REVIEW

Membranes and the clinician

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IN RECENT YEARS, A NUMBER OF ARTICLES dealing with membrane structure and function has made its way into clinical journals. This article reviews the newer developments in this area to provide clinicians with the necessary background to critically analyze and assess these studies. Given the complex and vast nature of the subject, this brief review will not be all encompassing but will attempt to deal, wherever possible, with selected aspects of this topic which are considered to have direct or at least indirect clinical relevance for the practising gastroenterologist or hepatologist.

STRUCTURE AND FUNCTION

It is necessary to review briefly certain aspects of intestinal and hepatic plasma membrane structure and function. These cell surface membranes, like all biological membranes, have a lipid bilayer structure which contains internal, external and transmembrane proteins (1). The latter traverse the bilayer presumably via stretches of hydrophobic amino acid residues. Both the lipids and proteins of these membranes are asymmetrically arranged in the inner or outer leaflets (1).

In the 1950s, the 'unit membrane theory' held that a single lipid bilayer was present at the core of all biological membranes. In the late 1960s, this theory lost favour for a number of reasons (1). In 1972, Singer and Nicholson (2) proposed a new concept of membrane structure which is currently believed to be correct. In their 'fluid mosaic model' the lipid bilayer is envisioned to contain scattered 'iceberg-like' proteins which either completely or partially span the bilayer with exposure of hydrophobic residues on both inner and outer surfaces (1,2). Moreover, the hydrophobic residues are turned outward, thereby protecting hydrophilic groups from the hydrophobic core, while the hydrophilic cores provide pathways through the bilayer for ions and other hydrophilic molecules.

Acceptance of this 'fluid' model provided the theoretical framework and impetus for studies on protein-lipid interactions in biological membranes. Over the past 15 years or so it has become increasingly clear that membrane lipids and their properties can influence membrane proteins and their specific functions and visa versa (3). In this regard, a key property of

membrane lipids is their 'lipid fluidity' which can be defined simply as the general motional freedom of the lipid molecules in a biological membrane.

Several recent reviews (3-5) have dealt with membrane lipid fluidity and its measurement in hepatic and intestinal plasma membranes, so this article touches only on certain key aspects of this topic and the reader is referred to the above reviews for further details. The fluidity of biological and model membranes has clearly been shown to depend upon a number of membrane compositional parameters including: lipid:protein (w:w) ratio; cholesterol: phospholipid (mol:mol) ratio; sphingomyelin:lecithin (mol:mol) ratio; and the length and degree of unsaturation of phospholipid fatty acyl chains (3). Any study on membrane fluidity should not only measure fluidity per se but also examine each of these compositional parameters. Failure to do this may lead to erroneous conclusions, particularly as alterations in the compositional parameters can be additive or even offset each other in terms of fluidity.

Recent studies have demonstrated that fluidity, as assessed by steady-state fluorescence polarization techniques using various lipophilic probes, the most widely used method of measuring fluidity in membranes, is more complex than originally thought. Certain probes, depending on their properties

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such as shape, etc, are markedly hindered in their rotation in biological membranes, whereas others are much less hindered (3). Thus, fluidity can be divided into two components: a 'static' or 'order component' and a 'kinetic' or 'dynamic component'. Failure to recognize this aspect of fluidity may also lead to erroneous conclusions.

POTENTIAL CLINICAL IMPLICATIONS

Studies from this laboratory (5) and others (3,4) have shown that alterations in the lipid composition and/or fluidity of intestinal or hepatic membranes may influence a number of protein-mediated activities. For example, alterations in small and large intestinal plasma membrane fluidity have been shown to influence certain enzyme activities such as adenylate and guanylate cyclase, alkaline phosphatase, Na^+ - K^+ -dependent ATPase, and Ca^{2+} -dependent ATPase as well as Na^+ -dependent glucose transport, Na^+ / H^+ exchange and water permeability (5). Alterations in hepatic plasma membrane lipid composition and/or fluidity have also been shown to influence bile salt dependent and independent bile flow as well as Na^+ - K^+ -ATPase activity (3,4).

Furthermore, this laboratory (5) has recently demonstrated that dietary lipids, luminal calcium ion concentrations, the normal physiological processes of ageing and differentiation, as

well as the administration of carcinogens, estrogen, vitamin D, glucocorticoids and insulin may influence the lipid composition and fluidity of intestinal plasma membranes which, in turn, modulates a number of their important protein-mediated activities.

Recently, the author has been able to detect 'pre-malignant' changes in the lipid composition, fluidity and phospholipid methyltransferase activity of colonic apical membranes of animals administered the procarcinogen 1,2 dimethylhydrazine (DMH) (6). These latter changes were confined to the distal colon, where DMH tumours predominantly occurred and were not seen in a strain of rats resistant to induction of cancers by DMH. These studies suggest that these membrane alterations may be related to the malignant transformation process induced by this carcinogen in the colon and also that these parameters may be useful in detecting pre-malignant or early colonic cancer. Based on these observations the author and colleagues are currently performing clinical studies in this area in human subjects.

Dietary manipulation, such as changing the triacylglycerol saturation of diets, has been shown to alter the lipid composition and/or fluidity of normal small and large intestinal antipodal plasma membranes, thereby, altering the function of these membranes (5,7,8). In the 1970s it became

evident that tumour cells might also be susceptible to membrane fatty acid composition via dietary manipulation (9,10). In this regard, in the last decade, studies from a number of investigators (9,10) have demonstrated that tumour membrane fatty acid composition and fluidity can be modified either in culture or by dietary means. These changes in membrane properties appeared to influence a number of important cellular processes including receptor binding, carrier-mediated transport, ion channels and eicosanoid production. While, to date, such tumour modifications have not been shown to alter tumour cell growth, they have been demonstrated to enhance the sensitivity of certain tumour cells to hyperthermia and adriamycin (9,10). It would, therefore, appear that this therapeutic approach may have significant potential in terms of augmentation of the cytotoxicity of anti-neoplastic agents.

In summary, the field of research involving membrane structure and function has never been more active. It is clear that many of the studies conducted have potential clinical implications. The next step is to take these observations to the 'bedside'. Over the next decade, I am sure that this will occur and lead to interesting and important modifications in our diagnostic and therapeutic approaches to patients with various pathological disorders, including cancer.

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