Alterations in the Pattern of Amine Excretion in Man Produced by a Monoamine Oxidase Inhibitor

Abstract. The administration of monoamine oxidase inhibitors produces an increase in the urinary excretion of many amines for which efficient alternate routes of metabolism are not available. These include tryptamine, paratyramine, and a "metatyramine-like" substance. The inhibitors can therefore be used to detect previously unsuspected pathways of amino acid decarboxylation. The finding that the excretions of norepinephrine, epinephrine, 3,4-dihydroxyphenylethylamine, and possible serotonin are not appreciably affected are consistent with previous reports of the existence of alternative metabolic routes.

Drugs which inhibit monoamine oxidase (MAO) are being widely used as tools in research and as therapeutic agents in conditions such as psychic depression, angina pectoris, and hypertension. At present their pharmacologic actions are being considered entirely from the standpoint of the inhibition of serotonin (5-hydroxytryptamine) and norepinephrine metabolism in tissues such as brain and heart. While it is true that MAO inhibitors block completely the oxidative degradation of these two amines in vitro, other pathways for metabolism of the amines exist in vivo (*1*). The presence or absence of efficient alternate pathways for a given amine can be detected by determining whether or not the amount of amine excreted in the urine is increased during MAO inhibition. It was decided, therefore, to study the excretion of amines in patients receiving the MAO inhibitor 1-phenyl-2-hydrazinopropane (JB-516, Catron), since it has already been shown that this drug, in tolerable clinical dosage (*2*), effectively inhibits amine oxidase in man.

Four patients with uncomplicated hypertension were used for these studies. Twenty-four-hour collections of urine were obtained before and during therapy with JB-516 in a daily dose of 25 mg. Free norepinephrine and epinephrine were assayed fluorometrically by a modification (*3*) of the trihydroxyindole method, following adsorption of catecholamines on alumina at *p*H 8.4 and elution with 0.2*N* acetic acid (*4*). Dopamine (3,4-dihydroxyphenylethylamine), was determined in the same eluates by the method of Carlsson and Waldeck (*5*). The method used for serotonin was that described by Udenfriend, Weissbach, and Brodie (*6*). Tryptamine was measured by a method described elsewhere (*7*). For paratyramine determinations, 10-ml samples of urine were extracted, as described by Mitoma *et al.* (*8*), and the final acid extract was assayed fluorometrically, as reported for tyrosine (*9*).

As shown in Table 1, there were no significant changes in the urinary excretions of norepinephrine, epinephrine, and dopamine with MAO inhibition; this indicated the existence of efficient alternate pathways for the metabolism of these amines. Data for serotonin are not presented in the table becaues the chemical methods of determination are not suitable when urinary excretion is less than 500 μg/day. However, comparisons for all four patients were made before and after administration of JB-516, and in no instance did the levels rise to detectable values. In contrast, the excretions of tryptamine and of paratyramine were increased markedly. In other experiments daily excretions of these two amines have risen as high as 1100 μg for the former and 2400 μg for the latter.

Preliminary studies have also shown that MAO inhibition produces a marked increase in many urinary amines, the majority of which are as yet unidentified. One such substance has been tentatively identified as metatyramine. It has been isolated by passing samples of urine (3 percent of a 24-hour volume) through a Dowex 50-NH_4^+ column at a neutral *p*H, followed by elution with 3*N* NH_4OH. Eluates were concentrated in a vacuum and chromatographed on paper with butanol, acetic acid, and water (8:2:2). Metatyramine yields a characteristic light blue color at R_f of 0.65 when the chromatograms are sprayed with 0.1-percent 2,6-dichloroquinone chloroimide in alcohol, followed by 0.5*M* borate buffer, *p*H 9.3. Tentative identification has been achieved by comparing the R_f values of the material obtained from urine with those of authentic metatyramine in four solvent systems. These, and the colors obtained with several reagents, were found to be identical with those of the authentic compound.

These results indicate that decarboxylation of amino acids is a more common phenomenon than has been suspected and that MAO inhibition should be viewed in the perspective of a general alteration in the metabolism of amines. The finding that the actions of an amine such as tryptamine, which has weak biologic activity, are greatly potentiated in animals treated with MAO inhibitors (*10*) supports this concept. Furthermore, the tryptamine content of tissues, including brain, can be greatly increased by administration of L-tryptophan to animals after MAO blockade (*11*). In six patients the administration of L-tryptophan (20 to 50 mg/kg) during therapy with JB-516 (25 mg/day) produced marked central effects, including hyperreflexia, clonus, and symptoms similar to those that follow the ingestion of ethanol (*7*). The absence of such symptoms when tryptophan alone was given suggests that the agent producing these effects is an amine metabolite of tryptophan.

The MAO inhibitors will undoubtedly prove valuable for the identification and study of many amines which are otherwise almost completely metabolized. The demonstration of such unsuspected products of amino acid decarboxylation is also of clinical interest, particularly in view of the findings with tryptophan, since it indicates that the dietary intake of amino acids is an important factor to consider in evaluating the actions of MAO inhibitors.

Table 1. Urinary excretion of amines before and during MAO inhibition with JB-516.

Case No.	Control (μg/day)	During inhibition* (μg/day)
	Norepinephrine	
1	33, 14	26, 49
2	15, 17	10, 8
3	26, 39	36
4	97	58
	Epinephrine	
2	8, 7	4, 5
3	8, 11	14
4	20	15
	Dopamine	
1	270, 160	240, 160
2	320, 270	360, 260
3	390, 160	410
	Tryptamine	
1	68, 45	640, 940
2	71, 52	412, 362
3	60, 50	834, 735
4	99, 101	555, 616
	p-*Tyramine*	
1	190, 370	1060, 1180
2	242, 300	784, 615
3	315, 361	1420, 1280
4	320, 430	805, 960

* After 5 to 10 days of treatment.

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26 March 1959