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SHORT COMMUNICATIONS

On the mechanism of release of norepinephrine by α-methyl-*m*-tyrosine and α-methyl-*m*-tyramine

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IT HAS recently been reported that α-methyl-3,4-dihydroxyphenylalanine (α-methyl-dopa) possesses hypotensive and sedative properties in man.[1] Biochemical studies in experimental animals have shown that α-methyl-dopa and the related compound, α-methyl-*m*-tyrosine, produce a marked and long-lasting lowering of norepinephrine levels in tissues (brain and heart)[2, 3] which could explain their pharmacological actions. However, the effects on norepinephrine do not arise as a result of inhibition of the biosynthesis of norepinephrine as might have been expected from the inhibitory actions of the two compounds on aromatic L-amino acid decarboxylase *in vitro*. The norepinephrine levels fall instead, through an effect on the ability of the tissues to take up or store the hormone.[2] Reserpine guanethidine and many sympathomimetic amines act in a similar manner.[4]

Studies with α-methyl-*m*-tyrosine and its decarboxylation product, α-methyl-*m*-tyramine, were undertaken in the guinea pig to determine the mechanism of the norepinephrine-release*; the amine is also a potent norepinephrine-releasing agent.[2]

TABLE 1. LACK OF CORRELATION BETWEEN NOREPINEPHRINE-RELEASE AND CONVERSION OF α-METHYL-*m*-TYROSINE TO ITS AMINE

	α-Methyl-*m*-tyramine in urine	Norepinephrine released (millimicromoles/g)	
	μg/24 hr	brain	heart
Normal	0	0	0
α-Methyl-*m*-tyrosine	470	1·3 ± 0·1	12·2 ± 0·7
α-Methyl-*m*-tyrosine following decarboxylase inhibitor	30	1·4 ± 0·1	10·8 ± 2·0
Decarboxylase inhibitor alone	0	0	0

α-Methyl-*m*-tyrosine (50 mg/kg) was administered intraperitoneally to guinea pigs and the animals were killed 24 hr later. The decarboxylase inhibitor, α-hydrazino-α-methyl-3,4-dihydroxyphenylpropionic acid (Merck, Sharpe and Dohme), was administered (25 mg/kg i.p.) 15 min before α-methyl-*m*-tyrosine and 30 min after. Each value for norepinephrine represents the average of findings obtained in from 3 to 5 individual animals.

It was found, first of all, that the norepinephrine-releasing action of α-methyl-*m*-tyrosine is not altered by agents which inhibit decarboxylation of the amino acid. In the experiment shown in Table 1, the decarboxylation of α-methyl-*m*-tyrosine was inhibited by the previous administration of α-hydrazino-α-methyl-3,4-dihydroxyphenylpropionic acid, which does not release norepinephrine from brain or heart. Although the formation of α-methyl-*m*-tyramine in test animals was diminished

* The term release is used for want of a better term. It is not meant to imply a mechanism for the lowering of tissue norepinephrine.

by more than 90 per cent, the amount of norepinephrine released was comparable to the amount released from control animals which received the α-methyl-*m*-tyrosine only. It would appear, therefore, that α-methyl-*m*-tyrosine is, by itself, an effective norepinephrine-releasing agent.

The availability of a sensitive and specific method for measuring α-methyl-*m*-tyramine in tissues* made it possible to investigate the stoichiometry of norepinephrine-release by the amine itself. The data in Fig. 1 show that, following its administration, α-methyl-*m*-tyramine reaches a level in heart about three times that of the control norepinephrine content. However, within a few hours, and lasting

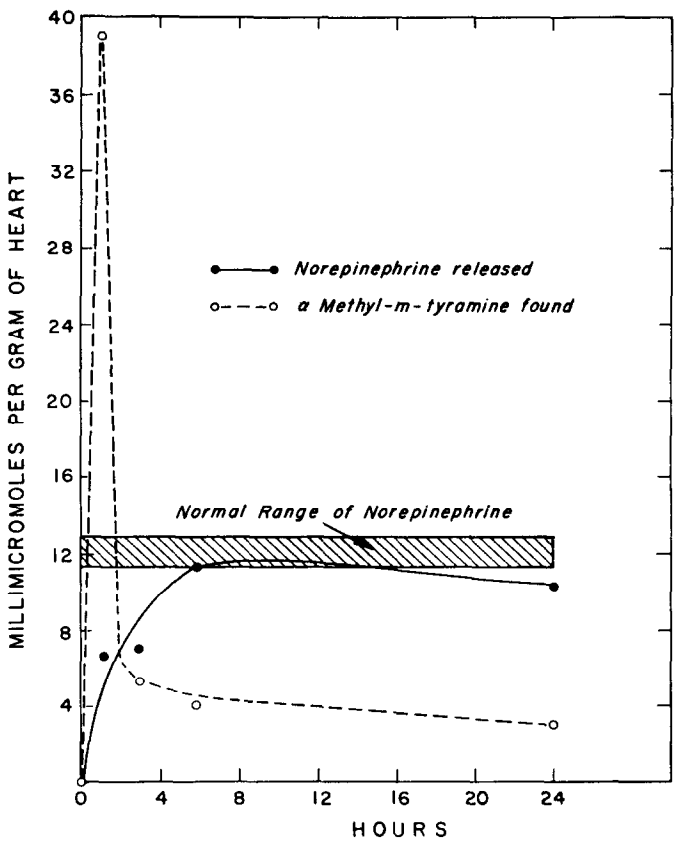

FIG. 1. Stoichiometry of the release of norepinephrine from guinea pig heart by α-methyl-*m*-tyramine. The drug (50 mg/kg) was administered intraperitoneally and individual animals were killed at the times indicated.

for at least 24 hr longer, when most of the norepinephrine had been released, the amount of α-methyl-*m*-tyramine in the brain had fallen to very low values, equivalent to only a fraction of the norepinephrine which was released. The levels of the tyramine-derivative at 5 and 24 hr may actually be lower than shown, since at these low levels the method is near the limits of its sensitivity. Similar data were obtained from studies of spleen and brain. It may be concluded that although the immediate release process may be a mole-for-mole displacement of norepinephrine by the administered α-methyl

* α-Methyl-*m*-tyramine was isolated by the same extraction procedure as is used for serotonin,[5] and was measured colorimetrically by the method described for *m*-tyramine by Mitoma *et al.*[6]

m-tyramine, the longer lasting depletion cannot be explained on a displacement basis. A prolonged effect on the norepinephrine-binding sites or a slow rate of norepinephrine turnover in the tissues are more likely explanations. When α-methyl-*m*-tyrosine was administered in doses producing a maximal depletion of norepinephrine, barely detectable amounts of α-methyl-*m*-tyramine were found in the tissues.

Another conclusion from these studies is that α-methyl-*m*-tyramine is a more potent releaser of norepinephrine than is apparent when considerations are pased on the administered dose. The highest levels found in brain and heart, following dosages of α-methyl-*m*-tyramine which produced maximal norepinephrine-depletion (50 mg/kg), were about 1 and 8 μg/g, respectively. Based on the amounts of the drug actually reaching the tissues, α-methyl-*m*-tyramine and probably α-methyl-*m*-tyrosine and α-methyl-dopa may be as potent releasers of norepinephrine as are the Rauwolfia alkaloids. More detailed studies are now in progress.

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Increased intestinal absorption of foreign organic compounds in the presence of ethylenediaminetetraacetic acid (EDTA)

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FOREIGN organic compounds of low lipid-solubility are poorly absorbed from the intestine mainly because of their inability to penetrate readily the lipid-like membrane of the intestinal epithelial cells.[1] It is also recognized that most organic compounds used as drugs have too large a molecular size to pass freely through the aqueous "pores" of the epithelial cell membrane or through the spaces which might exist between the cells.[2] Recently, Windsor and Cronheim[3] have reported that two lipid-insoluble acids, heparin and sulfopolyglucin, which are normally very poorly absorbed from the gastrointestinal tract, are absorbed to an appreciable extent when administered together with the chelating agent, sodium EDTA. The present investigation of the effect of EDTA on the intestinal absorption of several lipid-insoluble compounds shows that the chelating agent increases the extent of absorption of neutral and basic compounds, as well as that of acidic compounds, and suggests a possible mechanism for this action.