C. Isoproterenol

Isoproterenol is a direct-acting synthetic catecholamine that predominantly stimulates both \( \beta_1 \)- and \( \beta_2 \)-adrenergic receptors. Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on \( \alpha \) receptors is insignificant.

**Actions:**

**Cardiovascular:** Isoproterenol produces powerful stimulation of the heart to **increase its rate and force of contraction**, causing increased cardiac output. It is as active as epinephrine in this action and, therefore, is useful in the treatment of atrioventricular block or cardiac arrest. Isoproterenol also dilates the arterioles of skeletal muscle (\( \beta_2 \) effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure.

**Pulmonary:** A profound and rapid bronchodilation is produced by the drug (\( \beta_2 \) action). Isoproterenol is as active as epinephrine and rapidly alleviates an acute attack of asthma when taken by inhalation (which is the recommended route). This action lasts about 1 hour and may be repeated by subsequent doses.
**Other effects:** Other actions on $\beta$-receptors, such as increased blood sugar and increased lipolysis, can be demonstrated but are not clinically significant.

**Therapeutic uses:** Isoproterenol is now rarely used as a broncho-dilator in asthma. It can be employed to stimulate the heart in emergency situations.

**Pharmacokinetics:** Isoproterenol can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when given parenterally or as an inhaled aerosol. It is a marginal substrate for COMT and is stable to MAO action.

**Adverse effects:** The adverse effects of isoproterenol are similar to those of epinephrine.

**D. Dopamine**

Dopamine the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. Dopamine can activate $\alpha$ and $\beta$ adrenergic receptors. For example, at higher doses, it can cause vasoconstriction by activating $\alpha_1$ receptors, whereas at lower doses, it stimulates $\beta_1$ cardiac receptors. In addition, D1 and D2 dopaminergic receptors, distinct from the $\alpha$ and $\beta$ adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release.

**Actions:**

**Cardiovascular:** Dopamine exerts a stimulatory effect on the $\beta_1$ receptors of the heart, having both inotropic and chronotropic effects. At very high doses, dopamine activates $\alpha_1$ receptors on the vasculature, resulting in vasoconstriction.

**Renal and visceral:** Dopamine dilates renal and splanchnic arterioles by activating dopaminergic receptors, thus increasing blood flow to the kidneys.
and other viscera. These receptors are not affected by α or β blocking drugs. Therefore, **dopamine is clinically useful in the treatment of shock**, in which significant increases in sympathetic activity might compromise renal function. [Note: Similar dopamine receptors are found in the autonomic ganglia and in the CNS.]

**Therapeutic uses:** Dopamine is the drug of choice for shock and is given by continuous infusion. It raises the blood pressure by stimulating the β1 receptors on the heart to increase cardiac output, and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above. **An increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis.** In this regard, dopamine is far superior to norepinephrine, which diminishes the blood supply to the kidney and may cause renal shutdown.

**Adverse effects:** An overdose of dopamine produces the same effects as sympathetic stimulation. Dopamine is rapidly metabolized to homovanillic acid by MAO or COMT, and its adverse effects (nausea, hypertension, arrhythmias) are therefore short-lived.

**E. Dobutamine**

**Actions:**

Dobutamine is a **synthetic**, direct-acting catecholamine that is a β1-receptor agonist. It is available as a racemic mixture. One of the stereoisomers has a stimulatory activity. It increases cardiac rate and output with few vascular effects.

**Therapeutic uses:** Dobutamine is used to increase cardiac output in congestive heart failure as well as for inotropic support after cardiac surgery. The drug increases cardiac output with little change in heart rate, and it does not significantly elevate oxygen demands of the myocardium which is major advantage over other sympathomimetic drugs.
Adverse effects: Dobutamine should be used with caution in atrial fibrillation, because the drug increases atrioventricular conduction. Other adverse effects are the same as those for epinephrine. Tolerance may develop on prolonged use.

F. Oxymetazoline

Oxymetazoline is a direct-acting synthetic adrenergic agonist that stimulates both $\alpha_1$ and $\alpha_2$-adrenergic receptors. It is primarily used locally in the eye or the nose as a vasoconstrictor. Oxymetazoline is found in many short-term nasal spray decongestant products as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, or contact lens. The mechanism of action of oxymetazoline is direct stimulation of $\alpha$ receptors on blood vessels supplying the nasal mucosa and the conjunctiva to reduce blood flow and decrease congestion. Oxymetazoline is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. When administered in the nose, burning of the nasal mucosa and sneezing may occur. Rebound congestion is observed with long-term use.

G. Phenylephrine

Phenylephrine is a direct-acting, synthetic adrenergic drug that binds primarily to $\alpha$ receptors and favors $\alpha_1$ receptors over $\alpha_2$ receptors. It is not a catechol derivative and, therefore, not a substrate for COMT. Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but rather induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis (dilated eye pupils). Phenylephrine acts as a nasal decongestant and produces prolonged vasoconstriction. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the atrioventricular junction and atria). Large doses can cause hypertensive headache and cardiac irregularities.
H. Methoxamine

Methoxamine is a direct-acting, synthetic adrenergic drug that binds primarily to $\alpha$ receptors, with $\alpha_1$ receptors favored over $\alpha_2$ receptors. Methoxamine raises blood pressure by stimulating $\alpha_1$ receptors in the arterioles, causing vasoconstriction. This causes an increase in total peripheral resistance. Because of its effects on the vagus nerve, methoxamine is used clinically to relieve attacks of paroxysmal supraventricular tachycardia. It is also used to overcome hypotension during surgery involving halothane anesthetics. In contrast to most other adrenergic drugs, methoxamine does not tend to trigger cardiac arrhythmias in the heart, which is sensitized by these general anesthetics. Adverse effects include hypertensive headache and vomiting.

I. Clonidine

Clonidine is an $\alpha_2$ agonist that is used in essential hypertension to lower blood pressure because of its action in the CNS. It can be used to minimize the symptoms that accompany withdrawal from opiates or benzodiazepines. Clonidine acts centrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery.

J. Metaproterenol

Metaproterenol, although chemically similar to isoproterenol, is not a catecholamine, and it is resistant to methylation by COMT. It can be administered orally or by inhalation. The drug acts primarily at $\beta_2$ receptors, producing little effect on the heart. Metaproterenol produces dilation of the bronchioles and improves airway function. The drug is useful as a bronchodilator in the treatment of asthma and to reverse bronchospasm.
K. Albuterol, pirbuterol, and terbutaline

They are short-acting β2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler. Compared with the nonselective β adrenergic agonists, such as Metaproterenol, these drugs produce equivalent bronchodilation with less cardiac stimulation.

L. Salmeterol and Formoterol

They are β2-adrenergic selective, long-acting bronchodilators. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol. Unlike formoterol, however, Salmeterol has a somewhat delayed onset of action. These agents are not recommended as monotherapy and are highly efficacious when combined with a corticosteroid. Salmeterol and formoterol are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications.

Indirect-Acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause norepinephrine release from presynaptic terminals or inhibit the uptake of norepinephrine. They potentiate the effects of norepinephrine produced endogenously, but these agents do not directly affect postsynaptic receptors.

A. Amphetamine

The marked central stimulatory action of amphetamine is often mistaken by drug abusers as its only action. However, the drug can increase blood pressure significantly by α agonist action on the vasculature as well as β stimulatory effects on the heart. Its peripheral actions are mediated primarily through the blockade of norepinephrine uptake and cellular release of stored catecholamines; thus, amphetamine is an indirect-acting adrenergic drug. The CNS stimulant effects of amphetamine and its derivatives have led to their use for treating hyperactivity in children, narcolepsy, and appetite control. Its
use in pregnancy should be avoided because of adverse effects on development of the fetus.

**B. Tyramine**

Tyramine is not a clinically useful drug, but it is important because it is found in fermented foods, such as ripe cheese and Chianti wine. It is a normal byproduct of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but if the patient is taking MAO inhibitors, it can precipitate serious vasopressor (causing vasoconstriction) episodes. Like amphetamines, tyramine can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors.

**C. Cocaine**

Cocaine is unique among local anesthetics in having the ability to block the Na+/K+-activated ATPase (required for cellular uptake of norepinephrine) on the cell membrane of the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhancement of sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking cocaine as compared to those in one who is not. In addition, the duration of action of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by \( \alpha \) agonist actions and \( \beta \) stimulatory effects.

**Mixed-Action Adrenergic Agonists**

Mixed-action drugs induce the release of norepinephrine from presynaptic terminals, and they activate adrenergic receptors on the postsynaptic membrane.

**A. Ephedrine and pseudoephedrine**

They are plant alkaloids, that are now made synthetically. These drugs are mixed-action adrenergic agents. They not only release stored norepinephrine
from nerve endings but also directly stimulate both $\alpha$ and $\beta$ receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent. Ephedrine and pseudoephedrine are not catechols and are poor substrates for COMT and MAO; thus, these drugs have a long duration of action. Ephedrine and pseudoephedrine have excellent absorption orally and penetrate into the CNS; however, pseudoephedrine has fewer CNS effects. Ephedrine is eliminated largely unchanged in the urine, and pseudoephedrine undergoes incomplete hepatic metabolism before elimination in the urine. Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. Ephedrine produces bronchodilation, but it is less potent than epinephrine or isoproterenol in this regard and produces its action more slowly. It is therefore sometimes used prophylactically in chronic treatment of asthma to prevent attacks rather than to treat the acute attack (important). Ephedrine enhances contractility and improves motor function in myasthenia gravis (is a neuromuscular disease leading to irregular muscle weakness and fatiguability. It is an autoimmune disorder, in which weakness is caused by circulating antibodies that block acetylcholine receptors at the post-synaptic neuromuscular junction), particularly when used in conjunction with anticholinesterases. Ephedrine produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. Ephedrine has been used to treat asthma, as a nasal decongestant (due to its local vasoconstrictor action), and to raise blood pressure. Pseudoephedrine is primarily used to treat nasal and sinus congestion or congestion of the eustachian tubes. [Note: The clinical use of ephedrine is declining due to the availability of better, more potent agents that cause fewer adverse effects. Ephedrine-containing herbal supplements (mainly ephedra-containing products) were banned by the U.S. Food and Drug Administration in April 2004 because of life-threatening cardiovascular reactions. Pseudoephedrine has been illegally converted to methamphetamine. Thus, products containing pseudoephedrine have certain restrictions and must be kept behind the sales counter.]