings at 0 and 24, 48 hr after the administration were done in the fasting state before breakfast. Meals were not restricted, so that the 4- and 8-hr samples represented 4 hr after breakfast or lunch, respectively. Serum TG concentration was measured by the Kawade's modification (Kawade, 1962) of Van Handel's method (Van Handel and Zilversmit, 1957), total cholesterol by the modified Zak-Henly method (Zak, 1955; Henly, 1957; Shibata and Kitamura, 1963) and phospholipid by the phenylpyrazolidone method (Yoshida and Igarashi, 1962). Lipoprotein lipase activity was measured 10 minutes after heparin administration (0.1 U/kg BW) according to the method of Frederickson *et al.* (Frederickson *et al.*, 1962) using soybean oil (Intralipid, Apoteksvarucentralen Vitrum Ab, Sweden) as a triglyceride substrate. Serum free fatty acid concentration was measured by the microtitration method by Dole (Dole, 1956).

Fig. 1. Change in serum TG concentration (mg/dl) after ACTH administration in a patient Y. I. ACTH was injected either intravenously in an amount of 250 μ g (circles) or intramuscularly in an amount of 1.0 mg (triangles).

Results

Effect of ACTH on serum TG concentration

Figure 1 shows the results of ACTH administration either intravenously or intramuscularly to a patient (Y. I.) of carbohydrate

induced hyperlipemia. When administered intramuscularly in an amount of 1.0 mg, ACTH decreased the serum TG concentration from 1208, 890 mg/dl to 275, 80 mg/dl in 24 hr and to 130, 125 mg/dl in 48 hr, respectively. In another study, ACTH depressed the high TG concentration of 775 mg/dl to 83 mg/dl in 24 hr and remained to be less than 150 mg/dl for no less than 96 hr. The effect of ACTH became apparent within 4 hr by this route of administration. When administered intravenously, 250 μ g of ACTH lowered the serum TG concentration already in 30 min by nearly 50%. It is not only in this patient that the hypotriglyceridemic action of ACTH was observed, but in other hyperlipemic patients of various diseases responded in the same manner. In Table 1 is summarized the result in the patients who responded to the ACTH administration. Besides the patient described above (Y. I.), hyperlipemics of various diseases, namely acromegaly, essential hyperlipemia, diabetes or hypopituitarism, responded to ACTH. In Table 2 are listed those who did not respond to the ACTH administration. Most of the cases are clearly those whose fasting blood TG concentrations were low to begin with. However, 2 cases are included in the table who had high blood TG concentration and did not respond to ACTH. One of them was a patient of Cushing's syndrome associated with diabetes and the other was a diabetic. The blood TG concentration of either case fell within normal

Table 1. Change in serum TG concentration (mg/dl) after ACTH administration (Responders)

Patient	Diagnosis	0	4 hr	8 hr	24 hr	48 hr
Y. I.	Hypopituitarism	1210			275	130
Y. S.	Essential hyperlipemia	1100			409	391
K. To.	Acromegaly	580	556	481	314	239
K. Ta.	Diabetes mellitus	234	246		197	149
N. O.	Hypopituitarism	174		159	81	
Y. I.	Hypopituitarism	171	192	138	57	80
Y. I.	Hypopituitarism	141	109	77		
H. A.	Hypopituitarism		187	92	82	100

1 mg of synthetic ACTH was injected intramuscularly at 0 time.

Table 2. Change in serum TG concentration (mg/dl) after ACTH administration (Non-responders)

Patient	Deagnosis	0	4 hr	8 hr	24 hr	48 hr
T. I.	Diabetes mellitus	876			860	840
S. M.	Cushing's syndrome	118	128	353	187	177
S. E.	Diabetes Mellitus	85		82	66	
K. S.	Diabetes mellitus	76	100	105	75	78
K. K.	Hypopituitarism	34	41	36	43	34
T. T.	Essential hyperlipemia	33				42

1mg of synthetic ACTH was injected intramuscularly at 0 time.

limits after the initiation of insulin therapy. The difference between those of responders and of nonresponders to ACTH is not clear at present.

Effect of ACTH on blood cholesterol or phospholipid concentration

Although the effect of ACTH was so apparent in lowering TG concentration, ACTH had no remarkable effect on cholesterol or phospholipid concentration in blood. As shown in Tables 3 and 4 respectively, up to a 48 hr period of observation, no apparent change was observed in all cases.

Table 3. Change in serum total cholesterol concentration (mg/dl) after ACTH administration

Patient	0	4 hr	8 hr	24 hr	48 hr
T. T.	608				630
S. M.	388	369	402	364	314
K. Ta.		251	287	231	272
T. I.	247			261	258
H. A.		216	194	211	204
K. K.	142	143	138	131	136

1mg of synthetic ACTH was injected intramuscularly at 0 time.

Table 4. Change in serum phospholipid concentration (mg/dl) after ACTH administration

Patient	0	4 hr	8 hr	24 hr	48 hr
Y. S.	555			440	355
T. T.	445				473
K. Ta.	350	350	365	305	283
S. M.	338	323	363	313	298
T. M.	323			358	318
T. I.	310			318	303
Y. I.	298	313	288		
H. A.		263	205	218	200
Y. I.	248	245	268	253	245
N. O.	220		245	225	
K. S.	205	235	260	220	208
K. K.	170	178	178	165	175
S. E.	168		185	165	

1mg of synthetic ACTH was injected intramuscularly at 0 time.

Effect of ACTH on blood TG concentration in an Addisonian patient

The TG lowering effect of ACTH was also demonstrated in one patient of Addison's disease due to tuberculosis who had been under the steroid supplement therapy. As demonstrated in Figure 2, his fasting TG concentration in blood was 300 mg/dl prior to the administration of ACTH. Twenty-four hours after the administration, it decreased to 150 mg/dl and remained to be lowered in another 24 hr thereafter. Again, no change

T.T. 43 † Addison's Disease

Fig. 2. Change in serum TG concentrations after 1.0 mg ACTH injected intramuscularly.

pFig. 3. Change in serum FFA concentration after ACTH injected intravenously in an amount of 250 μg.

was observed in his cholesterol or phospholipid concentration by the ACTH administration.

Effect of ACTH on serum free fatty acid (FFA) concentration

ACTH has been known to stimulate lipolysis in adipose tissue when added *in vitro* or administered *in vivo* in animals of various species. However, in men no apparent effect on plasma FFA has been observed *in vivo*. Figure 3 shows the effect of ACTH on the plasma FFA concentration in the patients who responded to ACTH with a decrease of blood TG concentration. No consistent effect on plasma FFA was observed.

Effect of ACTH on postheparin lipoprotein lipase activity in blood

As shown in Table 5, lipoprotein lipase activity did not change significantly in samples of 4, 8, 24 or 48 hr after the ACTH administration in one patient (Y. I.), who showed the

Table 5. Postheparin lipoprotein lipase activity (LLA) after ACTH administration in a patient Y. I.

Time in hours	0	4	8	24	48
LLA*	0.098	0.100	0.102	0.099	0.060

* uEqFFA/min/ml

marked lowering of blood TG concentration in response to ACTH.

Discussion

In 1964, Friedman and others reported the hypotriglycedemic effect of ACTH in the literature for the first time (Friedman *et al.*, 1964). They found this effect incidentally while they were studying those hypertriglycedemic subjects exhibiting a particular behavior pattern (type A, according to their designation). Three years later, they reported that ACTH was capable of lowering the fasting and postprandial elevation of plasma TG of the hyperlipemic as well as normolipemic subjects, regardless of their behavior pattern (Friedman *et al.*, 1967). They observed that the injection of 100 U of ACTH prior to the ingestion of the fat meal reduced the average four-hour postprandial plasma triglyceride concentration. They also observed that the depot form of ACTH given 15 hr prior to the fat meal significantly lowered the preprandial and nine-hour postprandial plasma triglyceride levels.

Our results, mostly dealing with fasting plasma TG values, confirm theirs and add some interesting points. Firstly, we have proved that synthetic β^{1-24} ACTH was also effective in lowering the elevated plasma TG level. Friedman *et al.* excluded the effect of possible contaminants to their ACTH preparations by demonstrating that lipotropin and growth hormone failed to exhibit the effect (Friedman *et al.*, 1967). They also showed the administration of essentially pure ACTH to replicate the effect. Our results clearly show that ACTH per se can serve as a hypotriglycedemic agent in men and also the first 1 to 24 fragment of the peptide is sufficient to exhibit the effect. Secondly, our result shows that the effect of ACTH in lowering plasma TG concentration was so marked, which was not noted in their study. In one patient (Y. I.), the tremendous hypertrigly-

cedemia of more than 1000 mg/dl was decreased to a normal range within 24 hr on one occasion, and almost to a normal limit in 24 hr and to a subnormal range in 48 hr in another. In other patients, marked hyperlipemia was also amended almost completely in 24 hr. Thirdly, Friedman *et al.* failed to demonstrate the hypolipemic effect in Addisonian patients (Friedman *et al.*, 1964). In our patient of Addison's disease, the TG lowering effect was clearly demonstrated by ACTH. The reason for this discrepancy is not clear. However, in spite of their own result, they believed that ACTH itself was active, since a large amount of hydrocortisone did not replicate the effect of ACTH. Finally, the hypotriglycedemic effect of ACTH was apparent as early as 30 min after its intravenous administration. As for the duration of this effect of ACTH, it was apparent as long as 48 hr and on one occasion lowered plasma TG level remained normal up to 96 hr. Most of the study which Friedman *et al.* reported was up to 24 hr after the ACTH administration (Friedman *et al.*, 1964). They reported that the fasting and four-hour postprandial serum TG values returned to the control level 72 hr after the injection of ACTH (Friedman *et al.*, 1967). They studied the moderately hyperlipemic patients and we also observed a tendency to return toward their previous levels 48 hr after the administration of ACTH in those moderately hyperlipemic patients. The longer effective period we have observed in a patient of marked hyperlipemia may simply be because it takes more time to return to a markedly elevated initial level of plasma TG.

As possible cause(s) for this effect of ACTH, Friedman *et al.* excluded the participation of insulin which is known to be released by ACTH administration in some species of animals but not in men (Friedman *et al.*, 1967). Insulin pretreatment did not have any effect on pre- and postprandial hypertriglycedemia (Friedman *et al.*, 1967). Serum FFA concentration and postheparin lipoprotein lipase activity was not affected by the ad-

ministration of ACTH in one patient studied. Thus ACTH seems to have nothing to do with FFA mobilization or TG clearing by lipoprotein lipase. The mechanism of this hypotriglycemic action still remains to be elucidated. However, judging from its rapid action and prevention of postprandial hyperlipemia, it should be related to the removal of lipid from the blood stream by the liver, probably without the aid of a lipoprotein lipase activity. Judging from the relatively long lived effect, the effect should also be related to the synthesis and release of TG into the circulation from the liver.

As was mentioned in the results, there were some patients who did not respond to ACTH administration despite their elevated plasma TG level. The reason for this discrepancy is not clear at present. Also, further studies are certainly awaited as for the effect of long term administration on plasma lipid concentrations as well as on lipid content in peripheral tissues, especially in liver.

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