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High doses of atorvastatin (Sortis) modify the secretory process in the exocrine portion of the pancreas

The HMG-CoA reductase inhibitors, called statins, are medicines that reduce the increased cholesterol level most effectively (2, 9); they are generally well tolerated by patients. Nevertheless, in 0.1-0.2% of patients treated with statins (simvastatin, provastatin), the undesirable effects are: myopathy (7, 8, 14) hepatotoxicity (atorvastatin) (5). Among statins, atorvastatin is characterized by strong hypolipemic properties (5, 9, 15). Walsh examined the toxicity of atorvastatin (11, 12). It was similar to that of other HMG-CoA reductase inhibitors and was related only to high doses of atorvastatin. The doses above 150 mg lead to degeneration of liver cells and damage other organs.

The aim of this paper is the ultrastructural evaluation of rat pancreocytes after application of various doses of atorvastatin (Sortis).

MATERIAL AND METHODS

The studies were performed on white rats of body weight: 250 g, coming from laboratory animal breeding farm. A control group and two experimental groups of animals (5 rats in each) were formed. The experimental rats received the Sortis preparation (Atorvastatinum, PARKE-DAVIS GmbH, Germany), once, by means of a stomach tube, in water suspension, in two doses. The animals in experimental group I received the maximum human therapeutic dose of the drug – 80 mg, which is 2.8 mg/day for a rat. The animals in experimental group II were given a ten times larger dose than the therapeutic dose, i.e. 800 mg, which is 2.8 mg/day for a rat. The drug was administered for the period of 6 weeks. Then the animals were decapitated and their pancreases were collected for examination in an electron microscope. The ultrathin sections were watched and photographed in the transmission electron microscope Tesla BS 500.

RESULTS

The ultrastructure of the pancreatic acinar cells of the rats in the experimental groups was compared with the structure of the pancreocytes in control rats. In the group of animals receiving the maximum therapeutic dose (experimental group I) changes were observed in the structure of basic cellular organelle in pancreocytes. The nucleus usually contained two nucleoli with separated granular and fibrous part. Numerous pores were present in the nuclear envelope.The rough endoplasmic reticulum (RER) was slightly dilated. Besides the typical system of membranes, it was visible in the form of very numerous, enlarged follicles in the para- and supranuclear regions (Fig. 1). The paracanalicular part of the cells contained zymogenic granules of the similar electron size and density as in the pancreocytes of the

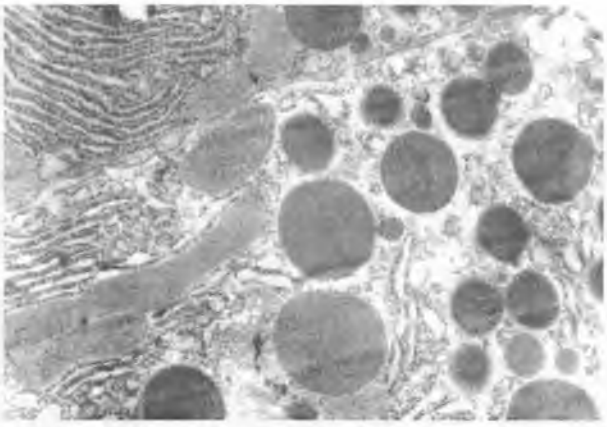

Fig. 1. Experimental group I. Supranuclear region of the pancreocyte. Magn. 14 000x

control animals. Polyribosomes occurred numerously in the whole cytoplasm. The follicular lumen was filled with microgranular material. In experimental group II, in the pancreocytes of animals that received the drug in the dose 10 times larger than the therapeutic one, the extent of ultrastructural changes in the image of cellular organelle was very conspicuous. The cellular nuclei were pycnotic – with condensed chromatinic stroma, and deep inclusions were present in the nuclear envelope (Fig. 2). In the paranuclear part a significant enlargement and distension of the RER canals were observed (Fig. 2). The zymogenic granules revealed various electron sizes and densities. We were finding granules containing material of varied electron density (Fig. 3). Mitochondria revealed the features of slight swelling.

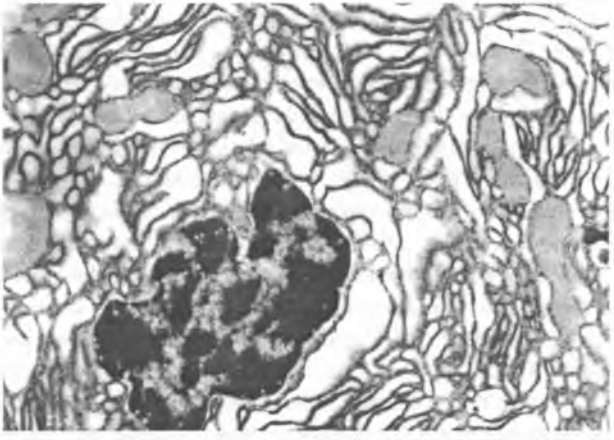

Fig. 2. Experimental group II. Ultrastructural changes in the image of cellular organelle in pancreocytes. Magn. 8000x

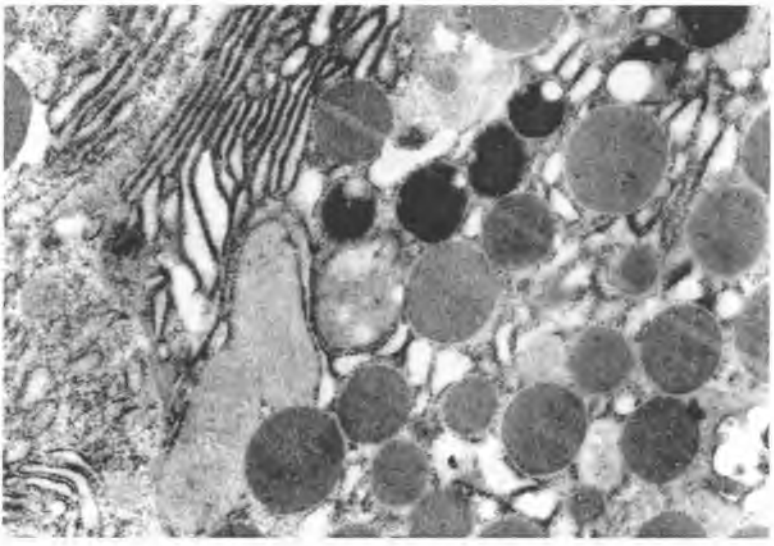

Fig. 3. Experimental group II. The zymogenic granules containing material of varied electron density. Magn. 10 000x

DISCUSSION

Statins as reductase inhibitors of HMG CoA – the enzyme catalyzing the early stages of cholesterol biosynthesis, inhibit the production of endogenous cholesterol, thus causing the indigence of the cholesterol pool in the hepatic cells, which is a stimulus to the increased synthesis of LDL receptors. The increased removal of cholesterol molecules by the LDL receptors causes reduction of the concentrations of these lipoproteins. Statins may cause an increase of activity of the hepatic enzymes in the serum (9). Besides, the symptoms of i.a. pancreatitis, not necessarily related to the application of atorvastatin, were observed (5, 9). The maximum therapeutic dose of atorvastatin (80 mg/24 h) is given to adults, whose increased blood cholesterol level is genetically conditioned (familial hypercholesterolemia). The Sortis preparation is designed for long-lasting therapy.

In the literature of the subject there are cases of pancreatitis described in a patient taking atorvastatin in the dose of 10 mg/day (1) and of an inflammatory status in the pancreas of a person taking drugs preventing HIV multiplication simultaneously with drugs decreasing cholesterol level (6).

Tardini (4) reports that neurohormonal factors (CCK, Ach) in small doses stimulate the secretion of exopancreas. He observed the distension of the RER cistern space and the formation of large secretory vacuoles. The high doses of pancreas stimulating factors distorted the order of the complicated secretory process. There occurred an uncontrolled fusion of the secretion granules (large vacuoles were formed) with lateral cellular membranes, which, together with other changes, gave the features of acute interstitial pancreatitis.

The pancreatic acinar cells, equipped with appropriate receptors situated in the cellular membrane, respond to the activity of neurohormonal factors with intracellular changes. Among others, there occur: the release of Ca^{+2} in the cell, increase of the contents of c-GMP or c-AMP, mobilization of enzyme secretion (3). Maintaining high concentrations of calcium ions in the cytoplasm is toxic for the cell. The excess of Ca^{+2} is removed by means of the calcium pump (10) or stored in the organelle, i.e. mitochondria and endoplasmic reticulum (13).

In our study, in the animals that were administered the maximum therapeutic dose of atorvastatin

(for the period of 6 weeks) – experimental group I, on the pancreocyte electronograms changes in the RER image were found (dilatation, the form of small and larger follicles), enlarged nucleolus and the abundance of polyribosomes would indicate the activated secretion synthesis. However, in animals that were given the drug in a ten times larger dose than the therapeutic one, a severe distortion of the secretory process occurred. It was revealed by very strong extensions of the RER cisterns, swelling of the mitochondria and deep inclusions of the nuclear membrane, as well as the accumulation of the zymogenic granules of various sizes and electron densities. These changes are probably the result of long-lasting activity of the secretion-stimulating factor. We suppose that what is distorted, is the process of the release of the secretion from the cell.

Like Lampel (4) we believe that the long-lasting activity and high doses of the factor that stimulates the exocrine portion of the pancreas lead to cellular destruction, which may induce the damage of the tissue

CONCLUSIONS

1. Atorvastatin administered to rats for the period of 6 weeks in the therapeutic dose (80 mg/day) stimulates the activity of exocrine portion of the pancreas.

2. After a 6-week application, atorvastatin in the dose ten times larger than the therapeutic one, distorts the secretory process of exocrine portion of the pancreas, which is revealed by morphological changes in the cellular organelle.

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SUMMARY

Changes were observed in the ultrastructure of the pancreatic acinar cells in rats after administration of atorvastatin (Sortis) in the therapeutic and ten times larger dose for the period of 6 weeks. It was found that atorvastatin given to rats in the therapeutic dose (80 mg/day) stimulated the secretion in pancreocytes, whereas the ten times higher dose of atorvastatin distorts the complicated process of the release of the secretion from the cell.

Wysokie dawki atorwastatyny (Sortis) modyfikują proces wydzielania egzokrynowej części trzustki

Obserwowano zmiany w ultrastrukturze komórek pęcherzykowych trzustki szczurów po podawaniu atorwastatyny (Sortis) w dawce terapeutycznej i dziesięciokrotnie większej przez okres 6 tygodni. Stwierdzono, że atorwastatyna podawana szczurom w dawce terapeutycznej (80 mg/dobę) stymuluje wydzielanie w pankreocytach, natomiast dawka atorwastatyny dziesięciokrotnie większa zaburza skomplikowany proces uwalniania wydzieliny z komórki.