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MINIREVIEW

Epithelial Ion Transport in the Developing Intestine

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Summary

The developing intestine is a complex organ that is responsible for absorption of nutrients, water and ions that are used either as a source of energy or are accumulated in the growing organism. This review describes the developmental profiles of ion transport at the organ level as well as the mechanisms that have been identified for mediating these transports. Information from studies of the developing intestine are integrated to derive a picture of maturation of transport functions. The maturation of intestinal structure and transport is not terminated at the time of birth. The transition from intrauterine parenteral nutrition to extrauterine enteral nutrition and later from maternal milk to solid food requires changes not only in morphology, but also in transport functions. The available data indicate that the development of intestinal transport represents the sequence of quantitative and qualitative changes resulting in a complete spectrum of nutrition, water and ion requirements of the growing organism.

Key words

Ionic transport – Developing intestine – Nutrition during development

The survival of newborns is dependent on their ability to adapt from intrauterine to extrauterine life. The maturation of gastrointestinal functions is one of the critical factors in their survival and further development. The changes, which occur perinatally, have been well studied from the biochemical and morphological points of view, particularly in rodents (Henning 1981, Koldovský 1984). These changes are largely related to the transition from intrauterine parenteral nutrition to extrauterine enteral nutrition and to the transition from maternal milk to solid food consumption. The developmental patterns differ in various mammals but the postnatal changes in the intestine have been observed in all the species studied. This review focuses mainly on the rat because most information available has been obtained in this species. The rat intestine is immature during the first two weeks of life (suckling period), undergoes major changes in enzymology and mucosal morphology during the second two weeks (weaning period), and acquires adult characteristics by the end of the first month of postnatal life.

Morphological development of the small and large intestine

In the rat small intestine, the increase in mucosa weight is greatest between the suckling and weaning period (Buts and DeMeyer 1981). During the third postnatal week, mucosal DNA synthesis, the RNA and DNA content, villus and crypt height and cell migration rate also increase (Herbst and Sunshine 1969, Koldovský *et al.* 1970, Buts and DeMeyer 1981, 1984). The enhanced cell proliferation leads to mucosal hyperplasia in the entire small intestine. In contrast, there is no change of cell kinetic parameters in the colon of weanlings (Buts *et al.* 1983). The developing colon differs considerably from the adult organ also due to the presence of villi (Lacy and Colony 1985, Potter and Burlingame 1986a). These villi disappear 10 days after birth and then the colon is covered by flat epithelium with interspersed crypts. The newborn rats are an example of a species with a short gestation, closely dependent on their dams for thermoregulation, locomotion and nutrition, with rapid postnatal growth, where weaning represents the major event of

gastrointestinal maturation. Though some other mammals such as the pig, sheep and especially the guinea-pig have a long gestational period and they are relatively more mature at birth than the rat, developmental changes have also been described in their intestinal morphology and cytokinetics (Smith 1988, Weaver and Carrick 1989, Attaix and Meslin 1991). In contrast to rats, the weaning period in species with a longer gestational period is not the major phase of progressive intestinal maturation. Suckling seems to be the phase of major changes. Weaning does not represent such an important period of changes due to the relatively long and gradual process of preceding maturation.

The fundamental question, as to what controls the maturation, is not yet answered (Lebenthal 1989, Klein 1989). The search for signals which might trigger the intestinal development has been centered on genetic, humoral, neural, and environmental factors (diet). Although there is temporal correlation between intestinal maturation and spontaneous weaning, the ontogenetic changes of morphology and cytokinetics are not initiated by a transition from relatively high-fat, low-carbohydrate diet (milk) to relatively low-fat, high-carbohydrate diet (solid food) (Buts and Nyakabasa 1985, Weaver and Carrick 1989). Changes in the diet can only modulate the full expression of intestinal development. The interpretation of such data is difficult because premature weaning stresses the pups and elevates the secretion of some hormones including glucocorticoids. Glucocorticoids and some other hormones or growth factors are intimately involved in the regulation of intestinal maturation (Henning 1981). It seems reasonable to suppose that hormones and dietary changes modulate the full expression of intestinal development but that genetic endowment initiates and controls it.

Development of ion transport at the organ level

Water absorption. Water absorption is a passive process when most of the water passes paracellular pathways in response to osmotic gradients created by transcellular absorption of Na^+ and other solutes. Water absorption from the small and large intestine of sucklings is considerably higher than in adult animals (Bentley and Smith 1975, Younoszai 1979, Finkel *et al.* 1988). Several observations suggest that this very high water transport reflects large paracellular pathways. First, an imposed osmotic gradient results in secretion of water in the small intestine. However, the relationship between water movement and the osmotic gradient is non-linear in adult rats and linear in sucklings. This finding implicates the age-dependent differences in the structure of paracellular pathways. Second, postnatal development is followed by a decrease of the water secretion (Younoszai *et al.* 1978). Similar marked age-related differences of colonic water transport were demonstrated by Marin and Aperia (1984).

Na^+ transport. The data that water absorption is increased during the early postnatal life suggest that intestinal epithelia share increased Na^+ absorption. It is difficult to propose a universal model for NaCl absorption. There are significant differences not only among various intestinal segments but also among species. High Na^+ transport has been disclosed in the rat and rabbit colon (Finkel *et al.* 1985, 1988, O'Loughlin *et al.* 1990) as well as in rat small intestine (Younoszai 1979). Morphometric analysis has indicated that other factors than the absorptive area are responsible for the decrease of water and Na^+ transport during postnatal development (Finkel and Larsson 1987). In contrast to the colon, net Na^+ transport in rabbit developing ileum and jejunum have a smaller capacity than in adult animals (Cooke and Dawson 1978, Shepherd *et al.* 1980, O'Loughlin *et al.* 1990). Similarly as in the rabbit small intestine the capacity of Na^+ transport in the pig colon does not change during development (Cremaschi *et al.* 1979, Argenzio and Whipp 1983). Direct measurements of Na^+ concentration in the colonic content suggest that the mechanisms for active Na^+ absorption are fully operative in the newborn pig (Bentley and Smith 1975).

Cl^- transport. The passage of digested food is carefully regulated by a balance of absorptive and secretory processes, with water generally moving secondarily to the active transport of solutes. Absorptive pathways are dominated by active Na^+ absorption, whereas Cl^- appears to be the principal ion determining active secretion. It seems that in most intestinal segments there is bidirectional active Cl^- transport, whose balance is responsible for the net Cl^- absorption or secretion. The dominant patterns of Cl^- absorption are transcellular or paracellular pathways which are frequently, but not always, linked to Na^+. Active Na^+ absorption generates electropositivity of the serosa when compared with the lumen and this transepithelial electrical potential difference favours positive absorption of Cl^-. During development the value of Cl^- absorption decreases in the rat jejunum and ileum and is constant in the pig colon similarly as Na^+ absorption (Bentley and Smith 1975, Younoszai 1979). Diarrhoeal diseases in infants and studies on laboratory animals have shown that the intestine is able to secrete Cl^- *via* an active transcellular pathway. The sensitivity of the intestine to agents that produce active Cl^- secretion undergoes developmental changes. There is an impressive high sensitivity of sucklings to *Escherichia coli* heat-stable enterotoxin (≈x600) and to the cholera toxin (≈x50) compared to adult animals (Cohen *et al.* 1986, Chu *et al.* 1989). On the other hand, the sensitivity of the colon to bile acids is decreased (Potter *et al.* 1991). This may have an important

meaning because the developing ileum does not actively absorb bile acids. In adult animals a failure to absorb bile acids by the ileum leads to Cl^- and fluid secretion in the colon.

Bicarbonate transport. Jejunal bicarbonate absorption has a similar developmental pattern as Cl^-. Bicarbonate transport is quite different in the ileum where it is absorptive only in the first 3 weeks of life and secretory later (Younoszai and Robillard 1980). In adult animals, the jejunum is the place of net bicarbonate absorption, whereas net secretion takes place in the ileum and colon (Charney and Goldfarb 1990). The observation of ileal bicarbonate absorption in sucklings is surprising. Maybe carbonic anhydrase, an enzyme that plays an important role in supplying the secreted H^+ and bicarbonate, has lower activity in the suckling ileum. In adult animals, this enzyme has a very low activity in the jejunum but high in the ileum and colon (Charney and Goldfarb 1990).

K^+ transport. Intestinal K^+ transport is also bidirectional. Usually both transport processes are active at the same time. Net K^+ transport reflects both processes and various manoeuvers are necessary to unmask one of the preexisting pathways (mostly K^+ absorption). In early postnatal life, these processes have not been clearly defined. Younoszai (1979) demonstrated net K^+ secretion in the jejunum and ileum of suckling and weanling rats while net K^+ absorption was seen in prepubertal animals. However, Meneely and Ghishan (1982) found net K^+ absorption in the jejunum, ileum and colon of suckling rats and Finkel *et al.* (1985) demonstrated a decrease of net K^+ absorption in the developing epithelium during the weaning period. These findings do not mean that the secretory pathway is not present in the young epithelium. Using furosemide and barium it is possible to unmask this transport in the distal colon (Pácha *et al.* 1987b). It is more active in suckling and weanling animals than in adults (Fig. 1) and is controlled by corticosteroids. The changes of corticosteroid status might explain the differences regarding the net K^+ secretion in sucklings.

Ca^{2+} transport. Intestinal maturation during the early postnatal period leads to considerable changes in the ability to absorb Ca^{2+}. All segments of the intestine, including the colon, are able to absorb Ca^{2+} after birth but later Ca^{2+} absorption decreases in the colon (Batt and Schachter 1969, Toverud and Dostal 1986). Absorption is a nonsaturable diffusional process *via* paracellular and maybe also transcellular routes. Duodenal nonsaturable absorption is modified during the period of weaning. Efficient absorption, which is insensitive to vitamin D, is replaced by a combination of less efficient nonsaturable and saturable vitamin D-dependent absorption. The induction of saturable Ca^{2+} absorption requires the development of mucosal receptors for 1,25-dihydroxyvitamin D_3 and the calcium-binding protein in duodenal cells (Toverud and Dostal 1986).

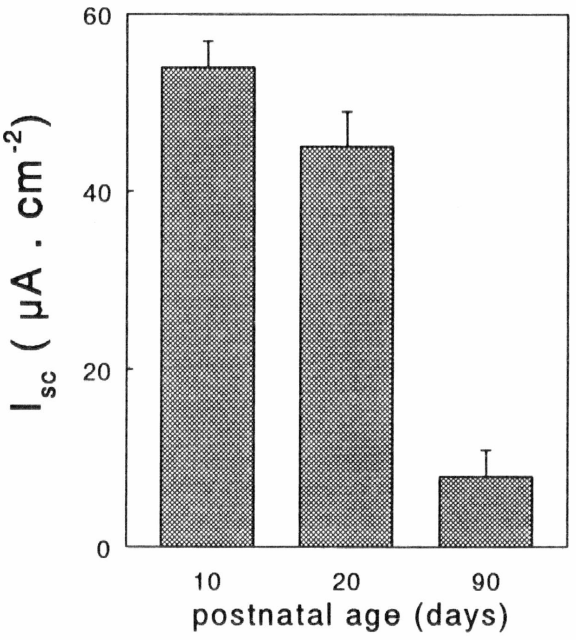

Fig. 1
Potassium secretion in rat distal colon during development. K^+ secretion was measured as barium-sensitive short circuit current (I_{sc}) after the addition of $BaCl_2$ (5×10^{-3} M) to the mucosal side of the epithelium (from Pácha *et al.* 1987b)

Development of ion transport at the cellular level

Observations made in the entire wall of the developing intestine do not help to determine the role played by particular pathways of epithelial ion transport. The *in vitro* transepithelial potential difference is qualitatively the same in adult and developing animals. It is serosa-positive and the respective short-circuit current roughly corresponds to the net mucosa-to-serosa flux of Na^+ or to the sum of the Na^+ and Cl^- fluxes (DeJesus and Smith 1974a, Cooke and Dawson 1978, O'Loughlin *et al.* 1990). Although many studies demonstrated the decisive role of Na^+ absorption in the determination of transepithelial electrical parameters under unstimulated conditions, there are marked species and segmental differences. During the last decade, four mechanisms by which Na^+ may cross the apical membrane have been established: 1) diffusion of Na^+ through Na^+ channels that can be inhibited by submicromolar concentrations of amiloride, 2) carrier-mediated Na^+/H^+ exchange which can be inhibited by micromolar concentrations of amiloride, 3) cotransport of Na^+ coupled to sugars or amino acids, and 4)

cotransport of Na^+ coupled to the entry of K^+ and Cl^- that can be inhibited by bumetanide or furosemide. Na^+ is extruded from the cytosol through the basolateral membrane by the Na^+, K^+-pump.

The first apical mechanism mentioned above was demonstrated in the distal colon of suckling and weanling rabbits, rats and pigs (Cremaschi *et al.* 1979, 1981, Potter and Burlingame 1986b, Pácha *et al.* 1987a, O'Loughlin *et al.* 1990). These observations are surprising since this pathway is missing in adult rats (Fig. 2). The occurrence of this pathway reflects the effect of mineralocorticoids, especially aldosterone, on colonic epithelium (Ferguson *et al.* 1979, Pácha *et al.* 1987a, O'Loughlin *et al.* 1990). Recent studies (Fuller and Verity 1990b, Pácha *et al.* 1988) demonstrated that mineralocorticoid receptor gene expression precedes the development of a full Na^+ transport response and that the sensitivity to aldosterone is increased in early postnatal life. It is unresolved whether the sensitivity of the epithelium is higher or whether it is the effect of age-dependent corticosteroid metabolism. There is no obvious explanation for the contradictory data in the rat. One possibility is that, during the rapid growth period, the pups are in a chronic Na^+ deficit because maternal milk is a low-sodium nutrient. The lack of Na^+ may increase the plasma level of aldosterone during the suckling and weaning period. The findings of increased plasma level of aldosterone in young rabbits and rats (O'Loughlin *et al.* 1990, Pácha and Pohlová *unpublished results*) support this suggestion.

Cotransport of Na^+ coupled to sugars or amino acids is responsible for most of Na^+ that is absorbed in the intestine. In adulthood these systems operate only in the small intestine. However, in very young animals, carbohydrate and amino acid cotransport systems are also active in the colon (James and Smith 1976, Potter and Burlingame 1986a). Perhaps the best explanation for the apparent discrepancy between suckling and adult animals can be derived from the existence of villi in the colon early after birth (Lacy and Colony 1985, Potter and Burlingame 1986a). In experiments designed to evaluate cotransport systems and their electrogenicity in the small intestine, several authors already noted the presence of these systems before birth and their transport activity soon after birth (DeJesus and Smith 1974b, Cooke and Dawson 1978, Shepherd *et al.* 1980, Buddington and Diamond 1989). The transport of whole proteins by pinocytosis very early after birth interferes with these processes (DeJesus and Smith 1974a,b).

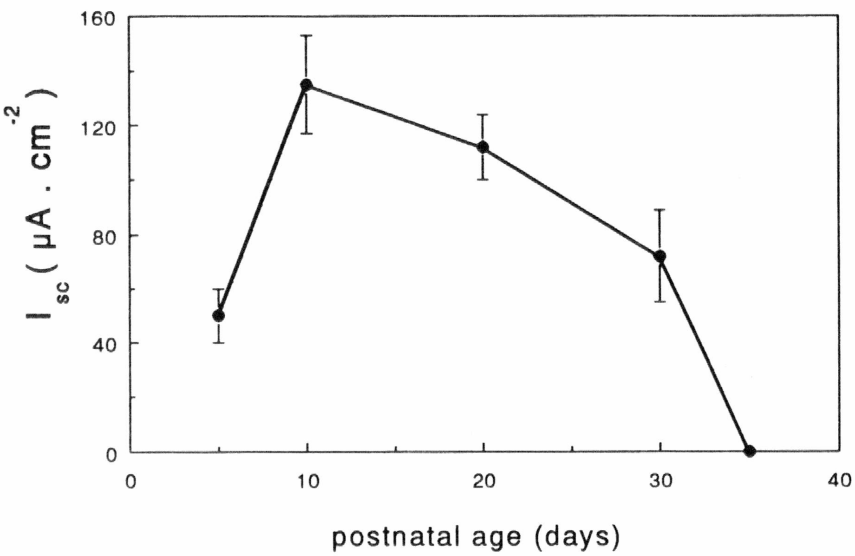

Fig. 2
Postnatal development of electrogenic amiloride-sensitive Na^+ transport in rat distal colon. The Na^+ transport was measured as the short circuit current (I_{sc}) sensitive to inhibition by 10^{-4} M amiloride (from Pácha *et al.* 1987a).

Countertransport of Na^+/H^+ as a member of the dual antiport system Na^+/H^+ and Cl^-/HCO_3^- is operative in the apical membrane of the small intestine (rabbit, rat) and colon (rat). Although *in vivo* perfusion studies demonstrated net bicarbonate transport (Younoszai and Robillard 1980), which may reflect the movement of bicarbonate *via* the exchange with Cl^- or the titration of bicarbonate by H^+ *via* Na^+/H^+ exchange or both processes, there is no direct evidence for the operation of these systems in early postnatal life. This is also the reason why mechanisms affecting Cl^- absorption in the developing intestine are poorly understood. It is likely that not only passive paracellular but also active transcellular Cl^-

absorption exist at least in the ileum and colon of suckling rabbits and in the newborn pig colon (Bentley and Smith 1975, Cooke and Dawson 1978, Potter and Burlingame 1986b). The dependence of Cl^- transport on the presence of bicarbonate (Potter and Burlingame 1986b) is consistent with the linkage of Cl^- and OH^- or bicarbonate.

Single carrier Na^+-K^+-Cl^- mediates the absorption of NaCl and most of K^+ in the teleost intestine. In the mammalian intestinal epithelium, this carrier, located in the basolateral membrane, enables the secretion of Cl^- and K^+. Cl^- and K^+ enter the cell from the serosal side and diffuse into the lumen *via* Cl^- or K^+ channels of the apical membrane. The mechanism and regulation of K^+ secretion was studied in the immature rat distal colon (Pácha *et al.* 1987b). K^+ enters the cell through the basolateral membrane together with Na^+ and Cl^- *via* a furosemide-sensitive pathway, Na^+ recycles across the basolateral membrane *via* the Na^+,K^+-pump, and apical barium-sensitive K^+ channels allow the extrusion of K^+ into the lumen. The velocity of this secretion is dependent on aldosterone but not on Na^+ absorption. Apical Cl^- conductance that may reflect Cl^- channels was demonstrated in the developing pig colon (Cremaschi *et al.* 1981).

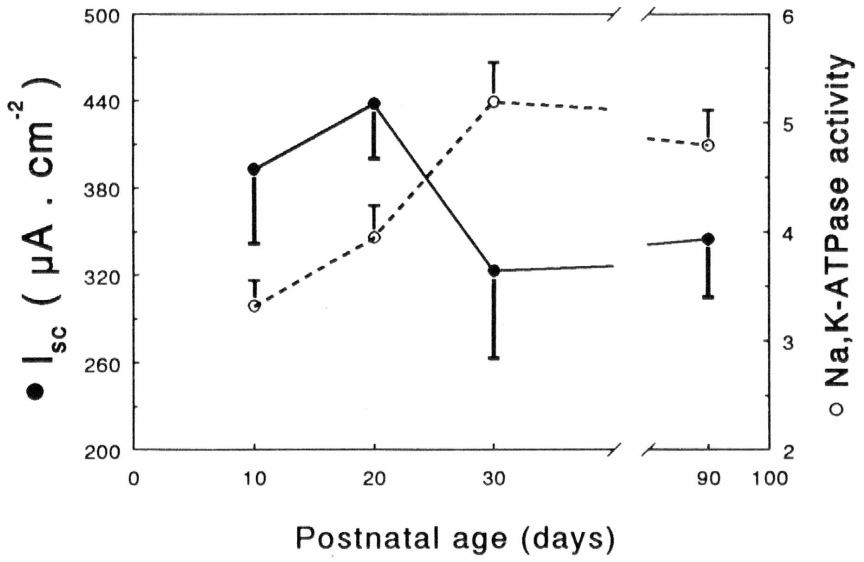

Fig. 3
Developmental changes of maximum Na^+-pumping activity and Na^+,K^+-ATPase activity in rat distal colon. Maximum Na^+-pumping activity was measured as the short circuit current (I_{sc}) after the addition of nystatin to the mucosal solution. Na^+,K^+-ATPase activity was estimated in homogenates of mucosal scrapings by determination of ouabain-sensitive release of inorganic phospate from ATP (μmol P_i . h^{-1} . mg $protein^{-1}$) (from Pácha *et al.* 1991).

The basolateral Na^+,K^+-pump is involved in Na^+ and Cl^- absorption as well as in K^+ and Cl^- secretion. Developmental studies carried out in various tissues demonstrated significant maturational changes of the Na^+,K^+-pump, or Na^+,K^+-ATPase that is the biochemical equivalent of the pump. However, there are some apparent discrepancies in the available studies that have investigated this enzyme in the developing intestinal epithelium. Pácha *et al.* (1991) and Finkel and Aperia (1986) in the rat distal colon as well as Walli *et al.* (1983) in the rat jejunum demonstrated a postnatal increase in its activity. In contrast, Colony *et al.* (1989) observed a decrease of activity in the developing rat colon. The data of Pácha *et al.* (1991) and Finkel and Aperia (1986) agree with a recent study showing that expression of Na^+,K^+-ATPase (mRNA level for α and β subunits) increases after birth to reach adult levels at the age of about 25 days (Fuller and Verity 1990b). How such developmental changes of Na^+,K^+-ATPase can increase Na^+ absorption in suckling and weanling animals was investigated in the rat colon (Pácha *et al.* 1991). Although the activity of the Na^+,K^+-ATPase (measured as hydrolysis of ATP under V_{max} conditions) and the number of pump molecules increase during development, the maximum pumping activity of Na^+,K^+-pump is constant (Fig. 3). This means that the turnover rate per single Na^+,K^+-pump is higher during the suckling and weaning period than in adulthood.

Conclusion

Maturation of intestinal ion and nutrient transport is essential for postnatal development and for the successful transition from milk to solid food. Nevertheless, our understanding of this vital function is limited and will require more study and the application of new techniques. Little is known regarding the role of individual intestinal cell types in transport phenomena and of the polarity of channels, pumps, carriers and regulatory systems in epithelial membranes. The heterogeneity of intestinal cell types and membranes contributes to the complexity of problems concerning the development of ion transport.

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