The Biochemical Basis of Spastic Paraplegia Type 5

Rebecca Schüle, Tom Wahlig Symposium 2011, Münster

Hereditary spastic paraplegias (HSP) comprise a group of neurodegenerative disorders characterized by slowly progressive lower limb spasticity and weakness due to degeneration of the pyramidal tracts. HSPs are genetically highly heterogeneous. To date almost 50 different genetic loci (SPG1-SPG48) and 22 HSP genes have been identified.

Recently mutations in the Oxysterol-7□-Hydroxylase gene CYP7B1 were identified to cause SPG5 {Tsaousidou, 2008}. SPG5 is inherited in an autosomal-recessive fashion and is associated with a predominantly pure childhood onset HSP; additional complicating features like optic atrophy and cerebellar ataxia are occasionally reported. 18 different CYP7B1 mutations in ~30 patients from 22 families have been reported so far {Biancheri, 2009; Goizet, 200; Schule, 2009; Tsaousidou, 2008}.

CYP7B1 is broadly expressed in liver, kidney, brain and endocrine tissue. It catalyzes the 7α-hydroxylation of *oxysterols* (25-hydroxycholesterol, 27-hydroxycholesterol) as well as *neurosteroid hormones* (dehydroepiandrosterone, pregnenolone) {Rose, 1997}; in addition it 6α-hydroxylates the estrogen receptor agonist 5α-androstane-3β,17β-diol {Sundin, 1987}.

The main metabolic route for cholesterol is degradation to polar bile acids that can be intestinally excreted. The bulk of cholesterol is degraded via the so-called "classic" pathway that is initiated by 7α-hydroxylation of cholesterol by CYP7A1. In the alternative „acidic" pathway, oxysterols are hydroxylated by CYP7B1.

We have shown, that loss of function mutations in CYP7B1 lead to accumulation oft he CYP7B1 substrates – oxysterols. In contrast to cholesterol, oxysterols can pass the blood brain barrier. They therefore also accumulate in CSF where concentration oft he oxysterol 27-hydroxycholesterol has been found to be about 40fold of normal concentrations {Schüle, 2010}.

Oxysterols, especially 27-OHC, have been repeatedly linked to neurodegeneration. They have a proapoptotic effect on cultured neuroblastoma cells, macrophages and smooth muscle cells {Rantham Prabhakara, 2008; Riendeau, 2009}. 27-OHC is proamyloidogenic by stimulating β-secretase activity {Famer, 2007} and cause Alzheimer disease (AD)-like pathology in human neuroblastoma SH-SY5Y cells {Prasanthi, 2009;Rantham Prabhakara, 2008}. 27-OHC has been shown to be elevated in brains of patients with AD {Heverin, 2004} as well as plasma of Parkinson's disease patients {Seet, 2010}. The spinal chord, that does not express CYP46A1, the main cholesterol-metabolizing enzyme in the brain, may be especially prone to 27-OHC effects.

Therapeutic modification of the cholesterol metabolism may provide a unique opportunity to modify disease progression in this otherwise incurable disease.