

“BIOCHEMICAL ENGINEERING” OF THE N-ACETYL SIDE CHAIN OF SIALIC ACID – A NEW TOOL TO MODIFY CELLULAR FUNCTIONS

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The crucial metabolic precursor of N-acetylneuraminic acid is N-acetylmannosamine (=ManNAc), which is converted into N-acetylneuraminic acid in four highly specific enzymic steps, starting with the bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE). The activation to CMP-sialic acid occurs, surprisingly, in the cell nucleus. This activated intermediate may function as transcription modifier. It passes from the nucleus to the Golgi apparatus, where it is used for synthesis of the glycans of glycoproteins and glycolipids. We found a simple biochemical procedure for modifying the N-acetyl side chain of N-acetylneuraminic acid (a sialic acid; about 50 sialic acids are known). The physiological precursor, ManNAc, is replaced by N-propionylmannosamine (=ManNProp), which possesses a slightly extended side chain (by one methylene group). The biosynthetic enzymes appear to be relatively unspecific with respect to modification of the side chain, since all cell-types studied so far investigated convert ManNProp into N-propionylneuraminic acid. The side chain may be modified also by the insertion of several methylene groups, or by use of N-levulinoylmannosamine (which possesses a reactive keto group) or N-acylmannosamine carrying an azido group as shown by Bertozzi's group.

The biosynthesis of these new neuraminic acids was surprising, but even more surprising is their subsequent influence on cellular functions. Stimulation of neurite growth, inhibition of the uptake of influenza A viruses by lymphoma cells, or an increased expression of sialyl-Lewis^x-factor in vitro and in vivo could be observed after supplying with ManNProp. Moreover, a pronounced increase in dopamine synthesis was observed in PC12 cells. Therefore, N-propionylmannosamine generates a metabolic state that counteracts Parkinson syndrome.

These substances appear to have little or no toxicity, since no harmful effects are observed after their administration to rats or mice for several weeks.

References:

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