SHORT COMMUNICATION

Normal adrenocortical response to adrenocorticotrophic hormone in patients with homozygous familial hypercholesterolaemia

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Summary

1. Plasma cortisol concentration was measured in three subjects with homozygous familial hypercholesterolaemia immediately before, and 30 and 60 min after, an intramuscular injection of adrenocorticotrophic hormone. The baseline values and the values at 30 and 60 min were within the normal range.

2. We conclude that in the presence of a genetic deficiency of low-density lipoprotein receptors, the human adrenal cortex can respond to a single injection of adrenocorticotrophic hormone with a normal increase in corticosteroid production.

Key words: corticosteroid production, familial hypercholesterolaemia, LDL receptors.

Introduction

The unesterified cholesterol required for the production of steroid hormones in the adrenal cortex can be derived either from synthesis in situ or from cholesterol-rich lipoproteins taken up from the extracellular medium; cholesteryl esters stored in cytoplasmic droplets provide an additional source of free cholesterol that can be released in response to sudden increases in demand for steroid hormone (see [1]). Observations on rats [2] and human subjects [3] in vivo have shown that nearly all the cholesterol used for steroid hormone synthesis by the adrenals in the basal state is derived from the plasma rather than from synthesis in situ. Mouse adrenal cells in culture express specific saturable receptors for low-density lipoprotein (LDL), similar to the LDL receptors discovered by Brown & Goldstein [4] on human fibroblasts (see [5]) and Faust et al. [6] have shown that when these cells are stimulated by adrenocorticotrophic hormone (ACTH), a maximal increase in corticosteroid production does not occur unless LDL can be taken up via the LDL receptor pathway. It is not known whether the human adrenal cortex is equally dependent upon receptor-mediated uptake of LDL for a maximal response to ACTH, but Brown et al. [5] have shown that membranes prepared from human foetal adrenal cortex are very rich in LDL receptors. If LDL receptors play an essential role in supplying the adult human adrenal cortex with cholesterol from the plasma, it should be possible to demonstrate defective corticosteroid production in patients with familial hypercholesterolaemia (FH) in the homozygous form, a condition characterized by an absence or marked deficiency of LDL receptors and a greatly increased plasma LDL concentration. In this study we have measured the serum cortisol concentration under basal conditions and after a standard ACTH test in three FH homozygotes.

Methods

Three male homozygotes aged 17 (no. 1), 21 (no. 2) and 30 years (no. 3) were investigated. Cultured skin fibroblasts from all three were receptor defective according to the criteria of Goldstein et al. [7]. A blood sample (25 ml) was taken at 09.00 hours after the subjects had fasted for 14 h. Each was then given 0.25 mg of ACTH 1-24 (Synacthen, Ciba Laboratories) by intramuscular injection and blood samples were taken after
TABLE 1. Serum cortisol concentrations in three patients with homozygous familial hypercholesterolaemia before and at 30 and 60 min after an injection of ACTH 1-24

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Serum cortisol (nmol/l)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Patient no. 1 Patient no. 2 Patient no. 3</td>
</tr>
<tr>
<td>0</td>
<td>254 591 237</td>
</tr>
<tr>
<td>30</td>
<td>549 749 691</td>
</tr>
<tr>
<td>60</td>
<td>621 867 832</td>
</tr>
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30 min and 60 min. Serum cortisol concentration was measured by a competitive protein-binding assay [8] with a pooled sample containing 430 nmol of cortisol/l as quality-control standard.

Results

Table 1 shows the baseline serum cortisol concentrations and the concentrations at 30 min and 60 min after the injection of ACTH in the three patients. The baseline values and the increases in serum cortisol concentration in response to the standard injection are within the range of values obtained from adults with normal adrenocortical function at Hammersmith Hospital, i.e. an increase in serum cortisol concentration of more than 200 nmol/l to a value exceeding 500 nmol/l after the standard injection of 0.25 mg of Synacthen.

Discussion

Our finding that the 1 h response to a single injection of Synacthen is normal in FH receptor-defective homozygotes suggests that an immediate increase in corticosteroid production does not require the presence of a normal complement of functioning LDL receptors in the adrenal cortex. However, it is possible that a brief increase in the supply of intracellular free cholesterol can be mediated by hydrolysis of stored cholesteryl esters, and that if we had given our patients a more prolonged challenge we would have uncovered a defect in their ability to respond maximally to ACTH. Against this, three of our FH homozygotes at Hammersmith Hospital have undergone major surgery for coronary artery bypass without showing clinical signs of adrenal insufficiency. It seems more likely that in FH homozygotes the adrenal cortex obtains the free cholesterol it needs for increased hormone synthesis, in response to a brief or prolonged stress, either by increasing cholesterol synthesis in situ or by increasing the uptake of lipoproteins from the plasma by routes other than the LDL receptor pathway. In keeping with the latter suggestion, Pittman et al. [9] have concluded that about 90% of the uptake of plasma LDL by the adrenals of a normal rabbit in vivo is mediated by the LDL receptor, but that in the WHHL rabbit (a strain with a genetic deficiency of LDL receptors leading to a 10-fold increase in plasma LDL concentration) the adrenals can nevertheless take up LDL at a rate approaching that observed in the normal animal. Pittman et al. [9] suggest that at very high plasma LDL concentrations, as occur in FH homozygotes, uptake of LDL by non-saturable mechanisms may partly compensate for the lack of normal receptor-mediated uptake. Thus our suggestion that the adrenal cortex in FH homozygotes responds to stress by increasing its uptake of LDL via receptor-independent pathways is compatible with the possibility that in normal human subjects the LDL receptor pathway makes a substantial contribution to the supply of cholesterol for hormone synthesis in the adrenal cortex. Nor does our suggestion exclude the possibility that there is also an increase in cholesterol synthesis in the adrenal cortex in response to ACTH, as in the mouse adrenal cells studied by Faust et al. [6].

Illingworth & Orwoll [10] have reported a subnormal increase in corticosteroid output in two abetalipoproteinaemic patients given intravenous infusions of ACTH for 24–36 h. However, in abetalipoproteinaemia there is a total deficiency of LDL. Hence, neither receptor-independent nor receptor-mediated uptake of LDL is available to supply the adrenal cortex with cholesterol from the plasma.

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References


