Inhaled Anesthetics

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Mc Graw Hill Boards&Beyond

Anesthetics

- Drugs that produce:
  - Analgesia
  - Loss of consciousness
  - Amnesia
  - Muscle relaxation

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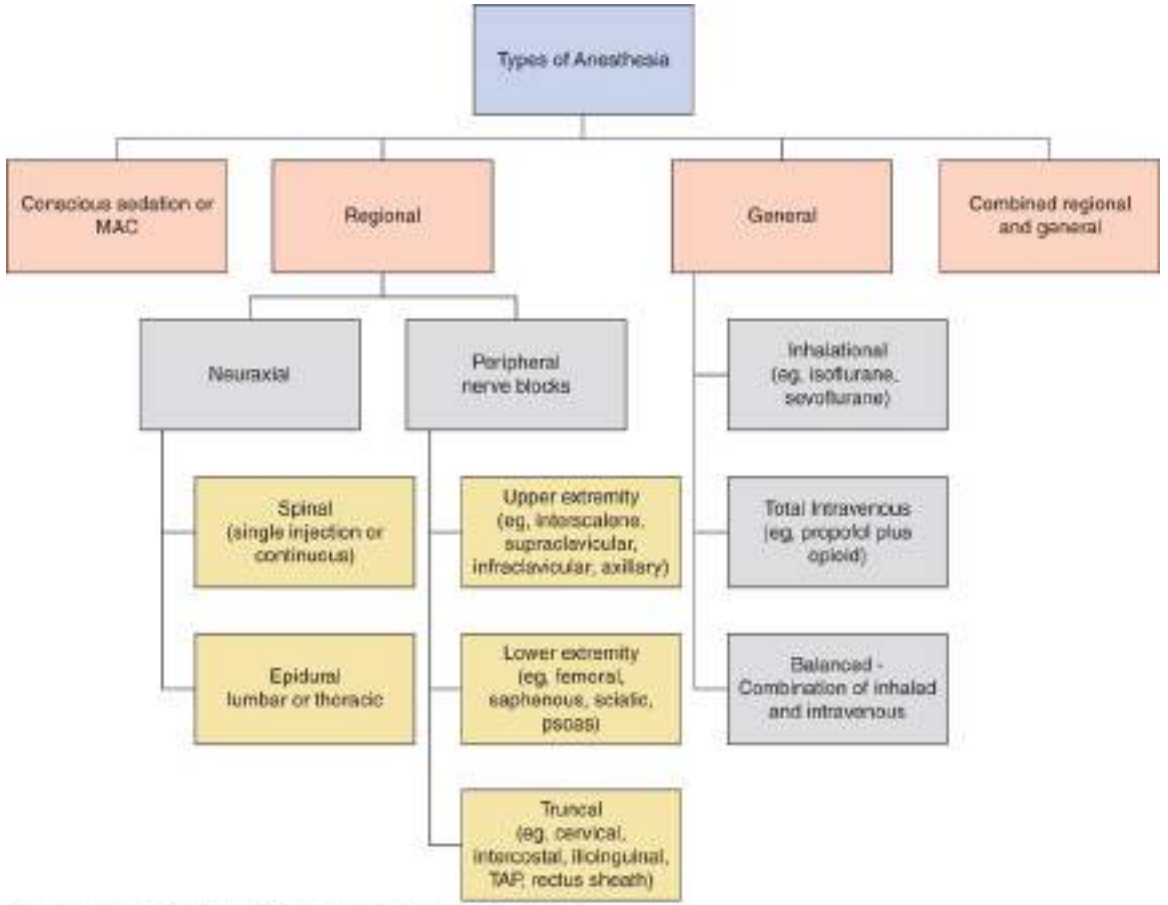
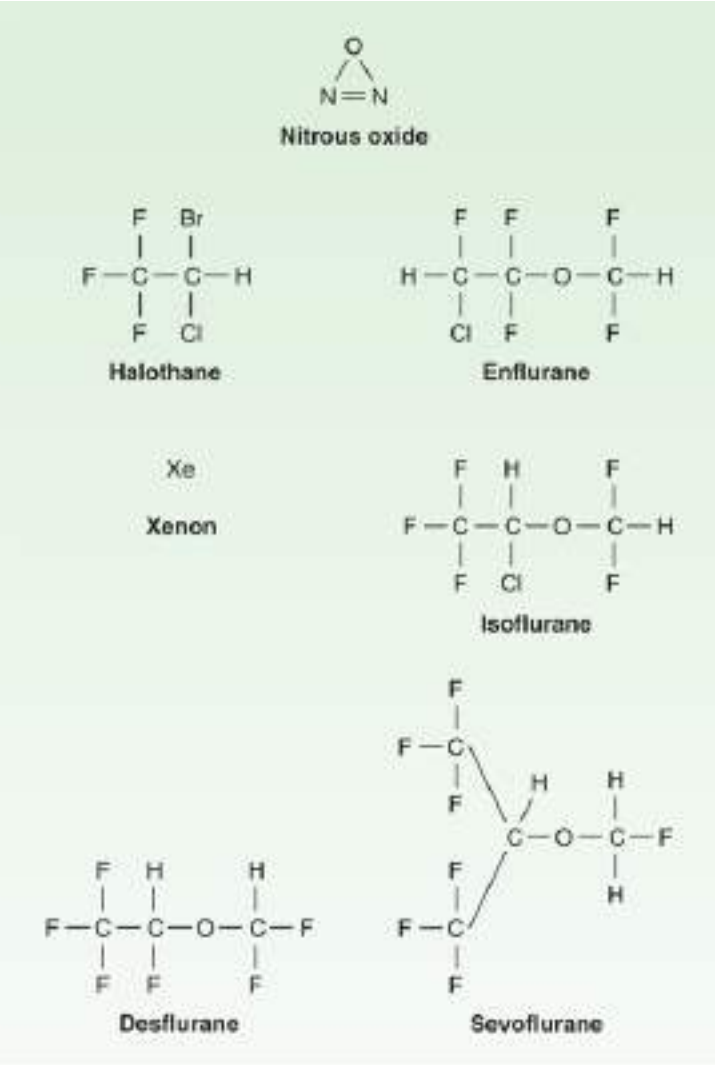
Types of Anesthesia Drugs

- Inhaled anesthetics
- Intravenous anesthetics
- Local anesthetics
- Neuromuscular blocking agents



Inhaled Anesthetic Principles

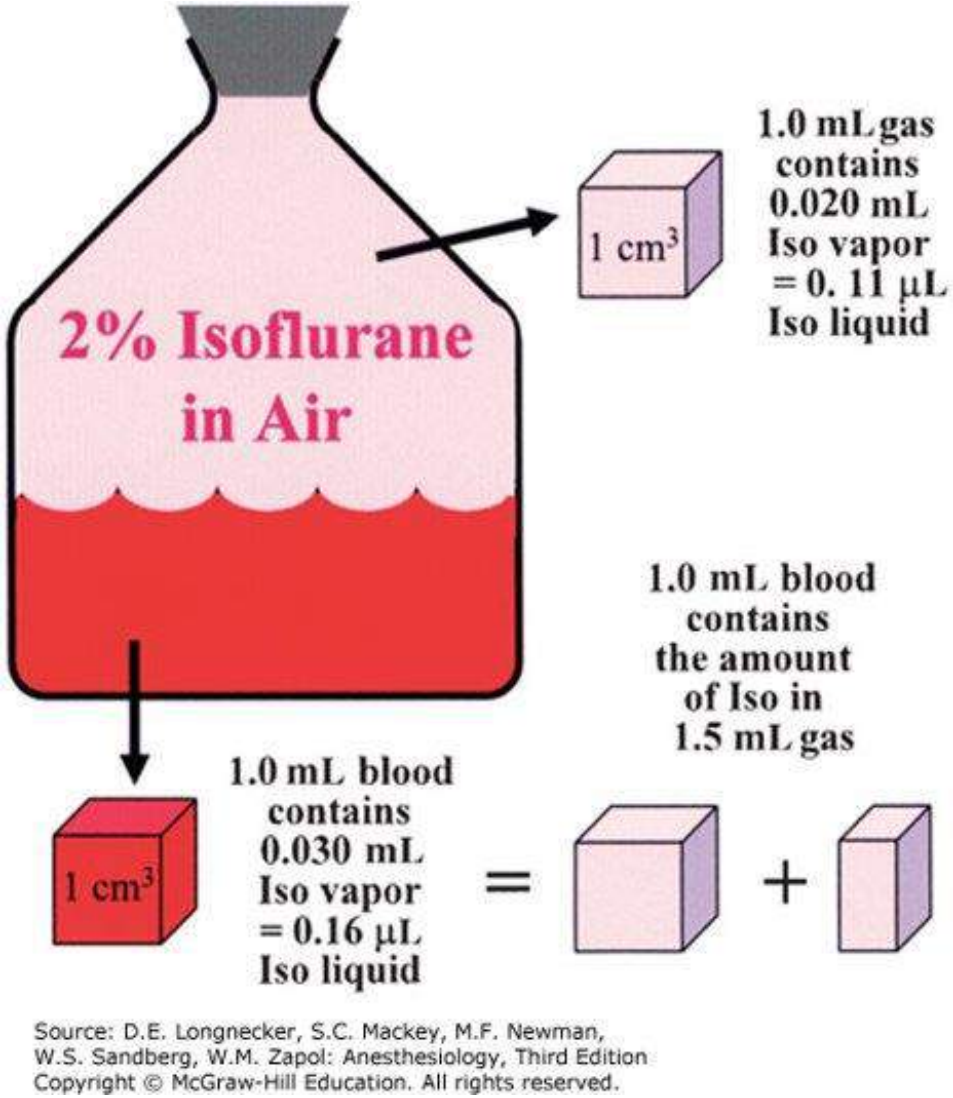
- Special properties determine effectiveness
- Solubility of gas for blood determines onset/offset
- Solubility of gas for lipids determines potency



Inhaled Anesthetics

Drug Uptake from Lungs

- Must enter blood of alveolar capillaries
- Must move from blood into CNS
- Speed of uptake depends on:
  - Inspired concentration of drug
  - Minute ventilation
  - Pulmonary blood flow
  - **Blood:gas partition coefficient**



Source: D.E. Longnecker, S.C. Mackey, M.F. Newman, W.S. Sandberg, W.M. Zapol: Anesthesiology, Third Edition

Blood:Gas Partition Coefficient

- Ratio solubility in blood to solubility in gas/alveoli
  - Example: Isoflurane: 1.4
  - [blood]1.4 > [alveoli]
- Proportional to the solubility of inhaled drug in blood
- More soluble drug = higher blood:gas PC
- More soluble = slower onset/offset

Gas	PC
Halothane	2.3
Isoflurane	1.4
Sevoflurane	0.69
Nitrous Oxide	0.47
Desflurane	0.42

Example 1: Desflurane

- 35yo healthy male undergoing elective surgery
- Desflurane
- Blood-gas partition coefficient: low (rapid uptake)
- Cardiac output: normal
- 2-4 min to reach desired level of anesthesia

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Example 2: Halothane

- 60yo female with heart failure undergoing elective procedure
- Halothane
- Blood-gas partition coefficient: high (slower uptake)
- Cardiac output: reduced
- 10-20 min to reach desired level of anesthesia

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Blood Solubility

Inhaled Anesthetics

- Molecules dissolved in blood: little/no anesthetic effect
- Molecules NOT dissolved: anesthetic effect
- Need to saturate blood to generate partial pressure
- MORE solubility in blood = LONGER to take effect

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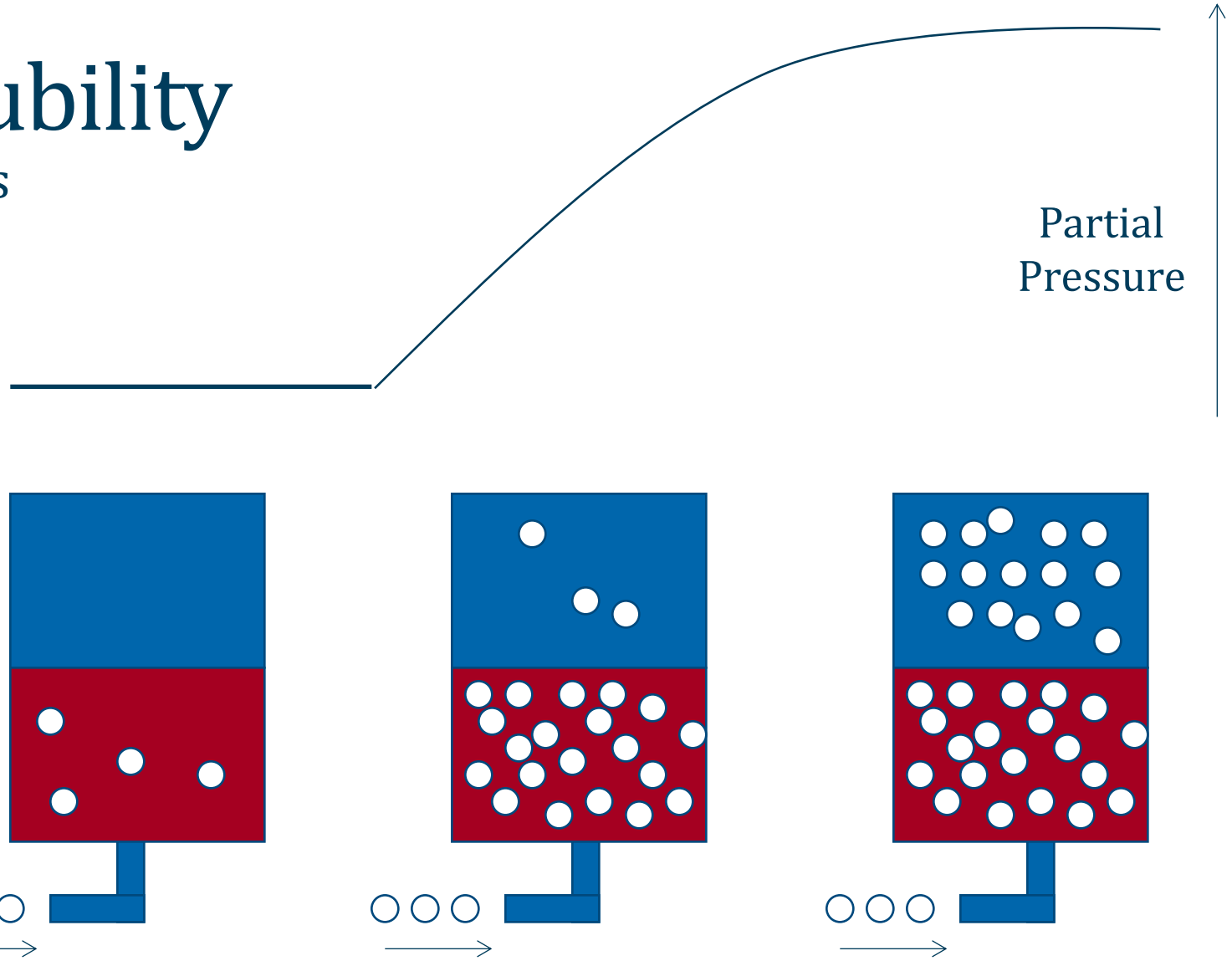
Blood Solubility

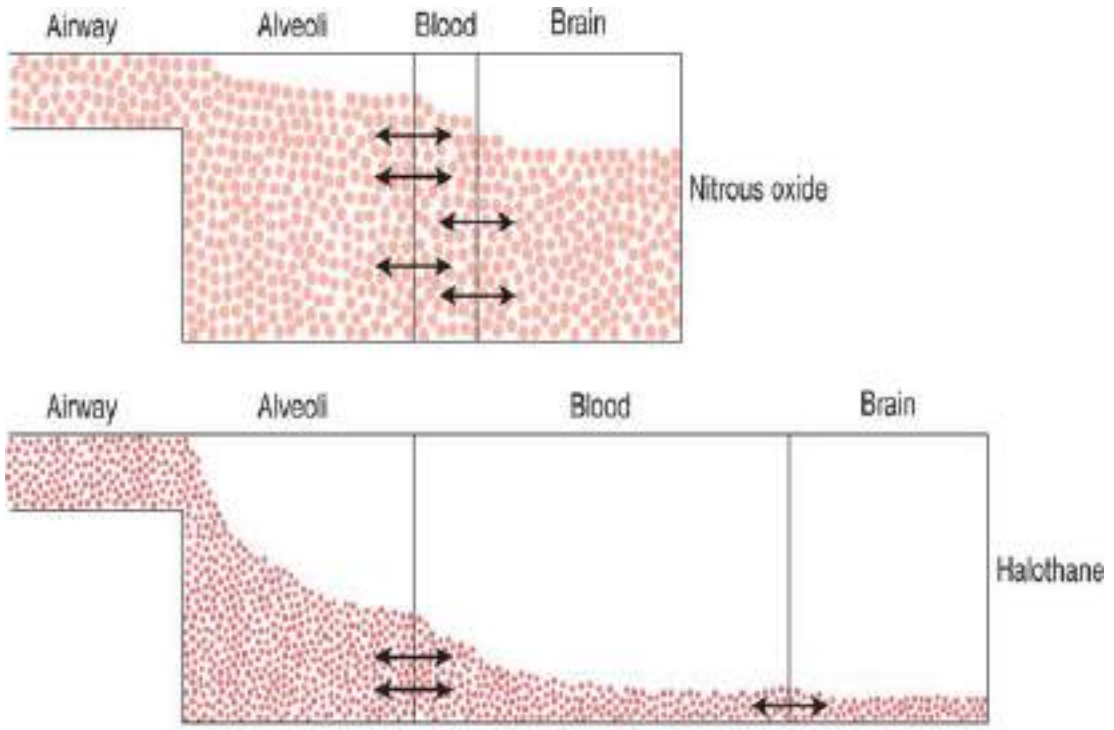
Inhaled Anesthetics



Blood Solubility

Inhaled Anesthetics

- Higher solubility
  - Longer time to saturate blood
  - SLOWER induction time (also washout time)
  - Example: Halothane (PC = 2.3)
- Low solubility
  - Quickly saturates blood
  - Quickly exert effects on brain
  - SHORTER induction time (also washout time)
  - Example: Nitrous oxide (PC = 0.47)



Source: E.E. Jobst, P.C. Panus, M. Kruidering-Hall
Pharmacology for the Physical Therapist, Second Edition

Blood:Gas Partition Coefficient

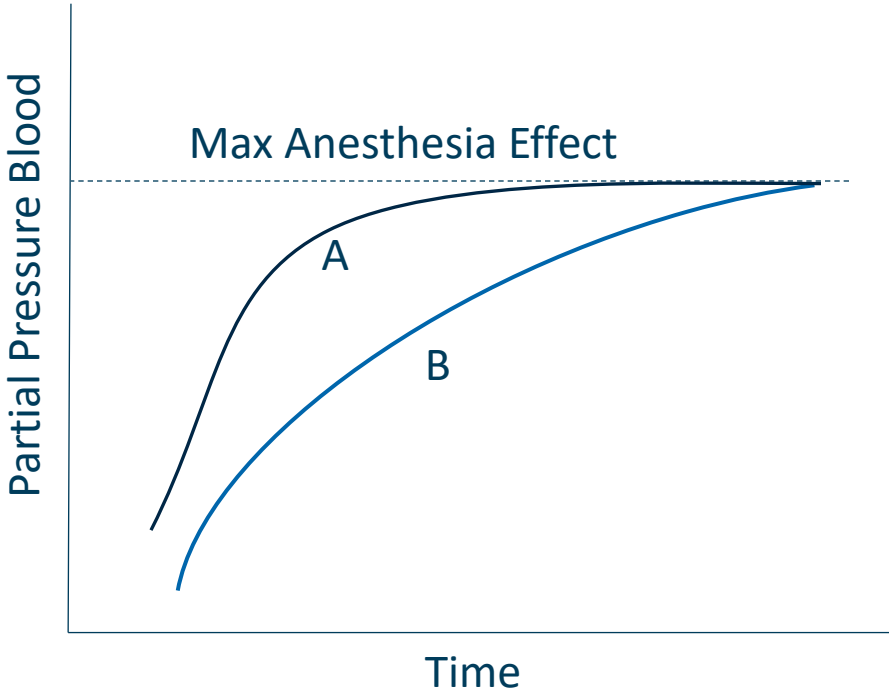
- **High blood:gas PC**
  - Drug relatively soluble in blood
  - More drug required to saturate the blood
  - **Slower** induction and emergence
- **Low blood:gas PC**
  - Drug relatively insoluble in blood
  - Less drug required to saturate the blood
  - **More rapid** induction and emergence

Gas	PC
Halothane	2.3
Isoflurane	1.4
Sevoflurane	0.69
Nitrous Oxide	0.47
Desflurane	0.42

Halothane → SLOW induction (slow saturation of blood)
Nitrous Oxide → FAST induction (rapid saturation of blood)

Blood Solubility

Inhaled Anesthetics

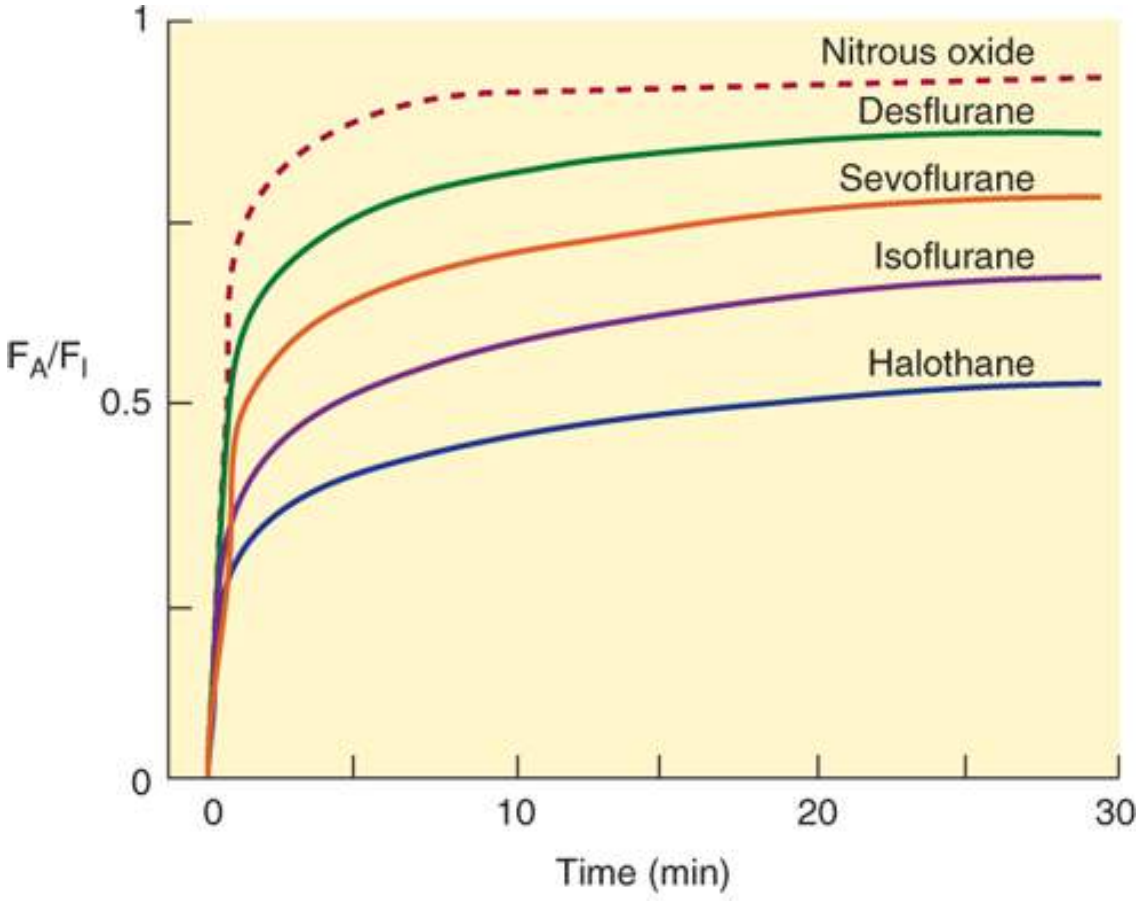


Drug A: Less soluble in blood, faster rise in pressure, fast anesthetic effect

Drug B: More soluble in blood, slower rise in pressure, slower effect

F_A/F_i

- F_A = alveolar concentration of drug
- F_i = inhaled concentration of drug
- F_A/F_i
  - Rate of rise of concentration in alveoli
  - Related to gas solubility in blood
  - More soluble = slower rise F_A/F_i



Source: Todd W. Vanderah:
Basic & Clinical Pharmacology, Sixteenth Edition

Lipid Solubility

Inhaled Anesthetics

- Affinity of gas for lipids
- Oil/gas partition coefficient
- ↑ lipid affinity = more potent (Meyer-Overton rule)
  - Less drug required to induce anesthesia

Gas	PC
Halothane	224
Enflurane	99
Isoflurane	98
Sevoflurane	47
Desflurane	28
Nitrous Oxide	<10

Inhaled Anesthetic Principles

- Minimum alveolar concentration
  - Concentration of anesthetic gas in alveoli
  - Prevents movement 50% of subjects
  - In response to pain
- Related to lipid solubility
- Low MAC = high potency
- MAC changes with age
- Lower in elderly

$$\text{Lipid Solubility} = \frac{1}{\text{MAC}}$$

Gas	MAC (%)	Oil:gas PC
Halothane	0.8	224
Enflurane	1.8	99
Isoflurane	1.3	98
Sevoflurane	2.5	47
Desflurane	7.2	28
Nitrous Oxide	>100	<10

Minimum Alveolar Concentration

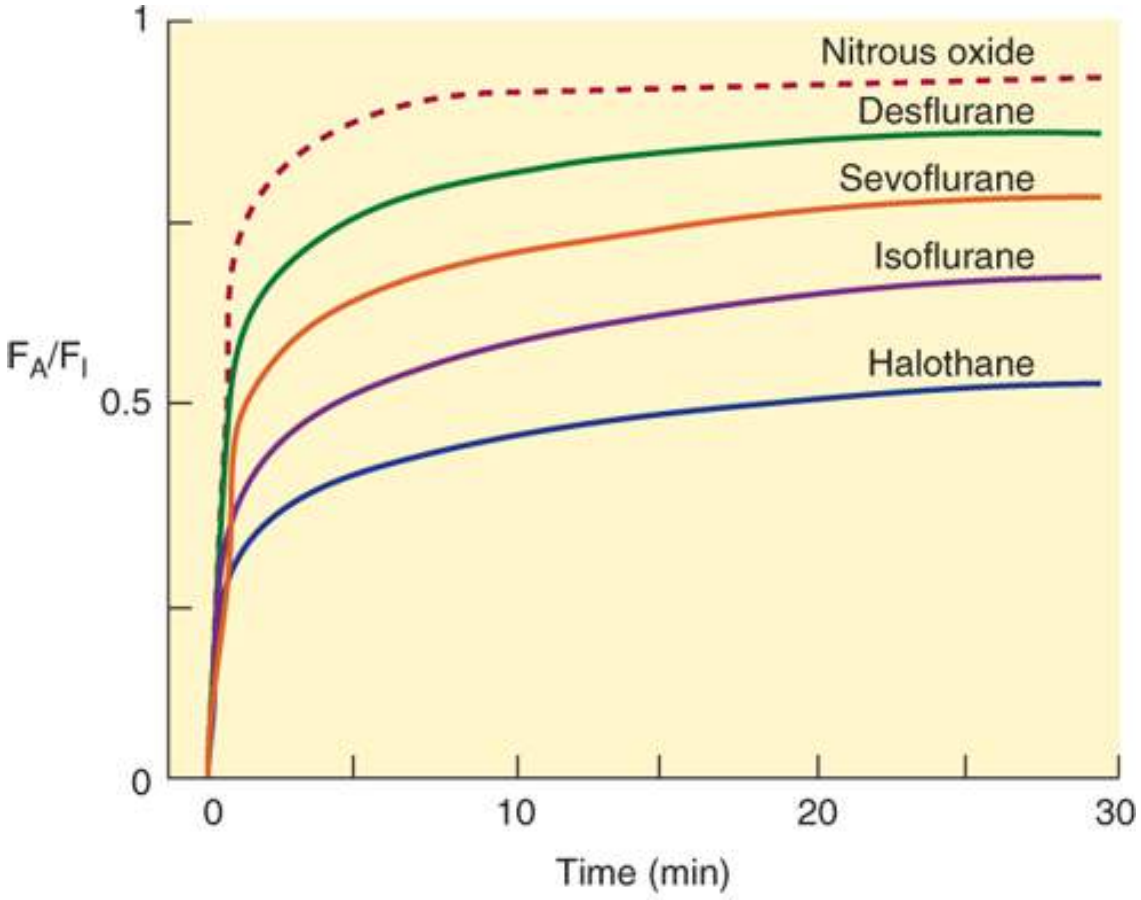
Additive Properties

- When using multiple drugs, MACs are additive
  - Allows use of lower concentration of each drug
- Example:
  - Sevoflurane ½ MAC – 25% efficacy
  - Nitrous oxide ½ MAC – 25% efficacy
  - Combination: 1 MAC, 50% efficacy
  - Patient exposed to less of each drug
  - Lower risk of adverse effects

Gas	MAC (%)	Oil:gas PC
Halothane	0.8	224
Enflurane	1.8	99
Isoflurane	1.3	98
Sevoflurane	2.5	47
Desflurane	7.2	28
Nitrous Oxide	>100	<10

Inhaled Anesthetics Summary

- Onset of action
  - Solubility in blood (↑ = slower)
  - Blood:gas partition coefficient (↑ = slower)
- Potency
  - Oil/gas partition coefficient (↑= more potent)
  - MAC (↓ = more potent)



Source: Todd W. Vanderah:
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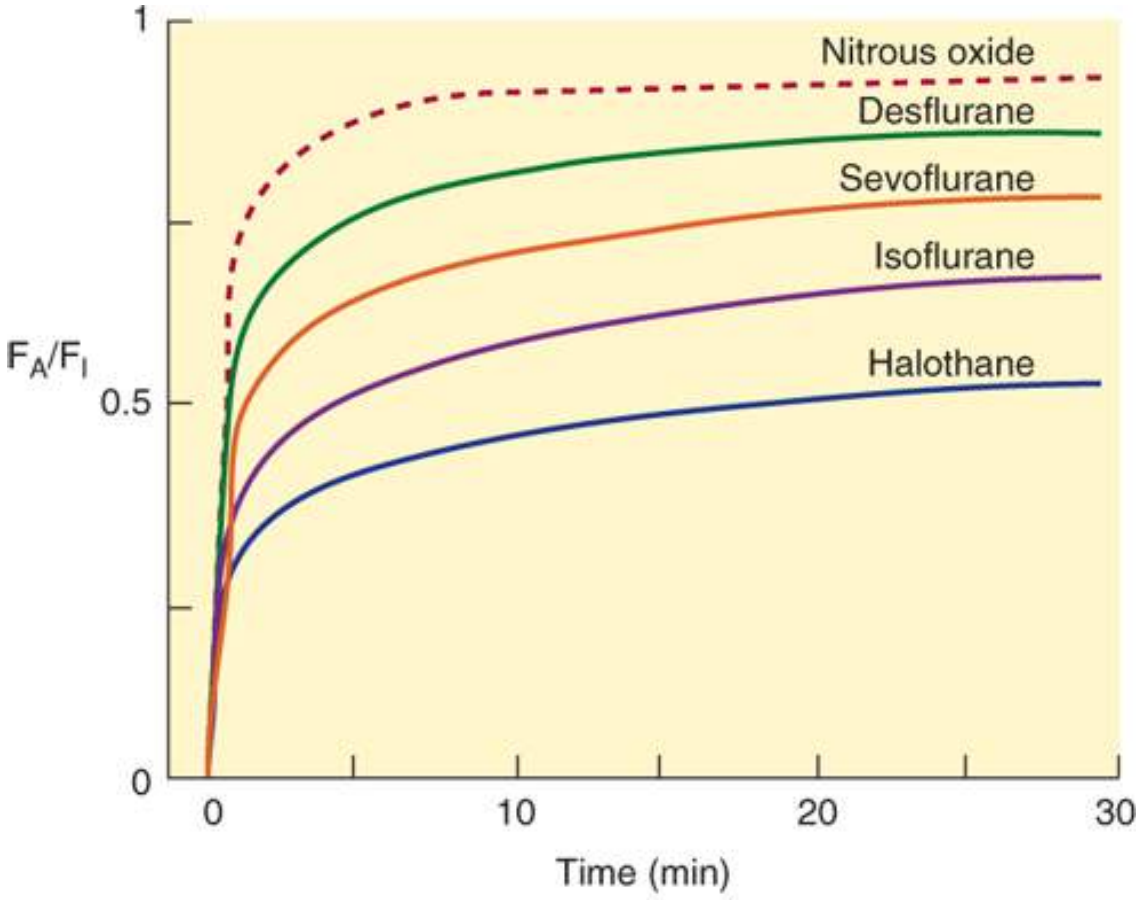
Inhaled Anesthetics

- Desflurane
- Sevoflurane
- Halothane
- Enflurane
- Isoflurane
- Methoxyflurane
- Nitrous oxide



Source: Todd W. Vanderah:
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Common Effects

- Myocardial depression
  - ↓CO
  - ↓BP
- Respiratory depression
- Decrease cough reflex
- Nausea and vomiting

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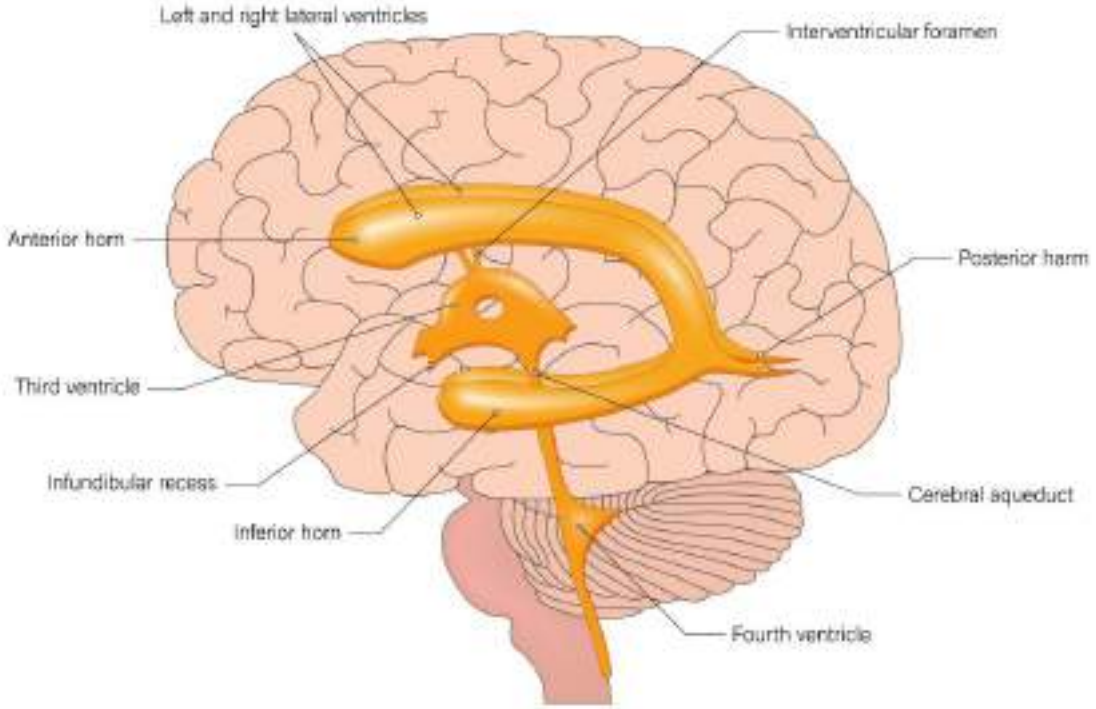
Common Effects

- ↑ cerebral blood flow
  - Cerebral vasodilation
  - Blood flow goes up
  - ICP goes up
- Decrease metabolic rate
- Decrease skeletal/smooth muscle tone



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Special Side Effects

- Halothane – Hepatotoxicity & malignant hyperthermia
  - Liver toxicity: Rare, life-threatening
  - Massive necrosis, increased AST/ALT
- Methoxyflurane – Nephrotoxicity
  - Renal-toxic metabolite
- Enflurane – Seizures
  - Lowers seizure threshold

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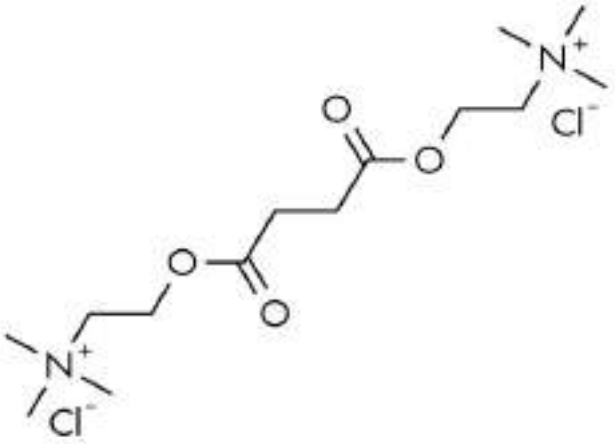
Malignant Hyperthermia

- Rare, dangerous reaction
- Inhaled anesthetics
  - Sevoflurane, desflurane, halothane
- Depolarizing muscle relaxants
  - Succinylcholine



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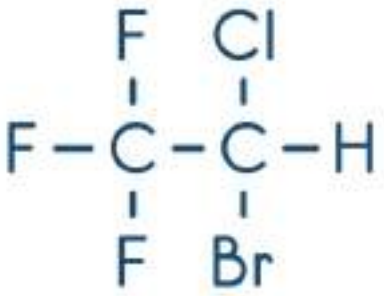

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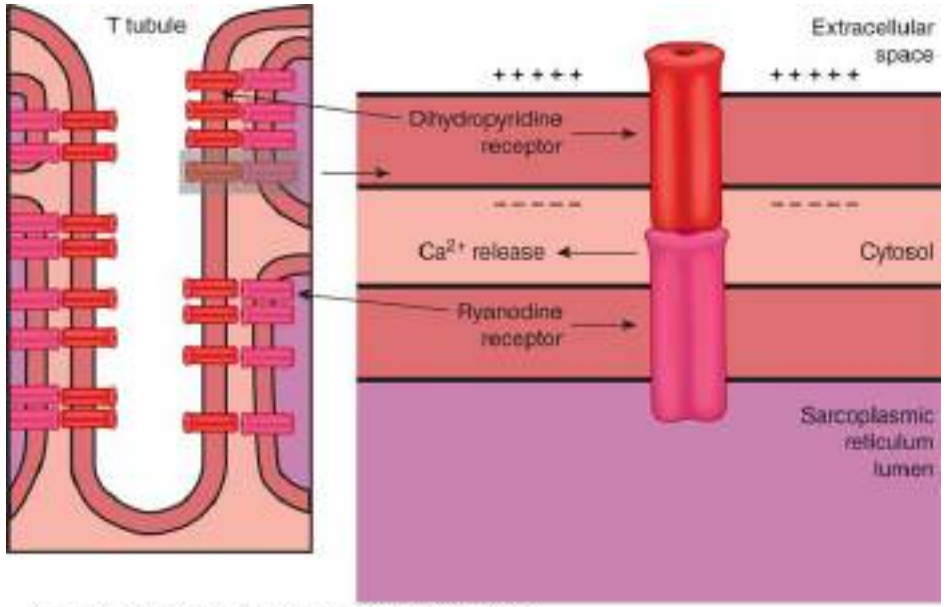
Malignant Hyperthermia

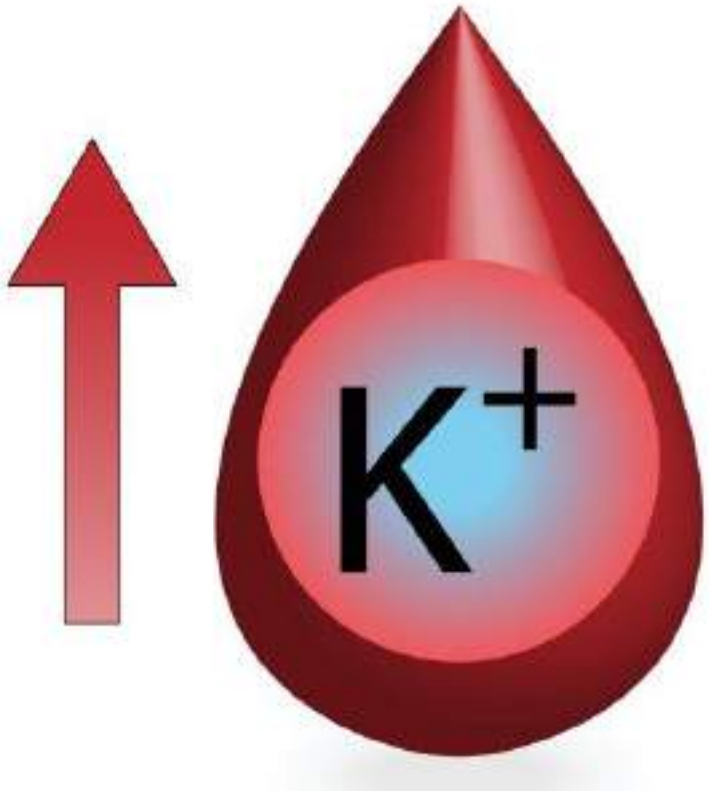
- Cause: ryanodine receptor (RyR) in the sarcoplasmic reticulum
  - Abnormal in patients who get MH (autosomal dominant)
  - Triggers excessive calcium release through the RyR
  - Ca overload causes continuous & uncontrolled muscle contractions
  - Hypermetabolic state
  - Increases heat production
  - Depletes ATP
  - Produces lactic acid, metabolic acidosis
  - Muscle breakdown



Source: K.E. Barrett, S.M. Barman, H.L. Brooks, Jason X.J. Yuan: Ganong's Review of Medical Physiology, Twenty-Sixth Edition

Malignant Hyperthermia

- Fever, muscle rigidity after surgery
- Tachycardia, hypertension
- Muscle damage: ↑K, CK
- Treat with dantrolene (muscle relaxant)



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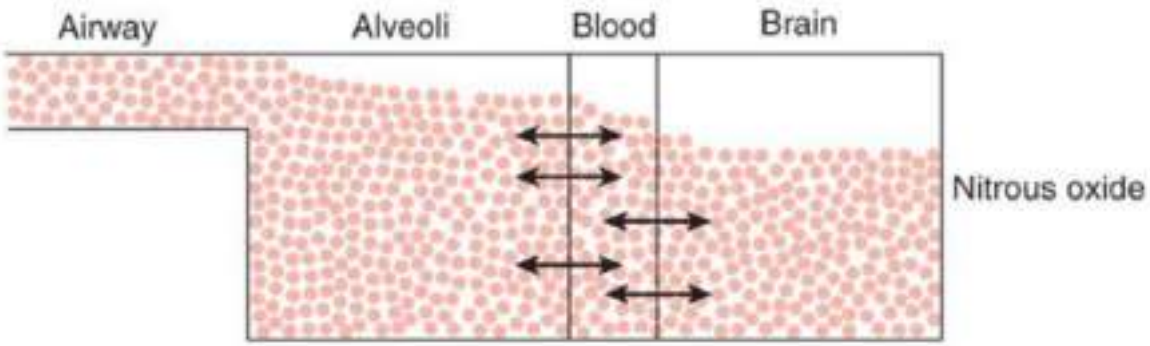
Nitrous Oxide

- Diffuses rapidly into air spaces
- Can increase volume
- Cannot use:
  - Pneumothorax
  - Abdominal distention



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Intravenous Anesthetics

Jason Ryan, MD, MPH

Mc Graw Hill Boards&Beyond

Intravenous Anesthetics

- Barbiturates
- Benzodiazepines
- Opioids
- Etomidate
- Ketamine
- Propofol

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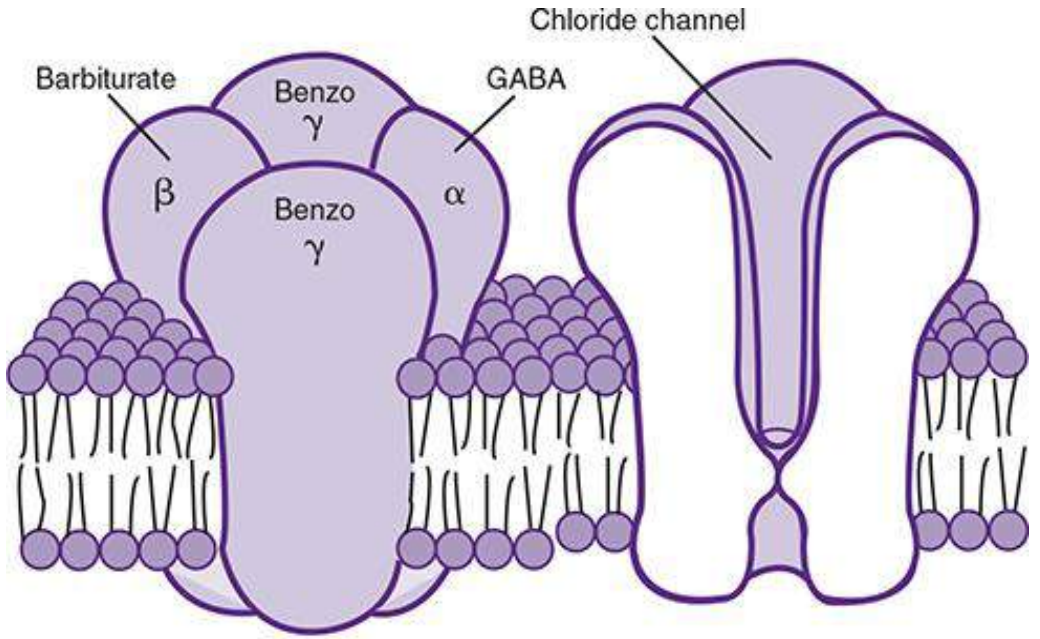
GABA Receptor

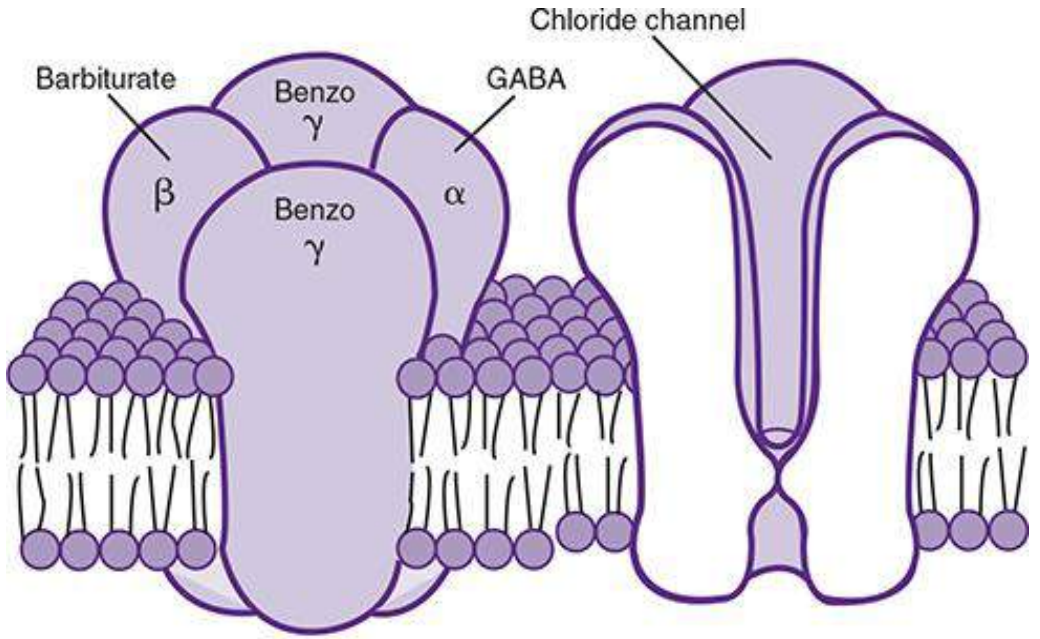
- GABA = Gamma-Aminobutyric Acid
- Binding to receptor opens chloride channel
- Multiple subunits around a central pore
- Primary inhibitor neurotransmitter
- Found in brain, spinal cord
- Increased activity = sedation/anesthesia



Source: Charles D. Ciccone: *Pharmacology in Rehabilitation*, 5th Edition:
www.FADavisPTCollection.com

Barbiturates

- Pentobarbital
- Binding to GABA-receptor
  - Positive allosteric modulator
  - Enhances activity
  - More chloride ion flux
- High potency from high lipid solubility
- Short-intermediate acting



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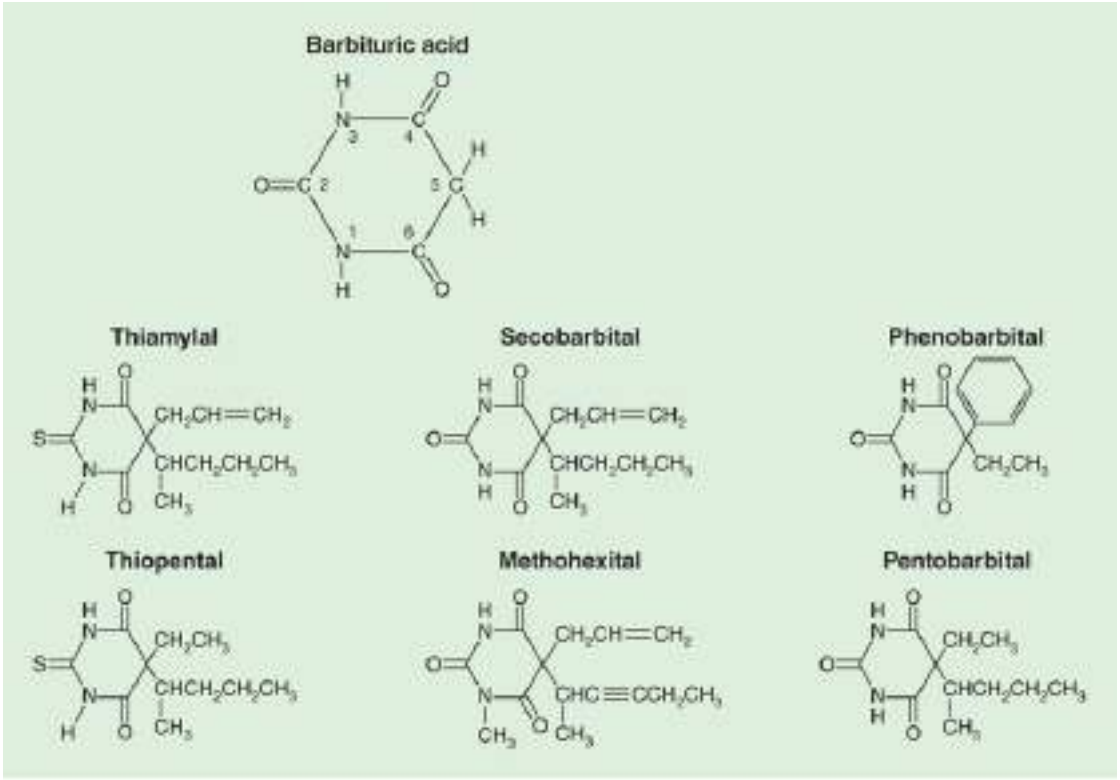
Barbiturates

- Respiratory depression
- Myocardial depression
- Peripheral vasodilation
- **Hypotension**
- Elevated ICP
- Seizures/coma
- Cause of celebrity deaths
  - Marilyn Monroe, Jimmy Hendrix
- Largely replaced by benzodiazepines

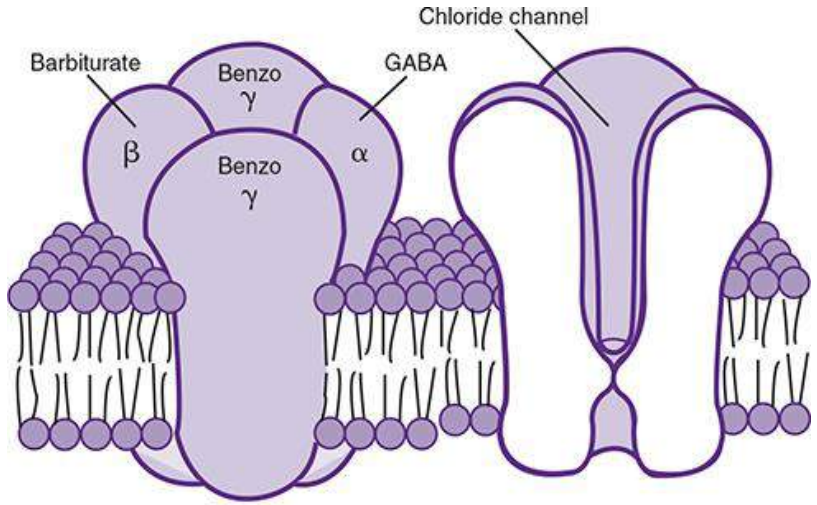


Source: John F. Butterworth IV, David C. Mackey, John D. Wasnick:
Morgan & Mikhail's Clinical Anesthesiology, 7e

Benzodiazepines

Midazolam, Lorazepam, Diazepam, Alprazolam

- Bind to GABA receptors
- Different mechanism from barbiturates
- ↑ frequency of GABA ion channel opening
- Low dose: anti-anxiety (anxiolytic)
- Midazolam (Versed): Short procedures (endoscopy)
- High dose: sedation, amnesia, anticonvulsant



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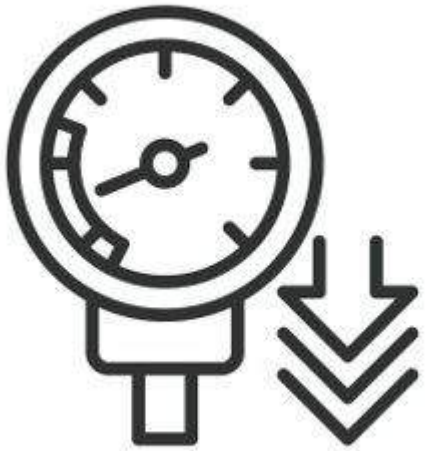
Benzodiazepines

Midazolam, Lorazepam, Diazepam, Alprazolam

- Cause cardio-respiratory depression
- ↓ blood pressure
- Overdose: Flumazenil



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Opioids

Morphine, Fentanyl, Hydromorphone

- Cause **pain relief and sedation** but no amnesia
- Opioid receptors
  - G protein-coupled receptors
  - Bind endorphins
  - Close presynaptic Ca channels
  - Open postsynaptic K channels
- Multiple subtypes
  - **Mu** =B-endorphin
  - Delta= enkephalin
  - Kappa =dynorphin

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Opioids Mechanism

Morphine, Fentanyl, Hydromorphone

- Close presynaptic Ca channels
- Leads to decreased synaptic transmission
- Inhibits the release of:
  - ACH
  - Norepinephrine
  - 5-HT
  - Glutamate
  - Substance P

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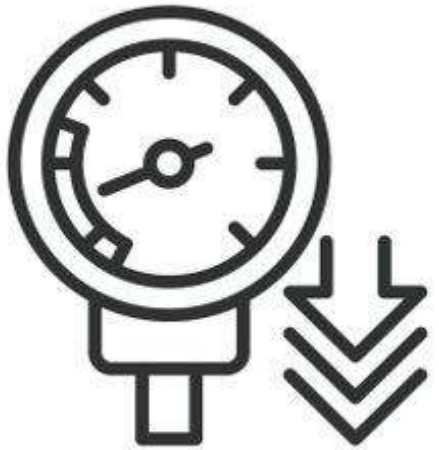
Opioids

Adverse Effects

- ↓ Respiratory drive
- ↓ BP
- Nausea/vomiting
- Constipation/Ileus
- Sphincter of Oddi spasm
- Urinary retention
- Miosis
- Addictive → opioid use disorder



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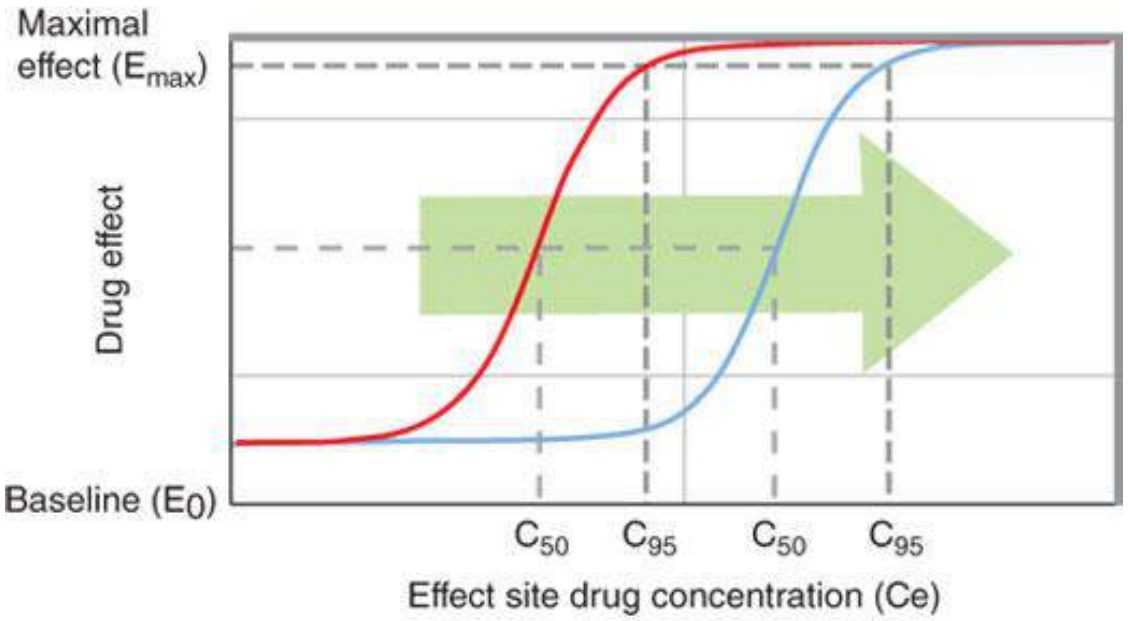
Opioid Tolerance

- Some effects wane with chronic use
- Major problem with cancer pain
- Decreased effect on
  - Pain/sedation
  - Nausea, vomiting
  - Respiratory depression
  - Cough suppression
  - Urinary retention
- No tolerance to **constipation or miosis**
  - These effects persist



Source: D.E. Longnecker, S.C. Mackey, M.F. Newman, W.S. Sandberg, W.M. Zapol: Anesthesiology, Third Edition

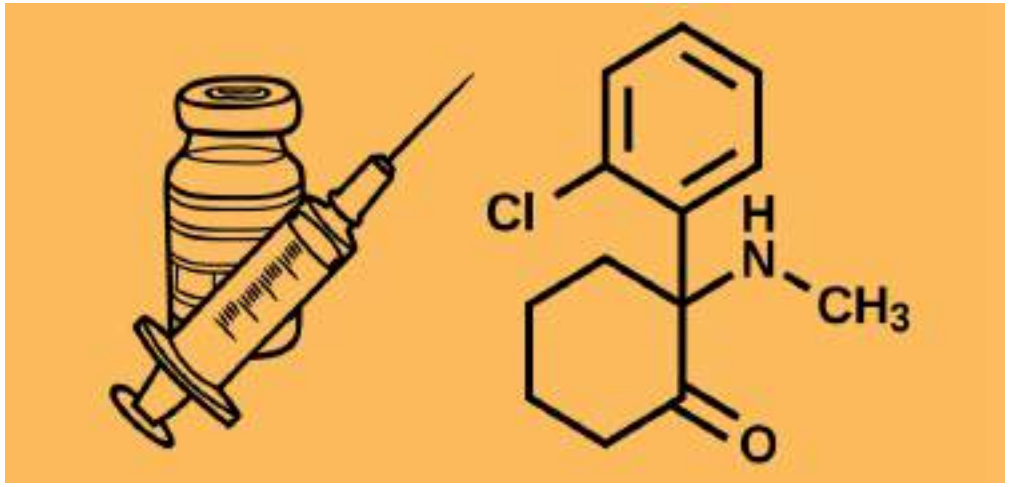
Naloxone

- Opioid antidote
- **Mu antagonist**
  - Also gamma & kappa
- Used for overdose
- Competes with opioids
- Displaces from binding site
- Reverses effects within minutes
- Must be given IV/nasal
- Inactivated by liver if PO

Source: Douglas D. Brunette
Extraordinary Cases in Emergency Medicine

Ketamine

- PCP derivative
- Antagonist of NMDA receptor
- Blocks effects of glutamate
- "Dissociative" drug
  - "Psychotomimetic effects"
  - Patient enters trancelike state
- Analgesia and amnesia
- Few respiratory or CV effects



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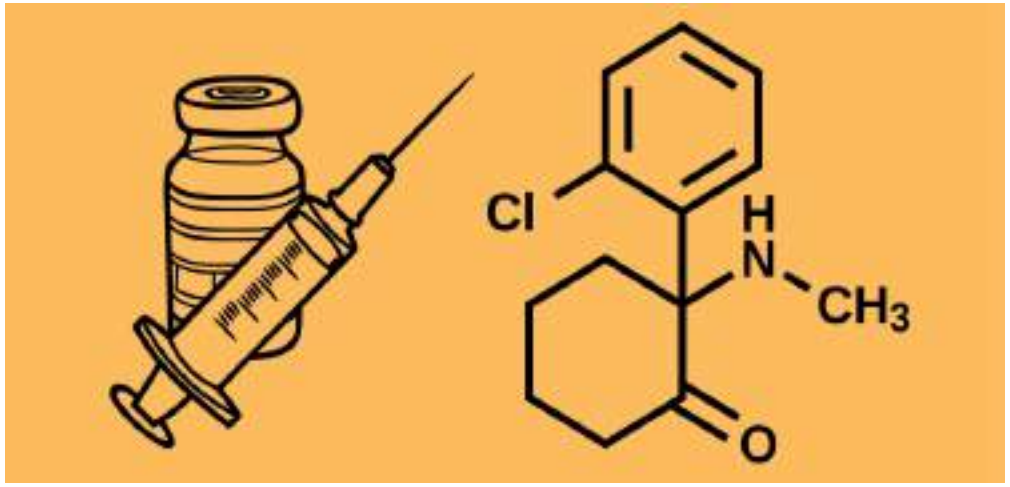
Ketamine

- Sympathomimetic drug
- **Increases BP and HR**
- Bronchodilation
- Increases cerebral blood flow (↑ ICP)



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Ketamine

- Used for depression/anxiety
- "Emergence Reactions"
  - Disorientation
  - Dreams, hallucinations
  - Can be frightening to patients
  - Co-administer midazolam to help

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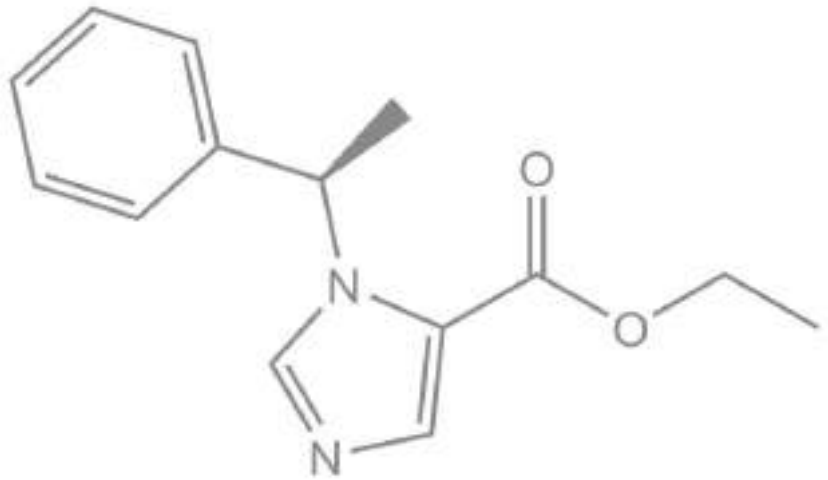
Etomidate

- Binds GABAa receptors → ↑ activity
  - "Potentiates" activity → blocks neuroexcitation
- Anesthesia but not analgesia
- Relatively hemodynamically neutral
  - Good for hypotensive patients
- Used in rapid sequence intubation
- Causes postoperative nausea and vomiting
- May cause myoclonic activity
  - 50-80% patients have muscle twitching/jerking
  - Attenuated with opioids or benzos



etomidate

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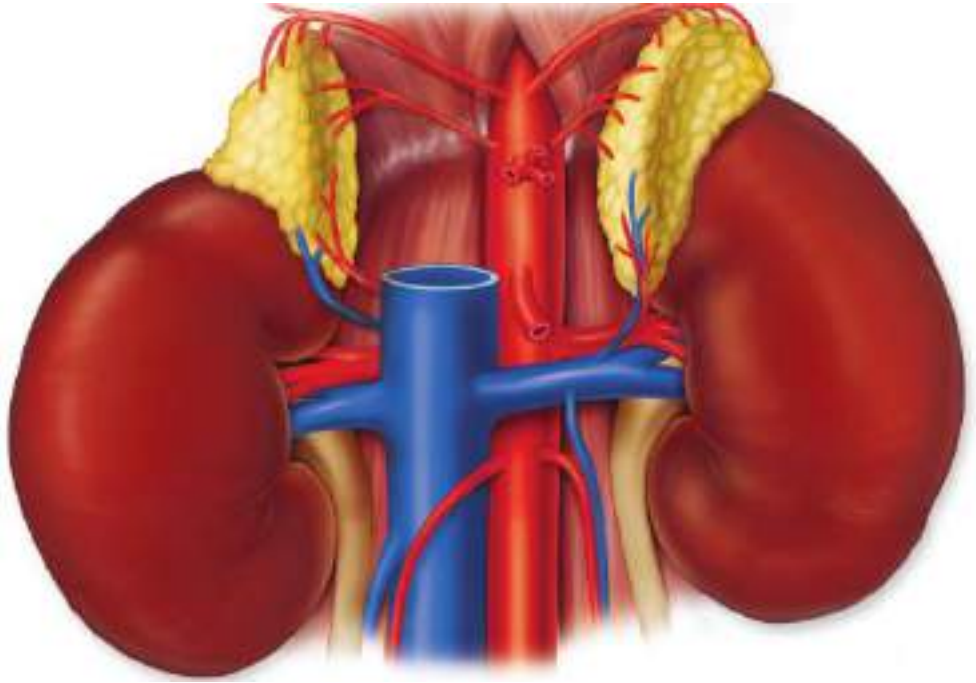
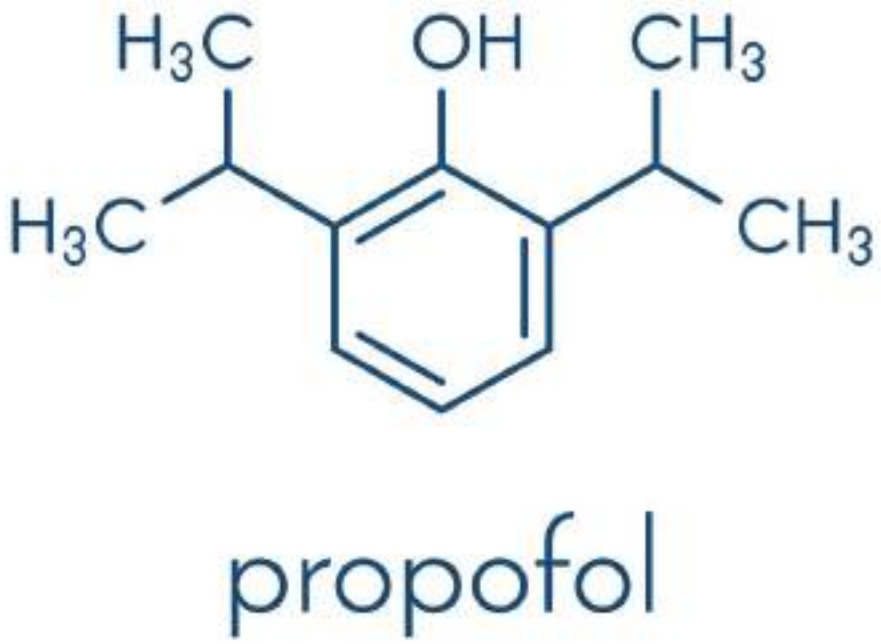
Etomidate

- Brief adrenal insufficiency
- Resolves < 24 hours
- Inhibits 11-beta-hydroxylase
- Cortisol rarely falls below normal range



Propofol

- Potentiates GABAa receptor
- Inhibits NMDA receptor
- Sedation, amnesia
- Respiratory depression
- Myocardial depression, hypotension



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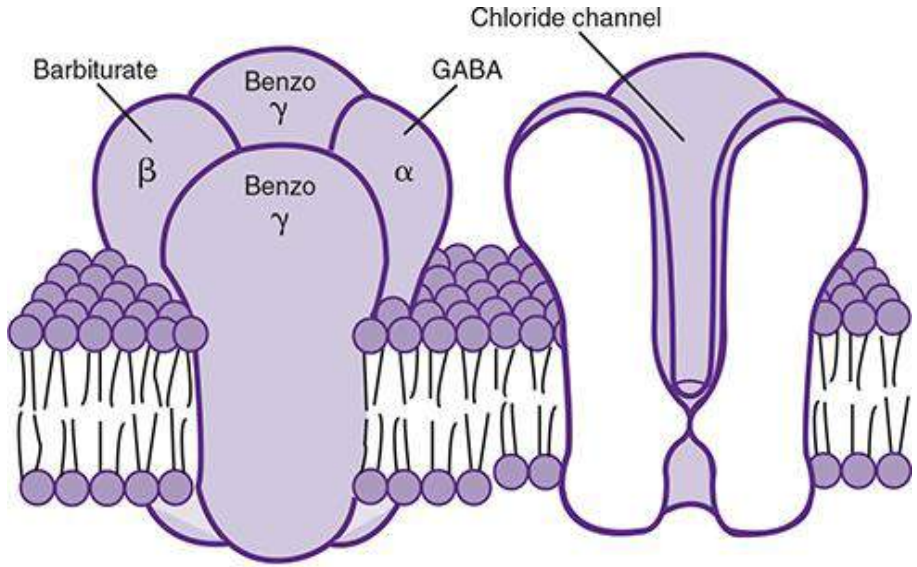
GABA Receptor Anesthetics

- Etomidate
- Propofol
- Benzodiazepines
- Barbiturates
- GABA is largely inhibitory
- These drugs activate receptor → sedation



Source: Charles D. Ciccone: *Pharmacology in Rehabilitation*, 5th Edition:
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Induction and Maintenance

- Induction – Render patient unconscious
  - Propofol, Etomidate, Ketamine
- Maintenance – Maintain unconscious state
  - Propofol, sevoflurane, desflurane

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Typical Open Heart Case

- Induction
  - Propofol, Midazolam
- Paralysis
  - Rocuronium
- Maintenance
  - Sevoflurane, fentanyl

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Rapid Sequence Intubation

- Standard practice for emergent intubation
- Renders patient sedated and flaccid
- Induction: Etomidate
  - Sometimes ketamine, benzos
- Paralysis: Succinylcholine
  - Ideal due to rapid onset/offset
  - Paralysis within 60 seconds
  - Rocuronium used if contraindication
  - HyperK, rhabdo, burns, denervation

A

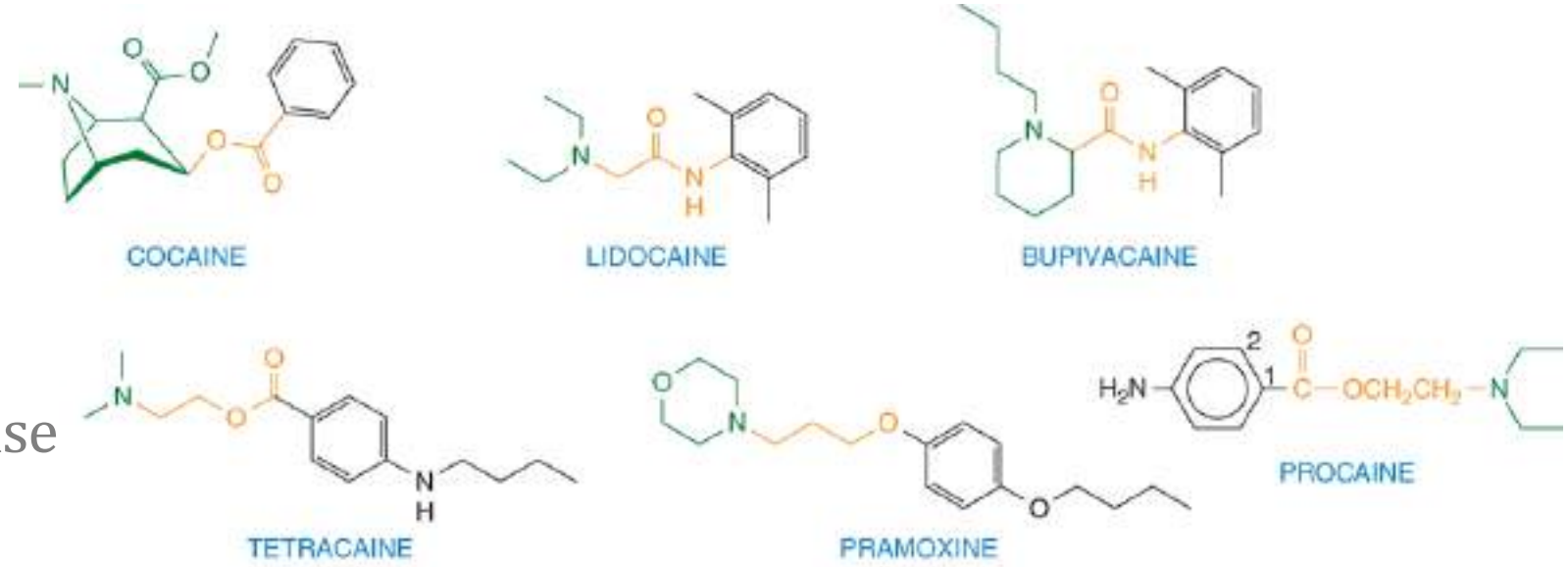
Local Anesthetics

Jason Ryan, MD, MPH

Mc Graw Hill Boards&Beyond

Local Anesthetics

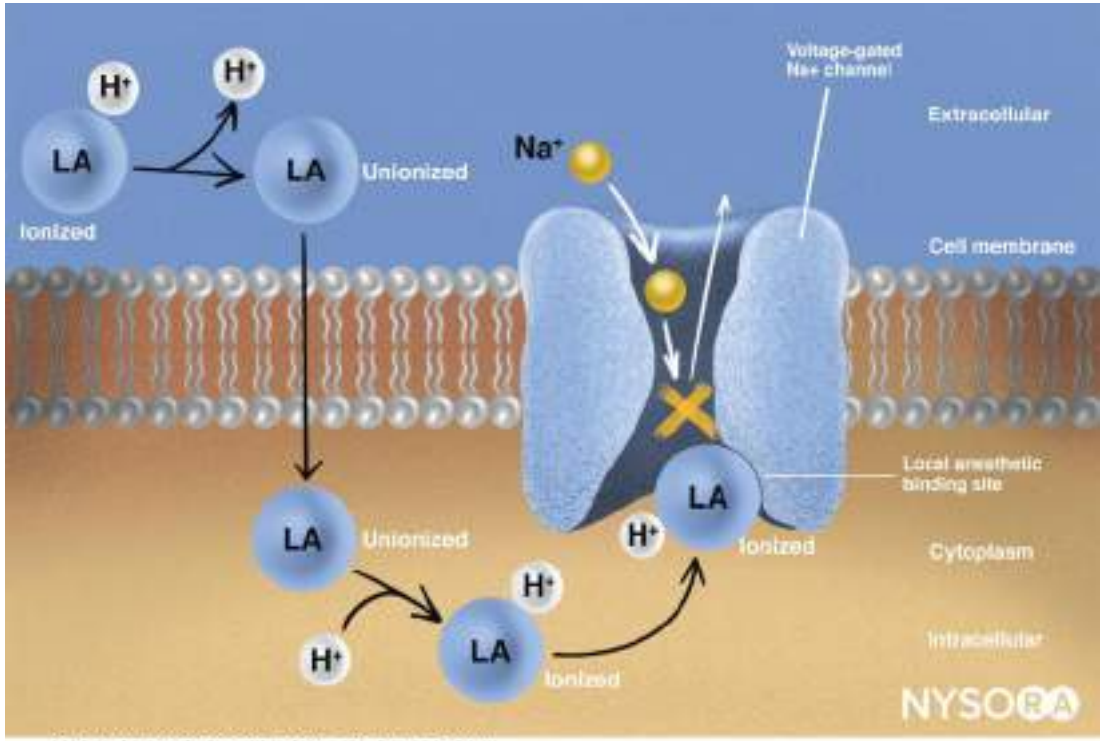
- Amides (2 i's)
  - Lidocaine
  - Mepivacaine
  - Bupivacaine
- Esters (1 i)
  - Procaine
  - Cocaine
  - Benzocaine
  - Tetracaine
- Can vary in allergic response



Local Anesthetics

Mechanism of Action

- Block sodium channels in nerves
- Greater effect on small myelinated nerves



Admir Hadzic: *Hadzic's Peripheral Nerve Blocks and Anatomy for Ultrasound-Guided Regional Anesthesia, 3ed.*

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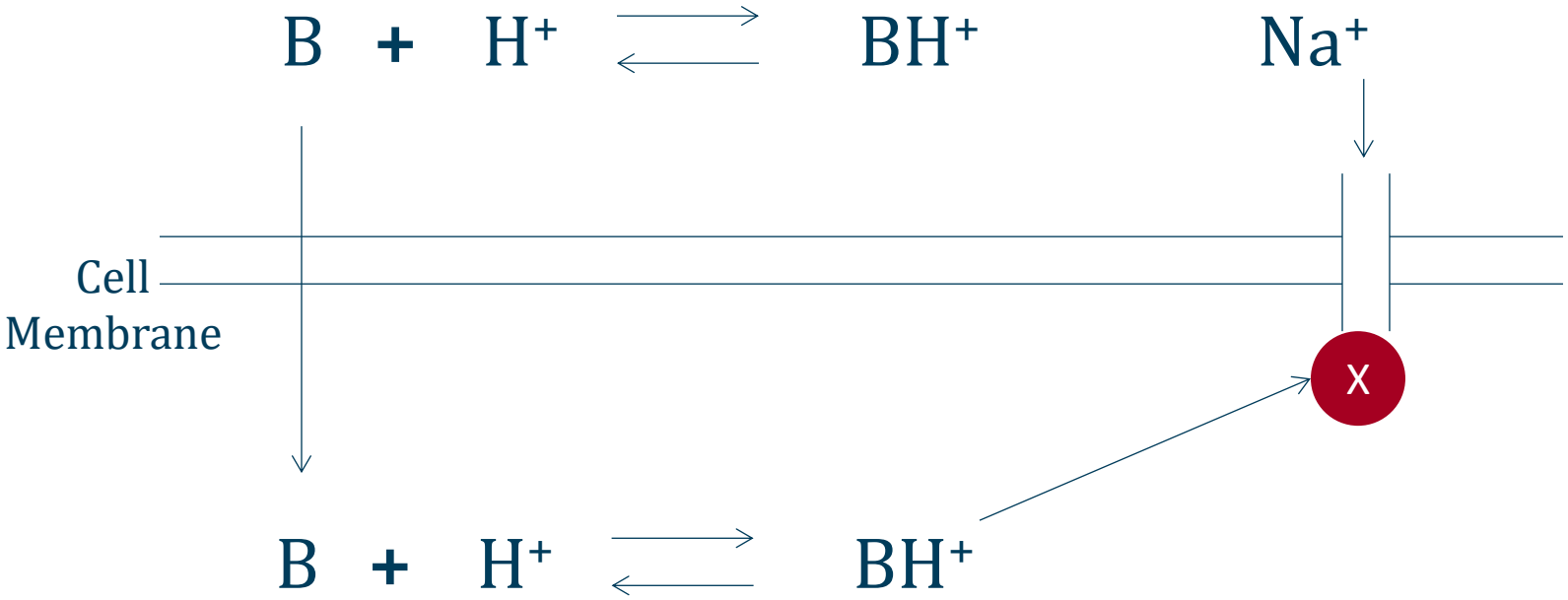
Local Anesthetic



Key Points

1. Uncharged form crosses membrane
2. Charged form blocks Na channel
3. Drugs work on inside of cell membrane
4. Acidic environments (infection) = more drug needed for effect

Local Anesthetic

Onset of Action

- **Determined by pKa**
- pH value with equal ionized/non-ionized forms of drug
- Higher p*K*a = **more ionized form**
- Less ability to cross cell membranes
- Slower onset of action

Drug	pKA
Lidocaine	7.8
Etidocaine	7.9
Prilocaine	8.0
Bupivacaine	8.1
Tetracaine	8.4

Local Anesthetic

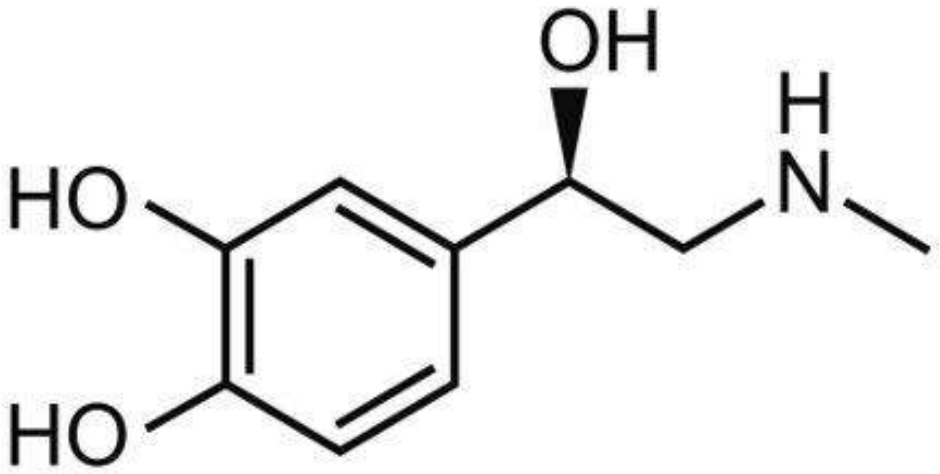
Other Characteristics

- **Potency**
  - Determined by lipid solubility
  - More lipid soluble = more potent
  - Less dose needs to achieve anesthesia
  - Measured by partition coefficient
- **Duration of action**
  - Determined by protein binding
  - High binding = long duration of action

Drug	Lipid Solubility	Protein Binding %
Lidocaine	110	70
Bupivacaine	560	95
Mepivacaine	42	77
Prilocaine	50	55

Adding Epinephrine

- All LA cause vasodilation except cocaine
- LA can be given with epinephrine
  - Causes vasoconstriction
  - Less bleeding
  - Less washout → more local effect



EPINEPHRINE
(Adrenaline)

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Differential Blockade

- Small fibers > large fibers
- Myelinated > unmyelinated

Order of Block	Fiber Type
1	Small, myelinated
2	Small, unmyelinated
3	Large, myelinated
4	Large, unmyelinated

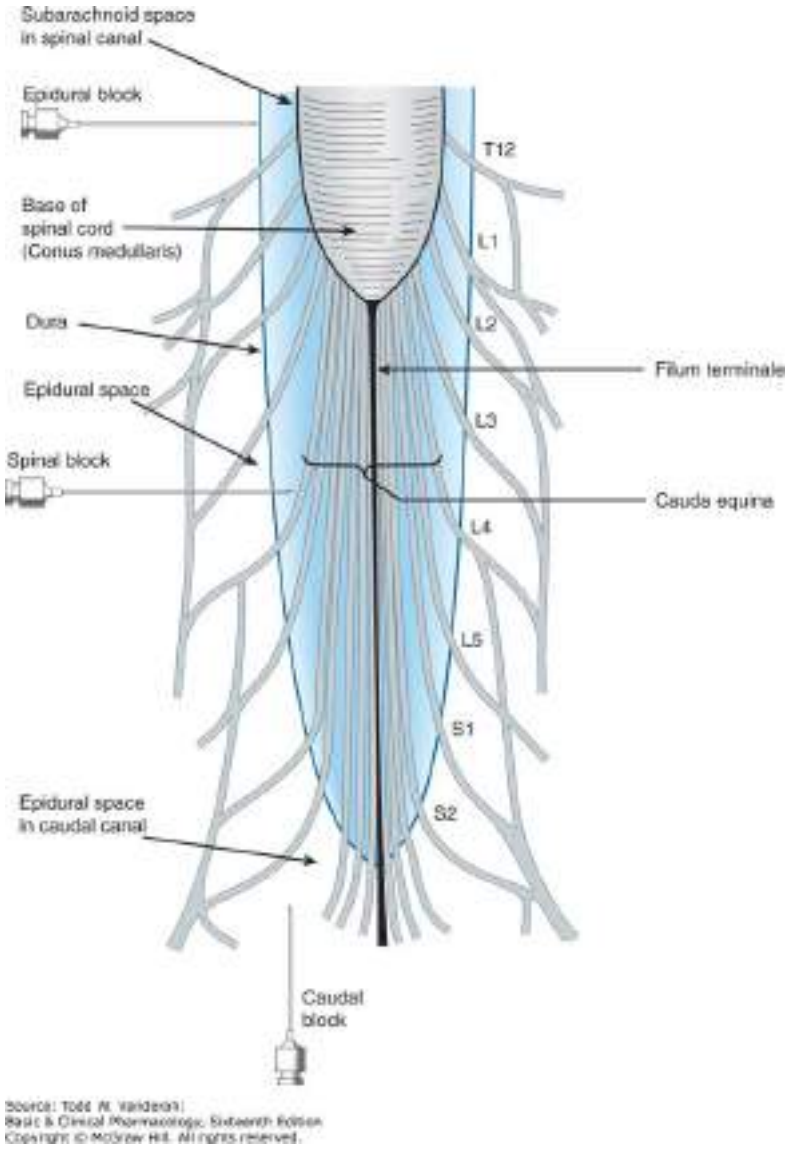
Differential Blockade

- Different effects on different senses
- Pain blocked first
- Pressure sense last

Order of Block	Fiber Type
1	Pain
2	Temp
3	Touch
4	Pressure

Local Anesthetics Uses

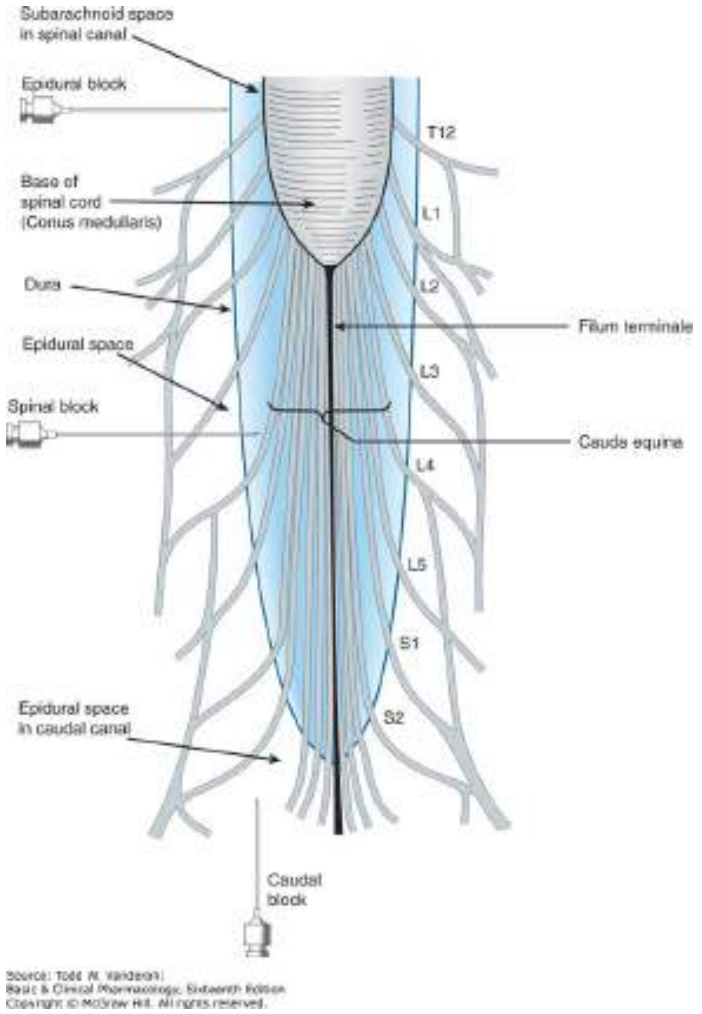
- Minor surgical procedures
- Epidural/spinal anesthesia



Needle Pathway

Epidural and Spinal Anesthesia

- Skin/subcutaneous tissue
- **Supraspinous ligament**
  - Connects tips of spinous processes
- **Interspinous ligament**
  - Between adjacent spinous processes
- **Ligamentum flavum**
  - Thick, elastic ligament – makes a "pop" when needle passes
- Epidural space – drug injected here for epidural anesthesia
- Dura mater – second "pop"
- Arachnoid mater
- Subarachnoid space (CSF) - inject here for spinal anesthesia



Local Anesthetics Side Effects

- CNS Stimulation
  - Initial (excitation): Talkativeness, anxiety, confusion, stuttering speech
  - Later: Drowsiness, coma
- Cardiovascular
  - Most cause vasodilation
  - Cocaine is exception: hypertension, vasoconstriction
  - Also bradycardia, heart block, arrhythmias
- Bupivacaine most cardiotoxic
  - Highly potent

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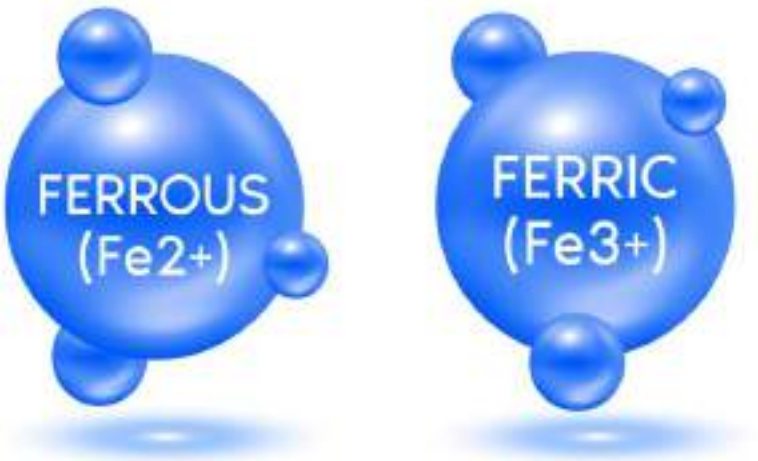
Methemoglobinemia

- Iron in hemoglobin normally reduced (Fe2+; ferrous)
- Certain drug oxidize iron to Fe3+ (ferric)
- When Fe3+ is present → methemoglobin
- Fe3+ cannot bind oxygen
- Remaining Fe2+ cannot release O2 to tissues
- Acquired methemoglobinemia from drugs
  - Local anesthetics (benzocaine)
  - Nitric oxide
  - Dapsone
- Treatment: methylene blue



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Clinical Scenario

- Endoscopy patient
- Benzocaine spray used for throat analgesia
- Post procedure shortness of breath
- “Chocolate brown blood”
- O2 sat (pulse oximetry) = variable (80s-90s)
- PaO2 (blood gas) = normal
- Also premature babies given NO for pulmonary vasodilation

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Neuromuscular Blockers

Jason Ryan, MD, MPH

Mc Graw Hill Boards&Beyond

Types of Anesthesia Drugs

- Inhaled anesthetics
- Intravenous anesthetics
- Local anesthetics
- Neuromuscular blocking agents

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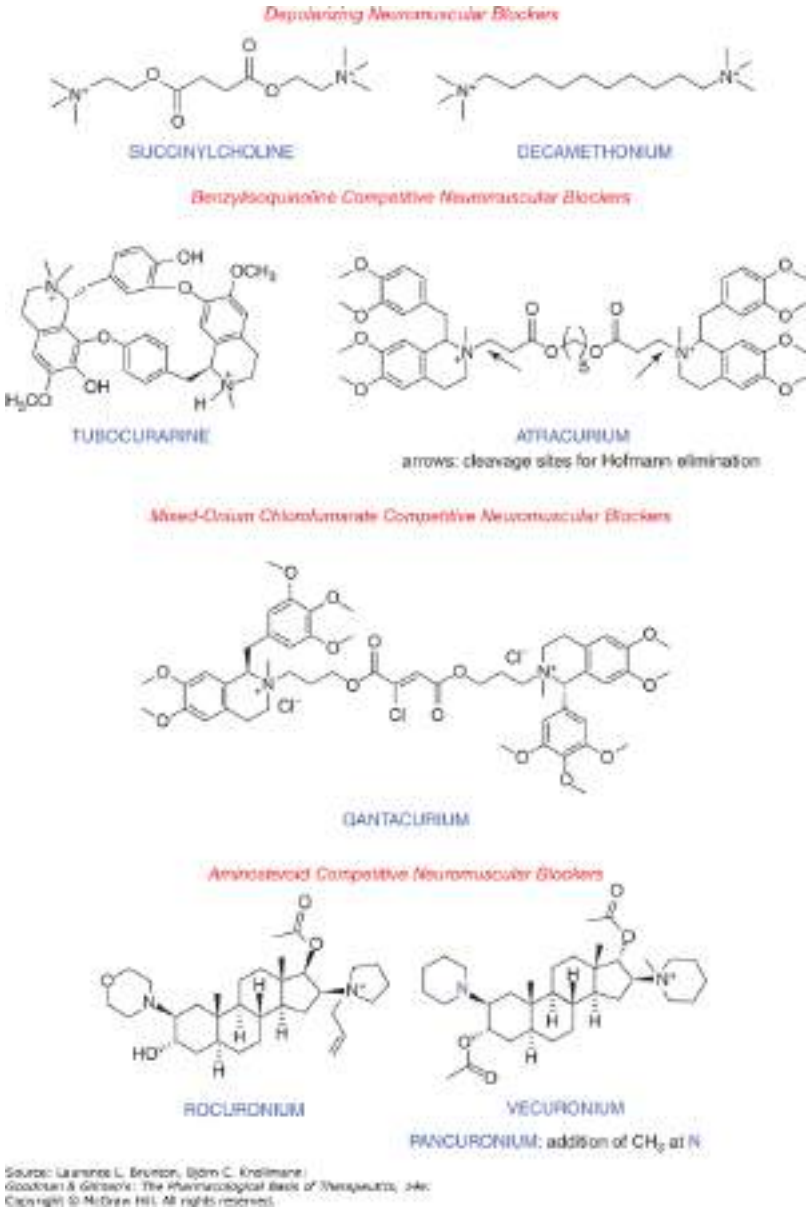
Paralytics

- Tubocurarine
- Atracurium
- Mivacurium
- Pancuronium
- Vecuronium
- Rocuronium
- Succinylcholine



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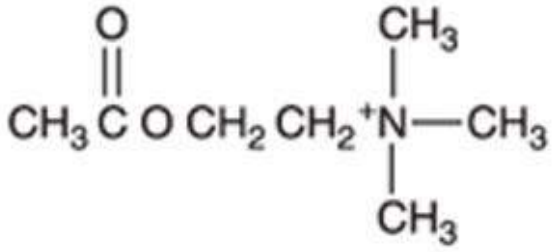
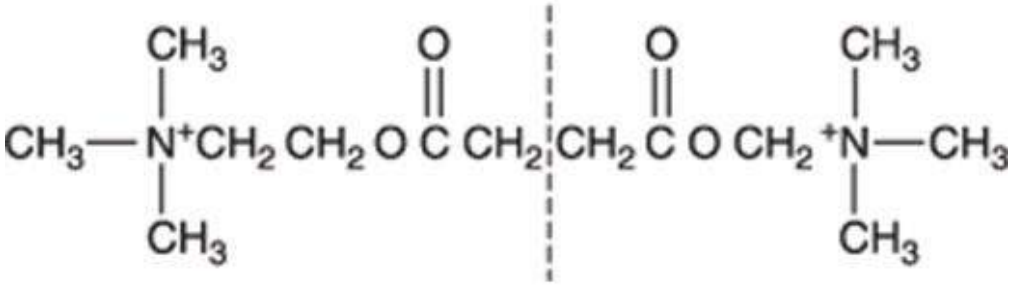
Succinylcholine

- Different from all other paralytics
- **DEPOLARIZING** neuromuscular blocker
- Two ACh molecules joined together
- Strong ACh (nicotinic) receptor agonist
- Sustained depolarization
- Prevents muscle contraction

Acetylcholine

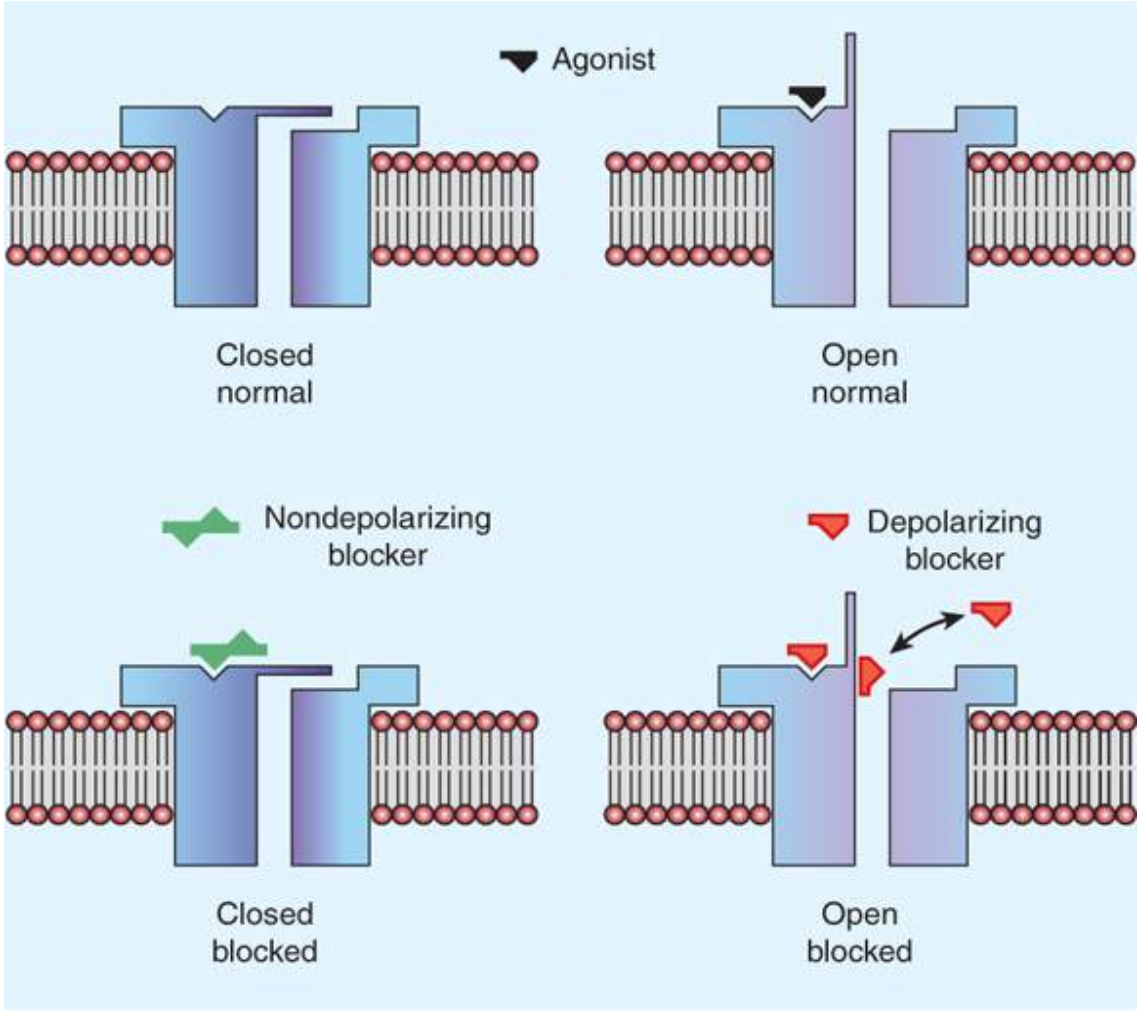


Succinylcholine (diacetylcholine)



Succinylcholine

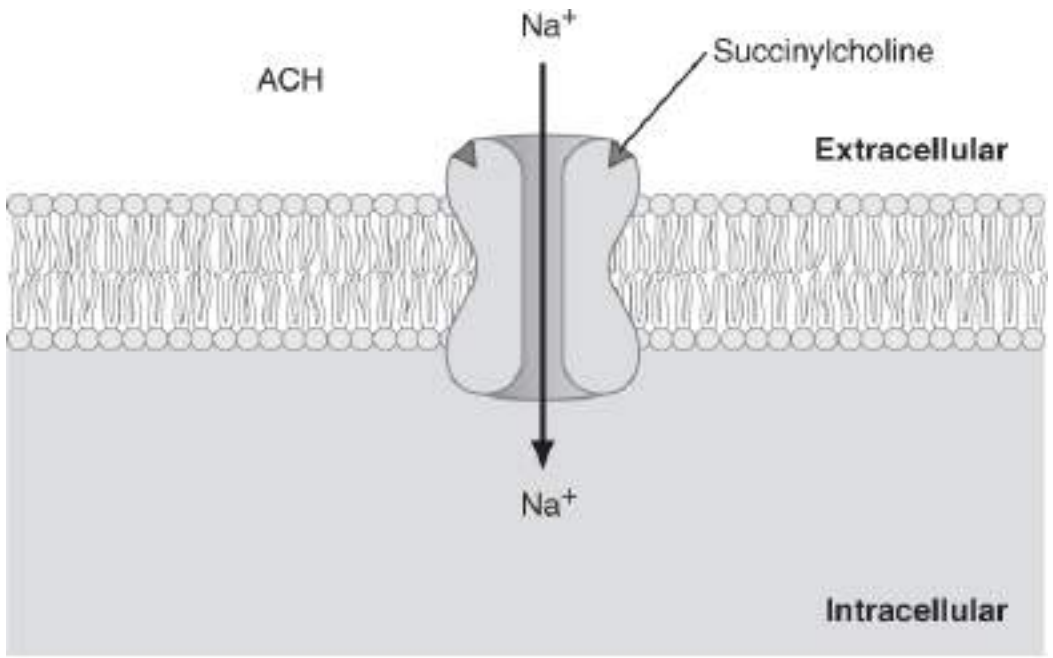
- Two phases to depolarizing block
- Phase 1
  - Depolarizing phase
  - **Muscle fasciculations occur**
- Phase 2
  - Desensitizing phase
  - Depolarization has occurred
  - Muscle no longer reacts to Ach
  - **Flaccid paralysis without fasciculation**



Source: E.E. Jobst, P.C. Panus, M. Kruidering-Hall
Pharmacology for the Physical Therapist, Second Edition

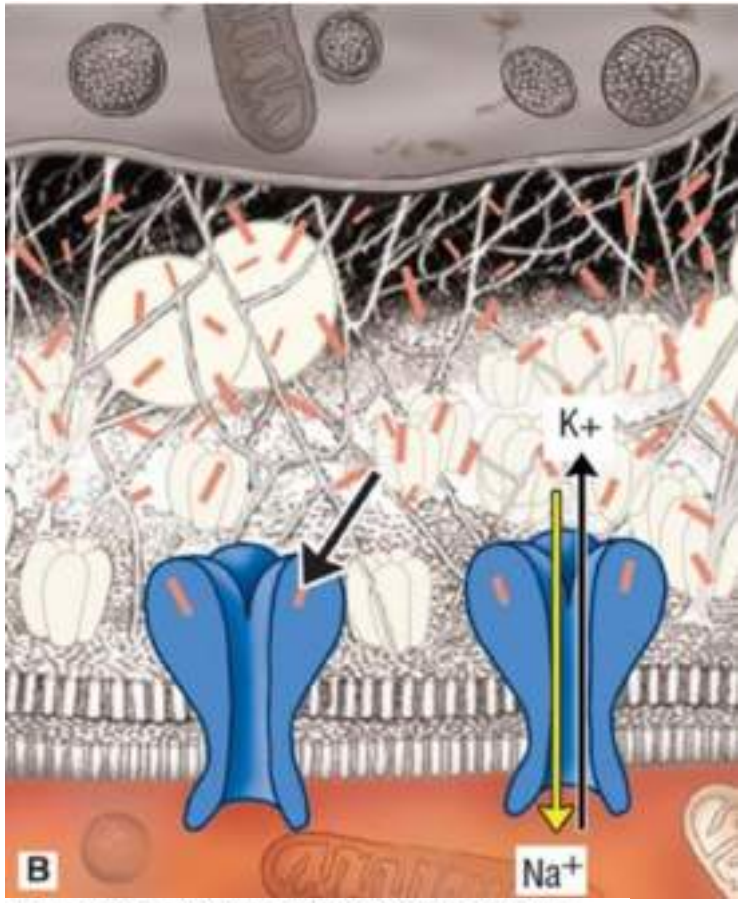
Succinylcholine – Phase 1

- Na channels open and then close - become inactivated
- **Muscle fasciculations occur**
- Membrane potential must reset
- Normally rapid as Ach hydrolyzed by AChE
- Succinylcholine NOT metabolized by AChE
- Prolonged activation of ACh receptors occurs
- No antidote
- Duration 5-10 min
- Desired type of block for brief paralysis



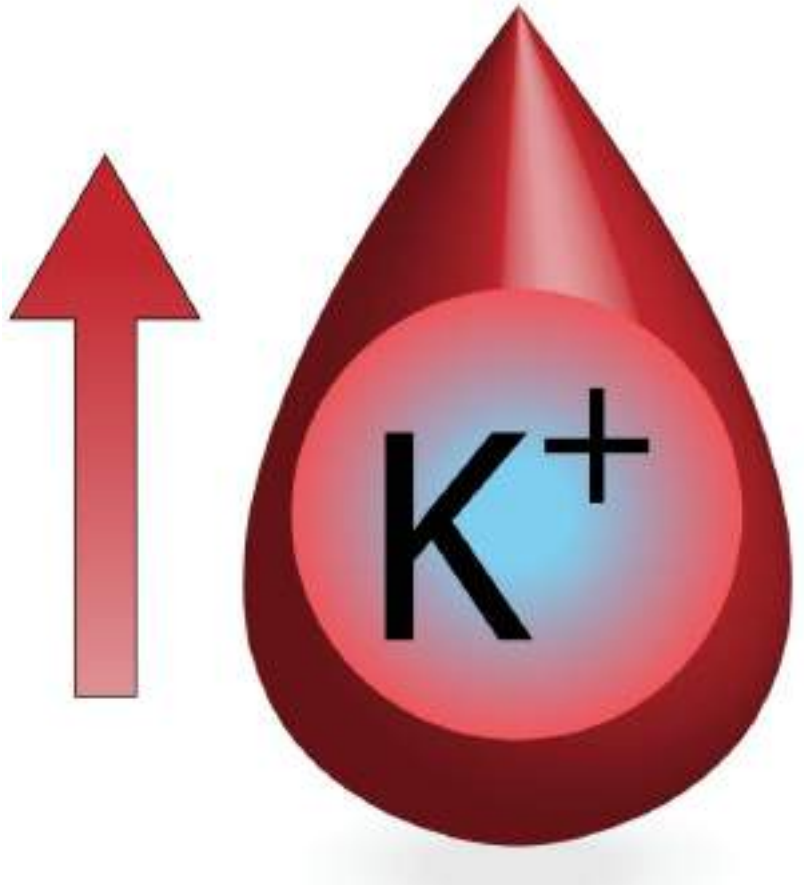
Succinylcholine – Phase 2

- Occurs with repeated doses or prolonged infusion
- **Flaccid paralysis without fasciculation**
- Desensitizing phase
- Normally ACh washed out quickly – no desensitization
- Longer depolarization (succ)→ desensitization
- May be reversed by cholinesterase inhibitors
- Similar to non-depolarizing block
- Duration 20min-several hours



Succinylcholine

- Fast acting
- Rapid washout
- Main side effect is ↑K
  - Caution in burn patients, dialysis patients
- Pseudocholinesterase deficiency
- Malignant hyperthermia



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Pseudocholinesterase Deficiency

- Unable to metabolize succinylcholine
- Prolonged paralysis
- “Slow to wake up” from anesthesia

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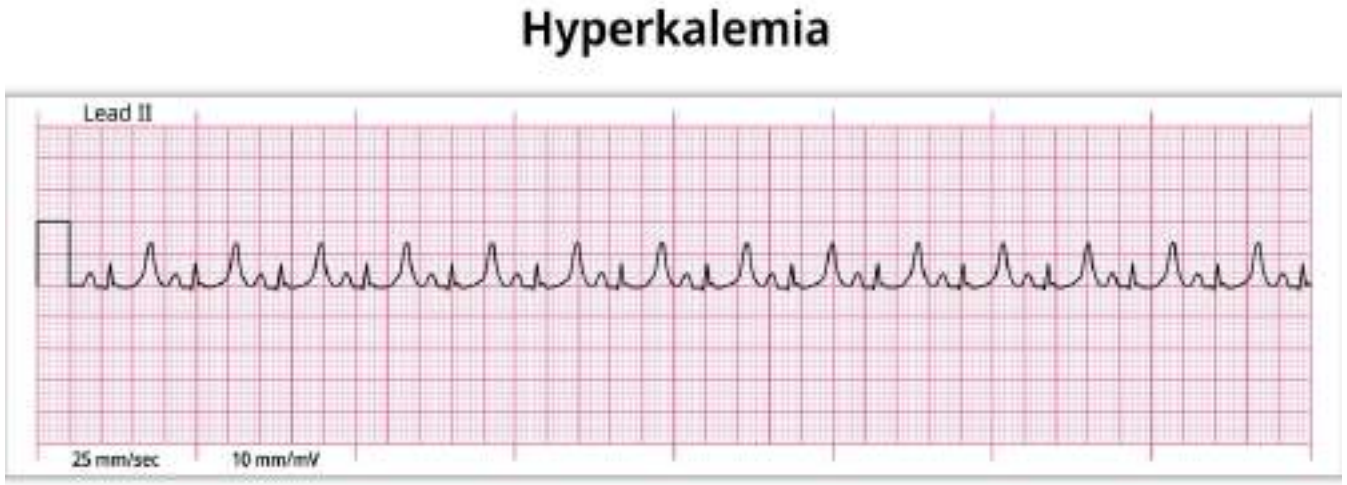
Succinylcholine

Adverse Effects

- Exaggerated hyperkalemia
- May cause life-threatening arrhythmia
- Especially in the setting of burn/crush injury
- Especially denervating quadriplegia (receptor upregulation)
- MG have altered receptor sensitivity



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Malignant Hyperthermia

- Rare, dangerous reaction to drugs:
  - Inhaled anesthetics (sevoflurane, desflurane, isoflurane)
  - Succinylcholine in susceptible patients
- De novo or inherited (AD) mutations
- Ryanodine receptor (RYR1)
- Dihydropyridine receptors (DHPR)

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Malignant Hyperthermia

- High fever, muscle rigidity after/during surgery
- Tachycardia, hypertension
- Muscle damage (rhabdomyolysis): ↑K, CK
- Symptoms occur 1-12 hours after exposure

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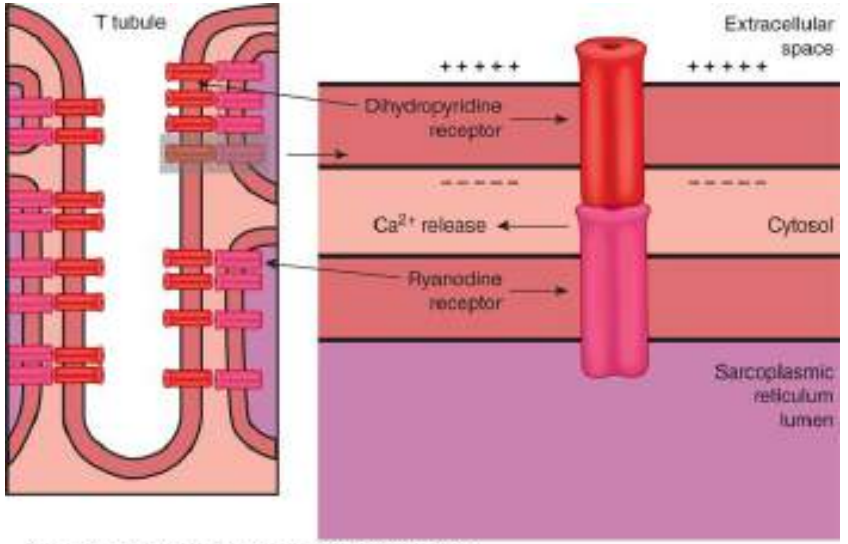
Malignant Hyperthermia

- Cause: ryanodine receptor sarcoplasmic reticulum
  - Ca channel in SR of muscle cells
  - Ca leads to consumption of ATP for SR reuptake
  - Sustained muscle contraction
  - ATP consumption leads to heat & therefore tissue damage
- Treat with dantrolene (ryanodine receptor antagonist)

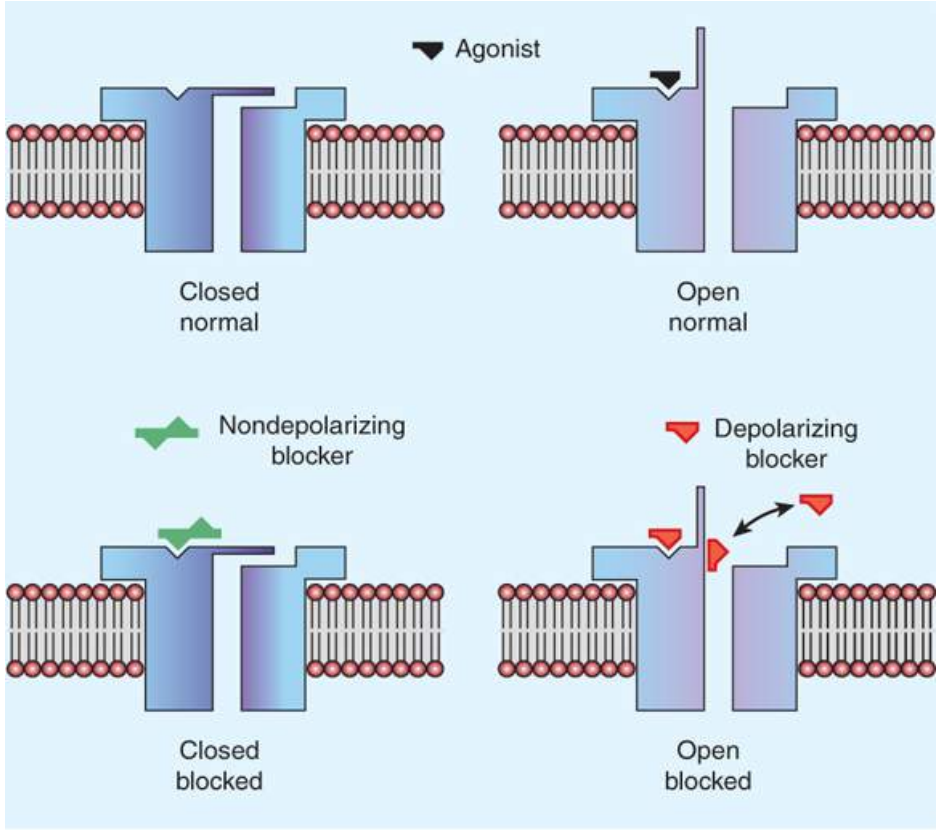


Source: K.E. Barrett, S.M. Barman, H.L. Brooks, Jason X.J. Yuan: Ganong's Review of Medical Physiology, Twenty-Sixth Edition

Non-depolarizing NMBA

Tubocurarine, Atracurium, Mivacurium, Pancuronium, Vecuronium, Rocuronium

- Competitive antagonists to ACh
- Compete with ACh for nicotinic receptors
- Produce paralysis
- Many cause marked histamine release
  - Hypotension → compensatory tachycardia
- Can be reversed by flooding synapse with ACh
- Done by inhibiting AChE



Source: E.E. Jobst, P.C. Panus, M. Kruidering-Hall
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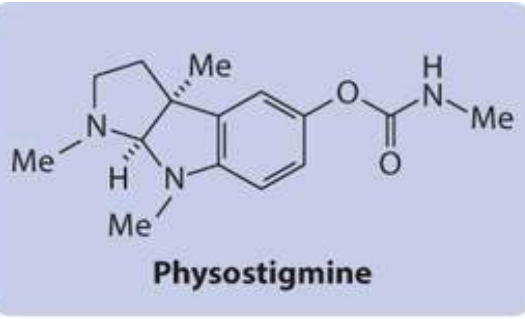
AChE Inhibitors

Reversal of non-depolarizing neuromuscular blockers

- Physostigmine
- Neostigmine
- Pyridostigmine
- Edrophonium
- Often given with anticholinergics
  - Atropine, glycopyrrolate
  - Prevent muscarinic effects like bradycardia

Neostigmine

Pyridostigmine



Physostigmine

Critical Illness Neuropathy/Myopathy

- Occurs in critically ill patients requiring ICU treatment
- Increased risk with older age
- May be associated with NMBA

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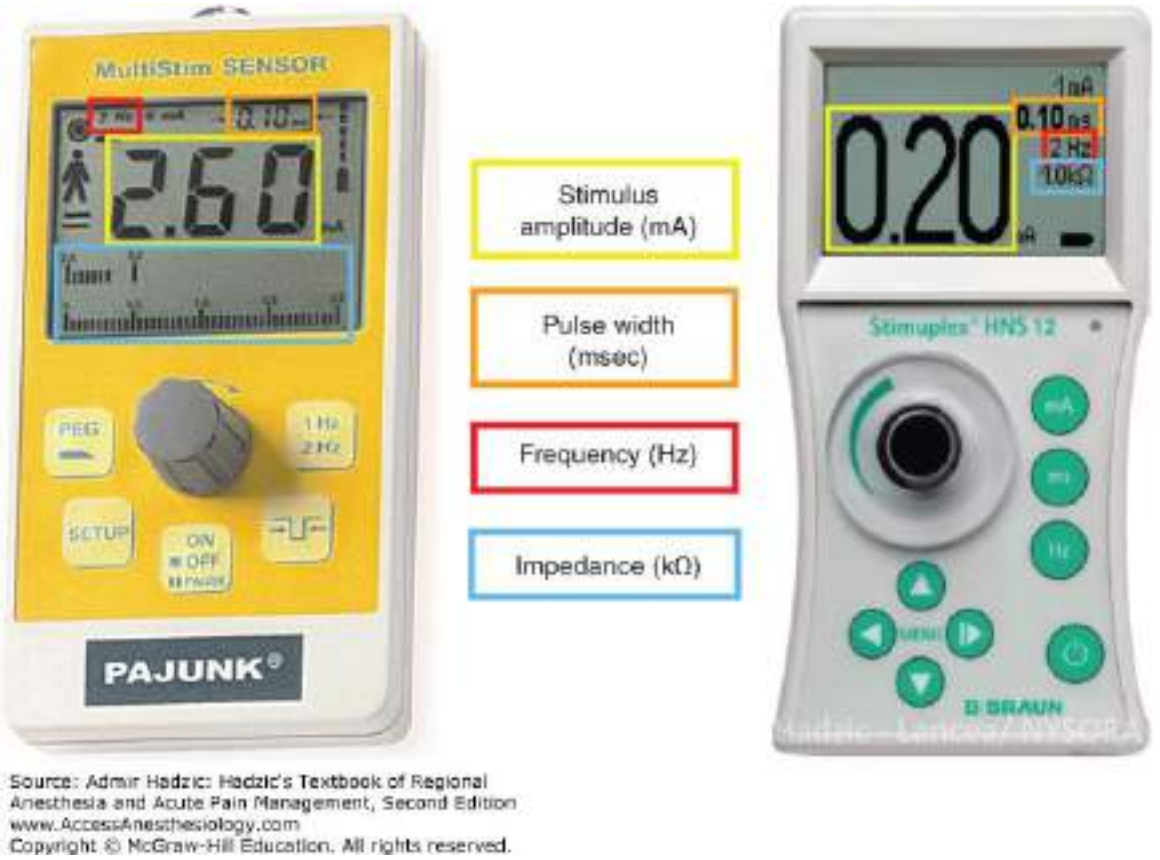
Assessing Neuromuscular Blockade

- Peripheral nerve stimulator
- Train of 4 impulses



Source: Admir Hadzic: Hadzic's Textbook of Regional Anesthesia and Acute Pain Management, Second Edition
www.AccessAnesthesiology.com

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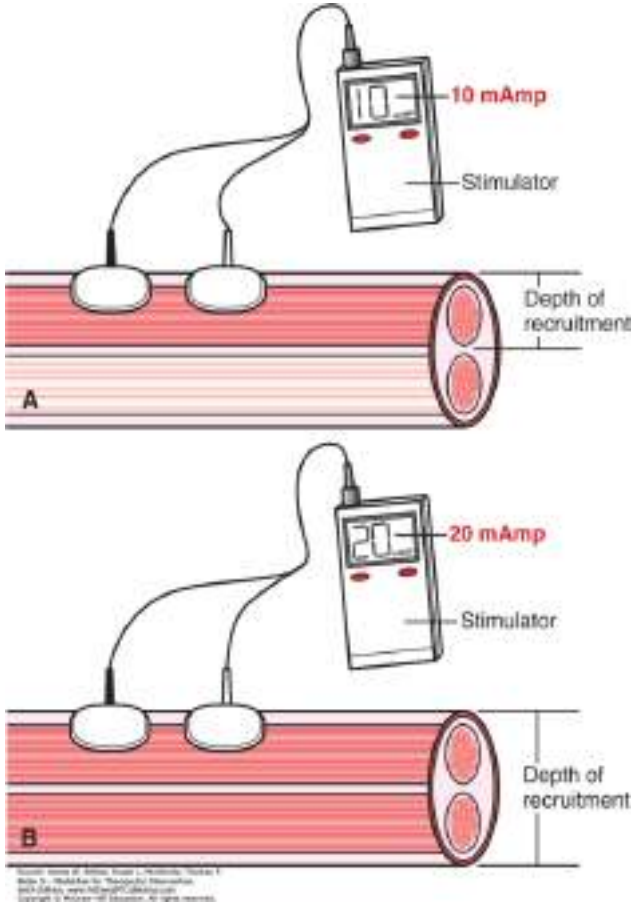
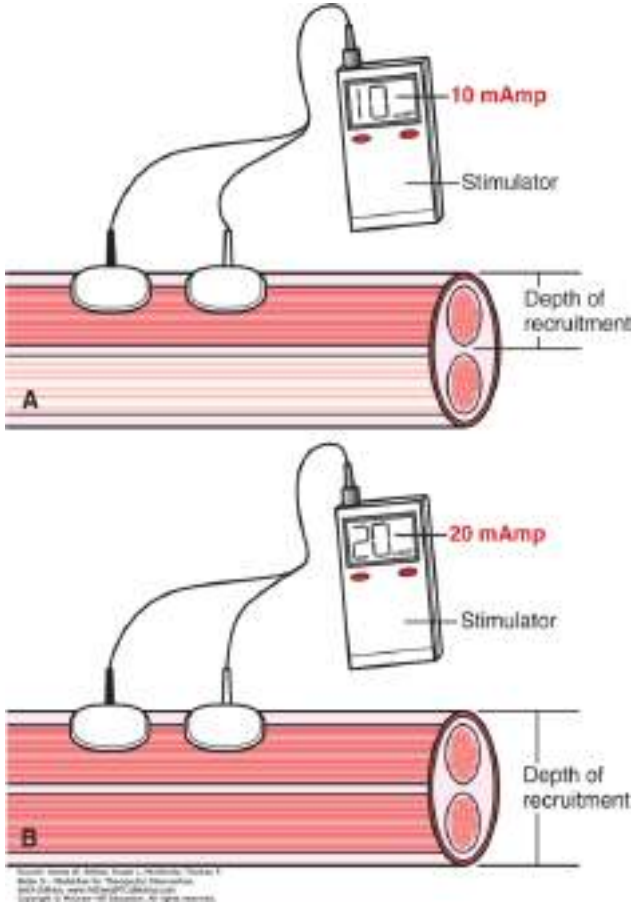
Train of 4

- Used to assess neuromuscular blockade in patients under anesthesia
- 4 electrical stimulations to nerve (i.e. ulnar)
  - Watch for finger twitches
- Goal usually 1/4 or 2/4
- Zero = all receptors blocked
  - No more drug needed
- Four = <75% of receptors blocked
  - May need more drug
  - Or may be okay to extubate



Train of 4

- **Nondepolarizing blockers**
  - Fade pattern
  - Progressively decreasing amplitude of responses
  - More block = twitches disappear
  - Fourth → third → second → first
- **Succinylcholine**
  - No fade pattern
  - All four twitches decline similarly
  - Unless phase 2 block: fade pattern



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