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Carbohydrate-based synthetic ion transporters

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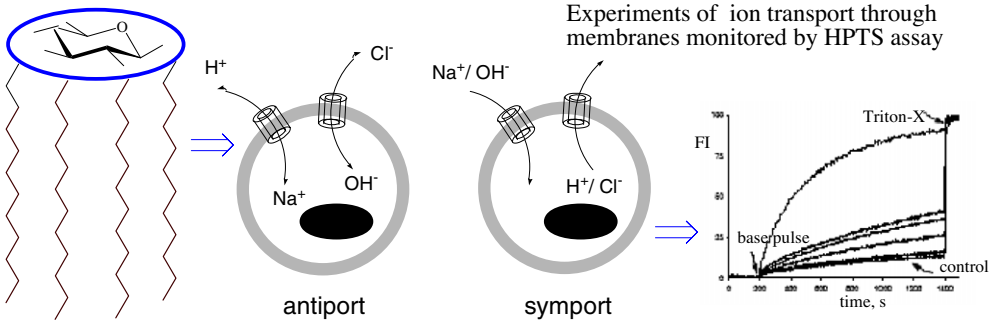
ABSTRACT

In this work, carbohydrate-based systems designed as artificial ion transporters have been surveyed. Despite the large structural diversity and ease of manipulations of carbohydrates, in principle endowed with a variety of desirable properties for ionophoric activity, only few examples of sugar-containing compounds have been reported in the literature for these purposes. The most remarkable example is the family of modified β-cyclodextrins, resulting in active cation and/or anion transporters when long, flexible *n*-alkyl or oligo-ethylene or butylene glycol chains are appended at the lower rim of the macrocycle. Interesting features have been also found in amphiphilic CyPLOS (Cyclic Phosphate-Linked Oligosaccharide) dimers, that is macrocycles with two phenyl-β-D-glucopyranoside residues, 4,6-linked through phosphodiester bonds, derivatized with tetraethylene glycol tentacles. A wider repertoire of available carbohydrate-based scaffolds is expected to largely stimulate the discovery of novel, efficient artificial ionophores, of great interest for both technological and biomedical applications.



1. Introduction

Biological membranes are organized assemblies of lipids and proteins and constitute the functional border of living cells insulating the cytosol from the external medium. The permeability properties of the membrane are governed by the phospholipid bilayer, which allows relatively free diffusion of nonpolar small organic molecules but prevents the permeation of polar species and biomacromolecules such as proteins or DNA. A typical example is the asymmetry of a cell: the concentration of sodium cation is 150 mM outside and 10 mM inside. In contrast, $[K^+]_{out}$ = 5 mM and $[K^+]_{in}$ = 150 mM. The bilayer acts as a barrier to the equilibration of these closely related cations while permitting the appropriate

Abbreviations: Bn, benzyl; BzCl, benzoyl chloride; CyPLOS, cyclic phosphate-linked oligosaccharides; DIEA, *N,N*-diisopropylethylamine; DMF, *N,N*-dimethylformamide; DMTCl, 4,4′-dimethoxy-triphenylmethylchloride; EYPC, egg yolk phosphatidyl choline; EYPG, egg yolk phosphatidyl glycerol; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HPTS, 8-hydroxy-1,3,6-pyrenetrisulfonic acid, trisodium salt; LUV, large unilamellar vesicles; MSNT, 1-mesitylen-sulfonyl-3-nitro-1,2,4-triazole; TEA, triethylamine; TEG, triethylene glycol; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

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concentrations to be maintained. However, an organized trafficking of molecules and ions across the membrane is needed to sustain the cellular metabolism. In Nature, this traffic is regulated by a variety of systems, mainly proteins, able to form ion channels or to act as molecular carriers. These ionophores, that is ion transporters, selectively affect the membrane permeability and regulate the functioning of healthy cells.[1]

Ion transport in Nature occurs via ion channels and pumps which promote, respectively, the passive (driven by the concentration gradient) and the active (against concentration gradient) flux of ions across membranes.[2] Natural ion channels and pumps are large protein assemblies consisting of a central channel portion that spans the membrane, and additional regions on one or both sides of the membrane that control access to the channel region. Recently reported high resolution structures of bacterial potassium[3] and chloride[4] channels have significantly contributed to the understanding of the molecular mechanism of ion transport.[5] The ion conducting portion of natural ion channels is typically a bundle of four to seven trans-membrane proteins. Hydrated ions approach the mouth of the channel and reach a region named 'selectivity filter' where the ion is partly dehydrated and the water of ionic solvation is replaced by polar interactions with functional groups belonging to the protein. The size of the filter, the topology of the binding site and the type of interactions (e.g., hard carbonyl oxygens for recognition of cations, and hydrogen-bonding groups for anions) determine the ion selectivity of the channel.

Besides large proteic ion channels, in Nature there is a wealth of smaller molecules able to alter membrane permeability and promote ion transport, by forming pores or acting as carriers. Ion carriers behave as 'ferry-boats': they complex ions on one side of the membrane, 'carry' them across the phospholipid bilayer and release them on the other side. On the contrary, pore forming molecules do not move in the membrane, but form holes, thus allowing the ions to get across them. These low molecular weight ionophores are produced by a variety of organisms essentially for their antibiotic properties. Most of them are peptides, like the well known channel forming gramicidin A,[6] the large family of linear amphipathic peptides,[7] or cyclic peptides that act as carriers, exemplified by valinomycin.[8] However, many other structural motifs are present: polyketide macrolides like amphotericin B,[9] polyketide polyethers like monensin,[10] polyamines like squalamine[11] and polyesters like polyhydroxybutyrate–polyphosphate complexes.[12] Very high diversity is observed both at the level of their structure and mechanism of action. However a common topological feature is frequently conserved in pore-forming molecules: many of them have elongated and amphiphilic structure with several polar groups (alcohols, amines, etc.) and are able to insert in the membrane by forming a self-assembled cylindrical structure with an inner polar conduit which favors the transmembrane transit of the ions (barrel stave model). In analogy with the more structurally defined protein channels, the polar groups solvate the dehydrated ion during the transport process.

Despite the structural diversity observed, the examples of natural ionophores based on carbohydrate scaffolds are not common. Sugar derivatives are present as polar headgroups in amphotericin B, and in structurally related macrolides like nystatin[13] and elaiophylin,[14] a family of antibiotics extracted by *Streptomyces* strains. In the case of amphotericin B, the better characterized system,[15] it is suggested that the aminosugar head group orients the molecule in the bilayer membrane with this polar portion in contact with the aqueous phase and the polyene tail inserted within the lipid hydrophobic region (Fig. 1). Several monomers in this orientation self-aggregate forming a barrel-stave structure with the interior lined by the hydroxyl groups on the edge of the amphotericin. Eventually, two of these structures align to form a conducting tube long enough to span the whole membrane. Ions cross the interior of the barrel being solvated by the hydroxyl groups of the ionophore.

A more complex structure decorated with carbohydrates is present in avicins, a family of triterpenoid saponins from *Acacia victoriae*.[16] Recent studies have demonstrated that avicin (Fig. 2) is able to form channels in phospholipid membranes. The 1.1 nm wide channel is formed by the self-assembly of ten monomers with the suggested participation of phospholipids recruited from the membrane. Interestingly, modifications of the avicin backbone have shown that chain A is essential for the channel activity. It has also been suggested that only this portion of the molecule is inserted in the membrane, while the two carbohydrate moieties are probably pointing out from the membrane surface, being in contact with bulk water.

Transmembrane ion transport is a typical supramolecular function.[17] The transport process requires specific non-covalent intermolecular interactions able to compensate the loss of hydration energy and the recognition of this characteristic has stimulated a large body of studies in the supramolecular chemistry community. The scope of this research is manifold. On one side, the modelling of complex natural systems may give important mechanistic information at a molecular level; on the other side, technological and biomedical applications are appealing, also extremely important for the understanding and treatment of channelopathies.[18,19] The last thirty years have witnessed an impressive increase in the complexity and efficiency of synthetic ionophores acting as carriers[20] or able to form channels.[21] Taking inspiration from natural systems, the structural diversity explored is really wide, ranging from simple linear polyethers to complex multiporphyrinic architectures and passing through almost all the typical scaffolds used in supramolecular chemistry (macrocycles, peptides, steroids, etc.).[22] In this context, with the notable exception of cyclodextrins,[23] synthetic ionophores structurally based on carbohydrates are rare. This is somehow surprising because carbohydrates may be ideal starting materials in the design of novel synthetic

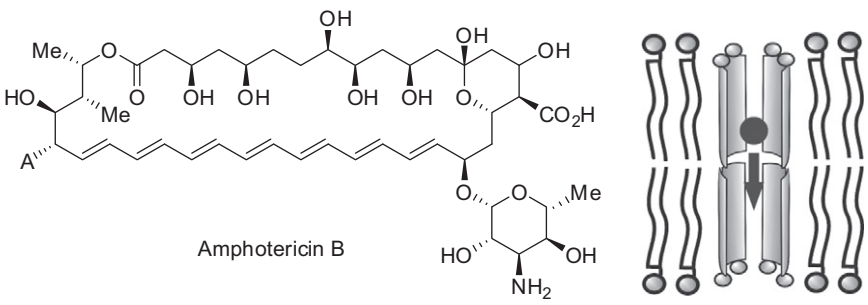

Figure 1. Chemical structure of amphotericin B and schematic representation of the barrel-stave pore this can form in the membrane.