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Title: Adrenal C11-oxy C₂₁ steroids contribute to the C11-oxy C₁₉ steroid pool via the backdoor pathway in the biosynthesis and metabolism of 21-deoxycortisol and 21-deoxycortisone.

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Adrenal C11-oxy C₂₁ steroids contribute to the C11-oxy C₁₉ steroid pool via the backdoor pathway in the biosynthesis and metabolism of 21-deoxycortisol and 21-deoxycortisone.

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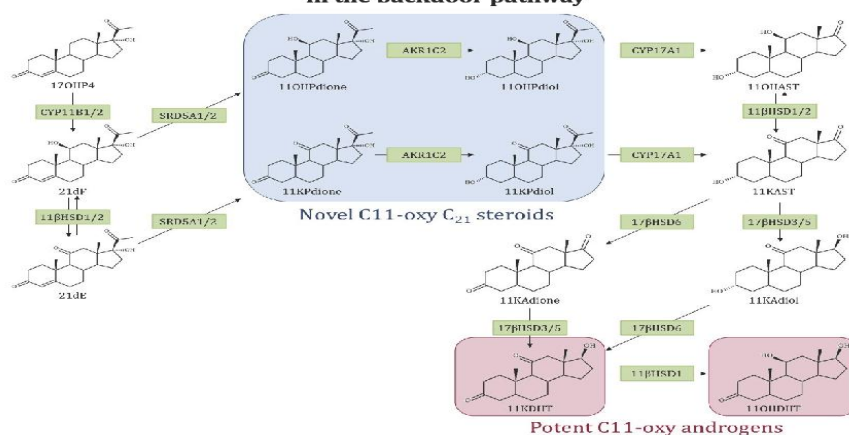
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Graphical abstract

Conversion of 21-deoxycortisol (21dF) and 21-deoxycortisone (21dE) to 11-ketodihydrotestosterone (11KDHT) and 11 β -hydroxydihydrotestosterone (11OHDHT) in the backdoor pathway



Highlights

- Adrenal CYP11B isozymes catalyze the 11 β -hydroxylation of 17 α -hydroxyprogesterone
- 11 β HSD1 and 11 β HSD2 convert 21-deoxycortisone (21dE) and 21-deoxycortisol (21dF)
- SRD5A catalyzes the conversion of 21dF and 21dE to 11OHPdione and 11KAdione
- AKR1C2 reduces the C3-hydroxyl moiety in the biosynthesis of 11OHPdiol and 11KAdiol
- 11OHPdiol and 11KAdiol are lysed by CYP17A1, yielding 11OHASt and 11KASSt

ABSTRACT

21-Hydroxylase deficiency presents with increased levels of cytochrome P450 21-hydroxylase substrates, progesterone and 17 α -hydroxyprogesterone, which have been implicated in the production of androgens via the backdoor pathway. This study shows the biosynthesis of C11-oxy C₂₁ steroids, 21-deoxycortisol and 21-deoxycortisone, and their metabolism by steroidogenic enzymes in the backdoor pathway yielding novel steroid metabolites: 5 α -pregnan-11 β ,17 α -diol-3,20-dione; 5 α -pregnan-17 α -ol-3,11,20-trione; 5 α -pregnan-3 α ,11 β ,17 α -triol-20-one and 5 α -pregnan-3 α ,17 α -diol-11,20-dione. The metabolism of 21-deoxycortisol was validated in LNCaP cells expressing the relevant steroidogenic enzymes showing for the first time that the steroid produced at high levels in 21OHD, is metabolised via the C11-oxy derivatives of 5 α -pregnan-17 α -ol-3,20-dione and 5 α -pregnan-3 α ,17 α -diol-20-one to substrates for the lyase activity of CYP17A1, leading to the production of C11-oxy C₁₉

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