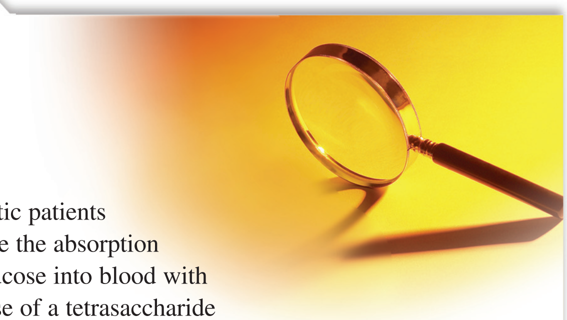
BIOCHEMISTRY IN PERSPECTIVE

Sweet Medicine



How does carbohydrate biochemistry impact human health? The importance of carbohydrates in human biological processes is emphasized by the following statistics: at least 200 genes code for glycan-processing enzymes, and at least 50% of all proteins are covalently linked to one or more carbohydrate groups. Thus it is not surprising that defects in glycan synthesis and degradation can have very serious health consequences. For example, there are at least 30 rare genetic diseases called *congenital disorders of glycosylation* (CDGs), in which various steps in N-glycan processing are defective. Other rare carbohydrate-related diseases include several forms of muscular dystrophy, as well as Tay-Sachs (p. 385) and Gaucher's diseases. Carbohydrates are now known to play roles in several more common illnesses.

For example, changes in the galactose content of the antibody class IgG have recently been shown to be directly related to the severity (i.e., the degree of inflammation) of juvenile arthritis. Additionally, recent evidence indicates that changes in glycosylation patterns accompany changes in the behavior of cancer cells. Infectious diseases are often initiated by the binding of pathogen CBPs to glycoconjugate receptors on host cell surfaces. Glycan research has increased the accessibility of these disorders to investigation.

Biological processes with prominent glycan involvement are potential targets for therapeutic intervention. With several notable exceptions, however, until the recent introduction of innovations that improved glycan analysis and synthesis technologies, attempts to develop carbohydrate-based therapies have failed. The most prominent examples of successful attempts are the DNA recombinant glycoprotein products erythropoietin (which stimulates red blood cell production) and tissue plasminogen activator (a blood-clot-dissolving serine protease, see Biochemistry in Perspective box on Enzymes and Clinical Medicine in Chapter 6), and heparin, a GAG that prevents blood clot formation. Currently, numerous carbohydrate-based drugs are either in use or in clinical trials. Among these are the following.

1. **Enzyme inhibitors**. Certain glycan molecules can be used to inhibit specific enzyme activities. For example, some diabetic patients reduce the absorption of glucose into blood with the use of a tetrasaccharide inhibitor of the intestinal enzyme α-glucosidase,
2. **Enzyme replacement**. The therapeutic replacement of missing enzymes can be effective only if the new enzymes can be targeted to their site of action within cells. The missing enzyme in Gaucher's disease (β-glucosidase) has been successfully engineered by altering its oligosaccharide group so that it binds to the intracellular mannose receptor that ensures delivery to lysosomes.
3. **Vaccines**. Vaccines, substances that protect against disease by triggering antibody production, are often composed of antigenic proteins. Despite current problems associated with large-scale synthesis, glycans are potentially useful in vaccine production because they have a lower risk of allergic reactions. In addition, they are more stable and therefore easier to convert into therapeutic agents. Because of their low immunogenic potential, glycan vaccines are usually composed of a glycan linked to certain proteins known to boost immune responsiveness. A glycan-based vaccine called Hib protects against infection by the bacterium *Hemophilus influenzae* type b, the leading cause of meningitis in children. Since its introduction, Hib has significantly reduced the occurrence of this potentially lethal disease.
4. **Redesigned drugs**. Careful analysis of the function and physiological processing of existing glycan-based drugs can result in the production of redesigned (or "second-generation") drugs. For example, the effectiveness of recombinant erythropoietin was increased by the attachment of additional N-linked glycans that both improved its biological activity and reduced its rate of excretion.

SUMMARY: Carbohydrate biochemistry provides insight into several human diseases. Carbohydrate biotechnology is being used to develop carbohydrate-based drugs and vaccines.