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C. DOPA DECARBOXYLASE: SUBSTRATES, COENZYME, INHIBITORS

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The concept of amino acid decarboxylation as a step in the formation of epinephrine (E) in animal tissues had its origin in the work of Hofmeister's pupils in Strasbourg at the beginning of this century. First, Spiro (51) claimed to have demonstrated the decarboxylation of phenylalanine by extracts of mammalian organs, and then Emerson (10) did the same for tyrosine. Friedmann (13) suggested that *p*-hydroxyphenylserine may be the precursor of E. A little later Halle (18), in Vienna, thought he had obtained the conversion of tyrosine to E in minced adrenal tissue. His evidence, based on a crude and entirely nonspecific chemical method, was justifiably and strongly contested by Ewins and Laidlaw (11) who employed biological assays, and failed to find significant formation of dopamine, epinine, or E from tryosine during their incubation experiments. They nevertheless considered tyrosine as the likely, but as yet undemonstrated, precursor.

In succeeding years dopa was synthesized by Funk (14) and isolated from a plant source (*Vicia faba*) by Torquati (52, 53) and Guggenheim (16). It was the latter investigator who established the structure of the natural product. These achievements focused attention on dopa as the probable precursor of melanin and of E, although Rosenmund and Dornsaft (39) dissented from this view.

Later the work of Raper and his colleagues on the tyrosine-tyrosinase reaction stressed the role of tyrosine as the parent substance from which E is formed. Indeed, the first direct evidence for the formation of pressor material from an amino acid was obtained by Dulière and Raper (9) in 1930, when they allowed a preparation of tyrosinase of plant origin to act on N-methyltyrosine. The next few years witnessed a renewed interest in amino acid decarboxylases, particularly in the laboratories of E. Werle and P. Holtz in Germany. This period culminated in the discovery of dopa decarboxylase in 1938 by Holtz, Heise and Lüdtcke (24); the ensuing history is documented in the proceedings of the first Symposium on Catecholamines, held in 1958 (Pharmacol. Rev. **11:** 241–566, 1959).

PROPERTIES AND ROLE OF DOPA DECARBOXYLASE

A decade ago three types of decarboxylase acting on compounds possessing the hydroxyphenylalanine structure were said to occur in mammalian tissues (*see* 44). These had been named tyrosine, dopa and hydroxyphenylserine decarboxylases, respectively. In addition, a phenylalanine decarboxylase was presumed to exist, but the experimental evidence for it was inadequate. With the discovery of serotonin and its precursor 5-hydroxytryptophan the question arose as to the nature of the enzyme carrying out that decarboxylation. From results of experiments with partially purified extracts, Clark *et al.* (4) concluded that the

decarboxylation of dopa and of 5-hydroxytryptophan occurs under the influence of different enzymes. But within a few years dopa decarboxylase was found to have a wider specificity and to be responsible, in fact, for the decarboxylation of 5-hydroxytryptophan, α-methyl-dopa, and other amino acids. Two sets of findings were responsible for this changed view. First of all, α-methyl-dopa was shown to inhibit the decarboxylation of 5-hydroxytryptophan as well as dopa, both *in vitro* and *in vivo* (23, 55), and it was natural to enquire whether it was acting on a single enzyme. Secondly, studies of substrate competition (58) and work with more highly purified preparations of dopa decarboxylase indicated that the latter enzyme acts on many substrates.

In their methods of purification Fellman (12) and Hagen (17) precipitated the enzyme from the supernatant liquid of homogenized and centrifuged beef adrenal medulla; the precipitant used was ammonium sulfate. Werle and Aures (54) used the same type of procedure but with extracts of guinea pig kidney. Awapara *et al.* (1) worked with rat liver, purifying the enzyme on DEAE-Sephadex. Finally, Lovenberg *et al.* (27) used a preliminary adsorption of extracts of guinea pig kidney (and dog brain stem) on alumina Cγ gel, followed by fractionation on DEAE-cellulose. The findings of all five researches have been reasonably uniform: through the various stages of purification the relative activity of the extract towards various substrates remains the same. Thus, Fellman found that *o*-tyrosine was decarboxylated at 41 % of the rate of 3,4-dopa in the high-speed supernatant fraction of beef adrenal medulla, 44 % in the material of highest potency obtainable by precipitation with ammonium sulfate, and 48 % in the purest preparation that he was able to get through a further adsorption on calcium phosphate gel. More important, the same type of relationship held for 5-hydroxytryptophan: the rate of decarboxylation of this amino acid was 10 and 7 % of that of dopa at two different stages of purification of the enzyme, respectively. This finding has been extensively confirmed, as shown in the data of table 1. Thus, recent investigations of dopa decarboxylase in five laboratories have shown that the ratio of activity of extracts of adrenal, kidney and liver on dopa, *m*-tyrosine, *o*-tyrosine, 5-hydroxytryptophan and *erythro*-dihydroxyphenylserine (or some of these) remains relatively constant during purification. Furthermore, the substrates when added together compete, rather than give additive results.

In their work with a partially purified dopa decarboxylase, Lovenberg *et al.* (27) had concluded that not only are 5-hydroxytryptophan and dopa decarboxylated by the same enzyme, but that phenylalanine, the tyrosines, histidine, tryptophan and α-methyl-dopa are also substrates. Because of this wide-ranging action they have proposed the new name "aromatic amino acid decarboxylase." Awapara *et al.* (1) have objected to the change of name, stating that recognition of the nonspecificity of the enzyme is an insufficient reason. Hagen (17) has disagreed with the new name also because his preparations were without action on histidine, tyrosine or tryptophan. It is of interest in this connection that the dopa decarboxylase purified from larvae of *Calliphora erythrocephala* acts on dopa and 5-hydroxytryptophan, but not on other aromatic amino acids that were tested (41).

TABLE 1

Decarboxylation of aromatic amino acids by dopa decarboxylase

Source and Preparation	Substrates					
	Dopa	*m*-Tyrosine	*o*-Tyrosine	5-Hydroxy-tryptophan	*erythro*-dihydroxy-phenylserine	References
Beef adrenal medulla						12
High-speed supernatant	0.46[a]		0.19			
Partly purified	2.01		0.89	0.20		
Purest preparation	7.05		3.39	0.48		
Guinea pig kidney						54
Crude extract (a)	2.14[b]				0.07	
Partly purified (a)	62.40				1.93	
Crude extract (b)	1.61			0.26		
Partly purified (b)	31.90			4.91		
Beef adrenal medulla						17
Partly purified (a)	37.90[c]			6.24		
Partly purified (b)	43.70	33.50	18.75	8.03		
Pheochromocytoma						17
Partly purified	32.83[c]	20.40	11.83	5.89		
Argentaffinoma						17
Partly purified	79.60[c]	26.35	16.04	9.47		
Rat liver						1
Crude preparation	1.81[c]	1.56	2.89	0.40		
Purest preparation	(100%)			(13%)		
Guinea pig kidney						27
Crude preparation	3.56[a]			0.39		
Partly purified	38.10			3.60		
Purest preparation	197.00			22.90		

[a] Micromoles/mg protein per hr.
[b] Micromoles/mg dry wt. per hr.
[c] Micromoles/ml enzyme extract per hr.

The next stage of research on dopa decarboxylase ought to reveal the exact limits of its specificity, along with clarification of the precise number of aromatic amino acid decarboxylases in the mammalian organism.

COENZYME-APOENZYME RELATIONSHIP

The activation of dopa decarboxylase of kidney cortex, prepared as a lyophilized powder, by pyridoxal phosphate (40, 47) has recently been studied in detail. Some pyridoxal phosphate is tightly bound to the apoenzyme as a Schiff's base, whereas another portion is dialysable (1). The relationship of these two portions of the coenzyme to the apoenzyme affects the action of the inhibitors, for the order of adding supplementary coenzyme, substrate and inhibitor determines the qualitative type of inhibition (26). Awapara *et al.* (1) state that the activation observed when pyridoxal phosphate is added to a preparation varies with the source of enzyme and the substrate used; two physical conditions affecting the process significantly are freezing of the enzyme and the pH of the medium in

which it acts. The loosely bound (or added) pyridoxal phosphate reacts nonenzymatically with D- (or L-) α-methyl-dopa, but the tightly bound coenzyme is not affected in this way (38). It should be noted that L-α-methyl-dopa, but not the D-isomer, inhibits the decarboxylase (36). Another interesting observation is the activation of kidney (but not brain) decarboxylase preparations by pretreating rats with chlorpromazine (15). Although the simple addition of pyridoxal phosphate to the reaction mixtures *in vitro* is more effective, Gey *et al.* (15) thought that the drug may protect endogenous coenzyme from metabolic degradation.

Some years ago Blaschko showed how uncertainly pyridoxine deficiency diminishes hepatic dopa decarboxylase in rat liver. Recently, we have confirmed this in the rat by tests *in vivo*, but have also found that the conversion of D-dopa to urinary dopamine is seriously affected by the vitamin deficiency. Presumably, the transamination reaction that is involved at one stage of this process is sensitive to the deficiency, whereas the decarboxylation step is much less so (50).

INHIBITORS OF DOPA DECARBOXYLASE (6, 7, 21, 46)

Since the first catecholamine symposium when Clark (5) reviewed this subject several new inhibitors have been synthesized. Some of these are shown in figure 1. Inhibitors of dopa decarboxylase, both old and new compounds, have been extensively studied in the living animal for assessment of their biochemical effects and other actions. There has been much interest in α-methyl-dopa and α-methyl-*m*-tyrosine because of their amine-releasing action in the brain (45) and elsewhere. This interest has been maintained not only because of their biochemical-pharmacological properties but also because of the introduction of L-α-methyl-dopa into therapeutics as an antihypertensive drug.

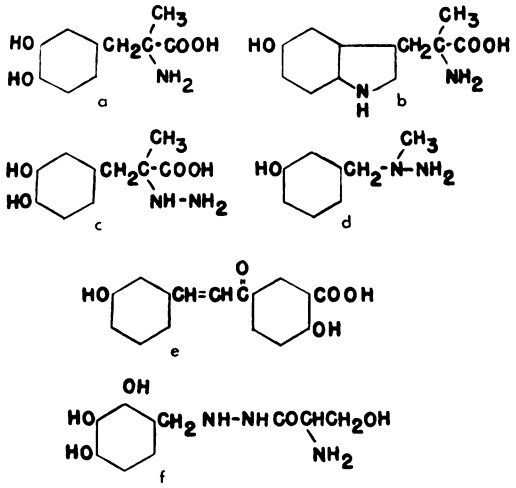

FIG. 1. Some inhibitors of dopa decarboxylase (with literature references): a, α-methyl-dopa (43, 46); b, α-methyl-5-hydroxytryptophan (26, 30, 49); c, MK-485, the hydrazino analog of α-methyl-dopa (20, 37, 42); d, NSD-1034, N-*m*-hydroxybenzyl-N-methylhydrazine (8, 20); e, 5-(3-hydroxycinnamoyl)-salicylic acid; f, Ro4-4602, N-(DL-seryl)-N′-(2,3,4-trihydroxybenzyl)hydrazine (20, 32, 33).

TABLE 2

Inhibition of formation of $C^{14}O_2$ by rat in vivo from D- and DL-dopa-$C^{14}OOH$

Inhibitor	Dose	Percent Inhibition of $C^{14}O_2$ Formation[a] from	
		D-Dopa-$C^{14}OOH$[b]	DL-Dopa-$C^{14}OOH$[b]
	mg/kg		
L-α-Methyl-dopa	200	75	60
Hydrazino analog of above (MK-485)	5	52	58
Hydrazino analog of above (MK-485)	30	74	72
L-α-Methyl-*m*-tyrosine	200	60	50
DL-α-Methyl-5-hydroxytryptophan	200		50
5-(3-Hydroxycinnamoyl)-salicylic acid	284		36

[a] During the first hour after injection of labeled dopa.

[b] In the first hour after administration of labeled dopa to control rats (no inhibitor given) 27.8% ± 5.0 (S.D.) and 46.3% ± 6.8 of the radioactivity was recovered in the respiratory gases as labeled CO_2 from D-dopa and DL-dopa, respectively.

The data in this table have been taken from references 28 and 50.

Tests of decarboxylase inhibition *in vivo* have proved useful in defining the efficacy of various substances. Dopa (30) or 5-hydroxytryptophan (36) is injected into small animals and the effect of the putative inhibitor, administered at the same time or earlier, on the output of dopamine or on the content of serotonin in the kidneys, respectively, is determined. Oates *et al.* (31) infused DL-5-hydroxytryptophan, L-tyrosine, or L-tryptophan into persons who had received α-methyl-dopa. Antidecarboxylase action was established by a reduction of 50 to 80% in the amount of the corresponding amine appearing in the urine, as compared with control infusions. Hansson and Clark (19) used carboxyl-labeled DL-dopa and estimated the inhibition of decarboxylation by the rate of excretion of $C^{14}O_2$ in the respiratory gases. DL-Dopa is not entirely satisfactory as a substrate for tests *in vivo*, because 1) the carboxyl group of the D-isomer is metabolizable, but not by direct decarboxylation, and 2) some inhibitors of dopa decarboxylase seem to inhibit the loss of $C^{14}O_2$ from the D-isomer more than from the L-dopa (28). The latter point is exemplified by the data in table 2. Even with L-dopa as substrate *in vivo* there is some possibility that a portion of the carboxyl group is detached after transamination of the amino acid to 3,4-dihydroxyphenylpyruvic acid.

Work with labeled tyrosine has shown that α-methyl-dopa, its hydrazino analogue, and α-methyl-*m*-tyrosine all inhibit the conversion of the carboxyl group to CO_2 (28, 29). Yet decarboxylation is a minor pathway of metabolism for tyrosine (34, 56). Indeed, these inhibitors also depress the formation of respiratory $C^{14}O_2$ from tyrosine that has been labeled in the methylene group of the side chain, although this inhibition is not as strong as for the carboxyl-labeled amino acid (28, 29). This is shown in table 3. These findings demonstrate very clearly the nonspecificity of the inhibitors mentioned. They also indicate the lack of validity of decarboxylation studies using tyrosine. We have considered L-α-methyl-dopa, labeled in the carboxyl group, as a substrate for testing of decar-

TABLE 3

Inhibition of the formation of $C^{14}O_2$ by rat in vivo from C^{14}-labeled tyrosine

Inhibitor	Dose	Percent Inhibition of $C^{14}O_2$ Formation from		
		L-Tyrosine-$C^{14}OOH$	D-Tyrosine-$C^{14}OOH$	DL-Tyrosine-β-C^{14}
	mg/kg			
L-α-Methyl-dopa	200	8	36	39
Hydrazino analog of above (MK-485)	100	94	54	48

Experiments with the carboxyl-labeled isomers were done at the same time; those with the methylene-labeled tyrosine were performed separately. Each value in the table is the average of 2 or 4 experiments, and represents the mean percentage inhibition of formation of respiratory $C^{14}O_2$ during the first hour after administration of the labeled substrate. The data are taken from reference 28.

TABLE 4

Some enzymes other than decarboxylases that are inhibited by α-methyl-dopa

Enzyme	System	Concentration	Reference
Tyrosine transaminase	Liver, *in vitro*	10^{-2} M	25
D-Amino acid oxidase	Rat, *in vivo*, using D-dopa and D-tyrosine		28
Tryptophan hydroxylase and Phenylalanine hydroxylase	Rat liver, *in vitro*	10^{-4} M	3
	Rat, *in vivo*		3
Dopamine-β-oxidase	Adrenal extract, *in vitro*	4×10^{-3} M[a]	22

[a] α-Methyl-*m*-tyrosine was used.

boxylase inhibitors *in vivo*. This compound is decarboxylated in the rat (28, 35) and to some extent in man (2, 35, 48, 57), although O-methylation and oxidative deamination are also important processes which may be affected by some of the inhibitors being tested for antidecarboxylase action. One of the drawbacks to the use of this amino acid is that, with so much of it reaching the kidney quickly, the effects observed with inhibitors are much influenced by enzymes that are present in that organ (35, 57). An interesting test of specificity is afforded by the use of α-methyl-5-hydroxytryptophan and 5-(3-hydroxycinnamoyl)-salicylic acid. These two compounds inhibit dopa decarboxylase *in vitro*, and are effective in tests *in vivo* using unlabeled dopa or 5-hydroxytryptophan. They have no inhibitory action on the catabolism of carboxyl-labeled L-tyrosine (28); they have some action on carboxyl-labeled DL-dopa (19, 28; see table 2); and they are very effective when carboxyl-labeled L-α-methyl-dopa is used (28).

A list of some enzymic inhibitions by α-methyl-dopa other than antidecarboxylase action, is presented in table 4.

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