Introduction to Glyconutritionals*

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THE CODE OF LIFE

When you eat, how does your digestive tract know which food components to grab and send into the blood stream and which ones to allow to pass through? How do the filters in your kidneys choose the correct molecules to expel? Unlike machines, living organisms are coded to perform many complex "involuntary" functions. The more complex the organism, the more such functions it must perform to live and thrive.

Science and medicine have long tried to break the biocode by which the cells of the body communicate with one other in order for these complex functions to occur. This mysterious code is truly the language of life. Biochemistry is the chemistry of life. It is the science concerned with the various molecules found in living cells and organisms and with their chemical reactions. The aim of biochemistry is to explain, in molecular terms, the chemical processes of living cells.

The four major classes of biomolecules are proteins, nucleic acids, lipids (fats) and carbohydrates. For many years, scientists focused on proteins as the primary communication molecules. Early in this century, however, a theoretical mathematician at the Weisman Institute calculated the number of molecular configurations possible with protein molecules and the number of known chemical command signals needed to run the body. She concluded that there were not enough protein configurations possible to supply all the messages. Another code was required.

RESEARCH ON GLYCOPROTEINS AND THE CODE OF LIFE

In the 1960s, research first began to appear on glycoproteins, protein molecules bound with carbohydrate molecules. ("Glyco" means "sweet" and refers to sugars, or carbohydrates. These terms are interchangeable.) Glycoprotein molecules coat the surface of every cell with a nucleus in the human body. Glycolipids, carbohydrate molecules bound with lipid (fat) molecules, are another kind of glycoform, or glycoconjugate, found on cell surfaces. In Figure A below the hair-like strands protruding from the section of cell surface are glycoproteins. The gold component represents protein molecules; the red component represents carbohydrate molecules.

FIGURE A

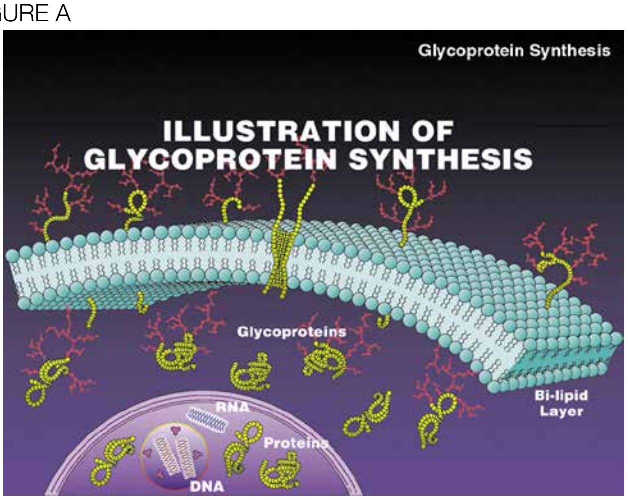


Figure D is drawn after the 1996 cover of Glycobiology: Official Journal of the Society of Glycobiology, Oxford University Press. The journal acknowledged permission to reprint the original illustration from Oxford GlycoSystems, Ltd.

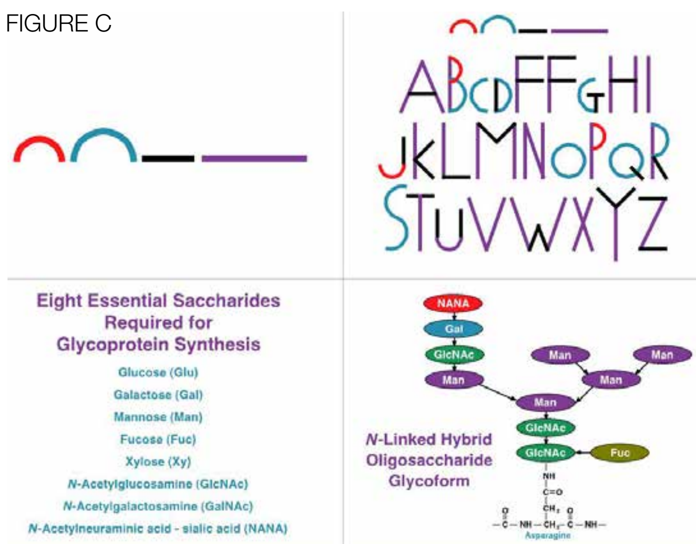
We now know that nature uses the carbohydrates on cell surface glycoconjugates as communication (or recognition) molecules. Carbohydrates are much more structurally complex than the simpler proteins. Many more molecular configurations are possible with a six-carbon sugar (e.g. glucose), which has two isomeric forms and six binding sites. For example, while only 24 oligopeptide configurations are possible with four peptides (proteins), more than 1000 different oligosaccharide configurations are possible with four carbohydrate molecules (1). So carbohydrate molecules provide the most specific form of biological information for the code of life.

Since the 1960s, the study of glycoconjugates has grown exponentially as the technological means to conduct the studies have been developed. Based on this research, by 1996 scientists had identified eight sugars found on human cell surface glycoforms that are involved in cellular recognition processes (2). Of the 200 such sugars occurring naturally in plants, to date only these eight had been identified as components of cellular glycoproteins (Figure B).

FIGURE B

For illustration purposes, molecular communication codes can be thought of like our own written language. Just as four different shapes can be combined to make many letters, and these letters can be combined to make many words, the different carbohydrate molecules combine within our bodies to make many cellular recognition "words" (Figure C). These precisely shaped words protrude from cell surfaces and are recognized and understood (or not understood) by neighboring cells through the "sense of touch".

FIGURE C

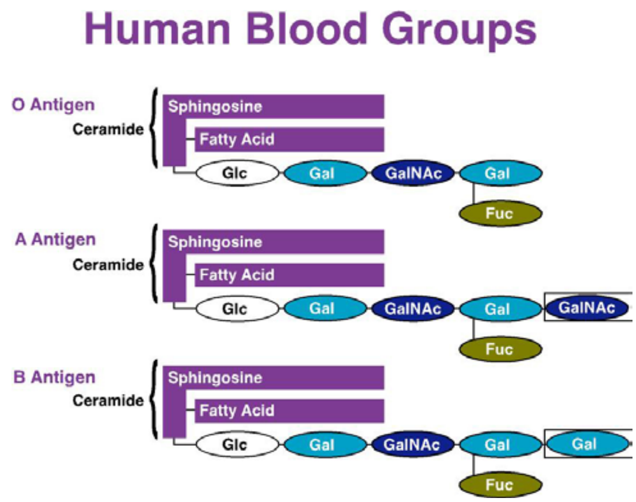


*This is a slightly abridged version of an article written in January 2000

SIGNIFICANCE OF THE SUGAR CODE ON GLYCOPROTEINS

The significance of these sugar components of glycoproteins is well illustrated by the different blood types. Figure D shows terminal glycoproteins in the various human blood groups. The only difference between Type O blood and Types A and B blood is that Types A and B contain an additional sugar molecule. Types A and B differ only in the terminal sugar. Type A contains N-Acetylgalactosamine (GalNAc), while type B contains galactose (Gal). Yet such a seemingly minor distinction makes the difference between life and death in a person given the wrong blood type (3).

FIGURE D

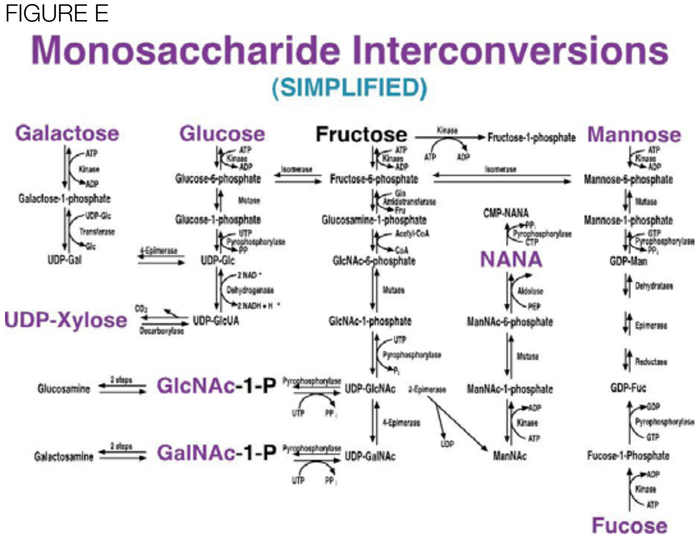


SOURCE OF THE SUGAR CODE ON GLYCOPROTEINS

If these sugar (glyco) molecules are so important, what is the source of them for our cells? What raw materials does the body use to build them? Ultimately, only plants can capture the sun's energy to produce the carbohydrates required by the body. Thus, the plants in our diet are the primary building blocks for the sugar portion of these molecules that are so vital to continued good health. A healthy body can break down plant carbohydrates, restructure them into small sugars, then use those sugars to build the glycoforms required for accurate cellular communication and overall wellness.

Enzymes are the tools the body uses to build the glyco-portion of glycoforms. Figure E illustrates the enzymes needed to convert one form of sugar to another in the body. Note that 15 enzymatic conversions are required to change galactose to fucose (4).

FIGURE E



LIMITATIONS OF ENZYMATIC CONVERSION TO BUILD THE SUGAR CODE

The effectiveness of the enzymatic conversion system to create the needed sugar molecules is not absolute. First, some individuals have inborn errors of metabolism. This means these individuals may be missing one or more of the enzymes needed to make the conversions. The conversion process also requires specific vitamins at certain steps, and these vitamins may be missing. Finally, the conversion process requires time and energy. Each step in the enzymatic conversion process for these sugars creates a new substrate that is one step closer to the needed molecule.

The following equation (Michaelis-Menten Equation) (Figure F), which defines the kinetic properties of most enzymes, demonstrates the energy expenditure required to make the conversions where V is the velocity of the reaction; Vmax is maximum velocity; [S] is substrate (sugar), concentration; and KM is the Michaelis constant. This equation shows that, in order to convert these sugars, the body expends energy. The more conversion steps required, the more energy is expended, and the speed at which a product is formed is proportional to available substrate (3).

FIGURE F

$$V = V_{max} \frac{[S]}{[S] + K_M}$$

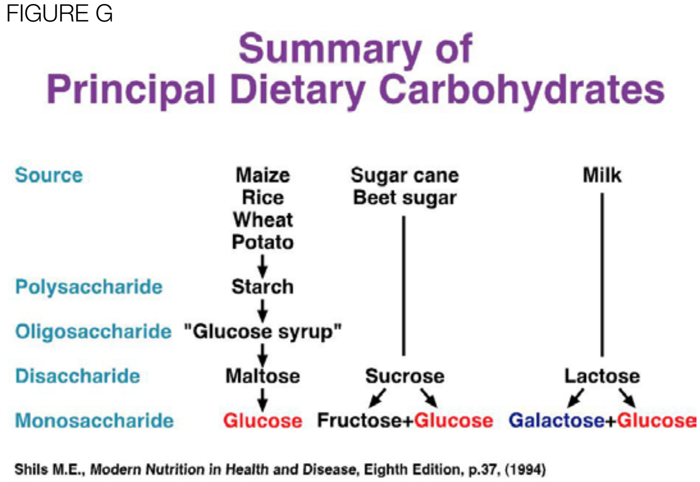
NUTRITIONAL SUPPLEMENTATION WITH SUGARS USED FOR GLYCOPROTEIN SYNTHESIS

Until now the fields of glycobiology and nutrition have never been adequately investigated together. This is true, even in light of 1) the above discussed current scientific knowledge concerning the importance of glycoproteins in cell-cell communication, 2) the importance of sugars in formation of glycoforms, and 3) in spite of the fact that diet is the major source of all carbohydrates.

Although current nutrition textbooks stress the importance of essential vitamins, minerals, proteins (amino acids) and fats in great detail, sugars are currently recognized only as a source of energy (5), not as substances essential to glycoform production for overall wellness.

Of the required eight sugars named in *Harper's Biochemistry*, only glucose and galactose are addressed in the classic nutrition texts; the other six are omitted. Modern nutrition textbooks give the principle sources of dietary carbohydrates as: 1) maize, rice, wheat, and potato which yield starches composed of glucose; 2) sugar cane and beet sugar which yield glucose; and 3) milk which yields galactose and glucose (Figure G) (5).

FIGURE G



Lactose-intolerant individuals who do not eat dairy products will be deficient even in galactose since the body manufactures galactose from the lactose in dairy products. The remaining six sugars used to make cellular words must either be synthesized by the body through the process described above or obtained from dietary supplements.

Glyconutritionals are dietary supplements designed to provide substrates for the body to use in building the glyco portion of glycoconjugates on cell surfaces. Glyconutritionals are designed to make the necessary sugars available to the cells quicker and in greater quantity.

The more substrate provided, the fewer steps the enzymatic conversion system has to take and the more the system functions at optimal capacity. At high substrate concentrations the rate of the reaction is maximized, i.e. V=Vmax (refer to equation above).

METABOLISM OF DIETARY SUGARS

Until recently, cellular use of dietary sugars for glycoform biosynthesis had not been studied because cellular sugars were theoretically assumed to be derived from glucose alone.(6-8) It was even theorized that when the necessary variety of sugars was consumed in the diet, the sugars were broken down into glucose and then rebuilt into the needed sugars in the cells. Note that this was a theory and had not been studied.

One of my professors told us that half of what we would learn in medical school would be wrong--he just don't know which half. Recent studies indicate that the "glucose alone" theory is falling into the wrong half.

A March 1998 published study showed that intact mannose molecules are rapidly absorbed from the intestine of rats into the blood, and mannose is cleared from the blood within hours. This study also showed that, contrary to current thinking, liver cells in tissue culture absorb most of the mannose for glycoprotein synthesis directly from mannose, not from glucose. One concludes from these experiments that mannose is absorbed, intact and unchanged, from the intestine into the blood and from the blood into the cells. These studies indicate, therefore, that dietary mannose may make a significant contribution to glycoform synthesis in mammals (6).

A 1998 literature review on the availability of specific sugars for glycoconjugate biosynthesis concluded that when humans were fed only glucose in state-of-the-art parenteral nutrition, they frequently developed liver dysfunction. This review also concluded that mixtures of the needed variety of sugars could improve clinical situations as compared to glucose alone. One hundred sixty papers were cited in this review (8).

In a December 1998 study by essentially the same group of scientists, healthy humans were given radioactively labeled galactose, mannose or glucose. This study showed that galactose and mannose were directly incorporated into human glycoproteins without first being broken down into glucose. These scientists concluded that specific dietary sugars could represent a new class of nutrients. They also concluded that use of these nutrients could have practical consequences, especially in parenteral nutrition, where only glucose is currently given (7).

Human and animal ingestion studies show that mannose is readily absorbed, elevates the blood mannose levels by 3- to 10-fold, and is cleared over several hours. Some oral mannose is incorporated into glycoproteins, especially those made by the liver and intestine (7).

CONCLUSION

The glycosciences are the last exciting frontier of biochemistry. Of the four major classes of biomolecules--proteins, nucleic acids, lipids (fats) and carbohydrates—carbohydrates are the most complex. Because of their complexity, technology has only recently developed the methods to study them, unlock their codes, and reveal their biological secrets.

As expected with any complicated field of study, the more we learn the more questions we develop. What are the precise connections with changes in the sugar portions of cell-surface glycoforms? How exactly does the body metabolize each of the necessary sugars when consumed in the diet? Such questions will take many years to finally resolve. The research sited in the above section on metabolism of dietary sugars is only little more than a year old. Science has only just begun to decipher the sugar (glyco) code and its importance in communicating the language of life.

At the same time that interest in glycoconjugates has been growing in the scientific community, the general population has begun to pay more and more attention to nutrition. Glyconutritionals came about as a combination of both trends--glycoconjugate research and the focus on nutritional supplementation for health. Glyconutritionals are nutritional dietary supplements designed to provide substrates for the body to use in building the glyco portion of glycoconjugates on cell surfaces. Glyconutritionals are designed to make the necessary sugars available to the cells quicker and in greater quantity.

We have much still to learn; we have only just begun to understand the biochemical story written in the sweet language of life, but what an exciting language to learn.

REFERENCES

1. Stryer L. Carbohydrates. In: Stryer L, ed. Biochemistry. New York: W. H. Freeman and Company 1995:477.
2. Murray RK. Glycoproteins. In: Murray RK, Granner DK, Mayes PA, Rodwell VW, eds. Harper's Biochemistry. Stamford: Appleton and Lange 2000:675-94.
3. Structure and Catalysis. In: Lehninger AL, Nelson DL, Cox MM, eds. Principles of Biochemistry. New York: Worth Publishers 1993:212-52.
4. Zubay GL, Parson WW, Vance DE. Principles of Biochemistry. Dubuque, IA: Wm. C. Brown, 1995.
5. Macdonald I. Carbohydrates. In: Shils ME, Olson JA, Shike M, eds. Modern nutrition in health and disease. Malvern: Lea and Febiger 1994:36-44.
6. Alton G, Hasilik M, Niehues R et al. Direct utilization of mannose for mammalian glycoprotein biosynthesis. Glycobiology 1998;8:285-95.
7. Berger V, Perier S, Pachiaudi C. Dietary specific sugars for serum protein enzymatic glycosylation in man. Metabolism 1998;47:1499-503.
8. Martin A, Rambal C, Berger V, Perier S, Louisot P. Availability of specific sugars for glycoconjugate biosynthesis: a need for further investigations in man. Biochimie 1998;80:75-86.