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Identification of 7 α ,24-Dihydroxy-3-oxocholest-4-en-26-oic and 7 α ,25-Dihydroxy-3-oxocholest-4-en-26-oic Acids in Human Cerebrospinal Fluid and Plasma

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Abstract

Dihydroxyoxocholestenoic acids are intermediates in bile acid biosynthesis. Here, using liquid chromatography – mass spectrometry, we confirm the identification of $7\alpha,24$ -dihydroxy-3-oxocholest-4-en-26-oic and $7\alpha,25$ -dihydroxy-3-oxocholest-4-en-26-oic acids in cerebrospinal fluid (CSF) based on comparisons to authentic standards and of $7\alpha,12\alpha$ -dihydroxy-3-oxocholest-4-en-26-oic and $7\alpha,x$ -dihydroxy-3-oxocholest-4-en-26-oic (where hydroxylation is likely on C-22 or C-23) based on exact mass measurement and multistage fragmentation. Surprisingly, patients suffering from the inborn error of metabolism cerebrotendinous xanthomatosis, where the enzyme CYP27A1, which normally introduces the (25R)26-carboxylic acid group to the sterol side-chain, is defective still synthesise $7\alpha,24$ -dihydroxy-3-oxocholest-4-en-26-oic acid and also both 25R- and 25S-epimers of $7\alpha,12\alpha$ -dihydroxy-3-oxocholest-4-en-26-oic acid. We speculate that the enzymes CYP46A1 and CYP3A4 may have C-26 carboxylase activity to generate these acids. In patients suffering from hereditary spastic paraplegia type 5 the CSF concentrations of the $7\alpha,24$ - and $7\alpha,25$ -dihydroxy acids are reduced, suggesting an involvement of CYP7B1 in their biosynthesis in brain.

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