*Kirk-Othmer Encyclopedia of Chemical Technology.*


# EPINEPHRINE AND NOREPINEPHRINE

(-)-Epinephrine (E), (-)-norepinephrine (NE), and dopamine (DA) belong to a class of compounds known as catecholamines, and are neurotransmitters and/or hormones in peripheral tissues and the central nervous system. NE is the principal postganglionic sympathetic neurotransmitter in the periphery and in adrenergic neurons in the central nervous system. It is released from nerve terminals, and acts to transmit a nerve impulse across the synapse (synaptic cleft) between the nerve terminal and postsynaptic site of action. Many neurotransmitters, including E and NE, can be both inhibitory and excitatory depending on which tissue or organ the neurotransmitter is acting on. For example, NE may be excitatory, as in the heart and vascularly, inhibitory, as in the intestine, or both excitatory and inhibitory, as in the central nervous system depending on location.

The chromaffin cells of the adrenal medulla may be considered to be modified sympathetic neurons that are able to synthesize E from NE by *N*-methylation. In this case the amine is liberated into the circulation, where it exerts effects similar to those of NE; in addition, E exhibits effects different from those of NE, such as relaxation of lung muscle (hence its use in asthma). Small amounts of E are also found in the central nervous system, particularly in the brain stem where it may be involved in blood pressure regulation. DA, the precursor of NE, has biological activity in peripheral tissues such as the kidney, and serves as a neurotransmitter in several important pathways in the brain (1, 2).

E occurs naturally in the adrenal medulla, and was one of the first chemical substances of biological importance to be isolated. In 1895 (3) extracts of adrenal glands were found to increase blood pressure and constrict smooth muscle. Numerous attempts were made to isolate the chemical compound that was responsible for the physiological effects, but the first positive findings were obtained in 1901 when E, together with small amounts of NE, was isolated and purified from bovine adrenal glands (4). Subsequently the structure of E was established (5). The chemical synthesis of the racemic form of E was published in 1904 (6). Although it was speculated after the discovery of E that another substance, probably NE, was released from stimulated sympathetic neurons (7, 8), it was not until 1946 that it was demonstrated that mammalian peripheral sympathetic adrenergic neurons used NE as a transmitter instead of E (9). At that time it was not technically possible to study the content of transmitter in terminal parts of the adrenergic neuron. However, it was predicted that NE was concentrated in the nerve terminal region from which it was released to act as a neurotransmitter. This was conclusively demonstrated about 10 years later with the development of methods for visualizing catecholamines in freeze-dried tissues, and the demonstration that NE was released when sympathetic neurons such as the splenic nerve were stimulated (10).

## 1. Physical Properties

Some of the physical properties of E and NE are summarized in Table 1.

**Table 1. Physical Properties of Epinephrine and Norepinephrine[a]**

| Property | D-(−)-Epinephrine | D-(−)-Norepinephrine |
|---|---|---|
| IUPAC name | (-)-3,4-dihydroxy-α-[(methylamino)methyl]benzyl alcohol | (-)-α(aminomethyl)-3,4-dihydroxybenzyl alcohol |
| CA name | (*R*)-(-)-4-[1-hydroxy-2-(methylamino)ethyl]-1,2-benzenediol | (*R*)-(-)-4-(2-amino-1-hydroxyethyl)-1,2-benzenediol |
| other names | epinephrine[b], adrenaline | levarternol, D-arterenol, D-noradrenaline |
| CAS Registry Number | [51-43-4] | [51-41-2] |
| formula | $C_9H_{13}NO_3$ | $C_8H_{11}NO_3$ |
| formula wt | 183.2 | 169.2 |
| description appearance | colorless microcrystals[c] | colorless microcrystals |
| mp | ca 209–210°C (dec) | ca 212°C (dec) |
| solubility | in water, ca 0.1 g/100 mL; insoluble in alcohol and most other organic solvents | slightly soluble in water |
| absorption spectrum | 0.1 *M* HCl $\lambda_{max}$ 221 nm, $\epsilon$ ca 6100; $\lambda_{max}$ 280 nm, $\epsilon$ ca 2700 | in 0.1 *M* HCl, $\lambda_{max}$ 221 nm, $\epsilon$ ca 5860; $\lambda_{max}$ 279 nm, $\epsilon$ ca 2560 |
| fluorescence spectrum | in 0.05 *M* sodium acetate buffer, pH 4, $\lambda_{ex}$ 283 nm, $\lambda_{em}$ 337 nm | in 0.05 *M* sodium acetate buffer, pH 4, $\lambda_{ex}$ 283 nm, λ337 nm; iodine oxidation in alkaline ascorbate[d], $\lambda_{ex}$ 412 nm, $\lambda_{ex}$ 505 nm |
| reaction product fluorescence | | color reactions with various reagents[e] |
| specific rotation | $[\alpha]^{25}_D$ −50 to −53.5°, *c* = 2g/100 mL, 0.5 *M* HCl[b]; | $[\alpha]^{25}_D$ 37.3°, *c* = 5g/100 mL water containing 1 equiv hydrochloric acid[f] |
| optical purity | determined on the *N*-acetyl-3,4-di-*O*-acetyl derivative, $[\alpha]^{21}_D$ −94.7°, *c* = 1.01 g/100 mL, $CHCl_3$[g] | determined on the *N*-acetyl-3,4-di-*O*-acetyl derivative, $[\alpha]^{25}_D$ 81.3°, *c* = 1 g/100 mL, $CHCl_3$[f] resolution of (±)-norepinephrine[h] |
| source | resolution of (±)-epinephrine with (+)-tartaric acid | |
| likely impurties | (+)-epinephrine | (+)-norepinephrine |

[a]Data given in: *Specifications and Criteria for Biochemical Compounds, Supplement: Biogenic Amines and Related Compounds.*(Courtesy of the National Academy of Sciences.)
[b]Ref. 11.
[c]Acceptable preparations may be slightly off-white.
[d]Ref. 12.
[e]Ref. 13.
[f]Ref. 14.
[g]Ref. 15; report $[\alpha]^{20}_D$ −87.4°, *c* = 1 g/100 mL, $CHCl_3$ for the triacetyl derivative, and the configuration of natural (−)-epinephrine is the same as D-(−)-mandelic acid.
[h]Ref. 16.

### 1.1. Stability

E is sensitive to air, light, heat, and alkalies. Metals, notably copper, iron, and zinc, destroy its activity. In solution with sulfite or bisulfite, it slowly forms an inactive sulfonate (17). The red color that forms when neutral or alkaline solutions are exposed to air is caused by adrenochrome.

NE is unstable in light and air, especially at neutral and alkaline pH. Oxidation to noradrenochrome occurs in the presence of oxygen and such divalent metal ions as copper, manganese, and nickel.

## 2. Analytical Methods

Bioassay methods were used in early studies as one of the more sensitive procedures for the estimation of E and NE in tissue extracts or biological fluids. However, the development of fluorescence methods (18) for the detection of nanomolar concentrations of E and NE in tissues, blood, and urine gradually displaced the original bioassays (19, 20). This was followed by the development of radioenzymatic (21, 22), gas chromatographic (gc) without (23) and with mass spectrometric detection (ms) (24). The latter, together with high performance liquid chromatographic (hplc) techniques, coupled with electrochemical detection (25), have replaced the earlier methods because of their increased sensitivity and specificity. In addition, their versatility and relative inexpensiveness as compared to gc–ms have gained widespread use and revolutionized the analytical procedures in this field. Improved techniques using capillary zone electrophoresis and combined hplc–ms have been developed, and will probably come into more general use (26).

## 3. Chemical Synthesis

The original commercial source of E was extraction from bovine adrenal glands (5). This was replaced by a synthetic route for E and NE (Fig. 1) similar to the original published route of synthesis (6). Friedel-Crafts acylation of catechol [120-80-9] with chloroacetyl chloride yields chloroacetocatechol [99-40-1]. Displacement of the chlorine by methylamine yields the methylamine derivative, adrenalone [99-45-6], which on catalytic reduction yields (±)-epinephrine [329-65-7]. Substitution of ammonia for methylamine in the sequence yields the amino derivative noradrenalone [499-61-6] which on reduction yields (±)-norepinephrine [138-65-8]. The racemic compounds were resolved with (+)-tartaric acid to give the physiologically active (−)-enantiomers. The commercial synthesis of E and related compounds has been reviewed (27). The synthetic route for L-3,4-dihydroxyphenylalanine [59-92-7] (L-DOPA) has been described (28).

## 4. Economic Aspects

The principal trade names and suppliers of (−)E, an adrenergic vasoconstrictor, are as follows: Adrenalin (Parke-Davis); Adrenalin in Oil (Parke-Davis); Primatene Mist (Whitehall); Bronkaid Mist (Sterling); and Epifrin (Allergan). The bitartrate salt [51-42-3] is used as an ophthalamic adrenergic vasoconstrictor; the principal trade names (suppliers) are Asmatane Mist (3M Riker); Epitrate (Wyeth-Ayerst); Medihaler-Epi (3M Riker); Primatene Mist Suspension (Whitehall); and Suprarenin (Sterling). (−)Norephinephrine bitartrate [69815-49-2], used similarly to (−)E, is supplied by Sterling under the trade name Levophed. Dopamine hydrochloride [62-31-7], a cardiovascular agent, is supplied under the name Dopestat from Parke-Davis and Intropin from Du Pont Pharmaceuticals. The total drugstore and hospital U.S. sales for 1991 were $78,008,000 for (−)E products, $6,851,000 for (−)NE products, and for dopamine $14,595,000 (IMS Pharmaceutical Database Division). Levodopa [59-92-7], an antiparkinsonian agent, is supplied under the following trade names (manufacturers) as Bendopa (ICN), Dopan (Norwich-Eaton), Larodopa (Hoffmann-LaRoche), and Levopa (SmithKline-Beecham), and is a component of Madopa (Hoffmann-LaRoche) and Sinemet (Merck). The total U.S. drugstore and hospital sales for 1991 were $63,535,000 with Sinemet controlling about 99% of this market (IMS Pharmaceutical Database Division).

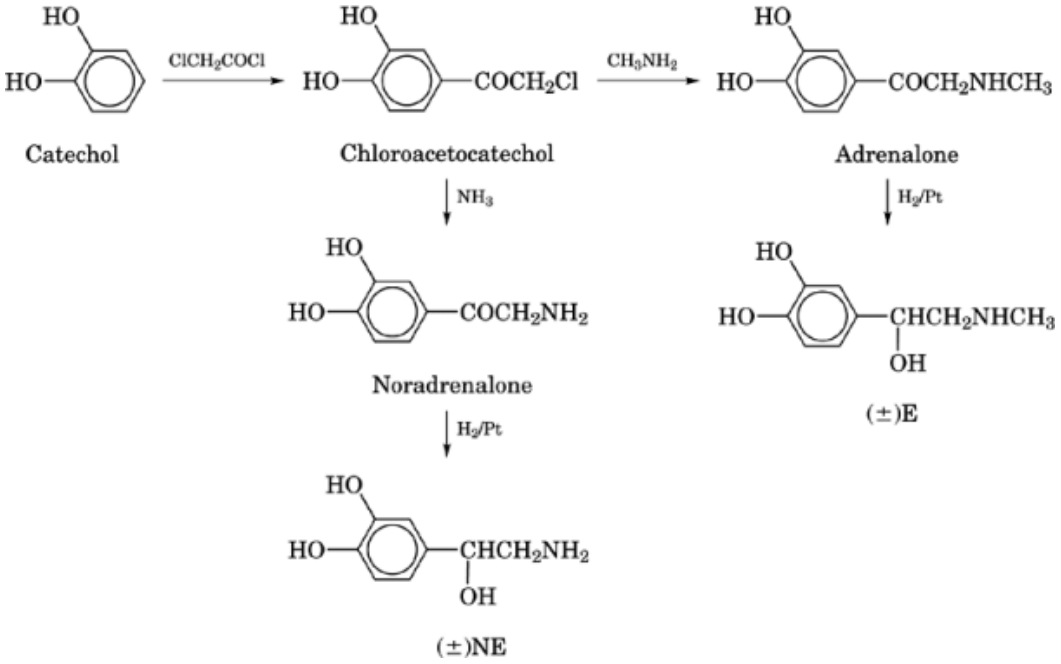


**Fig. 1.** Synthetic route to E and NE from catechol.

## 5. Metabolism of Catecholamines

The general scheme of the biosynthesis of catecholamines was first postulated in 1939 (29) and finally confirmed in 1964 (Fig. 2) (30). Although not shown in Figure 2, in some cases the amino acid phenylalanine [63-91-2] can serve as a precursor; it is converted in the liver to (-)-tyrosine [60-18-4] by the enzyme phenylalanine hydroxylase. Four enzymes are involved in E formation in the adrenal medulla and certain neurons in the brain: tyrosine hydroxylase, dopa decarboxylase (also referred to as L-aromatic amino acid decarboxylase), dopamine-$\beta$-hydroxylase, and phenylethanolamine *N*-methyltransferase. Neurons that form DA as their transmitter lack the last two of these enzymes, and sympathetic neurons and other neurons in the central nervous system that form NE as a transmitter do not contain phenylethanolamine *N*-methyl-transferase. The component enzymes and their properties involved in the formation of catecholamines have been purified to homogeneity and their properties examined. The human genes for tyrosine hydroxylase, dopamine-$\beta$-oxidase and dopa decarboxylase, have been cloned (31, 32). It is anticipated that further studies on the molecular structure and expression of these enzymes should yield interesting information about their regulation and function.

An outline of the metabolism of E and NE is shown in Figure 3. By the action of monoamine oxidase (MAO) (33) and an aldehyde dehydrogenase, acid metabolites are formed, and by the action of catechol-*O*-methyltransferase (COMT) (34) 3-*O*-methylation of either the parent compounds or of the metabolites is affected. A listing of the catecholamine and metabolite abbreviations together with the CAS Registry Numbers is found in Table 2. The metabolism of DA leads to the production of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) as shown in Figure 4. If 3-*O*-methylation first occurs, 3-methoxytyramine (3-MT) is formed which is then converted to 3-methoxy-4-hydroxyphenylethanol (MHPE). The aldehyde HAld can also be oxidized to the carboxylic acid HVA. Catecholamines can also be conjugated to glucuronic and sulfuric acid (4).

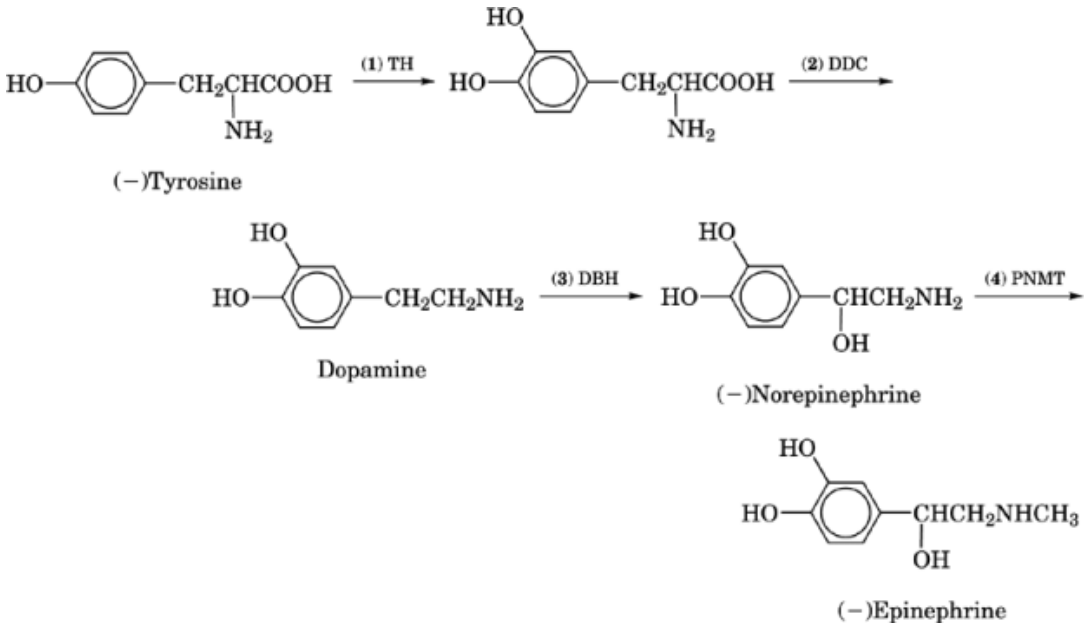


**Fig. 2.** Biosynthetic pathway for epinephrine, norepinephrine, and dopamine. The enzymes catalyzing the reaction are (**1**) tyrosine hydroxylase (TH), tetrahydrobiopterin and $O_2$ are also involved; (**2**) dopa decarboxylase (DDC) with pyridoxal phosphate; (**3**) dopamine-$\beta$-oxidase (DBH) with ascorbate, $O_2$ in the adrenal medulla, brain, and peripheral nerves; and (**4**) phenethanolamine *N*-methyltransferase (PNMT) with *S*-adenosylmethionine in the adrenal medulla and the brain.

## 6. Regulation of Synthesis, Storage, Release, and Metabolism

Catecholamine biosynthesis begins with the uptake of the amino acid tyrosine into the sympathetic neuronal cytoplasm, and conversion to DOPA by tyrosine hydroxylase. This enzyme is highly localized to the adrenal medulla, sympathetic nerves, and central adrenergic and dopaminergic nerves. Tyrosine hydroxylase activity is subject to feedback inhibition by its products DOPA, NE, and DA, and is the rate-limiting step in catecholamine synthesis; the enzyme can be blocked by the competitive inhibitor $\alpha$-methyl-*p*-tyrosine (31).

DOPA in the bloodstream can be taken up into neural tissue and into tissue devoid of tyrosine hydroxylase, thus bypassing the rate-limiting enzymatic synthetic step (35). Uptake of DOPA by the brain is the basis of the therapeutic effect of DOPA in the treatment of Parkinson's disease (a disease characterized by depletion of DA in basal ganglia due to loss of nerve cells in the substantia nigra). In addition, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (36) depletes DA in the striatum and produces a clinical syndrome like Parkinson's disease that responds to DOPA. DOPA in axonal cytoplasm is converted to DA by dopa decarboxylase. This enzyme is not specific for DOPA as its substrate, and is abundant in other neurons and tissues besides those containing catecholamines. The conversion of DOPA to DA outside the brain can be inhibited by carbidopa [28860-95-9], with the result that combined treatment with DOPA and carbidopa leads to greater brain DOPA levels than DOPA treatment alone.

DA in the cytoplasm of neurons is taken up into storage vesicles by an energy requiring process that can be inhibited by the alkaloid reserpine [50-55-5]. The depletion by reserpine is long lasting, and the storage granules are irreversibly damaged. Cytoplasmic NE can also be taken up stereoselectively into the vesicles. The vesicles contain dopamine-$\beta$-oxidase that catalyzes the conversion of DA to NE. In the vesicle NE can be

**Table 2. Catecholamines and Their Metabolites**

| Compound | Abbreviation | CAS Registry Number |
|---|---|---|
| dopamine | DA | [51-61-6] |
| (−)epinephrine (adrenaline) | E | [51-43-4] |
| (−)norepinephrine (noradrenaline) | NE | [51-41-2] |
| *Catecholamine metabolites* | | |
| 3,4-dihydroxymandelic acid (DHMA) | DOMA | [775-01-9][a] |
| 3,4-dihydroxymandelic aldehyde | D | [13023-73-9][a] |
| 3,4-dihydroxyphenylacetaldehyde | DAld | [5707-55-1] |
| 3,4-dihydroxyphenylacetic acid | DOPAC | [102-32-9] |
| 3,4-dihydroxyphenylethanol | DOPET | [10597-60-1] |
| 3,4-dihydroxyphenylethylene glycol | DOPEG | [3343-19-9][a] |
| homovanillic acid (4-hydroxy-3-methoxy-phenylacetic acid) | HVA | [306-08-1] |
| 4-hydroxy-3-methoxy-phenylacetaldehyde | HAld | [5703-24-2] |
| metanephrine | M | [5001-33-2][a] |
| 3-methoxy-4-hydroxymandelic acid | 3M4HMAld | [17592-23-3] |
| 3-methoxy-4-hydroxyphenylethylene glycol | MHPG | [534-82-7][a] |
| 3-methoxy-4-hydroxyphenyl ethanol (MOPET) | MHPE | [2380-78-1] |
| 3-methoxytyramine | 3MT | [554-52-9] |
| normetanephrine | NM | [97-31-4][a] |
| vanillylmandelic acid (4-hydroxy-3-methoxymandelic acid) | VMA | [55-10-7][a] |

[a]Unspecified stereochemistry.

stored, can leak back into the cytoplasm, or can be released into the synapse. Finally, at some sites, notably in adrenal medulla and brain stem, NE in *N*-methylated to form E by phenylethanolamine *N*-methyltransferase.

The storage vesicles play a dual role: they maintain a ready supply of catecholamines at the terminal (also in the adrenal medulla) available for release, and they mediate the process of release. For example, NE is liberated from nerve terminals of postganglionic sympathetic neurons (similarly E is released from adrenal medulla) when an electrical impulse or action potential propagates along the nerve and reaches the terminal and/or adrenal medulla. The mechanism(s) regulating the release in the adrenal medulla or neurons are complex and not entirely known. However, the final step is thought to be similar. When an action potential reaches nerve terminals, calcium channels open, allowing an influx of the cation; increased intracellular calcium promotes fusion of the vesicles with the neuronal membrane and promotes the release into the extracellular space, by a process of exocytosis, of the soluble contents of vesicles, including dopamine-$\beta$-oxidase, NE, adenosine triphosphate, and in most cases peptides, as co-transmitters (37). Indirectly acting agents such as tyramine [51-67-2] and amphetamine [300-62-9] release catecholamines by a mechanism that is independent of calcium and is not associated with release of dopamine-$\beta$-oxidase, ie, nonexocytotically. These agents displace NE from storage vesicles, resulting in leakage from nerve terminals probably by a reversal of the usual inwardly directed process of neuronal uptake. These concepts have been reviewed (38).

Efficient regulatory mechanisms operate to modulate the rate of synthesis and release of catecholamines, depending on the need. For example, changes in blood pressure activate pressure-sensitive baroreceptors, sending signals back to the vasomotor centers in the brain. The latter then sends signals to the vasoconstrictor or vasodilator nerves, producing the appropriate alterations in activity by way of a decrease or increase in firing rate of neurons. At the nerve terminal level, such mechanisms as end-product inhibition of tyrosine hydroxylase, transient activation by phosphorylation of tyrosine hydroxylase, and enzyme induction all enable the neuron to respond to alterations in utilization of catecholamine neurotransmitters. Besides the latter, another important regulatory mechanism is the ability of released NE to interact with responsive sites, or receptors present not only on the postsynaptic neuron but also located presynaptically (in the case of NE, $\alpha$-2 adrenergic receptors) on the neurons that are releasing the catecholamine to diminish NE release for

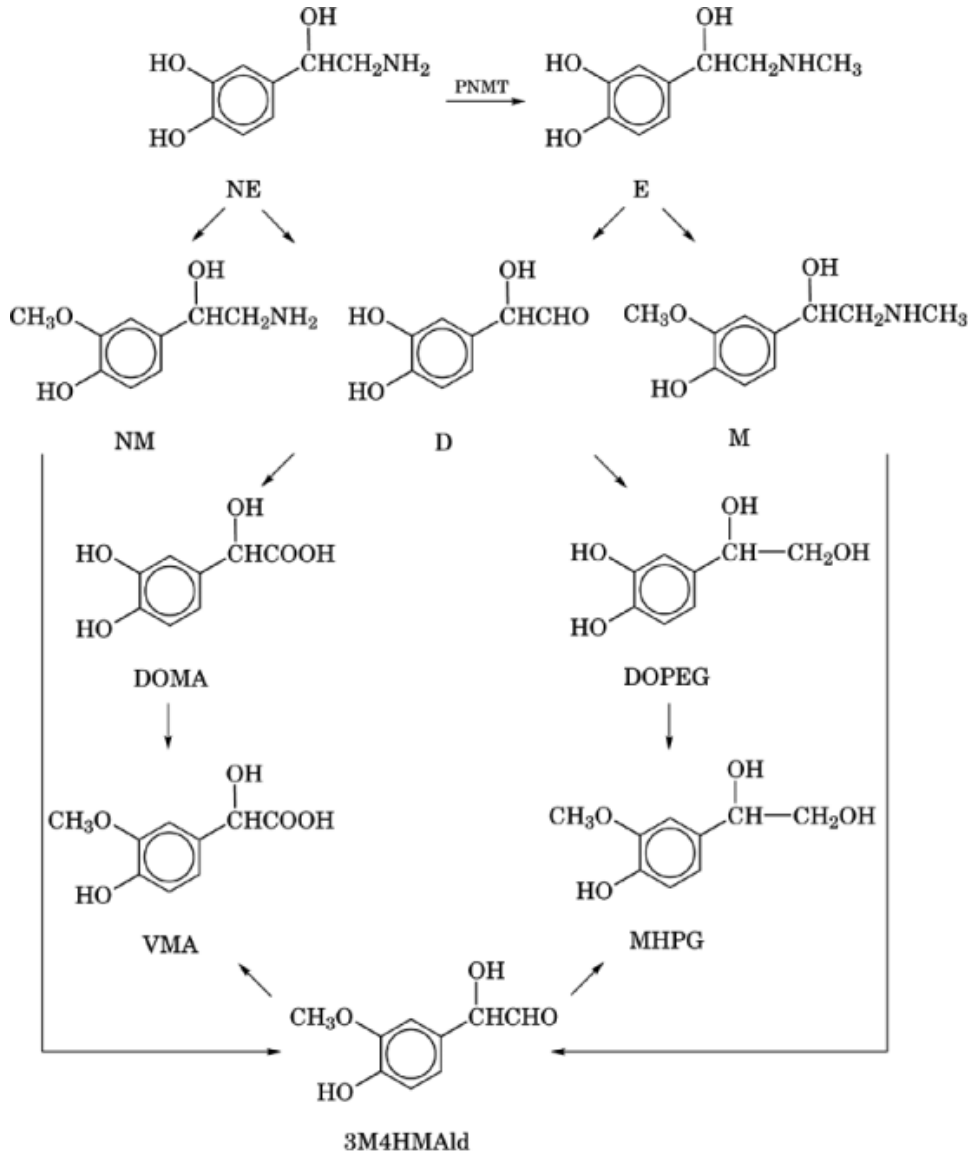


**Fig. 3.** Metabolism of norepinephrine and epinephrine (see Table 2 for abbreviations of amines and metabolites and CAS Registry Numbers).

a given amount of sympathetic nerve traffic. Thus, these presynaptic autoreceptors are believed to have the function of sensing the concentration of transmitter in the synaptic cleft and modulating the release and further synthesis of neurotransmitter accordingly. Other receptors such as muscarinic, dopamine, and opiate are also located presynaptically and are involved, for example, in adrenergic release. Similar presynaptic autoreceptor regulatory mechanisms appear to operate in the central nervous system for adrenergic and dopaminergic neurons (39).

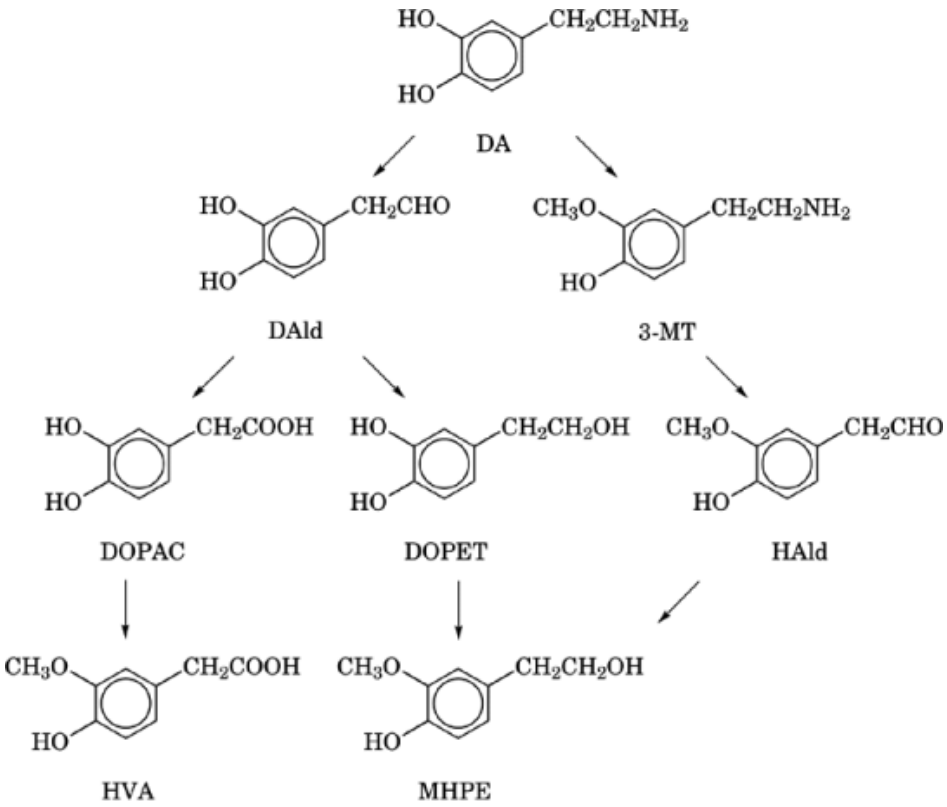


**Fig. 4.** Metabolism of dopamine (see Table 2 for abbreviations of amines and metabolites and CAS Registry Numbers).

Unlike the cholinergic system where the action of acetylcholine is terminated by cholinesterase, the action of catecholamine neurotransmitters released into the synaptic cleft is mainly brought to an end not by enzymatic degradation but by reuptake back into the nerve terminals (uptake 1) that released the catecholamines (40). Each of the three types of catecholamine neurons has its own uptake mechanism which is an energy-requiring, stereoselective process that can be blocked by certain classes of drugs such as tricyclic antidepressants (desipramine [50-47-5]), cocaine [50-36-2], and inhibitors of the Na–KATPase such as ouabain [630-60-4]. Nonneuronal uptake of catecholamines (uptake 2) also occurs, and is an energy-requiring, nonstereoselective process that can be blocked by adrenocorticosteroids such as corticosterone. A complementary DNA clone encoding a human NE transporter and more recently a DA transporter have been isolated.

Two important pathways for catecholamine metabolism are *O*-methylation by COMT, which is cytoplasmically localized, and oxidative deamination by the mitochondrial localized enzyme MAO. There are large amounts of MAO in tissues such as the liver and the heart which are responsible for the removal of most of the circulating monoamine, including some taken in from the diet. Tyramine is found in high concentrations in certain foods such as cheese, and in wine. Normally, this tyramine is deaminated in the liver. However, if MAO is inhibited, the tyramine may then be converted into octopamine [104-14-37] which may indirectly cause release of NE from nerve terminals to cause hypertensive crisis. Thus MAO, which is relatively nonspecific, plays an important role in the detoxification of pharmacologically active amines ingested from the diet.

MAO is known to occur in at least two forms, MAO A and MAO B, based on substrate selectivity, inhibition by various drugs, and cloning experiments. Clorgyline [17780-72-2] is a specific inhibitor of MAO A, which

displays a substrate specificity for NE and serotonin. Deprenyl [2323-36-6] is a selective inhibitor of MAO B, and displays a substrate preference for $\beta$-phenylethylamine and benzylamine. Dopamine and tyramine are substrates for both enzymes.

## 7. Catecholamine Receptors

When catecholamines are released from adrenergic neuronal terminals or adrenal medulla, they are recognized by and interact with specific receptor proteins (adrenergic) on plasma membranes of effector cells or tissues that mediate the action of the agonist, resulting in a physiological response. The diverse actions of E and NE led to the 1948 proposal of the concept of distinct subtypes of adrenergic receptors, classified as alpha and beta adrenergic receptors, on the basis of the differential responses elicited by six sympathetic amines in various effector systems (41). Beta receptors were subsequently subdivided into beta-1 and beta-2 (42). In the 1970s, studies from a number of laboratories using functional (43) and radioligand-binding techniques (44) signaled the beginning of an exciting era of pharmacology in which subtypes of receptors could be more readily assessed. These studies revealed that alpha receptors could be further divided into alpha-1 and alpha-2 subpopulations (43). Similarly, it was proposed that the effects of DA could be accounted for by the existence of two DA receptor subtypes, DA D-1 and D-2. More recent developments from several experimental approaches, in particular molecular biology, have led to the cloning and expression of six structurally related alpha adrenergic receptors, three beta adrenergic receptors, and five, and very likely more, distinct types of dopamine receptor subtypes.

## 8. Pharmacological Actions

In general, activation of alpha-1 adrenergic receptors causes a contraction of smooth muscle and of blood vessels, pilomotor muscles, dilator pupillae, vas deferens, nictitating membrane, splenic capsule, and sphincters of the intestine and urinary bladder and of the bile duct. An exception is the relaxation of the smooth muscle of the intestine. Prazosin [19216-56-9], indoramin [26844-12-2], and WB-4101 are relatively selective antagonists of these receptors.

Alpha-2 adrenergic receptors are found in a wide variety of tissues from the central and peripheral nervous system, and also in adipocytes, blood platelets, pancreatic islets, and cultured cell lines. As expected for receptors with a varied distribution, alpha-2 adrenergic receptors are associated with many physiological functions, including regulation of blood vessels, locomotor activity, platelet aggregation, memory, anxiety, and sexual activity. Receptors of the alpha-2 variety are located presynaptically on the terminals of sympathetic neurons, where they mediate inhibition of neurotransmitter release, but they are also found in the central nervous system and postsynaptically at the periphery. Clonidine [4205-90-7] and other imidazoline analogues are selective agonists, and yohimbine [146-48-5] and idazoxan are relatively selective antagonists.

Beta receptors of the beta-1 subtype mediate an increase in heart rate and increased force of contraction; they are also found in the central nervous system. E and NE are equally potent agonists and selective antagonists are atenolol [29122-68-7] and betaxolol [63659-18-7]. Beta-2 receptors are well known for their involvement in relaxing bronchioles. E is a more potent agonist than NE; procaterol [72332-33-3] is a selective agonist; ICI 118551 and $\alpha$-methylpropranolol are selective antagonists. A particular amine may act on both alpha and beta receptors or predominantly on one type. NE acts mainly on alpha-1, E on both alpha and beta, and isoproternol [7683-59-2] almost exclusively on beta receptors. Numerous antagonists also differentiate between alpha and beta receptors. The prototypic beta-adrenergic receptor antagonist propranolol [525-66-6] is essentially inactive at alpha receptors; the nonselective alpha-adrenergic receptor antagonist phentolamine is very weak or inactive at beta receptors.

## 9. Second Messengers

Adrenergic receptors comprise integral membrane proteins responsible for binding extracellular E and NE and initiating membrane signals through interaction with one of a series of guanine nucleotide binding regulatory proteins *G*-proteins) to activate second messenger systems. In this respect there are two significant mechanisms involved in the interaction of E and NE with their receptors, the first involving changes in calcium conductance and the phosphoinositol (PI) response, and the second related to inhibition or activation of adenylyl cyclase.

Excitation of smooth muscle via alpha-1 receptors (eg, in the uterus, vascular smooth muscle) is accompanied by an increase in intracellular-free calcium, possibly by stimulation of phospholipase C which accelerates the breakdown of polyphosphoinositides to form the second messengers inositol triphosphate ($IP_3$) and diacylglycerol (DAG). $IP_3$ releases intracellular calcium, and DAG, by activation of protein kinase C, may also contribute to signal transduction. In addition, it is also thought that alpha-1 adrenergic receptors may be coupled to another second messenger, a pertussis toxin-sensitive *G*-protein that mediates the translocation of extracellular calcium.

Effects mediated through beta- and alpha-2 adrenergic receptors are related to activation or inhibition of adenylyl cyclase through coupling of the receptors to the inhibitory ($G_i$) or stimulatory ($G_s$) regulatory proteins that influence adenylyl cyclase through guanosine triphosphate. Beta receptor activation leads to stimulation of adenylyl cyclase, resulting in generation of the second messenger *c*-AMP, whereas alpha-2 activation leads to inhibition. In a similar manner, the effects of DA were originally thought to be mediated by only two distinct *G*-protein-coupled receptor subtypes, DA D-1, inducing stimulation, and DA-2, inducing either inhibition or no effect on adenylyl cyclase, respectively.

## 10. Molecular Biology

Extensive pharmacological data together with the emergence of molecular biological approaches in the study of receptor structure and function, have yielded new information concerning the classification of alpha- and beta-adrenergic and dopaminergic receptors. This new information has resulted in the identification of a number of distinct subtypes. The following subdivision of receptor subtypes is based on data generated on endogenous receptors and cloned receptors. Three distinct alpha-1 (designated 1A, 1B, and 1C), three distinct alpha-2 (designated 2A, 2B, and 2C), three beta (designated beta-1, beta-2, and beta-3), and five or six DA (designated D-1, ie, D-1A, D-1B, and D-1C, also known as D-5, and D-2, ie, D-2A [2L], D-2B [2L], D-3, and D-4) receptors have been characterized. The D-2 receptor exists as two isoforms (2A and 2B), which are generated through alternative splicing of *m*RNA and differ by the presence or absence of a 29-amino acid insert in the third cytoplasmic loop. The reader is referred to reviews concerning structure, characterization, and pharmacology of alpha (45, 46), beta (47, 48), and DA (49, 50) receptor subtypes. The application of molecular biology to the study of adrenergic and dopaminergic receptors has occurred only in the last few years; much still has to be learned about the structure and function of these receptors, and the same for subtypes that have yet to be discovered.

A feature of the alpha and beta adrenergic and dopaminergic receptor subtypes is that they are members of a large superfamily of genes encoding numerous receptors that couple to guanine nucleotide regulatory proteins during signal transduction. Members of this family show common structural features, such as seven putative hydrophobic membrane spanning domains that are connected by hydrophilic loops that extend alternately into the extracellular and intracellular spaces from the plasma membrane. This model has the *N*-terminus outside the cell, with the protein weaving in and out of the membrane seven times with the C terminus in the cell. The seven putative transmembrane regions (about 175 amino acids) are relatively conserved among different family members (eg, the three alpha-2 adrenergic receptors share about 75% amino acid identity in their putative transmembrane regions) whereas the extra- and intracellular loop regions are more varied even between closely

related receptors. Other similarities of this receptor protein family are that the sites for *N*-linked glycosylation are found in the *N*-terminus extracellular portion of the molecule, and there are a number of highly conserved amino acids within the transmembrane regions. Moreover, among *G*-protein-coupled receptors, a high degree of variability has been observed in the third cytoplasmic loop and the carboxy tail. Generally, the protein coding regions of the genes in this family are without introns, but there are exceptions including the alpha-1 adrenergic and D-2, D-3, and D-4 genes.

The primary correlates or effector pathways of the various receptor subtypes are summarized as follows: most alpha-1 adrenergic subtype mediated responses involve the stimulation of phosphoinositide metabolism and the generation of the second messengers IP3 and DAG; alpha-2 adrenergic subtypes can inhibit adenylyl cyclase, acting through $G_i$ resulting in a decrease in the second messenger, *c*-AMP, although some alpha-2 adrenergic mediated responses cannot be explained by an action on adenylate cyclase, and other signal transduction mechanisms such as $Na^+/H^+$ exchange, or calcium ion channels, or as yet unknown mechanisms may be involved, particularly with regard to alpha-2A and 2B subtypes. DA D-1, including D-1C (also known as D-5), and beta adrenergic subtypes, are linked to adenylyl cyclase and induce stimulation, resulting in an increase of *c*-AMP levels. DA D-2A and 2B receptors are characteristic of receptors coupled to inhibition of adenylyl cyclase inducing a decrease in *c*-AMP; other signal transduction mechanisms such as activation of potassium and inhibition of calcium channel activity may also be involved. No functional correlate has been described for D-3 and D-4 receptors. In many cases there are few compounds that exhibit high selectivity for any particular subtype; moreover, some of the subtypes (particularly adrenergic) have only been found in a certain tissue or species and therefore may be endogenous only to that tissue or species. Thus further studies will be required to find out whether all subtypes are found in humans and what is their localization and function.

## 11. Therapeutic Uses

As described, E, NE, DA, and related compounds exhibit a wide diversity of physiological functions. Patients in clinical shock are usually treated with an iv administered pressor amine, including isoproterenol (beta agonist selective) NE, E, DA, and dobutamine [34368-04-2]. The choice of agents depends on the circumstances responsible for the decrease in blood pressure and the low rate of tissue perfusion that occurs in shock. E is also the primary treatment for anaphylactic shock. E is commonly included in local anesthetic solutions to promote hemostasis, and by vasoconstriction to reduce absorption resulting in prolongation of anesthesia. Several related sympathomimetic vasoconstrictor amines (eg, phenylephrine hydrochloride [61-76-7]) are used for nasal congestion. Because of their relaxation of bronchial smooth muscle, E and selected beta-2 agonists are used to antagonize the bronchospasm observed in asthma. NE is used for treating hypotension during anesthesia when tissue perfusion is good.

Alpha-adrenergic blocking agents such as prazosin (alpha-1 selective), which causes vasodilation in both arteries and veins without usually causing reflex tachycardia, are used to treat mild to moderate hypertension. Nonselective beta-adrenergic antagonists such as propranolol are used in the treatment of hypertension (usually with a diuretic), as prophylaxis in angina pectoris, and for prophylaxis of supraventricular and ventricular arrhythmias and other selected disorders. Selective beta-1 adrenergic antagonists such as metoprolol [37350-58-6] are used mainly for the treatment of hypertension. In addition, clonidine (an alpha-2 agonist) and methyldopa (metabolized to alpha-methylnorepinephrine in brain) act centrally on vasomotor centers of the brain to reduce sympathetic outflow to the peripheral vessels and thus are used, but to a lesser extent, in the treatment of hypertension.

In Parkinson's disease, treatment with the amine precursor DOPA (with the decarboxylase inhibitor carbidopa) (Fig. 2), has been shown to ameliorate the symptoms and signs of the condition and prolong life. Direct-acting dopamine agonists such as bromocriptine [25614-03-3] and pergolide [66104-22-1], plus the MAO B inhibitor deprenyl, which inhibits the breakdown of dopamine, are also being used, generally in

conjunction with DOPA therapy in the treatment of Parkinson's. There are several other disorders of the central nervous system in which catecholamines have been shown to be involved and drugs that affect the actions of catecholamines have a therapeutic action. Dopamine receptor antagonists that encompass several chemical classes such as phenothiazines (eg, chlorpromazine [50-53-5], butyrophenones (eg, haloperidol [52-86-8]), and thioxanthene derivatives (eg, chlorprothixene [113-59-7]), are prescribed for the management of both acute and chronic psychoses and in nonpsychotic individuals who are delusional or excited (eg, mania). The therapeutic as well as some of the side effects (eg, extrapyramidal) are thought to be the result of blockade of dopaminergic neurotransmission in the limbic, nigrostriatal, and hypothalmic, mesocortical systems (51). In the treatment of depression, most antidepressants are believed to improve mood by increasing catecholamine and/or serotonin concentrations. Tricyclic antidepressants such as imipramine [50-49-7] and amitriptyline [50-48-6] potentiate the actions of amines presumably by blocking the inactivating re-uptake of these amines after release from the presynaptic neuron. More selective agents, such as the selective serotonin re-uptake blocker fluoxetine [54910-89-3]have become available. MAO inhibitors block the metabolism of catecholamines, and the subsequent rise in amine levels in the brain are thought to underlie the antidepressant effect. The effects of drugs in the treatment of depression have been reviewed (52).

Besides behavior and blood pressure, catecholamine neurons also have important roles in other brain functions. Regulation of neuroendocrine function is a well-known action of catecholamines; for example, DA agonists reduce serum prolactin concentration, especially in conditions of hypersecretion. Ingestive behavior can be modulated by brain catecholamines, and some appetite-suppressing drugs are believed to act via catecholaminergic influences. Catecholamines also participate in regulation of body temperature.

## 12. Toxicity

Untoward effects of both E and NE (usually to a lesser degree) are anxiety, headache, cerebral hemorrhage (from vasopressor effects), cardiac arrhythmias, especially in presence of digitalis and certain anesthetic agents, and pulmonary edema as a result of pulmonary hypertension. The minimum subcutaneous lethal dose of E is about 4 mg, but recoveries have occurred after accidental overdosage with 16 mg subcutaneously and 30 mg intravenously, followed by immediate supportive treatment.

## BIBLIOGRAPHY

"Epinephrine" in *ECT* 1st ed., Vol. 5, pp. 763–768 by O. Kamm, Parke, Davis & Co.; in *ECT* 2nd ed., Vol. 8, pp. 231–238, by H. M. Crooks, Jr., Parke-Davis & Co.; "Epinephrine and Norepinephrine" in *ECT* 3rd ed., Vol. 9, pp. 241–250, by J. R. McLean, Warner-Lambert/Parke-Davis.

### Cited Publications

1. P. B. Molinoff and J. Axelrod, *Ann. Rev. Biochem.* **40**, 465 (1971).
2. U. Trendelenburg and N. Weiner, eds., *Catecholamines, Handbook of Experimental Pharmacology*, Vol. **90/II**, Springer-Verlag, Berlin, 1988, p. 427.
3. G. Oliver and E. Schaefer, *J. Physiol.* **18**, 230 (1895).
4. J. Takamine, *J. Soc. Chem. Ind.* **20**, 746 (1901); T. B. Aldrich, *Am. J. Physiol.* **5**, 457 (1901).
5. H. Pauly, *Chem. Berl.* **36**, 2944 (1903); H. A. D. Jowett, *J. Chem. Soc. Trans.* **85**, 192 (1904).
6. F. Stolz, *Chem. Berl.* **37**, 4149 (1904).

7. W. B. Cannon and J. E. Uridil, *Am. J. Physiol.* **58**, 353 (1921).
8. Z. M. Bacq, *Ann. Physiochem. Biol.* **10**, 467 (1934).
9. U. S. von Euler, *J. Physiol.* **105**, 38 (1946).
10. U. S. von Euler in H. Blaschko and E. Muscholl, eds., *Catecholamines, Handbuch der Experimentellen Pharmakologie*, Vol. **33**, Springer-Verlag, Berlin, 1972, p. 186.
11. *The U.S. Pharmacopeia*, 22nd rev., Mack Printing Co., Easton, Pa., 1989, p. 500.
12. P. A. Shore and J. S. Olin, *J. Pharmacol. Exp. Ther.* **122**, 295 (1958).
13. C. F. Schwender in K. Florey, ed., *Analytical Profiles of Drug Substances*, Vol. **1**, Academic Press, Inc., New York, 1972, p. 149.
14. L. H. Welsh, *J. Am. Pharm. Assoc. Sci. Ed.* **44**, 507 (1955).
15. L. H. Welsh, *J. Am. Chem. Soc.* **74**, 4967 (1952); P. Pratesi and co-workers, *J. Chem. Soc.* Part 1–2, 2069 (1958).
16. B. F. Tullar, *J. Am. Chem. Soc.* **76**, 2067 (1948); U.S. Pat. 2,774,789 (Dec. 18, 1956), B. F. Tullar (to Sterling Drug Inc.).
17. L. C. Schroeter, T. Higuchi, and E. E. Schuler, *J. Am. Pharm. Sci.* **47**, 723 (1958).
18. A. H. Anton and D. F. Sayre, *J. Pharmacol. Exp. Ther.* **138**, 360 (1962).
19. S. Udenfriend, *Fluorescence Assay in Biology and Medicine*, Vol. **2**, Academic Press, Inc., New York, 1969.
20. Y. Miura and M. Adachi in A. M. Krstulovic, ed., *Quantitative Analysis of Catecholamines and Related Compounds*, Ellis Horwood, Chichester, UK, 1986, p. 340.
21. P. G. Passon and J. D. Peuler, *Anal. Biochem.* **51**, 618 (1973).
22. M. G. Ziegler, L. C. Woodson, and B. Kennedy in Ref. 20, p. 263.
23. J.-M. Schmitter in Ref. 20, p. 24.
24. J. Roboz in Ref. 20, p. 46.
25. P. T. Kissinger and co-workers, *Clin. Chem.* **23**, 1449 (1977); B. Kagedal and D. S. Goldstein, *J. Chromatograph.* **429**, 177 (1988).
26. B. A. Davis, D. A. Durden, and A. A. Boulton, *J. Chromatograph.* **374**, 227 (1986).
27. K. R. Payne, *Ind. Chem.* **37**, 523 (1961); D. Lednicer and L. A. Metscher, *The Organic Chemistry of Drug Synthesis*, John Wiley & Sons, Inc., New York, 1977, p. 62.
28. U.S. Pat. 3,714,242 (Jan. 30, 1973), G. M. Jaffe and W. R. Rehl (to Hoffmann-LaRoche Inc.).
29. H. Blaschko, *J. Physiol.* **96**, 50P (1939).
30. T. Nagatsu, M. Levitt, and S. Udenfriend, *J. Biol. Chem.* **239**, 2910 (1964).
31. J. R. Cooper, F. E. Bloom, and R. H. Roth, *The Biochemical Basis of Neuropharmacology*, Oxford University Press, New York, 1991, p. 224.
32. H. Ichinose and co-workers, *Biochem. Biophy. Res. Commum.* **164**, 1024 (1989).
33. K. F. Tipton, *Br. Med. Bull.* **29**, 116 (1973).
34. J. Axelrod, *Pharmacol. Rev.* **18**, 95 (1966).
35. D. S. Goldstein and co-workers, *J. Clin. Endocrinol. Metab.* **64**, 861 (1987).
36. A. Y. Deutch and co-workers, *Neurosci. Lett.* **68**, 51 (1986).
37. R. M. Weinshilboum and co-workers, *Science* **174**, 1349 (1971).
38. H. Winkler in U. Trendelenberg and N. Weiner, eds., *Handbook of Experimental Pharmacology*, Vol **90/I**, Springer-Verlag, Berlin, 1988, p. 43.
39. S. Kalsner and T. C. Westfall, eds., *Presynaptic Receptors and the Question of Autoregulation of Neurotransmitter Release*, Vol. **604**, Annals of the New York Academy of Science, New York, 1990.
40. J. Axelrod, *Science* **173**, 598 (1971).
41. R. P. Ahlquist, *Am. J. Physiol.* **153**, 586 (1948).
42. A. M. Lands and co-workers, *Nature* **214**, 597 (1967).
43. S. Berthelsen and W. A. Pettinger, *Life Sci.* **21**, 595 (1977).
44. H. I. Yamamura, S. J. Enna, and M. J. Kuhar, *Methods in Neurotransmitter Receptor Analysis*, Raven Press, Ltd., New York, 1990.
45. J. K. Harrison, W. R. Pearson, and K. R. Lynch, *Trends Pharmacol.* **12**, 62 (1991).
46. R. R. Ruffolo, Jr. and co-workers, *Pharmacol. Rev.* **43**, 475 (1991).
47. R. J. Lefkowitz, J. M. Stadel, and M. G. Caron, *Annu. Rev. Biochem.* **52**, 159 (1983).
48. L. Emorine and co-workers, *Science* **245**, 1118 (1989).
49. O. Civelli and co-workers, *Eur. J. Pharmacol.,-Mol. Pharmacol. Sect.* **207**, 277 (1991).

50. R. K. Sunahara and co-workers, *Nature* **350**, 614 (1991).
51. K. L. Davis and co-workers, *Am. J. Psychiatry* **148**, 1474 (1991).
52. W. Z. Potter, M. V. Rudorfer, and H. Manji, *N. Engl. J. Med.* **325**, 633 (1991).

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