

## Intestinal absorption and liver uptake of medium-chain fatty acids in non-anaesthetized pigs

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In order to study the rate of intestinal absorption and hepatic uptake of medium-chain fatty acids (MCFA), six growing pigs, mean body weight 65 kg, were fitted with a permanent fistula in the duodenum and with three catheters in the portal vein, carotid artery and hepatic vein respectively. Two electromagnetic flow probes were also set up, one around the portal vein and one around the hepatic artery. A mixture of octanoic and decanoic acids, esterified as medium-chain triacylglycerols, together with maltose dextrine and a nitrogenous fraction was continuously infused for 1 h into the duodenum. Samples of blood were withdrawn from the three vessels at regular intervals for 12 h and further analysed for their non-esterified octanoic and decanoic acid contents. The concentration of non-esterified octanoic and decanoic acids in the portal blood rose sharply after the beginning of each infusion and showed a biphasic time-course with two maximum values, one after 15 min and a later one between 75 and 90 min. Only 65% of octanoic acid infused into the duodenum and 54% of decanoic acid were recovered in the portal flow throughout each experiment. The amounts of non-esterified MCFA taken up per h by the liver were close to those absorbed from the gut via the portal vein within the same periods of time, showing that the liver is the main site of utilization of MCFA in pigs. These results have been discussed with a special emphasis laid on the possible mechanisms of the biphasic time-course of MCFA absorption and the incomplete recovery in the portal blood of the infused fatty acids.

Medium-chain triacylglycerols: Pig: Intestinal absorption: Liver

Medium-chain fatty acids (MCFA) ranging from eight to ten carbon atoms are known to be absorbed according to a pathway which in some respect differs from that of long-chain fatty acids (LCFA). During their transit through the digestive tract medium-chain triacylglycerols (MCT) are assumed to undergo a rapid hydrolysis by the gastric, salivary or pancreatic lipases, which is most likely due to their better solubility and motility at the lipid droplet interface compared with long-chain triacylglycerols (LCT) (Greenberger *et al.* 1966; Clark *et al.* 1969). MCFA are then transported as non-esterified fatty acids into the portal blood stream and reach the liver directly, providing an easy supply of energy to this organ (Hashim *et al.* 1964; Playoust & Isselbacher, 1964; Bernard & Carlier, 1981, 1984). For these reasons MCT emulsions are commonly used for the clinical treatment of patients with fat malabsorption, pancreatic deficiency (Galabert *et al.* 1975) or suffering from stomach or oesophagus diseases requiring a permanent enteral infusion. MCT diets are increasingly used because they also reduce the lipid deposition in the fat stores compared with that resulting from LCT diets under identical energy intake conditions (Crozier *et al.* 1987). However, no difference between MCT and LCT has ever been found in terms of N retention. Because of these particular findings, MCT are of great interest and further studies should be performed on their intestinal absorption and hepatic uptake.

In most previous reports on this subject the efficiency of MCT digestion was only determined by stool analysis which is an indirect method for evaluating the intestinal absorption potency. Only very few attempts have yet been made to determine directly the rate and efficiency of MCFA absorption (Bernard & Carlier, 1981, 1984) and the kinetics of hepatic MCFA uptake from the portal blood have not been described in any of the previous studies. Moreover, these studies do not take into account the possible interactions between MCFA and the other diet components.

These are the reasons why we carried out a study in conscious pigs fitted with a permanent fistula in the duodenum enabling the infusion of a complex mixture containing both a MCT-rich lipid fraction, a carbohydrate and a nitrogenous component. The appearance of non-esterified MCFA in blood from the portal vein, carotid artery and right hepatic vein was then recorded throughout a 12 h period after the beginning of the infusion. This device allowed us to determine the time-course and efficiency of MCFA intestinal absorption and hepatic uptake. The influence of the type of nitrogenous component (free amino acids or peptides) was also investigated.

## MATERIALS AND METHODS

### *Animals*

Six castrated Large White pigs (65 (SE 1) kg initial body weight) were used. They had been fed on a standard growing diet (UFAC, Limours, France). Under halothane anaesthesia each animal was fitted with three catheters in the portal vein, carotid artery and one branch of the right hepatic vein respectively, and with two electromagnetic flow probes, one around the portal vein and one around the hepatic artery. A permanent fistulation was also set up in the duodenum. All these surgical techniques have already been described (Rérat *et al.* 1980; Simoes-Nunes *et al.* 1989).

### *Infusion mixtures*

Two infusion mixtures differing only by their nitrogenous fraction were used, i.e. either a peptide mixture (PEP) or a free amino acid mixture of the same composition as PEP; these mixtures have been described elsewhere (Rérat *et al.* 1988).

Each infusion mixture contained in a 2 litre total volume, 110 g nitrogenous fraction, 440 g maltose dextrine, 110 g of a MCT-rich lipid fraction described in Table 1. The MCT used contained octanoic and decanoic acids. Each mixture was supplemented with vitamins and trace elements. All these compounds were supplied by Sopharga (Puteaux, France).

### *Experimental design and infusion technique*

After a 1 week recovery period from surgery each animal was submitted to two successive 12 h experiments at 8 d intervals. During the interval pigs were fed orally on the previously mentioned growing diet. From one animal to the next a permutation of the nitrogenous component was used; thus, the first infusion was composed of PEP for three animals, and free amino acids for the other three. Each experiment was preceded by an 18 h fast. At the beginning of each experiment the infusion mixture was prepared extemporaneously; the lipid fraction was stirred with water for 3 min at a temperature decreasing progressively from 75° to 50°; the carbohydrate and nitrogenous fractions were then incorporated into the lipid emulsion at 30°. A sample was withdrawn from the mixture to control homogeneity. The warm (30°) stirred mixture (2 litres) was then continuously infused into the duodenum for 1 h through the permanent fistula. Blood samples (4 ml) were withdrawn from each vessel at 15 min intervals during the first 2 h after the beginning of infusion,

Table 1. *Composition of the lipid fraction in the infused mixture and its fatty acid pattern*  
(Values are expressed as g/100 g total lipids)

Composition of the lipid fraction	
Medium-chain triacylglycerols*	37.33
Evening Primrose ( <i>Oenothera biennis</i> L.) oil	24.20
Soya-bean oil	16.20
Glycerol monostearate	9.00
Ascorbyl palmitate	0.07
Soya-bean lecithin	13.20
Fatty acid composition of the lipid fraction	
Octanoic acid	28.8
Decanoic acid	11.7
Myristic acid	0.6
Palmitic acid	5.7
Stearic acid	4.3
Oleic acid	6.2
Linoleic acid	24.5
Linolenic acid	1.6

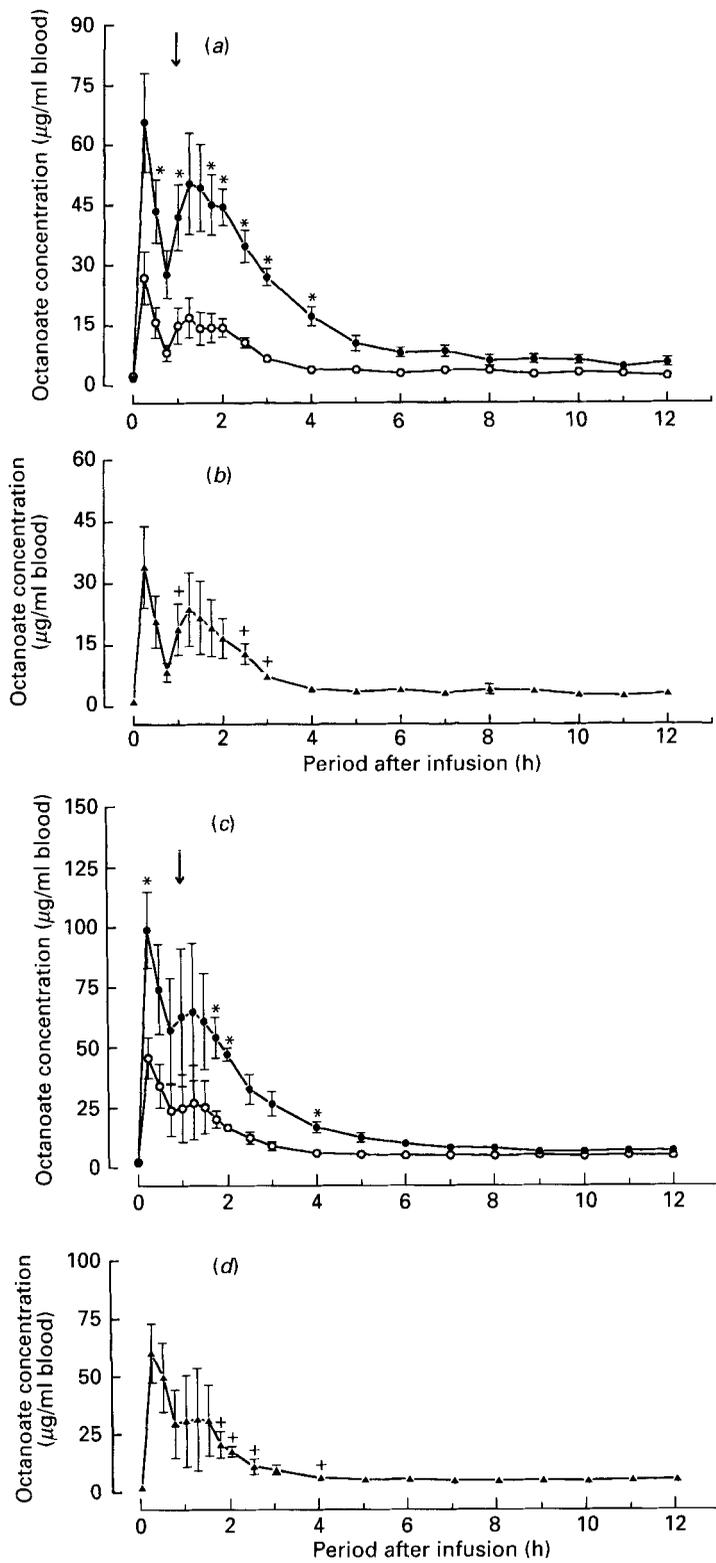
\* Octanoate and decanoate, obtained from Copra oil, were randomly esterified on the glycerol moiety.

every 30 min during the 3rd hour and every hour until the 12th hour, and poured into heparinized tubes. Blood plasma samples were prepared by centrifugation and stored at  $-80^{\circ}$  until assay. Packed cell volume was also measured every 2 h and portal and arterial flow rates were recorded continuously.

#### *Analytical methods*

Because of the volatility of octanoic acid and to a lesser extent that of decanoic acid, an extraction procedure using hexane-propan-2-ol (Hara & Radin, 1978; Wolff & Castera-Rossignol, 1987) avoiding any evaporation step was developed in our laboratory.

Each plasma sample (1 ml) was stirred for 15 min with 5 ml of a hexane-propan-2-ol mixture (3:2, v/v) and 50  $\mu\text{g}$  (in 50  $\mu\text{l}$  hexane-propan-2-ol solution) of nonanoic acid as an internal standard. After centrifugation for 3 min the two resultant phases (organic and aqueous) were simultaneously dried over anhydrous  $\text{Na}_2\text{SO}_4$  placed in a glass funnel; 0.5 ml of the resulting homogeneous organic solution was then applied over a 150 mm line to a thin-layer chromatoplate coated with silicagel H (Merck) and allowed to migrate using a hexane-diethyl ether-acetic acid solvent (57:41:2, by vol.). The non-esterified LCFA were revealed by iodine vapour. As the amounts of non-esterified MCFA were too low to be easily revealed and as preliminary assay had shown that they were located about 10 mm below the LCFA band, this band and the area 20 mm below it were both scraped off the plate and eluted together with 4 ml of a pentane-butanol mixture (3:2, v/v). This solution was then added to 100  $\mu\text{l}$  pure  $\text{H}_2\text{SO}_4$  and refluxed for 1 h (Clément & Bézard, 1961). The butyl esters were then extracted with pentane and analysed on a Gira gas-liquid chromatograph equipped with a 30 m cyanopropyl-polysiloxane capillary column (J & W Scientific, Folstom, CA, USA), at a helium flow rate of 1 ml/min. The temperature was maintained for 3 min at  $80^{\circ}$  and then increased to  $190^{\circ}$  at a rate of  $4^{\circ}/\text{min}$ . According to preliminary assay using pure octanoic and decanoic acids or  $[1-^{14}\text{C}]$ octanoic acid, the fatty acid recovery was higher than 96% in our experimental conditions. The plasma concentrations were corrected using the packed cell volume coefficient and the results expressed in  $\mu\text{g}/\text{ml}$  blood.



*Calculations*

The net appearance of MCFA (octanoic or decanoic acid) in the portal circulation was calculated, after concentration correction by the packed cell volume coefficient, by the formulas of Rérat *et al.* (1980):

$$q_i = (Cp_i - Ca_i) \cdot D_i \cdot t, \quad Q_n = \sum_{i=0}^{i=n} q_i,$$

and the hepatic uptake by the formulas of Simoes-Nunes *et al.* (1989):

$$\begin{aligned} \text{hepatic input} \quad h_i &= (Cp_i \cdot D_i + Ca_i \cdot A_i) \cdot t, \\ \text{hepatic output} \quad o_i &= Chv_i \cdot (D_i + A_i) \cdot t, \quad R_n = \sum_{i=0}^{i=n} r_i, \\ \text{hepatic uptake} \quad r_i &= h_i - o_i, \end{aligned}$$

where  $q_i$  is the amount of MCFA absorbed via the portal vein within a time unit  $t$  of 5 min during which all concentrations and flows are considered as constant;  $Q_n$  is the total amount of MCFA absorbed during  $n$  time units;  $Cp_i$ ,  $Ca_i$  and  $Chv_i$  the portal, arterial and hepatic vein blood concentrations respectively of MCFA;  $D_i$ ,  $A_i$ , the portal and hepatic artery flow rates, respectively;  $r_i$ , the amount of MCFA taken up by the liver during a time unit  $t$  of 5 min;  $R_n$ , the total amount of MCFA taken up by the liver during  $n$  time units.

In all Figs., values are expressed as means with their standard error of the mean. Differences between two variables (for example, MCFA concentration in the portal blood compared with that in the arterial blood) have been studied on a within-animal basis by comparing their mean value to zero using paired Student's  $t$  test (Snedecor & Cochran, 1967). A Bonferroni's procedure has been used to take into account the great number (twenty time-points for the quoted example) of  $t$  tests made (Miller, 1966).

RESULTS

*Blood flows in the portal vein and the hepatic artery*

Blood flows showed relatively constant values before and during the experiments and they were not modified by the infusion. The mean values were 2442 (SE 105) and 502 (SE 32.5) ml/min in the portal vein and the hepatic artery respectively showing that the portal flow represented 83 (SE 8.5)% of the total flow through the liver.

*Blood concentration of octanoic and decanoic acids*

The blood concentrations of non-esterified octanoic and decanoic acids from the three vessels studied (i.e. portal vein, carotid artery and hepatic vein) *v.* time were plotted in Figs. 1 and 2. Just before each infusion all basal concentrations were very low. The portal concentrations of the two MCFA rose sharply after the beginning of the infusion, reaching

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Fig. 1. Variations in octanoate concentration in the portal blood (●), arterial blood (○) and hepatic vein blood (▲) of non-anaesthetized pigs *v.* time-interval after infusion. Concentrations were determined after a duodenal infusion (during 1 h) of octanoic and decanoic acids esterified as medium-chain triacylglycerols, together with maltose dextrine and a nitrogenous fraction, i.e. either free amino acids (*a* and *b*) or peptides (*c* and *d*). ↓, End of the infusion. Values are means with their standard errors represented by vertical bars for six animals. \*†The statistical significance of the within-animal differences between portal and arterial blood concentrations and portal and hepatic venous blood concentrations respectively was determined by paired Student's  $t$  test:  $P < 0.05/k$  ( $k$ , twenty time-points). For details of procedures, see pp. 432–433.

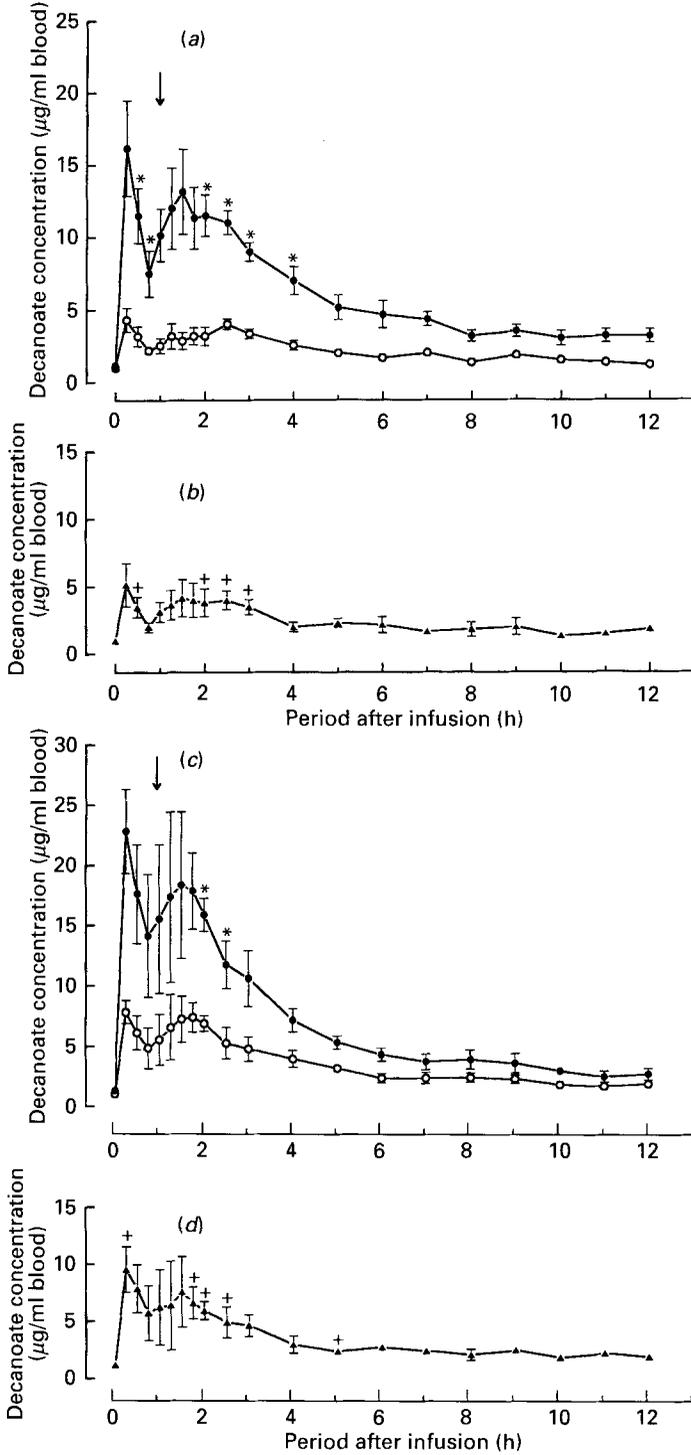


Fig. 2. Variations in decanoate concentration in the portal blood (●), arterial blood (○) and hepatic vein blood (▲) of non-anaesthetized pigs *v.* time-interval after infusion. Concentrations were determined after a duodenal infusion (during 1 h) of octanoic and decanoic acids esterified as medium-chain triacylglycerols, together with maltose dextrine and a nitrogenous fraction, i.e. either free amino acids (*a* and *b*) or peptides (*c* and *d*). ↓, End

maximal values that were 68 (SE 19) and 17 (SE 4) times higher than the basal concentrations for octanoic and decanoic acids respectively after 15 min. They decreased between 15 and 45 min, increased again to a maximum later (between 75 and 90 min) and then progressively decreased until the end of the experiment. Whatever the time-interval, the concentration of octanoic acid was higher than that of decanoic acid, particularly during the first 2 h when the former was about three times higher than the latter. This difference is consistent with the higher amount of octanoic acid infused as MCT (Table 1).

The concentrations of the two MCFA in the carotid and the hepatic vein blood samples showed variations with time similar to those encountered in the portal vein, but remained at a much lower level. The within-animal differences between the portal and arterial blood concentrations were significant (several significant differences,  $P < 0.05$ : twenty time-points, were obtained using the Bonferroni's corrected  $t$  test procedure) showing a direct absorption of MCFA from the gut. The differences between the portal and hepatic vein blood concentrations of MCFA were also significant, according to the same criterion. On the other hand, the blood concentration of MCFA in the hepatic vein was always very close to that in the artery whatever the time (the differences were not significant), suggesting that the liver removed a major proportion of MCFA present in the portal blood.

When comparing the results obtained with the two nitrogenous sources (free amino acids or peptides), there was no significant difference between the blood MCFA concentrations in any of the three vessels and at any time-interval after the beginning of the infusion.

#### *Amounts of MCFA absorbed from the gut and taken up by the liver*

On the basis of the blood MCFA concentrations and blood flow measurements it was possible to calculate the amounts of non-esterified MCFA absorbed per h via the portal vein and/or taken up by the liver during the same intervals of time. These results are shown in Figs. 3 and 4.

Portal MCFA absorption was highest during the first 2 h, resulting directly from the occurrence of the two concentration peaks in the portal blood within the first and the second hours respectively, as already shown in Figs. 1 and 2. It then decreased rapidly until 6 h and very slowly thereafter. About 50% of the total amount absorbed appeared in the portal vein within 3 h, and 80% within 6 h, whatever the type of mixture used (free amino acids or peptides). However, at the end of each experiment, i.e. 12 h after the beginning of the infusion, only 65% of the total quantity of octanoic acid infused as MCT was recovered in the portal blood as non-esterified fatty acid. The corresponding value for decanoic acid was 54%. In spite of an apparently higher absorption rate of MCFA with the PEP mixture than with the free amino acid solution during the first 2 h, the differences were not significant. The percentages quoted may slightly underestimate the total MCFA absorption, since minor, hardly detectable, amounts of MCFA were still being absorbed during the last hour of the experiment.

The amounts of non-esterified octanoic acid and decanoic acid taken up by the liver per h represented 80–100% of those absorbed from the gut via the portal vein in the same periods of time (non-significant differences). The total liver uptake in both experiments (free amino acid or peptide mixture) amounted at least to 90% of the intestinal absorption through the portal vein. It may be pointed out that the liver uptake efficiency seemed slightly lower during the first 2 h after the beginning of the infusion, when the portal concentration of MCFA showed the highest values.

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of the infusion. Values are means with their standard errors represented by vertical bars for six animals. \*†The statistical significance of the within-animal differences between portal and arterial blood concentrations and portal and hepatic venous blood concentrations was determined by paired Student's  $t$  test:  $P < 0.05/k$  ( $k$ , twenty time-points). For details of procedures, see pp. 432–433.

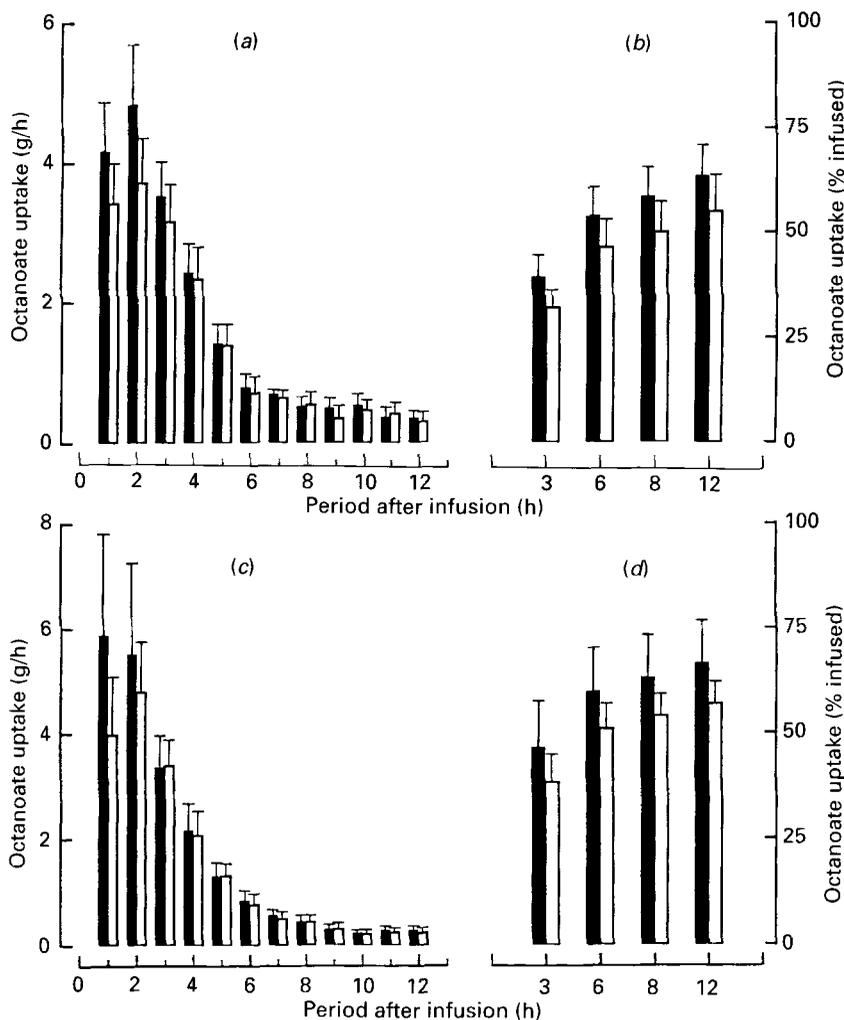


Fig. 3. Intestinal absorption (■) and liver uptake (□) of octanoate after the duodenal infusion of octanoic and decanoic acids esterified as medium-chain triacylglycerols together with maltose dextrine and a nitrogenous fraction, i.e. either free amino acids (*a* and *b*) or peptides (*c* and *d*); *a*, *c*, hourly intestinal absorption and liver uptake (g/h); *b*, *d*, cumulated amounts as a percentage of infused quantity. Values are means with their standard errors represented by vertical bars for six animals. For details of procedures, see pp. 432–433.

#### DISCUSSION

The present study on MCFA absorption, carried out for the first time in pigs, shows that the infusion of an octanoic and decanoic-rich triacylglycerol emulsion into the duodenum led to a rapid appearance of non-esterified octanoic and decanoic acids in the portal blood. The results confirm those previously obtained in dogs (Hashim *et al.* 1964; Bézard *et al.* 1966) and rats (Playoust & Isselbacher, 1964; Greenberger *et al.* 1966). This rapid absorption in the portal vein can be explained by (1) a rapid intraluminal hydrolysis of MCT, compared with LCT, by the pancreatic lipase (Entressangles *et al.* 1961; Greenberger *et al.* 1966), whatever the position of MCFA on the glycerol moiety (Entressangles *et al.* 1964); (2) a greater solubility of MCFA in an aqueous medium which would facilitate their

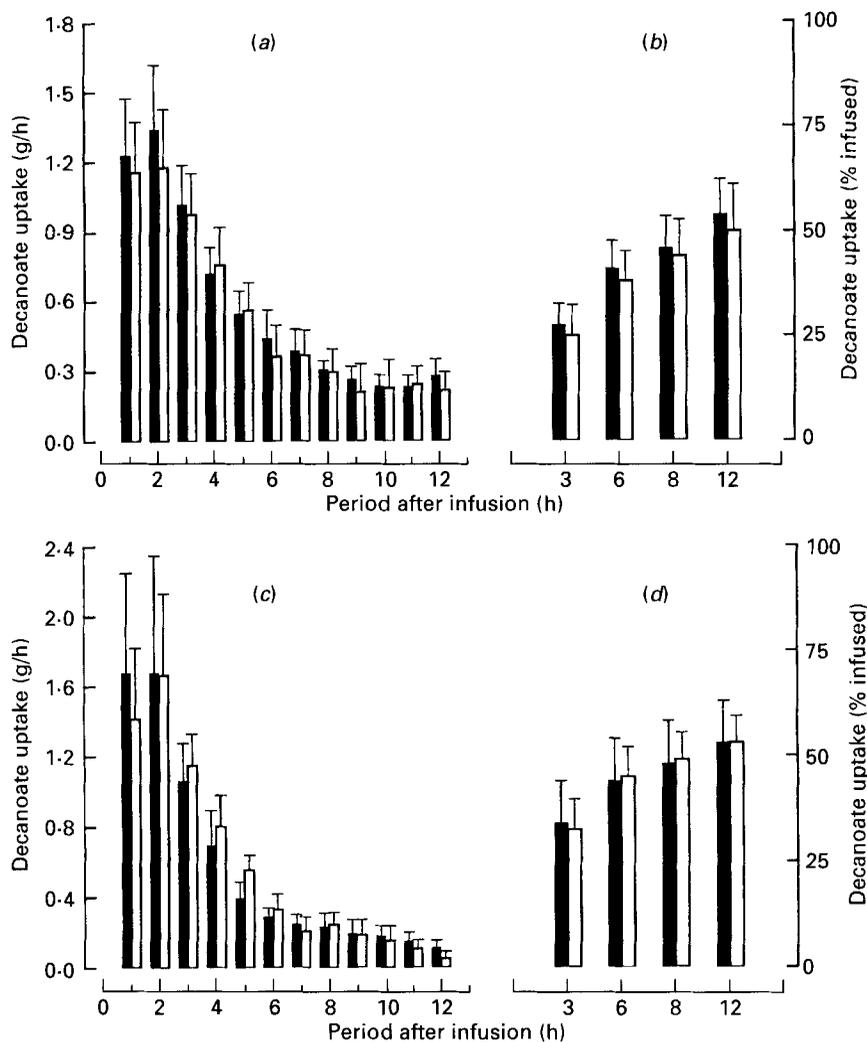


Fig. 4. Intestinal absorption (■) and liver uptake (□) of decanoate after the duodenal infusion of octanoic and decanoic acids esterified as medium-chain triacylglycerols together with maltose dextrine and a nitrogenous fraction, i.e. either free amino acids (a and b) or peptides (c and d); a, c, hourly intestinal absorption and liver uptake (g/h); b, d, cumulated amounts as a percentage of infused quantity. Values are means with their standard errors represented by vertical bars for six animals. For details of procedures, see pp. 432-433.

uptake by the intestinal mucosa and (3) a lower affinity of the intestinal fatty acid-binding protein (Ockner *et al.* 1972) and of acyl-CoA synthetase (*EC* 6.2.1.3) (Brindley & Hübscher, 1966) for MCFA compared with LCFA, which would then limit their re-esterification and incorporation into chylomicron triacylglycerols (Dawson & Isselbacher, 1960; Fernando-Warnakulasuriya *et al.* 1983).

The blood concentration of both MCFA in the portal vein showed a first maximum within 15 min, then a second one between 75 and 90 min. These fluctuations were not caused by corresponding variations in blood flows since all of them remained fairly constant throughout each experiment. In previous work in rats (Bernard & Carlier, 1981, 1984) a duodenal injection of tritiated decanoic acid was followed by variations of its concentration in the portal blood very similar to those found in our own experiments

during the short period (45 min) after the beginning of MCT infusion. The first MCFA concentration peak in the portal blood (after 15 min) observed in the present study could be due to the direct absorption of non-esterified octanoic and decanoic acids released after MCT hydrolysis in the intestinal lumen. However, this interpretation is only tentative and further research should be performed. A later MCFA concentration peak in the portal blood was repeatedly observed in the six experimental animals and is clearly evident in the mean curves reported in Figs. 1 and 2. This second peak might be due to another absorption mechanism of MCT. Several previous studies (Playoust & Isselbacher, 1964; Greenberger *et al.* 1966; Clark & Holt, 1968) carried out in pancreatic-deficient rats have brought both direct and indirect evidence of a possible intestinal absorption of MCT as such in the intestinal epithelial mucosa. As a microsomal lipase has already been reported in the enterocyte (Serrero *et al.* 1975), an alternative route for absorption of MCT, including their direct transport into the enterocyte, the subsequent intracellular hydrolysis and the secretion of MCFA into the portal vein, may be hypothesized. Whether this alternative pathway may contribute to the occurrence of the later absorption peak observed in our experiments is tested at the present time in pancreatic-deficient pigs and will be described in a forthcoming paper.

If we compare the total amounts of MCFA infused as MCT with those recovered as non-esterified fatty acids in the portal vein, the mean recovery values reached 65% for octanoic acid and 55% for decanoic acid, at the end of each experiment. This partial recovery may be due to various factors. First, the intraluminal hydrolysis of MCT could have been incomplete because of their direct introduction into the duodenum, thus bypassing the gastric hydrolysis. In animals fed orally, the gastric hydrolysis of MCT plays an important role, both directly in the stomach (Clark *et al.* 1969; Cohen *et al.* 1971; Egelrud *et al.* 1971; Aw & Grigor, 1980) and indirectly in the duodenum, since the non-esterified fatty acids released in the stomach and reaching the duodenum increase the activity of the lipase-colipase complex (Gargouri *et al.* 1986). However, to test this hypothesis it was not possible to analyse the duodenal content in our non-anaesthetized animals. A second, more reliable reason for this incomplete recovery is the metabolism of the enterocyte. Experiments *in vitro* in rats (Greenberger *et al.* 1965) demonstrated that MCFA are actively oxidized in the intestinal mucosa. Following an infusion of labelled decanoic acid into a rat intestinal loop, up to 5.6% of the radioactivity was recovered as acid-soluble catabolic products in the portal vein within a 1 h period (Bernard & Carlier, 1984). The chylomicron route should also be envisaged. Several experiments performed in milk-fed rats showed that the triacylglycerols of lymph lipoproteins contained 1 and 8% octanoic and decanoic acids respectively (Fernando-Warnakulasuriya *et al.* 1981, 1983). These results are consistent with values reported by Bloom *et al.* (1951) and Hyun *et al.* (1967) showing that after a duodenal infusion of labelled octanoic or decanoic acid in rats mean values representing 2 and 11% respectively of the radioactivity infused were recovered in lymph lipids. However, in these experiments it was not determined whether MCFA had been incorporated as such or after an elongation step or had first been oxidized to labelled acetate units used for further synthesis of LCFA. All these reports show that a minor fraction of octanoic acid and a more substantial fraction of decanoic acid would probably follow the lymph absorption route, which would explain the lower recovery of decanoic acid in the portal blood observed in the present experiment.

In our study each animal was successively submitted to two infusions that differed only in the type of nitrogenous component used (either free amino acids or peptides). The results obtained were very similar. Although the PEP mixture seemed to increase the MCFA absorption rate during the first 2 h after the start of the infusion, the small differences between the two time-courses of MCFA concentration in the portal blood and between

absorption rates were not significant. We were not able to show any interaction between the nitrogenous component and MCFA absorption.

Our results clearly demonstrate that in pigs the liver takes up almost the whole flux (80–100%) of non-esterified octanoic and decanoic acids from the gut via the portal vein. They confirm the findings of Hashim *et al.* (1964) and of Bézard *et al.* (1966) in dogs and those of Bézard & Monneret-Boquillon (1966) in the infused rat liver. Interestingly, in the latter experiment 2–5% of the amount of octanoic acid taken up by the liver was incorporated into the liver triacylglycerols while the corresponding value was 40% for decanoic acid. MCFA are known to be easily oxidized in the liver of several animal species (McGarry & Foster, 1971; Pégorier *et al.* 1989). However, isolated hepatocytes from newborn or 15-d-old piglets oxidize octanoic acid poorly (Pégorier *et al.* 1983), in contrast to newborn animals of other species such as rats or rabbits (Ferré *et al.* 1983; Pégorier *et al.* 1989). To our knowledge, no information on this subject has been published concerning growing or adult pigs.

Our study has shown that the liver is the main site of MCFA utilization in pigs and suggests that a substantial proportion of these acids may also be utilized in the intestinal mucosa. Further investigations are needed to determine the pathway preferentially followed by MCFA in these tissues, especially with a view to their use as MCT in pig feeding, but also for a better assessment of the role of MCFA in human nutrition on the basis of such studies using the pig as a model.

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