PERIPHERAL METABOLISM OF THE ADRENAL STEROID 11β-HYDROXYANDROSTENEDIONE YIELDS THE POTENT ANDROGENS 11KETO-TESTOSTERONE AND 11KETO-DIHYDROTESTOSTERONE

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The adrenal androgen precursors DHEA and androstenedione (A4) play an important role in the development and progression of castration resistant prostate cancer (CRPC) as they are converted to dihydrotestosterone (DHT) by steroidogenic enzymes expressed in CRPC tissue. We have recently shown that the adrenal C19 steroid 11β-hydroxyandrostenedione (11OHA4) serves as a precursor to the androgens, 11-ketotestosterone (11KT) and 11-keto-5α-dihydrotestosterone (11KDHT), and that the latter two steroids could play a role in CRPC. The aim of this study was therefore to characterise 11KT and 11KDHT in terms of their androgenic activity.

Competitive whole cell binding assays revealed that 11KT and 11KDHT bind to the human androgen receptor (AR) with affinities similar to that of testosterone (T) and DHT. Transactivation assays on a synthetic androgen response element (ARE) demonstrated that the potencies and efficiencies of 11KT and 11KDHT are comparable to that of T and DHT, respectively. Moreover, we show that both 11KT and 11KDHT induce the expression of AR-regulated genes (KLK3, TMPRSS2 and FKBP5) and cellular proliferation in the androgen dependent prostate cancer cell lines, LNCaP and VCaP. In most cases, 11KT and 11KDHT upregulated AR-regulated gene expression and increased LNCaP cell growth to a significantly higher extent than T and DHT. Mass spectrometry-based proteomics revealed that 11KT and 11KDHT, like T and DHT, results in the upregulation of multiple AR-regulated proteins in VCaP cells, with 11KDHT regulating more AR-regulated proteins than DHT. Using ultra-performance convergence chromatography tandem mass spectrometry (UPC²-MS/MS) we subsequently found that the apparent increased androgenic activity observed for 11KT and 11KDHT in both LNCaP and VCaP cells was likely due to the significantly lower rate of metabolism observed for these steroids as compared to T and DHT, respectively.

Taken together, our data clearly shows that 11KT and 11KDHT are potent and efficacious androgens, comparable to T and DHT. Most importantly, the reduced rate of metabolism observed for these steroids suggest that they have the potential to remain active longer than T and DHT, and in so doing drive the expression of AR-regulated genes and cell growth to a greater degree than equal concentrations of T or DHT. The role of 11OHA4 as an androgen precursor can therefore no longer be overlooked when considering androgen dependent diseases such as CRPC.

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