International Journal of Applied Research 2019; 5(2): 295-299

ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(2): 295-299
www.allresearchjournal.com
Received: 10-01-2019
Accepted: 19-02-2019

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Medicinal utilization of oligosaccharides in respect of chemical things

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Abstract
Oligosaccharides (carbohydrates) are composed from 2 to 10 simple units of monosaccharaides. Oligosaccharides possess many crucial functions in biological systems such as cell binding and cell recognition. The biological roles of oligosaccharides demonstrate to span the spectrum from those that are trivial, to those that are necessary for the growth, development, function or survival of an organism. Some general principles have been emerged. First, it is not easy to predict a priori the functions a given oligosaccharide on a provided glycoconjugate might be mediating, or their relative importance to the organism. Second, the sequence of same oligosaccharide may facilitate various functions at different locations within the same organism. Third, the more specific and promising biological functions of oligosaccharides are commonly mediated by unusual presentations of common-terminal sequences, unusual oligosaccharide sequences, or by further changes of the sugars themselves.

Keywords: Oligosaccharides, cell binding and cell recognition, glycoconjugate

Introduction
Complex carbohydrates are regarded as main source of energy for the living body. Carbohydrates supply the continuous fuel to body requirements for daily living activities, exercise, and even rest. Complex carbohydrates are usually single units (monosaccharaides), which are connected together. The oligosaccharides possess two to ten simple units of monosaccharaides. Polysaccharides can be considered as polymer, and possess hundreds and thousands of monosaccharide units as monomer. Complex carbohydrates contain long sustained energy. The different types of carbohydrates can be classified on the basis of number of sugar units (monomers). They are mainly categorized into three groups and nicely depicted in figure 1.

Carbohydrates play crucial roles in biological system as they are associated to numerous important activities regarding the immune system [1]. Moreover, they are often biocompatible, safe and well tolerated, which are intrinsic, favorable properties that make carbohydrate structures attractive targets for the development of vaccine adjuvants and immunomodulators. Considering the aforementioned properties, carbohydrates can be exploited by the scientific community of chemistry [2]. Carbohydrates exhibit several advantageous characteristics that make them promising adjuvant candidates, namely, high biocompatibility and tolerability and a strong safety profile [3]. A variety of natural carbohydrate structures, especially MPLA and QS-21, have been clinically assessed as adjuvants and are part of licensed Adjuvant Systems (AS) in human vaccines against HPV (AS04), herpes zoster and malaria (AS01).

Chemical synthesis is emerging as a powerful approach on this front, offering practical access to homogeneous carbohydrate compounds for adjuvant development, as well as enabling further SAR studies towards improved synthetic analogues. Recently Fernández-Tejada and his group reported the recent advances in natural and synthetic carbohydrate-based adjuvants, including current knowledge of their immune potentiation mechanisms, in addition to selected applications in the field of vaccines against infectious diseases and cancer [4]. It is expected that this progress will make it possible for both chemists and immunologists to rationally design and develop novel, carbohydrate-based adjuvants with enhanced efficacy and reduced toxicity for further clinical advancement in human vaccines.

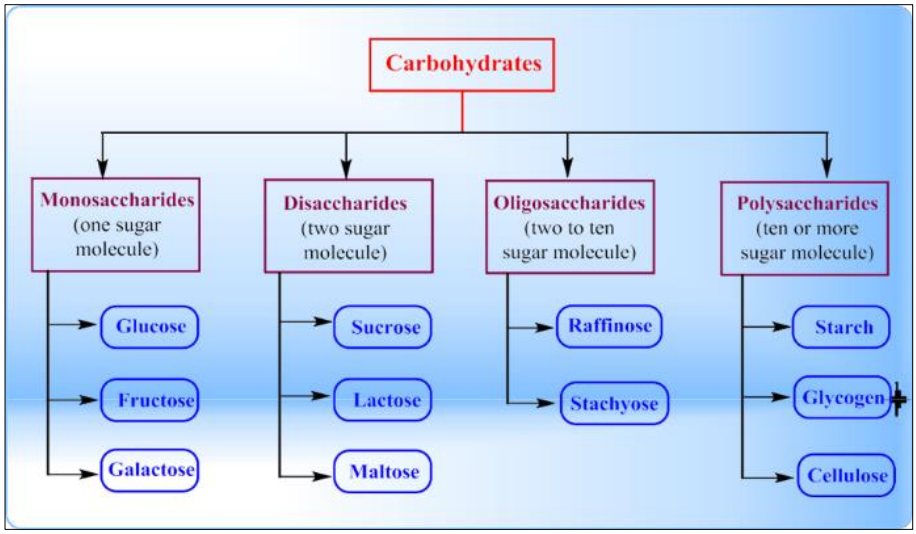

Fig 1: The general classification of carbohydrates

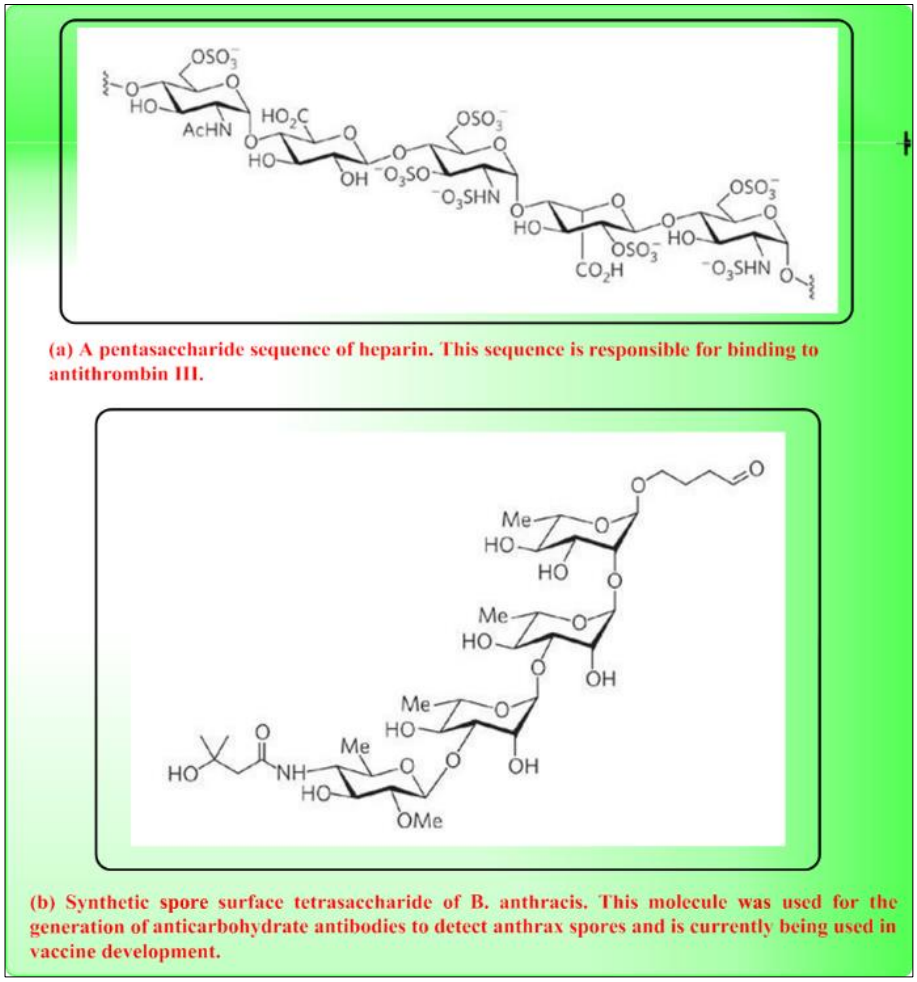

Fig 2: Carbohydrates employed in the development of medicine and for vaccine

The biological roles of oligosaccharides have not been properly studied in the past in comparison to other biopolymers e.g. proteins and nucleic acids. Although for many years it was known that the antigenic determinants of the ABO (H) blood group and the related Lewis blood groups are carbohydrate structures. Carbohydrate modifications of proteins and lipids are important processes that modulate the structures and functions of these biomolecules and affect intercellular recognition in infection, cancer, and immune response. Most recent efforts in the field are to develop new tools for use to understand the molecular-level carbohydrate recognition and to enable the carbohydrate-based drug discovery process. A great deal has been learnt in recent years about the biological role of oligosaccharides, and this has led to a new field named Glycobiology [5-6]. Understanding their biological significance and exploring their therapeutic value have driven the advancement of synthetic carbohydrate chemistry, glycobiology, and chemical Glycobiology [7].

Prevalent role of carbohydrates has been provided the in a broad spectrum of biological processes it may seem surprising that there are few carbohydrate-based therapeutics and diagnostics on the market. In addition to monosaccharide-inspired drugs such as the influenza virus treatment Tamiflu [8-9] (oseltamivir phosphate; Roche) two blockbuster drugs, acarbose (Precose, Glucobay; Bayer) and heparin, stand out. Both oligosaccharides were derived by isolation and reached the clinic before a detailed structure-activity relationship had been established. In addition, aminoglycosides naturally occurring pseudo-oligosaccharides have been used clinically to treat infectious diseases induced by a variety of Gram-negative bacteria [10]. The antibiotic activity of aminoglycosides is due to their inhibition of protein synthesis, which results from their binding to bacterial ribosomes.

Heparin

The oldest carbohydrate-based drug is isolated from animal organs and has been used clinically as an antithrombotic agent since the 1940s. Heparin activates the serine protease inhibitor antithrombin III, which blocks thrombin and factor Xa in the coagulation cascade [11]. This drug is a highly heterogeneous mixture of polysaccharides and is associated with severe side effects, including heparin-induced thrombocytopenia, bleeding and allergic reactions. Chemically or enzymatically fragmented heparins (low-molecular-weight heparins, LMWHs) are alsoheterogeneous, but are more bioavailable, with a longer half-life, a more predictable anticoagulant activity and fewer side effects *in vivo*.

After the specific pent saccharide responsible for the anticoagulant property was identified in the early 1980s (Figure 2), a herculean effort lasting more than 10 years was begun to establish a structure-function relationship using synthetic oligosaccharides [12]. As a result of this drug-development effort, a synthetic pent saccharide known as Arixtra (fondaparinux sodium; GlaxoSmithKline) has been available since 2002 [13]. However, Arixtra does have some clinical shortcomings, such as an exceedingly long half-life *in vivo* and little to no dose- dependent activity in certain indications [14]. Thus, LMWHs still have the highest market share of all antithrombotic, and the need for additional synthetic heparin molecules with specific activities persists.

Recent advances in heparin sequencing [15], heparin synthesis [16-18] and heparin microarray technology [19] have provided the tools to identify specific sequences or sequence families that interact with proteins such as chemokine's. The chemical synthesis of a broad range of heparin analogues should allow researchers to study the molecular mechanism of angiogenesis and to modulate wound healing and other medically relevant processes.

Acarbose

Carbohydrates such as starch and sucrose are principal components of food, and have to be enzymatically broken down in the intestinal tract. Acarbose, [20] a pseudo-oligosaccharide of microbial origin, is produced by fermentation. This α-glycosidase and α-amylase inhibitor interferes with and regulates intestinal carbohydrate digestion, controls the rate of absorption of monosaccharaides and influences the intermediary carbohydrate metabolism. It is used to treat type 2 diabetes.

Antibacterial vaccines

Synthetic advances made possible chemical assembly of complex oligosaccharide fragments of polysaccharide domains on the surface of human pathogenic bacteria. These oligosaccharides may be recognized by antibodies raised against high molecular weight, native, and polysaccharides. In addition to their antigenicity, synthetic oligosaccharides can also function as hastens in their protein conjugates that can elicit not only oligo- but also polysaccharide-specific IgG antibodies in animal models and in humans. A major milestone in the development of new generation vaccines was the demonstration that protein conjugates of synthetic fragments of the capsular polysaccharide of hemophilic influenza type b are as efficacious in preventing childhood meningitis and other diseases as is the corresponding licensed commercial vaccine containing the bacterial polysaccharide. The lessons learnt in this and other endeavors described herein are manifold. For example, they teach us about the significance of the oligosaccharide epitope size, the number of their copies per protein in the conjugate, the possible effect of the spacer on anti- saccharide immune response, and the proper choice of the carrier protein combined with the selection of the animal model. The H. influenza b story also teaches us that that the synthetic approach can be commercially viable [26].

A synthetic carbohydrate conjugate vaccine against *Haemophilus influenza* type b is now commercially available as Quimi-Hib (made from a tiny fragment of the bacteria's sugar-coat attached to a protein). It is a conjugate of a polyribosylribitol phosphate oligosaccharide and a carrier protein. Introduction of the conjugate Hib vaccine has reduced carriage rates of the bacteria (Figure 3) [27].

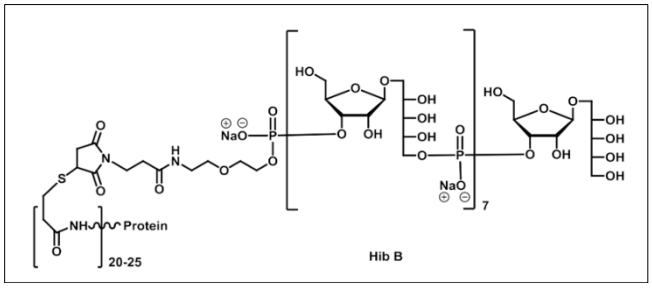

Fig 3: Structure of Quimi-Hib, the vaccine against meningitis

A tetra saccharide has been discovered on the surface of spores of the bio warfare agent *Bacillus anthracis* [28]. Once the durable form of the pathogen has been inhaled it will kill most victims if treatment is not commenced immediately. Synthesis of a species-specific tetra saccharide antigen [29-30] allowed the production of antibodies that specifically recognize B. anthracis in the presence of the closely related opportunistic human pathogen *Bacillus cereus* [31]. Challenge experiments to create a conjugate vaccine against anthrax are ongoing.

Ant parasite vaccines

Like bacteria, many parasites have unique glycoconjugates on their surfaces. The specific carbohydrates may serve as a starting point for the creation of conjugate vaccines, but efforts towards this goal have been hampered by the fact

that the parasites are very difficult to culture and because glycoconjugates cannot be obtained in pure form or sufficient quantity by isolation [32].

Malaria

Plasmodium falciparum is the most pathogenic of the single-celled parasites of the genus Plasmodium that are responsible for malaria. Malaria infects 5-10% of humans worldwide and kills more than 2 million people each year. Infected mosquitoes transmit the parasite, which leads to the common symptoms of chills and fever. Drug resistance is a growing problem at a time when there is still no effective vaccine. *P. falciparum* expresses a large amount of GPI on its cell surface [33]. This glycolipid triggers an inflammatory cascade that is responsible for much of malaria‟s morbidity and mortality. When a protein conjugate of a synthetic hexasaccharide GPI malaria toxin was administered to mice before infection, this resulted in a highly reduced mortality rate of only 10–20%, compared with 100% without vaccination [34]. Cross-reactivity of the antibodies with human GPI structures was not observed owing to the differences between human and *P. falciparum* GPI. Immunization of mice did not alter the infection rate or overall parasitaemia, indicating that the antibody against the GPI neutralized toxicity without killing the parasites.

Preclinical studies involving protein conjugates of synthetic GPI antigens are currently underway. To support such vaccine development efforts, methods for the large-scale synthesis of oligosaccharide antigens have been developed by taking advantage of the latest advances in carbohydrate synthesis technology. Very small amounts of synthetic antigen (10–9–10–7 g per person) are required, and the production of several kilograms of antigen per year will suffice.

Leishmaniasis

Leishmaniasis, which is caused by another protozoan parasite, is transmitted by sandflies and affects more than 12 million people worldwide. *Leis mania* resides in macrophages, making them difficult to treat. In a search for a potent vaccine, the lipophosphoglycans (LPGs) that are ubiquitous on the cell surfaces of the parasites and are composed of a GPI anchor, a repeating phosphorylated disaccharide and different cap oligosaccharides became a target. The cap tetra saccharide has been the focus of efforts towards a conjugate vaccine based on a synthetic antigen.

The branched tetra saccharide was assembled by automated solid phase synthesis [35] and conjugated to a virosomal particle to enhance immunogenicity. These highly immunogenic conjugates yielded antibodies that selectively recognize parasite-infected livers [36]. Challenge studies in an animal model are currently underway.

Recent advances and future development

In last decades, the lack of tools for studying glycobiology prevented biologists and medical researchers from addressing research problems that involve carbohydrates. During the past decade, sequencing and synthesis technologies that are commonly used to study nucleic acids and proteins have become available for glycemic as well. Now, carbohydrate sequencing of glycoconjugates is often possible even though sample preparation is complicated by Carbohydrate micro heterogeneity and the absence of amplification procedures. Automated solid- phase synthesis, improved methods for solution-phase oligosaccharide assembly, enzymatic methods and the use of engineered cells have complemented each other, allowing oligosaccharide synthesis to take a big step forward by granting access to different classes of glycoconjugate. In turn, these methods have helped procure oligosaccharides and their non- natural analogues for the creation of high-throughput screening methods such as carbohydrate arrays. The identification of specific oligosaccharides, by sequencing followed by comparison with synthetic oligosaccharides, has yielded insight into the interactions of carbohydrates and proteins. Oligosaccharide involvement at key positions of signaling pathways is beginning to emerge and a molecular understanding of carbohydrate binding to proteins is evolving. Detailed structural studies-including studies of protein-carbohydrate interactions-using X-ray crystallography will become commonplace in the near future. Further improvements in the methods by which oligosaccharides are sequenced and synthesized will be needed to make their routine use possible for non-specialists.

A better understanding of the biological roles of carbohydrates and improved sequencing and synthesis techniques are beginning to influence the design of diagnostic and therapeutic approaches. Carbohydrate arrays help to define new disease markers by screening the sera of patients. Bacterial and viral detection and typing can be achieved using carbohydrate microarrays. Synthetic access to oligosaccharides of infectious agents that are hard to culture and isolate (for example, *B. anthracis* and *P. falciparum*) facilitates antibody production for specific detection of these pathogens. These anti-carbohydrate antibodies may become important for passive immunization. The first conjugate vaccine candidates containing synthetic oligosaccharide antigens arereaching preclinical and clinical trials against bacterial (for example, Hib), viral (for instance, HIV) and parasitic (for example, malaria and Leishmaniasis) infections. The trend to produce defined vaccine antigens using chemical and enzymatic methods, as well as engineered cells, is likely to increase, and synthetic vaccines are expected to complement already existing vaccines containing purified polysaccharides.

Conclusion

As our understanding of carbohydrate involvement in signaling cascades in particular of those that involve glycosaminoglycan’s expands, carbohydrate-mediated processes will become the target of drug-development efforts using small organic molecules. Glycemic has just gone beyond the initial proof-of-principle studies for diagnostics and therapeutic candidates. Improved tools and a better molecular understanding should convince those biologists and medical researchers who previously avoided carbohydrates to address questions involving this class of molecule. The excitement of glycemic is just beginning, with many discoveries to

be made and applications to be developed.

Present chapter covers the basic concept as well as classification of carbohydrates. We have covered the fundamental understanding of medicinal importance of oligosaccharides. In addition, we have also discussed carbohydrates/oligosaccharide based vaccines, one of the most successful tools of medical sciences.

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