Chapter 1
Catecholamines

Lewis Landsberg

The naturally occurring, biologically important catecholamines are *epinephrine* (adrenaline in the UK), *norepinephrine* (noradrenaline in the UK), and *dopamine*. These compounds are synthesized in vivo from tyrosine which is sequentially hydroxylated to form dihydroxyphenylalanine (DOPA), decarboxylated to form dopamine (DA), β-hydroxylated to form norepinephrine (NE), and N-methylated to form epinephrine (E) (Fig. 1.1). The initial step, the hydroxylation of tyrosine by tyrosine hydroxylase, is rate limiting for the entire pathway. N-methylation of NE to E occurs only in the adrenal medulla and in those central neurons that utilize E as a neurotransmitter [1].

E is a circulating hormone, synthesized and stored in the adrenal medulla and secreted from that gland in response to acetylcholine released from the preganglionic splanchnic nerves. The latter originate in the intermediolateral column of the thoracic spinal cord (Fig. 1.2). E also serves as a neurotransmitter in the central nervous system (CNS) [2].

NE is the neurotransmitter at all sympathetic nerve endings (SNE) except those innervating the sweat glands which utilize acetylcholine as a neurotransmitter. The peripheral sympathetic nerves originate in the paravertebral sympathetic ganglia. Like the adrenal medulla, they are innervated by preganglionic nerves originating in the intermediolateral column of the spinal cord [1]. Although NE is also stored and released from the adrenal medulla, it does not function as a circulating hormone unless the levels are very high, as may occur from intense adrenal medullary stimulation or secretion from a pheochromocytoma. NE is also a neurotransmitter in the CNS.

DA is an important neurotransmitter in the CNS; in the periphery DA appears to generate its physiologic effects from the decarboxylation of its circulating precursor (DOPA) in effector tissues such as the kidneys and the gut. The origin of circulating

L. Landsberg (✉)
Northwestern University, Feinberg School of Medicine, Chicago, IL, USA
e-mail: l-landsberg@northwestern.edu

L. Landsberg (ed.), *Pheochromocytomas, Paragangliomas and Disorders of the Sympathoadrenal System*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-319-77048-2_1

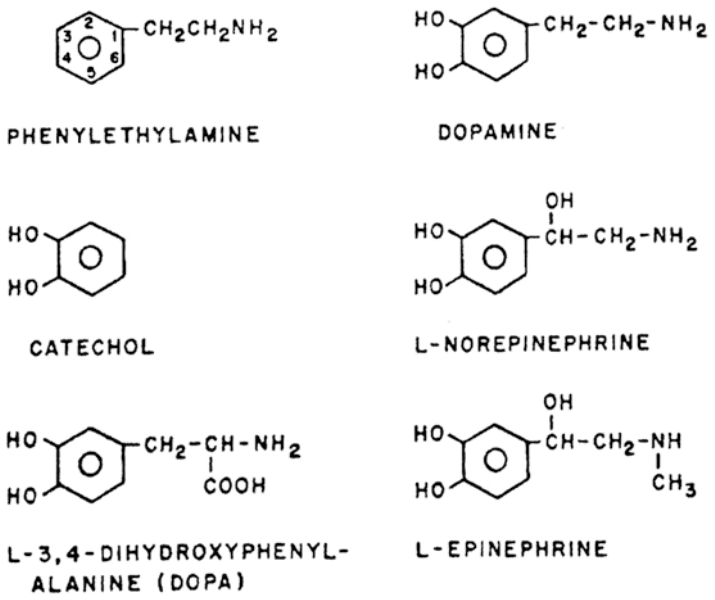

Fig. 1.1 Structures of naturally occurring catecholamines and related compounds. The conventional numbering system for ring and side chain substituents is shown for phenylethylamine, which may be considered the parent compound of many sympathomimetic amines. Catecholamines are hydroxylated at positions 3 and 4 on the ring (From Landsberg and Young [17], with permission)

DOPA is obscure, but a reasonable hypothesis localizes DOPA formation to the small intensely fluorescent (SIF) cells of the sympathetic ganglia [1, 3, 4].

Storage and Release of Catecholamines from Adrenal Medulla and Sympathetic Nerve Endings

Both the SNEs and the adrenal medulla contain large stores of catecholamines within discrete subcellular organelles known as chromaffin granules in the adrenal medulla and dense core vesicles in the nerve endings (Fig. 1.3). Storage within these structures provides a large functional reserve of catecholamines which are protected from enzymatic degradation by intracellular monoamine oxidase (MAO) [2, 5]. Catecholamine release is by exocytosis: fusion of the granule membrane with the cell wall and extrusion of the entire soluble contents of the granule or vesicle [1]. Exocytosis is triggered by the release of acetylcholine from the splanchnic preganglionic nerves that innervate the adrenal medulla and by depolarizing impulse traffic in the postganglionic sympathetic nerves (Fig. 1.4).

In the normal adrenal E constitutes about 75–80% of the total catecholamine content. In pheochromocytomas the relative concentration of NE is often increased.

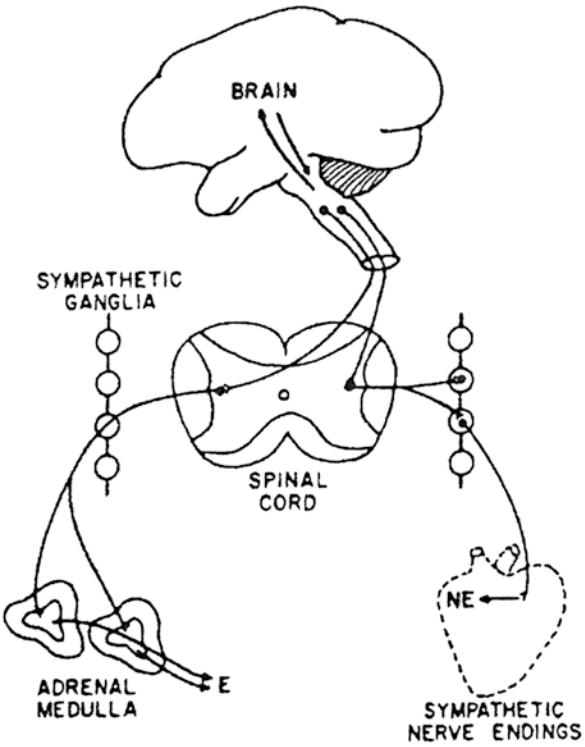

Fig. 1.2 Organization of the sympathoadrenal system. Descending tracts from the medulla, pons, and hypothalamus synapse with preganglionic sympathetic neurons in the spinal cord, which in turn innervate the adrenal medulla directly or synapse in paravertebral ganglia with postganglionic sympathetic neurons. The latter gives rise to sympathetic nerves, which are distributed widely to viscera and blood vessels. Release of epinephrine (E) or norepinephrine (NE) at the adrenal medulla or at sympathetic nerve endings occurs in response to a downward flow of nerve impulses from regulatory centers in the brain (From Landsberg and Young [17], with permission)

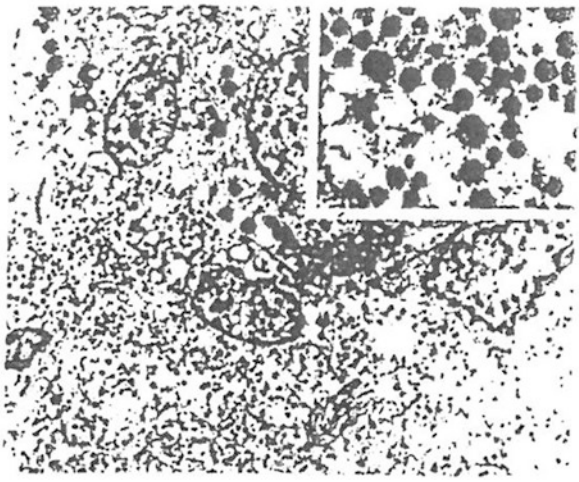

Fig. 1.3 Electron photomicrograph of human adrenal medulla. Cells at the lower left containing small, electro-dense particles are adrenomedullary chromaffin cells with chromaffin granules; those above are adrenocortical cells. Magnification ×7250. Inset (upper right) shows chromaffin granules with clearly defined limiting membranes under higher magnification (×50,000) (Courtesy of Dr. James Connolly)

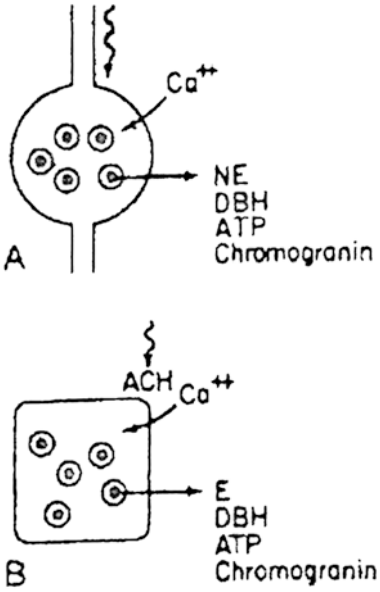

Fig. 1.4 Schematic representation of catecholamine release from a sympathetic nerve ending (**a**) and from an adrenomedullary chromaffin cell (**b**). Catecholamines, DBH, ATP, and chromogranin, as well as enkephalins (not shown), are released in stoichiometric amounts from the storage granule in response to nerve impulses. E, epinephrine; NE, norepinephrine (From Landsberg [18], with permission)

Central Regulation of Catecholamine Release

Descending tracts from the brainstem and the hypothalamus synapse with the preganglionic neurons in the intermediolateral cell column of the spinal cord (Fig. 1.2). Impulse traffic generated from these central neurons regulates the release of catecholamines from the adrenal medulla and SNS, thereby providing the CNS with control of the autonomic functions which maintain homeostasis and which react to external threats to the internal environment (fight or flight) [2, 6, 7]. The sympathoadrenal outflow is responsive to changes in arterial and venous pressure and to changes in the constituents of the circulating plasma such as oxygen and carbon dioxide tension, tonicity, pH, and the levels of hormones and substrates. In contrast the release of catecholamines from pheochromocytomas is unregulated since pheos are not innervated.

Termination of Action and Metabolism of Catecholamines

Reuptake of locally released NE from the SNEs is the major mechanism of transmitter inactivation; uptake into the nerve endings also plays an important role in the inactivation of circulating catecholamines (Fig. 1.5).

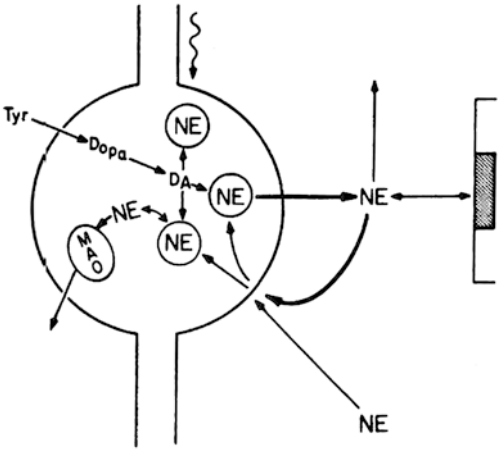

Fig. 1.5 Schematic representation of a sympathetic nerve ending. Tyrosine (Tyr) is taken up by the neuron and is sequentially converted to dopa and dopamine (DA); after uptake into the granule, DA is converted to norepinephrine (NE). In response to nerve impulses, NE is released into the synaptic cleft, where it may diffuse into circulation or be recaptured by a nerve. Accumulation of extragranular NE and DA is prevented by monoamine oxidase (MAO). NE within the synaptic cleft also interacts with presynaptic (or prejunctional) α- and β-adrenergic receptors on the axonal membrane that modulate NE release (not shown). A variety of other mediators also affect the presynaptic membrane and modulate NE release (From Landsberg and Young [17], with permission)

Table 1.1 Average[a] 24-h excretion of catecholamines and metabolites

Compound	μg/day	Major source(s)
Epinephrine (E)	5	Adrenal medulla
Norepinephrine (NE)	30	SNS
Conjugated NE + E	100	Dietary catechols
Metanephrine	65	Adrenal medulla
Normetanephrine	100	SNS
3-methoxy-4-hydroxy mandelic acid (VMA)	4000	SNS, adrenal, CNS
3-methoxy-4-hydroxyphenylglycol (MHPG)	2000	SNS, adrenal, CNS
Dopamine	225	Kidney
Homovanillic acid (HVA)	6900	CNS

[a]Not upper limit

Both E and NE are metabolized by catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO), enzymes with high concentration in the liver and kidney. The action of COMT produces normetanephrine (NMN) from NE and metanephrine (MN) from E. Both of these metabolites are important in the diagnosis of pheochromocytoma. The product of both enzymes, 3-methoxy-4-hydroxy mandelic acid (VMA), is no longer used in the diagnosis of pheos. Both DA and homovanillic acid (HVA) (the end product of DA metabolism) are useful in the diagnosis of neuroblastoma. Average normal values (not upper limits) for the excretion of catecholamines and metabolites are shown in Table 1.1 [1, 2].

Adrenergic Receptors

Catecholamines influence the function of every organ system. The effects are mediated by cell surface receptors. Stimulation of these receptors by the excessive amounts of catecholamines released from pheochromocytomas accounts for many of the clinical manifestations noted in this disease.

Differential responses to catecholamines and SNS stimulation had been noted, respectively, by Sir Henry Dale and Professor Walter Cannon in the early years of the twentieth century. It was, however, Professor Raymond Ahlquist, in 1948, who postulated the existence of two types of adrenergic receptors, based on the differential potency of sympathomimetic amines on a variety of physiologic responses. He designated these α and β adrenergic receptors. Over the ensuing decades, the structure and function of adrenergic receptors have been established and the intracellular cascades responsible for tissue-specific responses identified [8]. To summarize briefly, adrenergic receptors are cell membrane proteins with seven-membrane-spanning domains, an extracellular amino terminus, intracellular carboxy terminus, and three intracellular loops; the third intracellular loop and the carboxy terminus have regulatory phosphorylation sites that influence receptor function. Receptor occupancy triggers adrenergic responses that depend, in turn, upon regulatory G proteins that associate with the receptors and initiate the intracellular cascades that result in responses characteristic of the receptor stimulated and the effector tissue. The calcium ion is involved as a second messenger in these intracellular cascades [9–11].

Specific agonists and antagonists have been developed for each receptor type and have wide applicability in medical practice and in the treatment of patients with pheochromocytoma. Subsequent work has identified major subtypes of the α and β receptors (designated α1 and α2 and β1, β2, and β3) with clinically useful selective agonists and antagonists available for many of these subtypes [12].

Some classic physiologic effects of α receptor stimulation are vasoconstriction (arteries and veins), intestinal relaxation, and pupillary dilatation; activation of the β receptor results in cardiac stimulation, lipolysis, bronchodilation, vasodilation, and glycogenolysis. These receptor actions are summarized in Table 1.2 along with the relevant receptor subtypes.

Table 1.2 Adrenergic receptors and major catecholamine responses

	α1	**α2**	
Potency	**E = NE**	**E = NE**	
Effects	Vasoconstriction Smooth muscle relaxation Pupillary dilation	Vasoconstriction ↓ Prejunctional NE release ↓ Insulin secretion ↑ Platelet aggregation	
	β1	**β2**	**β3**
Potency	**E = NE**	**E >>> NE**	**NE >>> E**
Effects	Cardiac stimulation ↑ Lipolysis ↑ Renin secretion	Vasodilation Bronchodilation ↑Hepatic glucose output	↑ Lipolysis ↑ BAT heat production

Physiologic Effects of Catecholamines

The regulatory role of catecholamines in controlling organ function may be grouped into three major categories: circulatory, metabolic, and visceral. The manifestations of pheochromocytoma reflect the impact of excessive catecholamine stimulation in these three categories.

Circulatory effects Catecholamines cause vasoconstriction and cardiac stimulation resulting in high blood pressure and tachycardia, thereby accounting for two of the most common manifestations of pheochromocytoma: hypertension and palpitations. The vasoconstrictive effects involve the venous (capacitance) as well as the arterial (resistance) portions of the circulation and are mediated by the α1 and α2 receptors. Cardiac stimulation is mediated by the β1 receptor [12]. The multiple effects of catecholamines on the circulation are shown graphically in Fig. 1.6.

The effects of catecholamines to diminish plasma volume are particularly important. Contraction of the great veins increases venous pressure which stimulates the low pressure baroreceptors; this increase in pressure is read in the CNS as volume expansion, and a diuresis is initiated, thereby diminishing plasma volume. This mechanism reflects the fact that the body cannot assess volume status directly; it senses volume by changes in pressure in the capacitance (low pressure) portion of the circulation.

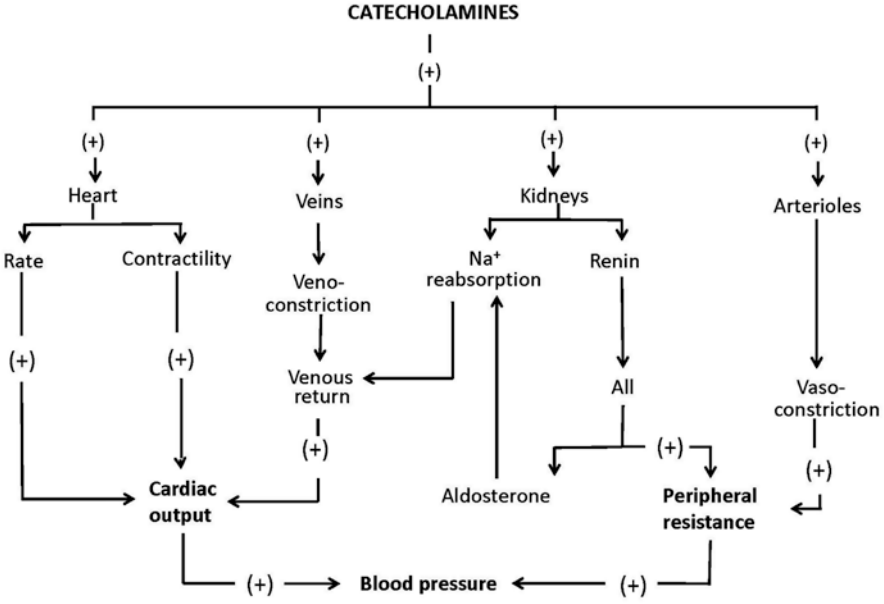

Fig. 1.6 Catecholamine effects on blood pressure. Sympathetic stimulation (+) increases blood pressure by effects on the heart, the veins, the kidneys, and the arterioles. The net result of sympathetic stimulation is an increase in both cardiac output and peripheral resistance. *AII* angiotensin II (Modified from Young and Landsberg [19])

The venoconstriction thus explains several important features of pheochromocytoma such as orthostatic hypotension and large swings in blood pressure: low volume reserve impairs the capacity to compensate for a fall in cardiac output by increasing venous return from the reservoir in the great veins. The diminished plasma volume also explains the high hematocrit occasionally noted (the so-called stress polycythemia) [2].

Metabolic effects Catecholamines have two major effects on metabolism: they cause substrate mobilization (lipolysis, glycogenolysis, and gluconeogenesis) [2, 13] and an increase in metabolic rate [1, 14–16]. The direct stimulatory effects on stored fuel are amplified by catecholamine induced suppression of insulin release, since substrate mobilization depends on a balance between catecholamines and insulin. Suppression of insulin (mediated by the α2 receptor) and stimulation of hepatic glucose output (β2 receptor) account for the carbohydrate intolerance frequently noted in pheochromocytoma patients. Lipolysis in white adipose tissue stores is mediated by the β1 and β3 receptor.

The increase in metabolic rate is secondary to catecholamine stimulation of brown adipose tissue (BAT). The latter has been noted for decades to be hypertrophied and activated in patients with pheochromocytoma. BAT is a heat generating organ that operates via a unique mechanism that uncouples fatty acid oxidation from ATP synthesis (Fig. 1.7). The generation of heat from BAT may be briefly summarized as follows:

1. When stimulated by catecholamines, hormone-sensitive lipase in BAT generates free fatty acids which activates uncoupling protein (UCP 1).
2. The latter, a mitochondrial carrier protein, is uniquely localized to BAT.

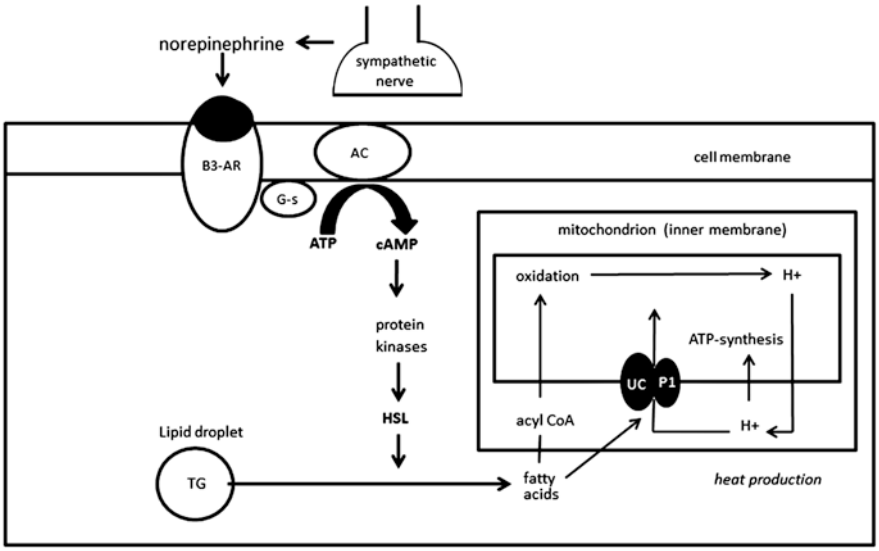

Fig. 1.7 BAT stimulation (see text for details)

3. UCP 1 permits hydrogen ions, formed from the action of the respiratory chain enzymes and excluded from the inner mitochondrial matrix during substrate oxidation, to reenter the inner mitochondrial matrix along its electromotive gradient without the synthesis of ATP.
4. In the normal coupled state reentry is tightly coupled to ATP synthesis which stores the energy released from the exothermic oxidative reactions.
5. When UCP1 is activated, ATP synthesis is bypassed, and the heat generated from the exothermic reactions increases the local temperature of BAT.
6. This heat is then exported to organs throughout the body via the vascular system [1].

During cold exposure this mechanism helps homoeothermic animals to maintain body temperature. Note that in patients with pheochromocytoma, this does not result in fever since the central set point for temperature regulation is not altered. The excess heat is dissipated by sweating, thereby accounting for a major symptom of pheochromocytoma.

Visceral effects Catecholamines relax visceral smooth muscle in the bronchial tree, the intestines, and the urinary bladder while stimulating the corresponding sphincters. The implications of these effects for patients with pheochromocytoma are less clear than the cardiovascular or metabolic effects described above, although alterations in GI motility are occasionally noted in pheochromocytoma patients. Both direct and indirect effects of catecholamines on the kidneys result in enhanced renal sodium reabsorption. The indirect effects are from stimulation of renin release and activation of the angiotensin-aldosterone system (Fig. 1.6). These effects might contribute to the hypertension in patients with a pheochromocytoma.

Pharmacology

The identification of adrenergic receptors was an important prelude to the development of agonists and antagonists to the classic α and β receptors and to several of their subtypes.

Adrenergic Agonists

The naturally occurring catecholamines, E and NE, stimulate α and β receptors and have limited but important therapeutic uses [8]. E is critical in the treatment of anaphylactic reactions, and its appropriate use is frequently lifesaving. E is also used as a cardiac stimulant in cardiac arrests. NE is a potent pressor agent used in the treatment of severe hypotension or shock. DA, administered intravenously, has a complex pharmacology that is dose dependent: at low doses it stimulates DA receptors and increases renal and mesenteric blood flow; at intermediate doses it stimulates, in addition, β receptors, while at high dose it activates α receptors which overrides the other effects.

Direct and Indirect Acting Sympathomimetic Amines

Sympathomimetic amines are congeners of the naturally occurring catecholamines that have been structurally modified to enhance one or more biologic properties [12]. These modifications influence, singly or in concert, various properties including reduction in metabolism and prolongation of action, increase in bioavailability via the oral route, effect specifically α or β receptors or their subtypes, and diminished or enhanced CNS penetration. Sympathomimetic amines are said to have direct effects when they interact with adrenergic receptors directly and indirect effects when they release the neurotransmitter, NE, from the SNEs. Some sympathomimetic amines have both direct and indirect effects; some are selective for the α1 receptor subtype. Some commonly utilized sympathomimetic amines, and their properties and indications are shown in Table 1.3. These drugs are useful in treating hypotension; they have also been used with limited success in patients with hepatorenal syndrome and pure autonomic neuropathy.

In pheochromocytoma patients, the catecholamine stores in the SNEs are increased due to the higher levels of circulating catecholamines; this results in an enhanced response to indirect acting sympathomimetic amines.

Adrenergic Prodrugs

Midodrine, droxidopa, α-methyldopa, and L-DOPA are prodrugs that are metabolized to active moieties in vivo. Midodrine is deglycinated to desglymidodrine, an α1 selective agonist used, with limited efficacy, in patients with hepatorenal syndrome

Table 1.3 Sympathomimetic amines

Agent	Action	Receptor	Therapeutic use
Phenylephrine	Direct	α1	Hypotension
Midodrine	Direct	α1	Orthostatic ↓ BP
Clonidine	Direct	α2	Hypertension
Isoproterenol	Direct	β1, β2	Bradycardia
Albuterol	Direct	β2	Bronchospasm
Terbutaline	Direct	β2	Bronchospasm
Formoterol	Direct	β2	Asthma (long acting)
Salmeterol	Direct	β2	Asthma (long acting)
Dobutamine	Direct	β1, β2, α1	CHF
Pseudoephedrine	Direct	α1, α2, β2	Decongestant
Ephedrine	Direct/indirect	α, β	Bronchospasm
Amphetamine	Indirect	α, β	Narcolepsy
Methylphenidate	Indirect	α, β	ADHD

CHF Congestive heart failure, *ADHD* Attention deficit hyperactivity disorder

and orthostatic hypotension. Droxidopa (L-dihydroxyphenylserine, L-DOPS), a synthetic amino acid that forms NE when decarboxylated by aromatic amino acid decarboxylase (DOPA decarboxylase), is an enzyme widely distributed throughout the body. The NE so formed functions as a circulating pressor rather than as a neurotransmitter. It is used with limited success in the treatment of orthostatic hypotension. α-methyldopa (Aldomet), an antihypertensive medication rarely used today except in pregnancy induced hypertension, is decarboxylated and β-hydroxylated to α-methyl NE, a centrally active α2 agonist that lowers BP. L-DOPA, when given orally, is decarboxylated by the same decarboxylase and forms DA in vivo. It is used in the treatment of Parkinson's disease with some success. It is given in combination with carbidopa, a decarboxylase inhibitor that does not cross the blood brain barrier, thereby allowing increased concentrations of L-DOPA to enter the CNS where it is converted to DA and partially restores DA mediated neurotransmission in the basal ganglia [12].

Adrenergic Antagonists (α- and β-Blockers)

Blocking the action of the excessive amounts of catecholamines in patients with pheochromocytoma is the goal of medical management. The judicious use of adrenergic blocking agents will almost always reverse the symptoms of catecholamine excess and permit safe surgical removal of the tumor [1].

α-Blocking Agents

Two *nonspecific α-blockers* are useful in the treatment of pheochromocytoma although their availability may be limited due to short supply and expense [12]. *Phentolamine* has been used intravenously to provide a short-acting competitive blockade in the treatment of pheochromocytoma paroxysms. Its use has been largely replaced by other short-acting specific α1-blockers as described below. *Phenoxybenzamine* provides long-acting, noncompetitive blockade of both the α1 and α2 receptors, features that make it the drug of choice for the treatment of pheochromocytoma patients prior to surgery. Disadvantages of phenoxybenzamine include hypotension after surgical removal of the tumor because of the long duration of action and accentuation of the tachycardia that occurs in pheochromocytoma patients after α2 blockade which antagonizes the presynaptic inhibition of NE release at adrenergic synapses. These adverse effects can be effectively managed by fluid administration on the one hand and β blockade on the other.

Selective α1-blockers with differing duration of action are available and have proved useful in the treatment of pheochromocytoma (Table 1.4). *Doxazosin* produces a

Table 1.4 Adrenergic blocking agents

Agent	Receptor	Major therapeutic uses
Phentolamine (iv)	α1, α2	Pressor crises (pheochromocytoma, cocaine, MAOI)
Phenoxybenzamine	α1, α2	Pheochromocytoma
Prazosin	α1	Pressor crises
Terazosin	α1	Hypertension, BPH
Doxazosin	α1	Pheochromocytoma, hypertension, BPH
Tamsulosin	α1	BPH
Propranolol	β1, β2	Pheochromocytoma, hyperthyroidism, tachycardia
Metoprolol	β1	CAD, CHF, tachycardia
Atenolol	β1	Hypertension, HCM, hyperthyroidism
Esmolol (iv)	β1	OR, ICU: Tachycardia, aortic dissection
Carvedilol	β1, β2, α1	Hypertension, CHF, CAD
Labetalol	β1, β2, α1	Hypertension

MAOI Monoamine oxidase inhibition reactions, *BPH* Benign prostatic hypertrophy, *CAD* Coronary artery disease, *HCM* Hypertrophic cardiomyopathy

long-acting competitive blockade making it a reasonable alternative to phenoxybenzamine for the medical management and preoperative preparation of pheochromocytoma patients. Postoperative hypotension may be less with doxazosin than with phenoxybenzamine, and the α1 selectivity may result in less tachycardia. Although the competitive nature of the blockade means that catecholamine surges from the tumor could overcome the blockade, doxazosin has been quite successful when used in the treatment of pheochromocytoma. *Prazosin* is a selective α1-blocker with a very short duration of action. It has established usefulness in the treatment of individual paroxysms in patients with pheochromocytoma. *Tamsulosin* is a selective α1-blocker with specificity for the prostate gland and is used to treat lower urinary tract symptoms related to prostatic hypertrophy and outflow tract obstruction.

β-Blocking Agents

β-blockers are among the most widely prescribed drugs with a variety of indications involving cardiovascular and non-cardiovascular diseases, as outlined in Table 1.4 [1, 12]. The so-called first-generation β-blockers nonselectively block β1 and β2 receptors. *Propranolol* is the prototypic agent in this class and is the drug used most frequently in the management of patients with pheochromocytoma. It should be administered to all pheochromocytoma patients but only after α blockade has been introduced to avoid unopposed α-mediated vasoconstriction. In addition to slowing the heart rate, β-blockers antagonize anesthesia-related arrhythmias.

Second-generation β-blockers are selective for the β1 receptor although this selectivity is only relative and less than that noted for the α1-selective agents. These are also referred to as cardioselective β-blockers and include *metoprolol*, *atenolol*, and *esmolol*. Esmolol is a very short-acting agent used intravenously in the intensive care unit and the operating room where rapid onset and offset are important.

Third-generation β-blockers have a vasodilating moiety which is applied in addition to blockade of the β receptor. *Carvedilol* and *labetalol* are the two commonly used agents in this class; they block the β1, β2, and the α1 adrenergic receptors. Carvedilol is used in the treatment of CHF and hypertension; the vasodilating moiety lessens the unfavorable metabolic effects of β blockade. Labetalol is available in intravenous as well as oral formulation and finds its greatest use in the treatment of severe hypertension. Of note, it may interfere with catecholamine measurements in the diagnosis of pheochromocytoma. The potency of the effects on the β receptor is much greater than the effects on the α receptor.

References

1. Landsberg L. Catecholamines; Philadelphia: Wolters-Kluwer; 2017.
2. Young JB, Landsberg L. Chapter 13. Physiology of the sympathoadrenal system. In: Williams textbook. Philadelphia: 9th ed. Saunders; 1998.
3. Hall AK, Principal Neurons LSC. Small intensely fluorescent (SIF) cells in the rat superior cervical ganglion have distinct developmental histories. J Neurosci. 1991;11:472–84.
4. Carey RM. Chapter 45. Dopamine mechanisms in the kidney. In: Primer on the autonomic nervous system. Amsterdam: Elsevier Inc; 2012. p. 221–3.
5. Winkler H. The adrenal chromaffin granule: a model for large dense core vesicles of endocrine and nervous tissue. J Anat. 1993;183:237–52.
6. Benarroch EE. Chapter 2. Central autonomic control. In: Primer on the autonomic nervous system; Amsterdam: Acdamic press (Elsevier) 2012. p. 9–12.
7. Morrison SF. Differential control of sympathetic outflow. Am J Physiol Regulatory Integrative Comp Physiol. 2001;281:R683–98.
8. Westfall TC, Westfall DP. Neurotransmission: the autonomic and somatic motor nervous systems. In: Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw Hill; 2011.
9. Gilman AG. G proteins: transducers of receptor-generated signals. Annu Rev Biochem. 1987;56:615–49.
10. Tobin AB. G-protein-coupled receptor phosphorylation: where, when and by whom. Br J Pharmacol. 2008;153(suppl 1):S167–S176.
11. Kohout TA, Lefkowitz RJ. Regulation of G protein-coupled receptor kinases and Arrestins during receptor desensitization. Mol Pharmacol. 2003;63:9–18.
12. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill; 2011.
13. Coppack SW, Jensen MD, Miles JM. In vivo regulation of lipolysis in humans. J Lipid Res. 1994;35:177–86.
14. Enerbäck S. Brown adipose tissue in humans. Int J Obes. 2010;34:S43–6.

15. Morrison SF, Madden CJ, Tupone D. Central control of brown adipose tissue thermogenesis. Front Endocrinol. 2012;3:1–19.
16. Ricquier D. Uncoupling protein 1 of brown adipocytes, the only uncoupler: a historical perspective. Front Endocrinol. 2011;2:1–7.
17. Landsberg L, Young JB. Catecholamines and the adrenal medulla. In: Bondy PK, Rosenberg LE, et al., editors. Metabolic control and disease. 8th ed. Philadelphia: W.B. Saunders; 1980. p. 1621–93.
18. Landsberg L. Catecholamines and the sympathoadrenal system. In: Ingbar SH, editor. The year in endocrinology. New York: Plenum; 1976. p. 177–231.
19. Young JB, Landsberg L. Obesity and circulation. In: Sleight P, et al., editors. Scientific foundations of cardiology. London: Heineman; 1983.