11β-Hydroxysteroid dehydrogenase type 1 modulates the activation of 11-oxygenated androgens by aldo-keto reductase 1C3

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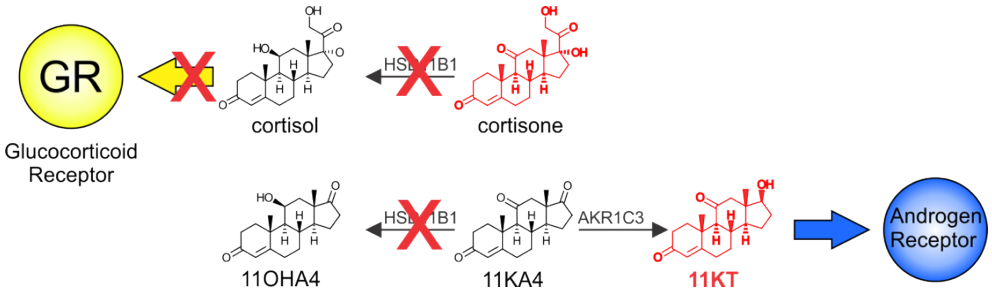

Inhibition of HSD11B1 to reduce glucocorticoid mediated metabolic effects may be counteracted by the increased levels of the potent 11-oxygenated androgen, 11-ketotestosterone (11KT).

Introduction: The enzyme aldo-keto reductase 1C3 (AKR1C3) plays a central role in the peripheral activation of androgens by converting androstenedione (A4) to testosterone (T). Recently it has been shown that 11-ketoandrostenedione (11KA4) is actually the preferred substrate for AKR1C3, yielding the potent androgen 11-ketotestosterone (11KT)[1,2]. In adipose tissue, a primary site of peripheral androgen activation, AKR1C3 is co- expressed with the enzyme 11β-hydroxysteroid dehydrogenase type 1 (HSD11B1), which converts 11KA4 to 11β-hydroxyandrostenedione (11OHA4) preventing activation by AKR1C3. We therefore propose that HSD11B1modulates the activation of 11-oxygenated androgens and that inhibition of HSD11B1 would lead to an increasein 11KT levels.

Methodology: Steroid conversion assays were performed in non-steroidogenic HEK293 cells expressing different ratios of AKR1C3 and HSD11B1, as well as in the human Simpson-Golabi-Behmel syndrome (SGBS) preadipocyte cell line, which endogenously expresses both enzymes after differentiation in-vitro. *Ex vivo* steroid incubations were performed using primary female paired subcutaneous and omental adipose tissue. All steroids were quantified by UHPLC-MS/MS.

Results: Increasing the ratio of HSD11B1 to AKR1C3 expression prevented the activation of 11KA4 to 11KT by AKR1C3, instead resulting in increased HSD11B1-catalyzed conversion of 11KA4 to 11OHA4, an inactive metabolite. Inhibition of HSD11B1 in SGBS and primary adipose tissue resulted in the accumulation of 11KT.

Discussion and Conclusion: HSD11B1 modulates the activation of 11-oxygenated androgens by AKR1C3, with the inhibition of HSD11B1 leading to the accumulation of the potent androgen 11KT. These findings may explain why HSD11B1 inhibitors, that are used to inhibit glucocorticoid activation, have not had the desired effects in the treatment of metabolic syndrome as increased 11KT may have metabolically adverse effects that counteract the potentially metabolically beneficial reduction of glucocorticoid activation.

References: [1]Barnard et al. (2018) *J. Steroid Biochem. Mol. Biol.* **183**, 192–201; [2]Pretorius et al. (2016) PLoS ONE 11(7): e0159867.

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