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PHARMACOLOGY

How abiraterone works

New research shows that abiraterone is converted to a metabolite that has a wider range of inhibitory activity and might be more clinically effective in the treatment of patients with prostate cancer than abiraterone itself.

Abiraterone is a steroidal compound that interferes with androgen synthesis by blocking the *CYP17A1*-expressed enzyme 17α-hydroxylase/17,20-lyase (CYP17A1). Inhibition of 17α-hydroxylase suppresses hydroxylation of pregnenolone and progesterone at C17. Block of 17,20-lyase limits the subsequent conversion of the hydroxylated metabolites to dehydroepiandrosterone and androstenedione, respectively, resulting in decreased tumour testosterone and dihydrotestosterone levels.

"Given the steroidal structure of abiraterone, we suspected that this agent would be metabolized by a steroidogenic enzyme to a novel metabolite: Δ^4-abiraterone (D4A)," explains Nima Sharifi, senior author of the paper, which was recently published in *Nature*. Specifically, abiraterone shares its Δ^5, 3β-OH structure with physiological substrates of the 3β-hydroxysteroid dehydrogenase (for example dehydroepiandrosterone), making abiraterone susceptible to conversion by that enzyme. The resulting D4A would have structural elements that are identical to testosterone, enabling it to interact with the androgen receptor (AR) and other enzymes involved in the steroidogenic pathway, but possibly retain abiraterone's CYP17A1-inhibitory function.

In their study, the researchers first demonstrated that D4A was present in serum from patients with prostate cancer who receive abiraterone acetate. *In vitro*, D4A was only detectable when 3β-hydroxysteroid dehydrogenase was overexpressed, highlighting the dependency of the conversion on the presence of this enzyme. In addition, the team discovered that D4A was able to inhibit several enzymes involved in the androgen synthesis pathway, including 3β-hydroxysteroid dehydrogenase itself, CYP17A1 and steroid 5α-reductase, some of which were not blocked by abiraterone.

Notably, a competition assay demonstrated that the affinity of D4A to the AR is comparable to that of enzalutamide. Abiraterone is known to only have limited affinity for the AR. Inhibition by D4A of dihydrotestosterone-induced AR binding of regulatory elements of, for example, *TMPRSS2* was slightly inferior to enzalutamide, but inhibition of expression of AR target genes and of dihydrotestosterone-induced cell growth was equivalent for D4A and enzalutamide. "D4A blocks CYP17A1 as well as its parental drug abiraterone, but also inhibits additional enzymes required for dihydrotestosterone synthesis," summarizes Sharifi. "It also directly blocks the AR at a level comparable to enzalutamide, the most potent antagonist used in the clinic at the moment."

The team also sought to validate their *in vitro* findings in mouse models of prostate cancer. In their first study, VCaP xenografts were grown subcutaneously in orchiectomized mice in whom dehydroepiandrosterone was supplemented via an implanted pellet. The time from initiation of treatment to >20% increase in tumour volume was significantly longer for D4A treatment in comparison with abiraterone acetate treatment ($P=0.011$). In a second study, using the same method but C4-2 cell xenografts, treatment with D4A was superior to both abiraterone acetate and enzalutamide treatment ($P=0.01$ and $P=0.02$, respectively).

Sharifi highlights two major implications of these results that could affect current clinical practice. "First, direct treatment with D4A should provide better clinical benefit in men with prostate cancer than giving the parent compound abiraterone acetate, as is current practice. Second, measurement of D4A levels might serve as a biomarker of response or resistance to abiraterone." In their paper, the authors remark that the mechanisms that confer resistance to abiraterone in patients have not been fully clarified to date, but that the potential clinical utility of D4A might be dependent on the exact nature of these mechanisms.

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Original article Li, Z. *et al.* Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. *Nature* doi:10.1038/nature14406