Introduction

Physical aspects of glycolipids in membranes are of interest because physical factors may have important bearing on their structural and receptor roles. However certain points remain very unclear. One would certainly like to know how glycolipids 'fit' into membranes: what forces hold them in place, what effect they have on the membrane, and how they are oriented. One would also like to know how the various portions of the molecule behave dynamically: the sugar headgroup, the acyl chains, and the structure as a unit. These things are beginning to be reasonably well understood. A number of experiments have been performed that aim at unravelling less well understood aspects, and this is probably a good time to stand back and think about them.

Results and Discussion

How do glycosphingolipids fit into the membrane?

Glycolipids share a basic molecular characteristic with phospholipids: they are elongated amphiphiles of low water solubility. Even gangliosides, with their extensive, hydrophilic, charged headgroups, seem to have small CMC values ($10^{-10}$ M, although higher values have been reported (1)). At the low mol ratios typical of cell membranes, glycolipids simply incorporate into the bilayer structures dictated by phospholipids – and this article will deal almost exclusively with such membranes (see 2 for references to pure glycolipid structures). Of course the lipid bilayer is a very special form of micelle peculiar to the phospholipid, so that
glycolipids would in general be expected to perturb it measurably. It has been pointed out that phospholipids have only acceptors for hydrogen-bond formation in the membrane-inserted portion (ester C = O), while glycosphingolipids have donor -OH and -NH, in addition to an amide C = O. Hydroxylated fatty acids (-OH group in the 2 position) are quite common in glycosphingolipids. The latter feature has been shown to substantially influence the effect of galactosyl ceramide on the headgroup region of dipalmitoyl phosphatidylcholine bilayers while not greatly changing its effect on the hydrophobic portion (3), and it had a relatively small effect on the melting behaviour of pure galactosyl ceramide (4). Clearly the headgroup of glycolipids is very different from that of phospholipids - having great potential for hydrogen-bonding. Gangliosides have the added feature of the -COOH function with its much-debated possible role as an ion chelator. Extensive data exists from monolayer studies and theoretical modeling of the dipolar forces to be expected in the glycolipid headgroup region (5-7). An interesting feature of the glycosphingolipid hydrophobic portion is the variability in chain length of the fatty acid chain relative to the sphingosine portion, which is generally C_{18} and thus behaves like a fatty acid of 14-15 carbons in terms of depth of bilayer penetration. The effect on phase behaviour of having unequal fatty acid chain length (up to 4 carbons different) in phosphatidylcholines has been measured in bilayer membranes, and the question of interdigitation raised (8-10). For glycolipids, with fatty acids up to C_{24}, interdigitation could be quite striking if it occurs - and of course at low mol ratios or in cell membranes this will be a 'one-way' phenomenon. A form of fatty acid interdigitation has been recorded in micelles of pure GalCer (11).

Some of the earliest physical questions asked about glycolipids concerned their fit into membranes. I remember that at a surface glyco-conjugate meeting in 1976 people were wondering whether certain sugars might be able to associate with lipid hydrophobic regions by having their -OH groups all on one side, or whether they simply stuck up into the water. Spin label probes the size of a sugar residue covalently attached to globoside or ganglioside sugars show no evidence of hydrophobic environment when the glycolipids are in phospholipid bilayers or cells (12, 13 and ref. therein). In fact the hyperfine spectral splitting was often slightly larger in cells, indicative of a more polar environment. The deuterium NMR spectrum of headgroup-labelled glucosylceramide in fluid dipalmitoyl phosphatidylcholine showed that the sugar projected upward