Expression of glucocorticoid receptor splice variants in peripheral blood mononuclear cells in hyper- and hypocortisolism

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Background. In addition to the wild-type glucocorticoid receptor (GRα), two GR splice variants exist which may decrease (GRβ) or increase (GR-P) glucocorticoid sensitivity. GR affinity may be decreased in patients with endogenous hypercortisolism due to Cushing's syndrome. We therefore examined GR number and affinity as well as GR splice variant expression in mononuclear leukocytes (PBML) in patients with Cushing's syndrome. In addition, the effects of relative hypocortisolism on GR splice variant expression were examined in patients who underwent metyrapone testing.
Methods. Blood was obtained from 14 healthy controls and from 13 patients with Cushing's syndrome: 9 with a pituitary adenoma, 3 with ectopic ACTH production and 1 with an adrenal adenoma. 9 patients were studied who underwent a Metyrapone test to evaluate pituitary-adrenal axis function. GR number and affinity were determined by a whole cell dexamethasone binding assay. GR isoform expression was assessed using real-time PCR.
sults. In Cushing patients, preoperative GR affinity in PBML's was decreased as reflected by a an increased Kd (14.4±2.0 vs. 9.3±0.5 in controls, $p<0.05$). GR number per cell was not significantly different. Postoperatively, the Kd decreased to 11.4±2.0. All three GR isoforms could be amplified in controls, patients with Cushing's syndrome and patients who underwent a metyrapone test ($\alpha : P : \beta = 1 : 0.25 : 0.001$). There was no difference in expression between these groups. In patients with Cushing's syndrome, mRNA expression of GR variants were correlated to the number of GRs per cell ($p<0.05$). Postoperative GR-β mRNA levels were lower compared to preoperative levels ($p<0.05$). The fall in cortisol levels in patients undergoing a metyrapone test was not accompanied by an altered GR isoform expression.
Conclusion. Decreased GR affinity in Cushing's syndrome is not explained by differential GR isoform expression. Relative hypocortisolism as induced by metyrapone does not induce an acute change in mRNA levels of the three GR variants.

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