Intestinal "Bioavailability" of Solute and Water: We Know How But Not Why

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Only minimal quantities of ingested and normally secreted solutes and water are excreted in the stool. This near 100% bioavailability means that the diet and kidneys are relatively more important determinants of solute, water and acid-base balance than the intestine. Intestinal bioavailability is based on excess transport capacity under normal conditions and the ability to adapt to altered or abnormal conditions. Indeed, the regulatory system of the intestine is as complex, segmented and multi factorial as in the kidney. Alterations in the rate and intestinal site of absorption reflect this regulation, and the diagnosis and treatment of various clinical abnormalities depend on the integrity of intestinal absorptive processes. However, the basis for this regulation is bioavailability and uncertain. Perhaps they had survival value for mammals, a phylogenetic class that faced the twin threats of intestinal pathogens and shortages of solutes and water.

INTRODUCTION

Many studies, including my own, have documented and examined the structural and functional complexity of the gastrointestinal tract. For this reason, some would suggest that this organ plays a pivotal role in the maintenance of water, electrolyte and acid-base balance. Certainly, the entire intake of fluids, electrolytes and dietary sources of acids and bases enters the body through intestinal absorption. In adults, this amounts to some three liters of water, 10 g NaCl and gram quantities of various other inorganic and organic salts. Infants and children consume even greater quantities per kilogram body weight. Remarkably, aside from organic cations and anions, most of which are generated in the intestinal lumen by bacteria, only a minimal quantity of ingested solutes and water are excreted in the stool. Expressed another way, the "bioavailability" of orally administered fluids, electrolytes, nutrients, acids and bases in the normal intestine is nearly 100 percent.

Near-100 percent bioavailability means that to maintain overall balance, i.e., homeostasis, any excess of absorbed solutes and water will require excretion. The degree of excess will depend to a large extent on the composition of the diet. The excretion of absorbed solutes and water beyond that needed to replenish what has been metabolized or lost by other routes is a function of the kidneys. Indeed, it is a primary function of the kidneys and one that must be replaced by a transplanted kidney, hemodialysis or peritoneal dialysis if patients with end-stage renal disease are to survive.

In this essay, I will consider the relative importance of the processes needed to maintain solute and water balance: dietary intake, intestinal absorption and renal excretion. Specifically, I will examine the apparent paradox of the intestinal contribution: this organ has enormous absorptive capacity, but performs its absorptive function regardless of the

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homeostatic needs of the body. Under these circumstances, can we speak of a meaningful role for the gastrointestinal tract in the regulation of water, electrolyte and acid-base balance?

**PHYSIOLOGIC CONSIDERATIONS**

The essentially complete absorption of water and solutes is based on two distinct characteristics of the intestinal epithelium: excess transport capacity under normal conditions, and the capacity to adapt to altered or abnormal conditions [1]. On a stable diet, the human small and large intestines have the capacity to absorb a two to three-fold greater quantity of fluid and absorbable solutes than are usually presented to them following meals. Although this excess was greatly overestimated in early studies, its presence and clinical significance is now well established [2-4].

Equally important is the ability of the intestine to regulate its absorptive capacity depending upon dietary intake and physiologic needs. This adaptation may be nutrient-specific as during the introduction or omission of a particular nutrient in the diet, or non-specific as during exercise, pregnancy or cold stress [5-7]. The adaptation occurs over a period of hours to days, and may include increases in specific cellular transport processes as well as overall mucosal hypertrophy. It also occurs as part of normal development from birth through adulthood and accounts for as much as a ten-fold increase in absorptive capacity. Together with the baseline excess capacity of the intestine, this adaptive response results in minimal stool losses of solute and water over a wide range of dietary habits.

The fact that diet does not affect the homeostatic arrangement between intestine and kidney is of particular interest. Intuitively, one would imagine that the timing of dietary intake and the composition and quantity of the diet would affect the efficiency of intestinal absorption. However, it makes no difference if one ingests the same quantity of food or fluid in one meal or in many small snacks [8-10]. It makes no difference whether the meal is protein, fat or carbohydrate-rich [11]. And, within broad limits, it makes no difference to the efficiency of intestinal function whether one ingests very small or very great quantities of a particular dietary constituent [12, 13]. There are exceptions to these generalizations, of course. Certain foods have effects on intestinal function when ingested in great quantities or in particular individuals. Such foods are particularly rich in capsaicin (certain peppers) [14], calcium (cheese) [15], or non-absorbable monosaccharides or oligosaccharides (dietetic foods, candies, pears, peaches and apple juice) [16-19]. Other examples have less well-analyzed effects: dried fruits, rice and bananas. In addition, the intestinal absorption of at least two solutes, iron and calcium, may be limited by the lumenal environment and regulation of epithelial transport processes [20, 21].

Of course, there are constraints on the quantities of food and fluid that one may ingest at one sitting. One factor involving the stomach is the feeling of nausea and the urge to vomit when certain foods or fluids are ingested. For example, saline ingestion is markedly restricted by the tendency to vomit. The size of the stomach is more commonly a limiting factor. The feeling of satiety that accompanies a full and distended stomach limits the quantity of food ingested [22, 23]. This serves to keep the quantities of solutes and water in need of absorption well within the functional capacity of the intestine. Evidence for this is of two types. First, the many *in situ* perfusion studies of the human small intestine and colon demonstrate an intestinal absorptive capacity many-fold greater than that required to absorb the flow of chyme exiting the stomach. Second, dietary intake represents only a fraction, perhaps 15 percent of the total quantities of solutes and water that the intestines absorb each day under normal circumstances. The greater fraction represents the secretions
of intestinal organs including saliva, gastric, pancreatic and biliary secretions and the succus entericus [24].

The minimal quantities of solutes and water excreted in the stool allow for their periodic exit from the body. In addition to solutes and water, intestinal excretions are largely bacteria and indigestible fibers that can be stored between bowel movements in the distal colon. If the intestine participated in the regulation of solute and water balance, whenever more fluid was ingested than was required by the body (and this is usually the case), a continuous stream of fluid would exit the intestine (as “diarrhea”). There is no storage organ for fluids in the intestinal tract. By contrast, the kidney excretes excess solutes and water continuously. Excess fluid and solute is stored in the bladder. The absence of an equivalent organ in the intestinal tract is the most obvious indicator that the intestine does not (continuously) regulate solute and water balance.

**BIOLOGIC IMPLICATIONS**

If, as suggested above, essentially all ingested (and normally secreted) solutes and water are absorbed, then why does the intestinal tract have a complex regulatory system controlling absorption? For an organ like the kidney, which controls the composition of body fluids, such a system fine-tunes the excretory process. Each segment of the nephron is under several and separate humoral and neural influences [25]; the glomerular filtration rate is independently regulated [26]; and the composition of the tubular fluid itself affects the functions of nephron segments upstream and downstream [27]. The regulatory system in the intestine is at least as complex, segmented and multifactorial [28, 29]. We can only answer this question incompletely in view of our limited understanding of intestinal function and regulation.

One approach to this question is to examine the functions that may be served by the physiologic stimulation or inhibition of electrolyte transport in the normal intestine. These functions appear homeostatic, but their value remains unproven. Perhaps most commonly, the overall rate of intestinal absorption may be changed without altering the total quantity of solute absorbed. This effect may be especially important following meals to speed or slow the digestive process. It may be important in states of extracellular volume depletion or overload when the rapid or delayed absorption of electrolytes and water may be critical. In this regard, the rate of intestinal sodium and water absorption is sensitive to the hormonal, neural and chemical responses to changes in extracellular fluid volume. These include responses to the renin-angiotensin-aldosterone system, enteric nervous system, acid-base balance and plasma electrolyte composition [28-33].

Second, modulation of intestinal transport may shift the site of absorption from one segment to another. A shift of sodium absorption, for example, would affect those solutes dependent on luminal sodium for their absorption. Some would be absorbed more efficiently, others less efficiently. The shift may alter the nature of the absorptive process from, for example, co-transport to ion-exchange [28, 29]. This would affect the mix of electrolytes absorbed in each segment. To the extent that the absorption of organic cations and anions are altered, this would influence the contribution of the intestine to the acid-base economy of the body. For example, a decreased rate of absorption of such anions would increase the amount of fixed, nonvolatile acid in need of renal excretion to maintain acid-base balance [34, 35].

The concentration of luminal solutes and the volume of luminal water in each intestinal segment would be affected as well. Carcinogens, enzymes, secretagogues and other lumen-active agents would all be delivered to distal sites in greater or lesser quantities of water (i.e., in altered concentrations) and in an altered chemical environment. Such changes may change the absorption and/or the effects of these agents.
CLINICAL IMPLICATIONS

The nearly complete bioavailability described above has two important clinical implications: First, the quantity and composition of the diet will affect body composition (at least temporarily) and determine the metabolic and excretory processes needed to restore homeostasis. This temporary imbalance may have diagnostic utility or cause clinical symptoms.

The influence of diet on the body balance of solutes and water is most apparent at the extremes of "normal" intake, especially when there is an abnormality in the disposition of the particular constituent. Very high intakes may reveal subtle abnormalities in assimilation or renal excretion. For example, the syndrome of inappropriate ADH secretion, congestive heart failure, hyperparathyroidism and hyporeninemic hypoaldosteronism (type IV renal tubular acidosis) each may become clinically evident in the presence of a specific (relative) dietary excess. These include water (syndrome of inappropriate ADH secretion) [36, 37], sodium (congestive heart failure) [38, 39], calcium (hyperparathyroidism) [40, 41] and potassium (type IV renal tubular acidosis) [42], respectively. Conversely, a very low intake of water, sodium or potassium may uncover the kidneys' inability to conserve a particular constituent. Examples include, respectively, partial diabetes insipidus (water) [43], Addison's disease (sodium) [44] and diuretic-induced potassium wasting (potassium) [45, 46].

The diet also is the ultimate source of most of the acid and base produced in the body each day. The ingestion, absorption and metabolism of potential acids and bases determine the quantity of fixed acid in need of renal excretion [34, 47, 48]. The metabolism of ingested proteins and organic acids, and the incomplete metabolism of glucose, triglycerides and nucleoprotein, yield a significant quantity of fixed, nonvolatile acids. Metabolism of dietary organic anions yields base (bicarbonate) or base equivalents. Even unabsorbed dietary constituents are metabolized by luminal bacteria and contribute net acid or base depending on the relative absorption of the metabolic products. Thus, high protein diets containing relatively greater quantities of meat, fish, rice, and eggs contribute net acid, whereas vegetarian diets containing vegetables, fruits, nuts and milk products contribute net base to overall acid-base balance [49, 50]. Although the intestinal absorption of these various foodstuffs is clearly regulated, the more important role of diet than the intestine in acid-base homeostasis is based on the fact that this absorption does not (directly) depend on the acid-base status of the body.

A second clinical implication of near-100 percent bioavailability is that many electrolyte and acid-base disorders, even those generated by gastrointestinal disorders, can be treated by the oral route. Orally administered fluids, electrolytes, acids and bases prescribed for various abnormalities may be assumed to be largely, if not completely, absorbed. The effects of these remedies are thought to depend on the appropriateness of the choice and the dose rather than on the extent of the remedy's absorption. As examples, hypokalemia is generally and most safely corrected by the oral administration of potassium salts [51], and chronic metabolic acidosis may be treated by the oral administration of NaHCO₃ or bicarbonate-generating salts [52].

The most dramatic example of this concept is oral rehydration therapy for diarrhea [53]. During the severe intestinal fluid and electrolyte secretion that occurs in cholera and other secretory diarrheas, solutions of electrolytes, sugars and amino acids are readily absorbed. Although severe extracellular volume depletion cannot be replenished with oral fluid replacement in all cases, the finding that net positive fluid balance can usually be achieved attests to the integrity of intestinal absorptive processes [54-58].
CONCLUSIONS

This description of the nearly complete bioavailability of ingested solutes and water presents two difficult questions: Does the gastrointestinal tract play a pivotal role in solute and water homeostasis? And, why is the intestinal absorption of these solutes and water so finely regulated? A tentative answer to the first question is a qualified "no." It is surprising yet self-evident that under normal circumstances this organ plays a passive role, absorbing potential acids and bases and nearly 100 percent of ingested solutes and water without regard to solute, water or acid-base balance. The answer to the second question remains uncertain. As discussed above, certain functions may be served by the complexity of the absorptive process including alterations in the rate or site of absorption. A more complete answer, as suggested by Powell [59], may come from studies of comparative physiology and the phylogeny of the intestinal tract.

Among phylogenic Classes, mammals have the most functionally-sophisticated kidneys. As a result, and in proportion, the role of the mammalian intestine in water, electrolyte and acid-base homeostasis has diminished [59]. The preservation of the complex intestinal regulatory machinery is perhaps based on the value of such machinery in the presence of both intestinal pathogens and environmental shortages of solutes and water. Such states of meager resources and diarrheal losses were very likely twin threats to survival throughout mammalian history. The survival value of near-100 percent bioavailability would be obvious, leaving to the kidney the job of dealing with dietary excess. Regulation of the rate, mechanism and site of intestinal absorption, in this view, may be "homeostatic" for mammals as a Class if not for individual mammals.

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