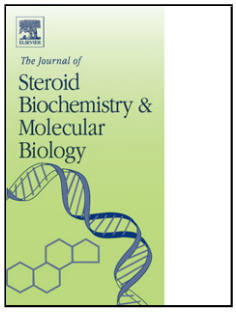


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PII: S0960-0760(17)30209-1
DOI: http://dx.doi.org/doi:10.1016/j.jsbmb.2017.07.034
Reference: SBMB 5000

To appear in: *Journal of Steroid Biochemistry & Molecular Biology*

Received date: 21-6-2017
Revised date: 27-7-2017
Accepted date: 28-7-2017

Please cite this article as: Lise Barnard, Rachelle Gent, Desmaré van Rooyen, Amanda C.Swart, 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., Journal of Steroid Biochemistry and Molecular Biologyhttp://dx.doi.org/10.1016/j.jsbmb.2017.07.034

# Adrenal C11-oxy $C_{21}$ steroids contribute to the C11-oxy $C_{19}$ steroid pool via the backdoor pathway in the biosynthesis and metabolism of 21-deoxycortisol and 21-deoxycortisone.

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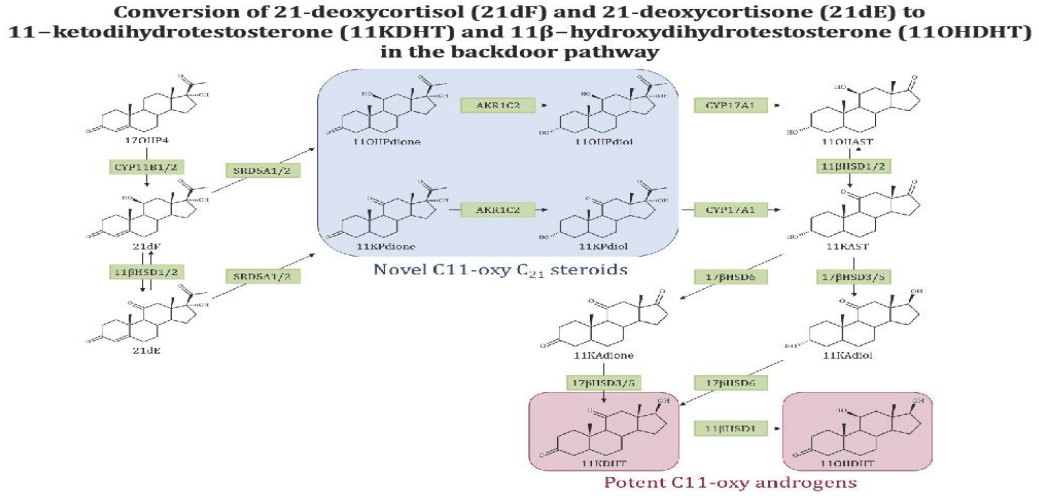
Graphical abstract




Highlights

- Adrenal CYP11B isozymes catalyze the 11β-hydroxylation of 17α-hydroxyprogesterone
- 11βHSD1 and 11βHSD2 convert 21-deoxycortisone (21dE) and 21-deoxycortisol (21dF)
- SRD5A catalyzes the conversion of 21dF and 21dE to 11OHPdione and 11KPdione
- AKR1C2 reduces the C3-hydroxyl moiety in the biosynthesis of 11OHPdiol and 11KPdiol
- 11OHPdiol and 11KPdiol are lysed by CYP17A1, yielding 11OHAST and 11KAST

**ABSTRACT**

**21-Hydroxylase deficiency presents with increased levels of cytochrome P450 21-hydroxylase substrates, progesterone and 17α-hydroxyprogesterone, which have been implicated in the production of androgens via the backdoor pathway. This study shows the biosynthesis of C11-oxy $C_{21}$ steroids, 21-deoxycortisol and 21-deoxycortisone, and their metabolism by steroidogenic enzymes in the backdoor pathway yielding novel steroid metabolites: 5α-pregnan-11β,17α-diol-3,20-dione; 5α-pregnan-17α-ol-3,11,20-trione; 5α-pregnan-3α,11β,17α-triol-20-one and 5α-pregnan-3α,17α-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 5α-pregnan-17α-ol-3,20-dione and 5α-pregnan-3α,17α-diol-20-one to substrates for the lyase activity of CYP17A1, leading to the production of C11-oxy $C_{19}$**