GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Histoprotective Effect of Antihypoxant Olifen during Experimental Acute Pancreatitis

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We evaluated the efficiency of perfusion with olifen in preventing oxidative stress at the early stage of acute pancreatitis. Transaortic perfusion with olifen prevented clinical and biochemical symptoms of acute pancreatitis, attenuated oxidative stress, reduced peritoneal exudation, and restricts the area of pancreatic necrosis to 6% tissue.

Key Words: *acute pancreatitis; transaortic olifen therapy*

Pancreatic hypersecretion, intrapancreatic activation of proteases and lipases, release of inflammatory cytokines [5,9], and oxidative stress (OS) manifested by systemic hypoxia and hyperperoxidation [10,11] are the major factors inducing local (destruction of the pancreas) and systemic (shock) pathological processes during acute pancreatitis (AP). Much attention is given to antihypoxic and antioxidant therapies of AP [4,6,8]. However, these procedures are not included in the gold standard of therapy for AP.

The aim of the present study was to evaluate the possibility and efficiency of inhibition of OS at the early stages of experimental AP.

MATERIALS AND METHODS

Experiments were performed on 36 cats weighing 3-5 kg. The animals were intraperitoneally narcotized with 30 mg/kg nembutal. AP was modeled by retrograde perfusion of 1 ml/kg bile and 2 mg/kg crystalline trypsin into the main pancreatic duct at 60 mm Hg. Control animals (n=14) received no drugs. Group 1 cats (n=4) with AP were subjected to transaortic perfusion of the splanchnic region with 10 ml/kg physiological saline for 1 h. Group 2 cats (n=18) received 10 mg/kg olifen in 10 ml/kg physiological saline (transaortic perfusion for 1 h). Olifen is a polyoxiphenylen compound possessing pronounced antihypoxic and antioxidant properties.

Total survival in experimental groups, coefficient of peritoneal exudation (EC, mm/kg/h), and parameters of enzyme toxicosis (amylase activity in the blood and exudate), systemic hypoxia (plasma lactate), and lipid peroxidation (malonic dialdehyde, MDA) were evaluated. Survivors were euthanized by intravenous injection of nembutal. The pancreases were subjected to macro- and microscopic examinations with semiquantitative measurements of pancreatic necrosis areas. The results were analyzed by Student's t test.

RESULTS

In all animals experimental AP was accompanied by fermentemia: amylase activity 1 h after AP modeling increased to 68.8±18.7 mg/ml/sec (*vs.* 25.5±12.4 mg/ml/sec in the control). Cats with AP had enzymatic peritonitis (amylase activity in the exudate was 98.8±22.4 mg/ml/h). All control cats developed massive destructive pancreatitis (Fig. 1, *b*): EC was 0.52±0.08

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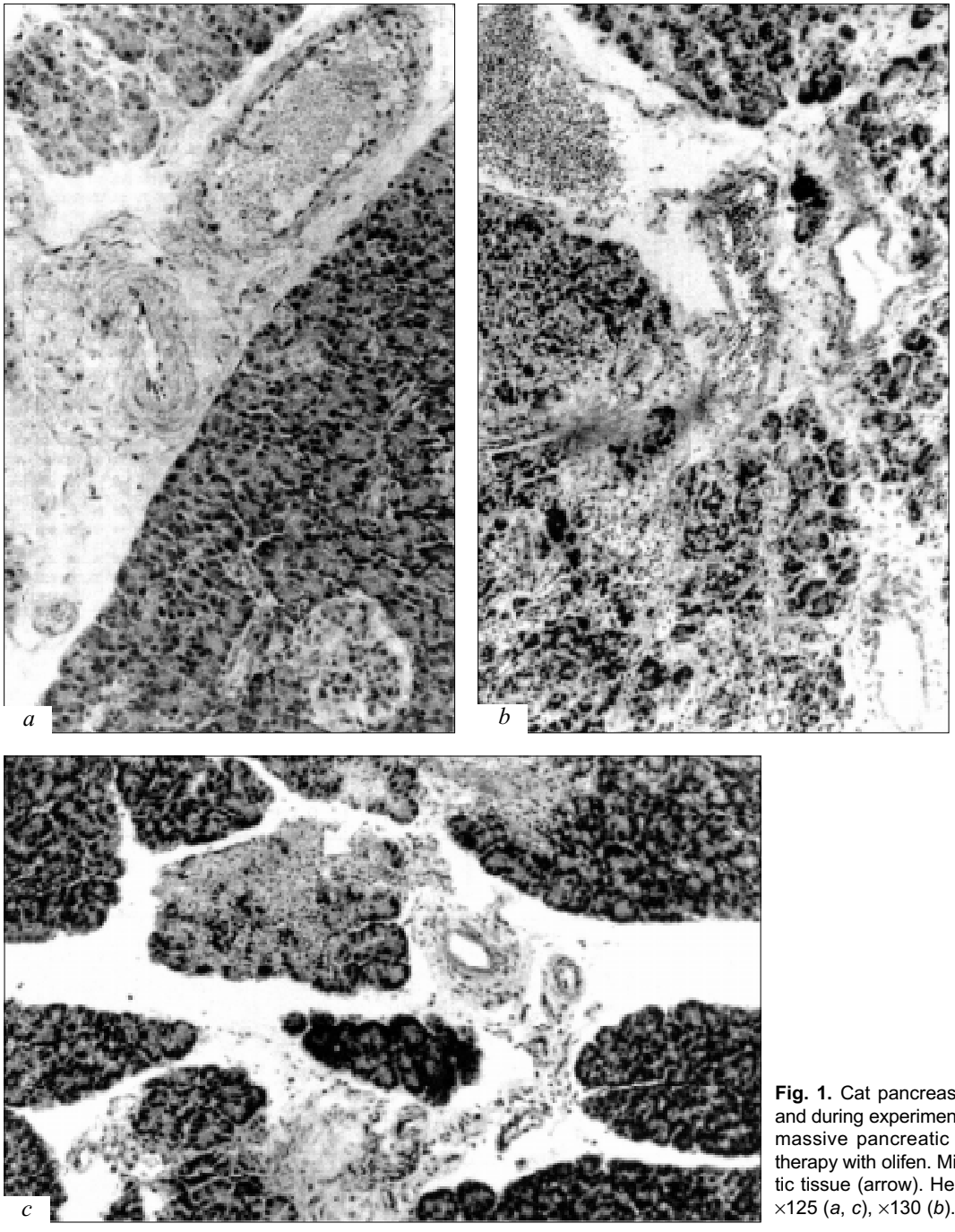

Fig. 1. Cat pancreas under normal conditions (*a*) and during experimental acute pancreatitis (*b, c*); *b*) massive pancreatic necrosis (control group); *c*) therapy with olifen. Microfocal necroses of pancreatic tissue (arrow). Hematoxylin and eosin staining, ×125 (*a*, *c*), ×130 (*b*).

ml/kg/h, plasma lactate concentration increased from 1.34±0.45 to 6.3±0.5 μmol/liter ($p<0.05$), and MDA concentration increased from 3.12±0.11 to 6.75±0.30 nmol/liter ($p<0.05$). The mean lifetime in the control group was 5±1 h and the area of pancreatic necrosis was 35±18% tissue.

In group 1 cats with AP receiving physiological saline, all parameters did not differ from the control. EC was 0.58±0.07 ml/kg/h, plasma lactate concentration increased from 1.38±0.36 to 5.85±0.44 μmol/liter, and MDA concentration increased from 2.97±0.16 to 6.18±1.05 nmol/liter. The lifetime of these animals was 6±1 h. The area of pancreatic necrosis was 27±9% tissue ($p>0.05$).

In group 2, 7 of 18 cats survived for 24 h and were euthanized. The mean lifetime was 18±4 h. EC decreased to 0.23±0.03 ml/kg/h. The contents of lactate and MDA increased to a lesser extent (3.18±0.68 μmol/liter and 4.48±0.27 nmol/liter, respectively, $p<0.05$ compared to the control group). The area of pancreatic necrosis in group 2 cats (6±1% tissue) was much lower than in animals of other groups. Pathohistolo-

gical changes included microfocal necroses, edema, and atrophy of pancreatic cells (Fig. 1, *c*).

Thus, transaortic splanchnic perfusion with 10 mg/kg olifen at the early stage of AP improved clinical and biochemical parameters, prolonged the lifetime and improved survival of experimental animals (40% cats), decreased the area of pancreatic necrosis, and prevented OS.

Previous experiments with AP demonstrated that forced diuresis [1] and intravenous injection of enzyme inhibitors and cytostatics [2] prolonged the lifetime of animals. However, these procedures did not reduce destructive changes in the pancreatic tissue. Probably, suppression of pancreatic hypersecretion and endotoxicosis during AP does not prevent the development of pancreatic necrosis, which is realized via circulatory hypoxia [7] and damages to pancreatic cell membranes [8] (*i.e.* OS syndrome).

There are ambiguous data on the effects of antioxidants during AP, probably due to the use of moderate AP models [6] and low or uncertain efficiency of test preparations (*e.g.*, tocopherol and sodium selenite) [4,8]. Our experiments on the model of severe destructive AP accompanied by local and systemic pathological processes demonstrate an important role of OS in the pathogenesis of this condition and positive effects of its prevention. Moreover, pharmacological effects of olifen are unambiguous and standard. The antihypoxic effect of olifen during hypoxia is associated with transfer of reduction equivalents in the respiratory chain from NADPH or succinate directly to complex 3 without involvement of complexes 1 and 2 [3]. Antioxidant properties of olifen are related to the presence of weak phenol hydroxyl groups scavenging peroxide radicals [3].

Thus, our experiments on the model of severe destructive pancreatitis showed that antihypoxic and antioxidant properties of olifen determine its protective effects on secretory pancreatic tissues. Olifen is recommended for clinical tests at the early stage of destructive AP.

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