Gut in diseases: Physiological elements and their clinical significance

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Abstract
The intestinal barrier function of GI tract is very important in the body except for the function of digestion and absorption. The functional status of gut barrier basically reflects the stress severity when body suffers from trauma and various stimulations. Many harmful factors such as drugs, illnesses, trauma and burns can damage the gut barrier, which can lead to the barrier dysfunction and bacterial/endotoxin translocation. The paper discusses and reviews the concepts, anatomy, pathophysiology of gut barrier and its clinical relations.

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INTRODUCTION
The gut has long been thought to be quiescent or inactive during illnesses. It has not been paid much attention and not protected just like other organs such as the heart, lung, and kidney in ICU patients. It is generally considered that biochemical metabolism of the body takes place mainly in the liver. Developments in studying technology and advances in surgical skills have led to a better understanding of nutrients metabolism, anatomic architecture and physiological functions of the gut. Gastrointestinal (GI) tract has functions not only to digest and absorb nutrients, but also to modulate systemic immunity and to prevent enteric bacterial/endotoxin’s invasion, so-called gut barrier function. Functional status of the gut sometimes determines the patients’ prognosis and recovery from diseases. Some traditional managements are not beneficial or completely harmful to intestinal barrier capability, and aggravate the primary diseases the body suffers. There is a practical significance to further study the physiological functions of GI tract. An overall understanding of the mechanisms of pathophysiological changes of the gut in illness would make us take measurable treatments to patients clinically. This review deals with a series of new concepts and advances in research of intestinal barrier that might be helpful to clinicians.

INTESTINAL BARRIER AND RELATED CONCEPTS

Intestinal barrier function
The definition of intestinal barrier function means that the gut can prevent the harmful materials in intestinal lumen such as bacteria and endotoxin from entering other aseptic organs, tissues and blood circulation through intestinal mucous membrane. The gut barrier is chiefly composed of three components: mucous epithelia, intestinal flora, and secreting immunoglobulin and gut associated lymphatic tissues (GALT)\(^1\), namely the ecological barrier (normal inhabitant flora within intestine), mechanical barrier (mucous epithelia) and immune barrier (or secreting IgA, miscellaneous immune cells including intraepithelial lymphocytes and macrophages, neutrophils, natural killer cells underlying the mucous membrane, Payer’s nodes and mesenteric lymph node). Among them mucous epithelium is the most important one that establishes a mechanical barrier between the lumen and blood circulation. The gut barrier in general term means this structural epithelia\(^2,3\).

Architecture of intestinal barrier
There are two pathways for materials in the lumen when entering into the blood circulation through mucous membrane. One is the transcellular route, the other is the paracellular route, which occupies 5 % of the total intestinal surface area. These two configurations are the main constituents of epithelial barrier\(^4,5\). It is considered that there are dispersively nonpolarized holes which are full of water and have a radius of 0.3-0.8 nm on the top of villous cells and a tight-junction of 0.95 nm in radius between villous cells. Substances with different sizes of radius get across intestinal epithelia through transcellular or paracellular way when entering into the body. Molecules smaller than 0.3-0.8 nm in radius could enter into the mucous membrane through these holes. Molecules bigger than those such as disaccharides (lactulose and cellobiose etc) and \(^{51}\)Cr-EDTA seem to enter into epithelia through paracellular tight-junctions. Based on this mechanism the intestinal permeability is measured by combining the smaller (such as monosaccharide) and bigger molecules (such as disaccharide) clinically and experimentally\(^5,6,7\). The two accesses are influenced by alterations of absorbing intestinal area. Substances absorbed by the intestine would reduce after atrophy of villi or bowel resection\(^5,7\).

Bacterial translocation
Bacteria come into aseptic tissues from the bowel lumen through mucosal barrier and colonize in tissues such as mesenteric lymph node, liver, spleen and blood. This process is called bacterial translocation (BT). Studies in experimental rodents showed that translocated bacteria seen most oftenly within intact epithelial cells were Candida, E. coli, Proteus mirabilis, Enterococcus faecalis and so on, whereas E. coli was common and anaerobes and fungi were rare in human beings\(^1,8\). Endotoxin could pass through bowel wall into the body easier than bacteria in the lumen\(^9\).

Mechanisms of intestinal barrier damage
Hunger, malnutrition and longer parenteral nutrition could cause intestinal mucosa atrophy and impair the mechanical bowel barrier\(^1,2,3,10,11\). Shock, ischemia/reperfusion damage, endotoxin of bacteria are the factors that lead to deterioration of intestinal barrier\(^4,9\). It was found that changes in
prostaglandin and related enzymes—Ca++ and cAMP system
within cells affected significantly the structure of gut barrier.
Non-steroid anti-inflammatory drugs (NSAIDs) could destroy
the system and increase the intestinal permeability. Thus it
caused bacteria/endotoxin translocating from intestinal lumen
into blood circulation and other aseptic tissues, and sepsis
would ensue[22,6]. Because of the increments of intestinal
permeability, a series of alterations occurred, such as edema
of tissues underlaid mucous membrane, microvasculature
compression, stasis of blood circulation and thrombosis in
microvasculature system. These patho-physiological changes
impaired the microvasculature underlaid mucosa and
aggravated further the damage of mucosal barrier[22]. Animal
experiments showed that treatment with non-steroid anti-
inflammatory drugs in aseptic rats did not cause impairment
of intestinal mucous membrane. The clinical symptoms were
remitted evidently by treatment with metronidazol to human
bowel lesions caused by NSAIDs[11]. Managements with
antibiotics in rats (it decreased the bacteria load within the
intestine) also prevented NSAIDs from inducing intestine
inflammation. In addition, the method of fasting for reducing
bacterial antigen in alimentary tract could counteract inflammatory
intestinal lesions that caused by NSAIDs either[2,14]. Studies
showed that factors causing alterations in hormones secreted
by mucous enterocytes and changes of related enzymatic
system caused damage of intestinal barrier, and the enteric
bacteria and endotoxin reinforced the damage. Prabhu et al[15]
concluded from researches in rats that surgical stress in the
small intestine caused structural and functional alterations in
the brush border membrane (BBM) through oxidative stress
which could affect gut barrier integrity and the generation of
arachidonic acid, might mediate distal organ dysfunction.
Activation of phospholipase A2 during the process was
considered as a pivotal step. Other investigations discovered
that the increment of intestinal permeability was mainly
due to the relaxation of the tight-junction between intestinal
epithelial cells, indicating that there are close connections
between changes in tight-junction and cytoskeleton. Any drugs
or chemical materials that could impact on cytoskeleton such as
lipopolysaccharide, growth factors, cytokines, and hormones,
would affect the intestinal permeability[16].

Nitric oxide and intestinal barrier
Nadler et al[12] considered that various insults working on
human body could cause overexpression of inducible nitric
oxide synthase (iNOS) and hence a redundant production of
nitrite oxide (NO) occurred. This higher concentration of NO
could lead to deposition of protein salts of nitrite-peroxide (and
nitric-peroxide) on mitochondrial membrane, impair
mitochondrial membrane potential (or permeability) or
decrease ATP production. It would destroy the cellular
respiratory function and aggravate cellular apoptosis, thus
resulting in a breakage in mucous epithelium continuity and
“bare area”. Bacteria entering through the “bare area”, so-called
bacterial translocation takes place. A number of researches
have shown that endotoxin increases NO over-production with
intestinal barrier damages[17-20]. Our animal experiments
confirmed this finding (data not published).

Gut is a central organ for surgical stress
The gut has long been thought to be quiescent or inactive during
illnesses[29]. A large number of animal experiments and clinical
investigations have suggested that functional changes in
gastrointestinal mucous membrane occur during illness.
Bacteria and endotoxin within the lumen enter into the other
aseptic tissues and blood circulation through disordered
functional and/or disorganized structural mucous epithelia,
which influence greatly on occurrence, progress and
transformation of illnesses[1-4,10,12,20-30]. In recent decades based
on large amounts of animal experiments and clinical investigations,
a series of new functions concerning gut metabolism and
nutrition, intestinal barrier and immunity function, have been
recognized. Following the elucidation on mechanisms of
systemic inflammatory response syndrome (SIRS) and
multiple-organ dysfunction syndrome (MODS)[11,37], the
action of the gut as a central organ for surgical stress has also
been put forward[29,30,32,35]. It is now known that the
gastrointestinal tract contains about 50% of reticular endothelia
and other immune cells, and occupies about 80% of the total
humoral immunity of a human body. It is therefore the largest
immune organ of the body[22-35]. Various insults such as trauma,
burn, infection, shock, ischemia/reperfusion, irradiation
therapy, chemical therapeutic medicines, and SIRS, could
directly or indirectly cause an overgrowth of bacteria in bowel
and lead to deterioration of intestinal barrier. Hence
translocation of enteric bacteria and/or endotoxin, SIRS, sepsis
and even MODS ensue[18-20], suggesting that the function of
the gut in illness determines the patient’s prognosis[38, 41].
Based on this theory and clinical practice above, Wilmore et al put
forward that gut was a reservoir of pathogens in illness and a
central organ for surgical stress[29, 41]. This has been accepted
by most scholars[8,38].

EVALUATION OF GUT BARRIER
There are many ways for measuring intestinal barrier function,
but no one is perfect. Three regular approaches are often used
to measure the function of gut barrier. The first is to examine
the morphologies of mucous membrane such as thickness of
mucosa, depth of crypts, architecture of villi, proliferating
cellular nuclear antigen (PCNA) and intraepithelial
lymphocytes (IELs). The second is to test translocation of
bacteria/endotoxin, or bacteria growth and endotoxin
concentration in mesenteric lymph node (MLN), liver, spleen,
portal vein and/or systemic circulation. The third is to measure
intestinal permeability[5,6], which is often carried out by using
some labeling substances in experimental and clinical
researches. Such substances could be water-soluble, nontoxic,
and freely permeated through numerous small ‘ water pores’
in the cell membranes of mucosal enterocytes. There is few or
no such substances in body tissues that could not be
metabolized. They should be excreted rapidly in an easily
measured form. The substances matching with conditions
mentioned above are lactulose, mannitol, 51Cr-EDTA, PEG400
and inulin[25,62]. The approaches that are most frequently used
to examine intestinal permeability are the two-sugar test, or
lactulose/mannitol test. There are two pathways for the
substances to get across the bowel mucous membrane,
transcellular (through plasma membrane of enterocyte in the
tip ) and paracellular (the tight-junction between cells) routes.
Smaller molecular substances (such as monosaccharide) pass
through enterocytes by transcellular route, whereas bigger
molecules (such as disaccharide) get across enterocytes by
paracellular pathway. Thus, the increase of small intestinal
permeability reflects the “leakage degree” of mucous
enterocytes[2,17].

DISEASES AND FACTORS CAUSING GUT BARRIER
DYSFUNCTION
Any insults that lead to an overgrowth of enteric bacteria, an
impairment of immune defence function and a damage to
mechanical barrier of the gut would result in disorders of the
intestinal barrier, and bacteria/endotoxin translocation would
ensue[1-4,6,10,11,27]. Followings are the causes that lead to an
increase of intestinal permeability.

...
**Infection**
This includes intestinal and intraperitoneal infections[38] and infections out of the intestinal tract (such as pneumonia)[43].

**Parenteral nutrition**
The issue has been confirmed by many animal experiments and clinical researches[10,11,21,25,44,45]. The reason is that 70 % of nutrients are absorbed directly from gut lumen, whereas only 30 % is provided by arterial blood supply[41]. Thus parenteral nutrition makes intestinal mucous membrane in a hunger state and leads to gut mucosa atrophy.

**Malnutrition**
Malnutrition could cause atrophy of intestinal mucosa, an insufficiency of protein synthesis and deficiency of body immunity. These would impair the gut barrier[13-27,28,32,34].

**Overgrowth of enteric bacteria**
Drugs or infection caused by some pathogens could lead to the overgrowth of intestinal bacteria and hence injures the gut barrier[3,27,39,65,46].

**Endotoxin**
Endotoxin could increase NO production in the body and lead to impairment of intestinal barrier function[27,46,47]. Our animal experiments were in accordance with this (not shown).

**Surgical stress**
Various injuries such as burn/scald[10], organ transplantation (reperfusion injury), surgery and trauma[46,50], haemorrhagic shock and many other insults that lead to SIRS, would bring about an increment of intestinal permeability and damage of gut barrier[4,21].

**Drugs**
Oral administration of castor oil would cause a physical damage of intestinal mucous membrane in mice. Diabetes mellitus induced by streptozotocin in mice caused an overgrowth of enteric bacteria and an immunity injury of the body. Cyclooxygenase inhibitors of prostaglandin such as meclofen acid block production of prostacyclin in bowel mucous membrane, which increases the permeability of mucous epithelium and bacterial translocation[4,11]. It can also bring about intestinal pathological changes[43,51]. Immunosuppressive agents such as chemotherapy drugs, anti-transplant rejection drugs[4,52], and antiacidics can destroy gut mucosal barrier[51].

**Multiple illnesses**
Various abdominal diseases could cause an increase of intestinal permeability. One of these is inflammatory bowel disease (IBD)[21,42]. Others are intestinal obstruction, biliary block[4,9], leukemia, endotoxemia, parenteral and enteral nutrition[1,4,10,11].

**Physical injury**
It includes radioactive intestinal damage[54].

**AGENTS DECREASING INTESTINAL PERMEABILITY**
Enteral nutrition could alleviate intestinal atrophy of mucous membrane during stress and could lower gut permeability, improve mucosal immunity. These have been confirmed by experiments and clinical practices[11,13,37]. Treatments with some special nutrients or immune-modulating drugs for patients with parenteral nutrition could also ameliorate intestinal barrier function[23,3,21].

**Glutamine**
Except for nutrient digestion and absorption, one of the functions of intestinal mucosa is to prevent enteric bacteria and endotoxin from entering into other parts and blood circulation of the body. It is now considered that gut barrier dysfunction is an important cause for infectious complications when patients suffer from hyper-metabolism after surgery and trauma[4,4,10,27,29,31]. It is still unclear what pathological mechanisms lead to gut barrier failure. It is taken for granted that two important factors causing intestinal barrier failure are the damage of intestinal blood supply and the lack of nutrient support[21]. It has been discovered from animal models and septic patients that the state is associated with insufficiency of perfusion (including disorders of microcirculation) and lack of essential nutrients (including glutamine) in their mucosa[2,21]. Except for antimicrobial therapy of selective decontamination aiming at getting rid of enteric pathogens, it has been carried out to protect gut barrier function from being injured or have been injured in patients threatened by enterogenous infection. A promising approach is to use glutamine parenterally, which is an essential nutrient for the gut in stress and decreases sharply in illness. A series of experiments and clinical researches showed that nutritional support supplemented with glutamine could improve gut barrier function and enhance the body immunity[8,10,21,32,34,42,44,55-58].

Glutamine exerts its effects on the body in many ways. It supplies fuels for mucous enterocytes and strengthens the barrier structure of the gut on the one hand, and increases secretion of IgA by regulating IL-4 and IL-10 on the other hand, thus preventing enteric bacteria from adhesion to intestinal mucosa and subsequent bacterial translocation[20].

**Arginine**
Arginine influences the body immune system extensively. First, it is the precursor of polyamines and nucleic acids, which are essential for cell hyperplasia and differentiation. Second, it can produce hydroxyproline through metabolism to promote collagenation. Third, it can stimulate different human cells to secrete hormones such as growth hormone, glyagon, insulin-like growth factor 1 and insulin etc., which have various effects on the immune reactions of the body. In addition, arginine is also a precursor of nitric oxide, an important immune molecule[12,44], and has functions to kill bacteria, protect or impair intestinal barrier[32,44,60,61]. Some scholars reported that arginine could alleviate the secondary damage of gut barrier[60,63], whereas others held a completely different opinion, which had also confirmative evidences[50,64]. Further investigations on the effects and mechanisms of arginine on the body are needed.

**Recombinant human growth hormone (rhGH)**
Growth hormone has many biological functions[22,44,64-66]. It could decrease intestinal permeability and improve gut barrier function in illness[19,58,69-71]. Possible mechanism of this may be that it promotes hyperplasia of intestinal epithelia[72], or enhances the mechanical barrier of mucous membrane.

**Insulin-like growth factor-(IGF-I)**
The main effects of IGF-I on the body are basically the same as rhGH[73,74]. It promotes hyperplasia of mucous membrane of the intestine, and increase the uptake and utilization of glutamine by the bowel when in sepsis[50].

**Nucleic acid**
Kishibuchi et al[75] observed the alterations of cellular ultrastructure under electronic microscope, variations of intestinal permeability and changes of protease in bowel...
mucous membrane, which showed that intestinal barrier function was significantly improved.

**Others**

Epidermal growth factors (EGF) have positive effects on the proliferation of mucous epithelium[16].

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