Corticosteroid Biosynthesis Revisited

Substrate Specificity of Steroid-21-Hydroxylase

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ABSTRACT

- Cytochrome P450 enzymes (CYP) are highly efficient biocatalysts
- CYP21 is crucial in the formation of corticosteroids out of progestins
- 3-oxo group as strict requirement for hydroxylation by CYP21
- biosynthesis of 21-hydroxyprogrenolone not from pregnenolone

METHODS

- Biotransformation experiments were performed with a fission yeast expressing human CYP21A2 (CAD75) in a whole-cell biotransformation assay
- Progesterone, pregnenolone and their corresponding 17-hydroxy analogs were used as substrates
- Analysis by GC-MS as TMS-derivatives
- Molecular docking were performed using GOLD software (CYP21A2 co-crystallized with progesterone)

RESULTS

- 21-hydroxylation of (17OH-)progesterone successful
- 21-hydroxylation of (17OH-)pregnenolone not prosperous
- Essential interaction between 3-oxo and Arg234 of CYP21 shown by molecular docking experiments

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Fig. 1 Substrate binding to the active site of CYP21A2. Progesterone binding mode from x-ray structure (A). Suggested binding modes of pregnenolone (B), 17OH-Progesterone (C) and 17OH-Pregnenolone (D) obtained from docking.