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Isomers of 2,4,5-Trihydroxyphenethylamine (6-Hydroxydopamine): Long-Term Effects on the Accumulation of [^{3}H]-Norepinephrine in Mouse Heart *in Vivo*

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SUMMARY

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The immediate and long-term effects of the six isomeric trihydroxyphenethylamines and 2,3,4,5-tetrahydroxyphenethylamine on the uptake and release of [^{3}H]norepinephrine from storage sites in cardiac tissue of the mouse *in vivo* have been compared. In addition, the rate of autoxidation of these amines has been measured. The order of potency of the various isomers for inhibition of uptake is: 3,4,5 = 2,4,5 = 2,3,4 > 2,3,4,5 > 2,3,5 ≫ 2,4,6 > 2,3,6; the order of activity for release is: 2,4,5 = 3,4,5 > 2,3,5 > 2,3,4 > 2,3,4,5 ≫ 2,4,6 ≫ 2,3,6. The α-methyl derivative of the 2,4,5-isomer (6-hydroxydopamine) is nearly twice as effective as the parent amine as a releasing agent, while the N,N-dimethyl derivative is completely inactive. The order for rate of autoxidation is: 2,3,4,5 ≫ 2,3,5 = 2,3,6 = 2,4,5 = N,N-dimethyl-2,4,5 > 2,3,4 > 3,4,5 ≫ 2,4,6. Only the 2,4,5-isomer, the α-methyl derivative of the 2,4,5-isomer, the 2,3,5-isomer, and the 2,3,4,5-tetrahydroxyphenethylamine cause long-term reduction in the cardiac uptake of [^{3}H]norepinephrine. These results support the hypothesis that neurodegeneration can only be initiated when a critical intraneuronal concentration of a readily autoxidizable amine is attained as a direct result of an affinity of the amine for the active uptake process at the neuronal membrane.

INTRODUCTION

2,4,5-Trihydroxyphenethylamine (6-hydroxydopamine), an autoxidation product of dopamine (1, 2), elicits a selective degeneration of noradrenergic nerve terminals, thereby providing an invaluable pharmacological tool for the study of both peripheral and central noradrenergic nerve function (3). The degenerative effect of 6-hydroxydopamine appears to be contingent upon attainment of a critical, rather high, intraneuronal concentration of the amine as a consequence of the active uptake of the amine at the neuronal membrane (3). Drugs, such as desmethylimipramine, that block the active uptake of norepinephrine and other amines through the neuronal membrane (4, 5) prevent the degenerative effect of 6-hydroxydopamine (6, 7), while drugs, such as reserpine, that interfere with the uptake of amines at the membrane of the intraneuronal

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storage vesicle have little effect on the degeneration induced by 6-hydroxydopamine (7–10). Thus uptake of 6-hydroxydopamine at the neuronal membrane, but not at the intraneuronal storage vesicle, appears to be essential for a degenerative effect.

A variety of amines, including 6-hydroxydopamine (9, 11), are actively transported both at the neuronal membrane and at the membrane of the intraneuronal storage vesicle. This process results in a transient release of norepinephrine from vesicles by the exogenous amine, followed by a gradual replacement of the exogenous "false transmitter" with newly synthesized norepinephrine, and usually occurs without producing any morphological change in the nerve terminal. However, it is now well established that a critical intraneuronal concentration of 6-hydroxydopamine will rapidly induce functional and morphological changes, which lead ultimately to a virtual ablation of the nerve terminal (3). The mechanisms by which this amine causes neurodegeneration are unknown. However, it appears quite likely that autoxidation of the amine, with the concomitant formation of both hydrogen peroxide and reactive quinones, is involved (12–15). Except for 6-aminodopamine (6, 16) and probably α-methyl-6-hydroxydopamine (6), no other amines are known to induce a selective destruction of noradrenergic nerve terminals. 6-Hydroxynorepinephrine and 6-hydroxyepinephrine (17) have been reported to cause depletion of cardiac norepinephrine (18). However, in spite of its structural similarity to 6-hydroxydopamine, 6-hydroxynorepinephrine did not cause neurodegenerative effects in mouse (19). A study of the six isomeric trihydroxyphenethylamines and certain other amines with regard to interaction with noradrenergic mechanisms and to ease of autoxidation was initiated with the expectation of providing further insight into the mechanism of chemically induced neural degeneration and perhaps of revealing more efficacious or selective neurodegenerative agents.

MATERIALS AND METHODS

2,4,5-Trihydroxyphenethylamine HBr, *N*,*N*-dimethyl-2,4,5-trihydroxyphenethylamine HCl, α-methyl-2,4,5-trihydroxyphenethylamine HCl, and 3,4,5-trihydroxyphenethylamine HCl were obtained from Regis Chemical Company under Research Contract SA 43-pH-3021 and were provided by Dr. A. A. Manian, Psychopharmacology Service Center, National Institute of Mental Health. 2,5-Dimethoxyphenethylamine HCl, 2,3,5-trimethoxyphenethylamine HCl, 2,3,6-trimethoxyphenethylamine HCl, and 2,3,4,5-tetramethoxyphenethylamine HCl were obtained from Drs. F. Benington and R. D. Morin, University of Alabama Medical College, and 2,3,5-trimethoxyphenethylamine from Dr. A. Furst, University of San Francisco. Demethylation of these compounds and of 2,3,4-trimethoxyphenethylamine HCl (Aldrich Chemical Company) was achieved by treatment with concentrated hydrobromic acid or with boron tribromide in dichloromethane. 2,4,6-Tribenzyloxyphenethylamine HCl was synthesized by standard methods from 2,4,6-trihydroxybenzaldehyde. Hydrogenation of the former afforded 2,4,6-trihydroxyphenethylamine HCl. Purity and identity of amines were determined by paper and thin-layer chromatography and by mass spectroscopy. Details of the synthesis and analyses will be published elsewhere.

Effect on uptake and release of norepinephrine into cardiac tissue. The technique used to study the inhibition of uptake of norepinephrine is based on the classical method developed by Axelrod and co-workers (4, 20–23), which consists of administration of a test substance to the animal *preceding* administration of a tracer dose of [^{3}H]DL-norepinephrine. This method, which has been used extensively (24–26), has provided results in essential agreement with those obtained using isolated, perfused hearts (27). [^{3}H]DL-Norepinephrine was used in the present report, since previous studies have demonstrated that this material, when employed as a tracer, provides indices which correlate with the behavior of endogenous cardiac norepinephrine (28–30). Both D- and L-norepinephrine utilize the same uptake mechanism in heart, with the uptake process showing a higher affinity for the natural isomer (31). Total radioactivity in heart after administration of [^{3}H]DL-norepineph-

rine has been shown to consist of greater than 80% radioactive norepinephrine under a variety of conditions (18, 24, 32). For this reason, total radioactivity in hearts has been measured in the present study to provide a simple index of the amount of [^{3}H]norepinephrine remaining at any time. The detailed protocol is described in the legend of Table 1.

The method for the study of release of norepinephrine is similar, and consists of administration of the test substance *after* administration of a tracer dose of [^{3}H]norepinephrine. This method has been widely used to study the effects of compounds that interact with the storage of cardiac norepinephrine (18, 21, 22, 29, 30, 32–40). The protocol described in the legend of Table 2 is a minor modification of a previously reported method (18).

Long-term effects of compounds on the uptake of [^{3}H]DL-norepinephrine were measured 5–20 days after administration of the test substance by a similar protocol (legend, Table 3). The uptake of [^{3}H]amines has been shown to provide indices related to degeneration of norepinephrine-containing nerve terminals in the heart (41–44).

RESULTS

Three aspects of the interaction of the isomeric trihydroxyphenethylamines and some related derivatives with the noradrenergic nerve terminals in the mouse heart were compared. First, a comparison of the initial effect of the amine on [^{3}H]norepinephrine uptake into mouse heart was carried out by a method that provides indices related to the affinity of the amine for the active uptake mechanism at the neuronal membrane (see refs. 4, 20–27). Second, a comparison of the rate of depletion of [^{3}H]norepinephrine from previously labeled stores of cardiac norepinephrine was carried out by a method that provides a measure of the ability of the amine to displace norepinephrine from the storage vesicles and/or cytoplasmic storage sites in the nerve terminal (see refs. 41–44). Finally, the rate of autoxidation of these compounds was compared as a relative measure of the ease of formation of quinones and hydrogen peroxide.

As shown in Table 1, all of the amines, except the 2,3,6- and 2,4,6-isomers, and the *N*,*N*-dimethyl derivative of the 2,4,5-isomer, inhibited the uptake of [^{3}H]norepinephrine by at least 25% at a dose of 80 μmoles/kg. At the lower dose, 20 μmoles/kg, only the 2,3,4-, 3,4,5-, and 2,4,5-isomers showed an effect on uptake.

All the isomeric trihydroxyphenethylamines cause release of [^{3}H]norepinephrine from cardiac storage sites, but their effectiveness varies widely (Table 2). As would be

TABLE 1

Acute effect of trihydroxyphenethylamines on uptake of [^{3}H]norepinephrine by mouse heart

Test compounds were administered subcutaneously as solutions of their hydrochloride or hydrobromide salts, dissolved in 0.9% NaCl immediately before injection. After 20 min [7-^{3}H]DL-norepinephrine (New England Nuclear Corporation, 10–15 Ci/mmole), 2.0 μCi in NaCl, was injected into the tail vein, and 15 min later the animal was killed by cervical fracture and the heart was removed. Tissue was dissolved by heating at 60° for 4 hr in a closed counting vial containing 30% hydrogen peroxide (0.4 ml) and 60% perchloric acid (0.2 ml). The vial was cooled in Dry Ice–alcohol, counting fluid was added (10 ml, Scintisol—complete, Isolab), and the total tritium per heart was determined by liquid scintillation spectroscopy at a counting efficiency of 29%. Recovery of tritium standards through the entire oxidation procedure was 99.8 ± 2.1% (SD). Male, National Institutes of Health, general-purpose mice, weighing 14–20 g, were used, with 10–20 individuals/group. Results are expressed as percentage of control ± standard deviation. The mean radioactivity obtained with control groups was 28,900 ± 2,000 cpm/heart.

Phenethylamine	Uptake of [^{3}H]norepinephrine	
	20 μmoles/kg	80 μmoles/kg
	% control	
2,3,4-Trihydroxy-	71 ± 6	55 ± 5
2,3,5-Trihydroxy-	101 ± 12	75 ± 10
2,3,6-Trihydroxy-	102 ± 6	94 ± 8
3,4,5-Trihydroxy-	47 ± 10	49 ± 9
2,4,5-Trihydroxy-[a]	52 ± 7	51 ± 5
N,*N*-Dimethyl-2,4,5-trihydroxy-[b]	101 ± 6	100 ± 5
2,4,6-Trihydroxy-	95 ± 14	87 ± 10
2,3,4,5-Tetrahydroxy-	102 ± 8	66 ± 11

[a] 6-Hydroxydopamine.

[b] *N*,*N*-Dimethyl-6-hydroxydopamine.

TABLE 2

Release of [³H]norepinephrine from mouse heart by phenethylamines and related compounds

Release was determined as described previously (18). One hour after intravenous administration of [³H]norepinephrine the test compound was given subcutaneously and the level of [³H]norepinephrine in heart was measured as described in Table 1 after an additional 2 hr. Results are expressed as percentages of control ± standard deviation for 5–10 individual mice. The mean activity in the control was 15,000 ± 1,000 cpm/heart.

Compound	Dose	Release	ED_{50}
	μmoles/kg	*% control*	*μmoles/kg*
Phenethylamine			
2,3,4-Trihydroxy-	25	74 ± 8	74
	50	59 ± 6	
	100	61 ± 7	
2,3,5-Trihydroxy-	25	62 ± 6	63
	50	53 ± 4	
	100	44 ± 3	
	320	28 ± 5	
2,3,6-Trihydroxy-	50	88 ± 6	>10,000
	100	95 ± 4	
	200	84 ± 6	
	400	79 ± 7	
3,4,5-Trihydroxy-	5	77 ± 8	10
	10	50 ± 5	
	20	22 ± 6	
3,5-Dihydroxy-4-methoxy-			1.4[a]
2,4,5-Trihydroxy-	5	56 ± 7	7[a]
	10	44 ± 8	
	25	30 ± 5	
	50	18 ± 6	
α-Methyl-2,4,5-trihydroxy-	2.5	62 ± 7	4
	5	45 ± 8	
	10	29 ± 5	
	25	15 ± 4	
2,4,-Dihydroxy-5-methoxy-	50	76 ± 7	91
	75	56 ± 8	
	100	47 ± 6	
2,4,6-Trihydroxy-	50	85 ± 4	>400
	100	75 ± 6	
	200	64 ± 7	
2,3,4,5-Tetrahydroxy-	25	75 ± 8	82
	50	58 ± 6	
	100	46 ± 7	
	300	22 ± 4	
4-Hydroxy-[b]			18.5[a]
Reserpine			0.3[a]

[a] Reference 30.

[b] Tyramine.

expected from the results in Table 1, the 2,3,6-, 2,4,6-, and *N*,*N*-dimethyl-2,4,5-derivatives are almost totally without effect. The 2,3,4-, 2,3,5-, and 2,3,4,5-derivatives are nearly equipotent with respect to release of [³H]norepinephrine, with ED_{50} values of 74, 63, and 82 μmoles/kg, respectively, whereas the 3,4,5- and 2,4,5-isomers are considerably more active. The α-methyl derivative of the 2,4,5-isomer is nearly twice as effective as the parent amine. The 4-*O*-methyl metabolite formed from the 3,4,5-isomer (30) is a potent releasing agent, while the 5-*O*-methyl derivative of the 2,4,5-isomer (46) is ineffective in this regard (Table 2).

The long-term effects of these amines are shown in Table 3. Only the 2,3,5-, 2,4,5-, α-methyl-2,4,5-, and 2,3,4,5-derivatives clearly produce a sustained reduction in the observed uptake of [³H]norepinephrine. The extent of the long-term damage to the uptake mechanism appeared to be dose-related at 5 days. An approximately 7-fold increase in effectiveness of the 2,3,4,5-tetrahydroxyphenethylamine was observed when 10% ascorbic acid was included in the injection solution.

The rates of autoxidation of the 2,3,5-, 2,3,6-, and 2,4,5-isomers, as well as the *N*,*N*-dimethyl derivatives of the 2,4,5-isomer, were virtually the same. At an amine concentration of 0.2 mM, the oxygen consumption was approximately 65–70

TABLE 3

Long-term effect of trihydroxyphenethylamines on uptake of [^{3}H]norepinephrine by mouse heart

Uptake of [^{3}H]norepinephrine was determined 15 min after administration as described in Table 1. Test compounds were given subcutaneously as a single dose 5–20 days prior to measuring uptake. Results are expressed as percentage of control ±standard deviation for 10–20 individuals.

Compound	Dose	Uptake of [^{3}H]norepinephrine		
		5 days	10 days	20 days
	μmoles/kg		*% control*	
Phenethylamine				
2,3,4-Trihydroxy-	100	98 ± 10		
	200	97 ± 13		
2,3,5-Trihydroxy-	30	65 ± 11	93 ± 16	
	80	58 ± 13	76 ± 6	87 ± 9
	200	30 ± 4	56 ± 8	70 ± 5
	400	12 ± 9		
2,3,6-trihydroxy-	80	97 ± 7		
	100	100 ± 5		
	150	102 ± 6		
3,4,5-Trihydroxy-	150	96 ± 7		
	300	94 ± 8		
2,4,5-Trihydroxy-	50	48 ± 15	48 ± 7	69 ± 10
	100	17 ± 10	28 ± 12	
	150	14 ± 7	36 ± 15	
α-Methyl-2,4,5-trihydroxy-	50	43 ± 10		
N,*N*-Dimethyl-2,4,5-trihydroxy-	150	102 ± 5		
2,4,6-Trihydroxy-	100	106 ± 10		
	200	100 ± 7		
2,3,4,5-Tetrahydroxy-	20	68 ± 8		
	40	54 ± 15	50 ± 6	
	50	50 ± 6	57 ± 7	64 ± 10
	75	41 ± 6		
	150	32 ± 10		
2,3,4,5-Tetrahydroxy-[a]	5	59 ± 5		
	10	43 ± 3		
	20	20 ± 6		
	50	22 ± 2		
	75	16 ± 8		
Reserpine	10	110 ± 16	91 ± 12	

[a] Administered in NaCl containing 10% ascorbic acid.

nmoles/min (Table 4). The rate observed for the 2,3,4,5-tetrahydroxyphenethylamine at this concentration was nearly 6 times faster, whereas the rate obtained with the 2,3,4- and 3,4,5-isomers was only about one-fifth as fast. The rates of oxygen uptake for the 2,4,6-isomer and for 2,5-dihydroxyphenethylamine and dopamine were much slower.

DISCUSSION

The present investigation was carried out *in vivo* to obtain direct and valid comparisons of both the acute and long-term effects of various isomeric trihydroxyphenethylamines and tetrahydroxyphenethylamine on uptake and storage of [^{3}H]norepinephrine in mouse heart. This approach suffers from the disadvantage that, with compounds of markedly different chemical properties, the pharmacokinetics of absorption, metabolism, and transport to the heart may differ widely. However, within a series of isomeric compounds such as those under study at present, such factors should be of reduced importance. Absorption and transport should be very similar, and should,

TABLE 4

Autoxidation rates of trihydroxyphenethylamines and related compounds

Initial rates of oxygen consumption were measured with a Clark oxygen electrode in a closed cell equipped with a magnetic stirrer. The total cell volume was 1.7 ml; temperature was maintained at 37°; the solvent was 0.2 M sodium phosphate buffer, pH 7.0. Test compounds were dissolved in deoxygenated water, 0.01–0.07 ml, immediately before injection into the cell via a sealed port.

Phenethylamine	Oxidation rate			
	0.1 mM[a]	0.2 mM	0.5 mM	1.0 mM
	nmoles O_2 consumed/min			
2,3,4-Trihydroxy-		14 ± 6.6	22.3 ± 2.6	42.0 ± 2.6
2,3,5-Trihydroxy-	34.1 ± 6.6	68.2 ± 5.2	288 ± 19.6	
2,3,6-Trihydroxy-	30.8 ± 2.6	66.8 ± 3.9		
3,4,5-Trihydroxy-		8.5 ± 3.9	20.4 ± 3.3	41.3 ± 2.6
2,4,5-Trihydroxy-	29.6 ± 2.6	66.3 ± 3.3	276 ± 13.1	
N,*N*-Dimethyl-2,4,5-trihydroxy-	34.1 ± 2.6	69.6 ± 3.3	269 ± 26.2	
2,4,6-Trihydroxy-				4.6 ± 1.0
2,3,4,5-Tetrahydroxy-	131 ± 23.6	394 ± 52.4		
2,5-Dihydroxy-			5.9 ± 2.6	11.8 ± 2.6
3,4-Dihydroxy[b]				<2

[a] Final concentration of amine.

[b] Dopamine.

indeed, be somewhat favored in certain more lipophilic amines, such as 2,4,6-trihydroxyphenethylamine and *N*,*N*-dimethyl-2,4,5-trihydroxyphenethylamine, compounds which are *inactive* toward the various parameters of [^{3}H]norepinephrine uptake and release *in vivo*. In addition, metabolism catalyzed by monoamine oxidase and/or catechol *O*-methyltransferase does influence to some extent the levels of various amines at cardiac sites; however, this metabolic factor cannot be of prime importance, since relatively low doses of dopamine (ED_{50} = 26.4 μmoles/kg), an excellent substrate for both enzymes, do cause marked release of [^{3}H]norepinephrine (30). One major factor which could greatly influence the attainment of effective concentrations of amine at cardiac sites is the rate of autoxidation of the amine during absorption and transport. Certainly, this factor must be considered with the readily autoxidizable amines, *i.e.*, the 2,3,5-, 2,3,6-, and 2,4,5-trihydroxyphenethylamines, and especially the 2,3,4,5-tetrahydroxyphenethylamine (Table 4). The marked potentiation of the long-term effect of the tetrahydroxyphenethylamine when administered in the presence of ascorbic acid (Table 3), in conjunction with the rapid loss of pharmacological effectiveness of the amine in solution, suggests that the protection from autoxidation afforded by ascorbic acid is exerted primarily during the injection and locally in the subcutaneous depot. The presence of ascorbic acid in the injection medium had little, if any, effect on the potency of the other amines.

The long-term effect of 2,3,5-trihydroxyphenethylamine and 2,3,4,5-tetrahydroxyphenethylamine on the uptake of [^{3}H]norepinephrine in mouse heart is similar to that produced by 2,4,5-trihydroxyphenethylamine and is probably the result of amine-induced neurodegeneration of noradrenergic terminals (41–44). The absence of this effect with the other amines studied, in conjunction with their other biochemical and physical properties, supports the hypothesis that neurodegeneration can only be initiated when a critical intraneuronal concentration of a readily autoxidizable amine is attained as a direct result of an affinity of the amine for the active uptake process at the neuronal membrane.

The inability of the 2,4,6- and 2,3,6-isomers significantly to inhibit the uptake or

enhance the release of norepinephrine suggests that the presence of two hydroxyl groups flanking the ethylamine side chain greatly reduces the affinity of the amine for uptake processes at either the neuronal or vesicular membrane. While the 2,4,6-isomer is autoxidized slowly, the 2,3,6-isomer is autoxidized at a rate equivalent to the 2,4,5-isomer. The lack of long-term effects with the 2,3,6-isomer probably results from an inability to attain a critical intraneuronal concentration. In like manner, the *N*,*N*-dimethyl derivative of the 2,4,5-isomer did not block uptake or promote release of [^{3}H]norepinephrine and produced no long-term effect, in contrast to the effect induced by the parent amine. The low affinity for the catecholamine uptake process of amines with increasingly bulky *N*-substituents was apparent from studies *in vitro* on the inhibition of [^{3}H]-epinephrine uptake in perfused hearts (45). Since the autoxidation of 2,4,5-trihydroxyphenethylamine and its *N*,*N*-dimethyl derivative is equivalent, it seems most likely that the lack of long-term effects of the latter amine is due to a failure to achieve the necessary intraneuronal concentration. The acute effect of 2,4,5-, 2,3,5-trihydroxy-, and 2,3,4,5-tetrahydroxyphenethylamines on [^{3}H]norepinephrine uptake after 20 min may represent not only competitive inhibition but neurodegenerative damage to the uptake processes, since others have reported that one of the earliest observable effects of amines such as the 2,4,5-isomer is damage to the amine uptake process (43, 44).

The 3,4,5- and 2,4,5-isomers were the most effective releasing agents in the series (Table 2). Part of the activity of the 3,4,5-isomer may result from release of [^{3}H]norepinephrine, elicited not by the amine itself but rather by its *O*-methylated metabolite, 3,5-dihydroxy-4-methoxyphenethylamine, a compound previously reported to be an extremely potent releasing agent (18). In the case of the 2,4,5-isomer, *O*-methylation (46) converts it into a relatively weak releasing agent, 2,4-dihydroxy-5-methoxyphenethylamine (Table 2). The lack of long-term effects on uptake of [^{3}H]-norepinephrine by active releasing agents such as the 3,4,5-isomer may be due to their markedly lower rates of autoxidation or their inability to form *p*-quinones (Table 4).

Metabolism of 2,4,5-trihydroxyphenethylamine by monoamine oxidase appears to play a minor role in determining the efficacy of the amine *in vivo*, since the α-methyl derivative is only twice as active as a releasing agent (Table 2) and is not significantly different from the parent amine in eliciting long-term reductions in the uptake of [^{3}H]norepinephrine in heart (Table 3). The enhanced activity of the α-methyl derivative as a releasing agent is in agreement with reports of potentiation of the effects of 6-hydroxydopamine (7, 10), or of 6-hydroxydopa (41, 47) by monamine oxidase inhibitors.

The 2,3,4,5-tetrahydroxyphenethylamine undergoes autoxidation at an extremely rapid rate (Table 4), but in spite of the extensive destruction probably occurring during transport from the subcutaneous site of injection to the heart, this amine exhibits moderate inhibition of the uptake of [^{3}H]-norepinephrine and moderate activity as a releasing agent (Tables 1 and 2). The long-term effects of this amine on uptake of [^{3}H]norepinephrine were consonant with the hypothesis that amines that have a significant affinity for uptake processes in the noradrenergic neuronal membrane and that are, in addition, readily autoxidizable will elicit neuronal degeneration. In view of the long-term effects of 2,3,5-trihydroxyphenethylamine and 2,3,4,5-tetrahydroxyphenethylamine in cardiac tissue, further studies to demonstrate the morphological correlates and other effects of these amines on peripheral and central noradrenergic, dopaminergic, and serotonergic neurons have been initiated. Studies, similar to the present report, on the factors involved in the release of cardiac norepinephrine and in the apparent degenerative effect of noradrenergic and/or serotinergic neurons elicited by 5,6-dihyroxytryptamine (18, 48–51) and related tryptamines are in progress.

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