EFFECT OF SODIUM THIOSULFATE ON VIABLE PARTS OF THE PANCREAS IN EXPERIMENTAL PANCREATITIS

A. S. Kanayan, N. A. Gabrielyan, and G. A. Gevorkyan

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KEY WORDS: experimental pancreatitis; sodium thiosulfate; morphometry of acinar cells; protein synthesis.

The use of proteinase inhibitors in the medical treatment of pancreatitis has not proved a sufficiently effective measure [1, 4] and, accordingly, intensive research is now in progress in order to find new substances with a specific action on one particular stage in the pathogenesis of this serious disease. Recently research workers have concentrated their attention on substances inhibiting protein synthesis in the pancreas [3, 6, 7-10]. The present writers showed previously that sodium thiosulfate limits the spread of necrotic and necrobiotic changes to undamaged parts of the pancreas in experimental pancreatitis [2].

The object of the present investigation was to study the effect of this compound on viable parts of the pancreas in the course of experimental pancreatitis.

EXPERIMENTAL METHOD

Experiments were carried out on 66 albino rats weighing 180-200 g, divided into three groups: 1) intact rats (n = 6); 2) control rats with experimental pancreatitis (n = 30), 3) experimental group of rats with experimental pancreatitis treated with sodium thiosulfate (n = 30). Pancreatitis was induced by cooling the splenic segment of the pancreas with ethyl chloride. Sodium thiosulfate, in the form of a 30% aqueous solution, was injected intraperitoneally into the animals of group 3 daily in a dose of 50 mg/100 g body weight. The rats of all three groups were decapitated after deprivation of food for 18 h on the 1st, 3rd, 7th, 14th, and 30th days after induction of pancreatitis. The test object was the duodenal (intact) segment of the pancreas, which was fixed in an alcohol–acetic acid–formalin mixture and embedded in paraffin wax. The area of the nucleus and cytoplasm of the acinar cells (AC) was determined by the dot counting method in paraffin sections 4 μ thick stained with hematoxylin and eosin. The intensity of incorporation of [^{14}C]leucine into proteins in this segment of the pancreas was determined *in vitro*. Radioactivity was measured on an SL-4221 liquid scintillation spectrophotometer (Intertechnique, France), in Bray's scintillator after preliminary solubilization of the proteins in 0.5 M protosol. The counting efficiency relative to ^{14}C was 95%. The numerical results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

Against a background of necrosis of the parenchyma of the splenic segment of the pancreas (24 h after induction of pancreatitis) interlobular and interacinar edema of the duodenal segment was observed in the control rats. AC appeared swollen with translucent cytoplasm. Meanwhile, under the influence of sodium thiosulfate edema of the duodenal segment did not develop and AC, on histological examination, had the usual appearance of the intact pancreas. Morphological investigation of the nuclei of AC (Fig. 1) in animals of the control group showed that their area varied within normal limits during the first 3 days. On the 7th and 14th days, against the background of pancreatic pseudocyst formation, the nuclei of AC in the control rats were significantly enlarged. In the stage of development of chronic pancreatitis (30th day) the area of the nuclei of AC was again close to the initial level. The use of sodium thiosulfate was accompanied by a gradual increase in areas of the nuclei of AC, although

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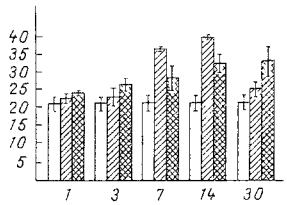

Fig. 1

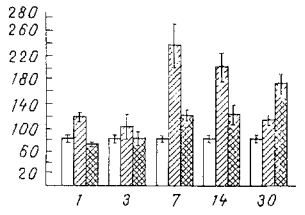

Fig. 2

Fig. 1. Mean area of AC in duodenal segment of pancreas. Abscissa, time of experiment (in days); ordinate, area of nucleus (in μ^2). Here and in Figs. 2 and 3 unshaded columns indicate intact rats, obliquely shaded columns — rats with pancreatitis, cross-hatched columns — pancreatitis + sodium thiosulfate.

Fig. 2. Mean area of cytoplasm of AC in duodenal segment of pancreas. Abscissa, time of experiment (in days); ordinate, area of cytoplasm (in μ^2).

it did not reach the highest values observed in the control rats. Changes in area of the AC cytoplasm in the duodenal segment of the control rats and of rats receiving sodium thiosulfate in the course of the experiment are illustrated in Fig. 2. The increase in area of the AC cytoplasm in the control animals after 24 h was in all probability the result of dystrophic changes during the development of intracellular edema, revealed by the histological study. By the 3rd day the cytoplasm of AC was back to the normal size, but later, on the 7th day, there was a sharp increase in area of the cytoplasm of AC, to 236.1 ± 36.4 μ^2 compared with 82.1 ± 6.6 μ^2 in intact rats. Later, although the area of the cytoplasm decreased, it did not reach the area of AC in intact rats. Under the influence of sodium thiosulfate some increase in area of the cytoplasm of AC was found on the 7th-14th days, reaching a peak on the 30th day of the experiment.

It will be clear from Table 1 that a decrease in the nucleo-cytoplasmic ratio of AC in animals of the control group took place on the 1st and 7th days of the experiment. However, this phenomenon was due to different causes. For instance, whereas after 24 h the increase in area of the AC cytoplasm developed as a result of intracellular edema, the area of the nucleus remaining unchanged, on the 7th day both nucleus and cytoplasm were hypertrophied, but the rate of increase of area of the nucleus was slower than that of the cytoplasm. The normal value of the nucleo-cytoplasmic ratio of AC in the control rats was restored on the 14th day against the background of hypertrophy of both nucleus and cytoplasm. After injection of sodium thiosulfate the nucleo-cytoplasmic ratio of the experimental rats was increased on the 1st-3rd day of the experiment as a result of some increase in area of the nucleus while the cytoplasm remained the same size. On the 30th day after injection of sodium thiosulfate the ratio decreased because the area of the nucleus increased more slowly than that of the cytoplasm.

A sharp increase in the intensity of incorporation of [^{14}C]leucine into protein of the duodenal segment of the pancreas (Fig. 3) was observed in the control rats on the 3rd day of the experiment, when it reached 2164.0 ± 89.8 cpm/mg protein compared with 748.8 ± 16.9 cpm/mg protein in intact animals. In all probability this intensification of protein synthesis reflected intracellular regeneration after degenerative changes in AC discovered in the phase of parenchymatous necrosis of the pancreas [6]. The high intensity of incorporation of labeled leucine observed in the subsequent periods of the experiment, together with hypertrophy of AC, may be evidence of increased secretory activity of the remaining AC in response to loss of a considerable part of the excretory parenchyma. The effect of sodium thiosulfate on incorporation of [^{14}C]leucine was manifested as follows: The value of this parameter was lower on the 1st day, but higher on the 7th and 30th days than in the control.

Experimental treatment of pancreatitis with sodium thiosulfate thus prevents the development of edema of the stroma and of the degenerative changes and intracellular edema of AC observed in viable parts of the pancreas in the phase of parenchymatous necrosis in control animals. Hypertrophy of AC under the influence of thiosulfate is observed later and is less marked than in the control. Sodium thiosulfate inhibits incorporation of [^{14}C]leucine, about 90% of which is known to be utilized in synthesis of secretory proteins [11], into proteins of the pancreas. The compound thus inhibits secretory activity of viable AC and creates con-

TABLE 1. Nucleo-cytoplasmic Ratios in Intact Segment of Rat Pancreas

Experimental conditions	Stage of experiment, days				
	1	3	7	14	30
Pancreatitis	0,19±0,01	0,25±0,03	0,16±0,03	0,2±0,02	0,22±0,02
P	<0,01	>0,5	<0,01	>0,05	>0,1
Pancreatitis + sodium thiosulfate	0,33±0,02	0,32±0,02	0,24±0,025	0,27±0,03	0,19±0,01
P	<0,05	<0,05	>0,5	>0,5	<0,01
P_1	<0,001	>0,1	>0,05	>0,05	>0,2

Legend. This ratio in intact rats was 0.26 ± 0.02. P) Relative to intact rats; P_1) relative to pancreatitis. Each group consisted of five animals.

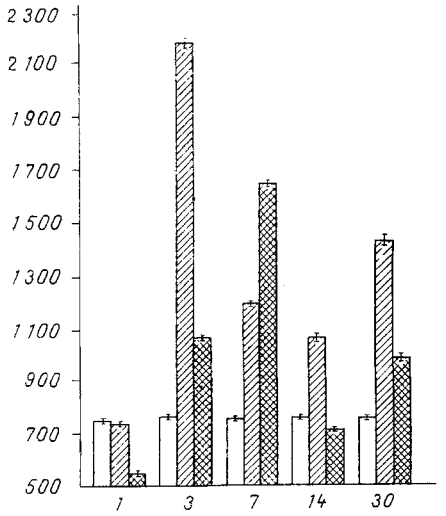

Fig. 3. Incorporation of [^{14}C]leucine into protein in duodenal segment of pancreas. Abscissa, time of experiment (in days); ordinate, incorporation of [^{14}C]leucine (in cpm/mg protein).

ditions of relative "rest" for them; this determines the increased resistance of the AC to the action of pathogenic agents originating from damaged parts of the pancreas.

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