Uses and abuses of intestinal permeability measurements

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ABSTRACT: Intestinal permeability has been assessed with three different classes of permeability probes, viz various sugar mixtures, ^{51}Cr-EDTA and poly(ethylene glycol). The former two methods are having increasing clinical applications in the screening and assessment of small intestinal damage and ^{51}Cr-EDTA is now the preferred probe for routine clinical use. Poly(ethylene glycol)s have numerous disadvantages and are not recommended. Probes may be used both in vitro and in vivo and have been applied to a wide variety of clinical problems. In particular, NSAID-induced enteropathy, a major complication of the chronic administration of these widely-used drugs, was recognized for the first time with ^{51}Cr-EDTA permeability measurements. The cytoprotective role of various prostanoids was also clearly demonstrated using ^{51}Cr-EDTA. It is anticipated that measurement of intestinal permeability will play an increasing role in clinical and research investigation and in the monitoring of intestinal disease. **Can J Gastroenterol 1988;2(3):127-132.**

Key Words: ^{51}Cr-EDTA, Intestinal permeability, Poly(ethylene glycol)s, Probes

DETERMINATION OF INTESTINAL permeability in both man and experimental animals is currently finding increasing application, both in research and clinical practice. This review briefly considers the historical development of ideas on mucosal permeability and reviews the current methodology and its application to clinical investigation.

HISTORICAL ASPECTS
Although there were early studies (1) on the apparent absorption of nonmetabolized sugars and unexplained observations on disacchariduria in intestinal disease (2), the real concepts behind measurement of intestinal permeability were first advanced by Menzies in the 1970s (3). It was, however, only in the 1980s that there was significant interest and progress, and the basis of disorders

of intestinal permeability were recognized (4). This may have been because of the methodological difficulties inherent in the assay of various urinary saccharides and the uncertainties of metabolism and/or endogenous production of certain of the probe molecules used in such studies (5,6).

There have been reports of altered intestinal permeability in certain experimentally induced mucosal lesions (7) and suggestions of altered permeability allowing antigens access to the mucosa (8). However, these studies used high molecular weight (more than 10,000 dalton) probes and they are likely to have reflected alterations in endocytic activity of the enterocytes, a very minor pathway, rather than changes in trans- and intercellular permeability.

Current interest in measurements of intestinal permeability was also stimulated by the well publicized reports from The Mayo Clinic and subsequently other groups on the use of poly(ethylene glycol)s (9-15). The findings with these polymers and with the sugars produced paradoxical results suggesting increased permeability to small sugar molecules but decreased permeability to large poly(ethylene glycol) molecules in damaged coeliac mucosa. It is now clear that poly(ethylene glycol)s are unsatisfactory probes for measuring mucosal permeability; they are lipophilic and show considerable transfer through normal mucosa and thus uptake is very dependent on mucosal surface area.

Another, more recent objection to the use of poly(ethylene glycol)s is the finding that urinary recovery of the various polymers following intravenous administration is proportional to their molecular size and thus claims of selective alterations in disease may simply reflect differential urinary excretion (16). Of even greater concern is the suggestion that poly(ethylene glycol)s may be oxidized enzymatically to potentially highly toxic aldehydes (17). Analytical difficulties and the need for complex mathematical modelling (18) means that these polymers play little role in the routine clinical investigations of disordered permeability. Nevertheless, these reports generated awareness of the importance of measuring intestinal permeability

TABLE 1
Pathways for permeability probes

Probe (mol wt)	Pathway	Clinical use
Rhannose (164)	Transmembrane pores	+
Mannitol (180)	Transmembrane pores	+
Xylose (150)	Passive carrier mediated	+
Lactulose (34)	Intercellular junctions	+
Cr-EDTA (342)	Intercellular junctions	+
Inulin (5000)	Intercellular junctions	–
Cyanocobalamin (1240)	Intercellular junctions	–
Poly(ethylene glycol)s (196-4,000)	Transmembrane, lipophilic	+
Horse radish peroxidase (40,000)	Endocytosis	–

and raised interest in methodological development.

In order to resolve the above paradox and to identify suitable probe molecules, a novel in vitro method was established for the measurement of permeability in intestinal biopsies (19). The procedure involves short term (5 to 10 mins) incubation of tissue fragments in oxygenated physiological medium. The technique determines selectively the permeability at the mucosal surface and is equally applicable to both human tissues and samples from experimental animals. It specifically avoids variations of apparent permeability due to gastrointestinal transit, mucosal water flux, blood and lymphatic flow, tissue distribution, renal excretion as well as tissue or luminal metabolism of the probes. Permeability was shown to be inversely linearly related to the log molecular weight of the probe both in normal and coeliac mucosa. Permeability was clearly increased to most probes in mucosa from patients with coeliac disease both in relapse and remission.

Probes used in in vitro studies included ^{51}Cr-EDTA, ^{57}Co-cyanocobalamin, ^{14}C-inulin (19), various labelled sugars (20), peptides (21) and macromolecules (7,22). These studies led to the use of ^{51}Cr-EDTA as an in vivo probe for measuring small intestinal mucosa in man (23-25), veterinary practice (26) and experimental animals (27,29) and is currently the most convenient, sensitive and simplest permeability probe used in clinical practice. Recent studies have compared ^{51}Cr-EDTA with both sugars and poly(ethylene glycol)s (16). Appropriately selected disaccharides, eg, lactulose, give good agreement with ^{51}Cr-EDTA and can be used more readily with children and in repeated studies. Combinations

of sugars can be used giving simultaneous determination of active and passive carrier mediated transport, and trans- and intercellular permeability (30). The optimal concentrations, etc, of these test substances, however, remain to be determined.

APPLICATIONS OF PERMEABILITY PROBES

Table 1 lists the main probes used in vitro and in vivo and the presumed pathways of entry into the mucosa. Although in vitro techniques have been invaluable in formulating concepts of intestinal permeability, in investigating the pathways taken by the individual probes and in localizing the region of gut showing the permeability change, the in vivo methods have generally proved the most clinically useful. Table 2 lists the disorders in which changes in permeability have been investigated.

Inflammatory bowel disease: Consistent increases in permeability have been reported with small bowel inflammation (23,31-35). A normal permeability to oral

TABLE 2
In vivo studies of intestinal permeability

Coeliac disease
Crohn's disease
Ulcerative colitis
Backwash ileitis
Alcoholic enteropathy
Parenteral nutrition — prolonged starvation
Drug toxicity
Nonsteroidal anti-inflammatory drugs and prostaglandins
Rheumatoid and osteoarthritis
Schizophrenia
Dermatitis herpetiformis
Atopic eczema, food intolerance
Infective enteritides
Cystic fibrosis

^{51}Cr-EDTA virtually excludes small bowel inflammation in Caucasians and is thus a useful screening test for small bowel disease. There is some controversy as to whether the in vivo permeability tests are increased (34) or normal (23) in ulcerative colitis. This may relate to the presence of various osmotic fillers (either absorbed or nonabsorbed) adminstered concomitantly with the probes in the various studies as well as the extent and activity of the colitis. Recent studies have measured large bowel permeability by direct rectal installation of the ^{51}Cr-EDTA with urinary radioassay (36,37). Clearly, saccharide probes are subject to rapid bacterial degradation and are unsuitable in this type of test. The clinical value of direct rectosigmoid permeability measurements are not yet established. They may, however, be of use in distinguishing functional bowel disorders from inflammatory bowel disease and in assessing response to treatment.

NSAID enteropathy: One of the most useful applications of permeability measurements particularly the ^{51}Cr-EDTA test has been the identification of chronic small bowel enteropathy due to nonsteroidal anti-inflammatory drugs (NSAIDs) (38). Nonspecific gastrointestinal symptoms have long been recognized as a frequent side effect of these drugs. An increased incidence of perforation (39) together with subjective gastroscopy findings suggested that the toxicity was confined to the stomach. However, recent studies (40-42) have shown that chronic NSAID therapy is frequently associated with small intestinal inflammation, ulceration and blood loss. Increased permeability is the initial lesion and probably is the key pathogenic mechanism of this important toxic effect. The similarities between this lesion and Crohn's disease are close and further studies of NSAID enteropathy should, both in man and experimental animals, considerably enhance understanding of the etiology, pathogenesis and treatment of this important challenge to gastroenterologists.

Coeliac disease: The increased permeability in patients with coeliac disease in relapse has already been noted (24, 43-45). Increased permeability also occurs in the associated dermatitis herpetiformis (46,47). Increased permeability in coeliac disease in relapse correlates with intraepithelial lymphocyte count suggesting a causal relationship (24). The increased permeability has been confirmed in vitro (18) and there is clearly no cut-off over the molecular weight range 300 to 5000 daltons. There is, however, disagreement over the response to treatment. Some studies suggest a return to normal with a gluten-free diet (48) but more recent studies both in vitro and in vivo indicate a reduced but persisting abnormality in these patients (49) even where the mucosa appears histologically normal. However, as very minor histological abnormalities (50) or changes in cell proliferation, only demonstrable by very sensitive biochemical methods (51), may be accompanied by increased permeability, the question remains open as to whether the permeability defect represents a primary or secondary lesion. Preliminary results indicate that coeliac patients treated with a nonantigenic elemental diet show a return to normality in their gut permeability.

Chronic psychiatric disorders: Dohan and colleagues (52) have claimed a relationship between coeliac disease and schizophrenia invoking the concept of exorphins associated with increased intestinal permeability (53). A report by Wood and colleagues (54) suggested that increased permeability was indeed present in approximately one-third of a series of chronic psychiatric inpatients. However, their low and very variable recovery of sugar probes indicates that the results should be interpreted with caution. In addition, these subjects were receiving a variety of unspecified drugs known to affect intestinal permeability, gastrointestinal transit and renal function. A more detailed study using ^{51}Cr-EDTA has failed to confirm these conclusions (55).

Miscellaneous disorders: Increased permeability is a highly sensitive measure of disruption of the normal mucosal barrier function of the small intestine and it is therefore not surprising that many potential toxic agents cause increased permeability. NSAIDs almost invariably increase permeability but alcohol abuse (56,57), cytotoxic drugs (27,58-62), cholecystokinin and bile salts (63), various detergents, (14,26,64,65), gold compounds (66), chelators (67,68), ischemia (69) and dietary idiosyncrasies (70) are also frequently accompanied by increased permeability without necessarily causing gastrointestinal symptoms. Increased permeability in premature infants (71) and following starvation (72) has been reported.

There have been several suggestions that increased gut permeability is a major pathogenic factor in a variety of allergic disorders particularly eczema. Measurements of permeability do show a higher prevalence of abnormal results, particularly in patients with severe systemic disease (73-77). Some of the patients show jejunal abnormalities and an increased prevalence of coeliac disease in these patients had been noted. It is unlikely that increased permeability represents a primary defect but merely reflects mucosal abnormalities associated with severe systemic disease. Summarizing the various reports, the data suggest that increased permeability is more frequently observed in children than in adults with eczema; the former more frequently show a dermatological response to dietary exclusion therapy.

Increased permeability has been consistently demonstrated in various small bowel infective enteropathies (74,78) due both to viral and bacterial infections. The time course of recovery has not been adequately documented but in certain individuals may be persistent and present clinically as irritable bowel syndrome.

OUTSTANDING QUESTIONS

Although the permeability pathways for the various probes are being increasingly understood, further studies are clearly indicated. Poly(ethylene glycol)s enter via a lipophilic pathway but whether specific domains of the cell membranes are involved has not been identified. Certain monosaccharides, eg, mannitol, enter via so-called 'pores' but the ultrastructural and biochemical basis for this physiological concept has not been identified.

Although various saccharides have been used in research they are not very suitable for routine clinical use. The analytical techniques are demanding

but, in addition, bacterial and cellular metabolism coupled with endogenous formation of certain sugars limit their use. The poor urinary recoveries of certain intravenously administered sugar probes is also a cause of concern. There is thus a need for a readily assayed, possibly radiolabelled, probe for assessing pore-mediated intestinal uptake.

The uniquely valuable properties of ^{51}Cr-EDTA have been discussed in detail elsewhere (4) but there is need for an assay procedure or alternative probe which does not use a radiolabelled tracer. Immunoassay with monoclonal antibodies offers a potentially useful approach (79). The exact pathway of these probes through the mucosa are uncertain, eg, whether there is selective uptake along the villus and the nature of the anatomical barrier, presumed to be the intercellular tight junction, are uncertain. Suitable ultrastructural studies with in vitro measurement of permeability should prove useful.

More detailed knowledge of the bio-chemical basis of mucosal integrity is needed. The observation that orally administered prostaglandins protects the small intestine against NSAID-induced injury (30) clearly has therapeutic implications but also implicates prostaglandins in the maintenance of the mucosal permeability barrier (80). This may also be relevant to the treatment of inflammatory bowel disease and indicate the biochemical processes underlying the structural integrity of the gut and offers exciting future research projects.

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