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Author	青山, 由利(Aoyama, Yuri) 吉田, 雄三(Yoshida, Yuzo) 園田, よし子(Sonoda, Yoshiko) 佐藤, 良博(Sato, Yoshihiro)
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Metabolism of 32-Hydroxy-24,25-dihydrolanosterol by Purified Cytochrome P-450$_{14DM}$ from Yeast*

Yuri AOYAMA**, Yuzo YOSHIDA**, Yoshiko SONODA and Yoshihiro SATO

青山由利**, 吉田雄三**, 園田よし子, 佐藤良博

Metabolism of 32-hydroxy-24,25-dihydrolanosterol (lanost-8-ene-3β-32-diol), a posturated intermediate of the 14α-demethylation (removal of C-32) of 24,25-dihydrolanosterol (lanost-8-en-3β-ol), by a reconstituted system consisting of yeast cytochrome P-450 which catalyzes lanosterol 14α-demethylation (P-450$_{14DM}$) and NADPH-cytochrome P-450 reductase was studied. The reconstituted system converted both 32-hydroxy-24,25-dihydrolanosterol and 24,25-dihydrolanosterol to 4,4-dimethyl-5α-cholesta-8,14-dien-3β-ol, the 14α-demethylated product of the latter. The metabolism of these compounds was inhibited by a low concentration of ketoconazole which is a potent P-450$_{14DM}$ inhibitor. Affinity of P-450$_{14DM}$ for 32-hydroxy-24,25-dihydrolanosterol was about 20 times higher than for 24,25-dihydrolanosterol and the cytochrome metabolized the former about 4 times faster than the latter under experimental conditions. Spectral analysis suggested that the 32-hydroxy group of 32-hydroxy-24,25-dihydrolanosterol interacted with the heme iron of the oxidized cytochrome and this interaction might support the high affinity of this compound for the cytochrome. These lines of evidence indicate that 32-hydroxy-24,25-dihydrolanosterol is the intermediate of the 14α-demethylation of 24,25-dihydrolanosterol by P-450$_{14DM}$. It is also clear that the cytochrome catalyzes further metabolism of the 32-hydroxylated intermediate to the 14α-demethylated product with higher efficiency than the 32-hydroxylation of the substrate. P-450$_{14DM}$ is thus classified as lanosterol C_{14}-C_{32} lyase.

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** 武庫川女子大学薬学部