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Absorption and Transportation of Amino acids in animals: A Review

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Abstract: Small peptides (primarily di- and tri-peptides) and amino acids are absorbed from the small intestine. Ileum and jejunum are the more active sites of amino acid absorption. Both peptide and amino acids can be absorbed against a concentration gradient and require energy in the form of ATP. The energy dependent transport of amino acids is linked with co-transport of Na^+, while in case of peptides it is linked with co-transport of protons (H^+). Animal's needs of the for body growth and maintenance is fulfilled by free amino acids and peptides. Although both are absorbed from the gastrointestinal tract, however, absoprtion of peptides occurs at much rate as compared to free amino acids. In ruminants peptides are more important form of amino acid than free amino acids, and major sites of peptide absorption includes rumen and omasum. Ruminal microorganisms potentially are vital in regulating the composition of peptides offered for absorption. These observations will have major effect on understanding the processes of digestion and absorption of proteins in ruminants. Furthermore, these observations will dramatically alter many strategies used in providing for the proper protein nutrition of ruminants.

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1. Introduction

The absorption and transporation of digested material through the biological membranes of digestive tract in animals are important biological phenomenon because optimum growth and lactation require adequate supplies of nutrients particularly the protein. The requirement of protein varies with age and stage of lactation. Protein reaching the small intestine of the ruminant is derived from three sources: (a) By pass protein; (b) Microbial protein (c) endogenous proteins coming from sloughed cells and secretions. Postruminal protein digestion and amino acid absorption are expected to occur in fashions similar to those observed in non-ruminants. Ruminants rely upon the same complement of pancreatic and intestinal proteases to affect breakdown of protein as do non-ruminants and absorb amino acids and small peptides by similar mechanisms (Chruch, 1988). In contrast, ruminants differ from their simple-stomached counterparts in the large fraction of protein of microbial origin reaching the lower gut, the relatively continuous flow of digest and the more acidic nature of the chyme arriving at the duodenum. The pH of digesta entering the duodenum increases slowly during passage through the intestine and protease activity (pH otima >7.5) was not maximized until 7-15 m past the pylorus in sheep (Church, 1988).

The discovery of trypsin and erupsin (different intestinal peptidases) in the early 1900's made it clear that proteins were at least hydrolyzed to amino acids (Matthews, 1975). Even though, this information was available, many early scientists believed that proteins were absorbed primarily as intact molecules which further hydrolyzed to amino acids in intestinal walls (Van Slyke, 1917). Processes involved with absorption of peptides and free amino acids by gastro intestinal tract (GIT) were complex and were mediated by a number of important factors (Webb, 1990; Saier, 2000). Peptides may play a leading role in amino acid absorption and thus information regarding supplementary dietary protein and amino acids absorption need to be examined closely.

The material presented in this review provides an overview of the current concepts of amino acid and peptide absorption. Attention is given to historical development of these concepts. Numerous reviews have been published on these topic areas; readers are directed to these for more information (Adibi, 1975, Adibi, 1976; Matthews, 1975; Adibi and Kim, 1981; Muck, 1981; Webb, 1986; Alpers, 1987; Hopfer, 1987; Webb, 1990; Webb et al., 1992; Saier. 2000; Sagne et al., 2001; Foltz et al. 2005).

The main objective of this review article is to furnish information regarding mechanism of

absorption of peptides and amino acids with respect to sites of GIT for their absorption.

2. Mechanism of absorption and transport systems

Proposals in the literature describing a wide variety of potential systems for amino acids transport are present but the only confusion exists because procedure differs; also there is considerable overlap of substrate specificity among amino acids transporters. Nevertheless, involvement of several carriers in movement of amino acids reported across the intestine. Presence of an amino or imino group along with a carboxyl group is mendatory for all carriers, regardless of the specific nature of transporter (Spencer et al., 1962; Schultz et al., 1972). Hydrophilic amino acids, with smaller molecular weight and neutral in nature, are taken up less readily than the hydrophobic amino acids with larger molecular weight. Whereas basic amino acids are traponsported with an intermediate rate (Sepulveda and Smith, 1978; Sepulveda and Smith, 1979). Table 1 describe the degree of hydrophobic nature of 20 amino acids.

The precise number of amino acid transporters present in the small intestine is un-known. Various carriers located on the brush border, the basolateral membrane and some are present on both (Bender, 1985; Hopper, 1987). Based on substrate preference amino acid transport systems are classified and is determined by kinetic and inhibition analysis measurements (Christensen, 1984).

Table 1. Residue Hydrophobicity of Amino acids

Amino acids	Free energy of transfer (KJ/mol)
Isoleucine	3.1
Phenyl alanine	2.5
Valine	2.3
Leucine	2.2
Tryptophan	1.5
Methionine	1.1
Alanine	1.0
Glycine	0.67
Cystein	0.17
Tryptophan	0.08
Proline	-0.29
Threonine	-0.75
Serine	-1.1
Histidine	-1.7
Glutathione	-2.6
Lysine	-4.6
Arginine	-7.5

Source: Sepulveda and smith, (1979)

Characteristics of amino acid side chains, including its onfiguration, size and charge apparently decides involvement of particular transport system. However, amino acids with quite diverse structures often share a common transport system (Christensen, 1984). Moreover, removal of the carboxyl group by formation of an ester, removal of the charge on the amino group by acetylation or introduction of charge into the side chain of a variety of amino acids, prevent active transport emphasizing the highly specific nature of the carrier system (Sarwar and Hasan, 2001).

In animal tissues, 12 amino acid transport systems are involved (Christensen, 1984). Across the biological membranes, various carriers contributes in the transportation of amino acid. Some of these carriers require energy to function and were said to be active transporters and Na^+ dependent. The Na^+ dependent active transport of glucose through the biological membrane was presented by Crane et al. (1961). They showed the active transport of glucose through the biological membranes. The similar experiment was conducted with amino acids by Curran et al. (1967). To understand the mechanism of absorption of amino acids across the biological membrane, one must review different systems present for the solute transport (Table 2). Three types of transport systems exist in the biological systems including a) Passive transport or simple diffusion, b) Active transport and c) Pinocytosis

2.1 Passive transport or simple diffusion

Molecules move through a permeable membrane with the concentration gradient, until two regions have equal solute concentration (Fig 1). Highly soluble solutes diffuse through the membranes by simple diffusion and the deriving force was the concentration gradient (Develin, 2006). The examples of solutes, which pass the membrane by simple diffusion, are passage of molecular O_2, N_2CO_2, NaCl, urea or other relatively non-polar solutes.

Fig. 1. Diffusion of dye molecules

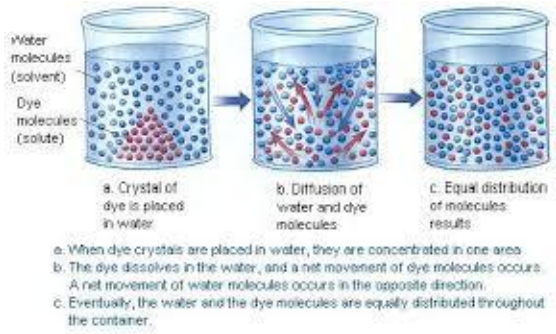

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Table 2. Major transport systems in mammalian cells

Substance Transported	Mechanism of Transport	Tissues
Sugars		
Glucose	Passive	Widespread
Fructose	Active symport with Na+	Small intestines and renal tubular
Amino acids	Passive	cells
All amino acid-specific	Active symport with Na+	Intestines and liver
Transporters	Active group translocation	
All amino acids except Proline	Passive	Intestines, kidney, and liver
specific amino acids	Antiport transport of nucleotides;	Liver
Other organic molecules	can be active transport	Small intestine
ATP-ADP	Active symport with Na+	Mitochondria
Ascorbic acid	--do--	Widespread
Biotin	--do--	Liver
Cholic acid, deoxycholic acid, and	--do--	Intestines
taurocholic acids	Active	Kidney
Folate	Active symport with H+	Widespread
Lactate and monocarboxylic acids		Widespread
Neurotransmitters (e.g., malate, a	Antiport with counter organic	Brain
ketoglutarate, glutamate)	anion	Mitochondria
Peptides (2 to 4 amino acids)		Intestines
Urea	Active symport with H+	Erythrocytes and kidney
Inorganic ions	Passive	Mitochondria
H+		Widespread lysosomes,
H+	Active	endosomes, and Golgi complex
Na+	Active; vacuolar ATPase	Distal renal tubular cells
Na+, H+	Passive	Proximal renal tubular cells and
Na+, K+	Active ATP driven	small Intestines
Na+,HPO_4^{2}-	ActiveAntiport	Plasma membrane of all cells
Ca^{2}+	Active co transport	Kidney
Ca^{2}+, Na+	Active ATP driven	Plasma membrane and
H+,K+	ActiveAntiport	endoplasmic (sarcoplasmic)
Cl^-/HCO_3^-	--do--	reticulum
	PassiveAntiport	Widespread
		Parietal cells of gastric mucosa
		secreting H+
		Erythrocytes and other cells

Kilberg and Haussinger (1992)

2.2 Active Transport

In passive transport, there is no accumulation of the transported species which always move down its concentration gradient while, active transport, results in the accumulation of a solute on one side of the membrane. Active transport is thermodynamically unfavorable (endergonic), and occurs only when coupled (directly or indirectly) to an exergonic process such as the absorption of sunlight, flow of some other chemical species down its concentration gradient (Develin, 2006 and Lehninger, 1993). In case of primary active transport, solute accumulation is directly connected to an exergonic reaction (e.g., ATP conversion to ADP + P1). Secondary active transport occurs when endergonic (uphill) transport of one solute is linked to the exergonic flow (downhill) of an other solute that was originally pumped uphill by primary active transport.

The mechanism of active transport is of fundamental importance in biological systems. The formation of ATP in mitochondria and chloroplasts occur by a mechanism that is essentially ATP-driven ion transport operating in reverse. Virtually every animal cell maintains a lower concentration of Na^+ and a higher concentration of K^+ than is found in its surrounding medium (Lehninger 1993; Fig 2). This balance was ascertained and sustained by a primary active transport system in the plasma

membrane, involving the enzyme Na^+ K^+ ATPase, which linked breakdown of ATP to the simultaneous movement of both K^+ and Na^+ against their concentration gradient For each molecule of ATP converted to ADP and Pi, this transporter moves two K^+ ions inward and three Na^+ ions outward, across the plasma membrane (Lehninger 1993).

The detailed mechanism by which ATP hydrolysis is coupled to transport is yet to be established, but a current working model (Fig 3) supposes that the ATPase cycles between two conformations: conformations 11,a phosphorylated form (designated P-Enz11) with high affinity for Na^+, and conformation 1, a phosphorylated form (Enz1) with low affinity for K^+ and high affinity for Na^+.

The conversion of ATP to ADP and Pi occurs in two steps catalyzed by the enzyme formation of phosphoenzyme:

$$ATP + EnzI \rightarrow ADP + P\text{-}Enz11$$

Hydrolysis of phosphoenzyme:

$$P\text{-}Enz11 + H_2O \rightarrow Enz1 + Pi$$

Which come to the hydrolysis of ATP: $ATP + H_2O \rightarrow ADP + Pi$

Three Na^+ ions move efflux for every influx of 2 K^+ ions, the process is an electrogenic in nature, it generates a net separation of charge across the membrane, resulting relative negative chage inside the cell. The resulting transmembrane potential of -50 to -70 mV (inside -ve relative to outside) is vital to the conduction of action potentials in neurons, and is also characteristic of most non-neuronal animal cells. The activity of this Na^+ K^+ ATPase in extruding Na^+ and accumulating K^+ is an essential cell function; about 25% of the energy-yielding metabolism of a human at rest goes to support the Na^+ K^+ ATPase (Lehninger, 1993).

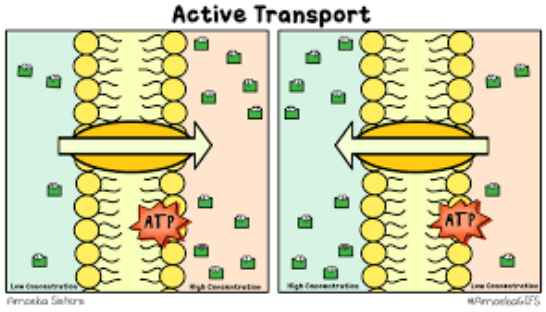

Fig. 2. Characteristics of Carrier-Mediated Peptide Transport

Several models for the absorption of peptides into epithelial cells have been proposed. Because it is likely that the physiological phenomenon of peptide absorption occurs by a combination of events, any model which must account for both luminal and cytosolic events. The combination of these separate and uncoordinated processes has been suggested by Matthews (1975) and Ganapathy and Leibach (1982) as being the most viable method due to its relative simplicity and because it accounts for all the distinctive features of peptide absorption. The model also allows for a high level of cytosolic peptidase activity, which is necessary to maintain downhill gradient for any diffusion of peptides that might occur. Although it is now generally accepted that peptide transport does not occur coupled with Na^+, early (Rubino et al., 1971; Shoaf et al., 1980) studies employing whole intestinal tissue showed that the removal of Na^+ from the incubation medium resulted in the reduction of peptide uptake. The use of hydrolysis-resistant peptides and the development of brush-border membrane vesicle (BBMV) techniques have enhanced the characterization of peptides transport by eliminating the confounding effects of peptide hydrolysis by cytosolic or brush-border (if papain-treated) peptidases on whole-tissue studies. The preponderance of experiments employing hydrolysis resistant peptides for intestinal tissue preparations and BBMV, especially have shown that peptide transport is not Na^+ dependent and that amino acid and peptide translocation across cellular membranes by unique and separate permeases (Ganapathy and Leibach, 1982; Ganapathy and Leibach, 1985; Hoshi, 1985, Burston and Matthews, 1987). The stimulation of peptide transport by an inwardly directed H^+ gradient (suggesting H^+ coupled transport) was first demonstrated in intestinal epithelial BBMV (Ganapathy and Leibach, 1983) and later in renal BBMV (Ganapthy et al.,1984; Takuwa et al.,1985)

The results of these investigations indicated that pH gradients stimulate peptide uptake, that an inward directed proton flow increases peptide uptake even in the absence of Na^+, and that peptide transport is an electrogenic process dependent on a transmembrane electrical potential. This last conclusion is supported by Boyd and Ward (1982) who showed that an increase in intracellular peptide concentration was accompanied by an increase in membrane depolarization. The observation is consistent with the hypothesized H^+/ peptide co-transport, model, which states that when positively charged protons cross a relatively negatively charged membrane region the

difference in electrical charges is reduced (depolarized). The evidence is conflicting as to whether peptide transport is actually energized, or driven, by a H^+ gradient. This is due to the lack of evidence for the ability of a H^+ gradient to drive the uphill transport of peptides from the relatively low concentration (extra vesicular) region into the higher concentration (intracellular) region. This ability, or lack of it, seems to be species-specific and not universal to all mediated transport systems for peptides. The ability of a H^+ gradient to derive the uphill transport of peptides has been demonstrated in rabbit (Ganapathy and Leibach, 1983; Hoshi, 1985) rat (Said et al., 1988; Iseki et al., 1989), and guinea pig (Himukai et al., 1983) using BBMV. Uptake studies characterizing di-peptide transport in rabbit, rat, and human intestinal BBMV (Rajendran et al.,1987) and tri-peptide transport in human jejunal BBMV, Wilson et al., (989) indicate that these tissues lack the ability to concentrate peptides against a concentration gradient in the presence of a H^+ gradient. Additionally the glutathione (GSH) transport in rabbit BBMV has been characterized as being energized by mono and divalent cations, especially Ca^{++}, but not H^+ (Vincenzini et al.,1989). These conflicting data seem to suggest the existence of at least two classes of carrier mediated peptide transporters, both of which are dependent of transmembrane electrogenic potential; one class which is energized by a H^+ gradient and a second class which is energized by cations other that H^+ or Na^+. Based on an interpretation of the results of Rubino et al. (1971) and evidence from Ganapathy and Leibach (1985) and their own cephalosporin uptake experiments (Inui et al., 1988; Kato et al., 1989) have proposed the existence of both an acidic pH-preferring class (uptake driven by an inward H^+) and neutral pH preferring class (no inward H^+ gradient) of peptide transporters. A transporter for the tri-peptide GSH has been characterized in rabbit intestinal tissue using BBMV (Vincenzini et al., 1988, 1989). This transporter is unique in its ability to be maximally stimulated by divalent cations (especially C^{++}) and the inability of other peptides to competitively inhibit GSH uptake.

Hypotheses have been proposed for models of peptide transport that include the integrated but separate functioning of H^+/peptide symporters and Na^+/H^+ exchangers (Ganapathy and Leibach, 1985) possibly ATP driven H^+ transporters (Hoshi, 1985) and Na^+/K^+ ATPases. In these models, an existing membrane potential would drive two protons across the brush border membrane with one peptide (Hoshi, 1985). As the intracellular pH drops, the Na^+/H^+ exchanger would be stimulated to exchange n intracellular H^+ for an extra cellular Na^+. Thus, both the intracellular pH and the trans-membrane electrical potential would be restored to basal levels. The Na^+/K^+ ATPases of the basolateral membrane would then pump the transported Na^+ out of the cell, thereby reestablishing the high extra cellular Na^+ gradient, at the cost of ATP hydrolysis.

The above discussion, at least for the H^+/ peptide transported, requires that a pH gradient exist across the apical border of intestinal enterocytes separating the lumen from the cell cytosole in order for peptide transport to occur. Additionally, the enterocytes require the biological mechanisms necessary to maintain normal cytosolic pH when protons are transported into the cell along with the peptides and to regenerate the inwardly directed pH gradient (Web, 1990). The presence of a pH gradient of a 1-log magnitude has been measured in rat proximal jejunal tissue (Lucas, 1983). Exchangers of Na^+/H^+ that function to pump H^+ out high intra-vesicular proton concentration have been shown to exist in intestinal brush border membranes in the rat (Murer et al., 1976), rabbit (Knickelbein et el., 1983), and human (Grimble and Silk. 1989). That peptide uptake stimulated Na^+ uptake, but that Na^+ failed to stimulate peptide uptake, provides evidence for the coordinated functioning of the N^+/peptide symporters and the H^+/N^+ antiporters (Cheeseman and Develin, 1985).

Recently, attempts have been made to characterize the chemical structure of peptide transporters with particular emphasis on the chemical group responsible for substrate binding. Using photoaffinity labeling techniques, Kramer et al. (1988) have identified a 127 kDa putative binding protein constituent of the carnosine and glycyco protein transport in rabbit intestinal BBMV that is H^+ dependent. In the same, tissue, Kato et al. (1989) suggest that histidine residues in the transporter are essential for H^+ coupled peptide transport because of their role as peptide binding sites under acidic conditions (pH 6.5). The investigations of these workers also suggest that thiole and sulfhydryl groups in the transporter are not essential for peptide binding. In contrast, maximal peptide transport in rabbit renal cortes BBMV reported to require the reduction of constitutive dithiole groups present on the transporter near the peptide-binding site (Miyamoto et al., 1986; Miyamoto et al., 1989). These workers suggested that an interchange between dithiole and sulfhydryl

groups may catalyze and regulate the functioning of the renal peptide transporter.

Although actual isolation of peptide transporters has not been responsible for glycyl-proline and glycy-sarcosine transport recently has been expression cloned in *Xenopus lavevis* oocytes (Miymoto et al., 1991). These researchers observed a three fold increase in the ability of the oocytes to take up these peptides, but not the constitutive amino acids (glycine or sarcosine), following micro injection of rabbit intestinal mucosal cell poly $[A]^+$ mRNA. This uptake was determined to be H^+ dependent.

It is now well established that peptide transport does not occur by Na^+ coupled transport. Instead, there is a large body of evidence indicating that peptides are co-transported with one type of symporter that is electric in nature, that requires a proton motive force, and that co-transports two H^+ for every peptide translocated into epithelial cells. It would seem that conditions within the gastrointestinal tract of ruminants are highly favorable for the existence of these types of peptide transporter. It is not unusual for the pH of the digesta to rumen acidic throughout the first one half to two thirds of the length of the small intestine in the ruminant (Bin-Ghedalia et al., 1974). Also, the digest within the ruminant stomach are essentially, always at least slightly acidic in nature. Evidence also continues to accumulate for the existence of second peptide transporter that is pH dependent but that is not energized by H^+ or Na^+ (Kato et al., 1989). Additionally, the GSH tri-peptide transporter seems to represent third type of transporter that apparently transports only GSH (Vincenzini et al., 1988; Vincenzini et al., 1989).

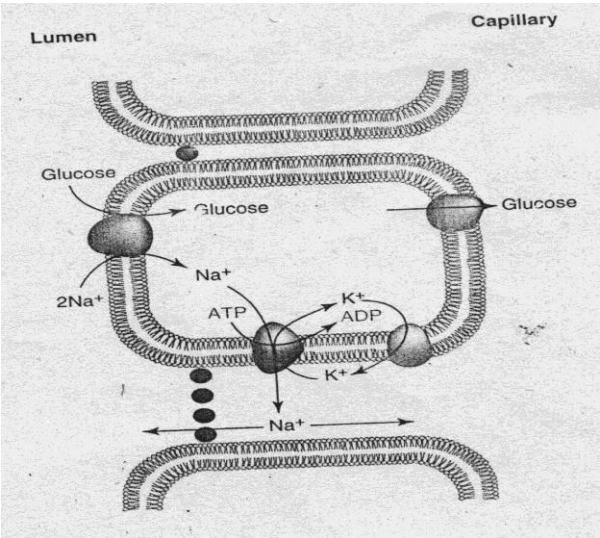

Fig. 3. Carrier mediated transport

2.3 Pinocytosis

Webb et al. (1992) reported that pinocytocis (endocytosis) mechanism would absorb intact protein that is the internalization of small vesicles ingested macromolecules of plasma membrane. Protein iinocytosis is seem to be vital for the transport of maternal antibodies (ß-globulin) to the offspring, particularly in rodents. For nutritional aspect pinocytotic uptake of proteins is not significant, and its magnitude usually declines after birth. The uptake of colostrum by young one is an important example in this regard (Webb et al., 1992). Persistence of low levels of this process beyond the neonatal period may, however, be cause for absorption of ample quantities is macromolecules to induce formation of antibody.

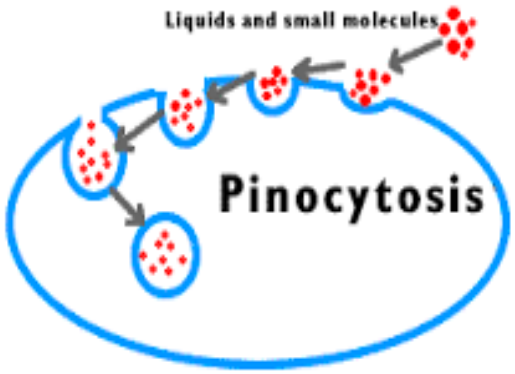

Fig. 4. Pinocytosis

3. Forms of amino acid absorption

Webb, (1990) discussed that the end products of protein hydrolysis absorbed through the GIT were free amino acids**.** Moreover, it was established for the first time by Newey and Smyth (1959; 1960), Mathews, et al. (1968) and Wolf et al. (1972) that peptides were absorbed. They demonstrated transport of intact di-glycine through the biological membrane. The possibility of alternative forms of amino acids absorption in ruminants; proteins are absorbed as such only in prenatal life of young ones by the process of pinocytosis (Sarwar and Hassan 2001).

3.1 Site of amino acid and peptide absorption

Many studies have addressed the question of site of absorption of amino acids. Bondies (1988) reported that the small intestine is the most important site of absorption of nutrients in mono gastric mammals and in avians. In addition, in all herbivores the large intestine is adopted for absorption, at least to a limited extent and in ruminants, in addition to the absorption from the intestine, some nutrients were absorbed through the walls of the forestomach (Webb, 1990; Sarwar and Hassan 2001). The small intestine

and particularly the duodenum serve this purpose because the inner surface area is greatly increased by folding of the epithelium and the presence of villi, tiny fingerlike projections extending into the intestinal lumen. The large surface area is increased at the brush borders, revealed by the electron microscope to be the villi. Each villus contains an arteriole and a venole together with a drainage tube of the lymphatic system, a lacteal. Thus, nutrients pass across the epithelial cells and enter either blood capillaries or the lymphatic system (Bondies, 1988). These nutrients are carried through the portal vein to the liner or through the lymphatic system to the heart. Villi undergo movements for facilitating contact with digested nutrients, particularly by the hormone villikinin (Fig. 1).

Schedke et al. (1968) reported that the middle region of the small intestine had the greatest capacity for amino acids absorption in the laboratory animals. Only a few studies using ruminant small intestine have been reported (Spencer and Samiy, 1961; Baker and George 1971). Amino acids absorption increased with distance from the pylorus, with maximum absorption occur in the ileum (William, 1969 and Phillips et al., 1976) but jejunum had also same absorption ability. Webb, (1990) reported the total Methionine and lysine uptake was higher by ileal brush border membrane vesicles than by Jejunal brush border membrane vesicles. Animals species and amino acid nature are important factors in determining the site of amino acid absorption

3.2 Absorption of amino acids

Absorption of amino acid is an example of secondary mediated transport system. Free amino acids and dipeptides are absorbed by carrier-mediated transport (Foltz et al. 2005). The small intestine has a high capability to absorb free amino acids and small peptides. Most L-amino acids can be transported across the epithelium against a concentration gradient. Although the requirement for concentrative transport *in vivo* is not obvious, since luminal concentrations are usually higher than the plasma level 0.1-0.2 mM. Peptide and amino acid transport in the small intestine has all the characteristics of secondary active carrier mediated transport, such as discrimination between L- and D- amino acids and energy and temperature dependence. On the basis of genetics, transport experiments and expression cloning. At least seven brush border specific transport systems for the uptake of L-amino acids or small peptides in the luminal membrane can be distinguished (Develin, 2006):

(1) for neutral amino acids with short or polar side chains (Ser, Thr, Ala);
(2) for neutral amino acids with aromatic or hydrophobic side chains (Phe, Tyr, Met, Val, Leu, Ile);
(3) for imino acids (Pro, Hyp);
(4) for ß-amino acids (ß-Ala, taurine);
(5) for basic amino acids and cystine (Lys, Arg, Cys-Cys);
(6) for acids (Asp, Glu); and
(7) for Dipeptides (Pept1) (Gly-sarcosine).

The concentration mechanisms for neutral L-amino acids appear to be identical to those discussed for D-glucose. Na^+-dependent transport systems have been identified in the luminal (brush border) membrane and Na^+-independent transports in the contra-luminal plasma membrane of small intestinal epithelial cells, Similarly as for active glucose transport, the energy for concentrative amino acid transport is derived directly from the electrochemical Na^+ gradient and only indirectly from ATP. Amino acids are not chemically modified during membrane transport, although they may be metabolized within the cytoplasmic compartment. The brush border transport for the other amino acids is energized in more complicated ways. For example, the acidic amino acid transporter mediates Co-transport of the amino acid with 2 Na^+ ions and counter transport with 1K^+ ion (Develin, 2006).

Neutral dipeptides are co-transported across the brush border membrane with a proton and thus are energized through the proton electrochemical gradient across this membrane. However, because of the Na^+ / H^+ exchange, both gradients tend to be similar and interdependent. The dipeptide transporter also accepts ß-lactam antibiotics (amino-penicillin) and is important for absorption of orally administered antibiotics of this class (Develin, 2006).

3.3 Relative contributions of amino acid transport systems

The transport of amino acids by intestinal enterocytes occurred by simple and facilitated diffusion (Na^+ dependent). The relative significance of each route is highly dependent on the concentration of substrate present. Active transport of Phenylalanine is the most important route of amino acid uptake when amino acid concentration is low. Only at very low substrate concentration (<1.0 mM) facilitated transport systems account for more transport than diffusion. Diffusion made a progressively larger contribution to total uptake as substrate concentration increased (Stevens et al.,1984;

Wilson and Webb, 1980) jejunal and ileal tissues was influenced dramatically by substrate concentration. In case of Methionine transport by ileal tissue, diffusion was the predominant form of transport throughout the range of substrate studies (Table 3 and 4).

Moe et al. (1987) reported that when bovine ileal brush border membrane vesicles were incubated in buffer containing .1mM substrate, Na^+-dependent, Na^+-independent and diffusion systems accounted for 14, 37 and 49% and 9,53 and 38% of Methionine and lysine transport, respectively. Guerino and Baumrucker (1987) reported siilar results as Moe et al. (1987) that in bovines the Na^+ -independent systems made the greatest contribution to total uptake for both lysine and Methionine at a substrate concentration of 1.0 mM.

3.4 Relative absorption of amino acids

When absorption rates of amino acids from equimolar mixtures of 18 common dietary amino acids or eight essential amino acids were studied in humans, Methionine and the branched-chain amino acids (leucine, Isoleucine and Valine) were absorbed most rapidly (Adibi and Gray, 1967; Adibi et al., 1967). As a group, essential amino acids were absorbed more rapidly than nonessential amino acids in human) jejunum with a mixture of 16 amino acids simulating lactalbumin (Silk et al. 1980). The absorption of top six amino acids, measured by percentage of amino acid absorbed, were methionine, leucine, valine, phenylalanine, arginine and isoleucine. The disappearance, as a percentage of amino acid present, was great for essential than for nonessential amino acids from the small intestine of sheep (Coelho da Silve et al., 1972; MacRae and Ulyatt, 1974; Christiansen and Webb, 1990a) and cattle (Christiansen and Webb, 1990b). In all the above studies with sheep and cattle, absorption, as a percentage of that present initially, was greater for methionine that for other amino acids.

When absorption of individual amino acid was measured as the percentage of amino acid present, dietary essential amino acids tend to be absorbed in greater amounts than nonessential amino acids. Methionine was the top of the list. The complex pattern of absorption of amino acids probably was attributable to differences in the affinities of carrier systems for individual amino acid and the effect that competitions for transport was greater among amino acids for which a carrier had greater affinity (Adibi, 1969). A 48% reduction in lysine absorption by ovine intestinal rings when leucine was present at three to four times the lysine concentration was reported by Johns and Bergen (1973). All the interactions that were observed among amino acids in the absorptive process were not negative. Some amino acids stimulated the transport of others, the ability of alanine and phenylalanine, leucine (Munck, 1966) and methionine (Reiser and Christiansen, 1971) to increase the intestinal transport of the basic amino acids arginine, lysine, ornithine and methionine stimulated the absorption of threonine when threonine concentrations were low was noted by Phillips et al. (1979).

4. Absorption of Peptides

Researchers suggested that it was necessary to hydrolyze proteins to free amino acids prior of alternative means of absorption. The possibility of peptide transport was mentioned over 100 years ago (Matthews, 1987). Newey and Smyth (1959) and Newey and Smyth (1960) are credited with providing the first convincing evidence that peptides were absorbed through the transport of intact di-glycine across the biological membrane . General acceptance that peptide absorption was significant physiologically was not rapidly forthcoming, however, interest and enthusiasm for this concept had to await the reports of substantial intestinal peptide absorption (Matthews et al., 1968). Both direct and indirect acceptance of peptide absorption was not to be commonplace in the 1970. Even in studies with ruminants, the possibility of alternative forms of amino acid absorption was suggested.

Small peptides resistant to intestinal hydrolysis are entered as such along with free amino acids but transportation was independent. So the brush border membrane thus fulfills a double function, in absorbing amino acids and peptides in enzymatic hydrolysis of small peptides to free amino acids (Lehninger, 1993; Ganapathy et al. 2000)

4.1 Absorption rate of peptides and the specificity of transport systems

Substantial evidence supports the hypothesis that peptides were absorbed more rapidly than free amino acids (Craft et al. 1968; Adibi 1971; Cheng et al. 1971; Burston et al. 1972; Webb 1990 and Brown et al. 2005). Absorption of amino acids from rat jejunum *in vivo* was greater from pancreatic hydrolysate of four proteins (casein, albumin, lysozyme and lactalbumin) than from equivalent mixtures of free amino acids (Matthews, 1974); Both rate and extent of absorption of amino acids from a partial enzymatic hydrolysate of lactalbumin consisting mainly of small peptides were greater that absorption of amino acids from an amino acid mixture simulating lactalbumin (Silk et al., 1980).

Hara et al., (1984) computed absorption of amino acids. The intensity of absorption of amino acids from an enzymatic hydrolysate of egg white of peptide amino acids was 70 to 80% higher than for amino acids from a corresponding amino acid mixture.

The fact that peptides are absorbed more rapidly than free amino acids suggests that independent transport systems for peptides may exist of that there is a competitive advantage by the peptide for carriers. The latter, however, has been largely discounted (Rubino et al., 1971). Studying several different amino acids and peptides, they demonstrated that free amino acids had no effect on the transport of di-peptides, and vice versa. In *Hartnup* disease, in which many neutral amino acids are poorly absorbed, the efficient absorption of phenyl-alanine as the di-peptide was demonstrated (Asatoor et al., 1970) This advantageous rate of absorption and specificity for transporters held by peptides had nutritional importance (Hellier et al., 1972). They were also reported similar results in case of lysine absorption as di-peptide and less absorption in case of free amino acids cystein, lysine, ornithine and arginine.

4.2 Peptide configuration and absorption

Configuration differences among peptides play a determining role in the transport of peptides across the intestinal mucosa. Peptide transport was limited primarily to di, tri and larger peptides separated by Peters et al., (1972); Evered and Wass, (1970); Vale et al. (1970); Addison et al. (1974) and Adibi and Morse, (1977), respectively. The early reports of Craft et al., (1968) and Mattews et al., (1968) demonstrated a progressive increase in the rate of transport from free glysine to the tripeptide.

4.3 Influence of peptides composition on amino acid absorption

Glutamic acid was absorbed at nearly twice the rate from rat small intestine when it was present as glutaminyl-tyrosine rather than glutaminyl-methionine (Burston et al., 1972). Not only do the particular amino acids present influence absorption, but whether an amino acid is in the N- or C-terminal position also important. Lysine was absorbed much more rapidly when it was present in the N-terminal position in a dipeptide with glycine than when it was in the C-terminal position in a dipeptide with glutamic acid (Burston et al., 1972) Peptides competed with one another for transport (Matthews et al., 1979; Taylor et al., 1980). In addition to inhibition, there may be some stimulatory effects of one peptide on the absorption of another, Addison et al., (1974a) showed a quantitatively greater absorption of camosine from hamster jejunum in the presence of glutaminyl-glutamate. They also showed that methionyl-methion and glycylglycine were potent inhibitor of carnosine absorption. Carrier specificity, therefore exists in peptide transport; this would influence the nature of absorption from mixtures of peptides.

4.4 Mechanisms of Peptide Transport

Peptides were transported against a concentration gradient by a system requiring energy (Matthews et al., 1974). These workers studied peptides that were resistant to hydrolysis by cytoplasmic peptidases and demonstrated concentrative uptake of peptides in intestinal mucosal cells in the presence of normal cellular metabolism and were able to inhibit this transport by the elimination of the presence of oxygen or by addition of metabolic inhibitors.

Because the role of Na^+ dependent transport of amino acids already was well understood, this led researchers to believe that peptide transport also was Na^+-dependent. In spite of the fact that many were able to demonstrate considerable concentrative transport in the absence of Na^+, Na^+-dependent transport was thought to be the driving force (Rubino et al., 1971; Cheeseman and Parsons. 1974; Himuki and Hoshi, 1980; Cheeseman and Johnston, 1982; Himuki, 1985). Isolated brush border membrane vesicles showed clearly the Na^+-independent nature of peptide transport was confirmed by Berteloot et al. (1981) Berteloot et al. (1982); Ganapathy and Leibach, (1982); Himukai et al., (1983); Ganapathy et al. (1984) and Rajendran et al. (1984).

Gananpathy and Leibch (1985), based on studies of pH effects on peptide transport, proposed that protons may be co-transported with peptides and that an electrochemical proton gradient may be the driving force for the concentrative transport of peptides. Takuwa et al. (1985) were the first to demonstrate the active accumulation of a peptide in brush border membrane vesicles in the presence of a H^+ gradient. Unequivocal evidence was provided for direct coupling between peptide and H^+ during transport and for energization of peptide transport by electrical as well as chemical components of the proton motive force when a membrane potential and a H^+ gradient were employed simultaneously (Miyamoto et al., 1986).

The presence of different carriers as well as different driving forces for active transport probably contributes to a more efficient absorption of total amino acids. This likely offers alternatives that allow the animal to adapt to a wider range of physiological and dietary conditions.

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5. Absorption from the Rumen and abomasum

Drainage of amino acids into the mesenteric vein come from the jejunum, ileum, cecum, colon, and pancreas, whereas the non-mesenteric drainage comes from the rumen, reticulum, omasum, abomasum, duodenum, and spleen. The fluxes of free and peptide amino acids across the mesenteric and non-mesenteric drained viscera are presented in Table 3. In both species (sheep and calves) the mesenteric flux of free and peptide amino acids was approximately equal. As anticipated, the flux of free amino acids cross the non-mesenteric-drained viscera was minimal. Particularly noteworthy is the observation that the fluxes of peptide amino acids across the amino acid flux in both calves and sheep (Webb, 1990; Matthews, 1991b).

The ability for absorption of peptides to occur across the epithelial tissues of the rumen and omasum has been confirmed with *in vitro* procedures employing both radiolabiled and non-radiolabiled peptides (Matthews, 1991b). Ruminal and omasal epithelia collected from four and seven sheep were used to study absorption of carnosine and methionyl-glycine, respectively. The data presented in Tables 4&5 are for the 60-min sampling only.

For both peptides, there was a linear increase in serosal appearance as concentration increased, Peptide appearance was an apparently nonsturable process suggests that absorption occurred by diffusion and not by carrier-mediated transport (Webb, 1990). Omasal epithelia seemed to have a greater ability than ruminal epithelia to absorb the peptides evaluated, when peptide uptake was expressed on an equal mucosal tissue weight basis.

If subsequent studies continue to substantiate current observations about peptide absorption from the rumen and omasum, then a serious reshaping of the currently accepted tenant concerning protein utilization by the ruminant will be necessary. The concept that the small intestine is the only site of amino acid absorption will be changed and efforts to influence dietary protein passage through the stomach will need to be re-evaluated. If the stomach is confirmed as the site of absorption of major portion of total amino acid in the form of peptides, this will explain many of the unpredictable responses observed with different sources of dietary proteins. Further experimentation to examine these observations is imperative.

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