Cholesterol Metabolism in SPG5: Potential for Diagnosis and Therapy

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The molecular determinant of hereditary spastic paraplegia type 5 (SPG5) is a deficiency in the enzyme oxysterol 7α-hydroxylase, also known as CYP7B1. CYP7B1 is the second enzyme in the acidic pathway of bile acid synthesis, it introduces a 7α-hydroxy group into side-chain oxidised forms of cholesterol. In this presentation, we show how SPG5 can be readily diagnosed by liquid chromatography – mass spectrometry (LC-MS) methods from small quantities of blood plasma (<100 µL). In SPG5 there is a large build up of the CYP7B1 substrates (25R)26-hydroxycholesterol (also called 27-hydroxycholesterol) and 3β-hydroxycholest-5-enoic acid, while a major reduction in the formation of 3β,7α-dihydroxycholest-5-enoic acid (3β,7α-diHCA), one of the products of CYP7B1. Another disease which can present with spastic paraplegia in later life is cerebrotendionous xanthomatosis (CTX). CTX is a consequence of a deficiency in the enzyme sterol 27-hydroxylase (CYP27A1), the first enzyme of the acidic pathway of bile acid biosynthesis which first introduces a hydroxy group at the terminal carbon of the cholesterol side-chain then converts it to a carboxylic acid. In CTX the acidic bile acid synthesis pathway is essentially "knocked out". Again, CTX is readily diagnosed by LC-MS methods.

CTX and SPG5 can both present with spastic paraplegia in later life and both show drastic reductions in concentration of 3β,7α-diHCA in both plasma and CSF, the fluid surrounding the brain. We postulated that 3β,7α-diHCA is a neuroprotective molecule and its reduced abundance in CSF and brain leads to the loss of motor neurons. Using a combination of studies in zebrafish and in mouse brain progenitor cultures we could show that 3β,7α-diHCA is protective towards motor neurons and when introduced to embryonic brain reduces motor neuron cell loss. We suggest that 3β,7α-diHCA or is relatives may have value in the treatment of HSP.

Acknowledgement

Zebrafish and cell culture work was performed in Karolinska Institute in collaboration with Ernest Arenas and Spyridon Theofilopoulos.

Reference

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