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EFFECTS OF SOME RADIOPROTECTIVE SUBSTANCES ON THE NADH-CYTOCHROME C REDUCTASE ACTIVITY OF ISOLATED LIVER MITOCHONDRIA

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Some neurotropic substances, sulphamides, biogenous amines, AET can influence the respiratory activity of isolated liver mitochondria by interaction with NADH-cytochrome C reductase. It has been proved that the moderate reduced state of respiratory enzymes may ensure radioprotection, a phenomenon which can explain the radioprotective effect of these substances.

In a previous work we presented the moderate and reversal effect of AET and of some neurotropes upon the activity of succin oxidase and cytochrome oxidase of liver mitochondria [1]. In the present work we shall present data obtained by using 20 substances (neurotropes, sulphamides, biogenous amines), having radioprotective effect, which can influence the respiratory activity by interaction with NADH-cytochrome C reductase enzyme from isolated liver mitochondria. The methods used for the isolation of liver mitochondria and for the determination of NADH-cytochrome C reductase activity (NCCR) were the same as described in our earlier published works [1], [2].

The 136 animals used for these experiments were Wistar male rats, weighing $150 \text{ g} \pm 10$. The substances used here were analytically pure and were purchased from different firms (E. Merck, La Roche-Hoffmann, I. R. Geigy, Richter Gedeon).

RESULTS

AET (S-2-Aminoethyl-isothiourea Br. HBr), as a reference substance, having an excellent radioprotective effect, significantly reduced the NCCR activity of isolated mitochondria, administered in 100–300 μg (Fig. 1).

The CNS acting substances with radioprotective effect

Imipramine had an inhibitory effect of 60 per cent, administered in doses of 125 μg ; this effect increased when larger doses were administered.

Dibenzocycloheptatriene derivatives in the doses of 100 μg showed an inhibitory effect depending on their radioprotective effect. Two sub-

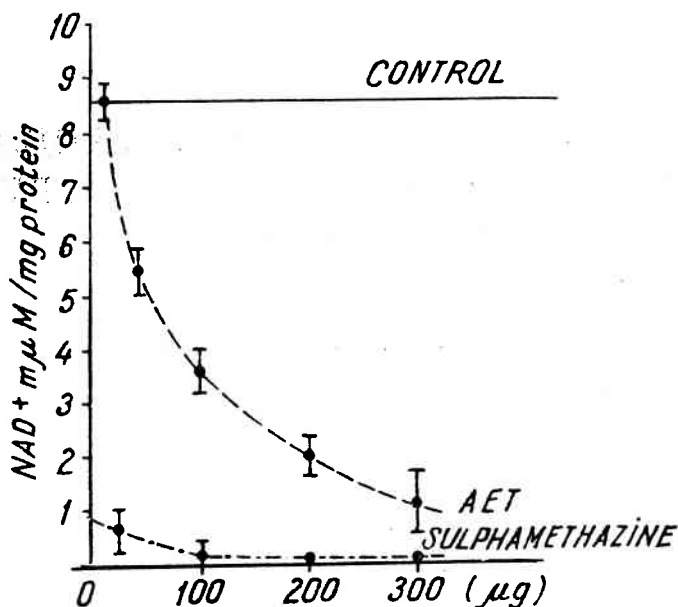


Fig. 1. — Action of AET and Sulphamethazine on the activity of NCCR of isolated liver mitochondria, depending on the administered doses.

stances: Ro-4-1577 and Ro-4-6011 inhibited NCCR activity with 22, respectively, 34 per cent (moderate inhibition). The other substances (no radioprotectors), Ro-4-8093, Ro-4-8711, Ro-4-7960, Ro-4-8624 had either a weak effect (15 per cent, Ro-4-8624) or a very strong one (99 per cent, Ro-4-8711).

Plegomasine, Nozinane, Laroxil and Taractan (Phenothiazine and thioxanthene derivatives), having radioprotective effect between 30—50 per cent, decreased NCCR activity in 100 μg doses with 60, 100, 52, respectively, 84 per cent. The effect of Plegomasine and Nozinane increased parallelly with the dosis (Fig. 2).

Administration of Sulphamethasine (radioprotective effect = 60 per cent) resulted in a very strong inhibition of NCCR activity, already in the dosis of 20 μg . This sulphamide is a weaker radioprotector than AET, but it is a stronger inhibitor of enzyme activity than AET (Fig. 1).

The action of biogen amines was measured in comparison with the action of tryptophan. Because tryptophan is not a radioprotector and has no effect on the NCCR activity of isolated mitochondria, serotonin had an inhibitory effect equal to 73 per cent at 100 μg doses. Histamine inhibited the above enzyme activity with 83 per cent at the same dosis (Fig. 3).

In the higher doses the effects of these substances were increased.

DISCUSSION

It has been proved that a moderately reduced state of respiratory enzymes may ensure radioprotection, a phenomenon that can be related

to the action of direct or indirect cytochrome oxidase inhibitors to produce hypoxia of all enzymes involved in mitochondrial oxidation pro-

Fig. 2. — Action of neurotropes on the activity of NCCR of isolated liver mitochondria, depending on the administered doses.

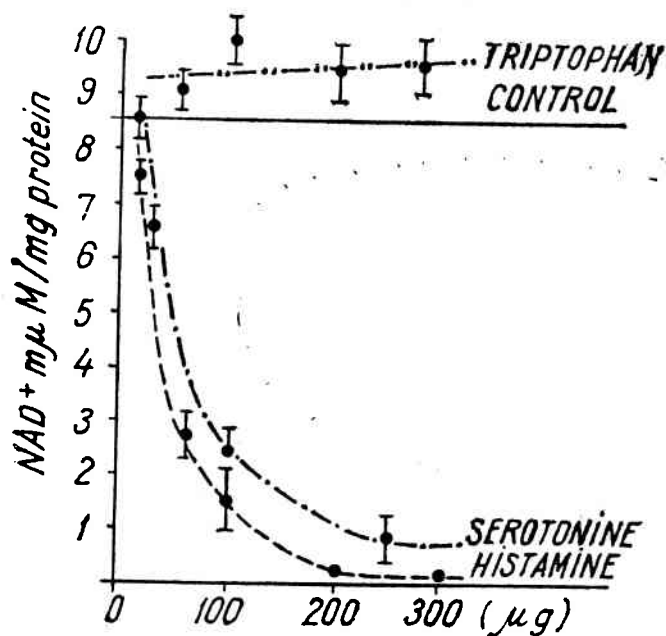
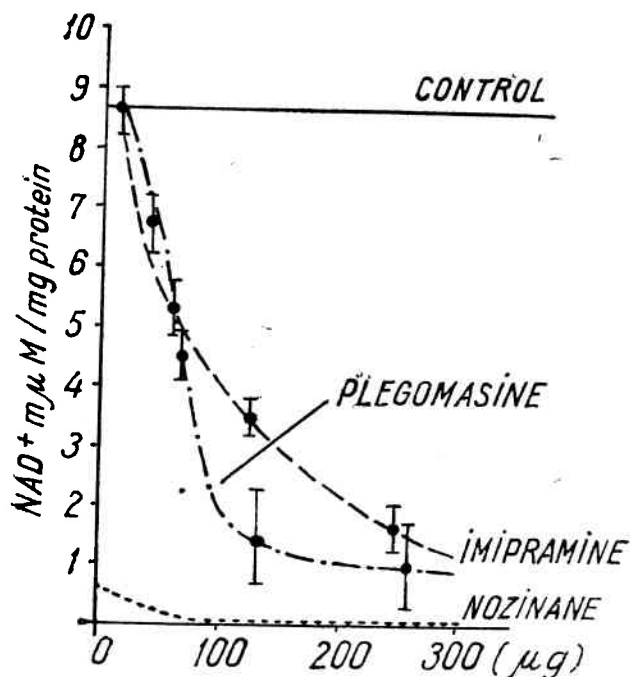
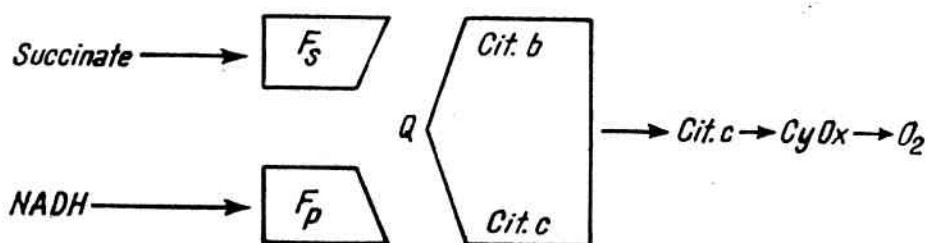


Fig. 3. — Action of Serotonin and Histamine on the activity of NCCR of isolated liver mitochondria, depending on the administered doses.

cesses. The central position of cytochrome oxidase is represented by Lehninger [2] in scheme 1:



Radioprotectors used in these experiments, which have an inhibitory effect on NCCR activity of isolated liver mitochondria, at the same time provoked an accumulation of NADH in the inside of mitochondria. This fact may be in relationship with the radioprotective effects of these inhibitors, in accordance with the well-known Pihl and Sanner's hypothesis [3] which presumed that NADH may act as hydrogen donors in transfer reactions, repairing target radicals induced by irradiation in biological systems.

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