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Intestinal phase of protein assimilation in man[1, 2]

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The importance of dietary proteins to optimal nutrition and health is well recognized. Digestion and absorption which are necessary for utilization of amino acid constituents of these proteins are quite complex. The initial step in protein digestion is the gastric phase: dietary proteins are denatured in the acidic environment of the stomach. Denaturation renders dietary protein a more suitable substrate for the action of proteolytic enzymes. Although the in vivo digestion of protein in human stomach has not been extensively studied, it is generally assumed that it is minimal (1). In contrast, digestion by pancreatic proteolytic enzymes is considered to be critical in the assimilation of dietary protein. Pancreatic resection or insufficiency results in both a considerable decrease in the intraduodenal hydrolysis of protein (2) and an increase in fecal nitrogen (1). Intraluminal digestion produces free amino acids and small oligopeptides (3, 4). This review examines the protein source and the intestinal fate of these free amino acids and oligopeptides in man.

Protein digestion

The conclusions of earlier studies were that after a meal: *a*) digestion and absorption of dietary protein are completed in the jejunum (5); *b*) the whole process of digestion and absorption is quite rapid, reaching its maximum at about 45 min or possibly earlier; and *c*) absorption may be largely complete within 75 to 90 min (6). However, recent studies (4) have shown that, as late as 4 hr after a meal, dietary protein can still be recovered from the ileum. Nevertheless, it appears reasonable to assume that under normal conditions the greatest portion of dietary proteins is digested and absorbed in the upper small intestine.

Concentrations of amino acids in the gut lumen are increased after ingestion of a nutritionally balanced meal containing 50 g of an animal protein (albumin). The increases in concentration are generally greater for amino acids that are linked together as small oligopeptides (two to four amino acid residues) than for amino acids in free form (4). Moreover, the increases in peptide amino acid concentrations are more pronounced in the jejunum than in the ileum. After ingestion of a protein-free meal, concentrations of individual amino acids in the jejunum and ileum do not increase and, in fact, in some cases actually decrease (4). These observations suggest that the increases in amino acid concentrations in the gut lumen after a protein meal are mostly of dietary origin. Nevertheless, the aspirates from human intestine always contain amino acids and peptides even when proteins have been excluded from the diet (4). The source of these endogenous amino acids and peptides are the proteins in the gastrointestinal secretions and the proteins released from desquamation of mucosal cells (7).

Peptide digestion

Although as early as 1901 it was discovered that the intestinal mucosa has the capacity to hydrolyze peptides (8), it is only within the past few years that studies in animal and human intestine have firmly established the

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role of mucosal peptide hydrolases in the final phase of protein digestion. When large amounts of tripeptides and dipeptides, such as triglycine and diglycine, are introduced into the gut lumen, there is rapid disappearance of these oligopeptides from the gut lumen (9–12). Intestinal hydrolysis must have taken place since no triglycine is detected in portal or peripheral plasma and only small amounts of diglycine appear in either portal or peripheral plasma, but there are large increases in glycine concentration (10–12). The location of hydrolysis must be in the mucosal cells since the intraluminal fluids, assayed in vitro, do not reveal hydrolase activity against these oligopeptides (11, 12).

Both brush border and cytoplasmic fractions of intestinal mucosal cells contain several different peptide hydrolases (13–18). Studies of electrophoretic mobility, heat stability, effects of inhibitors, and substrate specificity have indicated that the peptide hydrolases in the brush border fraction are not the same as those in the cytoplasmic fraction (16, 17, 19). The different responses of brush border and cytosol peptide hydrolases of rat intestine to dietary alterations are further evidence that these enzymes are distinct from each other. Kim et al. (20) have shown that in starvation the peptide hydrolase activity of the cytosol fraction is increased, while that of the brush border fraction is decreased. Nicholson et al. (21) have found that an increase in dietary protein intake increases the peptide hydrolase activity of the brush border fraction without affecting that of the cytosol fraction. However, peptide hydrolases of both fractions appear to have two common characteristics: *a*) all are amino-oligopeptidases, i.e., the N-terminal amino acid residue of peptides is the determinant of the rate and substrate specificity of the action of peptide hydrolases; and *b*) all have pH optima in alkaline range (17, 19, 22).

Studies of the subcellular distribution of peptide hydrolases in the mucosal cells of animal intestine have established that the major fraction (80 to 95%) of the enzyme activity against dipeptides and also probably against some tripeptides resides in the cytoplasmic component (16, 23). Kim et al. (17) have shown that cytoplasmic enzymes of human intestinal mucosa are capable of hydrolyzing dipeptides and tripeptides, but not peptides of greater chain length. In contrast, the brush border enzymes of human intestinal mucosa hydrolyze all the peptide substrates studied, including a heterohexapeptide (17).

Free amino acid absorption

Intestinal absorption of free amino acids is mediated by highly selective processes. This is apparent from comparison of rates of absorption of 18 common dietary amino acids or of eight essential amino acids, when infused in equimolar concentrations into the jejunum of healthy human volunteers (24, 25). Methionine and the branched chain amino acids (leucine, isoleucine, and valine) are absorbed most rapidly from both amino acid mixtures. Among the 18 common dietary amino acids, aspartate and glutamate were most slowly absorbed, as were tryptophan and threonine in the eight essential amino acids. As a group, essential amino acids are better absorbed than nonessential amino acids. These complex patterns of absorption have been attributed to differences in the affinities of amino acids for the free amino acid carrier systems (26); the competition for transport is stronger for amino acids with higher affinities (26).

The affinities of neutral amino acids for the amino acid carrier system depend to a great extent on the length of the amino acid side chain—the longer the side chain, the greater the affinity. Estimates of affinity of individual amino acids for the amino acid carrier system are based on comparisons of K_m values (concentrations which produce one-half of the maximal absorption rates) derived from jejunal perfusion studies in healthy human volunteers (26, 27). The K_m value is regarded as an index of apparent affinity for absorption sites—the lower the K_m value, the higher the apparent affinity. For example, leucine and valine are identical except for one less carbon atom in the valine side chain, but the K_m value of valine is twice that of leucine (26). Similarly, the K_m value of glycine is twice that of alanine (27).

In vitro and in vivo studies of amino acid transport in patients with hereditary disorders of amino acid absorption (28–32) have established the presence of at least two distinct membrane carrier systems in human intes-

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tine: one for basic and one for neutral free amino acids. The intestinal mucosa of cystinuric patients is defective in accumulation of basic free amino acids, but actively accumulates neutral ones (28, 29). In contrast, the intestinal mucosa of patients with Hartnup disease is defective in its accumulation of neutral amino acids (30). There have also been a few reports of defective intestinal transport of individual free amino acids, such as methionine (33), tryptophan (34), and proline (35), but there is as yet insufficient evidence to establish the existence of several different carrier systems for individual neutral amino acids in human intestine.

The potential for transport by their respective carrier systems is much smaller for basic free amino acids than for neutral amino acids (36). In the case of the basic amino acids, the presence of a positive charge in the side chain appears to exert an even greater influence than the chain length on the rate of transport.

Effect of luminal factors on amino acid absorption

In human jejunum, an acidic intraluminal pH (lower than 2.50) reduces leucine absorption (37). This reduction appears to be principally the result of protonation of the leucine molecule. The molecular alteration reduces the interaction of leucine with its carrier system, resulting in a comparatively slow transport.

In vitro studies have shown that the intestinal transport of amino acids in animals is markedly influenced by the concentration of sodium in the mucosal side of intestinal preparations (38, 39), but in vivo studies in man have demonstrated that wide variation in the intraluminal concentration (55 to 143 mM) of sodium does not significantly affect the jejunal absorption rate of free amino acids (40). Since the mechanism of interaction between sodium and free amino acid transport has not yet been fully established, the basis for disagreement between the in vitro and in vivo findings remains uncertain.

Several workers have reported that the transport of free amino acids is affected by the presence of hexoses (41, 42) in the gut lumen, but the results have been conflicting. Cook has shown that while glucose and galactose inhibit absorption of glycine in human jejunum, the absorption of methionine is not affected by glucose in this segment (43, 44). The physiological significance of these observations remains uncertain.

Peptide absorption

Evidence for intact absorption of dipeptides

In 1953, intestinal absorption studies in rats (45) unequivocally demonstrated the transmural transport (movement from the mucosal to serosal side) of unhydrolyzed dipeptides, such as glycylglycine. This observation was later confirmed by several other investigators (46, 47). Initially, it was not certain whether intact absorption was peculiar to glycylglycine or included other dipeptides, or whether dipeptide absorption was quantitatively an important pathway for the absorption of amino acid constituents of dietary proteins. In the past few years, extensive studies have demonstrated the physiological importance of dipeptide absorption in the intestine of experimental animals as well as in man. The evidence supporting intact dipeptide absorption in human intestine has included the following:

First, rates of disappearance of dipeptides from the gut lumen are not dependent on their rate of hydrolysis. For example, the rate of hydrolysis of glycylglycine by mucosal enzymes is much smaller than that of glycylleucine when examined in vitro (15, 18). However, disappearance rates of these two dipeptides from the jejunum are similar over a wide range of concentrations (11).

Second, if dipeptides were hydrolyzed to their constituent free amino acids before the absorption, rates of amino acid uptake from test solutions introduced into the gut lumen, and containing the same concentration of amino acids in either a free or dipeptide form, should be similar. However, rates of amino acid uptake are generally greater from infusion solutions containing dipeptides than from those containing corresponding free amino acid mixtures (11, 48-50).

Third, the competition between free amino acids for mucosal uptake is avoided or much reduced when solutions of dipeptides, instead

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of corresponding free amino acid mixtures, are introduced into the gut lumen (11, 48, 50). For example, when equimolar mixtures of free leucine and free glycine are infused into the jejunum of human volunteers, leucine is better absorbed than glycine (11); however, the difference between absorption rates of these two amino acids becomes much reduced or abolished when glycine and leucine are infused as glycylleucine (11). Similarly, uptake of glycine from glycylglycine or uptake of leucine and glycine from glycylleucine remains almost unimpaired when the free amino acid absorption sites in the intestine are saturated with large loads of leucine or isoleucine (11).

Fourth, acidic pH (below 5) abolishes the hydrolysis of dipeptides by the mucosal peptide hydrolases (15, 17). However, when the intraluminal pH was made highly acidic (pH lower than 3), there was only 40% reduction in the absorption rate of either glycylglycine or glycylleucine (51). Therefore, dipeptides were absorbed even when hydrolysis was prevented. Furthermore, the modest reductions in dipeptide absorption, under the condition of acidic pH, appear to be a function of protonation of dipeptides rather than reduced hydrolysis since the luminal disappearance of these dipeptides is less affected by acidification than that of free amino acids (51).

Fifth, patients with a hereditary deficiency of free amino acid carrier systems involving either neutral amino acids (Hartnup disease) or basic amino acids (cystinuria) have a serious reduction in the intestinal absorption of free amino acids (28–32, 52–55). When these patients were given oral solutions of free amino acid mixtures, there were no appreciable increases in the levels of free amino acids in plasma; however, the same patients showed considerable increases in the plasma amino acid levels when the same amino acids were given in dipeptide form (52–55). In addition, intestinal perfusion studies in patients with cystinuria have shown that rates of uptake of basic amino acids from dipeptides containing these amino acids are similar to those of normal volunteers (31, 32).

Sixth, dipeptides such as glycylglycine, carnosine (β-alanylhistidine), and anserine (β-alanyl-1-methylhistidine) which are slowly hydrolyzed by tissue enzymes are found intact in the peripheral venous blood of human subjects after either intestinal infusion, as in the case of glycylglycine (11), or after a protein meal, as in the case of imidazole dipeptides (56).

For studies of intestinal absorption, analysis of peripheral plasma may not always reveal the dipeptides that are transported by the mucosal cells and released to splanchnic circulation as dipeptides. Practically all tissues contain enzymes capable of hydrolyzing dipeptides at varying rates (57, 58). Therefore, these tissues may prevent the accumulation in the peripheral venous blood of a detectable concentration of dipeptides which have escaped hydrolysis by the enzymes in the intestinal mucosal cells. Indeed, analysis of peripheral venous plasma failed to show the presence of glycylleucine after intestinal perfusion with a large load of this dipeptide (11). On the other hand, analysis of blood samples taken from the superior mesenteric vein revealed each of the six dipeptides injected intraluminally in rats (59).

Dipeptide absorption in different segments of intestine

Although only limited studies have been performed in the ileum and the duodenum of human intestine, intact absorption of dipeptides has also been demonstrated in these segments (11, 60). In contrast to considerable differences in jejunal and ileal absorption rates of free amino acids (11, 26, 60, 61), the absorption rates of dipeptides are either similar in these two segments or only slightly greater in the jejunum (11, 60). A combination of greater dipeptide hydrolysis by mucosal enzymes (13) and a smaller rate of amino acid absorption in the ileum than in the jejunum (11, 26, 60, 61) appears responsible for the observed greater concentrations of amino acids accumulating in the lumen of the ileum than jejunum during dipeptide infusions (11, 60).

Is intact absorption common to all dipeptides?

Usually there are 20 different amino acids in dietary proteins. These amino acids may form 400 different dipeptides, and the intestinal absorption of all of these dipeptides has not yet been investigated. Therefore, the answer to the question of universality of

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intact absorption among dipeptides remains incomplete. However, intestinal perfusion studies and plasma and urine analyses after oral tolerance tests have indicated intact absorption for a wide range of dipeptides in man (11, 12, 31, 32, 48–56, 62–64). These include: glycylglycine, glycyl-L-leucine, L-leucylglycine, glycyl-L-lysine, glycyl-L-alanine, alanylglycine, β-alanyl-L-histidine, β-alanyl-L-1-methylhistidine, glycyl-L-tyrosine, L-arginyl-L-aspartate, L-arginyl-L-leucine, L-leucyl-L-leucine, and prolylhydroxyproline. Intestinal absorption of an even wider range of dipeptides has been shown in experimental animals (65).

Evidence for a specific carrier system for dipeptide transport

The movement of dipeptides from the gut lumen to the interior of mucosal cells can be achieved either by a simple process of diffusion or by the more complex process of carrier-mediated transport. The evidence required to establish carrier-mediated transport includes the demonstration of saturation, preferential absorption, and competitive inhibition. These phenomena have been demonstrated for the absorption of glycylglycine and glycyl-L-leucine in human jejunum (64). The saturation of the dipeptide absorption over a range of concentrations for both glycylglycine and glycylleucine allowed estimation of the absorption constants (K_m) of these dipeptides in human intestine. The K_m value of glycylglycine (43.3 mM) was almost twice the K_m value of glycylleucine (26.8 mM). These observations suggest that glycylleucine has a higher affinity for the peptide carrier system than glycylglycine.

While free amino acids did not alter the absorption rates of either glycylglycine or glycylleucine, the absorption of glycylglycine was markedly inhibited by glycylleucine (64). Kinetic analysis of this interaction revealed that inhibition was competitive in nature (64). These studies suggested that the absorption of both glycylglycine and glycylleucine is mediated by a carrier system which is not shared by neutral free amino acids. Of three dipeptides—glycylglycine, glycyl-L-leucine, and L-leucylglycine—glycylglycine was least rapidly absorbed, and there was no significant difference between absorption rates of the other two dipeptides (64). Therefore, both COOH- and NH_2-terminal amino acids appear influential in determining the affinity of a dipeptide for the absorption sites.

Studies in animal intestine have indicated that the stereoisomerism of amino acid residues of dipeptides also affects their affinity for the absorption sites; rates of transport of dipeptides made up of L-isomers are much greater than those for D-isomers (66). The studies of Cheeseman and Smyth (67) are suggestive of a common entry mechanism for dipeptides containing either L- or D-amino acids. However, dipeptides containing D-amino acids are not normally part of dietary protein, and the fact that they are not as well absorbed may not be physiologically relevant.

The rapidity of hydrolysis of dipeptides by the mucosal enzymes has hindered demonstration of active transport of dipeptides by preparations of animal intestine. To circumvent this problem, Addison et al. (68) and Matthews et al. (69) investigated the cellular accumulation of two dipeptides with slow rates of hydrolysis: glycylsarcosine, an analog of glycylglycine, and carnosine, a natural dipeptide. Rings of everted hamster jejunum accumulated these two dipeptides against an electrochemical gradient. Additional evidence in support of active transport for these dipeptides was the reduction of carnosine transport by hypoxia, by sodium replacement, and by metabolic inhibitors (69).

Das and Radhakrishnan (70) have recently studied the inhibitory effect of a wide range of dipeptides, including those containing acidic and basic amino acids, on the intestinal uptake of glycyl-L-leucine by monkey and human intestine in vitro. Their studies have suggested the presence of only one dipeptide uptake system with an extremely broad specificity. However, studies in hamster intestine have suggested the possibility of more than one dipeptide transport system, by showing that the uptake of carnosine is not inhibited by lysyllysine or glutamylglutamate, and that lysyllysine and glutamylglutamate do not affect uptake of each other (71).

Tripeptide absorption

Intestinal uptake of amino acids from tripeptides may be accomplished by one or more of the following mechanisms: *a*) com-

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plete hydrolysis of tripeptides by luminal and brush border peptide hydrolases to free amino acids, which are transported by free amino acid carrier systems; *b*) partial hydrolysis to free amino acids and dipeptides and the subsequent uptake of these products by free amino acid and dipeptide carrier systems, respectively; *c*) transport of tripeptides into the mucosal cell without prior hydrolysis.

The following observations have suggested that intact absorption is the major mode of intraluminal disappearance for triglycine in human jejunum (12).

a) Rate of uptake of glycine is significantly greater from triglycine than from either glycine or diglycine infusion solutions.

b) Saturation of amino acid carrier systems with free leucine does not impair glycine uptake from triglycine.

Since glycylleucine markedly inhibits the intestinal disappearance of triglycine, it appears that triglycine absorption is mediated partially or totally by the same carrier system used for dipeptides.

The following observations have suggested that the major mode of intraluminal disappearance of trileucine is by surface hydrolysis of trileucine to free leucine and dileucine and subsequent transport of these products by the membrane amino acid and dipeptide carrier systems in human intestine, respectively (12).

a) The uptake of leucine from trileucine solution is reduced by over 50% when a free amino acid such as isoleucine is added to the infusion solution, indicating that a large portion of trileucine is hydrolyzed by intraluminal and/or brush border enzymes. Since the peptide hydrolase activity of the intraluminal fluid is insufficient to account for the hydrolysis of trileucine, mucosal cell surface appears to be the major site of hydrolysis of this tripeptide.

b) The rate of leucine uptake is significantly greater from a trileucine than from a free leucine solution which indicates that there is either intact absorption of some trileucine or its constituent, dileucine. Since the intraluminal disappearance rate of trileucine is not affected by addition to the infusion solution of a dipeptide such as glycylleucine, intact absorption does not appear to be a significant mechanism for this tripeptide. However, the accumulation of dileucine in the lumen is increased 62-fold when glycylleucine is added to trileucine infusion solution, indicating that a large portion of trileucine is absorbed as dileucine.

Among the 8,000 possible tripeptides produced as a result of digestion of dietary proteins, there is information on the intestinal absorption of only a few tripeptides in man. In addition to the above trileucine and triglycine absorption studies, intestinal absorption of amino acids from alanylglycylglycine has been investigated in the human jejunum (72). The faster absorption of alanine and glycine from this tripeptide than from an equivalent free amino acid mixture of alanine and glycine suggests intact absorption of alanylglycylglycine and/or its dipeptide constituent. Further, the recovery of glycylprolylhydroxyproline in the urine of human subjects after ingestion of meals containing gelatin suggests intact absorption of this tripeptide (62).

Although as yet there is no evidence that transport of tripeptides in human intestine is active, studies of glycylsarcosylsarcosine (an analog of triglycine) uptake by hamster jejunum in vitro show active transport for this tripeptide (73). The slow rate of hydrolysis of glycylsarcosylsarcosine by mucosal enzymes allowed the demonstration of intracellular accumulation of this tripeptide against an electrochemical gradient (73).

The role of peptide absorption after a meal

Data on the proportion of dietary protein absorbed as peptides and that absorbed as free amino acids are limited. From studies in human volunteers, Nixon and Mawer (3) concluded that breakdown of dietary proteins to free amino acids is sufficiently rapid to account for the absorption of arginine, lysine, tyrosine, valine, phenylalanine, methionine, and leucine in free form, but is not rapid enough to account for the absorption of glycine, threonine, serine, imino acids, or the dicarboxylic amino acids in the free form. These conclusions were based on the measurement of release of free amino acids from the gut contents aspirated from the jejunum after a protein meal and incubated in vitro at 37 C for 5 to 80 min. The relevance of this

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observation to the complex situation in vivo is not yet clear, since the pattern of amino acid release from the gut content described above is not reflected in the increases in intraluminal concentrations of free amino acids after a protein meal (4). For example, the increases in the concentration of dicarboxylic amino acids are similar to or greater than the increases in the concentrations of amino acids with a rapid rate of release from the gut content. Relatively rapid absorption of di- and tripeptides together with either no or minimal intraluminal peptide hydrolase activities against dipeptides and tripeptides may not allow accumulation of substantial amounts of free amino acids in the gut lumen even after a large protein meal. Indeed, the increases in intraluminal concentrations of peptide-linked amino acids are much greater than the concentrations of individual free amino acids after a 50-g protein meal (4). Perhaps the most compelling evidence for the importance of absorption of a major portion of all amino acid constituents of dietary proteins in peptide form is the fact that individuals with hereditary deficiencies of the carrier system for either free neutral or basic amino acids do not appear to suffer from a state of protein malnutrition and they do absorb peptides normally (31, 32, 52–55).

Effect of altered nutrition and mucosal disorders on amino acid and peptide absorption

In vitro and in vivo studies of the intestine of human volunteers have shown that starvation for 2 weeks reduces the jejunal transport of amino acids (74, 75). Similarly, protein deprivation for 2 weeks also reduces the jejunal absorption rates of individual amino acids (75). Recent observations in man and rats have indicated that there are altered nutritional conditions which reduce the intestinal transport of amino acids but do not affect the absorption of dipeptides. Protein-calorie malnutrition, such as that induced by jejunoileal bypass, decreases the jejunal absorption rate of leucine while it does not alter the absorption rate of glycylleucine in the same individuals (76). Long-term protein deprivation decreases the intestinal absorption of methionine but has no effect on the intestinal absorption of dimethionine in rats (77).

Jejunal perfusion studies have shown reductions in absorption rates of free amino acids in patients with celiac sprue (61, 78, 79) and with tropical sprue (80). Schedl et al. (61) have found that the pattern of greater amino acid absorption in the jejunum than in the ileum is reversed in sprue patients. Although the cause for increased distal absorption in sprue patients is unknown, the decreased motility of the gut has been suggested as the basis for this change. In contrast to marked reductions in the jejunal absorption rates of amino acids in celiac sprue patients, intestinal absorption of dipeptides is either unimpaired or less severely decreased in the same patients (78, 79). That the absorption of dipeptides in human intestine is less affected by unfavorable nutritional or pathological conditions than is the absorption of free amino acids may have useful application in clinical conditions.

Clinical applications of oligopeptides in protein nutrition

The uptake of amino acids from individual dipeptides (11, 48–50), tripeptides (12, 72), and a tryptic hydrolysate of casein (81), which contains 66% of its amino acid content in the form of small peptides with a mean chain length of two to three amino acid residues, is greater than from the corresponding free amino acid mixtures in the intestine of healthy human volunteers. Therefore, oral administration of small oligopeptides might be useful in reestablishing or maintaining adequate protein nutrition of patients with absorptive and digestive disorders. The basis for this prediction is as follows:

a) *Reduced absorptive surface.* Disease processes involving the mucosa and surgical resection reduce the absorptive surface of the small intestine and often lead to serious protein-calorie malnutrition. Patients with this problem are commonly treated with elemental diets. Elemental diets enriched with free amino acids are highly hypertonic, and hypertonicity is poorly tolerated in situations of reduced absorption. Therefore, feeding of peptide instead of free amino acid diets to patients with reduced absorptive surface is

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more advantageous both in terms of lower hypertonicity and more efficient absorption.

b) Reduced pancreatic digestion. Impaired protein digestion in patients with pancreatic insufficiency might be better counteracted with the oral administration of oligopeptides as carriers of amino acids for protein nutrition rather than whole proteins. Brush border peptide hydrolases of intestine are capable of efficient digestion of oligopeptides with two to six amino acid residues (17). In fact, rats with exocrine pancreatic deficiency utilize a diet which contains 85% of its nitrogen content in the form of small oligopeptides better than a diet whose entire nitrogen content is in the form of free amino acids (82).

In addition to their usefulness for oral feeding, preliminary evidence has also indicated the potential usefulness of oligopeptides as substrates for parenteral nutrition (83).

Conclusion

Based on the available data discussed above, the following scheme of events can be proposed for the intestinal fate of dietary protein in man. Proteins are hydrolyzed to free amino acids and peptides by the pancreatic proteolytic enzymes in the gut lumen. This digestion increases the intraluminal concentrations of free amino acids and peptides. In general, peptide hydrolase activity in the gut lumen is insufficient to account for the hydrolysis of oligopeptides of two to six amino acid residues. However, the peptide hydrolases of brush border membrane are especially efficient in the hydrolysis of oligopeptides of three to six amino acid residues. Specific and selective processes are involved in the uptake of free amino acids, dipeptides, and some tripeptides by the intestinal mucosal cells. The peptide transport system allows intracellular hydrolysis of di- and tripeptides by enzymes which are more abundant in the cytoplasm than in the brush border region. Although the major products of protein digestion appearing in the portal blood are free amino acids, a small amount of a few oligopeptides escape hydrolysis by intestinal peptide hydrolases and reach splanchnic circulation. Dietary proteins are digested and the constituent amino acids and peptides are absorbed chiefly in the upper small intestine and, to a lesser extent, in the ileum. Finally, the greater absorption rates of amino acids when introduced in the gut lumen as dipeptides and tripeptides instead of free amino acid mixtures may have useful application in the nutritional therapy of patients with digestive and absorptive disorders.

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