EFFECT OF SEROTONIN ON ACTIVITY OF SECRETORY AND LYSOSOMAL ENZYMES IN PANCREATIC TISSUE AND ON THE INHIBITORY PROPERTIES OF BLOOD SERUM

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Serotonin is a biologically active substance with a varied effect on organs of the gastrointestinal tract [6, 7]. Data in the literature on the action of serotonin on secretory processes in pancreatic tissue are very limited. Such information as is available deals mainly with the effect of serotonin on the enzyme-liberating function of the pancreas [5, 9]. The possible role of serotonin in the pathogenesis of duodenal ulcer also is mentioned [1-3, 8]. Erspamer [13] considers that its role in inflammatory processes has been proved in some animals, the mast cells of whose organs contain serotonin. The object of the present investigation was to study the activity of secretory and lysosomal enzymes of pancreatic tissue and the inhibitory properties of the blood serum after injection of serotonin into intact animals.

EXPERIMENTAL METHOD

Experiments were carried out on 120 albino rats weighing 160-180 g. Serotonin was injected intramuscularly in a dose of 20 mg/kg. The rats were decapitated under ether anesthesia 30 min after the injection and their pancreatic tissue and blood were studied. Trypsin activity was determined in an extract of pancreatic tissue homogenate by Erlanger's method in Shaternikov's modification [4], elastase activity was determined by Geokas' method in the writer's own modification [11], cathepsins by Anson's method [12], and acid phosphatase by Bessey's method [4]. The antitryptic activity of the blood serum was determined by Haverback's method in Shaternikov's modification [4]. The serotonin and histamine concentrations in pancreatic tissue and blood were investigated by Sadavanquivad's method [2]. Elastase and acid phosphatase activity were calculated by means of a calibration curve and expressed in units or micromoles p-nitrophenol per gram native weight of pancreas; trypsin and trypsin inhibitor activity were calculated by a formula and expressed in milliunits per gram weight.

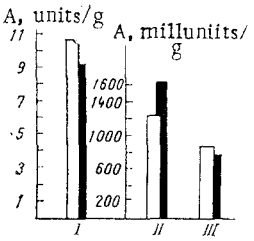

Fig. 1. Changes in total elastase (I) and trypsin (II) activity and in inhibitory properties of blood serum (III). Here and in Figs. 2 and 3, unshaded columns denote control, black columns experiments with injection of serotonin.

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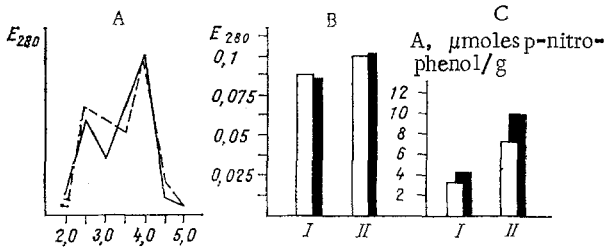

Fig. 2. pH curve of proteolytic activity in pancreatic tissue homogenate at acid pH values (A), cathepsin activity in pancreatic tissue homogenate at pH 3.0 in satiated (B, I) and hungry (B, II) rats before and after injection of serotonin, and acid phosphatase activity in pancreatic tissue homogenate before and after serotonin in satiated (C, I) and hungry (C, II) rats.

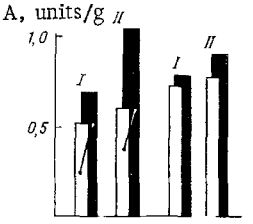

Fig. 3. Changes in serotonin (A) and histamine (B) concentrations in pancreatic tissue homogenate of satiated (I) and hungry (II) rats before and after injection of serotonin. Lines inside columns indicate changes in serum serotonin concentration before and after injection of serotonin.

The concentrations of serotonin and histamine were calculated in micrograms per gram weight of pancreas or per milliliter of blood. The significance of differences in the values was determined by the Wilcoxon–Mann–Whitney test.

There were three series of experiments. In series I changes in trypsin and elastase activity were determined in pancreatic tissue and the inhibitory properties of the blood serum were measured in fasting rats after administration of serotonin. In series II changes in protease activity at acid pH values and in acid phosphatase activity were studied in the pancreatic tissue of satiated and hungry rats after administration of serotonin. In series III the effect of serotonin on development of the pathological process was determined in pancreatic tissue after ligation of the pancreatic duct.

The rats were deprived of food for 18–20 h before the experiment but were allowed water *ad lib*.

EXPERIMENTAL RESULTS

Serotonin caused an increase in total trypsin activity (Fig. 1), but the small decrease in elastase activity was not significant ($P > 0.05$). The antitryptic activity of the blood serum was reduced under these conditions ($P > 0.025$).

In the experiments of series II (at pH 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0) the characteristic pH curve of protease activity was found in the hungry rats before and after injection of serotonin. Two peaks of proteolytic activity were found at pH 2.5 and 4.0. Serotonin caused no change in protease activity at acid pH values or in the character of the pH curve (Fig. 2A).

TABLE 1. Effect of Serotonin on Development of Pathological Changes in Pancreatic Tissue after Ligation of Pancreatic Duct

Experimental conditions	No. of animals	No. of animals dying during 1st day	Changes in pancreatic tissue
Intact animals + serotonin	10	0	No change
Animals with ligation of pancreatic duct	10	0	Slight edema of tissue
Animals receiving serotonin after ligation of pancreatic duct	10	10	Fatty necrosis of tissue, effusion of peritoneal fluid

Comparative studies at the same pH (3.0) showed that lysosomal protease activity was a little higher in the hungry rats than in the satiated animals, and this level continued to be found after injection of serotonin (Fig. 2B).

A different picture was observed when acid phosphatase activity was determined in satiated and hungry rats after injection of serotonin. Starvation for 18-20 h increased acid phosphatase activity in the pancreatic tissue ($P < 0.002$). After injection of serotonin, however, this increase became even more marked ($P < 0.005$). Activity of the enzyme increased more in the hungry rats than in the satiated animals after injection of serotonin (Fig. 2C).

It will be clear from Fig. 3 that before injection of serotonin its concentration in the pancreatic tissue and blood of the hungry animals was higher than in the satiated animals ($P < 0.05$), and after injection the difference became more marked still ($P < 0.01$). It was noted that the increase in the serotonin concentration in the pancreatic tissue of satiated rats was smaller than in the hungry animals, whereas changes in the blood serotonin concentration were opposite in character (Fig. 3A — lines inside columns).

Similar changes in the pancreatic tissue were detected in the case of histamine (Fig. 3B). Table 1 gives the results of the experiments of series III. Ligation of the pancreatic duct as a rule caused no changes in the pancreatic tissue, especially in the early stages. A combination of ligation of the duct with simultaneous injection of serotonin caused the development of pancreatitis and death of the animals during the first few hours after ligation (Table 1).

The results are thus evidence that changes in the serotonin levels in the body stimulate pancreatic function to some degree. Comparison of data in the literature indicating that serotonin, in the doses used (20 mg/kg), stimulates the secretion of juice and enzymes, and the results of the present investigation suggest that serotonin also acts on the synthetic function of the pancreas. This may perhaps be a manifestation of the combined action of serotonin and other biologically active substances, especially histamine, the concentration of which in the pancreatic tissue changes after administration of serotonin. Judging from the character of changes in the enzyme concentrations in pancreatic tissue, it can be postulated that cholinergic mechanisms are concerned in the secretory processes of the pancreas in response to injection of serotonin, for this substance causes an increase in sensitivity of cholinergic structures to acetylcholine [7].

Data on changes in the inhibitory properties of the blood serum following injection of serotonin are interesting. The fall in the blood concentration of inhibitors takes place parallel with the rise in the concentration of the corresponding enzymes in pancreatic tissue. A similar effect is observed during stimulation of the pancreas by pancreozymin [11]. It may perhaps be connected with an increase in the supply of active enzymes into the blood

stream, including from the intestine. As the results of the experiments of series III showed, serotonin may be a factor in the development of the pathological process. We know that serotonin modifies membrane permeability and that this effect is connected with its role in pathological processes in organs of the gastrointestinal tract (peptic ulcer and pancreatitis, for example). Substances which stabilize lysosomal membranes (glucagon, prostaglandin), on the other hand, reduce the severity of the pathological process [14, 15]. An increase in lysosomal enzyme activity coupled with an increase in permeability may, under certain conditions, be an additional pathological factor when serotonin levels in the body are high.

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