THE EFFECT OF COMPOUNDS DEPRESSING MITOTIC CELL DIVISION ON THE RESPIRATION OF RAT LIVER SLICES

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In previous research by one of the authors (Hadnad [1]) it was observed that certain drugs, acting as antimitotic poisons, had an inhibiting action on phosphorylation. It therefore appeared to be of interest to investigate the action of these antineoplastic substances on tissue respiration.

METHOD

Experiments were carried out on rats which were sacrificed after starvation for 24 hours. The liver was extracted and cut into slices weighing 0.2 g, and the O_2 absorption and CO_2 excretion by these slices were estimated in a Warburg apparatus in a buffered solution (pH 7.38). The effect of the following antitumor drugs was investigated: nitrogen mustard (Boots, Merck), urethane, colchicine, sarcomycin and degranol. Degranol is a nitrogen-mustard derivative (1, 6-desozy-D-mannitol-dihydrochloride), synthesized by Varga and tested at the Budapest Oncological Institute [2, 3]. It has been found to have low toxicity and has given good clinical results. Sarcomysin is an antitumor antibiotic, isolated by Hamao Umezawa from a strain of Streptomyces erythrochromogenes. Degranol was added to the Warburg flask in a dose of 10-200 γ, nitrogen mustard - 50-400 γ, urethane - 1-50 mg, colchicine - 0.1-10 γ and sarcomycin - 25-400 γ. Two to five parallel investigations were made with each concentration of the respective drug; mean results are given in the table.

TABLE. Effect of Antimitotic Drugs on the Respiratory Coefficient of Rat Liver Slices

Degranol			Nitr. Must.			Urethane			Colchicine			Sarcomycin		
quant. of drug added to Warburg flask (γ)	respiratory coefficient	number of tests	quant. of drug added to Warburg flask (γ)	respiratory coefficient	number of tests	quant. of drug added to Warburg flask (γ)	respiratory coefficient	number of tests	quant. of drug added to Warburg flask (γ)	respiratory coefficient	number of tests	quant. of drug added to Warburg flask (γ)	respiratory coefficient	number of tests
10	0,98	4	50	0,90	5	10	0,65	5	0,001	0,88	5	50	1,01	7
25	0,97	3	100	0,40	9	20	0,69	7	0,01	0,46	9	100	0,44	13
50	0,39	10	200	0,53	6	50	0,76	8	0,05	0,38	7	200	0,54	8
100	0,37	8	400	0,33	5				0,1	0,30	15	400	0,10	10
200	0,40	7							1,0	0,47	13			
									2,5	0,48	19			
									5	0,41	13			
									10	0,48	11			

RESULTS

Results relating to the effect of the substances which we tested on the respiration of the liver slices are shown in the table. It will be seen from this table that, in certain concentrations, these substances sharply lowered the respiratory coefficient.

We cannot yet give a precise explanation of the phenomenon observed, but we consider that the changes in this coefficient are the result of disturbance of the carbohydrate metabolism of the tissues.

The better therapeutic results from degranol than from nitrogen mustard are probably due to its low toxicity so that it could be given in doses ten times larger than nitrogen mustard. The effect of degranol of tissue metabolism, however, is far less pronounced than that of nitrogen mustard.

SUMMARY

The authors studied the effect of substances depressing the mitotic division of the cells, and employed as anticancer preparations, on the formation of CO_2 and the oxygen intake by slices of rat liver. The addition of degranol (50-200 γ) nitrogen mustard (100-400 γ), urethane (10-50 mg), colchicine (0.01-10 γ) and sarcomycin (100-400 γ) to 0.2 gm of the liver had no effect on its oxygen intake. However, the oxygen production by the liver was greatly reduced, resulting in a marked drop of the tissue respiratory coefficient, which then assumed very low values. With the addition of degranol this coefficient fell down to 0.037, with that of nitrogen mustard - to 0.33 urethane - to 0.65 colchicine - to 0.30 and of sarcomycin - to 0.10.

LITERATURE CITED

[1] B. Kellner and L. Nemeth, Ztschr. Krebsforsch. 61, 165 (1956).

[2] C. Sellei and Z. Antaloczy, Wien. Zschr. inn. Med. 37, 337 (1956).