LBP - 1259

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

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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.

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.

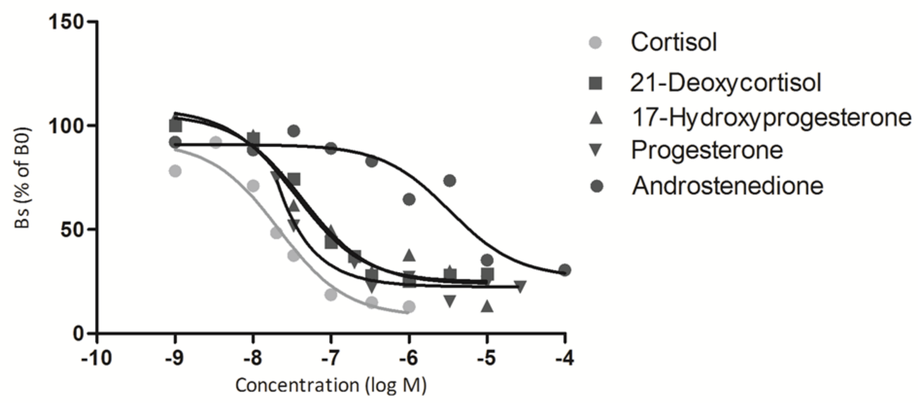
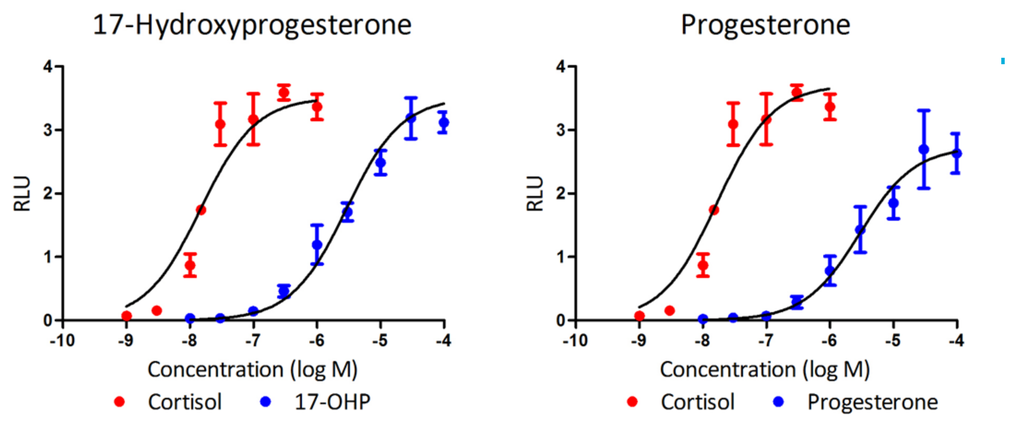


Figure 1. Competition of various steroids for binding of ^{3}H cortisol to the hGR in HeLa cells. Data are expressed as the percentage of specific binding (Bs) remaining after adding increasing amounts of competitor.



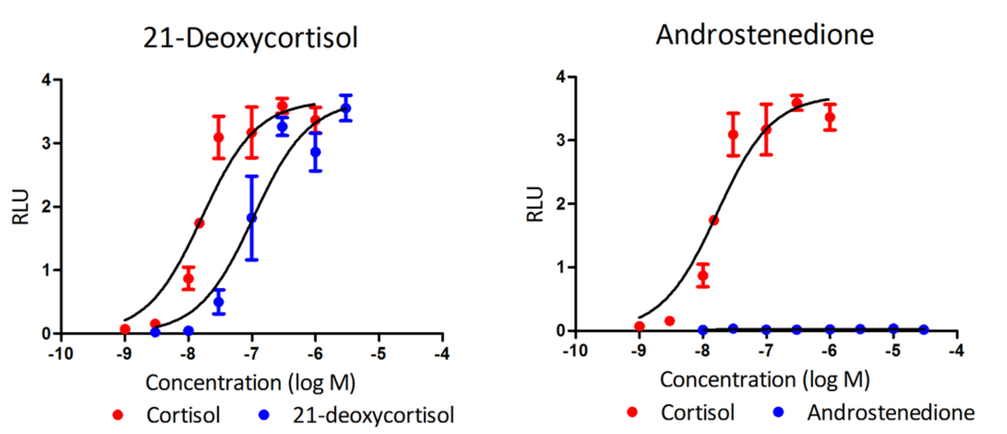


Figure 2. Transactivation of the hGR in COS-7 cells by various steroids, in comparison with the transactivation of the hGR by cortisol.

Results

21-deoxycortisol , 17-hydroxyprogesterone and progesterone are able to bind to the hGR with binding affinities of 24 – 43% compared to cortisol (fig. 1). Androstenedione has a low binding affinity. Incubation with 21-deoxycortisol led to complete nuclear translocation of the hGR, whereas treatment with 17-hydroxyprogesterone or progesterone resulted in partial nuclear translocation. 21-deoxycortisol transactivated the hGR with an EC50 approximately 6-fold the EC50 of cortisol (fig. 2). 17-hydroxyprogesterone and progesterone trans-activated the hGR with EC50s of more than 100 times the EC50 of cortisol. No hGR transactivation was detected after incubation with androstenedione.

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ESPE 2015 1259-LBP

Adrenals and HPA Axis

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DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

PosterSessionOnline.com