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Secondary ganglioside GM2 accumulation in mucopolysaccharidoses

In vivo, the lysosomal degradation of GM2 is catalyzed by HexA and its cofactor GM2AP, a lipid binding and transfer protein. The inherited deficiency of each of them causes a fatal neuronal accumulation of ganglioside GM2 in GM2-gangliosidosis [1,2]. The GM2-splitting activity of HexA does not only need GM2AP as an essential cofactor, but is furthermore strongly regulated by lipids of the GM2 carrying ILV (Intralysosomal Luminal Vesicle)-membranes and by other metabolites. For instance, the HexA catalyzed GM2 cleavage is heavily inhibited by chondroitin-6-sulfate and other primary storage compounds in some MPS diseases [3] and by sphingomyelin in ASM deficient Niemann- Pick disease [4]. Still, there is a good correlation between the clinical course of the disease on one hand and the turnover of its natural and radiolabeled GM2 in cultured patient's fibroblasts on the other hand, as assayed by their residual GM2-cleaving activity in vitro [5]. However, there is no correlation with the hydrolysis of the soluble artificial substrate 4MU-β-GlcNAc which is useful to assay the combined activities of hexosaminidases A, B and S [6,7].

Unfortunately, Derrick-Roberts et al. [9] do not correlate their GM2-relevant observations with the ganglioside GM2 splitting activity of their samples, but with their 4MU-β-GlcNAc hydrolyzing activity, which is not relevant at all [4]. Besides other correlations, genotype and the secondary accumulation of ganglioside GM2 in brains of MPS mice Type I, IIIA, and VII were correlated with the total hexosaminidase activity in the samples as assayed with the unspecific artificial soluble substrate 4MU-β-GlcNAc, which is not specific for the GM2-cleaving hexA, but is hydrolyzed by both, hexA and hexB. The latter hexB is not involved in GM2 degradation [7], which is supported by the observation, that HexB activity is increased more than twofold in postmortal human Tay-Sachs brain tissue, without preventing a fatal GM2 storage [8].

The authors write in their Abstract, “that genotype and residual enzyme activity are not indicative of severity of disease pathology in MPS disease and there exists a window when there are considerable storage products without detectable functional deficits, which may allow an alteration to occur with therapy”. This and further related statements in the text are not funded by experimental data. They are incorrect and need a correction.

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