EFFECT OF CHLORPROPAMIDE ON THE TISSUE RESPIRATION OF THE LIVER IN EXPERIMENTAL TOXIC HEPATITIS

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In a previous investigation [1] the author showed that administration of the oral antidiabetic preparation chlorpropamide, starting from the 15th day of carbon tetrachloride (CCl_4) poison, consistently inhibited the development of fatty infiltration of the liver and caused a parallel increase in the content of glycogen and protein in the liver and inhibition of proteolysis, at all stages of the investigation (for a period of 65 days). This action of chlorpropamide was interpreted as the result of stimulation of insulin secretion by the compound and depression of insulinase activity [2].

To discover the mechanism of the action of chlorpropamide on the pathochemical changes in the liver in chronic toxic hepatitis, the state of the respiration of the liver tissue must be investigated during administration of this preparation because, as has been shown [3, 4], toxic hepatitis is characterized by the development of histotoxic and circulatory hypoxia of the liver.

EXPERIMENTAL METHOD

The test objects were male albino rats weighing 180-280 g and kept on the ordinary laboratory diet.

Chronic toxic hepatitis was produced by subcutaneous injection of CCl_4 in a dose of 0.12 ml/100 g body weight twice a week.

Chlorpropamide (Diabenese, Pfizer) was given by mouth to the animals on alternate days in a dose of 5 mg/100 g, starting on the 15th day from the beginning of poisoning.

The experiments lasted from 15 to 65 days. The experimental rats were sacrificed on the 25th, 35th, 45th, 55th, and 65th days of poisoning. After sacrifice of the animals, liver slices were cut to a thickness of 0.4 ± 0.02 mm during cooling, by means of a special microtome. The tissue respiration was measured in a Warburg's apparatus in an atmosphere of oxygen at 37 ± 0.01°; the manometers were shaken at the rate of 100 times/min. Krebs'-Ringer phosphate solution was used as medium (in contrast to the original formula, no calcium salts were added to the mixture). The estimation continued for 1 h. The experimental results were calculated from the formula:

$$Q_{O_2(CO_2)} = \frac{h \times K}{m},$$

where h is the reading of the manometer after 1 h making allowance for the correction for the thermobarometer reading; K is the constant for the particular vessel, and m the weight of the tissue slice (in mg). The results were calculated per dry weight of slices, determined by taking parallel liver slices weighing 100 mg, placing them in special brass dishes, and drying them at 80-90° to constant weight.

The tissue respiration was expressed as Q_{O_2} and QCO_2, i.e., in microliters of oxygen absorbed and carbon dioxide eliminated per hour per milligram of dry tissue.

EXPERIMENTAL RESULTS

As the results given in the table show, during chronic administration of small doses of CCl_4, at all stages of the investigation a marked depression of respiration of the liver tissue was observed, as shown by a decrease both in the absorption of O_2 and in the elimination of CO_2. The decrease in the elimination

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Changes in Tissue Respiration of the Liver during Chronic CCl_4 Poisoning (0.12 ml/100 g twice a week) and Administration of Chlorpropamide (5 mg/100 g by mouth on alternate days) after the 15th Day of Poisoning. M ± m

Experiment No.	Character of experiment	Day of investigation	Number of animals	Weight of animals (in g)		Change in weight (in g)	Tissue respiration of liver (in μl/mg/h)		
				initial	final		Q_{O_2}	Q_{CO_2}	RQ
1	Control		15	192	260	+67	3.55 ± 0.19	2.89 ± 0.15	0.81 ± 0.008
2	Administration of CCl_4 .	25	5	198	234	+36	2.08 ± 0.14	1.43 ± 0.1	0.65 ± 0.01
3	Administration of CCl_4 and chlorpropamide after 15th day	25	10	194	211	+17	3.28 ± 0.2 P<0.001	2.44 ± 0.18 P<0.001	0.74 ± 0.02 P<0.001
4	Administration of CCl_4 .	35	5	196	206	+10	1.87 ± 0.2	1.17 ± 0.27	0.62 ± 0.04
5	Administration of CCl_4 and chlorpropamide after 15th day	35	10	194	233	+39	2.5 ± 0.1 P<0.05	1.41 ± 0.08 P>0.1	0.56 ± 0.03 P>0.1
6	Administration of CCl_4	45	5	186	236	+50	1.91 ± 0.05	1.01 ± 0.04	0.53 ± 0.03
7	Administration of CCl_4 and chlorpropamide after 15th day	45	10	175	254	+79	3.92 ± 0.24 P<0.001	2.76 ± 0.17 P>0.001	0.7 ± 0.01 P<0.001
8	Administration of CCl_4 .	55	5	184	230	+46	2.15 ± 0.07	1.26 ± 0.05	0.58 ± 0.02
9	Administration of CCl_4 and chlorpropamide after 15th day	55	10	180	265	+85	3.8 ± 0.08 P<0.001	2.57 ± 0.09 P<0.001	0.67 ± 0.01 P<0.001
10	Administration of CCl_4 .	65	5	188	243	+55	1.99 ± 0.2	1.27 ± 0.05	0.65 ± 0.04
11	Administration of CCl_4 and chlorpropamide after 15th day	65	10	180	280	+100	4.74 ± 0.23 P<0.001	3.1 ± 0.09 P<0.001	0.65 ± 0.02 P>0.1

of CO_2 was more marked than the decrease of absorption of O_2, so that the respiratory quotient fell significantly. This indicated the accumulation of incompletely oxidized metabolic products.

Administration of chlorpropamide on the 15th day after the beginning of poisoning increased the intensity of the tissue respiration at all stages of the investigation. This was shown by an increase in the absorption of oxygen and elimination of carbon dioxide with these indices in the control experiments. The increase in absorption of oxygen (except on the 35th day of the investigation) reached the same value as its absorption in normal animals, and at some stages (45th, 55th, and 65th days) it exceeded this level.

The increase in the elimination of carbon dioxide fell somewhat behind the increase in absorption of oxygen, but this lag was less marked than in the controls (animals receiving CCl_4 only). Correspondingly, the respiratory quotient was slightly higher on the 25th, 45th, and 55th days.

In the intact animals administration of chlorpropamide in the same dose (5 mg/100 g) and for the same period had no effect on the oxygen absorption by the liver tissue. The elimination of carbon dioxide was actually depressed.

Hence, administration of relatively small doses of chlorpropamide during chronic toxic hepatitis stimulates the tissue respiration of the liver besides causing the previously established increase in the glycogen and protein content of the liver and inhibiting the development of the liver and inhibiting the development of fatty infiltration.

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