Chapter

Pharmacology of the Autonomic Nervous System

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Abstract

This comprehensive chapter delves into the intricate landscape of autonomic nervous system (ANS) pharmacology. It meticulously explores both agonists and antagonists pharmacology that work on the sympathetic and parasympathetic divisions. This chapter covers direct and indirectly acting drugs and thoroughly explains receptor interactions. The content spans a wide array of examples, elucidating these agents' mechanisms and clinical applications. Through a detailed examination of pharmacokinetics, metabolism, adverse effects, and contraindications, healthcare professionals gain the insights needed to navigate the complexities of ANS modulation. This knowledge equips practitioners to harness the potential of autonomic drugs, facilitating optimal therapeutic outcomes across diverse medical scenarios.

Keywords: pharmacology, autonomic nervous system, sympathetic, parasympathetic, medications

1. Introduction

The autonomic nervous system (ANS) plays a pivotal role in maintaining homeostasis by modulating various vital processes, including heart rate, blood pressure, respiratory rate, gastrointestinal motility, and glandular secretions [1]. Understanding the pharmacology of the ANS is paramount in medicine, particularly in anesthesia and other acute medical specialities, as it allows healthcare professionals to manipulate autonomic pathways effectively and achieve desirable clinical outcomes [2]. This chapter aims to provide a comprehensive overview of ANS pharmacology, focusing on the sympathetic (SANS) and parasympathetic (PANS) divisions and their associated receptors.

Understanding the receptor selectivity of pharmacological agents is paramount in achieving desired clinical outcomes. Many drugs exhibit selectivity for specific adrenergic or cholinergic receptors, allowing for targeted modulation of the SANS and PANS [3]. Healthcare professionals can manipulate autonomic pathways to optimize patient care by carefully selecting and administering peripheral nervous system agonists or antagonists.

The knowledge of ANS pharmacology is particularly crucial in acute medical specialities, where precise control over the cardiovascular system, airway dynamics, and

other physiological parameters is essential. Physicians rely on drugs that selectively target specific adrenergic or cholinergic receptors to achieve optimal hemodynamic stability and other vital parameters [2].

Furthermore, pharmacists, physicians, intensivists, and medical students benefit from a comprehensive understanding of ANS pharmacology. By grasping the complexities of autonomic receptor modulation, healthcare professionals can make informed decisions regarding drug selection, dosing, and potential adverse effects. This knowledge enhances patient safety and improves clinical outcomes across various medical disciplines.

2. Pharmacology of the sympathetic nervous system

The SANS, often referred to as the "fight or flight" system, prepares the body for physical exertion and stressful situations. The primary neurotransmitter in the SANS is norepinephrine (noradrenaline), which interacts with adrenergic receptors located throughout the body. These receptors are categorized into two main subtypes: α and β [1].

The α-adrenergic receptors are further divided into α-1 and α-2 subtypes. α-1 receptors are predominantly located in blood vessels, leading to vasoconstriction when activated. This effect increases systemic vascular resistance, elevating blood pressure. α-1 agonists such as phenylephrine find clinical utility in managing hypotension during anesthesia. Conversely, α-1 antagonists like prazosin induce vasodilation and alleviate conditions such as benign prostatic hyperplasia and hypertension. α-2 receptors are primarily located presynaptically in sympathetic nerve terminals, where their activation inhibits the release of norepinephrine, resulting in negative feedback regulation of sympathetic outflow. Clonidine, an α-2 agonist, is commonly used in anesthesia and surgery to attenuate sympathetic responses, promote sedation, and enhance perioperative analgesia [1].

β-adrenergic receptors consist of three subtypes: β-1, β-2, and β-3. β-1 receptors are predominantly found in the heart, activating heart rate and contractility [1]. β-1 agonists like dobutamine enhance cardiac output in patients with heart failure or cardiogenic shock. β-1 antagonists, such as metoprolol, are widely used in to mitigate the adverse effects of excessive sympathetic stimulation on the cardiovascular system [3]. β-2 receptors are abundant in the bronchial smooth muscle and peripheral vasculature, leading to bronchodilation and vasodilation when stimulated [1]. β-2 agonists like salbutamol are commonly utilized to manage asthma and chronic obstructive pulmonary disease (COPD) [3].

Conversely, β-2 antagonists may be used in conditions like glaucoma, where reduced intraocular pressure is desirable [3]. β-3 receptors are primarily present in adipose tissue, where their activation promotes lipolysis. While the therapeutic significance of β-3 receptors is still being explored, their modulation may hold potential in treating obesity and metabolic disorders.

2.1 Sympathomimetics

2.1.1 α-1 receptor agonists

α-1 receptors dominate most of the smooth muscle of the autonomic target organs. They mediate primarily arterial and venous vasoconstriction when

activated. Drugs that mimic the action of epinephrine and norepinephrine can be called sympathomimetics. These drugs can be divided into direct and indirect agonists [4].

Direct agonists interact with the adrenoreceptor directly and subsequently activate them, while indirect agonists depend on their ability to enhance the effect of endogenous catecholamines. The indirect agonist can do so by (i) displacing catecholamine from their adrenergic nerve endings and inducing their release (e.g., the mechanism of action of tyramine), (ii) inhibiting the clearance of catecholamines by decreasing their neuronal reuptake (e.g., the mechanism of action of cocaine and tricyclic antidepressants), or (iii) preventing the enzymatic metabolism of norepinephrine (monoamine oxidase and catechol-O-methyltransferase inhibitors) [4].

2.1.1.1 Direct-acting α-agonists

2.1.1.1.1 Phenylephrine

The chemical formula of phenylephrine is $C_9H_{13}NO_2$. It is an α-1 adrenergic agonist that only affects β receptors at very high doses. As it is not a catechol derivative, it is not broken down by catechol-O-methyltransferase (COMT) and has a longer duration of action than catecholamines. It can cause an increase in blood pressure by venous and arteriolar vasoconstriction, and since it does not act on β receptors, there is no direct effect on cardiac muscle. The increase in blood pressure causes reflex bradycardia by stimulation of baroreceptors [5].

The intravenous (IV) phenylephrine hydrochloride increases blood pressure in adults with clinically significant hypotension resulting primarily from vasodilation in such settings as septic shock or anesthesia. Phenylephrine hydrochloride (HCL) is also used over-the-counter in ophthalmic formulations to promote mydriasis and conjunctival blood vessel vasoconstriction, intranasal administration as a treatment for uncomplicated nasal congestion, and as an over-the-counter additive to topical hemorrhoid medications [5].

The ophthalmic formulations of phenylephrine act for 3–8 hours, while intravenous solutions have a practical half-life of 5 minutes and an elimination half-life of 2.5 hours. The bioavailability orally is 38%, and ophthalmic solutions have clinically significant absorption, especially if the cornea is damaged. This drug is mainly metabolized by monoamine oxidase A, monoamine oxidase B, and sulfotransferase family 1A member 3 (SULT1A3). The primary metabolite it forms is the inactive meta-hydroxymandelic acid, followed by sulfate conjugates. It can also be metabolized to phenylephrine glucuronide. About 86% of the drug is recovered in urine; 16% of it is unmetabolized, and 57% of it is inactive meta-hydroxymendelic acid, and 8% is inactive sulfate conjugates [6].

The adverse effects of these drugs are nausea, vomiting, and confusion. Since phenylepinephrine increases the afterload more than the preload, the decreased cardiac output can also lead to severe bradycardia, exacerbating angina, heart failure, and pulmonary hypertension. Overdose can be treated by discontinuing the medication, chronotropic medications, and vasodilators [5].

There are no absolute contraindications for using this drug apart from hypersensitivity reactions such as anaphylaxis or less severe asthmatic episodes. Currently, no antidote is available to reverse this drug's effects. The treatment of hypertension and reflex bradycardia is discontinuing the administration of the drug [5].

2.1.1.1.2 Midodrine

Midodrine is a prodrug (medication that turns into active form once it enters the body). It is used to manage patients with orthostatic hypotension or hypotension secondary to other clinical conditions or drug therapies [7].

The chemical formula of this drug is C12H19ClN2O4. It is water-soluble and distributed as tablets for oral administration. Dosage forms are 2.5 mg, 5 mg, and 10 mg. Midodrine is almost completely absorbed after oral administration and undergoes enzymatic hydrolysis to form its pharmacologically active metabolite, de-glymidodrine. The drug should be stored in an airtight container [8].

The plasma levels of this prodrug peak at about half an hour and decline with a half-life of approximately 25 minutes. The peak concentration of the metabolites reaches about 1–2 hours, and their half-life is about 3–4 hours. The absolute bioavailability is 93% and is not affected by food. Midodrine deglycination to desglymidodrine appears in many tissues, and the liver metabolizes both compounds [9].

It does not act on cardiac β-adrenergic receptors and poorly diffuses across the blood-brain barrier. Increased embryo reabsorption is revealed in animal studies, as well as reduced fetal body weight and decreased fetal survival. There is no controlled data on human pregnancy. It is labeled US FDA Pregnancy category C, but the potential benefits may warrant the use in pregnant women, despite potential risks. No data is available for excretion in animal and human milk, but use should be avoided, and caution is recommended [8].

The contraindications to the drug are allergy to the drug, kidney disease, or, if one cannot urinate, pheochromocytoma (adrenal gland tumor), overactive thyroid, high blood pressure even while lying down, and liver disease. Taking this drug alongside other drugs that constrict the blood vessels can increase blood pressure. Common adverse effects (1–10%) of the drug are supine hypertension, paresthesia, headache, npiloerection, dysuria, nausea, dyspepsia, and vomiting [8].

The oral lethal dose (LD 50) is approximately 30–50 mg/kg in rats, 67.5 mg/kg in mice, and 125–160 mg/kg in dogs. Overdose symptoms could include hypertension, piloerection (goosebumps), a sensation of coldness, and urinary retention. The single doses associated with overdosage or potentially life-threatening symptoms in humans are unknown. Desglymidodrine is dialyzable [9].

2.1.1.2 Indirect-acting α-agonists

2.1.1.2.1 Ephedrine

Ephedrine is an α- and β-adrenergic agonist; however, it also causes the indirect release of norepinephrine from sympathetic neurons, inhibiting norepinephrine reuptake and displacing more norepinephrine from storage vesicles. Its use is indicated in treating hypotension under anesthesia, allergic conditions, bronchial asthma, and nasal congestion. Its chemical formula is $C_{10}H_{15}NO$ [10].

Ephedrine can be administered through oral, nasal, and intravenous routes (tablet/capsule:8–25 mg, Solution—0.5%, IV: 10–15 mg/1 mL). Ephedrine increases blood pressure by stimulating heart rate and cardiac output and variably increasing peripheral resistance. Activation of β-adrenergic receptors in the lungs causes bronchodilation. By stimulating α-adrenergic receptors in bladder smooth muscle cells, ephedrine also increases the resistance to the outflow of urine. Compared to when ephedrine is

used to treat hypotension, using ephedrine for hypotension prophylaxis is associated with a higher risk of hypertension [10].

The bioavailability of ephedrine is 88%, and oral ephedrine reaches an average maximum concentration (C_{max}) of 79.5 ng/mL, with a time-to-peak concentration (T_{max}) of 1.81 hours [10].

Ephedrine is largely unmetabolized in the body and can be N-demethylated to norephedrine or demethylated and deaminized to benzoic acid conjugates and 1,2-hydroxypropyl benzene. The route of elimination is through the urine; about 60% is excreted as unmetabolized parent compound and 13% as benzoic acid conjugates and 1% as 1,2-dihydroxypropylbenzene. There is a large degree of inter-patient variability on the half-life of this drug, but orally, the plasma elimination half-life is approximately 6 hours [10].

Its use is contraindicated in people with cardiovascular disease, hypertension, hyperthyroidism, pheochromocytoma, and closed-angle glaucoma [11]. Large doses of ephedrine cause nervousness, insomnia, vertigo, headache, tachycardia, palpitation, and sweating. Some patients have nausea, vomiting, and anorexia. Painful urination may occur as a result of a vesical sphincter spasm. Urinary retention may develop in males with prostatism. Cardiac arrhythmias and precordial pain may occur following administration of ephedrine sulfate injection, USP [11].

The LD50 in mice after oral administration is 785 mg/kg, after intraperitoneal administration is 248 mg/kg, and after subcutaneous administration is 425 mg/kg. An overdose of ephedrine will present with rapidly increasing blood pressure. The overdose can be managed with blood pressure monitoring and possibly administering parenteral antihypertensives [10].

2.1.1.2.2 Methamphetamine

It is a sympathomimetic agent widely used to treat attention deficit hyperactivity disorder (ADHD) and exogenous obesity. Its chemical formula is $C_{10}H_{15}N$. Methamphetamine is a white solid odorless crystal. The recommended storage temperature is −20°C. This drug is a potent stimulant of the central nervous system, and it affects the neurochemical mechanisms responsible for regulating body temperature, heart rate, blood pressure, appetite, attention, mood, and responses associated with alertness or alarm conditions. The drug's acute effects closely resemble the psychological and physiological effects of an epinephrine-provoked flight-or-fight response; these responses include increased heart rate, vasoconstriction, increased blood pressure, hyperglycemia, and bronchodilation. It causes the elimination of fatigue, increased mental alertness, increased focus, and decreased appetite [12].

When methamphetamine enters the brain, it causes a cascade of norepinephrine, dopamine, and serotonin release. It acts as a dopaminergic and adrenergic reuptake inhibitor to a lesser extent, and in a higher concentration, it can act as a monoamine oxidase inhibitor [12].

Absorption of methamphetamine occurs in the gastrointestinal tract, with peak concentrations occurring at 3.13–6.3 hours after ingestion, and its effects may continue up to 24 hours in larger doses. When the drug is administered by inhalation, or intranasally, a high degree of absorption occurs. The drug has a high lipophilicity; it is distributed across the blood-brain barrier and crosses the placenta. This drug should be avoided in breastfeeding mothers as it is excreted through milk. The drug excretion occurs through the urine and increases with the acidic pH metabolization of methamphetamine occurs in the liver by aromatic hydroxylation, N-dealkylation, and deamination; at least seven metabolites have been identified in urine [12, 13].

The concurrent use of monoamine oxidase inhibitors with methamphetamine is contraindicated as a hypertensive crisis may occur. It is also contraindicated in patients with glaucoma, advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity, or idiosyncrasy to sympathomimetic amines. It is a Pregnancy category C drug. It is shown to have teratogenic and embryocidal effects in mammals given multiple high human doses. There are no adequate and well-controlled studies in pregnant women, but it is recommended not to be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [14].

Acute overdose of methamphetamine is manifested by restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma [12].

Therapeutic methamphetamine blood concentration is 20–60 ug/dL; toxic methamphetamine blood concentration is 60–500 ug/dL, and lethal methamphetamine blood concentration is 1–4 mg/dL [12]. Benzodiazepines represent first-line treatment for methamphetamine toxicity but frequently require repeated and escalated dosing to achieve the effect [15].

2.1.2 α-2 receptor agonists

The α-2 receptors constitute a family of G-protein-coupled receptors (GPCRs) with three pharmacological subtypes, α-2A, α-2B, and α-2C [16]. Most α-2A and α-2C subtypes are located mainly in the presynaptic central nervous system. When stimulated, these receptor subtypes may be responsible for sedative, analgesic, and sympatholytic effects. On vascular smooth muscle, α-2B receptors are more prevalent and have been shown to mediate vasopressor effects. All three subtypes have been shown to inhibit adenylyl cyclase, resulting in decreased levels of cyclic adenosine monophosphate and hyperpolarization of noradrenergic neurons in the medial dorsal pons, specifically in the locus ceruleus [16]. As cyclic adenosine monophosphate is inhibited, potassium efflux via calcium-activated channels prevents calcium ions from entering the nerve terminal, inhibiting neural discharge. This process inhibits the release of norepinephrine and reduces the activity of ascending noradrenergic pathways, resulting in hypnosis and sedation. Activation of this negative feedback loop may also result in decreased heart rate and blood pressure, as well as a diminished sympathetic stress response. Stimulation of α-2 receptors in the spinal column's dorsal horn inhibits nociceptive neurons and reduces substance P release. Although there is evidence for supraspinal and peripheral sites of action, it is believed that the spinal mechanism accounts for the majority of the analgesic effects of α-2 agonist drugs [16].

Guanabenz, guanfacine, clonidine, tizanidine, medetomidine, and dexmedetomidine are all α-2 agonists with different potencies and affinities for different α-2 receptor subtypes. Clonidine, tizanidine, and dexmedetomidine have seen the most clinical use and will be discussed in greater depth.

2.1.2.1 Clonidine

Clonidine, an imidazole molecule, is a selective partial agonist for α-2 adrenoceptors with a 200:1 ratio (α_2–α_1).

Clonidine stimulates the brain stem's α-adrenoreceptors. This action diminishes central nervous system sympathetic outflow and decreases peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

Clonidine can be administered *via* various routes: oral, intravenous, transdermal, rectal, and different neuraxial routes. It is rapidly and nearly completely absorbed following the oral route, reaching peak plasma levels in 60–90 minutes. A time-release transdermal patch can also administer clonidine; however, therapeutic levels require at least 2 days. It has an elimination half-life of 8–12 hours, with 50% of the drug metabolized in the liver to inactive metabolites and the rest being excreted unaltered in the kidney [17].

2.1.2.2 Clinical uses

Clonidine and guanfacine may be used to treat children and adolescents with attention deficit hyperactivity disorder. The reduced firing of presynaptic neurons releasing norepinephrine into the prefrontal cortex decreases the impulsive and hyperactive behavior seen in ADHD. Because of their additive effects on serotonin and γ-aminobutyric acid receptors, α-2 agonists are the most commonly utilized drugs to treat lack of sleep in children with ADHD. Clonidine also treats chronic pain disorders and withdrawal from opiates, benzodiazepines, alcohol, cocaine, food, and cigarette smoke [17].

Clonidine as an adjuvant has several advantages, including a reduction in the amount of opioids necessary for analgesia and hence a likely reduction in opioid-related side effects, titrated sedation and anxiolysis with no additive respiratory depression when combined with opioids and vasodilation and enhanced circulation of the cerebral, coronary, and visceral vascular beds [17].

Clonidine has lately been utilized as a premedication in individuals with considerable pretreatment anxiety. It has been found to improve mask application during anesthesia induction and to reduce anesthetic requirements by 40–60% in the pediatric population.

2.1.2.3 Dexmedetomidine

Dexmedetomidine, as clonidine, is a highly selective α-2 agonist with a higher affinity for the α-2 receptor (**Figure 1**). Clonidine has a specificity of 220: 1 (α-2: α-1), while dexmedetomidine has a specificity of 1620: 1. It is a full agonist of α-2 adrenergic receptors and the pharmacologically active d-isomer of medetomidine [18].

Dexmedetomidine induces a state of unconsciousness equivalent to normal sleep by activating central pre- and postsynaptic α-2 receptors in the locus ceruleus, with the added benefit of patients remaining easily stimulated and cooperative.

Dexmedetomidine generates a dose-dependent biphasic blood pressure response. Low-dose intravenous infusion lowers mean arterial pressure due to selectivity for central and peripheral α-2 receptors. The subsequent decreases in heart rate and systemic vascular resistance indirectly diminish cardiac output and systolic blood pressure. These actions help modulate the stress response, improve stability, and guard against drastic changes in cardiovascular parameters after surgery [18].

Dexmedetomidine can be given orally, intravenously, intramuscularly, buccally, and intranasally. It has a two-compartment distribution and elimination model. It has a ($T_{1/2}$ β) of 2 hours for elimination. However, it is a highly lipophilic medication that rapidly dispersed and redistributed, with a ($T_{1/2}$ α) of only 6 minutes for distribution. This has a

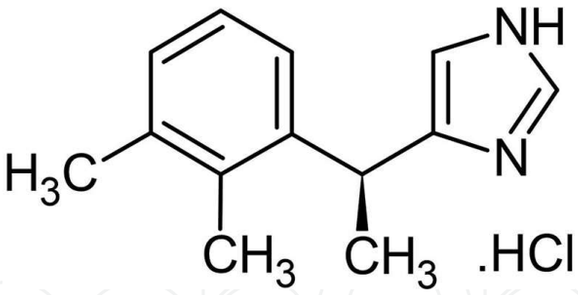

Figure 1.
Dexmedetomidine molecule.

rapid onset but only a short duration of clinical action. Because of its fast redistribution and removal, it is a suitable agent for infusion procedures. Dexmedetomidine is metabolized *via* direct glucuronidation and CYP2A6. Approximately 80–90% is eliminated in the urine, with the remaining 5–13% detected in the feces [18].

Pharmacokinetic interactions are unusual in most cases. However, dosage adjustments for concurrently administered sedatives may be required due to drug potentiation. Adding an α-2 agonist to a sedative regimen reduces the need for opioids by 50–75% and benzodiazepines by up to 80%. Dexmedetomidine's context-sensitive half-life ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion [18].

2.1.2.4 Clinical uses

Dexmedetomidine has three primary therapeutic applications: (a) in-hospital prolonged sedation, (b) procedure sedation and general anesthesia, and (c) obtunding emerging delirium. It is utilized as a sedative drug in critical care settings for critically ill patients who require prolonged sedation and mechanical ventilation. Dexmedetomidine possesses all of the features of an ideal critical care sedative. It does not cause respiratory depression, is analgesic and anxiolytic, has a fast onset, is titratable, and promotes drowsiness while maintaining hemodynamic stability. Finally, dexmedetomidine is exceptionally effective in treating the emerging delirium that can occur after general anesthesia, particularly in children. It has a significant relaxing effect without causing respiratory depression. This is a significant benefit over other medications typically used in such situations and requires additional study.

2.1.3 β-1 agonists

2.1.3.1 Dobutamine

Dobutamine is a synthetic sympathomimetic drug that selectively stimulates β-1 adrenergic receptors. It mimics the action of endogenous catecholamines like epinephrine but has a more specific effect on β-1 receptors. Dobutamine is typically available as a solution for intravenous infusion. The healthcare provider determines the concentration and dosage regimen based on the individual's specific needs.

Pharmacokinetically, dobutamine is administered intravenously due to its poor oral bioavailability. It has a rapid onset of action and a short duration of action. The drug is metabolized in the liver and excreted primarily in the urine.

Dobutamine acts primarily as a β-1 adrenergic receptor agonist. It increases the contractility of the heart muscle (positive inotropic effect) and enhances cardiac output. It also leads to mild vasodilation, primarily affecting the arterial system. In the clinical settings, dobutamine primarily treats acute heart failure or cardiogenic shock. It is used to improve cardiac contractility and increase cardiac output in these conditions.

2.1.3.2 Dopamine

Dopamine is a neurotransmitter and a sympathomimetic drug that acts on dopamine receptors in the central and peripheral nervous systems. It is crucial in physiological processes, including movement, motivation, reward, and blood pressure regulation. Dopamine is typically available as a solution for intravenous infusion. The healthcare provider determines the concentration and dosage regimen based on the individual's specific needs.

Pharmacokinetically, dopamine is administered intravenously due to its poor oral bioavailability. It has a rapid onset of action and a short duration of action. The drug is rapidly metabolized in the liver and excreted in the urine.

Dopamine acts on different receptors, including dopamine receptors, α-1 adrenergic receptors, and β-adrenergic receptors. Its effects vary depending on the dose administered. Dopamine primarily stimulates dopamine receptors at low doses, leading to renal and mesenteric vasodilation. It activates higher doses of α-1 and β-1 adrenergic receptors, increasing cardiac contractility and vasoconstriction.

Dopamine treats various conditions, including hypotension, shock, and low cardiac output states. It helps increase blood pressure and cardiac output by improving cardiac contractility and causing peripheral vasoconstriction.

2.1.3.3 Epinephrine (adrenaline)

Epinephrine, also known as adrenaline, is a naturally occurring catecholamine and a potent nonselective adrenergic agonist. It acts on α- and β-adrenergic receptors, producing various physiological effects. Epinephrine is available in different formulations, including solutions for intravenous injection, autoinjectors, and inhalers. The concentration and specific formulation may vary depending on the intended use.

Epinephrine can be administered *via* various routes, including intravenous, intramuscular, subcutaneous, and inhalation. It has a rapid onset of action and a short duration of action. The drug is metabolized in the liver and other tissues, and the metabolites are excreted in the urine. Epinephrine acts on both α- and β-adrenergic receptors. It produces various effects, including increased heart rate and contractility, bronchodilation, peripheral vasoconstriction, and increased blood pressure. These effects are beneficial in emergencies such as anaphylaxis, cardiac arrest, and severe asthma exacerbations.

Epinephrine is used in various emergencies, including anaphylaxis (severe allergic reactions), cardiac arrest, bronchospasm, and severe asthma exacerbations. It also restores blood pressure and maintains organ perfusion during resuscitation efforts.

2.1.4 β-2 agonists

β-adrenergic receptor agonists have long been used to treat both acute asthma symptoms and the prevention of exercise-induced asthma in adults and children

and to treat COPD. They mimic the actions of catecholamines such as epinephrine, norepinephrine, and dopamine in triggering various autonomic responses within the body. β-2 agonists significantly affect the smooth muscle of the airway, uterus, gut, and systemic vasculature.

As part of our functional autonomic system, circulating catecholamines stimulate adrenergic receptors, resulting in parasympathetic and sympathetic physiological reactions. β-2 agonists operate as ligands to adrenergic receptors with higher selectivity for β-2 adrenergic receptors, mimicking catecholamines. When the β-2 adrenergic receptor is activated, a transmembrane signal cascade is initiated that includes the heterotrimeric G protein, Gs, and the effector, adenylyl cyclase. Adenylyl cyclase then raises intracellular cAMP through ATP hydrolysis. The increased cAMP concentration activates the cAMP-dependent protein kinase A (PKA). PKA can phosphorylate intracellular substrates, which modulate various actions within the cell. PKA, in particular, operates in airway smooth muscle to phosphorylate Gq-coupled receptors, resulting in a cascade of intracellular signals that have been postulated to diminish intracellular Ca2+ or decrease Ca2+ sensitivity [19].

The increase in Ca2+ inhibits myosin light chain phosphorylation, which prevents airway smooth muscle contraction. This is the underlying mechanism of β-2 agonists, which boost bronchodilatory effects and are used to treat a variety of common respiratory disorders. There have been suggestions that β-2 agonists have anti-inflammatory effects within the airway smooth muscle by decreasing intercellular adhesion molecule-1, decreasing granulocyte-macrophage colony-stimulating factor release, and stabilizing mast cell degranulation by inhibiting multiple inflammatory pathways.[T16] The duration and start of the action of β-2 agonists influence their classification. The three categories are short-acting, long-acting, and, most recently, ultra-long-acting β-agonists.

2.1.4.1 Short-acting β-2 agonists

They are first-line drugs for treating acute asthma symptoms and exacerbations. They are also often used in treating COPD in conjunction with long-acting, inhaled corticosteroids or long-acting muscarinic agonists. These drugs are often administered through inhalation, either metered dosage, dry powder inhalation, or nebulization. Compared to alternative oral delivery, inhalation has a higher therapeutic benefit and fewer systemic side effects. This family includes Salbutamol (albuterol), Terbutaline, Levalbuterol, and Pirbuterol.

2.1.4.2 Salbutamol

Salbutamol absorption is highly dependent on both formulation and dosage as well as the way of delivery. A thorough description of the effect of delivery systems on salbutamol pharmacokinetics may occupy many book chapters and is beyond the scope of this piece; however, we will consider some of the key points. Salbutamol is usually administered *via* a compressed metered-dose inhaler with an immense buffer. This very efficient delivery mechanism assures good distribution, especially to small- to moderate-sized airways. It can, however, be inhaled using a dry powder inhaler, or nebulizer, orally or intravenously.

Salbutamol, a partial agonist, has the greatest bronchodilating action at low dosages. It binds to β2-adrenoceptors located on airway smooth muscle (ASM)

throughout the airways. This binding causes a postsynaptic action on adenyl cyclase, resulting in the formation of intracellular cyclic AMP (cAMP) from ATP, which in turn stimulates other effector molecules, including cAMP-dependent protein kinase A (PKA) and nucleotide exchange factor, which work together to cause intracellular Ca2+ sequestration, resulting in ASM relaxation. Despite that salbutamol's primary function is bronchodilation, it also suppresses mast cell mediator release and tumor necrosis factor α (TNF) release from monocytes. It also enhances mucus production and clearance of the mucociliary tract. It has extensive effects across numerous organ systems as a sympathomimetic, and it causes dose-dependent tachycardia, hyperglycemia, hypokalemia, and tremor. The systemic metabolic effects inducing glycogen breakdown and concomitant insulin release (possibly stimulated by pancreatic β2 cells) combine to cause high blood sugar levels and serum hypokalemia, with the former occurring as a consequence of cellular sodium excretion and potassium influx (Na-K-ATPase pump).

This side effect is beneficial in the emergency treatment of hyperkalemia, where ongoing salbutamol administration can decrease serum potassium between 1 and 1.5 mmol/L. However, it can also have complications such as dose-related tremors (the salbutamol shakes'), and when combined with cardiac receptor stimulation, stimulation can lead to tachyarrhythmias. Tachyphylaxis to β-2 agonists arises as soon as 1 week after starting regular medication and is more apparent with β 2-agonist monotherapy.

2.1.4.3 Terbutaline

It is also a selective β-2 adrenoceptor agonist used to prevent and reverse bronchoconstriction. Approximately, its volume of distribution is about 1.6 L/kg. After 72 hours, an oral dose of terbutaline gets eliminated in the urine by 40%. Terbutaline sulfate conjugated was the most predominant metabolite in the urine. Terbutaline parenteral levels are 90% removed in the urine, with roughly 2/3 as the unaltered primary substance. In the feces, less than 1% of a terbutaline dose gets eliminated.

2.1.4.4 Long-acting β-2 agonist

They are commonly used in managing asthma and COPD patients, often combined with inhaled corticosteroids. There is evidence that combination therapy is more effective than monotherapy. They have a longer onset time than short-acting medications, with salmeterol having an onset period of up to 15 minutes and lasting at least 12 hours. The suggested route of administration is inhalation, as with short acting. They are typically used as a second-line treatment in asthma patients who have failed to get clinical relief with short-acting medications. Salmeterol and formoterol are the commonest drugs in this group.

2.1.4.5 Salmeterol

In asthmatic patients, a 50 μg dose of inhaled salmeterol powder reaches a C_{max} of 47.897 pg./mL, with a T_{max} of 0.240 h and an AUC of 156.041 pg./mL/h. The distribution volume of the main compartment is 177 L, and the distribution volume of the peripheral one is 3160 L. Salmeterol is 96% protein linked to albumin and α-1-acid glycoprotein in plasma. It is primarily processed by CYP3A4 to α-hydroxysalmeterol1, with little contribution from an unknown process to an O-dealkylated metabolite.

Salmeterol is removed in the feces at 57.4% and the urine at 23%. Only around 5% of the dosage is excreted in the urine as unaltered salmeterol.

2.1.4.6 Formoterol

It has a fast onset of action (about 2–3 minutes) and an extended duration of action (up to 12 hours). In asthmatic patients, long-acting β-agonists such as formoterol without accompanying inhaled corticosteroids should be avoided, as long-acting monotherapy has been linked to an increased risk of asthma-related fatalities. Its pulmonary bioavailability is estimated to be around 43% of the delivered dose, whereas total bioavailability in the body is approximately 60% of the supplied dose (since systemic bioavailability comprises absorption in the stomach). Following inhalation, formoterol is rapidly absorbed into the plasma. Formoterol T_{max} in healthy adults ranged from 0.167 to 0.5 hours. C_{max} and AUC were 22 pmol/L and 81 pmol.h/L after a single dosage of 10 mcg, respectively. T_{max} in asthmatic adults ranged from 0.58 to 1.97 hours. C_{max} and $AUC_{0–12h}$ after a single dose of 10mcg were 22 pmol/L and 125 pmol.h/L, respectively; after several doses of 10 mcg, C_{max} and AUC0-12 h were 41 pmol/L and 226 pmol.h/L, correspondingly. Across normal dosing ranges, absorption appears to be dose proportionate. It is 34–38% binding to plasma protein. It is predominantly processed by direct glucuronidation of the primary drug and O-demethylation of the primary drug, followed by glucuronidation. Minor mechanisms include primary drug sulfate conjugation and primary drug deformylation followed by sulfate conjugation, albeit these minor pathways have not been completely studied.

2.1.4.7 Ultra-long-acting β-2 agonist

Ultra-long-acting medications provide the longest duration of action, up to 24 hours, with the added benefit of being a once-a-day therapeutic dosage. The FDA has approved Indacaterol as a maintenance medication for COPD patients in combination with other bronchodilators. Indacaterol can be taken as a dry powder with a 5-minute onset of action. Many different ultra-LABAs are now being researched, with the potential to increase compliance and efficiency over current asthma and COPD therapy choices. Indacaterol, Vilanterol, and Oladaerol are the drugs in this group.

2.1.4.8 Administration

Metered-dose inhalers, nebulizers, dry powder inhalers, orally, subcutaneously, or intravenously are the most common delivery methods for β-2 agonists. Inhalation is the primary mode of delivery for β-2 agonists in treating asthma and COPD. Inhalation concentrates the therapeutic impact of the medicine on the airway's smooth muscles while minimizing the drug's diffusion to the systemic circulation. There is no association between the therapeutic impact of inhaled β-2 agonists and their peak plasma levels. Oral β-2 agonists, which have been demonstrated to exacerbate systemic side effects, are used less commonly. Terbutaline can also be administered intravenously, intramuscularly, or orally.

2.1.4.9 Adverse effects

The most prevalent side effect of β-2 agonists is desensitizing the β-2 adrenergic receptor to the β-2 agonist. Because adrenergic receptors have comparable features, β-2

agonists can have an "off-target" effect by stimulating α-1, α-2, or β-1 receptors. β-2 agonists' most prevalent adverse effects include the cardiovascular, metabolic, or musculoskeletal systems. Because of the vasodilatory impact on peripheral vasculature and a concomitant decrease in cardiac venous return, mechanisms of compensation show as tachycardia is relatively prevalent, particularly in the first few weeks of treatment. According to several publications ranging from single case reports to case-control studies, cardiac toxicity in the form of arrhythmias, cardiomyopathy, and ischemia has been more strongly associated with earlier-generation β-2 agonists. β-2 agonists have been demonstrated to lower serum potassium levels by causing an inward influx of potassium into cells *via* an action on the membrane-bound Na/K-ATPase, which can lead to hypokalemia. β-2 agonists also accelerate glycogenolysis, which might result in unintentional increases in serum glucose. Musculoskeletal tremors are another possible side effect, which is more familiar with using oral β-2 agonists. The severity of these side effects is often related to factors such as the affinity of each β-2 agonist to its specific receptor and medication dosages. Several studies additionally discovered hypoxemia and hypercapnia to be aggravating variables for β-2 agonist cardiotoxicity.[T25]

2.2 Sympatholytics

2.2.1 α-blockers

Sympatholytic drugs inhibit the effects of catecholamines by acting on postsynaptic adrenergic receptors present in target organs or by inhibiting the synthesis and storage of the catecholamines. These drugs can be divided into two subtypes, selective and nonselective α-receptor blockers.

Nonselective α-receptor antagonists block both the α-1 receptors as well as α-2 receptors. Blocking α-1 receptor causes vasodilation, while α-2 receptor blockade will reduce the force of vasodilation due to increased release of Norepinephrine. These medications, such as pheochromocytoma, are widely used in patients with increased sympathetic activity.

Selective α-1 receptor blockers act on the receptors and cause vasodilation; therefore, they are widely used in patients with hypertension and cause smooth muscle relaxation, so they help manage benign prostate hyperplasia [20].

The mechanism of action of *α-2 receptor blockers* is not known, although, in principle, they are known to inhibit negative feedback of norepinephrine release by stimulating the norepinephrine system, and they inhibit the effects of norepinephrine on postsynaptic α-2 adrenoceptors [20, 21].

2.2.1.1 Nonselective α-receptor blockers

2.2.1.1.1 Phentolamine

It is a nonselective α-receptor blocker used mainly to diagnose pheochromocytoma and to control or prevent paroxysmal hypertension immediately before or during pheochromocytoma ectomy. It is used to reverse soft tissue anesthesia, such as the tongue and the lips, and the associated functional deficits resulting from an intraoral submucosal injection of a local anesthetic containing a vasoconstrictor.

The drug is available in injection forms from 0.235 mg/1 mL to 10 mg/1/mL. The chemical formula of the drug is $C_{17}H_{19}N_3O$. α-receptors are present in blood vessels;

when they are activated by phentolamine, the blood vessels widen as the muscles relax and therefore decrease blood pressure. This drug maintains long-acting chemical sympathectomy. Phentolamine also stimulates β-adrenergic receptors and therefore causes a positive inotropic and chronotropic effect on the heart and increases cardiac output.

Phentolamine is only about 20% as active after oral administration as after parenteral administration. About 10–13% of the drug is eliminated unchanged in the urine, while the fate of the rest of the drug is unknown. The Tmax is 30–60 minutes. After intravenous administration of the drug, the elimination half-life is 19 minutes; after oral administration, it is 5–7 hours.

Some common adverse effects of the drug are weakness, dizziness, flushing, orthostatic hypotension, and nasal congestion, which have been reported in patients receiving phentolamine. Adverse GI effects are common and include abdominal pain, nausea, vomiting, diarrhea, and exacerbation of peptic ulcer. Adverse cardiovascular effects include prolonged hypotension, tachycardia, cardiac arrhythmias, and angina, especially after parenteral administration. Myocardial infarction and cerebrovascular spasm or occlusion, usually associated with marked hypotension and a shock-like state, have been reported occasionally following parenteral administration of phentolamine. Deaths have occurred after IV administration of phentolamine for the diagnosis of pheochromocytoma.

No specific antidote is available for phentolamine toxicity; however, in shock-like conditions such as a dangerous decrease in blood pressure or other evidence of shock, the person should be treated promptly with supportive care, and IV norepinephrine infusion can be administered if necessary. Epinephrine should not be used as it can cause a paradoxical decrease in blood pressure [22].

The oral LD50's (mg/kg) in mice is 1000, and in rats, it is 1250. No teratogenic or embryotoxic effects were observed in the rat, mouse, or rabbit studies, and no adequate and well-controlled studies in pregnant women are available. If the potential benefit of phentolamine justifies the potential risk to the fetus, the drug can be used. Whether or not the drug is excreted in human milk is unknown. As many drugs are excreted through human milk and since there is potential for adverse reactions in nursing infants, a decision should be made whether or not to continue the drug, considering the importance of the drug to the mother [22].

2.2.1.2 Selective α-receptor blockers

2.2.1.2.1 Prazosin

Prazosin is an α-1 receptor blocker used to treat hypertension, and recently, many studies have evaluated the drug's benefits in controlling post-traumatic stress disorder symptoms and associated nightmares. Other members of this drug class include Doxazosin, Terazosin, Tamsulosin, and Alfuzosin. This effect likely occurs through the inhibition of adrenergic stimulation found in states of hyperarousal. As this agent does not negatively impact lung function, it can manage hypertension in chronic obstructive lung diseases [23].

The chemical formula of the drug is $C_{19}H_{21}N_5O_4$. The usual adult for hypertension is 1 mg orally 2 or 3 times a day, initially, and the maintenance dose is 1–20 mg orally per day in divided doses [24]. It can be used alone or alongside other blood pressure-lowering agents, including diuretics and β-adrenergic blocking agents. The decrease in blood pressure may occur in both standing and supine positions [23].

After administering the oral dose, the peak plasma level of the drug is reached by approximately 3 hours, and the half-life is about 2–3 hours. Prazosin is metabolized in the liver by demethylation and conjugation and is excreted mainly in the bile and feces. The clearance of the drug is decreased in people with congestive heart failure.

As the drug lowers blood pressure, it can cause a clinically significant decrease in cardiac output, heart rate, blood flow to the kidney, and glomerular filtration rate. The decrease in blood pressure may occur in both standing and supine positions [23]. Shock caused by low blood pressure should first be treated with volume expanders, and vasopressors should be used if deemed necessary. Renal function should be monitored and supported as needed [25].

The LD50 in humans is 285 μg/kg orally. Severe drowsiness and decreased reflex occurred with ingesting at least 50 mg of Prazosin. There was no fall in blood pressure, and the child recovered without complications. The drug is classified as a Pregnancy category C drug. There are no adequate studies for determining the drug's safety during pregnancy. Specific cases of emergent use for blood pressure control during pregnancy showed no effects on the fetus or neonate. As the drug is excreted in small amounts in breast milk, it should be used cautiously in breastfeeding mothers.

Avoid alcohol and licorice with the use of this drug. Its absorption is not affected by food. Acute symptomatic liver injury due to prazosin is rare, and severe hepatotoxicity must be rare if it occurs at all [26].

2.2.1.2.2 Tamsulosin

It is an α-1A and α-1B adrenergic receptor antagonist used to treat benign prostatic hyperplasia, ureteral stones, female voiding problems, and prostatitis. The chemical formula is $C_{20}H_{28}N_2O_5S$(R38). It is available in the form of tablets, and the dose for treatment of adult benign prostate hyperplasia is 0.4 mg orally once a day; the dose may be increased to 0.8 mg orally once a day in patients who fail to respond to 0.4 mg once a day within 2–4 weeks [27].

The most significant effect of this drug is in the bladder and prostate, where the α-1A and α-1B adrenergic receptors are most common. The drug's action leads to the relaxation of prostate and bladder muscles, allowing for better urinary flow. Tamsulosin binds to α-1A receptors 3.9–38 times more selectively than α-1B and 3–20 times more selectively than α-1D. A significant effect on urinary flow with a reduced incidence of adverse reactions like orthostatic hypotension is allowed through this selectivity [28].

Tamsulosin is absorbed 90% in patients who are fasting. Taking the drug with food increases the time to maximum concentration from 4 to 5 hours to 6–7 hours but increases bioavailability by 30% and maximum plasma concentration by 40–70% [28].

The drug is metabolized by cytochrome P450 (CYP) 3A4 and 2D6 in the liver, with some metabolism by other CYPs. There is a low rise in liver transaminases by tamsulosin, but clinically, apparent liver injury is rare [28].

The oral LD50 in rats is 650 mg/kg. In an overdose, the patients might have hypotension that should be managed supportively by lying supine, administering fluids, or if further progression occurs, vasopressors might be needed, and renal function should be closely monitored. As tamsulosin is highly protein-bound, dialysis does not assist in treating overdose [28].

Animal studies have not shown any fetal harm caused by tamsulosin, but this drug is not indicated for use in women. Tamsulosin is excreted in the milk of rats,

but no studies have been conducted about the effects of exposure to it. Male and female rats have been shown to have fertility affected by impairment of ejaculation and fertilization. In men, ejaculation problems have been recorded with the use of tamsulosin. At levels above the recommended dose, tamsulosin may be carcinogenic. There is a slight increase in mammary gland fibroadenomas and adenocarcinoma rates in female rats [28].

2.2.2 β-blockers

β-blockers block the physiological impacts of sympathetic nerve stimulation or circulating catecholamines on β-adrenoceptors, which exist across different organs in the body. Many organs have both β1 and β2 receptors coexisting (**Table 1**). For example, approximately 80% of the receptors are of the β-1 subtype in a typical individual heart. In heart failure, β1 receptors are downregulated, allowing a greater number of β2 receptors to be detected. The physiological and therapeutic effects of a β-blocker are determined by the actual quantity of β-1 or β-2 receptors in the various organs, the β-blocker's affinity, and the local drug concentration. When the bioavailability of β-blockers with a strong affinity for β-adrenoceptors is not too low, they can be helpful in small doses. Their effect persists even if they are washed out of the extracellular area. As a result, the plasma half-life of the β-phase of elimination cannot forecast their duration of activity. This is particularly true for many medicines that have a high affinity and a short plasma half-life (2–4 h for the β-phase).[T26]

Many β-blockers have additional features that may influence their value in individuals:

1. *Selectivity*: Considering β-blockers' desired effects are achieved by blocking β1-receptors, which dominate on the heart, "cardioselective" drugs with greater

Organ	Subtype	Function
Heart	β_1, (β_2)[a]	Increase sinus rate Increase contractility Increase AV conduction
Gastrointestinal tract	β_1	Reduce muscular tone
Kidney	β_1, (β_2)[a]	Increase Renin release
Fat cells	β_1, (β_2)[a]	Increase lipolysis
Bronchi	β2	Reduce muscular tone
Blood vessels	β_2, (β_1)[b]	Reduce muscular tone
Uterus	β_2	Reduce muscular tone
Pancreas (B-cell)	β_2, (β_1)[a]	Increase insulin release
Thyroid gland	β_2, (β_1)[a]	Increase T4 T3 conversion
Incretory glands	β_2 – (β_1)[a]	Increase secretion of parathyroid hormone Reduce calcitonin & glucagon

[a]*receptor subtype coexistence.*
[b]*human cerebral blood vessels.*

Table 1.
Presence of β_1–β_2 receptors in various organ.

Selective β-1 receptor blockers	Non-selective β-blockers
• Metoprolol	• Carvedilol
• Atenolol	• Labetalol
• Nebivolol	• Propranolol
• Bisoprolol	• Satalol
• Acebutolol[ISA]	• Timolol
• Betaxolol	
• Esmolol	

ISA: intrinsic sympathomimetic activity.

Table 2.
Selectivity of β-blockers.

sensitivity for this receptor are often recommended. However, "cardioselectivity" is not 100% and diminishes with increasing doses. Atenolol, bisoprolol, and metoprolol are examples of "cardioselective" β-blockers (**Table 2**).

2. *Partial agonist activity (intrinsic sympathomimetic activity)*: When baseline adrenergic firing is low (as during sleep), this manifests as a β-stimulant effect, but when adrenergic action is high (as during exercise), this manifests as β-blockade. Pindolol is a β-blocker with partial agonist action.

3. *Membrane-stabilizing activity*: Sotalol confers a local anesthetic and anti-arrhythmic effect.

4. *Additional characteristics*: Some β-blockers, such as carvedilol and labetalol, oppose effects conveyed at peripheral α-adrenoceptors, activate β2-adrenoceptors (e.g., celiprolol), or exhibit direct vasodilation effect (e.g., nebivolol).

The extent to which β-blockers are eliminated by the kidney or the liver varies, usually with considerable first-pass metabolism. Lipid-soluble β-blockers, such as labetalol, metoprolol, pindolol, and propranolol, are typically eliminated *via* the liver, whereas water-soluble β-blockers, such as atenolol, get eliminated by the kidney. The bioavailability of drugs removed by the liver varies significantly between populations. Most β-blockers have a short half-life; those removed through the kidney have a prolonged half-life.

2.2.2.1 Side effects

β-blockers have multiple unwarranted side effects secondary to their mechanism and site of actions, mainly:

1. Bronchoconstriction in susceptible individuals due to blockade of β-2 receptors, which mediate dilation in the bronchi. All β-blockers are contraindicated in the presence of asthma.

2. Bradycardia and cardiac contractility impairment.

3. Blockade of β-2 receptors, which serve vasodilation in blood arteries supplying skeletal muscle beds and cause peripheral vasoconstriction, resulting in cold hands and feet and possibly worsening Raynaud's phenomenon.

4. CNS symptoms related to diminished sympathetic discharge, such as malaise, intense dreams, nightmares, and, in rare cases, hallucinations, with highly lipid soluble β-blockers that have increased CNS penetration.

5. Restlessness and exhaustion are caused by β-2-receptor blockage in skeletal muscle, accompanied by increased muscular activity.

6. Hypoglycemia can be overlooked in insulin-dependent diabetes due to a reduction in sympathetic nerve stimulation.

3. Pharmacology of the parasympathetic nervous system (PANS)

The PANS, often called the "rest and digest" system, conserves energy and promotes homeostasis during periods of relaxation. Acetylcholine is the primary neurotransmitter in PANS signaling, acting on cholinergic receptors in various tissues. Cholinergic receptors are divided into two major types: nicotinic and muscarinic cholinergic receptors [1].

Nicotinic receptors are found at the neuromuscular junction and in the SANS and PANS ganglia. Activation of these receptors leads to subsequent muscle contraction or neurotransmitter release [1]. Nicotinic agonists, such as nicotine, are used primarily in smoking cessation therapies due to their stimulatory effects on the central nervous system [3]. In contrast, neuromuscular blocking agents, which act as nicotinic antagonists, are utilized in anesthesia to induce muscle relaxation during surgical procedures.

Muscarinic receptors: Muscarinic receptors are further classified into five subtypes, M1–M5. The PANS innervates these receptors in various target tissues, including the heart, smooth muscles, exocrine glands, and CNS structures. M1 receptors are predominantly located in the CNS, where their activation modulates cognitive function and memory. M2 receptors are primarily found in the heart, where activation slows heart rate and reduces contractility. M3 receptors are abundant in smooth muscles, glands, and endothelial cells. Stimulation of M3 receptors leads to bronchoconstriction, increased glandular secretions, and vasodilation.

The clinical utility of muscarinic agonists is limited compared to their antagonists. However, muscarinic antagonists, also known as anticholinergic drugs, play a crucial role in anesthesia. These agents, such as atropine and glycopyrrolate, counteract excessive PANS activity during anesthesia induction; prevent unwanted bradycardia, reduce salivary, and bronchial secretions; and facilitate intubation [1].

3.1 Parasympathomimetics

3.1.1 Muscarinic receptor agonist

3.1.1.1 Pilocarpine

Pilocarpine is a parasympathomimetic drug classified as a muscarinic receptor agonist. It is derived from the Pilocarpus plant and primarily acts on muscarinic

receptors to produce pharmacological effects similar to acetylcholine. Pilocarpine is available in various formulations, including eye drops, tablets, and solutions. Eye drops are commonly used for ophthalmic purposes. Concentrations may vary depending on the specific indication. Storage conditions may involve protecting the drug from light and excessive heat.

Pilocarpine can be administered topically to the eye or orally. When applied topically to the eye, it has poor systemic absorption. Oral pilocarpine is well-absorbed from the gastrointestinal tract. The drug undergoes hepatic metabolism, primarily *via* hydrolysis, and is excreted mainly in the urine.

Pilocarpine selectively activates muscarinic receptors, predominantly the M3 subtype. It stimulates cholinergic receptors in various tissues, leading to miosis (pupillary constriction), increased salivation, sweating, bronchoconstriction, and gastrointestinal motility.

Clinically, pilocarpine eye drops are commonly used to treat glaucoma, where they reduce intraocular pressure by increasing the drainage of aqueous humor from the eye. Pilocarpine can also manage dry mouth (xerostomia) associated with Sjögren's syndrome or radiation therapy.

Pilocarpine is contraindicated in individuals with a known hypersensitivity to the drug, uncontrolled asthma, acute iritis, or narrow-angle glaucoma. It should be used cautiously in patients with cardiovascular diseases or gastrointestinal disorders. Other common side effects of pilocarpine may include localized ocular effects like temporary blurred vision, eye discomfort, or burning sensation when used as eye drops. Systemic effects can include increased sweating, increased salivation, gastrointestinal disturbances (such as nausea, vomiting, or diarrhea), and bronchoconstriction.

In cases of overdose or excessive use, pilocarpine can lead to excessive cholinergic stimulation. Symptoms may include profuse sweating, salivation, miosis, gastrointestinal distress, and potentially life-threatening cardiovascular effects. Treatment may involve discontinuing the drug, supportive measures, and administering atropine as a competitive antagonist to counteract the excessive muscarinic effects.

3.1.2 Acetyl-cholinesterase inhibitors

3.1.2.1 Neostigmine

Neostigmine is a reversible acetylcholinesterase inhibitor, classified as a parasympathomimetic drug. It increases the concentration of acetylcholine at cholinergic synapses by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine. Neostigmine is available in various forms, including oral tablets and solutions for injection. The concentration and specific formulation may vary depending on the intended use.

Neostigmine can be administered orally, intramuscularly, or intravenously. It has poor oral bioavailability and is rapidly metabolized by esterases in the plasma and tissues. The elimination half-life is relatively short.

Neostigmine inhibits acetylcholinesterase, accumulating acetylcholine and exerting its effects at cholinergic synapses. It enhances neuromuscular transmission, leading to increased muscle strength and tone. It also affects cholinergic neurotransmission in other systems, such as the gastrointestinal tract.

Neostigmine is primarily used to manage myasthenia gravis, a neuromuscular disorder characterized by muscle weakness. It is also employed to reverse the effects

of non-depolarizing neuromuscular blocking agents after surgery and to treat urinary retention.

Neostigmine is contraindicated in individuals with known hypersensitivity to the drug or those with mechanical gastrointestinal or urinary tract obstruction. It should be used cautiously in patients with asthma, epilepsy, or bradycardia. Other common side effects of neostigmine include gastrointestinal disturbances such as nausea, vomiting, diarrhea, and abdominal cramps. It may also cause increased salivation, sweating, bronchoconstriction, and bradycardia. These effects are related to its cholinergic activity.

In cases of overdose or excessive use of neostigmine, symptoms of cholinergic crisis may occur, including profuse salivation, sweating, bronchoconstriction, bradycardia, and potentially life-threatening respiratory depression. Treatment involves discontinuing the drug, administering atropine as a competitive antagonist, and supportive measures as necessary.

3.1.2.2 Physostigmine

Physostigmine is a reversible acetylcholinesterase inhibitor classified as a parasympathomimetic drug. It increases the concentration of acetylcholine at cholinergic synapses by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine. Physostigmine is available in various forms, including oral tablets and solutions for injection. The concentration and specific formulation may vary depending on the intended use.

Physostigmine can be administered orally, intramuscularly, or intravenously. It is rapidly absorbed and metabolized by esterases in the plasma and tissues. The elimination half-life is relatively short. Physostigmine inhibits acetylcholinesterase, allowing acetylcholine to accumulate and exert its effects at cholinergic synapses. It enhances cholinergic neurotransmission in various systems, including the central nervous system and peripheral organs.

Physostigmine is primarily used to manage anticholinergic toxicity, including poisoning by anticholinergic drugs, such as certain medications, plants, or insecticides. It can reverse the effects of excessive anticholinergic activity, such as delirium, hallucinations, and peripheral manifestations. Physostigmine is contraindicated in individuals with known hypersensitivity to the drug or those with mechanical gastrointestinal or urinary tract obstruction. It should be used cautiously in patients with asthma, epilepsy, or bradycardia. Side effects of physostigmine include gastrointestinal disturbances such as nausea, vomiting, diarrhea, and abdominal cramps. It may also cause increased salivation, sweating, bronchoconstriction, and bradycardia. These effects are related to its cholinergic activity.

In cases of excessive use of physostigmine, symptoms of cholinergic crisis may occur, including profuse salivation, sweating, bronchoconstriction, bradycardia, and potentially life-threatening respiratory depression. Treatment involves discontinuing the drug, administering atropine as a competitive antagonist, and supportive measures as necessary.

3.1.2.3 Pyridostigmine

Pyridostigmine is a reversible acetylcholinesterase inhibitor classified as a parasympathomimetic drug. It increases the concentration of acetylcholine at cholinergic synapses by inhibiting the enzyme acetylcholinesterase, which breaks down

acetylcholine. Pyridostigmine is available in various forms, including oral tablets and extended-release formulations. The concentration and specific formulation may vary depending on the intended use.

Pyridostigmine is primarily administered orally and is well-absorbed from the gastrointestinal tract. It has a more prolonged action duration than other acetylcholinesterase inhibitors, allowing for less frequent dosing. Pyridostigmine inhibits acetylcholinesterase, increasing acetylcholine concentration and enhancing cholinergic neurotransmission. It primarily acts on skeletal muscles, improving muscle strength and tone. It also affects cholinergic neurotransmission in other systems, such as the gastrointestinal tract.

Therapeutically, pyridostigmine is primarily used to manage myasthenia gravis, a neuromuscular disorder characterized by muscle weakness. It helps improve muscle strength and function in individuals with this condition.

Pyridostigmine is contraindicated in individuals with known hypersensitivity to the drug or those with mechanical gastrointestinal or urinary tract obstruction. It should be used cautiously in patients with asthma, epilepsy, or bradycardia. Side effects of pyridostigmine include gastrointestinal disturbances such as nausea, vomiting, diarrhea, and abdominal cramps. It may also cause increased salivation, sweating, bronchoconstriction, and bradycardia. These effects are related to its cholinergic activity.

Overuse of pyridostigmine can lead to symptoms of cholinergic crisis may occur, including profuse salivation, sweating, bronchoconstriction, bradycardia, and potentially life-threatening respiratory depression. Treatment involves discontinuing the drug, administering atropine as a competitive antagonist, and supportive measures as necessary.

3.1.2.4 Rivastigmine

Rivastigmine is a reversible acetylcholinesterase inhibitor classified as a parasympathomimetic drug. It increases the concentration of acetylcholine at cholinergic synapses by inhibiting the enzyme acetylcholinesterase, which breaks down acetylcholine. Rivastigmine is available in oral capsules, oral solutions, and transdermal patches. The capsules and oral solution come in various strengths, typically 1.5–6 mg, while the transdermal patches are available in different doses.

Rivastigmine can be administered orally or transdermally. When given orally, it is well-absorbed from the gastrointestinal tract. It undergoes extensive metabolism in the liver, and the elimination half-life varies depending on the individual's genetic makeup. Rivastigmine inhibits acetylcholinesterase, increasing acetylcholine concentration and enhancing cholinergic neurotransmission. It primarily acts in the central nervous system, specifically targeting acetylcholinesterase in the brain.

Rivastigmine is primarily used for the treatment of mild to moderate Alzheimer's disease and Parkinson's disease dementia. It helps improve cognitive function in individuals with these conditions, including memory, attention, and daily living activities.

Rivastigmine is contraindicated in individuals with a known hypersensitivity to the drug or those with a history of hypersensitivity to carbamate derivatives. It should be used cautiously in patients with gastrointestinal conditions such as peptic ulcer disease or those at risk of developing bradycardia. It shares similar side effects to its sister medications.

In cases of overdose or excessive use of rivastigmine, symptoms of cholinergic crisis may occur, including profuse salivation, sweating, bronchoconstriction,

bradycardia, and potentially life-threatening respiratory depression. Treatment involves discontinuing the drug, administering atropine as a competitive antagonist, and supportive measures as necessary.

3.2 Parasympatholytics

Parasympatholytics are substances—or activities—that reduce the activity of the parasympathetic nervous system. They work by blocking the muscarinic receptors of the parasympathetic system. Most drugs with parasympatholytic properties are anticholinergics [29].

Parasympatholytic's pharmacodynamic effects include reduction of glandular secretion, dilatation of the pupil, paralysis of accommodation, increase of intraocular pressure, reduction of lacrimation, and more. These effects render parasympatholytics therapeutically valuable for treating slow heart rhythms, bronchioles constriction, and conditions such as benign prostatic hyperplasia, urinary retention, intestinal atony, and tachycardia [29]. It is worth mentioning, however, that parasympatholytics can interact with multiple drugs that can potentiate the antimuscarinic effect, such as antihistamines, neuroleptics, antidepressants, quinidine, or antiparkinson drugs [30].

Examples of parasympatholytics include atropine, methscopolamine bromide, flavoxate, orphenadrine, tiotropium, pinaverium, butylscopolamine, and anisodamine. However, atropine is the most used in the clinical setting.

3.2.1 Atropine

Atropine is classified as an anticholinergic or a parasympatholytic drug. Clinically, atropine is mainly indicated to treat bradyarrhythmias. Atropine also augments cardiac contractility by inhibiting cAMP-specific phosphodiesterase type 4, acting as a positive inotropic agent.

Atropine is a tropane alkaloid obtained from the deadly nightshade (*Atropa belladonna*) and other plants of the family Solanaceae. Its chemical formula is C17H23NO3, has a molecular weight of 289.4 g/mol (**Figure 2**), and is a racemic mixture of equimolar concentrations of (S)- and (R)-atropine. Atropine contains several functional groups, including an ester group, a hydroxyl group, and a tertiary amine group. The structure of atropine can be diagrammatically represented as benzene acetic acid, α-(hydroxymethyl)-8-methyl-azabicyclo {3.2. 1} oct-3-yl ester endo-(±). On hydrolysis, atropine gives (±)-tropic acid and tropine.

Atropine is an antimuscarinic agent that acts as a reversible, nonspecific antagonist of muscarinic receptors. It exerts its action by inhibiting the muscarinic actions of acetylcholine on structures innervated by postganglionic cholinergic nerves and smooth muscles, which respond to endogenous acetylcholine but are not so innervated. Atropine leads to both increased respiratory rate and depth, possibly due to the drug-induced inhibition of the vagus nerve. Generally, atropine counteracts the "rest and digest" activity of glands regulated by the parasympathetic nervous system.

Common medical uses of atropine include its role as an antisialagogue during surgery and anesthesia. It is also available in eye drops to treat uveitis and early amblyopia. Outside medicine, atropine is also used in the agricultural domain as a pesticide.

The pharmacological effects of atropine are due to binding to muscarinic acetylcholine receptors. Atropine is a competitive, reversible antagonist at muscarinic receptors, which blocks the effects of acetylcholine and other choline esters. Hence,

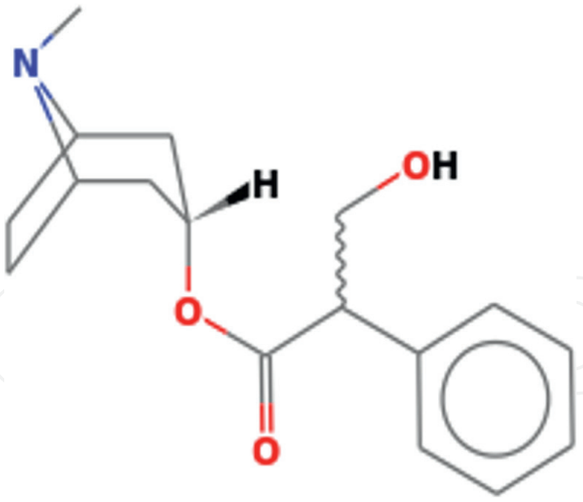

Figure 2.
Atropine molecule.

atropine is used as an antidote for poisoning by muscarinic agents, including organophosphates and other drugs.

Atropine can cause several side effects, mild or severe, depending on the dose and the individual's response to the drug. Some of the most common side effects of atropine include dry mouth, blurred vision, dry eyes, photophobia, confusion, headache, dizziness, fatigue, tachycardia, palpitations, flushing, urinary hesitance or retention, constipation, nausea, vomiting, and so on.

4. Conclusion

In conclusion, exploring autonomic nervous system (ANS) pharmacology presented in this chapter provides a comprehensive understanding of the intricate interplay between neurotransmitters, receptors, and drugs within the sympathetic and parasympathetic divisions. This chapter unveils the complexity of ANS modulation by dissecting the mechanisms of both agonists and antagonists and delving into direct and indirect drug actions.

The broad spectrum of examples discussed underscores the significance of ANS pharmacology across various medical disciplines. From managing hypotension and other medical problems, the clinical applications are far-reaching. The meticulous analysis of pharmacokinetics, metabolism, adverse effects, and contraindications empowers healthcare professionals to make informed decisions that optimize patient care.

For anesthesiologists, in particular, this knowledge is indispensable. The ability to finely tune autonomic responses during procedures can significantly impact patient outcomes and safety. A robust understanding of ANS pharmacology is a cornerstone of any physician toolkit, enabling them to navigate the intricate balance of autonomic control in the perioperative setting.

Conflict of interest

All authors declare no conflict of interest.

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