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ALTERATIONS IN INTESTINAL TRANSPORT OF OXALATE IN DISEASE STATES

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Abstract

Normally, absorption of oxalate from dietary sources can occur in all segments of the intestinal tract. However, alterations in both the magnitude and direction of oxalate fluxes across the intestine can occur in disease states. In enteric hyperoxaluria, enhanced absorption of oxalate by the large intestine is caused by increased permeability of a shunt conductance induced by malabsorbed bile salts and fatty acids. In this condition, the contribution of a paracellular passive flux of oxalate moving along its electrochemical gradient will predominate when intraluminal concentrations of free oxalate are high. In contrast, in chronic renal failure, secretion of oxalate can occur across both small and large intestine thereby facilitating extrarenal elimination with subsequent degradation by mucosal substrate-specific microorganisms. Clearly, in recent studies of oxalate transport, the intestine has emerged with an integral role in mass balance of oxalate in health and disease.

Key Words: Absorption, secretion, chronic renal failure, hyperoxaluria, dietary, fatty acid, bile salt, ileum, colon.

Introduction

The notion that intestinal transport of oxalate plays an important role in oxalate homeostasis is new and based upon recent studies demonstrating the ability of intestinal epithelia to regulate the magnitude and direction of oxalate transport (Hatch et al., 1984, 1993). Previously, the function of the intestine in oxalate handling in both health and disease was considered to be exclusively absorptive (or hyperabsorptive). It is now evident that there are segmental differences in oxalate transport along the length of the intestine (Hatch and Vaziri, 1991). Thus, in addition to the established routes for oxalate absorption, pathways for oxalate secretion from blood to lumen are also present (Hatch and Vaziri, 1991; Hatch et al., 1984, 1993). These absorptive and secretory pathways for transmural movements of oxalate across intestine can potentially contribute to oxalate homeostasis and to the pathogenesis of various disorders of oxalate metabolism.

Epithelial Transport Mechanisms for Oxalate

The epithelial transport mechanisms that are operative in intestinal absorption and secretion of oxalate have been described in some detail in the large intestine (Freel et al., 1980; Hatch and Vaziri, 1994a; Hatch et al., 1984, 1993, 1994a, 1994b). Furthermore, in the disease conditions discussed below, it is clear that the colon is the primary location for both the enhanced oxalate absorption in enteric hyperoxaluria and the secretion of oxalate in chronic renal failure. Alterations of small intestinal transport systems for oxalate have been suggested but not demonstrated experimentally. There is general consensus that the extent to which oxalate is absorbed by small intestinal epithelia depends upon the intraluminal concentration of free oxalate. The pathways that have been described for oxalate absorption and secretion across colonic epithelium are depicted in Figures 1a and 1b, respectively (Hatch and Vaziri, 1994a; Hatch et al., 1984, 1994b). Oxalate absorption occurs by parallel transcellular and paracellular routes.
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Figure 1. Proposed mechanisms for the transepithelial movements of oxalate across the mammalian distal colon. Figure 1a depicts net oxalate absorption across the distal colon under normal conditions. Transcellular oxalate absorption occurs via active, mediated anion exchange systems at the apical and basolateral membranes of the enterocyte. A passive, paracellular flux (arrows) will contribute to net absorption when the electrochemical potential of oxalate in the lumen is greater than that on the blood side of the epithelium. Figure 1b depicts active, transcellular mechanism of oxalate secretion. The magnitude of the net secretion of oxalate may be increased if the electrochemical gradient for oxalate in the lumen is greater than that on the blood side of the epithelium. Figure 1c depicts transmural oxalate movements in enteric hyperoxaluria. Despite bile salt and fatty acid-induced secretion of oxalate through transcellular pathways, the associated reduction in paracellular resistance results in the passive hyperabsorption of oxalate due to higher concentrations of free oxalate in the lumen compared to blood.

The electrochemical gradient of free oxalate across the epithelium will determine the magnitude and direction of passive, paracellular oxalate flux between the cells. The transcellular, absorptive flux of oxalate across the colon is an active, mediated process as judged by its sensitivity to metabolic and transport inhibitors (Hatch and Vaziri, 1994a; Hatch et al., 1984, 1994b) and exits across the basolateral membrane by a 4,4'-disothiocyanostilbene-2,2'-disulfonic acid (DIDS)-sensitive anion exchanger. The latter process may be coupled to intracellular pH, since inhibitors of Na⁺:H⁺ exchange (amiloride and its analogues) reduce oxalate absorption when applied serosally (Hatch et al., 1994b). The observed sodium dependence of oxalate absorption may be due to this exchange system in conjunction with the ouabain-sensitive basolateral Na⁺:K⁺:ATPase. This basolateral exit mechanism was also found to be sensitive to the thiazide diuretics, which reduced oxalate absorption across colonic mucosa (Hatch and Vaziri, 1994a). Other pathways for oxalate efflux across the basolateral membrane of the colonocyte may exist.

Colonic enterocytes, presumably in the crypt region, also exhibit the ability to secrete oxalate when presented with a secretagogue. Based on inhibitor sensitivities of the cyclic adenosine monophosphate (cAMP)-stimulated secretory process, it has been hypothesized that oxalate secretion occurs by mechanisms that are remarkably similar to that of chloride secretion (Hatch et al., 1994b). Thus, the colonic secretion of both chloride and, to a lesser degree, oxalate are reduced by mucosal application of the putative Cl⁻-channel blocker NPPB (5-nitro-2(3-phenylpropylamino benzoate), suggesting the possibility of a common exit pathway in the apical membrane (Figure 1b). Serosal application of furosemide, an inhibitor of Na⁺:K⁺:2Cl⁻ cotransport, also blocked chloride and oxalate secretion by the distal colon (Hatch et al., 1994b), further suggesting a common secretory mechanism for the two anions. It is noteworthy that cyclic AMP also stimulates oxalate secretion by the rabbit distal ileum (Freel et al., 1995). In a preliminary report, it was demonstrated that channel-like pathways for oxalate and chloride were present in brush border membrane vesicles and it was suggested that these may represent the apical exit avenues for the anion secretion by this tissue (Freel et al., 1995). Note also that passive, paracellular fluxes of oxalate may be important depending upon the permeability of the junctional complexes and the magnitude and direction of the blood to lumen electrochemical gradient for oxalate.

Given this brief backdrop regarding possible transport avenues for oxalate in the intestine, it is possible to consider some clinical consequences and manifestations of alterations in intestinal oxalate transport in the mass balance of oxalate.

Enteric Hyperoxaluria

In enteric hyperoxaluria increased absorption of oxalate occurs from the lumen of the large intestine (Dobbins and Binder, 1976, 1977; Hofmann et al., 1983; Modigliani et al., 1978). Two general mechanisms to explain enteric hyperoxaluria have emerged from diverse
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studies which have addressed this issue in a variety of ways. One scheme describes changes in mucosal permeability to oxalate resulting in increased oxalate absorption (Binder, 1974; Bright-Asare and Binder, 1973; Dobbins and Binder, 1976; Earnest, 1979; Fairclough et al., 1977; Gaginella et al., 1976; Hatch et al., 1982, 1983; Saunders et al., 1975) and the second scheme underscores the significance of the free oxalate concentration in intraluminal contents. Since a common finding in individuals with enteric hyperoxaluria is the malabsorption of bile salts and fatty acids, many investigators focused on whether these agents altered mucosal permeability. Using various techniques, including perfused colonic segments from humans (Fairclough et al., 1977) and both perfused loops and everted gut sac preparations from rats (Binder, 1974; Dobbins and Binder, 1976; Saunders et al., 1975), it was determined that dihydroxy bile salts or long chain hydroxy fatty acids increased oxalate absorption across the large intestine. In vitro experiments using isolated short-circuited sheets of colon from both rat (Kathpalia et al., 1984) and rabbit (Hatch et al., 1982, 1983) demonstrated that bidirectional fluxes of oxalate increased following the addition of bile salts or fatty acids. For example, the addition of one to four mM of the dihydroxy bile salt taurochenodeoxycholate (TCDC) to the isolated, short-circuited mucosa of rabbit distal colon enhanced the paracellular, passive flux of oxalate and at the same time promoted a transcellular net absorption (Hatch et al., 1982, 1983). Similar effects were observed with the addition of even lower concentrations (0.25 to 2 mM) of the hydroxy fatty acid ricinoleate (Hatch et al., 1983). The relative contribution of the transcellular, active, secretory flux of oxalate will, however, be negligible in vivo and oxalate absorption via gradient-driven, passive diffusion through the paracellular pathway will likely prevail in proportion to luminal activity of the oxalate ion (see Figure 1c).

The importance of the luminal activity of oxalate is evident from numerous patient studies which have demonstrated that oral administration of calcium or the resin cholestyramine effectively reduces hyperoxaluria by binding oxalate within the lumen (Earnest, et al., 1975; Hylander et al., 1980; Saunders et al., 1975; Smith et al., 1972; Stauffer et al., 1973). These conclusions were supported by results of in vitro experiments showing that oxalate solubility was reduced in solutions in the presence of calcium and also in the presence of the resin cholestyramine (Binder, 1974; Stauffer et al., 1973). In addition, when oxalate solubility was determined in the presence of both calcium and fatty acids likely to be malabsorbed, it was determined that the affinity of calcium for fatty acid was greater than for oxalate and the free concentration of oxalate was thereby increased (Binder, 1974; Earnest, et al., 1975). Therefore, enteric hyperoxaluria can be explained by large increases (induced by bile salts and fatty acids) in the predominantly passive, paracellular movement of oxalate from lumen to blood along a concentration gradient which ultimately depends on its intraluminal ionic concentration.

"Dietary" Hyperoxaluria

Increased absorption of oxalate from the small intestine leading to a hyperoxaluria that is not associated with malabsorption of bile salts or fatty acids is supported by a number of investigations (Barilla et al., 1978; Finlayson, 1977; Galosy et al., 1980; Hodgkinson, 1978; Lindsjö et al., 1989; Marshall et al., 1972; Sigmon et al., 1991; Smith, 1991). The general consensus appears to be that increased oxalate absorption is a direct consequence of oxalate bioavailability, rather than some defect in an oxalate transport system. It is noteworthy, however, that an increase in oxalate uptake was observed in intestinal rings (Farooqui et al., 1981) and isolated apical membrane vesicles (Gupta et al., 1988) prepared from vitamin B6 deficient rats. In another study of patients with an inheritable anomaly of red blood cell oxalate transport, it was suggested that the erythrocyte defect of enhanced uptake of oxalate might also be present in enterocytes (Baggio, et al., 1986; Borsatti, 1991). Yet, another consideration was prompted by recent in vitro studies identifying intestinal pathways for the secretion of oxalate into the gut lumen (Hatch and Vaziri, 1991; Hatch et al., 1993, 1994b). Using isolated short-circuited sheets of jejunum and ileum from both rats (Hatch and Vaziri, 1994b) and rabbits (Hatch and Vaziri, 1994a), it was demonstrated that the small intestine supports a basal net secretory flux of oxalate. These secretory pathways may be functionally more significant in stone-formers who are presumed to hyperabsorb dietary oxalate. That is, reduced intestinal oxalate secretion alone, or possibly in conjunction with an enhancement of the absorptive component could explain absorptive or "dietary" hyperoxaluria.

Enteric Excretion of Oxalate in Chronic Renal Failure

Oxalate homeostasis may also be expected to be affected by a decrease in renal function unless an extrarenal pathway for oxalate excretion compensates for reduced renal elimination. Two recent studies have provided evidence suggesting that enteric excretion of oxalate in rats with chronic renal failure (CRF) (Costello, et al., 1992; Hatch et al., 1994a) may contribute to oxalate homeostasis in this model. In one whole animal study, the fate of 14C-oxalate infused by a mini osmotic pump in normal rats and rats with experimentally induced chronic renal failure, was determined over several days (Costello et al., 1992). It was observed that fecal
excretion of the tracer was significantly higher in CRF rats when compared to normals, suggesting that excretion of oxalate by the intestinal route is important in renal failure. In a separate study, a direct examination of oxalate fluxes across isolated, short-circuited intestinal segments removed from a similar rat model demonstrated that colonic transport of oxalate is markedly changed (Hatch et al., 1994a). It was shown that basal oxalate absorption observed in the colon of control rats was changed to net oxalate secretion in CRF rats 6 weeks following 5/6 nephrectomy. The reversal in the direction of net oxalate transport under short-circuit conditions was due to an increase in the transcellular serosal to mucosal flux of oxalate across the colon. The basal secretory flux of oxalate across the jejunum and ileum, however, was not altered in this model of renal insufficiency. We now assume that CRF associated oxalate secretion by the rat colon observed in vitro is mechanistically similar to cAMP-dependent oxalate secretion previously described for the rabbit colon (Figure 1b). While significant changes in paracellular conductance were not evident in the in vitro rat model (Hatch et al., 1994a), enteric elimination through this shunt may also be significant in vivo, given the concomitant changes in transcellular oxalate gradient in CRF as considered below.

Several pieces of information suggest that in patients with oxalosis or renal failure, a chemical gradient favoring passive, paracellular oxalate secretion across the intestine may exist at times. First, it has been shown that these patients have serum oxalate levels up to 50-fold higher (0.1 mM) than healthy individuals (Kasidas et al., 1990). Second, in a pilot study in our laboratory, we observed that intraluminal concentrations of oxalate are relatively low (micromolar range). Oxalate was determined, by a double enzymatic method (Hatch, 1990), in acidified specimens of intestinal fluid obtained from eight surgical patients who were being fed parenterally for at least ten days. Samples of gastric juice obtained from five of the individuals yielded concentrations of oxalate ranging from 3.6 to 79 µM, with a mean and standard deviation of 23.3 ± 16 µM. In two individuals, oxalate concentrations in fluid removed from the small intestine were 37.7 and 51.1 µM, and in another individual, oxalate concentration in a colonic fluid specimen was found to be 41.7 µM. These initial estimates of intraluminal oxalate concentrations are most likely representative of concentrations that would be found under fasting conditions and post-prandial concentrations of oxalate will depend upon the dietary oxalate load in healthy individuals ingesting a normal diet. Nevertheless, in these patients, it would appear that the concentration gradients across enteric epithelia would favor the passive, paracellular elimination. Finally, the observation that an increased population of oxalate-degrading microorganisms was found in the large intestine of patients with CRF (Comici et al., 1982), suggests a metabolic sump for maintaining the transcolonic gradient for the passive oxalate movement into the lumen. These passive avenues, coupled with active colonic secretion of oxalate, may then represent an important extrarenal pathway for oxalate elimination in chronic renal failure.

**Summary**

There is no substantive evidence regarding an alteration or defect in small intestinal epithelial transport systems for oxalate which would result in oxalate hyperabsorption. There is general agreement, however, that increased oxalate absorption from the small intestine depends upon an increase in luminal oxalate bioavailability. In "leaky" epithelia, such as the small intestine, the contribution of the paracellular passive flux of oxalate will predominate when intraluminal oxalate concentrations are high resulting in oxalate absorption in vivo. Recent studies, demonstrating that the jejunum and ileum can actively secrete oxalate, suggest that transcellular secretory pathways may be functionally important in both health and disease. The potential contribution of these physiologically relevant secretory pathways in disease states requires consideration.

In contrast, more information is available regarding the involvement of large intestinal oxalate transport in the context of disease states. In enteric hyperoxaluria, the colon is the site of increased oxalate absorption as a consequence of increased epithelial permeability and increased concentrations of free oxalate within the lumen. In chronic renal failure associated hyperoxaluria, basal colonic absorption of oxalate is reversed to a secretory flux resulting in extrarenal excretion of oxalate.

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Discussion With Reviewers

V.R. Franceschi: The possibility is raised that a common exit pathway may exist in the apical membrane for chloride and oxalate ions. Have experiments been performed to look for competitive inhibition of transport of one ion by the other in the various systems upon which that hypothesis is based?

Authors: It is not possible to perform such experiments using whole tissues where the apical and basolateral membrane barriers are located in series with one another. While apical membrane vesicle preparations are more appropriate for such competition studies, we have not yet performed these kinds of experiments since they are difficult to interpret unless we know, a priori, that a single conductive pathway mediates the voltage-dependent accumulation of both anions. For example, an apparent cis-inhibition of oxalate uptake by chloride could be due to competition if a single pathway mediated their flux. However, separate pathways would produce a similar experimental result (apparent cis-inhibition) because chloride uptake via its pathway would short-circuit the imposed voltage (driving force) and thereby depress oxalate uptake via its pathway.

R.P. Holmes: Is the main purpose of the Cl⁻:HCO₃⁻ exchanger to prevent over-acidification of luminal contents? Similarly, in the reverse direction, is the secretion of Cl⁻ and oxalate to ensure that there is sufficient counter-ion for HCO₃⁻ secretion?

Authors: The Cl⁻:HCO₃⁻ exchanger located on the apical membrane of the enterocyte is one of the membrane transport systems involved in the regulation of intracellular pH. The membrane pathways involved in Cl⁻ secretion, i.e., basolateral Na⁺:K⁺:2Cl⁻ in series with an apical conductive pathway, may be indirectly coupled to intracellular pH regulatory transport mechanisms.

R.P. Holmes: Does acetate, the major anion in colonic fluid, compete with oxalate for active absorption?

Authors: We have demonstrated that the isolated, short-circuited rabbit colon supports a net absorptive flux of oxalate, however, this tissue does not support net acetate absorption under similar conditions (Hatch, 1987). A small, but insignificant net secretion of acetate was observed across the colon. Hence, it is difficult to conclude that acetate competes with oxalate for the membrane transport systems involved in the absorption of both organic anions. The observed secretion of acetate may reflect the existence of an anion secretory mechanism that can accommodate short chain fatty acids in an in vitro system. Studies using brush border membrane vesicles from rat colon suggest that oxalate is a poor substrate for the short chain fatty acid exchanger (Mascola et al., 1991). The fact that, in vivo, the large intestine can absorb large quantities of SCFAs underscores important physio-chemical differences between in vivo conditions and the symmetrical electrochemical environment of the Ussing chamber.

R.P. Holmes: Can an osmotic gradient in the colon contribute as a driving force for paracellular transport?

Authors: Yes, a hyperosmotic gradient can contribute to the driving force for paracellular transport of solutes. For example, luminal hypertonicity could support a serosal to mucosal flux of any solute entrained in the bulk flow of solution if no steric or electrostatic restrictions were imposed by the diffusion pathway.

R.P. Holmes: Could electroneutral complexes of calcium oxalate and magnesium oxalate be absorbed through the paracellular pathway?

Authors: Theoretically, this is a possible mode of transport that would be limited primarily by the size of the complex and the resistance of the paracellular pathway. There is no experimental evidence to either support or negate such a mode of transepithelial transport.

Additional References
