Does the fatty acid profile of dietary fat influence its trophic effect on the small intestinal mucosa?

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Abstract

To compare the enterotrophic effects of different triglycerides, five groups of eight rats were fed mixed diets giving 50% of calories as oils rich in either essential fatty acids (EFA), α -linolenic acid, fully saturated fatty acids, oleic acid, or medium chain fatty acids. After 21–24 days there were no significant differences between the groups in overall small intestinal whole gut weight, mucosal weight, or mucosal DNA; overall mucosal protein showed slight variation ($p < 0.05$) that was compatible with differences in food intake between the groups. However, long chain triglycerides (LCT) and medium chain triglycerides (MCT) differed in their regional effects on cell proliferation; all four LCT rich diets increased mucosal mass and cell proliferation maximally in the mid small intestine, while MCT had their greatest effect proximally. Subsequently, two groups of eight rats were fed diets in which EFA or MCT were given as twice daily boluses (29% of dietary calories) for 20 to 23 days and compared with a third group of eight rats receiving a glucose rich, low fat diet. EFA and MCT boluses increased the overall parameters of small intestinal mucosal mass and for both oils the effects were now maximal in the mid small intestine. Thus different triglycerides have similar effects on overall small intestinal mucosal mass, but MCT differ from LCT in their regional effects on mucosal cell proliferation when they are given in mixed diets, although not when given as boluses.

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The presence of food within the lumen maintains small intestinal mucosal structure and function, and this process has been called luminal nutrition.¹ It has been suggested that dietary long chain triglycerides (LCT) are particularly potent enterotrophic agents^{2–4} but we have shown that the enterotrophic effects of an oil rich in polyunsaturated fatty acids depend on how the oil is administered.^{5,6} Thus, when the oil is given to rats as part of a mixed diet over the course of 24 hours, it does not increase the overall mucosal mass of the small intestine relative to the effects of a diet rich in glucose substituted for the fat,⁵ while given in bolus doses it increases overall small intestinal mucosal mass compared with isocaloric amounts of the oil or glucose in a mixed diet.^{6,7} This enhanced enterotrophic effect of bolus doses of LCT may be caused by the release of an enterotrophic peptide from the distal gut.⁸

LCT also affect the distribution of mucosal mass and cell proliferation along the length of the small intestine, regardless of how they are

administered. Thus diets rich in LCT stimulate mucosal proliferation maximally in the mid small intestine, while glucose rich diets stimulate cell proliferation proximally.⁵ These differences may be explained by differences in the sites of absorption of glucose and lipid, with mucosal cell proliferation being most stimulated at the absorption sites of luminal nutrients.⁸ This implies that it is essential to make measurements of the whole small intestine when comparing high and low fat diets.

Earlier studies using mixed diets suggested that the relative enterotrophic effects of different LCT may vary.^{9–12} However, the findings have been inconsistent between experiments, and in each case measurements have been confined to short segments of proximal jejunum or distal ileum, or both, with no attempt made to measure changes in the mid small intestine or to assess the distribution of mucosal mass along the small intestine. Other studies have more consistently found that medium chain triglycerides (MCT), given either in mixed diets or by intraluminal infusion, exert a reduced enterotrophic effect compared with LCT,^{2,3,13} but again there has been little emphasis on the effects of the MCT on the distribution of mucosal mass along the length of the small intestine.

To clarify the relative enterotrophic actions of different triglycerides, five different oils were given initially in mixed diets and their effects on both the overall mass of the small intestine and on the distribution of mass along the small intestine were compared. Subsequently the enterotrophic effects of bolus doses of LCT and MCT were compared.

Methods

EXPERIMENT I

Five groups of eight female Wistar Rats (180–215 g) were fed mixed powder diets giving 50% of total calories as lipid, 35% calories as glucose, and 15% calories as an amino acid mixture (Albumaid Complete, Scientific Hospital Supplies Ltd, Liverpool, United Kingdom). All diets were supplemented equally (2.24 g/100 kcal) with a vitamin/mineral mixture (Special Diets Services Ltd, Essex, United Kingdom).

The nature of the lipid included in the diet varied with each group and the following oils and oil mixtures were used; Efamol (Scotia Pharmaceuticals Ltd, Surrey, United Kingdom; EFA), a 50% Efamol; 50% linseed oil (Hilton Banks Ltd, Surrey, United Kingdom) (w/w) mixture (LIN), a 98% coconut oil (Sigma Ltd, Dorset, United Kingdom); 2% Efamol (w/w) mixture (SAT), olive oil (Sigma Ltd; OA), and a 98% MCT oil (Mead Johnson Nutritionals,

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TABLE I Composition of the oils

Fatty acid	Composition (% by weight)				
	EFA	LIN	SAT	OA	MCT
6:0 caproic acid	—	—	—	—	2.9
8:0 caprylic acid	—	—	8.9	—	66.66
10:0 capric acid	—	—	5.9	—	23.5
12:0 lauric acid	—	—	47.0	—	4.9
14:0 myristic acid	—	—	17.6	—	—
16:0 palmitic acid	5.5	5.8	8.9	9.5	0.1
18:0 stearic acid	2.0	2.5	2.0	2.0	0.04
18:1 oleic acid	8.5	14.2	0.2	83.5	0.2
18:2 linoleic acid	75.0	45.5	1.5	4.0	1.5
18:3 γ linolenic acid	9.0	4.5	0.2	—	0.2
18:3 α linolenic acid	—	27.5	—	—	—
20:0 arachidic acid	—	—	2.9	1.0	—
Other	—	—	4.9	—	—

EFA=Efamol, LIN=50% Efamol/50% linseed oil, SAT=98% coconut oil/2% Efamol, OA=olive oil, MCT=98% medium chain triglyceride oil/2% Efamol.

Middlesex, United Kingdom): 2% Efamol (w/w) mixture (MCT). Efamol is rich in linoleic acid, linseed oil in α -linolenic acid, coconut oil in fully saturated fatty acids, and olive oil in oleic acid; the final compositions of the oils and oil mixtures are shown in Table I.

The animals were kept to a 12 hour light (07.00 to 19.00 hours): 12 hour dark cycle at an ambient temperature of 21–22°C. They were housed individually in cages with wire bottoms to reduce coprophagia and were allowed tap water *ad libitum*. The diets were delivered from low spillage glass containers¹⁴ and all the animals were allowed to feed from these *ad libitum*. Food intake was measured on a daily basis.

Two rats from each group were killed by overdose of inhaled halothane between 09.00 and 14.00 hours on each of four successive days, 21 to 24 days after the start of the experiment. Food was withdrawn at 23.00 hours the day before sacrifice and the animals were given intraperitoneal vincristine sulphate (Lilly France SA, Fegersheim, France; 1.0 mg/kg body weight) exactly 2 hours before being killed in order to measure crypt cell proliferation from the accumulation of vincristine arrested metaphases.

The small intestine, including part of the duodenum, was removed from the duodenal papilla to the ileocaecal valve. Its length was measured under 10g vertical tension and the intestine divided into three segments of equal length (proximal, middle, and distal). One cm samples for subsequent counting of arrested metaphases were taken from the proximal end, midpoint, and distal end of the proximal segment, and the midpoints and distal ends of the middle and distal segments; that is at distances 0%, 17%, 33%, 50%, 66%, 82%, and 100% along the length of the removed small intestine. The segments of small intestine were then flushed

with ice cold 0.9% sodium chloride solution followed by air. Adherent fragments of mesentery were carefully dissected free and the segments were weighed to give an estimate of the whole gut weight. The mucosa was gently blotted with tissue paper, scraped off with a glass slide, weighed and frozen at –20°C for subsequent determination of protein and DNA content.^{15,16}

The 1 cm samples of small intestine were slit open longitudinally and orientated mucosal side uppermost on small pieces of card. They were fixed in Carnoy's fluid and stored in 70% aqueous ethanol (v/v). A portion of each sample was bulk stained using the Feulgen reaction. The 2 hour accumulation of vincristine arrested metaphases was counted in 10 randomly selected, microdissected crypts,¹⁷ and the mean was calculated.

In addition to the small intestine, the pancreas was dissected free from its mesentery and its wet weight was determined.

EXPERIMENT 2

Two groups of eight female Wistar rats (190–220 g) were fed diets giving 48.2% of total calories either as twice daily intragastric 1.5 ml bolus doses of LCTs (Efamol, EFA; 8.4 kcal/ml), or twice daily 1.7 ml bolus doses of a 98% MCT oil: 2% Efamol mixture (MCT; 7.6 kcal/ml). After two days, the doses of EFA and MCT were respectively reduced to 0.9 ml and 1.0 ml twice daily, giving 29% of total calories as fat. The remaining calories were provided by a mixture of glucose (56% total calories) and amino acids (15% total calories) given separately. A third group of eight rats (190–220 g) was fed a mixed diet containing 1.2% Efamol, 15% amino acids, and 83.8% glucose. The final compositions of the three diets are shown in Table II and all rats were given a total of 52 kcal/day. As in experiment 1, the three diets were supplemented equally with vitamin/mineral mixture (2.24 g/100 kcal).

Two rats from each group were killed on successive days, 20 to 23 days after the start of the experiment and between 09.00 and 14.00 hours. On the day before sacrifice each animal was given half its normal intake of diet including oil.

As described for experiment 1, the small intestine was removed and divided into three equal length segments. The whole gut weight, mucosal weight, and mucosal protein and DNA were measured. The pancreas was also removed and weighed.

STATISTICAL METHODS

Between group comparisons of energy intake, weight gain, small intestinal length, small intestinal mass parameters, and pancreas weight were made using one way analysis of variance. If significant differences were found, individual comparisons were made using Student's unpaired *t* test. The effects of diet on 2 hour metaphase accumulation in experiment 1 were analysed using a repeated measures analysis of variance.¹⁸ The results are expressed as mean (SEM), unless otherwise indicated.

TABLE II Composition of the diets used in experiment 2

	Composition (% total calories)		
	EFA bolus	MCT bolus	Glucose diet
Efamol	29.0	—	1.2
MCT	—	29.0	—
Glucose	56.0	56.0	83.8
Amino acids	15.0	15.0	15.0

EFA=Efamol, MCT=98% medium chain triglyceride oil/2% Efamol mixture.

Results

EXPERIMENT I

Analysis of variance showed that there was a small but significant variation between the

TABLE III Effect of diet on daily energy intake, rat weight gain, and small intestinal length (Values mean (SEM); $n=8$)

	EFA	LIN	SAT	OA	MCT	ANOVA
Daily energy intake (kcal/rat)	54.5 (1.2)	55.7 (1.1)†	56.3 (0.9)‡	51.7 (1.1)*	54.0 (1.2)	$p<0.05$
Rat weight gain (g)	23.6 (3.2)	23.5 (4.2)	25.6 (2.5)	20.1 (2.4)	19.5 (3.4)	NS
Small intestinal length (cm)	106.1 (2.0)	106.8 (1.6)	108.9 (1.2)	107.6 (2.1)	107.4 (1.0)	NS

Student's t tests: *versus † $p<0.05$, *versus ‡ $p<0.01$.

TABLE IV Effect of diet on overall small intestinal whole gut weight, mucosal weight, and mucosal protein and DNA (Values mean (SEM); $n=8$)

	EFA	LIN	SAT	OA	MCT	ANOVA
Overall whole gut weight (mg/cm)	46.37 (1.25)	47.23 (1.39)	51.31 (1.57)	45.61 (1.15)	48.51 (1.80)	NS
Overall mucosal weight (mg/cm)	15.27 (0.63)	15.66 (0.68)	16.83 (0.91)	14.71 (0.66)	16.44 (1.19)	NS
Overall mucosal protein (mg/cm)	2.31 (0.13)	2.12 (0.08)‡	2.69 (0.14)*	2.22 (0.09)†	2.38 (0.17)	$p<0.05$
Overall mucosal DNA (μ g/cm)	174.80 (9.40)	165.76 (13.93)	183.42 (13.05)	183.54 (12.21)	187.66 (13.02)	NS

Student's t tests: *versus † $p<0.05$, *versus ‡ $p<0.01$.

Figure 1: Effect of diet on the distribution of (A) whole gut weight and (B) mucosal weight along the small intestine. Values mean (SEM); $n=8$; P=proximal, M=middle, D=distal segment. EFA=Efamol; LIN=50% Efamol/50% linseed oil; SAT=98% coconut oil/2% Efamol; OA=olive oil; MCT=medium chain triglyceride oil/2% Efamol.

groups in their energy intake (Table III), and individual comparisons with t tests showed significant differences between the intake of OA and LIN and of OA and SAT. However, there were no significant differences between the groups in weight gain or in small intestinal length (Table III).

There were no significant differences between the two groups in overall whole gut weight, overall mucosal weight, and overall mucosal DNA (Table IV). Analysis of variance, however, did show significant variation ($p<0.05$) in overall levels of mucosal protein, while individual comparisons showed significant differences between the mucosal protein levels for SAT and

LIN and SAT and OA. The individual intestinal segment mass parameters are plotted in Figures 1 and 2 to show their distribution along the small intestine. The four diets rich in LCT gave a similar distribution of mass parameters along the small intestine, with peak levels attained in the middle small intestinal segment. The diet rich in MCT, however, induced a different distribution of mass parameters; on this diet, mass was greatest in the proximal segment and declined successively in the middle and distal segments.

The data for 2 hour metaphase accumulation are plotted in Figure 3. The curves for the four diets rich in LCT were of similar shape, while that for MCT differed. Repeated measures analysis of variance confirmed that there was significant variation in the five slopes ($p<0.01$), but this was not present if the data for MCT were excluded from the analysis.

Table V shows that there was no significant difference between the groups in pancreas weight, although there was a trend for MCT to give the greatest weight.

EXPERIMENT 2

The rats tolerated the initial twice daily 1.7 ml bolus doses of MCT poorly; shortly after dosing they became subdued, cold to the touch, and developed severe diarrhoea. After 2 days, therefore, the dose of MCT was reduced to 1.0 ml twice daily giving 29% of total calories. This was better tolerated, although there was still some initial diarrhoea. The intake of the Efamol dosed animals was reduced correspondingly.

There were no significant differences in weight gain between the three groups or in total small intestinal length (Table VI), although small intestinal length seemed somewhat less after the glucose rich diet than after the other two diets.

Figure 2: Effect of diet on the distribution of (A) mucosal protein and (B) mucosal DNA along the small intestine. Values mean (SEM); $n=8$; P=proximal, M=middle, D=distal segment. (For other abbreviations see legend to Figure 1.)

Figure 3=Effect of diet on 2 hour metaphase accumulation. Each point is the mean of measurements from eight rats. (For abbreviations see legend to Figure 1.)

Overall small intestinal whole gut weight and mucosal weight were similar in the groups receiving bolus doses of Efamol and bolus doses of MCT and were increased compared with the group fed the glucose rich diet (Table VII). Overall mucosal protein and DNA showed a similar trend, although the changes for DNA did not achieve statistical significance ($p=0.08$). In this experiment the distribution of mucosal mass along the small intestine was similar for the Efamol rich diet and MCT rich diet, with greater levels of mass in the middle than in the proximal segment (Figs 4 and 5). As in earlier studies,^{5,7} the glucose rich diet gave levels of mucosal mass parameters that were greatest in the proximal segment and declined in the subsequent two segments.

There was significant variation in the absolute pancreatic weight and the pancreatic weight expressed relative to body weight between the diets (Table VIII). Individual comparisons with t tests showed a significant difference between pancreatic weights for the two high fat diets, with MCT giving the higher value.

Discussion

This study compared the enterotrophic actions of different triglycerides. In the first experiment the oils were given in mixed diets with the animals being deliberately allowed to feed *ad libitum*. If the intake of all the groups had been matched to that of the group with the lowest intake (OA), the remaining groups, and especially the SAT group, would have been effectively food restricted. These animals, therefore, might have gorged their food, and, in turn, this might have produced a bolus effect that could have created differences between the groups. It was also to avoid a confounding variable that two of the oils studied, SAT and MCT, contained supplements of Efamol. This was because the major constituents of these oils, coconut oil and MCT oil respectively, contain very low levels of essential fatty acids. It was important to avoid essential fatty acid deficiency, since this itself can cause small intestinal mucosal atrophy.¹⁹

The first experiment provided no evidence that the fatty acid composition of the ingested oil significantly affected overall small intestinal whole gut weight or mucosal weight and any trends between the groups were broadly in keeping with differences in energy intake. Thus, whole gut weight and mucosal weight were greatest in the group with highest energy intake, the SAT group, and least in the group with the lowest intake, the OA group. The variation in mucosal protein just attained statistical significance ($p<0.05$), but this was mainly because of the high level for the SAT group, which may have reflected the high intake of this group. Mucosal DNA, on the other hand, showed no significant variation and no obvious trend in relation to energy intake.

Although the LCT and MCT did not differ in their effects on the overall mass of the small intestine, the first experiment showed that their effects on the distribution of mass along the length of the small intestine did vary. The differences may relate to differences in the

TABLE V Effect of diet on pancreas wet weight. (Values mean (SEM); n=8)

	EFA	LIN	SAT	OA	MCT	ANOVA
Pancreas weight (mg)	882.33 (73.51)	775.45 (37.78)	820.24 (36.21)	814.79 (44.41)	940.55 (39.24)	NS
Pancreas weight per 100 g body weight (mg)	404.06 (31.75)	355.73 (20.67)	371.97 (13.55)	379.71 (18.72)	437.12 (18.08)	NS

TABLE VI Effect of diet on rat weight gain and small intestinal length. (Values mean (SEM); n=8)

	EFA bolus	MCT bolus	Glucose diet	ANOVA
Rat weight gain (g)	8.1 (4.7)	9.4 (3.4)	9.6 (2.5)	NS
Small intestinal length (cm)	108.9 (1.4)	110.8 (2.2)	105.8 (0.8)	NS

EFA=Efamol, MCT=98% medium chain triglyceride oil/2% Efamol mixture.

TABLE VII Effect of diet on overall small intestinal whole gut weight, mucosal weight, and mucosal protein and DNA (Values mean (SEM), n=8)

	EFA bolus	MCT bolus	Glucose diet	ANOVA
Overall whole gut weight (mg/cm)	57.81 (1.65)*	60.34 (2.53)*	49.41 (1.04)‡	p<0.001
Overall mucosal weight (mg/cm)	21.76 (0.70)*	23.37 (1.36)*	17.83 (0.52)‡	p<0.001
Overall mucosal protein (mg/cm)	3.02 (0.10)*	3.19 (0.19)*	2.60 (0.13)‡	p<0.05
Overall mucosal DNA (µg/cm)	214.38 (6.89)	234.57 (16.32)	193.79 (10.91)	NS

EFA=Efamol, MCT=98% medium chain triglyceride oil/2% Efamol mixture. Student's *t* tests: *versus †p<0.05; *versus ‡p<0.001.

Figure 4=Effect of diet on the distribution of (A) whole gut weight and (B) mucosal weight along the small intestine. Values mean (SEM); n=8; P=proximal, M=middle, D=distal segment; MCT=medium chain triglycerides.

absorption sites of these two classes of triglyceride and their digestive products. There is good evidence that luminal nutrients have a direct enterotrophic effect on the small intestinal mucosa, perhaps related to the 'workload' of their absorption²⁰⁻²² and this effect seems to be maximal at the site of absorption itself.* MCT are more rapidly hydrolysed and absorbed in the intestinal lumen than are LCT²³ and, therefore, would be expected to stimulate cell proliferation more proximally in the small intestine.

The results of this first experiment, therefore, did not support earlier studies^{2,3,9-13} which suggested that there may be differences between the enterotrophic effects of different LCT, and between LCT and MCT. Differences between the precise fatty acid composition of the oils used in the current experiment and those of the earlier studies may contribute to this discrepancy, but it is also relevant that in most of those studies,^{3,9-13} the overall small intestinal mucosal mass and distribution of mass along the small intestine were not measured. Without these measures it is therefore difficult to interpret the significance of differences in isolated short segments of small intestine.

In the second experiment, the enterotrophic effects of bolus doses of MCT were compared with those of LCT. Administration of LCT in bolus doses produces an enhanced enterotrophic effect compared with the same daily dose of oil consumed as a mixed diet,⁶ perhaps because there is increased delivery of lipid to the distal gut, where it may release an enterotrophic peptide.⁶ It was anticipated that boluses of MCT might have had a less potent enterotrophic effect than boluses of LCT, since MCT might have been so well absorbed proximally in the small intestine that little would have reached the distal ileum to enhance release of an enterotrophic peptide. Contrary to these expectations, however, the study showed that bolus doses of MCT had an overall enterotrophic action at least equivalent to that of isocaloric doses of LCT. Interestingly, administration of MCT in bolus doses also affected the distribution of mucosal mass along the small intestine; after the bolus doses of MCT mucosal mass was greatest in the middle small intestinal segment, whereas the first experiment had shown that MCT in the mixed diet most increased mucosal mass in the most proximal segment.

The enterotrophic effects of the bolus doses of MCT may have been related to the diarrhoea that they were observed to cause, for, as a result of accelerated transit, the oil might have travelled further along the small intestine before being absorbed, thus maximally enhancing cell proliferation in the mid rather than the proximal small intestine. The presence of unabsorbed MCT in the distal small intestine might also have released an enterotrophic peptide that enhanced their overall trophic effect to the small intestine.

Figure 5=Effect of diet on the distribution of (A) mucosal protein, and (B) mucosal DNA along the small intestine. Values mean (SEM); $n=8$; P=proximal, M=middle, D=distal segment; MCT=medium chain triglycerides.

It is noteworthy that MCT infused directly into the human ileum cause a release of enteroglucagon,²⁴ which has been proposed as an enterotrophic hormone.²⁵

The mechanism for the MCT induced diarrhoea is not clear, but recent studies in the rat suggest that MCT may stimulate greater release of cholecystokinin than do LCT.²⁶ Cholecystokinin may itself stimulate intestinal motility²⁷ and the output of pancreaticobiliary secretions into the lumen,²⁸ both of which could contribute to the diarrhoea. Cholecystokinin is also trophic to the pancreas²⁹ and it is interesting that the pancreatic wet weight was increased by the boluses of MCT. Indeed, even as part of a mixed diet (experiment 1, Table V), MCT

showed a non-significant trend to increase pancreatic weight.

The results of the current study are compatible with our earlier findings.¹⁶ The differences between the effects of MCT and LCT in mixed diets on the distribution of mucosal mass and cell proliferation along the small intestine are consistent with our proposal that regional variation in mucosal proliferation may reflect differences in the sites of absorption of ingested nutrients. Although surprising, the enterotrophic effects of bolus doses of MCT also do not contradict our earlier results. As discussed above, it is possible that accelerated intestinal transit accounts for the effects of MCT boluses on both regional and overall levels of small intestinal mucosal mass.

From a clinical viewpoint, it is disappointing that none of the oils in the current study has been shown to have an especially potent enterotrophic action. Such an action could be useful in the treatment of the short bowel syndrome, for example. It is still possible, however, that there are other oils with enhanced enterotrophic properties, and this has been suggested recently for both short chain triglycerides³⁰ and fish oil.³¹ This possibility is currently under investigation.

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TABLE VIII Effect of diet on pancreatic wet weight. (Values mean (SEM); $n=8$)

	EFA bolus	MCT bolus	Glucose diet	ANOVA
Pancreas weight mg	642.59 (30.17)*	805.26 (45.52)†	729.62 (60.36)‡	$p<0.05$
Pancreas weight per 100 g body weight (mg)	302.58 (6.11)*	372.66 (15.31)†	342.21 (19.31)‡	$p<0.05$

EFA= Efamol, MCT= 98% medium chain triglyceride oil/2% Efamol mixture. Student's t test: *versus †NS; *versus ‡ $p<0.01$; †versus ‡NS.

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