ACTH sc was the lowest dose to increase the plasma levels of the three steroids significantly. 30 µg CRH iv increased plasma cortisol and 18-OH-B but not aldosterone, while 100 µg CRH also raised aldosterone secretion. The dose-response curve (peak plasma ACTH level versus maximum increment of plasma cortisol within the first hour) was initially very steep. Plasma ACTH levels between 50 and 60 ng/l stimulated cortisol to almost 80% of the maximal increment obtained with plasma ACTH levels > 300 ng/l.

This dose-response relationship is similar to that found in clinical tests of the pituitary-adrenal axis (insulin test, metyrapone test). The effects of plasma ACTH released by CRH on cortisol secretion were not significantly different from those of injected ACTH. Our results argue against the hypothesis that the effect of CRH on steroid secretion is mediated or modulated by proopiomelanocortin-derived peptides other than ACTH.

144. Gel chromatographic characterization of immunoreactive adrenocorticotropic in patients with ACTH hypersecretion

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It has been established that the pituitary peptides ACTH, β-lipotropin and β-endorphin originate from a common precursor, pro-opiomelanocortin (POMC). Abnormalities in the processing of POMC have been described in the ectopic ACTH syndrome, resulting in the secretion of various large molecular weight forms of ACTH. However, these large forms of ACTH may also be observed in rare cases of pituitary-dependent Cushing’s syndrome (C.s.). We therefore investigated the molecular size of the circulating immunoreactive ACTH by gel chromatography in patients with ACTH hypersecretion.

4 patients with Addison’s disease, 2 with Nelson’s syndrome, 4 with Cushing’s disease (3 microadenomas, 1 macroadenoma), 1 with ACTH hypersecretion from a clinically nonfunctioning pituitary adenoma and 4 patients with ectopic Cushing’s syndrome (1 bronchial carcinoma, 1 metastatic carcinoid, 1 occult ectopic C.s., 1 bronchial carcinoma) were studied.

Analysis of the molecular size of immunoreactive ACTH was performed by gel chromatography. Acidified plasma was chromatographed on a Sephadex G-75 column (superfine; 100 × 1.5 cm) equilibrated with 1% formic acid. 2 ml fractions were collected and evaporated. The immunoreactive ACTH content of the recovered samples was determined by RIA.

In Addison’s disease, in Nelson’s syndrome and in the 3 patients with Cushing’s disease due to microadenomas the plasma showed one single peak of immunoreactive ACTH eluting at the same position as labeled 1–39 ACTH. The plasma of the patient with Cushing’s disease from a macroadenoma as well as the plasma of 3 patients with the ectopic ACTH syndrome revealed at chromatography besides the peak at the expected position of 1–39 ACTH another peak eluting between 1–39 ACTH and the void volume. This second peak was suggestive of a large molecular weight form of ACTH. The plasma sample of the patient with bronchial carcinoma showed at chromatography a heterogenous, large molecular weight peak which may be due to release of a variety of peptides with different molecular weight. The patient with the clinically nonfunctioning pituitary adenoma revealed a profile similar to the patients with carcinoid tumors. One very small ACTH peak eluted at the position of 1–39 ACTH, the second predominant peak eluted near the void volume.

Our conclusions are: 1. The secretion of high molecular weight ACTH is a typical feature of the ectopic ACTH syndrome. 2. In highly malignant carcinomas a variety of ACTH-related peptides is apparently released, whereas carcinoid tumors seem to be associated with the secretion of one high molecular weight form of ACTH. 3. In Cushing’s disease big ACTH seems to be a feature of macroadenomas. 4. Even in clinically silent pituitary adenomas the secretion of big ACTH without biological activity may be observed.