S21-5 Intracerebroventricular replacement effects of modified recombinant human enzyme on lysosomal disease model developing neurological manifestations

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Tay-Sachs disease and Sandhoff disease are lysosomal storage diseases caused by the mutations in *HEXA* and *HEXB* genes encoding α– and β-subunits of β-hexosaminidase A (HexA, αβ), respectively. These disorders are characterized by excessive accumulation of GM2 ganglioside (GM2) in the brain and neurological symptoms, and there is no effective treatment for these diseases. We have demonstrated that the yeast-derived recombinant human HexA carrying the oligosaccharides with terminal mannose-6-phosphate (M6P) residues could have therapeutic effects on Sandhoff disease model mice on intracerebroventricular (*icv*) administration. The HexB (ββ), which has structural similarity to HexA, is a very stable isozyme that could be incorporated into cells through binding with M6P receptors, although it does not exhibit GM2-degrading activity. Here we designed a modified HexB (β'β'), which should have substrate specificity similar to HexA and bind to GM2 activator protein essential for intracellular GM2 degradation, on the basis of structural comparison between HexA and HexB. We established a CHO cell line stably secreting the modified HexB that has HexA-like catalytic activity and the stability *in vitro*. The modified HexB was incorporated into the cultured fibroblasts derived from the patients to restore the HexA-like activity and reduce the accumulated GM2. It also reduced the GM2 accumulated in the brain parenchyma of Sandhoff disease model mice on *icv* administration. The novel modified HexB should be applicable for brain-directed enzyme replacement therapy for Tay-Sachs disease as a low-antigenic enzyme drug.