18 Mitochondrial Structure as a Controlling Factor of Monoamine-oxidase Activity and the Action of Amine-oxidase Inhibitors. H. AEBI (Switzerland).

The rate limiting factor was studied in suspensions of isolated mitochondria from rat liver, as well as in purified monoamine oxidase (MAO) preparations. Under a variety of experimental conditions the following activities were measured: (1) NH_3-production (Seligson's method); (2) total-O_2-consumption (Warburg's direct method); (3) rate of H_2O_2-production, using the coupled oxidation of [^{14}C] formate by catalase as an indicator reaction; and (4) the aldehyde formation by semicarbazide-trapping.

Mitochondrial suspensions behave quite differently according to their functional state. Compared with lysed mitochondria—as used usually—those suspended in isotonic saccharose and incubated in presence of pyruvate and tyramine exert a much smaller NH_3-production and H_2O_2-formation effect (about $\frac{1}{4}$), whereas their O_2-consumption is 4–5 times higher. Similar differences can be observed if pyruvate is omitted in the suspending medium, if the mitochondrial suspension is frozen before incubation, or if a detergent, i.e. 0·1 per cent Triton-X-100 is added. In all these instances there is reciprocity between the rate of pyruvate oxidation (requiring intact mitochondrial structure) and MAO-activity as well as coupled formate oxidation (either activity being limited by structural factors).

In presence of increasing amounts of MAO-inhibitors all the activities mentioned above are reduced to the same extent, except coupled formate oxidation. Thus, the I_{50}-value of $^{14}CO_2$ formation in isotonic suspensions of rat liver mitochondria is about twice. In presence of *cis*-2-phenyl-cyclopropylamine, added simultaneously with the substrate (0·02 M tyramine) the I_{50}-values for O_2 consumption and NH_3-production are $8{\cdot}0 \times 10^{-6}$ M; for coupled formate oxidation it is $1{\cdot}6 \times 10^{-5}$ M. Furthermore, these I_{50}-values largely depend on the functional state of the suspended mitochondria. In this respect Iproniazid behaves as follows: O_2-consumption and NH_3-production of liver mitochondria, lysed in distilled H_2O, are inhibited 50 per cent by $2{\cdot}5 \times 10^{-4}$ M Iproniazid, on the other hand, an approximate threefold inhibitor concentration (i.e. $7{\cdot}0 \times 10^{-4}$ M) is required if the mitochondrial suspension is incubated under conditions that essentially conserve structural integrity. The significance of these observations is discussed in view of the competitive behaviour of MAO-substrates and inhibitors in mitochondria and in the cell in general.

19 Action of Chlorethoxybutamoxane on Respiratory Enzymes of Rat's Brain in Traumatic Shock. H. NINOMIYA, R. W. BUXTON and M. MICHAELIS (U.S.A.).

Several dehydrogenases of rat brain including some which participate in the tricarboxylic acid cycle are depressed in Noble–Collip drum shock (500 turns). The degree of inhibition is in keeping with the severity of the shock, i.e. whether or not the rats' paws were taped or whether they were left unfettered to avoid or diminish impact of the drum. Rats tranquillized with chlorethoxybutamoxane (5-chloro-ethoxy-2-butylamino-methyl, 1-4-benzodioxane) prior to drumming show better resistance to shock. The dehydrogenases of such animals' brain are not significantly changed from controls, or from controls which had not been sedated. There is further differentation between the Pasteur effect in non-sedated shock cases, when repression occurs, and sedated ones, where the effect is lowered but remains at the control level after exposure to drumming. The protein-N contents of brain homogenates of non-sedated and drummed, and sedated, and drummed cases shows statistically highly significant differences.

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20 Drug-induced Alterations in the Intra-cellular Distribution of 5-Hydroxytryptamine in Rat's Brain. N. J. GIARMAN and S. M. SCHANBERG (U.S.A.).

Differential centrifugation of rat's brain in isotonic sucrose has shown that approximately 30 per cent of the endogenous 5-hydroxytryptamine (5-HT) is present in the non-particulate fraction, while about 70 per cent resides in granules. A number of neuro-active drugs have been found to alter this "normal" distribution. These drugs fall into two broad categories: (1) those which failed to change, increased, or decreased the level of 5-HT in the whole brain and, simultaneously, tended to shift the particulate to supernatant (^{P}/S; "bound"/"free") ratio from 2·5 toward unity (e.g. chlorpromazine, phenobarbital, reserpine, and α-methyl-DOPA); and (2) those which elevated the whole brain level of 5-HT and tended, at the same time, to maintain a normal ^{P}/S ratio or to raise it beyond 2·5 (e.g. iproniazid, phenylisopropylhydrazine, LSD-25, and certain adrenocortical steroids).

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21 Modern Concepts in Relationship between Structure and Biological Activity. Introductory Remarks. K. J. BRUNINGS (U.S.A.).

22 Size and Shape of Organic Molecules and Biological Activity. A. H. BECKETT (United Kingdom).

Biological processes involve three dimensions. Increasing attention is therefore being focused upon the size, shape and surface characteristics of enzymes, proteins, antigen–antibody reactions, drug–drug receptor interactions. Any chemically mediated, biological action involves interaction between suitably orientated surfaces.