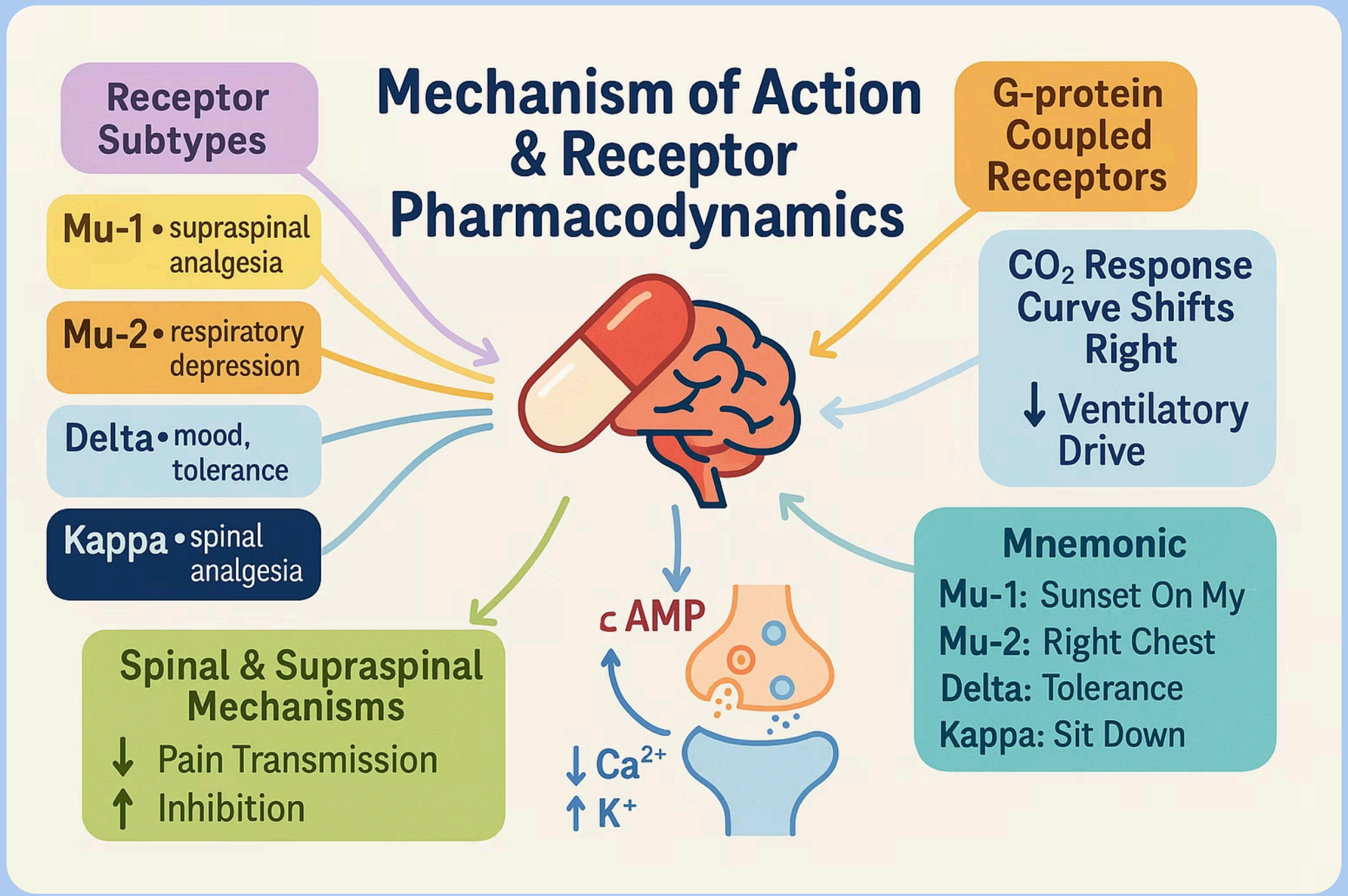
🧠 Mechanism of Action & Receptor Pharmacodynamics



Receptor Subtypes

Mnemonic: "Mu Makes You Merry, Delta Gives Dual Analgesia, Kappa Gets Krazy"

Receptor	Key Function	Mnemonic Aid
Mu-1 (μ_1)	Supraspinal analgesia	"Sunset On My" → Think 'Mu-1 = Morphine = Mood'
Mu-2 (μ_2)	Respiratory depression, constipation, dependence	"Right Chest" → Reminds you of respiratory suppression
Delta (δ)	Mood, analgesia, tolerance	"Delta = Dual" (acts at spinal + supraspinal sites)
Kappa (κ)	Spinal analgesia, sedation, dysphoria	"Kappa = Krazy Dreams" (causes hallucinations, sedation)

G-Protein Coupled Receptors

Mnemonic: "G-Protein = Go Slow"

Opioid receptors are Gi/o-protein coupled

Activation causes:

↓ cAMP

Decreased cyclic adenosine monophosphate

↓ Ca^{2+} influx

Reduced calcium entry into cells

↑ K^{+} efflux

Increased potassium exit from cells

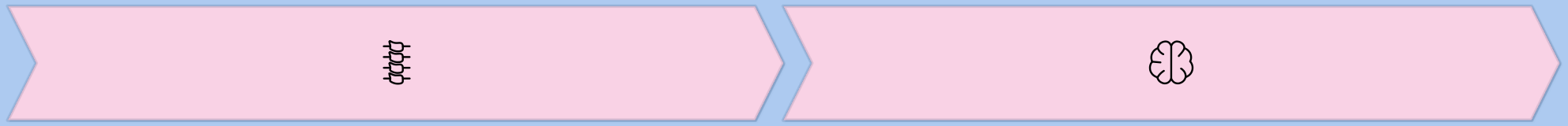
This leads to neuronal hyperpolarization and inhibition of neurotransmitter release, particularly:

- ↓ Substance P
- ↓ Acetylcholine (ACh)
- ↓ Norepinephrine (NE)

➡️ **Result:** Reduced neuronal excitability and decreased pain transmission.

Spinal & Supraspinal Mechanisms

Mnemonic: "S-to-S: Spinal to Supraspinal — Stop the Signal"



Spinal Level

Inhibits pain transmission at the substantia gelatinosa of the dorsal horn.

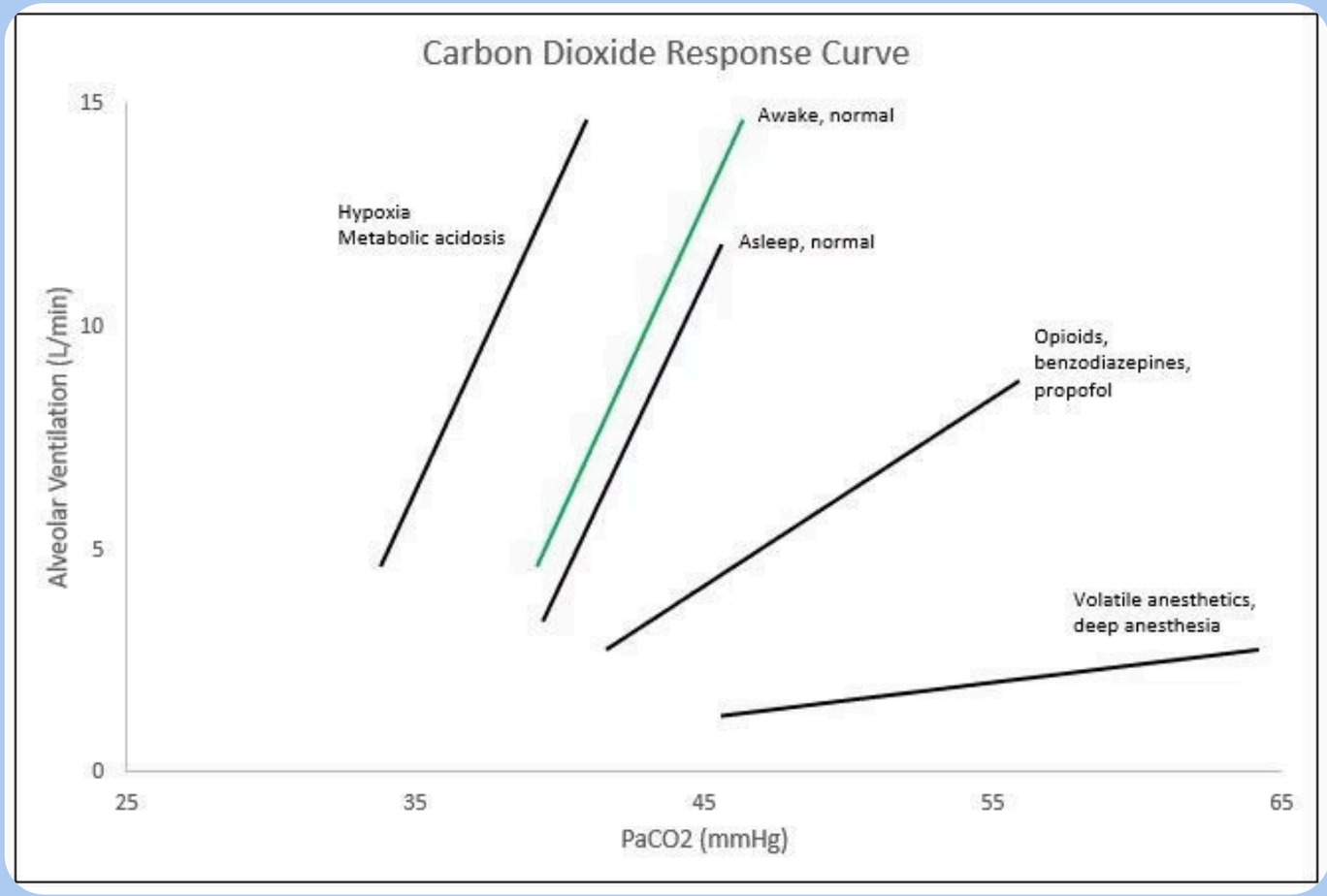
Supraspinal Level

Activates periaqueductal gray (PAG) and **rostral ventromedial medulla** (RVM) descending pathways to inhibit nociceptive signaling.

Net Effect: ↓ Pain transmission and ↑ Inhibition of ascending pathways.

CO_2 Response Curve

Mnemonic: "Shift Right, Stop Breathing"



Opioids shift the CO_2 ventilatory response curve to the right.

Patients need higher CO_2 levels to trigger ventilation → ↓ ventilatory drive.

Explains opioid-induced respiratory depression.

MORPHINES Breakdown

Letter	Effect	Mechanism
M	Miosis	Parasympathetic stimulation
O	Out of it (Sedation/Euphoria)	CNS depression
R	Respiratory depression	↓ CO_2 sensitivity
P	Pain relief	Spinal/supraspinal μ activation
H	Hypotension	Histamine release (esp. morphine)
I	Increased ICP	Due to ↑ $PaCO_2$
N	Nausea/Vomiting	Chemoreceptor trigger zone (CTZ)
E	Euphoria	Limbic μ receptor
S	Suppressed cough	Medullary cough center inhibition

6. Key Takeaways

- All opioid receptors are Gi-protein coupled → ↓ cAMP → neuronal hyperpolarization
- Analgesia results from inhibition of pain transmission and activation of descending inhibition
- Respiratory depression arises from the same receptor systems regulating ventilatory drive

> **Mnemonic Summary:**
>
> "Mu Makes You Merry, Delta Gives Dual Analgesia, Kappa Gets Krazy — All Go Slow through G-proteins."