of mineralocorticoid substitution because renin activity had been slightly elevated. On the other hand it cannot be ruled out that the lung metastases are partially hormone-active. Recently it has been shown by computerized tomography that a high percentage of patients with CAH develop adrenal adenomas and that the incidence of adrenal tumors corresponds to age and insufficient substitution [1]. This particular case supports the hypothesis that also malignant transformation of hyperplastic adrenocortical tissue may be ACTH-dependent.

Table 1

<table>
<thead>
<tr>
<th>ACTH-test</th>
<th>Dexamethasone</th>
<th>Basal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min 60 min</td>
<td>1 day 3 mg</td>
<td>1 day 8 mg</td>
</tr>
<tr>
<td>17-OH-P ng/ml</td>
<td>14.7</td>
<td>18.8</td>
</tr>
<tr>
<td>Cortisol µg/dl</td>
<td>2.7</td>
<td>3.2</td>
</tr>
<tr>
<td>ACTH pg/ml</td>
<td>&lt; 5.5</td>
<td>&lt; 5.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> 25 mg hydrocortisone at 9 a.m.
<sup>b</sup> 15 mg hydrocortisone at 1 p.m.

References


Supported by the Landesamt für Forschung, Nordrhein-Westfalen.

168. Do heterozygote carriers of an adrenogenital syndrome also show an enhanced frequency of adrenal tumors?

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According to our recent investigations 82% of all homozygote patients with an adrenogenital syndrome (AGS) have adrenal tumors. These develop under the continuously increased activity of the pituitary-adrenal axis. Histological examinations show that adenoma (silent), lipomatous transformed myelolipoma and myelolipoma are the main tumor types. Since these tumors are benign they do not constitute a primary indication for surgery (Jaresch et al. 1987).

The aim of this study was to find out whether also the heterozygote carriers of an AGS, especially the parents, brothers and sisters of homozygotes, would show an enhanced occurrence of adrenal tumors.

We examined the heterozygote families of patients with 21-hydroxylase deficiency, performed a computer tomography of the adrenals and took blood samples for the determination of plasma hormone concentrations (androstendione, 17-hydroxyprogesterone and testosterone).

Adrenal tumors were found in 30% of the heterozygote patients. The tumors mainly measured between 10–20 mm in diameter. No correlation was found between tumor size and the plasma concentrations of androstendione, 17-hydroxyprogesterone, testosterone or clinical signs of androgenization.

The incidence of these tumors in heterozygotes strongly suggests that periodically enhanced ACTH-stimulation might be the reason for adrenal tumors in these subjects.

Histologically these tumors may also be adenomas (silent), as in the homozygote patients.

Since the frequency of adrenal tumors accidentally detected by CT has increased in recent years, the heterozygotes should also be regarded as a possible source. Therefore it is suggested that in case
of accidental detection of silent adrenal tumors, an adrenogenital syndrome should be ruled out in these patients and also in their families by endocrinological tests. Furthermore all known heterozygote carriers of an AGS should be informed about the possibility of these adrenal tumors in order to avoid unnecessary operations.

References


169. Leukotriene B₄ synthesis inhibition: a mechanism involved in lymphoma growth suppression by glucocorticoids


Glucocorticoid action on certain lymphoma cells is characterized by a growth arrest followed by cytolysis. Therefore two phases of the steroid effect can be distinguished, i.e. a cytostatic and a cytolytic one. The cytostatic phase in murine S49.1 lymphoma cells lasts for about 24 hours, and during this time the growth inhibition appears to be fully reversible, as suggested by growth and cloning experiments. Glucocorticoid-induced cell lysis involves the activation of endonucleases (Wyllie 1980). The basis of the cytostatic effect, however, has not yet been clarified.

Since the extent of corticosteroid "toxicity" on lymphoma cells varies with the growth rate, a high degree of cytolysis being observed in slowly proliferating cultures compared to a low degree in rapidly growing cultures, the antiproliferative action of glucocorticoids can possibly be attributed to an interference with the synthesis of growth factors. An autocrine and paracrine mechanism of growth control is also suggested by a drastic reduction of the S49.1 lymphoma growth rate in dilute cultures. The finding that the addition of conditioned medium can reconstitute normal growth in dilute cultures further supports the idea of proliferation control by endogenous factors. Since treatment of conditioned medium by charcoal or dialysis abolished growth stimulation, the limiting growth factor under these conditions appears to be a small molecule. Since arachidonic acid metabolites have been reported to have a stimulating effect on certain cell lines, we tested the possibility that the growth stimulating agent in conditioned medium is an eicosanoid. Among the substances examined only leukotriene B₄ exerted a growth-stimulating effect on S49.1 cells and reversed growth reduction in dilute cultures, pointing to a participation of this substance in the control of lymphoma proliferation. Further evidence for the involvement of LTB₄ in lymphoma proliferation was provided by the strong growth suppression mediated by nordihydroguaiaretic acid, an inhibitor of LTB₄ production. Since glucocorticoids interfere with leukotriene synthesis via the induction of a phospholipase A₂-inhibitor leading to a block of arachidonic acid release, the steroid-induced growth arrest might be at least partially attributed to a suppression of LTB₄ formation. In fact, this idea was validated by quantitation of LTB₄ in lymphoma cell cultures treated ± dexamethasone by means of a radioimmunoassay: While 3–4 ng LTB₄ per ml of cell suspension were present in untreated cultures, no LTB₄ was detectable in treated ones.

The lack of a LTB₄ (or arachidonic acid) reversal of glucocorticoid-induced growth arrest, however, suggests that inhibition of LTB₄ production is not the sole target of the steroid. Lymphoma growth possibly depends on other factors that are also under corticosteroid control, or glucocorticoids additionally interfere with growth factor receptor synthesis or function as well as with post-receptor processes. Therefore it can be concluded that glucocorticoids exert their cytostatic effect on lymphoma cells by interference with autocrine and paracrine growth mechanisms.

References


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