Adrenal Steroid Metabolites Accumulating in Congenital Adrenal Hyperplasia lead to Transactivation of the Glucocorticoid Receptor

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Introduction

Congenital adrenal hyperplasia (CAH) patients are clinically often less severely affected by cortisol deficiency than anticipated from their enzymatic defect. We hypothesize that adrenal steroid hormone precursors that accumulate in untreated or poorly controlled CAH have glucocorticoid activity and partially compensate for cortisol deficiency. We aimed to determine the in vitro binding, translocation and transactivation potential of the steroid hormone precursors 21-deoxycortisol, 17-hydroxyprogesterone, progesterone and androstenedione on the human glucocorticoid receptor.

Methods

Competitive binding assays were performed in HeLa cells. Nuclear translocation of the hGR was studied by transfection of COS-7 cells with a GFP-tagged hGR and fluorescence microscopy. Transactivation assays were performed in COS-7 cells and repeated in HEK 293 cells using a dual luciferase assay after co-transfection of the cells with the hGR and luciferase reporter vectors.

Results

21-deoxycortisol, 17-hydroxyprogesterone and progesterone are able to bind, translocate and transactivate the glucocorticoid receptor (hGR) in vitro and thus may have glucocorticoid activity. Mainly 21-deoxycortisol might have a clinically relevant agonistic effect on the hGR and could potentially partially compensate the cortisol deficiency in congenital adrenal hyperplasia patients.

Conclusion

21-deoxycortisol, 17-hydroxyprogesterone and progesterone are able to bind, translocate and transactivate the glucocorticoid receptor (hGR) in vitro and thus may have glucocorticoid activity. Mainly 21-deoxycortisol might have a clinically relevant agonistic effect on the hGR and could potentially partially compensate the cortisol deficiency in congenital adrenal hyperplasia patients.