A. Introduction

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Sialic acids comprise a family of derivatives of neuraminic acid (5-amino-3,5-dideoxy-**D**-*glycero*-**D**-*galacto*-nonulosonic acid) occurring widespread in nature, especially in the animal kingdom. From an evolutionary point of view, they probably have a long history, dating back to precambrian times, as they have already been found in *Echinodermata* (chapter B). It took a number of years (1936–1962) to establish the structure of N-acetylneuraminic acid by chemical and enzymic means, as has been reviewed by GOTTSCHALK (1972), LEDEEN and YU (1976) and TUPPY and GOTTSCHALK (1972).

In the past 20 years the number of well-characterized sialic acids has increased to 23. Largely due to the enormous progress in analytical instrumentation such as gas-liquid chromatography in combination with mass-spectrometry (chapter F) and nuclear magnetic resonance spectroscopy (chapter G), many sialic acids could be identified, even when present in small amounts in more or less complex mixtures. As substituents at the amino group acetyl and glycolyl residues have been found. The hydroxyl functions show a greater variety in the type of substituents, since acetyl, lactyl, phosphate, sulfate and methyl groups have been shown to occur. Furthermore, unsaturated N-acetylneuraminic acid has been detected as a natural compound.

The different sialic acids exhibit an interesting species- and tissue-specific distribution. However, the biological implications of the various sialic acids and of the different substitution patterns are not fully understood. There is some evidence that different N and O substituents influence enzymic reactions, particularly in the catabolic pathways of sialoglycoconjugates (chapter I). Moreover, effects of substitution of sialic acids on immunological properties of sialoglycoconjugates have been observed (chapter J). Further elucidation of the role of sialic acid modifications remains a challenge for future research.

Sialic acids rarely occur as free molecules, they are usually α-glycosidically linked to carbohydrate chains. They can be attached to different positions of various monosaccharides including sialic acids. By consequence, they can occupy

terminal as well as internal positions in the carbohydrate chain. The variability in binding type, too, gives rise to physico-chemically distinguishable sialic acids and may thus contribute to the great diversity of biological phenomena sialic acids are involved in. A further structural and functional modulation may be obtained by introducing substituents on sialic acid residues. In higher organisms, sialic acids frequently occur in terminal positions in carbohydrate chains of glycoconjugates. This feature may be relevant for the architecture and function of the cell membrane. The spatial arrangement in conjunction with the different chemical aspects of glycosidically-bound sialic acids can be held responsible for phenomena such as the masking of antigenic sites or of recognition markers on cell surfaces. In addition, such sialic acids affect the dynamic properties of cell membranes, including their communication with the environment. However, these and possible other functions are only partially understood at the molecular level.

In evolutionary low organisms, which have no sialic acid, it would be interesting to study which compounds substitute for sialic acids. The solution of this question might provide further insight into the essential roles of sialic acids in cell function and may clarify the importance of the negative charge of sialic acids at physiological pH. The availability of mutants of cells from higher organisms lacking sialic acid would also be helpful in the investigation of the precise biological role of this sugar. The fact that such mutants have never been observed suggests that such a mutation is lethal.

The regulation of biological processes requires, as far as sialic acids are involved, effective control mechanisms of the metabolism of these substances. This can take place at genetic, enzymic and/or hormonal levels. Little is known of this fascinating area, although some feedback mechanisms and hormonal influences on the metabolism of sialic acids have been demonstrated (chapter I). Elucidation of metabolic regulations is relevant for an understanding of cell and tissue growth and differentiation, as well as of malignant transformation. There are indications that changes occur in sialic acid metabolism during the aging of mature cells. Several diseases are known, which involve abnormalities in sialic acid metabolism. Remarkable examples are sialuria and Salla's disease, which are accompanied by an urinary excretion of unusually large amounts of free sialic acids. The causes of these diseases have only been speculated upon. More information is available on sialidoses (chapter K), where genetic defects in sialidases are involved.

The introduction of exogeneous sialidase e.g. due to bacterial or viral infections can lead to a decrease in the amount of glycosidically bound sialic acids. Consequently, an exposure of cellular antigens may occur as well as an enhanced clearance of serum glycoproteins and cells (chapter J). In general, alterations in the activity of anabolic (sialyltransferases) or catabolic (exogeneous and endogeneous sialidases) enzymes of sialic acid metabolism may play a part in chronic, (auto)immunological diseases.

It is noteworthy that some low organisms like a few bacterial and protozoan species possess sialic acids. This may help these parasites to survive in the host. For a similar reason it may be advantageous for some microorganisms to have at their disposal catabolic enzymes of sialic acid metabolism like sialidase and N-acetylneuraminate lyase. Strikingly, many of these organisms are pathogenic for mammals. It could well be that sialidase is required for a faster spreading of

bacteria in tissues by an attack on sialic acid residues of cell surfaces. The role of sialidase for viral attachment to the host cell has long been known.

In connexion with these considerations, it is intriguing to ask whether the bacteria developed biochemical pathways for the synthesis of sialic acids independently, or whether they acquired the genome for the enzymes involved from host organisms. The similarity in the biosynthetic pathways leading to sialic acid in bacteria and in higher animals lends support to the latter possibility. It is tempting to presume that such a genome transfer is also responsible for the acquisition of sialidase and N-acetylneuraminate lyase by some bacteria. Comparison of the properties of these enzymes obtained from mammalian and bacterial sources does not contradict such an event.

Further research on the manifold chemical and biological aspects of sialic acids will contribute to the understanding of the molecular organization of living systems.

Bibliography

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