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研究報告 :

(a) Abstract

Biological meanings of diversity and complexity of glycan chains comprising glycoproteins and glycolipids have been a central issue in glycoscience. As nearly three decades already passed after the research filed of glycobiology emerged, paradigm shift from diversity/complexity to commonality/simplicity would be required to open new era of this research field.

So-called hexosamine biosynthetic pathway (HBP) is highly important in producing a variety of glycans. It generates UDP-GlcNAc, a donor substrate of a group of enzymes, *N*-acetylglucosaminyltransferases (GlcNAc-Ts). UDP-GlcNAc is also an important precursor of sialic acid biosynthesis pathway, a downstream event of HBP. Sialic acid containing molecules are highly important in a number of recognition events in biological systems. In this case, UDP-GlcNAc is converted to *N*-acetylmannosamine (ManNAc) by an isomerizing enzyme (GNE) which catalyzes epimerization at of the 2-position. Dysfunction of the HBP results in various problems in multicellular living systems, in association with the shortage of sialic acid. Several studies in recent years reported results that point toward potentials of simple monosaccharides, which are either related to or able to perturb HBP as master key glycol-molecules.

To this end, we conducted systematic synthesis of ManNAc derivatives as potential 1) inducers of orexin neurons and 2) modulators of epigenetic control of gene expression. Although orexin receptor antagonists and agonists have been examined as drug candidates of various diseases such as narcolepsy, depression and metabolic disorders, direction of our research is clearly distinct. Our study revealed that the HCRT gene was silenced by the hyperglycemia condition, and ManNAc and its derivatives were useful for restoring the orexin neurons. Supporting evidences were provided which indicate that ManNAc derivatives exhibit the effects in a sialic acid-independent manner. We believe our results are influential in opening a novel research field ranging carbohydrate chemistry, glycobiology, epigenetics and psychiatry.

