

## BIOACTIVE CONFORMATIONS OF GANGLIOSIDE TYPE OLIGOSACCHARIDES BINDING TO MYELIN ASSOCIATED GLYCOPROTEIN (MAG) FROM TRANSFER NOE EXPERIMENTS

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Myelin-associated glycoprotein (MAG) is a member of the siglec family, a group of sialic acid-binding Ig like lectins that is characterized by sequence homology with members of the IgSF family. It is a key factor in the complex regulation of the development and regeneration of the central nervous system (CNS), and it has been shown that binding to gangliosides such as GD1 $\alpha$ , GT1b, or GQ1b $\alpha$  leads to the inhibition of neurite outgrowth. Therefore, we studied the binding of synthetic fragments of GQ1b $\alpha$  to MAG employing transfer NOE (trNOE) experiments. The experiments yielded bioactive conformations for the trisaccharide  $\alpha$ -D-Neu5Ac-(2,3)- $\beta$ -D-Gal-(1,3)- $\beta$ -D-Gal-O(CH<sub>2</sub>)<sub>2</sub>SiMe<sub>3</sub>, the tetrasaccharide  $\alpha$ -D-Neu5Ac-(2,3)- $\beta$ -D-Gal-(1,3)-[ $\alpha$ -D-Neu5Ac-(2, 6)]- $\beta$ -D-GalNAc-O(CH<sub>2</sub>)<sub>2</sub>SiMe<sub>3</sub>, the tetrasaccharide  $\alpha$ -D-Neu5Ac-(2,3)- $\beta$ -D-Gal-(1,3)-[ $\alpha$ -D-Neu5Ac-(2, 6)]- $\beta$ -D-Gal-O(CH<sub>2</sub>)<sub>2</sub>SiMe<sub>3</sub>, and the tetrasaccharide mimic  $\alpha$ -D-Neu5Ac-(2,3)- $\beta$ -D-Gal-(1,3)-[(S)-Lac-(2,6)]-Cyc. A homology model of MAG allowed docking of the saccharide ligands into the hypothetical binding pocket of MAG. On the basis of these models we performed a quantitative analysis of the bound conformations of the tetrasaccharides and the tetrasaccharide mimic using the program CORCEMA. Our study indicates that all saccharides are bound in the Sialyl Lewis<sup>x</sup>/E-Selectin type bioactive conformation, and that Lys67 is critical for the binding of the tetrasaccharide fragments of GQ1b $\alpha$ . This important result is the basis for ongoing research aiming at the design of potent MAG inhibitors.

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