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The effects of adrenocorticotrophic hormone and an equivalent dose of cortisol on the serum concentrations of lipids, lipoproteins, and apolipoproteins

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Abstract

Previous studies have shown a strong lipid-lowering effect of adrenocorticotrophic hormone (ACTH) in healthy individuals and in patients with different kinds of dyslipoproteinemia. The mechanism behind this effect has not been established and its direct ACTH-specific nature has been questioned. Therefore, the present study was performed. Thirty healthy young males were randomized into 3 groups of equal size: one group received $ACTH_{1\text{-}24}$ 1 mg IM, daily for 4 days, another group was treated with cortisol 150 mg ID (50 mg tid) daily for 4 days, whereas a control group was observed for 4 days. Fasting blood samples were collected before and after treatment or observation. The serum concentrations of cholesterol (12%, $P < .05$), low-density lipoprotein cholesterol (24%, $P < .01$), and apolipoprotein (apo) B (31%, $P < .01$) decreased significantly in the ACTH group but not in the cortisol and control groups. The statistical workup confirmed that only ACTH had a lowering effect on the apo B–containing lipoproteins. In contrast, the results indicated conformity between the treatment groups with respect to increases in the serum apo E concentrations. There were inconsistent changes in the serum concentrations of the triglycerides, high-density lipoprotein cholesterol, apo A, and lipoprotein(a). The main results were clear: the lowering effect of ACTH on the serum concentration of apo B–containing lipoproteins could not be ascribed to cortisol. These, in combination with previous in vitro results, indicated an ACTH-specific effect.

1. Introduction

In 1991, the lipid-lowering effect of short-term treatment with adrenocorticotrophic hormone (ACTH) was first described [1]. The question arose as to whether this effect was mediated directly by ACTH or by the steroids released. To answer this question, two different courses were taken. The responses of healthy individuals to ACTH treatment and steroid treatment were investigated, finding a lipid-lowering effect during ACTH treatment but not during steroid treatment [2]. Also, the uptake of labeled low-density lipoprotein (LDL) particles in human hepatoblastoma cells (HepG2 cells) was studied, revealing an increase during the addition of ACTH to the culture medium, which was not seen in control experiments [2]. Thus, it was concluded that ACTH had a direct effect on lipoprotein metabolism. Since then, the lipid-lowering effect of ACTH has been confirmed in studies of patients with different kinds of dyslipoproteinemia [3-5]. However, the notion of a direct lipid-lowering effect of ACTH has been challenged for several reasons. First, in the above-mentioned treatment study comparing ACTH and a steroid, dexamethasone was given instead of the physiologically relevant steroid species, cortisol [2]. Second, in that study, the steroid load of the 2 groups was not documented, precluding estimation of equivalency [2]. Third, in a recent ACTH study, there was a similar dose-response relationship between the

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lipid-lowering properties and cortisol release, suggesting a link between these two effects [6]. Thus, before continuing the research on ACTH, it was imperative to retest the hypothesis that ACTH has a direct lipid-lowering effect. This was done by comparing a group treated with ACTH; a group treated with an equivalent dose of cortisol, which is the predominant physiologic steroid species in question; and a control group.

2. Subjects and methods

2.1. Subjects

Thirty male subjects with mean age of 25 ± 3 years were recruited. They had no relevant medical history, their physical examination was normal, none of them received any medication, and their hemoglobin, white cell, and platelet counts, as well as their serum concentrations of creatinine, glucose, liver enzymes, thyroid-stimulating hormone, and C-reactive protein, were normal.

2.2. Procedure

The participants were randomized to 1 of 3 groups: one group received $ACTH_{1-24}$ (Synacthen Depot, Novartis, Basel, Switzerland) 1 mg IM at 8 AM for 4 days; another group received Solu-Cortef (Pfizer, Puur, Belgium) 50 mg intramuscularly tid at 8 AM, 3:00 PM, and 10:00 PM for 4 days; and the third group received no treatment (control). Blood sampling (after 10 hours fast) and a 24-hour urine collection were performed before and after treatment or observation according to the following scheme:

Day 0: 24-hour collection of urine
Day 1: Physical examination, blood sampling, treatment according to group
Days 2 to 4: Treatment according to group
Day 4: 24-hour collection of urine
Day 5: Physical examination, blood sampling

On days 1 and 5, the participants were seen by an internist. Inquiries were made about the actual state of health, to detect an ongoing infection or inflammation, and, at the second visit, possible side effects. On these occasions, weight, pulse rate, and blood pressure were documented, and a full physical examination performed when needed.

The blood samples were transported to the clinical chemistry department of the hospital for routine analysis of albumin, cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglycerides, lipoprotein(a) [Lp(a)], apolipoprotein (apo) A1, and apo B. Blood samples were also centrifuged within 1 hour, and the serum then stored frozen at −80°C. The serum was shipped to the Pasteur Institute (Lille, France) for analysis of apo E in one series.

Cortisol was analyzed in an aliquot of the 24-hour urine collection, and the concentration was then multiplied by the urine volume in liters.

Table 1
Serum lipid, lipoprotein, and apo concentrations in 3 groups of healthy individuals

		ACTH (n = 10)	Cortisol (n = 10)	Control (n = 10)	Kruskal-Wallis (*P*)
Cholesterol (mmol/L)	Before	4.4 ± 1.0	4.3 ± 1.1	3.6 ± 0.6	.007
	After	3.9 ± 0.6*	4.3 ± 0.8	3.6 ± 0.6	
	Change	−12† ‡	0	1	
LDL cholesterol (mmol/L)	Before	2.6 ± 0.6	2.8 ± 0.7	2.1 ± 0.6	<.001
	After	2.0 ± 0.6**	2.9 ± 0.9	2.2 ± 0.5	
	Change	−24†† ‡‡‡	7	2	
HDL cholesterol (mmol/L)	Before	1.36 ± 0.26	1.40 ± 0.13	1.39 ± 0.22	.034
	After	1.51 ± 0.25**	1.47 ± 0.18	1.40 ± 0.20	
	Change	11†	4	1	
Triglycerides (mmol/L)	Before	1.09 ± 0.37	1.11 ± 0.68	0.82 ± 0.46	.042
	After	0.81 ± 0.33**	1.21 ± 0.69	0.87 ± 0.59	
	Change	−25	24	6	
Apo A1 (g/L)	Before	1.19 ± 0.12	1.29 ± 0.14	1.32 ± 0.20	.001
	After	1.39 ± 0.10**	1.24 ± 0.12	1.28 ± 0.22	
	Change	17†† ‡‡	−3	−2	
Apo B (g/L)	Before	0.81 ± 0.17	0.86 ± 0.25	0.63 ± 0.18	<.0001
	After	0.57 ± 0.21**	0.83 ± 0.15	0.60 ± 0.16	
	Change	−31†† ‡‡	1	−4	

ACTH, before and after 4 days of intramuscular injections with $ACTH_{1-24}$ 1 mg daily. Cortisol, before and after 4 days of intramuscular injections with cortisol 50 mg tid. Control, before and after 4 days of observation. Data are given as means ± SD. Changes are given as percentages.

* $P < .05$, comparing before and after treatment.
** $P < .01$, comparing before and after treatment.
† $P < .05$, comparing ACTH and control.
†† $P < .01$, comparing ACTH and control.
‡ $P < .05$, comparing ACTH and cortisol.
‡‡ $P < .01$, comparing ACTH and cortisol.
‡‡‡ $P < .001$, comparing ACTH and cortisol.

Table 2
Serum apo E and Lp(a) concentrations in 3 groups of healthy individuals

		ACTH (n = 10)	Cortisol (n = 10)	Control (n = 10)	Kruskal-Wallis (*P*)
Apo E (mg/L)	Before	84 ± 23	80 ± 27	90 ± 27	<.0001
	After	118 ± 36**	93 ± 24*	70 ± 15**	
	Change	41††	19‡	−20	
Lipoprotein(a) (mg/L)	Before	336 ± 439	215 ± 247	353 ± 359	.002
	After	243 ± 321**	171 ± 190*	342 ± 351	
	Change	−28†	−14	−0	

Data are given as means ± SD. Changes are given as percentages.
* $P < .05$, comparing before and after treatment.
** $P < .01$, comparing before and after treatment.
† $P < .01$, comparing ACTH and control.
†† $P < .001$, comparing ACTH and control.
‡ $P < .01$, comparing cortisol and control.

2.3. Analyses

Cholesterol, LDL cholesterol, HDL cholesterol, Lp(a), apo A1, apo B, and albumin were measured with routine methods (Modular Analytics P, Roche Diagnostics, Mannheim, Germany). Cortisol was measured with a radioimmunoassay (Spectria Cortisol RIA, Orion Diagnostica, Espoo, Finland). Apolipoprotein E was analyzed with immunoelectrodiffusion with reagents from SEBIA (Issy les Moulineaux, France) [7].

2.4. Statistical analyses

Data are given as means ± standard deviations. The changes during treatments or observation were estimated by the Wilcoxon test. The Kruskal-Wallis analysis of variance followed by the Dunn's test was used to compare the changes between the groups. The level of significance was set at .05.

2.5. Permission and ethical considerations

The study was performed at the Department of Nephrology, University Hospital in Lund, Sweden. Formal permission to perform the study was obtained from the local ethics committee. Owing to the short period of treatment, no serious or long-standing adverse reactions were expected. Precautions were taken in case of intolerance to the substances that were injected.

The study participants received both oral and written information, and they signed an informed-consent form.

3. Results

3.1. Serum concentrations of the apo B– and apo A–containing lipoproteins

In the ACTH group, significant changes took place in all the variables (Table 1). Most importantly, there were decreases in LDL cholesterol and apo B. No such changes were seen in the cortisol or control groups. The Kruskal-Wallis test was also significant for the changes in all the variables, allowing comparisons between groups. With regard to the changes in cholesterol, LDL cholesterol, and apo B, these comparisons revealed significant differences between the ACTH and cortisol groups, the ACTH and control groups, but not between the cortisol and control groups. The changes in apo A1 and HDL cholesterol manifested the same pattern except that there were no significant differences between the changes in HDL cholesterol in the ACTH and cortisol groups. There were no significant differences between the groups with respect to the changes in the triglycerides.

Table 3
Serum albumin concentration, body weight, and 24-hour urinary cortisol excretion in 3 groups of healthy individuals

		ACTH (n = 10)	Cortisol (n = 10)	Control (n = 10)	Kruskal-Wallis (*P*)
Albumin (g/L)	Before	42 ± 4	41 ± 1	42 ± 3	.661
	After	42 ± 3	41 ± 1	41 ± 3	
	Change	1	0	−1	
Body weight (kg)	Before	78.5 ± 11.0	86.5 ± 15.9	79.9 ± 8.2	.089
	After	78.6 ± 11.0	87.1 ± 15.7	79.9 ± 8.2	
	Change	0	1	0	
U-cortisol (nmol/24 h)	Before	251 ± 91	244 ± 110	209 ± 78	<.0001
	After	19052 ± 1584*	15779 ± 2508*	240 ± 78	
	Change	8306†	7787‡	37	

Data are given as means ± SD. Changes are given as percentages.
* $P < .01$, comparing before and after treatment.
† $P < .001$, comparing ACTH and control.
‡ $P < .001$, comparing cortisol and control.

3.2. Serum concentrations of apo E and Lp(a)

There were significant increases in apo E in the ACTH and cortisol groups, whereas there was a significant decrease in the control group (Table 2). The Kruskal-Wallis test was significant for the changes in apo E, as were the comparisons between the ACTH and control groups, the cortisol and control groups, but not the ACTH and cortisol groups.

Lipoprotein(a) decreased significantly in the ACTH and cortisol groups but not in the control group. The Kruskal-Wallis test was significant for the changes in Lp(a). The difference between the ACTH and control groups was significant, whereas the other comparisons between groups were not.

3.3. Other variables

Neither body weight nor the serum albumin concentration changed significantly in any group (Table 3). The 24-hour urinary excretion of cortisol increased significantly in the ACTH and cortisol groups, but did not change in the control group. The Kruskal-Wallis test was significant for the changes in the urinary cortisol excretion, and there were significant differences between the changes in the ACTH and control groups, as well as between the cortisol and control groups, but not between the ACTH and cortisol groups.

4. Discussion

In the ACTH group, a significant decrease was observed in the serum concentrations of cholesterol, LDL cholesterol, and apo B of a similar magnitude as seen in previous ACTH treatment studies both in healthy individuals and in patients with different types of dyslipoproteinemia [1-5]. Moreover, the changes in the serum concentrations of the triglycerides, HDL cholesterol, and apo A1 were inconsistent, which is in accordance with previous findings [1-5]. In contrast, no significant changes were observed in the serum concentrations of the apo B– and apo A1–containing lipoproteins in the cortisol and control groups. In the ACTH group, there were significant changes in the serum concentrations of apo E and Lp(a), an increase in the former variable and a decrease in the latter, but there were also corresponding changes in the cortisol group, although these were less pronounced.

The main goal of the present short-term lipoprotein study was to compare the effects of ACTH and steroids in a manner that reflected the influence of ACTH on steroid release as accurately as practically possible. Because stimulation of cortisol synthesis is the primary action of ACTH, cortisol is the most relevant steroid species in the circumstances. To closely imitate the response to ACTH, cortisol would have to be given as a continuous infusion at a variable rate. For practical reasons, this was impossible. Instead, the cortisol injections were given 3 times a day, at a dose that resulted in a similar total cortisol load during 24 hours as evidenced by the urinary excretion of cortisol. Thus, in the present study, the relevant physiologic steroid species was given at a dose that was documented to be equivalent to the influence of ACTH on the synthesis of this species, conditions that were not met in a previous study comparing the effects of ACTH and steroids on the serum lipoprotein profile [2]. The main results of the study were clear-cut: there was a strong reduction in the serum concentration of the apo B–containing lipoproteins in the ACTH group; such a change was not seen in the other groups and the significance of the findings was corroborated by the Kruskal-Wallis and Dunn's tests. These findings, in combination with previous in vitro findings [2,8], indicated that the changes in the serum lipoprotein profile were induced by ACTH as such.

The mechanism behind the lipid-lowering effect of ACTH has eluded clarification. The first studies suggested an upregulated hepatic LDL receptor activity [2,8], which generally explains decreases in the serum LDL cholesterol concentration of the magnitude in question, that is, 25% to 30%. Moreover, this would be in accord with the effect of ACTH on the adrenal LDL receptor activity [9]. A recent study failed to demonstrate a change in the expression of the LDL receptor mRNA in response to the addition of ACTH to the culture medium of HepG2 cells [10]. Thus, it seems that ACTH increases the uptake of the LDL particles by other means than inducing increased LDL-receptor activity such as by increasing the activity of some other receptor. Another possible mechanism is linked to the repeatedly documented increase in the serum apo E concentration during ACTH treatment [5,6,11]. This could contribute, at least theoretically, to the elimination of apo B–containing lipoproteins, as apo E–enriched, apo B–containing lipoprotein particles are easily taken up by the LDL receptor in experimental studies [12]. In the present study, there was a significant increase in the serum apo E concentration in the ACTH group of a similar magnitude as in previous studies. However, there was also a significant increase in the cortisol group, which was less pronounced but not significantly different from that in the ACTH group. The apo E results were somewhat weakened by a significant, probably coincidental, decrease in the control group; but taken together with findings from an in vitro study, showing no increase in the apo E mRNA when ACTH was added to the culture medium of HepG2 cells [10], they suggest that the changes in apo E in both treatment groups were cortisol-induced.

The changes in the serum Lp(a) concentrations manifested a similar pattern as those in the serum apo E concentrations except that the post hoc tests showed no difference between the cortisol group and the other groups. Thus, the changes observed in the serum Lp(a) concentrations in both treatment groups might have been cortisol-induced, which would be in accordance with the results of a previous study [2].

The information in Table 3 allows us to conclude that the observed changes could not be explained by hemodilution associated with ACTH-induced fluid retention. Moreover, it shows that there was no statistical difference between the cortisol loads of the treatment groups.

In summary, the message is clear: the pronounced and statistically significant decrease in the serum concentration of apo B–containing lipoproteins in the ACTH group could not be ascribed to cortisol. In contrast, the changes in the serum concentrations of apo E and Lp(a) were probably cortisol-induced. These results encourage further studies on the lipid-lowering mechanism of ACTH.

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