Adrenal steroid precursors with glucocorticoid activity are able to prevent adrenal crises in untreated congenital adrenal hyperplasia (CAH) patients

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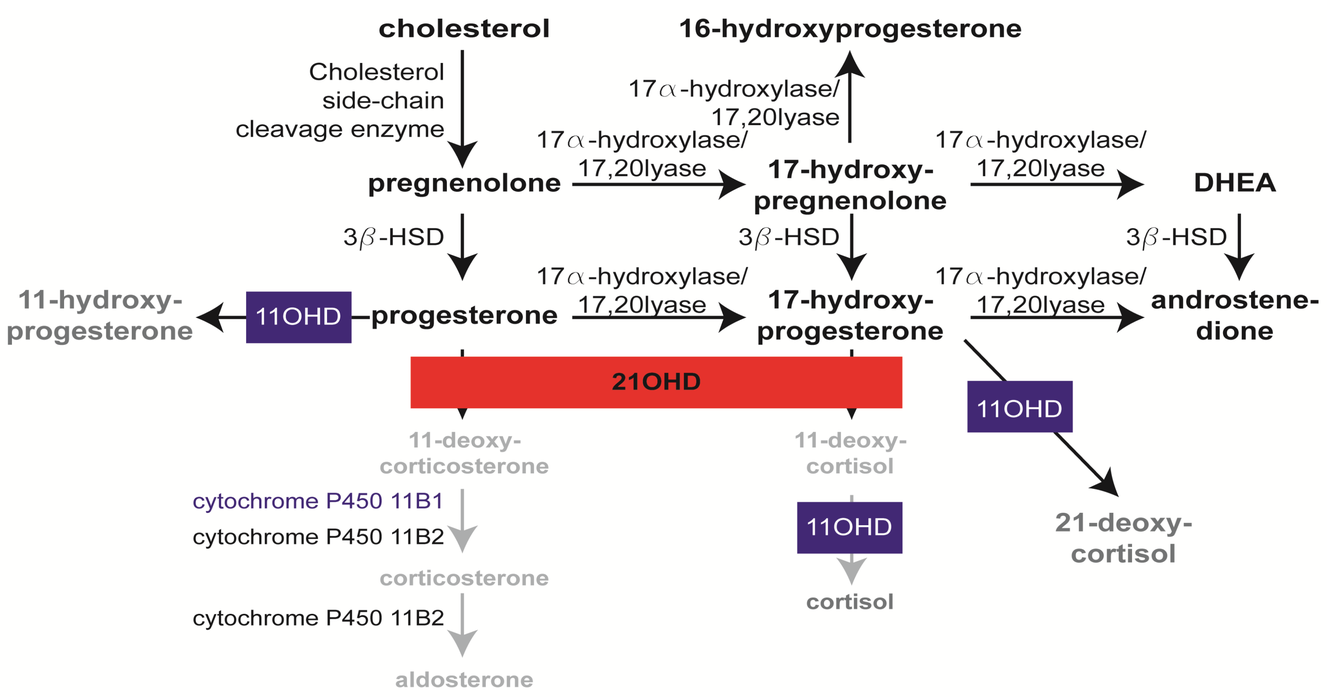
Adrenal steroidogenesis and CAH



Cohort description

24 severely affected **untreated** CAH patients:

Age 0 – 46 years

19x 21-hydroxylase deficiency (21OHD)

5x 11-hydroxylase deficiency (11OHD)

13/22 patients had reported episodes of severe stress

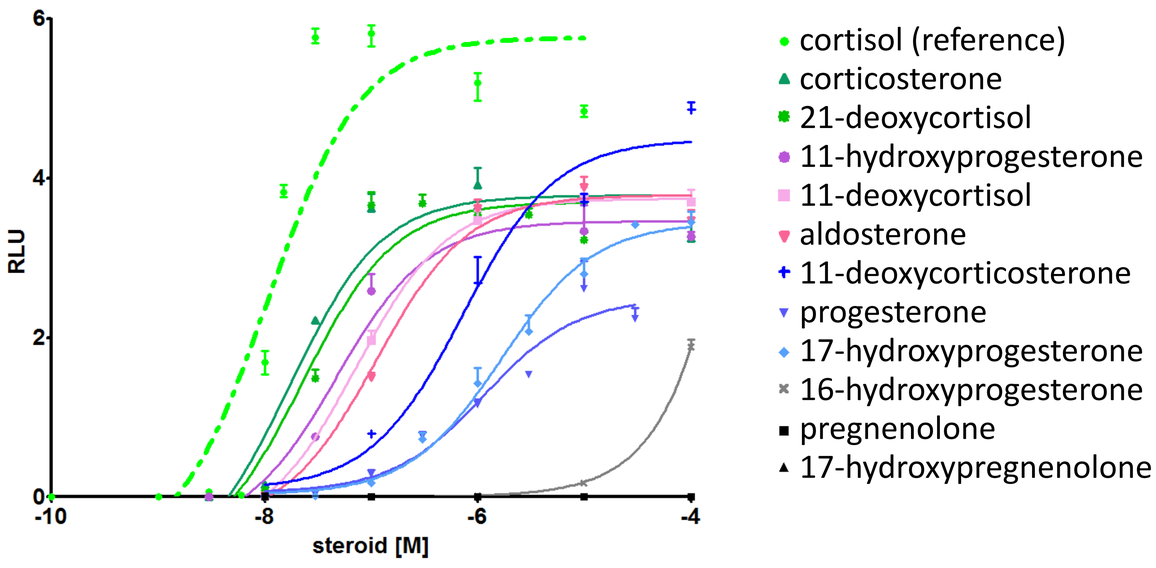
Aim: to determine the role of adrenal steroid precursors in CAH patients

Increased concentrations of adrenal steroid precursors in untreated CAH patients

Steroid	Median concentrations (nmol/L) 60 minutes after ACTH stimulation (LC-MS/MS) Mann-Whitney-U test compared to control		
	21OHD	**Control**	**11OHD**
cortisol	**73**	>500	**180**
11-deoxycortisol	1.9	3.2	**457 (p=0.003)**
11-deoxycorticosterone	0.4	0.5	**55 (p=0.003)**
17-hydroxyprogesterone	**610 (p<0.001)**	4.8	20 (p=0.003)
progesterone	**29 (p<0.001)**	1.0	3.6 (p=0.003)
21-deoxycortisol	**73**	-	-
corticosterone	7.1 (p<0.001)	72	4.3 (p=0.003)

Steroid precursors have glucocorticoid activity

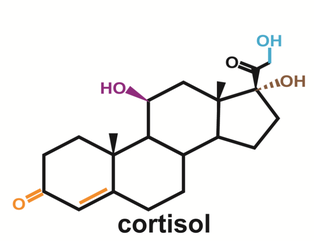
Dual-luciferase assay in human embryonic kidney cells transfected with the glucocorticoid receptor



Structure-activity relationship:

Dehydrogenation is a prerequisite
no activity of (17-hydroxy) pregnenolone

Most potent steroids are 11-hydroxylated *(corticosterone, 21-deoxycortisol, 11-hydroxyprogesterone, aldosterone)*



21-hydroxylated
17-hydroxylated
11-hydroxylated
3β-hydroxysteroid dehydrogenated

Conclusion: Strongly elevated adrenal steroid precursor concentrations are able to compensate for cortisol deficiency in untreated CAH patients

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Adrenals and HPA Axis

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