# Physiology Exam 1 — Study Packet, Rewritten

## Section 1: Cell and Muscle Physiology

**PHYM 1010 — Mammalian Physiology, Fall 2026, New York Medical College**

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# Why This Version Exists

The first pass of this packet followed the lecture structure directly. On review, that source material had real problems: the professors split membrane transport awkwardly across two lectures and re-taught the same basics twice, several receptor tables and answer keys contradict either the assigned textbook or the notes' own figures, and a number of explanations are wordy without being precise. None of that is a reason to avoid the material — it's what's on the exam — but it's worth fixing before you memorize it.

This version is reorganized by concept instead of by lecture number, corrects every verified error found in the source material (each correction is stated explicitly, not just silently fixed), and is written at graduate level throughout — no simplification for its own sake. It draws on Costanzo and Berne & Levy where they explain something more clearly or with a better clinical example than the lecture notes did, and it leans hard on your EMT background: real prehospital drugs and scenarios are used as worked examples wherever the mechanism actually supports it, set apart in their own boxes so they never blur into the core material. A few memory hooks (mnemonics, wordplay, one pop-culture analogy) are included the same way — clearly marked as "on the side," never mixed into the graduate-level explanation itself.

**The six modules**, reorganized:

| # | Module | Corresponds to |
|---|---|---|
| 1 | Cells, Tissues & Homeostasis | S1.1 (minus transport) |
| 2 | Membrane Transport & Electrochemistry | S1.1 (transport) + S1.2, merged into one pass |
| 3 | Excitable Membranes & Action Potentials | S1.3 |
| 4 | Synaptic Transmission & the Neuromuscular Junction | S1.4 |
| 5 | The Autonomic Nervous System | S1.5 |
| 6 | Skeletal Muscle Mechanics | S1.6 |

# How to Use This Packet

Each module has a real illustration for its most important concepts (AI-generated, built from your source material's own facts — not copied from any textbook), plus a **"Draw it" box** for every major concept, including some that don't have a reference figure. Sketch it yourself before checking the illustration; that's the part that actually builds recall, the picture is just the answer key.

Watch for two box types as you read: **field notes** ( 🚑 ) tie a concept to a real prehospital drug or scenario — read these for the "why this matters" hook, not as pharmacology to memorize beyond what's already asked. **Memory hooks** ( 🧠 ) are mnemonics and analogies, kept deliberately separate from the graduate-level explanation around them.

Case studies and the full practice test from the original packet are unchanged in the appendix — that material was already well-written and clinically framed, and didn't need a rewrite.

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# Module 1 — Cells, Tissues & Homeostasis

## What "physiology" actually means, and why hierarchy matters

Physiology is the study of function — not what structures look like (that's anatomy/histology) but what they *do*, and how doing it keeps an organism alive. For mammals, that means: how does a 37°C bag of mostly water, running on a couple thousand kilocalories a day, hold its internal conditions inside a survivable range while the outside world does whatever it wants?

The body is organized as a strict hierarchy: **cells → tissues → organs → systems → organism.** This isn't just an org chart — each level's function is *built from* the level below it. A cell's histological classification (its size and shape) is a direct clue to its job: a flattened squamous cell is built for fast diffusion across a thin barrier, a long excitable muscle cell is built to conduct a signal and shorten. Tissue function is the aggregate behavior of the cells composing it, and organ function is the aggregate behavior of its component tissues. This matters practically: when something goes wrong at the organ level (say, kidney failure), the physiological explanation is almost always traceable to a specific cell-level defect (a transporter, a channel, a receptor) rather than the organ failing as an undifferentiated blob.

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

✎ **Draw it — structural hierarchy ladder**

The four tissue types, briefly, since this part of the source material is solid and doesn't need reworking: **epithelium** (polarized sheets covering surfaces and lining cavities — one free surface, one surface anchored to a basement membrane, built for unidirectional transport and barrier function), **connective tissue** (the most abundant and varied type — binds, supports, and protects; includes bone, cartilage, and adipose), **muscle** (long, specialized cells built to actively shorten — striated skeletal and cardiac vs. smooth), and **nervous tissue** (neurons for polarized, rapid, one-directional signal propagation, plus neuroglia acting as the nervous system's own connective-tissue-like support cells).

> 🧠 **Memory hook**
>
> *think of the four tissue types as a superhero team with fixed roles — Epithelium is the Wall (the barrier/shield that separates inside from outside), Connective Tissue is the Support Crew (holds everyone and everything together), Muscle is the Hulk (raw contractile force), and Nervous tissue is the team's own JARVIS — the fast, wired-in communication system relaying signals everywhere at once.*

✎ **Draw it — four tissue types, one-line function each**

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## Homeostasis: what it actually claims, and what regulates it

**Homeostasis** is the maintenance of a relatively constant *internal* environment despite a variable *external* one. The precise version of that idea, stripped of filler: the body doesn't hold every internal variable at a fixed point because the outside world is calm — it holds them constant *because* control systems are actively working against a constantly changing

outside world. That's the entire concept in one sentence; if a definition of homeostasis doesn't mention "despite change," it hasn't said anything.

Homeostatic variables are regulated by two categories of control:

- **Intrinsic controls** — regulatory mechanisms built into the organ or tissue itself (e.g., a blood vessel's own smooth muscle responding directly to local stretch or local metabolite buildup, independent of any nerve or hormone).
- **Extrinsic controls** — mechanisms that originate outside the organ, almost always neural or endocrine.

> 🚑 **Field note**
>
> this intrinsic/extrinsic split is exactly what you're watching during compensated vs. decompensated shock. Early on, local (intrinsic) autoregulation and the global sympathetic (extrinsic) surge — tachycardia, peripheral vasoconstriction, that thready radial pulse that's still there because the body is shunting flow centrally — are holding blood pressure in range even as volume is dropping. When you finally see the blood pressure fall, the extrinsic compensation has been overwhelmed; the number didn't "start" dropping then, your monitoring just caught up to a failure that was already happening underneath a masked vital sign.

When a homeostatic variable is pushed off its set point, the correcting response is called **feedback**, and it comes in two forms:

- **Negative feedback** — the overwhelmingly dominant mode. The response *opposes* the original disturbance, driving the variable back toward baseline. This is the mechanism of homeostasis itself.
- **Positive feedback** — comparatively rare and, critically, *self-limiting*: the response reinforces the original change in the same direction, and the loop runs until something outside the loop breaks it (delivery of the fetus stops the oxytocin surge of labor; clot formation physically closes off the platelet-aggregation cascade). Positive feedback is not "bad homeostasis" — it's a different tool used precisely when a fast, decisive, one-way push is the correct physiological answer.

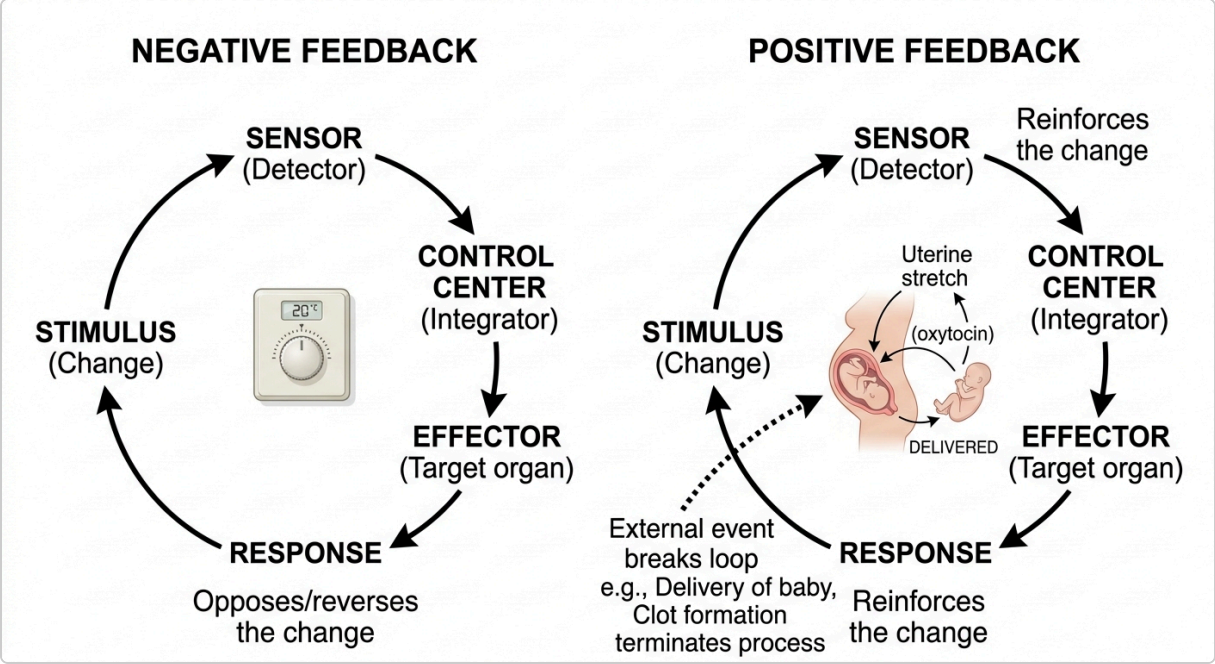
Feedback corrections also differ in speed and precision, and the lecture's own vocabulary for this is worth keeping: **low-gain** corrections are fast (seconds to minutes) but imprecise, and are the signature of neural control; **high-gain** corrections are slow (minutes to days) but accurate, and are the signature of endocrine control. Gain, formally, is the ratio of correction to remaining error — a system with higher gain closes more of the gap.

### 🚑 Field note

a positive feedback loop that fails to get externally interrupted is one useful way to think about a physiological death spiral. In severe hemorrhage, falling blood pressure reduces coronary perfusion, which weakens the heart, which drops cardiac output further, which drops pressure further — each step making the next step worse. Nothing about that loop is self-limiting the way labor or clotting is; it only stops with an outside intervention (fluid, blood product, source control), which is the entire physiological argument for why “permissive hypotension and get to a trauma center” beats waiting to see if the body corrects itself.

### 🧠 Memory hook

*negative feedback is a thermostat — heat rises, the AC kicks on, the room cools, the AC shuts off; it always pushes back the other way. Positive feedback is microphone feedback squeal — a little noise gets picked up by the mic, amplified through the speaker, picked up again louder, amplified again — the loop reinforces itself in the same direction until someone (an outside force) cuts the gain or unplugs it.*




Negative vs. positive feedback loops — *AI-generated illustration; verify against your own notes/slides.*

✎ **Draw it — negative vs. positive feedback loop pair**

A homeostatic variable is not "special" because it has a physiological system uniquely built for it (many variables share overlapping systems), and it is not held constant by accident — it's characterized by having a real, defended set point *and*, typically, multiple redundant systems working in parallel to keep it in range (neural, endocrine, renal, cardiovascular, and pulmonary systems frequently all have a hand in the same variable). That redundancy is a feature: it's why losing one regulatory system rarely causes immediate collapse of a variable — other systems partially cover for it, at least for a while.

Representative homeostatic variables and normal reference points:

| Variable | Normal value |
|---|---|
| Blood pH | ≈ 7.4 |
| Plasma osmolality | ≈ 290 mOsm |
| Core temperature | ≈ 37°C (98.6°F) |
| Arterial $pO_2$ | ≈ 100 mmHg |
| Arterial $pCO_2$ | ≈ 40 mmHg |
| Hematocrit | ≈ 42% |
| Mean arterial pressure | ≈ 100 mmHg |
| Extracellular $Na^+$ | ≈ 140 mM |
| Extracellular $K^+$ | ≈ 4 mM |
| Extracellular $Cl^-$ | ≈ 100 mM |

| Variable | Normal value |
|---|---|
| Extracellular $HCO_3^-$ | ≈ 24 mM |

Two corrections worth flagging explicitly, not just filed away in the table: fasting blood glucose is conventionally cited around 70–99 mg/dL (ADA "normal"), not a flat 120 mg/dL — the lecture material's number is more consistent with a postprandial or borderline-impaired reading than a fasting set point, and the two shouldn't be quoted interchangeably. And while urea and creatinine (common "waste products" listed alongside these) do sit at trended baseline concentrations clinicians monitor directly, free ammonia is a different case — it's not "held at a normal level" the way urea is, it's actively suppressed toward zero (via the urea cycle) because even modest elevations are neurotoxic. Grouping ammonia with urea/creatinine as parallel "homeostatic waste variables" overstates how comparable they are.

**Field note**

nearly every one of these "homeostatic variables" is a vital sign or a point-of-care number you already read off a monitor or a strip — pulse ox estimates the $pO_2$/hemoglobin saturation side of gas exchange, capnography trends $pCO_2$, a temporal or tympanic probe gives you core temp, a cuff or arterial line gives you MAP, and a glucometer gives you blood glucose directly. Trending a vital sign in the field is, mechanistically, watching a control system's gain in real time — a heart rate that's climbing despite your fluid bolus is telling you the compensatory (extrinsic, low-gain) response is losing ground, not that the vital sign itself is the problem.

**✎ Draw it — homeostatic variables table with values**

## Fluid compartments: ICF, ECF, and where blood actually fits

Water is roughly 60% of adult body weight (higher in infants, ~75%, falling to the adult value by about age one; lower in people with more adipose tissue, because fat holds less water than lean tissue does — fat content is the main driver of individual variation in %body water, not age alone once past infancy). That total body water splits, unevenly, into two compartments:

- **Intracellular fluid (ICF)** — all fluid inside all cells of the body. This is the larger share, roughly two-thirds of total body water. ICF is rich in $K^+$, $Mg^{2+}$, and phosphate ($HPO_4^{2-}$/$PO_4^{3-}$ — note the correct ion is phosphate, $PO_4^{3-}$, not the "$PO_3^{4-}$" that sometimes appears in course notes) as its major ions, plus intracellular proteins.
- **Extracellular fluid (ECF)** — everything outside cells, roughly one-third of total body water. ECF itself has two subcompartments: **interstitial fluid** (bathing cells directly, essentially an ultrafiltrate of plasma) and **plasma** (the fluid that stays inside blood vessels). ECF is dominated by $Na^+$, $Cl^-$, and $HCO_3^-$.

The distinction the source material blurs is worth stating precisely, because it's tested exactly where it's blurry: **plasma is not the same thing as whole blood, and "suspended in plasma" is not the right description for everything blood contains.** Whole blood = plasma + formed elements (red cells, white cells, platelets). Within plasma, proteins (albumin, globulins, clotting factors) are *dissolved solutes* — they're part of the ECF composition and they're largely excluded from interstitial fluid because the capillary wall is nearly impermeable to a molecule that size (which is exactly why plasma protein, not interstitial protein, is what generates oncotic pressure). Red blood cells, by contrast, are not an ECF solute at all — a red cell is a cell, its interior is a small parcel of ICF, and it happens to be carried *within* the plasma rather than dissolved *in* it. Calling proteins and RBCs both "suspended in plasma" erases that distinction at the exact point it needs to be sharp.

> **🚑 Field note**
>
> this is the whole reason crystalloid (normal saline, lactated Ringer's) is not a blood substitute. Crystalloid replaces ECF volume — it distributes across plasma and interstitium — but it carries no red cells and no clotting factors, so it can restore blood pressure without restoring oxygen-carrying capacity or coagulation. That's the physiological basis for damage-control resuscitation moving away from large-volume crystalloid toward earlier blood product administration in hemorrhagic shock: you're not just replacing "fluid," you're trying to replace the actual compartments and components that were lost.

> **🚑 Field note**
>
> the ICF/ECF potassium gradient (roughly 140 mM inside cells vs. 4 mM in ECF) is also the mechanism behind crush syndrome and reperfusion hyperkalemia. A crushed or ischemic limb has cells leaking their ICF contents; as long as circulation to that limb stays occluded, that potassium stays local. The moment a prolonged tourniquet or heavy entrapment is released and circulation resumes, that ICF potassium load washes back into the systemic ECF all at once, and a patient who looked stable on extrication can go into a lethal arrhythmia within minutes — which is why crush syndrome protocols emphasize fluids, and in some systems empiric treatment for hyperkalemia, *before* release of a long entrapment, not after.

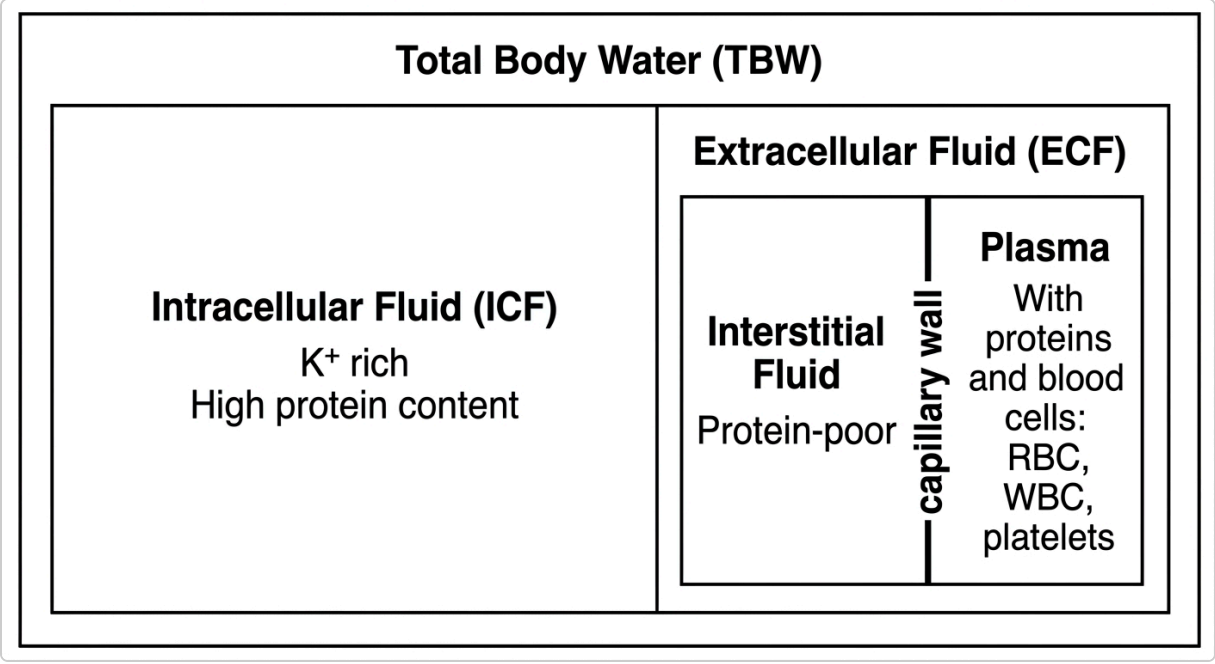
> **🧠 Memory hook**
>
> *picture the cell membrane as a castle wall. Sodium is the army camped outside the walls (high $Na^+$ in ECF — think of blood plasma as being almost as salty as seawater). Potassium is the king kept safely guarded inside the castle (high $K^+$ in ICF). Anything that breaches the wall — trauma, cell lysis, a ruptured membrane — lets the king's guard ($K^+$) spill out where it doesn't belong.*

Approximate concentrations worth anchoring (in mM or mEq/L):

| Ion | ECF | ICF |
|---|---|---|
| $Na^+$ | 140 | 15 |
| $K^+$ | 5 | 120 |
| $Cl^-$ | 100 | 20 |
| $HCO_3^-$ | 24 | 10 |

ICF proteins and organic phosphates (not shown in the table — they don't have a single standard concentration figure) provide most of the intracellular anion charge that $Cl^-$ and $HCO_3^-$ provide extracellularly. One more precise point Costanzo makes that the lecture notes gloss over: despite these individual solute concentrations being wildly different between ICF and ECF, the *total* solute concentration — osmolality — is essentially identical in both compartments (≈290 mOsm/L), because water moves freely across cell membranes and equalizes it within seconds of any transient difference. If you ever see an exam question implying ICF and ECF have different total osmolality at steady state, that premise is wrong.

> **Field note**
>
> this osmolality-equality principle is exactly why a large free-water deficit or excess shows up first as a *sodium* number on a chem panel, not as two different compartments visibly out of balance — and it's the mechanism behind conditions like SIADH-driven hyponatremia, where excess water reabsorption dilutes ECF $Na^+$ and drags water into cells (including brain cells) to re-equalize osmolality, causing cerebral edema. It's also why the field/ED treatment for that specific picture is hypertonic saline rather than more isotonic fluid — you're deliberately raising ECF osmolality back toward normal, not just adding volume.




Body fluid compartments — *AI-generated illustration; verify against your own notes/slides.*

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

✎ **Draw it — nested fluid compartment diagram, ICF/ECF/interstitial/plasma, with the ion table alongside**

## A note on how this section is organized

S1.1's "Transport" section and S1.2 ("Ions and Membranes") were taught as two separate lectures, but they cover the same ground twice before S1.2 finally adds anything new: both re-establish that membranes separate compartments with different ionic compositions, both re-explain that ions cross membranes via channels and carriers, and both print near-duplicate (and, on closer inspection, not-quite-matching) ion concentration tables. What follows is that material taught once. Part 1 covers every general transport mechanism a membrane has — the vocabulary and machinery. Part 2 then asks the quantitative question those mechanisms set up: given a concentration gradient and a membrane's permeability to it, how many millivolts is that gradient actually worth? Everything in Part 2 assumes Part 1 and will say so explicitly rather than re-teaching it.

One correction up front, because it's load-bearing for everything downstream: the $Na^+/K^+$-ATPase pump moves **3 $Na^+$ out of the cell for every 2 $K^+$ pumped in**, not 3-for-1. The lecture notes state 1 $K^+$, which is incorrect — a 1-for-1 ratio (3 out, 3 in, net charge zero) would make the pump electrically silent, when in fact the 3:2 mismatch is exactly what makes it electrogenic. That correction is used, correctly, throughout the active transport section below.

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# Module 2A — Membrane Transport & Electrochemistry: General Transport Mechanisms

## Simple diffusion: the default, and its limits

Simple diffusion is what happens when nothing stops a molecule from moving down its concentration gradient — no protein intermediary, no energy input, just random thermal motion producing net movement from high to low concentration until the gradient is gone. It's bidirectional by nature (a molecule crosses whichever way its local gradient points), and its rate depends on the concentration gradient, the membrane's surface area, its thickness, and — critically — the *lipid solubility* (partition coefficient) of the molecule in question, since the phospholipid bilayer is a hydrophobic barrier. This is why the list of things that diffuse simply is short and specific: respiratory gases ($O_2$, $CO_2$, $N_2$) and small uncharged lipophilic molecules (ethanol, steroid hormones). Everything else — anything charged, anything polar, anything larger than a handful of atoms — needs help.

## Facilitated diffusion: carriers vs. channels

Facilitated diffusion is still passive (still downhill, still no ATP) but requires a membrane protein to get a charged or bulky solute across. There are two structurally and mechanistically distinct ways this happens, and the distinction matters because it resurfaces constantly later in the course (renal transport, GI absorption, everywhere):

**Channels** are pore-forming proteins — essentially a hole through the membrane. When open, they provide a continuous aqueous path, and ions flow through by simple electrodiffusion at very high rates. A channel doesn't change shape to move its cargo; it just is or isn't open.

**Carriers** work by binding their solute, then undergoing a conformational change that physically relocates the binding site (and the solute with it) to the other side of the membrane. Because a carrier has to complete that whole cycle for one cargo molecule to cross, carriers move solutes far more slowly than channels — but they can also transport ATP-dependently (see Part 1's active transport section) which channels cannot. Carriers are also *saturable*: each carrier protein has a finite number of binding sites, so as solute concentration rises, more binding sites get occupied until every carrier is cycling as fast as it can. Beyond that point, adding more solute doesn't increase transport rate — you've hit the transport maximum, Tm. This is the exact same idea as Vmax in enzyme kinetics (a carrier is, mechanistically, just an enzyme whose "product" is the same molecule on the

other side of the membrane), which is why carrier-mediated transport curves look like Michaelis-Menten curves rather than the straight line of simple diffusion.

> 🚑 **Field note**
>
> The GLUT family of glucose carriers is the textbook facilitated-diffusion example, and it is directly relevant to why you push D50 or D10 IV dextrose on a hypoglycemic patient rather than expecting it to diffuse in on its own — glucose is too large and polar to cross the membrane by simple diffusion, so it depends entirely on GLUT carrier density and saturation kinetics, which is also part of why insulin (which recruits more GLUT4 to the membrane in muscle and fat) matters so much in that picture.

## Gated ion channels: four ways to open a pore

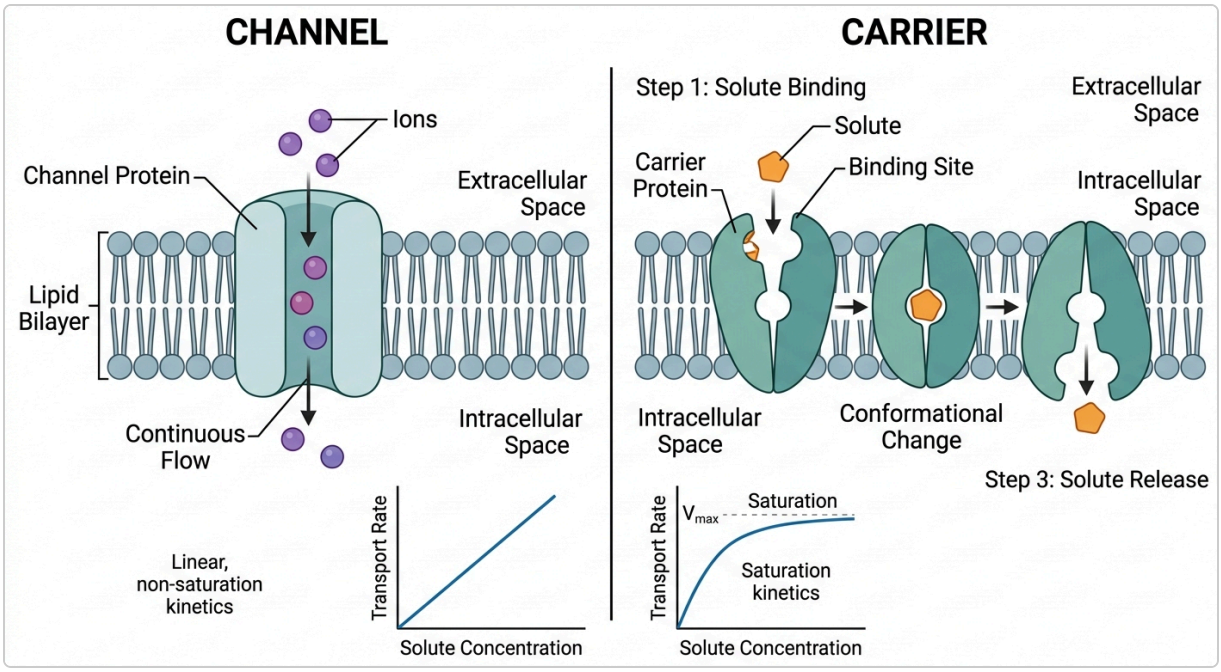
Not all channels are open all the time. A gated channel has a sensor that controls a physical gate, and there are four categories based on what that sensor responds to:

1. **Ligand-gated** — opens when a specific molecule (a neurotransmitter, most classically) binds a receptor site on the channel. The nicotinic ACh receptor at the neuromuscular junction is the canonical example.
2. **Mechanically-gated** — opens in response to physical force/pressure/stretch on the membrane. Relevant to touch receptors and baroreceptors.
3. **Voltage-gated** — opens (or closes) in response to a change in membrane potential. These are the channels that generate the action potential upstroke, and you'll spend the entirety of S1.3 on them.
4. **Leak (non-gated) channels** — no sensor, no gate; open essentially at random/constantly. These set the baseline permeability that establishes the resting membrane potential, which is the whole subject of Part 2.

Some ions move through gated channels via passive facilitated diffusion (the ion just flows down its existing electrochemical gradient once the gate opens); others are moved by channels that are directly coupled to active transport, which is a separate mechanism covered below.

> 🧠 **Memory hook**
>
> *LMVL — think of four different ways to get through a locked door: someone hands you a key (Ligand), you shoulder it open (Mechanical), the power flips and the maglock releases (Voltage), or it was just never locked in the first place (Leak).*

✎ **Draw it — Channels vs. carriers — mechanism and kinetics**




Channel vs. carrier transport — *AI-generated illustration; verify against your own notes/slides.*

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## Osmosis: water follows solute

Osmosis is water crossing a semipermeable membrane along its own gradient — and to state the direction unambiguously (a place the lecture notes leave room for confusion):

water moves toward the compartment with the **higher solute concentration** (equivalently, the compartment with *lower* water concentration/activity), diluting that side until the effective osmotic pressure difference is eliminated or until something (like a rigid cell wall, or in our case the cytoskeleton and membrane tension) opposes it. A solution that would cause no net water movement relative to another is isotonic to it; one that would draw water in is hypertonic; one that would lose water is hypotonic. Note that osmolarity (total dissolved particle concentration) and tonicity (the *effective* osmotic pressure, which depends on how well the membrane actually reflects a given solute) are not the same thing — a solute that crosses the membrane freely doesn't contribute to tonicity even if it raises osmolarity.

> 🚑 **Field note**
>
> Hypertonic saline (3% NaCl) is a real prehospital/ED intervention for suspected cerebral edema or elevated ICP, and it works by exactly this mechanism — driving the effective osmotic gradient so water moves out of swollen brain cells and interstitium into the vasculature. It is also literally the plot mechanism behind the same drug's use in symptomatic hyponatremia: raising serum $Na^+$ pulls water back out of overhydrated cells, which is the same physiology in the opposite clinical direction.

## Filtration: pressure, not concentration

Filtration is bulk movement of water *and* whatever small solutes are dissolved in it, driven by a hydrostatic (mechanical pressure) gradient across a membrane with pores large enough to let both through together — this is fundamentally different from osmosis, which moves only water and is driven by a concentration difference. The reason this deserves more than a one-line mention: filtration across the capillary wall is opposed by the oncotic (colloid osmotic) pressure of plasma proteins that can't cross, and the balance of those two forces (Starling forces) is what determines whether fluid moves into or out of capillary beds. You'll use this explicitly in cardiovascular and renal physiology — worth filing away now rather than re-deriving later.

✎ **Draw it — Osmosis vs. filtration — what moves, and what drives it**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## Active transport: primary

Active transport moves a solute *against* its electrochemical gradient — uphill — which by definition requires energy input, because nothing does uphill work for free. **Primary active transport** couples that uphill movement directly to ATP hydrolysis. The workhorse example, and the one most of the rest of this course depends on, is the **$Na^+/K^+$-ATPase**: per cycle of ATP hydrolysis, it pumps 3 $Na^+$ out of the cell and 2 $K^+$ into the cell, both moving against their own concentration gradients. Because three positive charges leave for every two that enter, each cycle exports one net positive charge — the pump is *electrogenic*, meaning it makes a small direct contribution to making the cell interior more negative, on top of its much larger *indirect* contribution: it's what builds and maintains the steep $Na^+$ and $K^+$ gradients that every other mechanism in Part 2 depends on. Other primary active transporters follow the same logic with different cargo — the $Ca^{2+}$-ATPase (PMCA) that keeps intracellular $Ca^{2+}$ vanishingly low, and the SERCA pump that sequesters $Ca^{2+}$ into the sarcoplasmic reticulum in muscle, both directly relevant when you get to excitation-contraction coupling.

🚑 **Field note**

Digoxin (and the older cardiac glycoside ouabain) works by directly inhibiting the $Na^+/K^+$-ATPase. Block the pump and intracellular $Na^+$ rises, which (via the secondary active transport described next) raises intracellular $Ca^{2+}$ — the intended therapeutic effect in heart failure, since more intracellular $Ca^{2+}$ means stronger contraction. But in digoxin toxicity, the same pump inhibition also lets extracellular $K^+$ rise (less $K^+$ being pumped in) and intracellular $Ca^{2+}$ overload becomes arrhythmogenic — which is exactly why digoxin toxicity classically presents with hyperkalemia and a garden variety of dysrhythmias, and why you'll see it flagged on every cardiac-arrest-reversible-causes card you carry.

## Active transport: secondary

**Secondary active transport** doesn't touch ATP directly — instead, a transporter couples the *downhill* movement of one ion (almost always $Na^+$, occasionally $H^+$) to the *uphill* movement of another solute, spending the energy that was already stored in that ion's electrochemical gradient by the primary active transporter that built it. Two geometries exist: **cotransport (symport)** moves both solutes in the same direction across the membrane (e.g., the $Na^+$/glucose cotransporter, SGLT, which uses the inward $Na^+$ gradient to drag glucose into the cell against its own gradient); **countertransport (exchange/antiport)** moves them in opposite directions (e.g., the $Na^+/H^+$ exchanger). Note that "carrier" and "channel" from Part 1 still apply here — every active transporter, primary or secondary, is a carrier-type protein (binds, changes conformation, releases), never a simple channel, because channels can't do uphill work.

🧠 **Memory hook**

*Sym- means "same" (as in symmetry, symphony) — symport moves both passengers the same direction. Anti- means "against/opposite" — antiport swaps them in opposite directions. And for primary vs. secondary: primary active transport pays its own ATP bill; secondary active transport is riding on a gradient someone else (the $Na^+/K^+$-ATPase) already paid for.*

**🚑 Field note**

Loop diuretics (furosemide) and potassium-sparing diuretics (spironolactone, amiloride) are a clean real-world channel/carrier contrast. Loop diuretics block the $Na^+$-$K^+$-$2Cl^-$ secondary active cotransporter in the thick ascending limb — a carrier. Potassium-sparing diuretics act downstream, either blocking the ENaC sodium *channel* directly (amiloride) or blocking the aldosterone receptor that upregulates it (spironolactone) — which is why the potassium-wasting seen with loop and thiazide diuretics (which increase distal $Na^+$ delivery and drive more $K^+$ secretion through those same ENaC-adjacent $K^+$ channels) doesn't happen with the potassium-sparing class.

**✎ Draw it — Primary vs. secondary active transport — who spends the ATP**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

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# Module 2B — Membrane Transport & Electrochemistry: Putting a Number on the Gradient

Everything above explains *how* something crosses a membrane. Nothing above tells you *how much electrical potential* a given concentration gradient is worth, or *why* the resting cell interior sits at roughly −70 mV rather than 0. That's a quantitative question, and it's the entire point of this half.

## Electrochemical gradients and electroneutrality

An ion crossing a membrane experiences two forces simultaneously: a diffusive force proportional to its concentration gradient (the same force from Part 1), and an electrical force from any potential difference across the membrane, since the ion is charged. Both forces existed all along for uncharged solutes too, but for uncharged molecules only the first one applies — ions are the special case where both matter, and where they can work with or against each other.

A cell's cytoplasm and the fluid outside it are each electrically neutral in bulk — total cation charge equals total anion charge on each side (electroneutrality) — even though the *individual* ion concentrations are wildly different between the two sides. The canonical numbers, worth memorizing once (this replaces the two separate, slightly-mismatched tables you may have seen taught twice):

| Ion | Outside (mM) | Inside (mM) |
|---|---|---|
| $Na^+$ | 140 | 15 |
| $K^+$ | 5 | 120 |
| $Cl^-$ | 100 | 20 |
| $Ca^{2+}$ | 1.5 | 0.0001 |

Inside the cell, the charge balance is completed mostly by impermeant anions — proteins, DNA, organic phosphates — that never cross the membrane at all and so don't figure into any of the transport mechanisms from Part 1.

## Driving force: the concept Part 1 needs to actually predict ion flow

Before the Nernst equation, one more concept, because without it "equilibrium potential" is just a number with no way to use it: for any ion, at any given actual membrane potential Em, the **driving force** on that ion is Em − Eion (its equilibrium potential, defined below). If Em equals Eion, the electrical and chemical forces on that ion are equal and opposite — no net flow, by definition. If Em is more negative than Eion, that's a *net inward* driving force for a cation (it will flow in if the membrane has a pathway open) or net outward for an anion; if Em is more positive than Eion, it's reversed. This is the tool you'll use for the rest of the course to answer "which way does this ion actually move right now," as opposed to "what would this ion's gradient be worth in isolation."

✎ **Draw it — Electroneutrality + the driving force concept**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## The Nernst equation: one ion's equilibrium potential

For a single permeant ion species with a concentration gradient across a membrane, there is exactly one membrane potential at which the electrical force on that ion exactly balances the diffusive force — the point where net flux is zero. That's the ion's **equilibrium potential** (also called Nernst potential or reversal potential), given by the Nernst equation:

$$E_{ion}\,(mV) = \frac{2.303\ RT}{zF} \times \log_{10} \frac{[ion]_{out}}{[ion]_{in}}$$

where z is the ion's valence (a sign-and-magnitude term — this is why anions and cations behave oppositely for the same concentration ratio) and R, T, F are the gas constant, absolute temperature, and Faraday's constant respectively. (If you've seen this written with a 2.23 coefficient instead of 2.303, that's an arithmetic slip — 2.303 is ln(10), the fixed conversion factor from natural log to $\log_{10}$, and it's not optional or approximate.) At normal body temperature, 2.303RT/F works out to about 61 mV, giving the commonly used shortcut:

$$E_{ion}\ (\text{mV}) \approx \frac{61}{z} \times \log_{10} \frac{[\text{ion}]_{out}}{[\text{ion}]_{in}}$$

**Worked example**, using the concentration table above:

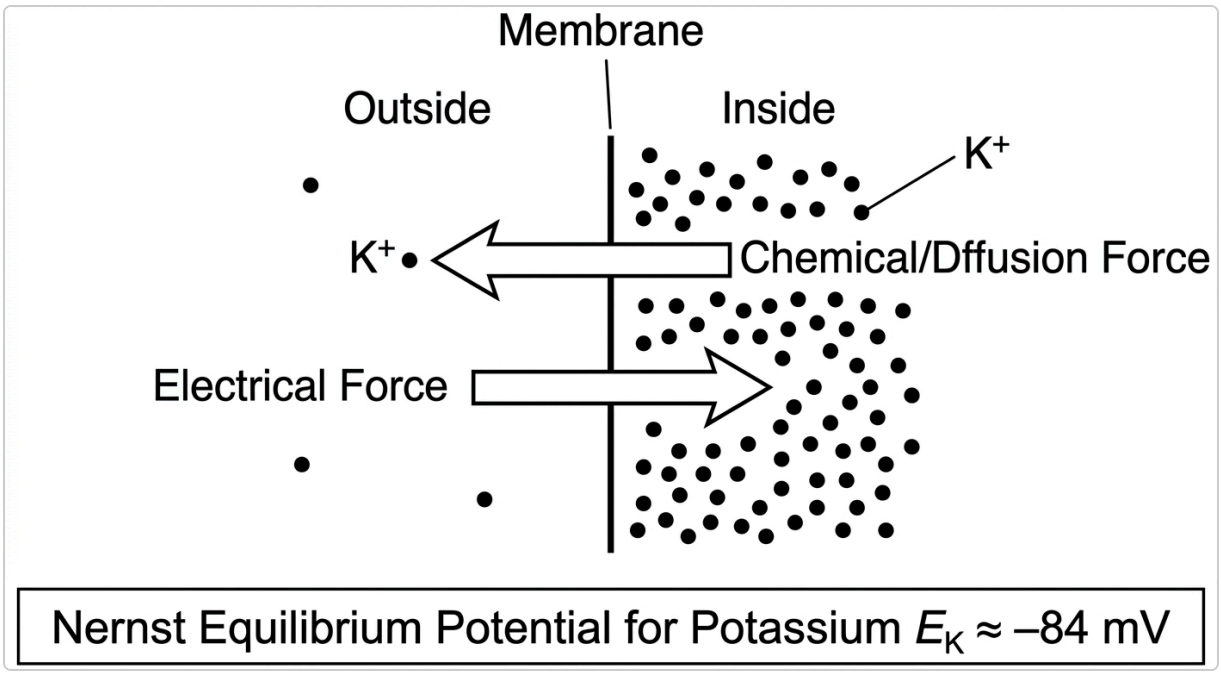
| Ion | z | $[\text{ion}]_{out}$ | $[\text{ion}]_{in}$ | ratio (out/in) | $\log_{10}$(ratio) | $E_{ion}$ |
|---|---|---|---|---|---|---|
| $K^+$ | +1 | 5 | 120 | 0.042 | −1.38 | **−84 mV** |
| $Na^+$ | +1 | 140 | 15 | 9.33 | 0.97 | **+59 mV** |
| $Cl^-$ | −1 | 100 | 20 | 5.00 | 0.70 | **−43 mV** (sign flips for anions) |
| $Ca^{2+}$ | +2 | 1.5 | 0.0001 | 15,000 | 4.18 | **+127 mV** |

The $Ca^{2+}$ result cross-checks closely against Costanzo's own worked example, which uses different absolute concentrations but a similar 15,000-to-20,000-fold ratio and lands at +129 mV — a good sign the *method*, not the specific numbers, is what to trust. Two things worth noticing beyond the table: first, none of these calculations required knowing anything about how permeable the membrane actually is to that ion — permeability plays no role in where equilibrium sits, only in how fast the system gets there and how much that ion actually contributes to the real membrane potential (next section). Second, if you've been taught elsewhere that $E_{Cl^-}$ is closer to −61 mV, that number comes from a different (10-fold, not 5-fold) $Cl^-$ concentration ratio — a reminder to always check which concentration table a quoted equilibrium potential was actually computed from, because "the" Nernst potential for an ion isn't a fixed constant, it's a function of whatever gradient is currently in place.

### 🚑 Field note

This is exactly the mechanism behind why hyperkalemia is immediately dangerous and why calcium chloride is a first-line arrest drug for it. Raising extracellular $K^+$ shrinks the $K^+$ concentration ratio (out/in), which by the Nernst equation makes $E_K$ less negative — the resting potential (driven mostly by $K^+$, see below) drifts up toward threshold, partially inactivating voltage-gated $Na^+$ channels and slowing conduction, which is what produces the peaked T-waves, widened QRS, and eventual sine-wave pattern you're taught to recognize. Calcium chloride doesn't fix the $K^+$ gradient at all — it works by raising the *threshold* potential back away from the now-elevated resting potential, restoring the gap between them (membrane stabilization) without touching $E_K$ itself.

### ✎ Draw it — The Nernst equation and equilibrium potential




Nernst equilibrium for potassium — *AI-generated illustration; verify against your own notes/slides.*

## The Goldman-Hodgkin-Katz (Goldman) equation: when every ion votes, weighted by permeability

Real membranes are permeable to several ions simultaneously, and each one is pulling the membrane potential toward its own individual Nernst potential at the same time. The Goldman equation extends the same logic to that multi-ion case — but instead of a single concentration ratio, each ion's concentration terms get weighted by that ion's relative membrane permeability, P:

$$V_m\ (\text{mV}) = 61 \times \log_{10} \frac{[Na^+]_{out}P_{Na} + [K^+]_{out}P_K + [Cl^-]_{in}P_{Cl}}{[Na^+]_{in}P_{Na} + [K^+]_{in}P_K + [Cl^-]_{out}P_{Cl}}$$

(Notice $Cl^-$'s inside/outside terms are flipped relative to the cations' — that's the anion sign convention built directly into the equation rather than requiring a separate z term.) The key conceptual payoff: an ion with permeability of essentially zero contributes essentially nothing to Vm no matter how large its concentration gradient or how attractive its individual Nernst potential is — permeability, not gradient size, is what buys an ion a vote. At rest, a typical cell's relative permeabilities are roughly $P_K = 1.00$, $P_{Cl} = 0.45$, $P_{Na} = 0.04$, with $P_{Ca}$ effectively negligible. Because $K^+$'s permeability dominates so

heavily, the resting Vm sits close to $E_K$ (≈ −84 mV from above) even though $E_{Na}$ is nearly +60 mV — $Na^+$'s gradient is enormous, but its door is barely open.

**Worked example**, using the permeabilities and concentration table above:

| Term | $Na^+$ | $K^+$ | $Cl^-$ | Sum |
|---|---|---|---|---|
| Numerator (out × P) | 140 × 0.04 = 5.6 | 5 × 1.00 = 5.0 | 20 × 0.45 = 9.0 | **19.6** |
| Denominator (in × P) | 15 × 0.04 = 0.6 | 120 × 1.00 = 120 | 100 × 0.45 = 45 | **165.6** |

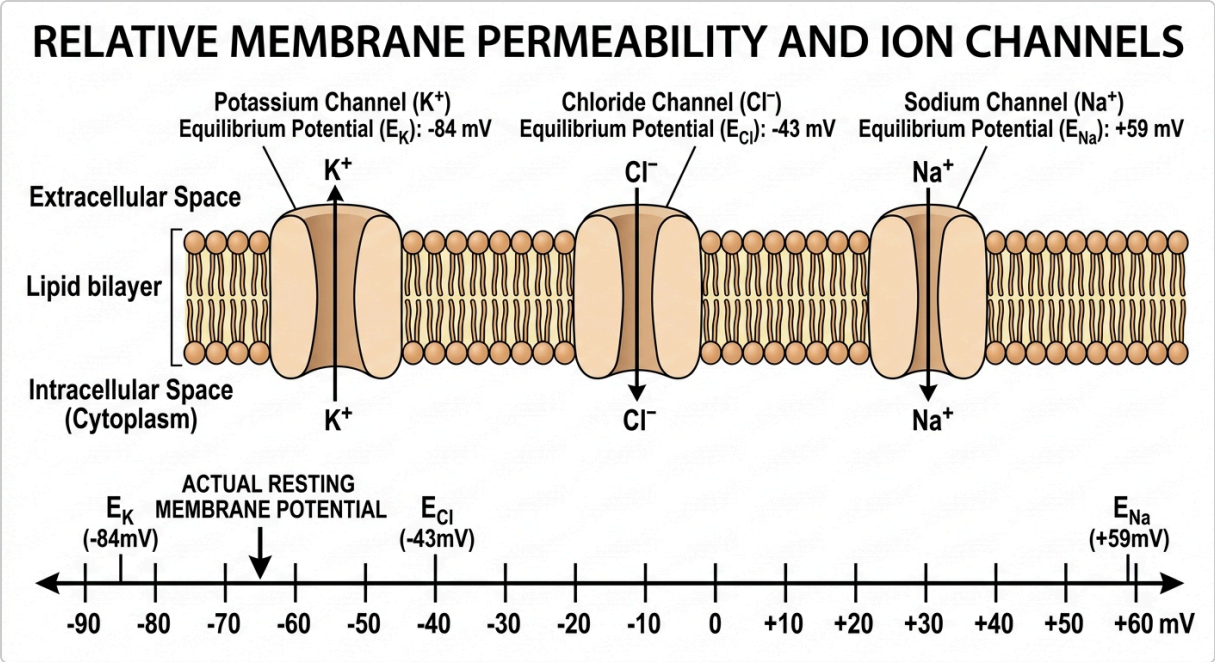
$$V_m = 61 \times \log_{10} \frac{19.6}{165.6} = 61 \times (-0.927) \approx \mathbf{-57\ mV}$$

That lands closer to $E_K$ than to $E_{Na}$ or $E_{Cl}$, exactly as the permeability ratios predict — real neurons typically report resting potentials in the −70 to −90 mV range, and the exact number shifts with the specific permeability ratios and concentrations of the tissue in question, but the direction of the logic (whoever has the highest permeability wins) is the fixed part.

A second, faster way to reason through Goldman-style problems without grinding the full equation: check the two extremes. Set one ion's permeability to zero and see what Vm becomes (it collapses to a pure Nernst calculation for the remaining ion); do the same for the other ion; whichever extreme your measured/given Vm sits closer to tells you which ion the real membrane is more permeable to.

> **Field note**
>
> The $Na^+/K^+$-ATPase's *indirect* contribution (Part 1) is what makes this whole equation mean anything physiologically — it's constantly re-establishing the $Na^+$ and $K^+$ gradients that leak channels are constantly dissipating. Stop the pump (profound hypoxia, certain toxins) and the gradients run down, $P_K$'s dominance stops mattering because there's no gradient left to be dominant over, and Vm drifts toward zero. This is part of why cellular ischemia is electrically catastrophic before it's anything else.

✎ **Draw it — The Goldman equation and permeability-weighted dominance**




Goldman equation: permeability-weighted resting potential — *AI-generated illustration; verify against your own notes/slides.*

**🧠 Memory hook**

*Nernst is a solo act — one ion, one equilibrium potential, no permeability term at all. Goldman is the full band — every permeant ion gets a part, but the one holding the microphone (highest permeability) is the one you actually hear. At rest, $K^+$ has the mic.*

# Module 3 — Excitable Membranes & Action Potentials

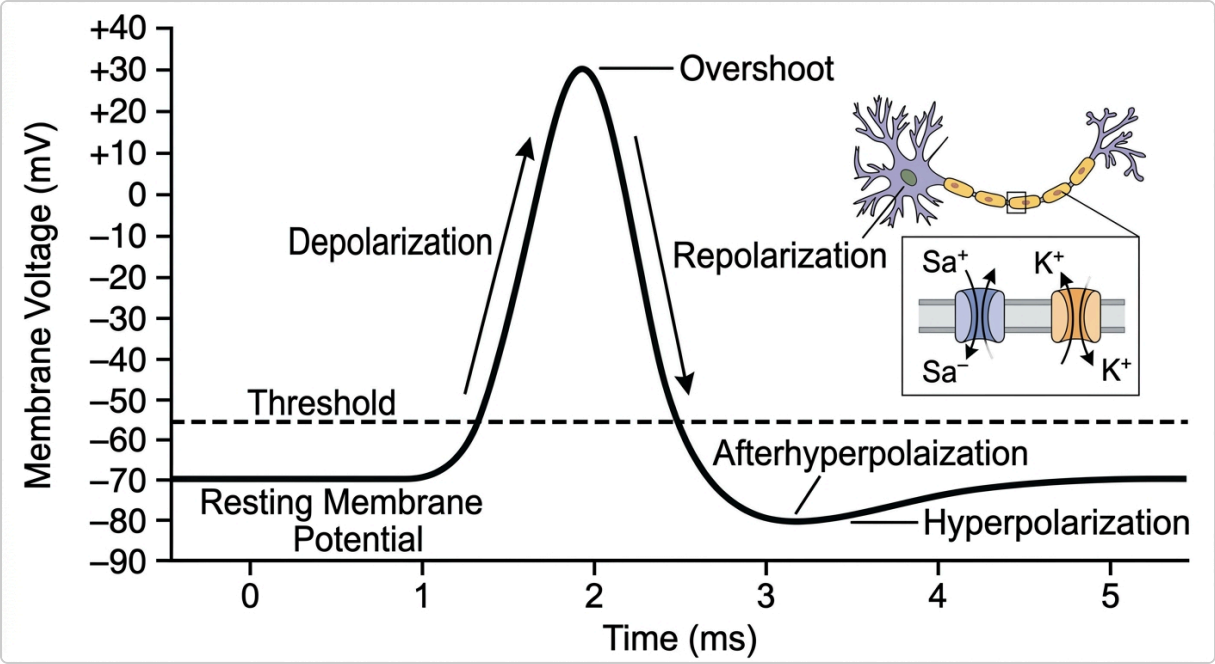
## The Action Potential as a Time-Dependent Solution to GHK, Not a New Equation

You already have the tools: GHK sets Vm as a permeability-weighted average of the ion equilibrium potentials, and at rest that average sits close to EK (and ECl) because gK dominates and gNa is nearly silent. The action potential adds nothing to that framework except time. It is what happens when gNa and gK stop being fixed constants and become steep, offset functions of both voltage and time. For roughly a millisecond, gNa spikes by a factor of ~1000, GHK's weighted average swings hard toward ENa (~+60 mV), and Vm follows; then gNa collapses and a delayed, larger-than-baseline gK pulls the same weighted average back past its resting value toward EK. Every feature of the waveform — the explosive upstroke, the overshoot, the undershoot — is GHK being re-solved continuously as the conductance ratio whipsaws and settles.

Put numbers on the landmarks once, so every "threshold"/"peak"/"rest" reference below has something concrete to attach to: a typical neuron rests around **−70 mV**, fires once depolarization crosses **threshold at roughly −55 mV** (this is the number this course's own practice materials use — you may also see −50 mV in other sources; treat it as "approximately −55," not a fixed constant), and overshoots to a peak around **+30 mV** before repolarizing and undershooting slightly below rest.

The engine behind the upstroke is positive feedback, not a strength-dependent stimulus response: depolarization opens voltage-gated Na+ channels, which admit Na+, which depolarizes further, which opens more channels. This loop is self-terminating for two independent reasons — the shrinking driving force (Vm - ENa) as Vm approaches ENa, and, more importantly, time-dependent inactivation that shuts channels regardless of how depolarized the membrane still is. Confusing these two brake mechanisms is a common exam trap: the AP does not stop at the peak because it "runs out of driving force" (there's still ~10-15 mV of driving force left at the peak, since Vm overshoots to about +30-35 mV while ENa is nearer +60 mV) — it stops because inactivation gates, which have been closing on a slower clock than the activation gates opened, finally catch up.

✎ **Draw it — annotated action-potential graph with Vm trace, gNa and gK traces, and ENa/EK/threshold/resting reference lines**




The action potential — *AI-generated illustration; verify against your own notes/slides.*

## Three Phases, Two Independent Gates on One Channel

Model the voltage-gated Na+ channel as carrying two separate gates in series, both of which must be open for current to flow: a fast activation gate (m) and a slow inactivation gate (h). Three functional states result — closed-but-available (rest: m closed, h open), open (both gates briefly open during the upstroke), and inactivated (m open, h closed — the channel is shut and cannot be reopened by any further depolarization until the

membrane repolarizes and h resets). The three phases map onto this gating scheme directly:

- **Depolarization (rising phase).** Activation gates snap open on reaching threshold; gNa overtakes gK for the first time since rest; the regenerative loop above drives Vm to its peak.
- **Repolarization (falling phase).** Inactivation gates, lagging behind activation by design, finally close — gNa collapses toward zero. Simultaneously, voltage-gated (delayed-rectifier) K+ channels, which opened on the same depolarizing trigger but with slower kinetics than Na+ channels, are now fully engaged; gK exceeds its resting value and drives Vm back down.
- **Hyperpolarization (undershoot).** Delayed-rectifier K+ channels are still open and closing only slowly; with gK still elevated above baseline, Vm is pulled past resting potential toward EK before K+ conductance finally relaxes and the leak/pump balance re-establishes rest.

Get the timing claim precise, because it's a common exam trap: gNa is at its highest at or immediately before the peak — that's the mechanistic reason the peak occurs where it does — and only reaches its true minimum during the falling phase and undershoot, once inactivation is complete. "Lowest Na+ permeability" belongs to the tail of the waveform, not the peak itself.

> 🧠 **Memory hook**
>
> *Na+ channels are Cinderella at the ball. The activation gate is the door swinging wide open the instant she arrives (fast, voltage-triggered) — she's in and having the time of her life while gNa is high. The inactivation gate is midnight: a slower, time-locked event that shuts her out no matter how loud the music (how depolarized the membrane) still is. She can't get back in — no matter how hard anyone pushes on the door — until she's gone all the way home and the clock has reset, which is the membrane repolarizing back near rest.*

## Refractory Periods: Two Different Mechanisms, One Word

**Absolute refractory period (ARP)** spans essentially the entire upstroke and most of repolarization. During this window, no stimulus of any magnitude can evoke a second action potential, because the limiting factor isn't voltage sensitivity at all — it's channel availability. The h-gates are shut across essentially the whole Na+ channel population; there is nothing for any stimulus, however large, to open.

**Relative refractory period (RRP)** occupies the hyperpolarization/undershoot tail. Two things are simultaneously true here, and both matter: a growing fraction of Na+ channels have recovered to closed-but-available (h has reopened), but gK is still elevated above its resting baseline, which (a) hyperpolarizes Vm farther from threshold and (b) shunts depolarizing current as it arrives. Net effect: an AP can be evoked, but only by a stronger-than-normal stimulus, and the resulting AP has reduced amplitude (fewer available Na+ channels to recruit) and a slower rising phase.

✎ **Draw it — refractory-period timeline aligned under the AP trace, ARP and RRP windows shaded and labeled with channel-availability annotations**

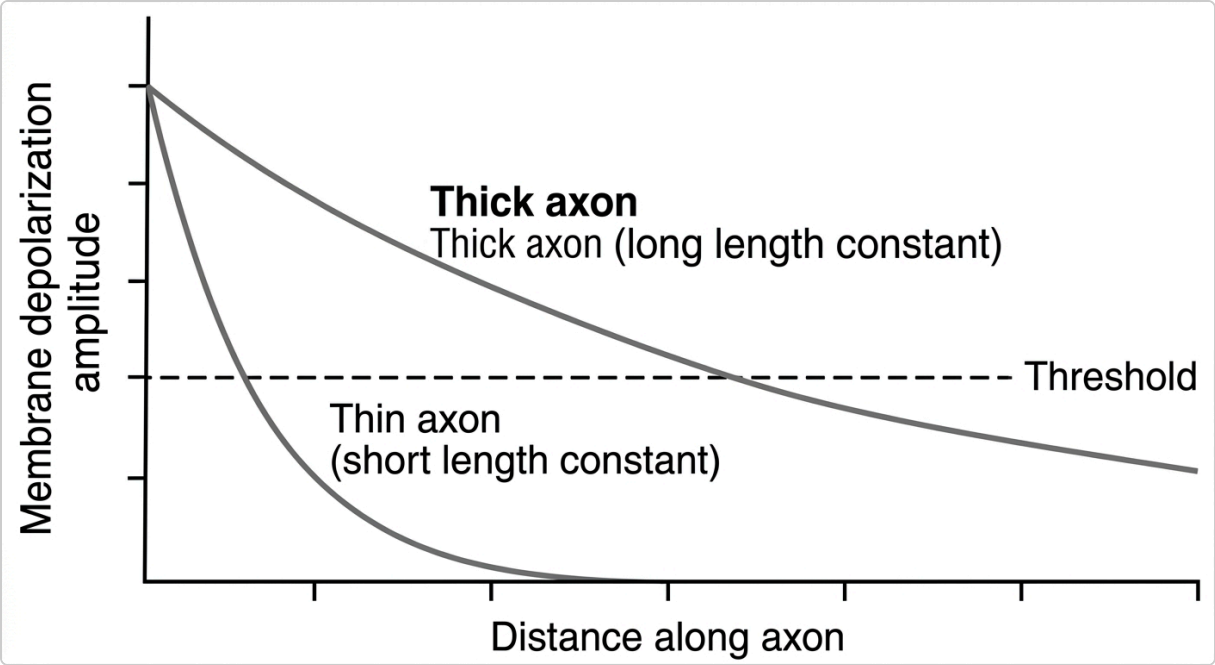
Two direct functional consequences follow, and both are worth stating explicitly because they're the kind of thing exam questions build around: the ARP sets a hard ceiling on maximum firing frequency (an ARP of ~1-2 ms caps theoretical firing well below what most neurons actually achieve, since other factors intervene first), and the refractory period is the entire reason propagation is unidirectional — the patch of membrane just traversed by an AP is, by definition, still refractory, so the wave cannot double back into its own wake.

> **Field note**
>
> defibrillation and synchronized cardioversion both exploit the refractory period directly rather than working around it. A defibrillation shock forces a critical mass of myocardial cells into simultaneous depolarization and inactivation at once — effectively imposing one shared, synchronized absolute refractory period across the ventricles. With no excitable tissue left for a chaotic re-entrant wavefront to invade, ventricular fibrillation or pulseless VT loses its substrate and stops; the SA node, having the fastest intrinsic pacemaker rate, is typically first to emerge from that shared refractory state and recaptures the rhythm. Synchronized cardioversion times the shock to the R wave specifically to avoid landing during the vulnerable relative refractory period on the T wave, where a poorly-timed stimulus could itself trigger a re-entrant arrhythmia instead of terminating one.

## Propagation I: Electrotonic Spread Is the Substrate, Regeneration Is the Engine

Nothing about propagation requires new machinery beyond what you already have for passive cable properties. The length constant ($\lambda = \sqrt{(Rm/Ri)}$) and time constant ($\tau = Rm \cdot Cm$) that govern how far and how fast a graded potential decays now determine something more specific: whether electrotonic current spreading from an actively-firing patch of membrane reaches the next patch of voltage-gated channels while it's still above threshold. Propagation is not a single AP "moving" down the axon — it is a chain of independently regenerated, full-amplitude events, each one a fresh all-or-none response triggered by its upstream neighbor's passive spread.

This reframes the diameter/resistance relationships without inventing anything new: larger diameter lowers axoplasmic (internal) resistance Ri, which lengthens λ, which lets electrotonic depolarization reach farther down the axon while still exceeding threshold — hence faster conduction in thicker axons. Membrane resistance Rm works the same direction, not the opposite one: higher Rm means less current leaks back out across the membrane per unit length, which also lengthens λ. Any framing that treats "membrane resistance" as something that slows propagation has the sign backward — raising Rm is exactly the trick myelin uses to speed things up (see below).




Electrotonic decay: thin vs. thick axon — *AI-generated illustration; verify against your own notes/slides.*

## Propagation II: Saltatory Conduction

Myelin is a Cm-lowering, Rm-raising insulator wrapped around the axon in internodal segments roughly 100 μm long, interrupted by Nodes of Ranvier where voltage-gated channel density is high and the axonal membrane is exposed. Under the myelin, gNa is negligible — there's essentially nothing to regenerate there — so depolarization at one node must reach the next node by electrotonic spread alone. But because myelin has driven Rm way up and Cm way down, λ under the myelin is now long enough (and the membrane too electrically "slow" to charge, via τ, to leak the signal away) that the depolarization arrives at the next node still comfortably above threshold. The AP effectively skips from node to node — saltare, "to leap" — regenerating only where channels actually exist. The result is roughly a 100-fold increase in conduction velocity over an unmyelinated axon of the same diameter, plus a substantial energy saving: the Na+/K+-ATPase only has ionic bookkeeping to do at the nodes, not across the entire membrane surface.

🧠 **Memory hook**

*think hopscotch. The AP touches down only on the numbered squares — the Nodes of Ranvier, where channels live — and glides over the chalk lines between them (the myelinated internodes) on momentum alone (electrotonic spread), never needing to "regenerate" mid-line.*

🚑 **Field note**

demyelinating disease is a direct, mechanistic stress test of this model rather than a separate topic. In multiple sclerosis or Guillain-Barré, loss of myelin drops Rm and raises Cm at what used to be internodal segments — λ shortens, electrotonic spread decays before reaching the next node, and conduction slows or blocks even though the axon and its Na+ channels remain structurally normal. This is why the hallmark finding on a nerve conduction study is reduced conduction velocity, not reduced amplitude at the stimulation site — the channels still work fine, they're just no longer reachable by the signal in time.

✎ **Draw it — saltatory vs. continuous conduction schematic, node density and channel distribution contrasted side by side**

## Channel Pharmacology: What You Can Block and Why It Matters in the Field

Voltage-gated Na+ and K+ channels are distinct, druggable proteins, and their pharmacology is where this topic earns its clinical weight. Tetrodotoxin (TTX) and local anesthetics both block voltage-gated Na+ channels, but not identically: local anesthetics like lidocaine bind preferentially to the channel's open and inactivated states (use-dependent block), which is exactly why they hit rapidly, repetitively firing fibers — pain

fibers, ectopic ventricular foci — harder than quiescent, normally-conducting tissue. Tetraethylammonium (TEA) is the classic voltage-gated K+ channel blocker, useful experimentally for isolating the Na+ current in patch-clamp work.

> 🚑 **Field note**
>
> lidocaine is the same drug whether it's infiltrating a laceration or running as an antiarrhythmic, and the mechanism is identical — use-dependent block of voltage-gated Na+ channels, preferentially in their open/inactivated conformation. That's why it numbs a wound (blocking sustained nociceptor firing) and why it historically suppressed ventricular ectopy (blocking the abnormally frequent, inactivated-state-rich firing of an irritable ventricular focus) without shutting down normal, low-frequency cardiac conduction nearly as much. It's also why lidocaine toxicity tracks so tightly with total dose and injection rate — perioral numbness and tinnitus first, then seizures, then cardiovascular collapse as block extends from the intended peripheral fibers to central and cardiac Na+ channels.

> 🚑 **Field note**
>
> amiodarone gets filed next to lidocaine in a lot of ACLS mnemonics as "another Na+ blocker," which undersells what it actually does. Its dominant action is blocking delayed-rectifier K+ channels, which prolongs phase 2-3 repolarization and extends the action potential duration and refractory period — a longer refractory period starves a re-entrant circuit of excitable tissue to invade, which is the actual mechanism by which it helps terminate refractory V-fib or pulseless VT after defibrillation and epinephrine. It also carries real Na+-channel, calcium-channel, and beta-blocking activity, which is precisely why it resists being filed cleanly into one Vaughan-Williams class and is usually described as broad-spectrum.

## Ionic Bookkeeping: Why Concentrations Barely Move, and When That Stops Being True

A useful sanity check, straight from capacitor math ($Q = CV$): the actual number of ions crossing per action potential is tiny relative to total intracellular Na+ and K+ stores, so a single AP — or even a modest train of them — causes a negligible shift in bulk cytoplasmic concentration. This is precisely why the resting potential doesn't visibly degrade after ordinary neuronal firing. It stops being negligible only with sustained high-frequency activity, at which point the Na+/K+-ATPase's job shifts from "housekeeping" to "keeping up," and its ATP demand rises accordingly — the physiological basis for activity-coupled local blood-flow increases that PET and functional MRI actually detect.

The clearest place this bookkeeping actually breaks is hyperkalemia, and the mechanism is a genuine paradox worth sitting with rather than memorizing as a fact. Raising extracellular K+ makes EK less negative, which depolarizes the resting membrane potential — nothing new there, it's the same GHK relationship you already know. The naive prediction is that a resting potential sitting closer to threshold should make cells more excitable. What actually happens is the opposite: sustained depolarization progressively shifts Na+ channels from closed-but-available into the inactivated state (a process sometimes called accommodation), shrinking the pool of channels available to fire on demand. Excitability falls, not rises, as extracellular K+ climbs.

**🚑 Field note**

hyperkalemia is the cleanest clinical demonstration of Na+ channel inactivation kinetics you'll encounter as an EMT. Elevated serum K+ depolarizes resting Vm, which sounds like it should make cardiac and skeletal muscle more excitable — but the dominant effect is accommodation: a growing fraction of Na+ channels sit inactivated rather than closed-but-available, so fewer channels are recruitable when a stimulus arrives. Clinically this shows up as skeletal muscle weakness and, on the monitor, peaked T waves progressing to widened QRS complexes as cardiac conduction slows. It's also why the field/ED treatment targets channel availability directly rather than just the lab number: calcium gluconate stabilizes the cardiac membrane by restoring the threshold-to-resting-potential gap (buying time, not lowering K+), while insulin/glucose and albuterol actually shift K+ intracellularly to fix the underlying gradient.

**🧠 Memory hook**

*picture Na+ channels as bouncers who lock the door if the crowd outside leans on it slowly and steadily (gradual, sustained depolarization from hyperkalemia) — but the same door opens just fine for a single sharp, sudden knock (a normal, fast action potential upstroke). Same door, same bouncers; it's the speed and duration of the push that decides whether you get in or get locked out.*

✎ **Draw it — gNa/gK/Vm time-course overlay annotated with the site of action of TTX, lidocaine, TEA, and amiodarone**

# Module 4 — Synaptic Transmission & the Neuromuscular Junction

## From axon to another cell: why synapses exist at all

Everything in S1.3 got a signal from one end of an axon to the other, non-decrementally, at the cost of an all-or-none rule. Synapses solve the next problem: how does that signal get to a *different cell*, and how does the nervous system get anything resembling computation — summation, gating, learning — out of what is otherwise a chain of identical binary events? The answer is that synapses convert a digital signal (the action potential) back into an analog one (a graded postsynaptic potential), and that conversion step is where all the interesting regulation happens.

Two fundamentally different hardware solutions exist: electrical and chemical synapses. They are not different flavors of the same mechanism — they trade off in almost every dimension that matters.

## Electrical synapses: sacrificing gain for speed

At an electrical synapse, the pre- and postsynaptic membranes are physically joined by gap junctions — hexameric assemblies of connexin subunits (a connexon) docking end-to-end with a connexon on the other cell to form a continuous aqueous pore (~1.5-2 nm effective diameter) connecting the two cytoplasms directly. Current — literally ionic current, not neurotransmitter — flows straight across. Because there is no diffusion step and no receptor-binding kinetics, transmission is essentially instantaneous and bidirectional, and it is not amplified: a small presynaptic depolarization produces a smaller postsynaptic one, since it's spreading passively (electrotonically) exactly as it would down an unmyelinated stretch of the same axon — no regeneration, no threshold, no gain. That's the tradeoff: electrical synapses buy synchrony at the cost of amplification. This is why they show up wherever a population of cells needs to fire as a single unit — cardiac and smooth muscle gap junctions, some interneuron networks that need to oscillate in lockstep.

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## Chemical synapses: paying a time cost for the ability to modulate

Chemical synapses insert an actual gap (the synaptic cleft) and a molecular relay: an arriving action potential opens voltage-gated $Ca^{2+}$ channels in the presynaptic terminal, $Ca^{2+}$ influx triggers vesicle fusion, neurotransmitter diffuses across the cleft, and it binds postsynaptic receptors. That relay costs roughly 0.2 ms of synaptic delay — trivial for a single synapse, but it compounds across a multisynaptic pathway. What you buy for that latency is everything electrical synapses can't do: amplification (one presynaptic vesicle's contents can gate hundreds of postsynaptic channels), sign inversion (a depolarizing presynaptic event can produce a hyperpolarizing postsynaptic one, which is structurally impossible at a gap junction), and, critically, *modulable strength* — the same synapse can be weakened or strengthened based on its own recent history. That last property is what makes learning and memory possible at the cellular level, and it has no electrical-synapse analog.

## Vesicle exocytosis: the SNARE cycle

The molecular machinery converting "$Ca^{2+}$ arrived" into "neurotransmitter is in the cleft" divides cleanly into vesicle-resident and plasma-membrane-resident proteins that together form the SNARE complex:

- **Synaptobrevin** (vesicle) and **synaptotagmin** (vesicle, the $Ca^{2+}$ sensor) pair with **syntaxin** and **SNAP-25** (both presynaptic plasma membrane).
- Sequence: (1) the vesicle docks at the active zone, near the voltage-gated $Ca^{2+}$ channels; (2) synaptobrevin, syntaxin, and SNAP-25 zipper together into a four-helix SNARE bundle that pulls the two membranes into close apposition; (3) the arriving $Ca^{2+}$ (entering preferentially during the *falling* phase of the presynaptic action potential, when the electrochemical driving force on $Ca^{2+}$ is largest) binds synaptotagmin; (4) $Ca^{2+}$-bound synaptotagmin drives the final membrane fusion step, opening a pore through which transmitter empties into the cleft.

This is a fast, high-fidelity, and — this matters for the field notes below — a mechanically vulnerable process: it depends on a small, specific set of proteins, all of which are druggable and toxin-targetable individually.

✎ **Draw it — Vesicle exocytosis sequence — dock, SNARE zippering, Ca2+-synaptotagmin binding, fusion**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

> 🚑 **Field note**
>
> Botulinum toxin and tetanus toxin are both zinc metalloproteases that cleave SNARE proteins — botulinum typically cleaves SNAP-25 or synaptobrevin at peripheral motor nerve terminals, tetanus toxin travels retrograde up motor axons to cleave synaptobrevin in inhibitory interneurons in the spinal cord. The clinical pictures are opposite because the location differs, not the mechanism: botulism presents as a descending flaccid paralysis (no ACh release at the NMJ means no muscle contraction at all — this is why wound botulism and infant botulism from honey are on your differential for a floppy, weak patient with a dry mouth and dilated pupils), while tetanus presents as rigid, spastic paralysis with trismus (lockjaw) and opisthotonus, because you've disabled the inhibitory brake on motor neurons rather than the motor neurons themselves. Same broken machine part, different location, opposite presentation — a useful example of why "where" a toxin acts matters as much as "what" it does.

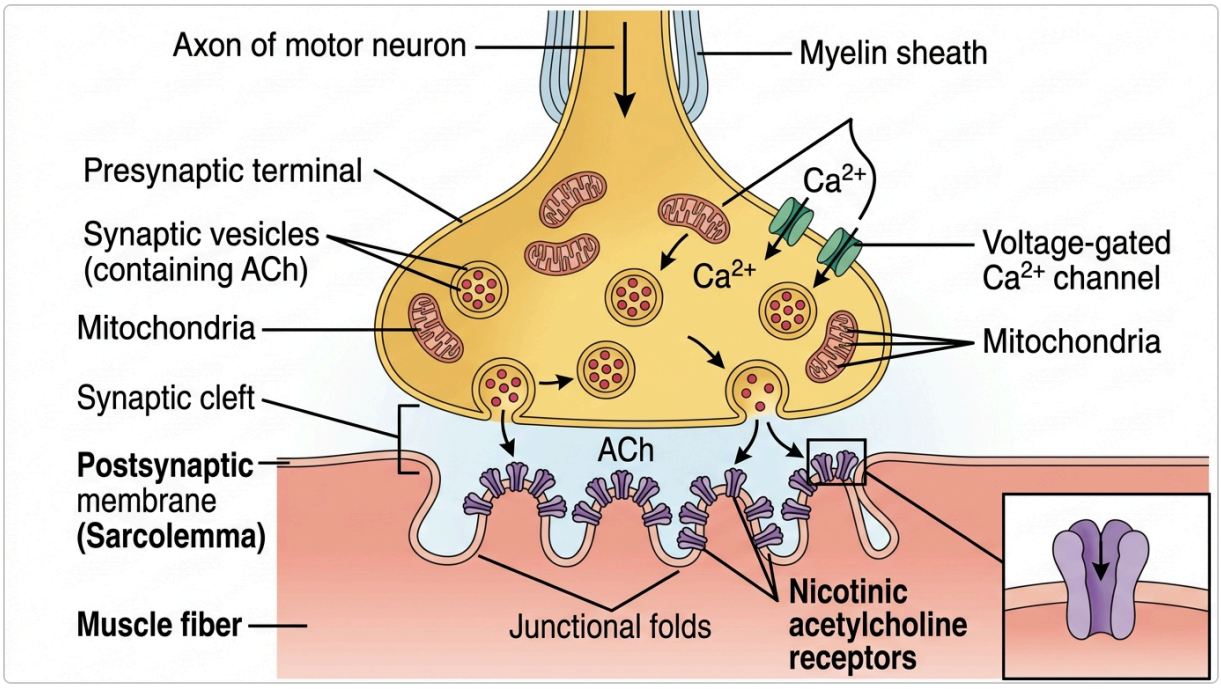
## The neuromuscular junction: a synapse engineered for certainty, not flexibility

The NMJ is the one-to-one synapse: a single presynaptic action potential should produce a single postsynaptic action potential, every time, with no room for failure — skeletal muscle doesn't get to "maybe" contract. Everything about its structure exists to eliminate variability that a CNS synapse would tolerate or even exploit:

1. Voltage-gated $Ca^{2+}$ channels cluster at dense bars (active zones) directly across the cleft from the highest density of postsynaptic ACh receptors — minimizing diffusion distance, which minimizes both the time transmitter spends in transit (where it's vulnerable to enzymatic degradation) and the fraction lost to lateral diffusion out of the cleft.
2. Postsynaptic junctional folds massively increase local membrane surface area, packing far more nicotinic ACh receptors into the region directly beneath each release site than a flat membrane could hold.
3. The transmitter itself — acetylcholine — is released in enormous excess of what's strictly required. Each vesicle ("quantum") contains ~10,000 ACh molecules and produces a small, fixed depolarization at the end plate called a miniature end plate potential (MEPP, ≈0.4 mV). Getting the end plate from its resting potential (~-90 mV) up to threshold (~-50 mV — a muscle fiber's own threshold, slightly less negative than the ~-55 mV commonly cited for a generic neuron in Module 3; different excitable tissue, not a contradiction) requires about 40 mV of depolarization — roughly 100 quanta's worth. A single action potential normally releases on the order of 100-200 quanta. That's not a coincidence; it's a deliberately engineered *safety factor* — release is calibrated to exceed the minimum needed by roughly two-fold, which is precisely why the NMJ is a reliable one-to-one relay while a typical central synapse, releasing far fewer quanta per action potential, is not.

This safety-factor framing also explains a disease you'll see clinically: myasthenia gravis, an autoimmune disease in which antibodies attack postsynaptic nicotinic ACh receptors. ACh release from the presynaptic side is completely normal — the defect is that fewer of the released quanta find an intact receptor to bind, which erodes the safety margin. With enough receptors lost, a normal-sized EPP no longer reaches threshold and transmission fails — classically worsening with repetitive use as vesicle stores deplete slightly with each successive stimulus (this is why the diagnostic maneuver is repetitive nerve stimulation showing a decremental response, and why the classic complaint is progressive fatigable weakness — ptosis and diplopia by the end of the day, difficulty finishing a meal).

✎ **Draw it — NMJ structural sequence — Ca2+ channel/AChR alignment, junctional folds, quantal safety factor**




Neuromuscular junction — *AI-generated illustration; verify against your own notes/slides.*

🚑 **Field note**

This is exactly the receptor you're blocking during rapid sequence intubation. Succinylcholine is a depolarizing neuromuscular blocker — it's a nicotinic ACh receptor agonist that isn't degraded by AChE, so it keeps the end plate depolarized (you'll often see visible fasciculations first, as every motor unit fires once, before flaccid paralysis sets in because voltage-gated Na+ channels near the end plate inactivate and won't reset). Rocuronium and vecuronium are nondepolarizing blockers — competitive nicotinic antagonists that simply occupy the receptor without activating it, so there's no fasciculation phase, just progressive weakness. Both drugs hit the exact postsynaptic receptor described above; they differ only in whether they turn the channel on before blocking it or just block it outright.

🧠 **Memory hook**

*For the SNARE proteins, think of them as a heist crew: SNAP-25 and syntaxin are the inside crew already stationed at the wall (presynaptic membrane), synaptobrevin is the getaway rope thrown from the vesicle, and synaptotagmin is the lookout who only gives the "go" signal (fusion) once Ca2+ shows up — no Ca2+, no green light, no job.*

## Termination: why acetylcholine can't be allowed to linger

A synapse that only turns on would be useless — muscle would stay contracted. ACh's off-switch is enzymatic, not reuptake-based, and that distinction matters: acetylcholinesterase (AChE), anchored in the basement membrane running through the synaptic cleft itself, hydrolyzes ACh into choline and acetate essentially as fast as ACh diffuses past it — among the fastest enzymes known. Roughly half the resulting choline is recovered by a $Na^+$-choline cotransporter back into the presynaptic terminal and recombined with acetyl-CoA by choline acetyltransferase (ChAT) to make new ACh. Note that this is a fundamentally different clearance mechanism from the reuptake transporters that clear monoamines like dopamine, norepinephrine, or serotonin from CNS synapses — there is no ACh reuptake transporter pulling intact ACh back into the terminal; the transmitter itself is destroyed and only its choline backbone is recycled.

🚑 **Field note**

Organophosphates (nerve agents, and — the one you'll actually see in the field — agricultural pesticides) irreversibly inhibit AChE. Block the enzyme and ACh accumulates everywhere it's normally released — not just the NMJ, but every muscarinic synapse in the parasympathetic system too. That's the SLUDGE presentation: Salivation, Lacrimation, Urination, Defecation, GI distress, Emesis — plus the muscular side, which starts as fasciculations and progresses to a depolarizing-block-style flaccid paralysis once every nicotinic receptor is chronically activated, exactly as with succinylcholine above, and often ends in respiratory failure from diaphragmatic paralysis combined with bronchorrhea. The antidote, atropine, is worth pausing on: atropine is a muscarinic receptor antagonist. It will dry the secretions and slow the heart back down (the SLUDGE side) but it does nothing for the nicotinic NMJ paralysis, because atropine doesn't touch nicotinic receptors at all — that's why severe organophosphate poisoning also gets pralidoxime (2-PAM), which reactivates AChE itself, and why "atropinize and reassess" doesn't mean the patient's muscles are safe yet.

🚑 **Field note**

Neostigmine and pyridostigmine are reversible AChE inhibitors used therapeutically, at doses far below organophosphate toxicity, specifically to treat myasthenia gravis: by slowing ACh degradation, they keep transmitter available at the end plate longer, partially compensating for the antibody-mediated loss of postsynaptic receptors described above and restoring enough safety factor to get transmission back above threshold.

## Postsynaptic receptors: ionotropic speed versus metabotropic reach

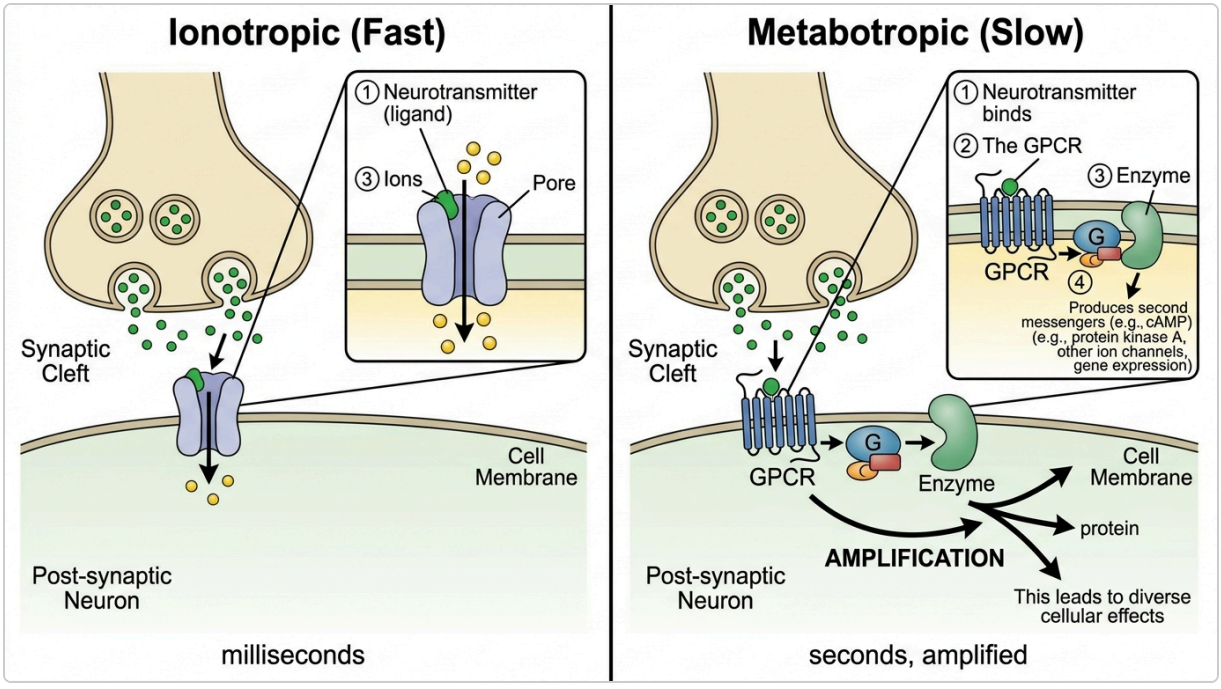
Every neurotransmitter receptor falls into one of two structural classes, and this distinction — not just a vocabulary pair to memorize — determines the speed, sign, and duration of everything downstream.

**Ionotropic (ligand-gated ion channel) receptors** are the channel: neurotransmitter binding directly opens a pore built into the same protein complex. Effect is fast (milliseconds) and short-lived, lasting only as long as transmitter occupies the site. The nicotinic ACh receptor at the NMJ is the prototype — five subunits arranged around a central pore, two of which must each bind an ACh molecule before the channel opens, and the open channel is permeable to both $Na^+$ and $K^+$ (which is why activating it drives the membrane toward a depolarized value roughly midway between the $Na^+$ and $K^+$ equilibrium potentials, not all the way to $E_{Na}$). Glutamate receptors in the CNS work the

same way and are the major source of fast excitatory transmission there. GABA-A receptors are also ionotropic, but selectively conduct $Cl^-$ instead of $Na^+/K^+$ — same structural logic, opposite ionic consequence.

**Metabotropic receptors** are not channels at all — they're G-protein-coupled receptors (GPCRs) with seven transmembrane domains. Transmitter binding activates an associated G protein, which then modulates a separate effector (commonly adenylyl cyclase, generating cAMP, which activates protein kinase A). The signal is slower to develop (hundreds of milliseconds to seconds), it amplifies (one receptor can activate many G proteins, each activating many downstream effector molecules), and its effects can persist well beyond the transmitter's presence and can extend all the way to gene expression. Muscarinic ACh receptors, dopamine receptors, and serotonin receptors are the standard metabotropic examples.

The single most important thing to internalize here is that the *same* transmitter can act through either class depending only on which receptor it happens to bind — ACh is ionotropic (nicotinic) at the NMJ and metabotropic (muscarinic) at parasympathetic target organs, which is exactly why a drug can be surgically selective for one tissue and leave the other completely alone.




Ionotropic vs. metabotropic receptors — *AI-generated illustration; verify against your own notes/slides.*

> **Field note**
>
> This ionotropic/metabotropic split is exactly why atropine is safe to give for a symptomatic bradycardia or as an organophosphate antidote without touching skeletal muscle at all: atropine blocks muscarinic (metabotropic) ACh receptors on cardiac and smooth muscle/glands, and simply has no affinity for nicotinic (ionotropic) ACh receptors at the NMJ. Same transmitter, structurally distinct receptor, and the drug's selectivity rides entirely on that receptor-class difference — not on some difference in the ACh molecule itself, because there isn't one.

> **Field note**
>
> Naloxone is a useful second example of receptor pharmacology because it's a competitive antagonist at opioid receptors — themselves metabotropic (GPCRs coupled to inhibitory G proteins that reduce cAMP and hyperpolarize neurons, notably in the respiratory centers of the brainstem). Naloxone doesn't "cancel" the opioid chemically; it has higher affinity for the same receptor and physically displaces the opioid off of it, which is why an opioid with a long half-life can outlast a single dose of naloxone (itself short-acting) and why re-sedation after apparent reversal is a real risk you monitor for, not a training-manual footnote.

## Inhibition: GABA, glycine, and the other half of postsynaptic potentials

Not every postsynaptic potential pushes toward threshold. GABA (gamma-aminobutyric acid) is the dominant inhibitory transmitter in the brain; glycine plays the equivalent role in the spinal cord. The GABA-A receptor is built exactly like the ionotropic receptors above — a ligand-gated channel — except selectively permeable to $Cl^-$ rather than $Na^+/K^+$. Since the $Cl^-$ equilibrium potential in most CNS neurons sits below resting potential (around -80 mV, versus a resting potential closer to -65 mV), opening this channel drives the membrane potential *away* from threshold: an inhibitory postsynaptic potential (IPSP), i.e., hyperpolarization. There's also a GABA-B receptor, which is metabotropic (GPCR-coupled to a $K^+$ channel) — so the ionotropic/metabotropic split applies to inhibitory transmission exactly as it does to excitatory transmission; it's not a special exception.

> 🚑 **Field note**
>
> Benzodiazepines (midazolam, lorazepam, diazepam) don't activate GABA-A receptors on their own — they're positive allosteric modulators, binding a separate site on the receptor complex and increasing the frequency of $Cl^-$ channel opening in response to GABA that's already present. That's exactly why benzodiazepines are first-line for status epilepticus: a seizure is, at the network level, runaway excitatory activity that's outstripped inhibitory restraint, and boosting GABA-A-mediated $Cl^-$ influx directly restores that inhibitory brake. It's also why benzodiazepine overdose is comparatively survivable on its own (there's a ceiling — you're modulating a receptor's response to endogenous GABA, not driving it independent of GABA) while combination with another CNS depressant that also potentiates GABA-A, like alcohol, removes much of that safety margin.

## Summation: how a cell actually decides whether to fire

A single EPSP at a typical central synapse is small and brief (rise and decay over roughly 5-10 ms) — nowhere near enough on its own to reach threshold. A postsynaptic neuron's decision to fire is therefore a real-time integration problem, solved two ways:

- **Spatial summation**: EPSPs arriving simultaneously from different presynaptic inputs onto the same postsynaptic cell add together, because they're all spreading passively across the same membrane at the same moment. If one input is excitatory and another inhibitory, they partially or fully cancel — this is how a single neuron performs something like a weighted vote across hundreds to thousands of inputs.
- **Temporal summation**: rapid, repeated firing from a single presynaptic input produces EPSPs that arrive before the previous one has fully decayed, so they stack.

Either mechanism, or both together, can bring the membrane potential from several individually subthreshold EPSPs up past threshold, at which point the postsynaptic cell fires its own action potential — the point where the analog computation (summation) gets converted back into a digital signal (a new all-or-none spike) to be relayed onward.

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## Synaptic plasticity: two mechanisms, two timescales, and why they get confused

"Synaptic strength" is not fixed — the same presynaptic input can produce a bigger or smaller postsynaptic response depending on the synapse's recent history, and conflating

the short- and long-term mechanisms is one of the most common ways this topic gets muddled.

**Facilitation** is fast and purely presynaptic: repeated stimulation within a few hundred milliseconds causes residual $Ca^{2+}$ to accumulate in the presynaptic terminal faster than it can be cleared, and since $Ca^{2+}$ concentration is what drives vesicle fusion (via synaptotagmin, above), each successive action potential releases progressively more neurotransmitter than the last, transiently increasing EPSP amplitude. It decays within roughly a second once stimulation stops, because it's entirely a function of a $Ca^{2+}$ concentration that's actively being pumped back down.

**Long-term potentiation (LTP)** operates on a completely different timescale (days to weeks) and, unlike facilitation, is not purely presynaptic — sustained high-frequency stimulation drives molecular changes on *both* sides of the synapse: increased presynaptic machinery for neurotransmitter synthesis and vesicle formation, and increased postsynaptic receptor expression/insertion. The mechanisms are still incompletely understood, but the functional upshot is durable: this is the leading cellular model for how learning and memory are physically encoded, whereas facilitation is a millisecond-to-second-scale adjustment with no lasting trace once the stimulus train stops.

The two are easy to mix up on an exam because both are described as "repeated stimulation increases response" — the discriminating facts are the timescale (hundreds of ms vs. days-to-weeks) and the locus (presynaptic-only vs. bilateral pre- and postsynaptic).

**✎ Draw it — Facilitation vs. long-term potentiation — contrast timescale, locus (pre-only vs. bilateral), and persistence**

> 🧠 **Memory hook**
>
> *Facilitation is a jump-scare — brief, startling, gone as soon as the stimulus stops, like the adrenaline spike from a good horror movie that fades within minutes of leaving the theater. LTP is closer to actually training for a marathon — the changes (in this case, more receptors, more release machinery) are structural, took repeated sustained effort to build, and are still there weeks later. Same starting move (repeated stimulation) — completely different durability.*

## Neurotoxins as a diagnostic lens on the whole pathway

Because synaptic transmission is a fixed sequence of discrete molecular steps, natural toxins that target synapses are functionally organized by *which step* they disable — and once you know the sequence (AP arrival → $Ca^{2+}$ entry → vesicle fusion → transmitter diffusion → receptor binding → clearance), you can predict a novel toxin's effect from its stated mechanism rather than memorizing it as a fact.

- **Black widow spider venom (α-latrotoxin)** acts presynaptically, forcing massive, uncontrolled $Ca^{2+}$ influx (and $Ca^{2+}$-independent vesicle fusion through pore formation) at the axon terminal — the result is a flood of neurotransmitter release rather than a blockade. At the NMJ specifically this produces excessive muscle contraction: cramping, rigidity, and painful spasm, essentially the opposite failure mode from botulinum toxin acting on the same general vesicle-release machinery.
- **Cobratoxin and bungarotoxin** (elapid snake venoms) act postsynaptically as nicotinic ACh receptor antagonists — structurally, α-bungarotoxin binds the nicotinic receptor essentially irreversibly, which is precisely why radiolabeled α-bungarotoxin became the standard laboratory tool for counting ACh receptor density at the end plate. Clinically this produces flaccid paralysis, the same endpoint as a nondepolarizing NMJ blocker like rocuronium, because it's the same receptor being disabled by the same competitive-antagonism logic.
- **Botulinum toxin**, already discussed above, blocks release entirely at the first step (SNARE cleavage) rather than acting downstream at the receptor.

The pattern across all three: presynaptic-release toxins (latrotoxin, botulinum) act on the vesicle fusion machinery and produce opposite phenotypes depending on whether they cause runaway release or total blockade, while postsynaptic-receptor toxins (cobratoxin, bungarotoxin, and pharmacologically, curare/rocuronium/succinylcholine) all converge on flaccid paralysis because they all remove functional nicotinic signaling at the end plate, regardless of whether they do it by simple competition or irreversible binding.

**🚑 Field note**

This mechanism-first approach is exactly the skill NBME-style toxin questions are testing, and it's the same skill you already use in the field: you don't need to have memorized every toxidrome by name if you can reason from "blocks ACh release presynaptically" to "expect a total, progressive flaccid paralysis starting with cranial nerves and descending" (classic botulism) versus "floods the terminal with Ca2+" to "expect involuntary muscle rigidity and autonomic storm" (black widow envenomation, which in the field often gets mistaken for an acute abdomen because of the muscle rigidity it produces).

# Module 5 — The Autonomic Nervous System

## The Two-Neuron Relay: Sympathetic and Parasympathetic Architecture

Every autonomic pathway is a two-neuron relay: a preganglionic neuron with its cell body in the CNS, synapsing in a peripheral ganglion onto a postganglionic neuron, which then reaches the effector organ. This is the single structural fact that explains almost everything else in this topic, so it's worth deriving rather than memorizing.

The **sympathetic (thoracolumbar) division** originates from spinal cord segments T1–L3. Its ganglia sit close to the spinal cord — the paravertebral (sympathetic chain) ganglia running alongside the vertebral column, and the prevertebral ganglia (celiac, superior and inferior mesenteric) out along the abdominal aorta. Because the ganglia are close to the cord, the preganglionic fiber is short. But the ganglion-to-organ distance is long, so the postganglionic fiber is long. Preganglionic fibers also diverge widely — one preganglionic neuron can synapse on postganglionic neurons at multiple levels up and down the chain (roughly a 1:20 ratio) — which is structurally why sympathetic activation reads as a diffuse, whole-body event.

The **parasympathetic (craniosacral) division** originates from four cranial nerve nuclei (III, VII, IX, X) and sacral segments S2–S4. Its ganglia sit on or inside the target organ itself — the opposite geometry. The preganglionic fiber is now the long one (it has to travel nearly the whole distance to the organ), and the postganglionic fiber is short (barely more than the width of the ganglion). Fewer postganglionic neurons per preganglionic fiber (roughly 1:4) means the effect stays localized to whatever organ that ganglion sits in, rather than spreading system-wide.

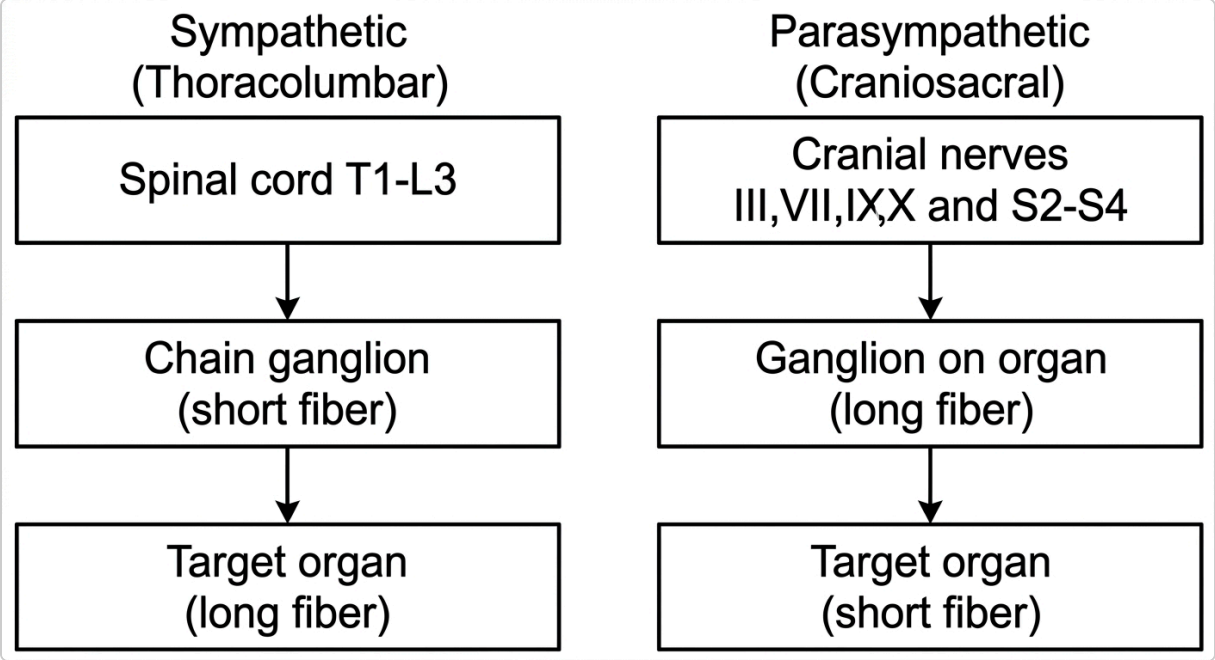
This single geometric fact — where the ganglion sits — is the cause, and everything else (widespread vs. localized effect, "fight-or-flight" vs. "rest-and-digest") is the downstream consequence. It's worth internalizing it that way instead of as two separate lists to memorize.

> 🧠 **Memory hook**
>
> *the length of the word matches the length of the fiber — "sympathetic" (shorter word) has the shorter preganglionic fiber; "parasympathetic" (longer word) has the longer preganglionic fiber.*

**🧠 Memory hook**

*picture the spinal cord as a club sandwich — parasympathetic outflow is the bread, top and bottom (cranial nerves at the very top, sacral segments at the very bottom), and sympathetic outflow is the filling, packed into the middle slice (thoracolumbar, T1–L3). If the outflow comes from the top or bottom of the cord, it's parasympathetic; if it comes from the middle, it's sympathetic.*

✎ **Draw it — sympathetic vs. parasympathetic structural comparison — ganglion location, fiber length ratio, divergence ratio, single table, built once**




Sympathetic vs. parasympathetic pathway architecture — *AI-generated illustration; verify against your own notes/slides.*

## Neurotransmitters and Receptor Logic at Each Synapse

Every preganglionic neuron, sympathetic or parasympathetic, releases acetylcholine (ACh) onto **nicotinic (N2)** receptors on the postganglionic cell body — this part never varies. What varies is the postganglionic transmitter: parasympathetic postganglionic neurons release ACh again, this time onto **muscarinic** receptors on the effector organ. Sympathetic postganglionic neurons release **norepinephrine** onto adrenergic receptors on the effector organ — with two well-defined exceptions: sweat glands and some skin/skeletal-muscle vasculature, which are sympathetically innervated but cholinergic (ACh onto muscarinic receptors), because the fibers there arose developmentally as cholinergic despite belonging to the sympathetic chain.

The adrenal medulla is the outlier that proves the rule: it's a modified sympathetic ganglion where the preganglionic fiber synapses directly on a chromaffin cell with no postganglionic neuron at all. ACh still acts on nicotinic receptors there, but instead of releasing a local neurotransmitter, the chromaffin cell dumps catecholamines straight into the bloodstream — about 80% epinephrine and 20% norepinephrine, a ratio set by an enzyme (PNMT) that needs cortisol delivered locally from the adjacent adrenal cortex to convert norepinephrine to epinephrine. That's why an ectopic pheochromocytoma, sitting too far from any adrenal cortex to bathe in that cortisol, secretes mostly norepinephrine instead — a real oral-boards-style detail worth holding onto.

Nicotinic receptors are ligand-gated ion channels — ACh binds, the channel opens, $Na^+$ and $K^+$ flow, the cell depolarizes in milliseconds. Muscarinic receptors are G-protein–coupled — slower, amplified, and capable of producing very different downstream effects (excitatory or inhibitory) depending on which muscarinic subtype and which G-protein is involved. This speed difference is the actual reason the ganglionic synapse (nicotinic) and the effector-organ synapse (muscarinic, in the parasympathetic division) behave so differently even though both use ACh.

> 🧠 **Memory hook**
>
> *nicotinic receptors are a light switch — flip it and the room is instantly lit, because ACh is directly gating an ion channel. Muscarinic receptors are a thermostat — you turn the dial and the room temperature drifts there over several seconds, because ACh is triggering a G-protein cascade that has to build before anything changes. Same building, two completely different response times.*

✎ **Draw it — neurotransmitter release map — preganglionic ACh/nicotinic universal, postganglionic ACh/muscarinic (parasympathetic + sympathetic-cholinergic exceptions) vs. NE/adrenergic (sympathetic), adrenal medulla direct nicotinic-to-bloodstream pathway**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## The Adrenergic Receptors: Mechanism Before Memorization

Don't memorize the α/β organ-effect table as disconnected trivia — every entry falls out of one of three second-messenger mechanisms, and once you have the mechanism the "which organ does what" becomes something you can derive under exam pressure instead of recall from a list you half-remember.

**α1** couples to Gq → phospholipase C → IP3 and diacylglycerol → intracellular $Ca^{2+}$ release. Rising intracellular $Ca^{2+}$ is a contraction signal in smooth muscle. So wherever you see α1, expect **contraction/constriction**: vascular smooth muscle in skin, kidney, and splanchnic beds (not cerebral vessels — see below); GI and bladder internal sphincters; the radial (dilator) muscle of the iris, producing mydriasis.

**α2** couples to Gi → inhibits adenylyl cyclase → falling cAMP. It sits presynaptically on the same sympathetic terminal that released the norepinephrine in the first place, so it functions as an autoreceptor — a negative-feedback brake that throttles further NE release once local concentration is high enough. It also inhibits insulin release from pancreatic β-cells, which is teleologically sensible: in a fight-or-flight state you want blood glucose to stay high and available, not being pulled into cells.

**β1, β2, and β3** all couple to Gs → stimulate adenylyl cyclase → rising cAMP → PKA activation. Same mechanism, three different postal codes: β1 is concentrated in the heart (SA node rate, AV node conduction velocity, ventricular contractility) and the kidney

(renin release from juxtaglomerular cells — the first step of the renin-angiotensin-aldosterone cascade you'll meet again in cardiovascular and renal physiology). β2 is concentrated in smooth muscle you want to *relax* — bronchioles, GI wall, bladder wall, and vascular smooth muscle of skeletal muscle beds — because rising cAMP in smooth muscle, unlike in the heart, produces relaxation rather than a bigger contraction. β3 is a genuinely more recently characterized receptor, most consistently tied to lipolysis in adipose tissue and (per newer pharmacology, though not universally taught the same way across textbooks — check what your specific slide deck and Costanzo each assign, since they don't fully agree) detrusor relaxation.

Epinephrine and norepinephrine are not interchangeable at these receptors. Both activate α1 about equally. Norepinephrine is a strong β1 agonist but weak at β2. Epinephrine activates β2 preferentially at concentrations norepinephrine can't reach it at. That asymmetry is the whole reason the postganglionic-NE-only sympathetic nervous system and the epi-dominant adrenal medulla produce overlapping but distinct physiology — and it sets up several of the field notes below.

> 🚑 **Field note**
>
> norepinephrine (Levophed) is the first-line vasopressor in septic and other distributive shock precisely because it is an α1-dominant agonist with only modest β1 activity and essentially no β2 activity — it raises mean arterial pressure through vasoconstriction without the reflex tachycardia and peripheral vasodilation you'd get from a drug that also hits β2. That's the pharmacologic reason it's chosen over epinephrine when the problem is "vessels are too dilated" rather than "the heart isn't pumping."

> 🚑 **Field note**
>
> dopamine is the textbook case of dose-dependent receptor selectivity, and it's worth knowing even though it's fallen out of first-line use in most services. At low infusion rates it preferentially activates dopaminergic D1 receptors, producing renal and mesenteric vasodilation (the old "renal-dose dopamine" concept, now considered largely without clinical benefit but still tested). At moderate rates it recruits β1 receptors, increasing heart rate and contractility. At high rates it spills over onto α1, producing vasoconstriction and a pressor effect. Same molecule, three different receptor stories, purely a function of concentration at the receptor.

**🚑 Field note**

phenylephrine is a pure α1 agonist with essentially no β activity, which makes it a clean vasoconstrictor/pressor that doesn't directly speed the heart — in fact, because it raises blood pressure sharply, the baroreceptor reflex often produces a reflex bradycardia on top of it. That's why it shows up both as a nasal decongestant (local α1 vasoconstriction shrinking swollen nasal mucosa vessels) and as a peri-anesthesia pressor when you specifically want to avoid tachycardia.

**🚑 Field note**

albuterol is a β2-selective agonist, and its bronchodilation is the Gs → cAMP → PKA → smooth muscle relaxation pathway acting on bronchiolar smooth muscle rather than the vasculature. Its familiar side effects — tremor and mild tachycardia — are the mechanism leaking outside the lungs: skeletal muscle also carries β2 receptors (tremor), and no β2 agonist is perfectly selective, so there's always a little β1 spillover (tachycardia) at higher doses.

**🚑 Field note**

nitroglycerin isn't an autonomic-receptor drug at all — it releases nitric oxide, which raises cyclic GMP in vascular smooth muscle rather than cyclic AMP — but it's worth holding next to β2 agonism precisely because it converges on the same functional endpoint (smooth muscle relaxation) through a completely separate second-messenger pathway. That's a useful contrast for understanding that "relax smooth muscle" is an outcome multiple mechanisms can reach, not a single receptor's private property. Clinically it's used mainly for its venodilating effect, which drops preload and myocardial oxygen demand in angina.

✎ **Draw it — adrenergic receptor mechanism table — receptor, G-protein, second messenger, cellular effect (contract vs. relax vs. modulate release), representative organs, prototype agonist/antagonist**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## The Cholinergic Receptors: Nicotinic Fast, Muscarinic Slow

Nicotinic receptors show up in exactly three places worth knowing: the skeletal muscle motor end plate (N1), all autonomic ganglia — both divisions (N2), and the chromaffin cells of the adrenal medulla (N2). Muscarinic receptors show up in every parasympathetic effector organ, plus the sympathetically-innervated sweat glands.

Atropine is the drug that makes this distinction earn its keep clinically.

**🚑 Field note**

atropine is a nonselective muscarinic antagonist — it blocks M2 as readily as M1/M3/M5. Its most field-relevant action is at the M2 receptor on the SA node: normally, vagal (parasympathetic) tone keeps resting heart rate below its intrinsic pacemaker rate by activating M2, which opens potassium channels directly through the Gi-protein subunit and slows depolarization. Block that receptor with atropine and you remove the brake, which is exactly why atropine is used for symptomatic bradycardia — you're not stimulating the heart, you're unmasking the SA node's true intrinsic rate by silencing vagal inhibition. In organophosphate poisoning, acetylcholinesterase is inhibited, ACh accumulates at every muscarinic synapse, and you get the classic muscarinic toxidrome remembered by the mnemonic SLUDGE — salivation, lacrimation, urination, defecation, GI upset, emesis — plus bronchorrhea, bronchospasm, and bradycardia. Atropine competitively displaces that excess ACh from muscarinic receptors and reverses those symptoms, but it does nothing for the nicotinic effects of the same poisoning (muscle fasciculations, weakness, potential respiratory muscle failure), which is why pralidoxime (2-PAM) has to be given alongside it to actually regenerate acetylcholinesterase.

**✎ Draw it — nicotinic vs. muscarinic receptor comparison — mechanism (ion channel vs. GPCR), location, prototype agonist/antagonist, speed of response**

## Organ-by-Organ Effects, Tied to Receptor and Mechanism

Most organs receive both divisions, working reciprocally — one activates, the other inhibits the same function. A handful of structures are sympathetic-only: sweat glands, most vascular smooth muscle, pilomotor (arrector pili) muscles, the liver, adipose tissue, and the kidney. There is no parasympathetic backup system for these — which is worth

remembering, because it means drugs or lesions that knock out sympathetic tone to these tissues have no compensating division to fall back on.

Heart: sympathetic β1 increases SA node firing rate, AV node conduction velocity, and ventricular contractility (Gs/cAMP raising intracellular $Ca^{2+}$ handling). Parasympathetic vagal M2 does the reverse at the SA and AV nodes — Gi acting directly on potassium channels, no second messenger needed, which is part of why vagal effects on heart rate are so fast.

> **Field note**
>
> glucagon's relevance to a beta-blocker overdose is a direct payoff of understanding that β1's downstream effect (raised intracellular cAMP → increased contractility and heart rate) doesn't require the β1 receptor itself if you can raise cAMP through a different receptor entirely. Glucagon receptors on cardiac myocytes are also Gs-coupled, so glucagon activates adenylyl cyclase and raises cAMP independent of the (pharmacologically blocked) β1 receptor. In a patient who has overdosed on a beta-blocker and is bradycardic/hypotensive because β1 is competitively occupied, glucagon bypasses the blockade entirely and restores inotropy and chronotropy through a parallel Gs pathway — a genuinely elegant piece of receptor pharmacology hiding inside what looks like an endocrinology drug.

Bronchioles: sympathetic β2 relaxes bronchial smooth muscle (bronchodilation); parasympathetic muscarinic (M3) contracts it (bronchoconstriction) and stimulates mucus secretion.

> **Field note**
>
> epinephrine is first-line in both anaphylaxis and cardiac arrest, but the receptor logic behind each indication is different, and understanding that difference is worth more than memorizing "epi for both." In anaphylaxis, the crisis is combined distributive shock (mast-cell-mediated vasodilation and capillary leak) plus bronchospasm and laryngeal edema — epinephrine's α1 action reverses the vasodilation and vascular permeability, and its β2 action bronchodilates and stabilizes mast cells, so all three receptor actions are pulling in the direction you need. In cardiac arrest, by contrast, the therapeutic value during CPR is almost entirely the α1-mediated peripheral vasoconstriction, which raises aortic diastolic pressure and therefore coronary perfusion pressure during chest compressions — the β1 inotropic/chronotropic effect is largely irrelevant to a heart that isn't perfused enough to respond, and the β effects raise myocardial oxygen demand, which is arguably a cost rather than a benefit in that setting. Same drug, same three receptors, but you're leaning on a different one depending on which crisis you're treating.

GI tract: sympathetic (α2 and β2, both ultimately lowering activity) relaxes the wall and contracts the sphincters — net effect, slow things down. Parasympathetic muscarinic does the opposite — contracts the wall, relaxes the sphincters — net effect, move contents forward. The wall-vs-sphincter reciprocity (relax wall + contract sphincter = stop; contract wall + relax sphincter = go) is the same logic reused at the bladder.

Bladder: sympathetic α1 contracts the internal sphincter and β2 relaxes the detrusor wall — together, this is the "storage" configuration, letting the bladder fill without leaking. Parasympathetic muscarinic reverses both — contracts the detrusor, relaxes the internal sphincter — the "voiding" configuration. The external sphincter is skeletal muscle under voluntary somatic control layered on top of this autonomic circuit, which is why continence has both an involuntary and a voluntary component.

Eye: sympathetic α1 contracts the iris's radial (dilator) muscle → mydriasis. Parasympathetic muscarinic contracts the iris's circular (sphincter) muscle → miosis, and also contracts the ciliary muscle for near-vision accommodation.

Salivary glands: both divisions stimulate secretion, but with different character — sympathetic input yields a smaller volume of thick, protein-rich (amylase-heavy) saliva, while parasympathetic input yields a larger volume of thin, watery, serous saliva. This is a genuine acinar-cell secretory difference, not just "more vs. less."

✎ **Draw it — organ-by-organ receptor and mechanism table — organ, sympathetic receptor + effect, parasympathetic receptor + effect, one line of mechanism each**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

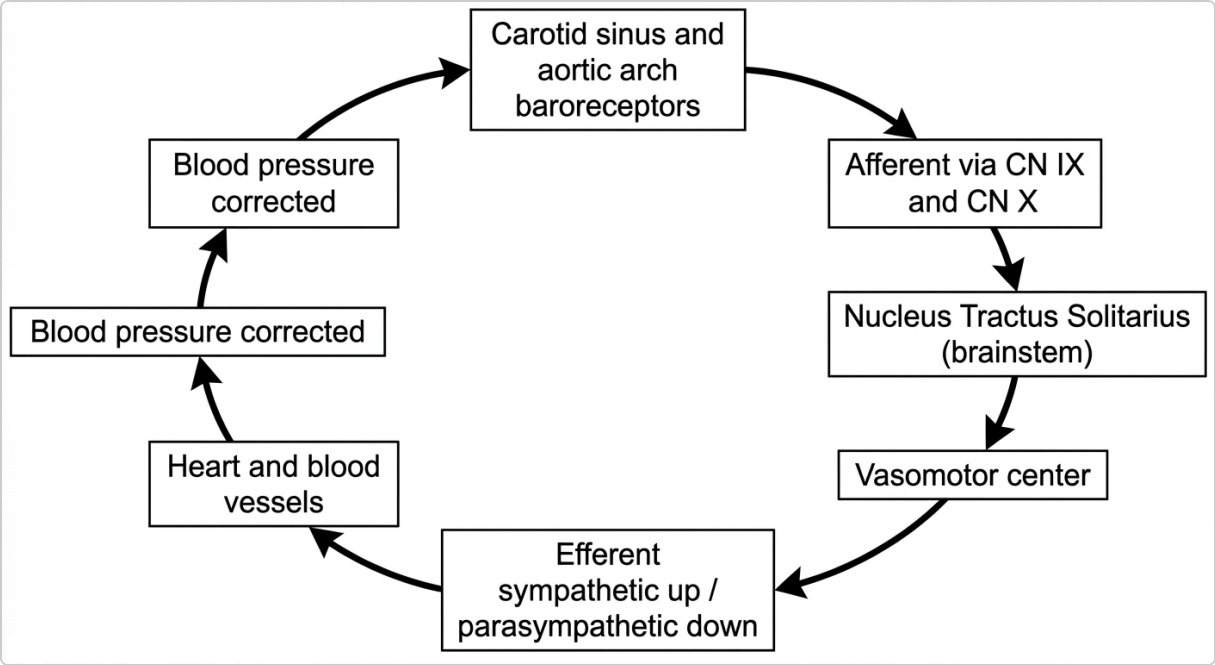
*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

## The Baroreceptor Reflex: Autonomic Blood Pressure Control

Stretch receptors in the carotid sinus and aortic arch continuously report blood pressure to the brainstem — carotid sinus input travels via the glossopharyngeal nerve (CN IX), aortic arch input via the vagus (CN X), both converging on the nucleus tractus solitarii (NTS) in the medulla. The NTS compares this input to a set point and adjusts sympathetic and parasympathetic outflow to the heart and vessels to correct any deviation — and, critically, it does this by adjusting both divisions in a coordinated (not competing) direction. A drop in blood pressure produces a simultaneous increase in sympathetic output (raising heart rate, contractility, and vascular resistance) and a decrease in parasympathetic output (removing the vagal brake on heart rate) — two levers pulled in the same direction at once.

> 🚑 **Field note**
>
> this reflex is why orthostatic hypotension (the lightheaded, occasionally syncopal drop in blood pressure on standing) is a baroreceptor-reflex problem worth taking seriously in the field, especially in dehydrated, hemorrhaging, or elderly patients, or patients on beta-blockers or other agents that blunt the reflex response. Standing pools blood in the lower extremities, transiently dropping venous return and arterial pressure; a healthy baroreceptor reflex corrects it within seconds via the exact sympathetic surge/parasympathetic withdrawal described above. When that reflex is blunted — autonomic neuropathy, volume depletion, or pharmacologic beta-blockade removing the compensatory tachycardia — the correction doesn't happen fast enough, and the patient goes down. It's also the physiologic reason orthostatic vital signs (lying vs. standing heart rate and blood pressure) are a real, mechanistically grounded field assessment rather than a box-checking exercise.

**✎ Draw it — baroreceptor reflex arc — sensor (carotid sinus/aortic arch stretch receptors), afferent pathway (CN IX, CN X), integration center (NTS → vasomotor center), efferent output (sympathetic ↑ / parasympathetic ↓ on a pressure drop, and the mirror image on a pressure rise)**




The baroreceptor reflex arc — *AI-generated illustration; verify against your own notes/slides.*

## Central Control: Brainstem, Hypothalamus, and the NTS

The hypothalamus is the highest coordinating center for autonomic output — it integrates temperature regulation, thirst, feeding behavior, and circadian input with autonomic and neuroendocrine (pituitary) output, and it can trigger the fight-or-flight response as an integrated package rather than organ-by-organ. The brainstem (midbrain, pons, medulla) houses the specific control centers — vasomotor, respiratory, micturition — and the NTS specifically functions as the major sensory relay station, receiving visceral afferents from the vagus, glossopharyngeal, and peripheral chemoreceptors and baroreceptors, then distributing that integrated information onward to the hypothalamus and cortex.

Cortical input runs both directions through this system. Fear, panic, chronic stress, and sleep deprivation can all measurably shift autonomic output (a panic attack is, physiologically, a real sympathetic surge, not just a subjective experience) — and conversely, strong visceral input (severe pain, nausea, dyspnea, bladder/bowel distension) can dominate cortical processing to the point that it's genuinely difficult to think about anything else. This bidirectional coupling is why a patient in visceral crisis is often a poor historian, and it's a real physiologic fact worth carrying into how you approach a patient assessment, not just a throwaway line.

✎ **Draw it — central autonomic control hierarchy — hypothalamus (integration, neuroendocrine link) → brainstem (midbrain/pons/medulla, specific control centers) → NTS (visceral sensory relay) → spinal cord/peripheral outflow**

## Exercise and the Redistribution of Cardiac Output

The ANS doesn't just react to deviations from a set point — it anticipates upcoming demand. At the onset of exercise, sympathetic output redirects cardiac output away from resting-state priorities (kidney, splanchnic circulation) and toward active skeletal muscle, via a combination of increased cardiac output (β1) and selective vasodilation in working muscle beds versus vasoconstriction in kidney and gut. At rest, roughly 20% of cardiac output goes to skeletal muscle; at peak whole-body exercise, that can approach 80%, almost entirely at the expense of renal and splanchnic flow. If muscle vasodilation is aggressive enough to threaten systemic blood pressure, the sympathetic nervous system will partially constrict even the working muscle vasculature to protect perfusion pressure — a real-time trade-off between local metabolic demand and systemic pressure maintenance, running continuously rather than as a single switch thrown at the start of exercise.

✎ **Draw it — exercise blood flow redistribution — resting vs. peak-exercise percent cardiac output to skeletal muscle, renal, and splanchnic beds, with the competing constrict/dilate signals labeled**

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

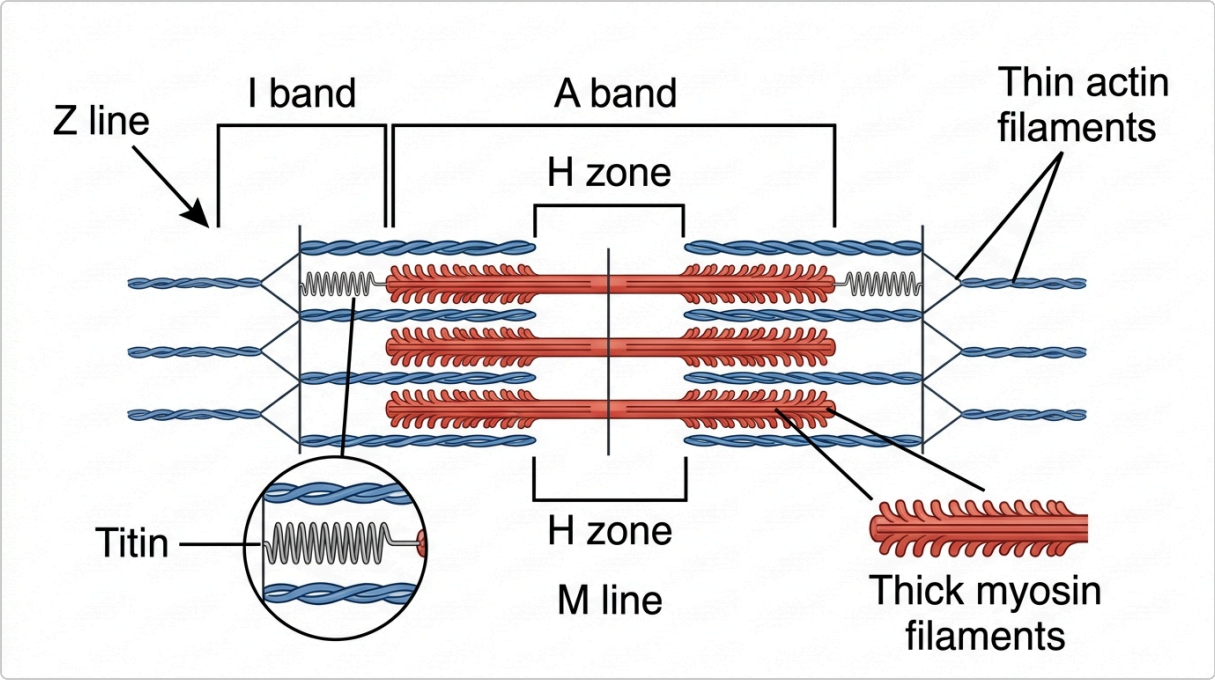
# Module 6 — Skeletal Muscle Mechanics

## Sarcomere Structure: The Machine Itself

Skeletal muscle is built as a hierarchy: muscle → fascicle → muscle fiber (a single, multinucleated cell, 10–80 μm in diameter, up to tens of centimeters long) → myofibril (up to ~8,000 per fiber) → sarcomere, the repeating contractile unit, roughly 2 μm at resting length. The sarcomere is bounded by two **Z lines**, which anchor thin (actin) filaments extending toward the center. Thick (myosin) filaments occupy the center and overlap the thin filaments at each end. This overlap pattern produces the classic bands: the **I band** (thin filament only, bisected by the Z line), the **A band** (the full length of the thick filament, including the zone of overlap), and the **H zone** (thick filament only, no overlap, centered on the **M line**).

Thin filaments are more than actin. Each is a two-stranded helix of globular actin (G-actin) monomers polymerized into filamentous actin (F-actin). Wound around this helix are **tropomyosin** dimers, each spanning seven actin monomers, physically blocking the myosin-binding sites at rest. Sitting on each tropomyosin is a **troponin complex** with three functionally distinct subunits: troponin C (binds $Ca^{2+}$), troponin I (inhibits the actin-myosin interaction at rest), and troponin T (anchors the complex to tropomyosin). Additional structural proteins — nebulin (a molecular ruler that sets thin filament length), tropomodulin and CapZ (cap each end) — aren't independently testable trivia; they exist because a sarcomere has to build filaments of *exact*, reproducible length every time, across trillions of sarcomeres in a single muscle, without a blueprint being re-read at each one.

Thick filaments are bundles of ~300 myosin molecules arranged tail-to-tail from the M line outward, giving the filament a bipolar structure that is the mechanical reason contraction pulls both Z lines *toward the center* rather than sliding the whole sarcomere in one direction. Each myosin molecule has two heavy chains forming an α-helical rod (the tail) and a pair of globular heads, each carrying an actin-binding site and $Mg^{2+}$-dependent ATPase activity — the myosin head is both the engine and the fuel gauge. The thick filaments themselves are tethered to the Z line by **titin**, a giant elastic protein (>3,000 kDa) that acts as a spring, keeping the thick filament centered and generating the passive, non-cross-bridge-dependent tension you feel when a resting muscle is stretched.




Sarcomere structure — *AI-generated illustration; verify against your own notes/slides.*

**🧠 Memory hook**

*Remember the troponin subunits by what each letter actually does — TnC Catches calcium, TnI Inhibits the interaction at rest, TnT Ties the whole complex down to Tropomyosin. C-I-T, in the order calcium arrives, the brake releases, and the anchor holds.*

**✎ Draw it — Sarcomere structure**

## Excitation-Contraction Coupling: From Nerve Signal to $Ca^{2+}$ Release

You already know the neuromuscular junction mechanism cold from the synaptic transmission module — α-motor neuron fires, ACh is released, binds nicotinic receptors on the motor end plate, opens ligand-gated cation channels, depolarizes the sarcolemma. What's new and skeletal-muscle-specific starts *after* that depolarization reaches the T tubules.

T tubules are invaginations of the sarcolemma that carry the action potential deep into the fiber, positioned where they abut the **terminal cisternae** of the sarcoplasmic reticulum (SR) — this T-tubule/two-cisternae arrangement is called a **triad**. The voltage-gated $Ca^{2+}$ channel in the T-tubule membrane (Ca_V1.1, historically called the **dihydropyridine receptor**, DHPR, after the drug class used to isolate it) sits mechanically coupled to the **ryanodine receptor** (RYR1), the SR's $Ca^{2+}$ release channel, across a ~15 nm gap. Depolarization causes a conformational change in Ca_V1.1 that is transmitted as a direct protein-protein interaction to RYR1 — no actual $Ca^{2+}$ needs to flow through Ca_V1.1 for this to work. This is **electromechanical coupling**, and it's a defining, testable difference from cardiac muscle, where the analogous channel (Ca_V1.2) instead *lets in* a trigger dose of extracellular $Ca^{2+}$ that then opens RYR2 (calcium-induced calcium release, "electrochemical coupling"). It's the reason skeletal muscle keeps contracting normally with zero extracellular $Ca^{2+}$, while cardiac muscle stops.

$Ca^{2+}$ released into the myoplasm binds troponin C, which repositions the troponin-tropomyosin complex and exposes the myosin-binding sites on actin — this is the step that actually licenses the cross-bridge cycle described next. Relaxation requires **SERCA** (sarco/endoplasmic reticulum $Ca^{2+}$-ATPase) to pump $Ca^{2+}$ back into the SR against its concentration gradient, consuming a substantial fraction of the ATP used during a contraction-relaxation cycle.

> 🚑 **Field note**
>
> succinylcholine, the paralytic most services carry for rapid-sequence intubation, works by binding the same nicotinic ACh receptor on the motor end plate and refusing to let go — a persistent depolarization that first causes visible fasciculations, then flaccid paralysis once voltage-gated $Na^+$ channels inactivate and stop responding. That's the NMJ side of the story you already know. But the reason succinylcholine is also on the anesthesia crash-cart nightmare list is downstream of what you just read: in a genetically susceptible patient (RYR1 mutation), succinylcholine — and volatile anesthetics like halothane — can trigger uncontrolled RYR1-mediated $Ca^{2+}$ release from the SR, producing malignant hyperthermia: sustained rigidity, tachycardia, hyperthermia, and a metabolic crisis that is fatal without immediate dantrolene, which works by blocking RYR1 directly. If you ever hear "history of malignant hyperthermia" in a patient handoff before a procedure requiring paralytics, that's not incidental trivia — it changes the drug choice.

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

**✎ Draw it — Excitation-contraction coupling (electromechanical, skeletal-specific)**

## The Cross-Bridge Cycle: How Filaments Actually Slide

Once myosin-binding sites are exposed, contraction proceeds as a four-state cycle, repeating as long as $Ca^{2+}$ stays elevated:

1. **Attachment.** In the resting state, myosin has already partially hydrolyzed ATP (it's "cocked," like a loaded spring) and has low affinity for actin. When $Ca^{2+}$ exposes the binding site, myosin binds actin, forming a cross-bridge.

2. **Power stroke.** The bound myosin head releases inorganic phosphate ($P_i$), triggering a conformational change — the "ratchet" — that pulls the thin filament roughly 10 nm toward the M line. ADP is released during or just after this step.
3. **Detachment.** A new ATP molecule binds the myosin head. ATP binding — not hydrolysis — is what drops myosin's affinity for actin and releases the cross-bridge. This point matters enormously downstream.
4. **Re-cocking.** Myosin partially hydrolyzes the newly bound ATP, recocking the head into the high-energy configuration, ready to bind actin again if $Ca^{2+}$ is still present.

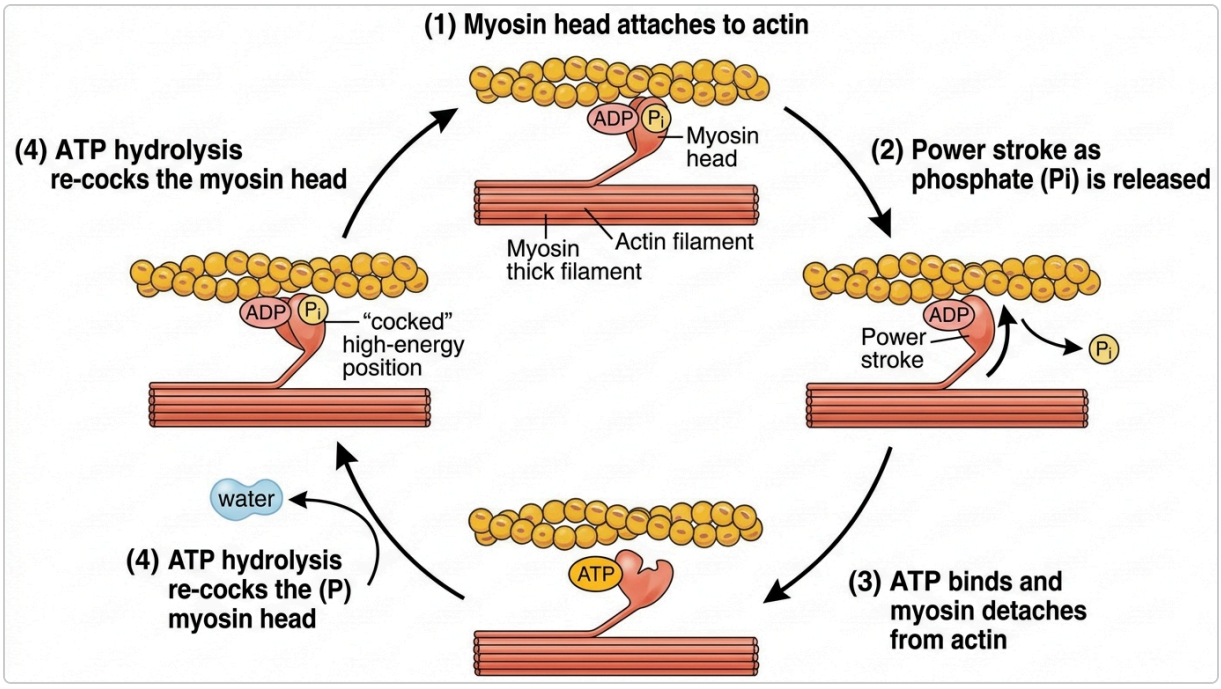
Each cycle only moves the filament ~10 nm, so generating a meaningful, sustained shortening requires many myosin heads cycling asynchronously and repeatedly — a molecular equivalent of a rowing team where each rower's stroke is independent, but the boat still moves smoothly because someone is always mid-pull.

The cycle stops in two very different ways, and confusing them is a classic exam trap. If $Ca^{2+}$ falls (SERCA has done its job, troponin releases $Ca^{2+}$, tropomyosin re-blocks the site) the cycle halts at step 1, in the relaxed, detached state — this is normal relaxation. If **ATP runs out** instead, the cycle halts at step 2→3, with myosin still bound to actin and unable to detach, because step 3 specifically requires ATP binding to break the cross-bridge. Every myosin head in the muscle locks onto actin and stays there: this is **rigor mortis**.

> 🚑 **Field note**
>
> rigor mortis is a direct, mechanistic readout of step 3 failing for lack of ATP — cellular ATP production stops within minutes of death, existing ATP is consumed finishing the cycles already in progress, and then every cross-bridge that completes its power stroke gets stuck because there's no ATP left to bind and pop it back off. Onset (typically 2–6 hours after death, complete by ~12 hours, resolving by 24–36 hours as the muscle proteins themselves begin to degrade) is one of the tools used for time-of-death estimation in the field, though it's temperature- and activity-dependent — a hot environment or a body that was seizing or fighting at the moment of death burns through ATP and glycogen faster and can shift the timeline earlier. It is not a permanent state of the tissue; it resolves once proteolysis breaks the actin-myosin linkage regardless of ATP.

**🧠 Memory hook**

*The cross-bridge cycle is a Groundhog Day loop — bind, pull, let go, reset, repeat, identical every time, and the only way out is either the $Ca^{2+}$ "alarm clock" turning off (relaxation) or someone taking away the day itself (no ATP — rigor). Bill Murray's character escapes his loop by changing something internally; a myosin head can't escape at all without ATP showing up to unstick it.*




The cross-bridge cycle — *AI-generated illustration; verify against your own notes/slides.*

**✎ Draw it — Cross-bridge cycle**

## The Length-Tension Relationship

Total tension in a muscle at any given length is the sum of two independent components. **Passive tension** comes from titin's elastic resistance to stretch — it behaves like a rubber band, contributing essentially nothing at short-to-moderate lengths and rising steeply once the muscle is stretched well beyond its resting range. **Active tension** comes from the cross-bridge cycle itself and depends entirely on how much thick-thin filament overlap is available for cross-bridges to form — this is a direct structural prediction of the sliding filament theory, and it's why the length-tension curve is one of the strongest pieces of evidence *for* that theory rather than just a description of it.

The active curve is a parabola with a real physical explanation at each landmark, not just a shape to memorize: at very long sarcomere lengths (~3.7 μm) actin and myosin no longer overlap at all, so no cross-bridges can form and active tension is zero. As length shortens toward the optimum (~2.0–2.2 μm, labeled L_O), overlap — and therefore the number of possible cross-bridges — increases, and active tension rises to its peak. Shorten the sarcomere further, below roughly 2.0 μm, and thin filaments from opposite ends of the sarcomere begin to overlap each other and collide near the M line, interfering with cross-bridge geometry and reducing force again. This is a real anatomic constraint, not a hand-wavy "too much of a good thing": you can predict, from a given sarcomere length alone, roughly where a muscle sits on this curve and how much force it can generate — which is exactly the kind of number-to-mechanism reasoning a boards-style question will ask for.

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

✎ **Draw it — Length-tension relationship**

## Motor Units, Recruitment, and Tetanus: Grading Force

A **motor unit** is one α-motor neuron plus every muscle fiber it innervates; because all fibers in a unit are the same fiber type and contract synchronously, the motor unit — not the individual fiber — is the smallest independently controllable unit of force. Skeletal muscle grades force by two independent mechanisms, and it's worth being precise about which does what:

**Recruitment (spatial summation)** increases force by activating *more* motor units. The **size principle** governs the order: small motor neurons have low firing thresholds and are recruited first, innervating small numbers of slow, fatigue-resistant fibers — appropriate for fine control and posture. As demand increases, progressively larger, higher-threshold motor neurons join in, recruiting large numbers of fast, powerful, fatigue-prone fibers. This is why picking up a pencil and picking up a barbell engage almost entirely different populations of motor units, not the same units firing harder.

**Frequency summation and tetanus** increase force from a *single* motor unit by increasing its firing rate, without recruiting any additional fibers. A single action potential produces a brief **twitch**: $Ca^{2+}$ release and reuptake happen faster than the mechanical response can fully develop, so twitch tension is submaximal. If a second stimulus arrives before the fiber has relaxed, the mechanical responses summate (**incomplete tetanus**); at a high enough stimulation frequency, myoplasmic $Ca^{2+}$ never drops back to baseline between stimuli, and the fiber sustains near-maximal tension continuously (**complete tetanus**). Critically, the peak $Ca^{2+}$ concentration reached during tetanus is *not* higher than during a single twitch — force increases because elevated $Ca^{2+}$ is *sustained*, giving the series-elastic elements in the muscle (connective tissue, titin, the cross-bridges themselves) time to fully stretch and transmit the tension the cross-bridges are generating. Slow-twitch fibers, with their longer twitch duration, fuse into tetanus at lower stimulation frequencies than fast-twitch fibers do.

> 🧠 **Memory hook**
>
> *Recruitment is "how many musicians are playing," frequency summation is "how fast each musician is playing" — you can make an orchestra louder either way, and a real crescendo (heavy lift) uses both at once.*

✎ **Draw it — Motor unit recruitment vs. frequency summation**

## Skeletal Muscle Fiber Types

Fiber types are classified by which myosin heavy chain isoform they express, and that single molecular difference — myosin ATPase activity — is the mechanistic root of essentially every other difference between fiber types. In humans, the three physiologically relevant types are **Type I (slow oxidative)**, **Type IIa (fast oxidative)**, and **Type IIx (fast glycolytic)**. Note: Type IIb is a real, distinct myosin isoform, but it's essentially a rodent fiber type — human skeletal muscle does not meaningfully express it, so when you see "Type IIb" in older or animal-model literature, mentally translate it to "the human equivalent is IIx." All fibers within a single motor unit express the same myosin isoform, because fiber type is a property conferred by the innervating motor neuron, not an intrinsic, fixed property of the muscle cell — this is demonstrable experimentally: cross-innervating a slow muscle's motor neuron onto a fast muscle (and vice versa) converts the contractile phenotype to match the new nerve, over weeks.

The differences compound across several parallel axes, not just contraction speed:

| | Type I | Type IIa | Type IIx |
|---|---|---|---|
| Myosin ATPase | Slow | Fast | Faster |
| SR $Ca^{2+}$-pumping rate | Moderate | High | High |
| Oxidative capacity (mitochondria) | High | High | Low |
| Glycolytic capacity | Moderate | High | High |
| Capillary density | Moderate | Moderate | Lower |

| | Type I | Type IIa | Type IIx |
|---|---|---|---|
| Fatigue resistance | High | Fairly high | Low |
| Motor neuron size / threshold | Small / low | Medium | Large / high |

High oxidative capacity and dense capillary supply are just as responsible for Type I fatigue resistance as low ATPase — a slow-twitch fiber isn't just "using energy slowly," it's also *better supplied* with the oxygen and enzymatic machinery to keep resynthesizing ATP indefinitely, which is why postural muscles can stay tonically active for hours without fatiguing.

> 🚑 **Field note**
>
> myasthenia gravis is a NMJ disease, not a fiber-type disease, but it presents in a way that's easy to mistake for one — progressive weakness that gets *worse* with sustained or repeated activity and improves with rest. Autoantibodies deplete or block nicotinic ACh receptors on the motor end plate, so with each successive action potential, fewer receptors are available to depolarize the end plate above threshold — the muscle isn't fatiguing metabolically the way a Type IIx fiber does after a max lift, it's failing to even get reliably activated. Classic field presentation: ptosis and diplopia that worsen through the day, or a patient who reports difficulty chewing that gets worse partway through a meal. It's an important differential to hold when a patient's "weakness" doesn't fit a clean myopathy or fatigue pattern.

> 🧠 **Memory hook**
>
> *"Type I, One speed, all day" (slow, oxidative, marathon-grade endurance) versus "Type IIx, the sprinter's proxy" for a short, explosive burst that gases out fast — think of the Tortoise (Type I, wins on endurance and reliability) versus the Hare (Type IIx, explosive but bonks) from Aesop's fable everyone already knows.*

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

✎ **Draw it — Skeletal muscle fiber types**

## Types of Contraction: Concentric, Eccentric, Isometric

**Concentric** contraction: the muscle generates more force than the load and shortens (curling a weight up). **Eccentric** contraction: the load exceeds the force the muscle is generating, so the muscle is fully activated but is forced to lengthen anyway (lowering that same weight slowly, or your quadriceps controlling a descent down stairs). **Isometric** contraction: force equals load, and muscle length doesn't change (holding a weight steady in front of you). A genuinely useful, testable point: eccentric contractions can generate tension well above a muscle's own maximal *tetanic* (concentric-equivalent) tension — you can lower more than you can lift — and the cross-bridge model that explains concentric shortening so cleanly does not fully explain eccentric mechanics; it remains an area of active research, not a settled textbook fact.

🚑 **Field note**

eccentric loading is the mechanistic reason downhill running or a heavy negative-rep training session leaves you far sorer the next day than a comparable amount of concentric work — the high force per cross-bridge during forced lengthening produces disproportionate microtrauma near the myotendinous junction, and delayed-onset muscle soreness peaks 24–48 hours later. It's also relevant on scene: a patient found down after a prolonged seizure, a crush injury, or a multi-hour extrication with sustained isometric/eccentric muscle loading against restraint is a rhabdomyolysis risk — muscle breakdown dumps myoglobin, potassium, and creatine kinase into circulation. Crush syndrome specifically refers to the reperfusion phase after a prolonged compression injury is released: that sudden washout of intracellular contents (especially $K^+$) into the bloodstream can produce life-threatening hyperkalemia and cardiac arrhythmia within minutes of extrication — which is why some protocols call for fluids and even empiric treatment for hyperkalemia *before* a long-pinned limb is freed, not after.

✎ **Draw it — Types of contraction**

## Muscle Architecture: Fiber Arrangement and Force

How fibers are arranged within a whole muscle — independent of fiber type — determines the muscle's force/range-of-motion tradeoff. **Parallel** architecture (fusiform, like the biceps, or non-fusiform/strap-shaped) runs fibers along the axis of force, maximizing shortening velocity and range of motion at the cost of raw force (fewer fibers per cross-sectional area). **Pennate** architecture (uni-, bi-, or multipennate, depending on how many rows of fibers angle into a central tendon) packs more fibers into a given volume by angling them relative to the axis of force, trading range of motion for a higher

**physiological cross-sectional area** and therefore more force — this is why densely pennate muscles like the gastrocnemius are built for power, not reach. **Convergent** architecture (pectoralis major) is a pennate variant where fibers fan out from a broad origin to a single narrow insertion point, concentrating force. **Circular** architecture (orbicularis oris/oculi) forms sphincters, where "shortening" means closing an opening rather than moving a joint.

✎ **Draw it — Muscle architecture and fiber arrangement**

## Bone-Muscle Lever Systems

A lever has three components: fulcrum (the joint), load (the resistance/weight being moved), and effort (the muscle's pull). The three classes are defined entirely by the *relative position* of these three points, and mixing up the tweezers example is a common source of confusion, so anchor it carefully:

- **First-class lever** (fulcrum between load and effort): a seesaw. Rare in the body — the joint between the skull and C1 vertebra, where posterior neck muscles (effort) balance the weight of the head (load) around the atlanto-occipital joint (fulcrum).
- **Second-class lever** (load between fulcrum and effort): a wheelbarrow. Standing on tiptoes — the ball of the foot is the fulcrum, body weight is the load in the middle, and the calf muscle pulling on the heel (behind the load) is the effort.
- **Third-class lever** (effort between fulcrum and load): by far the most common arrangement in the body, because it trades force for speed and range of motion — exactly what limbs need. A pair of tweezers: the hinge is the fulcrum, your fingers pinching *in the middle* are the effort, and whatever the tips are squeezing at the far

end is the load. Elbow flexion is the classic physiologic example: the elbow joint is the fulcrum, the forearm/hand is the load at the far end, and the biceps inserting on the radius — between the elbow and the hand — is the effort.

Because third-class levers place the effort closer to the fulcrum than the load, they always sacrifice mechanical force for a large gain in speed and excursion at the hand or foot — a small shortening of the biceps produces a much larger swing of the hand. That tradeoff, not raw strength, is why the vast majority of limb muscles are arranged this way.

*(No reference illustration built for this one — use the box above to sketch it, or check the lecture slides.)*

**✎ Draw it — Bone-muscle lever systems**

# Appendix A — Section 1 Case Studies (with Answers)

## Case Study 1 — Digoxin and the Cardiac Action Potential

**Vignette:** Digoxin is a drug used to treat heart conditions such as heart arrhythmias. The drug's primary mechanism of action involves inhibiting the $Na^+/K^+$ pump, mainly in the myocardium. The net result is an increase in intracellular $Na^+$, which subsequently alters the cardiac action potential and, ultimately, decreases heart rate. This change is not so much due to altered membrane potential as it is due to a resulting inactivation of the $Na^+/Ca^{2+}$ exchanger, and a consequent increase in intracellular $Ca^{2+}$ which directly affects the cell's contractile properties.

Cardiac muscle cells (which are primarily affected by the drug) are electrically excitable, contractile cells. Consider a situation where intracellular/extracellular ionic conditions are altered under Digoxin as follows:

| | **Intracellular (mM)** | **Extracellular (mM)** |
|---|---|---|
| $[Na^+]$ (normal) | 15 | 142 |
| $[K^+]$ (normal) | 150 | 4 |
| $[Cl^-]$ (normal) | 5 | 120 |
| $[Na^+]$ (Digoxin) | **50** | 142 |
| $[K^+]$ (Digoxin) | 150 | 4 |
| $[Cl^-]$ (Digoxin) | 5 | 120 |

**Question 1:** Use the Nernst equation below to calculate the Nernst potential for $Na^+$ under normal conditions and under the numbers attributed to Digoxin.

$E\_Na^+ (mV) = 61 \times \log_{10} ([Na^+]\_out / [Na^+]\_in)$

**Answer (1):** - Normal: $E\_Na^+ = 61 \times \log_{10}(142/15) =$ **59.5 mV** - Digoxin: $E\_Na^+ = 61 \times \log_{10}(142/50) =$ **27.6 mV**

**Case review-session note:** What does this mean? Reducing the concentration gradient reduces the potential required to maintain it.

**Question 2:** Use the Goldman equation below to calculate how the altered $[Na^+]\_in$ would affect the resting membrane potential. Calculate the value for normal and Digoxin conditions (tabulated above):

$E_{resting}$ (mV) = 61 × $\log_{10}$ ( ($[Na^+]_{out} \cdot P_{Na^+} + [K^+]_{out} \cdot P_{K^+} + [Cl^-]_{in} \cdot P_{Cl^-}$) / ($[Na^+]_{in} \cdot P_{Na^+} + [K^+]_{in} \cdot P_{K^+} + [Cl^-]_{out} \cdot P_{Cl^-}$) )

Relative permeabilities: $P_{K^+} = 1.0$, $P_{Cl^-} = 0.44$, $P_{Na^+} = 0.04$

**Answer (2):** - Normal: $E = 61 \times \log_{10}[(142 \times 0.04 + 4 \times 1 + 5 \times 0.44) / (15 \times 0.04 + 150 \times 1 + 120 \times 0.44)]$ = **−75.2 mV** - Digoxin: $E = 61 \times \log_{10}[(142 \times 0.04 + 4 \times 1 + 5 \times 0.44) / (50 \times 0.04 + 150 \times 1 + 120 \times 0.44)]$ = **−75.4 mV**

**Case review-session note:** Why is there such a small difference between the normal and Digoxin resting potentials? The two values barely differ under resting conditions **because the permeability for sodium is so small**. Contrast this with what happens during an action potential, when permeability abruptly changes due to the opening of voltage-gated sodium channels.

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## Case Study 2 — Ischemic Stroke and the Ischemic Cascade

**Vignette:** During ischemic stroke, blood flow is impeded due to a blockage in the cerebral vasculature. This typically results in a decrease in blood flow to a select region of the brain, determined by the location of the blockage in the cerebral vasculature. Among a host of adverse events, collectively referred to as the ischemic cascade, is a significant increase in intracellular $Ca^{2+}$. This can ultimately lead to uncontrolled excitation among many interconnected excitatory neurons.

**Question 3:** What are pre-synaptic and postsynaptic mechanisms that could lead to uncontrolled excitation? (Note that the glutamate channel is also somewhat permeable to $Ca^{2+}$, and entry will depend on the time the receptors spend open.)

**Answer (3):** - **Presynaptic:** At the presynaptic side, this will elicit synaptic vesicle fusion and release of neurotransmitter. This dumps a significant amount of neurotransmitter (largely excitatory) at synapses, which will bind to and open glutamate receptors. These ligand-gated ion channels are permeable to $Ca^{2+}$ as well, so constant excitation causes an even greater accumulation of $Ca^{2+}$ in the cell, which further promotes synaptic fusion and neurotransmitter release in the next cell. - **Postsynaptic:** Ischemia causes a decrease in ATP (oxygen depletion), causing $Na^+/K^+$ pumps to stop working. $Na^+$ accumulates inside the cell, $K^+$ accumulates outside. The membrane potential is destroyed, and the new membrane potential keeps voltage-gated calcium channels (VGCC) open. $Ca^{2+}$ accumulates inside the cell, activating enzymes that cause disarray inside the cell, including those that send vesicles to the membrane — glutamate is

released into the synaptic cleft constantly. Constant glutamate release plus anoxic depolarization keeps NMDA (N-methyl-D-aspartate) channels open, and $Mg^{2+}$ ions are no longer blocking $Ca^{2+}$ entry through them. The postsynaptic neuron then has other processes failing or changing direction; cell death usually happens to all cells involved.

**Case review-session note:** As far as *why* the increase in intracellular $Ca^{2+}$ occurs: $Ca^{2+}$ concentration is partly also held down through $Na^{+}/Ca^{2+}$ exchangers. At elevated intracellular $Na^{+}$ concentrations, which happens when $Na^{+}/K^{+}$ pumps are inactive due to a lack of energy, $Ca^{2+}$ can accumulate intracellularly.

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## Case Study 3 — Mary, Multiple Sclerosis and Visual Evoked Potentials

**Vignette:** While on a biking trip, Mary, a 29-year old piano instructor experienced unusual difficulty reading signage and clumsiness using her arms while steering her bike. Upon completing her route she felt excessively fatigued. These symptoms persisted for a few days, after which she also began experiencing difficulty coordinating her hands while teaching. This prompted her to visit her primary care physician, who subsequently referred her to a neurologist. MRI findings revealed demyelination & plaques in the corpus callosum. The physician classified her event as a clinically isolated syndrome of multiple sclerosis (MS), which is a neuroinflammatory/neurodegenerative disease that degrades the myelin insulation of neurons in the central nervous system. Specifically, it affects oligodendrocytes (as opposed to the Schwann cells of the peripheral nervous system). Approximately 10 months later, however, Mary's symptoms resurfaced: she experienced the same fatigue, vision disturbances and arm issues. A secondary MRI revealed more distal demyelination & plaques; prompting a diagnosis of relapsing-remitting MS (RRMS). By taking Rebif (interferon beta, which decreases inflammatory cells in the brain), staying rested, and avoiding hot weather, Mary finds that her relapses are much less frequent.

Prior to Mary's first MRI, she was sent to neurophysiology to check her visual evoked potentials (VEPs). This involves measuring the transmission of sensory information throughout the brain, typically in response to changing patterns on a video screen. When patterns change, electrodes at the scalp record a series of "waves." They show a summed representation of large numbers of action potentials, and each peak/trough represents a major processing station in the brain (e.g., thalamus, primary visual cortex). The spacing

between the peaks is proportional to the speed of sensory information conduction from structure to structure in the brain.

*(This question references normal-vs-abnormal VEP waveform figures — not reproducible here, check the original PDF.)*

**Question 4:** Mary's VEPs are shown compared with a healthy recording. What feature is the clearest indication of the abnormal condition? Can you explain what leads to it?

**Answer (4):** The negative "peak" at ~100 ms latency in the normal condition appears closer to ~140 ms in the MS case (a decrease in amplitude is also seen). This represents a **delay in conduction of action potentials** from the sensory organs through the other regions in the brain. This is due to degradation of the myelination that surrounds the axons of neurons (loss of myelin on axons — whether oligodendrocytes or Schwann cells — causes conduction velocity to be reduced or halted altogether; saltatory conduction is lost). Myelination increases the speed of action potential propagation because it reduces the membrane's electrical capacitance. Thus, reduced myelination reduces the speed of conduction, and the action potentials will arrive at target structures at later times. In Mary's VEP specifically, the delay reflects decreased continuous conduction in the visual pathway due to oligodendrocytes being affected (a CNS process).

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## Case Study 4 — Tetanus Infection

**Vignette:** A 21-year-old man presents to a rural emergency center with a 1-day history of progressive stiffness of the neck and jaw, difficulty swallowing, stiff shoulders and back, and a rigid abdomen. Upon further questioning, the patient reports that the stiff jaw was the first symptom, followed by the stiff neck and difficulty swallowing. On examination he is noted to have stiffness in the neck, shoulder, and arm muscles. He has a grimace on his face that he cannot stop voluntarily and an arched back from contracted back muscles. The physician concludes that the patient has "tetanic" skeletal muscle contractions. A 3-cm laceration is noted on his left foot. The patient reports sustaining the laceration about 7 days ago while he was plowing the fields on his farm. He has not had a tetanus booster. He is diagnosed with a tetanus infection, and an injection of the tetanus antitoxin is given.

**Question 5:** What is the molecular basis for initiation of contraction in skeletal muscle?

**Answer (5):** Muscle tension and the process of contraction is regulated by release of $Ca^{2+}$ from internal stores of the sarcoplasmic reticulum (SR) into the sarcoplasm (the cytoplasm of the sarcomere). Without $Ca^{2+}$, myosin cannot bind to actin. The release of

$Ca^{2+}$ is regulated by nerve impulses sent down through the somatic nervous system via motor neurons. The nerve impulse triggers the release of acetylcholine (ACh) across the synaptic cleft of the neuromuscular junction (NMJ), where it binds to acetylcholine receptors on the motor end plate on the surface of the sarcolemma (the membrane of a muscle fiber). Upon binding ACh, the ligand-gated channels open to permit cations to pass through, including both $Na^+$ and $K^+$. Because of the higher driving force on $Na^+$, the net effect is an influx of $Na^+$, which depolarizes the membrane (this summed depolarization is the end-plate potential, EPP). If the membrane potential reaches threshold for opening voltage-gated $Na^+$ channels, an action potential may be initiated, propagating along the sarcolemma and down the transverse tubules (T tubules, invaginations into the sarcolemma). The action potential triggers dihydropyridine (DHP) receptors in the T tubules, which then subsequently signal the connected ryanodine receptors (RyR) to open the "doorway" of the sarcoplasmic reticulum and let $Ca^{2+}$ out into the sarcomere. The $Ca^{2+}$ then binds to the troponin complex (specifically troponin C), causing a conformational change that shifts tropomyosin and exposes myosin-binding sites on actin, allowing myosin-actin (cross-bridge) interaction and contraction.

Cross-bridge cycle: (1) $Ca^{2+}$ binds troponin C, causing a conformational change; (2) myosin head + ADP + Pi binds the exposed actin site, and Pi is released; (3) power stroke occurs, ADP is released; (4) ATP binds to myosin, breaking the cross-bridge; (5) ATP is hydrolyzed and the myosin head cocks back to reset the cycle. The sum of all sarcomere cross-bridge cycles produces sarcomere contraction, and the sum of sarcomere contractions produces whole muscle contraction. Relaxation occurs when ACh is degraded by acetylcholinesterase in the NMJ and the SERCA pump (using ATP) pumps $Ca^{2+}$ back into the sarcoplasmic reticulum.

**Question 6:** Tetanus toxin is retrogradely propagated along motor neurons up to the synapses of inhibitory neurons in the spinal cord, where it blocks the release of γ-aminobutyric acid (GABA) from inhibitory interneurons that synapse onto motor neurons (those motor neurons extend from the spinal cord into muscles and synapse at the NMJ with muscle fibers). How could blocking the release of GABA from the inhibitory neurons that synapse with motor units in the spinal cord subsequently affect downstream signaling of these motor units with skeletal muscle? How would this lead to uncontrolled rigid muscle contraction and muscular stiffness, such as "lockjaw"?

Answer choices given in the review session: A) Downstream signaling would not be affected B) Downstream signaling would be weakened and reduced in rate and intensity C) Downstream signaling would be completely interrupted and stopped **D)**

**Downstream signaling would be increased in intensity and repetition (correct)**

**Answer (6):** Blocking the release of GABA from spinal interneurons causes a downstream effect. Somatic motor neurons at the NMJ are purely excitatory. GABA normally elicits inhibitory postsynaptic potentials (IPSPs) in the postsynaptic cell by opening channels that selectively permit $Cl^-$ to enter, hyperpolarizing the motor neuron and reducing its firing rate (GABA → GABA_A receptor → increased $Cl^-$ influx → hyperpolarizes the cell and decreases action potentials in motor neurons). This normally counterbalances excitatory postsynaptic potentials and tempers the continuous action potentials that repeatedly evoke muscle contraction. As tetanus toxin prevents GABA release, this "braking" effect on stimulation of the sarcolemma is lost. Constant release of ACh maintains action potentials, and without an inhibitory signal, the motor neuron fires continuously (constant wave summation without inhibitory postsynaptic potentials causes tetanus). Because of the increased repetitive stimulation of the motor neuron, the $Ca^{2+}$ released from the SR remains bound to troponin and extends the time for cross-bridge cycling, resulting in muscles that do not relax. This produces rigid, unopposed muscle contraction and spasm — on both flexor and opposing muscles, causing stiffness, lockjaw, and an arched back. The overactivity of muscle contraction due to failed inhibition of motor neurons causes generalized continuous contraction of the musculature.

**FYI (review-session):** Tetanus is a neurologic disorder caused by the toxin produced by the bacterium *Clostridium tetani*, an anaerobic gram-positive motile rod found worldwide in soil, inanimate environments, animal feces, and occasionally human feces. Contamination of wounds with C. tetani spores is common. With diminished GABA-mediated inhibition, the resting firing rate of motor neurons increases; because calcium released from the SR remains bound to troponin, muscles do not relax. Symptoms often begin in facial muscles ("lockjaw") and progress down the neck, shoulder, back, and extremities. Generalized spasms may jeopardize breathing. Antitoxin is administered to bind and neutralize circulating, unbound toxin; wounds should be explored, cleaned, and debrided. Muscle spasm can be controlled with medications such as diazepam (a GABA agonist). Protection of the airway is essential.

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## Case Study 5 — Pufferfish Poisoning (Tetrodotoxin)

**Vignette:** One evening during a recent trip to New York City, Dr. Marshall Westwood from the Montana Technical Institute sat down to a meal of pufferfish and rice at a

seafood restaurant. Within an hour of returning to his hotel room, Dr. Westwood felt numbness in his lips and tongue, which quickly spread to his face and neck. Before he could call the front desk, he began to feel pains in his stomach and throat, which produced feelings of nausea and eventually severe vomiting. Fearing that he had eaten some "bad fish" for dinner, Dr. Westwood called a local hospital to describe his condition. The numbness in his lips and face made it almost impossible for him to communicate, but the hospital staff managed to at least understand the address he gave them and they sent an ambulance in response. As Dr. Westwood was rushed to the hospital, his breathing became increasingly difficult and he suffered paralysis that spread to the upper body, arms, face, and head. At the hospital, after a quick examination by the doctors (including talking to the hotel staff which told them Dr. Westwood had eaten pufferfish), they determined he was a victim of pufferfish poisoning. The active toxin in the tissues of this fish is a chemical called tetrodotoxin (TTX). TTX is in a class of chemicals known as neurotoxins due to the fact that it has its effects on neurons. Specifically, tetrodotoxin blocks voltage-gated sodium ion channels on neurons. Dr. Westwood was treated with intravenous hydration, gastric lavage, and activated charcoal. Symptoms gradually resolved, and he was discharged the following day with no residual symptoms.

**Question 7:** Why would Dr. Westwood have experienced numbness after eating pufferfish?

**Answer (7):** TTX (the active toxin in pufferfish) interrupts transduction and relay of sensory information in sensory nerve fibers by impeding the generation of action potentials. Blocking voltage-gated $Na^+$ channels prevents sensory neurons from depolarizing and firing action potentials, so touch, temperature, and pain signals never reach the brain — this loss of sensory information is experienced as "numbness."

**Case review-session note:** Of the listed choices, only "Block the opening of voltage-gated $Na^+$ channels" would impede *initiation* of the action potential (blocking $K^+$ channels would impair repolarization instead; depolarizing the resting membrane potential or increasing excitatory neurotransmitter release would each make an action potential easier, not harder, to trigger).

**Question 8:** Why did Dr. Westwood also experience paralysis (the loss of function of muscle)?

**Answer (8):** TTX inhibition of voltage-gated $Na^+$ channels prevents action potentials in motor neurons. Paralysis can be caused by failure of motor neurons to fire — muscles contract only after receiving signals from motor neurons. Since TTX prevents the generation of action potentials in these neurons (a decrease in axonal action potentials

means voltage-gated $Ca^{2+}$ channels at the nerve terminal don't open, ACh exocytosis decreases, and not enough ACh reaches across the synaptic cleft — the motor end plate doesn't get activated and skeletal fibers don't depolarize or contract), every aspect of muscle contraction would be prevented. The result is paralysis in the affected areas ("flaccid" paralysis, since the muscle can't be activated at all).

**Question 9:** *(References a labeled action-potential graph with points A–E — not reproducible here, check the original PDF.)* If TTX blocks voltage-gated $Na^+$ channels, which part of the action potential would be impacted?

Answer choices: A) Point A, B) Point B, C) Point C, D) Point D, E) Point E

**Answer (9): C** — Voltage-gated $Na^+$ channels must open to enable $Na^+$ to diffuse into the cell, depolarizing it. When TTX binds to $Na^+$ channels, it prevents $Na^+$ from passing through, which prevents the cell from depolarizing and blocks the cell from generating an action potential. Point C corresponds to the rapid depolarizing upstroke that normally occurs once the cell reaches threshold — with TTX bound, this upstroke would not occur. (Point A = resting potential; B = subthreshold depolarization/EPSP toward threshold at −55 mV; D = repolarization; E = afterhyperpolarization/return to rest.)

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## Case Study 6 — Shy-Drager Syndrome and the Autonomic Nervous System

**Vignette:** A 54-year-old male is diagnosed with having Shy-Drager Syndrome. This syndrome is a neurological disease resulting in the degeneration of preganglionic neurons of the sympathetic and parasympathetic nervous system, along with autonomic control centers in the hypothalamus. As a result, both the sympathetic and parasympathetic divisions of the autonomic nervous system are profoundly impaired.

**Question 10:** Which organ systems and bodily functions would you expect to be adversely affected by degeneration of the autonomic nervous system?

**Answer (10):** The autonomic nervous system controls the function of virtually every organ system and every bodily function, usually as a result of interplay between the sympathetic and parasympathetic divisions. Impaired function of the autonomic nervous system, as seen in Shy-Drager syndrome, would be predicted to adversely affect every organ system. This failure affects control of arterial blood pressure; function of the lung bronchioles, which regulate the flow of air into the lungs; motility, secretion, digestive, and absorptive functions of the gastrointestinal tract; filling and emptying of the bladder;

male sexual response, including erection and ejaculation; function of the eye muscles that control near and far vision; activity of sweat glands involved in thermoregulation; and metabolic functions of the liver. For these reasons, the patient would be expected to be very sick and experience things such as impotence, urinary difficulties, dizziness when standing up (orthostatic hypotension, from loss of sympathetic vasoconstriction/baroreflex), double vision, indigestion, diarrhea, and heat intolerance.

Practice-test-style detail (from the case-study answer sheet, organized by control center):

| **Control Center** | **Organ/System** | **Effect of ANS degeneration** |
|---|---|---|
| Upper thoracic spinal cord; dorsal motor nucleus of vagus (CN X) | Cardiovascular system | SA node loses reciprocal control — heart rate no longer adjusted; baroreflex stops working; loss of sympathetic vasoconstriction; low BP |
| Lumbar spinal cord L1–L3; sacral S2–S4 (pelvic splanchnic nerves) | Urinary bladder | Problem filling the bladder; problem emptying (incontinence) |
| Same as bladder | Male genitals | Erection (parasympathetic) and ejaculation (sympathetic) both affected |
| Midbrain → CN III; upper thoracic cord → superior cervical ganglion | Eye | Radial muscle (dilator) and circular muscle (constrictor) both affected |
| Thoracolumbar cord → celiac/superior mesenteric ganglia; vagus (CN X); sacral cord S2–S4 | GI tract | GI dysmotility, constipation, gastroparesis, impaired gastric secretions |
| Sympathetic system | Skin | Thermoregulation impaired |
| Thoracic spinal cord; vagus (CN X) | Respiratory | Bronchial tone regulation decreased |
| Hypothalamus | — | Autonomic reflexes lose their control as well |

# Appendix B — Section 1 Practice Test (Full, with Answer Key)

*Correct answers are marked in bold immediately after each question; explanations from the official answer key follow in italics where provided.*

**1)** Complete the table below to compare and contrast modes of membrane transport and diffusion.

| | **Passive Transport** | **Active Transport** | **Simple Diffusion** | **Facilitated Diffusion** |
|---|---|---|---|---|
| Moves molecules down a gradient | X | | X | X |
| Occurs without additional energy | X | | X | X |
| Moves molecules against a gradient | | X | | |
| Requires protein assistance | (not all forms of passive transport require a transport protein) | X | | X |
| Requires energy input | | X | | |
| Aquaporin | X | | | |
| Transports small, nonpolar molecules (i.e. $O_2$, $CO_2$) | X | | X | |
| Osmosis | X | | X | X |
| Occurs without protein | X | | X | |
| Na+/K+ Pump | | X | | |

| | Passive Transport | Active Transport | Simple Diffusion | Facilitated Diffusion |
|---|---|---|---|---|
| Transports large, polar, or charged molecules | X | X | | X |

**2)** Increasing the firing rate of a nerve axon from 1/sec to 2/sec, will cause the muscle fibers in the activated single motor unit to: A) Increase the number of fibers that are activated from 20 to 60 percent of the total B) Decrease tension (force strength) due to reduced frequency summation **C) To be activated more frequently, but not change the number of fibers contracting** *Increasing the firing rate of a nerve axon (motor neuron) that innervates a specific group of muscle fibers will activate the motor unit more frequently (leading to frequency summation and tetanus), which increases muscle tension, but will not increase the number of muscle fibers that are activated.*

**3)** If ATP is depleted in a skeletal muscle fiber then: A) Overall $Ca^{2+}$ concentration decreases B) The muscle fiber relaxes **C) The muscle fiber becomes rigid (such as occurs during rigor mortis)** D) Myosin polymerizes E) The SERCA pump continues to move $Ca^{2+}$ back into the sarcoplasmic reticulum *The binding of ATP to myosin is required for myosin to release actin. Without ATP, myosin will not release actin and the muscle fiber remains rigid (not relaxed). Depletion of ATP does not affect overall $Ca^{2+}$ concentration in the muscle fiber nor does it affect myosin polymerization. The SERCA pump requires ATP to pump $Ca^{2+}$ back into the sarcoplasmic reticulum, so without ATP, $Ca^{2+}$ will not be pumped back into the sarcoplasmic reticulum after its release.*

**4)** A fusiform (parallel fiber) muscle, such as the sartorius, is preferentially designed to generate: A) A greater torque B) Power **C) Greater range of motion** D) Heat *The sartorius muscle is a thin, long, superficial muscle in the anterior compartment of the thigh and is a classic example of a fusiform parallel muscle. Many parallel muscles do not generate much strength (and thus do not generate much heat since their consumption of ATP is relatively low) or torque, but instead offer a greater range of motion.*

**5)** The advantage for generating force that a pennate muscle (fibers oriented at an oblique angle) has lies in: A) Its greater length B) The lesser number of mitochondria interfering with the contractile process **C) The greater number of muscle fibers for a given volume of muscle** D) The fewer number of muscle fiber in each motor unit E) The greater amount of myoglobin in each fiber *Pennate muscles typically have a greater amount of muscle fibers for a given volume of muscle, which adds to their strength.*

**6)** Within a skeletal muscle, increasing the ratio of slow twitch fibers to fast twitch fibers improves the resistance to fatigue because: **A) The increased aerobic capacity of the slow twitch fibers will make the muscle more fatigue resistant** B) The increased glycolytic capacity of the IIA fibers will make the muscle more fatigue resistant C) The greater number of sarcomeres in the IIB fiber will lessen the amount of work a muscle fiber will have to do D) The increased blood supply to the vastus lateralis will decrease the volume of that muscle E) The greater number of fibers in a motor unit will mean that fewer fibers are recruited at any one time *Fast twitch muscle fibers depend on stored ATP, creatine phosphate and glycogen for energy (ATP), which are all fairly shallow energy pools that cannot maintain sustained substantial ATP quantities. In contrast, slow twitch muscles contain myoglobin and utilize oxygen and the Krebs cycle to generate ATP. The Krebs cycle is a much more robust and prolonged generator of ATP in slow twitch muscle fibers, and thus the slow twitch muscles fibers are more resistant to fatigue.*

**7)** Simple diffusive flux is inversely proportional to: A) Temperature **B) Molecular size** C) Mobility of solute D) Surface area E) Concentration gradient *All of the answer options affect simple diffusion flux, but only molecular size has an inverse relationship with flux. In other words, the larger the molecule, the more reduced its ability to move across a membrane by simple diffusion.*

**8)** If eserine (an acetylcholinesterase inhibitor) is applied to the NMJ then: **A) The rate and number of action potentials elicited in the postsynaptic muscle fiber will increase** B) More acetylcholine will be formed and released from the motor neuron C) DHP receptor will no longer be able to detect an action potential and signal the ryanodine receptor to trigger $Ca^{2+}$ release D) The duration of the action of acetylcholine present in the NMJ would be decreased *By blocking and reducing the activity of acetylcholinesterase in the synaptic cleft of the neuromuscular junction, acetylcholine remains longer in the synaptic cleft thus increasing its activation of nicotinic acetylcholine receptors on the motor end plate. This would increase the rate and number of actions potentials elicited in the postsynaptic muscle fiber.*

**9)** $Ca^{2+}$ ions regulate skeletal muscle contraction by: A) Releasing myosin from actin **B) Binding to troponin C** C) Polymerizing G-actin into actin filaments D) Promoting the synthesis of ATP E) Increasing the rate constant for binding of ATP to myosin *$Ca^{2+}$ binds to troponin C of the troponin complex, which consequently causes a shift in tropomyosin's position on actin. This shift reveals the myosin binding sites on actin thus allowing myosin-actin interaction to occur.*

**10)** All of the following are correlated with smaller motor units (as compared to larger units) EXCEPT: A) Small number of activated muscle fibers B) Associated muscle fibers are relatively fatigue-resistant **C) Associated slow twitch muscle fibers are mostly larger in size than fast twitch muscle fibers** D) High rate of tonic (slower long lasting) activity E) Muscle fibers predominantly use oxidative metabolism *Smaller motor units fire early on during activity and are mostly made up of slow twitch muscle fibers (Type I fibers). In general, slow twitch muscle fibers are smaller and less powerful than fast-twitch muscles.*

**11)** Which of the following would be important for increasing skeletal muscle tension: A) Increasing the diameter of muscle fibers B) Increasing the number of active motor units C) Increasing the firing rate of motor neurons D) Increasing the size of the activated motor units **E) All of the above** *Increasing the thickness (diameter) of the activated muscle fibers, the number of activated motor units, the firing rate of motor neurons and the size of activated motor units would all increase skeletal muscle tension.*

**12)** The rate of free diffusion of a lipid soluble molecule across the plasma cell membrane is influenced by all of the following, EXCEPT: A) Temperature B) The substance's mass C) The substance's electrical charge D) The substance's shape E) The substance's size **F) All of the above** *All of these variables affect the free diffusion movement of a lipid soluble molecule across a plasma membrane. The greater the temperature and the smaller the mass, shape and size of a molecule will all increase the rate of free diffusion for that molecule. As for a substance's electrical charge, electrically charged molecules do not pass through a membrane by simple diffusion and thus the molecule's rate of free diffusion would be affected as it would be zero. Recall that for free diffusion of a molecule to occur, that molecule must not have a charge.*

**13)** Which of the following is NOT a regulated variable: A) Plasma glucose concentration B) Concentration of $O_2$ and $CO_2$ **C) Respiration rate** D) The pH (concentration of $H^+$) E) Temperature *Respiration rate is controlled by the brainstem, but it does not have a super tight range that it always has to fall within. Depending on what a person is doing, respiration rate might need to be increased (such as occurs during exercise) or may fall considerably (such as during sleep). In contrast, the other variables are all normally controlled in a very tight range regardless of activity.*

**14)** At rest when a postural muscle is exerting minimal force, you would expect that the force is being contributed primarily by: A) Large motor units of Type I fibers B) Large motor units of Type II fibers **C) Small motor units of Type I fibers** D) Small motor units of Type II fibers *Type I fibers are the weakest and are the first to be recruited to fire, particularly when minimal force is needed.*

**15)** Homeostatic variables are special because: A) Only homeostatic variables can be regulated B) There is a unique physiological system to control them C) There is no set range to maintain the level **D) There are typically multiple systems working to limit the range of the variable** E) They have no pre-determined set-point *Homeostatic variables do have a pre-determined set-point to some extent and have multiple systems (both neural and multiple endocrine/humoral systems) to control them.*

*Questions 16–19 use the terms: A. Type I Fiber, B. Type II_A Fiber, C. Type II_B Fiber*

**16)** The fiber type **least** susceptible to injury: **A** *The weakest muscles are also the least prone to injury.*

**17)** During a prolonged high intensity exercise, the rise in plasma levels of lactate are contributed most by recruitment of: **C** *Type IIB fibers utilize anaerobic respiration the most and thus are inclined to generate the most lactate of any muscle fiber type.*

**18)** The fastest rate of contraction: **C** *Type IIB fibers offer the greatest strength and speed of any muscle fiber type.*

**19)** The most prevalent fiber type in a large powerful fusiform muscle: **C** *Since it is a large powerful muscle, it must contain Type IIb fibers.*

**20)** The permeability coefficient: A) is the amount of a particular substance that diffuses across a unit area B) is only specific to water filtration across a membrane **C) is the rate at which a molecule can cross a membrane such as a lipid bilayer** D) is not factor in the simple diffusion of small lipid soluble molecules across a membrane *The permeability coefficient is the rate at which a molecule can cross a membrane, such as a lipid bilayer, and this affects the simple diffusion of that molecule. It refers to a molecule, not a liquid. The filtration coefficient refers to water filtration across a membrane, while the diffusion coefficient refers to the amount of a particular substance that diffuses across a unit area.*

**21)** Which is a true statement regarding passive facilitated transport: A) There is no maximum rate of transport for carriers **B) The rate of transport for an ion is dependent on the number of participating channels** C) Carrier mediated transport is typically faster than ion channel transport D) Metabolic energy is required to maintain transport *Increasing the number of participating passive channels increases the rate of passive facilitated transport. Carriers have a maximum rate of transport and are typically slower in transporting molecules than ion channels are because they require a conformation change. Passive facilitated transport does not require (metabolic) energy.*

**22)** What kind of channel increases ionic permeability when neurotransmitter binds to it? **A) Ligand-gated channels** B) Voltage-gated channels C) Mechanosensitive channels D) Co-transporters *Ion channels that require a neurotransmitter to open its "gate" are ligand gated channels. These channels move just one type of ion and thus are not co-transporters. Voltage-gated channels open in response to a change in the membrane potential. Mechanosensitive channels open in response to mechanical force, such as pressure.*

**23)** For neurons to bring more potassium ions ($K^+$) inside the cell than outside, which type of transport is most likely to be used? A) Simple diffusion B) Facilitated diffusion **C) Active transport** D) None of the above *$K^+$ is in greater concentration inside cells than outside. Thus, to move $K^+$ into a cell against its concentration gradient, active transport (which utilizes energy in the form of ATP) is required.*

**24)** Glutamate receptors at excitatory synapses in the central nervous system are examples of what type of channel? **A) Ligand-gated channel** B) Voltage-gated channel C) Mechanosensitive channel D) Leakage channel *Glutamate binding to the glutamate receptors opens the gating of the channel and allows ions to flow through. Thus, since the glutamate receptor channel is opened by ligand binding, it is referred to as a ligand-gated channel.*

**25)** What type of transporter or channel will restore the ion balances and move ions against their gradient? **A) Uniporter B) Symporter** C) Ligand-gated channel D) Voltage-gated channel E) Mechanosensitive channel *(Answer key highlights both A and B.) Ligand-gated, voltage-gated and mechanosensitive channels are all passive channels that allow ion flux down their gradient, not against their gradients. Uniporters are membrane transport proteins that transport a single species of molecules across a membrane; they may be used to transport a molecule down or against its gradient, and thus can be involved in active or passive transport. Symporters are integral membrane proteins that transport two different molecules across the cell membrane in the same direction; like uniporters, they can move molecules down or against a concentration gradient, and thus can be involved in passive or active transport.*

**26)** Which steps in muscle contraction require ATP? A) Cross bridge detachment B) $Ca^{2+}$ sequestration C) $Na^+/K^+$ ATPase to establish the $Na^+$ gradient across the cell membrane **D) All of the above** *ATP binding to myosin permits myosin to release actin, and thus promotes cross bridge detachment. $Ca^{2+}$ sequestration back into the sarcoplasmic reticulum requires activity of the SERCA pump, which is an ATPase…thus requires ATP. $Na^+/K^+$ ATPase uses ATP to generate the $Na^+$ and the $K^+$ gradient across the cell membrane.*

*INFORMATION for questions 27–29: $Na^+$ and $Cl^-$ are placed on opposite sides of a cell with a semi-permeable membrane: Outside = 10 mM $Na^+$, 10 mM $Cl^-$; Inside = 100 mM $Na^+$, 100 mM $Cl^-$. Using the Nernst Equation, $E_{Na^+} = -60$ mV. Approximate combined-ion membrane potential formula: $E(mV) = 60 \times \log_{10}( ([Na^+]_{out} \cdot P_{Na^+} + [Cl^-]_{in} \cdot P_{Cl^-}) / ([Na^+]_{in} \cdot P_{Na^+} + [Cl^-]_{out} \cdot P_{Cl^-}) )$. Recall $\log(1) = 0$.*

**27)** A membrane potential of –30 mV is recorded. This membrane is: A) Impermeable to $Na^+$ B) Impermeable to $Cl^-$ C) Equally permeable to $Na^+$ and $Cl^-$ D) More permeable to $Cl^-$ **E) More permeable to $Na^+$**

**28)** A membrane potential of 0 mV is recorded. This membrane is: A) Impermeable to $Na^+$ B) Impermeable to $Cl^-$ **C) Equally permeable to $Na^+$ and $Cl^-$** D) More permeable to $Cl^-$ E) More permeable to $Na^+$

**29)** A potential of +30 mV is recorded. This membrane is: A) Impermeable to $Na^+$ B) Impermeable to $Cl^-$ C) Equally permeable to $Na^+$ and $Cl^-$ **D) More permeable to $Cl^-$** E) More permeable to $Na^+$

*Explanation for 27–29: A great way to handle these "relative permeability" questions is to consider the extremes: take the case where the membrane is impermeable to one of them. If it's permeable ONLY to $Na^+$, set $P_{Cl^-}$ to 0, and $E = 60 \times \log_{10}([Na^+]_{out}/[Na^+]_{in}) = 60 \times \log_{10}(10/100) = 60 \times \log_{10}(0.1) =$ **$-60$ mV**. If the membrane is only permeable to $Cl^-$, set $P_{Na^+} = 0$, and $E = 60 \times \log_{10}([Cl^-]_{in}/[Cl^-]_{out}) = 60 \times \log_{10}(100/10) = 60 \times \log_{10}(10) =$ **+60 mV**. If the membrane is equally permeable, E = 0 mV. So, anything closer to –60 mV indicates the membrane is closer to the negative extreme (only permeable to $Na^+$), and anything closer to +60 mV indicates greater permeability to $Cl^-$.*

**30)** Which channels play the most significant role in repolarizing a neuron following the peak of an action potential? A) Voltage-gated $Ca^{2+}$ channels B) Voltage-gated $Na^+$ channels C) Nicotinic acetylcholine receptors **D) Voltage-gated $K^+$ channels** E) Ligand gated chloride channels *After the peak of the action potential, voltage-gated $K^+$ channels open, which increases the permeability to $K^+$ and, given that voltage-gated $Na^+$ channels have just inactivated, those $K^+$ channels provide the only permeability and thus their permeability dominates the membrane potential.*

**31)** In a neuron with generic electrochemical properties and presence of voltage-gated $Na^+$ and $K^+$ channels, if the membrane permeability for $Na^+$ is abruptly increased, in the first 1 msec: A) The influx of $Na^+$ will significantly increase the intracellular concentration of $Na^+$ B) The outward flux of $K^+$ will exactly counter the influx of $Na^+$ C) The membrane potential for the neuron will not change D) The Nernst potential for $Na^+$ will decrease **E)**

**The membrane potential will depolarize relative to its resting potential** *Why the others are incorrect: (A) During an action potential, relatively few ions actually enter or leave the cell — membrane potential is determined by the permeabilities and resting concentrations (Goldman equation). (B) Increasing $Na^+$ permeability affects $Na^+$ current, not $K^+$. (C) Permeability has changed, so membrane potential will change. (D) The Nernst equation does not give information on net membrane potential when there are multiple ion species (that's the Goldman equation) — if a membrane were permeable only to one ion, the equilibrium potential for that cell would equal the Nernst potential for that ion.*

**32)** The peak of the action potential in a neuron usually does not reach E_Na (Nernst potential) primarily because: A) Voltage gated potassium channels begin to open while the voltage-gated $Na^+$ channels are still open B) The concentration gradient of $Na^+$ is only a tenth of that of $K^+$ **C) Voltage-gated $Na^+$ channels begin to inactivate before the E_$Na^+$ is reached** D) Voltage-gated $K^+$ channels begin to inactivate before the peak is reached E) The $Na^+$ concentration gradient reduces significantly within 2 msec

**33)** Action potential threshold is reached when: A) The membrane potential is halfway between the Nernst potentials E_$K^+$ and E_$Na^+$ B) The $Na^+$ conductance equals the $K^+$ conductance C) The $Na^+$ Nernst potential is greater than the potassium Nernst potential **D) The membrane potential surpasses the opening threshold for voltage-gated $Na^+$ channels but is less than the inactivation threshold for the channels** E) The number of inactivated $Na^+$ channels equals the number of activated channels

**34)** All of the following statements about the refractory period are correct EXCEPT: A) The relative refractory period duration depends on the number of de-inactivated sodium channels B) It partly determines the maximum firing rate of the cell **C) A neuron is completely unable to fire another action potential during the relative refractory period** D) The amplitude of an action potential elicited during the relative refractory period depends in part on the kinetics of voltage-gated potassium channels E) The definition of a refractory period is unaffected by the activity of ligand-gated channels *C is the answer because it is untrue: during the relative refractory period, some $Na^+$ channels have become de-inactivated, thus they are able to open again and initiate another action potential.*

**35)** All of the following are true statements about voltage-gated $Na^+$ channels EXCEPT: A) In a generic neuron, their probability of opening increases following an EPSP B) They can exist in three conformations that differ in terms of $Na^+$ conductance C) They can be blocked with tetrodotoxin D) In myelinated neurons, they are highly expressed at Nodes

of Ranvier **E) The duration of their open state depends only on time rather than membrane potential** *E is the answer because the open state is dependent on membrane potential (after all, it is a "voltage-sensitive" channel).*

**36)** All of the following statements about acetylcholine are true EXCEPT: A) It is synthesized in the presynaptic terminal from choline and acetylCoA B) It can elicit EPSPs at some synapses C) In some acetylcholine receptors its effects can be mimicked by nicotine **D) It directly activates voltage gated channels in the muscle membrane** E) At the neuromuscular junction, its effects are always excitatory *D is the answer because the only thing that activates voltage gated channels is voltage — they are not ligand-gated channels.*

**37)** All of the following are true statements about nicotinic acetylcholine (Ach) receptor channels at the neuromuscular junction (NMJ) EXCEPT: A) The NMJ Ach channels are permeable to both $Na^+$ and $K^+$ **B) The current that flows through the channel (when open) is independent of the postsynaptic cell's membrane potential** C) At the neuromuscular junction, the junctional fold increases the surface area over which these channels are expressed D) More generally, there are a variety of ACh receptors that differ based on specific subunits E) The ACh receptors at the NMJ can be agonized by nicotine *B is the answer because a cell's voltage will impact the force that drives ions across the membrane.*

**38)** *(References a figure showing an action potential waveform with a "Stimulus" arrow pointing to its descending/falling phase — not reproducible here, check the original PDF.)* During an action potential, the postsynaptic cell receives an EPSP delivered at the time point indicated by the arrow. In response to the stimulus: A) An action potential of smaller magnitude may occur B) An action potential of normal magnitude will occur C) An action potential of normal magnitude will occur but will be delayed D) An action potential will occur but will not have an overshoot **E) An action potential will not occur** *This is because this is the point at which $Na^+$ channels become inactivated, and it is the $Na^+$ permeability change that causes the initial spike.*

*Questions 39–41 reference a diagram of a nerve action potential with labeled points 1 (at −70 mV baseline), 2 (rising phase), 3 (peak, +35 mV), 4 (falling phase), and 5 (undershoot below −70 mV) — not reproducible here, check the original PDF.*

**39)** At which labeled point on the action potential is $Na^+$ closest to its equilibrium (a.k.a. reversal) potential? A) 1 B) 2 **C) 3** D) 4 E) 5 *For same reason as explained in the previous question (this is the peak, where $Na^+$ permeability/conductance is at its highest relative dominance).*

**40)** What process is responsible for the change in membrane potential that occurs between point 1 and point 3? **A) Increased $Na^+$ permeability** B) Movement of $Na^+$ out of the cell C) Increased $K^+$ permeability D) Movement of $K^+$ out of the cell E) Activation of the $Na^+/K^+$ pump F) Inhibition of the $Na^+/K^+$ pump *The first step of an action potential is depolarization, which is due to voltage-gated $Na^+$ channels opening, meaning permeability increases for them.*

**41)** What process is responsible for the change in membrane potential that occurs between point 3 and point 4? A) Increased $Na^+$ permeability B) Movement of $Na^+$ out of the cell **C) Increased $K^+$ permeability** D) Movement of $K^+$ out of the cell E) Activation of the $Na^+/K^+$ pump F) Inhibition of the $Na^+/K^+$ pump *During this period, voltage-gated $K^+$ channels open, and combined with the fact that voltage-gated $Na^+$ channels have become inactivated, the membrane potential will basically draw toward the $K^+$ Nernst potential (which you get if the membrane is only permeable to $K^+$).*

**42)** A muscle cell has an intracellular [$Na^+$] of 14 mM and an extracellular [$Na^+$] of 140 mM. What would the membrane potential be if the muscle cell membrane were permeable only to $Na^+$? ($E_{ion} = 60 \times \log_{10}([ion]_{out}/[ion]_{in})$) A) −80 mV B) −60 mV C) 0 mV **D) +60 mV** E) +80 mV *$60 \times \log10(140/14) = 60 \times \log10(10) = 60$.*

**43)** The velocity of conduction of action potentials along a nerve will be increased by: A) Stimulating the $Na^+/K^+$ pump B) Inhibiting the $Na^+/K^+$ pump C) Decreasing the diameter of the nerve **D) Myelinating the nerve** E) Lengthening the nerve fiber *Myelination reduces loss of current through the membrane and also reduces the membrane capacitance, which means that charges inside the axon are less attracted to charges outside the axon, consequently the action potential can travel faster and further.*

**44)** A newly developed local anesthetic blocks voltage-gated $Na^+$ channels in neurons. Which of the following effects on the action potential would it be expected to produce? **A) Reduce the neuron's ability to fire an action potential** B) Shorten the absolute refractory period C) Abolish the hyperpolarizing after potential D) Increase the $Na^+$ equilibrium potential E) Decrease the $Na^+$ equilibrium potential *An action potential is initiated when voltage-gated $Na^+$ channels open, thus preventing them from opening would suppress action potentials.*

**45)** At the muscle end plate, acetylcholine (ACh) directly: A) Opens voltage-gated $Na^+$ channels, causing the cell to depolarize toward the $Na^+$ equilibrium potential B) Opens $K^+$ channels, causing the cell to depolarize toward the $K^+$ equilibrium potential C) Opens $Ca^{2+}$ channels, causing the cell to depolarize toward the $Ca^{2+}$ equilibrium potential **D) Increases permeability to $Na^+$ and $K^+$ causing the cell to depolarize toward the**

**equilibrium potential of $Na^+$** E) Increases $Na^+$ and $K^+$ permeability, causing the cell to hyperpolarize to a value halfway between the $Na^+$ and $K^+$ equilibrium potentials *This happens because the ions that have the most pressure to move are the ones furthest from their equilibrium potentials. For example, if a membrane's permeability is closER to the equilibrium potential for one ion, there will not be much force driving that current — so the mixed $Na^+/K^+$ permeability drives the cell toward $Na^+$'s equilibrium potential (the ion further from its own equilibrium), not exactly halfway*.

**46)** An inhibitory postsynaptic potential: A) Depolarizes the postsynaptic cell due to the opening of $Na^+$ channels B) Depolarizes the postsynaptic cell due to the opening of $K^+$ channels C) Hyperpolarizes the postsynaptic cell due to the opening of $Ca^{2+}$ channels **D) Hyperpolarizes the postsynaptic cell due to the opening of channels permeable to $Cl^-$**

**47)** Which of the following is generally an inhibitory neurotransmitter in the central nervous system (CNS)? A) Norepinephrine B) Glutamate **C) γ-Aminobutyric acid (GABA)** D) Serotonin E) Histamine

**48)** What effect will the destruction of myelin have on the signaling capability of a neuron? **Answer:** The action potential will travel much more slowly than it should, or it may even die out before it reaches the axon terminal.

**49)** In motor neurons, Botulinum toxin (a.k.a. Botox) prevents the fusion of synaptic vesicles with the membrane for acetylcholine release, thereby effectively blocking acetylcholine release. If small concentrations of the toxin are injected, how could this cosmetically reduce facial wrinkles? **Answer:** Botox is the common name of the toxin botulinum toxin type-A produced by the bacteria *Clostridium botulinum*. If injected intramuscularly, it blocks action potentials' downstream effect at the NMJ (by preventing ACh release), thereby causing paralysis of the muscles at the site of injection. When injected into muscles in the face, the muscles are unable to contract (contraction normally would cause skin to furrow). Paralysis lasts for 3–6 months. This toxin enters the motor neuron and prevents the normal formation of SNARE complexes required for synaptic vesicle exocytosis and release of neurotransmitters. Thus, the muscle cell associated with this neuromuscular junction is much less likely to be activated.

**50)** The correct temporal sequence for events at the neuromuscular junction is: A) Action potential in the motor nerve; depolarization of the muscle end plate; uptake of $Ca^{2+}$ into the presynaptic nerve terminal **B) Uptake of $Ca^{2+}$ into the presynaptic terminal; release of acetylcholine (ACh); depolarization of the muscle end plate** C) Release of ACh; action potential in the motor nerve; action potential in the muscle D)

Uptake of $Ca^{2+}$ into the motor end plate; action potential in the motor end plate; action potential in the muscle E) Release of ACh; action potential in the muscle; action potential in the muscle end plate *(A) is incorrect because uptake of $Ca^{2+}$ into the presynaptic nerve terminal occurs before the depolarization of the muscle (motor) end plate. (C) is incorrect because the action potential in the motor nerve occurs before release of ACh. (D) is incorrect because the action potential in the motor end plate occurs before the uptake of $Ca^{2+}$ into the motor end plate. (E) is incorrect because action potential in the muscle end plate occurs before the action potential in the muscle is generated.*

**51)** A 42-year-old man with myasthenia gravis notes increased muscle strength when he is treated with an acetylcholinesterase (AChE) inhibitor. The basis for his improvement is: A) Increased amount of acetylcholine (ACh) released from motor nerves **B) Increased levels of ACh at the muscle end plates** C) Increased number of ACh receptors on the muscle end plates D) Increased amount of norepinephrine released from motor nerves E) Increased synthesis of norepinephrine in motor nerves *AChE inhibitors increase strength because they block the breakdown of acetylcholine in neuromuscular junctions, and thus the presence of acetylcholine remains high enough in the synaptic cleft to continue activating ACh receptors and generating end plate potentials and action potentials in muscle fibers. Norepinephrine is not synthesized or released from motor nerves. AChE inhibitors do not increase ACh release from motor nerves and do not increase ACh receptors on the muscle end plate.*

**52)** Which of the following temporal sequences is correct for excitation–contraction coupling in skeletal muscle? A) Increased intracellular [$Ca^{2+}$]; action potential in the muscle membrane; cross-bridge formation **B) Action potential in the muscle membrane; depolarization of the T tubules; release of $Ca^{2+}$ from the sarcoplasmic reticulum (SR)** C) Action potential in the muscle membrane; splitting of adenosine triphosphate (ATP); binding of $Ca^{2+}$ to troponin C D) Release of $Ca^{2+}$ from the SR; depolarization of the T tubules; binding of $Ca^{2+}$ to troponin C *(A) is incorrect because increased intracellular [$Ca^{2+}$] occurs after the generation of action potentials in the muscle membrane. (C) is incorrect because the splitting of ATP in myosin occurs after binding of $Ca^{2+}$ to troponin C (which allows myosin to bind to actin). (D) is incorrect because the depolarization of the T tubules occurs before the release of $Ca^{2+}$ from the SR.*

**53)** In skeletal muscle, which of the following events occurs before depolarization of the T tubules in the mechanism of excitation-contraction coupling? **A) Depolarization of the sarcolemmal membrane** B) Opening of $Ca^{2+}$ release channels on the sarcoplasmic reticulum (SR) C) Uptake of $Ca^{2+}$ into the SR by $Ca^{2+}$-adenosine triphosphatase (ATPase)

D) Binding of $Ca^{2+}$ to troponin C E) Binding of actin and myosin *After ACh is released by the motor nerve and activates the motor end plate on the muscle, depolarization of the sarcolemmal (muscle) membrane occurs, resulting in depolarization of the T tubules that extend inward through the muscle fibers around the myofibrils. Events in the other four answer options occur after T tubule depolarization.*

**54)** Which of the following causes rigor mortis in skeletal muscle? A) Lack of action potentials in motoneurons B) An increase in intracellular $Ca^{2+}$ level C) A decrease in intracellular $Ca^{2+}$ level D) An increase in adenosine triphosphate (ATP) level **E) A decrease in ATP level** *ATP binding to myosin is required for myosin to release actin after performance of the power stroke. Without ATP, myosin stays connected to actin causing prolonged muscle contraction as myosin cannot release actin, thus muscle fibers remain stiff.*

**55)** The effector organs for the somatic motor nervous system are: A) Cardiac muscle B) Smooth muscle C) Glands **D) Skeletal muscle** E) All of these 4 *The somatic nervous system exclusively innervates skeletal muscle, not visceral organs. The ANS innervates internal organs (such as the heart), glands and even smooth muscle…but not skeletal muscle.*

**56)** In the ANS, the preganglionic axons synapse with postganglionic neurons in the: **A) Autonomic ganglia of the peripheral nervous system** B) Brain stem C) Spinal cord D) Dorsal root ganglia E) Skeletal muscle cells *In both the sympathetic and parasympathetic divisions of the ANS, preganglionic axons synapse with postganglionic neurons in the peripheral nervous system, not in the central nervous system (which includes the brain stem and spinal cord). The dorsal root ganglia lie right next to the spinal cord and vertebrae, but are not the major site of preganglionic and postganglionic neuron synapse. The ANS does not synapse with skeletal muscle.*

**57)** Which autonomic receptor predominantly mediates dilation of the bronchus? A) Adrenergic α receptors B) Adrenergic β1 receptors **C) Adrenergic β2 receptors** D) Cholinergic muscarinic receptors E) Cholinergic nicotinic receptors *α1 adrenergic receptors constrict blood vessels, including vessels of the skin, GI tract, kidney and brain. α2 adrenergic receptors play a role in negative feedback and reduce norepinephrine and insulin release. β1 adrenergic receptors increase heart rate, blood pressure, renin release (kidneys) and ghrelin release in the GI tract. β2 adrenergic receptors relax smooth muscle (including dilating arteries and bronchi), the GI tract, the bladder and will slightly reduce blood pressure. Nicotinic cholinergic receptors are found in the synapse between pre- and postganglionic neurons (for both divisions of the*

*ANS). Muscarinic cholinergic receptors are found on the target tissues where the postsynaptic ganglion of the parasympathetic division synapses.*

**58)** Which of the following characteristics is correct for the parasympathetic division of the ANS: **A) Preganglionic neurons emerge from the brainstem and sacral region of the spinal cord** B) Pre- and postganglionic neurons synapse in the paravertebral ganglion C) Many postganglionic neurons for each preganglionic neuron D) Short preganglionic neurons, long postganglionic neurons E) All of these are correct *All parasympathetic nerves emerge from the brainstem and sacral region of the spinal cord. The other 3 answer options are true for the sympathetic, but not parasympathetic, division of the ANS.*

**59)** About 80% of the cells in the adrenal medulla secrete: A) Acetylcholine **B) Epinephrine** C) Norepinephrine *After activation by the sympathetic nervous system (via acetylcholine release by the preganglionic neuron at its synapses on the adrenal gland), the adrenal gland releases epinephrine and norepinephrine, although 80% of what is released is epinephrine, while the other 20% is norepinephrine.*

**60)** All preganglionic neurons of the sympathetic and parasympathetic divisions are: A) Adrenergic B) Cholinergic C) Myelinated D) Unmyelinated **E) Both B and C** *All preganglionic neurons of the sympathetic and parasympathetic divisions are indeed myelinated and release acetylcholine at their synapse with their target, thus making them cholinergic.*

**61)** Which autonomic receptor is activated by epinephrine released from the adrenal medulla and causes vasodilation? A) Adrenergic α receptors B) Muscarinic M3 receptors **C) Adrenergic β2 receptors** D) Cholinergic muscarinic receptors E) Cholinergic nicotinic receptors

**62)** Which of the following is a feature of the sympathetic, but not the parasympathetic nervous system? A) Ganglia located in the effector organs B) Long preganglionic neurons C) Preganglionic neurons release norepinephrine D) Preganglionic neurons release acetylcholine (ACh) **E) Preganglionic neurons originate in the thoracic segment of the spinal cord** F) Postganglionic neurons synapse on effector organs G) Postganglionic neurons release epinephrine H) Postganglionic neurons release Ach *Answer option A is not true of the sympathetic as sympathetic ganglia are typically relatively far from effector organs (in the parasympathetic, postganglionic neurons can synapse as short as 1 mm from effector organs). Options B and H are features of the parasympathetic, not the sympathetic. Options D and F are features of both divisions. Options C and G are not features of either division.*

**63)** Which autonomic receptor predominantly mediates an increase in heart rate? A) Adrenergic α receptors **B) Adrenergic β1 receptors** C) Adrenergic β3 receptors D) Cholinergic muscarinic receptors E) Cholinergic nicotinic receptors

**64)** Which autonomic receptor mediates secretion of epinephrine by the adrenal medulla? A) Adrenergic α receptors B) Adrenergic β1 receptors C) Adrenergic β2 receptors D) Cholinergic muscarinic receptors **E) Cholinergic nicotinic receptors** *After activation by the sympathetic nervous system, acetylcholine binds to and activates cholinergic nicotinic receptors on the adrenal gland; the adrenal gland then releases epinephrine and norepinephrine (80% epinephrine, 20% norepinephrine).*

**65)** The vagus nerve (CN X) interfaces with parasympathetic control of the: A) Heart B) Lungs C) Stomach D) Intestines **E) All of the above** *The vagus nerve is the longest and most complex of the 12 pairs of cranial nerves. It transmits information to and from the brain to tissues and organs throughout the body, including the heart, lungs and GI system.*

**66)** Both the somatic nervous system and the preganglionic neurons of the autonomic nervous system have myelinated axons to speed transmission of nerve impulses. **A) True** B) False

**67)** Activation of the sympathetic nervous system will do all of the following EXCEPT: A) increase heart rate B) increase respiration rate C) inhibit digestion **D) constrict pupils** *Sympathetic activation is fight-or-flight, which includes increasing heart rate, increasing respiration, reducing GI activity, shifting blood flow to skeletal muscle, and dilation (not constriction) of the pupils.*

**68)** What is the primary basis of the length-tension relationship in skeletal muscle? A) Recruitment of motor units of longer muscle lengths B) The amount of $Ca^{2+}$ released at different muscle lengths **C) The degree of overlap between thick and thin contractile filaments** D) The amount of tetanization at different muscle lengths E) All of the above *The length-tension relationship of skeletal muscle describes the amount of tension produced by a muscle fiber as a feature of its length. Under isometric conditions, the maximal force produced will differ as the muscle lengthens or shortens, and the reason for that change depends on the degree of overlap between thick (myosin) and thin (actin) filaments.*

**69)** The nucleus tractus solitarii (NTS) integrates input from variable sources (sympathetic and parasympathetic afferent nerves, brainstem structures, hypothalamus, cerebral cortex, chemoreceptors and baroreceptors) to match the correct autonomic nervous system output. **A) True** B) False *The NTS, located in the medulla oblongata of*

*the brainstem, integrates input from all these sources and helps exert appropriate response and control over autonomic output.*

**70)** Preganglionic sympathetic neurons use norepinephrine as the major neurotransmitter. Postganglionic parasympathetic neurons use acetylcholine as the major neurotransmitter. A. Both statements are true B. Both statements are false C. The first statement is true; the second statement is false **D. The first statement is false; the second statement is true** *Preganglionic neurons of both the parasympathetic and sympathetic divisions release acetylcholine (not norepinephrine), while postganglionic neurons of the parasympathetic division release acetylcholine.*

**71)** The glossopharyngeal nerve (CN IX) provides afferent fibers to which of the following? **A) Carotid body baroreceptors** B) Aortic arch baroreceptors C) Gastrointestinal tract D) A and B E) All of the above *The glossopharyngeal nerve (CN IX) provides afferent fibers to the carotid receptors in the neck, while it is the vagus nerve (CN X) that provides afferent fibers to the GI system and baroreceptors in the aortic arch.*

**72)** You decide to take a break after a long study session. As you get started on the treadmill, which of the following would *not* likely occur? A) Increased cardiac output **B) Decreased β1 adrenergic receptor activity** C) Increased heart contraction D) Decreased vagus nerve stimulation of SA node *As your activity level increases on the treadmill, the sympathetic nervous system would be activated to increase heart contractility and cardiac output via increased (NOT decreased) activity of β1 adrenergic receptors in the heart. As sympathetic activity ramps up, parasympathetic activity (and vagus nerve stimulation of the SA node) is reduced.*

**73)** β2 adrenergic agonists cause which of the following? A) Increase lipolysis **B) Bronchodilation** C) Reduce insulin secretion D) Increase heart rate E) Increase ghrelin release *α1 adrenergic receptors constrict blood vessels. α2 adrenergic receptors play a role in negative feedback and reduce norepinephrine and insulin release. β1 adrenergic receptors increase heart rate, blood pressure, renin release and ghrelin release. β2 adrenergic receptors relax smooth muscle (including dilating arteries and bronchi), the GI tract, and the bladder, and will slightly reduce blood pressure.*

**74)** Gastric emptying is stimulated by which of the following? A) CN III B) CN IX **C) CN X** D) Spinal nerves E) All of the above *CN X (vagus nerve) is the most complex of the 12 cranial nerves and transmits information to and from the brain to organs throughout the body, including the GI system. CN III (oculomotor) and CN IX (glossopharyngeal) are part of the parasympathetic nervous system but do not play a role in the GI system.*

*Spinal nerves that innervate the GI system are sympathetic, and when activated, inhibit (not stimulate) GI function/gastric emptying.*

**75)** Negative feedback offered by the neural system to make a small adjustment to heart rate is an example of which of the following: A) a high gain correction B) an intrinsic control **C) an extrinsic control** *Since the adjustment to heart rate is made by an organ system outside of the heart itself (the nervous system), this is an example of extrinsic (not intrinsic) control. Such neuronal corrections are usually small, quick and fairly accurate, thus making it a low gain correction. Endocrine corrections, by contrast, are usually large, slow and fairly inaccurate, thus they are referred to as high gain corrections. Gain is calculated by dividing the amount of correction by the amount of error.*

**76)** A single contraction of skeletal muscle is most likely to be terminated by which of the following actions? A) closure of the postsynaptic nicotinic acetylcholine receptor B) removal of acetylcholine from the neuromuscular junction C) removal of $Ca^{2+}$ from the terminal of the motor neuron **D) removal of sarcoplasmic $Ca^{2+}$** E) return of the dihydropyridine receptor to its resting conformation *While all options would be involved in the termination of a single skeletal muscle contraction, as long as sarcoplasmic $Ca^{2+}$ is sufficiently high, none of the other events (A, B, C & E) would have any effect on the contractile state of muscle.*

**77)** What is the likely basis for the muscle weakness symptoms of a patient with myasthenia gravis? **A) Autoimmune response** B) Botulinum toxicity C) Depletion of voltage gated $Ca^{2+}$ channels in certain motor neurons D) Overexertion *While B, C and D lead to muscle fatigue, myasthenia gravis is an autoimmune disease characterized by the presence of anti-acetylcholine receptor antibodies in the plasma, which reduces functional acetylcholine receptors in the neuromuscular junction and subsequently reduces muscle contraction.*

*Questions 78–79 reference a graph with two saturable/linear transport-kinetics curves labeled Trace A (saturating, hyperbolic) and Trace B (linear, non-saturating) plotting "Transport across membrane" vs. "Concentration of transported molecule" — not reproducible here, check the original PDF.*

**78)** Trace A best describes the kinetics of which event? A) Movement of $CO_2$ across the plasma membrane B) Movement of $O_2$ across a lipid bilayer C) $Na^+$ flux through an open nicotinic acetylcholine receptor channel **D) Transport of $K^+$ into muscle cell** E) Voltage-dependent movement of $Ca^{2+}$ into the terminal of a motor neuron *A and B are simple diffusion, which does not have a transport maximum. C and E are passive*

*facilitated diffusion through a channel, which does not have a transport maximum. In D, transport of $K^+$ in a muscle cell occurs via $Na^+/K^+$ ATPase, which is primary active transport involving a carrier protein. Carrier proteins undergo a conformation change during transport of a molecule across the membrane, and thus have a transport maximum, as illustrated in Trace A in the figure.*

**79)** Trace B best describes the kinetics of which of the following events? A) $Na^+$-dependent transport of glucose into an epithelial cell B) Transport of $Ca^{2+}$ into the sarcoplasmic reticulum of a smooth muscle cell C) Transport of $K^+$ into a muscle cell D) Transport of $Na^+$ out of a nerve cell **E) Transport of $O_2$ across an artificial lipid bilayer** *A is secondary active transport that uses a carrier protein. B, C and D are primary active transport that use a carrier protein. Carrier proteins exhibit a rate maximum, which is trace A. Transport of $O_2$ across a lipid bilayer is simple diffusion and does not have a transport maximum (trace B).*

**80)** A 17-year-old soccer player sustained a fracture to the left tibia. After her lower leg has been in a cast for 8 weeks, she is surprised to find that the left gastrocnemius (calf) muscle is significantly smaller in circumference than it was before the fracture. What is the most likely explanation? A) Decrease in the number of individual muscle fibers in the left gastrocnemius B) Decrease in blood flow to the muscle caused by constriction from the cast **C) Temporary reduction in actin and myosin protein synthesis** D) Increase in glycolytic activity in the affected muscle E) Progressive denervation *Skeletal muscle continuously remodels in response to its level of use. When a muscle is inactive for an extended period of time, the rate of synthesis of the contractile proteins in individual muscle fibers decreases, resulting in an overall reduction in muscle mass. This reversible reduction in muscle mass is called atrophy.*

**81)** Sam was feeling very nervous when he heard a banging on his window. However, when he found it was just a tree branch in the wind, he found his heartbeat slowing down and his blood pressure decreasing back to normal. The decreases in heartbeat and blood pressure were regulated by his: A) Sympathetic nervous system **B) Parasympathetic nervous system** C) Somatic nervous system D) Voluntary nervous system *The parasympathetic nervous system slows heartbeat and reduces heart contractility during a state of relaxation and calmness. It does this through the vagus nerve and its interaction with the pacemakers of the heart, the SA and AV nodes. Stimulation of the vagus nerve slows heart rate. The sympathetic nervous system does the opposite — it increases heart rate. The somatic nervous system (voluntary nervous system) does not innervate the heart, it only innervates skeletal muscle.*

**82)** Which of the following is not under the dual control of the autonomic nervous system? A) Pupil diameter B) Heart rate C) Salivary gland activity **D) Adrenal medulla activity** E) Gastrointestinal motility *Both the parasympathetic and sympathetic nervous systems innervate and regulate pupil diameter, heart rate, salivary gland activity and gastrointestinal motility (with contrasting effects). However, the adrenal medulla is influenced only by the sympathetic nervous system.*

**83)** Describe the following events as being either parasympathetic (P) or sympathetic (S) induced activities. - **S** — Dilation of pupil - **P** — Decrease in heart rate - **P** — Constriction of the bladder and subsequent urination - **S** — Dilation of bronchioles and subsequent increased respiration - **S** — Decreased digestion - **P** — Erection