Decoding Physiology

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1ST EDITION

PATHOPHYSIOLOGY AND CASE QUESTIONS FOR
USMLE EXAMS, MEDICAL STUDENTS, AND NURSING
PREPARATION COURSES

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The author strongly encourages readers to submit any errors they find to the author via email at alrubaye@gakclinic.com. This will enable us to address any misunderstandings or errors in preparation for the second edition. Additionally, we welcome you to join our team as part of the reviewer panel for the second edition, and we would be more than happy to have you on board.

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To my parents, who raised me with the values of compassion and generosity and instilled in me the desire to help others: thank you for your unwavering love and guidance.

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To my precious daughters, Dana and Rima, your love and light illuminate my world. Thank you for bringing endless joy and meaning to my life.

PREFACE

Welcome to the world of Decoding Physiology! As you embark on this journey through the intricacies of the human body's functions, allow me to share a personal reflection on the challenges and triumphs that have shaped my understanding of this fascinating subject.

During my time in medical school, I grappled with the complexities of medical physiology, often feeling overwhelmed by dense textbooks and obscure concepts. The lack of clear illustrations and explanations left me spending countless hours trying to decipher fundamental principles, unsure if I was truly comprehending or merely memorizing to pass exams.

My struggles became most apparent as I prepared for the USMLE Step 1. This pivotal exam demanded a deeper understanding and application of physiological concepts, challenging me to move beyond rote memorization. It was during this time that I realized the need for a different approach.

I began to focus on grasping simple facts and applying them across various body systems. For example, understanding the concept of compliance allowed me to extrapolate its implications to different physiological contexts, such as compliance of the chest wall, lungs, and vascular system. The same applies when implicating the concept of resistance to vascular and pulmonary systems.

One of the pure physiology challenges I encountered was understanding the mathematical equations. We were taught to memorize the equations and plug in numbers without truly grasping the underlying concepts. However, I learned how to explain the meaning of the equations; for example, the negative sign of free water clearance indicates the body's retention of water, which is a crucial concept in understanding the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Understanding curves and graphs is another struggle, particularly vascular function curves, which often left me feeling perplexed and frustrated. Understanding these curves became even more daunting when considering how changes in preload and afterload could alter their shape and implications. Furthermore, the integration of vascular and cardiac function curves added another layer of complexity, especially in understanding how changes in cardiac output affect these curves. These concepts were not only challenging to grasp but also difficult to apply within the time constraints of exams. To overcome this hurdle, I adopted a methodical approach. I dissected each curve into distinct areas, such as Area A, B, and C, and focused on describing the changes in the curve visually rather than relying solely on text-based explanations. Additionally, I supplemented theoretical concepts with simple drawings to enhance visual understanding.

My journey didn't end there. Along the way, I observed common struggles among fellow students, particularly in interpreting clinical cases and applying pathophysiological concepts. For instance, the presentation of a patient with chronic shortness of breath could indicate various underlying causes, such as pulmonary issues, cardiac problems, or anemia. Understanding whether the shortness of breath is due to decreased compliance, decreased myocardial contractility, or decreased hemoglobin concentration adds another layer of complexity to diagnosis and treatment.

I integrated clinical pathophysiology concepts into the book, emphasizing the importance of approaching different clinical scenarios with tailored strategies. For instance, hypoxia with a A-a gradient requires a different approach than hypoxia with large A-a gradient. Similarly, understanding how to approach a patient with hypokalemia in the context of normotension versus hypertension is crucial for effective diagnosis and management.

Driven by a desire to share my insights and help others navigate the challenges of medical physiology, I embarked on the journey of writing this book. Drawing from my own experiences and the lessons learned, my aim is to provide a comprehensive yet accessible resource that bridges the gap between basic science and clinical application. In this book, you'll find not only clear explanations of physiological principles but also practical examples and clinical correlations to aid in understanding and application.

Riyadh R. AlRubaye

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1 CELLULAR PHYSIOLOGY AND AUTONOMIC NERVOUS SYSTEM (ANS)

Movement of Solutes across the Cell Membrane

Solutes move across the cell membrane by either passive diffusion or active transport.

Solutes can move across the cell membrane in response to a concentration gradient which is the difference between their concentration inside and outside the cell. Larger concentration gradients will promote more diffusion.

Solutes can also respond to an electrical or voltage gradient which is the difference in charge across the cell membrane. Larger differences in electrical charge will also promote more diffusion.

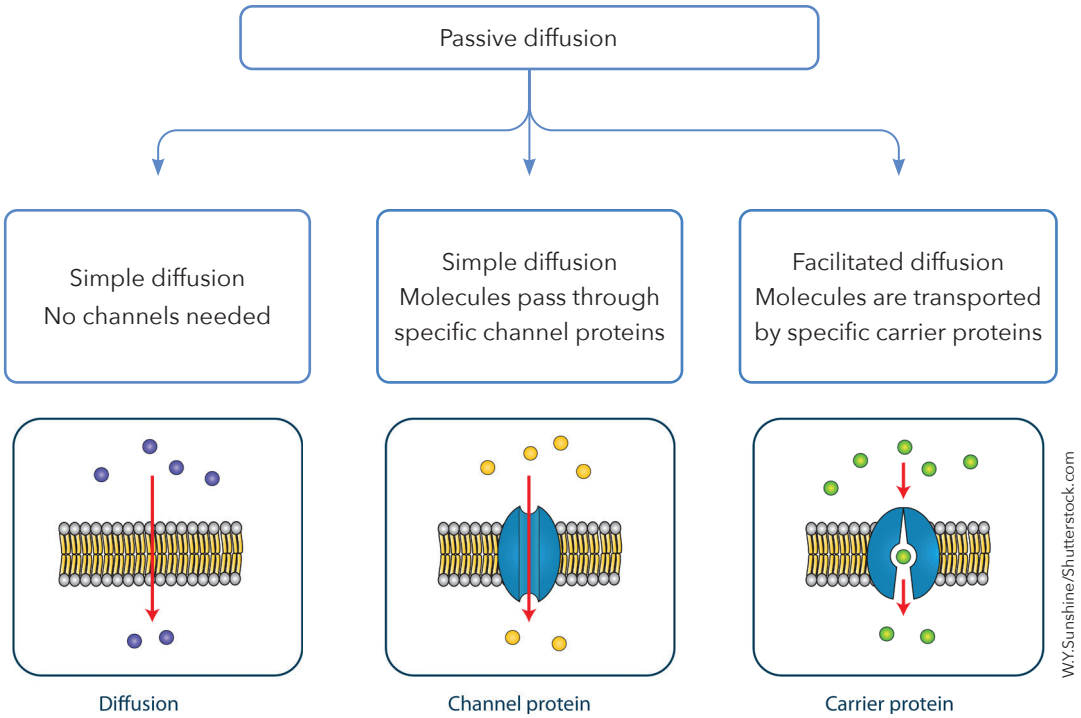
Passive Diffusion

Solutes diffuse down the electrochemical gradient. No energy is needed for solutes to be transported by this process. Molecules have different modes of diffusion across the cell membrane:

A. Gases (e.g., oxygen and carbon dioxide) and lipid-soluble molecules (e.g., steroid hormones) can diffuse directly through the lipid bilayer.

B. By contrast, sodium (Na^+) and potassium (K^+) diffuse through ion-specific protein channels. These channels promote the continuous transport of these ions along their concentration gradients.

C. Diffusion of other molecules (e.g., glucose) across the cell membrane is facilitated by specific carrier proteins.



Active Transport

Molecules are transported against a concentration or an electrochemical gradient. Active transport is always mediated by specific proteins or channels. Energy is always required either directly in the case of primary active transport or indirectly via secondary active transport.

Primary active transport

Energy is acquired directly from the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and free phosphate (P_i).

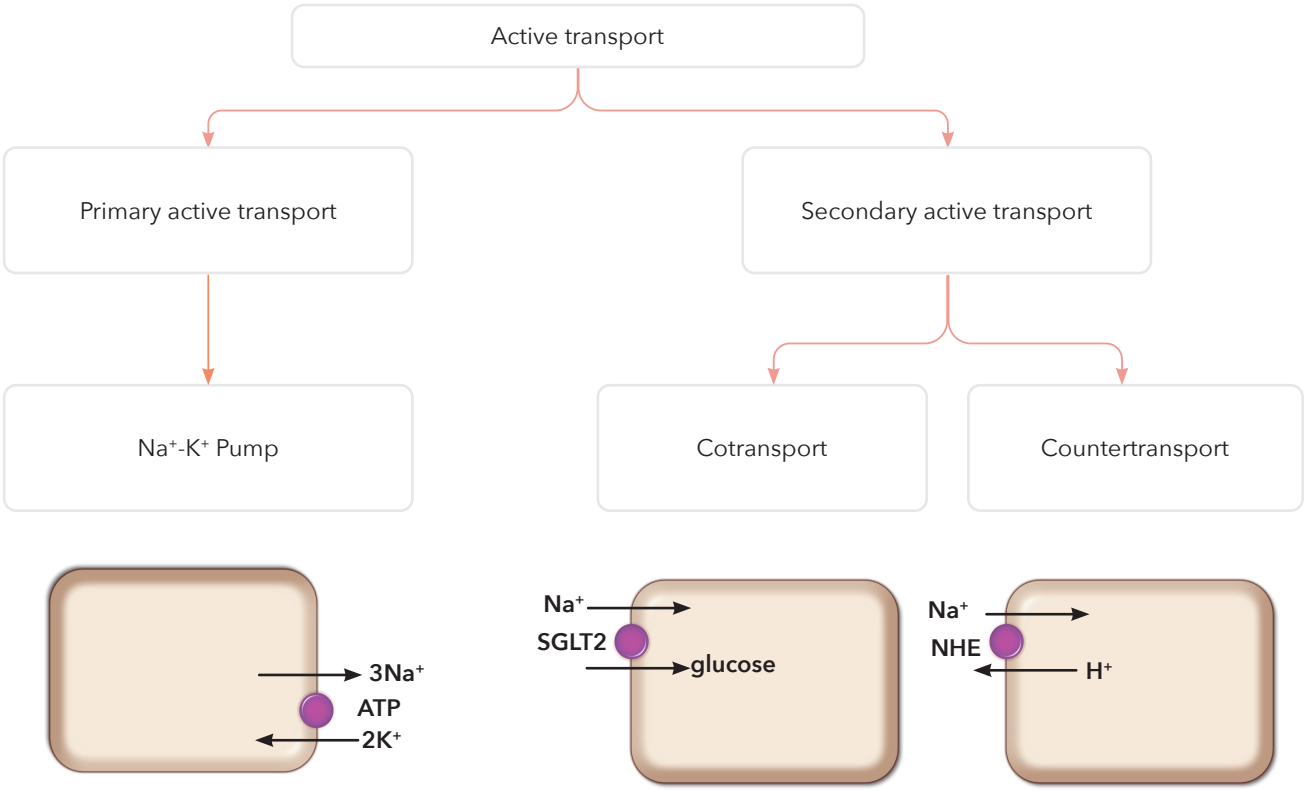
The Na^+-K^+ pump is a classic example of primary active transport. The Na^+-K^+ pump is expressed in all cells in the body and functions by exchanging three intracellular Na^+ ions for two extracellular K^+ ions.

Secondary active transport

Energy is provided indirectly by the hydrolysis of ATP. Two solutes are transported at the same time by a specific membrane transport protein. The transport protein has two binding sites, i.e., one distinct binding site for each of the two molecules.

Na^+ interacts with one of the binding sites and is transported down its electrochemical gradient. The other solute interacts with the second binding site and is transported against a concentration gradient. There are two types of secondary active transport:

- Cotransport is the transfer of two solutes in the same direction. The transporter protein is identified as a symporter. Na^+-glucose transport in the proximal convoluted tubule of the kidney by Na^+-glucose-linked cotransporter protein (e.g., SGLT2) is an example of cotransport.
- Countertransport is the term used to describe the transfer of two solutes in opposite directions. The transport protein that performs this function is known as an antiporter. Na^+-H^+ exchange in the proximal convoluted tubule carried out by the Na^+-H^+ exchanger protein (NHE) is an example of this process.



Medical Case

A scientist attempted to decrease blood glucose levels by decreasing glucose reabsorption in the proximal convoluted tubules. Which of the following strategies can directly reduce glucose reabsorption at this site?

A. Active Na^+-K^+ ATPase in tubular cells
B. Blockade of NHE countertransport
C. ↑ Na^+-electrochemical gradients
D. Blockade of SGLT co-transporters

- Answer: D

The Autonomic Nervous System

The ANS controls the functions of visceral organs, including glands, cardiac muscles, vascular smooth muscle, the gastrointestinal tract, and the bladder, among others. The ANS includes both the sympathetic and parasympathetic nervous systems.

Features of the Sympathetic Nervous System (SNS)

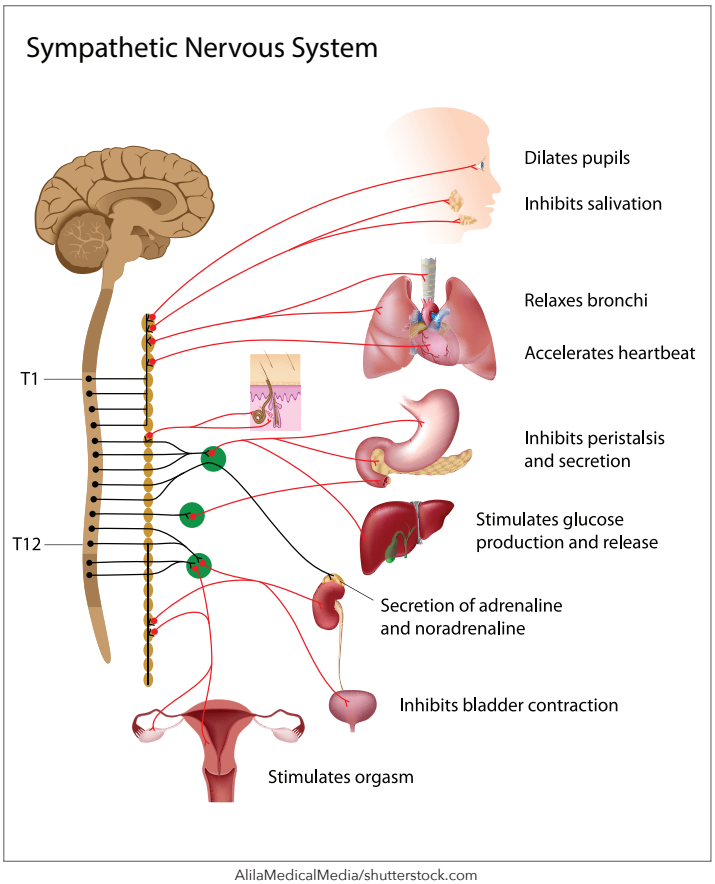
The SNS works quickly to respond to emergency and stressful conditions by increasing the heart rate, blood pressure, sweating, and other involuntary activities.

The preganglionic sympathetic neurons arise from the cell bodies of the intermediolateral horn of the spinal cord through the thoracolumbar outflow (T1–L3). Acetylcholine (Ach) released from these fibers activates nicotinic receptors in the autonomic ganglia. The autonomic ganglia are located far from the target organs. The postganglionic neurons communicate using norepinephrine (NE), except the postganglionic fibers that use Ach to innervate the sweat glands.

Features of the Parasympathetic Nervous System (PNS)

The PNS works to reverse the function of the SNS and restore the body to its original resting state.

The Preganglionic fibers arise from cranial nerve (CN) nuclei, including CN III (the oculomotor nerve), CN VII (the facial nerve), CN IX (the glossopharyngeal nerve), CN X (the vagus nerve), and from sacral segments of the spinal cord (S2–S4). These fibers release Ach which activates nicotinic receptors in the autonomic ganglia. The autonomic ganglia are located near or within the target organs. The post ganglionic fibers communicate using Ach.



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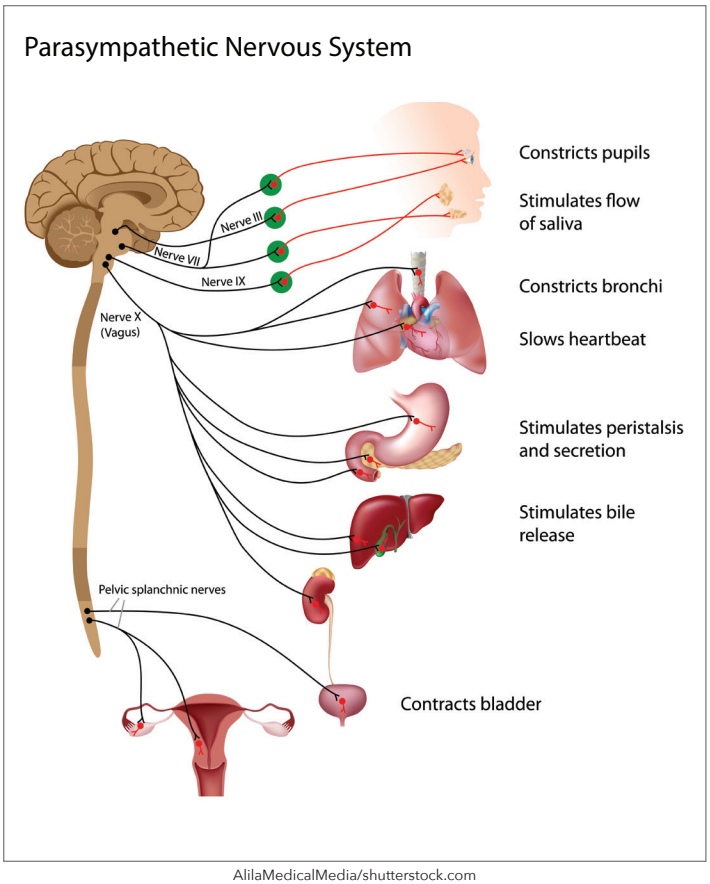

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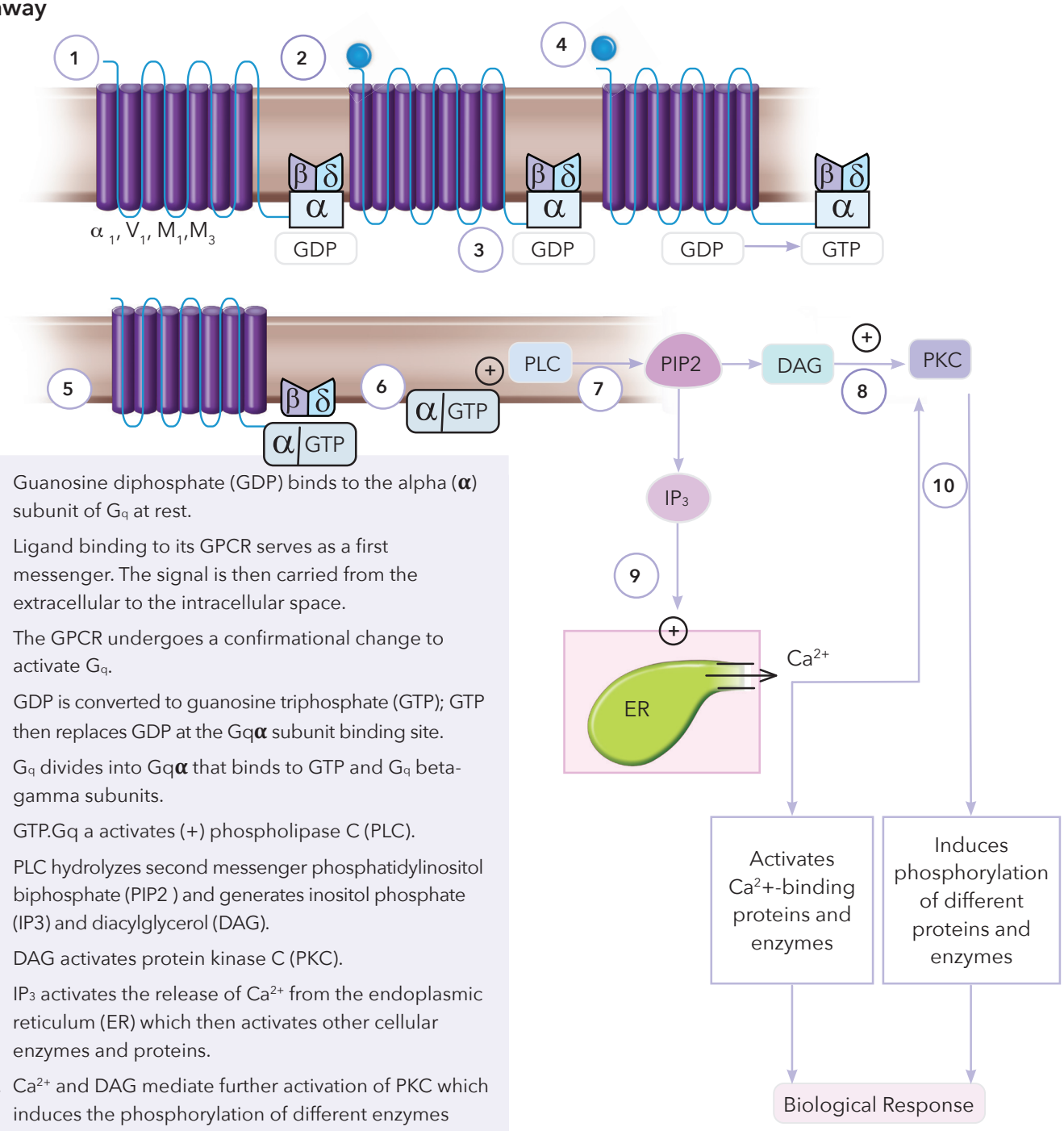
Signaling Molecules and Receptor-Mediated Interactions

A signaling molecule is a ligand that binds to a specific extracellular site on its receptor. Receptors are proteins that transmit signals from the cell membrane into the cytoplasm via their capacity to activate various intracellular pathways to achieve specific physiological responses.

G-protein coupled receptors (GPCRs) have seven transmembrane regions with G proteins coupled to intracellular sites.

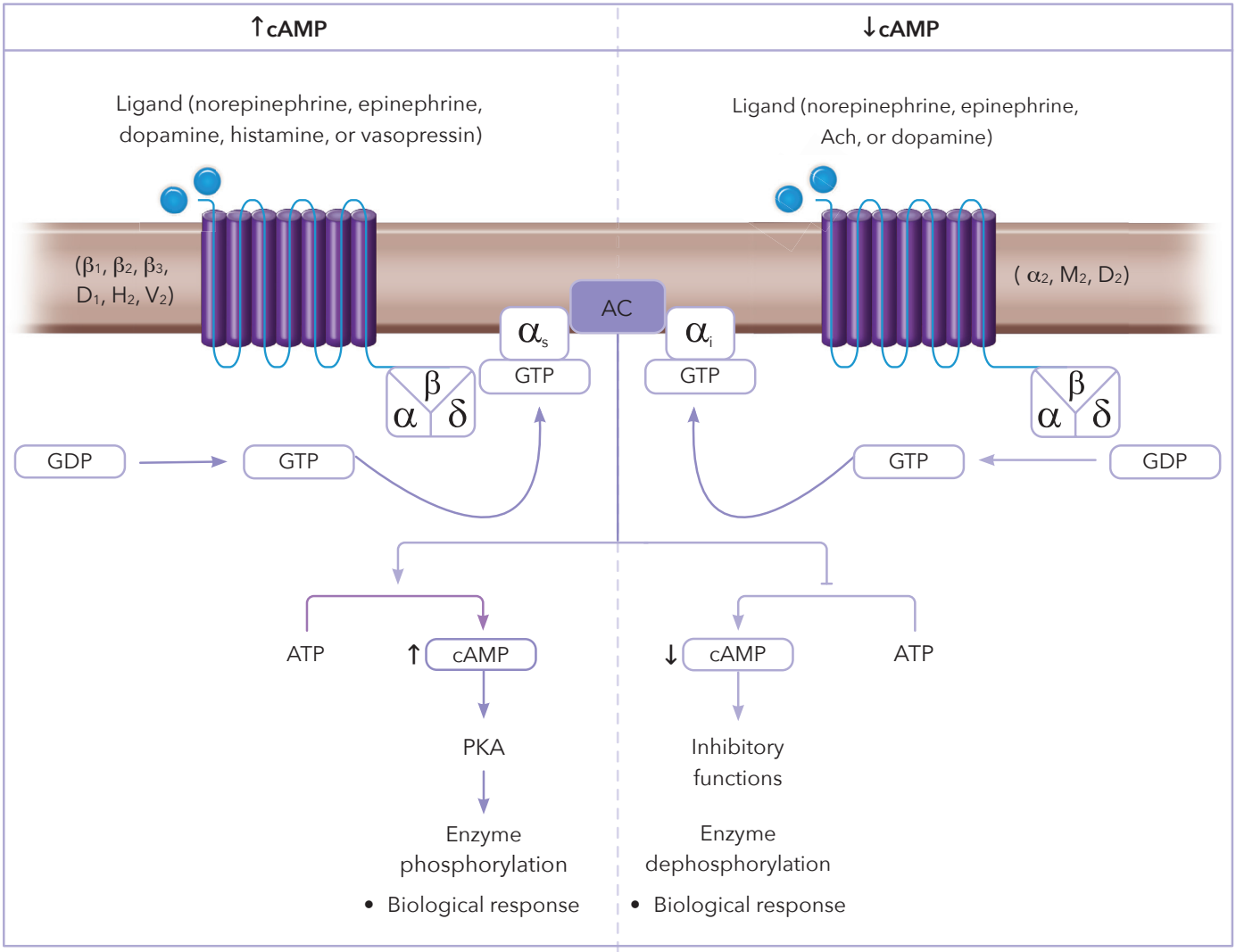
GPCRs can transmit signals that activate the phosphatidylinositol and cyclic AMP pathways.

The Phosphatidylinositol Pathway



1. Guanosine diphosphate (GDP) binds to the alpha (**α**) subunit of G_q at rest.
2. Ligand binding to its GPCR serves as a first messenger. The signal is then carried from the extracellular to the intracellular space.
3. The GPCR undergoes a confirmational change to activate G_q.
4. GDP is converted to guanosine triphosphate (GTP); GTP then replaces GDP at the Gq**α** subunit binding site.
5. G_q divides into Gq**α** that binds to GTP and G_q beta-gamma subunits.
6. GTP.Gq a activates (+) phospholipase C (PLC).
7. PLC hydrolyzes second messenger phosphatidylinositol biphosphate (PIP2) and generates inositol phosphate (IP3) and diacylglycerol (DAG).
8. DAG activates protein kinase C (PKC).
9. IP_3 activates the release of Ca^{2+} from the endoplasmic reticulum (ER) which then activates other cellular enzymes and proteins.
10. Ca^{2+} and DAG mediate further activation of PKC which induces the phosphorylation of different enzymes leading to specific biological responses.

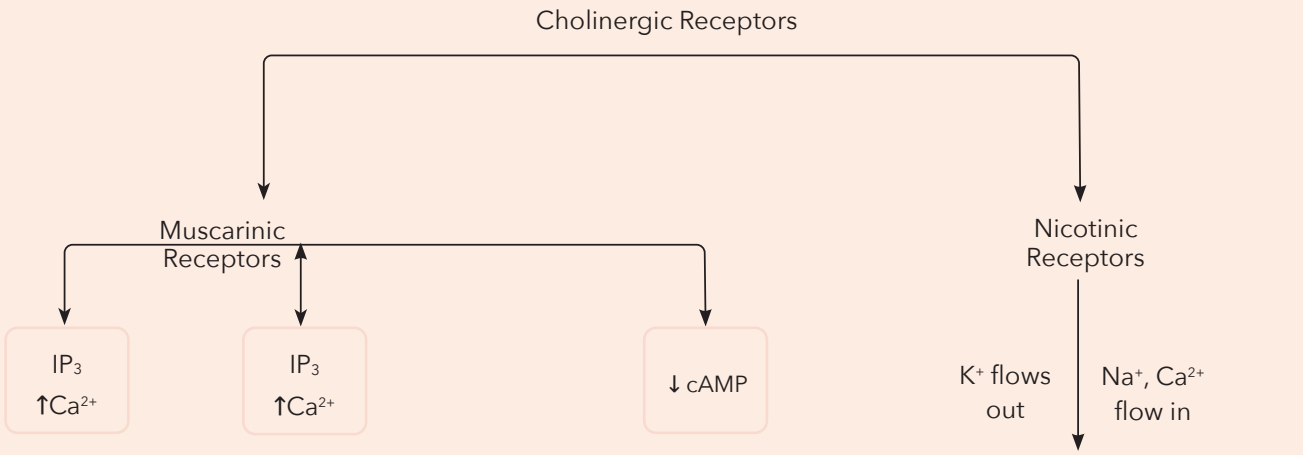
The Cyclic Adenosine Monophosphate (cAMP) Pathway



- Ligand (first messenger) binds to its GPCR.
- Conformational changes of the GPCR lead to the activation of the G protein, G_s.
- GDP is converted into GTP; GTP binds to the **α** subunit of G_s.
- Gs uncouples from the GPCR and is converted into G_s**α** and G_s beta-gamma subunits.
- GTP.G_s**α** activates adenylate cyclase (AC).
- AC converts ATP into cAMP (second messenger) which activates protein kinase A (PKA).
- PKA phosphorylates various enzymes and other proteins to induce a specific biological response.

- Ligand (first messenger) binds to its GPCR.
- Conformational changes of the GPCR lead to the activation of the G protein, G_i.
- GDP is converted into GTP; GTP binds to the **α** subunit of G_i.
- G_i uncouples from the GPCR and is converted into G_i**α** subunits and G_i beta-gamma subunit.
- GTP.G_i inhibits the activity of adenylate cyclase (AC).
- ATP will not undergo conversion to cAMP and PKA will not be activated.
- Various enzymes and proteins will become dephosphorylated which will result in a different biological response.

Cholinergic Receptors: Types, Locations, and Functions



M_1

CNS

Memory
Excitation

Parietal cells and glands

↑ secretion

M_3

Exocrine glands

Increased secretion from thermoregulatory sweat glands via the activation of sympathetic neurons

Endothelial cells

↑ Nitric oxide-mediated vascular smooth muscle relaxation

Sphincters relaxation

M_2

Heart

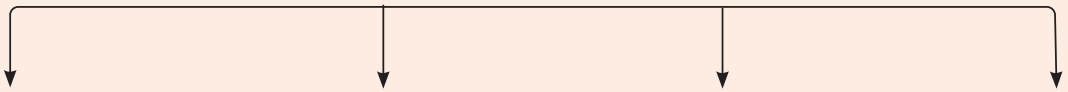
↓ Heart rate
↓ AV nodal conduction velocity

Nicotinic receptors are located in:

- Neuromuscular junctions (NMJs)
- Autonomic ganglia at the synapses between preganglionic and postganglionic neurons
- Adrenal medulla

Stimulation of nicotinic receptors on skeletal muscles leads to an increased inflow of Na^+ and Ca^{2+} ions. The rate of inflow exceeds the rate of K^+ outflow, resulting in cell depolarization and increased muscle contraction.

M_3 receptors found on smooth muscle cells



Eyes

Sphincter muscle contraction (miosis)

Ciliary muscle contraction and accommodation for near vision

Bronchioles

Bronchoconstriction

Gastrointestinal

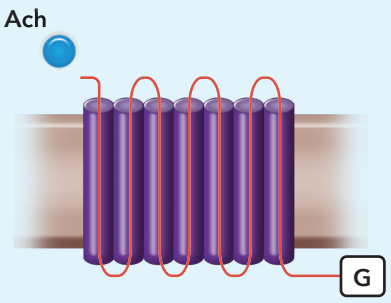
Smooth muscle contraction and sphincter relaxation
↑ motility
diarrhea

Bladder

Detrusor muscle contraction and sphincter relaxation
↑ urination, urinary incontinence

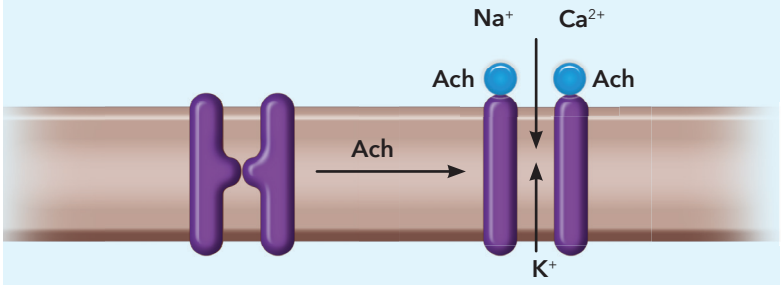
Molecular Anatomy of the Cholinergic Receptors

Muscarinic Receptors



- Muscarinic receptors are GPCRs transmembrane receptors with seven segments that pass through the cell membrane.
- Ach binds to an extracellular site.
- A G protein is linked to an intracellular site.
- Signal can be transduced by IP_3, DAG, Ca^{2+}, or cAMP pathways.
- No ion flow is involved.

Nicotinic Receptors



- Nicotinic receptors are transmembrane proteins composed of two alpha, one beta, one gamma, and one delta subunit. These five subunits create a ligand-responsive ion channel.
- The channel opens when two Ach molecules bind to specific sites on the alpha subunits.
- The net inflow of Na+ and Ca^{2+} ions exceeds the net K^+outflow. The ions diffuse down their respective electrochemical gradients, resulting in membrane depolarization.

Medical Case

A 65-year-old man who is a smoker with a long history of chronic obstructive pulmonary disease (COPD) presented to the emergency department with a three-day history of shortness of breath and increasing cough that was productive of sputum. He was diagnosed with a COPD exacerbation. The patient was treated with ipratropium bromide to relieve his symptoms. Which receptor-mediated pathway responses were involved in the response to this drug?

A. Inhibition of cAMP
B. Activation of IP_3/Ca^{2+}
C. inhibition of IP_3/Ca^{2+}
D. Activation of cAMP

- Answer: C

Adrenergic Receptors

Alpha$_1$ Receptors

Activate biological responses via IP_3, DAG, and Ca^{2+}.

Locations	Actions	Agonist (stimulatory)	Antagonist (blocking)
Eyes radial pupillary muscle	Dilation (mydriasis)		
Vascular smooth muscle of skin, skeletal muscles and abdominal vessels	Vasoconstriction ↑ Blood pressure	Phenylephrine Used to treat nasal congestion	Prazosin (α_1 blocker) that ↓ blood pressure slightly
Bladder sphincter Penis Gastrointestinal tract	Contracts internal urethral sphincter (urinary retention) ejaculation ↓ peristalsis sphincter contraction		Tamsulosin dilates the internal urethral sphincter and thus can be used to treat benign prostatic hypertrophy

Alpha$_2$ Receptors

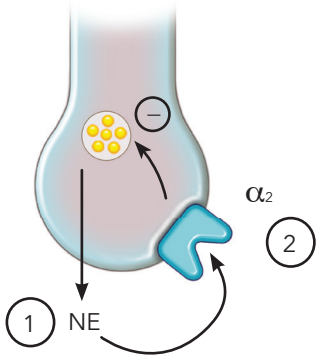
α_2 receptors transmit signals via G_i proteins and thus inhibit AC. Receptor activation results in ↓ cAMP. No second messengers are involved.

Molecular Functions

NE release from nerve terminals.
NE binds to **α_2** receptors in presynaptic membranes.
Stimulation of **α_2** receptors inhibits NE release secondary to negative feedback.

Locations

Presynaptic regions of adrenergic neurons.
Central nervous system (CNS) in locus coeruleus (sedation).
Dorsal horn of spinal cord (pain modification).
Pancreas (↓ insulin release).
Platelets (↑ aggregation).



Medications that stimulate α_2 receptors

1. Clonidine – used to treat hypertension.
2. Tizanidine – used as muscle relaxant.
3. Dexmedetomidine – used to promote sedation.

Medical Case

A 45-year-old man with a long history of excessive alcohol intake presents to the hospital with severe agitation, confusion, hallucinations, and general shakiness. His symptoms began two days after ceasing alcohol use. He was admitted to the intensive care unit and sedated with dexmedetomidine. Which receptor-mediated pathway is engaged by this drug?

A. Adrenergic receptor activation leading to decreased cAMP levels.
B. Adrenergic receptor activation leading to increased cAMP levels.
C. Muscarinic M2 receptor decreasing cAMP
D. Muscarinic M1 receptor increasing IP3/Ca

- Answer: A

Beta (β) Receptors

β_1 Receptors

These are stimulatory receptors, they work through the G protein and cAMP pathway.

Locations	Actions	Agonists	Blockers
Sinoatrial (SA) node	↑ Firing rate ↑ HR	Dobutamine is a positive inotrope used in cardiogenic shock to increase cardiac contractility.	Metoprolol and propranolol are beta blockers used to treat tachycardia and improve survival in patients with heart failure and coronary artery disease.
Atrioventricular (AV) node	↑ Conduction velocity from atria to ventricles		
Ventricles	↑ Contractility → ↑ Stroke volume (SV)		

Kidney: Juxtaglomerular cells ⟶ ↑ Renin release

β_2 Receptors

These are stimulatory receptors present in various smooth muscles that transmit signals via cAMP.

Locations and Functions

Vascular smooth muscles of skeletal muscles: peripheral vasodilation

Bronchioles: bronchodilation
Bronchodilators include albuterol and salmeterol.
These medications are used to treat asthma and chronic bronchitis.

Pancreas: ↑ Insulin release.
Gastrointestinal tract: relaxation.

Uterus: ↓ uterine contraction.
Ritodrine and terbutaline are β_2 agonists that can be used during delivery to prolong pregnancy.
Bladder: detrusor muscle relaxation.

Eye: ciliary muscle dilation and accommodation for far vision
Increased production of aqueous humor.

Medical Case

A 60-year-old man with a history of coronary artery disease and hypertension presents with sudden onset of atrial fibrillation and a heart rate of 130 beats per minute (bpm). How can you slow down his heart rate (HR)?

A. β_1 agonist agent
B. β_2 agonist agent
C. β_3 stimulation
D. β_1 blocker agent

Autonomic Control of the Urinary Bladder

The autonomic and somatic nervous systems play specific roles in maintaining bladder function. Bladder function includes both filling and emptying phases.

Filling phase

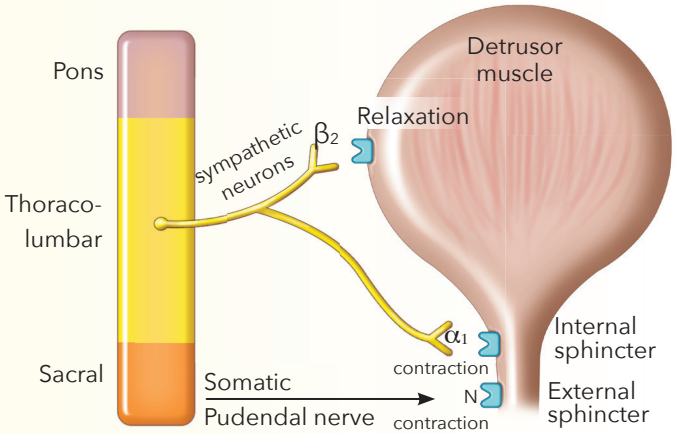
Bladder filling is achieved by the actions of both sympathetic stimulation and somatic neurons.

Sympathetic nerve stimulation induces:

- Detrusor muscle relaxation through β_2 receptors which inhibits bladder contraction.
- Internal sphincter contraction through an α_1 effect which prevents urinary leak.

The results of somatic stimulation include:

- Activation of alpha-motor neurons to contract the external sphincter voluntary through nicotinic (N) receptor stimulation.



Emptying phase (micturition reflex)

The sequence of events begins with stretching of the mechanoreceptors when the bladder is full which stimulates the afferent sensory pelvic nerve. The impulse is then transferred from the spinal cord to the micturition center in the pons to inhibit sympathetic outflow and stimulate the parasympathetic outflow.

Emptying phase is achieved by the actions of both Parasympathetic stimulation and somatic neurons:

- Parasympathetic outflow act on muscarinic M_1 receptors to stimulate detrusor muscle contraction and internal sphincter relaxation.
- Somatic stimulation relaxes the external sphincter.