Somatostatin therapy of acute experimental pancreatitis¹

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SUMMARY Because somatostatin (SRIF) reduces exocrine pancreatic secretion, its effect on acute pancreatitis was investigated in rats. Linear SRIF reduced serum amylase and lipase but had no effect on pancreatic necrosis, oedema, leucocyte infiltration, and enzyme content. The mortality rate was not reduced. These results do not recommend the use of SRIF in the treatment of acute pancreatitis.

Cyclic somatostatin (SRIF) significantly reduces hormonal (Creutzfeldt *et al.*, 1975; Dollinger *et al.*, 1976; Domschke *et al.*, 1976) and non-hormonal (Lankisch *et al.*, 1975) stimulated pancreatic volume and enzyme secretion in man. Linear SRIF inhibits basal and hormonal stimulated enzyme secretion in the rat (Fölsch *et al.*, 1976). As 'rest to the gland' is generally considered to be a major aim in the treatment of acute pancreatitis (Trapnell, 1972) the effect of SRIF was investigated in acute experimental pancreatitis in the rat.

Methods

Acute experimental pancreatitis was induced by retrograde injection of 0.6 ml of 0.8, 2.0, 2.5, and 3.0 Na-taurocholate (Serva Feinbiochemica, Heidelberg) into the pancreatic ducts of 101 male Wistar rats (180-220 g) (Lankisch *et al.*, 1974). Linear SRIF (Serono, Freiburg) was given subcutaneously at a dosage of 200 µg during operation as a bolus injection followed by infusion of 100 µg/100 g body weight/h for three hours. This regime had been found to decrease significantly pancreatic enzyme secretion for more than four hours (Fölsch *et al.*, 1976). Controls received saline infusions. To investigate the SRIF influence upon the survival rate the following groups were formed (Figure):

1.2%-Na-taurocholate-

pancreatitis : (a) SRIF-therapy : n = 12;
(b) controls : n = 11;

2.2.5%-Na-taurocholate-pancreatitis : (a) SRIF-therapy : n = 12;
(b) controls : n = 10;

3.3%-Na-taurocholate-pancreatitis : (a) SRIF-therapy : n = 6;
(b) controls : n = 5;

0.8%-Na-taurocholate-pancreatitis was not used for survival experiments as the mortality rate of this model is too low to demonstrate the success of a treatment.

To study the effects of SRIF upon morphological and enzymatic factors rats were killed four hours after induction of pancreatitis by 0.8, 2.0, and 3.0%-Na-taurocholate—that is, one hour after the treatment was stopped. 2.5%-Na-taurocholate-pancreatitis was not used as there were no distinct differences between 2.0 and 3.0%-Na-taurocholate-pancreatitis where the above mentioned factors were concerned (Table). Ascites was measured and tissue from the head and the tail of the pancreas was fixed in Bouin's solution, embedded in paraffin, cut in 5 µm sections, and stained with haematoxylin and eosin.

Histologically, the degree of necrosis, oedema, and leucocyte infiltration was estimated as absent (0), slight (1), moderate (2), and severe (3) as reported before (Lankisch *et al.*, 1974). The remaining pancreas was used for enzyme assays: α-amylase (EC3211) according to Rick and Stegbauer (1970)

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Table Morphological and enzymatic parameters of three groups of experimental pancreatitis in treated and non-treated rats

n	Pancreatitis induced by:					
	0.8% Na-taurocholate		2% Na-taurocholate		3% Na-taurocholate	
	SRIF 12	Controls 11	SRIF 6	Controls 5	SRIF 6	Controls 5
Ascites (ml)	4.3 ± 1.9	5.7 ± 2.2	6.3 ± 1.9	5.6 ± 2.7	4.2 ± 2.1*	6.8 ± 1.3
Necrosis	2.4	2.6	2.2	2.2	3.0	2.6
oedema	2.4	2.3	2.7	2.8	2.8	2.6
leucocyte infiltration	1.2	1.1	0.7	0.6	1.0	1.0
Serum amylase (SCE/100 ml)	1869†	2234	1941	3220	1852	2054
Serum lipase (U/ml)	± 271	± 413	± 447	± 1390	± 167	± 331
Ascites amylase (10*SCE/100 ml)	7.61*	10.32	5.74‡	9.77	7.88*	12.32
Ascites lipase (U/ml)	± 1.52	± 4.05	± 0.43	± 1.85	± 1.09	± 4.73
Amylase (U/pancreas)	20.18	18.0	14.54	19.94	17.47	15.64
Trypsin (mU/pancreas)	± 6.0	± 5.91	± 3.84	± 3.94	± 5.16	± 3.69
	179.5	185.6	128.7	128.9	201.2	181.2
	± 53.3	± 58.0	± 39.7	± 27.8	± 52.7	± 69.5
	9696	8778	11429	10902	7211	8807
	± 3456	± 1594	± 1268	± 2342	± 1169	± 1570
	6687	6646	5670	4712	7562	10907
	± 2692	± 2860	± 1308	± 881	± 1470	± 3380

* P < 0.05, † P < 0.02, ‡ P < 0.001, all versus controls.

SURVIVAL RATE

Figure Influence of SRIF-treatment (black symbols) on the survival rate of acute experimental pancreatitis compared with non-treated controls (white symbols). □—□ 2% Na-taurocholate pancreatitis; SRIF-treatment n = 12; controls n = 11; ○—○ 2.5% Na-taurocholate pancreatitis; SRIF-treatment n = 12; controls n = 10; △—△ 3% Na-taurocholate pancreatitis; SRIF-treatment n = 6; controls n = 5.

and trypsin (EC3444) according to Erlanger *et al.* (1961). Enterokinase (EC3448) was obtained from Hoechst, Frankfurt/Main-Höchst.

Amylase and lipase were measured in serum and ascites according to Street and Close (1956), Close and Street (1958), and Rick (1969), respectively. Statistical analysis was performed using Student's *t* test.

Results

ENZYMES IN SERUM AND ASCITES

When rats were killed four hours after induction of pancreatitis serum lipase was significantly lower after SRIF therapy in all three groups (Table). Serum amylase was also lowered, although only significantly so with 0.8%-Na-taurocholate-pancreatitis. Enzyme values in the ascites did not differ from those in non-treated controls.

MORPHOLOGY AND ENZYMES IN PANCREAS

As the Table shows, SRIF did not influence the degree of pancreatic necrosis, oedema, and leucocyte infiltration or the enzyme content of the pancreas after pancreatitis was induced.

SURVIVAL RATE

After induction of 3.0%-Na-taurocholate-pancreatitis all rats, treated and untreated, died within 20 hours. In the less severe forms of experimental pancreatitis the survival rate was 50% versus 50% and 73% versus 75% for treated and untreated animals (Figure).

Discussion

It is generally accepted that the reduction of pancreatic exocrine secretion is beneficial in the treatment of acute pancreatitis. For this purpose several hormones with inhibitory effects on the pancreas have been recommended, such as glucagon (Zajtcuk *et al.*, 1967; Dyck *et al.*, 1970), calcitonin (Schmidt *et al.*, 1971), and SRIF (Creutzfeldt *et al.*, 1975), which all markedly depress the exocrine and to a lesser extent the hydrokinetic pancreatic secretion. Knight *et al.* (1971) first introduced glucagon in the treatment of acute pancreatitis and this was followed by several reports in favour of this new therapy. Unfortunately, animal experiments failed to show a beneficial effect of glucagon in acute pancreatitis in rats (Lankisch *et al.*, 1974; Fodor *et al.*, 1975) and dogs (Condon *et al.*, 1974). In controlled studies in man neither glucagon (Dürr *et al.*, 1976) nor calcitonin (Goebell, 1976) significantly influenced the course of acute pancreatitis.

In our experiments treatment with SRIF reduced

serum enzymes, a feature which was also found after the application of glucagon (Lankisch *et al.*, 1974). This effect is of no clinical importance. The significance of the degree of decrease in the rise of serum enzymes remains controversial for the course of the disease (Brooks, 1972) and serum enzyme levels have been reported to be inversely related to the severity of pancreatitis (Adams *et al.*, 1968).

SRIF therapy had no influence upon the morphology and the pancreatic enzyme content and did not change the survival rate of acute experimental pancreatitis.

These results do not encourage the introduction of SRIF in the treatment of acute pancreatitis as proposed by some authors (Boden *et al.*, 1975; Dollinger *et al.*, 1976). Nor do they support the hypothesis that inhibition of pancreatic secretion may change the course of acute pancreatitis.

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