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Steroid hormone biosynthesis meets biotechnology

Key words: cytochromes P450, steroid hormone biosynthesis, test systems

Six cytochromes P450 are involved in steroid hormone biosynthesis. We investigated the regulation of crucial steps by protein-protein interactions as well as steroid hormone intermediates. Special attention is given to glucocorticoid and mineralocorticoid formation catalyzed by CYPs of the CYP11B subfamily. Molecular genetic and biochemical analyses of patients with defects in theses CYPs were performed. Since CYP11B2 and CYP11B1 are targets for the development of drugs against hypertension, congestive heart failure and metabolic syndrome, systems for testing new potential drugs had to be developed. We were able to establish reliable test systems using stable cell cultures, yeast expression and purified proteins. In addition, to better understand structure-function relationships of steroid hydroxylases, corresponding bacterial enzymes have been cloned and analyzed. The structural basis for the regio- and stereo-selectivity of hydroxylation by human and bacterial steroid hydroxylases was characterized using computer modeling, protein design and directed evolution of steroid hydroxylases. Furthermore, protein crystallization revealed the structural basis for the stereo- and regio-selectivity of hydroxylation of steroid molecules. Finally, by analyzing CYPs for their potential to hydroxylate steroids and using the possibilities of protein design and evolution, important results for the application of these enzymes in biotechnology for the sustainable production of drugs were obtained.

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