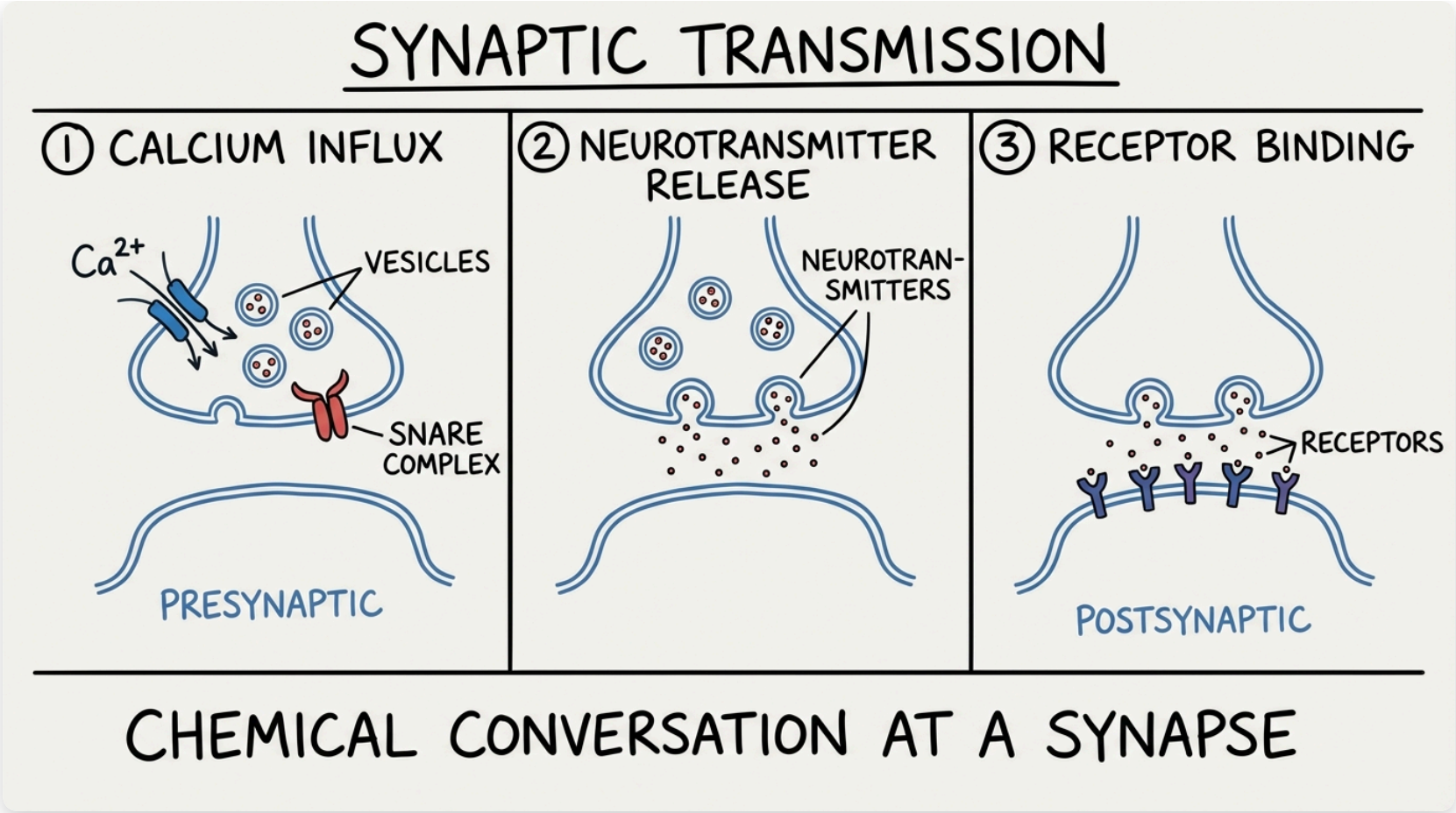
Synaptic Transmission

Chemical Conversations: Synaptic Transmission and Neurotransmitters Chemical Conversations Visual Summary LECTURE OUTLINE (80 minutes) I. The Neuromuscular Junction: A Model Synapse (20 min) • Otto Loewi's "Vagusstoff" and the chemical hypothesis • Anatomy of the motor endplate • The endplate potential and curare experiments • Quantal release and Bernard Katz's discovery II. Mechanisms of Neurotransmitter Release (15 min) • Calcium as the trigger: voltage-gated Ca^{2+} channels • The SNARE hypothesis: synaptobrevin, syntaxin, SNAP-25 • Synaptotagmin as the calcium sensor • Vesicle pools and recycling III. Synaptic Transmission in the CNS (15 min) • EPSPs and IPSPs: excitation and inhibition • Spatial and temporal summation • The reversal potential and driving force • Synaptic integration at the axon hillock

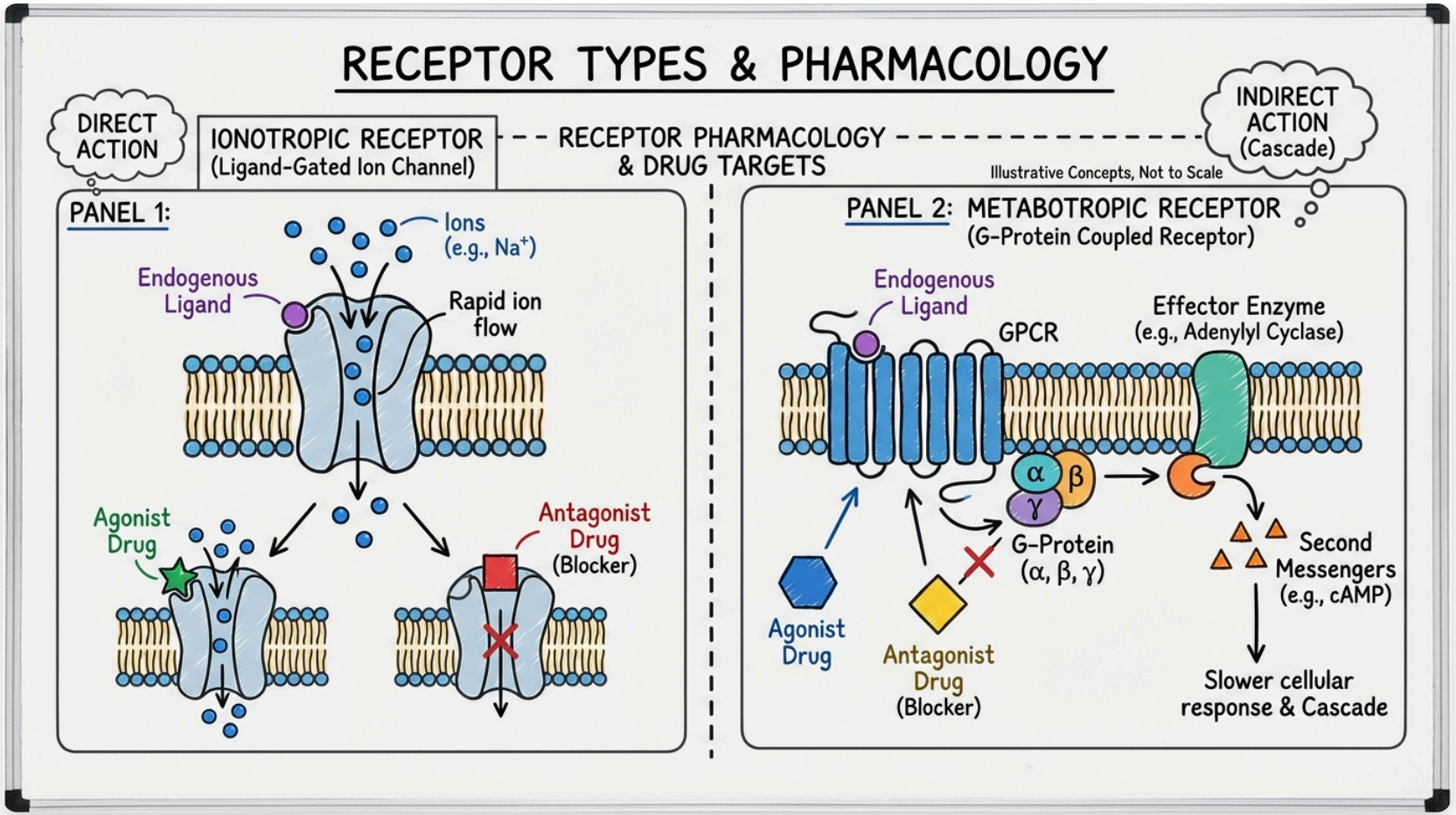
- Here are 3-5 main points from the text:
- Nerve cells communicate by sending chemical signals called neurotransmitters.
- Calcium ions trigger the release of neurotransmitters from special sacs inside the nerve cell.
- The brain uses both excitatory and inhibitory signals to control nerve cell activity.
- Nerve cells add up these different signals to decide whether to send their own message.


SYNAPTIC TRANSMISSION
① CALCIUM INFLUX
Ca2+
VESICLES
SNARE COMPLEX
PRESYNAPTIC
② NEUROTRANSMITTER RELEASE
NEUROTRAN-SMITTERS
③ RECEPTOR BINDING
RECEPTORS
POSTSYNAPTIC
CHEMICAL CONVERSATION AT A SYNAPSE

Fast Slow Receptors

IV. Receptor Types: Fast and Slow (15 min) • Ionotropic receptors: ligand-gated ion channels • Metabotropic receptors: G-proteins and second messengers • Receptor pharmacology and drug targets

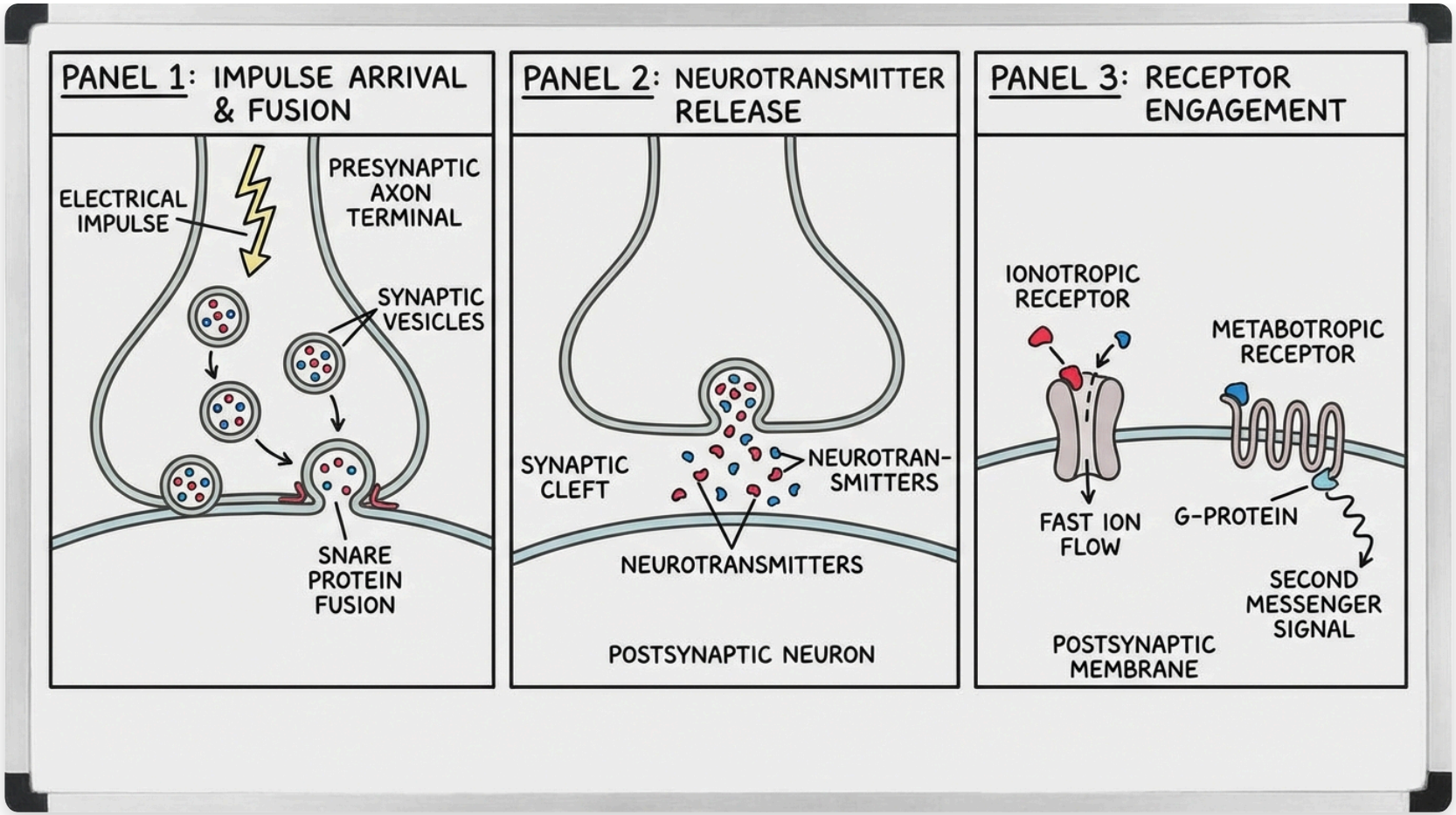
- Here are 4 main points from the text:
- Receptors are categorized into different types based on how fast they act.
- Ionotropic receptors function as ligand-gated ion channels.
- Metabotropic receptors work using G-proteins and second messengers.
- Receptor pharmacology studies how drugs target these receptors.


RECEPTOR TYPES & PHARMACOLOGY
DIRECT ACTION
IONOTROPIC RECEPTOR (Ligand-Gated Ion Channel)
RECEPTOR PHARMACOLOGY & DRUG TARGETS
INDIRECT ACTION (Cascade)
Illustrative Concepts, Not to Scale
PANEL 1:
Ions (e.g., Na+)
Endogenous Ligand
Rapid ion flow
Agonist Drug
Antagonist Drug (Blocker)
PANEL 2: METABOTROPIC RECEPTOR (G-Protein Coupled Receptor)
Endogenous Ligand
GPCR
Effector Enzyme (e.g., Adenylyl Cyclase)
α
β
γ
G-Protein (α, β, γ)
Second Messengers (e.g., cAMP)
Agonist Drug
Antagonist Drug (Blocker)
Slower cellular response & Cascade

Neurotransmitter Diversity

V. Neurotransmitter Diversity (15 min) • Acetylcholine and the cholinergic system • Amino acids: glutamate and GABA • Biogenic amines: dopamine, serotonin, norepinephrine • Neuropeptides and unconventional transmitters Last time, we traced the electrical signal to the axon terminal and stopped. Now we cross the 20-nanometer synaptic cleft—a gap that action potentials cannot jump. Here, electricity must become chemistry. Today we'll discover how Otto Loewi proved chemical transmission with a frog heart in 1921, how Bernard Katz revealed that neurotransmitters are released in discrete packets called quanta, and how SNARE proteins execute membrane fusion with atomic precision. We'll explore the fundamental dichotomy between fast ionotropic transmission (milliseconds) and slow metabotropic modulation (seconds to minutes), understand why the brain uses over 100 neurotransmitters when one would seem to suffice, and see how drugs from caffeine to cocaine to curare exploit synaptic machinery. From the neuromuscular junction that moves your muscles to the central synapses that generate your thoughts, we'll trace the complete chemical conversation between neurons.

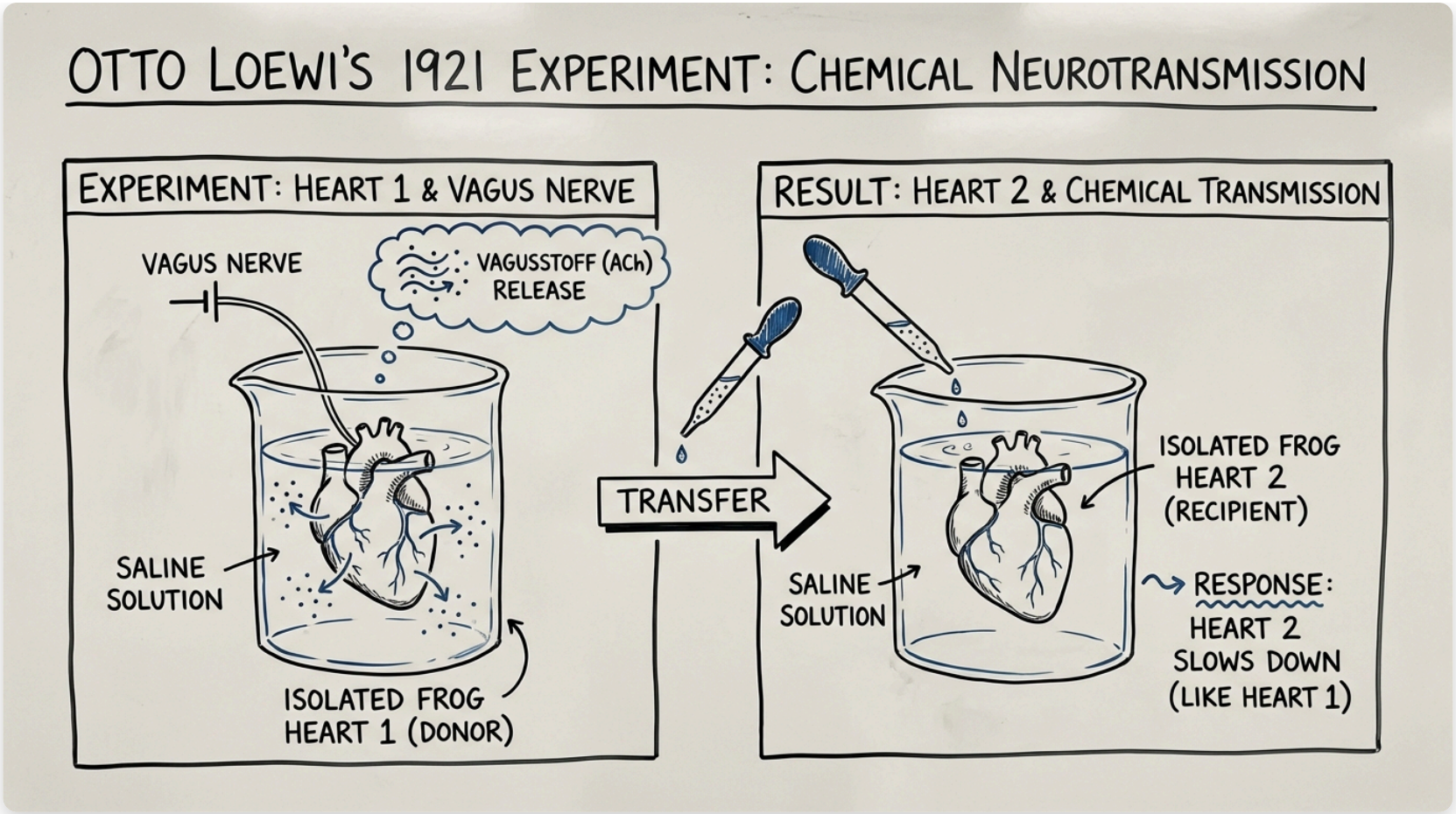
- → Here are 4 main points from the text:
- → Electrical signals change into chemical signals at the synapse. Action potentials cannot cross the synaptic gap directly.
- → Neurotransmitters release from the neuron in tiny packets called quanta. SNARE proteins help release these packets with precision.
- → Neurotransmission can be fast (ionotropic) or slow (metabotropic). These types work at different speeds.
- → The brain uses more than 100 different kinds of neurotransmitters.


PANEL 1: IMPULSE ARRIVAL & FUSION
ELECTRICAL IMPULSE
PRESYNAPTIC AXON TERMINAL
SYNAPTIC VESICLES
SNARE PROTEIN FUSION
PANEL 2: NEUROTRANSMITTER RELEASE
SYNAPTIC CLEFT
NEUROTRAN-SMITTERS
NEUROTRANSMITTERS
POSTSYNAPTIC NEURON
PANEL 3: RECEPTOR ENGAGEMENT
IONOTROPIC RECEPTOR
METABOTROPIC RECEPTOR
FAST ION FLOW
G-PROTEIN
SECOND MESSENGER SIGNAL
POSTSYNAPTIC MEMBRANE

Chemical Transmission

Today's journey: From Loewi's dream experiment to molecular machines. We'll see how evolution solved the problem of transmitting information across a gap too wide for electricity but small enough for chemistry. The Neuromuscular Junction: Where Chemical Transmission Was Born In 1921, Otto Loewi woke at 3 AM with an idea from a dream. He stimulated the vagus nerve of a frog heart floating in saline, slowing its beat. Then he transferred the saline to a second heart—and that heart slowed too, though no nerve had touched it. A diffusible chemical—he called it "Vagusstoff," later identified as acetylcholine (ACh)—had carried the message. This elegant experiment ended decades of debate between "sparks" (electrical transmission) and "soup" (chemical transmission). Loewi shared the 1936 Nobel Prize with Henry Dale, who had first isolated acetylcholine.

- Main Points:
- Otto Loewi's dream inspired an important experiment in 1921. He used frog hearts to study nerve signals.
- Loewi showed a chemical, later named acetylcholine, transmitted signals from one heart to another. This chemical slowed the heart's beat.
- His experiment proved that chemical transmission occurs in the body. It settled a long scientific debate about how nerves transmit signals.
- Otto Loewi received a Nobel Prize in 1936 for his discovery. He shared it with Henry Dale, who isolated acetylcholine.

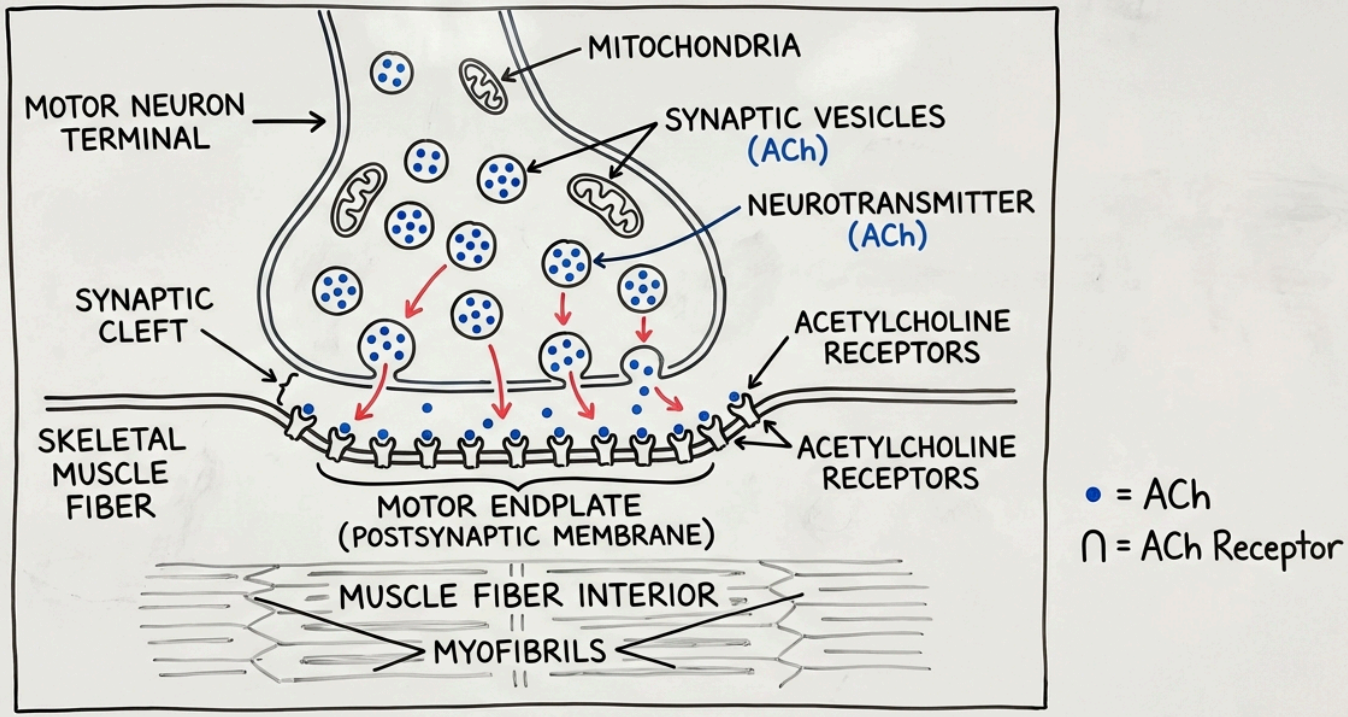

OTTO LOEWI'S 1921 EXPERIMENT: CHEMICAL NEUROTRANSMISSION
EXPERIMENT: HEART 1 & VAGUS NERVE
VAGUS NERVE
VAGUSSTOFF (ACh) RELEASE
SALINE SOLUTION
ISOLATED FROG HEART 1 (DONOR)
TRANSFER
RESULT: HEART 2 & CHEMICAL TRANSMISSION
ISOLATED FROG HEART 2 (RECIPIENT)
SALINE SOLUTION
RESPONSE: HEART 2 SLOWS DOWN (LIKE HEART 1)

Neuromuscular Junction

The neuromuscular junction (NMJ) became the model synapse because of its accessibility and simplicity. Motor neurons from the spinal cord innervate skeletal muscle fibers at specialized regions called motor endplates. The synapse here has three characteristic features visible in electron microscopy: (1) a 20-nm synaptic cleft separating pre- and postsynaptic membranes, (2) clusters of synaptic vesicles in the presynaptic terminal containing neurotransmitter, and (3) a postsynaptic density—thickening of the muscle membrane due to high concentrations of acetylcholine receptors.

- Here are 3 main points from the text:
- The neuromuscular junction (NMJ) is an important model for studying synapses. Researchers use it because it is easy to access and simple in structure.
- Motor neurons from the spinal cord connect to skeletal muscle fibers. These connections happen at special areas called motor endplates.
- The NMJ synapse has a small gap between the nerve and muscle. The nerve holds sacs of neurotransmitters, and the muscle has many receptors for these chemicals.

NEUROMUSCULAR JUNCTION (NMJ)

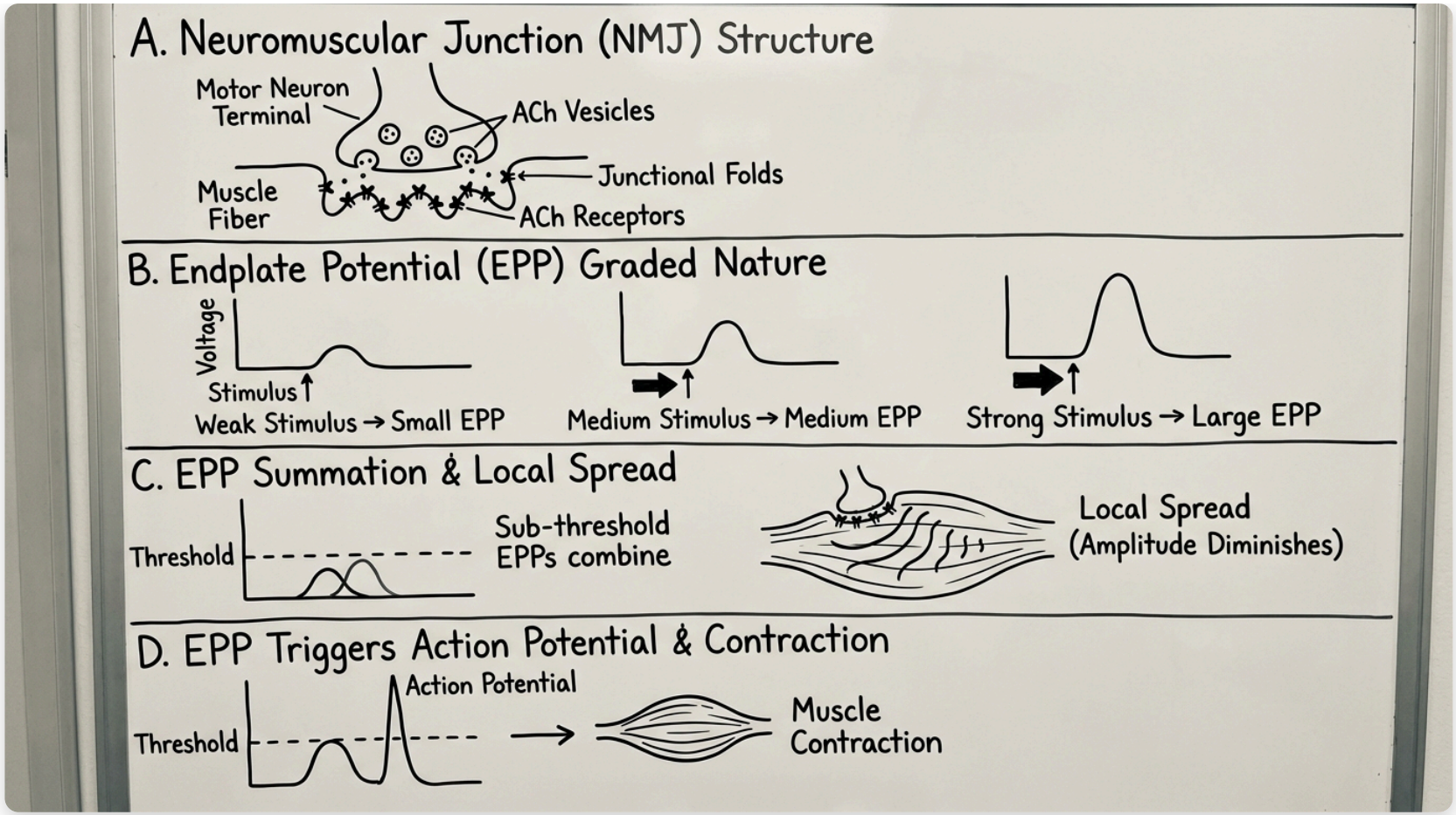


Action potential triggers ACh release, leading to muscle contraction.

EPP Fundamentals

The Endplate Potential and Curare Experiments When an action potential invades the motor neuron terminal, the muscle fiber depolarizes. This endplate potential (EPP)—a special case of the more general excitatory postsynaptic potential (EPSP)—triggers a muscle action potential and contraction. The EPP differs fundamentally from the action potential: it's graded (larger stimuli produce larger EPPs), it's local (it doesn't regenerate but spreads passively), and it can summate (multiple EPPs add together).

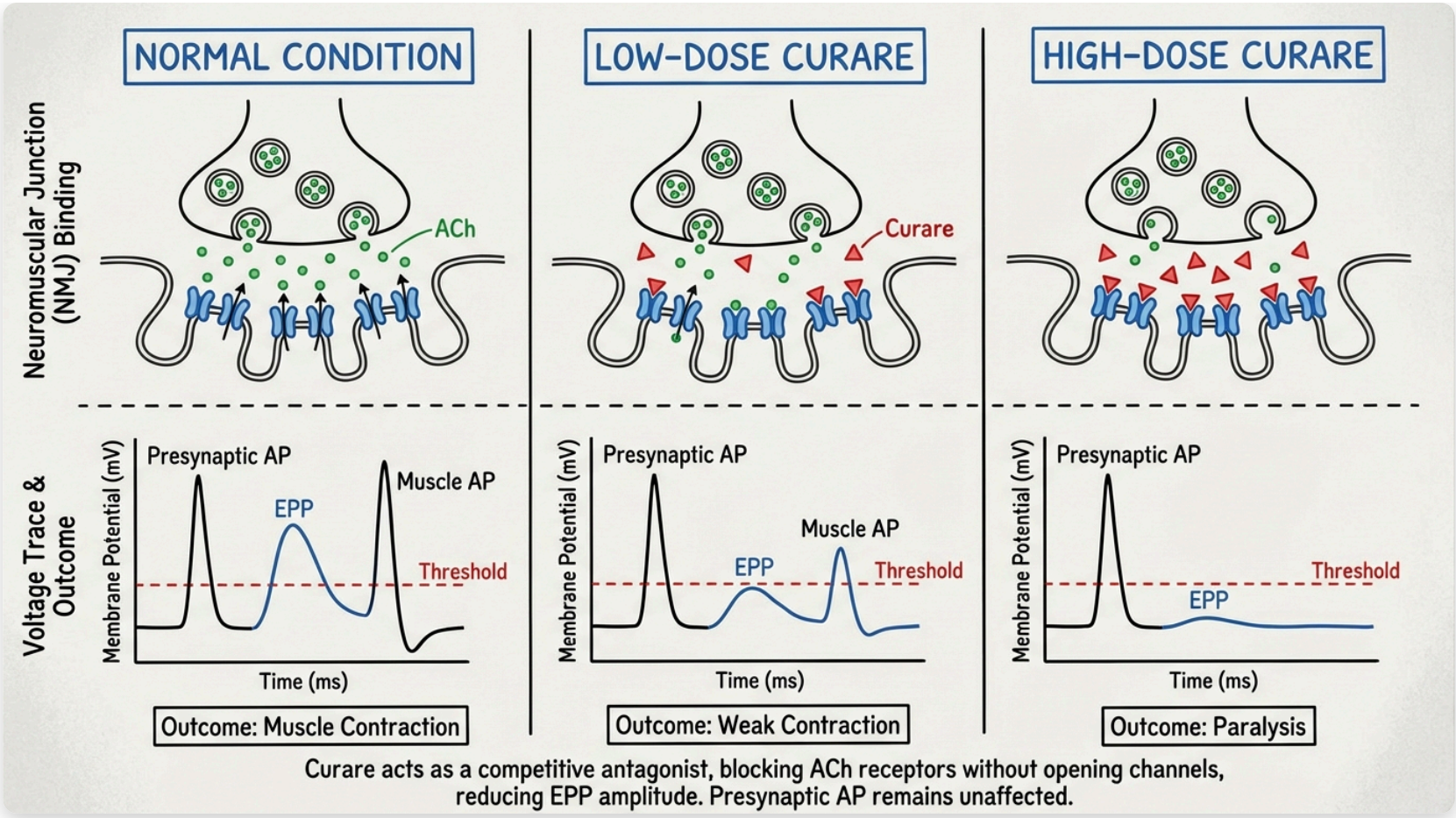
- Main Points:
- An endplate potential (EPP) depolarizes muscle fibers, which then triggers a muscle action potential and contraction.
- Endplate potentials (EPPs) are graded, meaning stronger signals produce larger EPPs.
- EPPs are local and spread passively through the muscle fiber without regenerating.
- Multiple endplate potentials (EPPs) can add together, a process called summation.


A. Neuromuscular Junction (NMJ) Structure
Motor Neuron Terminal
ACh Vesicles
Junctional Folds
Muscle Fiber
ACh Receptors
B. Endplate Potential (EPP) Graded Nature
Voltage
Stimulus
Weak Stimulus → Small EPP
Medium Stimulus → Medium EPP
Strong Stimulus → Large EPP
C. EPP Summation & Local Spread
Threshold
Sub-threshold EPPs combine
Local Spread (Amplitude Diminishes)
D. EPP Triggers Action Potential & Contraction
Action Potential
Threshold
Muscle Contraction

Curare Neurotransmission

Curare, the arrow poison used by South American Indigenous peoples, proved essential to understanding synaptic transmission. At low doses, curare reduces the EPP amplitude but it still reaches threshold. At higher doses, the EPP becomes subthreshold—the muscle doesn't contract. Curare is a competitive antagonist of ACh receptors: it binds to the receptor without opening the channel, blocking ACh from binding. Crucially, curare doesn't affect the action potential mechanism—it specifically blocks synaptic transmission. This dissociation proved that synaptic and action potential mechanisms are distinct.

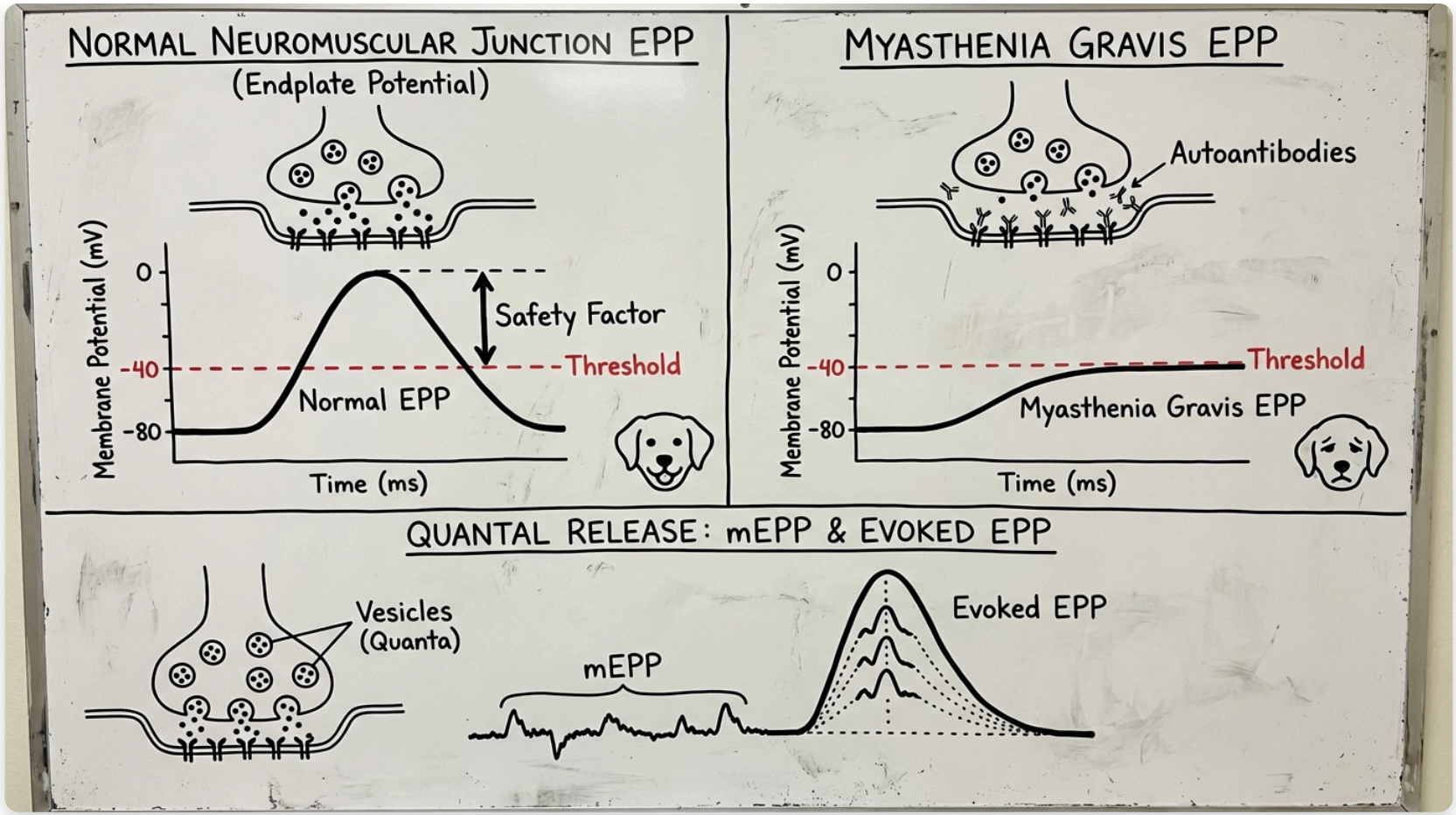
- Here are 4 main points from the text:
- Curare helped scientists understand how nerve signals pass between cells (synaptic transmission).
- Curare blocks specific receptors on nerve cells, stopping a chemical called ACh from connecting.
- Curare blocks synaptic transmission, while action potentials (nerve signals) continue to work.
- Curare's action showed that synaptic transmission and action potentials are separate processes.


NORMAL CONDITION
LOW-DOSE CURARE
HIGH-DOSE CURARE
Neuromuscular Junction (NMJ) Binding
ACh
Curare
Voltage Trace & Outcome
Membrane Potential (mV)
Presynaptic AP
EPP
Muscle AP
Threshold
Time (ms)
Outcome: Muscle Contraction
Outcome: Weak Contraction
Outcome: Paralysis
Curare acts as a competitive antagonist, blocking ACh receptors without opening channels, reducing EPP amplitude. Presynaptic AP remains unaffected.

EPP Safety Factor

The EPP amplitude normally far exceeds what's needed to reach threshold—about 50 mV when only 30 mV is required. This 20 mV safety factor ensures reliable transmission despite fatigue or minor pathology. In myasthenia gravis, autoantibodies attack ACh receptors, reducing the safety factor until EPPs fail to reach threshold—patients experience progressive weakness, especially in muscles used repeatedly. Quantal Release: Bernard Katz's Discovery Bernard Katz discovered that neurotransmitter release is quantized—it occurs in discrete packets. Even without stimulation, tiny spontaneous potentials (~0.5 mV) occur randomly at the NMJ. Katz called these miniature endplate potentials (mEPPs). The evoked EPP amplitude is always a multiple of the mEPP amplitude—you never see 1.5 or 2.3 mEPPs, only 1, 2, 3, etc. This quantal nature suggests that ACh is released not as individual molecules but as packages.

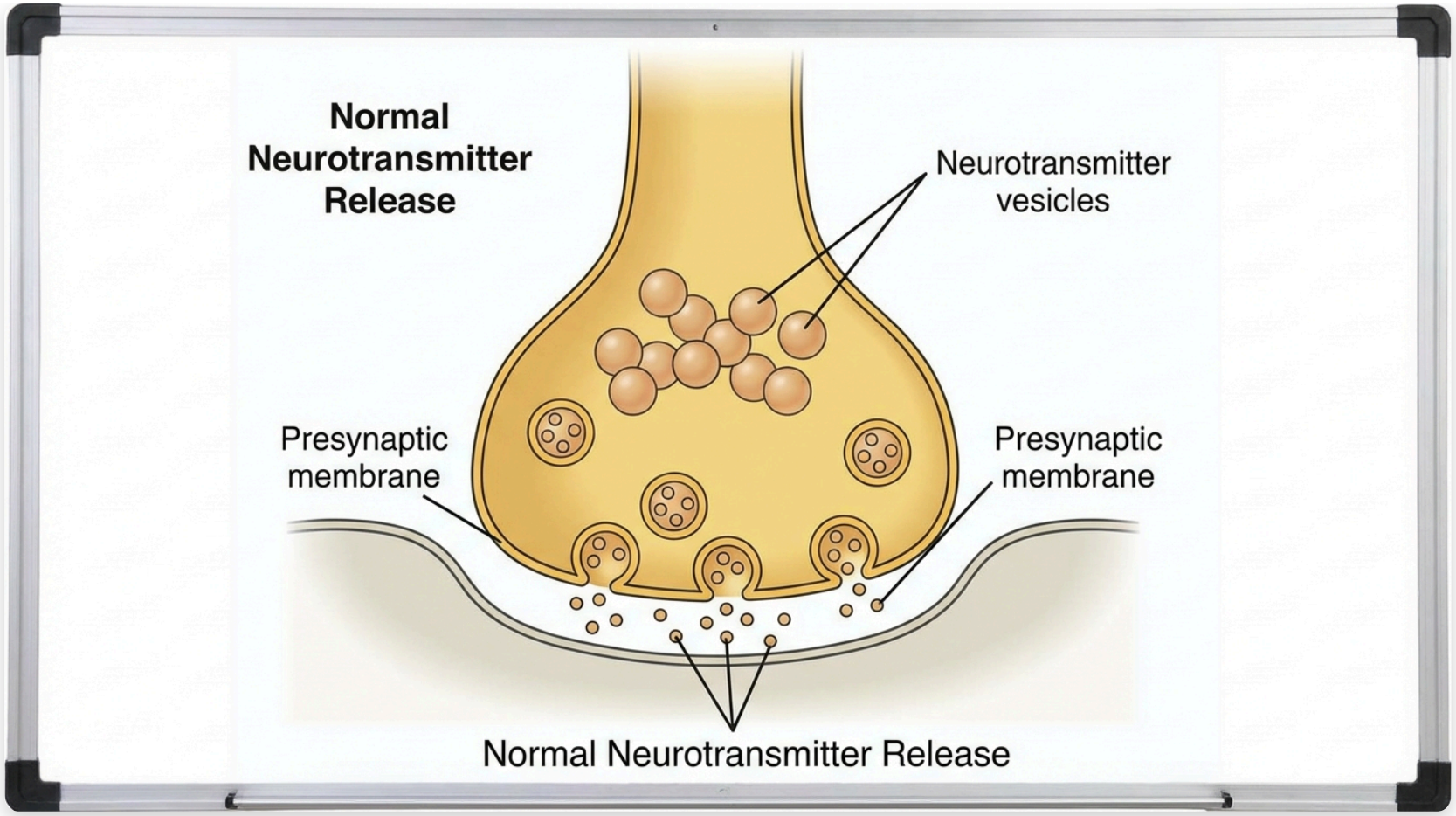
- Main Points:
- The body's natural electrical signals (EPPs) are stronger than required, creating a safety margin for reliable muscle movement.
- Myasthenia gravis is a disease where autoantibodies attack acetylcholine receptors, which weakens muscle signals and causes progressive muscle weakness.
- Bernard Katz discovered that neurotransmitters release in fixed, discrete packets, a process called quantal release.
- Tiny, spontaneous electrical signals (mEPPs) occur even without stimulation. Larger electrical signals (EPPs) are always a direct multiple of these mEPPs, suggesting neurotransmitters release in packages.


NORMAL NEUROMUSCULAR JUNCTION EPP
(Endplate Potential)
Membrane Potential (mV)
0
-40
-80
Safety Factor
Threshold
Normal EPP
Time (ms)
MYASTHENIA GRAVIS EPP
Autoantibodies
Membrane Potential (mV)
0
-40
-80
Threshold
Myasthenia Gravis EPP
Time (ms)
QUANTAL RELEASE: mEPP & EVOKED EPP
Vesicles
(Quanta)
mEPP
Evoked EPP

Synaptic Vesicle Release

Electron microscopy later revealed the packages: synaptic vesicles, ~40 nm spheres each containing thousands of neurotransmitter molecules. Each mEPP corresponds to the spontaneous fusion of one vesicle. A normal EPP results from the coordinated release of ~200 vesicles. Katz received the 1970 Nobel Prize for this work, which established the vesicular basis of synaptic transmission. Clinical Connection: Botulinum toxin (Botox) cleaves SNARE proteins, preventing vesicle fusion and blocking ACh release—causing flaccid paralysis. Tetanus toxin travels retrogradely to spinal cord interneurons and blocks GABA release, causing rigid paralysis (lockjaw) through disinhibition of motor neurons. Mechanisms of Neurotransmitter Release

- Here are 5 main points:
- Synaptic vesicles are small spheres containing thousands of neurotransmitter molecules.
- A normal nerve signal happens when many vesicles release neurotransmitters together.
- Katz established that vesicles are key to transmitting nerve signals.
- Botulinum toxin (Botox) stops vesicles from releasing neurotransmitters, causing flaccid paralysis.
- Tetanus toxin blocks neurotransmitter release in the spinal cord, causing rigid paralysis.


Normal
Neurotransmitter
Release
Neurotransmitter
vesicles
Presynaptic
membrane
Presynaptic
membrane
Normal Neurotransmitter Release

Calcium Trigger

Calcium: The Universal Trigger Katz and colleagues demonstrated that calcium is essential for transmitter release. Remove extracellular Ca^{2+}, and EPPs vanish despite normal presynaptic action potentials. The mechanism: when an action potential reaches the terminal, voltage-gated calcium channels (primarily P/Q-type and N-type in neurons) open. Calcium floods in, rising from ~100 nM to >100 µM in microdomains near channels—a 1000-fold increase within microseconds. The relationship between calcium and release is highly nonlinear: release probability scales with approximately the fourth power of calcium concentration. This steep dependence means that small changes in calcium entry cause large changes in release—providing a mechanism for synaptic modulation. Diseases affecting calcium channels (like Lambert-Eaton myasthenic syndrome, where antibodies attack presynaptic calcium channels) severely impair neuromuscular transmission.

- → Main Points:
- → Calcium must be present for neurons to release neurotransmitters.
- → Action potentials cause specific calcium channels to open, allowing calcium to flood into the neuron.
- → A small change in the amount of calcium entering a neuron causes a large change in neurotransmitter release.
- → Diseases that affect calcium channels greatly reduce nerve communication with muscles.

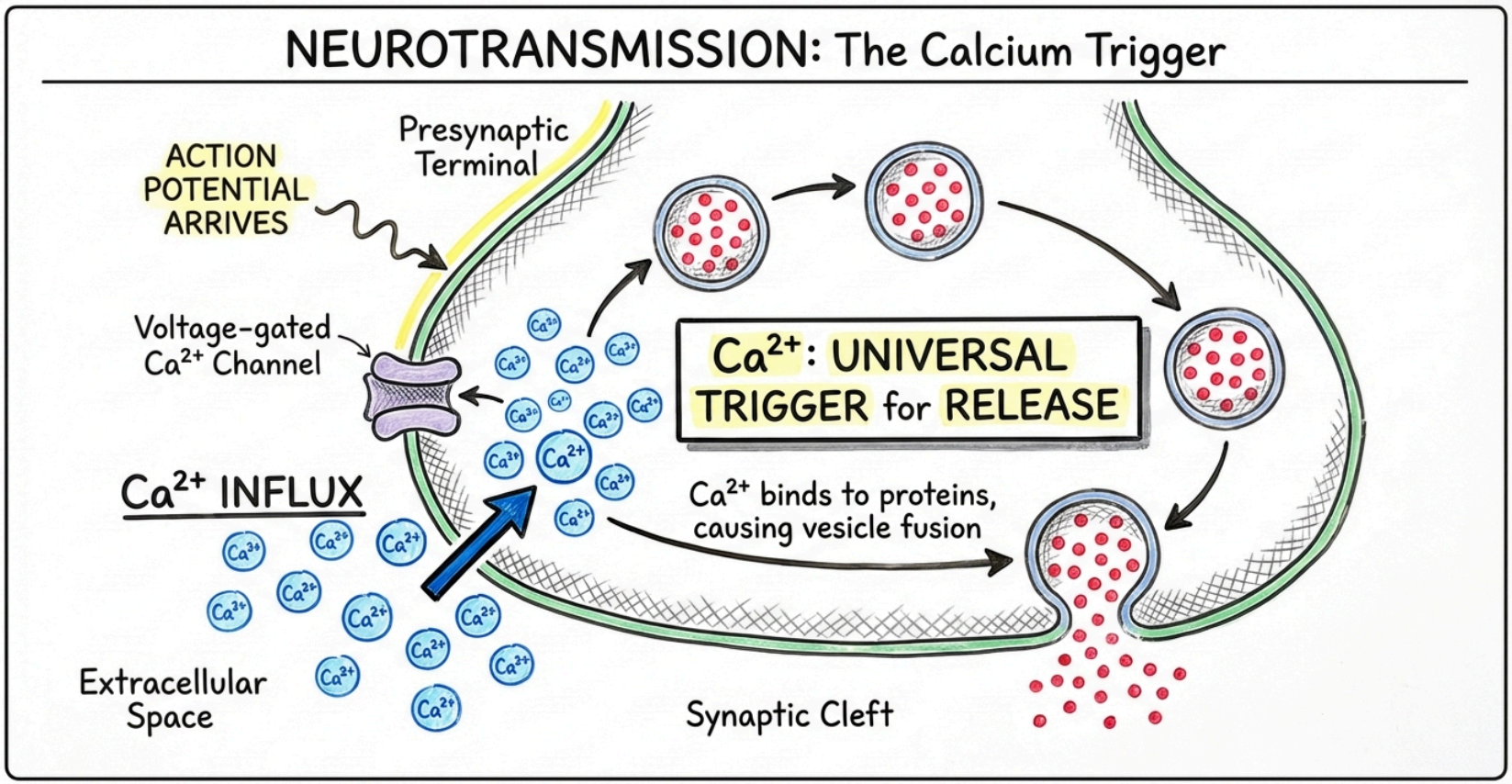
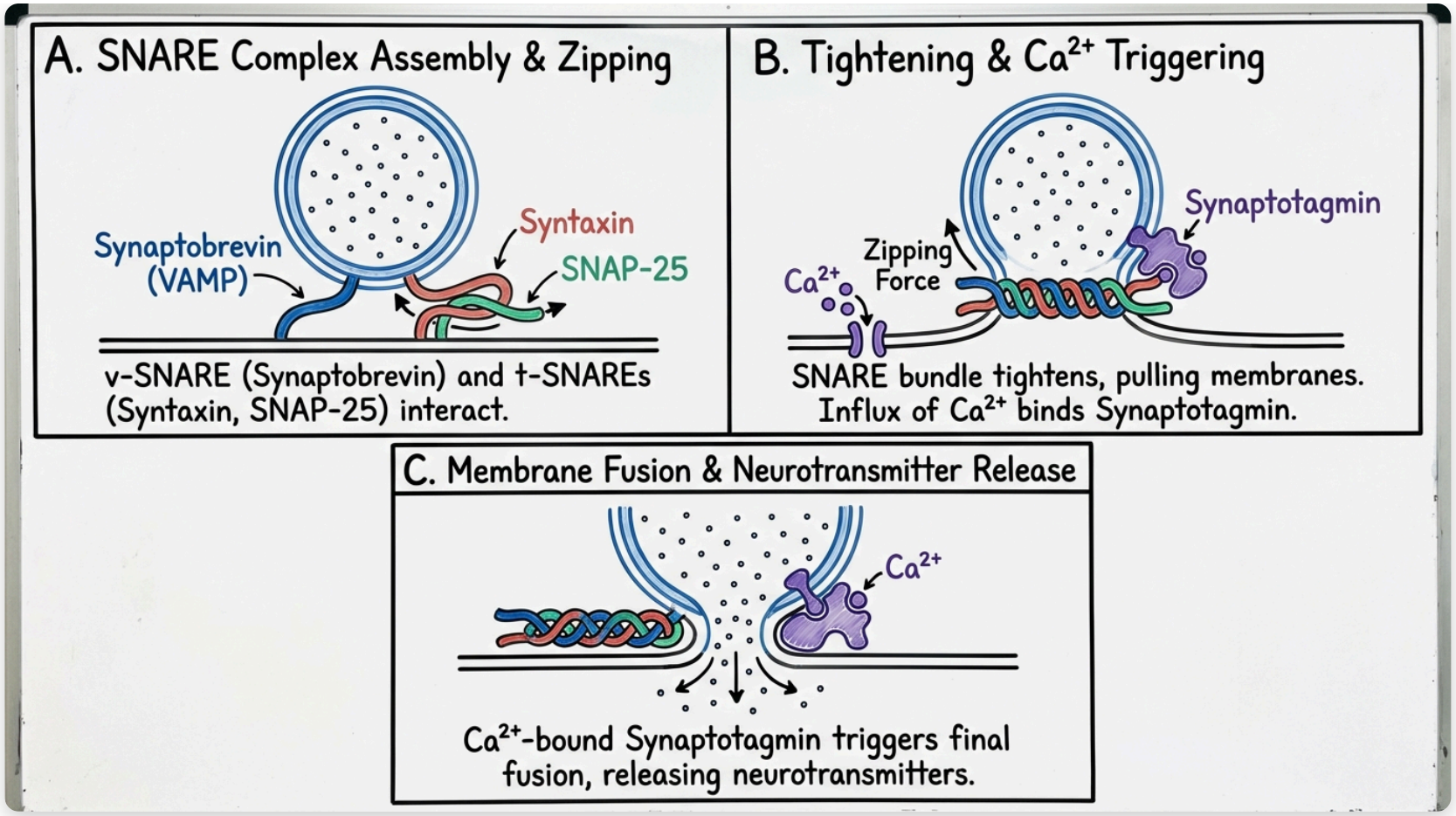


Figure 1. Action potential-triggered calcium influx causes synaptic vesicle fusion and neurotransmitter release.

SNARE Machinery

The SNARE Machinery: Molecular Zippers How does calcium trigger vesicle fusion? The SNARE hypothesis (soluble NSF attachment protein receptors), developed by James Rothman, Randy Schekman, and Thomas Südhof (2013 Nobel Prize), describes a molecular machine for membrane fusion: • Synaptobrevin (VAMP) is anchored in the vesicle membrane • Syntaxin and SNAP-25 are anchored in the presynaptic plasma membrane • These three proteins "zip" together from their N-termini toward the membranes, forming an extraordinarily stable four-helix bundle that pulls the membranes together, overcoming their natural repulsion The SNARE complex is primed and ready, but a molecular brake prevents spontaneous fusion. Synaptotagmin, the calcium sensor, has two C2 domains that bind calcium with micromolar affinity. When calcium enters, synaptotagmin binds it, undergoes a conformational change, and triggers the final membrane fusion event within 200 microseconds—among the fastest biochemical processes known.

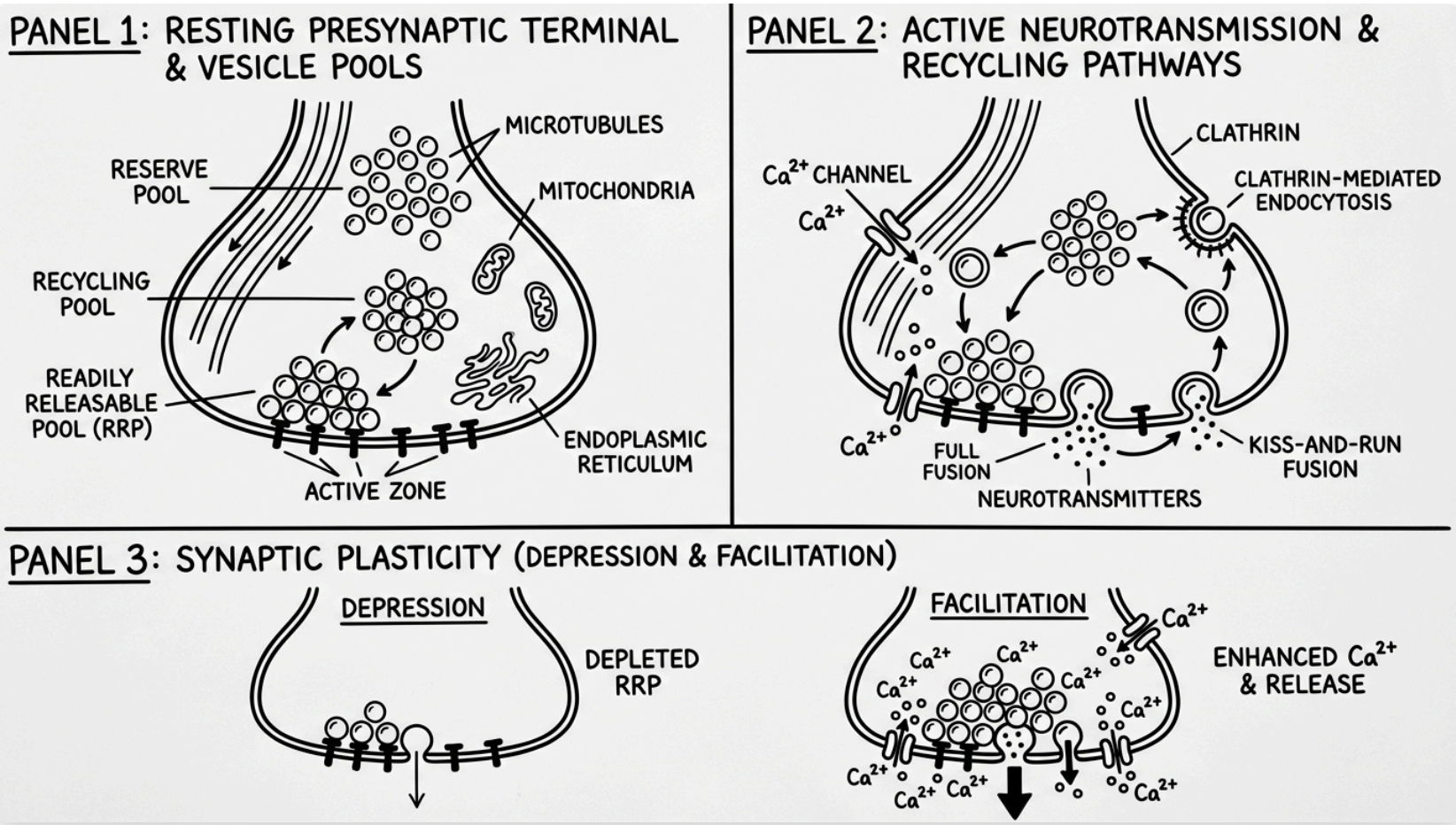
- Main Points:
- SNARE proteins form a molecular machine that helps cell membranes fuse together.
- Three specific SNARE proteins—Synaptobrevin, Syntaxin, and SNAP-25—zip together, pulling cell membranes close. This action overcomes the membranes' natural repulsion.
- Synaptotagmin acts as a calcium sensor. When calcium enters, synaptotagmin binds to it and triggers the quick membrane fusion.
- This membrane fusion process happens extremely fast, completing within 200 microseconds.


A. SNARE Complex Assembly & Zipping
Synaptobrevin (VAMP)
Syntaxin
SNAP-25
v-SNARE (Synaptobrevin) and t-SNAREs (Syntaxin, SNAP-25) interact.
B. Tightening & Ca2+ Triggering
Synaptotagmin
Zipping Force
Ca2+
SNARE bundle tightens, pulling membranes. Influx of Ca2+ binds Synaptotagmin.
C. Membrane Fusion & Neurotransmitter Release
Ca2+
Ca2+-bound Synaptotagmin triggers final fusion, releasing neurotransmitters.

Vesicle Plasticity

Vesicle Pools and Recycling Synaptic terminals contain distinct vesicle pools: the readily releasable pool (RRP, docked at active zones, ~10-20 vesicles), the recycling pool (~200 vesicles), and the reserve pool (hundreds more). During high-frequency firing, the RRP depletes faster than it can be replenished, causing synaptic depression. Conversely, residual calcium from previous spikes can enhance release probability of subsequent spikes—synaptic facilitation. These short-term plasticity mechanisms shape how information is processed in neural circuits. After fusion, vesicles are recycled through clathrin-mediated endocytosis, refilled with neurotransmitter, and returned to vesicle pools—a process requiring ~30 seconds for full recycling. During sustained activity, faster "kiss-and-run" fusion may occur, where vesicles release contents through a transient pore without full membrane merger. Synaptic Transmission in the Central Nervous System

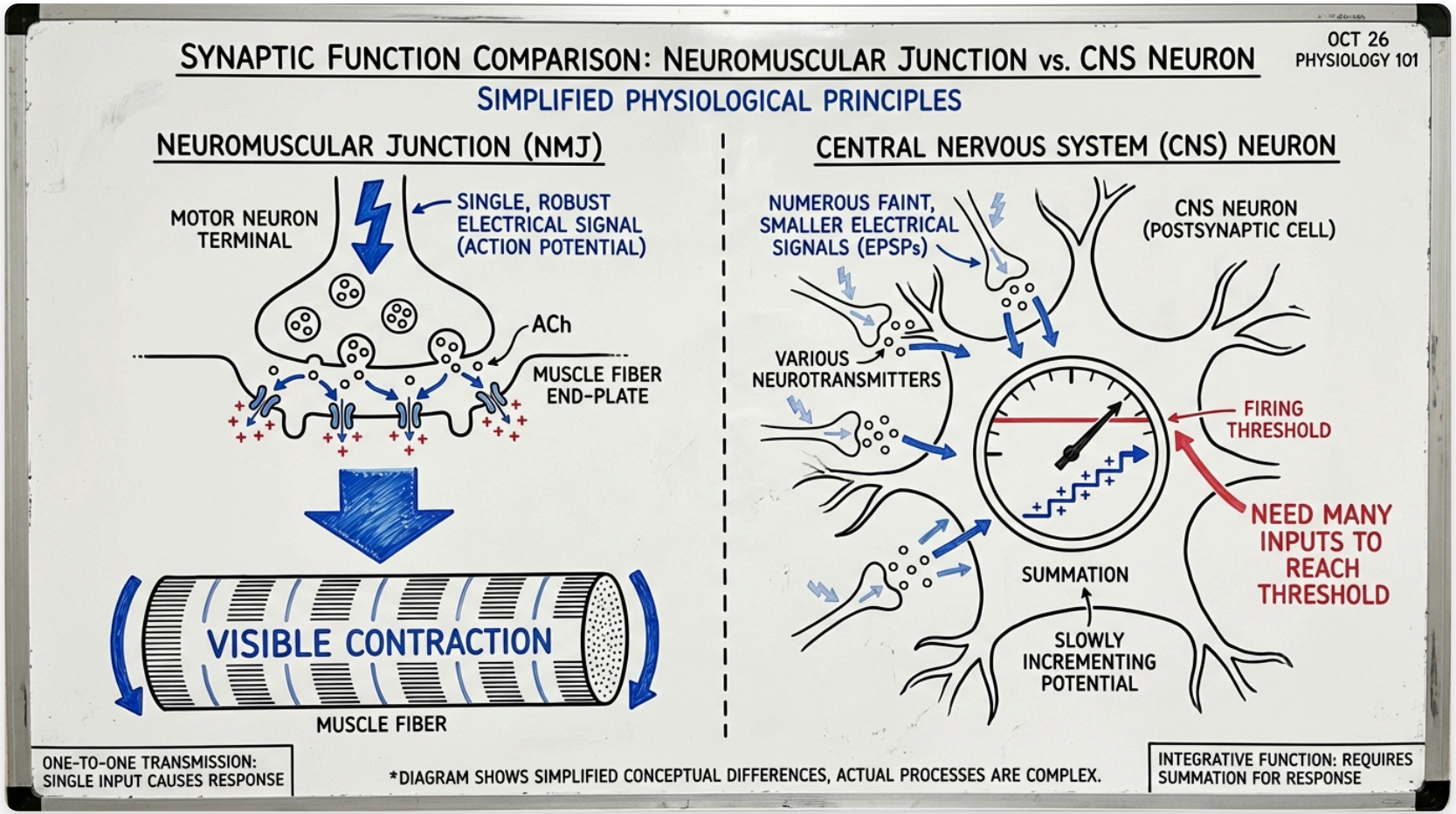
- Here are 4 main points from the text:
- Synaptic terminals store neurotransmitters in three distinct vesicle pools: the readily releasable, recycling, and reserve pools.
- Synapses show short-term changes in their release ability. High activity can reduce neurotransmitter release, while leftover calcium can increase it.
- After releasing neurotransmitters, vesicles undergo recycling through endocytosis. They refill with neurotransmitter and return to the pools, taking about 30 seconds.
- During sustained activity, vesicles may use a faster "kiss-and-run" method, releasing contents through a temporary pore without fully merging.


PANEL 1: RESTING PRESYNAPTIC TERMINAL & VESICLE POOLS
MICROTUBULES
RESERVE POOL
MITOCHONDRIA
RECYCLING POOL
READILY RELEASABLE POOL (RRP)
ENDOPLASMIC RETICULUM
ACTIVE ZONE
PANEL 2: ACTIVE NEUROTRANSMISSION & RECYCLING PATHWAYS
CLATHRIN
Ca2+ CHANNEL
Ca2+
CLATHRIN-MEDIATED ENDOCYTOSIS
Ca2+
FULL FUSION
KISS-AND-RUN FUSION
NEUROTRANSMITTERS
PANEL 3: SYNAPTIC PLASTICITY (DEPRESSION & FACILITATION)
DEPRESSION
DEPLETED RRP
FACILITATION
Ca2+
ENHANCED Ca2+ & RELEASE

CNS Synaptic Strength

Vesicle Pools and Recycling CNS synapses differ from the NMJ in crucial ways. A single motor neuron–muscle fiber synapse reliably triggers muscle contraction (1:1 relationship). But a single CNS synapse produces only a tiny EPSP (~0.5 mV)—far below the ~15 mV needed to reach threshold. A neuron must integrate thousands of synaptic inputs to decide whether to fire.

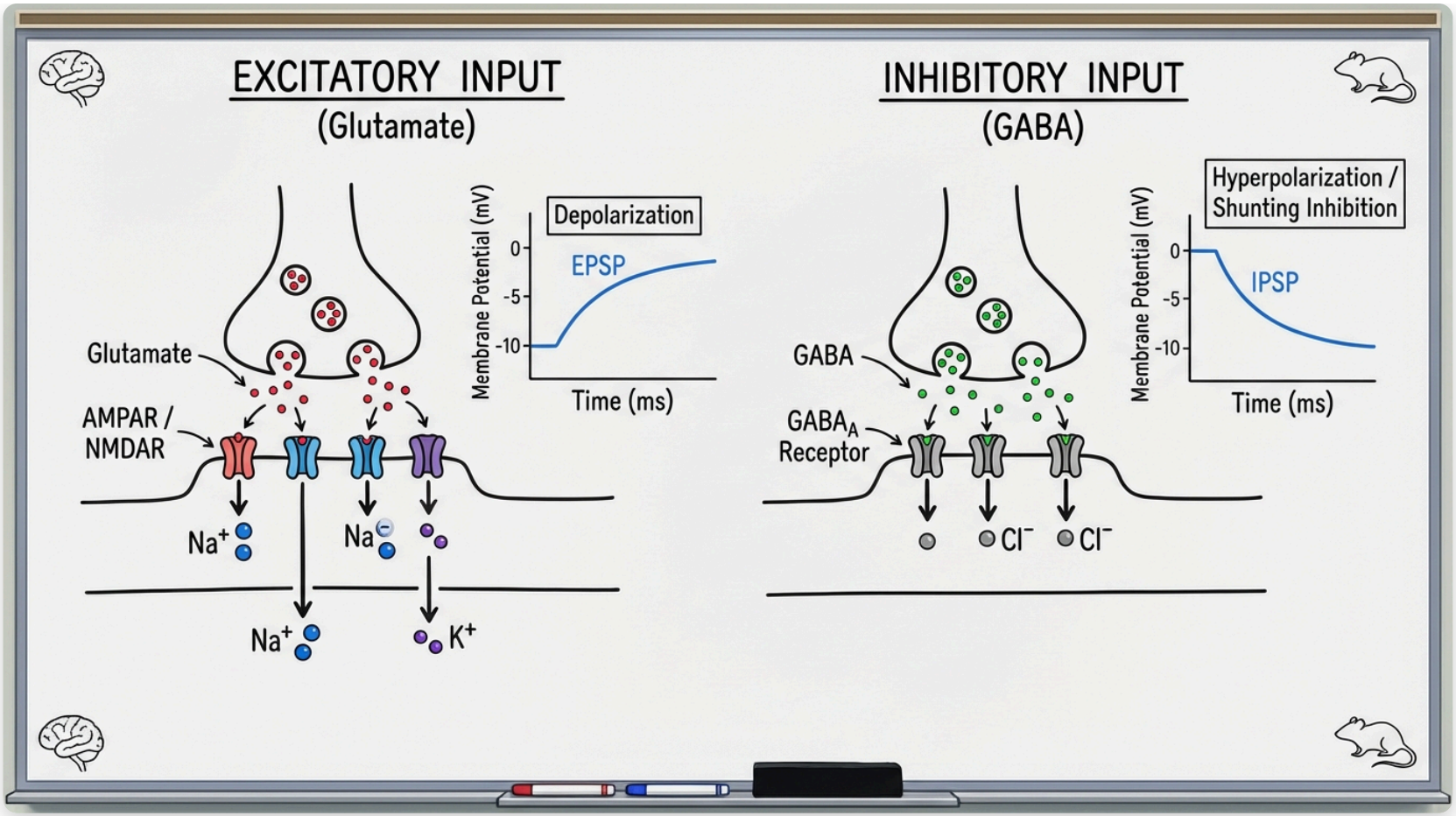
- Here are 4 main points from the text:
- Synapses in the central nervous system work differently compared to those connected to muscles.
- One motor neuron synapse on a muscle fiber always makes the muscle contract.
- A single CNS synapse produces only a tiny electrical signal.
- Central nervous system neurons must gather thousands of small signals to send their own message.


SYNAPTIC FUNCTION COMPARISON: NEUROMUSCULAR JUNCTION vs. CNS NEURON
OCT 26
PHYSIOLOGY 101
SIMPLIFIED PHYSIOLOGICAL PRINCIPLES
NEUROMUSCULAR JUNCTION (NMJ)
MOTOR NEURON TERMINAL
SINGLE, ROBUST ELECTRICAL SIGNAL (ACTION POTENTIAL)
ACh
MUSCLE FIBER END-PLATE
VISIBLE CONTRACTION
MUSCLE FIBER
CENTRAL NERVOUS SYSTEM (CNS) NEURON
NUMEROUS FAINT, SMALLER ELECTRICAL SIGNALS (EPSPs)
CNS NEURON (POSTSYNAPTIC CELL)
VARIOUS NEUROTRANSMITTERS
FIRING THRESHOLD
NEED MANY INPUTS TO REACH THRESHOLD
SUMMATION
SLOWLY INCREMENTING POTENTIAL
ONE-TO-ONE TRANSMISSION: SINGLE INPUT CAUSES RESPONSE
*DIAGRAM SHOWS SIMPLIFIED CONCEPTUAL DIFFERENCES, ACTUAL PROCESSES ARE COMPLEX.
INTEGRATIVE FUNCTION: REQUIRES SUMMATION FOR RESPONSE

Postsynaptic Potentials

Excitatory and Inhibitory Postsynaptic Potentials Excitatory postsynaptic potentials (EPSPs) depolarize the neuron, moving it toward threshold. At glutamatergic synapses, binding of glutamate opens channels permeable to Na^+ and K^+, with a reversal potential near 0 mV—well above threshold. Current flows inward (Na^+ entry exceeds K^+ exit), depolarizing the cell. Inhibitory postsynaptic potentials (IPSPs) hyperpolarize the neuron or hold it at the resting potential. At GABAergic synapses, GABA opens Cl^--permeable channels. In mature neurons, E_Cl (~−80 mV) is more negative than the resting potential, so Cl^- flows in, hyperpolarizing the cell. Even if E_Cl equals the resting potential, opening Cl^- channels provides "shunting inhibition"—the increased conductance short-circuits excitatory currents.

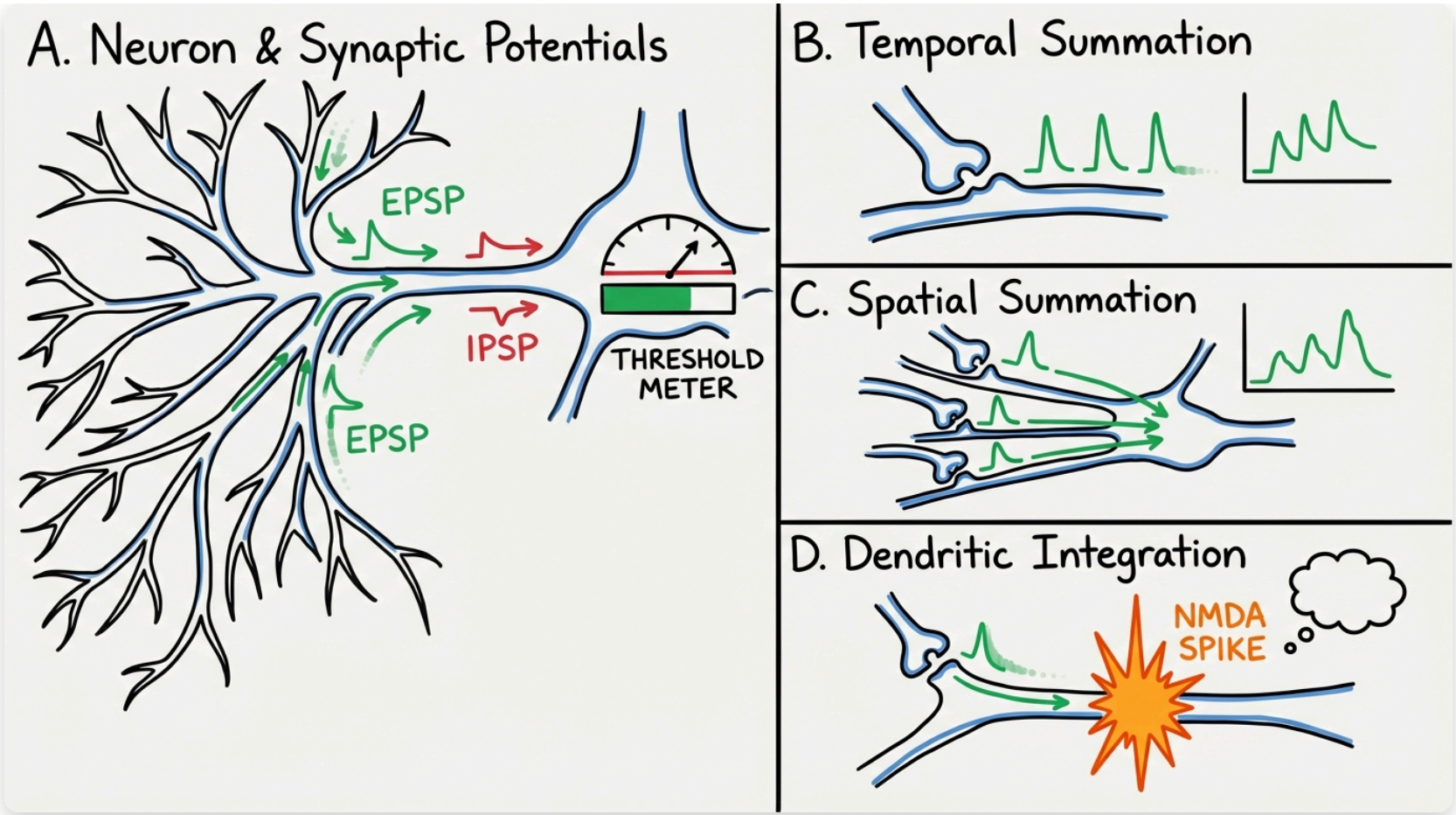
- Main Points:
- Excitatory postsynaptic potentials (EPSPs) make a neuron more positive, pushing it closer to firing an electrical signal.
- At certain connections, a chemical called glutamate opens channels that allow positive ions to flow into the neuron, causing this positive change.
- Inhibitory postsynaptic potentials (IPSPs) make a neuron less likely to fire by making it more negative or by stabilizing its electrical state.
- At other connections, a chemical called GABA opens channels for negative chloride ions to enter the neuron, causing these inhibitory effects.


EXCITATORY INPUT
(Glutamate)
Glutamate
AMPAR /
NMDAR
Na+
Na+
Na+
K+
Membrane Potential (mV)
0
-5
-10
Depolarization
EPSP
Time (ms)
INHIBITORY INPUT
(GABA)
GABA
GABAA
Receptor
Cl−
Cl−
Membrane Potential (mV)
0
-5
-10
Hyperpolarization /
Shunting Inhibition
IPSP
Time (ms)

Spatial Temporal Summation

Excitatory and Inhibitory Postsynaptic Potentials Spatial and Temporal Summation A single EPSP (~0.5 mV) decays passively with a time constant of ~20 ms. To reach threshold, neurons use temporal summation—rapid successive EPSPs from the same synapse add together before earlier ones decay—and spatial summation—simultaneous EPSPs from multiple synapses add together. Dendritic integration is sublinear (inputs on the same branch interact) or supralinear (NMDA spikes), adding computational richness beyond simple addition.

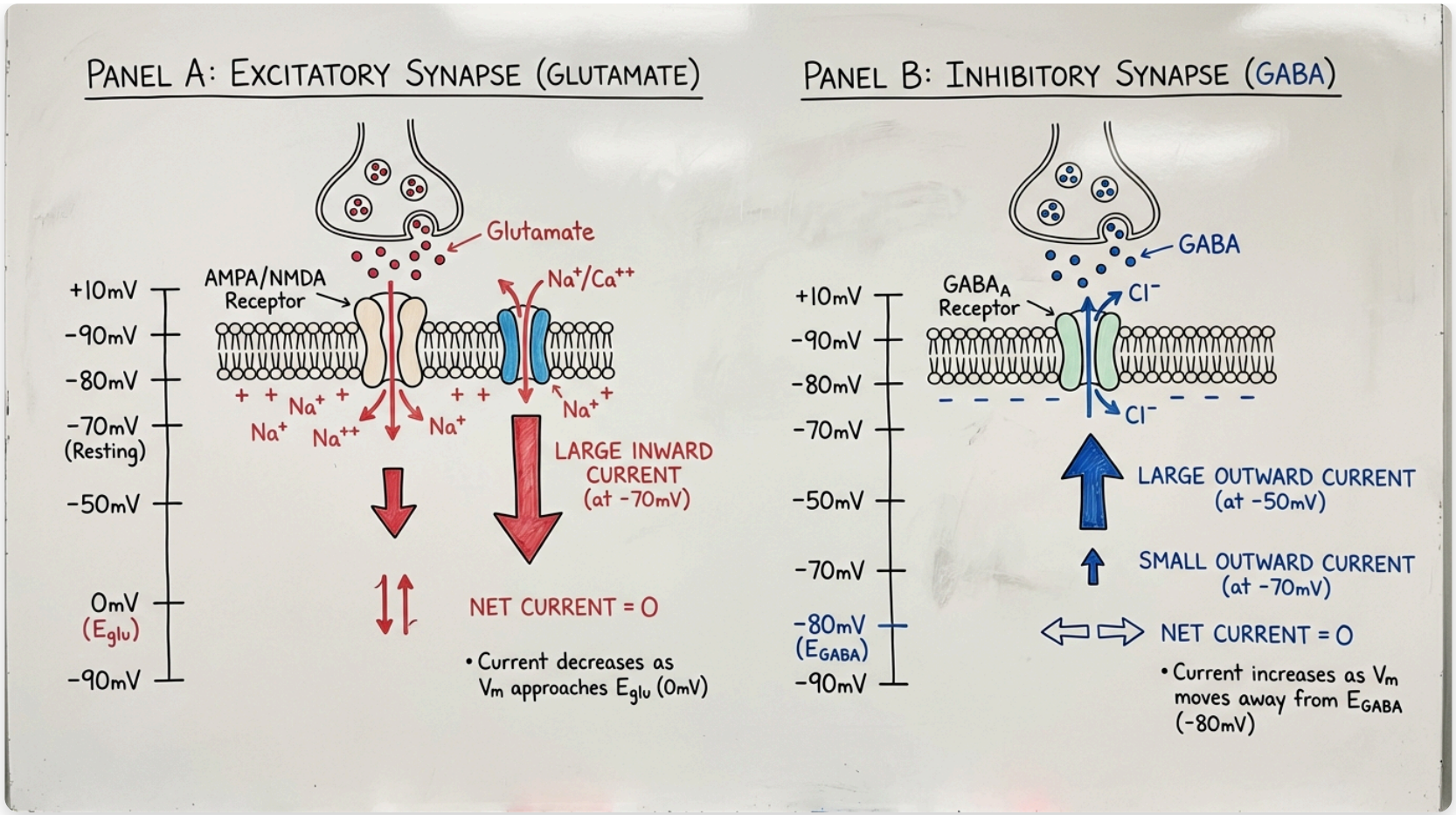
- Here are 4 main points from the text:
- A single excitatory signal (EPSP) is small and decays quickly.
- Temporal summation combines rapid, successive signals from the same neuron connection. This helps a neuron reach its activation threshold.
- Spatial summation combines signals that arrive at the same time from multiple different neuron connections. This also helps the neuron activate.
- Signal combination in dendrites can be more complex than simple addition. This allows for rich calculations within the neuron.


A. Neuron & Synaptic Potentials
EPSP
IPSP
EPSP
THRESHOLD METER
B. Temporal Summation
C. Spatial Summation
D. Dendritic Integration
NMDA SPIKE

Reversal Driving Force

Excitatory and Inhibitory Postsynaptic Potentials Reversal Potential and Driving Force Every synaptic current follows Ohm's law: $I = g(V_m - E_{rev})$. The reversal potential (E_{rev}) is where current reverses direction—at this voltage, equal cation influx and efflux produce no net current. For glutamate receptors permeable to Na^+ and K^+, $E_{rev} \approx 0$ mV. The term ($V_m - E_{rev}$) is the driving force. At resting potential (−70 mV), the driving force for glutamate receptors is $-70 - 0 = -70$ mV, driving strong inward current. As the cell depolarizes toward 0 mV, driving force shrinks—EPSPs become smaller. This self-limiting property prevents runaway excitation. For GABAergic synapses, $E_{rev} \approx -80$ mV (E_{Cl} in mature neurons). At rest (−70 mV), the driving force is $-70 - (-80) = +10$ mV—a small outward current that hyperpolarizes slightly. But during excitation, if V_m reaches −50 mV, driving force becomes +30 mV—stronger inhibition precisely when it's most needed.

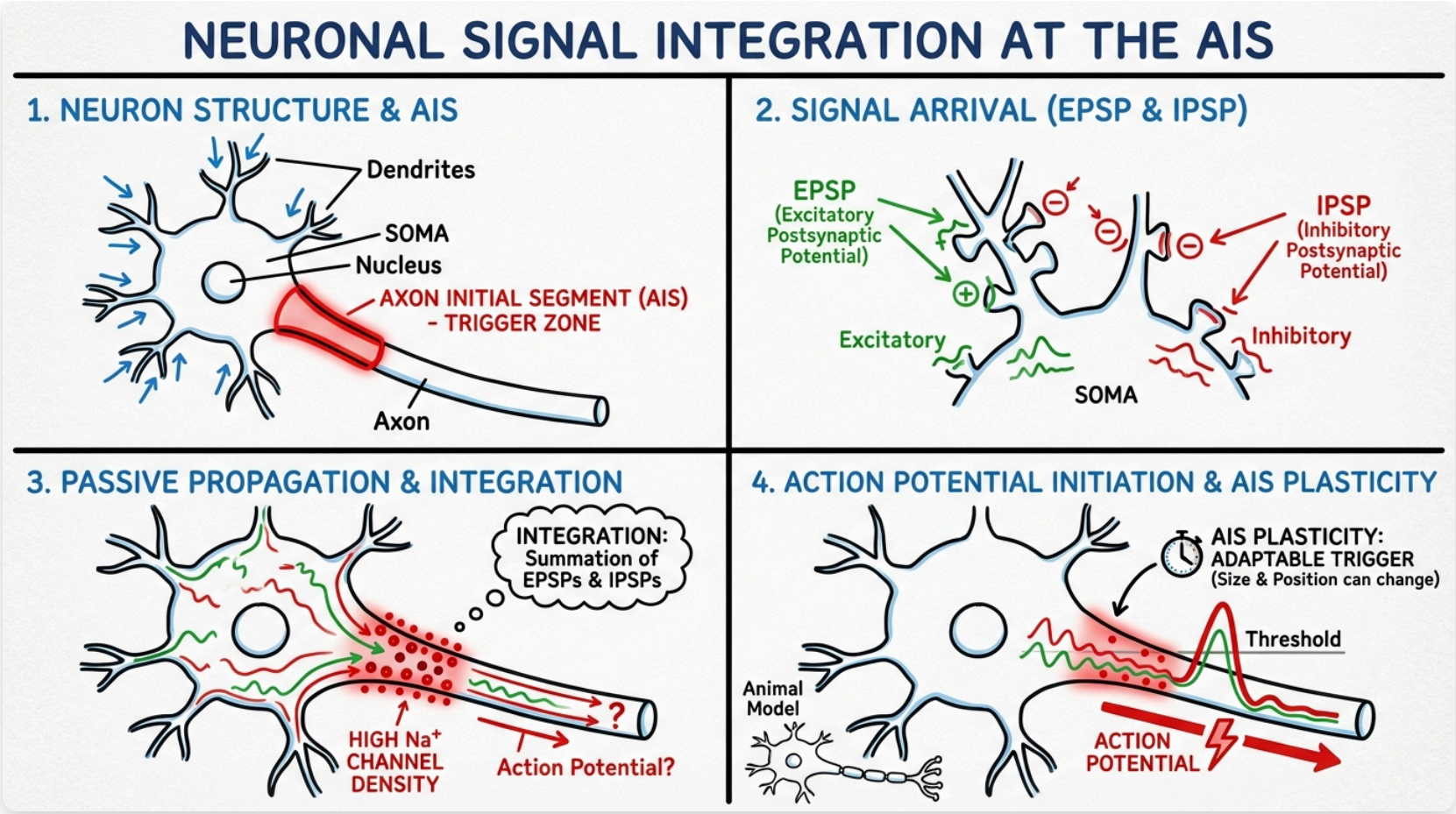
- Here are 4 main points from the text:
- The reversal potential is the specific voltage where a synaptic current changes its direction. At this voltage, the flow of positive ions into and out of the cell is equal, resulting in no net current.
- The driving force determines the strength and direction of a synaptic current. It measures the difference between the cell's membrane voltage and the reversal potential.
- Excitatory synapses, such as those that use glutamate, have a reversal potential around 0 mV. They create a strong inward current, causing the neuron to become excited.
- Inhibitory synapses, like those using GABA, have a reversal potential around -80 mV. They provide stronger inhibition when the neuron is highly excited, helping to control activity.


PANEL A: EXCITATORY SYNAPSE (GLUTAMATE)
Glutamate
AMPA/NMDA Receptor
Na+/Ca++
+10mV
-90mV
-80mV
-70mV (Resting)
-50mV
0mV (Eglu)
-90mV
Na+
Na++
Na+
Na+
LARGE INWARD CURRENT (at -70mV)
NET CURRENT = 0
• Current decreases as Vm approaches Eglu (0mV)
PANEL B: INHIBITORY SYNAPSE (GABA)
GABA
GABAA Receptor
Cl-
Cl-
+10mV
-90mV
-80mV
-70mV
-50mV
-70mV
-80mV (EGABA)
-90mV
LARGE OUTWARD CURRENT (at -50mV)
SMALL OUTWARD CURRENT (at -70mV)
NET CURRENT = 0
• Current increases as Vm moves away from EGABA (-80mV)

AIS Synaptic Integration

Excitatory and Inhibitory Postsynaptic Potentials Integration at the Axon Initial Segment The final decision—fire or not—occurs at the axon initial segment (AIS), where sodium channel density is highest (~1000/μm², vs ~10/μm² on the soma). EPSPs and IPSPs propagate passively from dendrites and soma to the AIS, which acts as the trigger zone. If integrated input exceeds threshold at the AIS, an action potential initiates and propagates down the axon. Recent research shows the AIS is plastic—its position and length can change with experience, tuning neuronal excitability. Receptor Types: Fast and Slow Signaling

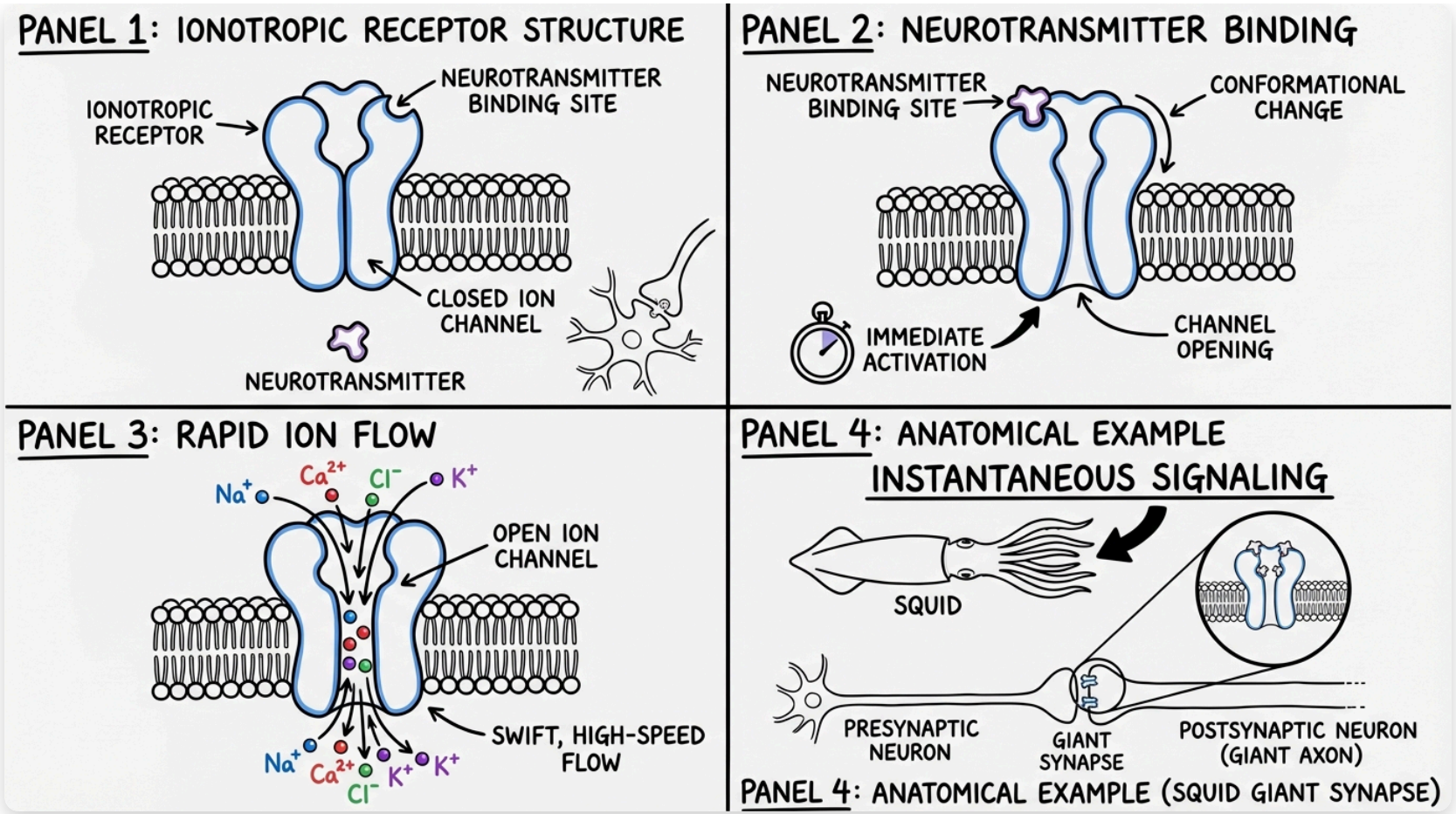
- Here are 4 main points from the text:
- The axon initial segment (AIS) makes the final decision about whether a neuron fires. It has a very high number of sodium channels.
- Electrical signals from dendrites and the cell body travel to the AIS. The AIS acts as the neuron's trigger zone.
- An action potential starts at the AIS if incoming signals reach a certain strength. This electrical signal then moves down the axon.
- The AIS can change its position and length based on a neuron's experiences. These changes adjust how easily a neuron fires.


NEURONAL SIGNAL INTEGRATION AT THE AIS
1. NEURON STRUCTURE & AIS
Dendrites
SOMA
Nucleus
AXON INITIAL SEGMENT (AIS)
- TRIGGER ZONE
Axon
2. SIGNAL ARRIVAL (EPSP & IPSP)
EPSP
(Excitatory
Postsynaptic
Potential)
IPSP
(Inhibitory
Postsynaptic
Potential)
Excitatory
Inhibitory
SOMA
3. PASSIVE PROPAGATION & INTEGRATION
INTEGRATION:
Summation of
EPSPs & IPSPs
HIGH Na+
CHANNEL
DENSITY
?
Action Potential?
4. ACTION POTENTIAL INITIATION & AIS PLASTICITY
AIS PLASTICITY:
ADAPTABLE TRIGGER
(Size & Position can change)
Threshold
Animal
Model
ACTION
POTENTIAL

Ionotropic Speed

Ionotropic Receptors: Speed Ionotropic receptors (ligand-gated ion channels) are fast because the receptor IS the channel. Neurotransmitter binding causes a conformational change that directly opens the ion pore—response time is microseconds to milliseconds. Examples include: • Nicotinic ACh receptors: pentameric channels ($\alpha_2\beta\gamma\delta$ at NMJ, various α and β subunits in brain), permeable to Na^+ and K^+ • AMPA receptors: tetrameric glutamate-gated channels mediating fast excitatory transmission • NMDA receptors: voltage-dependent (Mg^{2+} block), Ca^{2+}-permeable, requiring both glutamate and glycine—coincidence detectors critical for learning • GABA_A receptors: pentameric Cl^- channels mediating fast inhibition; targets for benzodiazepines, barbiturates, alcohol, and anesthetics • Glycine receptors: pentameric Cl^- channels mediating inhibition in spinal cord and brainstem

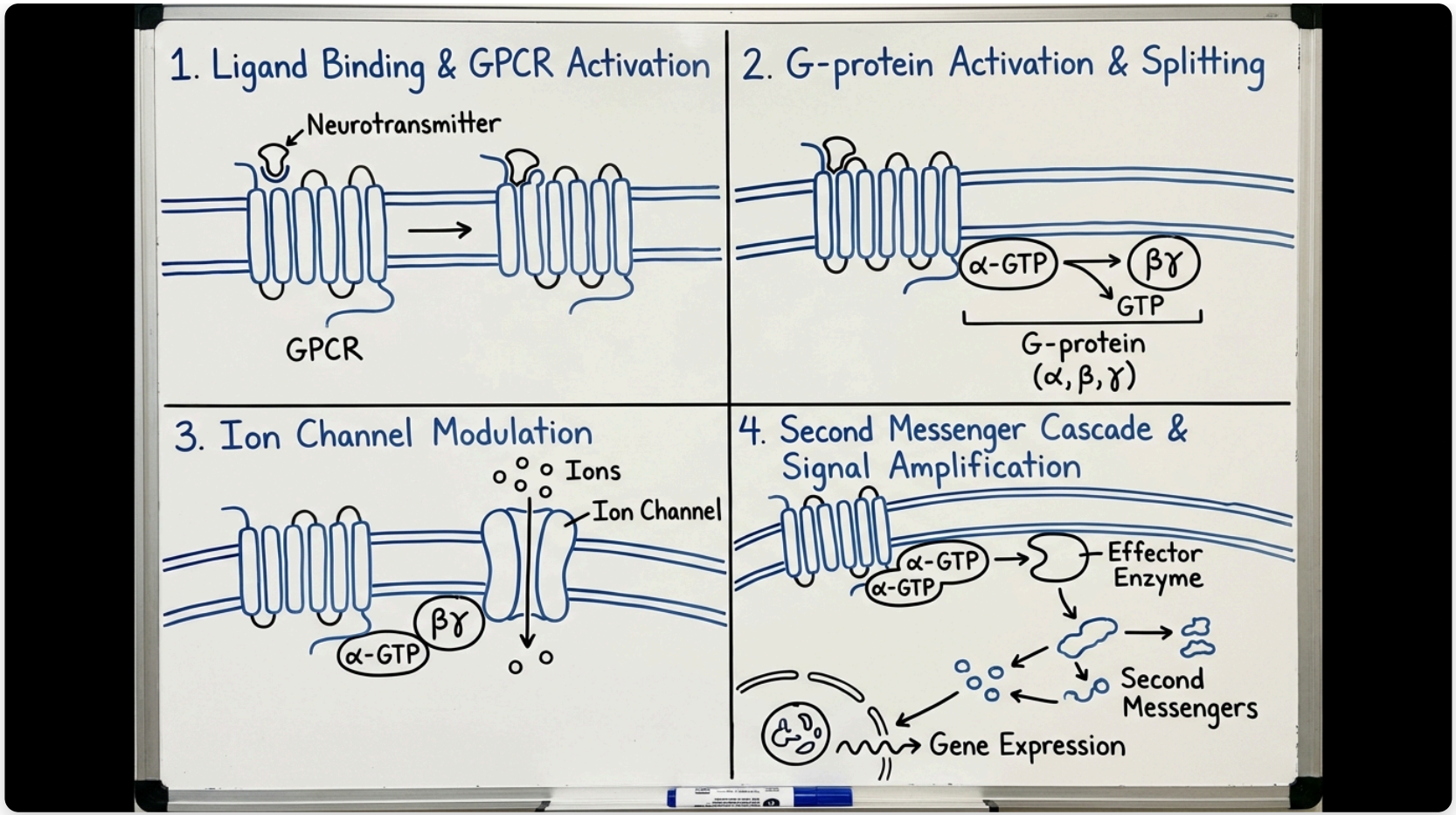
- Here are 3 main points about ionotropic receptors:
- Ionotropic receptors are channels that open directly when a neurotransmitter binds. This allows for very fast responses.
- These receptors help create fast excitatory or inhibitory signals in the nervous system. Specific types, like NMDA receptors, are important for brain functions such as learning.
- There are many different types of ionotropic receptors, each letting specific ions pass through. Some of these receptors are targets for common medications and substances.


PANEL 1: IONOTROPIC RECEPTOR STRUCTURE
IONOTROPIC RECEPTOR
NEUROTRANSMITTER BINDING SITE
CLOSED ION CHANNEL
NEUROTRANSMITTER
PANEL 2: NEUROTRANSMITTER BINDING
NEUROTRANSMITTER BINDING SITE
CONFORMATIONAL CHANGE
IMMEDIATE ACTIVATION
CHANNEL OPENING
PANEL 3: RAPID ION FLOW
Na+
Ca2+
Cl−
K+
OPEN ION CHANNEL
SWIFT, HIGH-SPEED FLOW
PANEL 4: ANATOMICAL EXAMPLE
INSTANTANEOUS SIGNALING
SQUID
PRESYNAPTIC NEURON
GIANT SYNAPSE
POSTSYNAPTIC NEURON (GIANT AXON)
PANEL 4: ANATOMICAL EXAMPLE (SQUID GIANT SYNAPSE)

Metabotropic Receptors

Metabotropic Receptors: Flexibility Metabotropic receptors (G-protein coupled receptors, GPCRs) are slow but powerful. They don't form channels themselves but activate G-proteins that modulate ion channels indirectly or trigger second messenger cascades. Response time is seconds to minutes, but effects are amplified and can alter gene expression. • Muscarinic ACh receptors (M1-M5): G-protein coupled, mediate slow ACh effects in heart (slowing), smooth muscle, and brain • Metabotropic glutamate receptors (mGluR1-8): modulate synaptic transmission and plasticity • GABA_B receptors: activate K^+ channels (hyperpolarizing) and inhibit Ca^{2+} channels (reducing release); target of baclofen • Dopamine receptors (D1-D5): D1-like activate adenylyl cyclase; D2-like inhibit it—targets for antipsychotics and Parkinson's drugs

- Here are 4 main points from the text:
- Metabotropic receptors work slowly but have powerful, long-lasting effects.
- These receptors activate G-proteins. G-proteins then indirectly control ion channels or start other processes inside the cell.
- Their effects develop over seconds to minutes. These actions are amplified and can even change how genes work in a cell.
- They mediate diverse effects in the heart, muscles, and brain, and many drugs target them.

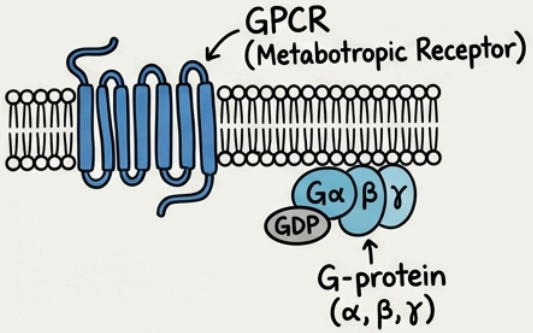

1. Ligand Binding & GPCR Activation
Neurotransmitter
GPCR
2. G-protein Activation & Splitting
α-GTP
βγ
GTP
G-protein
(α, β, γ)
3. Ion Channel Modulation
Ions
Ion Channel
βγ
α-GTP
4. Second Messenger Cascade & Signal Amplification
α-GTP
α-GTP
Effector Enzyme
Second Messengers
Gene Expression

GTPase Cycle

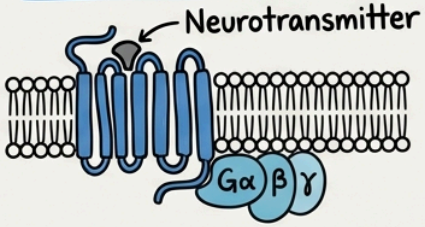
Metabotropic Receptors: Flexibility G-proteins act as molecular switches. In the inactive state, the α subunit binds GDP. Receptor activation catalyzes GDP→GTP exchange; the GTP-bound α subunit (and/or βγ dimer) then modulates effectors—adenylyl cyclase, phospholipase C, ion channels—until GTP hydrolysis returns the system to baseline. This GTPase cycle provides temporal control and signal amplification. Pharmacology Note: Most CNS drugs target synaptic transmission. Benzodiazepines (Valium, Xanax) enhance GABA_A receptor function. SSRIs (Prozac) block serotonin reuptake. Cocaine blocks dopamine reuptake. Opioids activate μ receptors. Caffeine blocks adenosine receptors. Understanding synaptic mechanisms is understanding the molecular basis of drug action. Neurotransmitter Diversity: Why 100+ Messengers?

- Here are 3-5 main points from the text:
- G-proteins act as molecular switches within metabotropic receptors.
- When activated, G-proteins exchange GDP for GTP, which then modulates other cellular effectors.
- The GTPase cycle helps control the timing of signals and amplifies them.
- Most drugs that affect the central nervous system target synaptic transmission.
- Understanding synaptic mechanisms explains the molecular basis of how drugs work.

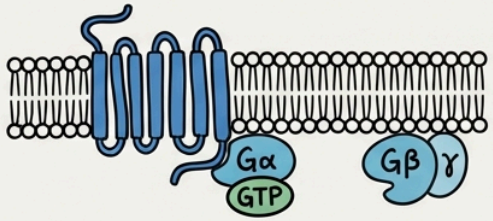
1. RESTING STATE



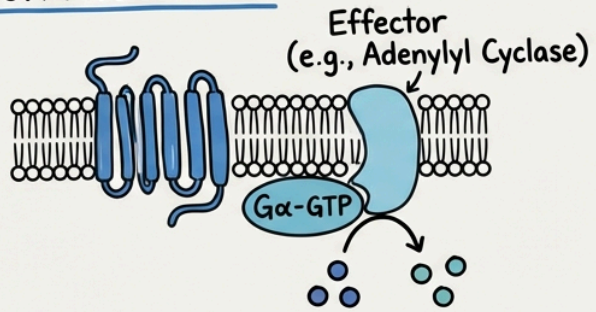
2. NEUROTRANSMITTER BINDING & ACTIVATION



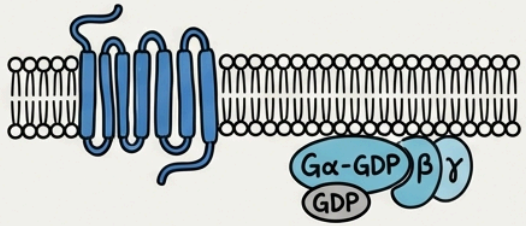
3. GDP-GTP EXCHANGE & DISSOCIATION



4. EFFECTOR MODULATION



5. TERMINATION & RESET

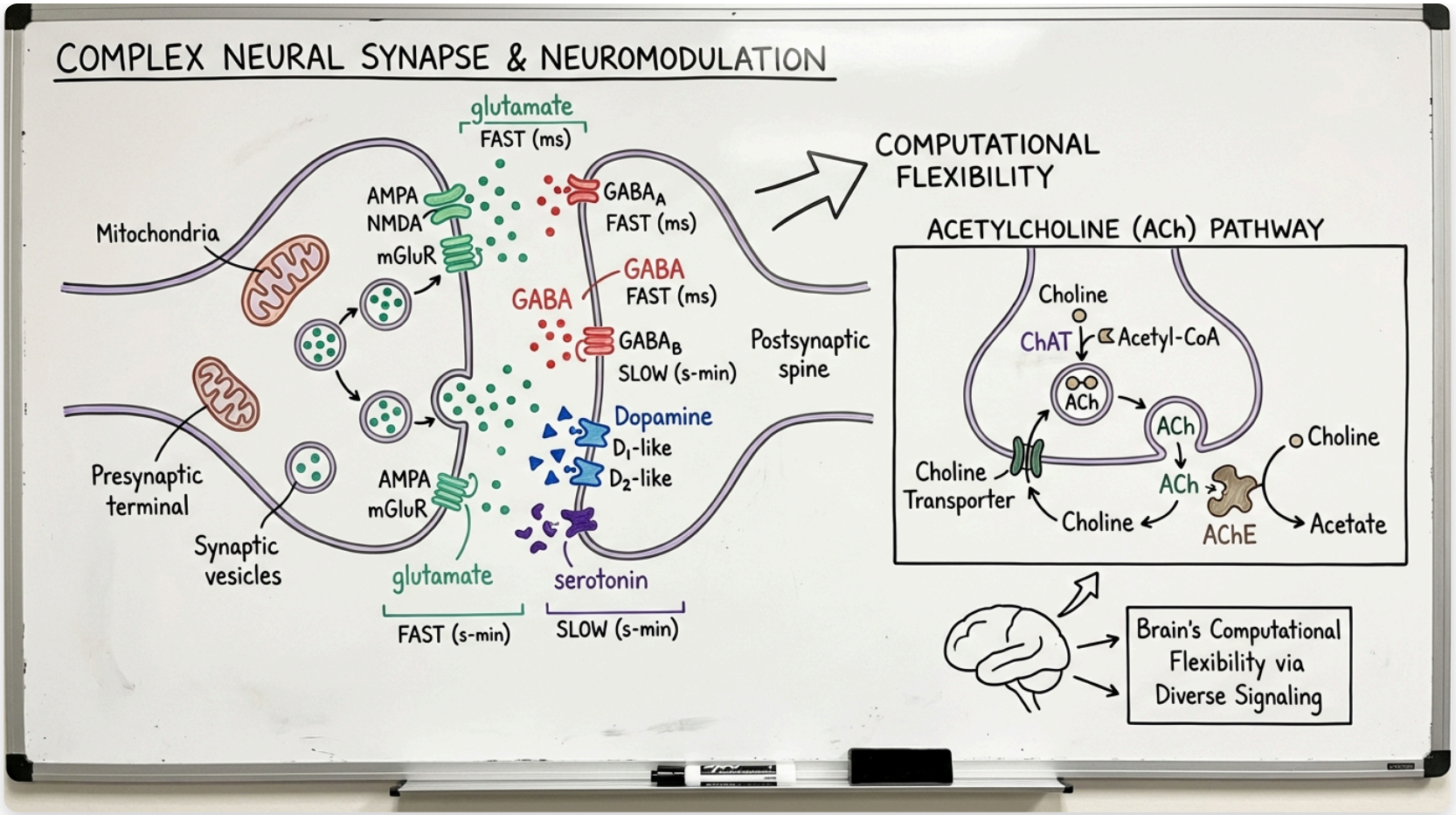


PHARMACOLOGICAL TARGETS: Drugs can modulate receptors, G-proteins, or effectors to alter signaling.

Neurotransmitter Diversity

Metabotropic Receptors: Flexibility If neurons just need to say "more" or "less," why does the brain use over 100 neurotransmitters? The answer: each transmitter system serves distinct functions, operates on different timescales, and can be independently regulated. This chemical diversity enables computational flexibility impossible with a single transmitter. Acetylcholine: The Original Neurotransmitter Acetylcholine is synthesized from choline and acetyl-CoA by choline acetyltransferase (ChAT). After release, it's hydrolyzed by acetylcholinesterase (AChE)—one of the fastest enzymes known, processing 25,000 molecules per second. The choline is recycled into the terminal.

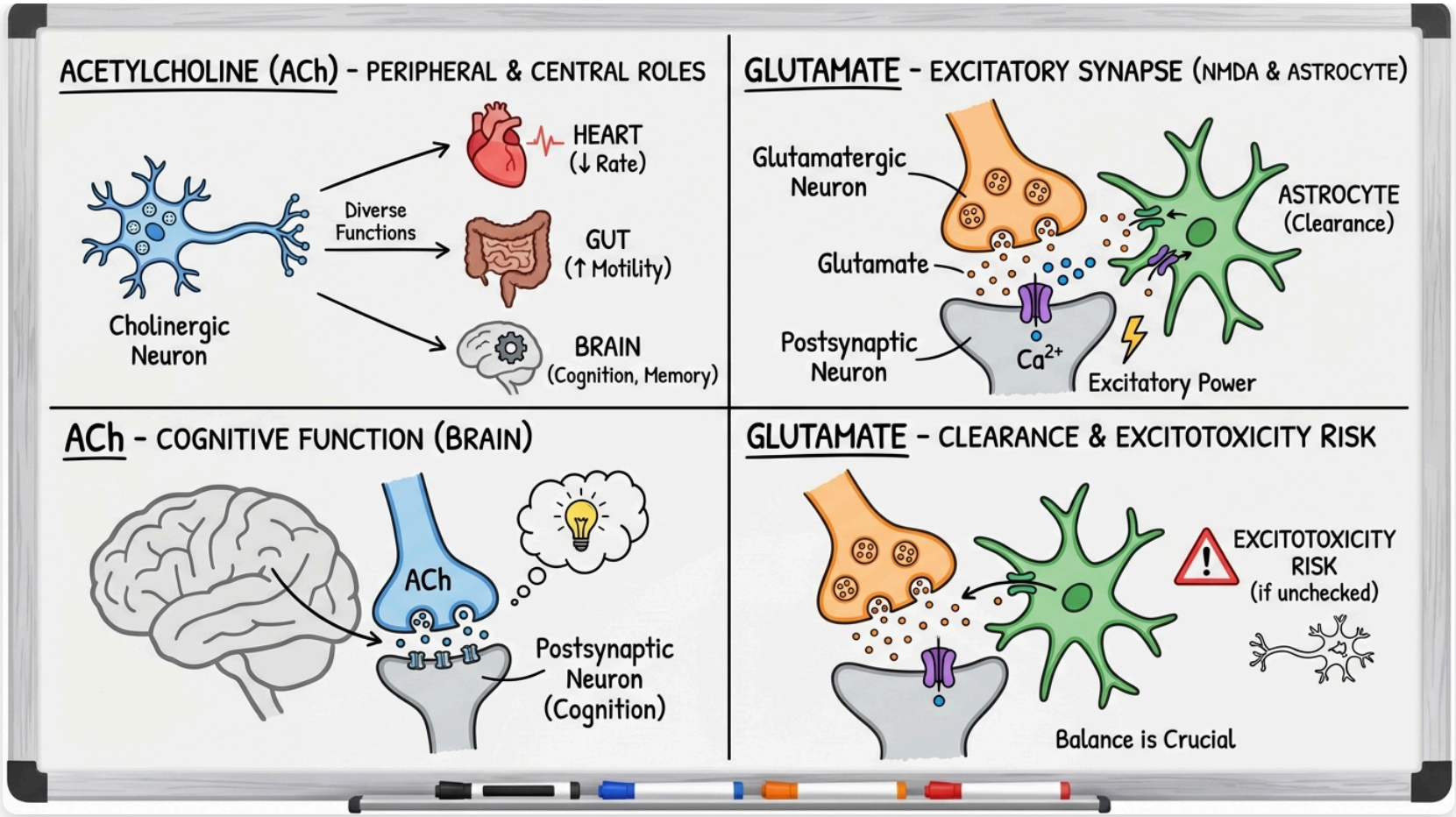
- Here are 3 main points from the text:
- The brain uses many different neurotransmitters because each has unique functions and operating speeds. This diversity allows for complex and flexible brain processing.
- The enzyme ChAT synthesizes acetylcholine from choline and acetyl-CoA.
- After acetylcholine is released, the enzyme acetylcholinesterase (AChE) rapidly breaks it down. The brain then recycles the choline for new use.


COMPLEX NEURAL SYNAPSE & NEUROMODULATION
glutamate
FAST (ms)
AMPA
NMDA
mGluR
Mitochondria
GABA$_A$
FAST (ms)
GABA
GABA
FAST (ms)
GABA$_B$
SLOW (s-min)
Postsynaptic spine
Dopamine
D$_1$-like
D$_2$-like
Presynaptic terminal
AMPA
mGluR
Synaptic vesicles
glutamate
serotonin
FAST (s-min)
SLOW (s-min)
COMPUTATIONAL FLEXIBILITY
ACETYLCHOLINE (ACh) PATHWAY
Choline
ChAT
Acetyl-CoA
ACh
ACh
Choline
Choline Transporter
ACh
Choline
AChE
Acetate
Brain's Computational Flexibility via Diverse Signaling

Cholinergic System

Metabotropic Receptors: Flexibility In the periphery, ACh mediates neuromuscular transmission (nicotinic receptors) and parasympathetic functions (muscarinic receptors—slowing heart, stimulating digestion). In the brain, cholinergic projections from the basal forebrain modulate attention and memory. Alzheimer's disease involves degeneration of these neurons; acetylcholinesterase inhibitors (donepezil, rivastigmine) provide modest symptomatic benefit. Organophosphate nerve agents irreversibly inhibit AChE, causing fatal cholinergic crisis. Amino Acid Transmitters: The Workhorses Glutamate is the brain's primary excitatory transmitter, used by ~80% of cortical neurons. It's synthesized from glutamine by glutaminase, packaged into vesicles by VGLUTs, and cleared by astrocyte transporters (EAATs). Excess glutamate causes excitotoxicity—calcium overload through NMDA receptors triggers cell death—contributing to stroke and neurodegenerative disease.

- Here are 5 main points:
- Acetylcholine plays important roles in muscle movement, body functions like heart rate and digestion, and brain functions like attention and memory.
- Alzheimer's disease affects neurons that use acetylcholine, and medicines can offer some relief for symptoms.
- Dangerous nerve agents can block an enzyme that breaks down acetylcholine, which can be deadly.
- Glutamate serves as the main chemical messenger that excites brain cells, especially in the outer layer of the brain.
- Too much glutamate in the brain can damage and kill brain cells, which contributes to conditions like stroke and other brain diseases.

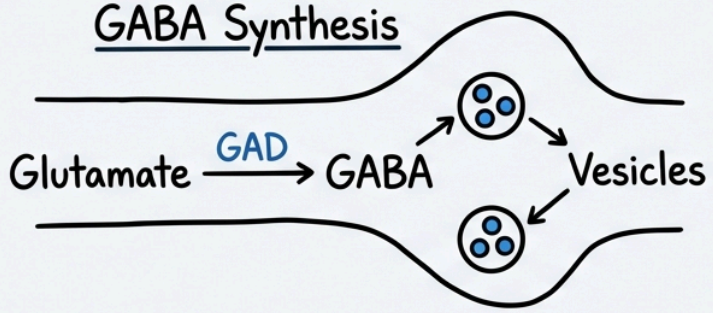

ACETYLCHOLINE (ACh) - PERIPHERAL & CENTRAL ROLES
HEART
(↓ Rate)
Diverse
Functions
GUT
(↑ Motility)
Cholinergic
Neuron
BRAIN
(Cognition, Memory)
GLUTAMATE - EXCITATORY SYNAPSE (NMDA & ASTROCYTE)
Glutamatergic
Neuron
ASTROCYTE
(Clearance)
Glutamate
Postsynaptic
Neuron
Ca2+
Excitatory Power
ACh - COGNITIVE FUNCTION (BRAIN)
ACh
Postsynaptic
Neuron
(Cognition)
GLUTAMATE - CLEARANCE & EXCITOTOXICITY RISK
EXCITOTOXICITY
RISK
(if unchecked)
Balance is Crucial

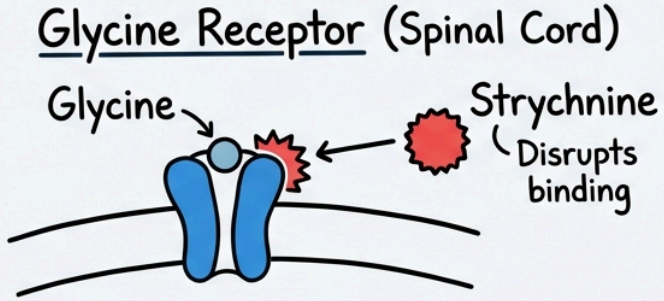
Neurotransmitter Systems

Metabotropic Receptors: Flexibility GABA is the primary inhibitory transmitter, synthesized from glutamate by glutamic acid decarboxylase (GAD)—the same molecule converted from excitatory to inhibitory. GABA is packaged by VGATs and cleared by reuptake (GAT1) and astrocyte uptake. Glycine serves as the primary inhibitory transmitter in spinal cord and brainstem; strychnine (glycine receptor antagonist) causes fatal convulsions. Biogenic Amines: Modulators of Mood and Movement The monoamines—dopamine, norepinephrine, serotonin—are synthesized from amino acid precursors (tyrosine, tryptophan) and degraded by monoamine oxidase (MAO) and COMT. Their cell bodies are concentrated in small brainstem nuclei that project diffusely throughout the brain, modulating global states rather than carrying specific information.

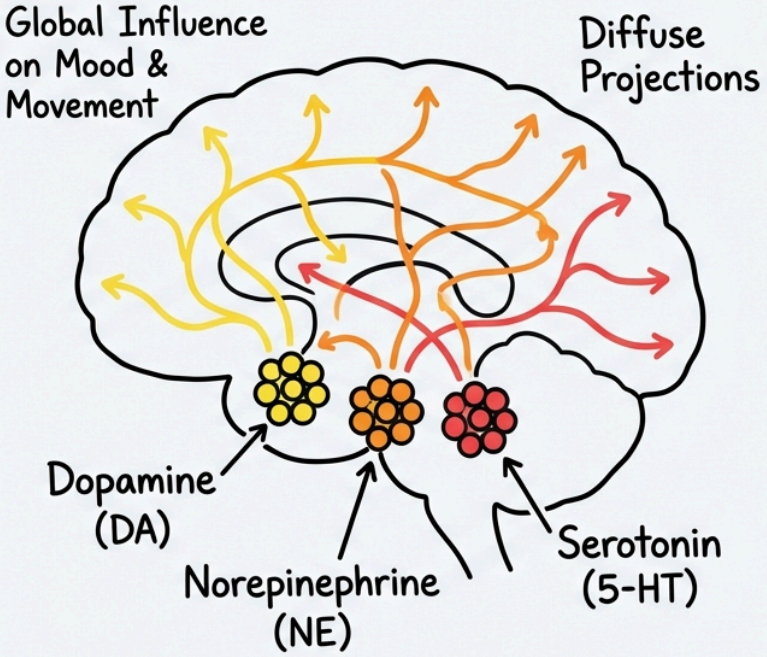
- GABA serves as the brain's primary inhibitory neurotransmitter. The body synthesizes GABA from glutamate.
- Glycine functions as the main inhibitory neurotransmitter in the spinal cord and brainstem.
- Dopamine, norepinephrine, and serotonin are crucial monoamine neurotransmitters. The body creates them from amino acids and degrades them with specific enzymes.
- These monoamines modulate overall brain states, affecting mood and movement. Their cell bodies are in the brainstem and project widely across the brain.

Inhibitory Neurotransmission (GABA & Glycine)





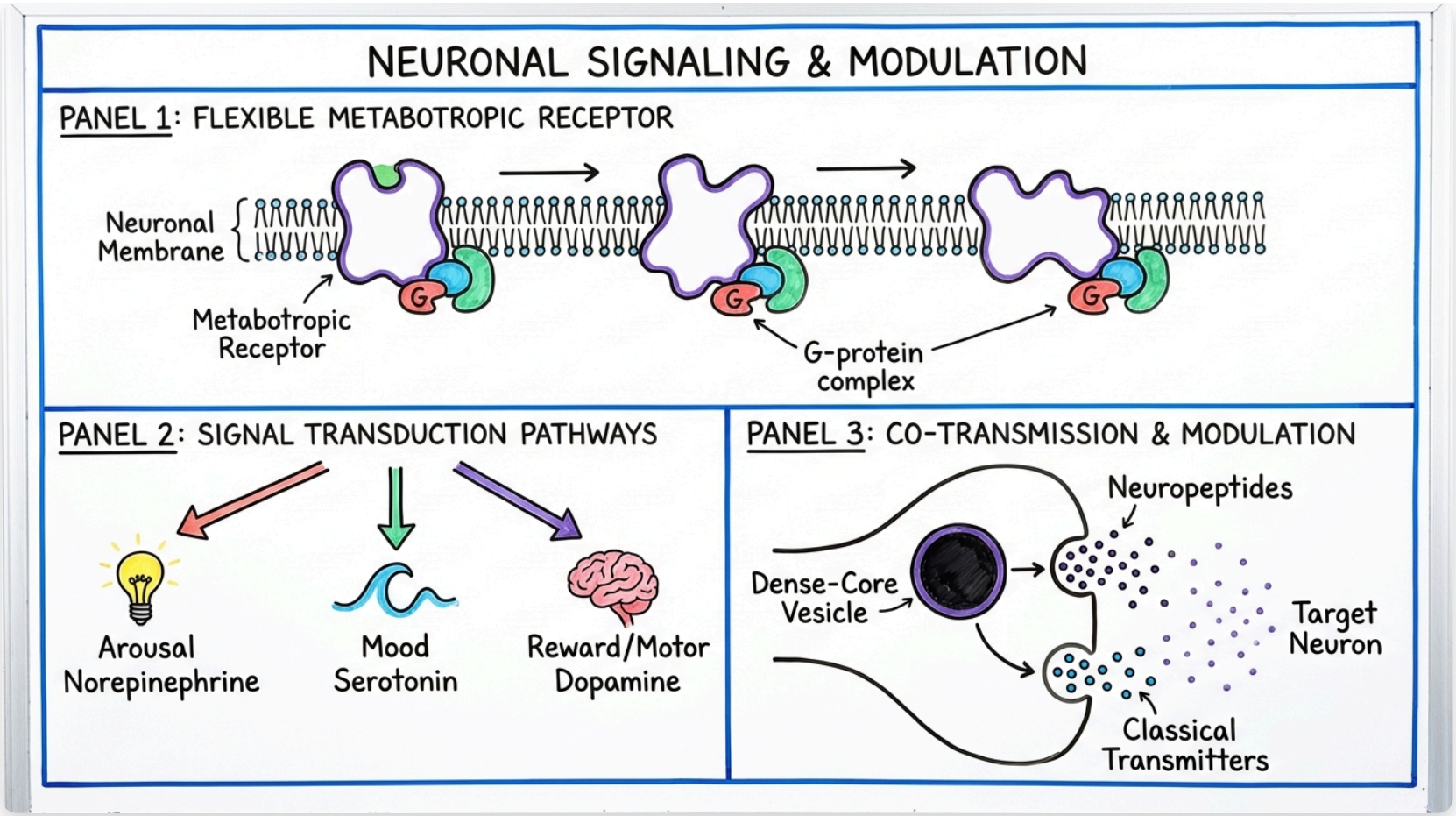
Biogenic Amine Modulation (DA, NE, 5-HT)



Neurotransmitter Systems

Metabotropic Receptors: Flexibility Dopamine pathways include the mesolimbic system (reward, motivation—implicated in addiction), the mesocortical system (cognition—implicated in schizophrenia), and the nigrostriatal system (motor control—degeneration causes Parkinson's). Norepinephrine from the locus coeruleus modulates arousal and attention. Serotonin from the raphe nuclei modulates mood, sleep, and appetite—the primary target of antidepressants. Neuropeptides and Unconventional Transmitters Neuropeptides—chains of 3-40+ amino acids including endorphins, substance P, and neuropeptide Y—are synthesized in the cell body, packaged into large dense-core vesicles, and transported to terminals. They act on GPCRs and are cleared by diffusion and enzymatic degradation (no reuptake). Neuropeptides are often co-released with classical transmitters, providing modulatory effects on longer timescales.

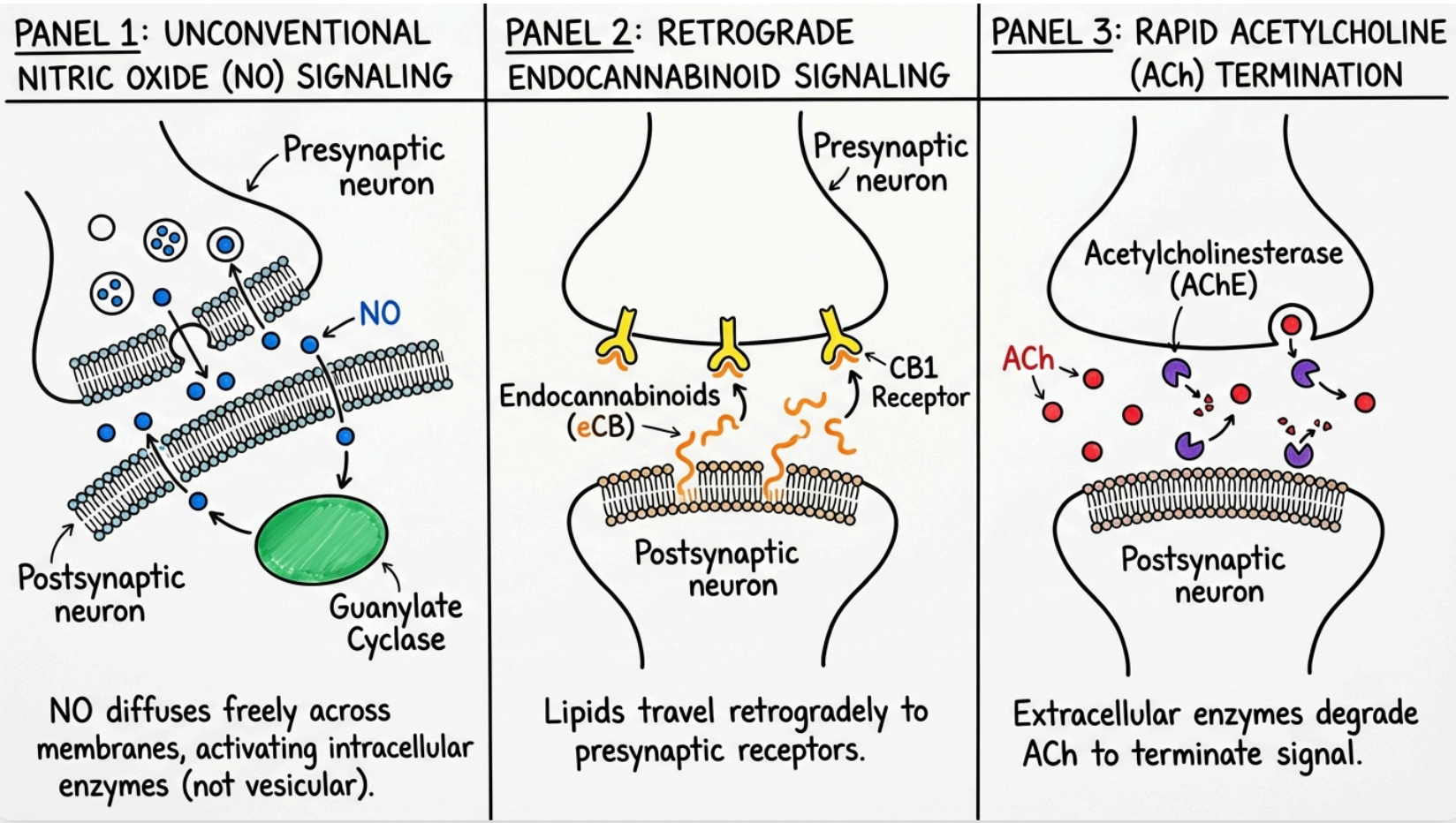
- Here are 3 main points from the text:
- Dopamine pathways control important functions like reward, thinking, and body movement.
- Norepinephrine regulates arousal and attention. Serotonin controls mood, sleep, and appetite and is a primary target for antidepressants.
- Neuropeptides are amino acid chains made in the cell body and moved to nerve terminals. They often release with other transmitters and cause longer-lasting effects.


NEURONAL SIGNALING & MODULATION
PANEL 1: FLEXIBLE METABOTROPIC RECEPTOR
Neuronal Membrane
Metabotropic Receptor
G
G
G
G-protein complex
PANEL 2: SIGNAL TRANSDUCTION PATHWAYS
Arousal Norepinephrine
Mood Serotonin
Reward/Motor Dopamine
PANEL 3: CO-TRANSMISSION & MODULATION
Neuropeptides
Dense-Core Vesicle
Target Neuron
Classical Transmitters

Unconventional Transmitters

Metabotropic Receptors: Flexibility Unconventional transmitters include nitric oxide (NO) and endocannabinoids. NO is a gas that diffuses freely across membranes, activating guanylyl cyclase; it's synthesized on demand (no vesicle storage). Endocannabinoids (anandamide, 2-AG) are lipids synthesized postsynaptically and released to act on presynaptic CB1 receptors—retrograde signaling that suppresses further transmitter release. This is the system activated by cannabis. Neurotransmitter Clearance: Terminating the Signal Synaptic signaling must be terminated rapidly to allow repeated transmission. Three mechanisms clear neurotransmitters from the cleft: 1. Enzymatic degradation: ACh is hydrolyzed by AChE in the synaptic cleft. This is the only transmitter cleared primarily by extracellular enzymes.

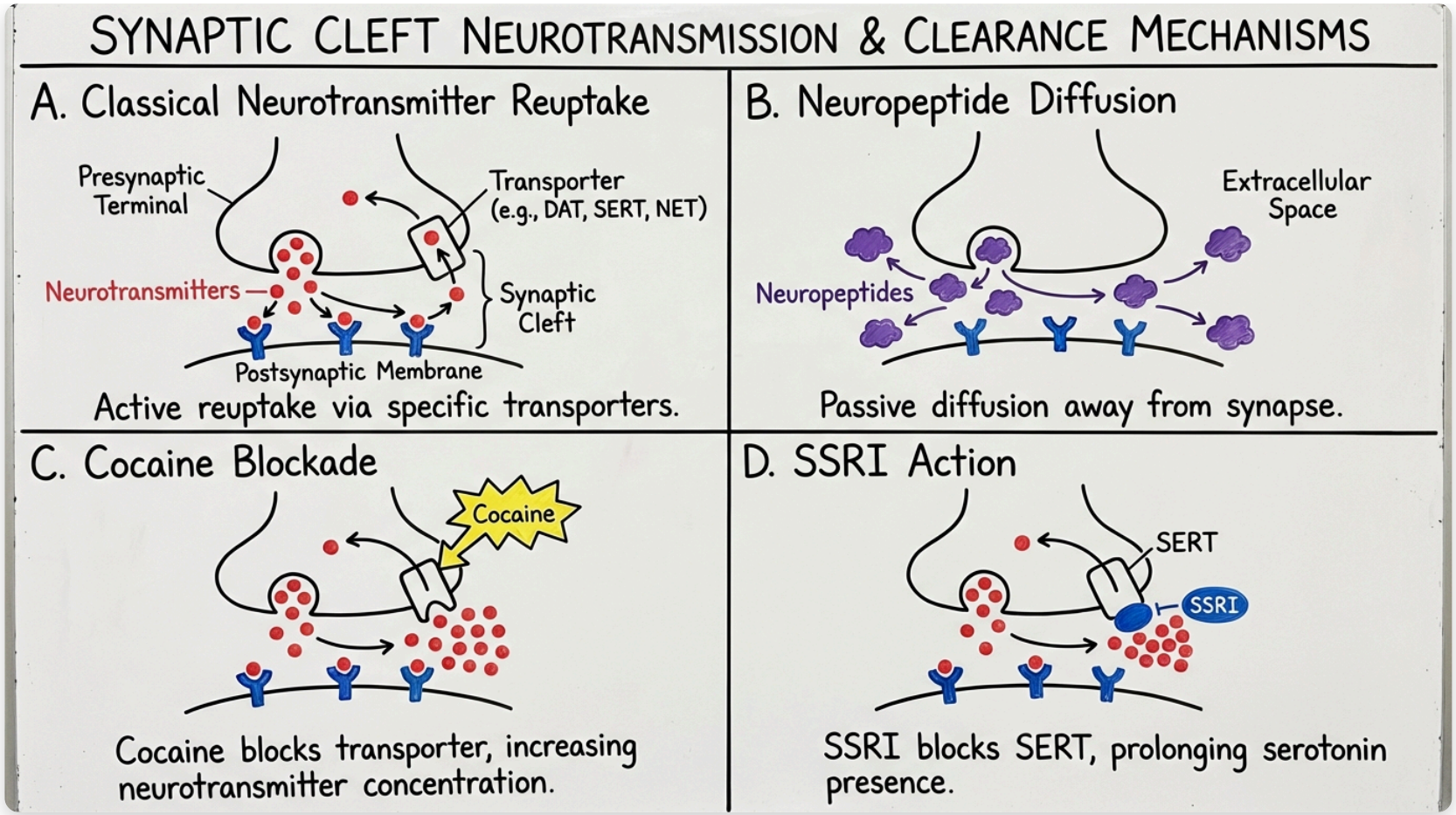
- Main Points:
- Nitric oxide (NO) and endocannabinoids are examples of unconventional neurotransmitters.
- Nitric oxide is a gas that easily moves across cell membranes and is created when needed.
- Endocannabinoids are fats made by the receiving neuron that act on the sending neuron to reduce further release.
- Synaptic signals must end quickly so that new signals can be sent.
- Enzymes break down neurotransmitters in the synaptic gap as one way to stop the signal.


PANEL 1: UNCONVENTIONAL NITRIC OXIDE (NO) SIGNALING
Presynaptic neuron
NO
Postsynaptic neuron
Guanylate Cyclase
NO diffuses freely across membranes, activating intracellular enzymes (not vesicular).
PANEL 2: RETROGRADE ENDOCANNABINOID SIGNALING
Presynaptic neuron
Endocannabinoids (eCB)
CB1 Receptor
Postsynaptic neuron
Lipids travel retrogradely to presynaptic receptors.
PANEL 3: RAPID ACETYLCHOLINE (ACh) TERMINATION
Acetylcholinesterase (AChE)
ACh
Postsynaptic neuron
Extracellular enzymes degrade ACh to terminate signal.

Neurotransmitter Clearance

Metabotropic Receptors: Flexibility 2. Reuptake: Most transmitters are transported back into the presynaptic terminal by specific transporters (DAT for dopamine, SERT for serotonin, NET for norepinephrine, GAT for GABA, EAAT for glutamate). These are major drug targets: cocaine blocks DAT, SSRIs block SERT, tricyclics block multiple transporters. 3. Diffusion: Especially important for neuropeptides, which lack dedicated transporters and are cleared slowly by diffusing away from the synapse. Clinical Correlations: When Synapses Fail • Myasthenia gravis: Autoantibodies attack nicotinic ACh receptors at the NMJ. Progressive weakness, worse with use, improved by rest. Treatment: acetylcholinesterase inhibitors (pyridostigmine), immunosuppression. • Lambert-Eaton syndrome: Autoantibodies attack presynaptic calcium channels. Weakness that improves with use (repeated stimulation allows calcium accumulation). Often paraneoplastic (small cell lung cancer).

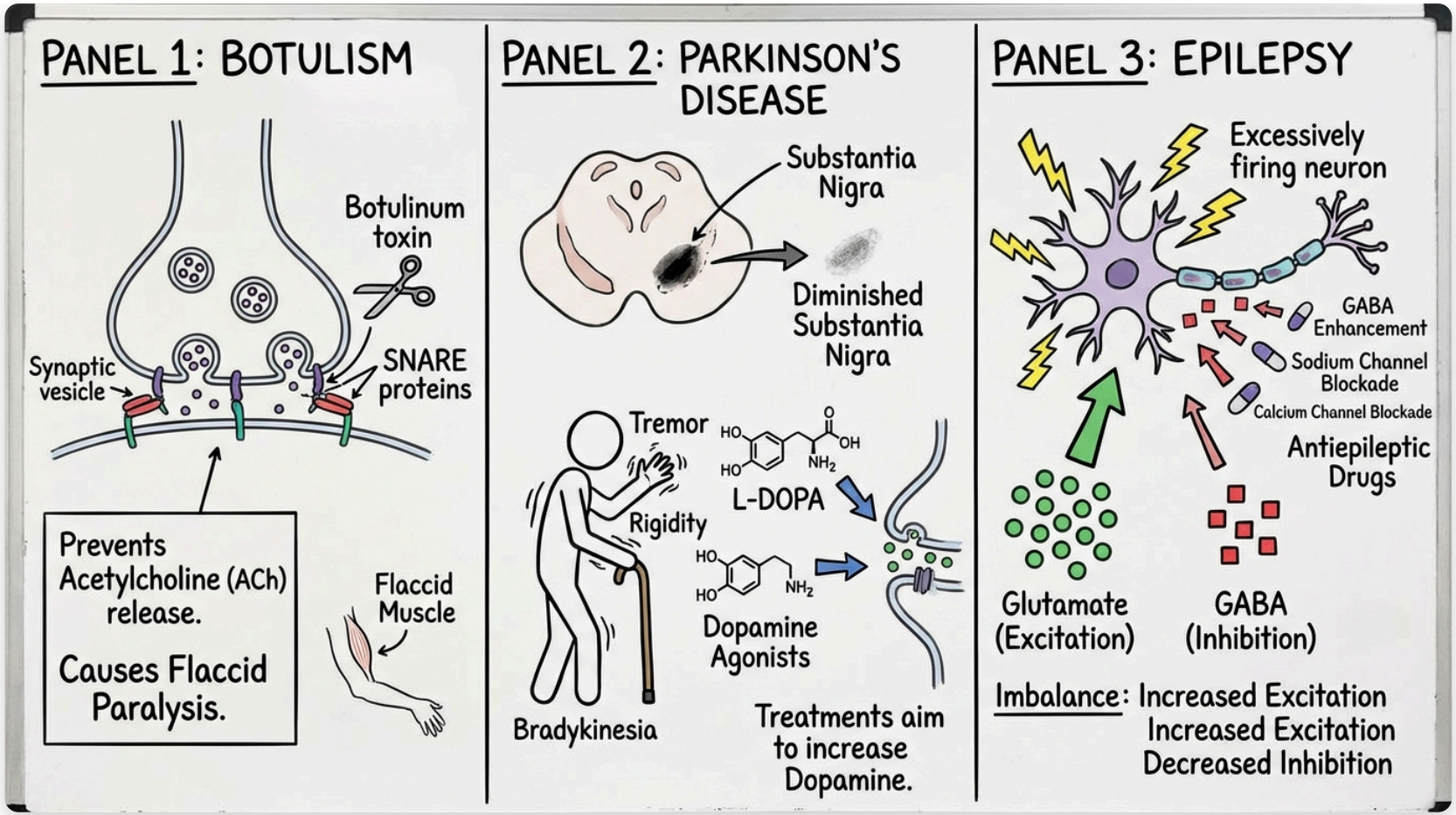
- Here are 4 main points from the text:
- The body clears most neurotransmitters by transporting them back into nerve cells using specific transporters.
- Neuropeptides clear the synapse by slowly diffusing away because they do not have special transporters.
- Myasthenia gravis involves autoantibodies that attack acetylcholine receptors, causing progressive muscle weakness.
- In Lambert-Eaton syndrome, autoantibodies attack presynaptic calcium channels, leading to muscle weakness that gets better with activity.


SYNAPTIC CLEFT NEUROTRANSMISSION & CLEARANCE MECHANISMS
A. Classical Neurotransmitter Reuptake
Presynaptic Terminal
Transporter (e.g., DAT, SERT, NET)
Neurotransmitters
Synaptic Cleft
Postsynaptic Membrane
Active reuptake via specific transporters.
B. Neuropeptide Diffusion
Extracellular Space
Neuropeptides
Passive diffusion away from synapse.
C. Cocaine Blockade
Cocaine
Cocaine blocks transporter, increasing neurotransmitter concentration.
D. SSRI Action
SERT
SSRI
SSRI blocks SERT, prolonging serotonin presence.

Neurotransmitter Disorders

Metabotropic Receptors: Flexibility • Botulism: Botulinum toxin cleaves SNAREs, preventing ACh release. Descending flaccid paralysis beginning with cranial nerves. Can occur from contaminated food or wound infections. • Parkinson's disease: Loss of dopaminergic neurons in the substantia nigra. Tremor, rigidity, bradykinesia. Treatment: L-DOPA (dopamine precursor), dopamine agonists, MAO-B inhibitors. • Epilepsy: Imbalance between excitation (glutamate) and inhibition (GABA). Antiepileptics enhance GABA (benzodiazepines, barbiturates), block sodium channels (phenytoin, carbamazepine), or block glutamate receptors.

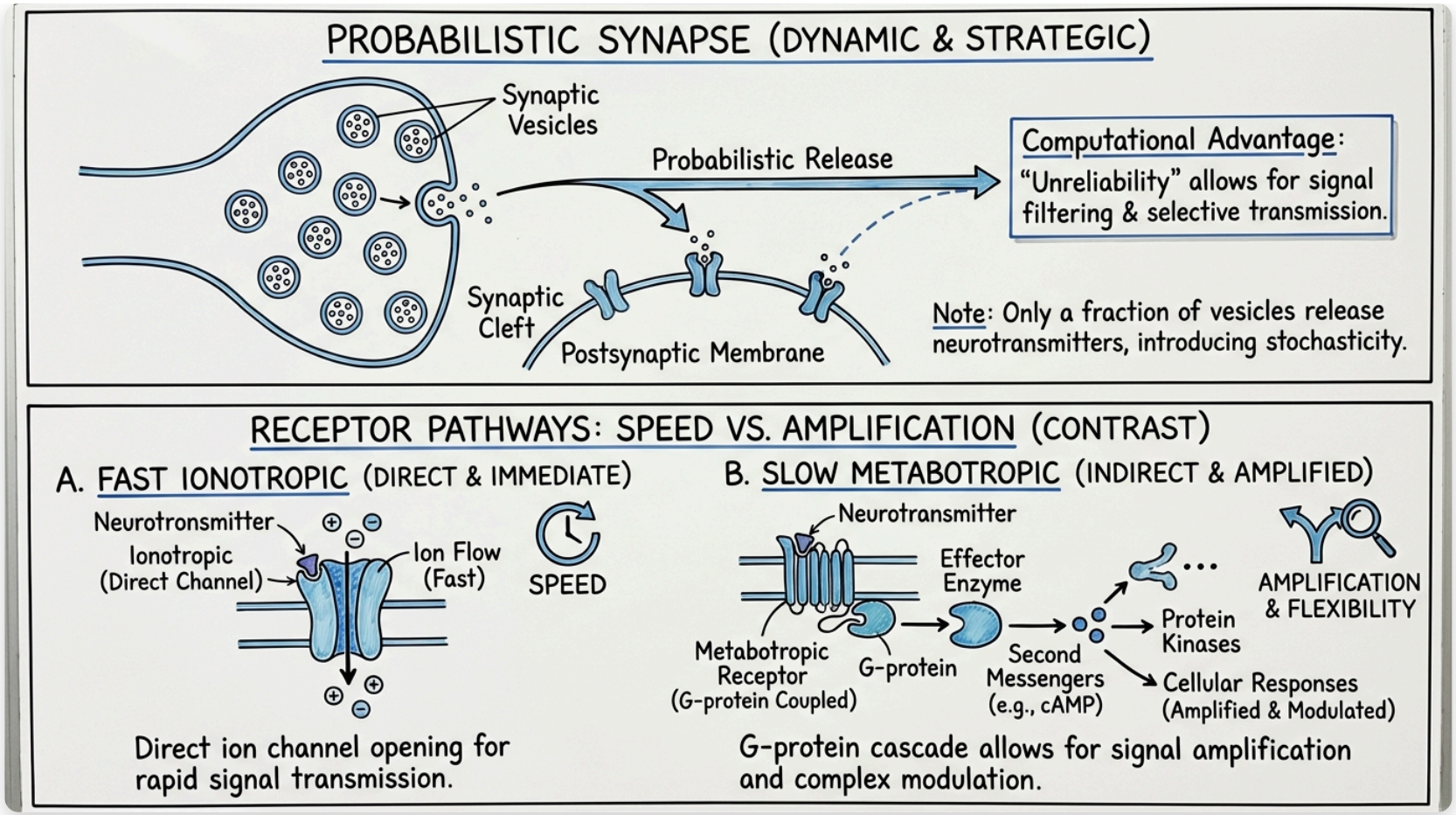
- Here are 3 main points from the text:
- Botulism occurs when a toxin prevents nerve cells from releasing a chemical signal, causing paralysis. This can result from contaminated food or wound infections.
- Parkinson's disease happens when brain cells that produce dopamine are lost, causing symptoms like tremors, stiffness, and slow movement. Treatments aim to replace or increase dopamine in the brain.
- Epilepsy results from an imbalance in brain chemicals that control nerve activity, leading to seizures. Medications for epilepsy work by enhancing calming signals or blocking exciting signals in the brain.


PANEL 1: BOTULISM
Botulinum toxin
Synaptic vesicle
SNARE proteins
Prevents Acetylcholine (ACh) release.
Causes Flaccid Paralysis.
Flaccid Muscle
PANEL 2: PARKINSON'S DISEASE
Substantia Nigra
Diminished Substantia Nigra
Tremor
Rigidity
Bradykinesia
L-DOPA
Dopamine Agonists
Treatments aim to increase Dopamine.
PANEL 3: EPILEPSY
Excessively firing neuron
GABA Enhancement
Sodium Channel Blockade
Calcium Channel Blockade
Antiepileptic Drugs
Glutamate (Excitation)
GABA (Inhibition)
Imbalance: Increased Excitation
Increased Excitation
Decreased Inhibition

Quantal Release Probability

Metabotropic Receptors: Flexibility Thought Questions for Discussion Three questions to spark discussion before your next class: The Quantal Puzzle: Bernard Katz showed that neurotransmitter release is quantized—always in multiples of single vesicle contents. But release probability per vesicle is typically only 10-30% per action potential. Why might evolution have favored unreliable synaptic transmission? Consider the computational advantages of probabilistic release for learning, gain control, and energy efficiency. The Speed-Flexibility Tradeoff: Ionotropic receptors respond in microseconds; metabotropic receptors take seconds. Yet both exist at many synapses. Why maintain two parallel signaling systems rather than optimizing one? Consider situations where speed matters most versus situations where amplification, duration, and modulation of response are more important.

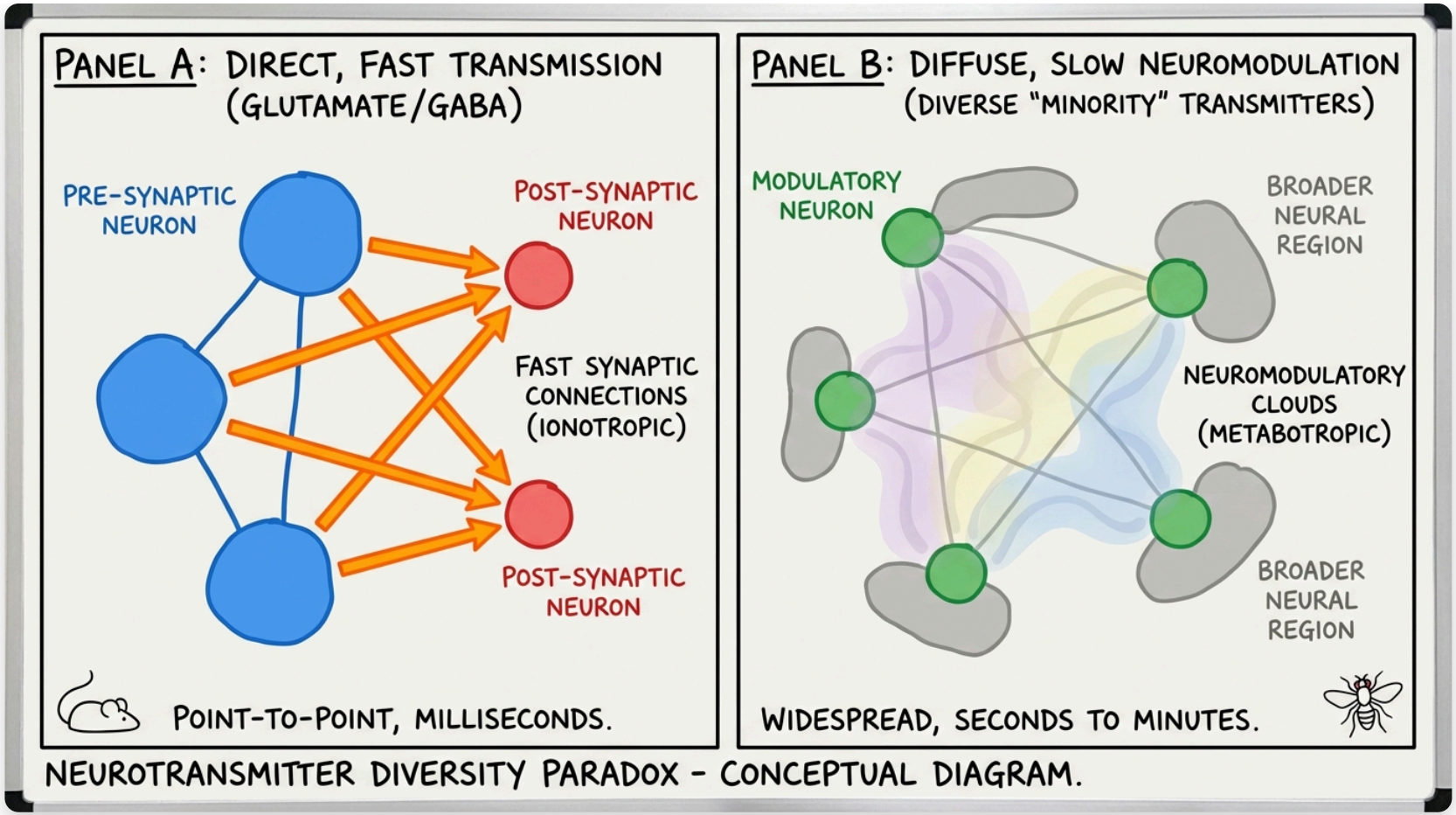
- Here are 4 main points from the text:
- Neurotransmitters release in fixed amounts, but the chance of release for each signal is typically low.
- Probabilistic neurotransmitter release provides benefits for learning, controlling signal strength, and saving energy.
- Synapses use two main types of receptors: ionotropic and metabotropic.
- Ionotropic receptors respond quickly, while metabotropic receptors respond more slowly. They each play important roles in different brain processes.


PROBABILISTIC SYNAPSE (DYNAMIC & STRATEGIC)
Synaptic Vesicles
Probabilistic Release
Computational Advantage:
"Unreliability" allows for signal filtering & selective transmission.
Synaptic Cleft
Postsynaptic Membrane
Note: Only a fraction of vesicles release neurotransmitters, introducing stochasticity.
RECEPTOR PATHWAYS: SPEED VS. AMPLIFICATION (CONTRAST)
A. FAST IONOTROPIC (DIRECT & IMMEDIATE)
Neurotransmitter
Ionotropic (Direct Channel)
Ion Flow (Fast)
SPEED
Direct ion channel opening for rapid signal transmission.
B. SLOW METABOTROPIC (INDIRECT & AMPLIFIED)
Neurotransmitter
Effector Enzyme
Metabotropic Receptor (G-protein Coupled)
G-protein
Second Messengers (e.g., cAMP)
Protein Kinases
Cellular Responses (Amplified & Modulated)
AMPLIFICATION & FLEXIBILITY
G-protein cascade allows for signal amplification and complex modulation.

Neurotransmitter Diversity

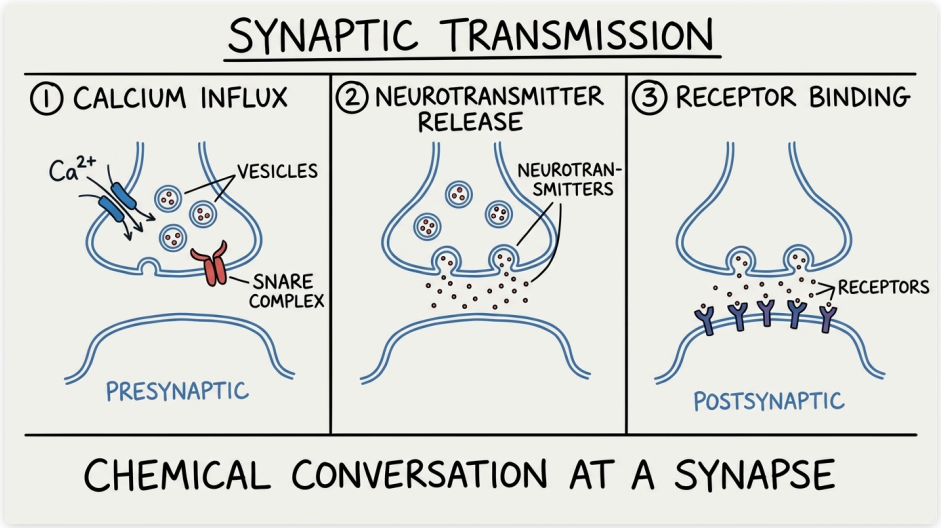
Metabotropic Receptors: Flexibility The Neurotransmitter Diversity Paradox: The brain uses 100+ neurotransmitters, yet glutamate and GABA account for ~95% of fast synaptic transmission. Why maintain so many "minority" transmitters? Consider the distinction between point-to-point transmission and neuromodulation, and how different transmitter systems enable different types of computation.

- Here are 3-5 main points from the text:
- The brain uses more than 100 different kinds of neurotransmitters.
- Glutamate and GABA handle almost all (about 95%) of the brain's rapid communication between cells.
- The brain maintains many other neurotransmitters, suggesting they have different roles.
- These varied neurotransmitter systems allow for different types of brain computations and neuromodulation.



NEUROTRANSMITTER DIVERSITY PARADOX - CONCEPTUAL DIAGRAM.

Synaptic Transmission

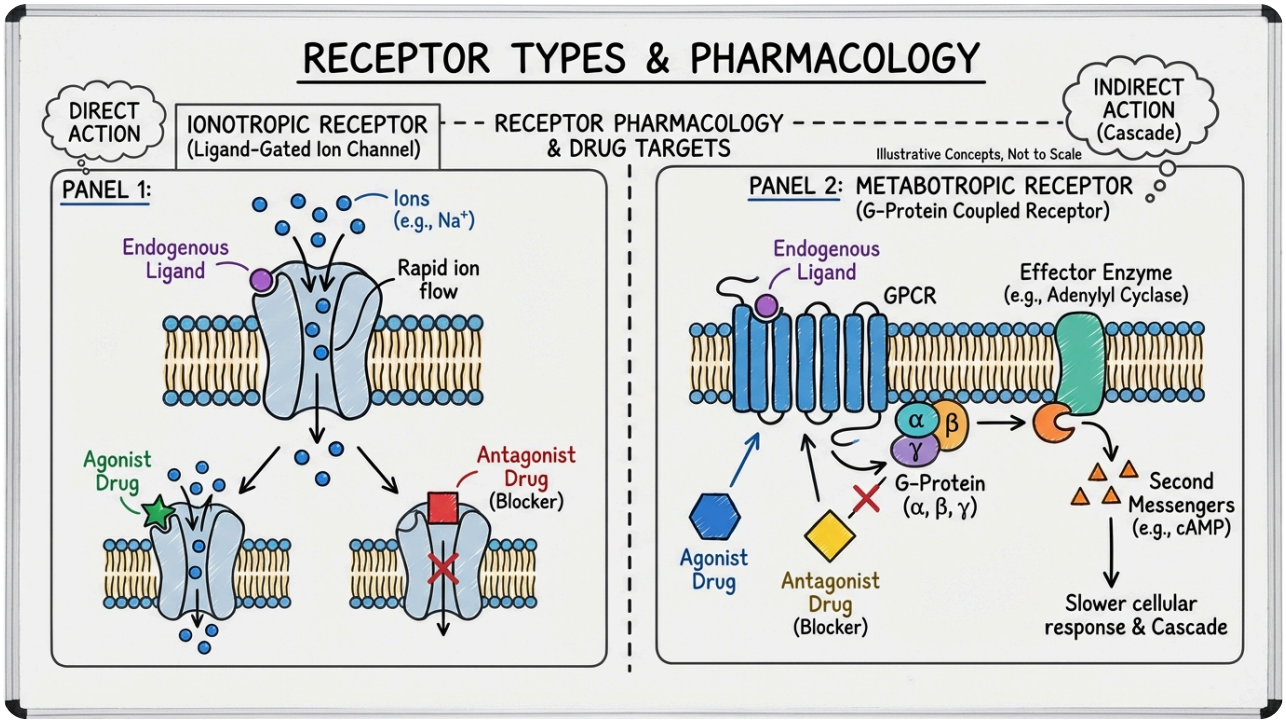


- Here are 3-5 main points from the text:
- Nerve cells communicate by sending chemical signal neurotransmitters.
- Calcium ions trigger the release of neurotransmitters special sacs inside the nerve cell.
- The brain uses both excitatory and inhibitory signals control nerve cell activity.
- Nerve cells add up these different signals to decide to send their own message.

Full Text

Chemical Conversations: Synaptic Transmission and Neurotransm
Chemical Conversations Visual Summary LECTURE OUTLINE (80
The Neuromuscular Junction: A Model Synapse (20 min) • Otto L
"Vagusstoff" and the chemical hypothesis • Anatomy of the moto
• The endplate potential and curare experiments • Quantal releas
Bernard Katz's discovery II. Mechanisms of Neurotransmitter Rele
min) • Calcium as the trigger: voltage-gated Ca^{2+} channels • The
hypothesis: synaptobrevin, syntaxin, SNAP-25 • Synaptotagmin a
calcium sensor • Vesicle pools and recycling III. Synaptic Transmi
the CNS (15 min) • EPSPs and IPSPs: excitation and inhibition • Sp
temporal summation • The reversal potential and driving force • S
integration at the axon hillock

Fast Slow Receptors

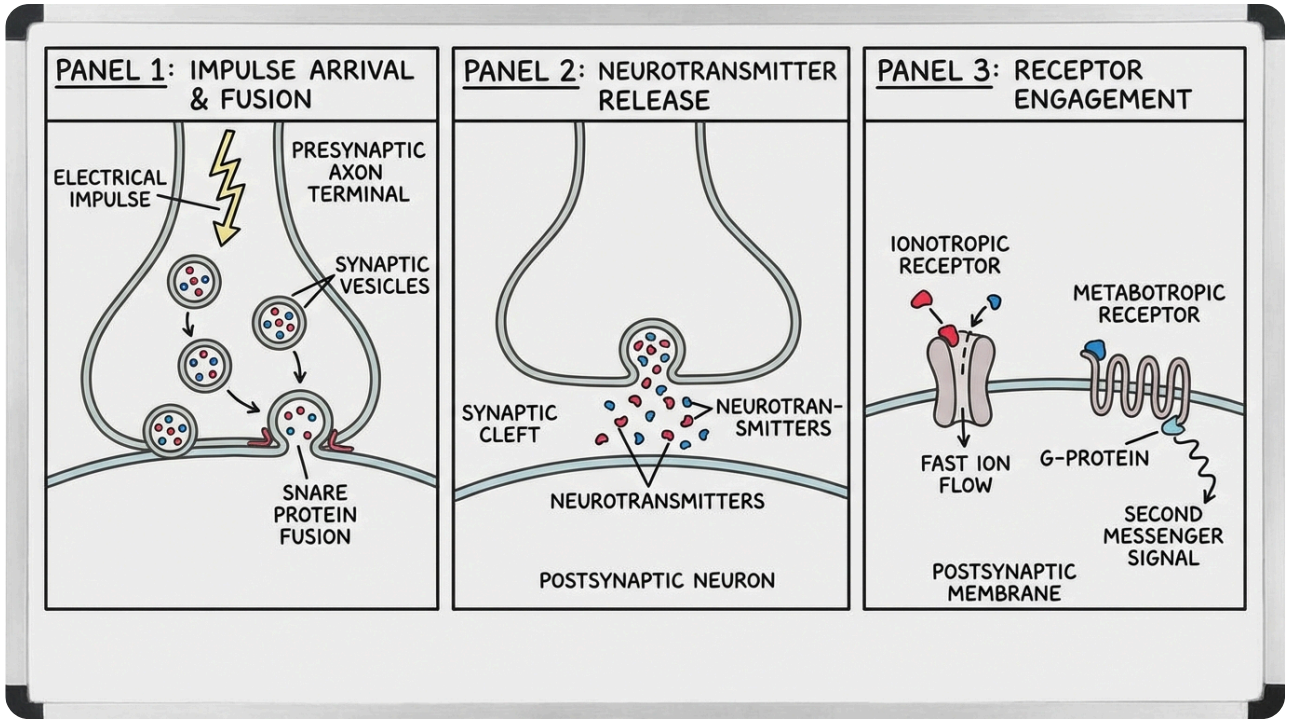


- Here are 4 main points from the text:
- Receptors are categorized into different types based fast they act.
- Ionotropic receptors function as ligand-gated ion cha
- Metabotropic receptors work using G-proteins and s messengers.
- Receptor pharmacology studies how drugs target the receptors.

Full Text

IV. Receptor Types: Fast and Slow (15 min) • Ionotropic receptors gated ion channels • Metabotropic receptors: G-proteins and sec messengers • Receptor pharmacology and drug targets

Neurotransmitter Diversity

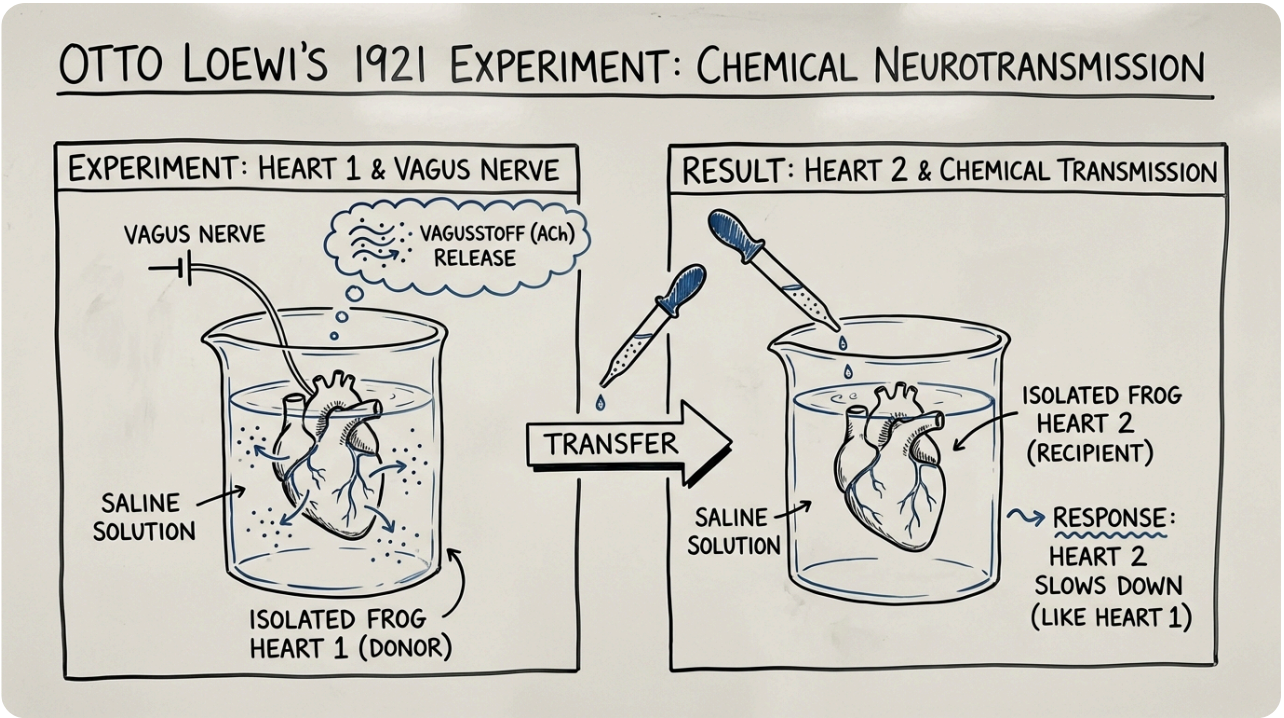


- Here are 4 main points from the text:
- Electrical signals change into chemical signals at the Action potentials cannot cross the synaptic gap direc
- Neurotransmitters release from the neuron in tiny pa called quanta. SNARE proteins help release these pa with precision.
- Neurotransmission can be fast (ionotropic) or slow (metabotropic). These types work at different speed
- The brain uses more than 100 different kinds of neurotransmitters.

Full Text

V. Neurotransmitter Diversity (15 min) • Acetylcholine and the cho system • Amino acids: glutamate and GABA • Biogenic amines: do serotonin, norepinephrine • Neuropeptides and unconventional tr Last time, we traced the electrical signal to the axon terminal and Now we cross the 20-nanometer synaptic cleft—a gap that action cannot jump. Here, electricity must become chemistry. Today we' how Otto Loewi proved chemical transmission with a frog heart in Bernard Katz revealed that neurotransmitters are released in disc packets called quanta, and how SNARE proteins execute membra with atomic precision. We'll explore the fundamental dichotomy b fast ionotropic transmission (milliseconds) and slow metabotropic modulation (seconds to minutes), understand why the brain uses neurotransmitters when one would seem to suffice, and see how caffeine to cocaine to curare exploit synaptic machinery. From the neuromuscular junction that moves your muscles to the central sy that generate your thoughts, we'll trace the complete chemical conversation between neurons.

Chemical Transmission

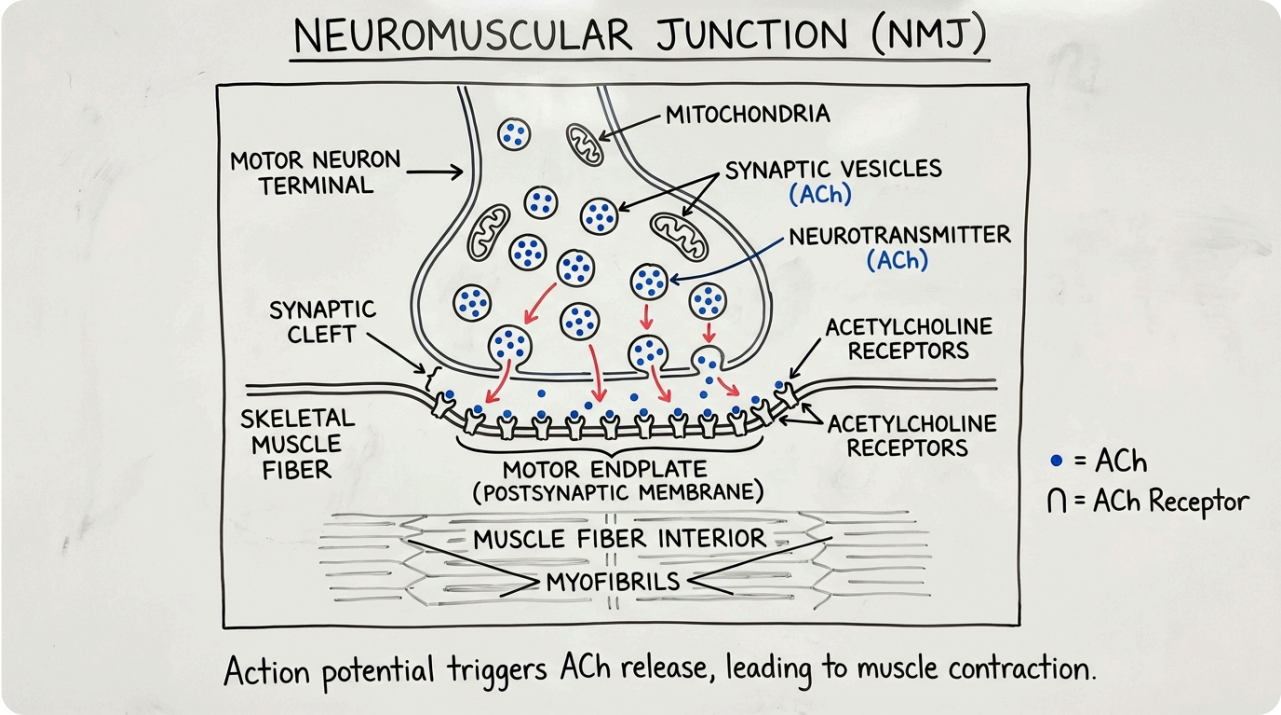


- Main Points:
- Otto Loewi's dream inspired an important experimen
  He used frog hearts to study nerve signals.
- Loewi showed a chemical, later named acetylcholine
  transmitted signals from one heart to another. This c
  slowed the heart's beat.
- His experiment proved that chemical transmission oc
  the body. It settled a long scientific debate about hov
  transmit signals.
- Otto Loewi received a Nobel Prize in 1936 for his dis
  He shared it with Henry Dale, who isolated acetylcho

Full Text

Today's journey: From Loewi's dream experiment to molecular ma
We'll see how evolution solved the problem of transmitting inform
across a gap too wide for electricity but small enough for chemist
Neuromuscular Junction: Where Chemical Transmission Was Borr
Otto Loewi woke at 3 AM with an idea from a dream. He stimulate
vagus nerve of a frog heart floating in saline, slowing its beat. The
transferred the saline to a second heart—and that heart slowed tc
no nerve had touched it. A diffusible chemical—he called it "Vagu
later identified as acetylcholine (ACh)—had carried the message.
elegant experiment ended decades of debate between "sparks" (
transmission) and "soup" (chemical transmission). Loewi shared t
Nobel Prize with Henry Dale, who had first isolated acetylcholine.

Neuromuscular Junction

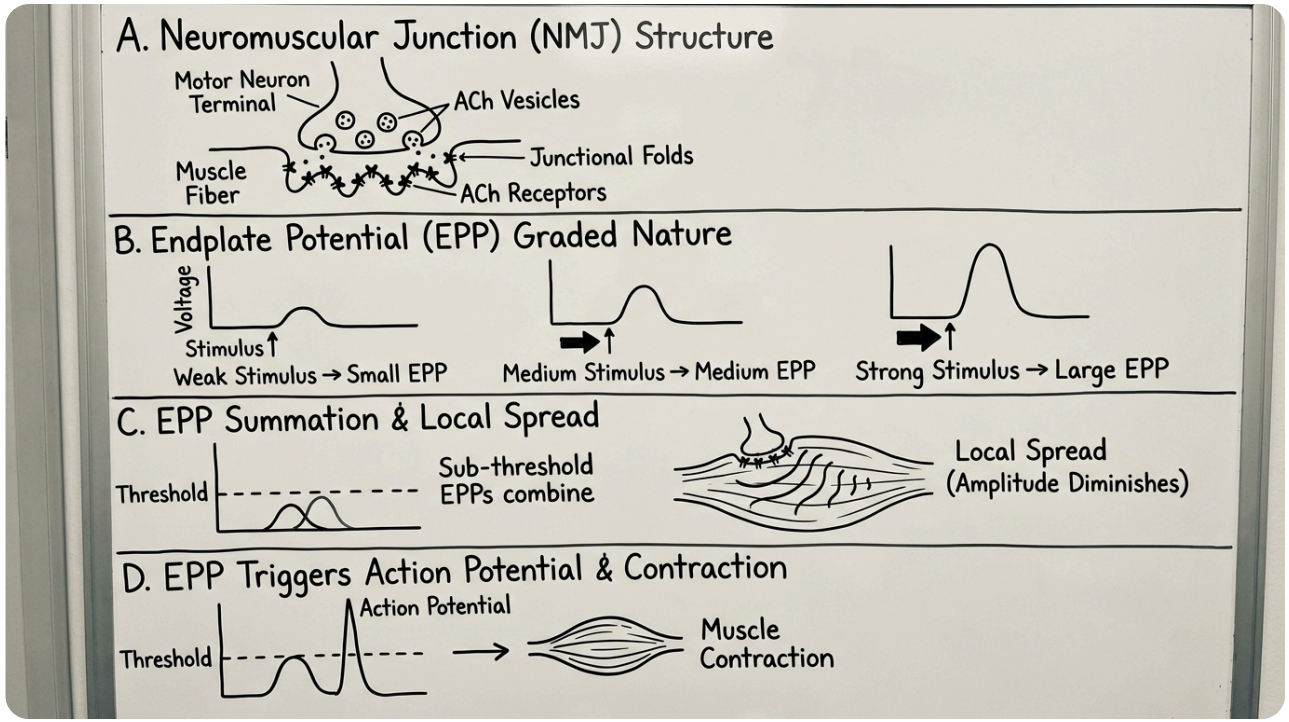


- Here are 3 main points from the text:
- The neuromuscular junction (NMJ) is an important m studying synapses. Researchers use it because it is e access and simple in structure.
- Motor neurons from the spinal cord connect to skele muscle fibers. These connections happen at special called motor endplates.
- The NMJ synapse has a small gap between the nerve muscle. The nerve holds sacs of neurotransmitters, a muscle has many receptors for these chemicals.

Full Text

The neuromuscular junction (NMJ) became the model synapse be its accessibility and simplicity. Motor neurons from the spinal cor skeletal muscle fibers at specialized regions called motor endplat synapse here has three characteristic features visible in electron microscopy: (1) a 20-nm synaptic cleft separating pre- and posts membranes, (2) clusters of synaptic vesicles in the presynaptic te containing neurotransmitter, and (3) a postsynaptic density—thicl the muscle membrane due to high concentrations of acetylcholin receptors.

EPP Fundamentals

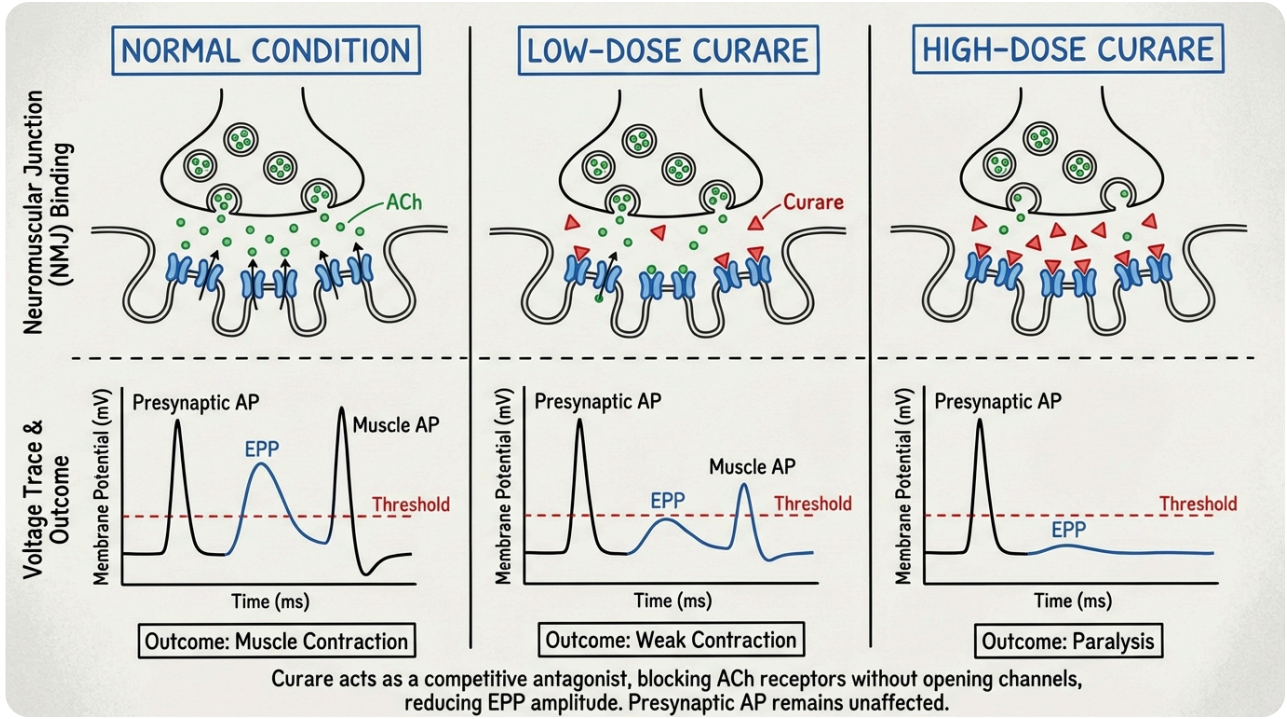


- Main Points:
- An endplate potential (EPP) depolarizes muscle fiber then triggers a muscle action potential and contracti
- Endplate potentials (EPPs) are graded, meaning stro signals produce larger EPPs.
- EPPs are local and spread passively through the mus without regenerating.
- Multiple endplate potentials (EPPs) can add together process called summation.

Full Text

The Endplate Potential and Curare Experiments When an action p invades the motor neuron terminal, the muscle fiber depolarizes. endplate potential (EPP)—a special case of the more general exci postsynaptic potential (EPSP)—triggers a muscle action potential contraction. The EPP differs fundamentally from the action poten graded (larger stimuli produce larger EPPs), it's local (it doesn't r but spreads passively), and it can summate (multiple EPPs add to

Curare Neurotransmission

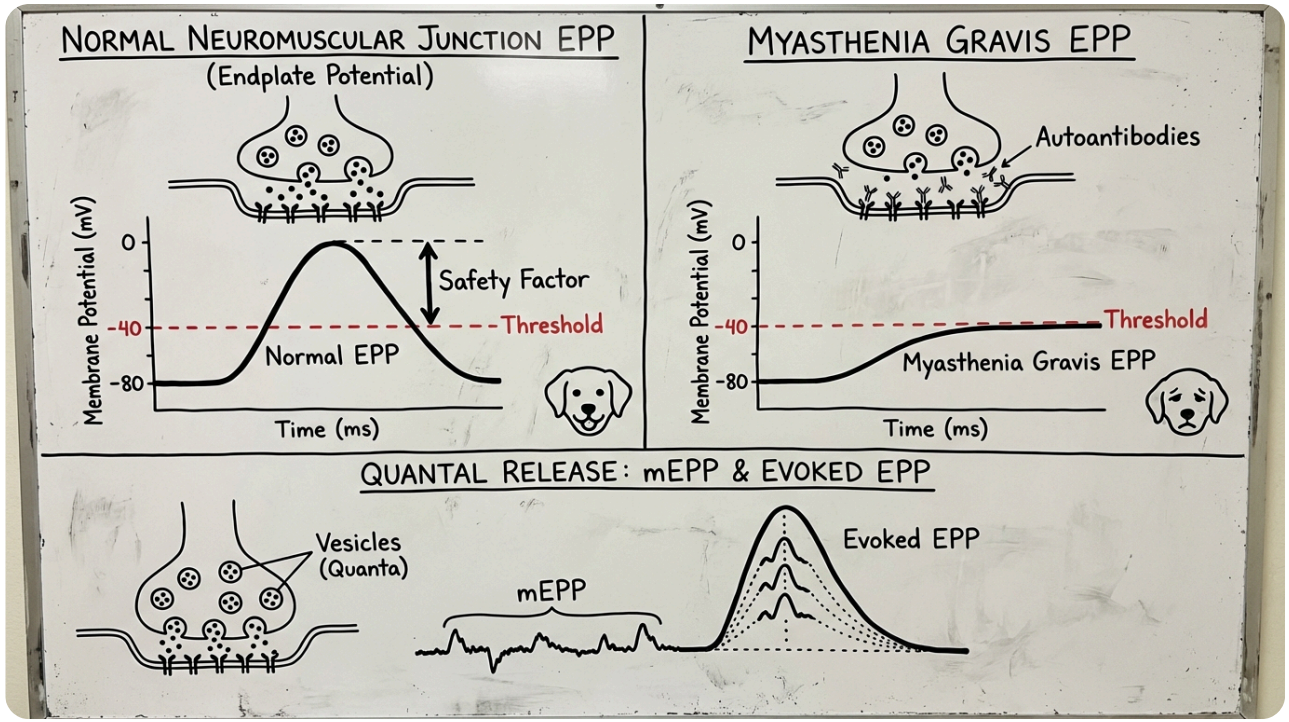


- Here are 4 main points from the text:
- Curare helped scientists understand how nerve signa between cells (synaptic transmission).
- Curare blocks specific receptors on nerve cells, stop chemical called ACh from connecting.
- Curare blocks synaptic transmission, while action po (nerve signals) continue to work.
- Curare's action showed that synaptic transmission a potentials are separate processes.

Full Text

Curare, the arrow poison used by South American Indigenous pec proved essential to understanding synaptic transmission. At low c curare reduces the EPP amplitude but it still reaches threshold. A doses, the EPP becomes subthreshold—the muscle doesn't contr Curare is a competitive antagonist of ACh receptors: it binds to th without opening the channel, blocking ACh from binding. Crucially doesn't affect the action potential mechanism—it specifically bloc synaptic transmission. This dissociation proved that synaptic and potential mechanisms are distinct.

EPP Safety Factor

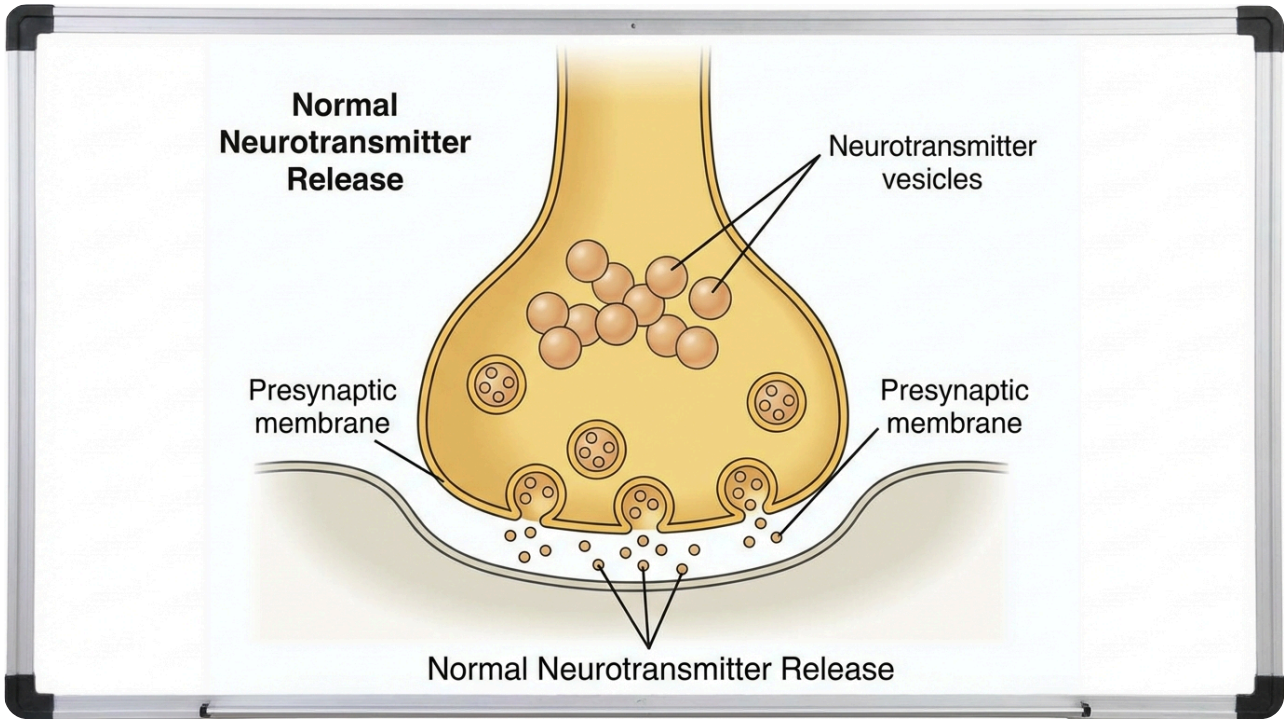


- Main Points:
- The body's natural electrical signals (EPPs) are stron required, creating a safety margin for reliable muscle movement.
- Myasthenia gravis is a disease where autoantibodies acetylcholine receptors, which weakens muscle signa causes progressive muscle weakness.
- Bernard Katz discovered that neurotransmitters relea fixed, discrete packets, a process called quantal rele
- Tiny, spontaneous electrical signals (mEPPs) occur e without stimulation. Larger electrical signals (EPPs) a always a direct multiple of these mEPPs, suggesting neurotransmitters release in packages.

Full Text

The EPP amplitude normally far exceeds what's needed to reach t —about 50 mV when only 30 mV is required. This 20 mV safety fa ensures reliable transmission despite fatigue or minor pathology. myasthenia gravis, autoantibodies attack ACh receptors, reducing safety factor until EPPs fail to reach threshold—patients experienc progressive weakness, especially in muscles used repeatedly. Qu Release: Bernard Katz's Discovery Bernard Katz discovered that neurotransmitter release is quantized—it occurs in discrete packe without stimulation, tiny spontaneous potentials (~0.5 mV) occur at the NMJ. Katz called these miniature endplate potentials (mEPI evoked EPP amplitude is always a multiple of the mEPP amplitude never see 1.5 or 2.3 mEPPs, only 1, 2, 3, etc. This quantal nature s that ACh is released not as individual molecules but as packages.

Synaptic Vesicle Release



- Here are 5 main points:
- Synaptic vesicles are small spheres containing thous neurotransmitter molecules.
- A normal nerve signal happens when many vesicles r neurotransmitters together.
- Katz established that vesicles are key to transmitting signals.
- Botulinum toxin (Botox) stops vesicles from releasing neurotransmitters, causing flaccid paralysis.
- Tetanus toxin blocks neurotransmitter release in the cord, causing rigid paralysis.

Full Text

Electron microscopy later revealed the packages: synaptic vesicle spheres each containing thousands of neurotransmitter molecule mEPP corresponds to the spontaneous fusion of one vesicle. A nc results from the coordinated release of ~200 vesicles. Katz receiv 1970 Nobel Prize for this work, which established the vesicular ba synaptic transmission. Clinical Connection: Botulinum toxin (Boto SNARE proteins, preventing vesicle fusion and blocking ACh relea causing flaccid paralysis. Tetanus toxin travels retrogradely to spi interneurons and blocks GABA release, causing rigid paralysis (lo through disinhibition of motor neurons. Mechanisms of Neurotran Release

Calcium Trigger

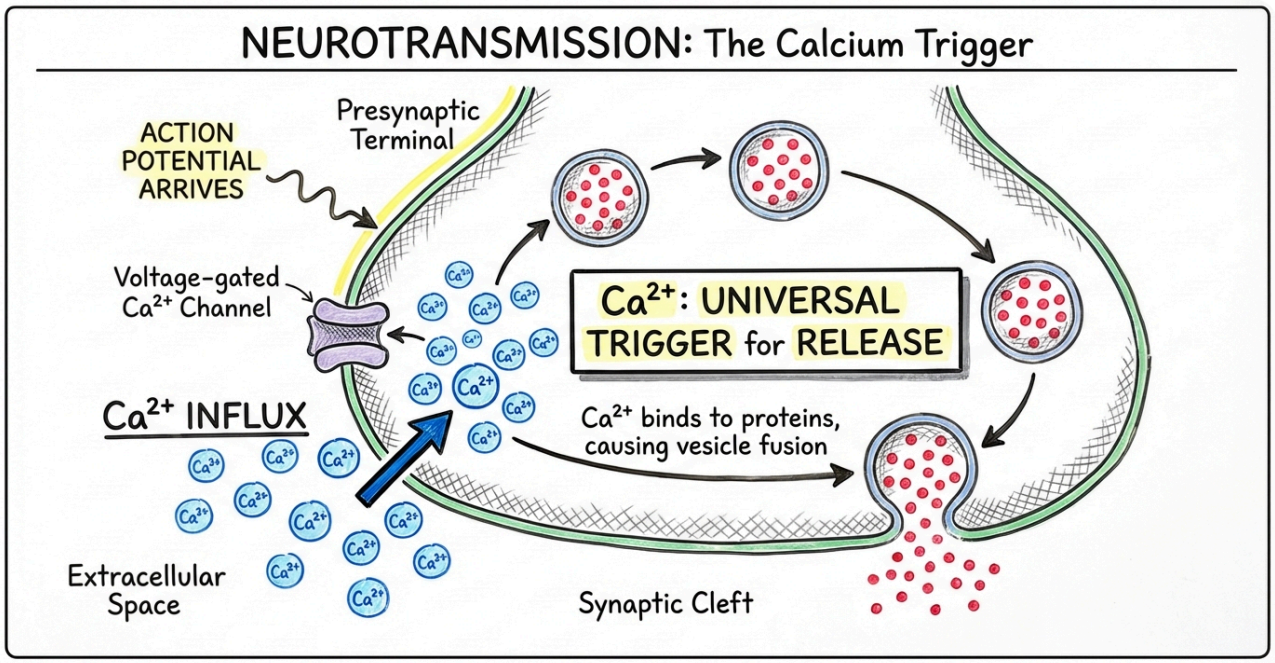


Figure 1. Action potential-triggered calcium influx causes synaptic vesicle fusion and neurotransmitter release.

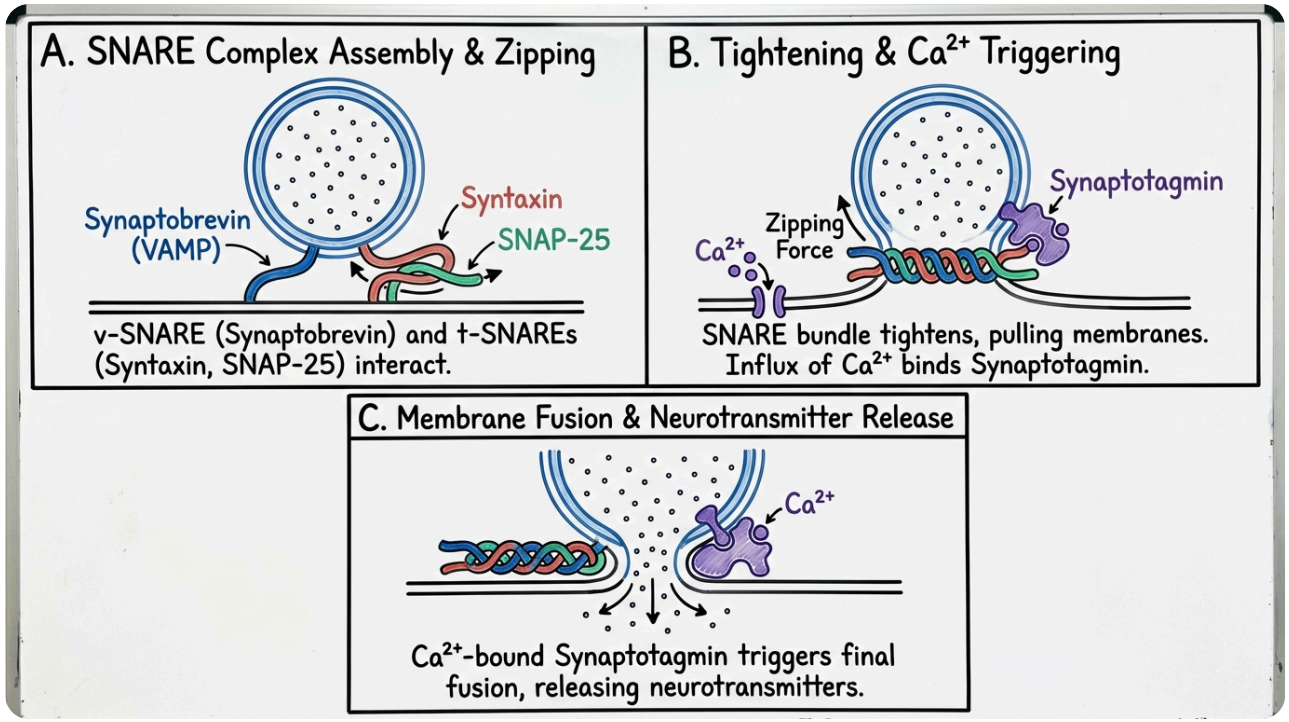
Main Points:

- Calcium must be present for neurons to release neurotransmitters.
- Action potentials cause specific calcium channels to allowing calcium to flood into the neuron.
- A small change in the amount of calcium entering a r causes a large change in neurotransmitter release.
- Diseases that affect calcium channels greatly reduce communication with muscles.

Full Text

Calcium: The Universal Trigger Katz and colleagues demonstrated calcium is essential for transmitter release. Remove extracellular EPPs vanish despite normal presynaptic action potentials. The me when an action potential reaches the terminal, voltage-gated calc channels (primarily P/Q-type and N-type in neurons) open. Calciu in, rising from ~100 nM to >100 µM in microdomains near channel 1000-fold increase within microseconds. The relationship betwee and release is highly nonlinear: release probability scales with approximately the fourth power of calcium concentration. This ste dependence means that small changes in calcium entry cause lar changes in release—providing a mechanism for synaptic modulati Diseases affecting calcium channels (like Lambert-Eaton myasthe syndrome, where antibodies attack presynaptic calcium channels impair neuromuscular transmission.

SNARE Machinery

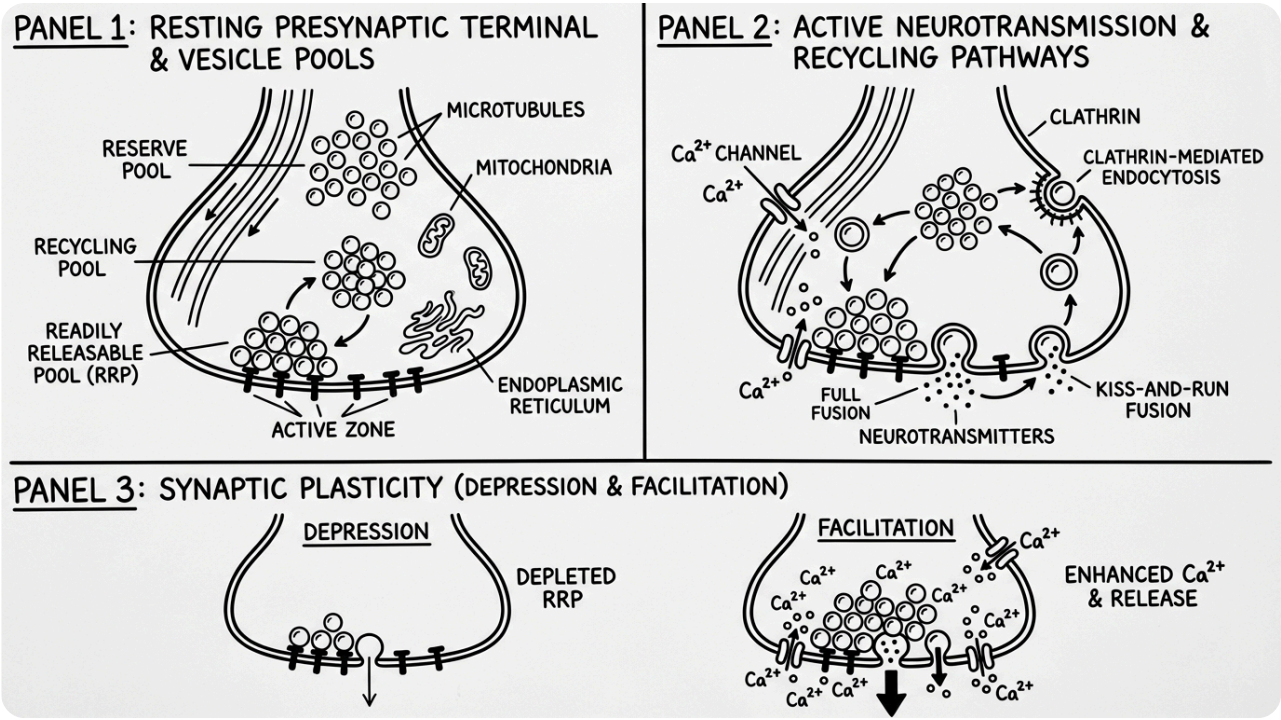


- Main Points:
- SNARE proteins form a molecular machine that helps membranes fuse together.
- Three specific SNARE proteins—Synaptobrevin, Synt SNAP-25—zip together, pulling cell membranes clos action overcomes the membranes' natural repulsion.
- Synaptotagmin acts as a calcium sensor. When calci enters, synaptotagmin binds to it and triggers the qu membrane fusion.
- This membrane fusion process happens extremely fa completing within 200 microseconds.

Full Text

The SNARE Machinery: Molecular Zippers How does calcium trigg fusion? The SNARE hypothesis (soluble NSF attachment protein r developed by James Rothman, Randy Schekman, and Thomas Sü Nobel Prize), describes a molecular machine for membrane fusion Synaptobrevin (VAMP) is anchored in the vesicle membrane • Syr SNAP-25 are anchored in the presynaptic plasma membrane • Th proteins "zip" together from their N-termini toward the membrane an extraordinarily stable four-helix bundle that pulls the membran together, overcoming their natural repulsion The SNARE complex and ready, but a molecular brake prevents spontaneous fusion. Synaptotagmin, the calcium sensor, has two C2 domains that bin with micromolar affinity. When calcium enters, synaptotagmin bin undergoes a conformational change, and triggers the final membr event within 200 microseconds—among the fastest biochemical p known.

Vesicle Plasticity

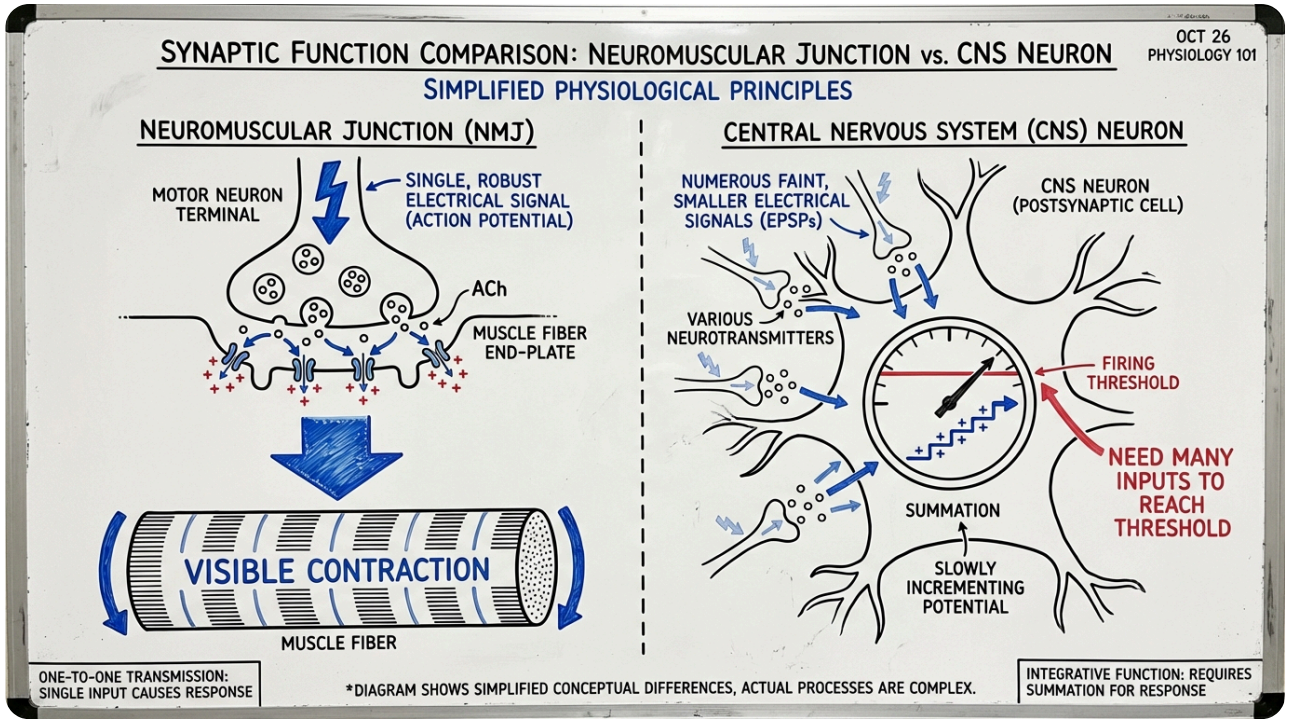


- Here are 4 main points from the text:
- Synaptic terminals store neurotransmitters in three d vesicle pools: the readily releasable, recycling, and r pools.
- Synapses show short-term changes in their release a High activity can reduce neurotransmitter release, w leftover calcium can increase it.
- After releasing neurotransmitters, vesicles undergo r through endocytosis. They refill with neurotransmitte return to the pools, taking about 30 seconds.
- During sustained activity, vesicles may use a faster " run" method, releasing contents through a temporary without fully merging.

Full Text

Vesicle Pools and Recycling Synaptic terminals contain distinct ve pools: the readily releasable pool (RRP, docked at active zones, ~ vesicles), the recycling pool (~200 vesicles), and the reserve poo (hundreds more). During high-frequency firing, the RRP depletes than it can be replenished, causing synaptic depression. Convers residual calcium from previous spikes can enhance release proba subsequent spikes—synaptic facilitation. These short-term plastic mechanisms shape how information is processed in neural circuit fusion, vesicles are recycled through clathrin-mediated endocyto with neurotransmitter, and returned to vesicle pools—a process re ~30 seconds for full recycling. During sustained activity, faster "k run" fusion may occur, where vesicles release contents through a pore without full membrane merger. Synaptic Transmission in the Nervous System

CNS Synaptic Strength

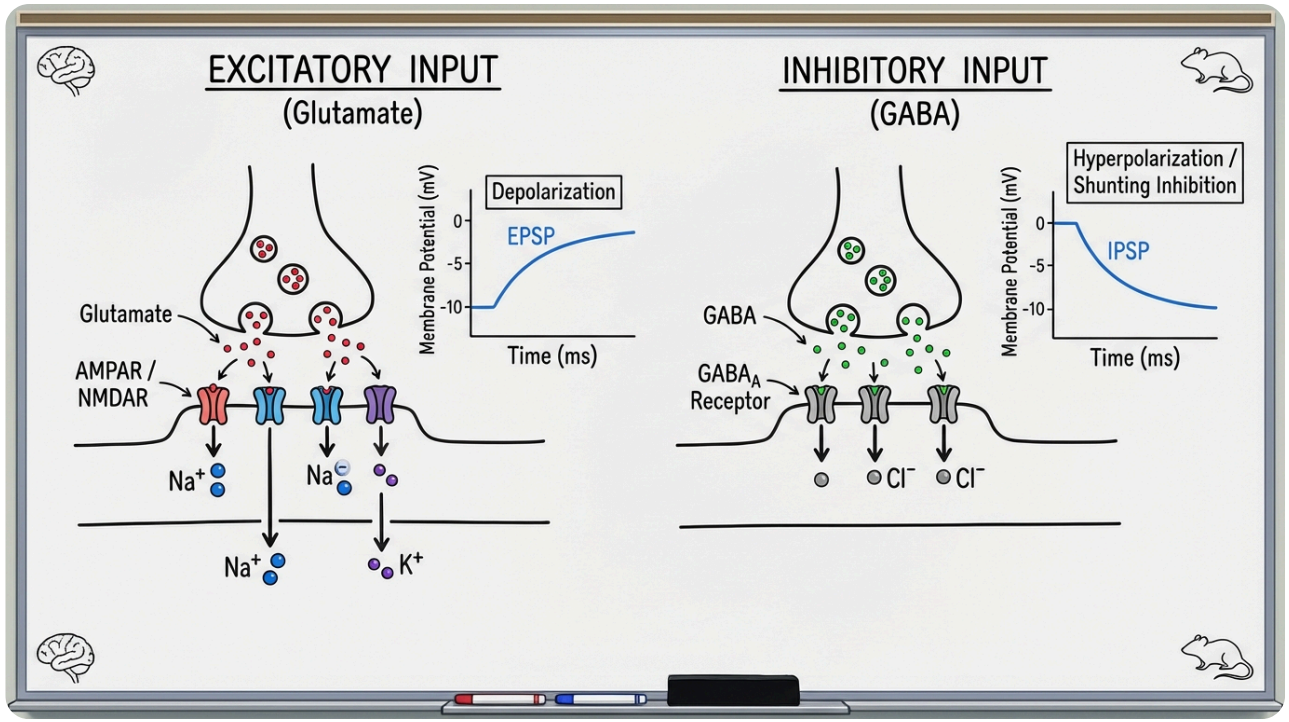


- Here are 4 main points from the text:
- Synapses in the central nervous system work differe compared to those connected to muscles.
- One motor neuron synapse on a muscle fiber always the muscle contract.
- A single CNS synapse produces only a tiny electrical
- Central nervous system neurons must gather thousa small signals to send their own message.

Full Text

Vesicle Pools and Recycling CNS synapses differ from the NMJ in ways. A single motor neuron–muscle fiber synapse reliably trigge contraction (1:1 relationship). But a single CNS synapse produces tiny EPSP (~0.5 mV)—far below the ~15 mV needed to reach thres neuron must integrate thousands of synaptic inputs to decide wh fire.

Postsynaptic Potentials

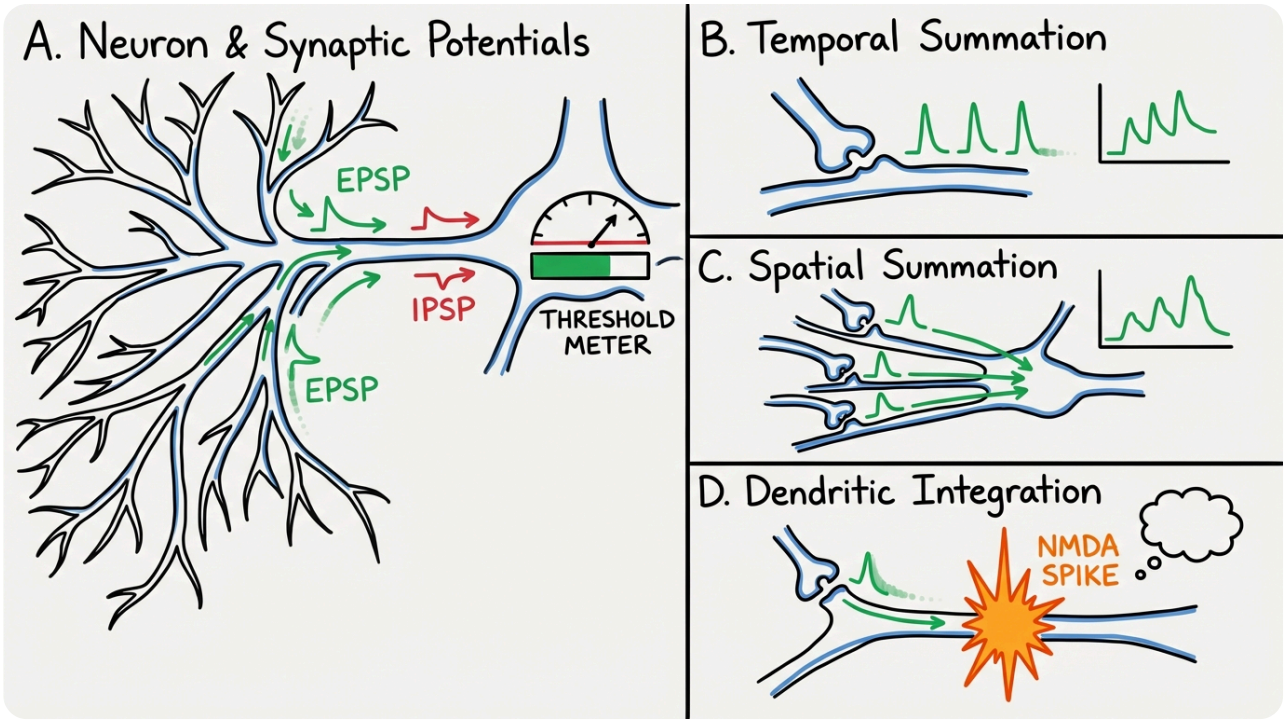


- Main Points:
- Excitatory postsynaptic potentials (EPSPs) make a ne more positive, pushing it closer to firing an electrical
- At certain connections, a chemical called glutamate channels that allow positive ions to flow into the neu causing this positive change.
- Inhibitory postsynaptic potentials (IPSPs) make a neu likely to fire by making it more negative or by stabiliz electrical state.
- At other connections, a chemical called GABA opens for negative chloride ions to enter the neuron, causir inhibitory effects.

Full Text

Excitatory and Inhibitory Postsynaptic Potentials Excitatory posts potentials (EPSPs) depolarize the neuron, moving it toward thresh glutamatergic synapses, binding of glutamate opens channels pe Na^+ and K^+, with a reversal potential near 0 mV—well above thresh Current flows inward (Na^+ entry exceeds K^+ exit), depolarizing the Inhibitory postsynaptic potentials (IPSPs) hyperpolarize the neurc it at the resting potential. At GABAergic synapses, GABA opens C permeable channels. In mature neurons, E_Cl (~−80 mV) is more than the resting potential, so Cl^- flows in, hyperpolarizing the cell E_Cl equals the resting potential, opening Cl^- channels provides " inhibition"—the increased conductance short-circuits excitatory c

Spatial Temporal Summation

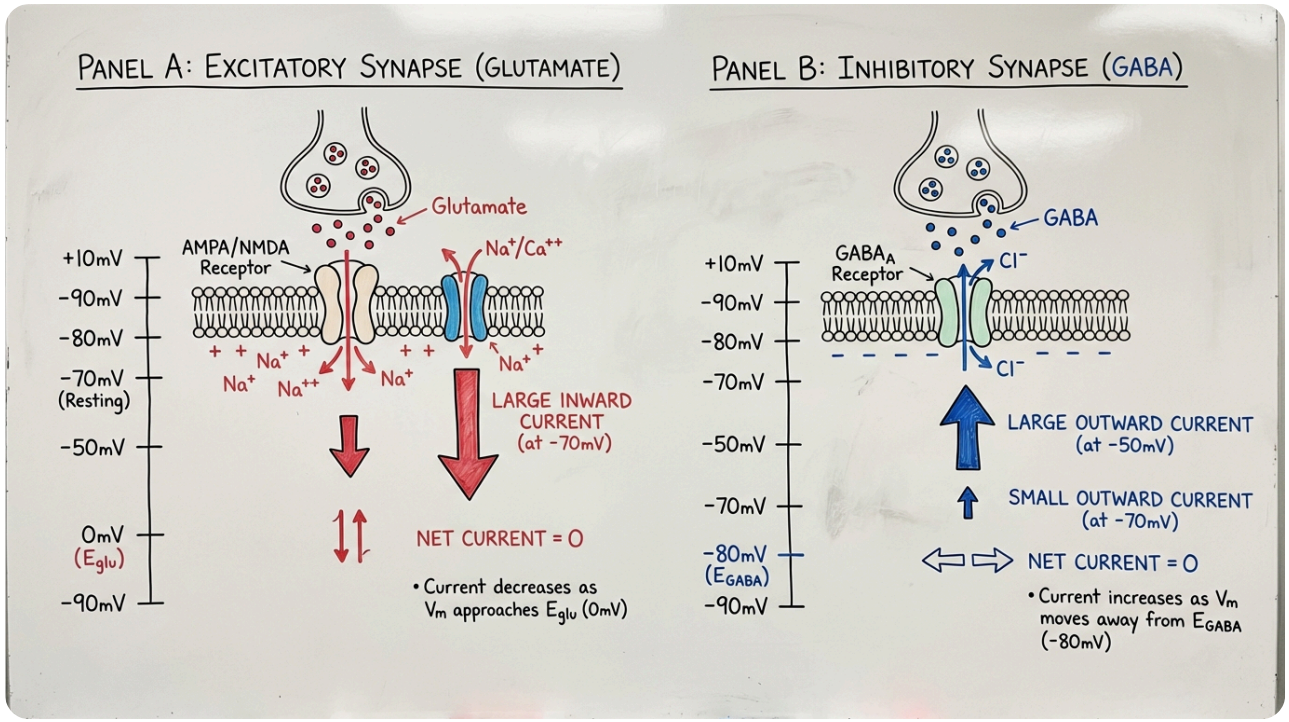


- Here are 4 main points from the text:
- A single excitatory signal (EPSP) is small and decays
- Temporal summation combines rapid, successive sig the same neuron connection. This helps a neuron rea activation threshold.
- Spatial summation combines signals that arrive at th time from multiple different neuron connections. This helps the neuron activate.
- Signal combination in dendrites can be more comple simple addition. This allows for rich calculations with neuron.

Full Text

Excitatory and Inhibitory Postsynaptic Potentials Spatial and Temp Summation A single EPSP (~0.5 mV) decays passively with a time of ~20 ms. To reach threshold, neurons use temporal summation- successive EPSPs from the same synapse add together before ea decay—and spatial summation—simultaneous EPSPs from multipl synapses add together. Dendritic integration is sublinear (inputs o same branch interact) or supralinear (NMDA spikes), adding comp richness beyond simple addition.

Reversal Driving Force

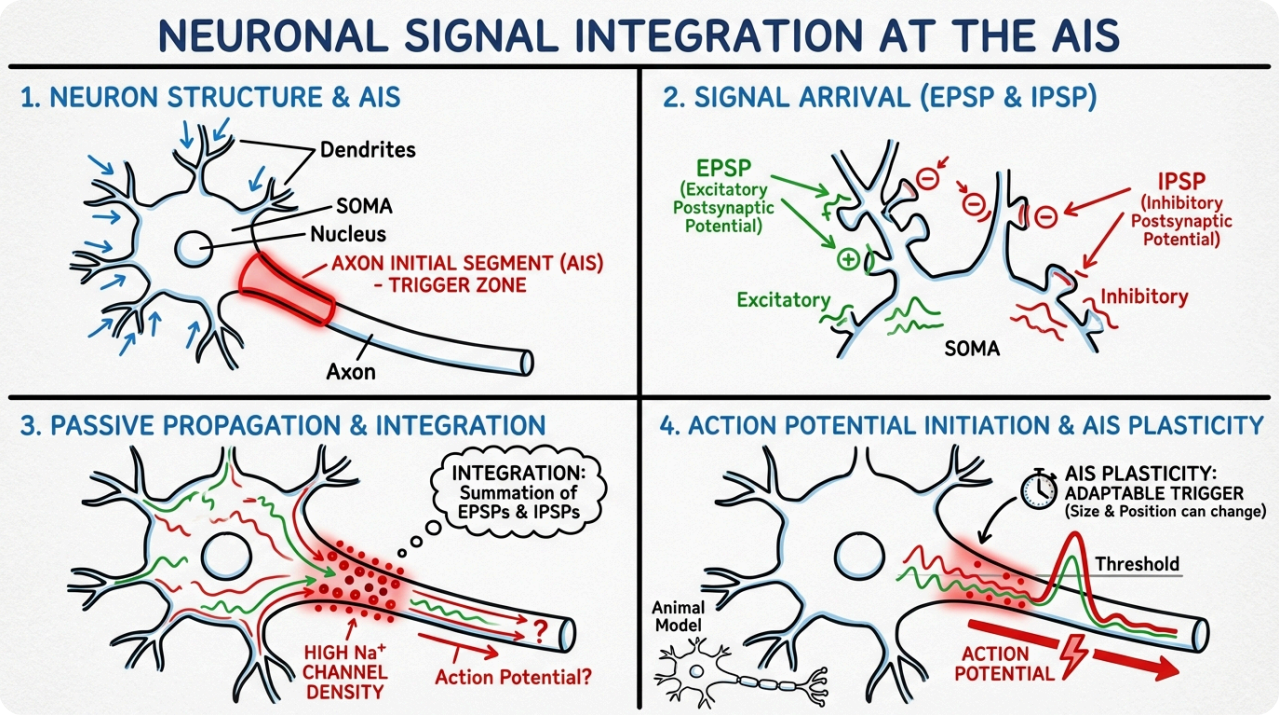


- Here are 4 main points from the text:
- The reversal potential is the specific voltage where a current changes its direction. At this voltage, the flov positive ions into and out of the cell is equal, resultin net current.
- The driving force determines the strength and direct synaptic current. It measures the difference betweer cell's membrane voltage and the reversal potential.
- Excitatory synapses, such as those that use glutama reversal potential around 0 mV. They create a strong current, causing the neuron to become excited.
- Inhibitory synapses, like those using GABA, have a re potential around -80 mV. They provide stronger inhib when the neuron is highly excited, helping to control

Full Text

Excitatory and Inhibitory Postsynaptic Potentials Reversal Potenti Driving Force Every synaptic current follows Ohm's law: I = g(V_m The reversal potential (E_rev) is where current reverses direction· voltage, equal cation influx and efflux produce no net current. For glutamate receptors permeable to Na^+ and K^+, E_rev ≈ 0 mV. The t – E_rev) is the driving force. At resting potential (–70 mV), the dri for glutamate receptors is –70 – 0 = –70 mV, driving strong inwar As the cell depolarizes toward 0 mV, driving force shrinks—EPSPs smaller. This self-limiting property prevents runaway excitation. F GABAergic synapses, E_rev ≈ –80 mV (E_Cl in mature neurons). A (–70 mV), the driving force is –70 – (–80) = +10 mV—a small outv current that hyperpolarizes slightly. But during excitation, if V_m r –50 mV, driving force becomes +30 mV—stronger inhibition preci it's most needed.

AIS Synaptic Integration

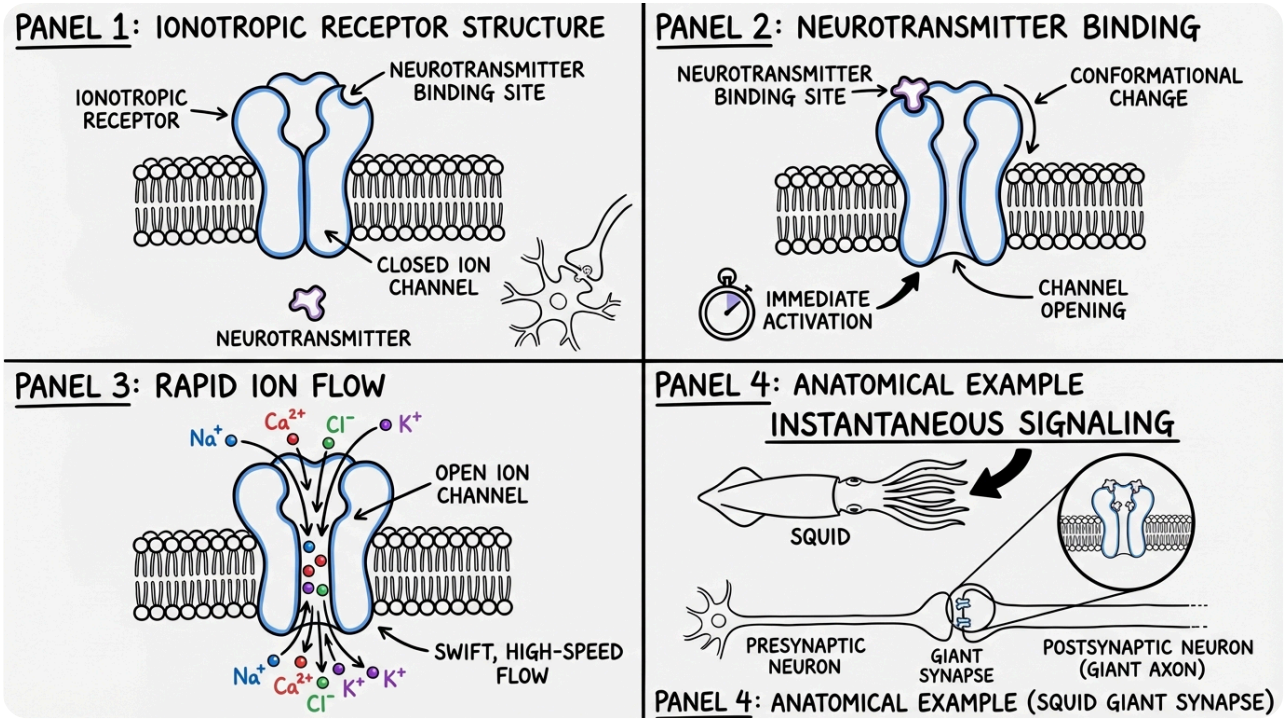


- Here are 4 main points from the text:
- The axon initial segment (AIS) makes the final decisi whether a neuron fires. It has a very high number of s channels.
- Electrical signals from dendrites and the cell body tra the AIS. The AIS acts as the neuron's trigger zone.
- An action potential starts at the AIS if incoming signa a certain strength. This electrical signal then moves axon.
- The AIS can change its position and length based on neuron's experiences. These changes adjust how eas neuron fires.

Full Text

Excitatory and Inhibitory Postsynaptic Potentials Integration at the Initial Segment The final decision—fire or not—occurs at the axon segment (AIS), where sodium channel density is highest (~1000/μ ~10/μm² on the soma). EPSPs and IPSPs propagate passively from and soma to the AIS, which acts as the trigger zone. If integrated exceeds threshold at the AIS, an action potential initiates and pro down the axon. Recent research shows the AIS is plastic—its posi length can change with experience, tuning neuronal excitability. R Types: Fast and Slow Signaling

Ionotropic Speed

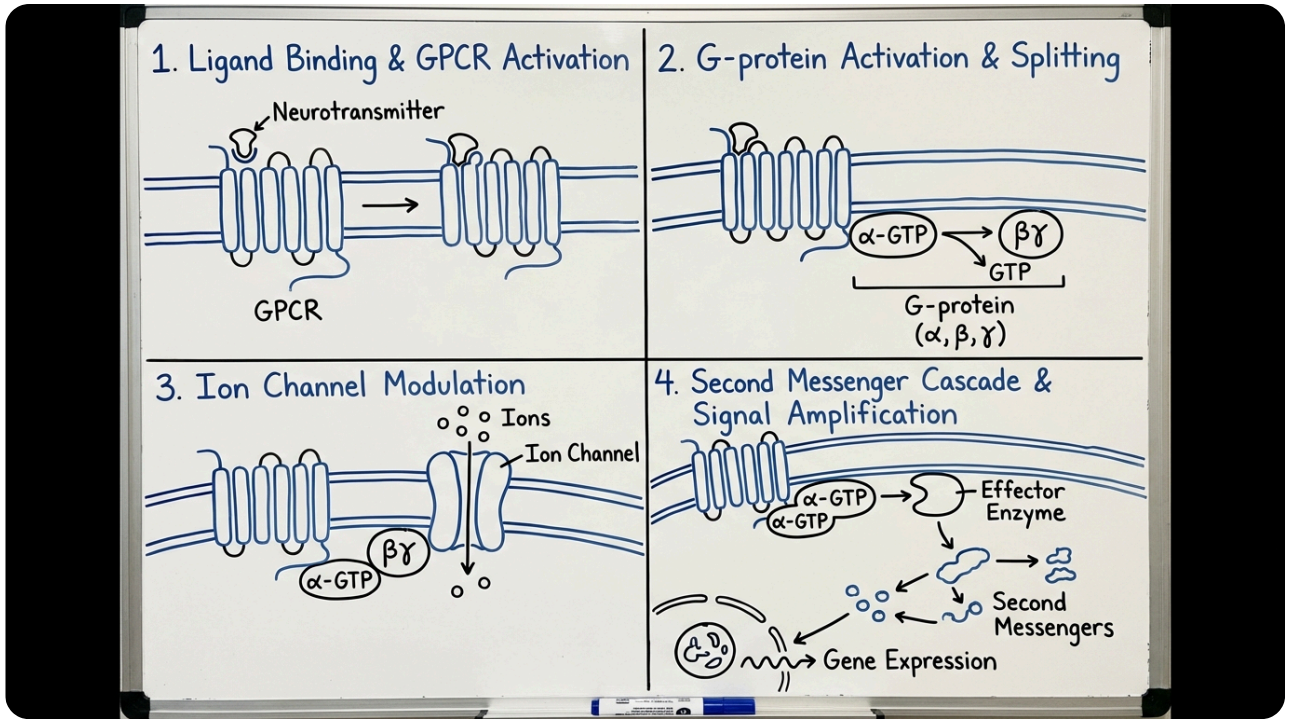


- Here are 3 main points about ionotropic receptors:
- Ionotropic receptors are channels that open directly neurotransmitter binds. This allows for very fast resp
- These receptors help create fast excitatory or inhibit signals in the nervous system. Specific types, like NM receptors, are important for brain functions such as l
- There are many different types of ionotropic recepto letting specific ions pass through. Some of these rec are targets for common medications and substances

Full Text

Ionotropic Receptors: Speed Ionotropic receptors (ligand-gated ic channels) are fast because the receptor IS the channel. Neurotrar binding causes a conformational change that directly opens the ic response time is microseconds to milliseconds. Examples include Nicotinic ACh receptors: pentameric channels ($\alpha_2\beta\gamma\delta$ at NMJ, vari β subunits in brain), permeable to Na^+ and K^+ • AMPA receptors: t glutamate-gated channels mediating fast excitatory transmission receptors: voltage-dependent (Mg^{2+} block), Ca^{2+}-permeable, requ glutamate and glycine—coincidence detectors critical for learning GABA_A receptors: pentameric Cl^- channels mediating fast inhibit targets for benzodiazepines, barbiturates, alcohol, and anesthetic Glycine receptors: pentameric Cl^- channels mediating inhibition ir cord and brainstem

Metabotropic Receptors

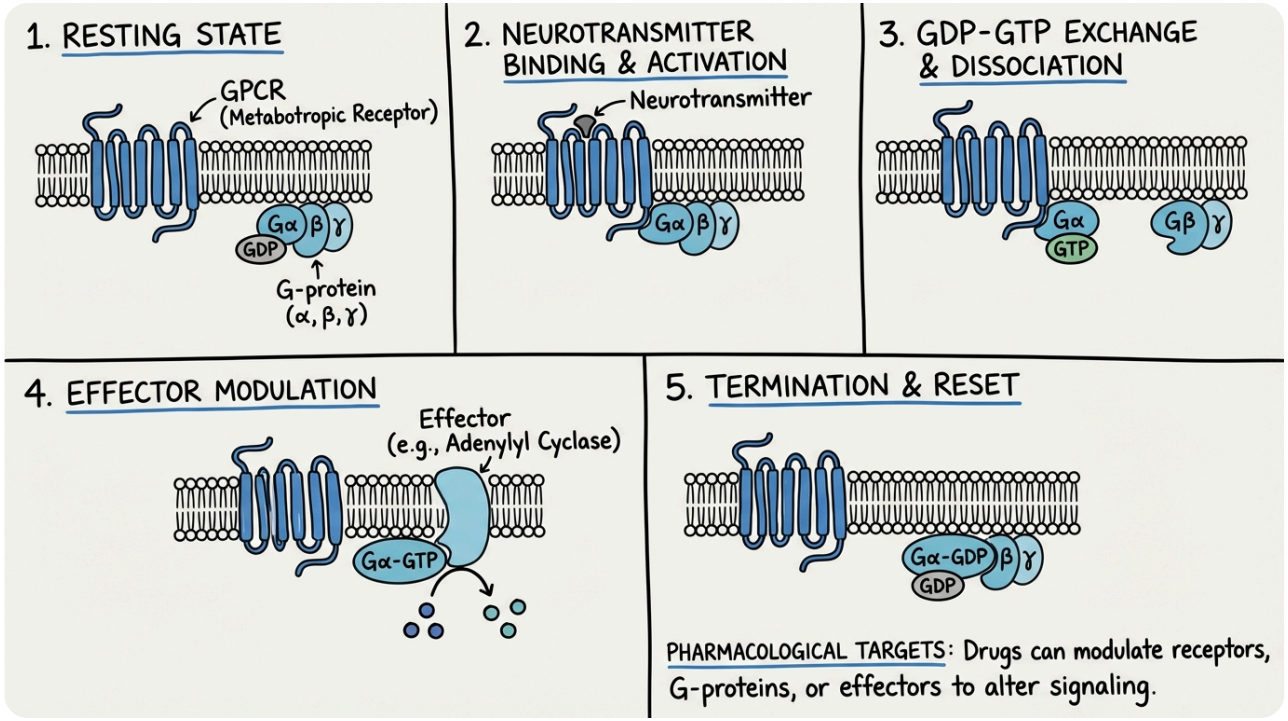


- Here are 4 main points from the text:
- Metabotropic receptors work slowly but have powerf lasting effects.
- These receptors activate G-proteins. G-proteins ther indirectly control ion channels or start other process the cell.
- Their effects develop over seconds to minutes. Thes are amplified and can even change how genes work i
- They mediate diverse effects in the heart, muscles, a and many drugs target them.

Full Text

Metabotropic Receptors: Flexibility Metabotropic receptors (G-pr coupled receptors, GPCRs) are slow but powerful. They don't forr themselves but activate G-proteins that modulate ion channels in trigger second messenger cascades. Response time is seconds t but effects are amplified and can alter gene expression. • Muscar receptors (M1-M5): G-protein coupled, mediate slow ACh effects (slowing), smooth muscle, and brain • Metabotropic glutamate re (mGluR1-8): modulate synaptic transmission and plasticity • GAB receptors: activate K^+ channels (hyperpolarizing) and inhibit Ca^{2+} (reducing release); target of baclofen • Dopamine receptors (D1-I like activate adenylyl cyclase; D2-like inhibit it—targets for antips and Parkinson's drugs

GTPase Cycle

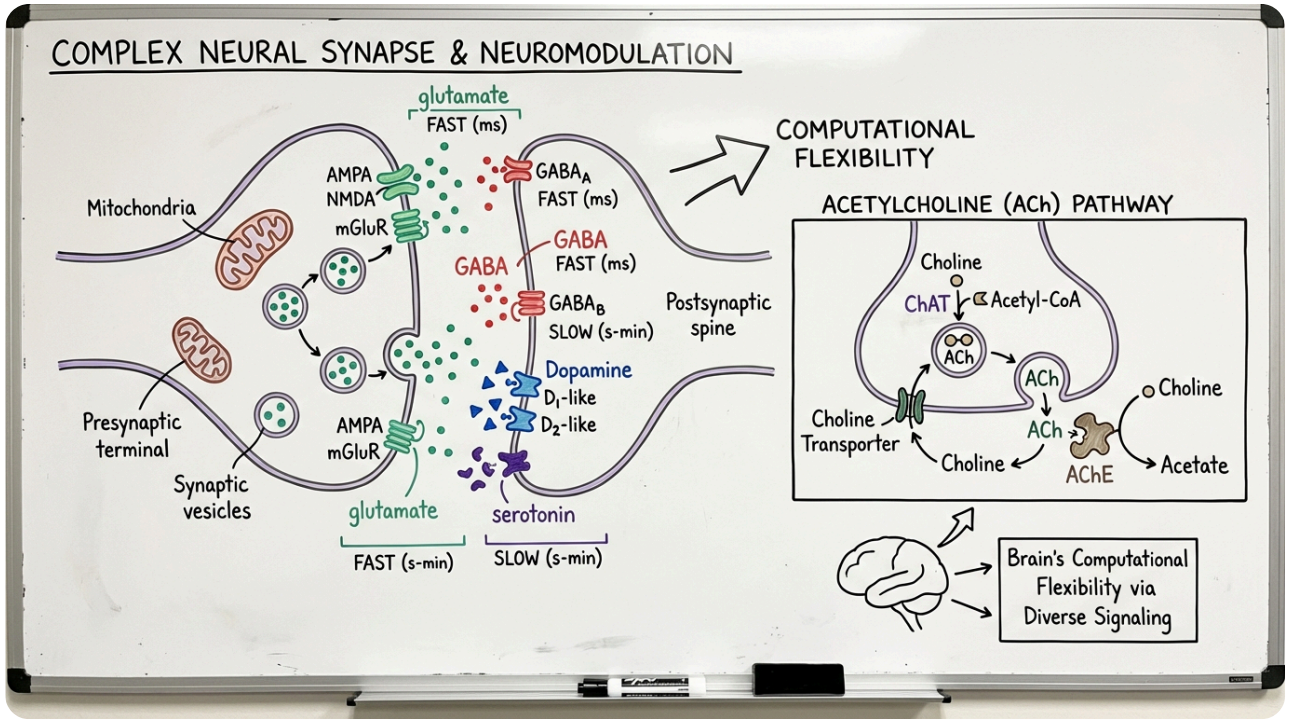


- Here are 3-5 main points from the text:
- G-proteins act as molecular switches within metabot receptors.
- When activated, G-proteins exchange GDP for GTP, then modulates other cellular effectors.
- The GTPase cycle helps control the timing of signals amplifies them.
- Most drugs that affect the central nervous system ta synaptic transmission.
- Understanding synaptic mechanisms explains the mo basis of how drugs work.

Full Text

Metabotropic Receptors: Flexibility G-proteins act as molecular s the inactive state, the α subunit binds GDP. Receptor activation c GDP→GTP exchange; the GTP-bound α subunit (and/or βγ dimer) modulates effectors—adenylyl cyclase, phospholipase C, ion char until GTP hydrolysis returns the system to baseline. This GTPase provides temporal control and signal amplification. Pharmacology Most CNS drugs target synaptic transmission. Benzodiazepines (Xanax) enhance GABA_A receptor function. SSRIs (Prozac) block reuptake. Cocaine blocks dopamine reuptake. Opioids activate μ Caffeine blocks adenosine receptors. Understanding synaptic me is understanding the molecular basis of drug action. Neurotransm Diversity: Why 100+ Messengers?

Neurotransmitter Diversity

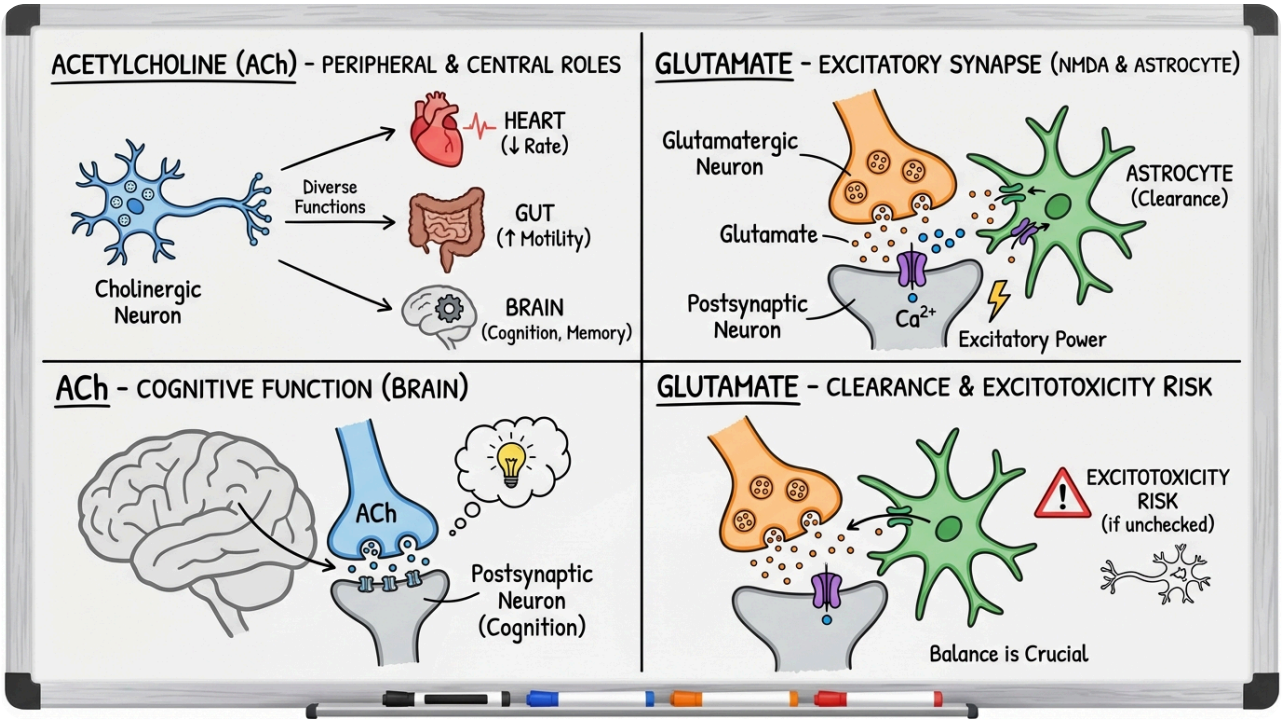


- Here are 3 main points from the text:
- The brain uses many different neurotransmitters bec each has unique functions and operating speeds. Th diversity allows for complex and flexible brain proces
- The enzyme ChAT synthesizes acetylcholine from ch acetyl-CoA.
- After acetylcholine is released, the enzyme acetylcholinesterase (AChE) rapidly breaks it down. then recycles the choline for new use.

Full Text

Metabotropic Receptors: Flexibility If neurons just need to say "m "less," why does the brain use over 100 neurotransmitters? The a each transmitter system serves distinct functions, operates on di timescales, and can be independently regulated. This chemical di enables computational flexibility impossible with a single transmit Acetylcholine: The Original Neurotransmitter Acetylcholine is synt from choline and acetyl-CoA by choline acetyltransferase (ChAT). release, it's hydrolyzed by acetylcholinesterase (AChE)—one of th enzymes known, processing 25,000 molecules per second. The c recycled into the terminal.

Cholinergic System

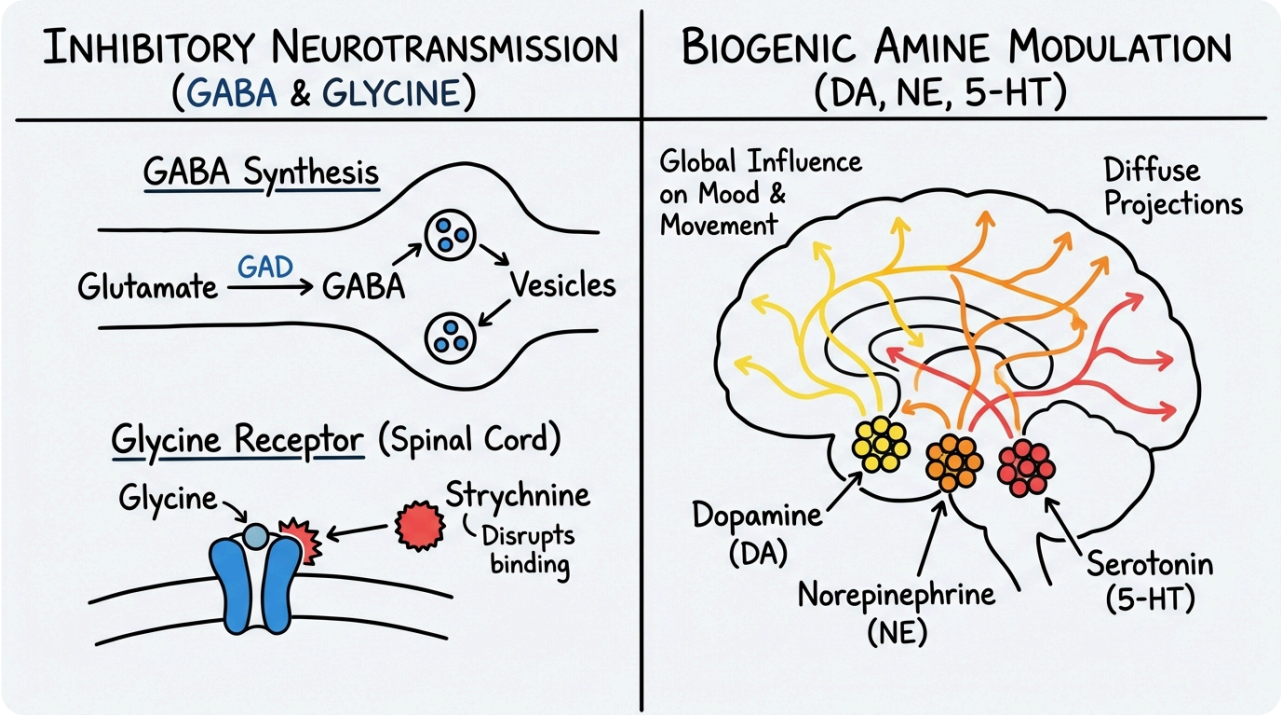


- Here are 5 main points:
- Acetylcholine plays important roles in muscle movem body functions like heart rate and digestion, and bra functions like attention and memory.
- Alzheimer's disease affects neurons that use acetylc and medicines can offer some relief for symptoms.
- Dangerous nerve agents can block an enzyme that b down acetylcholine, which can be deadly.
- Glutamate serves as the main chemical messenger tl excites brain cells, especially in the outer layer of the
- Too much glutamate in the brain can damage and kill cells, which contributes to conditions like stroke and brain diseases.

Full Text

Metabotropic Receptors: Flexibility In the periphery, ACh mediate neuromuscular transmission (nicotinic receptors) and parasympat functions (muscarinic receptors—slowing heart, stimulating diges the brain, cholinergic projections from the basal forebrain modula attention and memory. Alzheimer's disease involves degeneration neurons; acetylcholinesterase inhibitors (donepezil, rivastigmine) modest symptomatic benefit. Organophosphate nerve agents irre inhibit AChE, causing fatal cholinergic crisis. Amino Acid Transmit Workhorses Glutamate is the brain's primary excitatory transmitte ~80% of cortical neurons. It's synthesized from glutamine by glut packaged into vesicles by VGLUTs, and cleared by astrocyte trans (EAATs). Excess glutamate causes excitotoxicity—calcium overloa NMDA receptors triggers cell death—contributing to stroke and neurodegenerative disease.

Neurotransmitter Systems

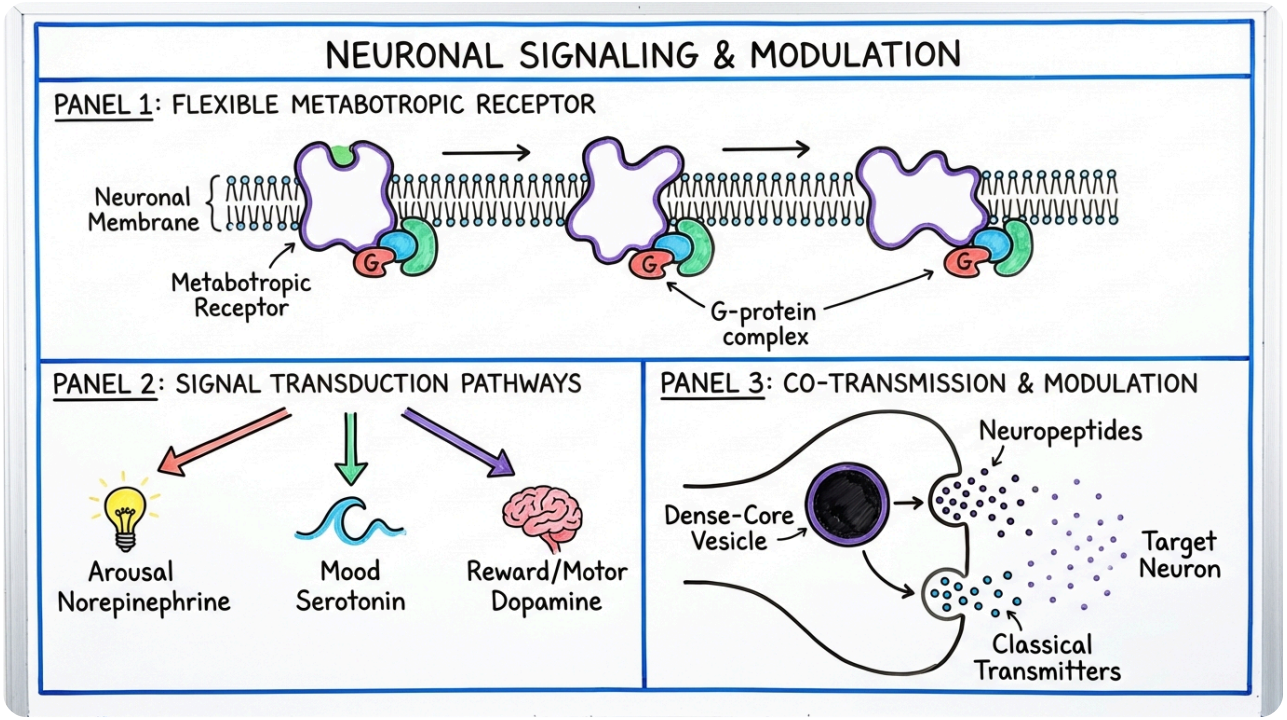


- GABA serves as the brain's primary inhibitory neurotransmitter. The body synthesizes GABA from glutamate.
- Glycine functions as the main inhibitory neurotransm the spinal cord and brainstem.
- Dopamine, norepinephrine, and serotonin are crucial monoamine neurotransmitters. The body creates the amino acids and degrades them with specific enzym
- These monoamines modulate overall brain states, aff mood and movement. Their cell bodies are in the bra and project widely across the brain.

Full Text

Metabotropic Receptors: Flexibility GABA is the primary inhibitory transmitter, synthesized from glutamate by glutamic acid decarbo (GAD)—the same molecule converted from excitatory to inhibitory packaged by VGATs and cleared by reuptake (GAT1) and astrocyt Glycine serves as the primary inhibitory transmitter in spinal cord brainstem; strychnine (glycine receptor antagonist) causes fatal convulsions. Biogenic Amines: Modulators of Mood and Movemer monoamines—dopamine, norepinephrine, serotonin—are synthesi amino acid precursors (tyrosine, tryptophan) and degraded by mo oxidase (MAO) and COMT. Their cell bodies are concentrated in s brainstem nuclei that project diffusely throughout the brain, modu global states rather than carrying specific information.

Neurotransmitter Systems

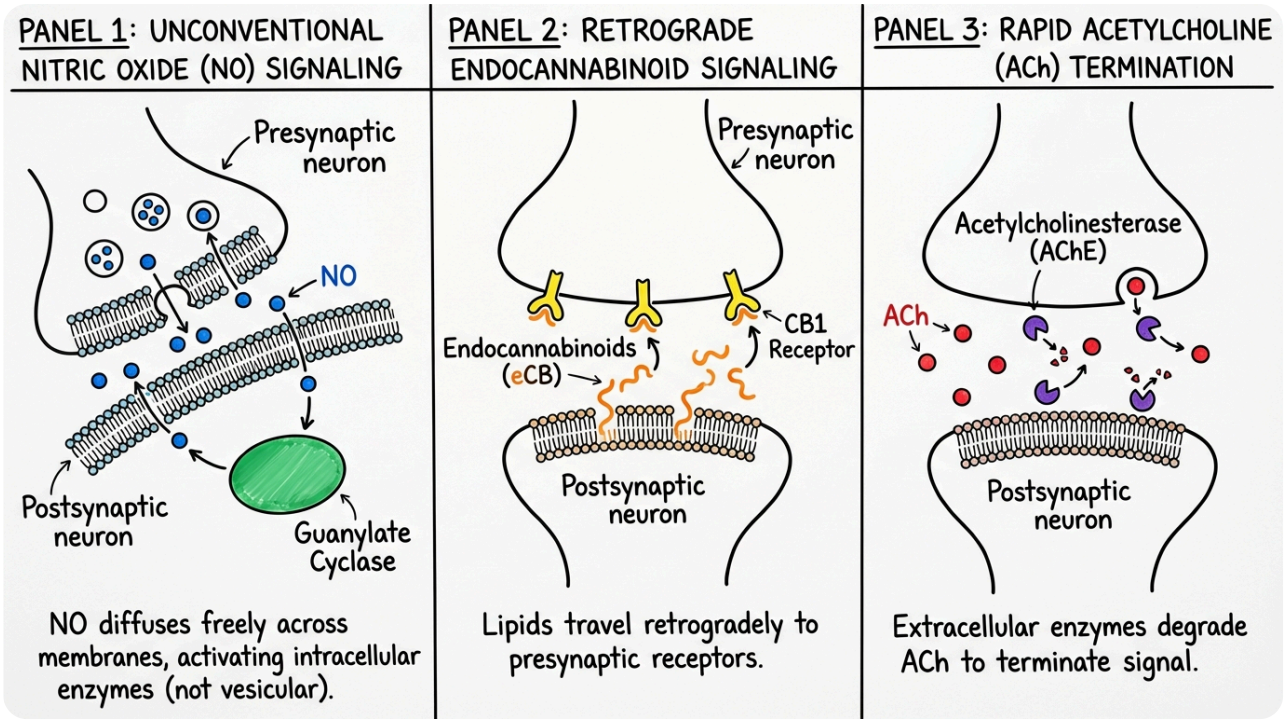


- Here are 3 main points from the text:
- Dopamine pathways control important functions like thinking, and body movement.
- Norepinephrine regulates arousal and attention. Serc controls mood, sleep, and appetite and is a primary t antidepressants.
- Neuropeptides are amino acid chains made in the ce and moved to nerve terminals. They often release wi transmitters and cause longer-lasting effects.

Full Text

Metabotropic Receptors: Flexibility Dopamine pathways include th mesolimbic system (reward, motivation—implicated in addiction), mesocortical system (cognition—implicated in schizophrenia), and nigrostriatal system (motor control—degeneration causes Parkins Norepinephrine from the locus coeruleus modulates arousal and a Serotonin from the raphe nuclei modulates mood, sleep, and appe primary target of antidepressants. Neuropeptides and Unconvent Transmitters Neuropeptides—chains of 3-40+ amino acids includ endorphins, substance P, and neuropeptide Y—are synthesized in body, packaged into large dense-core vesicles, and transported t terminals. They act on GPCRs and are cleared by diffusion and er degradation (no reuptake). Neuropeptides are often co-released classical transmitters, providing modulatory effects on longer tim

Unconventional Transmitters

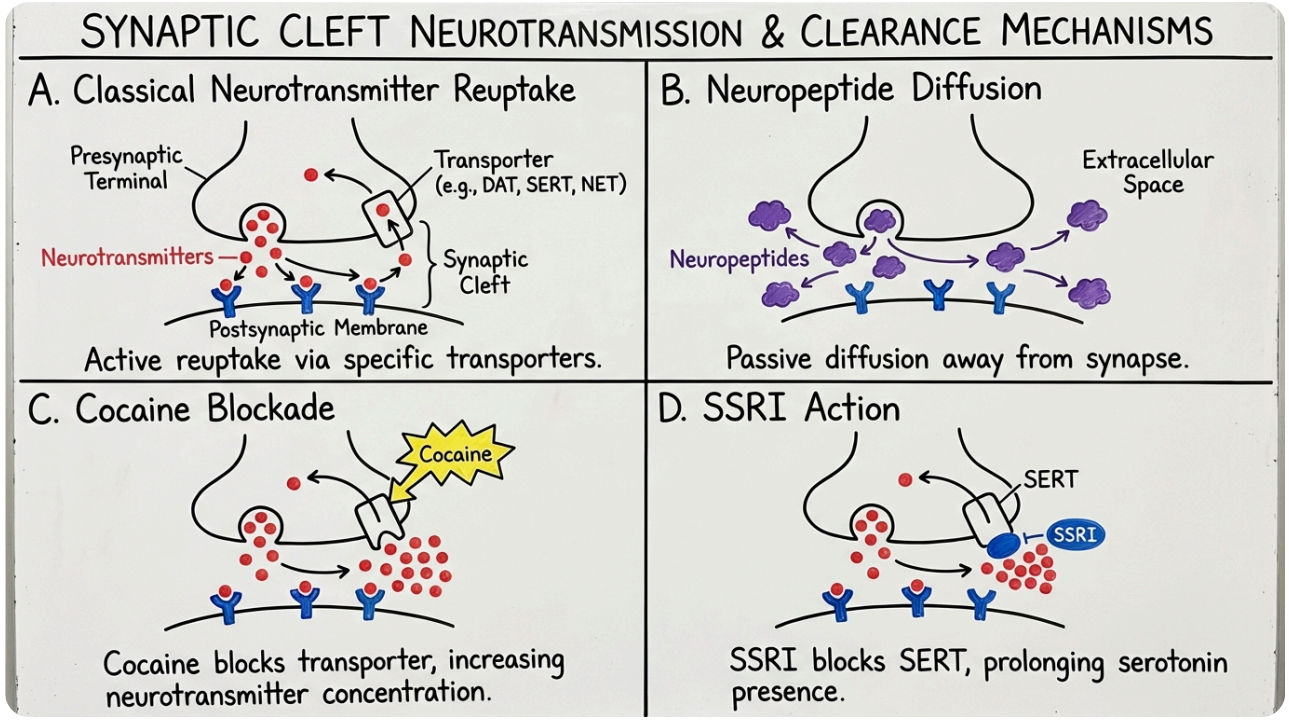


- Main Points:
- Nitric oxide (NO) and endocannabinoids are example unconventional neurotransmitters.
- Nitric oxide is a gas that easily moves across cell me and is created when needed.
- Endocannabinoids are fats made by the receiving ne act on the sending neuron to reduce further release.
- Synaptic signals must end quickly so that new signal sent.
- Enzymes break down neurotransmitters in the synap one way to stop the signal.

Full Text

Metabotropic Receptors: Flexibility Unconventional transmitters i nitric oxide (NO) and endocannabinoids. NO is a gas that diffuses across membranes, activating guanylyl cyclase; it's synthesized c (no vesicle storage). Endocannabinoids (anandamide, 2-AG) are l synthesized postsynaptically and released to act on presynaptic receptors—retrograde signaling that suppresses further transmitt This is the system activated by cannabis. Neurotransmitter Clear Terminating the Signal Synaptic signaling must be terminated rap allow repeated transmission. Three mechanisms clear neurotrans from the cleft: 1. Enzymatic degradation: ACh is hydrolyzed by AC synaptic cleft. This is the only transmitter cleared primarily by ext enzymes.

Neurotransmitter Clearance

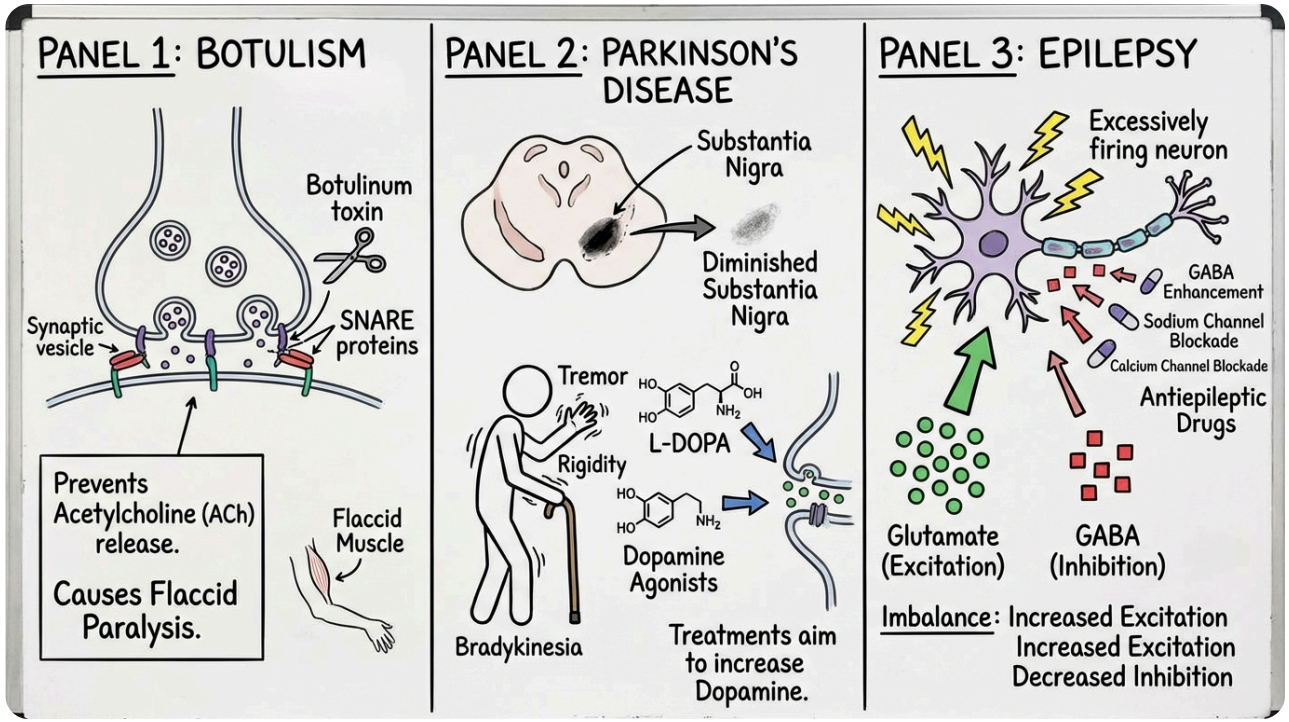


- Here are 4 main points from the text:
- The body clears most neurotransmitters by transport back into nerve cells using specific transporters.
- Neuropeptides clear the synapse by slowly diffusing because they do not have special transporters.
- Myasthenia gravis involves autoantibodies that attac acetylcholine receptors, causing progressive muscle weakness.
- In Lambert-Eaton syndrome, autoantibodies attack presynaptic calcium channels, leading to muscle wea that gets better with activity.

Full Text

Metabotropic Receptors: Flexibility 2. Reuptake: Most transmitter transported back into the presynaptic terminal by specific transpo (DAT for dopamine, SERT for serotonin, NET for norepinephrine, C GABA, EAAT for glutamate). These are major drug targets: cocain DAT, SSRIs block SERT, tricyclics block multiple transporters. 3. D Especially important for neuropeptides, which lack dedicated trar and are cleared slowly by diffusing away from the synapse. Clinic Correlations: When Synapses Fail • Myasthenia gravis: Autoantibo attack nicotinic ACh receptors at the NMJ. Progressive weakness with use, improved by rest. Treatment: acetylcholinesterase inhib (pyridostigmine), immunosuppression. • Lambert-Eaton syndrome Autoantibodies attack presynaptic calcium channels. Weakness th improves with use (repeated stimulation allows calcium accumula Often paraneoplastic (small cell lung cancer).

Neurotransmitter Disorders

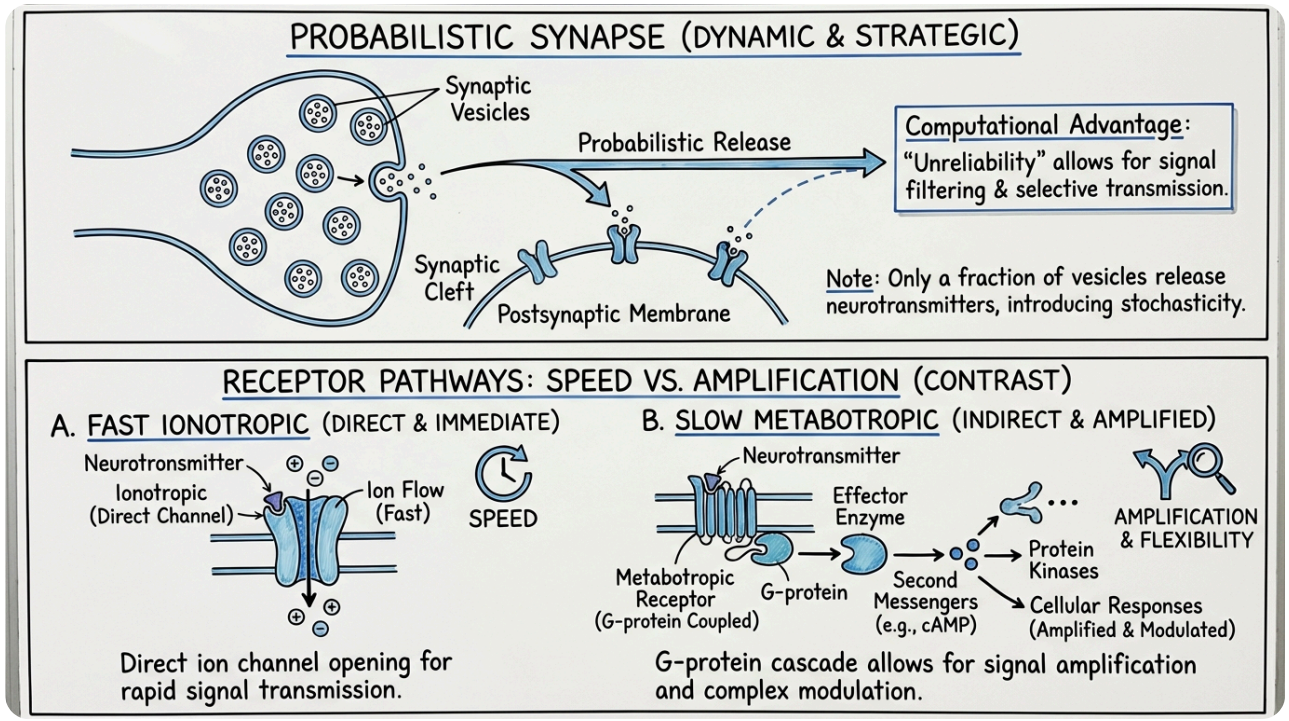


- Here are 3 main points from the text:
- Botulism occurs when a toxin prevents nerve cells fr releasing a chemical signal, causing paralysis. This c from contaminated food or wound infections.
- Parkinson's disease happens when brain cells that p dopamine are lost, causing symptoms like tremors, s and slow movement. Treatments aim to replace or in dopamine in the brain.
- Epilepsy results from an imbalance in brain chemical control nerve activity, leading to seizures. Medicatio epilepsy work by enhancing calming signals or block exciting signals in the brain.

Full Text

Metabotropic Receptors: Flexibility • Botulism: Botulinum toxin cl SNAREs, preventing ACh release. Descending flaccid paralysis be with cranial nerves. Can occur from contaminated food or wound • Parkinson's disease: Loss of dopaminergic neurons in the subst nigra. Tremor, rigidity, bradykinesia. Treatment: L-DOPA (dopamir precursor), dopamine agonists, MAO-B inhibitors. • Epilepsy: Imb between excitation (glutamate) and inhibition (GABA). Antiepilept enhance GABA (benzodiazepines, barbiturates), block sodium ch (phenytoin, carbamazepine), or block glutamate receptors.

Quantal Release Probability

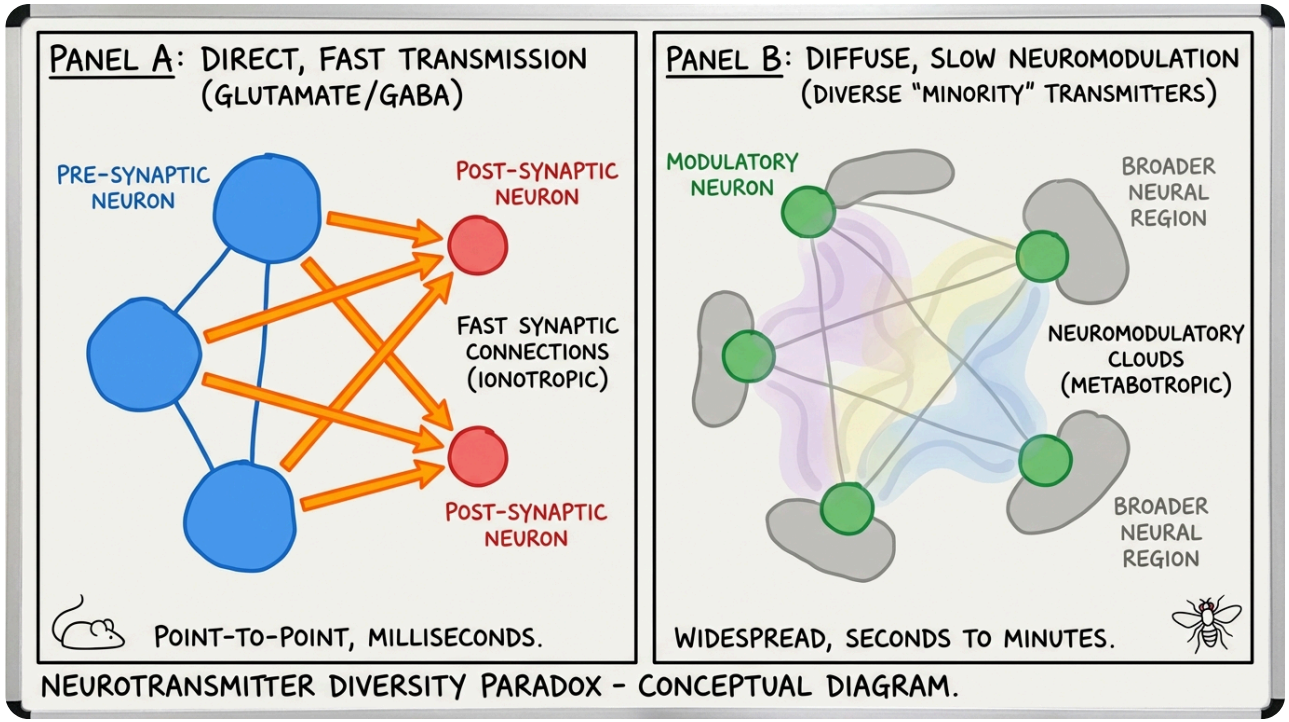


- Here are 4 main points from the text:
- Neurotransmitters release in fixed amounts, but the c release for each signal is typically low.
- Probabilistic neurotransmitter release provides bene learning, controlling signal strength, and saving ener
- Synapses use two main types of receptors: ionotropi metabotropic.
- Ionotropic receptors respond quickly, while metabotr receptors respond more slowly. They each play impo roles in different brain processes.

Full Text

Metabotropic Receptors: Flexibility Thought Questions for Discus questions to spark discussion before your next class: The Quanta Bernard Katz showed that neurotransmitter release is quantized— multiples of single vesicle contents. But release probability per ve typically only 10-30% per action potential. Why might evolution h favored unreliable synaptic transmission? Consider the computati advantages of probabilistic release for learning, gain control, and efficiency. The Speed-Flexibility Tradeoff: Ionotropic receptors re microseconds; metabotropic receptors take seconds. Yet both ex synapses. Why maintain two parallel signaling systems rather tha optimizing one? Consider situations where speed matters most ve situations where amplification, duration, and modulation of respo more important.

Neurotransmitter Diversity



- Here are 3-5 main points from the text:
- The brain uses more than 100 different kinds of neurotransmitters.
- Glutamate and GABA handle almost all (about 95%) brain's rapid communication between cells.
- The brain maintains many other neurotransmitters, s they have different roles.
- These varied neurotransmitter systems allow for diff types of brain computations and neuromodulation.

Full Text

Metabotropic Receptors: Flexibility The Neurotransmitter Diversit The brain uses 100+ neurotransmitters, yet glutamate and GABA for ~95% of fast synaptic transmission. Why maintain so many "n transmitters? Consider the distinction between point-to-point tra and neuromodulation, and how different transmitter systems enab different types of computation.