Peptide digestion and absorption in humans: portal vein, hepatic vein, and peripheral venous amino acid concentrations

M Yamakawa[1] MD, J Maeda[1] MD, K Sugisaki[1] MD, T Fujita[1] MD, T Oohara[1] MD, H Hara[2] PhD and S Mitani[3] MD

[1] *Third Department of Surgery, Faculty of Medicine, University of Tokyo, Tokyo*
[2] *Department of Agriculture, University of Hokkaido, Sapporo City*
[3] *Yamato Tokushukai Hospital, Yamato City, Japan*

An oligopeptide preparation and an amino acid mixture with an identical composition were administered intraduodenally to a patient with a catheter in the portal vein, and blood samples were collected over time from the portal vein, the hepatic vein, and a peripheral vein to investigate amino acid digestion and absorption.

When the oligopeptide preparation was administered, amino acids appeared rapidly in the portal blood and monomodal well-balanced absorption curves were obtained. When the amino acid mixture was given, however, amino acid levels in the portal blood indicated a bimodal pattern of absorption. Evaluation of the kinetics of various amino acids after administration of the two preparations showed that they could be classified into the following four groups: 1) amino acids showing hepatic uptake (threonine, methionine, phenylalanine, lysine, histidine, arginine, serine, and proline), 2) amino acids released from peripheral tissues and taken up by the liver (alanine, glutamine, and glycine), 3) amino acids not showing hepatic uptake (leucine, valine, and isoleucine), and one amino acid released from the liver for peripheral uptake (glutamic acid).

These findings suggest that the nature of the protein source and the kinetics of individual amino acids should be taken into account in nutritional therapy and nutritional assessment.

Key words: Oligopeptides, amino acids, digestion absorption, human, portal vein, hepatic vein, peripheral vein, hepatic uptake, peripheral release, peripheral uptake, BCAA, enteral nutrition

Introduction

Disturbances of digestion and absorption develop after surgery as well as in the short-bowel syndrome and with inflammatory bowel disease. For patients with such conditions, amino acid mixtures have been used successfully as a nitrogen source that can be rapidly digested and absorbed. According to Matthews *et al*[1], and Silk *et al*[2], some ingested protein is degraded to amino acids, but a considerable portion is absorbed in the form of dipeptides or tripeptides (oligopeptides), with the absorption rate of the latter being higher.

To investigate the behaviour of oligopeptides and amino acids as nitrogen sources, portal vein, hepatic vein, and peripheral venous amino acid concentrations were measured in a human subject after administration of an oligopeptide preparation and an amino acid mixture. The kinetics of various amino acids were also investigated.

Patient and methods

The patient was a 45-year-old man who had a catheter inserted into the portal vein at the time of subtotal gastrectomy for pyloric stenosis secondary to duodenal ulcer. The catheter was intended for insulin infusion for the treatment of chronic active hepatitis. The patient showed GOT and GPT levels over 200 IU/l preoperatively, and received a drip infusion containing regular insulin (40 units/day) and glucose (200g/day) through the catheter for 70 days postoperatively. Serum GOT level and GPT levels fell to less than 70 IU/l, 60 IU/l respectively after this therapy. The patient fully recovered from the operative stress, and no medication or therapy were necessary except the insulin therapy. A catheter for right hepatic vein angiography was inserted via the right long saphenous vein 85 days postoperatively to evaluate what ongoing pathological change accompanied his chronic hepatitis and was left *in situ*.

After an overnight fast, 15 g of an oligopeptide preparation (egg albumen hydrolysate containing >70% dipeptides and tripeptides: Terumo Inc, Tokyo Japan) was dissolved in 100 ml of lukewarm water and administered via a nasoduodenal tube over 1 minute. Table 1 shows the amino acid composition of the oligopeptide preparation. Three days after the study, a mixture of amino acids (Terumo Inc, Tokyo, Japan) with an identical composition to the oligopeptide preparation was administered in a similar fashion. The patient was stable in the interval between these studies. Blood samples were collected from the portal vein, the hepatic vein, and the left cubital vein at the start (0 min) of administration as well as 10, 20, 30, 60, 90, and 120 min after administration (total blood volume: 63 ml). Plasma amino acid concentrations were measured using an amino acid analyser (HITACHI 835: HITACHI Co Ltd, Hitachi-city, Japan) after separation of amino acids and peptides using the copper complex-DEAE Sephadex technique. The study protocol was approved by the hospital ethics committee, and informed consent was obtained from the patient.

Correspondence address: Dr Mitsuru Yamakawa, Third Department of Surgery, Faculty of Medicine, University of Tokyo, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo, Japan
Tel: 03 3943 1151; Fax: 03 3943 8530

Table 1. Amino acid composition of the oligopeptide preparation.

Amino acid	g/ 100g
Aspartate	4.92
Threonine	4.58
Serine	6.85
Glutamate	8.23
Glycine	3.40
Alanine	5.95
Cysteine	2.30
Valine	6.62
Methionine	4.81
Isoleucine	4.88
Leucine	7.13
Tyrosine	3.92
Phenylalanine	5.70
Lysine	7.12
Histidine	2.42
Tryptophan	1.15
Arginine	5.97
Proline	3.66
Asparagine	4.93
Glutamine	5.40
Total	**100.00 (wt%)**

Results

Absorption of the oligopeptides and amino acid preparations: Figures 1-4 show amino acid concentrations in the portal vein, hepatic vein, and peripheral vein. When the oligopeptide preparation was administered, the levels of all amino acids showed a sharp rise in the portal vein with a peak at 30 min after administration. No oligopeptides were detected in portal, hepatic, or peripheral venous blood.

When the amino acid monomer mixture was administered, some amino acids showed rapid absorption, but others showed more gradual absorption and lower peak levels. A bimodal absorption pattern was also observed with some amino acids. The amino acids could be divided into the following 4 groups on the basis of differences in their portal, hepatic, and peripheral venous concentrations.

1) Amino acids showing hepatic uptake (Fig. 1). Threonine, methionine, and phenylalanine showed a positive concentration difference between the portal and hepatic veins after administration of both the oligopeptide and amino acid monomer preparations, and the magnitude of the difference increased with time, suggesting active hepatic uptake. Similar findings were obtained for lysine, histidine, arginine, serine, and proline (data not shown).

2) Amino acids released peripherally with subsequent hepatic uptake (Fig. 2). Alanine and glutamine showed a negative concentration difference between the hepatic and peripheral veins, suggesting release from the peripheral tissues (probably from the muscles). The difference between the portal and hepatic veins was positive, indicating hepatic uptake of the released amino acids. Similar findings were obtained for glycine (data not shown).

3) Amino acids without hepatic uptake (Fig. 3). Leucine, valine, and isoleucine exhibited a positive concentration difference between the portal and hepatic veins after oligopeptide and amino acid monomer administration, but the differences were small, suggesting that hepatic uptake was slight.

4) An amino acid released from the liver and metabolised peripherally (Fig. 4). Glutamic acid showed a large negative concentration difference between the portal and hepatic veins, suggesting release from the liver. In addition, the concentration difference between the hepatic and peripheral veins was positive, indicating that glutamic acid was taken up by the peripheral tissues.

Figure 1. Kinetics of amino acids undergoing hepatic uptake.

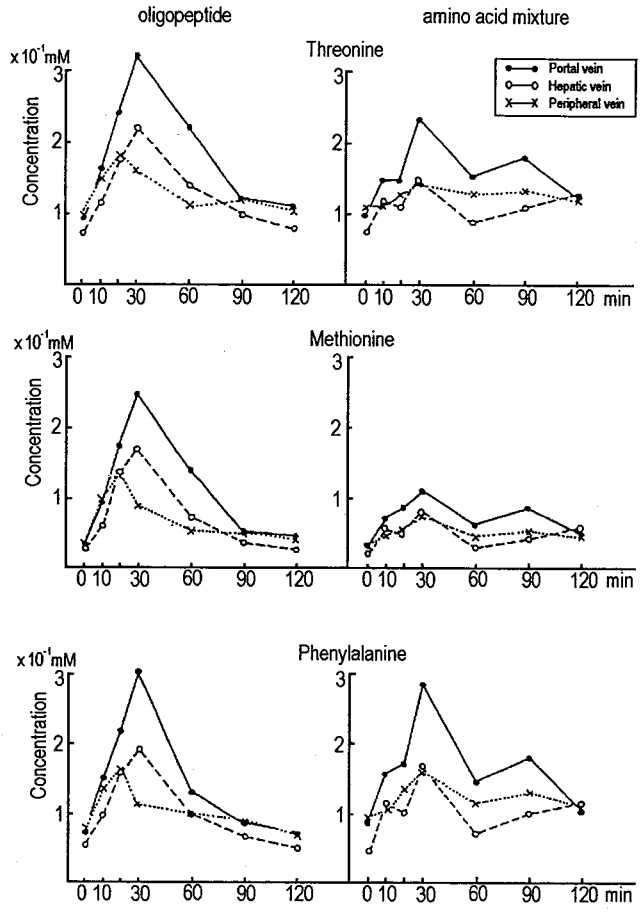


Figure 2. Kinetics of amino acids released from the peripheral tissues with subsequent hepatic uptake.

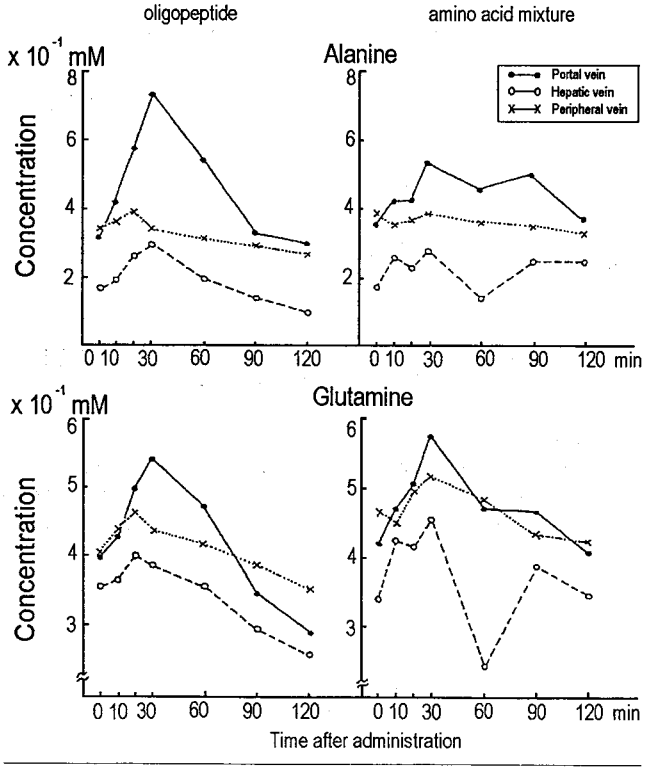


Figure 3. Kinetics of amino acids not undergoing hepatic uptake.

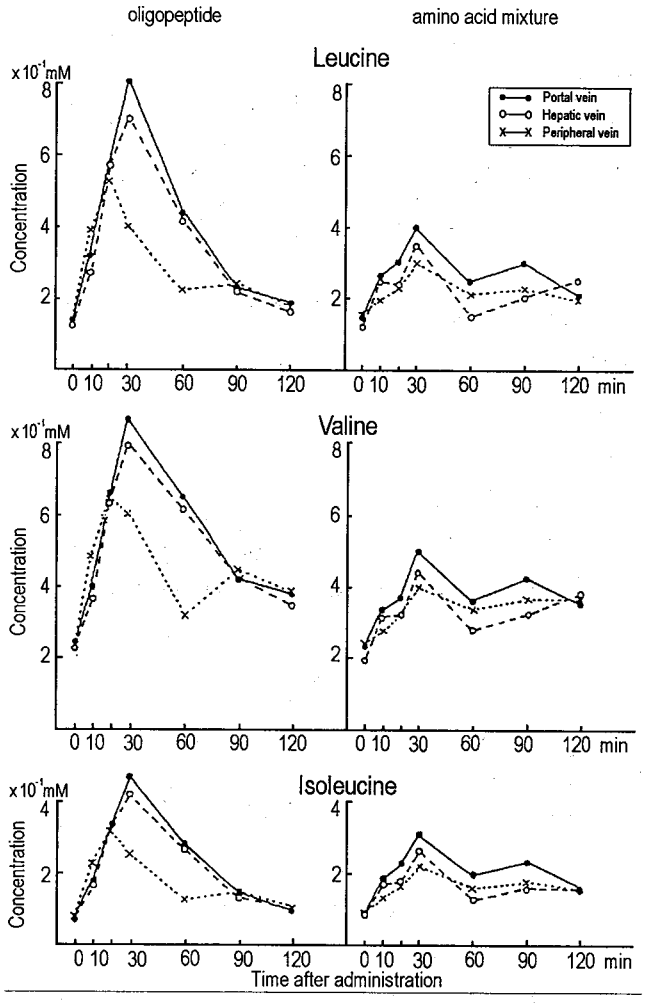
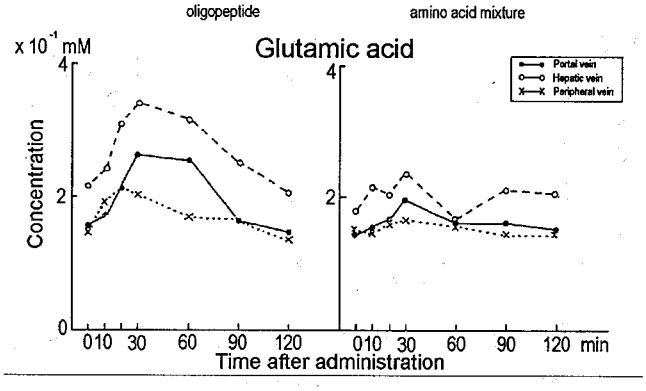


Figure 4. Kinetics of glutamic acid.



Discussion

Digestion and absorption of oligopeptides has been suggested to be more physiologic than that of amino acids[1,2]. In the present study, oligopeptide administration generally produced absorption curves with a sharp peak, and blood levels returned to the pre-administration baseline after 90-120 min, indicating rapid and well-balanced digestion and absorption.

After administration of the amino acid mixture, however, bimodal absorption curves were generally observed. This may have been because there was competition for absorption between various amino acids, or because the extent of absorption of the amino acids varied between different parts of the small intestine and absorption occurred throughout the small bowel. In contrast, oligopeptide preparations have been reported to be absorbed in the proximal small intestine (mainly the jejunum), suggesting their usefulness in patients with short-bowel syndrome and inflammatory bowel disease[3], and our findings in the present study supported these previous observations.

We also investigated the kinetics of various amino acids after absorption. Threonine, methionine, phenylalanine, lysine, histidine, arginine, serine, and proline showed large concentration differences between the portal and hepatic veins, indicating uptake by the liver. Alanine and glutamine showed similar concentrations in the portal and hepatic veins, but showed a large negative concentration difference between the hepatic and peripheral veins, suggesting release from the peripheral tissues. It is worth noting that these amino acids can transfer amino groups[4].

The concentration difference between the portal and hepatic veins was small for leucine, valine, and isoleucine, which are branched-chain amino acids (BCAA), suggesting that they were taken up by the liver in the minimum amounts necessary as essential amino acids. The BCAA showed large concentration differences between the hepatic and peripheral veins after administration of the oligopeptide preparation, indicating peripheral tissue uptake. The patient had a good appetite and gained body weight postoperatively, and was clinically stable throughout. Therefore, we considered the patient to be unstressed. BCAA uptake by peripheral tissues during stress has been studied previously[5]; their kinetics appear to be similar in the absence of stress, on the basis of our present findings. The BCAA concentration patterns were somewhat different when the amino acid monomer mixture was administered, suggesting that BCAA may have different kinetics when given as oligopeptides and as amino acid monomers.

Unlike other amino acids, glutamic acid was clearly released from the liver. This may have been due to the hepatic production of glutamate by release of an amino group from glutamine[4] or the supply of an amino group to α-ketoglutarate.

The methodology of on this study provides an indirect way to demonstrate amino acid kinetics. Radiolabeling would enable more direct study of kinetics and could distinguish between the fate of administered amino acids and those derived from endogenous turnover. Nevertheless, the concentration differences reflect amino acid kinetics, in the liver of a patient who was not cirrhotic and where there were no alterations of the hepatic venous bed. Although, we have only a single data set in one patient, we consider the study valuable as a human study.

In conclusion, when nutritional therapy is formulated or nutritional assessment is made, it is important to take into account the differing kinetics of various amino acids as well as differences in digestion and absorption between oligopeptide and amino acid preparations.

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人體對肽的消化與吸收: 門靜脈, 肝靜脈和末梢靜脈的氨基酸濃度

摘要

作者使用同一組成的寡肽制劑和氨基酸混合液, 從十二指腸注入具有門靜脈導管的病人體內. 然后在門靜脈和末梢靜脈收集血樣本, 研究氨基酸的消化與吸收. 當給與寡肽制劑時, 門靜脈血中氨基酸迅速出現, 并得到單峰的良好平衡吸收曲綫. 當給與氨基酸混合液時, 門靜脈血中氨基酸水平顯示了雙峰的吸收曲綫. 估計兩種制劑攝入后, 各種氨基酸的動力學可分爲如下四 種: (1). 被肝攝取的氨基酸有蘇氨酸, 蛋氨酸, 苯丙氨酸, 賴氨酸, 組氨酸, 精氨酸, 絲氨酸和脯氨酸; (2). 從末梢組織釋放被肝攝取的氨基酸有: 丙氨酸, 谷胺酰氨和甘氨酸; (3). 不被攝取的氨基酸有: 亮氨酸, 纈氨酸和异亮氨酸; (4). 一種從肝釋放, 由末梢組織攝取的氨基酸是谷氨酸. 這些發現指出, 進行營養治療和營養評估時, 應考慮蛋白質來源和個别氨基酸動力學的特性.

生体においては，蛋白はアミノ酸にまで加水分解されるとともに，かなり多くの部分が，dipeptide，あるいは tripeptide (oligopeptide) の形で消化吸収され，しかもその吸収速度が速いことが示唆されている．

われわれは，門脈内にカテーテルを留置した患者において，oligopeptideと，それと全く同じ組成のアミノ酸配合物を経十二指腸的に投与して，門脈血，肝静脈血，末梢静脈血を経時的に採取して，その消化吸収の状態を観察した．

Oligopeptideを投与した場合，各アミノ酸は門脈内に急速に出現してその濃度曲線は一峰性を示し，バランスよい吸収状態を示唆した．アミノ酸配合物を投与した場合には，門脈血中のアミノ酸濃度曲線は二峰性を示した．

また，臓器を介した各アミノ酸の動態を検討した処，①肝臓で主に取り込まれるアミノ酸(threonine, methionine, phenylalanine, lysine, histidine, aeginine, serine, proline), ②末梢組織から放出されるアミノ酸 (alanine, glutamine, glycine), ③肝臓で取り込まれないアミノ酸(leucine, valine, isoleucine), ④肝臓から放出されるアミノ酸 (glutamic acid) に分類された．

蛋白源やアミノ酸の特性を活かした栄養法と栄養評価を考えることが大切である.

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