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EFFECT OF TAGEFLAR, A SYNTHETIC L-ENKEPHALIN ANALOG, ON MORPHOGENESIS OF EXPERIMENTAL PANCREATITIS

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KEY WORDS: experimental pancreatitis; morphogenesis, tageflar

Much clinical and experimental evidence has now been obtained to show that, despite the existence of a wide range of drugs, the effectiveness of conservative treatment of pancreatitis is not yet sufficient to meet the demands of clinical medicine. In the last decade research workers have paid close attention to natural neuropeptides and to their synthetic analogs, which have a broad spectrum of biological action. The enkephalins and their synthetic analogs, notably dalargin, are known to be able to inhibit basal and stimulate pancreatic secretion [3, 5], to inhibit activity of the pancreatic enzymes and kinins, potentiate the inhibitory system of proteolytic enzymes [1], and to limit and prevent progression of the pathological process in the pancreas during pancreatitis under both clinical and experimental conditions [1, 4].

The aim of this investigation was to test a new synthetic enkephalin analog — tageflar (synthesized in the Laboratory of Peptide Synthesis, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR) as an agent for the pathogenetic treatment of experimental pancreatitis.

EXPERIMENTAL METHOD

Pancreatitis was produced in 197 noninbred albino rats weighing 180-200 g by cooling the splenic segment of the pancreas with ethyl chloride. Of this total number of rats, tageflar was injected intraperitoneally in a dose of 0.1 mg/kg into 70 rats, immediately after injury to the pancreas, and also 2 and 24 h later. The remaining animals served as the control. Rats of both groups were killed by decapitation 1, 3, 6, and 24 h and 3, 7, 14, 21, and 30 days after injury to the pancreas. The pancreas was fixed in 10% formalin, buffered by Lillie's method, and embedded on paraffin wax. Paraffin sections 4 μ thick were stained with hemotoxylin and eosin, by the Jenner–Giemsa and Gram–Weigert methods. Amylolytic activity of the blood was determined by Caraway's method, and trypsin-like activity and the trypsin inhibitor level in the blood by Shaternikov's method.

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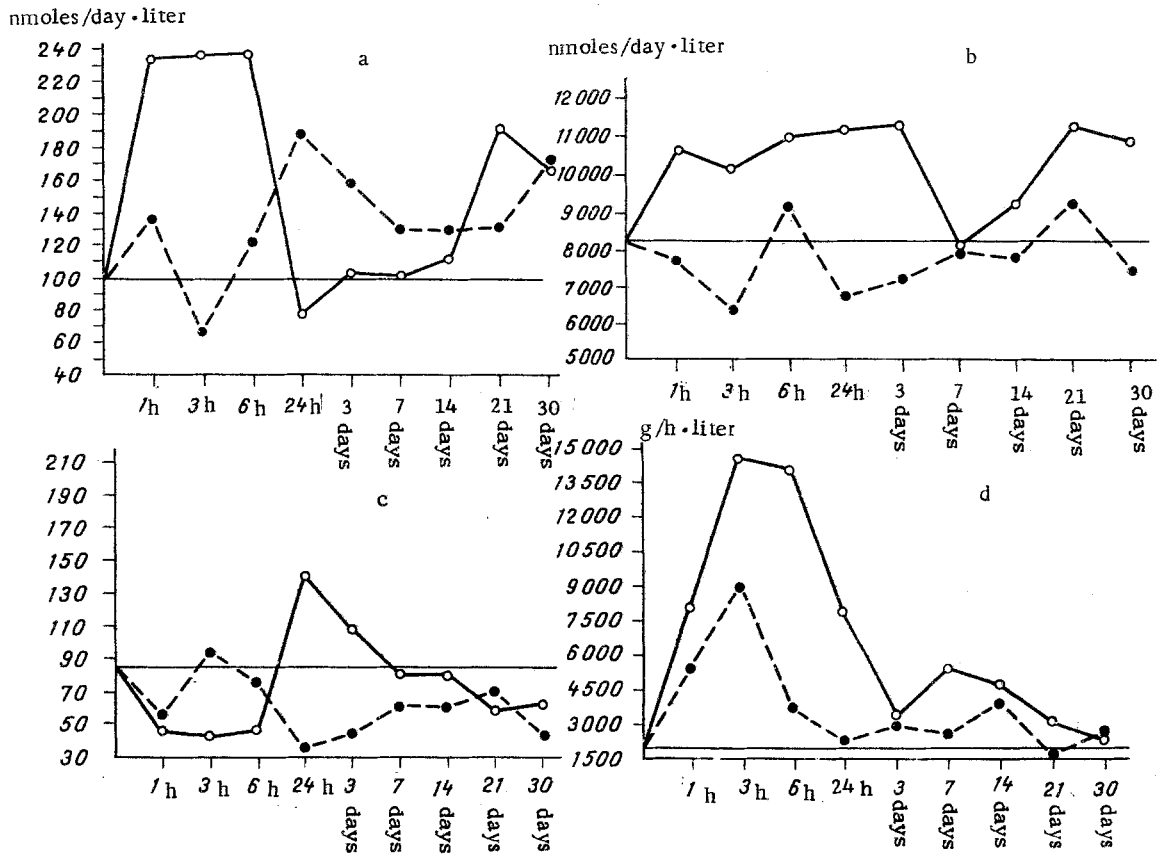

Fig. 1. Time course of changes in tryptic (a) and antitryptic (b) activity, trypsin—inhibitor ratio (c), and α-amylase activity (d) in experimental pancreatitis (broken line) and against the background of treatment with tageflar (continuous line). Horizontal line— normal. Abscissa, period of experiment; ordinate, enzyme activity (in units of measurement).

EXPERIMENTAL RESULTS

Under the influence of tageflar a substantial fall occurred in the amylolytic (Fig. 1d) and tryptic (Fig. 1a) activity of the blood, and this was particularly marked in the hemorrhagic stage of pancreatitis (1-6 h). By contrast with the control (pancreatitis) the trypsin level was increased in the necrotic stage (24 h) and on the 30th day of experiment (flare-up of chronic parcreatitis). Throughout the duration of the experiment tageflar depressed the antitryptic activity of the blood (Fig. 1b), while maintaining a normal trypsin—inhibitor ratio at the height of development of the hemorrhagic stage (Fig. 1c).

The macroscopic picture of the pancreas in the control and experimental rats was characterized by similar changes until the 7th day of experiment: congestion, edema, hemorrhages, suffusion of blood into the injured and "vitreous" edema of the uninjured segments of the gland after 1-6 h, necrosis formation after 24 h, and pseudocyst formation on the 7th day after induction of pancreatitis [2]. However, later under the influence of the compound there was a sharp decrease in size of the pseudocyst, which underwent partial and then complete absorption by the 30th day. The injured segment of the pancreas under these circumstances consisted of bands of semitransparent connective tissue. In the control, however, a massive pseudocyst was found until the 90th day of observation.

Microscopic investigation of the damaged segment of the pancreas in the control rats in the hemorrhagic stage revealed marked loss of structure of the acini, and the exocrine pancreocytes (EP) were in a state of necrobiosis, with diffusion of zymogen (ZG) granules among the cytoplasm and their escape into the edematous interstices. The cytoplasm of EP was mainly diffusely oxyphilic, highly vacuolated in places. The periacinar capillaries were congested, with evidence of erythrostasis and microthrombosis, and the stroma of the organ was in a state of marked edema. The whole of the damaged segment of the gland was suffused with blood. The duodenal (intact) segment of the pancreas was in a state of vitreous edema:

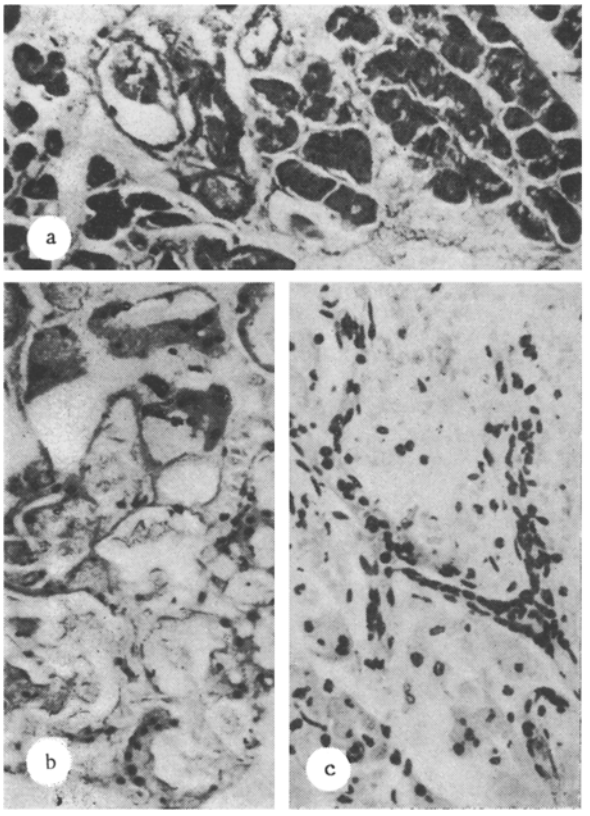

Fig. 2

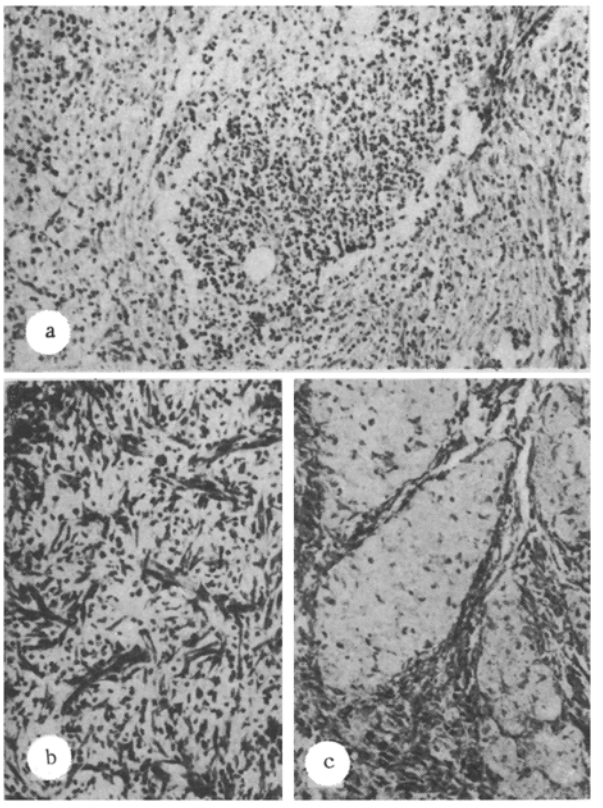

Fig. 3

Fig. 2. Zone of injury to pancrease 24 h after induction of pancreatitis (a) and the same under treatment with tageflar (b, c). a) Coagulation necrosis of pancreatic parenchyma; b) lysis of EP; c) denudation of microvessels. Hematoxylin and eosin. 100 ×.

Fig. 3. Pseudocyst in pancreas in animal treated with tageflar (14th day). a) Microabscesses in capsule; b) proliferation and vertical orientation of vessels in capsule of pseudocyst; c) ingrowth of bands of connective tissue and vessels into contents of pseudocyst. Jenner–Giemsa stain. 100 ×.

the edema fluid was not strained by histological dyes and did not contain inflammatory cells. In the experimental (tageflar) rats the identical picture was observed in both segments of the pancreas, the only difference being that in the cytoplasm of necrobiotically changed EP there were no ZG, and by this stage of the experiment foci of infiltration of the zone of injury by polymorphonuclear leukocytes (PML) had formed. Hemorrhages were localized mainly by the interlobular stroma, and much less frequently in the acini.

Destructive processes in the parenchyma progressed in the damaged segment of the pancreases in both groups of animals. Under these circumstances (24 h-3 days) the picture in the control rats was dominated by coagulation necrosis of EP (Fig. 2a) but in the experimental rats by cloudy-swelling degeneration and lysis of EP, with the result that denudation of the periacinar capillaries took place (Fig. 2b, c). Under the influence of tageflar, PML-infiltration of the necrotic pancreatic tissues through vessels in the boundary zone and surviving microvessels of the epicenter of injury increased. Tageflar also led to the formation of microabscesses in the capsule of the pseudocyst (Fig. 3a) which, in turn, was accompanied by the more rapid liquefaction and elimination of the components of the pseudocyst. At the same time, marked vascularization of the capsule took place (Fig. 3b) with invasion of bands of connective tissue and blood vessels into the contents of the pseudocyst (Fig. 3c). By the 30th day of observation the zone of injury to the pancreas in the experimental rats was composed of connective tissue, rich in cells but extremely poor in fibrous structures. Besides fibroblasts, there were large numbers of mast cells and macrophages and concentrations of lymphocytes. Meanwhile in the control group, PML-infiltration of the zone of necrosis was on a small scale, perifocal in distribution, and the infiltrating cells did not penetrate into the depth of the necrotic tissues. The capsule of the pseudocyst was formed by coarse bun-

dles of collagen fibers hyalinized in places. In areas of the gland adjacent to the pseudocyst sclerosis and lipomatosis progressed.

In the group of animals treated with tageflar the boundary zone was greatly reduced in size. In it, just as in the control, tubulo-epithelial reconstruction of the acini took place. However, unlike in the control the tubulo-epithelial complexes were less numerous and were formed by flattened, dystrophic EP, which were subsequently replaced by connective tissue.

Administration of tageflar in a dose of 0.1 mg/kg thus had a marked effect on the morphogenesis of experimental pancreatitis. The most important and characteristic features of the pathomorphosis of pancreatitis in this case are: 1) accelerated formation of complete necrosis of irreversibly damaged EP and reduction in size of the perifocal zone of necrobiosis with reconstruction of acini into tubulo-epithelial complexes; 2) considerable preservation of the microcirculation in the zone of necrosis of the parenchyma with intensification of PML-infiltration of necrotic tissues of the gland, acceleration of their elimination and organization of foci of injury; 3) inhibition of sclerosis and lipomatosis formation in the pancreas; 4) lowering of the blood levels of pancreatic enzymes in the hemorrhage stage of experimental pancreatitis.

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EFFECT OF ZIXORIN ON DIURESIS AND RENAL TRANSPORT OF XENOBIOTICS

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KEY WORDS: zixorin; diuresis; tubular secretion of kidneys

Zixorin (Gedeon Richter, Hungary), a new inducer of the mono-oxygenase system, has been widely used in a number of conditions when stimulation of glucuronide formation and excretion of foreign substances has been required. In the character of this action it resembles phenobarbital [6]. It was shown previously that an inducer of microsomal enzymes, studied at the Institute of Cytology and Genetics, Siberian branch, Academy of Sciences of the USSR, potentiates tubular secretion in the kidneys [1].

It was decided to study zixorin in this respect. This was important also because zixorin has an immunomodulating action, and in particular, it stimulates antibody formation and phagocytosis [4]. Meanwhile it has been shown that immunostimulators accelerate tubular transport of foreign substances [2]. Besides tubular secretion, it was also decided to study the effect of zixorin on other processes in the kidneys, namely diuresis and sodium and potassium excretion, which may be of practical importance.

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