Hyperlipaemia intensifies the course of acute oedematous and acute necrotising pancreatitis in the rat

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Abstract

Background—Serum triglyceride concentrations higher than 10 to 20 mmol/l are probably a risk factor for developing acute pancreatitis in humans.

Aims—To therefore analyse the influence of hyperlipaemia on the course of acute oedematous and acute necrotising pancreatitis in rats.

Subjects—Male Wistar rats were used in all experiments.

Methods—Six different groups of animals were used: two groups without pancreatitis (controls), two with acute oedematous pancreatitis, and two with acute necrotising pancreatitis. One group from each pair was treated with Triton WR 1339, which induces endogenous hyperlipaemia. Blood samples were taken from all subjects to measure triglyceride, cholesterol, amylase, and lipase. Pancreatic tissue samples were taken and the degree of pancreatic damage was judged microscopically.

Results—In the control groups no significant changes occurred, either in serum enzyme activities or in histology. The hyperlipaemic subgroup of animals with acute oedematous pancreatitis developed significantly higher ($p < 0.001$) serum amylase activities and a greater degree of histological damage ($p < 0.01$) than the animals of the non-hyperlipaemic acute oedematous pancreatitis group. In the animals with necrotising pancreatitis, serum lipase activity and the histological degree of pancreatic damage were significantly higher in the hyperlipaemic animals than in the non-hyperlipaemic animals.

Conclusion—This study shows that hyperlipaemia intensifies the course of acute oedematous and acute necrotising pancreatitis in rats.

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Keywords: hyperlipaemia, acute oedematous pancreatitis, acute necrotising pancreatitis.

Acute pancreatitis is a disease with an incidence varying from 47 to 110 cases per million per year in Western countries.¹⁻³ Usually it is characterised clinically by acute abdominal pain and increased pancreatic enzymes in blood or urine, or both. Clinically, two different courses can be distinguished: acute oedematous

pancreatitis and acute necrotising pancreatitis. In general, patients with acute oedematous pancreatitis respond well to conservative treatment,^{4,5} having a low morbidity and mortality. In contrast, 10-20% of the patients with acute pancreatitis develop intrapancreatic or extrapancreatic necrosis⁶ and life threatening systemic, metabolic, and organic complications.⁷⁻⁹ The most common aetiological factors in acute pancreatitis are alcohol abuse (40%) and biliary tract stones (40%). Other aetiologies, such as trauma, drugs or tumours, are rare and occur in about 20% of the cases.¹⁰

Hyperlipaemia is another aetiological factor and is often associated with relapsing periods of acute pancreatitis. A prevalence of hyperlipaemia in acute pancreatitis of between 4.5% and 47% has been reported in previous studies.¹¹⁻¹⁶ This wide range of hyperlipaemia in acute pancreatitis seems to result from the patient populations, because patients with alcoholic pancreatitis have hyperlipaemia more frequently than patients with biliary pancreatitis.^{11,14-15} Serum triglyceride values higher than 10 to 20 mmol/l seem to be a serious risk factor for developing acute pancreatitis.^{14,15} Particularly in patients suffering from familial hyperlipoproteinaemia (types I, IV, and V according to the classification of Frederickson), acute pancreatitis occurs with an incidence of up to 21%.^{11,12,19} In those cases, patients have increased serum concentrations of chylomicrons and triglycerides. In type V of familial hyperlipoproteinaemia there are also high concentrations of pre- β -lipoproteins of very low density (VLDL) containing high concentrations of triglycerides.^{17,18}

Several studies in humans and animals have been performed to evaluate hyperlipaemia as a risk factor for developing acute pancreatitis. Those studies showed that a high fat diet can change the susceptibility to experimental pancreatitis. Haig *et al* ascertained that overfed mongrel dogs had an increased likelihood of developing at least pancreatic oedema or even acute pancreatitis.²⁰ Those findings confirmed the results of other studies that showed that acute experimental pancreatitis is more severe in normally fed animals than in semistarved animals. An explanation for this finding was that there is an adaptation of pancreatic enzymes because of the diet the animals were fed before developing pancreatitis.^{21,22} But this hypothesis was considered controversial in another study.²³

Other studies using the isolated pancreatic acini model have suggested that damage to the

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TABLE I Histological classification of acute pancreatitis according to the Spormann classification³⁹

Histology	Points
Oedema	
Mild	1
Moderate	2
Severe	3
Inflammatory infiltration	
Mild	1
Moderate	2
Severe	3
Fat necrosis	
Mild	3
Moderate	5
Severe	7
Parenchymal necrosis	
Singular	3
Sub lobular <1/3	5
Lobular >1/3	7
Haemorrhage	
Mild	3
Moderate	5
Severe	7

acinar cells is caused by the cytotoxic effect of free fatty acids. These fatty acids are broken down products of triglycerides and were generated within the pancreas by the hydrolytic activity from the pancreatic lipase acting on triglycerides.^{24,25} There are two other hypotheses that could explain the mechanism by which hyperlipaemia causes parenchymal necrosis during acute pancreatitis. Trypsinogen could be activated by acidosis due to the presence of free fatty acids,^{26,27} or the free fatty acids may disturb the microcirculation of the pancreas by damaging the vessels endothelium.²⁵

However, there is not much information about the influence of hyperlipaemia on the course of acute pancreatitis. Previously, Buch *et al* confirmed that hyperlipaemia does not induce pancreatitis in humans directly, but can predispose to it or amplify it if there are other risk factors for acute pancreatitis.¹⁴ In this study the effect of endogenous hyperlipaemia on acute experimental pancreatitis was studied in rats using a caerulein model for acute oedematous pancreatitis and retrograde taurocholate injection in the pancreatic duct to induce acute necrotising pancreatitis.

Methods

Male Wistar rats with a body weight between 270 g and 300 g were used in all experiments. They were kept in single cages exposed to a 12 hour light/dark cycle with free access to chow and water. The chow (Altromin 1314, obtained from Altromin GmbH, Lage, Germany) contained 23% protein, 5% fat, 6.5% ashes, 4.5% fibre, 47.5% nitrogen free extracts, and 3.5% water, minerals, and vitamins.^{28,29}

After an overnight fast the animals were anaesthetised with a halothane-oxygen narcosis and a plastic catheter was placed in the right and left external jugular veins to take blood samples or to inject Triton WR 1339, saline solution, or infuse caerulein, or a combination of those.²⁸

Blood samples were taken from all animals eight hours before and 0, 45, 90, 135, and 180 minutes after inducing pancreatitis. The blood samples were centrifuged at 3000 rpm and the serum was stored in a -30°C freezer until further analysis. The samples were then thawed at +4°C and taken to measure triglyceride, cholesterol, amylase, and lipase.

Hyperlipaemia was induced by an intravenous injection of 0.25 ml of a 10% Triton WR 1339 solution (Thomae GmbH, Biberach, Germany) in the right external jugular vein. Triton WR 1339 (polymeric p-iso-octyl polyoxyethylene phenol) is a non-ionic surface active detergent that leads to an increase of the endogenous triglyceride and cholesterol blood concentrations.^{30,31} We determined the required amount of Triton WR 1339 earlier in a test series of eight rats treated with rising volumes of a 10% Triton solution. A volume of 0.25 ml of 10% Triton WR 1339 solution was found to induce maximal hyperlipaemia (data not shown). The non-hyperlipaemic animals received an injection of 0.25 ml of a physiological saline solution intravenously instead of 0.25 ml 10% Triton WR 1339 solution.

Acute oedematous pancreatitis was induced by infusion of 5 µg/kg body weight caerulein with a flow of 0.6 ml/h intravenously within three hours, as described in earlier studies.³²⁻³⁵

Acute haemorrhagic necrotising pancreatitis was induced by retrograde injection of 0.1 ml/0.1 kg body weight of 3% Na-taurocholate solution into the pancreatic duct with a pressure of 30 cm H₂O, as previously described by other authors.³⁶⁻³⁸

For histopathological analysis, small pancreatic tissue samples were taken 90 and 180 minutes after inducing pancreatitis and immediately fixed in Bouin solution for 24 hours. Afterwards the tissue samples were stored in alcohol (50%) and embedded in paraffin wax. The resulting 5 µm sections were stained with haematoxylin and eosin reagent. To quantify the histological changes, two blinded independent pathologists judged the tissue samples using a point score as described by Spormann *et al*³⁹ (Table I).

To explore the influence of hyperlipaemia on acute experimental pancreatitis we used six different groups of animals with 10 animals in each group (Table II). The animals of the first group C_(Sal) received 0.25 ml saline (Sal) solution, and the animals of the second group C_(Tri) received 0.25 ml of 10% Triton WR 1339 (Tri) solution both intravenously. In those two groups (C_(Sal) and C_(Tri)) no pancreatitis was induced. They formed the control (C) group.

Acute oedematous pancreatitis (OP) was induced in the third group OP_(Caer) and the fourth group OP_(Caer+Tri) by infusing caerulein (Caer) as described above. The animals of group OP_(Caer+Tri) received an injection of 0.25 ml of 10% Triton WR 1339 (Tri) intravenously eight hours before inducing pancreatitis with the caerulein infusion.

Acute necrotising pancreatitis (NP) was induced in the fifth group NP_(Tau) and the sixth group NP_(Tau+Tri) by retrograde injection of 3% Na-taurocholate solution (Tau) into the main pancreatic duct. The animals of group NP_(Tau+Tri) received an injection of 0.25 ml of 10% Triton WR 1339 (Tri) intravenously eight hours before pancreatitis was induced.

Results

Overall, 68 male Wistar rats were used in this study. Eight of the 68 animals died prematurely from thrombo-embolism or circulatory breakdown, leaving 60 animals for experimentation, 10 in each of six groups.

In the clinical course, no changes occurred in the animals of both control groups C. The

TABLE II Experimental design. The animals were divided into six groups. Each group contained 10 rats

Control groups (C)	
I:	C _(Sal) : saline solution
II:	C _(Tri) : Triton WR 1339
Oedematous pancreatitis (OP)	
III:	OP _(Caer) : saline and caerulein
IV:	OP _(Caer+Tri) : caerulein and Triton WR 1339
Necrotising pancreatitis (NP)	
V:	NP _(Tau) : saline and Na-Taurocholate
VI:	NP _(Tau+Tri) : Na-Taurocholate and Triton WR 1339

TABLE III Serum triglyceride and cholesterol concentrations

	-8 Hours	±0 Hours	+90 Minutes	+180 Minutes
Triglyceride (median; mmol/l)				
Controls				
Saline	0.56	0.42]	0.09]	0.08]
Triton	0.73	9.05]***	7.51]***	6.63]***
Oedematous pancreatitis				
Caerulein+saline	0.50	0.39]	0.23]	0.16]
Caerulein+Triton	0.60	8.59]***	6.68]***	7.05]***
Necrotising pancreatitis				
Taurocholate+saline	0.71	0.41]	0.24]	0.25]
Taurocholate+Triton	0.59	6.88]***	6.77]***	6.07]***
Cholesterol (median; mmol/l)				
Controls				
Saline	1.69	1.79]	1.54]	1.29]
Triton	1.57	4.24]***	4.21]***	3.95]***
Oedematous pancreatitis				
Caerulein+saline	1.49	1.52]	1.57]	1.43]
Caerulein+Triton	1.55	4.24]***	4.04]***	3.87]***
Necrotising pancreatitis				
Taurocholate+saline	1.53	1.60]	1.49]	1.26]
Taurocholate+Triton	1.59	3.71]***	3.72]***	3.21]***

***p<0.001.

animals of group OP, with oedematous pancreatitis, developed the typical macro and microscopical changes of oedematous pancreatitis after infusion of caerulein. Retrograde infusion of Na-taurocholate into the pancreatic duct led to haemorrhage and typical necrosis in all animals of the two necrotising pancreatitis (NP_(Tau), NP_(Tau+Tri)) groups. All animals treated with Triton WR 1339 developed hypertriglyceridaemia.

CONTROL GROUPS (C), WITHOUT PANCREATITIS

Triglycerides

The infusion of 0.25 ml of 10% Triton WR 1339 (minus eight hours) resulted in an increase in serum triglyceride concentrations in group C_(Tri). The median serum triglyceride concentration before Triton WR 1339 infusion was 0.73 mmol/l (range: 0.1–1.69 mmol/l), and after eight hours the median triglyceride value increased to 9.05 mmol/l (range: 2.05–17.42 mmol/l). At 180 minutes after infusion of Triton WR 1339 the serum triglyceride concentrations decreased slightly (not significant) (Table III). The serum triglyceride values of group C_(Sal), the animals receiving only physiological saline solution, remained unchanged during the experiment (Table III).

TABLE IV Serum amylase and lipase activity

	-8 Hours	±0 Hours	+90 Minutes	+180 Minutes
Amylase (median; U/l)				
Controls				
Saline	2493	2268	2275	2383
Triton	2543	1941	1856	1885
Oedematous pancreatitis				
Caerulein+saline	2546	1963	3900]	8130]
Caerulein+Triton	2719	2003	5680]***	11 010]***
Necrotising pancreatitis				
Taurocholate+saline	2705	2268	2816	4220
Taurocholate+Triton	2531	1979	4200	4070
Lipase (median; U/l)				
Controls				
Saline	10	10	10	29
Triton	10	10	10	45
Oedematous pancreatitis				
Caerulein+saline	10	10	1540]	3480]
Caerulein+Triton	10	10	2540]**	5430]***
Necrotising pancreatitis				
Taurocholate+saline	10	10	366]	475]
Taurocholate+Triton	10	10	1460]**	1310]**

* p<0.05, **p<0.01, ***p<0.001.

Cholesterol

In the animals receiving 0.25 ml Triton WR 1339 (group C_(Tri)), the serum cholesterol concentrations showed the same courses as the serum triglyceride concentrations. The median cholesterol value before Triton WR 1339 injection was 1.57 mmol/l (range: 0.9–2.26 mmol/l), increasing to 4.24 (range: 2.10–5.15) after eight hours. At 180 minutes after infusion of Triton WR 1339 the serum cholesterol values decreased slightly (not significant) (Table III). The cholesterol concentrations of the animals receiving only saline solution (group C_(Sal)) remained unchanged throughout the investigation (Table III).

Amylase

The serum amylase activities of the animals without pancreatitis decreased eight hours after the beginning of the investigation, both in the animals receiving only saline solution (group C_(Sal)) and in the animals treated with Triton WR 1339 (group C_(Tri)) (Table IV). The decrease was not significant (Table IV).

Lipase

The serum lipase activities in the control groups (C) increased slightly in the last 90 minutes of the experiment, both in the hyperlipaemic animals (group C_(Tri)) and in the non-hyperlipaemic animals (group C_(Sal)) (Table IV). However, the difference between the two groups was not significant (Table IV).

Histology

The animals of the control groups (C) showed no changes in the clinical course, whether receiving physiological saline solution (group C_(Sal)) or Triton WR 1339 (group C_(Tri)). There were no macroscopic changes of the pancreas in these two groups of animals during the whole examination time. The tissue samples taken at 90 and 180 minutes were judged histologically according to the point score of Spormann *et al* (Figure). Four hyperlipaemic animals of group C_(Tri) showed mild

Histological degree of pancreatic damage in rats without pancreatitis, with caerulein induced pancreatitis, and with taurocholate induced pancreatitis. Animals with endogenous hyperlipaemia had a higher degree of pancreatic damage than animals without endogenous hyperlipaemia.

pancreatic oedema, whereas no histological changes occurred in the saline treated animals (group C_(Sal)).

OEDEMATOUS PANCREATITIS, GROUP (OP)

Oedematous pancreatitis was induced as described previously by infusing 5 µg/kg body weight caerulein intravenously. Macroscopically, within one hour of caerulein infusion the animals developed a smooth oedema of the pancreas. This became more pronounced after three hours.

Triglycerides

The serum triglyceride concentrations of group OP_(Caer), the animals receiving only caerulein, remained unchanged during the experiments. In comparison, infusion of Triton WR 1339 resulted in a 14-fold increase in serum triglyceride values in group OP_(Caer+Tri). This difference between the OP_(Caer) group and the OP_(Caer+Tri) group was significant ($p < 0.001$). The median serum triglyceride concentration of the OP_(Caer+Tri) group was 0.6 mmol/l (range: 0.3–1.33 mmol/l) (minus eight hours) before Triton WR 1339 infusion and increased to 8.59 mmol/l (range: 4.05–20.28 mmol/l) eight hours after Triton WR 1339 infusion. Eleven hours after the Triton WR 1339 infusion the serum triglyceride concentrations decreased only a little (Table III). Induction of acute pancreatitis by itself did not lead to a change in serum triglyceride values.

Cholesterol

The animals receiving 0.25 ml Triton WR 1339 (group OP_(Caer+Tri)) had significantly ($p < 0.001$) higher serum cholesterol values than the non-hyperlipaemic animals (group OP_(Caer)). The median cholesterol value rose in group OP_(Caer+Tri) from 1.55 mmol/l (range: 1.33–1.89 mmol/l) before to 4.24 mmol/l (range: 2.10–5.15 mmol/l) eight hours after Triton WR 1339 infusion. Eleven hours after the Triton WR 1339 infusion the serum cholesterol values decreased only a little (Table III).

The cholesterol concentrations of the animals without Triton WR 1339 treatment (group OP_(Caer)) remained unchanged throughout the investigation (Table III).

Amylase

After induction of acute oedematous pancreatitis with caerulein, the amylase activities were increased, as expected. In comparison with the OP_(Caer) group, the amylase activities of the animals of the OP_(Caer+Tri) group were significantly higher ($p < 0.001$) (Table IV).

Lipase

The serum lipase values increased within 45 minutes of induction of pancreatitis with caerulein and showed a steep increase throughout

the experiment. The animals of group OP_(Caer+Tri) developed significantly higher ($p < 0.001$) serum lipase activities than the non-hyperlipaemic animals (Table IV).

Histology

Seven of the hyperlipaemic (group OP_(Caer+Tri)) and seven of the non-hyperlipaemic (group OP_(Caer)) animals developed smooth oedema 90 minutes after pancreatitis induction. In addition, two hyperlipaemic animals had moderate oedema. No additional histological changes occurred after 90 minutes in the OP_(Caer) group. One hundred and eighty minutes after induction of acute oedematous pancreatitis, the cumulative point scores of the tissue samples were significantly higher ($p < 0.01$) in the hyperlipaemic animals (group OP_(Caer+Tri)) than in the animals receiving only caerulein infusion (group OP_(Caer)) (Figure). The hyperlipaemic animals also showed singular parenchymal necrosis, whereas no parenchymal necrosis was seen in group OP_(Caer).

NECROTISING PANCREATITIS, GROUP (NP)

Beginning with the retrograde infusion of Na-taurocholate into the pancreatic duct, extended areas of the pancreas turned red and developed a pronounced oedema. The gland lobules were pushed apart by severe swelling of the gland. In some areas haemorrhage occurred and the animals developed sanguineous ascites.

Triglyceride and cholesterol

The course of the serum cholesterol and triglyceride concentrations in the animals with necrotising pancreatitis were again the same as in the animals without pancreatitis. The triglyceride values of the animals not receiving Triton WR 1339 (group NP_(Tau)) also did not change throughout the investigation (Table III). Infusion of Triton WR 1339 again led to endogenous hyperlipaemia in group NP_(Tau+Tri); eight hours after Triton WR 1339 application, the serum triglyceride and cholesterol values increased 11.6-fold and 2.3-fold, respectively (Table III). Induction of acute pancreatitis by itself did not lead to a change in serum triglyceride values.

Amylase

The serum amylase activities in the animals with necrotising pancreatitis were significantly increased after the induction of pancreatitis, but reached only half that of the animals with oedematous pancreatitis. Within 90 minutes of the induction of pancreatitis, the median amylase values rose from 1979 U/l (± 0) to 4200 U/l (+90 min) in the NP_(Tau+Tri) group. Three hours after pancreatitis induction the amylase values decreased a little (Table IV).

In the NP_(Tau) group the increase of the amylase values was slower than in the NP_(Tau+Tri) group (Table IV).

Lipase

In the first eight hours of the experiment no changes in the lipase activities occurred in group NP_(Tau) or group NP_(Tau+Tri). After induction of acute necrotising pancreatitis, the increase of the lipase values was greater in the NP_(Tau+Tri) group than in the NP_(Tau) group. The difference between the hyperlipaemic (NP_(Tau+Tri)) group and the non-hyperlipaemic (NP_(Tau)) group was of less significance than the difference seen in group OP (Table IV).

Histology

Microscopically, all tissue samples taken from the animals suffering from necrotising pancreatitis showed oedema and a significantly ($p < 0.01$) higher cumulative point score in the hyperlipaemic animals (NP_(Tau+Tri)) (point score 107) than in the non-hyperlipaemic animals (NP_(Tau)) (point score 67) 90 minutes after pancreatitis induction. Subsequently, 180 minutes after the induction of necrotising pancreatitis the point scores were 145 in the NP_(Tau+Tri) group and 110 in the NP_(Tau) group. These differences were statistically significant ($p < 0.01$).

Discussion

Compared with the main aetiological factors like gall stones and alcohol abuse, hyperlipaemia is of minor incidence in the development of acute pancreatitis. Nevertheless, several authors have reported that acute pancreatitis and hyperlipaemia coincide in 12% to 38% of patients. Also, patients suffering from hereditary hyperlipaemia have an incidence of up to 21% of acute pancreatitis.^{11 12 19} However, the mechanisms by which hyperlipaemia leads to acute pancreatitis are not known. One concept is that the damage of the acinar cells is caused by the cytotoxic effect of free fatty acids. These fatty acids are thought to be generated within the pancreas by the hydrolytic action from pancreatic lipase on triglycerides.²⁵ In 1989, Nagai *et al* postulated that interstitial fission of triglycerides by the pancreatic lipase might lead to a detergent-like destruction of the cell membrane.⁴⁰

The aim of this study was to analyse the effect of hyperlipaemia on the course of acute experimental pancreatitis in rats. Therefore, we divided the animals into six groups: two without pancreatitis, serving as the control; two with acute oedematous pancreatitis based on a caerulein model³²⁻³⁵; and two with acute haemorrhagic necrotising pancreatitis, based on the Na-taurocholate model.³⁶⁻³⁸ One group from each pair was pretreated with Triton WR 1339, which causes a significant increase of endogenous triglyceride and cholesterol blood concentrations.^{30 31} Animals in the other three groups received saline solution.

The rats without pancreatitis showed no clinical differences eight hours after Triton WR 1339 infusion compared with the animals with saline infusion. Macroscopically, the pancreases of the hyperlipaemic and the normal

animals showed no differences. Microscopically, however, the animals treated with Triton WR 1339 showed smooth oedema, whereas no changes occurred in the non-hyperlipaemic animals. These morphological changes in the pancreases of rats with hyperlipaemia seem not to be caused by direct toxic effects of Triton WR 1339 administration. In our test series, rats were treated with rising volumes of Triton WR 1339 to determine the optimal dose of this drug needed to induce hyperlipaemia. Using twofold and fourfold higher doses of Triton WR 1339 in these experiments, we found mild oedema in four of 10 and three of 10 animals, respectively. The smooth pancreatic oedema in some of the rats treated with Triton WR 1339 could be the effect of the concentration of free fatty acids and decomposition products of fatty acids, which have cytotoxic effects. Saharia *et al* proposed that trypsinogen is activated in the acid milieu of the fatty acids and leads to autodigestion of the pancreas.²⁵ Also, the detergent theory of Nagai *et al*, postulated in 1989, could explain these minor histological differences.⁴⁰ Hyperlipaemia seems to make the pancreas more susceptible to additional changes.

In the animals with acute oedematous pancreatitis (groups OP_(Caer+Tri) and OP_(Caer)) there were also no detectable differences macroscopically, either 90 or 180 minutes after inducing pancreatitis by a caerulein infusion. Histologically, smooth oedema and small vacuoles were detectable in both groups after 90 minutes of pancreatitis, being more noticeable in the hyperlipaemic group. The second samples, taken 180 minutes after the induction of pancreatitis, showed an increase in the Spormann point score of up to sixfold in the OP_(Caer) group and up to 10-fold in the hyperlipaemic animals (OP_(Caer+Tri)) in comparison with the control groups (C_(Sal), C_(Tri)). The animals receiving Triton (OP_(Caer+Tri)) showed increased inflammation, fat necrosis, haemorrhage, and even pancreatic necrosis, which did not occur in the OP_(Caer) group. Secretory vacuoles are increased in size and number in animals with acute oedematous pancreatitis. These vacuoles are typically seen in the early stages of acute pancreatitis. They are the result of a fusion of lysosomal and zymogen granules, with subsequent activation of proteases and cell destruction.^{41 42} The loss of activated enzymes into the interstitial tissue might lead to higher concentrations of free fatty acids in the hyperlipaemic animals, probably resulting from the generation of fatty acids by pancreatic lipase from the increased triglyceride values.^{25 40} Subsequently, the cytotoxic effects of free fatty acids might lead to a significant increase in histological damage in the animals having the Triton injection (group OP_(Caer+Tri)) before the induction of pancreatitis.

In the animals having acute necrotising pancreatitis, the serum lipase activity was significantly higher in the hyperlipaemic animals compared with the animals with normal triglyceride and cholesterol serum values. By histological analysis, pancreatic damage occurred earlier and

was more severe in the hyperlipaemic than in the non-hyperlipaemic animals. The degree of pancreatic damage was significantly higher ($p < 0.01$) in the hyperlipaemic necrotising pancreatitis group after 90 and 180 minutes compared with the non-hyperlipaemic groups.

Similar results were reported by Haig *et al.*²⁰ who induced acute pancreatitis in mongrel dogs. Dogs that had been maintained on a high fat diet for six weeks before pancreatitis became more acutely ill and sustained greater injury to the pancreas than those animals ingesting a balanced diet. The hypothesis that hyperlipaemia does not induce pancreatitis directly but rather causes a predisposition to or amplifies acute pancreatitis if there are other risk factors for acute pancreatitis has been supported in other studies.^{14 19 43} Also, in this study only the animals that received a Triton WR 1339 injection developed hyperlipaemia, regardless of whether acute pancreatitis was present. Other authors have hypothesised that pancreatitis might induce hyperlipaemia by itself.⁴⁴ Because our investigation was limited to three hours, it is probable that there was not enough time for hyperlipaemia to develop.

It is well known that relapsing episodes of acute pancreatitis are occasionally associated with hyperlipaemia.¹¹⁻¹⁶ Particularly in patients suffering from familial hyperlipoproteinaemia (types I, IV, and V according to the classification of Frederickson), acute pancreatitis has an incidence of up to 21%.^{12 19} Those clinical findings have been confirmed in several studies of experimental pancreatitis.^{20-22 25 38} Our experimental data show that hyperlipaemia intensifies the course of both acute oedematous and acute necrotising pancreatitis in rats. These findings suggest that hyperlipaemia might also be an important risk factor in the course of acute pancreatitis in humans. Additional studies are needed to explore the clinical significance of these findings.

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