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Histoenzymatic Investigations of White Rat Liver after Partial Hepatectomy and Experimental Haloperidolum Administration

Badania histoenzymatyczne wątroby szczura białego po częściowej hepatektomii i doświadczalnym podawaniu haloperidolu

Гистоэнзиматические исследования печени белой крысы после частичной гепатэктомии и опытного введения галоперидола

Haloperidolum (*v*-4-(*p*-chlorophenyl)-4-hydroxypiperydyne-*p*-fluorbutyrophenone) is characterized by a wide range of antipsychotic action. It is an essential specimen in treatment of different forms of schizophrenia (5). This drug penetrates quickly from blood to all parenchymatous organs as well as penetrates easily through the blood-cerebrospinal fluid obstacle. Its highest concentration is reached in the liver, where its biotransformation takes place leading to N-dealkilation and oxidation. Haloperidolum is excreted very slowly in a metabolic form mainly in urine and to a smaller degree in stol (12).

The side symptoms i.e. decrease of blood pressure, difficulties of urine returning, drying in mouth, leukopenia, increased lactation, hyperglycemia and others appear after haloperidolum administration, though not so often as after phenotiazyne neuroleptics.

The purpose of this paper to investigate haloperidolum action on morphology and behaviour of some liver enzymes after removal of one of its lobes is justifiable from the clinical point of view mainly because of contraindications in drug taking in the case of liver and kidney diseases (6).

MATERIAL AND METHODS

The experiment was carried out on white rats — sexually mature males weighing about 250 g. The animals were divided into two experimental groups and one control group, including five animals each.

Control group: non-operated animals receiving no haloperidolum.

Experimental group I: non-operated animals, fasting, receiving haloperidolum in ampoules of Polfa firm in the dose 8 mg/kg of body mass by the stomach-tube for 7 successive mornings. This

dose of drug giving no visible effects in animals behaviour was established in the piloting experiment. Each animal received 56 mg of drug.

Experimental group II: the animals with a removed liver lobe, received haloperidolum in the same way as the animals of group I. The administration of the drug began one week after hepatectomy carried out by Higgins and Anderson's method modified by Staszyc.

The animals were fed with standard granulated fodder and had enough drinking water. They were killed by ether anaesthesia two weeks after operation. During the dissection total regeneration of the removed liver lobe in all animals was seen. It differed from the primary lobe by the rounded edge.

The dexter lobe lying directly under the removed lobe in the operated animals was taken for investigations. The histochemical investigations for the presence of glycogen according to PAS McManus's method, acid phosphatase according to Gomori's method, TPP-ase (thiamin pirophosphatase) according to Novikoff and Goldfischer's method, succinic dehygrogenase according to Nachlas's method, lactic dehydrogenase according to Hass Scarpelli and Pearse's method were made. The review slides were stained with hematoxylin and eosin (H + E).

RESULTS

Staining with hematoxylin and eosin

In experimental group I the small lymphocyte concentrations lying usually in the light of central veins or in vessels of portal spaces were found. Eosinophiles were also present. Lymphocytes contained a nucleus and chromatin granules, however its arrangement has not been typical for plasmatic cells yet. A number of cells with darker cytoplasm and smaller strongly stained, single or double nucleus, was observed.

In experimental group II when compared with the experimental group I a greater number of cells with small, double nuclei was found. A number of central veins in the organ section was smaller but their light extended. In some places a distinct, radial arrangement of hepatic trabeculae and typical lobules were not observed. In the portal spaces as well as in the light of central veins the presence of lymphocytes and small lymphocyte infiltrations in one of the animals was noticed.

Glycogen

On the liver slides derived from the control animals different distribution of staining indicating the presence of glycogen was observed. In some places, larger quantity of this sugar was present in the zones adherent to the portal spaces, in others — close to the central veins. The places in which the cells rich and poor in glycogen were arranged alternately from the portal space to central vein were observed in the gland section.

After administration of haloperidolum (experimental group I), distinct changes in quantity and glycogen arrangement in the liver cells in comparison

with the control animals were not noticed. In the hepatectomized animals, the glycogen quantity increased to a small degree compared with the control animals.

The succinic dehydrogenase (SDH) activity

The succinic dehydrogenase activity was shown in all liver cells of the control animals, however, it was considerably stronger in the zones adherent to the portal spaces.

In liver parenchyma of the animals receiving haloperidolum, a slight increase of SDH activity close to the portal spaces was observed. In the animals with the removed liver lobe and receiving haloperidolum a slight decrease of SDH activity was found in the whole organ parenchyma in comparison with control slides, in spite of typical localization i.e. weaker activity in the central and medial zone of lobule, stronger in the circumference.

The lactic dehydrogenase (LDH) activity

In the whole liver parenchyma of the control animals, the strongest reaction indicating LDH presence was shown in the cells adjacent directly to the central and portal space veins. In the other cells the reaction was also intensive.

After haloperidolum treatment, a slight increase of enzyme activity in the whole liver parenchyma and occurrence of single hepatocytes with a strong reaction far from the vein vessels was observed. After hepatectomy and haloperidolum administration, the reaction increase was distinct, mainly at veins in the portal spaces and in many cells on the lobule circumferences.

The acid phosphatase (Fk) activity

In the liver of control animals, the greater enzyme activity on lobule circumference, smaller — close to the central veins was observed. Thick enough granules of PbS were distributed mainly near the cell membrane of hepatocytes.

After haloperidolum administration, the slight increase of reaction to Fk with the distribution of a reaction product typical for the liver of the control animals was observed. After removal of the liver lobe and haloperidolum administration only a slight increase of reaction to Fk on the circumference of some lobules was shown. In the PbS granules were smaller than those in the liver cells of control and experimental group I animals and distributed steadily in the whole cytoplasm. However, in two animals reaction was evidently stronger in the zones adjacent to many portal spaces and the product of reaction was distributed first of all near the biliary ducts.

The thiamin pirophosphatase (TPP-ase) activity

The biliary ducts demarcated by the reaction product were visible in whole liver parenchyma in the same quantity. No distinct differences in the enzyme activity connected with the functional zones were found.

After haloperidolum treatment, a small increase of reaction on circumference and decrease in the centre of lobules were observed. After partial hepatectomy and haloperidolum treatment the TPP-ase activity was the same as in the control animals except the small decrease in the middle part of lobules.

DISCUSSION

In our experiment the higher daily dose of haloperidolum (8 mg/kg of body mass) in comparison with the highest daily doses of drug (5 mg/kg of body mass) applied in other experimental investigations (2) was applied considering the fact that drug was given into stomach, which retards and weakens its action in comparison with intraperitoneal administration.

The investigated liver lobe in the animals of experimental group II did not differe in size from the analogous lobe of the control animals. Histological and histochemical investigations however, showed the presence of more distinctly marked changes in the hepatectomized animals. Occurrence of the greater number of binuclear cells and small lymphocyte concentrations in light of the blood vessels were observed in the animals of experimental group I. On one hand it points to the trophic stimulation of the organ, on the other hand to the increase of protective reactions accompanying the drug biotransformation. The small lymphocytic infiltrations in kidneys after haloperidolum administration were observed by Zarębska and Staszyc (14).

The lack of differences in comparison with the control in relation to glycogen contents in the animals receiving only haloperidolum as well as in the operated animals receiving haloperidolum points to the proper carbohydrate economy and also indirectly to the lack of drug influence on pancreas hormone secretory.

The slight increase of SDH activity in the highest oxidative zone is a tantamount to the increase of oxidative processes taking place in mitochondria in this part of the lobule. The increase of the LDH enzyme which exists in the soluble form of cytoplasm in the whole organ parenchyma and particularly in some single cells indicates that the cell utilizes the energy obtained by anaerobic glycolyse. Activity of this enzyme has shown some oscillations connected with day and night rhythms (3). The increase of SDH and LDH activities in kidneys after treatment with haloperidolum (14) and reserpine (13) was also observed.

The Fk localization demonstrated in the experiments on lobule circumference and in the cells at the biliary ducts is the same as that reported by Schär et al. (7).

The increase of Fk activity is the evidence for the increase of lytic processes or moblilization towards a phagocytosis.

TPP-ase weaker activity in the centre of lobuli is connected with weakening of Golgi system function in this part with the enzyme activity increase on the circumference.

The removal of one lobe and then haloperidolum administration caused histological changes in the lobe close to the operated one. This is tantamount to extension of the distance between central veins, light increase of these veins and less regular arrangement of hepatic trabecules in some places. The observed changes showed the presence of hypertrophic processes taking place in the non-damaged lobe. Our observations confirmed the conclusion drawn by Ungváry et al. (10) namely that regeneration of a damaged liver is a result of the two processes: formation of new lobes and hypertrophy of others. As for hypertrophy, Jatropulos (4) showed that the distance between a triad and central vein in a normal liver is 280–520 μ, generally 370–420 μ, however, in the second week of regeneration — 460 μ, and in the ninth week as much as 490 μ. In young animals in which growth of the body is still going on creating new lobes is possible. A venous system capacity also increases most distinctly in the period between 2–7 days. In our experiments, slight hypertrophy of only some lobules was observed. It is connected with the removal of only a small part of parenchyma.

Weakening of SDH activity with the simultaneous distinct increase of LDH activity mainly at the portal spaces points to greater utilization of anerobic glycolyse at the expense of oxidative processes by cells to produce quicker but less effective energy. It is connected with less metabolic and detoxic efficiency of the cells engaged in regeneration processes. Tuczek et al. (8) reported that the albumin level — proteinaceous compounds whose synthesis is the most energy consuming have distinctly decreased in the regenerating liver cells.

The slight increase of Fk activity in three animals in comparison with the control animals but smaller than in experimental group I suggested less detoxic efficiency of liver cells in the second week after operation. In two animals the distinct increase of enzyme activity greater than in experimental group I but only at the portal spaces, i.e. in a zone of the highest oxidation. A differentiated Fk activity in liver cells of experimental group II animals indicated the different individual sensibility.

Slight weakening of the TPP-ase activity in the middle part of the lobule is probably connected with lower secretory activity of the cells lying in the zone of the lowest oxidation. The activity decrease of the investigated enzyme can also be a result of enzyme escape into the blood circulation. Some authors (1) report the activity increase of some indicatory enzymes including succinic and lactic dehydrogenases in a blood serum after psychotropic drugs. These enzymes are of multiorganeous origin point to a damage first of all of the liver, heart muscle, skeletal muscles and pancreas.

To conclude it can be said that changes in the activity of the investigated enzymes are characterized by the temporary decrease of metabolic activity of the cells most actively engaged in the regenerative processes during the first two weeks (9). However, for normal functioning of the cells, appropriate innervation is necessary. Regeneration of nervous fibres in the rat liver is delayed in relation to regeneration of blood vessels and cells and is completed only after about 6 weeks (11).

Conclusions

1. Trophic stimulation of a white rat liver, increase of protective reactions and greater metabolic activity of hepatocytes are found after haloperidolum administration.

2. Slight hypertrophy of some lobules, stronger protective reaction and metabolic activity decrease of hepatocytes are found after removal of one lobe and haloperidolum treatment rather than after only haloperidolum treatment.

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STRESZCZENIE

Badano zmiany morfologiczne i histochemiczne w wątrobie szczura białego po podawaniu haloperidolu oraz usunięciu jednego płata i podawaniu haloperidolu. U zwierząt otrzymujących haloperidol stwierdzono pobudzenie troficzne narządu, objawiające się większą liczbą komórek 2-jądrzastych w porównaniu ze zwierzętami kontrolnymi. Obserwowano także wzmożenie reakcji obronnych (obecność niewielkich skupień limfocytów w świetle żył centralnych i naczyń przestrzeni bramnych). Zwiększona aktywność dehydrogenazy bursztynianowej i mleczanowej, fosfatazy kwaśnej, a na obwodzie zrazika — pirofosfatazy tiaminowej wskazuje na zwiększoną aktywność metaboliczną hepatocytów.

Po usunięciu jednego płata i podawaniu leku, w płacie sąsiednim obserwowano przerost niektórych zrazików oraz miejscowe mniej regularne ułożenie beleczek wątrobowych. Osłabienie aktywności dehydrogenazy bursztynianowej i pirofosfatazy tiaminowej oraz wyraźne wzmożenie aktywności dehydrogenazy mleczanowej i fosfatazy kwaśnej może być równoznaczne z przejściowym obniżeniem aktywności metabolicznej hepatocytów zaangażowanych w procesy regeneracyjne.

РЕЗЮМЕ

Исследовано морфологические и гистохимические изменения в печени белой крысы после введения галоперидола и после устранения одной доли печени и введения галоперидола. У животных, получающих галоперидол, определено трофическое возбуждение печени проявляющееся увеличением 2-ядерных клеток по сравнению с контрольными животными. Замечено также усиление защитной реакции (выступление небольших концентраций лимфоцитов в просвете центральных вен и в сосудах воротных промежутков.) Увеличенная активность сукцинатной и лактатной дегидрогеназы, кислой фосфатазы, а в области дольки тиаминовой пирофосфатазы, указывает на увеличение метаболической активности гепатоцитов.

После удаления одной доли печени и введения препарата в соседнюю долю замечено гипертрофию некоторых долек и местное менее регулярное положение печеночных балок. Ослабление активности сукцинатной дегидрогеназы и тиаминовой пирофосфатазы и четкое усиление активности лактатной дегидрогеназы и кислой фосфатазы равнозначно с временным понижением метаболической активности гепатоцитов участвующих в регенерационных процессах.