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*The influence of Atorvastatin on ultrastructure of rat pancreatic
exocrine cells in the course of experimental intoxication with ethanol*

The undesired action of Atorvastatin on the organism is similar to the toxicity of other statins (4, 5). Quite often pathological symptoms from digestive tract occur, i.e. pancreatitis (3). Considering the damaging action of ethanol (1, 2) we decided to observe an interaction between Atorvastatin and ethanol on the level of cell ultrastructure in exocrine tissue of pancreas.

MATERIAL AND METHODS

The experiment was carried out on Wistar rat males weighting about 300 g. The animals were divided into two experimental groups and two control groups. Control group I received water and standard granulated fodder. Control group II received 20% ethanol instead of water. Each animal drank about 20 ml of ethanol for 24 h. Experimental group I received Atorvastatin (the preparation Sortis PARKE-DAVIS GmbH, Berlin) in the dose 0.28 mg/24h. This dose corresponds to the maximal therapeutic dose for human being. Experimental group II received ethanol like the control group II and Atorvastatin like the experimental group I. The drug dissolved in 1 ml of water was administered by intragastric bougie, each day for three successive weeks. All the time animals from control group II and experimental group II drank 20% ethanol instead of water. Each group included three animals. At the end of experiment the animals were decapitated and specimens of the pancreas were collected for an electron microscope examination. Specimens of tissue material were fixed with buffered glutaraldehyde and OsO₄ and then em-

bedded in Epon 812. Ultrathin sections were contrasted with uranyl acetate and lead citrate according to the Reynold's method. They were investigated and pictures were taken in Tesla BS-500 transmission electron microscope.

RESULTS AND DISCUSSION

The decreased amount of zymogene granules, a dilatation of endoplasmic reticulum and swollen mitochondria were observed in a large number of pancreocytes of animals from control group II (ethanol) in comparison with control group I. The changes in rough endoplasmic reticulum (a dilatation of cisternae, the decreased amount of ribosomes) seem to point to a diminished rate of cell secretory processes. Ethanol reduces a synthesis of ribonucleic acid and proteins. Some investigators (7, 8) link together the decrease in number of ribosomes and the transformation of rough endoplasmic reticulum in smooth endoplasmic reticulum, which is responsible for detoxication. The changes in pancreatic cells under the influence of ethanol are characteristic of early stages of pancreatic cell damage (Fig. 1). The administration of Atorvastatin (experimental group I) causes the increase in secretory granule number. Also, the state of cell nuclei indicates the increased metabolic activity (excentrically located nucleoli, open pores in the nuclear envelope). The ultrastructural picture of pancreas indicates the increased

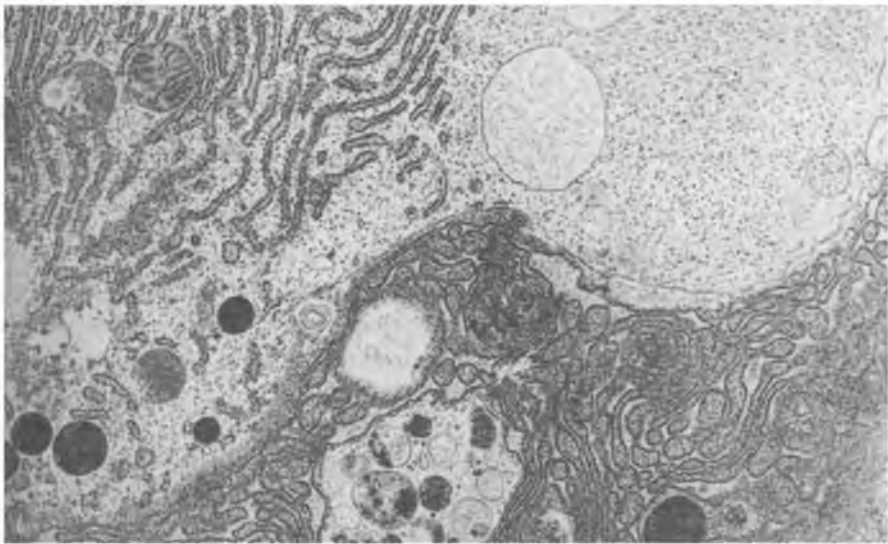


Fig. 1. Pancreas from animal which received ethanol. A dilatation of spaces between membranes of endoplasmic reticulum and swelling of mitochondria are visible. Not numerous zymogene granules and vacuoles different in size filled with secretion. Magn.

4000x

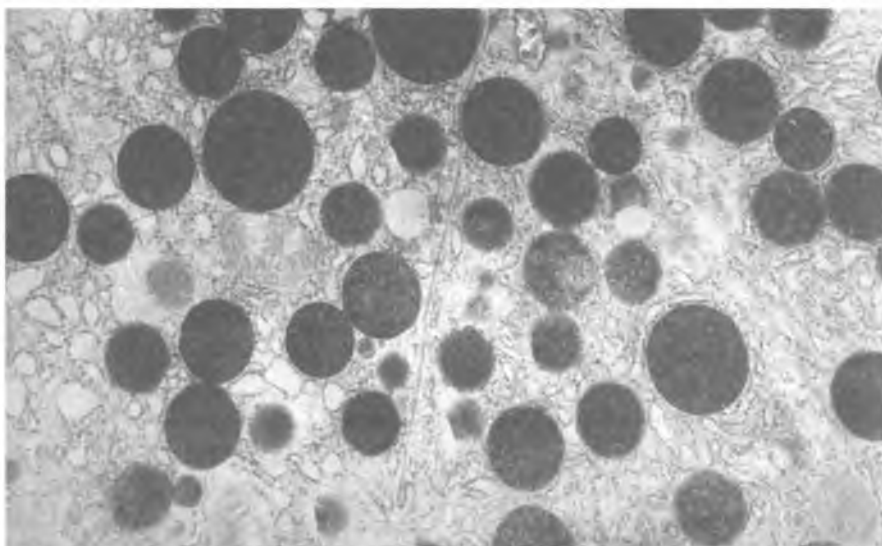


Fig. 2. Pancreas from animal which received Atorvastatin. Numerous zymogene granules are visible in cytoplasm of pancreaticocytes. Cell organelles have regular structure

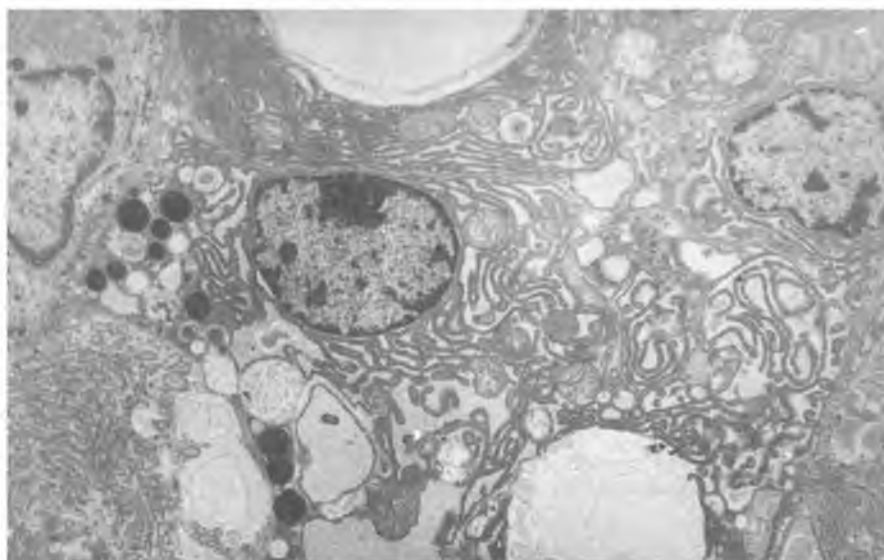


Fig. 3. Pancreas from animal which received ethanol and Atorvastain. Disintegration of organelles, autophagal vacuoles and dilated endoplasmic reticulum are present. Zymogene granules – maturing and mature – are visible. Cell nuclei show signs of activation (excentrically located nucleoli, open pores in the nuclear envelope). Magn. 4000x

production of zymogene (Fig. 2). The infusion of cerulein (6) – cholecystokinin-pancreozymin analogue causes a dilatation of endoplasmic reticulum cisternae and formation of vacuoles in pancreocytes.

Chemical compounds stimulating the pancreatic secretion can damage cell organelles and in excessive doses can cause the tissue damage. Experimental group II (Atorvastatin and ethanol – Fig. 3) showed that changes occurring in pancreocytes after administration of both chemical compounds are related to the stimulation of secretory process. Significant destruction of cytoplasmic organelles is observed and sometimes myelinic structures occur in swollen mitochondria, which can indicate unreversible damage of the cell.

CONCLUSIONS

1. Atorvastatin administered in rats for three weeks causes a stimulation of zymogene secretion.

2. The administration of Atorvastatin and ethanol causes the damage of cell organelles, which is more intensive than in the case of the action of ethanol, only.

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SUMMARY

The experiment was carried out on mature Wistar male rats. The animals from experimental group I received Atorvastatin in the dose 0.28 mg/24h for 3 weeks. Experimental group II received 20% ethanol *ad libitum* apart from Atorvastatin. Ultrastructural examinations of pancreatic exocrine cells showed the stimulation of secretory processes in cells of animals receiving Atorvastatin and considerable damage of cell organelles in experimental group II, more intense than in the pancreas of control animals which drank ethanol.

Wpływ Atorwastatyny na ultrastrukturę komórek zewnątrzwydzielniczych trzustki szczura w przebiegu doświadczalnego zatrucia etanolem

Badania wykonano na szczurach samcach rasy Wistar, dojrzałych płciowo. Zwierzęta z grupy doświadczalnej I otrzymywały Atorwastatinę w dawce 0,28 mg na dobę codziennie przez 3 tygodnie, grupa doświadczalna II oprócz Atorwastatyny była pojoną 20% etanolem *ad libitum*. Badania ultrastruktury komórek zewnątrzwydzielniczych trzustki wykazały pobudzenie procesów wydzielniczych w komórkach zwierząt otrzymujących Atorwastatinę i znaczne uszkodzenie struktur komórkowych w drugiej grupie doświadczalnej, większe aniżeli w trzustce zwierząt kontrolnych, które piły etanol.