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INTESTINAL TRANSPORT DURING FASTING AND MALNUTRITION

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■ **Abstract** Fasting or malnutrition (FM) has dramatic effects on small intestinal mucosal structure and transport function. Intestinal secretion of ions and fluid is increased by FM both under basal conditions and in response to secretory agonists. Intestinal permeability to ions and macromolecules may also be elevated by FM, which increases the potential for fluid and electrolyte losses and for anaphylactic responses to luminal antigens. Mucosal atrophy induced by FM reduces total intestinal absorption of nutrients, but nutrient absorption normalized to mucosal mass may actually be enhanced by a variety of mechanisms, including increased transporter gene expression, electrochemical gradients, and ratio of mature to immature cells. These observations underscore the value of enteral feeding during health and disease.

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INTRODUCTION

Nutrients and electrolytes absorbed by the intestinal epithelium are eventually utilized to fulfill the metabolic needs of the body. Fasting or malnutrition (FM) and similar conditions deprive the body of essential nutrients and may result in electrolyte imbalances that perturb physiological homeostasis. The gastrointestinal tract is the first organ system that is directly affected by changes in nutrient intake, and it also displays the most rapid and dramatic changes to nutrient deprivation. These changes alter intestinal mucosal structure and function, which, in turn, may alter the processing of food when feeding resumes. The intestinal responses induced by FM have both beneficial and detrimental effects on nutrient and ion transport. Functional responses to FM may help alleviate structural changes that reduce total intestinal absorptive capacity. On the other hand, ion transport responses to FM can exacerbate the effects of enteric pathogens and other secretory agents.

Fasting often connotes a voluntary abstinence from food, whereas starvation implies an involuntary cessation of food intake. In this review, we do not distinguish between the two terms, as both conditions have the same effects on the gastrointestinal tract. The duration of experimentally induced cessation of food intake varies widely among studies, and differences in duration of a fast can result in marked differences in effects on the gastrointestinal tract. Experimental starvation is often acute and lasts only 24–72 h. Malnutrition can be defined in a number of ways. For example, semistarvation denotes a partial cessation of food intake, whereas protein or carbohydrate deficiency denotes reduction in consumption of these specific macronutrients. Terms related to malnutrition are often unique to each study, and comparisons with other studies may be difficult. Experimental malnutrition is usually acute (only several days duration) and involves a dramatic reduction in protein or protein/calorie intake. We distinguish malnutrition from dietary or calorie restriction, which is perhaps the most uniformly defined term related to conditions that reduce food intake. In studies on aging and life span, calorie restriction is typically defined as a daily caloric intake ∼60–70% of that of an animal fed to satiety, and it is usually administered throughout the life span of the experimental animal. Calorie-restricted animals consume the same amount of vitamins and minerals as those fed to satiety.

Fasting is almost routine among overweight human populations in developed countries, and in peoples observing certain religious practices. For otherwise healthy individuals eager to manage their body weight, short-term fasting or dieting is an option with relatively few side effects. Chronic starvation and malnutrition are conditions that often afflict animals in nature, as well as human populations in severely underdeveloped countries. Fasting is also an accepted presurgical

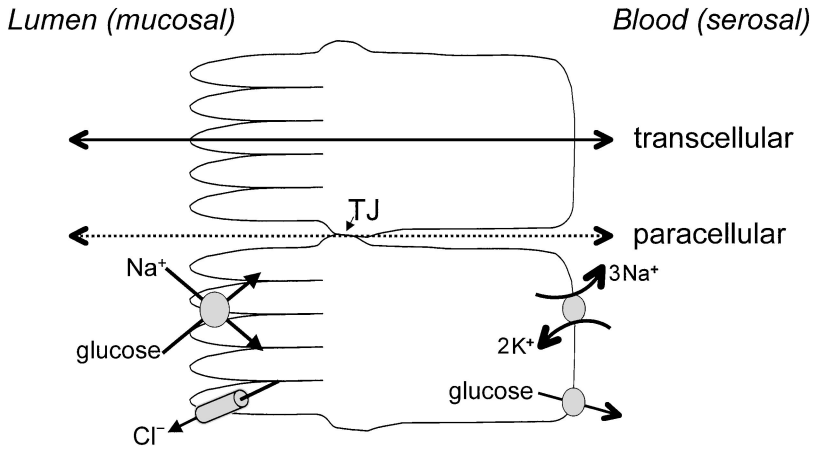

Figure 1 Pathways for ion and nutrient transport across intestinal epithelia. Transcellular transport constitutes solute movement through membrane-bound channels and transporters. Glucose is representative of any Na^+-coupled luminal solute whose absorption is driven by the Na^+-electrochemical gradient generated by the action of the basolateral Na^+, K^+-ATPase pump. Glucose and many nutrients exit the cell across the basolateral membrane by facilitated diffusion. Cl^- is transported into the lumen via apical channels. Paracellular transport of ions and other solutes may occur between enterocytes through the tight junction (TJ).

procedure. Calorie restriction has attracted enormous interest not only because it prolongs mammalian life span (91), but also because its anti-aging effects may benefit primates, including humans (54). Moreover, calorie restriction is used in the treatment of obesity (28) and in the management of non–insulin-dependent diabetes (94).

There is little information on the mechanisms that regulate intestinal absorption and secretion during fasting and related conditions. This is surprising because the small intestine is the site of the first step in nutrient assimilation and metabolism in animals and is, therefore, the site of the major regulatory mechanisms that may be altered by reductions in nutrient intake. This review focuses mainly on the responses of the small intestinal absorptive and secretory systems (Figure 1) to fasting, calorie restriction, and malnutrition. There is a vast literature, beyond the scope of this review, on neuroendocrine responses to FM and the effects of neuroendocrine mediators on intestinal transport. Only a few examples pertinent to this review are mentioned here. Studies on effects of FM on digestive enzymes and lipid absorption and on nutrient deprivation of intestinal cell cultures are not included. Total parenteral nutrition has been used to distinguish the effects of starvation on intestinal function from those resulting only from a reduction in luminal contents in otherwise well-nourished animals. Only those studies directly relevant to this review are discussed.

EFFECT OF FASTING AND MALNUTRITION ON MUCOSAL MASS

This review begins by summarizing how fasting and malnutrition alter intestinal structure, because these anatomical changes often result in alterations in intestinal nutrient and ion transport. The small intestine is responsible for 17–25% of whole-body oxygen consumption (12), hence it is a metabolically expensive organ to maintain and is markedly affected if nutrient intake decreases or ceases entirely.

Fasting

Significant decreases in mucosal mass are evident after fasts of 24 h or more. What is the anatomical counterpart of this marked weight loss? In rats and mice, microvilli and villi amplify the intestinal surface area by 50–80 and 5–10 times, respectively (34); hence, changes in microvillus and villus widths, heights, and densities per unit area are important indicators of fasting-induced changes in intestinal surface area. The reported effects of fasting on microvillus dimensions are inconclusive. Height of microvilli decreased in fasted hamsters (65). However, both microvillus height and number per unit area either increased (39, 90) or did not change (63) in fasted rats. Fasting also altered microvillus membrane fluidity in rats (39, 90), although this has not been observed in other studies (see below).

Although studies on the effect of fasting on microvillus dimensions are inconclusive, total intestinal surface area almost always decreases with fasting (63), which suggests that the underlying cause of the fasting-related reduction in surface area is mainly at the villus level. There is indeed almost unanimous agreement that fasting markedly affects villus measurements. Villus heights decreased with fasting (15, 45, 56, 62, 82, 87, 97) because of significant reductions in the number of cells along the crypt-villus axis (76). The decrease in cell number likely resulted from decreases in cell proliferation and migration rates (37, 45, 97), as well as from increases in rates of cell loss (4) and apoptosis (7).

Malnutrition

The effects of protein or protein/calorie malnutrition on intestinal mucosal structure are similar to those of fasting. Villus heights typically decreased with malnutrition (9, 10, 84) because of significant decreases in the number of cells as well as in enterocyte proliferation and migration rates along the crypt-villus axis. This led to reductions in total surface area and mucosal mass. Even fetuses of malnourished pregnant sheep showed markedly decreased intestinal mass and enterocyte maturation rates (88).

Infant rabbits subjected to protein-energy malnutrition exhibited changes in cholesterol and phospholipid composition of brush border membranes, including an elevated lipid:protein ratio (10). Although this change would be expected to increase membrane fluidity in the malnourished state, no changes in brush

border membrane fluidity were observed between control or malnourished animals. Both cholesterol and phospholipid membrane components increased in malnourished animals, and the cholesterol:phospholipid ratio was increased. The latter effect, which would tend to reduce membrane fluidity, might have counteracted the fluidizing effect of the increased lipid:protein ratio. An increase in the cholesterol:phospholipid ratio was also found in intestinal mucosal membranes of malnourished piglets, although in that situation cholesterol, phospholipid, and triglyceride levels were reduced (58).

Calorie Restriction

Unlike fasting and malnutrition, which dramatically decrease intestinal surface area and mucosal mass in parallel with a marked decrease in body weight, chronic calorie restriction leads to dramatic decreases in body weight with relatively modest effects on intestinal structure. In calorie-restricted mice, there was no (16) or little (17) decrease in villus height and intestinal mass. There were no diet-related differences in the number of cells on the villus columns or in the crypts (51). The number of proliferative cells and the rate of cell proliferation, however, decreased (52, 57). Because enterocyte migration rate and cell turnover decreased with calorie restriction, the lifetimes of cells were longer, and consequently cells stayed on the villus for a longer duration. Absorptive functions are attained only after enterocytes reach a certain age; hence, changes in cell lifetime induced by calorie restriction may alter the ratio of intestinal absorptive cells (see below). The relatively mild effects of calorie restriction on mucosal structure may be evident only under chronic conditions. For example, the ileal hyperplasia often seen in aged rodents fed to satiety throughout their life span can be prevented by chronic calorie restriction (33, 42).

In summary, FM is typically associated with significant reductions in body weight, mucosal mass, intestinal protein content, and total intestinal surface area. These effects are closely associated with the loss of luminal nutrition and not the metabolic consequences of nutrient deprivation per se because similar changes are induced by total parenteral nutrition (46, 74). The general role of luminal contents in regulating gastrointestinal growth is reviewed elsewhere (47). In contrast to FM, calorie restriction dramatically decreases body weight but has little effect on intestinal anatomy. Thus, it is extremely important for investigators to be aware of how absorption or secretion rates are normalized, and to incorporate relevant clinical data such as body weight or intestinal mass in publications.

INTESTINAL ION TRANSPORT

The active transport of ions (principally Na^+, Cl^-, and HCO_3^-) across the small intestinal epithelium provides the electrical and chemical forces that drive the coupled absorption of nutrients as well as the net absorption or secretion of water.

Because ions can move bidirectionally across the intestinal mucosa, i.e. from luminal (mucosal) to blood (serosal) sides and vice versa, it is the difference between the two unidirectional fluxes, or the "net" ion flux, that determines the direction of net transport (Figure 1). A variety of absorptive and secretory agents, including local and systemic hormones, neurotransmitters, toxins released by enteric pathogens, and other molecules that gain access to the intestinal lumen, stimulate ion and water transport. Although normal ion absorption and secretion drive transport of other solutes and maintain proper luminal consistency in a healthy intestine, excessive ion and fluid transport in either direction can lead to pathophysiologic states (e.g. constipation or diarrhea). In this section, we discuss the evidence for FM-induced alterations in ion and fluid transport under basal conditions, as well as the effects of such alterations on ion transport stimulated by absorptive and secretory agents. In addition to active transport mediated by membrane-associated channels and transporters, solutes can traverse the intestinal epithelium through two other mechanisms, often collectively referred to as intestinal permeability: endocytotic uptake from the lumen followed by exocytotic delivery to the basolateral compartment, and intercellular transport through the tight junctions that separate enterocytes (the "paracellular pathway") (Figure 1). There is evidence that FM can also influence the transepithelial transport of solutes via these two routes.

Basal Ion and Fluid Transport

Net movement of ions and fluid across the small intestinal epithelium in the basal state varies considerably among species, and within species, it varies along the length of the small intestine. For a given intestinal segment, basal transport tone is influenced by a variety of factors, including age, reproductive status, body fluid and electrolyte balance, behavioral state (stress), diet composition, and meal frequency. Changes in basal ion transport induced by FM reflect the importance of diet history on intestinal epithelial function.

Most studies that have examined the effects of FM on intestinal ion transport in vitro have relied on the change in basal short-circuit current (Isc) as an indicator of active ion movement. The Isc is the external current required to null out the spontaneous transepithelial potential difference across epithelial tissues mounted in Ussing chambers and bathed with solutions of similar ionic composition. Under these conditions, changes in Isc reflect only active (electrogenic) ion movements mediated by cellular transport processes. Changes in Isc per se yield only limited information unless the specific ion fluxes responsible for Isc changes have been documented. This is best done by measuring transepithelial fluxes of radiolabeled ions such as ^{22}Na and ^{36}Cl, although ion replacement studies can also been used.

FM has been shown to induce a shift in basal ion transport in the small intestine from a neutral state or net absorptive flux to a more secretory state. This effect is most commonly reported as elevated basal Isc of jejunal or ileal tissues (9, 15, 22–24, 99). The ionic basis for elevated basal Isc after 48–72 h of fasting has been identified in piglets and rats as an increase in net Cl^- and, in some cases, HCO_3^-

secretion (15, 99). In infant rabbit intestine, the elevated Isc induced by protein-calorie malnutrition involved no change in net Na^+ transport (9), which suggests that increased anion secretion was most likely responsible for the change in basal Isc. In vivo, net anion secretion provides the electrical driving force for passive Na^+ movement into the lumen through the paracellular pathway (Figure 1), and both ions then provide the osmotic drive for fluid secretion.

Basal fluid accumulation in jejunal segments was similar in fed rats and in rats fasted for 1–3 days (98), but in ileal segments, basal fluid absorption was reversed to net secretion after 2 days of fasting (99, 100). The higher rates of basal ion and fluid secretion in the nutritionally deprived intestine may predispose the gut to fluid and electrolyte losses, a condition that can be further exacerbated by a second major consequence of FM, hypersecretion in response to intestinal secretagogues.

Stimulated Ion and Fluid Transport

FM enhances the responsiveness of the small intestinal epithelium to agents that stimulate ion and fluid transport. Enhanced responses to absorptive and secretory agents typically occur concomitant with reductions in mucosal mass and surface area, although functional alterations induced by fasting have been observed in rodent intestine before the appearance of any gross morphological changes in the epithelium (13). Thus, the extent to which FM-induced changes in ion and fluid transport are dependent on the structural changes induced by nutrient deprivation is not clear.

Hypersecretion FM enhances ion transport responses to a broad range of intestinal secretagogues. They include agonists of cyclic nucleotide-dependent pathways (cAMP and cGMP), as well as those that stimulate intracellular calcium mobilization (15, 22, 98). Many of these are endogenous mediators of secretory pathways that regulate normal intestinal responses to feeding, immune defense, and other processes (21), which suggests that FM has the potential to induce a hypersecretory state in an otherwise healthy gut with no other underlying disease. Hypersecretion also occurs in jejunal tissues of parenterally fed rats (74). Of perhaps more clinical relevance are the observations that FM also enhances the sensitivity of the small bowel to factors released by enteric pathogens that induce diarrhea, such the heat-stable enterotoxin of *Escherichia coli* (STa) (15, 19, 98, 101). FM also enhances the anaphylactic secretory response to luminal antigens, such as β-lactoglobulin, in sensitized animals (22). In general, FM sensitizes the intestine to agents that cause diarrhea and exacerbates the extent and severity of diarrheal symptoms (19, 73, 103, 104).

The ionic basis for the effect of FM on stimulated secretion is essentially the same as its effect on basal ion transport, i.e. an increase in net anion, typically Cl^-, secretion. This has been confirmed in vitro through ion flux (15) and anion replacement experiments (13, 98, 99) and by measurement of Cl^- and HCO_3^- concentrations in luminal fluid before and after secretagogue administration in

vivo (98, 99). Although the effect of FM in some cases appears to be enhancement of the same secretory mechanisms that are observed in the fed state, there is also evidence that FM may alter the cellular mechanism by which net secretion occurs. For example, in fed piglets, the cholinergic agonist carbachol increased the serosal-to-mucosal flux of Cl^- and thereby increased net Cl^- secretion (15). In fasted animals, carbachol induced a significantly greater increase in net Cl^- secretion than in the fed state, but it did so by inhibiting the net absorptive flux (mucosal to serosal) of Cl^- with no further increase in serosal-to-mucosal Cl^- flux (which was already elevated by the fast).

Fasting-induced increases in stimulated ion transport observed in vitro are paralleled by altered fluid secretion in vivo. Intraperitoneal administration of a variety of secretory agonists (carbachol, bethanechol, prostaglandin E_2, and *E. coli* STa) to anesthetized rats evoked significantly greater rates of fluid secretion in jejunal and ileal tissues of fasted rats compared with fed controls (98–100).

Hyperabsorption Although intestinal hypersecretion is more commonly observed in animals subjected to FM, nutrient deprivation can also enhance responses to agents that stimulate intestinal ion absorption. For example, FM causes a greater increase in Isc when Na^+-coupled nutrients, such as D-glucose, are added to solutions bathing the mucosal surface of tissues mounted in Ussing chambers (15, 24, 98). This change in Isc reflects the mucosal-to-serosal Na^+ current that is generated during nutrient uptake across the brush border membrane (Figure 1). In addition, tyramine, which releases norepinephrine from sympathetic nerve terminals, causes a greater fall in Isc in intestinal tissues of fasted compared with fed rats (98). The fall in Isc is due to activation of adrenergic receptors on enterocytes that increase Cl^- absorption.

Permeability

Enhanced permeability of the small intestine to ions and larger solutes has been reported in animal models of FM as well as in humans (92). This section describes the effects of FM on transcellular passage of macromolecules (>40 kDa) and on movement of solutes through the paracellular pathway.

Endocytosis FM increased the movement of macromolecules across the intestinal epithelium in adult rats, infant rabbits, infant mice, and children (7, 43, 81, 89, 96). The FM-induced enhancement of macromolecular absorption appeared to be due to increased endocytotic uptake across the brush border membrane (43, 96). Enhanced endocytotic uptake of macromolecules may represent an adaptive response to maximize protein absorption during malnutrition. On the other hand, it may also increase the likelihood of antigenic stimulation of the mucosal immune system and hypersensitivity responses (81, 89, 96). The mechanisms responsible for enhanced uptake of intact macromolecules after FM are unknown. However, the enteric nervous system, which has been implicated in FM-induced changes in

ion transport (see below), has been proposed as a regulator of transcellular uptake of macromolecules in the small intestine (50).

Paracellular Transport Over 80% of total ionic conductance across the small intestinal epithelium can be attributed to ion movement through the paracellular pathway. This means that changes in conductance observed in tissues mounted in Ussing chambers largely reflect changes in the size and/or selectivity of the tight junctions that separate adjacent enterocytes. Fasts of 48- to 72-h duration and malnutrition significantly increase basal tissue conductance (9, 13, 15, 22, 41, 80, 95, 98). Direct measurement of the in vitro flux of paracellular markers such as inulin and mannitol support an increase in permeability due to FM (15, 22, 41, 80). There is also increased paracellular movement of macromolecules such as ovalbumin and bovine serum albumin during FM (7, 96). In vivo tests of intestinal permeability, such as the lactulose:mannitol excretion ratio, have shown an increase in paracellular permeability in malnourished humans (92), although not all studies observe such an effect (30). These disparate results may be due to differences in duration and severity of malnutrition. As is the case for endocytotic uptake of macromolecules, the relative costs and benefits of FM-induced increases in paracellular permeability are unknown. Although an increase in paracellular permeability may enhance uptake of nutrients under the compromised nutritional state associated with FM, it may also increase the risk for inappropriate passage of food antigens and other noxious substances across the mucosal barrier.

Mechanisms Underlying Changes in Ion Transport and Permeability

Therapeutic interventions to correct intestinal epithelial derangements induced by FM will ultimately depend on knowledge of the mechanisms by which FM exerts its effects. Despite the numerous reports that have now documented the effect of FM on intestinal ion transport and permeability, we still do not clearly understand how, and even why, these changes occur. There are several mechanisms that have been proposed to account for FM-induced changes in intestinal ion transport and permeability.

Enterocyte Microvillus Membrane Composition and Fluidity Diet composition can affect the biophysical properties of plasma membranes, which in turn influence membrane permeability and activity of membrane transport proteins and signal transduction pathways (93). Thus, FM may influence intestinal ion transport and permeability through changes in enterocyte membrane composition and fluidity.

Changes in Enterocyte Brush Border Membrane Potential Fasting for as little as 24 h significantly increased brush border membrane potential in rat jejunal enterocytes that were impaled with microelectrodes while still attached to villi (25). This suggests that FM may alter intestinal ion transport through changes

in electrical driving forces across the enterocyte brush border membrane. An effect of FM on brush border membrane potential may account for both the enhanced Na^+-coupled nutrient absorption and the increased Cl^- secretion that are typically observed. The reasoning is that an increase in the steepness of the electrical gradient from the luminal (positive) to intracellular (negative) compartments would increase both the electrical driving force for cation entry into enterocytes and the driving force for anion secretion from cells into the lumen (100). The mechanism responsible for brush border membrane hyperpolarization is not known, except for evidence that fasting may reduce membrane permeability to Na^+ (25). An effect of FM on brush border membrane potential was not observed by other investigators using fasted guinea pigs (67), but because the latter study involved enterocytes that were fully isolated from the mucosa and whose polarity was unknown, methodological differences may be responsible for the disparate results.

Another mechanism that could lead to a steeper Na^+ electrochemical gradient is increased activity of the basolaterally located Na^+K^+-ATPase pump. However, studies that have examined Na^+K^+-ATPase activity in animals subjected to FM report no effect or reduced enzyme activity (9, 11, 68, 69).

Hormonal Changes Fasting and malnutrition can alter levels of endocrine and paracrine factors, making them potential candidates for extracellular signaling molecules that mediate changes in intestinal epithelial function after FM. The hormone that has received the most attention in this regard is pancreatic glucagon (55, 100). In support of this hypothesis, intraperitoneal administration of glucagon significantly increased brush border membrane potential of rat jejunal enterocytes (87). The membrane depolarization induced by addition of galactose to solutions bathing enterocytes was also greater in glucagon-treated rats. Glucagon injections into fed rats for 3 days increased basal Isc and enhanced cholinergically mediated intestinal Cl^- secretion (53). Glucagon also increased basal Isc and net Cl^- secretion when added to solutions bathing mouse intestine mounted in Ussing chambers (49).

Despite these observations, the link between elevated circulating glucagon levels and FM-induced epithelial changes is still tentative. Changes in plasma glucagon levels have not been reported in the many studies that document significant effects of FM on intestinal ion transport. In piglets fasted 48 h whose tissues show significant changes in ion transport from fed values (15), plasma glucagon levels are unchanged [although levels of another hormone associated with fasting, cortisol, are nearly threefold higher (UL Hayden & HV Carey, unpublished data)]. Species differences may explain some of these contradictory observations.

Neural Influences Enteric nerves respond to physical and chemical stimuli that originate in the intestinal lumen and initiate reflex pathways that regulate epithelial function (20, 83). In rats and piglets, FM-induced changes in basal and stimulated ion transport are mediated in part by altered activity of enteric nerves (41, 70).

Nutritional status may also influence the neural regulation of paracellular permeability in the small intestine (41). The primary signal responsible for changes in neurally mediated ion transport in animals subjected to FM is not known, but the absence of glucose in mucosal solutions activates enteric neural reflexes that subsequently influence basal ion transport (14, 20). These studies suggest that enteric sensory fibers, perhaps acting through release of products from enteroendocrine cells that "taste" the luminal contents (77), may mediate FM-induced changes in epithelial function. Whether FM directly affects the activity of enteric nerves has received little attention. However, the intestinal atrophy associated with surgical bypass of nutrients from the intestinal lumen for 10 days caused changes in expression of enteric neurotransmitters and neurally mediated contractile activity of the musculature (29). Thus, the intestinal atrophy that is associated with FM may affect not only the cells directly involved in epithelial function but also other cells in the mucosa that play regulatory roles.

Oxidative Stress FM has been associated with oxidative stress to the intestinal mucosa, including changes in levels of antioxidant enzymes (2, 24, 48) and in production of free radicals (24). Oxidative stress induced by FM could affect epithelial function by increased lipid peroxidation and subsequent damage to enterocyte plasma membranes, leading to alterations in ion channels, membrane permeability, and tight junctional proteins that regulate paracellular permeability. Chemical oxidants such as hydrogen peroxide and monochloramine increase intestinal Cl^- secretion (24, 38) and intestinal permeability (38). The association of FM with oxidative stress and epithelial dysfunction may be due to increased release of oxidants from mucosal immune cells. For instance, the enhanced intestinal permeability associated with malnutrition in human patients was accompanied by greater numbers of activated T cells and macrophages in the mucosa, as well as by enterocytes expressing the major histocompatibility complex class II antigen, human leukocyte antigen-DR (92). However, caution must be taken in interpreting these and other correlations between FM, intestinal epithelial dysfunction, and specific immune mediators because the cause-and-effect relationships among them are not yet known (92).

INTESTINAL NUTRIENT TRANSPORT

Functional Considerations Underlying Regulation of Nutrient Absorption

In animals fed to satiety, an increase in dietary levels of sugars (and presumably in levels of luminal signals) monotonically increases sugar transport rates (31). In contrast, intestinal absorption of vitamins and minerals typically decreases with increasing levels of these micronutrients in the diet. Amino acid and peptide transport rates usually vary with dietary protein (decreasing rates with lower dietary

protein) until minimum required dietary protein concentrations are reached. Further decreases in concentration of dietary protein below minimum requirements are accompanied by increases in essential but not nonessential amino acid transport (32). The functional considerations that help us interpret these patterns in fed animals, and that may be relevant to unfed animals, follow.

Biosynthetic costs of synthesizing transporters should cause a transporter to be repressed if the cost of its synthesis exceeds the benefits the transporter provides. In the case of metabolizable nutrients such as sugars and nonessential amino acids yielding energy in proportion to the quantity of nutrient absorbed, there should be increased transporter activity with increasing dietary substrate levels. Optimal daily requirements for essential nutrients, such as vitamins and certain amino acids, should cause low dietary concentrations of each nutrient to up-regulate the transporter because the transporter would then yield greatest benefits. Nutrients toxic at high concentrations, such as certain minerals and amino acids, should down-regulate their transporters at high dietary levels.

Dietary or luminal nutrients generally act as signals for these transport patterns to develop in well-fed animals (31). What happens to transporter gene expression during FM? This is a difficult question to answer because FM limits the amount of dietary signals emanating from the lumen, and therefore regulatory mechanisms activated during FM involve direct responses to diminished amounts of luminal signals, or indirect responses to factors released by absence of luminal signals. The functional considerations predict that absorption of sugars and nonessential amino acids should decrease with starvation, whereas absorption of vitamins, minerals, and essential amino acids should increase with starvation.

Mechanisms Underlying Changes in Nutrient Absorption

Nonspecific Mechanisms Several of the proximate mechanisms proposed for FM-induced changes in intestinal ion transport discussed earlier may also be involved in the nonspecific regulation of intestinal nutrient transport. These include a reduction in mucosal surface area (27), an increase in transcellular electrochemical gradient for Na^+ (25), and a change in plasma membrane lipid composition and fluidity (10, 39). Alterations in membrane composition and fluidity may alter the turnover number (number of moles of substrate absorbed per mole of transporter per unit time) of nutrient transporters. Another nonspecific mechanism, an increase in the ratio of mature (absorbing) to immature (nonabsorbing) enterocytes, may occur with the reduction in mucosal mass (31). This combination can explain an increase in transport rates per unit intestinal mass.

Specific Mechanisms Increases in site density of transporters increase transport rates of their substrates (31). In normally fed animals, a change in transporter gene expression and in site density of transporters involves the interaction of a signal with promoter elements. For example, a 70-bp sequence in the intestinal fructose transporter GLUT5 promoter region responds to glucose (60). The removal of

substrates during FM may act as a signal for regulating the site density of a transporter, hence changing the transport V_{max}. The molecular regulation of nutrient transport during starvation is yet to be studied. However, there is a close relationship between the growth state of the intestinal epithelium and the expression of genes that regulate brush border enzymes (44).

There may also be changes in substrate affinity or turnover number of specific transporters (1), or in synthesis of a new transporter type (8). In the latter case, fasting stimulates one type of glucose transporter whereas malnutrition stimulates another type.

A change in concentration gradient can affect the transport of nutrients, particularly those transported by facilitated mechanisms. Oxygen consumption increases by 40% in enterocytes isolated from FM rats (67) whereas protein synthesis rates increase in intestines of calorie-restricted rats (64). If metabolic activity during FM reduces the intracellular pool of the transported nutrient, the transcellular concentration gradient will be enhanced, thereby increasing the driving force for facilitative transport of that nutrient from the lumen or blood into the enterocyte.

Luminal Nutrient Concentrations

FM reduces the amount but not the concentration of certain nutrients in the intestinal lumen. This is an important consideration because luminal nutrient concentrations are important signals that regulate activities of nutrient transporters in well-fed animals (31). Luminal contents do not exactly mirror the types of nutrients ingested. This is because (*a*) the intestinal epithelium is continuously replaced and cells are always being exfoliated into the lumen, (*b*) it secretes proteins and nitrogenous compounds into the lumen (36), and (*c*) it is relatively permeable and therefore can permit passage of substances from the blood. Thus, the intestinal epithelium is an active contributor to the contents of the intestinal lumen.

Surprisingly, there are no time-related and very little diet- or fasting-related differences in osmolality and in Na^+ and K^+ concentrations in vivo between the intestinal contents of fasted (12–36 h) dogs, rabbits, or rats and those of control animals fed a variety of diets (35). These similarities in osmolality and ion concentrations were generally independent of the type of diet being ingested and of the volume of luminal contents, which was much greater in fed control animals. Remarkably, the luminal concentration of α-aminonitrogen compounds (total free amino acids and peptides) is also similar between fed and fasted dogs or rabbits (RP Ferraris, S Yasharpour, KC Lloyd, & JM Diamond, unpublished observations). However, fasting affected the amino acid composition of jejunal contents. In contrast to those of α-aminonitrogen compounds and of Na^+ and K^+, glucose concentrations in the intestinal lumen of dogs, rabbits, or rats were markedly reduced by starvation and varied with diet composition (35). This suggests that FM markedly decreases the luminal concentration of those nutrients that are not secreted by the mucosa and are obtainable mainly from the diet: sugars, minerals, many vitamins, and certain amino acids.

Effect of Fasting and Malnutrition on Nutrient Absorption

Because total mucosal mass, total number of cells, and total surface area decrease during FM, total intestinal absorption of all types of nutrients will likely decrease under these conditions. What other types of adaptations does FM elicit?

Sugars Site density of intestinal glucose transporters increases monotonically with carbohydrate levels in the diet (31). Because there is little glucose in the intestinal lumen during starvation, there is no luminal signal to maintain a high number of transporters, and consequently, intestinal glucose absorption per milligram should decrease with starvation. This FM-related decrease in transport per milligram, coupled with nonspecific decreases in mucosal mass, would logically result in marked decreases in glucose transport per intestine and per centimeter of intestine during fasting.

Many studies, however, observed increases in brush border glucose transport per milligram of intestine or per milligram of protein, independent of decreases in mucosal mass, during FM (8–10, 15, 25, 39, 59, 102). These findings indicate that transport rates may increase even when luminal sugar concentrations are very low. The significance of the absence of luminal carbohydrates during FM was emphasized when glucose uptake per centimeter and per milligram increased in fasted mice previously fed a carbohydrate-free diet (27). The carbohydrate-free diet removed glucose from the intestinal lumen well before fasting began, and it distinguished the effect of removal of carbohydrate in well-fed animals from the effect of removal of carbohydrate during starvation. Because the lumen of fasted mice previously fed a carbohydrate-free diet had no sugar before or after fasting, there should not be any change in glucose uptake during fasting if the regulatory signals were solely luminal sugars. In fact, after 2–3 days of fasting, uptake per centimeter and per milligram increased by 50–100% in these mice. In contrast, in fasted mice previously fed a high-carbohydrate diet, uptake per centimeter decreased whereas uptake per milligram increased transiently before decreasing. This study underscores the relevance of diet history prior to experimental starvation in FM studies.

What can up-regulate sugar transport in the absence of luminal sugars during FM? FM-related hyperpolarization of the membrane potential (25) and/or decreases in intracellular Na^+ concentration would increase the driving force for Na^+-coupled glucose transport. In support of this hypothesis, transepithelial Na^+-dependent glucose transport and glucose-induced Na^+ absorption increased in fasted rats, fasted piglets, and malnourished rabbits (9, 10, 15, 25, 102). Other studies, however, do not support this hypothesis. In fasted guinea pigs and malnourished rats, there were no FM-related differences in either membrane potential or intracellular Na^+ concentration (59, 67), although methodological differences may be responsible for these differences. Moreover, Na^+-independent transport of many nutrients also increases markedly with FM (see below), observations that cannot be explained by the hyperpolarization hypothesis.

FM increased glucose transport in brush border membrane vesicles about two-fold that of well-fed rats or rabbits (8, 10, 39, 59) but decreased glucose transport in monkeys (75). In mildly malnourished rats that lost body weight but had no change in intestinal mass or in intestinal protein and DNA content, glucose absorption per milligram increased (18). These FM-related increases in transport rates were variously ascribed to increases in the Na^+ electrochemical gradient, to a stimulation of a different glucose transporter type, or to increases in microvillus surface area and membrane fluidity. A new transporter type would specifically increase glucose transport during FM but cannot explain the FM-related increases in transport of other nutrients. In adult rat (39), FM-related increases in membrane fluidity have been invoked to explain FM-induced increases in intestinal glucose transport. In neonatal rabbits, however, there were FM-related changes in intestinal transport with no changes in membrane fluidity (10).

The role of nerves in mediating FM-related and diet-related changes in sugar transport has received little attention. There is evidence that nerves may regulate adaptive changes in intestinal sugar transport because chemical ablation of vagal afferent nerves of well-fed guinea pigs eliminated dietary carbohydrate-induced changes in glucose transport (3). However, others have reported no effects of neural isolation on net glucose absorption (40).

A detailed discussion of the potential effects of hormones on FM-induced changes in glucose transport is beyond the scope of this review; however, one example merits attention. Pancreatic glucagon, which may be elevated under fasted conditions, has been suggested to mediate FM effects on intestinal glucose transport. Infusions of glucagon into fed rats have been shown to increase intestinal glucose transport (19a, 24a). However, as with ion transport (see above), a direct linkage between FM-induced increases in plasma glucagon concentrations and intestinal glucose transport needs to be firmly established.

The FM-induced increases in transport per milligram, however, may be insufficient to offset the FM-related decreases in mucosal mass, and total intestinal transport of sugars may still decrease. For example, in rats maintained on a low-protein diet for 8 weeks, total glucose and fluid transport by the entire small intestine decreased (71). Total intestinal sugar absorption, as measured by the rate of change in plasma xylose and 3-*O*-methyl-D-glucose concentrations, also decreased in healthy patients starved for 1.5 days and in obese patients starved for 11 days (61). In humans considered to be clinically malnourished by anthropometric data (but not dietetically malnourished), there was, however, no effect of "malnutrition" on intestinal carbohydrate absorption as measured by breath hydrogen (5). Perhaps there has to be a reduction or cessation of enteral nutrient intake before intestinal carbohydrate absorption can decrease.

What is the effect of parenteral nutrition, which results in marked decreases in mucosal mass, on sugar transport? The data available yield conflicting conclusions. For example, in parenterally fed rats, in vivo glucose transport rates normalized to intestinal mass decreased (66). Glucose transport per milligram of brush border membrane protein decreased markedly in humans on total parenteral nutrition

for 1 week (46), even though calorie and nitrogen intakes were similar between enterally and parenterally fed patients. In contrast to these studies, glucose-induced increases in Na^+ current increased in parenterally fed rats (74). Clearly, further studies are needed to determine the effects of parenteral nutrition on intestinal sugar transport.

Like FM, chronic (14–24 mo) calorie restriction increases brush border glucose transport per milligram of tissue or protein in mice; unlike FM, there were no marked reductions in mucosal mass (16, 17). Hence, there is an increase not only in glucose absorption normalized to mucosal mass, but also in glucose absorption per centimeter and per small intestine. Intestinal fructose absorption per milligram, mediated by the Na^+-independent transporter GLUT5, also increased dramatically with chronic calorie restriction. The increases in sugar transport rates were not accompanied by increases in transporter mRNA abundance. There were no calorie restriction–related changes in brush border membrane permeability to L-glucose (17). The mechanism underlying the increased transport rate may be an increase in the ratio of absorptive to nonabsorptive cells because of decreases in enterocyte migration rate during calorie restriction (57). In rats subjected to calorie restriction, the increase in brush border sucrase activity was due to this same mechanism (51). It is interesting that calorie restriction of a shorter duration (28 days) had no effect on intestinal sugar transport.

Little is known about the effect of FM on basolateral sugar transport mediated by GLUT2. In rats whose brush border uptake and transepithelial transport of glucose were enhanced with semistarvation, basolateral transport was not affected (59).

In summary, FM leads to decreases in luminal concentrations of sugars, which not only decrease intestinal mucosal mass but also remove a known signal for up-regulating sugar transport in well-fed animals. Paradoxically, intestinal sugar transport per milligram of intestine increases with FM, a finding that cannot be explained by the absence of luminal sugars or by the loss of mucosal mass. It is possible that FM can lead to direct increases in transporter gene expression and transporter activity. The molecular mechanism for this regulatory step is unknown, although a recent study on circadian periodicity in rats and monkeys is relevant (79). Immediately before the onset of darkness and of feeding (but after 12 h of limited or no feeding) when SGLT1 mRNA levels were high, elements of the hepatocyte nuclear factor 1 bind to the SGLT1 promoter to regulate its transcription. FM can also lead to increases in electrochemical gradient for Na^+ and to changes in membrane fluidity, thereby increasing transport. There may also be changes in the ratio of absorptive to nonabsorptive cells, but more convincing evidence for this hypothesis has arisen mostly from amino acid transport studies (see below).

Amino Acids and Peptides As would be expected from postulated increases in the brush border Na^+ electrochemical gradient, intestinal absorption of essential and nonessential amino acids transported mainly or in part through a Na^+-dependent pathway increased with FM in rats and chickens (18, 25, 78, 84, 90). Enhanced

amino acid absorption via the Na^+-dependent system A transporter can even be observed in enterocytes isolated from the small intestine of starved guinea pigs (67), which suggests increased transport on a per cell basis. Evidence against this hypothesis includes the FM-enhanced absorption of many amino acids and dipeptides by Na^+-independent pathways in rats and guinea pigs (67, 86, 90). Moreover, absorption of amino acids by several Na^+-dependent transporter systems did not increase with starvation (67), indicating that mechanisms other than brush border membrane hyperpolarization may be an important factor in modulating the effects of fasting on intestinal transport.

It is interesting to note that the protein synthesis inhibitor cycloheximide abolished the FM-induced increase in amino acid uptake by guinea pig enterocytes (67). Cycloheximide could affect the synthesis of transporters themselves or of other proteins regulating transporter synthesis or function. By increasing the transcellular concentration gradient, potential intracellular metabolism (64, 67) of transported amino acids may also modulate the effects of starvation on amino acid absorption. Evidence against this hypothesis is the finding that brush border absorption of the nonmetabolizable amino acids cycloleucine and methylisobutyric acid still increases with FM (67). Recall, however, that transport of a single amino acid may occur by different transporters, each of which may be affected differently by FM.

In fasted rats, twofold increases in dipeptide absorption rates are paralleled by fourfold increases in Pept-1 (the H^+-dependent oligonucleotide transporter) protein and mRNA levels (72, 86). These substantial increases in transporter expression probably more than compensate for any FM-related decreases in intestinal mucosal mass. Drinking an amino acid mixture markedly decreased the number of Pept-1 transporters in previously unfed rats, to levels even lower than those of well-fed rats (72). Fasting enhanced by twofold the levels of Pept-1 transporter proteins in the villus tip and mid-villus regions. Moreover, Pept-1 transporters appeared in the villus base of fasted rats and were not present in the villus base of control, well-fed rats (72). Perhaps the mechanism underlying the fasting-related increase in peptide transport may be a combination of a starvation-related increase in Pept1 gene expression and an increase in the ratio of transporting to nontransporting cells.

An increase in the ratio of transporting to nontransporting cells may also be responsible for FM-induced increases in valine absorption. Fasting not only enhanced the density of valine transporting sites (as measured by autoradiography) in the villus tip, it also resulted in their appearance in the lower villus regions of rat intestine (87). This resulted in recruitment of 60% more valine transport sites along the villi, which were themselves reduced in height by the fast. In protein-malnourished rats, the top 60% of a short villus column absorbed valine, whereas in well-fed rats, only the top 40% of a tall villus absorbed valine (85). In both diet groups, only enterocytes 30 h or older absorbed valine, indicating that the shortened villi of malnourished rats were occupied by cells older than those found at the same height in the longer villi of well-nourished rats.

Other studies have not reported FM-induced changes in amino acid absorption. In contrast to findings in guinea pigs, rats, and chickens, glutamine and arginine

transport per milligram of protein decreased in the brush border of fasted rabbits (82). Malnutrition (as defined by anthropometric data) also had no effect on protein absorption, as measured by stool nitrogen in humans (5). These disparate results may reflect species differences in response to FM, duration of FM, diet history, and method used in amino acid uptake determinations.

Although FM generally increased intestinal amino acid transport, the effects of parenteral nutrition on nutrient transport are less clear. In vivo aspartic acid, valine, and lysine absorption per milligram (our recalculations) was much higher in the intestine of fasted and parenterally fed rats compared with that in enterally fed rats (6). In contrast, parenteral nutrition had no effect on rat intestinal glycine and glycylglycine absorption per milligram in vivo (66). There were >50% decreases in intestinal mass per centimeter, so that amino acid absorption per centimeter, in all cases, was lower in parenterally fed compared with enterally fed animals (66). Brush border membrane vesicle transport of leucine, arginine, alanine, and meAIB, a nonmetabolizable amino acid, each decreased with parenteral nutrition in humans (46).

Chronic calorie restriction of mice markedly enhanced the absorption per milligram or per centimeter of amino acids, particularly proline (16, 17), which may be due to an increase in the ratio of absorptive to nonabsorptive enterocytes. However, as with sugar absorption, short-term calorie restriction did not alter intestinal proline transport. This suggests that the signal regulating the effects of calorie restriction on amino acid transport is not luminal in nature, as there likely was no difference in luminal contents between chronic calorie restriction and calorie restriction of shorter durations.

The effect of FM on basolateral transport of amino acids has received little attention. It does appear that, as for sugar transport, FM increases the rate of brush border uptake with no change in the rate of basolateral transport of amino acids (67). This finding is interesting. It implies that certain nutrients whose brush border but not basolateral transport increases may remain in the enterocyte (59) and be metabolized because oxygen consumption and protein synthesis increase in the intestine of fasted or calorie-restricted rats (64, 67).

In summary, intestinal amino acid and peptide absorption generally increases during FM. Regulation of this increase may differ from that of well-fed animals, in which reduction of dietary protein levels increases transport of only the essential amino acids. Proposed mechanisms for FM-induced increases include an increase in the ratio of absorptive to nonabsorptive cells and an increase in transporter gene expression and protein abundance. Like sugar absorption, amino acid absorption per intestine will decrease with fasting if the decrease in absorptive mucosal mass will be much greater than the paradoxical increases in absorption per milligram of tissue or membrane protein.

Water-Soluble Vitamins and Minerals The few studies on effects of FM on vitamin and mineral absorption do not indicate any general trends. Total absorption in vivo of folate did not change in fasted dog jejunum (40), perhaps because dogs

were fasted only overnight. In contrast, calcium absorption in vitro increased in malnourished rats (18). It is likely that FM-related reductions in mucosal mass can lead to an overall reduction in vitamin and mineral absorption per intestine.

PERSPECTIVES

What can be concluded about the overall effects of FM at the level of the whole organism? Are the changes described in this review adaptive, in the sense that they are beneficial to the individual experiencing FM? Certainly, the most noticeable response of the small intestine to FM is the reduction in absorptive surface area. Although this reduces total absorptive capacity, it also reduces the proportion of total body energy and nutrient stores that must be diverted to the gut for its maintenance. During FM, it may be beneficial to redirect nutrients to those organs that must receive adequate energy and nutrients to insure survival. From this perspective, the somewhat paradoxical findings of enhanced rates of nutrient absorption normalized to absorptive cell mass with simultaneous decreases in total intestinal absorptive capacity may turn out to be of benefit to the organism. Valuable energy and nutrient reserves are no longer spent on maintaining the normal mass of absorptive tissue during FM, whereas mechanisms that maintain or even enhance nutrient transport at the level of individual enterocytes are utilized. These may include an increase in the proportion of transporting to nontransporting cells along the shortened crypt-villus axis, an increase in expression of nutrient transporters, and alterations in electrochemical gradients across the brush border membrane. Future studies must confirm these mechanisms and identify extracellular signals and intracellular pathways that mediate them.

What is the physiological significance underlying the increase in ion secretion and intestinal permeability typically observed during FM? If, as has been suggested, FM leads to hyperpolarization of the enterocyte brush border membrane and a more favorable gradient for Na^+-coupled nutrient absorption into cells, the same membrane hyperpolarization may also favor increased rates of electrogenic anion secretion from cells into the intestinal lumen. Thus, the seemingly maladaptive secretory response of the intestine to FM could be a deleterious outcome of the primary adaptive response to increase nutrient absorption in the atrophic, malnourished intestine. This would insure that even with greatly reduced concentrations of certain luminal nutrients and the loss of absorptive surface area induced by FM, nutrient uptake could still occur against substantial concentration gradients via a physiological change in existing enterocytes that enhances the active uptake of Na^+-coupled solutes.

There is a higher incidence of diarrheal diseases in areas in which malnutrition and starvation are common, particularly among infants and children. Although the role of infectious agents that evoke secretory diarrheas (e.g. *Vibrio cholerae*) is well documented, in some cases, the severity of diarrheal symptoms in undernourished populations is less clear. The ability of FM to enhance ion secretion and intestinal

permeability in animal models may help explain some of these cases. It is unlikely that FM-induced changes in ion transport and permeability lead to significant losses of fluid and electrolytes in healthy individuals because of the substantial absorptive capacity of the colon. However, the effects of nutrient deprivation on the intestinal epithelium may be important in those situations in which colonic function is impaired, or in pathologic conditions that directly stimulate intestinal secretion. These considerations underscore the value of maintaining enteral feeding when at all possible.

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