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Splanchnic fluxes of amino acids after duodenal infusion of carbohydrate solutions containing free amino acids or oligopeptides in the non-anaesthetized pig

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Seven non-anaesthetized pigs (mean body-weight 64·6 kg) were used to study the intestinal absorption and hepatic metabolism of glucose and amino acids (AA) using carbohydrate solutions (maltose dextrin; 440 g/2 l), containing 110 g of either an enzymic milk-protein hydrolysate (PEP) with a large percentage of small peptides (about 50% with less than five AA residues) and very few free AA (8%) or a mixture of free AA (AAL) with an identical pattern, infused intraduodenally. Each pig was previously fitted under anaesthesia with electromagnetic flow probes around the portal vein and the hepatic artery, and with permanent catheters in the portal vein, carotid artery, one hepatic vein and the duodenum. Each solution was infused for 1 h after a fasting period (18 h) and each pig received both solutions at 8 d intervals. The observation period lasted 8 h. For most AA (his, lys, phe, thr, arg, tyr, pro) the absorption rate after infusion of PEP was significantly higher than after that of AAL during the 1st hour, but the differences quickly disappeared. After 8 h, the only differences concerned his and tyr (PEP > AAL) and met, glu and asp (AAL > PEP). There was a large uptake of blood AA by gut-wall cells, higher after AAL infusion than after PEP infusion, particularly for branched-chain AA (BCAA). The absorption of ammonia-nitrogen after both infusions was equivalent to two-thirds of urea-N passing from blood to intestinal tissues and lumen. Glucose absorbed within 8 h represented only 76% (PEP) or 69% (AAL) of the infused amounts. The cumulative hepatic total AA (TAA) uptake increased from 13 to 27% of the infused amounts between the 1st and the 8th hour after PEP infusion, and from 8 to 31% after AAL infusion. Most essential AA were largely taken up by the liver, with the exception of met (PEP) and thr and of BCAA, which were poorly retained for both solutions; there was a high uptake of ala and gly, and a release of asp, glu, and gln. Urea-N released by the liver within 8 h was equivalent to 23–25% absorbed amino-N and to around 1·5 times ammonia-N taken up by the liver within 8 h. Glucose was highly taken up by the liver during the first hours then released, the total uptake within 8 h representing about half the absorbed amount. There was a lactate release tending to be higher after PEP than after AAL infusion and a liver pyruvate release identical for both solutions. From calculations of net non-catabolic metabolism in the liver the possible synthesis of liver proteins within 8 h may be estimated at 35 g for both solutions. The cumulative peripheral TAA uptake increased from 12 to 27% of the infused amounts between the 1st and 8th hour after PEP and from 9 to 11% after AAL infusion. At 8 h after the infusion the larger uptake concerned BCAA, arg, glu and asp and there was a marked release of gln, gly and ala for both solutions; the peripheral balance was zero for met (PEP) or characterized by a release of phe and thr (AAL). Thus, protein synthesis seemed only to be possible with the aid of plasma proteins synthesized in the liver. The 8 h peripheral balance of glucose, lactate and pyruvate was characterized by the same level of uptake for both solutions. The time-course of AA absorption, depending on the physicochemical structure of nitrogenous mixtures present in the digestive tract, had an influence on the pattern of liver and peripheral AA uptake.

Amino acids: Glucose: Intestinal absorption: Liver metabolism: Peripheral metabolism: Pig

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Protein hydrolysis in the proximal digestive tract leads to the release of a mixture of free amino acids and small peptides in the intestinal lumen (Adibi & Mercer, 1973). According to the review of Matthews (1975) the enterocyte is able to transport not only amino acids (AA) but also some natural or artificial small peptides. During their transport the latter are hydrolysed into their constituent AA by the enterocyte (Kim *et al.* 1974) so that apparently only free AA appear in the portal blood coming from the gastrointestinal tract. There is now evidence that the intestinal transport systems of small peptides are different from those of free AA and this might minimize the competition for transport sites (Sleisinger *et al.* 1976). This could explain why the efficiency and speed of absorption observed after intestinal infusion of small peptides are greater than after that of free AA (Rérat *et al.* 1988*b*). However, this type of experiment is generally conducted with solutions containing only small peptides or free AA without any other nutrients except minerals for balancing the osmotic pressure as well as oligoelements and vitamins (Rérat *et al.* 1988*b*). As it is generally admitted that sugars and AA inhibit each other during intestinal transport (Munck, 1981), it may be asked whether this would be true for sugars and small peptides. Furthermore, the fate of absorbed nutrients according to their absorption rate has not been established, particularly in the liver which is known to store and release nutrients as necessary. The presence of these nutrients in the intestinal lumen and their appearance in the 'milieu intérieur' could result in the production of variable amounts of hormones such as insulin, glucagon and somatostatin which are very important for the general body metabolism. Thus, the present study was designed to examine the influence of the physicochemical structure of nitrogenous substances infused into the duodenum together with a carbohydrate on the kinetics of intestinal absorption, hepatic uptake and release of glucose, amino acids, some metabolites and production of regulatory peptides. In the present paper, findings relating to nutrients and metabolites will be analysed and discussed. In a second paper, findings on production of regulatory peptides will be given. Some preliminary results have already been reported (Rérat & Simoes-Nunes, 1988; Rérat *et al.* 1990).

MATERIALS AND METHODS

Animals

Seven castrated Large White male pigs (about 45 kg body-weight) originating from the herd of the Nutrition Department of the National Institute for Agricultural Research (INRA, la Minière) were used. For 1 month before the experiment they received a well-balanced pre-experimental diet (800–1000 g/meal according to appetite) twice daily at 09.00 and 17.00 hours. The mean growth rate of the animals during this period exceeded 600 g/d. At the time of surgery their mean body-weight was 64·6 (SEM 1·9) kg. Each animal was anaesthetized and fitted with an electromagnetic probe around the portal vein and another around the hepatic artery for measuring the splanchnic blood flow-rate. A catheter was placed in the portal vein, another in a hepatic vein, and a third in the left brachiocephalic arterial trunk through the carotid route (Rérat *et al.* 1980; Simoes-Nunes *et al.* 1989). A permanent cannula was also placed in the duodenum (Rérat *et al.* 1988*b*). The animals began to eat the pre-experimental diet 1–2 d after surgery according to a progressive scale increasing from 100 g for the first meal, by steps of 100 g/meal twice daily, up to 800–1000 g/meal on day 5 or day 6. They were given penicillin (1 200 000 IU) and streptomycin (1 g/d) for 3 d after surgery. The catheters permitted painless blood sampling in conscious animals placed in restraining cages. Throughout their experimental life the animals were maintained according to the principles for care of laboratory animals.

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Table 1. *Amino acid (AA) composition and peptide molecular weight (MW) distribution of the milk-protein hydrolysate**

AA composition (%)	His	2·5	Lys	8·5	Phe	4·6	Leu	10·1	Ile	5·1	Met	2·3
	Val	5·9	Thr	4·4	Arg	3·3	Cys	1·6	Tyr	4·9	Asp	8·4
	Pro	8·4	Ser	4·7	Glu†	15·9	Gly	1·8	Ala	3·6	Try	1·8
MW distribution (%)	< 1500‡				1500 < MW < 5000				5000 < MW < 6000			
	80				17				3			
Free AA (mol/100 mol mixture)					8							

* Nitrogen content (g/kg) 125·79.
† Mixture of glutamic acid and glutamine in the hydrolysate.
‡ More than 60% with less than five AA residues.

Experimental design

Experimental trials began 6–8 d after surgery and when the animals had recovered normal appetite and growth rate. Each animal was subjected to two 8 h trials at 8 d intervals; during the recovery period between trials they were fed the pre-experimental diet (two meals daily under the same conditions as before surgery). Each trial started at 09.00 hours after a fasting period of 18 h, the last evening meal being fed at 15.00 hours. Each trial involved the duodenal infusion of a solution (2000 ml) containing 440 g maltose-dextrin + 110 g (i.e. 107·5 g total AA (TAA)) of either a milk-protein mild hydrolysate (Rérat *et al.* 1988*b*) mainly composed of small peptides (PEP; Table 1) or a mixture of free AA of the same composition (AAL). No information was available concerning the distribution of individual AA in the different fractions of the small peptide mixture according to their size. It was not possible to determine the gln content of PEP because of the conversion of gln into glu during the acid-hydrolysis necessary for the analysis; thus, glu (Table 1) represents the sum of glu + gln in the hydrolysate. The mineral content was adjusted to obtain equal osmotic pressures in the two experimental solutions; the supply of trace elements and vitamins was the same. In the first trial PEP was infused to three animals and AAL to the other four animals. In the second trial each pig received the alternative infusion.

Measurements

On the day of each infusion, the blood flow-rate was recorded continuously in the portal vein and the hepatic artery and samples of blood (6 ml) were taken simultaneously from the portal and hepatic veins and carotid artery from the start until 8 h after the beginning of the infusion, every 15 min during the first hour, every 30 min during the 2nd and 3rd hours and every 60 min thereafter. Loss of blood was compensated by a saline (9 g sodium chloride/l) injection into the bloodstream. Determinations were made on 2 ml of each blood sample for glucose (glucose oxidase (*EC* 1.1.3.4) technique; Hill & Kessler, 1961), urea (Mather & Roland, 1969), ammonia (Dropsy & Boy, 1961), lactic acid (Minaire *et al.* 1965) and pyruvic acid (Minaire *et al.* 1966). The remainder of each blood sample was used for determination of individual amino acids (except tryptophan) and regulatory peptides according to techniques already described (Rérat *et al.* 1985; Rérat *et al.* 1988*a*). For simplicity, cys and tyr, which are semi-essential AA, were included with the essential AA (EAA). The electromagnetic technique used to determine the blood flow has been validated previously (Rérat *et al.* 1980; Rérat & Vaugelade, 1983). The sources of potential random errors were as follows: phase adjustment in vitro and in vivo (maximum 5%), and specific sensitivity of the probe (maximum 4%). For blood AA concentration the mean potential

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errors assessed from assay in twelve pairs of subdivided blood samples were 4·3% for EAA and 6·4% for non-essential amino acids (NEAA).

Calculations and limits of the method

The method used for studying absorption (Rérat, 1971; Rérat *et al.* 1980) is based on the quantitative determination of the increase in the intestinal blood level of nutrients after the infusion by measuring the porto-arterial differences ($C_p - C_a$) in nutrient concentrations at any moment after the infusion and by multiplying these differences by the corresponding flow-rate (D_p) and by the duration of digestion. The amount of nutrients (q) appearing in the portal vein within the short time (dt 5 min) during which variables studied can be considered as constant is given by $q = (C_p - C_a)\ D_p\ dt$ when the differences $C_p - C_a$ are positive, i.e. when the portal concentration is higher than the arterial concentration. The total amount (Q_{apv}) appearing over a longer period is obtained by adding the quantities (q) obtained over this period.

However, this formula only gives an apparent estimate of the absorption. Thus, some nutrients coming from the intestinal lumen or the blood can be metabolized or catabolized in the gastrointestinal wall (Rérat, 1981). According to the rate of metabolism of these nutrients in the gut wall, the differences ($C_p - C_a$) may be positive or negative. During periods when these differences are positive, the values represent the overall excess of absorption relative to gut tissue metabolism. During periods when these differences are negative, i.e. when the arterial concentration is higher than the portal concentration, the values represent the excess of uptake from the blood relative to absorption. When adding values for all these periods, i.e. when using the differences ($C_p - C_a$) irrespective of whether they are positive or negative, an apparent intestinal balance is obtained which is the overall result of absorption processes. Of course, in the case of a non-ingested nutrient its apparent synthesis by the cells of the gastrointestinal wall can be measured by this technique.

The study of liver metabolism (Simoes-Nunes *et al.* 1985, 1987, 1989; Rérat, 1986; Rérat & Simoes Nunes, 1988) is based on measurements of the concentration differences between venous blood from a hepatic vein (C_{vs}) on the one hand, and portal and arterial blood on the other hand, as well as on measurements of the blood flow-rate in the hepatic artery (D_a) and the portal vein. Different formulas are used to determine the flux of splanchnic input (qES), the flux of hepatic input (qEH) and the flux of hepatic or splanchnic output (qSH) during the short time-interval dt:

$$qES = C_a(D_p + D_a)dt,$$
$$qEH = [(C_p \times D_p) + (C_a \times D_a)]dt,$$
$$qSH = C_{vs}(D_p + D_a)dt.$$

The total amounts (QES, QEH and QSH) over a longer period are obtained by adding the quantities (q) obtained over this period.

Three variables based on the outflux–influx values may be deduced from these formulas: the intestinal balance (BI), the hepatic balance (BH) and the balance in the peripheral tissues (BT) which includes urinary excretion:

$$\mathrm{BI} = QEH - QES, \quad \text{which by substitution gives}$$
$$\mathrm{BI} = \Sigma(C_p - C_a)D_p dt, \quad \text{whether } (C_p - C_a) \text{ is negative or positive,}$$
$$\mathrm{BH} = QSH - QEH,$$
$$\mathrm{BT} = QES - QSH.$$

All these balances result from a series of steps involving uptake and release within these different tissues. Using these formulas, a negative value means an uptake, a positive one a release.

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Referring to the TAA intake, the infused amount was calculated to be 105·57 g on the basis of the AA content in the hydrolysate (97·8 %) and because tryptophan was not assayed in the blood. As for gln, its intake was included with that of glu.

Statistical methods

Statistical analyses (Snedecor & Cochran, 1967) involved standard error of the mean, and comparison of two groups of data by Student's paired t test.

RESULTS

Hepatic blood flow-rate

The mean blood flow-rates in the portal vein and hepatic artery were calculated for each infusion from continuous recordings throughout the trial. No relationship was found between the mean flow-rate and the type of infusate. For all animals and experiments, the portal blood flow-rate (8 h mean) was 2499 (SEM 155) ml/min, i.e. 37·9 (SEM 1·6) ml/min per kg body-weight; the hepatic artery blood flow-rate was 433 (SEM 58) ml/min, i.e. 6·32 (SEM 0·72) ml/min per kg body-weight. The hepatic artery flow: total hepatic flow ratio was, thus, 0·149. An increase of up to 16% was seen in the portal flow 145 min after infusion, followed by a decrease, but no real change was found in the arterial flow.

Splanchnic influx and hepatic influx and outflux

Cumulative fluxes and balances of nutrients and metabolites are given in Table 2. At the beginning of infusions (t_0) the fluxes of glucose (IF; g/min) were not different, whether they were splanchnic influxes (PEP 1·75 (SEM 0·22), n 7; AAL 1·80 (SEM 0·24), n 7), hepatic influxes (PEP 1·73 (SEM 0·21), n 7; AAL 1·78 (SEM 0·26), n 7) or hepatic outfluxes (PEP 1·84 (SEM 0·22), n 7; AAL 1·85 (SEM 0·25), n 7). Thereafter, because of the exogenous supply of maltose dextrin, the fluxes increased up to the 2nd hour after PEP infusion and the 3rd hour after AAL infusion, and were greater for hepatic influx (PEP 308% IF, AAL 332% IF) than for hepatic outflux (PEP 252% IF, AAL 288% IF) or splanchnic influx (PEP 233% IF, AAL 271% IF). Then they decreased until the 8th hour to values which were slightly higher than the initial values (PEP 110–113% IF, AAL 119–121% IF). All over the 8 h observation period the hourly fluxes were lower ($P < 0{\cdot}01$–$P < 0{\cdot}001$) after PEP than after AAL infusion (Table 3).

The fluxes of circulating TAA (Fig. 1) were similar for both infusions at time t_0 whether they were splanchnic or hepatic influxes or hepatic outfluxes. They increased up to the 2nd hour (PEP 263–284% IF, AAL 240–270% IF) then decreased to values slightly higher than the initial ones at the 8th hour (PEP 110–120% IF, AAL 117–129% IF). This variation corresponded to the increase in blood NH_2-N levels depending on the large AA supply which occurred very early in the portal blood and which lasted until the end of the 2nd hour as shown by differences between splanchnic and hepatic influxes (Fig. 1). This supply subsequently decreased substantially. All over the 8 h observation period the mean hourly fluxes were lower ($P < 0{\cdot}01$) after PEP than after AAL infusion (Table 3).

Mean fluxes of circulating urea in and out of the splanchnic bed registered at time t_0 (IF; g/min) were similar for both infusions (splanchnic influx: PEP 0·445 (SEM 0·044), n 7; AAL 0·408 (SEM 0·029), n 7; hepatic influx: PEP 0·435 (SEM 0·044), n 7; AAL 0·402 (SEM 0·028), n 7; hepatic outflux: PEP 0·443 (SEM 0·044), n 7; AAL 0·404 (SEM 0·028), n 7). They increased until the 3rd hour (PEP 137–140% IF) or the 5th hour (AAL 157–161% IF) and then decreased until the 8th hour to low (PEP 108–110% IF) or moderate values (AAL 140–142% IF). On average, the hourly fluxes were lower ($P < 0{\cdot}05$–$P < 0{\cdot}001$) during the 8 h observation period after PEP infusion than after AAL infusion (Table 3).

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Table 2. *Cumulative (g/8 h) splanchnic and hepatic fluxes and balances after duodenal infusion of carbohydrate solutions† containing small peptides† (PEP) or free aminoacids† (AAL) in the pig*

(Mean values with their standard errors for seven animals)

		Glucose		Total amino acids		Urea		Ammonia		Lactate		Pyruvate	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Splanchnic influx	AAL	1592	152	1048·4	67·0	276·0	17·9	0		154·6	15·2	13·68	1·66
(QES)	PEP	1374**	120	949·9*	68·8	253·6	12·1	0		156·8	16·6	14·66	1·88
Hepatic influx	AAL	1888	192	1092·7	73·9	274·6	18·7	1·34	0·12	165·5	14·4	13·70	1·62
(QEH)	PEP	1702*	158	1007·6	77·3	250·9	12·2	1·55	0·12	159·0	15·0	14·27	1·94
Hepatic outflux	AAL	1734	155	1059·5	66·8	277·9	17·4	0		167·8	14·2	16·17	2·31
(QSH)	PEP	1522**	133	978·9	67·7	255·0	12·3	0		167·8	15·1	17·26	2·12
Amounts appeared	AAL	302	44	78·74	8·78	2·41	0·97	1·34	0·12	11·22	3·10	0·71	0·25
in the portal blood	PEP	334	39	83·09	10·60	1·33	0·23	1·55	0·12	5·72	0·69	0·49	0·09
Intestinal balance	AAL	296	46	44·28	10·05	−1·44	1·00	1·34	0·12	10·83	3·23	0·02	0·54
(QEH−QES)	PEP	328	40	57·71	10·32	−2·67	0·36	1·55	0·12	2·16*	1·91	−0·40	0·21
Hepatic balance	AAL	−154	41	−33·11	13·77	3·28	2·62	−1·34	0·12	2·29	2·90	2·48	0·88
(QSH−QEH)	PEP	−180	42	−28·75	13·81	4·12	1·75	−1·55	0·12	8·83	2·83	2·99	1·15
Peripheral balance	AAL	−142	19	−11·17	7·09	−1·84	2·58	0		−13·12	4·46	−2·50	0·88
(QES−QSH)	PEP	−148	35	−28·96	10·67	−1·45	1·52	0		−11·00	3·27	−2·59	1·07

−, indicates uptake of nutrients; positive data indicate release.

Mean values were significantly different from those of AAL: * $P < 0{\cdot}05$, ** $P < 0{\cdot}01$.

† Maltose-dextrin 440 g/2 l; PEP or AAL containing 105·6 g amino acids except tryptophan; for details of infusions, see p. 113.

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Table 3. *Mean hourly fluxes (g/h) of nutrients and metabolites within 8 h after the start of duodenal infusion of carbohydrate solutions† containing oligopeptides† (PEP) or free amino acids† (AAL) in the pig*

(Mean values with their standard errors for fifty-six hourly fluxes (seven animals × eight time intervals))

	Splanchnic influx				Hepatic influx				Hepatic outflux			
	PEP		AAL		PEP		AAL		PEP		AAL	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Glucose	171·7***	8·9	199·0	11·9	212·7**	13·3	236·0	15·8	190·2***	10·4	216·7	13·0
Total amino acids	118·7***	6·3	131·0	5·9	125·9**	7·7	136·6	6·7	122·4**	6·8	132·4	6·2
Urea	31·70**	0·76	34·5	0·99	31·36*	0·76	34·32	1·03	31·87**	0·78	34·74	1·00

Mean values were significantly different from those of AAL: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

† Maltose-dextrin 440 g/2 l; PEP or AAL containing 105·6 g amino acids except tryptophan; for details of infusions, see p. 113.

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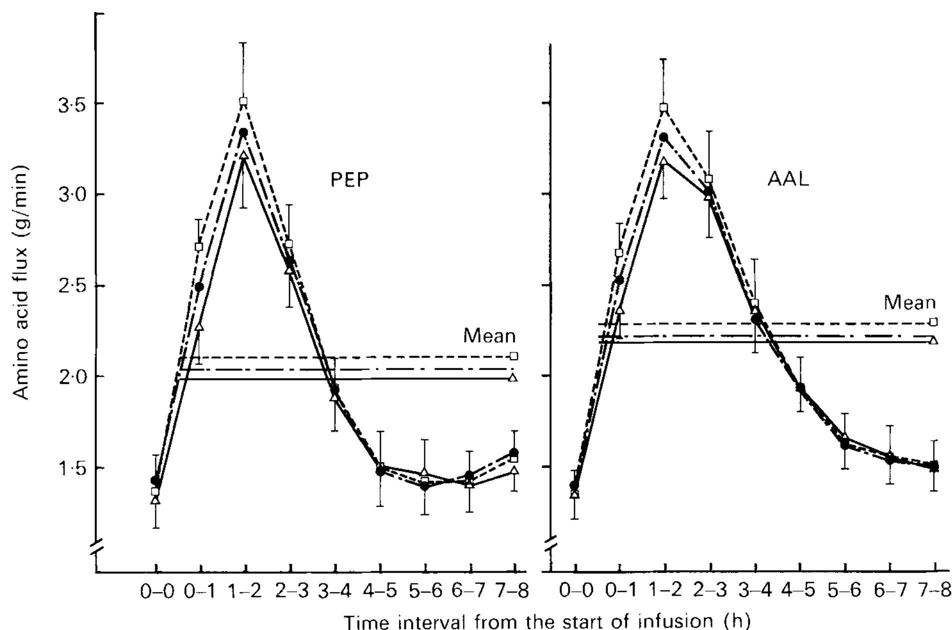

Fig. 1. Changes with time of total amino acids (TAA) on an hourly basis (g/min) for splanchnic influx (△—△), hepatic influx (□--□), and hepatic outflux (●-·●), during 8 h after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP) or free amino acid mixture (AAL) with the same pattern (TAA except tryptophan: 105·6 g). Values are means with their standard errors represented by vertical bars for splanchnic and hepatic influxes. For details of infusions, see p. 113.

Circulating fluxes of lactate at time t_0 (IF; g/min) were identical, whatever the site of measurement and type of infusion (splanchnic influx: PEP 0·195 (SEM 0·027), *n* 7; AAL 0·199 (SEM 0·032), *n* 7; hepatic influx: PEP 0·195 (SEM 0·027), *n* 7; AAL 0·190 (SEM 0·028) *n* 7; hepatic outflux: PEP 0·180 (SEM 0·033), *n* 7; AAL 0·197 (SEM 0·028), *n* 7). They increased until the 3rd hour after infusion (PEP 232–260% IF, AAL 223–247% IF) then decreased until the 8th hour (PEP 141–188% IF, AAL 121–146% IF). There were no significant differences between the two infusates in the average hourly fluxes during the 8 h observation period.

The same changes with time were seen with pyruvate whose fluxes, which were identical at time t_0 (IF; g/min) whatever the site of measurement and type of infusion (splanchnic influx: PEP 0·016 (SEM 0·003), *n* 7; AAL 0·019 (SEM 0·003), *n* 7; hepatic influx: PEP 0·018 (SEM 0·004), *n* 7; AAL 0·020 (SEM 0·003), *n* 7; hepatic outflux: PEP 0·016 (SEM 0·003), *n* 7; AAL 0·021 (SEM 0·003), *n* 7), increased until the 3rd to 4th hour (PEP 208–289% IF, AAL 176–182% IF) then decreased until the 8th hour (PEP 155–281% IF, AAL 120–180% IF). The average hourly fluxes during the 8 h observation period were not different according to the type of infusate.

Appearance of nutrients and metabolites in the portal blood and intestinal balances

The amounts of glucose appearing in the portal blood (Table 4) were not significantly different within 8 h after the infusion of PEP (76 (SEM 9) % of the infused amount) or that of AAL (69 (SEM 10) % of the infused amount). The bulk of the absorptive phenomena was performed during 4 h after infusion (PEP 83% of the total absorbed, AAL 81% of total absorbed). The exchanges between intestinal lumen and blood during 8 h represented about

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Table 4. *Changes in amounts (g) of glucose appearing in the portal blood, taken up by the liver, taken up by the peripheral tissues and taken up by the gut cell wall according to time elapsed after the start of duodenal infusion of carbohydrate solutions† containing small peptides† (PEP) or free amino acids† (AAL) in the pig*

(Mean values for seven animals)

Time interval after the beginning of the infusion (h)	Appearing in the portal blood		Taken up by the liver		Taken up by the peripheral tissues		Taken up by the gut cell wall	
	PEP	AAL	PEP	AAL	PEP	AAL	PEP	AAL
0-1	69·1	62·0	−38·6	−31·3	−30·5	−30·6	0	0·1
1-2	74·3	72·9	−42·4	−35·9	−31·9	−37·0	0	0
2-3	64·5	62·7	−38·9	−34·6	−25·6	−28·1	0	0
3-4	68·4*	48·1	−45·3	−30·3	−23·1	−17·8	0	0
4-5	38·8	34·9	−24·7	−24·7	−14·0	−10·2	−0·1	0
5-6	10·2	12·9	−3·6	−4·5	−6·2	−7·7	−0·4	−0·7
6-7	5·8	5·5	3·1	1·0	−7·6	−4·6	−1·3	−1·9
7-8	2·8	3·4	10·4	5·9	−9·2	−6·0	−4·0	−3·3
0-8	333·9	302·3	−179·9	−154·3	−148·2	−142·0	−5·8	−6·0

−, indicates uptake of nutrients; positive data indicate release.

Mean values were significantly different from those of AAL: * $P < 0.05$.

† Maltose-dextrin 440 g/2 l; PEP or AAL containing 105·6 g amino acids except tryptophan; for details of infusions, see p. 113.

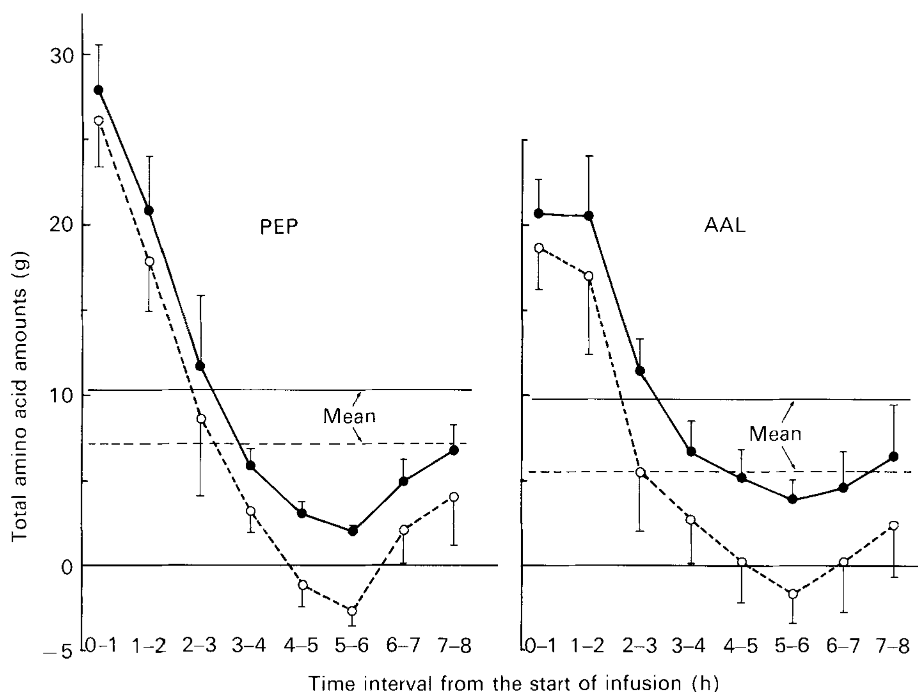

Fig. 2. Changes with time of total amino acids (TAA) amounts appearing in the portal blood (●—●) and TAA intestinal balances (○---○) after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP) or free amino acids mixture (AAL) with the same pattern (TAA except tryptophan: 105·6 g). Values are means with their standard errors represented by vertical bars. For details of infusions, see p. 113.

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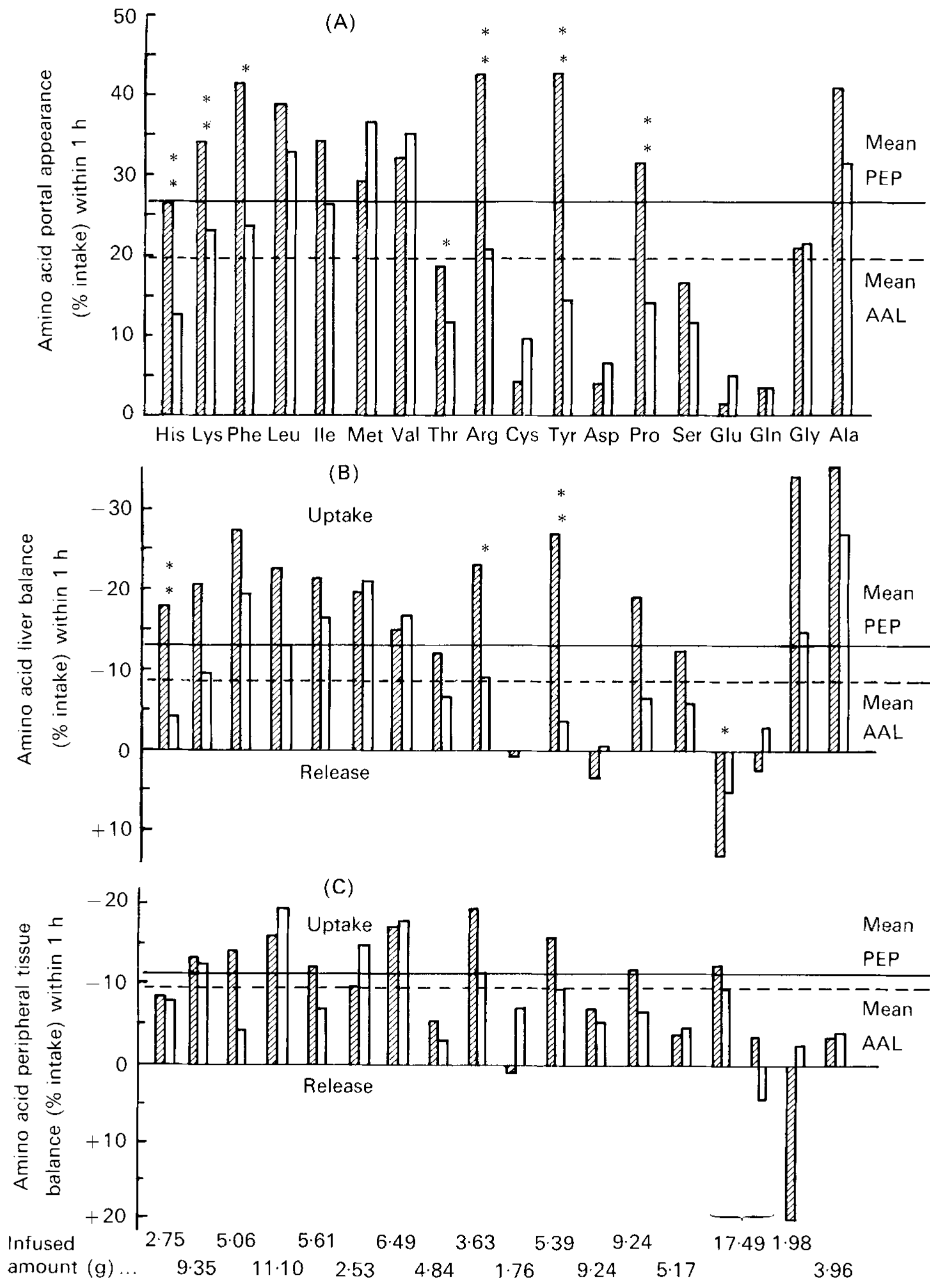

Fig. 3. Percentages of infused individual amino acids (A) appearing in the portal blood (B) taken up or released by the liver (C) taken up or released by peripheral tissues within 1 h after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing 110 g oligopeptides (PEP; ▨) or free amino acid mixture (AAL; □) with the same pattern (total amino acids except tryptophan: 105·6 g). Statistical significance of difference between infusates (n 7): * $P < 0·05$, ** $P < 0·01$. For details of infusions, see p. 113.

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Table 5. *Amounts (g) of some non-essential amino acids appearing in the portal blood, taken up by the liver, taken up by the peripheral tissues and taken up by the gut cell wall from arterial blood after the start of duodenal infusion of carbohydrate solutions† containing small peptides† (PEP) or free amino acids† (AAL) in the pig*

(Mean values for seven animals)

	Appearing in the portal blood		Taken up by the liver		Taken up by the peripheral tissues		Taken up by the gut cell wall	
	PEP	AAL	PEP	AAL	PEP	AAL	PEP	AAL
During 1 h after the infusion								
Glu	0·26	0·87	2·31*	0·85	−2·19	−1·63	−0·38	−0·09
Gln	0·60	0·58	0·41	−0·49	−0·53	0·75	−0·48	−0·84
Cit	0·28	0·10	−0·04	0·01	−0·11	0	−0·13	−0·11
Orn	0·42	0·25	−0·21*	0·06	−0·18	−0·27	−0·03	−0·04
Tau	0·32	0·39	−0·22	−0·11	0·24	−0·15	−0·34	−0·13
Within 8 h after the infusion								
Glu	1·93*	4·01	15·75	9·80	−14·63	−11·93	−3·05	−1·88
Gln	1·19	1·17	1·36	1·79	5·49	6·50	−8·04	−9·46
Cit	2·17	1·23	−2·09	−0·59	0·36	−0·21	−0·44	−0·43
Orn	1·90	1·45	−1·21	−0·53	−0·21	0·40	−0·48	−1·32
Tau	2·26	2·59	−0·28	−0·38	0·42	0·87	−2·40	−3·08

−, indicates uptake of nutrients; positive data indicate release.

Mean values were significantly different from those for AAL: * $P < 0.05$.

† Maltose-dextrin 440 g/2 l; PEP or AAL containing 105·6 g AA except tryptophan; for details of infusions, see p. 113.

98% of the amounts appearing in the portal blood (Table 2) because of periods of small apparent uptake of blood glucose by the intestinal cell wall during the last 4 h (Table 4).

The amounts of TAA appearing in the portal blood (Fig. 2) were the highest during the 1st 2 h, the absorption representing more than 50% of that performed during the 8 h period. The total amounts appearing during 8 h (Table 2) were almost the same in the two cases (79 and 75% of the amount infused of PEP and AAL respectively; not significant). The balance of intestinal TAA exchanges (Fig. 2) showed a pattern similar to that of the appearance of TAA in the portal blood. The total amounts resulting from these exchanges during 8 h represented only 69 (PEP) and 56% (AAL) of the amounts corresponding to the AA enrichment of the portal blood.

The absorption ratios (amounts appearing in the portal vein: amounts infused) of each AA calculated for a period of 1 or 8 h can be used to show the differences in the absorption rates of a given AA according to the type of infusion, and between the various AA for a given type of infusion. At 1 h after infusion of PEP (Fig. 3(A)) the absorption rate differences between AA were particularly marked: for an overall ratio of 26% (TAA) the absorbed amount ranged from 4 to 43% for EAA (mean 34%) and from 1 to 41% for NEAA (mean 17%). The early absorption rate was higher than the mean for lys, phe, leu, ile, val, arg, tyr, pro and ala and lower than the mean for thr, cys, asp, ser, glu+gln and gly. During the same period of time the initial mean absorption rate of individual AA after AAL infusion was lower (TAA 19%); it represented 24% for EAA (range 4–43%) and 14% for NEAA (range 3–32%). The initial absorption rate was higher than the mean for lys, phe, leu, ile, met, val and ala and lower than the mean for his, thr, cys, tyr, asp, pro, ser and glu+gln. The initial absorption differences between the two solutions were significantly in favour of PEP for his, lys, phe, arg, thr, tyr and pro. Some AA absent in

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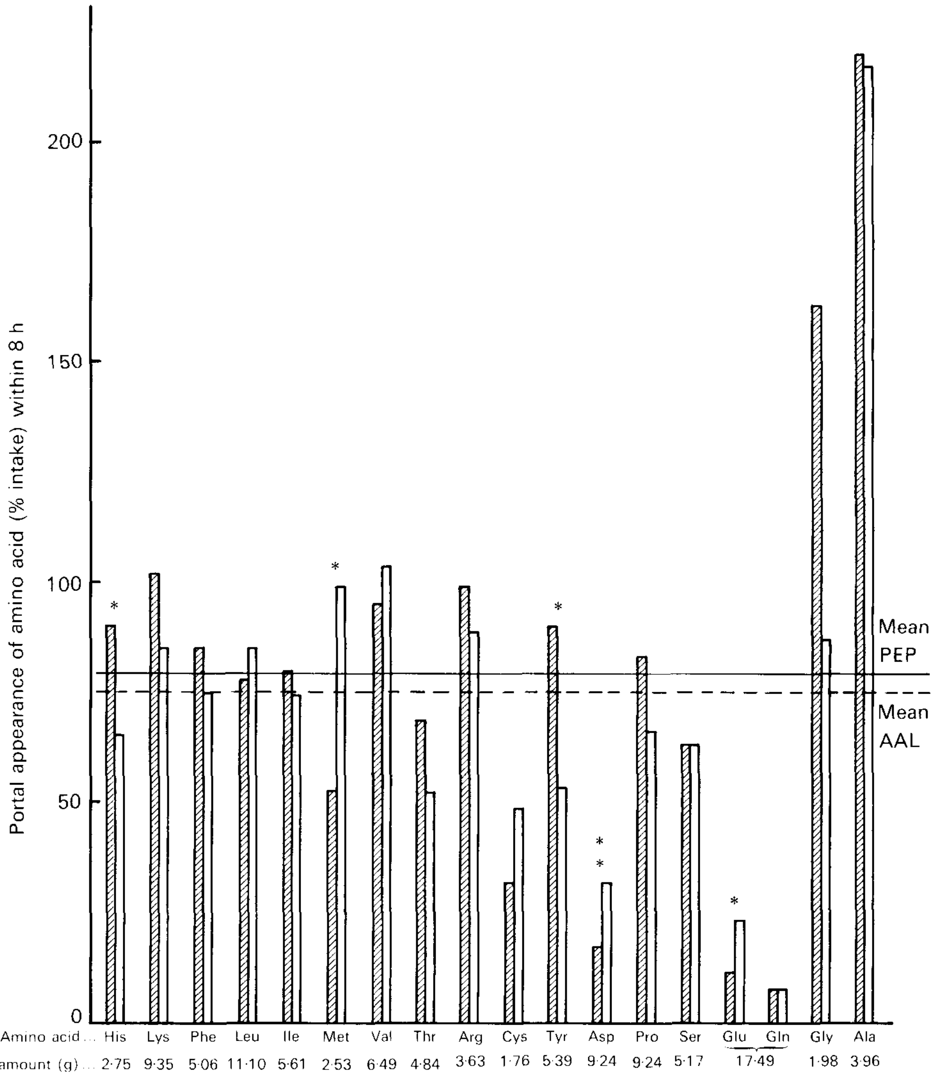

Fig. 4. Percentages of infused individual amino acids appeared in the portal blood within 8 h after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP; ▨) or free amino acids mixture (AAL; □) with the same pattern (total amino acids except tryptophan: 105·6 g). Statistical significance of difference between infusates (*n* 7): * $P < 0.05$; ** $P < 0.01$. For details of infusions, see p. 113.

the infusions (cit, orn and tau) appeared initially in small quantities in the portal blood (Table 5), but there were no significant differences between the two solutions.

At 8 h after infusion (Fig. 4) the same trends were observed. After PEP infusion the absorption rate was higher than the mean in the case of his, lys, val, arg, tyr, gly and ala and lower than the mean for met, thr, cys, asp, ser and glu+gln. After AAL infusion the absorption rate was higher than the mean for lys, leu, met, val, arg, gly and ala and lower than the mean for his, thr, cys, tyr, asp, pro, ser and glu+gln. The appearance in the portal blood of cit, orn and tau within 8 h was identical for both solutions. The only significant

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Table 6. *Cumulative intestinal cell wall uptake of individual amino acids (AA; g) within 8 h following the start of duodenal infusion of carbohydrate solutions† containing oligopeptides† (PEP) or free amino acids† (AAL) in the pig*

(Mean values with their standard errors for seven animals)

Essential AA	PEP			AAL			Non-essential AA (NEAA)	PEP			AAL		
	Amounts (g)		Percentage absorbed	Amounts (g)		Percentage absorbed		Amounts (g)		Percentage absorbed	Amounts (g)		Percentage absorbed
	Mean	SEM		Mean	SEM			Mean	SEM		Mean	SEM	
His	−0·20	0·07	8·1	−0·31	0·09	17·2	Asp	−0·11	0·06	7·2	−0·19	0·05	6·1
Lys	−1·01	0·33	10·5	−1·67	0·39	20·9	Pro	−2·64	0·95	34·2	−4·65	1·61	75·8
Phe	−0·29	0·06	6·6	−0·60	0·20	15·8	Ser	−0·73	0·20	22·1	−1·32	0·42	40·7
Leu	−0·54	0·11	6·3*	−2·07	0·54	22·2	Glu	−3·05	0·45	158·2	−1·88	0·68	46·9
Ile	−0·26	0·06	6·0*	−1·14	0·28	27·2	Gln	−8·04	1·54	676·2	−9·46	2·17	809·1
Met	−0·33	0·10	25·0	−0·17	0·07	6·8	Gly	−1·01	0·22	31·2	−0·83	0·05	48·3
Val	−0·82	0·12	13·2*	−1·72	0·37	25·7	Ala	−0·64	0·35	7·3	−0·36	0·13	4·2
Thr	−0·79	0·23	23·9	−1·36	0·43	54·8	Cit	−0·44	0·15	20·1	−0·43	0·07	34·7
Arg	−0·35	0·09	9·7	−0·22	0·10	7·0	Orn	−0·48	0·19	25·6	−1·32	0·50	90·6
Cys	−0·72	0·21	131·6	−0·85	0·17	100·7	Tau	−2·40	0·38	106·2	−3·08	0·36	118·9
Tyr	−0·53	0·21	11·1	−0·83	0·31	28·8	NEAA	−19·54	2·68	57·5	−23·52	2·88	71·1
EAA	−5·84	0·75	11·9*	−10·94	1·66	24·0							
TAA	−25·38	3·31	30·5*	−34·46	2·43	43·8							

−, indicates uptake of nutrients; positive data indicate release.
Mean values were significantly different from those of AAL: * $P < 0.05$.
† Maltose-dextrin 440 g/2 l; PEP or AAL containing 105·6 g AA except tryptophan; for details of infusions, see p. 113.

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differences between the two solutions concerned his and tyr (PEP > AAL) and met, asp and glu (AAL > PEP).

The differences between the appearance of TAA and individual AA in the portal blood and the intestinal balance of exchanges with blood correspond to transient ($C_p - C_a$) negative values and, thus, to the apparent uptake of AA from the arterial blood (Table 6). After 8 h the apparent uptake of TAA was lower ($P < 0.05$) after PEP than after AAL infusion (24 and 33% of infused amounts respectively); the same was true for EAA whose uptake was reduced by half after PEP infusion ($P < 0.05$). The amounts of NEAA taken up were three and two times those of EAA after PEP and AAL infusion respectively. The amounts of EAA taken up represented between 10 (PEP) and 19 (AAL) % of EAA infused and those of NEAA between 41 (PEP) and 50 (AAL) % of NEAA infused. For the individual AA the only significant differences concerned the branched-chain AA (BCAA) whose uptake by the intestinal wall after PEP infusion was one-third that registered after AAL infusion. There was a very large gut-wall uptake of gln (representing 40% of all NEAA) and a smaller one of thr, lys, glu, pro and tau. In the case of tau the amounts appearing in the portal vein were equivalent to those taken up by the gut wall from the blood (Table 5).

Levels of urea appearing within 8 h in the portal blood were small and not significantly different (Table 2) after both infusions. There was a simultaneous high uptake from the arterial blood by the intestinal wall so that intestinal balances within 8 h were negative (Table 2).

The appearance of ammonia in the portal blood was constant over the post-infusive period; the total amount appearing within 8 h (Table 2) was not significantly different for both solutions. The amount of NH_3-N appearing in the portal blood was equivalent to 68 (PEP) and 61 (AAL) % of urea-N taken up from the blood by the intestinal wall.

Changes with time of lactate appearance in the portal blood and of lactate intestinal balances showed a similar pattern, but the balances were generally lower than the appearance in the portal blood due to lactate uptake by the intestinal cell wall. The cumulative intestinal balance within 8 h was lower ($P < 0.05$) after PEP than after AAL infusion (Table 2), the total apparent uptake of lactate by the cell wall being 3·56 (PEP) and 0·39 (AAL) g/8 h.

Pyruvate appearance in the portal blood was highly variable with time and rather low within 8 h (Table 2). There was a large gut-wall uptake (PEP 0·69 g/8 h, AAL 0·89 g/8 h; Table 2) rendering the intestinal exchanges negative (PEP) or zero (AAL).

Liver exchanges of nutrients and metabolites

The liver uptake of glucose (Table 4) was high within the first 5 h then decreased sharply, a slightly increasing release being seen during the last 2 h. There was no significant difference in the total liver uptake of glucose between the two infusions (54 and 51% of absorbed amounts respectively for PEP and AAL).

The TAA uptake by the liver (Fig. 5) paralleled that of the intestinal balance and was, thus, larger during the first hours than afterwards. It was followed by a release during the last 2 h of observation after PEP infusion while it persisted slightly until 8 h after AAL infusion. The amounts of TAA taken up were not significantly different after both infusions (PEP −27 (SEM 13) % of infused amounts, AAL −31 (SEM 13) % of infused amounts). The amounts of TAA taken up by the liver within 1 h (Fig. 3(B)) tended to be higher (56%, not significant) after PEP than after AAL infusion, but the percentages of hepatic retention relative to infused amounts was rather low (PEP −13%, AAL −8%). The bulk of the liver retention during this period came from EAA representing 86 (PEP) and 78 (AAL) % of the mixtures taken up. The differences between liver uptake measured 1 h after both infusions

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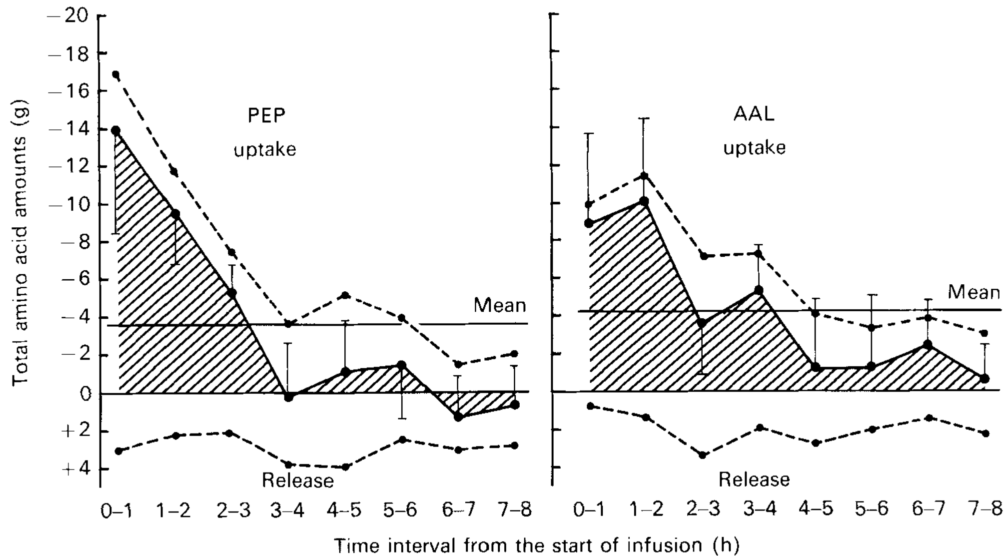

Fig. 5. Changes with time of total amino acid liver exchanges (●---●) or balances (uptake minus release; (●—●), (▨) after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP) or free amino acids mixture (AAL) with the same pattern (total amino acids except tryptophan: 105·6 g). Values are means with their standard errors (for balances) represented by vertical bars. For details of infusions, see p. 113.

concerned all AA except met, val, asp and cys, but they were only significant for his, arg, tyr, orn (in favour of PEP) and glu (in favour of AAL). After PEP infusion the hepatic balance relative to infused amounts (%) varied between +0·5 (cys) and −27 (phe) for EAA (mean uptake −20) and between +13 (glu) and −36 (ala) for NEAA (mean uptake −4%). There was a small release of asp and gln and a larger release of glu. After AAL infusion the hepatic balance of EAA (mean uptake −12%) varied between 0% (cys) and −21% (met); that of NEAA (mean uptake −4%) varied between +5% (glu) and −27% (ala); there was only a small release of glu. During this period the amounts of TAA retained in the liver were less than half the amounts appearing in the portal blood (PEP 49%, AAL 43%), this percentage being higher for EAA (PEP 60%, AAL 48%) than for NEAA (PEP 24%, AAL 30%).

The liver uptake was larger after 8 h (Fig. 6) than after 1 h (PEP 208%, AAL 374%). In the case of PEP the total uptake of EAA by the liver within 8 h (−29·1 g) was slightly higher than the total amount of TAA (−28·8 g) because of a small cumulative release of NEAA (+0·4 g). Thus, it represented more than 100% of the TAA mixture apparently taken up but only 60% of the AA retained by the liver (−48·3 g) when discarding a large release (19·5 g) of some NEAA (asp, gln, glu). In the case of AAL infusion the total amount of EAA taken up by the liver (−23·7 g) represented 71·6% TAA, but when discarding hepatic losses (12·6 g) of cys and some NEAA (asp, glu, gln) they represented only 52% of the AA retained by the liver (−45·7 g). However, the difference in liver uptake within 8 h was in favour of PEP for EAA (−50% of infused amounts *v.* −40% in the case of AAL) and in favour of AAL for NEAA (−20% of infused amounts *v.* a release of +0·8% in the case of PEP). Whatever the infusion, the AA mixture taken up within 8 h by the liver was very different from the mixture infused (Fig. 6), which can be seen by comparison between uptake ratios of individual amino acids and the mean. After PEP infusion the EAA mixture showed an enrichment in his, lys, phe, arg and tyr and an impoverishment in BCAA, met,

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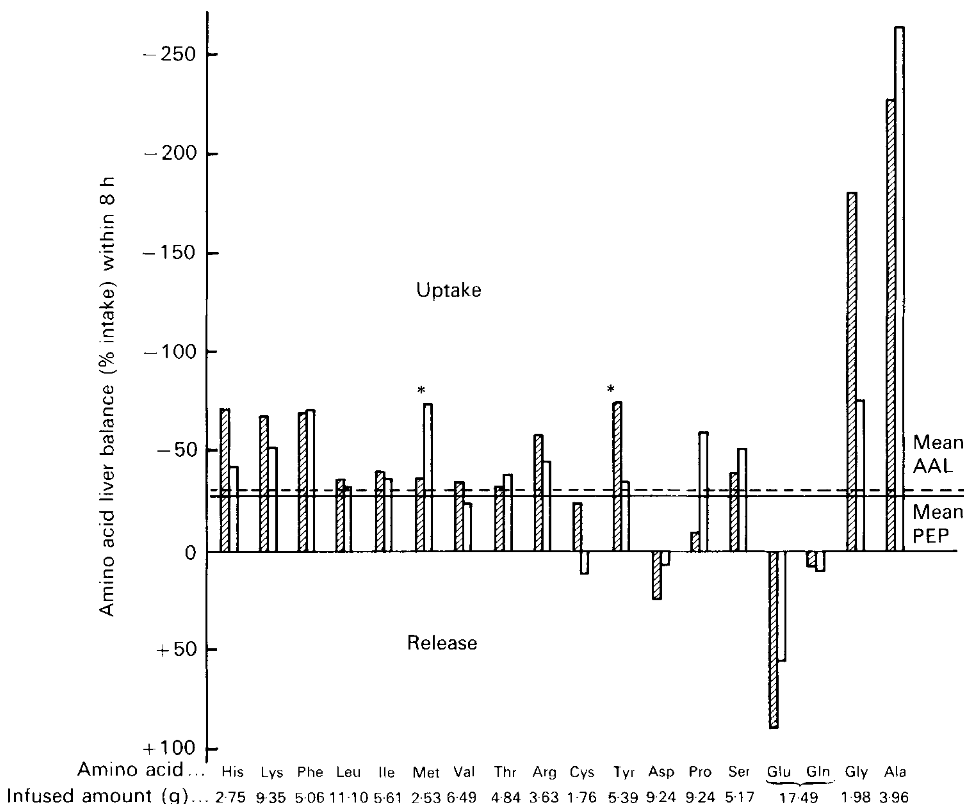

Fig. 6. Percentages of infused individual amino acids taken up or released by the liver within 8 h after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP; ▨) or free amino acids mixture (AAL; □) with the same pattern (total amino acids except tryptophan: 105·6 g). Statistical significance of difference between infusates (*n* 7): * $P < 0.05$. For details of infusions, see p. 113.

cys and thr. A similar trend was observed after AAL infusion except for thr, the liver uptake of which was identical to the mean and to that of met (enrichment). The NEAA balance was characterized by a very large uptake of ala and a smaller uptake of gly and ser, and a release which was moderate for gln and asp and very large for glu; the uptake for pro was low after PEP infusion and high after AAL infusion. With cit and orn (Table 5), a large percentage of these AA appearing in the portal blood was taken up by the liver after PEP infusion (cit 96%, orn 64%) and a smaller proportion after AAL infusion (cit 48%, orn 36%). The only significant differences of liver uptake between the two infusions concerned tyr, (PEP > AAL) and met (AAL > PEP).

With regard to urea, there was a similar liver output for both infusates throughout the observation period. The cumulative amounts released within 8 h (Table 2) were not significantly different and represented between 1·6 (PEP) and 1·2% (AAL) of the total hepatic influx of urea. Meanwhile, the absorbed NH_3 (Table 2) was completely taken up by the liver since the NH_3 concentrations in the hepatic venous blood and in the arterial blood were close to zero. NH_3-N uptake by the liver within 8 h was about two-thirds (PEP 66%, AAL 72%) the urea-N release or 63% (PEP)–81% (AAL) the NEAA (glu, gln and asp) release during the same period. Lactate metabolism in the liver showed a transient uptake for some hours, then a release; the cumulative balance (Table 2) was characterized by a release which showed a trend to be larger within 8 h after PEP than after AAL

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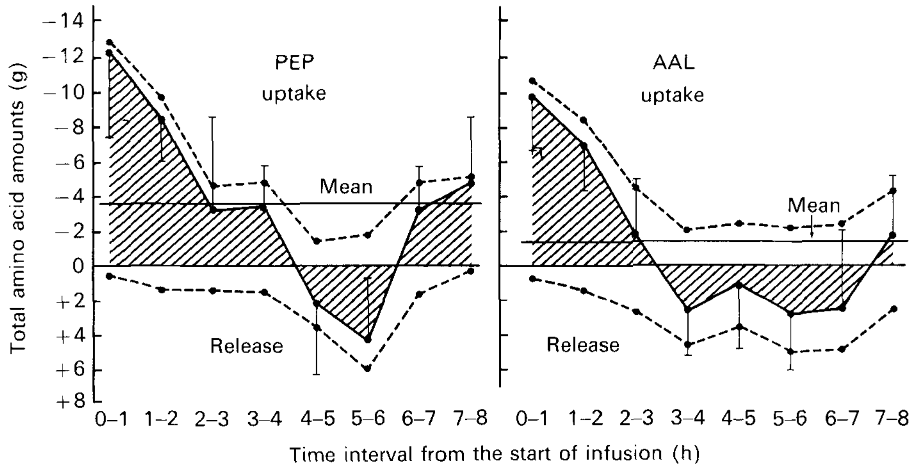

Fig. 7. Changes with time of total amino acid peripheral tissue exchanges (●---●) or balances (uptake minus release; (●—●), (▨) after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP) or free amino acids mixture (AAL) with the same pattern (total amino acids except tryptophan: 105·6 g). Values are means with their standard errors (for balances) represented by vertical bars. For details of infusions, see p. 113.

infusion. With pyruvate there was a permanent liver release throughout the observation period and the cumulative release within 8 h (Table 2) was not significantly different after the two infusions.

Uptake and release by peripheral tissues (including urinary excretion)

The uptake of glucose by the peripheral tissues (Table 4) was high during the 1st 2 h, then decreased slowly until the 8th hour. The cumulative uptake within 8 h was similar after PEP and AAL infusions, and was not significantly different from the amounts taken up by the liver during the same period.

The hourly uptake of TAA by the peripheral tissues (Fig. 7) was large during the 1st 2 h whatever the type of solution; it was followed by a release of TAA during the 5th and 6th hours after PEP infusion and from the 4th to the 7th hour after AAL infusion. The cumulative amounts of TAA taken up by the peripheral tissues more than doubled from the 1st (−12·3 g/h) to the 8th hour (−29·0 g/8 h) after PEP infusion; this uptake increased slightly after AAL (−9·8 g during the 1st hour *v.* −11·2 g after 8 h). At 8 h after the infusion it was in favour (259%, not significant) of PEP because of a generally larger hourly uptake and a smaller hourly release of AA than after AAL infusion.

The TAA peripheral tissue balance at the end of the 1st hour (Fig. 3(C)) was quite similar after the infusion of both solutions and the peripheral uptake (+renal excretion) relative to infused amounts (%) was rather low (PEP −12, AAL −9). The amounts of EAA represented between 63% (PEP) and 71% (AAL) of TAA; taking into account losses due to release (PEP 0·64 g, AAL 0·75 g) they represented 60% (PEP) to 66% (AAL) of the mixture taken up within 1 h.

At 1 h after PEP infusion the percentage of peripheral tissue balance of individual AA relative to infused amounts (Fig. 3(C)) varied between +0·5% (cys) and −19% (arg) for EAA (mean uptake −13%) and between +20% (gly) and −12% (glu) for NEAA (mean uptake −9%). The EAA mixture taken up was richer in phe, leu, val, arg and tyr than the infused mixture and poorer in his, met and thr; the NEAA mixture was richer in glu+gln and

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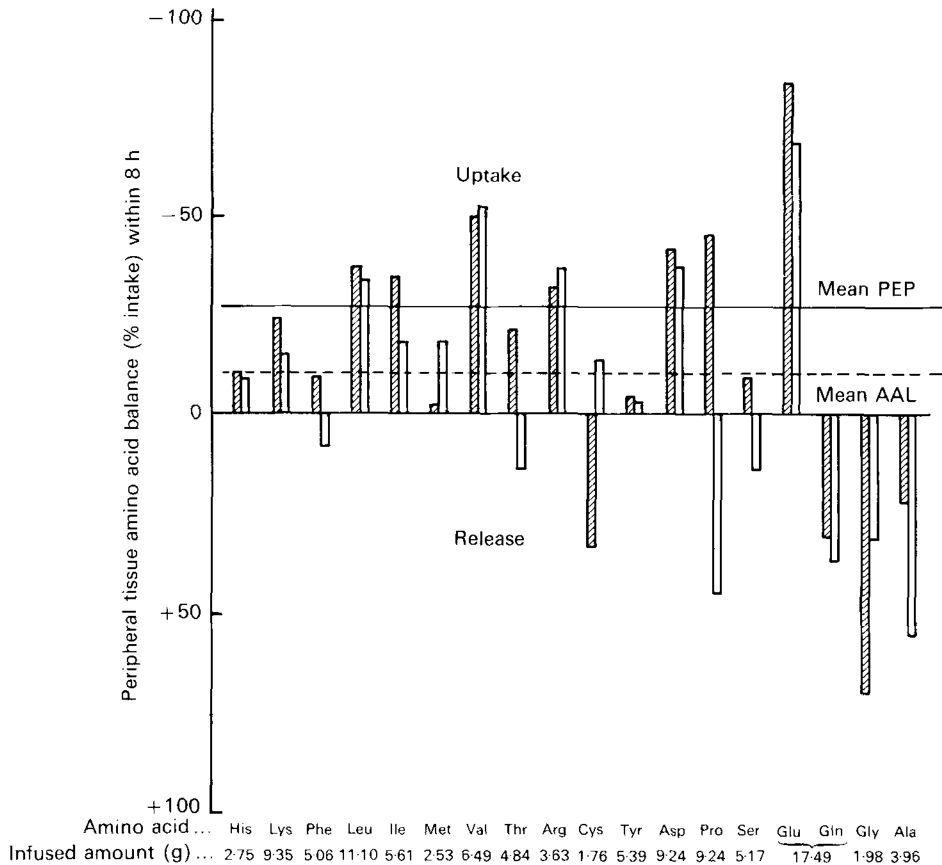

Fig. 8. Percentages of infused individual amino acids taken up or released by peripheral tissue within 8 h after the start of duodenal infusion of carbohydrate solutions (440 g maltose-dextrin/2 l) containing oligopeptides (PEP; ▨) or free amino acids mixture (AAL; □) with the same pattern (total amino acids except tryptophan: 105·6 g). For details of infusion, see p. 113.

pro and poorer in ser and ala; there was also a marked release of gly. At 1 h after AAL infusion (Fig. 3(C)) the peripheral tissue balance of individual AA relative to infused amounts (%) varied between −3 (thr) and −19 (leu) for EAA (mean uptake −12) and between +4 (gln) and −9 (glu) for NEAA (mean uptake −6). The EAA mixture taken up was richer in leu, met and val than the infused one and poorer in his, phe, ile, thr, tyr and cys; there was also a release of gln. There was no significant difference between the two solutions for peripheral uptake of individual AA, but some trends could be observed including a higher uptake of phe, ile, arg, tyr, pro and glu+gln and a lower uptake of met and gly after PEP than after AAL infusion.

At 8 h after PEP infusion (Fig. 8) the uptake by the peripheral tissues considerably increased (236% relative to the 1st hour), the major part of this increase being due to NEAA. Thus, when discarding losses due to a cumulative release (9·13 g/8 h), the EAA uptake (−14·73 g/8 h) represented 39% of the TAA mixture retained (−38·09 g/8 h). The peripheral balance relative to infused amounts (TAA mean uptake −27%) varied for EAA (mean uptake −24%) between +33% (cys) and −50% (val) and for NEAA (mean uptake −31%) between +70 (gly) and −84% (glu). The EAA mixture taken up showed a large

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BCAA and a smaller arg enrichment as well as a very marked his, phe, met, tyr and cys impoverishment. The NEAA mixture was richer mainly in glu (representing 63% of all NEAA uptake), asp and pro than the infused mixture; there was also a large release of gln, ala and gly and a smaller release of cit. At 8 h after AAL infusion the cumulative TAA peripheral uptake (Fig. 8) increased slightly (115% compared with the 1st hour) and represented only −11% of the infused amount. It was almost exclusively composed of EAA (99% of the total) because of a large release of NEAA. Thus, when discarding losses due to release (16·56 g/8 h) the peripheral retention of EAA (−12·13 g/8 h) represented 44% of the total TAA mixture retained (−27·73 g/8 h). The peripheral balance relative to infused amounts (%) (Fig. 8) varied for EAA (mean uptake −19) between +14 (thr) and −52 (val) and for NEAA (mean −0·3) between +56 (ala) and −68 (glu). In comparison with the infused mixture, the EAA mixture taken up was richer in BCAA (except ile) and arg and poorer in his and tyr; there was also a net release of phe and thr. As for the NEAA mixture, it was richer in glu (76% of all NEAA uptake) and asp; there was a slight uptake of cit (Table 5) and a release of all the other NEAA, the largest being that of gln and pro. Thus, 8 h after the infusion some similar trends could be seen in the two cases, i.e. a peripheral enrichment in BCAA and arg, an impoverishment in his and aromatic AA (becoming a release in the case of AAL), a high uptake of glu and a smaller uptake of asp, and a high release of gln, gly and ala. However, some marked differences appeared: a release (zero balance for met) of sulphur-AA after PEP infusion, and a release of thr and phe after AAL infusion; a pro and ser uptake after PEP infusion *v.* a release after AAL infusion and the opposite for cit; a higher release (not significant) of ala after AAL infusion.

The cumulative peripheral balance of urea (Table 2) was negative, i.e. an uptake which was similar for both solutions. Lactate and pyruvate peripheral metabolism was characterized by a permanent uptake throughout the observation period; the cumulative peripheral uptake was not significantly different whatever the solution infused (Table 2).

DISCUSSION

Appearance of nutrients in the portal blood and intestinal balances

During the present experiment a duodenal infusion of small peptides led to an earlier and more homogeneous absorption rate of most AA than the infusion of free amino acids of the same pattern. However, the divergences recorded between the two types of solutions were much less marked than in a previous experiment in which infusions of similar peptide mixtures did not contain any carbohydrate (Rérat *et al.* 1988*b*). This difference between the two experiments does not seem to be due to the peptide component of the solution since the starter protein and the method of enzyme hydrolysis were the same in the two cases, resulting in a similar distribution of small and longer peptides and probably in a similar distribution of individual AA in the different fractions of the peptide mixture. Thus, the peptide chain length which markedly affects uptake of AA residues (Grimble *et al.* 1986) was not involved in this difference. In fact, the most important difference between the two experiments concerned the presence of carbohydrate which resulted in an almost parallel slowing down of the absorption rate of most AA from the two solutions during the 1st hour; the exception was met whose absorption was accelerated after PEP infusion (Rérat *et al.* 1990). Whereas the reduced absorption rate in the presence of carbohydrate persisted for 5 h after infusion of small peptides (PEP), resulting in a mean depression of AA appearance in the portal blood of 30% (met 14%), this was no longer the case for the solution of free AA whose overall absorption for 5 h reached a similar level in the presence or in the absence of carbohydrate (Rérat *et al.* 1990). It should be pointed out that the

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opposite effect of maltose dextrin on the absorption rate of met according to its bound or free form disappeared after 2 h, which resulted again in a quicker appearance (within 5 or 8 h) of this AA in the portal blood after infusion of AAL than after that of PEP, as shown in the absence of carbohydrate. The short-lasting inhibition of the transport by the enterocyte of various free AA in the presence of glucose has already been demonstrated in vivo, particularly for gly (Cook, 1971), met, his and glu (Annegers, 1966), and in vitro (Chez *et al.* 1966; Hindmarsh *et al.* 1966). However, the presence of carbohydrate may have no effect (Cook, 1972*a*) or may, on the contrary, be favourable (gly; Newey & Smyth, 1964). On the other hand, the interactions between transport of small peptides and glucose by the enterocyte have received very little attention; it is only known that the addition of glucose to a solution containing glycylglycine causes a marked decrease in the transport by the enterocyte in vivo (Cook, 1972*b*), which is consistent with the results of the present experiment. The mechanisms of such interactions should be further elucidated. It is noteworthy that despite the presence of carbohydrate, the previously described hierarchy of absorption using solutions with the same pattern and quantity was also observed in the present experiment.

The amounts of each AA appearing in the portal vein, measured from the positive porto-arterial differences, were generally larger than the corresponding amounts representing the intestinal balance (intestinal blood outflux – intestinal blood influx) which takes into account the apparent intestinal uptake from the arterial blood, calculated from the negative porto-arterial differences. The uptake was only apparent since a proportion of the absorbed AA coming from the lumen could also be taken up during the transport by the enterocyte. It was variable from one AA to another, the mean for TAA being significantly higher (36%) 8 h after AAL than after PEP infusion. The difference may be due to the fact that fluxes of circulating AA were larger after AAL than after PEP infusion. Because of the high metabolic rate of intestinal tissues, this may result in a larger uptake of the higher amounts of blood AA available for these tissues. As for EAA, these differences concerned mainly BCAA which means that intestinal tissues behave like muscle tissues which are avid for these AA (Harper *et al.* 1984), and this confirms results of other authors in the dog (Ferrannini *et al.* 1988; Abumrad *et al.* 1989). BCAA could be at the origin of the synthesis of ala in the gut wall and also be used for protein synthesis when combined with other AA taken up by the gut wall during their transport from the digestive lumen. Concerning NEAA, there was a large uptake of blood gln, which agrees with observations of Windmueller & Spaeth (1974, 1975) and Rérat *et al.* (1988*a, b*), and a smaller uptake of glu resulting in a low apparent absorption rate of the sum of the two AA; conversely, there was a marked synthesis of ala which appeared in the portal vein in amounts exceeding widely the dietary supply. Ala production proceeds from gln and glu metabolism (Pion *et al.* 1964; Windmueller & Spaeth, 1980) but probably also from the metabolism of BCAA and pyruvate as in muscle tissues (Felig, 1973; Chang & Goldberg, 1978). The origins of orn and cit synthesis in the gut cell wall have already been discussed (Rérat *et al.* 1988*a, b*). The exchanges of tau between the blood and the intestine resulted in a near zero balance, the uptake by the intestinal wall being equivalent to the appearance in the portal vein. On the contrary, in other species like sheep there is a net output of tau from portal-vein-drained viscera (Wolff *et al.* 1972).

The uptake of blood amino acids by the gut cell wall might indicate that there was a synthesis of proteins, the extent of which depends on the contribution of other sources of AA because some individual blood AA were poorly retained and could be limiting factors of this synthesis. It is rather difficult to estimate accurately this synthesis, generally considered as large, because in addition to the exchanges of AA between the gut cell wall and the blood there are also exchanges of serum proteins. Some of the blood serum proteins

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could be taken up and secreted into the digestive lumen where they are broken down; some serum proteins could also be synthesized from the absorbed end-products of exogenous and endogenous origin and secreted into the blood. It seems that in normal subjects the amounts of serum proteins catabolized or synthesized (Fauconneau & Michel, 1970) are low, but this emphasizes that accurate inter-organ balances must involve not only free AA but also circulating peptides and proteins.

The appearance of glucose in the portal vein was not modified by the type of infusate. As in former experiments performed in pigs given the same amount of glucose, sucrose or starch (Rérat *et al.* 1984), a percentage of the glucose, which was similar for the two solutions (about 20–30%), did not appear in the portal blood. As the appearance during the last 3 h was small, it may be assumed that the absorption was almost completed and that the lost amount (i.e. 107–138 g) was actually taken up directly by the gut wall during its transport by the intestinal cells or excreted into the hind-gut, which seems highly improbable. The hourly glucose uptake by the cell wall could, thus, be estimated to be 13–17 g/h, i.e. 250 mg/h per kg body-weight, which is ten times the estimates in the dog (Barrett *et al.* 1985).

Urea appeared in the portal blood during the entire experimental period whichever solution was used. However, when considering the whole intestinal urea balance the amount of urea delivered by the arterial blood to the intestinal wall and lumen was larger than the amount appearing in the portal blood. This type of exchange has already been reported (Rérat & Buraczewska, 1986). Blood urea uptake by the intestine is partly due to the free urea diffusion to the intestinal lumen (Ewe & Summerskill, 1965) and to its partial metabolism in the gut wall (Gibson *et al.* 1976). The appearance of urea in the portal vein may be due to the catabolism of part of the dietary arg (Windmueller & Spaeth, 1976) and partly to the reabsorption of urea excreted into the gut lumen. In the present case the total mean hourly uptake of urea by the intestine was about −0·5 g/h, which is in keeping with previous experiments (Rérat, 1986). The resulting uptake and absorption balance varied between −0·33 (PEP) and −0·18 (AAL) g/h.

Amounts of NH_3 appearing in the portal vein were a little lower than in a previous experiment (Rérat & Buraczewska, 1986). Absorbed NH_3 may originate from its production by the micro-organisms of the large intestine from dietary or endogenous nitrogenous residues such as urea (Salter, 1973), or by the gut wall from blood or dietary gln (Windmueller & Spaeth, 1975) through the action of glutaminase *EC*3.5.1.2 (McFarlane-Anderson *et al.* 1976).

There was a large appearance of lactate in the portal vein and a smaller appearance of pyruvate without any significant differences between the two solutions. It is well known that they are metabolites resulting from the 'anaerobic' catabolism of the intestinal tissues involving glutamine (Windmueller & Spaeth, 1974). The higher production (not significant) in the case of AAL infusion could be due to a higher gut metabolic rate already indicated by the larger uptake of BCAA.

Hepatic and peripheral balances

Amino acids. The experimental design makes it possible to differentiate the liver from the other organs of the splanchnic area (e.g. gut and spleen). As regards the peripheral tissues, the organs and tissues involved (e.g. muscle, brain, kidneys) are very heterogeneous so that the findings should be considered as a whole and the conclusions drawn with caution. It should also be underlined that exchanges of AA between tissues may take place in other chemical forms as liver-secreted proteins (McFarlane, 1964) or glutathion which, in some cases, could constitute more than 50% of the liver output of AA-N (Elwyn *et al.* 1968).

During the entire post-infusive period total absorbed ala as well as a high percentage of

other neoglucogenic AA were fully taken up by the liver: mainly gly, phe, tyr and ser after PEP infusion and, phe, ser and pro after AAL infusion. The total uptake of all neoglucogenic AA by the liver represented −75% (PEP)–−83% (AAL) of the infused amounts. In contrast, the well absorbed BCAA were only slightly retained by the liver, the mean for the three AA being −43% of absorbed amounts 8 h after PEP infusion and −35% after AAL infusion. These BCAA values are similar to those of Elwyn (1970) and higher than those of other authors who found in the dog that 15–20% (Barrett *et al.* 1986; Ferrannini *et al.* 1988) or even less (Bloomgarden *et al.* 1981) of the amounts appearing in the portal blood were extracted by the liver. However, this difference may be explained by the high level of AA intake in the dog, the absorption of which exceeds the small extraction capacities of these BCAA by the liver. Absorbed thr was also poorly taken up by the liver during this period, but only after PEP infusion (−46% of the amount absorbed *v.* −73% after AAL) which levelled out the differences due to the higher rate of thr absorption after PEP than after AAL infusion (68 *v.* 51%). In contrast, absorbed his, aromatic AA, met and lys were extracted by the liver at higher rates than the mean absorbed EAA mixtures, and at a higher rate for PEP (except met) than for AAL. This hierarchy agrees with that found by Elwyn (1970) and Barrett *et al.* (1986) in vivo and by McMenamy *et al.* (1962) in vitro. During the post-infusive period of 8 h the liver output of gln, asp and mainly glu was high after PEP infusion (19·5 g/8 h) and little less (not significant) after AAL infusion (12·4 g/8 h). These findings are completely divergent from those of Elwyn (1970) who found a high uptake of gln and a small release of glu in the dog. The 8 h balances did not take into account the events between the 1st and the 8th hour characterized by alternate uptakes and releases of AA. Accordingly, the true uptake and release were much higher than those reflected by this crude balance but can only be estimated with tracers.

The peripheral uptake of EAA for 8 h varied according to the individual AA studied. It was large for BCAA, corresponding to more than one-third of amounts infused for leu (mean −36%), and around half for val (mean −51%), ile showing a difference between PEP (−35%) and AAL (−18%). This peripheral uptake of BCAA is well documented (Harper *et al.* 1984). It probably includes incorporation of these AA into tissue proteins, as well as a simple transamination with release and oxidative metabolism of the keto acid analogue (Harper *et al.* 1984; Ferrannini *et al.* 1988). Some of the branched-chain keto acids are probably transferred to the liver for oxidation (Krebs & Lund, 1977; Livesey & Lund, 1980). Some EAA had a high uptake by peripheral tissues: arg (about one-third of infused amounts), lys (higher after PEP (−24%) than after AAL (−15%)), thr after PEP infusion (−20%) and met after AAL infusion (−18%); the uptake of some was lower: phe after PEP infusion (−9%) and tyr after the two infusions (−4%). Conversely, there was a release of thr and phe after AAL infusion, and neither uptake nor release of met after PEP infusion.

There was a large peripheral uptake of glu and asp and a lower output mainly of gln and ala but also of gly, cit and tau. It should be underlined that peripheral production of gln was underestimated because of renal catabolism for NH_3 production and excretion (Owen & Robinson, 1963; Welbourne *et al.* 1972). Peripheral disposal of glu and asp after meal intake is well documented (Elwyn, 1970; Wahren *et al.* 1976; Abumrad *et al.* 1982; Gelfand *et al.* 1986) as well as peripheral release of gln and ala (Aoki *et al.* 1976; Wahren *et al.* 1976; Abumrad *et al.* 1982). For ala Gelfand *et al.* (1986) found a peripheral uptake but it was after parenteral perfusion of an amino acid solution containing large amounts of this AA, which is not in keeping with the usual composition of the mixture of AA present in the arterial blood. Gly metabolism in the muscle results in either an output (Wahren *et al.* 1976) or an uptake (Gelfand *et al.* 1986). No significant movements were found for tau, cit and orn (Wahren *et al.* 1976; Abumrad *et al.* 1982). All these discrepancies may be explained

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by the large differences in experimental conditions (meal feeding *v.* infusion, nature of the infusate and species differences).

In the muscle ala- and gln-N is partly derived from BCAA (Galim *et al.* 1980; Golden, 1981; Haymond & Miles, 1982), but there is no explanation for the relative distribution of BCAA-N between these two compounds, and the possible mechanisms for their synthesis in muscle have been discussed (Harper *et al.* 1984). The source of carbon for synthesis of these compounds in the muscle has been debated: pyruvate from glycolysis (Felig, 1975; Goldberg & Chang, 1978), or plasma and tissue AA (Garber *et al.* 1976; Snell, 1980) in the case of ala probably, and primarily AA in the case of gln (Goldberg & Chang, 1978). Thus, the main result of peripheral tissue metabolism is the formation of carbon dioxide and branched-chain keto acids which represent a form of transfer of energy to the liver, and that of ala and gln which represent the 'shuttle' for transfer of BCAA-N from the peripheral tissues to the liver for urea formation (Mallette *et al.* 1969). Furthermore, gln is the source of NH_3 in the kidney (Welbourne *et al.* 1972) and an energy fuel for gut tissues (Windmueller & Spaeth, 1978, 1980).

Thus, the overall balance of free AA in the peripheral tissues within 8 h after the infusion was characterized by severe imbalances. The imbalance was less severe in the case of PEP (no met uptake) than in that of AAL (release of thr and phe, absence of NEAA uptake). This could mean that the two solutions were unable to promote peripheral protein synthesis unless some input of AA in a combined form was available to compensate for these imbalances. There might be a peripheral hydrolysis of the labile plasma proteins synthesized in the liver which could, thus, contribute to the inter-organ transport of AA and repletion of peripheral proteins (Elwyn, 1970). The possibility of a high rate of protein synthesis by the liver during the infusions is suggested by the comparative study of urea

Urea and NH_3. There was no difference in liver urea release during the experimental period, which was related to the solution infused into the duodenum. Urea production partly originates from the deamination of some EAA (Miller, 1962). As shown by Elwyn (1970) for most EAA, their uptake by the liver is greater than that required for liver protein synthesis, or their liver output is less than that required for protein breakdown, indicating that they are partly catabolized in the liver. In the present case the amount of urea produced in the liver (N 1·5–1·9 g/8 h) was small, which is in agreement with the level of urinary excretion of N in pigs of the same weight fed on 80 g protein/kg diet (Rérat & Henry, 1964). This low level of production could be explained by the preliminary fasting period and the relatively low level of N infusion. It is at variance with the imbalances of free AA in the peripheral tissues within 8 h which should result in an almost complete catabolism of infused AA and a high level of urea production by the liver. This low production of urea must, thus, be linked to a proper use of AA by the peripheral tissues, probably due to the peripheral input of blood-transported proteins synthesized by the liver.

According to Elwyn (1970) the rate of net protein synthesis or breakdown in the liver may be estimated by measuring the net non-catabolic AA metabolism from the differences between the liver uptake of TAA and NH_3-N and the output of urea-N. Even if this estimate suffers errors due to the determination of urea concentrations in the blood, it is considered that these errors would tend to cancel out over the total course of the experiment (Elwyn, 1970). In the present experiment these differences resulted in both cases in an 8 h uptake of 4·9 g N by the liver which, on the basis of the liver protein-N content calculated from the protein-AA pattern (Pion & Fauconneau, 1968), could mean about 35 g liver proteins. These findings are in agreement with the estimations of Elwyn (1970). They are in excess of the possible synthesis of liver proteins calculated from the percentage of EAA retained in the liver and available to build proteins, taking into account their limiting factors (Block & Mitchell, 1946), i.e. 63% with S-AA as limiting factors for PEP

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v. 60% with val for AAL. Furthermore, because of the absence of NEAA in the mixture retained in the liver after PEP infusion, transamination reactions must occur for the synthesis of NEAA which represent 44% of the liver proteins (Munro & Fleck, 1969). Taking into account all these findings relating to the liver-protein AA pattern, the possible synthesis of proteins by the liver during 8 h can be estimated to be 29 g (PEP) and 25 g (AAL).

The peripheral apparent balance is the result of the uptake and output of nutrients in the peripheral tissues. Since there is no important source of urea besides the liver, and since urea is not used by the tissues for their metabolism, the apparent uptake of urea by the peripheral tissues corresponds to urea excretion. In the present experiment the renal excretion for 8 h was higher (AAL 128%) or lower (PEP 54%) than the intestinal urea balance, but the amounts excreted by the kidney or taken up by the gut were not significantly different.

The NH_3 concentration was rather high in the portal blood but was zero in the systemic blood, which is in keeping with reports of other authors (Visek, 1972). This means that the absorbed NH_3 was completely taken up by the liver. This uptake could result in the formation of purines and pyrimidines and NEAA (Powers-Lee & Meister, 1988), particularly a part of the gln released by the liver (Jahoor, 1981). Liver conversion of NH_3 also results in the formation of urea (Powers-Lee & Meister, 1988).

Glucose, lactate and pyruvate. Hepatic uptake of glucose within 8 h represented about half the amount of glucose appearing in the portal blood, the rest being delivered to the peripheral tissues. This confirms that there is direct uptake of glucose by the liver during hyperglycaemia (Barrett *et al.* 1985). In the present case the contribution of the liver to glucose disposal was high in spite of the large amount infused (about 7 g/kg body-weight), which does not agree with the assumption that the relative contribution of the liver to total glucose tolerance is greater with smaller glucose loads (Madison *et al.* 1960). This hepatic glucose uptake was observed mostly during the first 5 h when the insulin production was at its highest rate in the same animals (A. Rérat and C. Simoes-Nunes, unpublished results) which favoured glycogenogenesis. Later there was a small apparent hepatic glucose release, which was observed in the same animals at the same time as higher glucagon production (A. Rérat and C. Simoes-Nunes, unpublished results), which favoured glycogenolysis. The delayed production of lactate by the liver could be due to a trend in liver metabolism towards glycolysis. Release of lactate was also observed after a glucose meal in the dog (Cherry & Crandall, 1937; Barrett *et al.* 1985). Part of liver pyruvate production could derive from glucogenic amino acids, and more directly from ala, ser and cys (Kaplan & Pitot, 1970), and another part from lactate derived from glucose metabolism in intestinal tissues and resulting in liver formation of glucose-6-phosphate and sugar nucleotides through the gluconeogenic pathway (Hellerstein & Munro, 1988). Thus, in the absence of an estimation of glycogen formation it seems difficult to appreciate the net movement of C substrates through the glucogenic and glycolytic pathways.

Glucose disposal by the peripheral tissues was large during the first hours when insulin production was high (A. Rérat and C. Simoes-Nunes, unpublished results) and decreased with time. After 8 h it represented −44% (PEP) and −47% (AAL) of the amounts appearing in the portal blood. In the present case its metabolism did not result in a release of pyruvate and lactate as emphasized by other authors (Elia *et al.* 1988; Kelley *et al.* 1988); in contrast these two metabolites were retained by the peripheral tissues in rather large amounts which confirms the muscle uptake of lactate observed after glucose ingestion (Jackson *et al.* 1987). Glucose is, thus, probably used for energy needs in these tissues (Kelley *et al.* 1988) and part of it might return to the liver in the form of alanine (Felig, 1973; Chang & Goldberg, 1978).

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In conclusion, the duodenal infusion of carbohydrate solutions containing mixtures of AA in the free form or as small peptides resulted in marked differences in the pattern of early AA absorption, these differences being smaller than in the absence of carbohydrate. At 8 h after infusion these differences were followed by large imbalances in the pattern of free AA taken up by the liver and mainly by peripheral tissues. The peripheral tissues were lacking free met after PEP infusion and showed a lack of NEAA and a release of thr and phe after AAL infusion. Thus, peripheral protein synthesis seems only to be possible with the contribution of some proteins synthesized by the liver. This protein synthesis by the liver could be estimated to be 25 g or more, but further studies should be performed to determine its capacity to balance the peripheral AA uptake.

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