Alteration of glycoprotein glycans often contributes to a wide variety of diseases. Here we focused on the N-glycans of amyloid precursor protein whose cleaved fragment, beta-amyloid, is related to the pathology of Alzheimer's disease (AD). We previously determined the N-glycan structures of normal and mutant amyloid precursor proteins (the Swedish type and the London type) (Glycoconj. J., 25, 775-786, 2008). In comparison with normal amyloid precursor protein, mutant amyloid precursor proteins had higher contents of bisecting GlcNAc. The results prompted us to measure GnT-III mRNA levels in the brains of AD, because N-acetylgalcosaminyltransferase III (GnT-III) is the glycosyltransferase responsible synthesizing bisecting GlcNAc. Interestingly, GnT-III mRNA expression was increased in AD brains. Furthermore, b-amyloid treatment increased GnT-III mRNA expression in Neuro2a cells. Then we examined the influence of bisecting GlcNAc on the production of beta-amyloid. Both beta-amyloid 40 and beta-amyloid 42 were significantly decreased in GnT-III transfected Neuro2a cells unexpectedly. When activities and expression levels of secretases were analyzed in GnT-III transfectant cells, alpha-secretase activity was increased and BACE expression was decreased. These results suggest that up-regulation of GnT-III in AD may represent an adaptive response to protect from additional beta-amyloid production.