THE ROLE OF AMINE OXIDASES IN THE DESTRUCTION OF CATECHOLAMINES

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One of the early observations on the enzymic degradation of epinephrine was made by C. Neuberg who found in 1908 that an adrenal melanoma extract converted epinephrine into a black pigment (46). A few years later J. Neumann discovered the rapid destruction of this amine by the blood of pregnant women (47). In 1936 another epinephrine oxidizing enzyme was found (15, 17) which turned out to be identical with monoamine oxidase (MO) (16, 42, 53). Soon more epinephrine inactivating agents were described and the question arose as to what degree all these reactions were responsible for the catabolic destruction of this amine. This problem was discussed by several distinguished authors (6, 12, 13, 14, 22, 27, 28, 35). Z. M. Bacq (6) flatly denied the participation of MO, while others, *e.g.*, D. Bovet and H. D. Patton, recently stated with regard to MO that "it is still uncertain how important the enzyme may be in the inactivation of the sympathetic mediators" (19), and that "doubts are accumulating as to whether this is the main enzyme concerned with sympathin destruction" (48).

Today we again tackle this thorny problem together, wondering whether we shall be able to get farther than the previous reviewers or whether we have to reshuffle the same stack of cards. The situation, however, looks more promising, thanks mainly to three recent developments:

1) Introduction of isotopically labeled catecholamines, a field in which R. W. Schayer has pioneered (56).

2) Discovery of the metabolic methylation of the *meta*-hydroxyl group of catecholamines.

3) Blocking of MO *in vitro* and *in vivo* by iproniazid (1-isonicotinyl-2-isopropylhydrazine, Marsilid) and other hydrazine derivatives.

But even if it were true that we stand in a better position than a short while ago, it is impossible to re-evaluate and organize all experimental information within the allotted time. Instead of trying to squeeze a great number of individual facts into this review, I prefer to concentrate on a few points hoping that this approach will help to simplify future discussion. Only three topics will be presented here:

1) Definition, classification and nomenclature of amine oxidases.

2) Review of reactions which have been considered to be instrumental in the destruction of catecholamines.

3) Comparison of the inactivation of catecholamines by methylation and by oxidative deamination.

1. Classification of amine oxidases. Before we discuss the role of amine oxidases it seems advisable to define and name these enzymes in such a way that misunderstandings are reduced to a minimum. This becomes more imperative the more biologists apply enzymological concepts to their special fields of interest

without having all the experimental details and facts of modern enzymology constantly in mind. Inappropriate nomenclature could be and has been misleading in applied enzymology.

Oxidative deamination of amines consists of replacing of aliphatic amino groups by carbonyl residues. This formulation is broad enough to cover enzymes not only such as MO and diamine oxidase (DO) but also spermine oxidase and amphetamine oxidase. This class of enzymes is called amine oxidases (or dehydrogenases) a name which logically belongs to the whole group rather than to a subdivision thereof.

The amine oxidases can be separated operationally into subdivisions, one which attacks α-methylamines such as phenylisopropylamine (amphetamine oxidase) and one which does not. The latter is separated by 1 mM semicarbazide. One subdivision remains practically unaffected by this agent, while the other is completely or almost completely blocked by it (23, 74). In this definition semicarbazide cannot be replaced by the term carbonyl reagent, since many carbonyl reagents such as monosubstituted alkyl- and arylhydrazines act on both enzymes efficiently (69), while only monosubstituted acylhydrazines and hydrazine itself exclusively inhibit the second group (68). Both agents represent whole families of homologous enzymes. To the semicarbazide-resistant enzymes belong the classical monoamine oxidases. Within this group only small differences are observed. Some monoamine oxidases, such as mouse liver and hog liver mitochondria MO, slightly attack mescaline, while others do not (rabbit liver mitochondria) (74). To the group of semicarbazide-sensitive amine oxidases, which is considerably heterogeneous in its composition belong diamine oxidases (DO) (11, 45, 67), beef and sheep plasma spermine oxidase (37, 61, 74), benzylamine oxidase (9), and mescaline oxidase (10, 74).

As an example of the hazards of naming enzymes the degradation of histamine is mentioned. This compound, the classical substrate of DO (histaminase), is also a weak substrate of MO (78). Its N_1-methylated derivative is fairly well attacked by MO (43, 75). Since this compound appears in the metabolic degradation of histamine, it is not surprising that a substantial part of histamine metabolism in man is governed by MO (55). Thus histaminase, in some instances at least, may have little to do with the catabolism of histamine.

The ultimate solution of this problem should come from a reliable insight into the structure of the active center of these enzymes. While our knowledge in this field is still far from satisfactory, a start has been made. On the basis of experiments carried out with a great number of substrates and hydrazine inhibitors, new models for MO and for DO (23) have been proposed.

In Figure 1, the letter A indicates the hydrogen accepting residue of MO. The solidly drawn structure represents a phenylalanine residue (or a related aromatic amino acid), and the two circles stand for two electrophilic residues, presumably two consecutive peptide bonds in a peptide chain. MO has only *one* kind of receptor in its active center. On the other hand, DO displays *two* types of receptors. This difference became apparent when it was shown that the structural requirements of the two amino groups of a DO substrate are markedly different

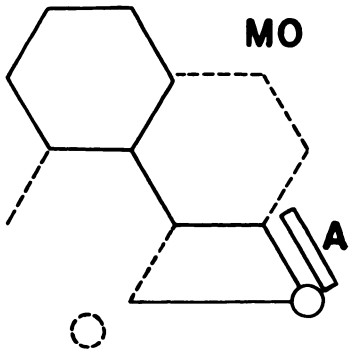

FIG. 1. Model of monoamine oxidase.

(77). The terminal amino group, which cannot be substituted, is attracted by an aldehyde residue, while the other amino group interacts with an enzyme group which is similar to that found in MO.

2. Elimination of catecholamines. Many reactions have been claimed as being responsible for the *in vivo* destruction of catecholamines (Table 1). But not all of them, according to our present knowledge, are acceptable for this function. In some instances related amines, but not catecholamines, have been demonstrated as being attacked. Even when we eliminate the questionable and improbable components of our list, a tremendously rich situation remains, defying quantitative description. Even if we knew much more about the individual systems than we actually do, it still could be very difficult to draw a clear picture of the metabolic inactivation of catecholamines. The *in vivo* action of a single enzyme is such a complex function, depending on so many variables, that at best only crude approximations can be made. The variables pertain to the concentration of a given catecholamine at the cellular and at the enzyme level, to the orientation of the substrate molecule near the active center, to the concentration of other substrates and of the reaction products at various levels, to the oxygen supply, etc. To these many complexities we must add the temporary or final elimination of catecholamines by storage in particulate matter, by noncovalent bonding with proteins, and by excretion.

3. Comparison of inactivation of catecholamines by methylation and by oxidative deamination. The study of the termination of the catecholamine activity cannot be limited to the analysis of the individual enzymes alone and more integrated systems have to be investigated. One promising way would consist of blocking one enzyme specifically in an otherwise intact organism and of observing the metabolic and pharmacologic deviations which may ensue. With this concept in mind we should then scan all the reactions given in Table 1. Since this goal obviously is out of reach, I propose instead to compare the methylation of the *meta*-hydroxy group of catecholamines, discovered by Armstrong (1) and Axelrod (3, 4, 5), and their associates, with the process of oxidative deamination.

This promising approach just referred to seemed to come into realization when it was found that iproniazid and related hydrazine derivatives are efficient

TABLE 1

Inactivation of catecholamines

Process	Remarks	References
I. Reactions involving the catechol residue		
A. Oxidations		
1. Tyrosinases		46
2. Ceruloplasmin		38, 44, 47
3. Cytochrome c		31
4. Peroxidases		36
5. Ferritin		32
6. Nonenzymic oxidations	heavy metal traces	40
B. Nonoxidative reactions		
7. Sulfate-esterification		54
8. Glucuronide-conjugation		26
9. Formation of methoxy derivatives		1, 3
II. Reactions involving side-chain		
10. Dehydrogenation of β-hydroxyl group		—
11. Monoamine oxidase		14, 15, 53
12. Diamine oxidase	mescaline, serotonin	70, 74
13. Amphetamine oxidase	phenylethylamine	2
III. Miscellaneous reactions		
14. Incorporation into proteins	mescaline	18
15. Destruction by receptor		21
16. Destruction during interaction with metabolic reactions		—
17. Inactivation by aldehydes		62

inhibitors of this enzyme *in vitro* and *in vivo* (8, 41, 49, 57, 65, 71–73, 76). The first experiments on the potentiation of sympathomimetic amines were carried in the laboratories of the Departments of Pharmacology (33) and of Medicine (51) of Northwestern University, in cooperation with my research unit in the Department of Biochemistry. The results from experiments on the action of tyramine on the nictitating membrane of the cat (33) and on the body temperature of guinea pigs (51) were clearly consistent with the assumption that substances such as tyramine are protected from degradation by the blocking of MO by iproniazid. These results were confirmed by G. B. Koelle and his associates (39).

Through many outstanding investigations in the fields of metabolism, physiology and pharmacology (7, 24, 25, 30, 58, 60, 64) it was established that iproniazid is able to protect serotonin *in vivo*. For a while this interpretation of a large body of data was rendered difficult by an observation which seemed to indicate that iproniazid was unable to penetrate to the site of monoamine oxidase in the intact cells (63). In the meantime, this phenomenon found another explanation (66).

Not only tyramine and serotonin, but also catecholamines were found to be protected by iproniazid against metabolic inactivation, notably in brain (59) and in heart (50). However, in other experimental situations, no potentiation by iproniazid in the action of epinephrine on the nictitating membrane occurred (33, 39). Furthermore, the blocking of MO by iproniazid did not increase the

quantity of norepinephrine which appeared in the venous blood of the spleen on stimulation of the sympathetic nerves (20, 21). One possible contribution to the understanding of this unexpected result came from the observation that iproniazid, isosterically related to epinephrine, competes with epinephrine for the receptor (34). Although this adrenergic blocking effect has been confirmed (7, 29, 39), it does not seem to explain completely the failure of the potentiation of catecholamines by iproniazid. For one thing, the concentration required for the adrenergic blocking effect is very high (10^{-3} M).

A more promising approach for answering this difficult question came from the recent work on the inactivations of catecholamines by the enzyme O-methyl transferase (3, 4, 5). However, the compound 3-methoxy-4-hydroxymandelic acid found in the urine (1, 52) does not permit one to decide whether methylation or oxidative deamination occurs first.

From a purely enzymological viewpoint there is no reason to assume that catecholamines have to be methylated before they become substrates of MO. Actually, the replacement of phenolic hydroxylic groups by methoxy residues reduces the rate of degradation of phenylethylamine derivatives by MO (74). Since O-methyl transferase acts on catechol itself and on all catechol derivatives thus far tested it probably accepts as substrates catecholamines as well as their degradation products by MO. On the other hand, the occurrence of nonmethylated catecholamines in the animal cell seems to indicate that these amines and their precursors are not methylated immediately after their appearance and that a chance remains for the catechol derivatives to be attacked by MO first: CA → MO → TR (CA = catecholamines, TR = transferase). The protection and potentiation of catecholamines by iproniazid mentioned before is a strong point in favor of this concept. It seems, therefore, probable that both pathways, CA → TR → MO as well as CA → MO → TR are open. When one route is blocked, the other may be used more.

In an attempt to settle this issue, iproniazid again was summoned (3, 4, 5). By pretreating animals with this drug, the urinary excretion of metanephrine was more than doubled (5). This was taken as evidence for the existence of the sequence CA → TR → MO. These results indeed offer clear-cut proofs for the ability of the animal metabolism to methylate epinephrine before this compound is deaminated. They also demonstrate the usefulness of iproniazid as a biochemical tool. But there is no reason to assume that in every instance the catecholamine goes through methylation before it is attacked by MO. In addition, the iproniazid experiments do not offer any information as to whether all or only a part of the epinephrine which appears as metanephrine increase after iproniazid treatment goes through CA → TR → MO in nontreated animals. Once again the study of a given situation disturbs the system under observation.

According to our present information catecholamines and other sympathomimetic amines seem to be inactivated by MO in those cases where potentiation and protection through iproniazid and related hydrazines occurs. Lack of potentiation is a strong indication that methylation is involved in the process of inactivation. However, enough question marks remain to induce us to work even harder in our attempt to elucidate some of the processes responsible for the

degradation of catecholamines. But I do hope I have demonstrated that we are moving out of the flat field of speculation and toward the mountains of hard facts, thanks to the outstanding work done by many investigators present at this meeting.

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