The physicochemical environment of the neonatal intestine

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ABSTRACT    Dietary intake, bacterial metabolites, and the secretion of factors (eg, proteins, electrolytes, lipid-soluble molecules, and water) by the body each contribute to the physicochemical environment of the gastrointestinal tract. Peristalsis regulates the changes along the length of the intestine. However, coordinated peristaltic responses develop as premature infants mature. In addition, the physicochemical environment of the center of the intestinal lumen differs from that of the epithelial surface. The area adjacent to the small intestinal epithelium is more acid than the bulk phase. Na+/H+ exchange antiporters in the epithelial cell apical membrane generate this acidity. Mucus maintains the acid microclimate by preventing free diffusion of hydrogen ions into the bulk phase. Development also affects these mechanisms. Changes in the lumenal environment may alter the synthesis of signaling molecules expressed by the intestinal epithelium. Thus, the epithelium, through changes in gene regulation, may act as an active interface that transmits information about the composition of the intestinal lumen to the mucosal immune system. Premature neonates are at risk of necrotizing enterocolitis, a disease almost exclusively associated with oral feeds. The pathogenesis of this condition may, in part, be due to the immaturity of the interactions between the physicochemical environment of the lumen and intestine. Am J Clin Nutr 1999;69(suppl):1028S–34S.

KEY WORDS Infant, peristalsis, unstirred layer, acid microclimate, nutrient regulation of gene expression, epithelial signaling, intestine

INTRODUCTION

The intestinal lumen is a space topologically outside the living organism, the composition of which is regulated by the body. The physicochemical environment of the intestine determines how nutrients are absorbed and how potential pathogens are controlled. The ability of the intestine to dominate this space is therefore critical to life. The key evolutionary event in the development of multiorgan animals was containment of this external environment in a tube to gain effective control over it. The intestine was then able to select from this area those things that were beneficial while leaving behind those that were of no benefit or even harmful. Unicellular organisms, sponges, and other collections of cells cannot regulate their absorptive surface. They, therefore, have not solved the essential problem of allowing other cells in the body to specialize into organs whose environment is bathed in more consistent surroundings than are found in nature. The evolution of the intestine led to the evolution of many different tissue types including muscles and nerves, which ultimately resulted in intelligent life. This review will examine how the intestinal environment is regulated, with particular reference to neonates.

The environment of the intestine is derived from 3 main factors: dietary intake, bacterial ecology, and factors such as peristalsis and glandular secretions that are intrinsic to the intestine. Regulation of the physicochemical environment therefore depends on the body’s ability to control each of these areas effectively. Control of the microbial ecology is the subject of another review in this supplement. Dietary intake is controlled by active ingestion. As the development of the gut led to the evolution of complex organisms, so also the appearance of coordination in multiorgan animals resulted in the control of ingestion. Animals of higher order select what they eat. Thus, the ability of the intestine to enable complex organisms to evolve in turn resulted in the control of ingestion. Interplay therefore occurred between intestinal evolution and phylogeny of the complex animal. This concept of “evolutionary reinforcement” is an underinvestigated area of biology. It occurs in other examples, notably the coevolution of color sensing by insects and color display by flowers.

This article presents evidence that not only does the intestine control the environment of the lumen but that the reverse also occurs; namely that a change in the intestinal lumen can alter the epithelial cell. Short-chain fatty acids will be used to illustrate some of these points; both diet and bacterial flora alter their concentrations, and their uptake by the gut is subject to changes in the environment of the epithelial cell surface. They also affect the expression of genes within the epithelium.

PERISTALSIS

The intrinsic mechanisms that alter the intestinal environment include many distinct components (Figure 1). Factors such as

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proteins, electrolytes, lipid-soluble molecules, and water are swept along the intestine together with digested food by peristalsis. This longitudinal propulsion limits the variation in intestinal contents at any one point along the gastrointestinal tract. In health, the greatest changes occur in different distances down the intestine. To a great extent, therefore, peristalsis replaces temporal distinctions (as would be seen with reactions in a static receptacle) with spatial differences. This fundamental characteristic of the gut allows specialized activity, such as absorption and glandular secretion, to be located at strategic points along the length of the tract.

Peristalsis is developmentally regulated. In term infants, as in adults, migrating motor complexes pass as waves along the gastrointestinal tract (1). Feeding results in further complexes superseding the background wave pattern. In preterm neonates, however, migrating complexes are not present until around 34 wk gestation (2, 3). Thus, the mechanisms necessary for maintaining a stable temporospatial relation in the intestine are not developed.

In fetuses, the environment of the intestine is mostly controlled by the amniotic fluid and thus the role of peristalsis in regulating lumenal homeostasis is correspondingly less important. In infants born before term, however, the intestinal environment is affected by the outside world. Thus the possibility of buildup of substances within the intestine exists because the propulsive action of the intestine is not yet developed.

THE ENVIRONMENT OF THE EPITHELIAL SURFACE

The changes that occur in the gastrointestinal tract longitudinally are determined to a large extent by peristalsis. However, the environmental changes that occur transversely from the center of the intestinal lumen are regulated by different factors. Molecules passing from the bulk phase (ie, the contents of the intestine that are propelled by peristalsis) of the intestine to the epithelial cell apex encounter 2 specific regions, the unstirred layer and the acid microclimate. Both are present in the neonatal intestine. The effect of each entity on the absorption of molecules depends on the chemical nature of the molecule in question. For example, the unstirred layer is a significant barrier to lipid-soluble molecules, whereas the acid microclimate has a large effect on weak electrolyte uptake.

Unstirred layer

The unstirred layer may not be a distinct layer on the mucosal surface, but a diffusion barrier in which molecules diffuse at a rate different from that predicted by the diffusion coefficient of water. Winne (4) has used the term preepithelial diffusion resistance to describe this notion. However, the term unstirred layer better expresses the idea that the greater the agitation of the bulk phase the less resistant the diffusion barrier becomes. In preterm neonates, the degree of mixing of lumenal contents may be small because of immature peristaltic activity, and might result in an unstirred layer of greater thickness than is present in neonates born at term.

Although the thickness of the unstirred layer has only been estimated (5), we do know that it is a significant barrier to highly lipid-soluble molecules. To a great extent the effect of the unstirred layer on fat absorption is minimized by micelle formation, allowing lipids to be taken directly into the epithelial cell. However, in premature neonates, pancreatic and biliary functions are not as well developed as in adults, making the unstirred layer a significant barrier to lipid absorption. The propensity for lipids to remain in the bulk phase in preterm infants may make long-chain fatty acids (6) possible factors in the etiology of necrotizing enterocolitis, a disease with a high mortality (see below). Water-soluble molecules are not greatly impeded by the unstirred layer, and short-chain fatty acids are readily able to reach the epithelial cell surface.

One component of the unstirred layer that has been difficult to quantify in neonates is the role of mucus. Smithson et al (7) measured the size of the unstirred layer in rat intestines by using hydrolysis rates of sugars, resulting in a thickness estimate of ≈700 μm, assuming that the fluid had the same diffusion coefficients as water. These investigators concluded that this size was untenable because such an unstirred layer would occupy most of the intralumenal area. They suggested that the diffusion barrier could have been thicker over a smaller volume by the contribution of mucus. Mucus secretion is well developed in neonates, although, as in rodents, its composition may change during development (8).

Acid microclimate

The mucus coat and outer glycocalyx of the intestinal epithelium are composed of negatively charged carbohydrate side
chains. This negative charge reduces the diffusibility of hydrogen ions within the surface layer of the cell. Any pH at the apical surface of the epithelium will thus be maintained in the region. In an absorption study on salicylic acid, a weak electrolyte, uptake was much greater than expected when the bulk phase of the intestine was alkaline (9). In fact, the absorption of salicylate in experiments was equivalent to that expected if the bulk phase had a pH value of 2 units lower than it was. Absorption rates of weak bases were altered in the opposite direction to weak acids in rat small intestines (10). In a relation of absorption against pH, the uptake of a weak electrolyte should be at 50% of its maximum when the pH of the absorptive surface is equal to the pK of the electrolyte. These data resulted in the hypothesis that the microclimate of the small intestinal surface is acidic. Direct experiments measuring the pH of the surface with micro-electrodes have confirmed this prediction in both humans and rodents (11–14). In the proximal small intestine, the pH of the microclimate was significantly more acidic than in the bulk phase, but differences in pH in other parts of the intestine were not significant. Indeed, in the stomach, the pH at the epithelial cell surface was higher than in the bulk phase of the stomach. Therefore, changes at the surface of the epithelium are less variable than those in the bulk phase in different parts of the gastrointestinal tract.

The pH of the intestinal microclimate changes during development (15). In suckling rats the microclimate is even more acidic than in adult rats (Figure 2). Weak acids (such as short-chain fatty acids) are particularly well absorbed under these conditions. Studies by Said et al (15) showed that the pH of the acid microclimate differed with age and was maintained by mucus. The addition of a mucolytic agent (N-acetylcysteine) reduced the acidity of the apical surface.

Mucus impedes the free diffusion of hydrogen ions into the bulk phase but it does not generate the acidity. Hydrogen ions are secreted by the epithelial cells in exchange for sodium ions by Na+/H+ antiporters in the intestinal apical membrane. Sodium passes readily into epithelial cells down its concentration gradient, causing hydrogen ions to be pumped into the apical space where they are trapped by the negatively charged mucopolysaccharide side chains, as discussed above. Removal of sodium from the bulk phase causes a pH reduction in the microclimate (16). For weak electrolytes (such as short-chain fatty acids), sodium removal would indirectly alter absorption by increasing the pH, which normally maintains the weak acid in its more soluble form. The acid microclimate has a direct effect on transport of dipeptides (17) which, unlike amino acids, are transported into the cell in association with hydrogen ions. On the basis of studies in rodents (15), it appears that human neonates would produce a microclimate sufficient for these absorptive functions. However, little is known about the microclimate in preterm neonates, and this remains an interesting area for further study.

**LUMENAL MOLECULES AND GENE EXPRESSION IN EPITHELIAL CELLS**

The ability of the intestine to regulate its environment has been acknowledged for decades. How this is achieved and how it varies throughout development are more recently being understood. On the other hand, the converse relation of how the lumen might affect the intestinal epithelium has not been fully realized.

The possibility that the epithelium may respond to luminal molecules, signaling their presence to the mucosal immune system, is only now being appreciated. The epithelium has mainly been regarded as a passive barrier with points of selective filtration (Figure 3A), surveillance of the luminal contents occurs after this filtration has taken place (18).

It has long been known that nutrients may alter the expression of genes whose actions are restricted to the confines of the epithelial cell monolayer of the intestine (Figure 3B). As an example of this cellular adaptation, changes in the luminal milieu can cause variations in the expression of disaccharidases and nutrient transporters. The relevance of luminal factors on gene expression of proteins whose actions occur away from the epithelium, such as that of cytokines and growth factors, is quite different. In this situation (Figure 3C) the epithelium acts as a mediator between the luminal contents of the intestine and target cells beyond the epithelial barrier. Such target cells include immunocytes in the mucosa and cells recruited from the circulation. This epithelial signaling (Figure 3C) represents a higher level of evolutionary complexity than does cellular adaptation (Figure 3B). Although epithelial cellular adaptation is beneficial to the body as a whole, it involves only 1 cell type. Epithelial signaling, on the other hand, requires the cooperation of 2 different cell types, those of the epithelium and of the mucosal immune system.

The epithelium of the small intestine interacts with other cells of the mucosal immune system (20) by secreting cytokines, which directly alter immune responses, and growth factors and their binding proteins, which may affect the proliferation of immune cells. Furthermore, the small-intestinal epithelium may present antigens directly to T cells through class II major histocompatibility complex (MHC) molecules or through CD1 molecules. The molecular mechanisms governing the expression of these genes have features in common with those of other enterocyte genes (such as disaccharidases and nutrient transporters that respond to dietary nutrients and factors in the lumen). For example, the epithelial cell must still recognize the nutrient or other luminal factor, and other mechanisms must then transduce this recognition into molecular changes that alter directly the expression of immunologic genes. The main difference in molecular terms in this adaptive response (Figure 3B) is that the resulting actions of the proteins escape from the influence of the epithelium and interact with receptors on target cells (Figure 3C).

Epithelial signaling (Figure 3C) enables luminal factors to alter immune responses while the integrity of the epithelial bar-

![Figure 2](https://example.com/f2.png)

**FIGURE 2.** The microclimate at the surface of the intestine is more acidic than that in the bulk phase. In suckling rats the microclimate is even more acidic than in adults. However, there are no data in the premature human neonate. Data from reference 15. Error bars indicate SE.
A) Epithelial Transfer  
B) Change in Epithelial Phenotype  
C) Epithelial Signalling

**FIGURE 3.** Possible interactions of molecules from the intestinal lumen with the epithelium. Traditionally, the epithelium has been seen as a selective barrier to molecules, admitting those required for energy intake or immunosurveillance and excluding others (A). However, nutrients can alter the phenotype of the epithelium to adapt to changing nutritional needs (B). When changes in the intestinal lumen induce new proteins that interact with mucosal immune cells, the epithelium can act as a membrane signaling information from the lumen to the immune system (C). Reproduced from reference 18 with permission.

**Chemokines**

Chemokines are a family of low molecular weight (8–12 kD), basic, heparin binding proteins that are related by both primary structure and position of 4 cysteines in the amino acid sequence. They are involved in the multistep process of selective adhesion, activation, and migration of leukocytes and can both initiate and perpetuate inflammation. They are generally induced by proinflammatory signals [eg, interleukin (IL)-1 or lipopolysaccharide]. In contrast with classic chemoattractants, chemokines can direct the migration of defined leukocyte subpopulations. The chemokine family has been divided into 2 subfamilies (α- and β-chemokines) based on the arrangement of the first 2 cysteines and the chromosomal location of their genes. In general, α-chemokines are potent attractants and activators of neutrophils but not monocytes; β-chemokines are potent attractants and activators of monocytes but not neutrophils. However, each specific chemokine has its own spectrum of activity that includes an array of different possible effects. Several chemokines are expressed in the intestinal mucosa, by lamina propria leukocytes, fibroblasts, and intestinal epithelial cells (22, 23). Intestinal epithelial cells may therefore participate in the processes that regulate the composition of the various leukocytes in the lamina propria that control inflammation. Chemokines have a long half-life in vivo relative to other cytokines, making them feasible candidates for long-lasting control over mucosal immune responses.

IL-8 is a member of the α-family of chemokines. It is a potent chemotactic factor for neutrophils and may be important in recruiting them into the gastrointestinal tract during inflammation. IL-8 also stimulates the release of superoxide radicals in neutrophils as well as other potential mediators of damage in intestinal inflammation. Furthermore, it increases the permeability of vascular endothelium to albumin resulting in tissue edema. It is increased in inflamed intestine in several conditions (24). Its production in intestinal epithelial cells has been documented in response to bacterial invasion and by other agents including phorbol myristate acetate and IL-1 (25), but evidence is now emerging that its expression is altered by dietary factors.

n-Butyrate is a short-chain fatty acid derived from the bacterial metabolism of unabsorbed carbohydrate. The type of fiber consumed in the diet alters the amount of butyrate produced in the stool (26). In addition, the populations of butyrate-producing bacteria in the intestine may themselves vary with diet. Infants fed casein-based artificial milk formulas (27, 28) produce large amounts of butyric acid and propionic acid in the stool, whereas the predominant short-chain fatty acid in breast-fed infants is acetic acid. Furthermore, casein inhibits the bacterial flora (lactobacilli) responsible for high acetate production (29). Butyrate concentrations, therefore, depend on both the type of bacteria in the

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**INTESTINAL ENVIRONMENT IN THE NEONATE**

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Nutrient control of body growth in the gut and the amount of substrate available for butyrate production. Signaling alterations in butyrate production to the mucosal immune system would provide information about events in the intestinal lumen, in addition to being an epithelial nutrient. Butyrate increases IL-8 secretion by cultured enterocytes and acts in synergy with inflammatory stimuli, such as lipopolysaccharide and IL-1β (30). The changes in the pattern of chemokine secretion induced by butyrate show that luminal factors may alter the involvement of epithelial cells in mucosal immune responses. In rodent, the family member that performs a comparable function to IL-8 is macrophage inflammatory protein 2 (MIP-2). Cell lines derived from rodent intestinal epithelium secrete MIP-2 in response to lipopolysaccharides and sodium butyrate (31). Each effect of butyrate was associated with corresponding changes in chemokine messenger RNA (mRNA). Future studies are needed to show whether, in vivo, epithelial cells secrete MIP-2 in response to inflammatory mediators and what the effect of butyrate and other dietary factors on this expression might be. However, the effect of dietary factors on class II MHC and invariant chain expression (32) has been examined in vivo in our laboratory.

Class II major histocompatibility complex and invariant chain expression

The initiation of an immune response to protein antigen normally requires the help of T lymphocytes. Activation of T lymphocytes in turn depends on the processing and presentation of peptides by an antigen-presenting cell (APC) (33). Class II MHC heterodimers (αβ in the rodent) are the molecules that present the processed exogenous antigen to the T cell receptor. In addition to classic APCs (dendritic cells, macrophages, B lymphocytes, and Langerhans cells), several other cell types, including intestinal epithelial cells, express class II MHC and may function as APCs. Electron micrographs showing lymphocytes in contact with enterocytes in vivo lend support to this possibility (34). The processing and presentation of exogenous antigen require an additional protein, the invariant chain (li chain) (35).

Diet has a marked effect on the expression of class II MHC and li chain in the mouse intestinal epithelium. The expression of both genes is regulated developmentally (36) in the epithelium, appearing normally in the first week of life (unlike in lamina propria cells, where it is expressed from before birth). In addition, the timing of expression can be altered by delaying the age of weaning from mother’s milk to a normal feed diet (37). The expression of class II MHC and li chain is normally apparent 3–4 d after weaning onto normal feed. However, weaning onto an elemental diet (containing chemically synthesized amino acids, simple sugars, and fats) does not induce the expression of class II MHC or li chain. Differences in the expression of these 2 molecules and their transcripts were observed in cells isolated from intestinal epithelium at different time points after birth in mice changed on day 17 from mother’s milk either to an elemental diet (lanes 1–3) or normal mouse feed (lanes 4–7). The blot was probed with invariant chain complimentary DNA and autoradiographed for 48 h. Mice were examined at days 23, 25, 27, and 29. Blots were also probed with y-actin complimentary DNA to verify uniformity of enterocyte extraction. Reproduced from reference 32 with permission. mRNA, messenger RNA.

Insulin-like growth factor binding proteins

Immune responses depend not only on the activation of T cells, but also on the ability of T cells to proliferate. One factor involved in lymphocyte proliferation is insulin-like growth factor I (IGF-I). This agent is normally thought of as the primary molecule responsible for nutrient control of body growth in health (37, 38) and disease (39).

IGF-I also acts on cells of the immune system. Activated T cells and B cells possess receptors for IGF-I. IGF-I increases the proliferation of both of these cell types and is chemotactic for activated T cells. Treatment of adult mice with recombinant human IGF-I induces striking modifications in lymphocyte number and function (40). Fourteen days of treatment with IGF resulted in increases in both CD4+ T cells and splenic B cells. Mitogenic responses of T cells and B cells were also enhanced, showing that IGF-I increases lymphocyte numbers and activity.

In extracellular fluids, IGF-I is bound to IGF binding proteins (IGFBPs), of which 6 have been described and cloned (41). Their biological functions include regulating the stability and clearance of IGFs, acting as shuttles for IGF transport, and modulating the actions of IGFs at a cellular level. Cultured intestinal epithelial cells (42, 43) secrete IGFBPs, and it is possible that the epithelium can influence the proliferation of activated mucosal lymphocytes by this means. Furthermore, data have shown that nutritional factors affect the production of IGFBPs in cells line in vitro (44). Butyrate, for example, increases IGFBP-2 (the protein with the greatest affinity for IGF-II) while reducing the secretion of IGFBP-3 (which binds avidly to IGF-I). Glutamine, on the other hand, increases IGFBP secretion without altering the relative secretion of one binding protein over another. These changes in IGFBP secretion are correlated with alterations in IGFBP mRNA. Thus, not only may nutritional factors influence IGF and IGFBP secretion by the liver into the circulation (45), resulting in changes in growth of the whole individual, but nutrients may also affect the IGF-IGFBP system in the intestinal epithelium, leading to alterations in the proliferation of the mucosal immune system.

Necrotizing enterocolitis

Necrotizing enterocolitis is a disease that occurs almost exclusively during the neonatal period. It is characterized by ulceration and necrosis of the gastrointestinal tract, primarily the distal small intestine and colon. It has an incidence of 1–3 cases per 1000 live births (46). Infants weighing <1000 g are at most risk for necrotizing enterocolitis. Despite the high degree of experience with...
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may be important in the pathogenesis of intestinal disorders.

beneath, and speculated that in the immature gut this signaling be signaled by the epithelium to the mucosal immune system described how variations in the environment of the intestine may described how variations in the environment of the intestine may in preterm infants are likely to be important in the pathogenesis of necrotizing enterocolitis. Finally, this article environment in preterm infants are likely to be important in the pathogenesis of necrotizing enterocolitis. Long-chain fatty acids in piglet small intestines to short-chain fatty acids. Whereas these molecules serve as sources of nutrition for colonic epithelium, it is possible that in the small intestine they may increase the risk of necrotizing enterocolitis (49). Clarke et al (6, 50) showed that excessive fermentation of carbohydrate in the small intestine may cause an inflammatory condition resembling necrotizing enterocolitis. However, other nutrients have also been implicated in necrotizing enterocolitis. Long-chain fatty acids in piglet small intestines induce a necrotizing enterocolitis–like condition (51, 52).

Although many theories could account for how changes in the lumen of the intestine may alter inflammatory responses, one possibility is that luminal molecules alter the signaling between the intestinal epithelium and the mucosal immune system. In premature neonates, this interplay between lumen and intestine may not be sufficiently developed to deal with molecules derived from the extraterrine environment.

CONCLUSION

This article examined some of the factors that regulate the physicochemical environment of the intestine and illustrated how these factors may be altered in neonates. Changes in the luminal environment in preterm infants are likely to be important in the pathogenesis of necrotizing enterocolitis. Finally, this article this condition, its associated mortality rate is still ~30% (47). The disease has been well described (47) and this review provides more information on its clinical features, treatment, and prognosis. Necrotizing enterocolitis is relevant to the present article because the physicochemical environment is important in its pathogenesis. At present the mechanisms responsible for development of this disease are speculative. However, it is known that almost all infants with necrotizing enterocolitis have received milk feeds, pointing to changes in the intestinal lumen as central to the disease process. Israel (46) compiled 6 studies with a total of 537 infants and noted that all but 7% had been fed enterally. Various possibilities exist as to which aspect of enteral feeds causes the pathology. Because lactase activity is relatively low in premature infants, undigested carbohydrate was proposed as a possible agent (48). Bacteria metabolize carbohydrates in the intestinal lumen to short-chain fatty acids. In this condition, its associated mortality rate is still ~30% (47). The disease has been well described (47) and this review provides more information on its clinical features, treatment, and prognosis. Necrotizing enterocolitis is relevant to the present article because the physicochemical environment is important in its pathogenesis. At present the mechanisms responsible for development of this disease are speculative. However, it is known that almost all infants with necrotizing enterocolitis have received milk feeds, pointing to changes in the intestinal lumen as central to the disease process. Israel (46) compiled 6 studies with a total of 537 infants and noted that all but 7% had been fed enterally. Various possibilities exist as to which aspect of enteral feeds causes the pathology. Because lactase activity is relatively low in premature infants, undigested carbohydrate was proposed as a possible agent (48). Bacteria metabolize carbohydrates in the intestinal lumen to short-chain fatty acids. In premature neonates, this interplay between lumen and intestine may not be sufficiently developed to deal with molecules derived from the extraterrine environment.

CONCLUSION

This article examined some of the factors that regulate the physicochemical environment of the intestine and illustrated how these factors may be altered in neonates. Changes in the luminal environment in preterm infants are likely to be important in the pathogenesis of necrotizing enterocolitis. Finally, this article described how variations in the environment of the intestine may be signaled by the epithelium to the mucosal immune system beneath, and speculated that in the immature gut this signaling may be important in the pathogenesis of intestinal disorders.

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