Postprandial hyperlipemia in pigs

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Summary
The ability to induce postprandial hyperlipemia is essential for using certain animal species as models for short-term consequences of fat intake in humans. We present the results from two studies on postprandial hyperlipemia and triglyceride metabolism in young slaughter pigs using the proprietary lipid-containing product, Intralipid®. In the first study we demonstrated that postprandial hyperlipemia in slaughter pigs was insignificant (p=0.16) when fed Intralipid® in doses of 2 g fat/kg administered in two fractions: the first 1/3 1 1/2 hours after feeding, and the second 2/3 1 1/2 hours later. In the second study, induction of postprandial hyperlipemia was performed by administering Intralipid® in single doses of 2 g fat/kg 5 1/2 hours after feeding, which resulted in the development of significant postprandial hyperlipemia (p<0.001). To assess the half-life (T1/2) of triglycerides in the circulation, Intralipid® was administered intravenously in doses of 0.1 g fat/kg, which gave T1/2 (mean ± std.)=13.3±3.7 minutes. Furthermore, inhibiting the lipoprotein lipase by administering Triton WR-1339 intravenously in doses of 150 mg/kg exerted a significant inhibitory effect on the triglyceride catabolism in the circulation as determined by increments in peak value (p<0.05), increased area under the curve (iAUC) (p<0.01), and T1/2 (p<0.05). In conclusion, the slaughter pigs developed significant postprandial hyperlipemia when fed Intralipid® in doses of 2 g fat/kg 5 1/2 hours after feeding, while it was difficult to induce significant postprandial hyperlipemia when the same amount of fat was administered in two fractions in close proximity to feeding. We hypothesize that the high activity of the endothelial lipases, determined by the T1/2, constitutes the physiological threshold counteracting the development of postprandial hyperlipemia in young slaughter pigs.

Introduction
Postprandial hyperlipemia is a physiological phenomenon described by an increase in the serum lipid concentration generated primarily from triglycerides following the ingestion of a fat-rich meal. A field of major concern and interest in human medicine is the possible correlation between diet, lipoproteins, and coronary heart disease (CHD), especially with the development of atherosclerotic lesions and thrombosis (Austin, 1997; Karpe, 1997). It is widely accepted that diets high in fat and/or energy play an essential etiological role in the causation of CHD, and are as such considered as coronary risk factors due to the subsequent excessive hydrolysis of triglyceride-rich lipoproteins (Grundy & Denke, 1990; Goldberg, 1996; Hennig & Toborek, 2001). Epidemiological studies have demonstrated that hypertriglyceridemia is associated with an increased risk of CHD, most likely in combination with decreased levels of HDL-cholesterol, and the development of

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chylomicron remnant particles and small, dense LDLs (Ryu et al., 1992; Havel, 1994; Austin, 1997; Mangiapane & Salter, 1999b; Fielding, 2000). Furthermore, investigations have shown that increases in late postprandial triglyceride values, especially between 6 and 10 hours, constitute a significant risk factor for CHD (Cohen et al., 1988; Patsch et al., 1992; Uiterwaal et al., 1994). Thus, the capacity of catabolising triglycerides in the circulation is considered an important physiological mechanism, not only indispensable in fulfilling the energy demands of peripheral tissues, but also essential in diminishing the unfavourable long-term consequences of prolonged postprandial hyperlipemia.

The lipoprotein lipase is the major enzyme responsible for hydrolysing triglycerides in circulating lipoproteins, and the binding of lipoproteins to the lipoprotein lipases comprises the rate-limiting step in the enzymatic process of eliminating triglycerides from the circulation (Santamarina-Fojo & Dugi, 1994; Olivecrona & Olivecrona, 1995; Goldberg & Merkel, 2001). Consequently, it seems highly plausible that the activity of lipoprotein lipase and its ability to interact with various lipoproteins, assessed by its capacity for eliminating triglycerides from the circulation, represents a quantifiable physiological risk factor for CHD and atherosclerosis equal to other well-established risk factors, such as age, hypertension, body weight, diabetes mellitus, and cigarette smoking (Ridker & Antman, 1999; Mangiapane & Salter, 1999a).

Present knowledge supports using the domestic pig as a viable animal model in this particular field of biomedical research due to wide similarities in the anatomy and physiology of the digestive and cardiovascular system (Swindle & Smith, 2000; Gootman, 2001) and considerable homology between human and pig lipoprotein structure and metabolism (Chapman & Goldstein, 1976; Chapman, 1986; Black et al., 1990; Luhman et al., 1992; Travlos, 1999; Mersmann & Pond, 2001). Thus, the use of the domestic slaughter pig as an animal model is considered a valuable alternative because it is relatively cheap and readily accessible worldwide, especially in comparison with various breeds of minipigs, although the strong out-bred characteristics of the commercially available slaughter pig may affect the individual variation and statistical analysis. The applicability of the Göttingen minipig as an animal model of postprandial hyperlipemia in man has recently been investigated (Olsen et al., 2002). The impact of applying different fat-loads of Intralipid® on the subsequent generation of postprandial hyperlipemia in the Göttingen minipig revealed a dose-dependent response similar to that seen in humans consuming high-fat diets. The Göttingen minipigs received Intralipid® in doses of 2 g fat/kg, either as two fractions (the first 1/3 1 1/2 hours after feeding, and the second 2/3 1 1/2 hours later) or in a single fraction 1 1/2 hours after feeding. No significant inhibitory effect of either pre-feeding or fractionation of Intralipid® was demonstrated as both regimes induced significant (p<0.001) postprandial hypertriglyceridemia. Consequently, it was hypothesized that young domestic slaughter pigs ingesting similar amounts of Intralipid® would respond identically in terms of postprandial hyperlipemia as recorded in humans consuming similar fat-rich diets (Cohen et al., 1988; Patsch et al., 1992; Uiterwaal et al., 1994; Larsen et al., 1997; Gill et al., 2001), and in Göttingen minipigs receiving Intralipid® (Olsen et al., 2001; Olsen et al., 2002). Thus, it was of particular interest for this study to establish a pattern of postprandial hyperlipemia in young slaughter pigs compared with previous results in the Göttingen minipig by administering Intralipid® orally. To assess the elimination kinetics and half-life (T½) of triglycerides in the circulation, Intralipid® was administered intravenously. In order to demonstrate the significance of the endothelial lipases in clearing triglycerides from the circulation, Triton WR-1339, an inhibitor of the lipoprotein lipase, was administered intravenously. In contrast to several other animal species, studies using Triton in pigs have apparently never been published. Therefore, considering results from previous animal studies (Yamamoto et al., 1984b; Edelstein et al., 1985; Li et al., 1996;
Chirieac et al., 2000; Hall et al., 2000), a short preliminary Triton dose-range study was performed to verify a safe and effective dosage of Triton used in slaughter pigs.

**Materials and Methods**

**Animals**

The present experiment was conducted in accordance with the Institutional Guidelines and the Danish Animal Experimentation Act on a license granted by the Ministry of Justice, and all procedures were performed in agreement with the European Convention For The Protection Of Vertebrate Animals Used For Experimental And Other Scientific Purposes, ETS no 123 (Council of Europe, 1986). Fifteen 10-12 weeks old domestic Danish crossbred slaughter pigs (Danish Landrace*Yorkshire*Duroc) were obtained from a SPF herd (The Research Farm “Sjaelland 3”, Roskilde, Denmark). All pigs were weighed twice during the experiment, and had an average body weight of 29.3±2.3 kg (mean±std.). The herd was declared free from the microbiological agents causing pleuropneumonia, atrophic rhinitis, dysentery, the porcine reproductive and respiratory syndrome (PRRS), Aujeszky’s disease, and sarcoptic mange. The distribution by sex was four barrows and eleven gilts. The pigs were accommodated in a controlled environment with solid concrete floor pens covered with straw bedding at the Research Facility at the Division of Laboratory Animal Science and Welfare (The Royal Veterinary and Agricultural University, Denmark). During the period of the trials clinical health monitoring was performed daily. The pigs were acclimatized for two days before the dose-range study and at least six days before all other experiments. Five pigs were used in the first study, and ten pigs in the second study.

**Materials**

Tyloxapol (Triton WR-1339) was purchased from Sigma-Aldrich Co (St. Louis, MO, USA), and dissolved in 0.9% sterile saline as a 10% wt/vol solution, autoclaved at 121°C for 15 min, and kept at room temperature until injection within 24 hours after production. Intralipid® was purchased from Fresenius Kabi AB (Uppsala, Sweden), supplied as a 20% wt/vol solution containing 200 g purified soybean oil, 12 g purified egg phosphatides, 21.3 g glycerol per litre, and with an energy content of approximately 8.4 MJ/l, and pH about 7.5.

**Diets**

All animals were fed a standard pig diet, approximately 0.4-0.5 kg per pig twice a day (pig-feed no 5, NAG A.m.b.a., Helsinge, Denmark). The diet contained 23 g crude fat/kg, 170 g crude protein/kg, and 7874 kJ metabolizable energy/kg. Water was available ad libitum. On days when experiments were performed, feeding was carried out at 6.30 a.m. in the morning, and feeding in the afternoon was postponed until all procedures were completed.

**Infusion and blood sampling**

Oral administration of Intralipid® in doses of 2 g fat/kg was given by gastric intubation through a stallion catheter (Equivet Stallion Catheter Luer, 6.5*1350mm, Kruuse, Denmark), while keeping the pig in an upright sitting position and using a mouth dilator. Intravenous infusion of Triton and Intralipid® was performed with the pig placed in a Y-shaped trough using a 22 gauge Venflon® catheter (I.V. Cannula 0.8x25mm, Becton Dickinson, Infusion Therapy AB, Helsingborg, Sweden) inserted in a peripheral ear vein. Intralipid® was administered intravenously in doses of 0.1 g fat/kg within a period of approximately 1½ minutes. Triton was administered intravenously in doses of 50, 150 or 300 mg/kg at approximately 50 mg/kg/min. Blood samples were collected from the jugular vein both before (baseline values, t = 0 h) and after the administration of Intralipid® while keeping the pig standing, as briefly as possible, using a hog snare. Following intravenous infusion of Intralipid®, blood samples were successively taken at t = 2½, 5, 15, and 30 minutes, and after oral infusion of Intralipid®, blood samples were taken at t = 1, 2, 3, 4, 5, and 6 hours. The blood samples were with-
drawn by a 21 gauge, 38 mm long needle and collected in 4 ml tubes (BD SSTTM Vacutainer Systems, Belliver Industrial Estate, Plymouth, UK) with clot activator and gel for serum separation. Blood samples were withdrawn in volumes of 3-4 ml and centrifugated at 2000g for 15 minutes at 20-25°C. A minimum of 0.5 ml serum was pipetted into 1.5 ml plastic microcentrifuge tubes (Plastibrand®, Brand GmbH, Wertheim, Germany), and stored at -18°C until analysis.

Analytic methods
The total triglyceride content in the serum sample was analysed in an ADVIA® 1650 (ADVIA® 1650 Chemistry System, Bayer Diagnostics GmbH, München, Germany) at the Central Laboratory of the Department of Clinical Studies, Royal Veterinary and Agricultural University, Frederiksberg, Denmark. The analytical method was based on the triglyceride test kit (Product No. B01-4133-01, ADVIA® 1650 Chemistry System).

Protocols
The first study.
Five pigs received Intralipid® orally in doses of 2 g fat/kg divided in two fractions: the first 1/3 1 1/2 hours after feeding, and the second 2/3 1 1/2 hours later. Blood samples were taken as previously described.

The second study.
In advance of the main experiment, the Triton dose-range study was performed. Three pigs received Triton intravenously in doses of 50, 150, and 300 mg/kg, respectively. Subsequently, each pig received Intralipid® intravenously 18 hours later in doses of 0.1 g fat/kg and orally 47 hours later in doses of 2 g fat/kg.
The remaining seven pigs were used in the main experiment, and were divided into two groups (3+4). The two groups were subjected to identical trials, however, performed on successive days. The main experiment was initiated by a one-factor response study implicating Intralipid® alone. Intralipid® was infused intravenously at 07.30 and orally at 12.00. A period of four days rest followed. The following trials included both Triton and Intralipid®, administering Triton in advance of Intralipid®. Based on findings in the Triton dose-range study, Triton was administered in doses of 150 mg/kg, and Intralipid® was subsequently administered intravenously at 07.30 and orally at 12.00, approximately 42 1/2 and 47 hours after the infusion of Triton, respectively. Blood samples were taken as previously described.

Statistical analysis
A modified cross-over design was used, the pigs being their own controls. The concentration of serum triglycerides was plotted against time. The increased area under the curve (iAUC) was calculated by the trapezoidal method after subtracting the baseline value from each individual measurement. The peak-value was calculated by subtracting the baseline value from the highest registered triglyceride concentration. The T 1/2 of triglycerides in serum was determined by linear regression of the log-transformed serum triglyceride concentrations over time intervals of 2 1/2-30 minutes post injection, while the T 1/2(mean) was calculated by linear regression of the means of log-transformed triglyceride values. The statistical calculations were made on MINITAB Release 12.1 (Minitab Inc., USA). Distribution of variables was assessed by normal probability plots, and the Shapiro-Wilk test and the Anderson-Darling test assessed normality of data. Drawing Dunnett’s intervals enabled multiple comparisons of means minus control mean. The paired t-test was used to assess differences in iAUC, peak-value, and T 1/2, and the two sample t-test was used to compare T 1/2. When results were not consistent with the Gaussian distribution, the Kruskal-Wallis Test was used to test whether triglyceride concentrations were significantly different. The level of statistical significance was p<0.05.
Results
As presented in figure 1, the pigs that received Intralipid® in two fractions did not develop a statistically significant postprandial hyperlipemia (p=0.16), although some fluctuations were present. In the Triton dose-range study (Figure 2), a noticeable dose-dependent increment in the postprandial triglyceride concentration seemed evident. Pig no 2 appeared to have a more prolonged and sluggish elimination of triglycerides from the circulation compared with pig no 1, allowing a more pronounced postprandial hyperlipemia to evolve. Pig no 3, receiving 300 mg/kg of Triton, developed considerable hypertriglyceridemia, which exceeded 20 mmol/l and 5 mmol/l 42½ hours and 72 hours after administration, respectively. Additionally, this pig experienced severe and acute side effects such as convulsions and paresis, which vanished within the first hours after dosing. As the progression in postprandial triglyceride concentrations observed in pig no 2 (Figure 2) displayed obvious quantitative and qualitative similarities with fluctuations observed in both humans (Cohen et al., 1988; Patsch et al., 1992; Uiterwaal et al., 1994; Larsen et al., 1997; Gill et al., 2001) and Göttingen minipigs (Olsen et al., 2001; Olsen et al., 2002) ingesting similar diets, it was decided that the dose of Triton applied in the main experiment should be 150 mg/kg. Further, the time interval between the Triton injection and the oral administration of Intralipid® should be 47 hours as this allowed a relatively stabilized triglyceride concentration to be achieved in

Figure 1. The first study. Postprandial triglyceride (Tg) concentrations in five (n=5) slaughter pigs (all gilts). Intralipid® was administered in doses of 2 g fat/kg by gastric intubation divided in two fractions: the first ½ 1½ hours after feeding, and the second ½ 1½ hours later. Arrows indicate time of Intralipid® administration. Results were not consistent with the Gaussian distribution, and non-parametric tests were used. Medians are connected, and whiskers indicate 95% confidence intervals. Triglyceride concentrations were not significantly different (p=0.16) (The Kruskal-Wallis Test).
Due to the long half-life of Triton (3-4 days) (Scanu & Page, 1962; Yamamoto et al., 1984b), and in order to avoid undue extension of the experiment and the need of applying Triton twice, it was decided that Intralipid® should be administered intravenously approximately 4½ hours in advance of the oral administration, and not as previously performed in the dose-response study. This time interval of 4½ hours was established as a compromise between enabling us to assess the lipoprotein lipase activity just prior to the Intralipid® ingestion, while allowing the Intralipid® to be substantially cleared from the circulation before Intralipid® was given orally.

As both trials (Figure 3) demonstrated, ingestion of Intralipid® gave rise to statistically significant postprandial hypertriglyceridemia as compared with baseline (p<0.001) (n=4). Comparing the iAUC, peak values and T½ in a paired design enabled us to assess the impact of administering Triton (Table I). Inhibiting the enzymatic actions of lipoprotein lipase caused significant increments in iAUC (p<0.01), peak values (p<0.05) and T1/2 (p<0.05) (n=4).

Based on linear regression analyses, the T½ values were calculated: the T1/2 (min.-max.)=12.5-20.8 minutes (Table II), and the T1/2 (mean±std.)=13.7±3.7 minutes (Figure 4). The results from pig no 9 were excluded because they did not comply with first-order elimination kinetics. Furthermore, as depicted in figure 5, pig no 10 did not seem to absorb triglycerides. During the following autopsy of pig no 10, considerable amounts of Intralipid® were found in the stomach and the small intestine approximately 7-8 hours after Intralipid® was given.

Figure 2. The second study. Postprandial triglyceride (Tg) concentrations from the Triton dose-range study in two slaughter pigs ingesting Intralipid® (at baseline, t = 0 h) in doses of 2 g fat/kg 5½ hours after feeding. Triton was administered 47 hours previously. Pig no 1 received 50 mg/kg Triton, and pig no 2 received 150 mg/kg Triton. Pig no 3 receiving 300 mg/kg Triton is not included due to excessive accumulation of triglycerides.
ingestion, but no corresponding anatomical anomalies or pathological lesions, which could possibly explain the lack of triglyceride absorption, were identified. However, this phenomenon may have been induced by diarrhoea, which occurred during the experiment in this pig.

**Discussion**

The consequence of administering Triton to domestic slaughter pigs in doses of 150 mg/kg was not entirely unambiguous. Some pigs experienced transient and very brief symptoms of in-coordination. However, the experiment was continued because no signs of discomfort, pain, or anxiety were observed, and all pigs regained normal motor and behavioural activity within a few minutes. Furthermore, differences in the susceptibility to and elimination of Triton were indicated by divergences in the baseline triglyceride values (Figure 6). Interpreting results derived from pigs expressing relatively high triglyceride concentrations after Triton infusion may be biased by less accuracy in the analysis results, and furthermore, may be under the influence of different elimination kinetics, thus altering the effect and consequences of administering Intralipid®. Consequently, exclusion criteria were made in order to obviate that those pigs displaying rather extreme baseline triglyceride values should possibly bias further analyses. Therefore, a cut-off value was defined. It was decided that the baseline triglyceride values obtained 47 hours after Triton administration would not be allowed to exceed the equiva-

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Figure 3. The second study. Postprandial triglyceride (Tg) concentrations in slaughter pigs (n=4). Means are connected, and whiskers indicate 95% confidence intervals. Intralipid® was administered in doses of 2 g fat/kg (at baseline, t = 0 h) 5½ hours after feeding (broken line). Four days later Triton (150 mg/kg) was infused, and after 47 hours Intralipid® (2 g fat/kg) was administered (at baseline, t = 0 h) 5½ hours after feeding (un-broken line). Postprandial triglyceride concentrations were significantly different from baseline values in both trials (p<0.001). Asterisks indicate statistically different triglyceride concentrations compared with baseline concentrations.
Table I. Paired observations of iAUC, peak value and T½ tested by the one-sided paired t-test.

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>iAUC (mmol/l*6h)</th>
<th>peak (mmol/l)</th>
<th>T½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-Tr</td>
<td>+Tr</td>
<td>Difference</td>
</tr>
<tr>
<td>5</td>
<td>2.6</td>
<td>6.3</td>
<td>3.7</td>
</tr>
<tr>
<td>6</td>
<td>3.3</td>
<td>5.9</td>
<td>2.6</td>
</tr>
<tr>
<td>7</td>
<td>2.6</td>
<td>3.8</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>4.1</td>
<td>6.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean</td>
<td>2.6</td>
<td>0.68</td>
<td>1.4</td>
</tr>
<tr>
<td>95% c.i.</td>
<td>1.4 - 3.8</td>
<td></td>
<td>1.02 - 1.11</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.01</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

iAUC = increased area under the curve (mmol/l*6h) in per-oral challenge study; peak = peak value (mmol/l) in per-oral challenge study; T½ = half-life (min) of triglycerides in serum after administration of Intralipid® intravenously; -Tr = without Triton; +Tr = with Triton; c.i. = confidence interval calculated by: mean +/- t(0.975;df=3)*SE (n=4); p-value = statistical significance of one-sided paired t-test.

Table II. Linear regression analyses of log-transformed data obtained after administration of Intralipid® intravenously.

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>R² (%)</th>
<th>T½ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (-/+ Tr)</td>
<td>99.7 / 96.3</td>
<td>13.6 / 77.2</td>
</tr>
<tr>
<td>5 (-/+ Tr)</td>
<td>99.0 / 98.5</td>
<td>14.7 / 41.2</td>
</tr>
<tr>
<td>6 (-/+ Tr)</td>
<td>99.8 / 94.7</td>
<td>12.5 / 25.7</td>
</tr>
<tr>
<td>7 (-/+ Tr)</td>
<td>98.5 / 98.9</td>
<td>13.2 / 18.1</td>
</tr>
<tr>
<td>8 (-/+ Tr)</td>
<td>99.1 / 96.4</td>
<td>20.8 / 31.7</td>
</tr>
<tr>
<td>10 (-/+ Tr)</td>
<td>92.9 / 92.1</td>
<td>20.4 / 83.6</td>
</tr>
</tbody>
</table>

R² = square of the correlation coefficient; T½ = half-life (min) of triglycerides in serum after administration of Intralipid® intravenously; -Tr = without Triton; +Tr = with Triton.
 lent baseline values obtained before Triton administration by more than three times (Figure 5 and 6). Three pigs (no 4, 9, and 10) were excluded on behalf of this criterion because they displayed baseline triglyceride increments of 8, 29, and 26 times, respectively. Thus, only four pigs (n=4) (all gilts) were employed in the statistical analyses using a paired design. However, although this sample size may seem small, all statistical analyses using this design turned out to be significant.

Although the handling of pigs and blood samplings were performed as quickly and gently as possible, it has to be acknowledged that this procedure may have inflicted some degree of stress on the animals. It is well known that inflammatory conditions and substantial stress interfere with lipid metabolism by altering the activity of endothelial lipases. However, we believe that the level of stress imposed on the animals during the experiment did not noticeably affect the subsequent triglyceride analyses since all base-line measurements after the intravenous administration of Intralipid® were within normal limits, and since the triglyceride concentration after six hours was not statistically different from base-line measurements (Figure 3 and 5).

The divergences in results between the first study (Figure 1) and the second study (Figure 3) are mainly based on three aspects. Firstly, the administration of Intralipid® in two fractions obviously prolonged the time needed to absorb the same amount of fat compared with administering Intralipid® in a single fraction. Thus, a less amount of Intralipid® was available for immediate absorption when administered in two fractions, thereby not straining the catabolic processes in the circulation to the same extent. Secondly, the relatively short time intervals between feeding and administration of Intralipid® in the first study probably gave rise to significant

\[
\text{T}_{1/2} \text{(mean, Göttingen minipigs)} = 25.7 \text{ minutes} \\
R^2 = 0.9403
\]

\[
\text{T}_{1/2} \text{(mean, slaughter pigs)} = 13.3 \text{ minutes} \\
R^2 = 0.9766
\]

Figure 4. Linear regression analyses of log-transformed triglyceride (Tg) concentrations in the slaughter pigs and the Göttingen minipigs after intravenous injection of Intralipid®. The T_{1/2} (Slaughter pigs) was significantly different (p<0.001) from the T_{1/2} (Göttingen minipigs). R^2 = square of the correlation coefficient.
mixing, which impaired the immediate absorption of triglycerides. Thirdly, the baseline triglyceride values in the first study were relatively high (median > 1 mmol/l). This may have been induced by the preceding feeding, although this seems unlikely because none of the seven pigs in the second study experienced baseline triglyceride concentrations exceeding 0.6 mmol/l in the hours immediately after ingesting similar diets. Thus, the relatively high median baseline triglyceride value in the first study made it difficult to demonstrate a statistically significant postprandial hyperlipemia, especially when the subsequent triglyceride concentration measurements showed quite large variation. However, it seems likely that some kind of interaction between these postulated mechanisms exists, which together makes it difficult to induce significant postprandial hyperlipemia when Intralipid® is administered in two fractions in close proximity to feeding.

The Göttingen minipig readily develops postprandial hyperlipemia (Olsen et al., 2001, Olsen et al., 2002). This appears to be at variance with the results from our first study using slaughter pigs (Figure 1). The difference may be partly explained by comparing data describing the capacity to eliminate triglycerides from the circulation. When performing this comparison it is assumed, with reasonable justification, that both pig breeds readily digest Intralipid® and absorb triglycerides as no steatorrhea was observed. Consequently, this makes the T1/2 an essential and determinant factor for the development and magnitude of forthcoming postprandial hyperlipemia. On the basis of data acquired from the investigation performed by Larsen and co-workers (Larsen et al., 2003), which administered Intralipid® intravenously, we were able to assess the T1/2 across variables in the Göttingen minipig: the T1/2 (min.-max.)=18.5-37.5 min-

Figure 5. The second study. Postprandial triglyceride (Tg) concentrations in all seven slaughter pigs without the use of Triton. Intralipid® was administered in doses of 2 g fat/kg (at baseline, t = 0 h) 5½ hours after feeding.
utes, and the $T_1/2$ (mean±std.)=25.7±7.4 minutes (n=12) (Figure 4). Using the two sample t-test we demonstrated that the $T_1/2$ (mean) from the slaughter pigs ($T_1/2$ (mean±std.)=13.3±3.7 minutes (n=6)) was significantly different (p<0.001) from the $T_1/2$ (mean) in the Göttingen minipigs. Therefore, the capacity to eliminate triglycerides from the circulation, determined by the magnitude of the $T_1/2$, seems to constitute a cornerstone when attempts are made to clarify and comprehend basic differences in lipid metabolism between slaughter pigs and the Göttingen minipig.

Another important aspect that needs to be considered is the actual age of the animals. The slaughter pigs were 10-12 weeks old, while the Göttingen minipigs were approximately one year old and almost full-grown. Thus, one would expect the metabolic rates to be similar, since the body weights were almost identical (Hau & Poulsen, 1988). However, young slaughter pigs need relatively more energy to cover basic requirements of rapid growth and therefore have an attendant physiological need of a high turnover of nutrients in the body (Mitchell et al., 2001). This may explain the differences in $T_1/2$, although other genetic and physiological parameters may also be involved. Indication of some age-related variation in lipid metabolism in slaughter pigs is substantiated by the investigation performed by Johansson and Karlsson (Johansson & Karlsson, 1982), who demonstrated that young slaughter pigs have approximately twice as much HDL in the serum compared with the adult pig. The need and importance of HDL in the transport of apolipoproteins is documented, and HDL facilitates the continuous transformation of triglyceride-rich lipoproteins in peripheral tissues (Goldberg, 1996). Thus, the high levels of HDL in young slaughter pigs may to some extent reflect the basic physiolog-

Figure 6. The second study. Postprandial triglyceride (Tg) concentrations in all seven slaughter pigs. Triton was administered 47 hours previously in doses of 150 mg/kg. Intralipid® was administered in doses of 2 g fat/kg (at baseline, t = 0 h) 5 1/2 hours after feeding.
ical requirement of rapid catabolism of triglyceride-rich lipoproteins needed in order to sustain rapid growth.

The effect of Triton on the intravascular triglyceride concentration displayed obvious dose-dependent tendencies. All seven slaughter pigs receiving Triton in doses of 150 mg/kg regained baseline triglyceride concentrations within normal limits 72 hours after administration, while the pig receiving 300 mg/kg still had a triglyceride concentration in serum exceeding five mmol/l. This dose-dependent physiological effect of Triton corresponds well with other experimental studies using other animal species (Schultz & Esdale, 1971; Yamamoto et al., 1984a; Yamamoto et al., 1984b; Okazaki et al., 1990; Hall et al., 2000). Although significant postprandial hyperlipemia was induced by administering Intralipid® alone, the consequences of administering Triton was statistically significant as demonstrated by the iAUC, peak-value, and T½. Thus, the application of Triton in trials on slaughter pigs in quantities of 150 mg/kg inhibited the intravascular elimination of triglycerides for at least 47 hours significantly increasing the postprandial hypertriglyceridemia, and did not cause detrimental side-effects. However, it should be remembered that Triton has substantial adverse effects when administered in too high amounts (as demonstrated in the pig receiving Triton at a dose of 300 mg/kg) or in repeated infusion regimes (Scanu & Page, 1962; Wrenn et al., 1971; Hall et al., 2000).

Whether slaughter pigs develop significant postprandial hyperlipemia if administered 2 g fat/kg of Intralipid® in a single dose 1½ hours after feeding has not been investigated. However, feeding may still interfere considerably, consequently increasing the variability of results and decreasing the significance of postprandial hyperlipemia. Therefore, if a substantial and significant postprandial hyperlipemia is to be induced in young slaughter pigs it seems sensible to administer the fat in a single fraction and not in near proximity to feeding.

In summary, the present investigation demonstrated that the slaughter pigs developed statistically significant postprandial hyperlipemia ingesting Intralipid® in doses of 2 g fat/kg 5½ hours after feeding. However, ingesting the same amount of fat in two fractions in the immediate proximity to feeding proved difficult for achieving statistically significant postprandial hyperlipemia when using a realistic group size. It was demonstrated that the administration of Triton WR-1339 in doses of 150 mg/kg significantly influenced the degree of postprandial hyperlipemia (iAUC, peak value, and T½), which became intensified. We hypothesize that the high activity of the endothelial lipases, as measured by the T½, constitutes the physiological threshold countering the development of postprandial hyperlipemia in young slaughter pigs.

References


Edelstein C, RE Byrne, K Yamamoto, C Zarins & AM Scanu: Plasma lipoprotein changes attending the intravenous administration of Triton WR-1339 in normolipidemic dogs: preferential


