Insulin Receptor Antibody-α-N-Acetylglucosaminidase Fusion Protein Penetrates the Primate Blood-Brain Barrier and Reduces Glycosoaminoglycans in Sanfilippo Type B Fibroblasts.

Mucopolysaccharidosis Type IIIB (MPSIIIB) is caused by mutations in the gene encoding the lysosomal enzyme, α-N-acetylglucosaminidase (NAGLU). MPSIIIB presents with severe disease of the central nervous system, but intravenous NAGLU enzyme replacement therapy has not been developed because the NAGLU enzyme does not cross the blood-brain barrier (BBB). A BBB-penetrating form of the enzyme was produced by re-engineering NAGLU as an IgG-enzyme fusion protein, where the IgG domain is a monoclonal antibody (mAb) against the human insulin receptor (HIR). The HIRMAb traverses the BBB via transport on the endogenous insulin receptor and acts as a molecular Trojan horse to ferry the fused NAGLU across the BBB from blood. The NAGLU was fused to the carboxyl terminus of each heavy chain of the HIRMAb via an extended 31-amino acid linker, and the fusion protein is designated HIRMAb-LL-NAGLU. The fusion protein retains high affinity binding to the HIR, and on a molar basis has an enzyme activity equal to that of recombinant human NAGLU. Treatment of MPSIIIB fibroblasts with the fusion protein normalizes intracellular NAGLU enzyme activity and reduces sulfate incorporation into intracellular glycosoaminoglycan. The fusion protein is targeted to the lysosomal compartment of the cells as shown by confocal microscopy. The fusion protein was radiolabeled with the [(125)I]-Bolton-Hunter reagent and injected intravenously in the adult Rhesus monkey. The fusion protein was rapidly cleared from plasma by all major peripheral organs. The high brain uptake of the fusion protein, 1% injected dose/brain, enables normalization of brain NAGLU enzyme activity with a therapeutic dose of 1 mg/kg. The HIRMAb-LL-NAGLU fusion protein is a new treatment of the brain in MPSIIIB, which can be administered by noninvasive intravenous infusion.