REVIEW

MONOAMINE OXIDASE IN HEALTH AND DISEASE

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Summary: The enzyme MAO plays an important role in the metabolic degradation of catecholamines which are closely related to the activities of different centres of brain and the sympathetic nervous system. It is now well established that it is present mainly in the outer mitochondrial membrane of the neurones and also in the cells of receptors. It is comparatively a staole enzyme with a molecular weight of 100,000. It is inactivated at pH values below 6 or above 9 and the optimum pH for its activity is 7.3. Recently some workers have suggested that MAO is not only one enzyme, but a mixture of different enzymes. It is distributed widely in the liver, kidney, stomach, and intestines and moderately in brain and lungs and scantily in the heart and skeletal muscles. Its main function is the oxidative removal of the amino group of the catecholamine molecule intraneuronally and extraneuronally followed by further oxidation of the aldehyde to form the corresponding carboxylic acid which is then excreted as such in the urine. In the brain the MAO has an important role to play in the behavioural pattern of the animal and functional activity of the brain. Because of this, recently several competitive inhibitors of MAO have been introduced such as Iproniazid, Nardil, Niamid, etc. which inactivate the enzyme by dehydrogenation. Therefore, in depressive disorders of mind, when there is depletion of catecholamines, these MAO inhibitors have much role to play since by their use the catecholamine content of the brain increases. By the use of these drugs one could demonstrate a good correlation between clinical improvement and the degree of enzyme inhibition in patients. Though MAO has not been completely purified and isolated, it is still possible to estimate the MAO activity in the tissues by partially purifying it by homegenisation and disruption of mitochondria by ultra-sonic waves. Amongst the methods of estimating the activities, Flurometric and Radiometric methods seem to be the most accurate ones.

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INTRODUCTION

Although monoamine oxidase (MAO) was first discovered by Hare in 1928, its important role at the adrenergic nerve endings was discovered relatively recently (2). It has now been well established that it is found in the outer membrane of the mitochondria and its main function seems to be the inactivation of catecholamines liberated by the stimulation of the adrenergic nerve endings (8). This enzyme inactivates noradrenaline and adrenaline by deaminating them and then converting them into aldehydes. These aldehydes are then repidly metabolized by oxidation to corresponding acids. In certain circumstances the aldehydes are also reduced to alcohol or glycol. In this way, MAO plays an important role in the metabolic degradation of catecholamines (4). As the catecholamines are closely related to the functions of the nervous

system, especially the various centres of the brain and the sympathetic nervous system, the study of (MAO) has attained a great importance in recent years. Therefore, a review encampassing the existing knowledge and covering the recent literature on the subject will be much value to all those interested in the study of this topic.

1. HISTORICAL BACKGROUND:

The enzyme M.A.O. was first discovered in 1928 as tyramine oxidase in the mammalian livers by Miss M.L.C. Hare. Initially she did not see any oxidation of adrenaline and it was only in 1937 that Blaschko and others observed the oxidatively deaminating action of MAO on adrenaline, noradrenaline, dopamine and other monoamines (3). In this reaction the following chemical transformation was observed :

$$RCH_2NH_2 + H_2O + O_2 = RCHO + NH_3 + H_2O_2$$

Here one molecule of oxygen was found to be absorbed for every molecule of substrate oxidized. It was further observed that this enzyme activity could be conveniently estimated manometrically by determining oxygen uptake with a suitable substrate, like tyramine, or by using the Conway diffusion technique for ammonia estimations. Later on, by using isotopically labelled amines, it was found that this oxidative process is a slow one and some other mechanism for inactivating the catecholamines was predicted by Blaschko in 1957. Soon afterwards Axelrod and his colleagues discovered another enzyme called catechol-o-methyl transferase (COMT) with the property of inactivating the catecholamines by transmethylation, (1). It was soon found that these two enzymes have two differing properties. Whereas MAO is an intracellular enzyme and mainly worked at the adrenergic neurones, the enzyme COMT, was found active in the extracellular region.

Further, it was also found that the enzyme MAO had mainly a mitochondrial distribution and more recently it was found that the enzyme was located in the outer mitochondrial membrane (5). This intraneuronal existence of the enzyme indicated that the catecholamines were reabsorbed into the neuron, after they were liberated and secreted. Such a mechanism could be stimulated or depressed by using sympathicomimetic drugs.

Soon, Blaschko again showed that there occurred a competition between various amines such as adrenaline, tyramine, tyrptamine etc. for the action of amine oxidase. They also found that drugs like ephedrine and amphetamine which were not attacked by amine oxidases have greater affinity for the enzyme and therefore they inhibited the oxidation of other amines present in the area (2, 3). Thus, as a result of this observation a large number of MAO inhibitors were soon discovered which had mainly the antidepressant action in the body. Amongst them iproniazid, nialamide, harmala alkaloids were the important ones. These MAO inhibitors were expected to increase the concentration of intraneuronal catecholamines in the various centres of the brain and hence elevate the mood. Therefore, this group of drugs were also labelled as mood elevators (16). On the other hand, a decrease in the concentration of catecho-

lamines in the brain by use of reserpine group of drugs, caused a sedative action (26). In spite of these advancements, the exact mechanisms of the action of MAO were still incompletely understood. Similarly, its exact molecular structure and other characteristics are still under active investigation by a large number of workers (7). These are some of the areas which need immediate attention for clarifying the action of this enzyme which plays such an important role in the management of psychosomatic disorders.

2. CHEMICAL PROPERTIES:

The chemistry of this enzyme is still not clear because of its relative insolubility. A number of solubilizing agents such as lysolecithin, Triton x 100 and others have been found to be useful in producing a moderate purification of this enzyme. Treatment with sonic oscillations in the presence of deoxycholate appears to have a similar purifying effect. A high speed centrifugation yielded about one-fifth of the enzymatic activity in the supernatant fluid. However, none of these enzyme preparations have so far thrown any light on the chemistry of this enzyme. The only thing that can be said at present is that it contains sulfhydryl groups since antisulfhydryl regents produce inhibition of this enzyme.

Zeller (29) had given a formula for this enzyme which contains the following three residues:
(i) Hydrogen accepting residue, (ii) A Phynylalanine residue (—),
(iii) electrophilic residue.

Since this enzyme is located in the mitochondria, the washed mitochondria form a convenient preparation for it. It is comparatively a stable enzyme and can be kept in phosphate buffer at room temperature for a day without any loss of activity. Heating for 10 mins at 50°C destroys half of its activity. It is inactivated at pH below 6 and above 9. The optimum pH for its activity is 7.3. There is no known coenzyme or prosthetic group associated with it (8). It has been observed recently that MAO is a flavoprotein enzyme and the diamine oxidase is a copper pyridoxal phosphate protein. According to Tipton (24), the Molecular weight varies from 100,000 to over 1,000,000 and some preparations form aggregates readily. According to him the multiple forms of MAO described by Youdim seem to be due to different degrees of polymerization rather than the separate form. Despite these differences in molecular weights, the minimum molecular weight based on flavine content seems to be 100,000 in all cases.

According to Youdim, MAO is not one enzyme, but a mixture of different enzymes. The studies so far conducted by him and his colleagues indicated that MAO enzymes from different organs differ in their action on different substrates. These differences in their form and action indicate that either the enzyme in different tissues is entirely different or that each organ contains a mixture of different kinds of MAO in varying proportions (27). However, this matter needs further investigation.

3. METHODS OF DETECTIONS AND ESTIMATION:

The enzyme MAO can be detected in the tissues by the following histochemical method.