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SPECIAL REVIEW SERIES: Molecular morphological approach for pathogenesis of hepatogastrointestinal diseases

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Molecular morphology of the digestive tract; macromolecules and food allergens are transferred intact across the intestinal absorptive cells during the neonatal-suckling period

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Abstract Food allergies represent an important medical problem throughout the developed world. The epithelium of the digestive tract is an important area of contact between the organism and its external environment. Accordingly, we must reconsider the transport of intestinal transepithelial macromolecules, including food allergens, in vivo. The intestinal epithelium of the neonatal-suckling rat is a useful model system for studies into endocytosis and transcytosis. Macromolecules and food allergens can be transferred intact with maternal immunoglobulins across the absorptive cells of duodenum and jejunum during the neonatal-suckling period. This review summarizes these observations as well as our recent molecular morphological studies.

Key words Neonatal-suckling · Small intestine · Duodenum · Jejunum · Ileum · Absorptive cells · Endocytosis · Transcytosis · Macromolecule · Food allergen

Introduction

The digestive tract communicates directly with the external environment. The function of the digestive tract is to reduce ingested foods to small molecules that can be absorbed by the absorptive cells of the small intestine, thus removing nutrients from food and passing them into the general circulation.[1–3] The absorptive cells throughout the small intestine of neonatal-suckling mammals are developmentally specialized to take up macromolecules from maternal milk, and in the duodenum and jejunum such cells transport maternal antibodies into circulation without lysosomal degradation.[4–6] In the ileum, absorptive cells are specialized for massive endocytosis and intracellular lysosomal degradation of maternal milk macromolecules.[7–10] At 3 weeks of age, these cells are replaced abruptly with absorptive cells of apparently adult form and function in the rat.[11–19]

Food allergies are the result of abnormal immunological responses to food proteins.[20–26] In the first stage of such an immunological response, food allergens are known to be transferred intact across the epithelium into the lamina propria mucosa of the digestive tract.[27] The intestinal absorptive cells of neonatal-suckling rats are a useful model system for studies into the endocytosis and transcytosis pathways, by which large amounts of maternal immunoglobulins, nonspecific macromolecules, and food allergens are transferred intact across the absorptive cells.[28]

This review focuses on molecular morphological studies, as well as membrane-bound or fluid-phase endocytosis, transcytosis, transepithelial food allergen transport, and prevention of food allergies during the neonatal-suckling period.

Absorptive cells of small intestine during the neonatal-suckling period

The absorptive cells of the small intestine are columnar cells with a brush border of closely packed microvilli on their luminal surface. Adult absorptive cells do not absorb macromolecules from the lumen. On the other hand, neonatal-suckling absorptive cells are capable of endocytosing macromolecules from maternal milk, including immunoglobulins. An apical endocytic membrane system of cells is specialized for uptake, transport, and intracellular digestion of macromolecules.[4–10] It is known that absorptive cells differ in structure and function between the proximal and distal small intestine during the neonatal-suckling period. We previously reported that absorptive cells could be morphologically categorized into three types in the small intestine of suckling rats.[29] The first type is observed in the epithelium of the duodenum and proximal jejunum (Fig. 1a). These

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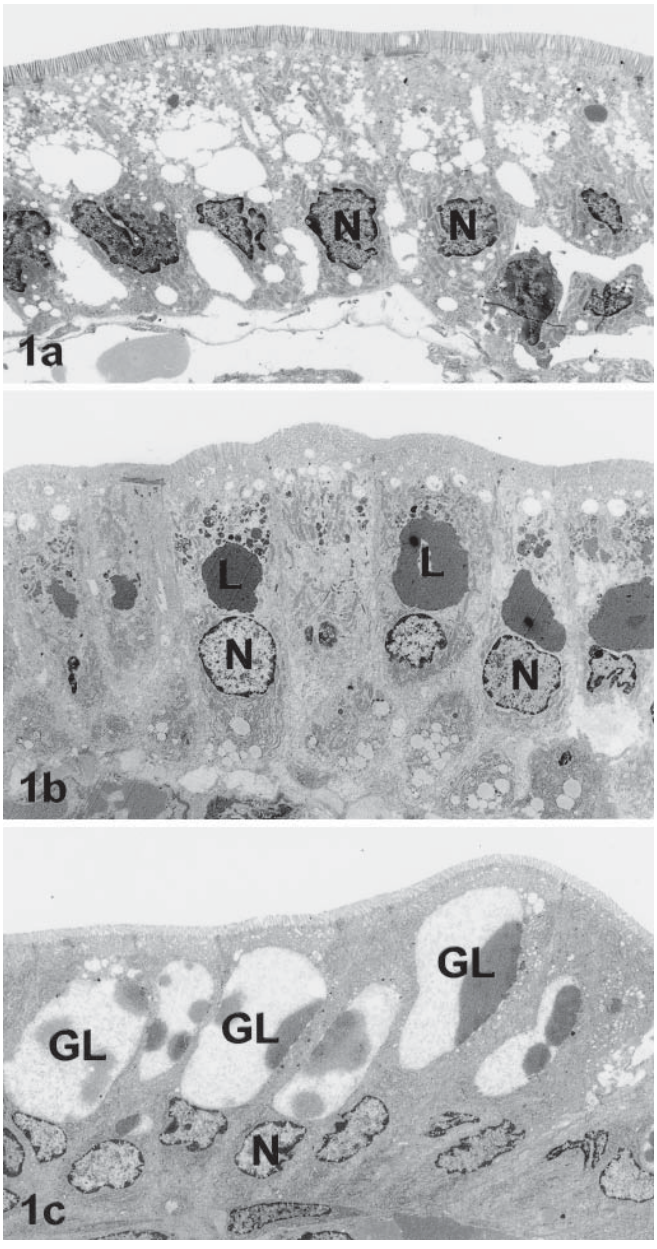


Fig. 1. Electron micrographs of the suckling rat small intestine. **a** Jejunum. Many lipids are observed in the absorptive cells and intercellular spaces. **b** The middle segment of the small intestine. In the absorptive cells, an apical endocytic membrane system including a large homogeneous electron-dense lysosome (*L*) is observed. **c** Ileum. In the absorptive cells, an apical endocytic membrane system including a heterogeneous giant lysosome (*GL*) is observed. *N*, nucleus

cells, called jejunal absorptive cells, possess numerous lipid particles and droplets in the cisternae of the smooth endoplasmic reticulum in the apical region, the vacuoles of the Golgi apparatus in the supranuclear region, and the intercellular spaces between adjacent cells. These absorptive cells also contain an apical endocytic membrane system; apical coated pits, small tubular pits, coated vesicles, vesicles, tubules, early endosomes, late endosomes, and small homogeneous lysosomes. The second type is observed in the epithelium of the distal ileum (Fig. 1c). These cells, called ileal absorptive cells, have an apical endocytic membrane system; apical coated pits, large apical invaginations, coated vesicles, vesicles, tubules, early endosomes, late endosomes, small lysosomes, and a heterogeneous giant lysosome. The last type is observed in epithelium from the distal jejunum and proximal ileum (Fig. 1b). These absorptive cells, called the middle type, have an apical endocytic membrane system similar to ileal absorptive cells. However, they have a large homogeneous electron-dense lysosome instead of a heterogeneous giant lysosome. In middle-type absorptive cells, lipid particles and droplets are observed in the smooth endoplasmic reticulum and Golgi apparatus, as in the jejunal absorptive cells.

The developing intestine is able to establish and maintain differences in the differentiation programs of each lineage as a function of their location along the proximo-to-distal and crypt-to-villus gradient; the three types of absorptive cells appear to shift gradually along the proximo-to-distal gradient. In addition, it appears that the suckling absorptive cells gradually shift to adult absorptive cells during the weaning period.[11–19] Thus, absorptive cells apparently differentiate along two axes, their position in the small intestine and the age of the animal.

Macromolecular uptake into absorptive cells

Membrane-bound endocytosis

Expression of Fc receptors is transcriptionally regulated and is maximal within the proximal duodenum, declining progressively in the distal bowel. Recent morphological studies have indicated that the absorptive cells of suckling rat jejunum selectively transport maternal antibodies into circulation without lysosomal degradation. Maternal immunoglobulin G (IgG) first binds to Fc receptors on the luminal surface membranes in the absorptive cells of the duodenum and proximal jejunum. The bound IgG enters the cells through endocytic tubules that form at the bases of the microvilli, is transferred to coated vesicles, and is released into the intercellular space at the lateral surface.[30–38] In contrast, absorptive cells in the ileum are specialized, not for transcytosis of IgG, but for endocytosis, storage, and digestion of milk macromolecules.[39–41] The permeability of the intestinal epithelium for macromolecules declines after birth, and this transfer of milk macromolecules is terminated completely at 21 days after birth in rats.

In our experiments, horseradish peroxidase (HRP)-labeled IgG (IgG-HRP), gold-labeled IgG (IgG-gold), or peroxidase antiperoxidase (PAP) were used as tracers for membrane-bound (receptor-mediated) endocytosis in vivo, and were found to bind to the apical coated pits or small tubular pits at the bases of microvilli in jejunal absorptive cells. The tracers were found within the coated vesicles, vesicles, tubules, basal vesicles surrounding the Golgi apparatus, and lateral plasma membrane. IgG-HRP was frequently visualized within the coated vesicles and the vesicles

bordering and apparently fusing with the lateral plasma membrane. It was also detected freely within the intercellular spaces (Fig. 2). This observation suggests that IgG binds to Fc receptors on the apical surface membrane of absorptive cells, enters into the endosomal compartment, and is released into intercellular spaces at the lateral surface without lysosomal degradation.

Lectins recognize the specific oligosaccharides on cell-surface glycolipids and glycoproteins.[42–45] We used lectin-HRP conjugates (wheat germ agglutinin-HRP, WGA-HRP; concanavalin A-HRP, Con A-HRP; peanut agglutinin-HRP, PNA-HRP; soybean agglutinin-HRP, SBA-HRP; phytohemagglutinin E4-HRP, PHA-E4-HRP; *Lens culinanis* agglutinin-HRP, LCA-HRP; *Ricinus communis* agglutinin 120-HRP, RCA120-HRP; *Dolichos biflorus* agglutinin-HRP, DBA-HRP) as tracers for membrane-bound endocytosis in vivo.

Con A-HRP, PNA-HRP, LCA-HRP, and RCA120-HRP strongly bound to components of glycocalyx on the plasma membranes of microvilli, apical coated pits, and small tubular pits at the bases of microvilli of absorptive cells in the suckling rat jejunum. Lectin-HRP on the plasma membrane was endocytosed from the coated pits and small tubular pits and was then transported into coated vesicles, vesicles, and small tubules. It was subsequently seen in the intercellular space. WGA-HRP induced the jejunal absorptive cells of suckling rats to form deep and wide apical invaginations at the bases of microvilli. WGA-HRP strongly bound to the glycocalyx components on the plasma membranes of microvilli, the deep and wide apical invaginations, apical coated pits, and small tubular pits. It was confirmed in the coated vesicles, tubules, early endosomes, late endosomes, multivesicular bodies, and lysosomes, and within the intercellular space. WGA-HRP on the plasma membrane, however, was largely transported into early endosomes, late endosomes, multivesicular bodies, and lysosomes. In contrast, SBA-HRP and DBA-HRP bound weakly to the plasma membrane. Absorptive cells exhibited little uptake and transepithelial transport.

Lectin-HRP conjugates induce different membrane formations for apical endocytosis by adsorption to specific glycoconjugates on the apical plasma membranes of absorptive cells in the suckling rat jejunum. In addition, observations suggest that WGA induces deep and wide invaginations at dynamic (not static) membrane domains of the apical plasma membrane in suckling rat jejunum in vivo.

Cationized ferritin and cationized gold studies have shown similar results in vivo.

Fluid-phase endocytosis

HRP is useful for tracing fluid-phase endocytosis[46–50] in vivo. In the jejunal absorptive cells of suckling rats, HRP enters the small coated pits, small tubular pits, coated vesicles, vesicles, tubules, early endosomes, late endosomes, multivesicular bodies, and lysosomes. Tracer was also observed within the intercellular space (Fig. 3a). This finding indicates that nonspecific macromolecules are also transported across the absorptive cells, or transcytosis, of suckling rat jejunum. In ileal absorptive cells, HRP enters the apical coated pits, invaginations, coated vesicles, vesicles, tubules, early endosomes, late endosomes, and lysosomes as a heterogeneous giant lysosome (Fig. 3b). However, no reaction products are seen in the intercellular spaces.

Native ferritin and colloidal gold studies have shown similar results in vivo.

Transepithelial transport of food allergen

The initial stage of a food allergy involves an allergen invading the lamina propria mucosa of the digestive tract. However, it is not clearly understood how allergens pass through the epithelium. Although little has been observed other than tracers, intraluminally injected ovalbumin-HRP was endocytosed into the apical endosomal system of jejunal absorptive cells and was then transcytosed into the intercellular space in a manner similar to other tracers (Fig. 4). We have confirmed that nonspecific macromolecules, including food allergens, were also transferred across duodenal and jejunal absorptive cells without lysosomal degradation during the suckling period, but to differing degrees (Fig. 5). β-Lactoglobulin studies have shown similar results in vivo.

When there is little or no mucus covering the intestinal lumen, larger amounts of IgG-HRP, HRP, or ovalbumin-HRP were endocytosed into jejunal and ileal absorptive cells, and larger amounts were transcytosed into the intercellular spaces of jejunal absorptive cells. No macromolecular tracer, however, was transcytosed into the intercellular space in the ileum. This result suggests that various macromolecules, including food allergens (such as ovalbumin and β-lactoglobulin), easily invade the lamina propria mucosa when mucous secretion declines.

Absorptive cells during weaning period

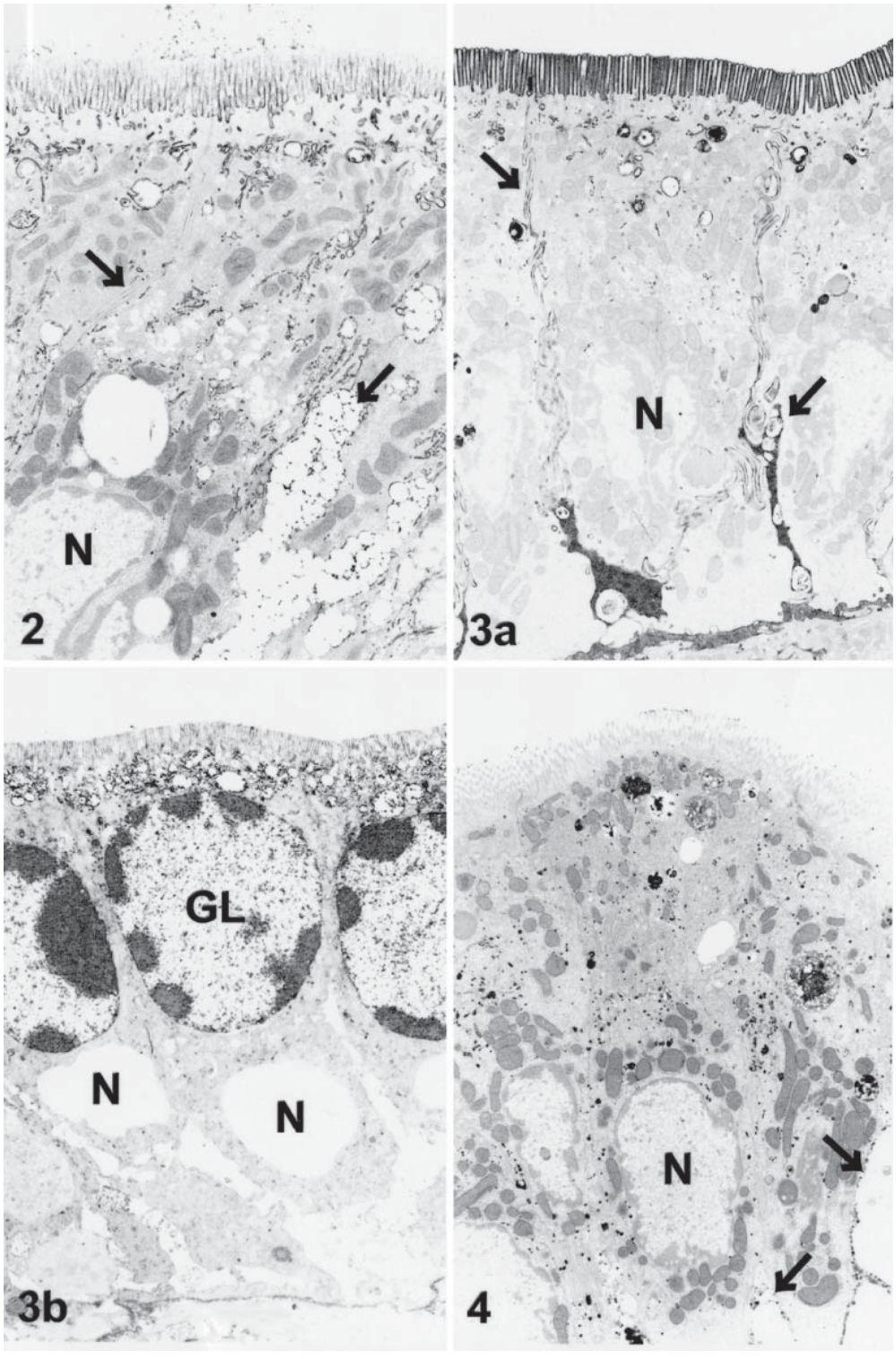
The absorptive cells of a suckling rat's small intestine are replaced at 3 weeks of age by cells having adult form and function.[11–19] The small intestinal absorptive cells of neonatal mammals take up milk macromolecules by endocytosis, whereas adult absorptive cells take up small molecules. During the weaning process, the jejunal absorptive cells stop transcytosing luminal macromolecules and reduce the apical endocytic membrane system. In the ileum, absorptive cells reduce the apical endocytic membrane system while expanding supranuclear giant lysosomes. This change decreases macromolecular transport into the giant lysosome. At 0 to 2 days into the weaning period, suckling absorptive cells are completely replaced by adult absorptive cells in both the jejunum and ileum.

In rats weaned in the neonatal or early suckling period, the apical endocytic membrane system of the jejunal and ileal absorptive cells changes within a few days. IgG-HRP and PAP do not bind to the apical plasma membrane of jejunal absorptive cells and are not observed in cells or the

Fig. 2. Electron micrograph of a jejunal absorptive cell 60 min after intraluminal injection of HRP-labeled IgG (IgG-HRP). IgG-HRP reaction product can be seen in the apical coated pits, coated vesicles, vesicles, tubules, early endosomes, late endosomes, lysosomes, and intercellular spaces (*arrows*) of the absorptive cells. *N*, nucleus

Fig. 3. Electron micrographs of the absorptive cell 60 min after intraluminal injection of HRP. **a** Jejunum. HRP reaction product can be seen in the apical coated pits, coated vesicles, vesicles, tubules, early endosomes, late endosomes, lysosomes, and intercellular spaces (*arrows*) of the absorptive cells. **b** Ileum. HRP reaction product can be seen in the apical coated pits, invaginations, coated vesicles, vesicles, tubules, early endosomes, late endosomes, lysosomes, and giant lysosome (*GL*) of the absorptive cells. *N*, nucleus

Fig. 4. Electron micrograph of a jejunal absorptive cell 60 min after intraluminal injection of ovalbumin-HRP. Ovalbumin-HRP reaction product can be seen in the apical coated pits, coated vesicles, vesicles, tubules, early endosomes, late endosomes, lysosomes, and intercellular spaces (*arrow*s) of the absorptive cells. *N*, nucleus



intercellular space. IgG-HRP, PAP, and HRP are found in the apical coated pits, coated vesicles, vesicles, early endosomes, late endosomes, and lysosomes, but are not observed in the intercellular space. This observation suggests that transcytosis in the absorptive cells of suckling rat jejunum is mediated by the presence or absence of IgG receptor.

In rats weaned at 14 days of age, the apical endocytic membrane system in the jejunal and ileal absorptive cells also changes within a few days. However, the apical endocytic membrane system disappears in both types of absorptive cell a few days earlier than in the normal weaning process. When weaning was postponed to beyond 21 days of age, the changes in absorptive cells were the same as

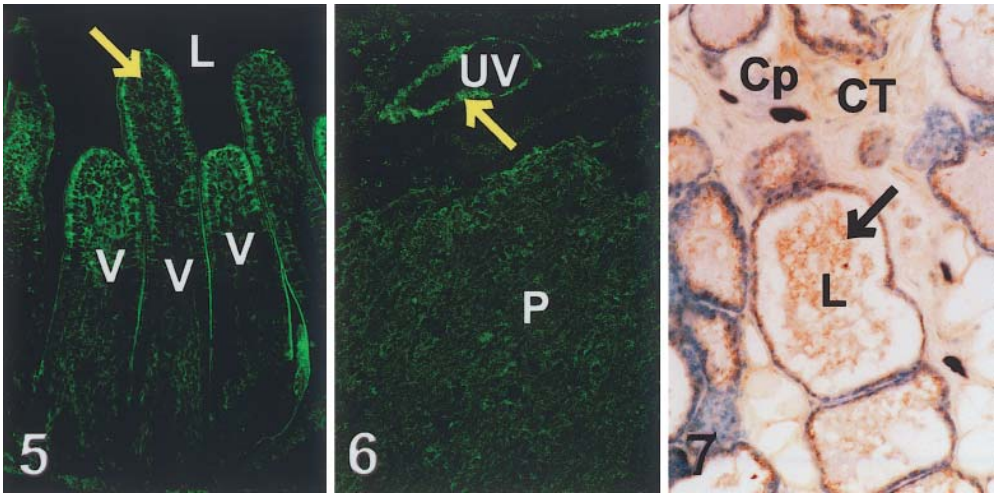


Fig. 5. Immunofluorescent image of jejunal villi (*V*) indirectly stained with an antibody directed against β-lactoglobulin antigen. Staining is evidence in the epithelium and lamina propria mucosa (*arrow*). *L*, lumen

Fig. 6. Immunofluorescent image of placenta indirectly stained with an antibody directed against ovalbumin antigen. Staining is evidence of intravenously injected ovalbumin in the trophoblasts (*P*) and umbilical vein (*UV, arrow*)

Fig. 7. In the lactating rat mammary glands, intravenously injected ovalbumin is detected in the blood vessels (*Cp*), connective tissues (*CT*), mammary epithelial cells, and lumina of the alveoli (*L*)

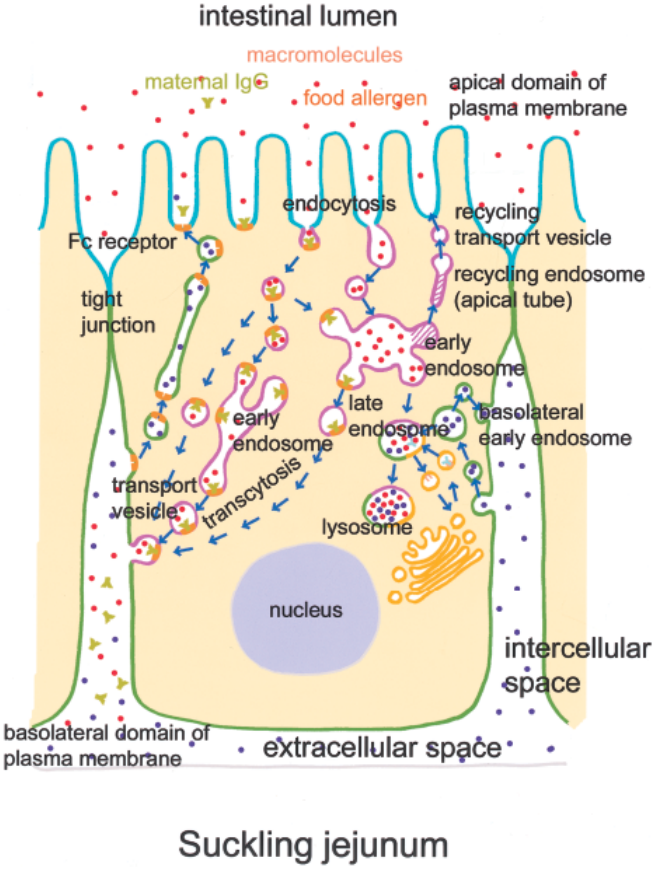


Fig. 8. Diagram of a neonatal-suckling rat jejunal absorptive cell illustrating the major futures of the endocytosis and transcytosis pathways

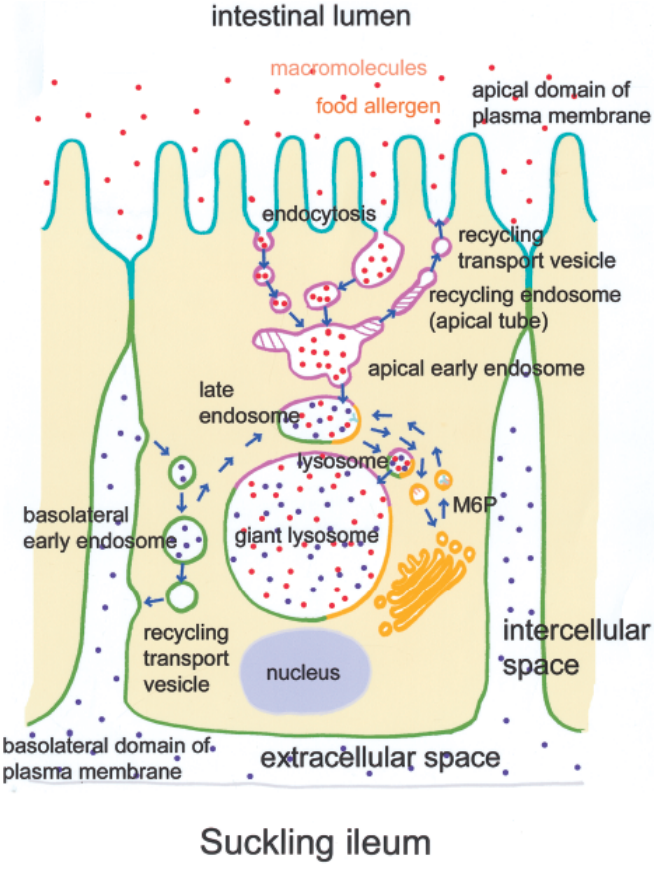


Fig. 9. Diagram of a neonatal-suckling rat ileal absorptive cell illustrating the major futures of the endocytosis and transcytosis pathways

normally seen during the weaning process. These results suggest that the timing of the weaning process is determined by genetic factors, although early weaning causes changes in the absorptive system of the suckling rat.

Placental barrier

The primary function of the placenta is to permit substances dissolved in the maternal blood to diffuse into the fetal blood.[51–55] Under normal conditions the blood of the fetus and the blood of the mother neither mix nor come into direct contact with one another; they are always separated by the placental barrier.

The trophoblast is composed of three layers: cytotrophoblast, syncytiotrophoblast I, and syncytiotrophoblast II. Nonspecific macromolecular tracers, including ovalbumin, injected into maternal veins are observed in maternal blood vessels, in the interspaces between the cytotrophoblast and syncytiotrophoblast I layers, in the vesicles of syncytiotrophoblast I and syncytiotrophoblast II, and in fetal connective tissue and fetal blood vessels (Fig. 6).

These results suggest that nonspecific macromolecules or food allergens can pass from maternal blood into fetal blood through the blood–placental barrier.[56–59]

Mammary gland

In lactating mammary glands, the epithelial cells secrete milk.[60–64] HRP or ovalbumin injected intravenously is detected in the blood vessels, connective tissue, mammary epithelial cells, and lumina of the alveoli ducts in lactating rat mammary glands (Fig. 7). These results suggest that maternal allergens pass through the mammary epithelial cells and are secreted with breast milk in lactating rats.[20,65]

Conclusions

Intestinal absorptive cells of neonatal-suckling rats provide a useful model for studies into the endocytosis and transcytosis pathways by which large amounts of maternal immunoglobulins, nonspecific macromolecules, and food allergens are transferred intact across the absorptive cells (Figs. 8, 9). During the neonatal-suckling period, membrane-bound and fluid-phase macromolecules can be transferred intact across duodenal and jejunal absorptive cells. In this period, allergens or macromolecules readily invade the duodenal and jejunal epithelia, subsequently entering the lamina propria mucosa. We have clearly shown that macromolecules and food allergens are transferred intact across the absorptive cells of the duodenum and jejunum during the neonatal-suckling period (Fig. 8). In the future, studies into endocytosis and transcytosis in human intestinal absorptive cells of newborns, placental syncytiotrophoblasts, and mammary epithelial cells are necessary.

This review has suggested that primary prevention of food allergy is better than cure.

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