

Pharmacology

Drugs That Affect The:
Nervous System

Topics

- Analgesics and antagonists
- Anesthetics
- Anti-anxiety and sedative-hypnotics
- Anti-seizure / anti-convulsants
- CNS stimulators
- Psychotherapeutics
- ANS/PNS/SNS agents

But first...

A colorful review of
neurophysiology!

Nervous System

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graph TD; A[Nervous System] --> B[CNS]; A --> C[PNS]; C --> D[Autonomic]; C --> E[Somatic]; D --> F[Sympathetic]; D --> G[Parasympathetic];
```

CNS

PNS

Autonomic

Somatic

Sympathetic

Parasympathetic

Analgesics

- Decrease in sensation of pain.
- Classes:
 - Opioid.
 - Agonist.
 - Antagonist.
 - Agonist-antagonist.
 - Non-opioids.
 - Salicylates.
 - NSAIDs.
 - Adjuncts.

Opioids

- Generic reference to morphine-like drugs/actions
 - Opiate: derivative of opium
- Prototype: morphine
 - Morpheus: god of dreams
- Act on endorphin receptors:
 - Mu (most important)
 - Kappa



Actions of Opioid Receptors

Response	Mu	Kappa
Analgesia	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Respiratory Depression	<input checked="" type="checkbox"/>	
Sedation	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Euphoria	<input checked="" type="checkbox"/>	
Physical Dependence	<input checked="" type="checkbox"/>	
↓ GI motility	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Actions at Opioid Receptors

Drugs	Mu	Kappa
Pure Agonists -morphine, codeine, meperidine (Demerol [®]), fentanyl (Sublimaze [®]), remifentanyl (Ultiva [®]), propoxyphene (Darvon [®]), hydrocodone (Vicodin [®]), oxycodone (Percocet [®])	Agonist	Agonist
Agonist-Antagonist -nalbuphine (Nubaine [®]), butorphanol (Stadol [®])	Antagonist	Agonist
Pure Antagonist -naloxone (Narcan [®])	Antagonist	Antagonist

General Actions of Opioids

- Analgesia
- Respiratory depression
- Constipation
- Urinary retention
- Cough suppression
- Emesis
- Increased ICP
 - Indirect through CO₂ retention

- Euphoria/Dysphoria
- Sedation
- Miosis
 - Pupil constriction
- ↓↓ Preload & afterload
 - Watch for hypotension!

Non-opioid Analgesics

- Salicylates
 - Aspirin (Bayer[®]) * (prototype for class)
- Non-Steroidal Anti-Inflammatory Drugs
 - Ibuprofen (Motrin[®], Advil[®])
 - Propionic Acid derivative
 - Naproxen (Naprosyn[®])
 - Naproxen sodium (Aleve[®])
 - All compete with aspirin for protein binding sites
 - Ketorolac (Toradol[®])

NSAID Properties

Drug	Fever	Inflammation	Pain
Aspirin	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Ibuprofen	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Acetaminophen	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>

Aspirin Mechanism of Action

- Inhibit synthesis of cyclooxygenase (COX)
 - Enzyme responsible for synthesis of:

Prostaglandins

- Pain response
- Suppression of gastric acid secretion
- Promote secretion of gastric mucus and bicarbonate
- Mediation of inflammatory response
- Production of fever
- Promote renal vasodilation (↑ blood flow)
- Promote uterine contraction

Thromboxane A₂

- Involved in platelet
- aggregation

Aspirin Effects

Good

- Pain relief
- ↓↓ Fever
- ↓↓ Inflammation

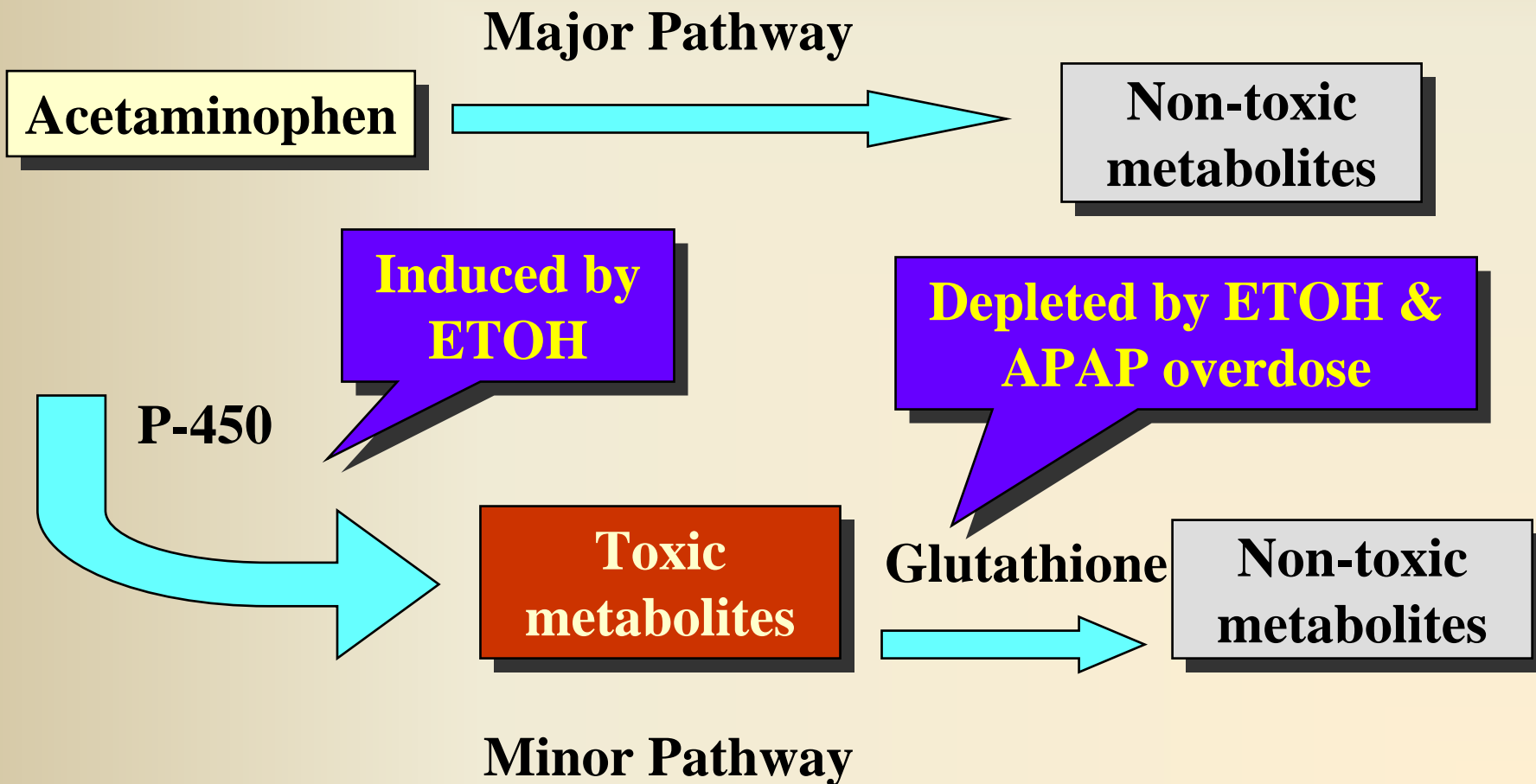
Bad

- GI ulceration:
 - ↑↑ Gastric acidity
 - ↓↓ GI protection
- ↑↑ Bleeding
- ↓↓ Renal elimination
- ↓↓ Uterine contractions during labor

Acetaminophen (Tylenol®)

- NSAID similar to aspirin
- Only inhibits synthesis of CNS prostaglandins
 - Does not have peripheral side effects of ASA:
 - Gastric ulceration
 - ↓↓ Platelet aggregation
 - ↓↓ Renal flow
 - ↓↓ Uterine contractions

Acetaminophen Metabolism



Anesthetics

- Loss of all sensation
 - Usually with loss of consciousness
 - ↓ propagation of neural impulses
- General anesthetics
 - Gases
 - Nitrous oxide (Nitronox[®]), halothane, ether
 - IV
 - Thiopental (Pentothal[®]), methohexital (Brevitol[®]), diazepam (valium[®]), remifentanil (Ultiva[®])

Anesthetics

- Local
 - Affect on area around injection
 - Usually accompanied by epinephrine
 - Lidocaine (Xylocaine[®]), topical cocaine

Anti-anxiety & Sedative-hypnotic Drugs

- Sedation: ↓ anxiety & inhibitions
- Hypnosis: instigation of sleep
- Insomnia
 - ↑ Latent period
 - ↑ Wakenings
- Classes:
 - Barbiturates
 - Benzodiazepines
 - Alcohol

**Chemically different,
Functionally similar**

Mechanism of action

- Both promote the effectiveness of GABA receptors in the CNS
 - Benzodiazepines promote only
 - Barbiturates promote and (at high doses) stimulate GABA receptors
- GABA = chief CNS inhibitory neurotransmitter
 - Promotes hyperpolarization via $\uparrow\uparrow$ Cl^- influx

Benzodiazepines vs. Barbiturates

Criteria	BZ	Barb.
Relative Safety	High	Low
Maximal CNS depression	Low	High
Respiratory Depression	Low	High
Suicide Potential	Low	High
Abuse Potential	Low	High
Antagonist Available?	Yes	No

Benzodiazepines

Benzodiazepines

- diazepam (Valium[®])
- midazolam (Versed[®])
- alprazolam (Xanax[®])
- lorazepam (Ativan[®])
- triazolam (Halcion[®])

“Non-benzo benzo”

- zolpidem (Ambien[®])
- buspirone (BusPar[®])

Barbiturates

Subgroup	Prototype	Typical Indication
Ultra-short acting	thiopental (Pentothol [®])	Anesthesia
Short acting	secobarbital (Seconal [®])	Insomnia
Long acting	phenobarbital (Luminal [®])	Seizures

Barbiturates

- amobarbital (Amytal[®])
- pentobarbital (Nembutal[®])
- thiopental (Pentothal[®])
- phenobarbital (Luminal[®])
- secobarbital (Seconal[®])

Anti-seizure Medications

- Seizures caused by hyperactive brain areas
- Multiple chemical classes of drugs
 - All have same approach
 - Decrease propagation of action potentials
 - \Downarrow Na^+ , Ca^{++} influx (delay depolarization/prolong repolarization)
 - \Uparrow Cl^- influx (hyperpolarize membrane)

Anti-Seizure Medications

Benzodiazepines

- diazepam (Valium®)
- lorazepam (Ativan®)

Barbiturates

- phenobarbital (Luminal®)

Ion Channel Inhibitors

- carbamazepine (Tegretol®)
- phenytoin (Dilantin®)

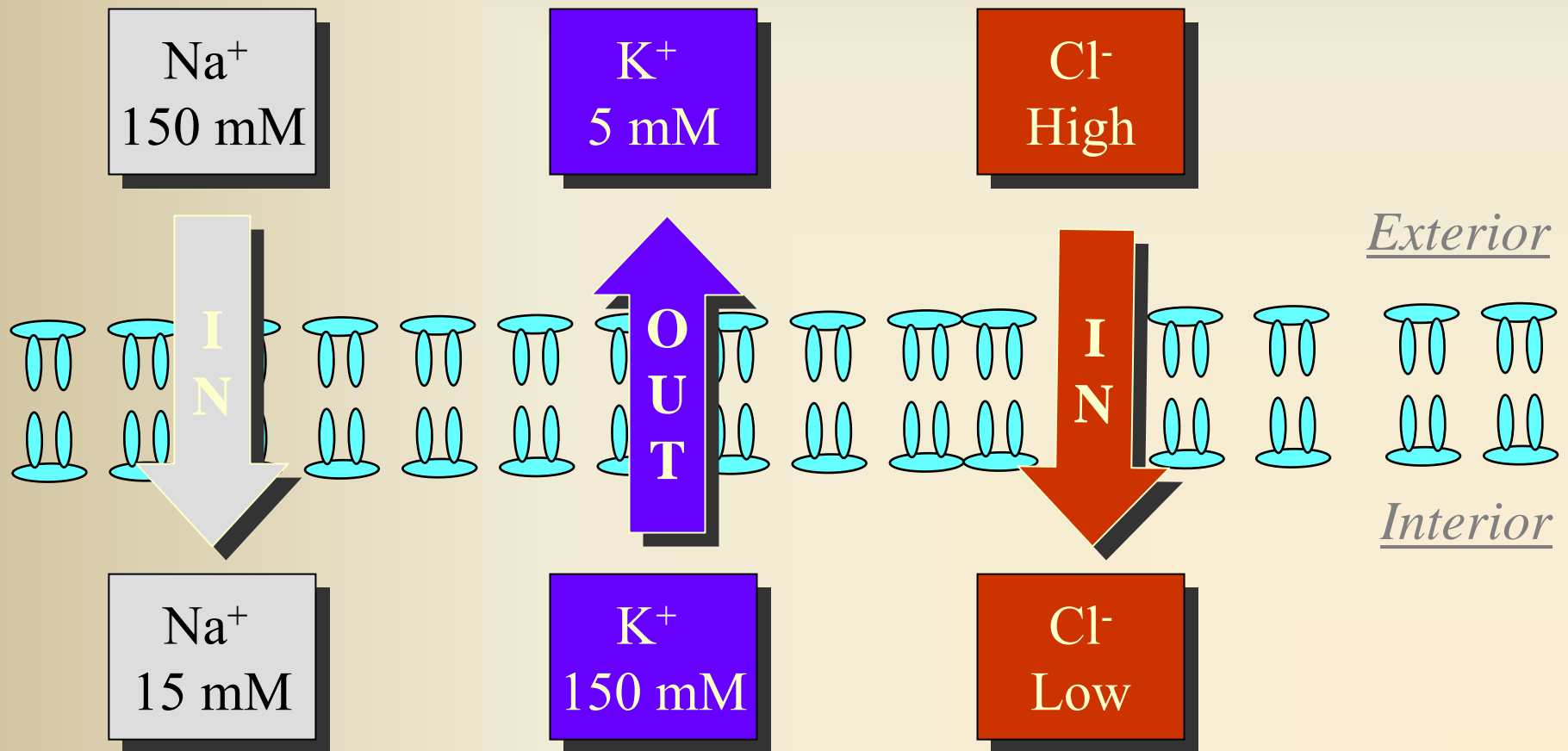
Misc. Agents

- valproic acid (Depakote®)

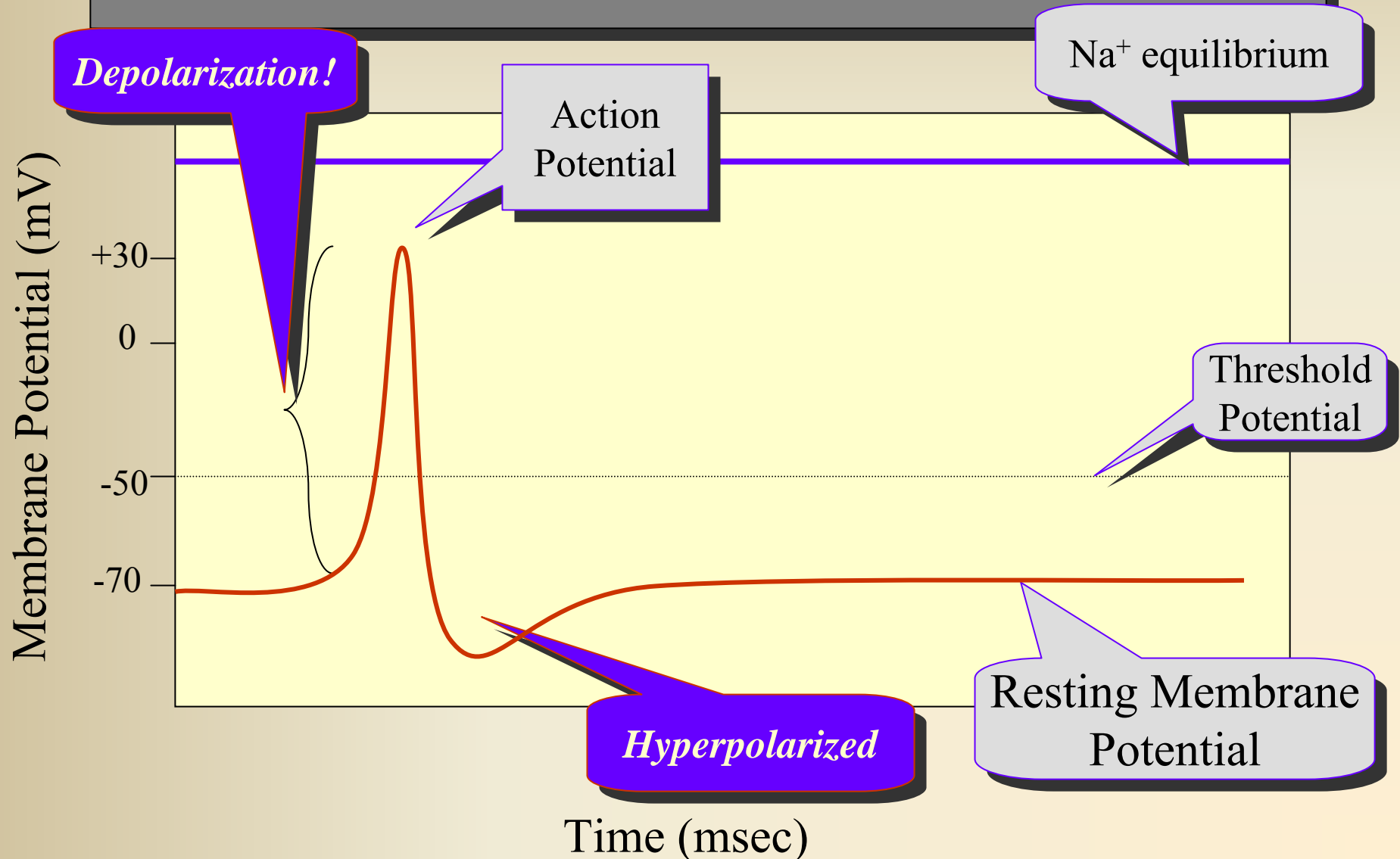
Ion Diffusion

- Key to neurophysiology
- Dependent upon:
 - Concentration gradient
 - Electrical gradient
- Modified by:
 - ‘Gated ion channels’

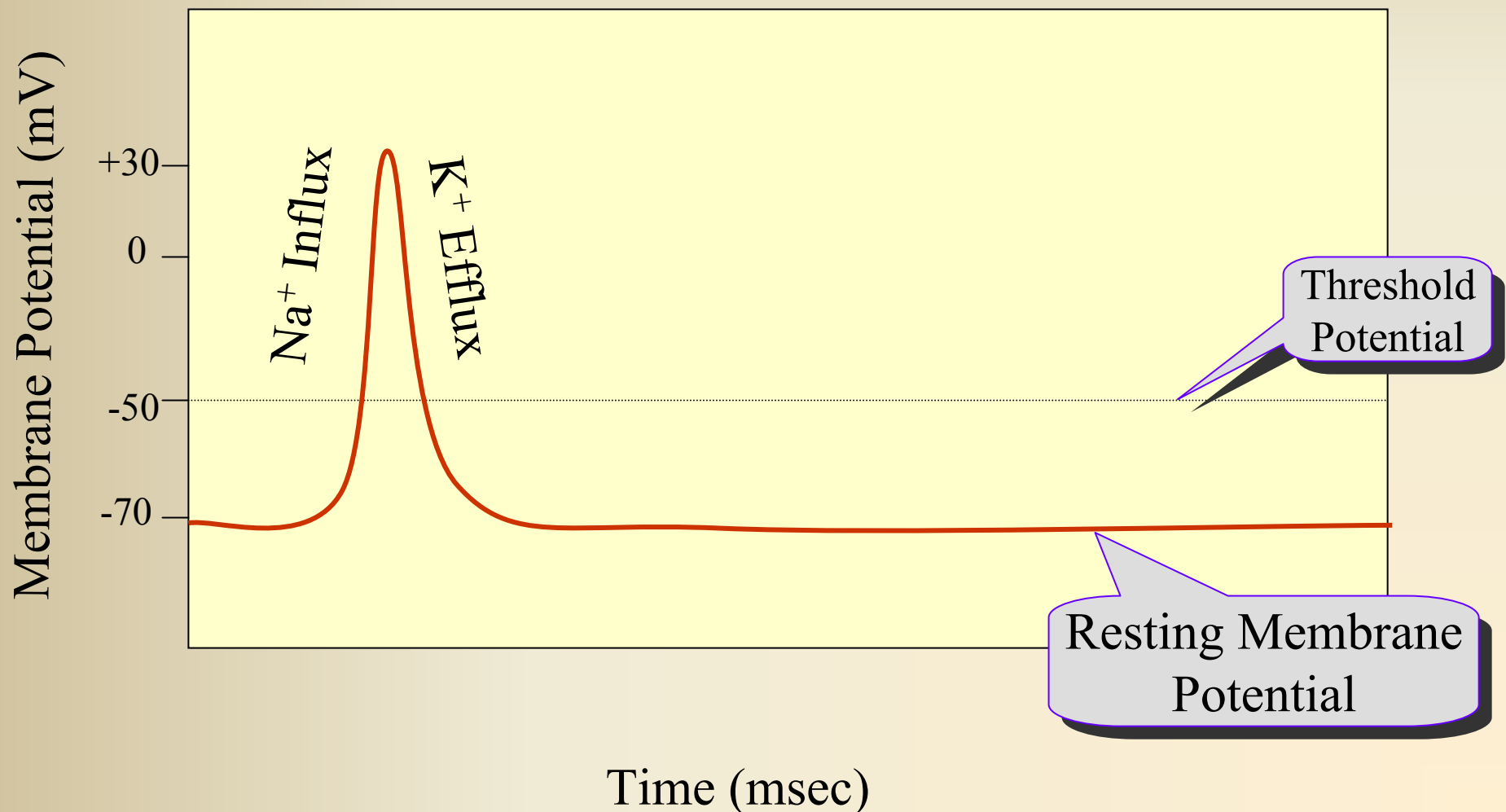
Where Does Diffusion Take the Ion?



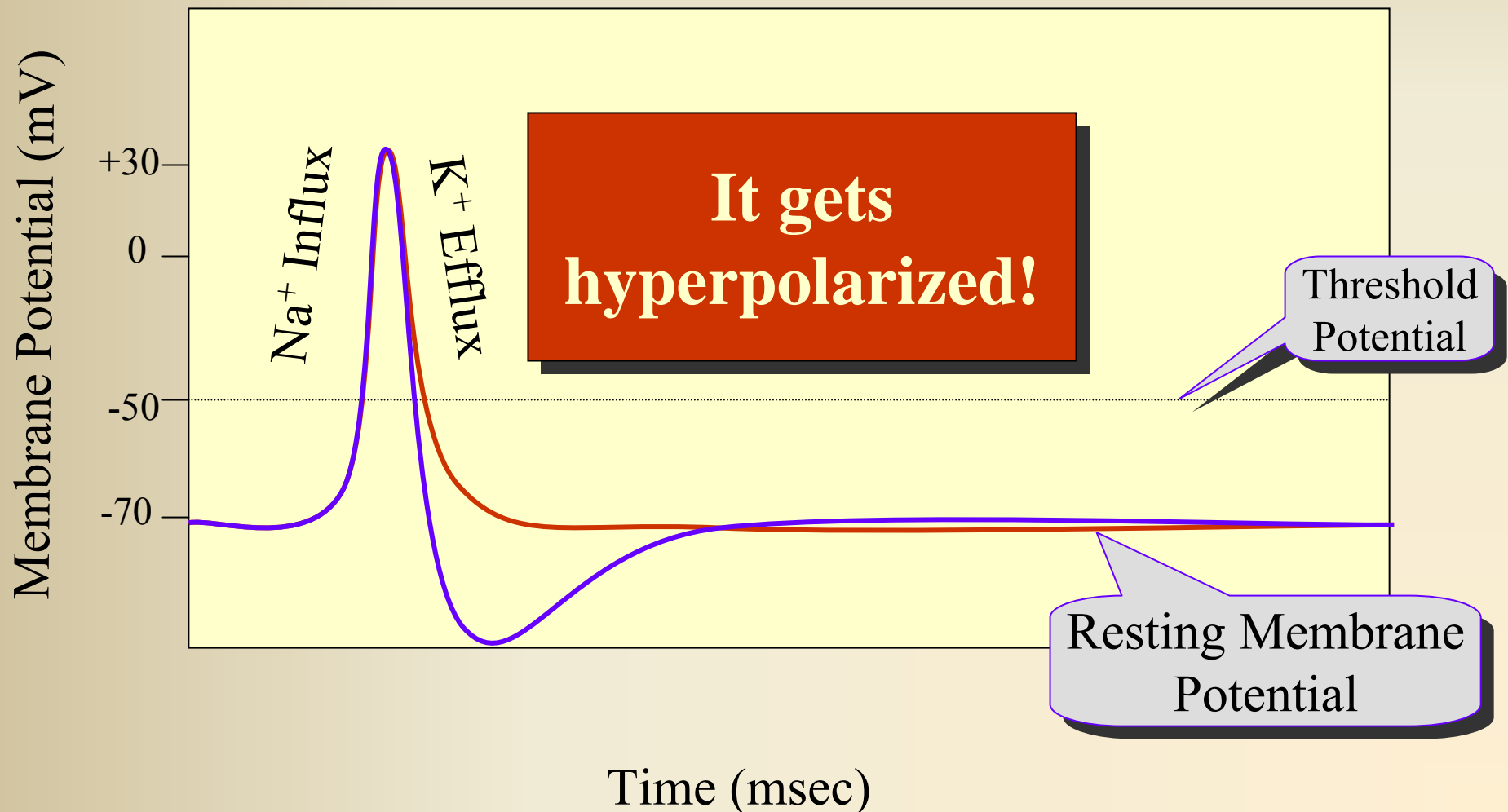
Action Potential Components



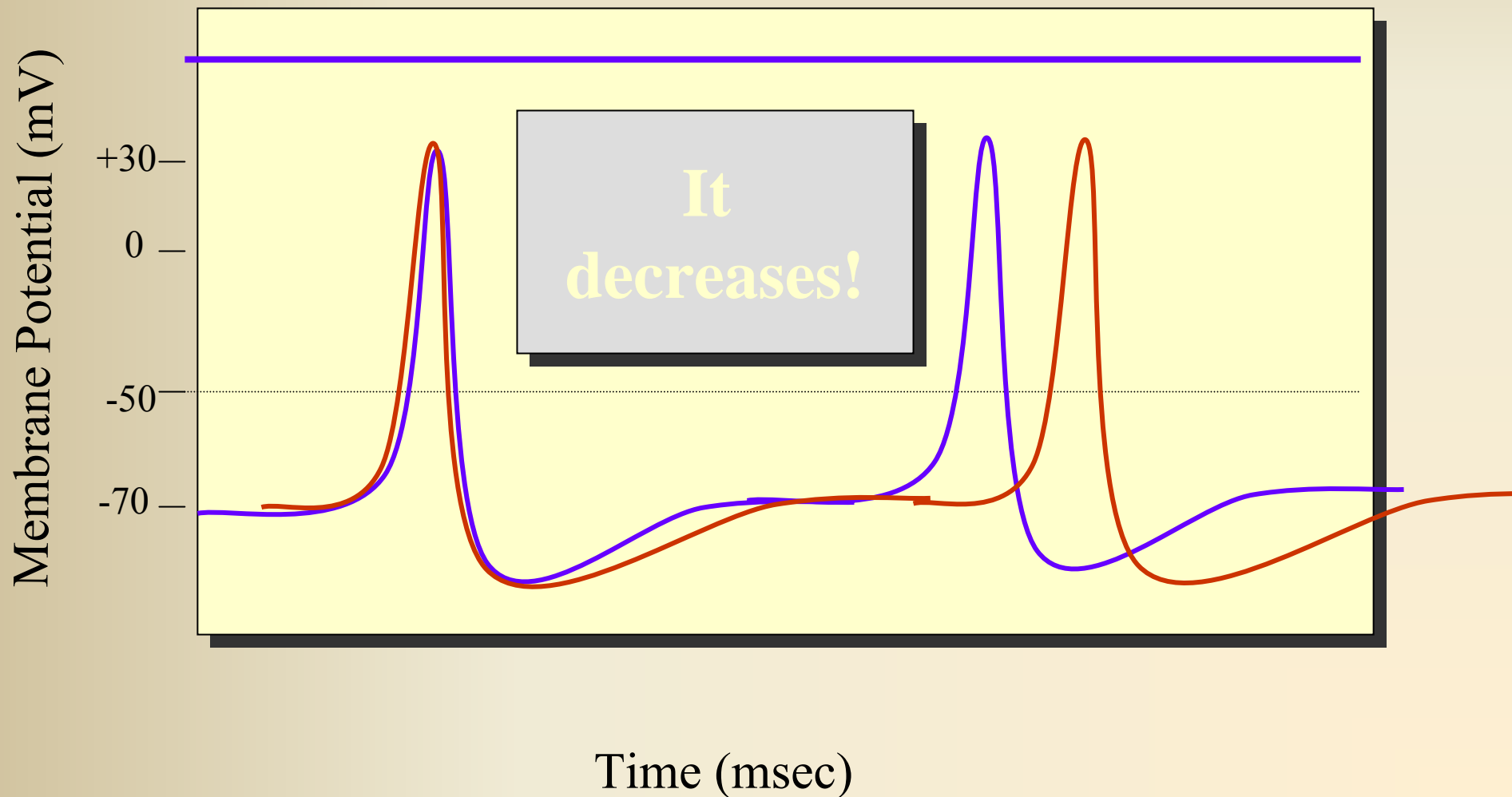
Membrane Permeability



What Happens to the Membrane If Cl^- Rushes Into the Cell During Repolarization?



What Happens to the Frequency of Action Potentials If the Membrane Gets Hyperpolarized?



Clinical Correlation

- Remember that it is the rate of action potential propagation that determines neurologic function.
 - Determined by frequency of action potentials.

What would be the effect on the membrane of $\uparrow\uparrow$ Cl^- influx during a seizure?

What is a seizure?

***Hyperpolarization &
 $\downarrow\downarrow$ seizure activity!***

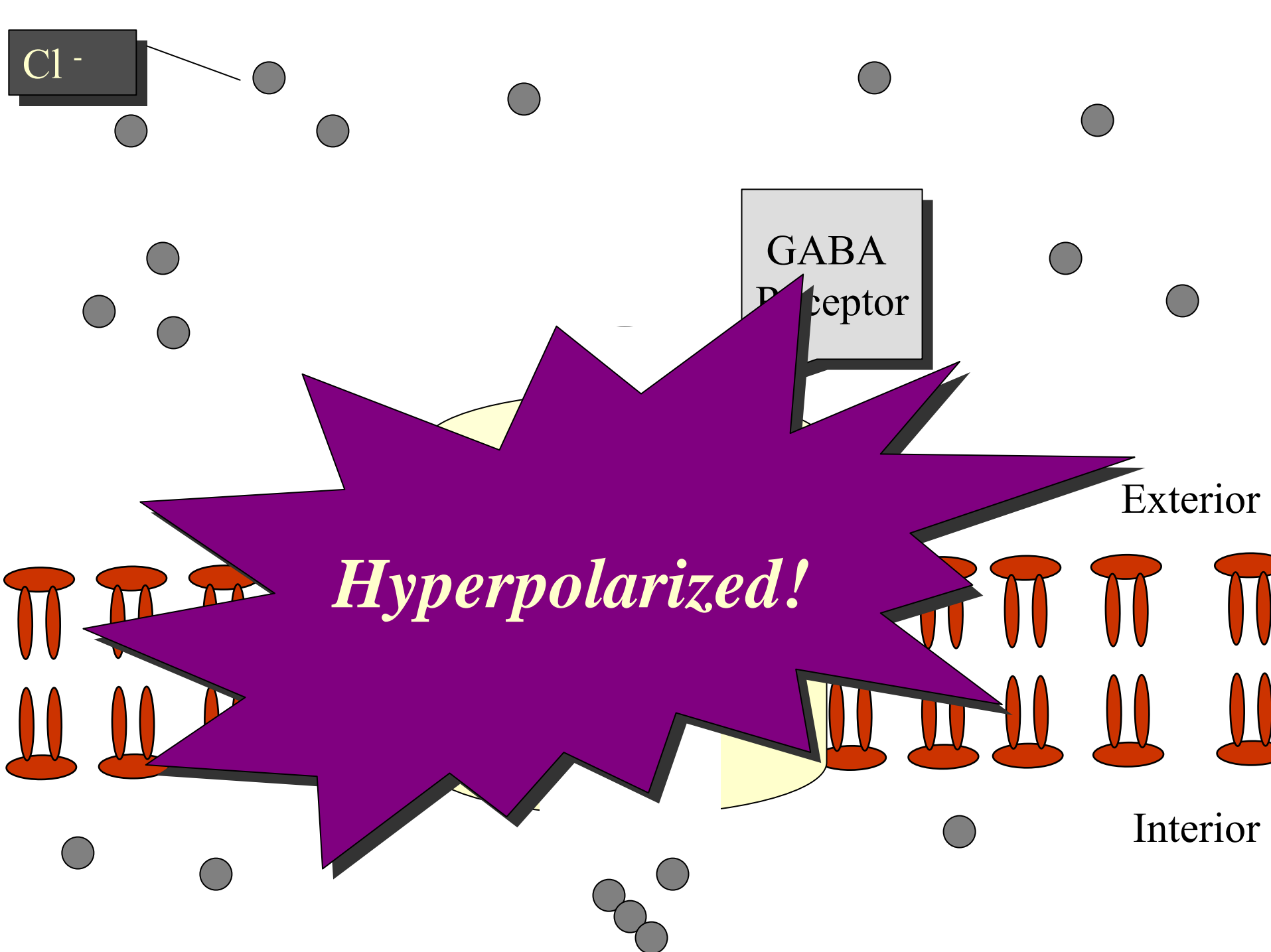
Cl⁻

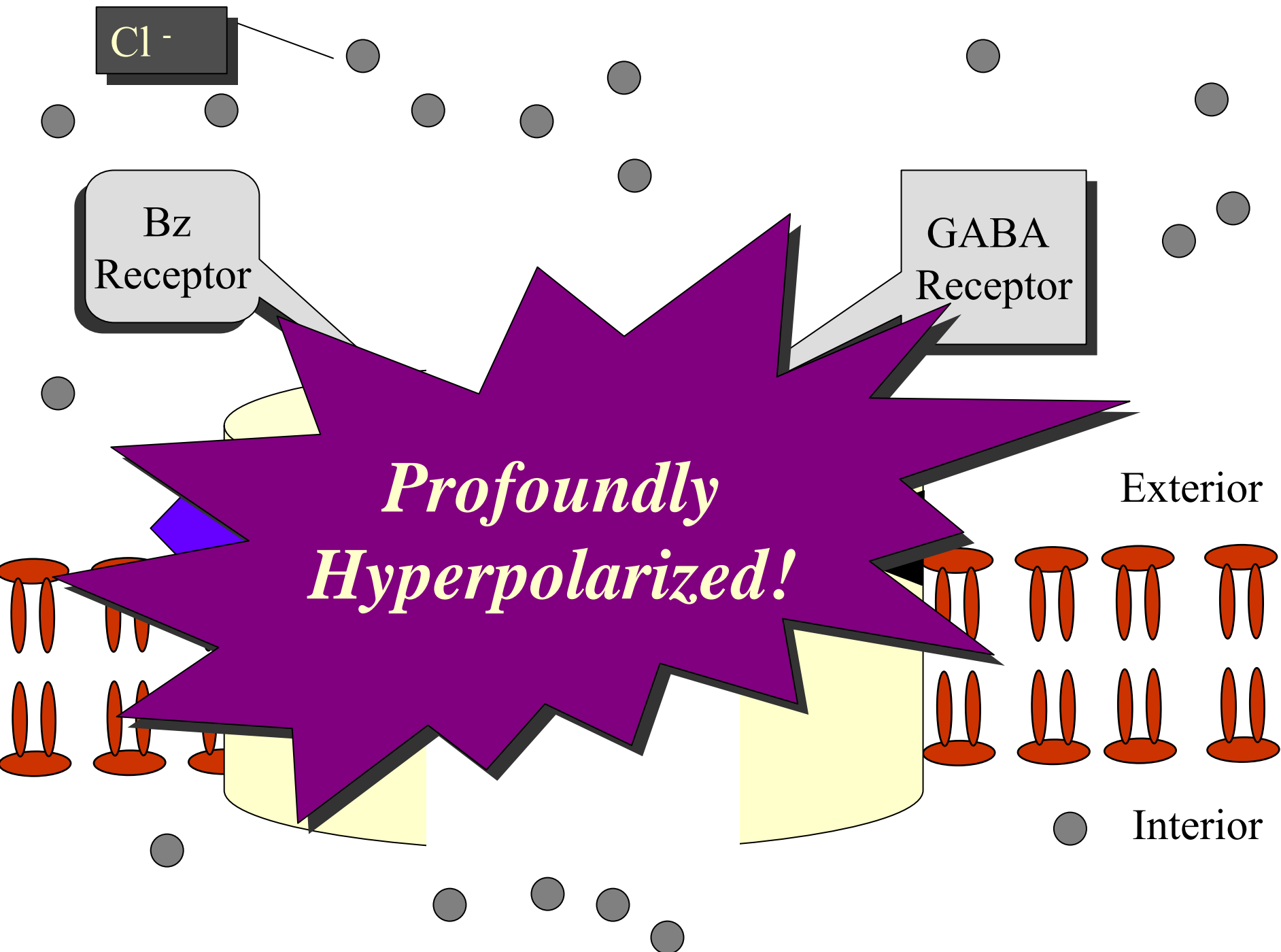
GABA
Receptor

Hyperpolarized!

Exterior

Interior





Are You Ready for a Big Surprise?

Many CNS drugs act on GABA receptors to effect the frequency and duration of action potentials!

SNS Stimulants

- Two general mechanisms:
 - Increase excitatory neurotransmitter release
 - Decrease inhibitory neurotransmitter release
- Three classes:
 - Amphetamines
 - Methylphenidate
 - Methylxanthines

Amphetamines

amphetamine
methamphetamine
dextroamphetamine
(Dexedrine®)

MOA:

promote release of
norepinephrine,
dopamine

Indications

- Diet suppression
- ↓ Fatigue
- ↑ Concentration

Side Effects

- Tachycardia
- Hypertension
- Convulsion
- Insomnia
- Psychosis

Methylphenidate (Ritalin[®])

- Different structure than other stimulants
 - Similar mechanism
 - Similar side effects
- Indication: ADHD
 - Increase ability to focus & concentrate

Methylxanthines

- Caffeine
- Theophylline (Theo-Dur®)
- Aminophylline

Mechanism of action

- Reversible blockade of adenosine receptors

A patient is taking theophylline and becomes tachycardic (SVT). You want to give her adenosine. Is there an interaction you should be aware of? How should you alter your therapy?


Methylxanthines blocks adenosine receptors. A typical dose of adenosine may not be sufficient to achieve the desired result.

Double the dose!

News You Can Use...

Source	Amount of Caffeine
Coffee	
•Brewed	40 – 180 mg/cup
•Instant	30 – 120 mg/cup
Decaffeinated Coffee	2 - 5 mg/cup
Tea	20 – 110 mg/cup
Coke	40 – 60 mg/12 oz

Psychotherapeutic Medications

- Dysfunction related to neurotransmitter imbalance.
 - Norepinephrine.
 - Dopamine.
 - Serotonin.
-  ***Monoamines***
- Goal is to regulate excitatory/inhibitory neurotransmitters.

Anti-Psychotic Drugs (Neuroleptics)

- Schizophrenia
 - Loss of contact with reality & disorganized thoughts
 - Probable cause: increased dopamine release
 - Tx. Aimed at decreasing dopamine activity

Two Chemical Classes:

- **Phenothiazines**
 - chlorpromazine (Thorazine[®])
- **Butyrophenones**
 - haloperidol (Haldol[®])

Other Uses for Antipsychotics

- Bipolar depression
- Tourette's Syndrome
- Prevention of emesis
- Dementia (OBS)
- Temporary psychoses from other illness

Antipsychotic MOA

- Mechanism is similar
 - Strength ([]) vs. Potency ('oomph')
 - Phenothiazines – low potency
 - Butyrophenones – high potency
 - Receptor Antagonism
 - Dopamine₂ in brain → *Therapeutic effects*
 - Muscarinic cholinergic
 - Histamine
 - Norepi at alpha₁
- } *Unintended effects*

Antipsychotic Side Effects

- Generally short term
- Extrapyramidal symptoms (EPS)
- Anticholinergic effects (atropine-like)
 - Dry mouth, blurred vision, photophobia, tachycardia, constipation)
- Orthostatic hypotension
- Sedation
- Decreased seizure threshold
- Sexual dysfunction

Extrapyramidal Symptoms

Reaction	Onset	Features
Acute dystonia	Hours to 5 days	Spasm of tongue, neck, face & back
Parkinsonism	5 – 30 days	Tremor, shuffling gait, drooling, stooped posture, instability
Akathesia	5 – 60 days	Compulsive, repetitive motions; agitation
Tarditive dyskinesia	Months to years	Lip-smacking, worm-like tongue movement, ‘fly-catching’

Treatment of EPS

- Likely caused by blocking central dopamine₂ receptors responsible for movement
- Anticholinergic therapy rapidly effective
 - diphenhydramine (Benadryl®)

Antipsychotic Agents

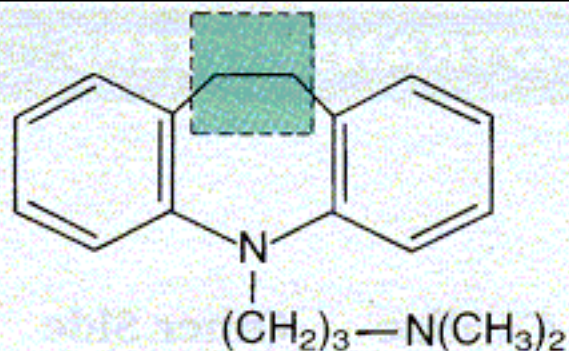
- chlorpromazine (Thorazine®)
- thioridazine (Mellaril®)
- trifluoperazine (Stelazine®)
- haloperidol (Haldol®)

Antidepressants

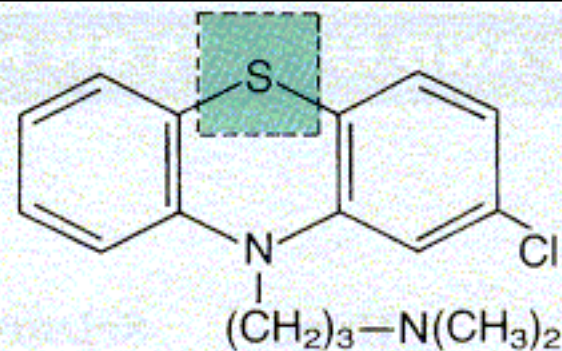
- Likely cause: inadequate monoamine levels
- Treatment options:
 - Increasing NT synthesis in presynaptic end bulb
 - Increasing NT release from end bulb
 - Blocking NT 'reuptake' by presynaptic end bulb

Tricyclic Antidepressants (TCAs)

- Block reuptake of both NE & serotonin
 - Enhance effects
- Similar side effects to phenothiazines



Imipramine
(a tricyclic antidepressant)



Chlorpromazine
(a phenothiazine antipsychotic)

TCA Side Effects

- Orthostatic hypotension
- Sedation
- Anticholinergic effects
- Cardiac toxicity
 - Ventricular dysrhythmias

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Block only serotonin (not NE) reuptake
 - Elevate serotonin levels
- Fewer side effects than TCS
 - No hypotension
 - No anticholinergic effects
 - No cardiotoxicity
- Most common side effect
 - Nausea, insomnia, sexual dysfunction

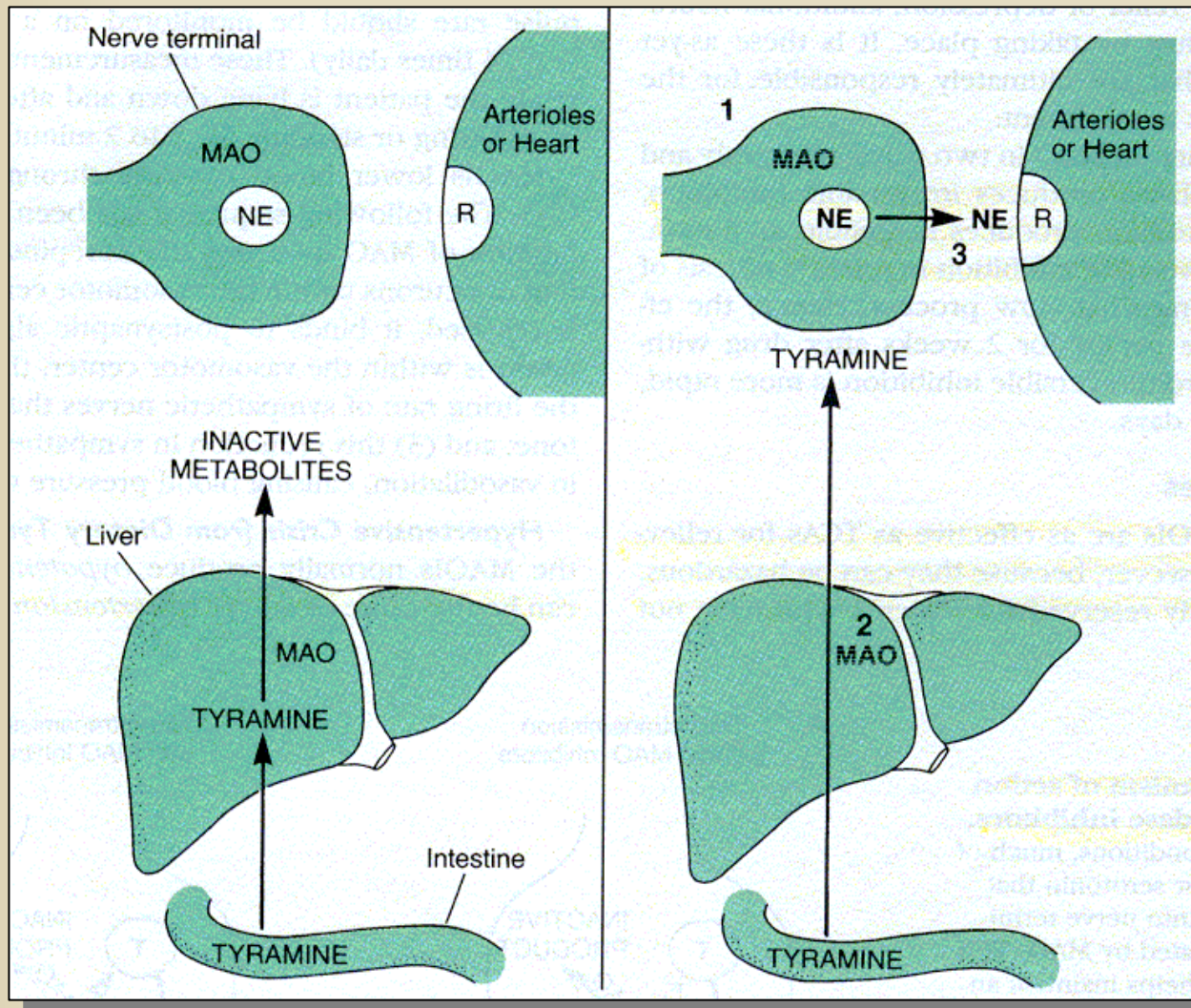
Monoamine Oxidase Inhibitors (MAOIs)

- Monoamine oxidase
 - Present in liver, intestines & MA releasing neurons
 - Inactivates monoamines
 - Inactivates dietary tyramine in liver
 - Foods rich in tyramine: cheese & red wine

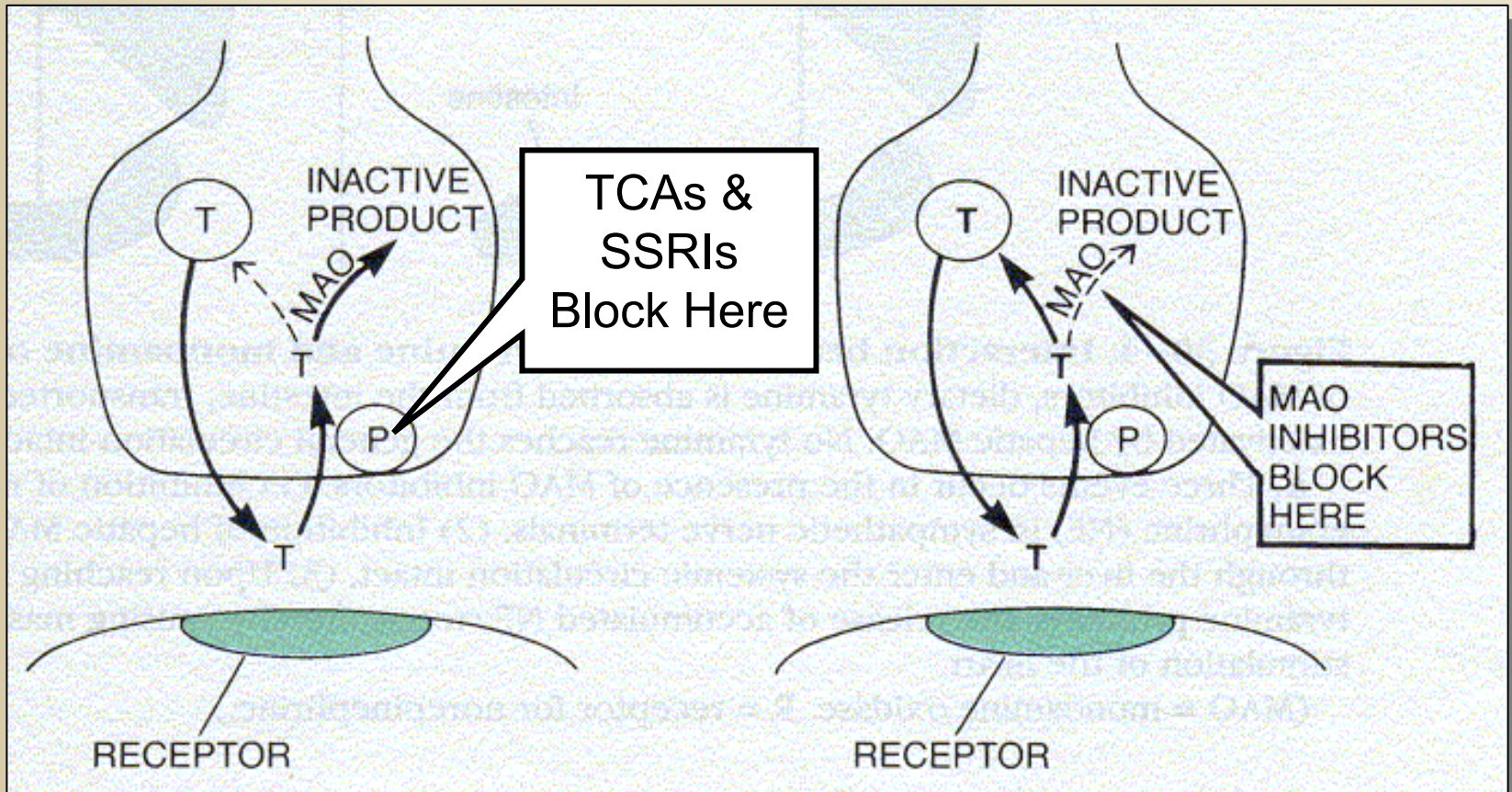
MAOI Side Effects

- CNS Stimulation
 - Anxiety, agitation
- Orthostatic hypotension
- Hypertensive Crisis
 - From increased tyramine consumption
 - Excessive arteriole constriction, stimulation of heart

MAOI & Dietary Tyramine



Antidepressant Mechanism



Antidepressants Agents

TCA_s

- imipramine (Tofranil[®])
- amitriptyline (Elavil[®])
- nortriptyline (Pamelor[®])

SSRIs

- fluoxetine (Prozac[®])
- paroxetine (Paxil[®])
- sertraline (Zoloft[®])

MAOIs

- phenelzine (Nardil[®])

Atypical Antidepressants

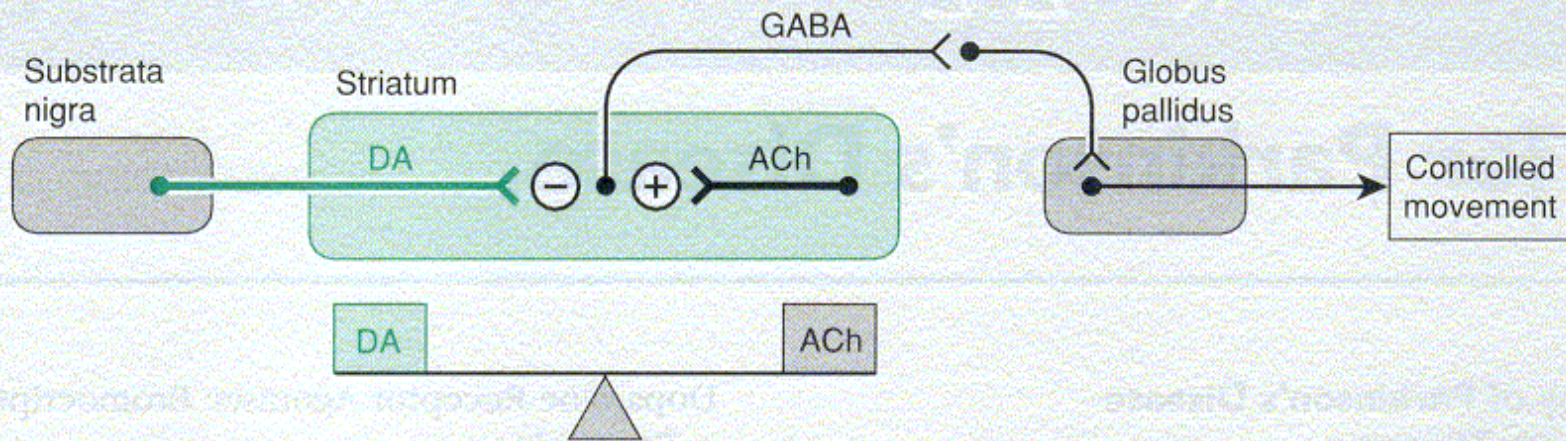
- bupropion (Wellbutrin[®])

Parkinson's Disease

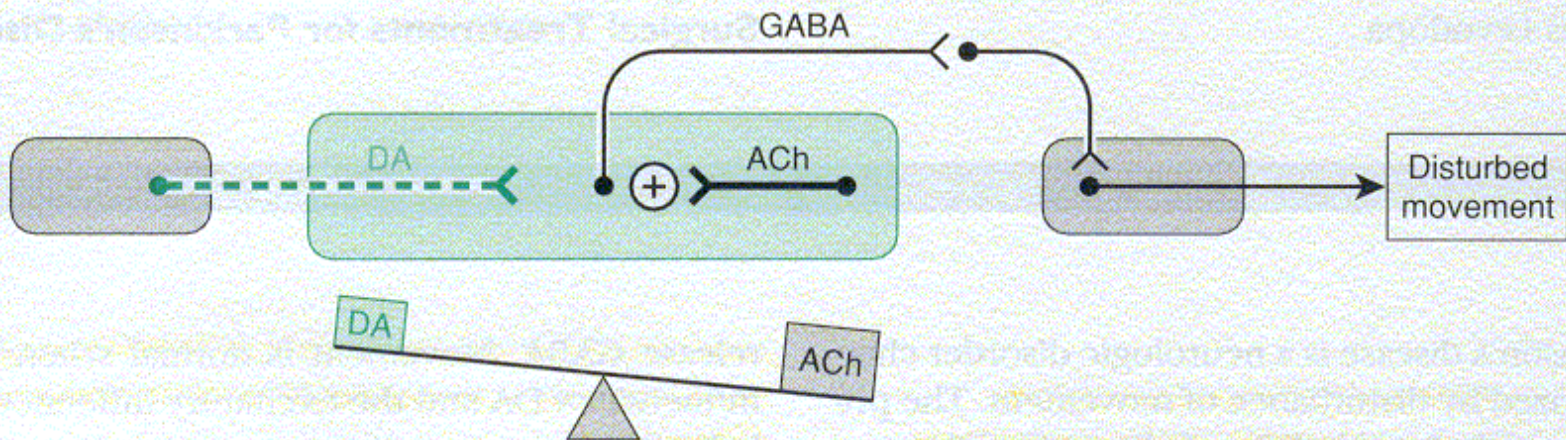
- Fine motor control dependent upon balance between excitatory and inhibitory NT
 - Acetylcholine = excitatory
 - Dopamine = inhibitory
- GABA = inhibitory
- } Control GABA release

Parkinson's Disease

A Normal



B Parkinson's Disease



Parkinson's Symptoms:

- Similar to EPS
- Dyskinesias
 - Tremors, unsteady gait, instability
- Bradykinesia
- Akinesia in severe cases

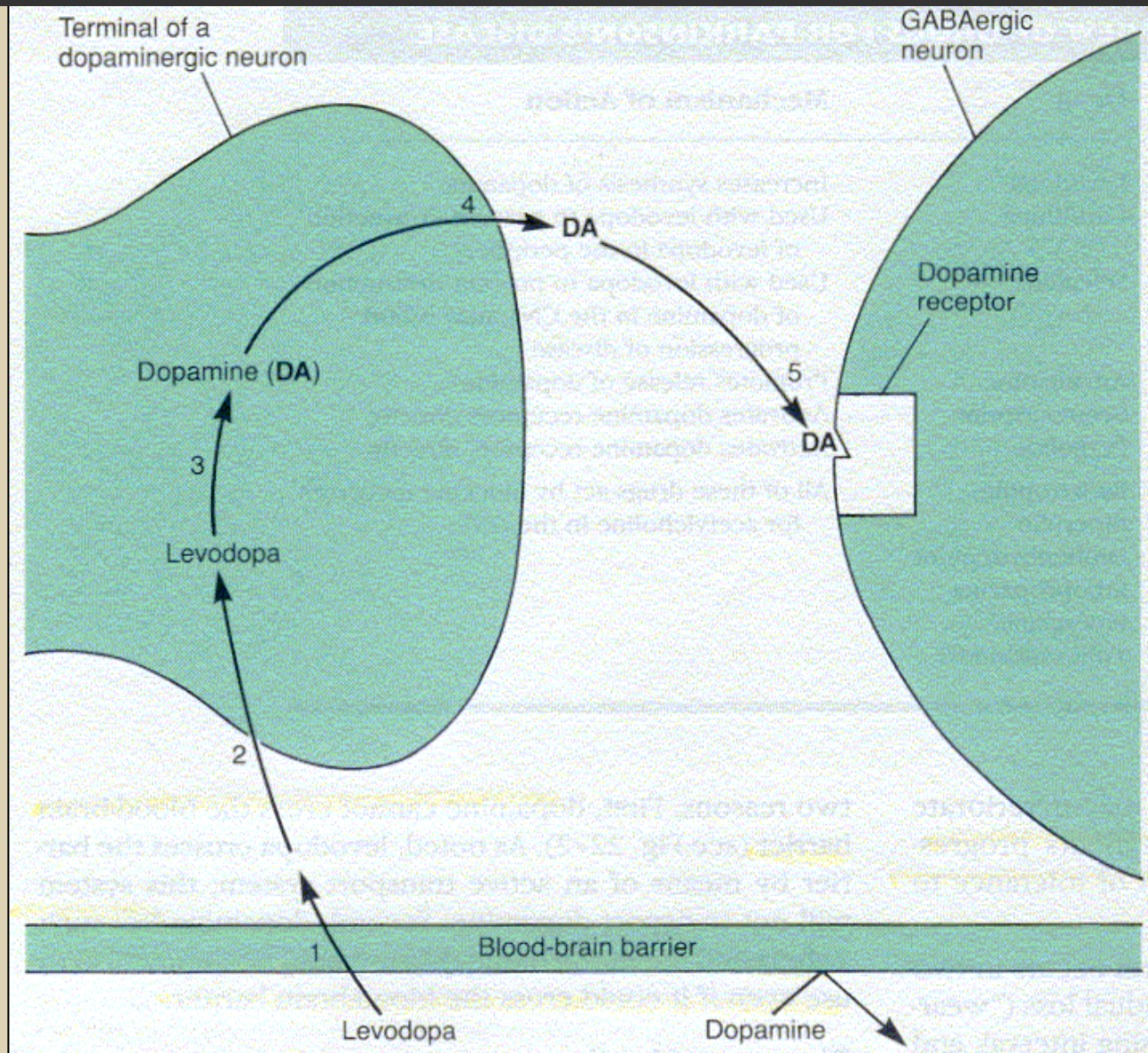
Parkinson's Treatment

- Dopaminergic approach
 - $\uparrow\uparrow$ Release of dopamine
 - $\uparrow\uparrow$ [Dopamine]
 - $\downarrow\downarrow$ Dopamine breakdown
- Cholinergic approach
 - $\downarrow\downarrow$ Amount of ACh released
 - Directly block ACh receptors
- All treatment is symptomatic and temporary

Levodopa

- Sinemet ® = levodopa + carbidopa
- Increase central dopamine levels
- Side effects:
 - Nausea and vomiting
 - Dyskinesia (~80% of population)
 - Cardiovascular (dysrhythmias)

Levodopa Mechanism



Other Agents

- amantadine (Symmetrel[®])
 - ↑↑ release of dopamine from unaffected neurons
- bromocriptine (Parlodel[®])
 - Directly stimulated dopamine receptors
- selegiline (Carbex[®], Eldepryl[®])
 - MAOI selective for dopamine (MAO-B)
- benztropine (Cogentin[®])
 - Centrally acting anticholinergic

Drugs That Affect the Autonomic Nervous System

Word of Warning

Carefully review the A&P material &
tables on pages 309 – 314 and 317 – 321!

PNS Drugs

- Cholinergic
 - Agonists & Antagonists (Anticholinergics)
 - Based on response at nicotinic_(N&M) & muscarinic receptors

Acetylcholine Receptors

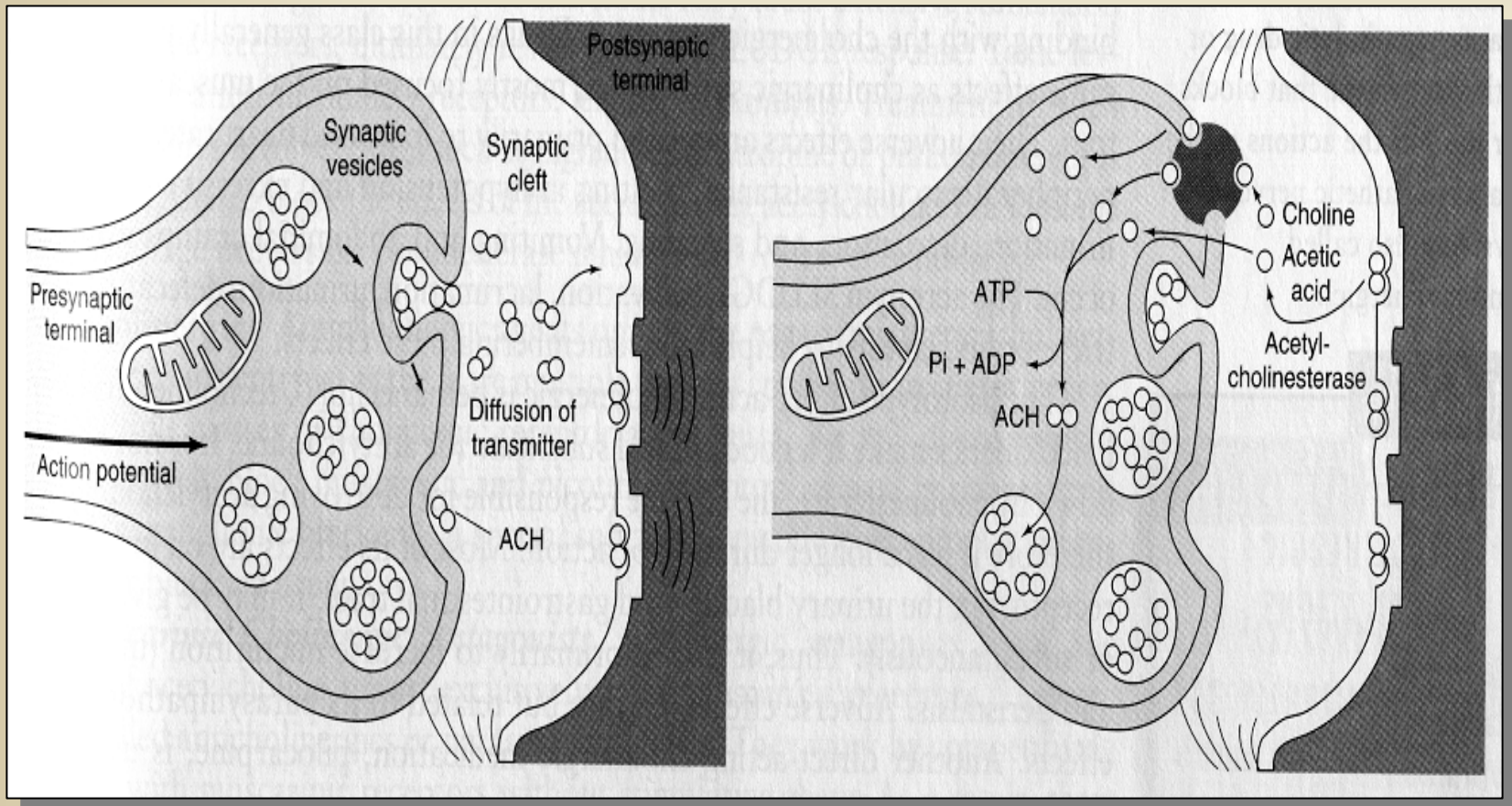


Figure 9-8, page 313, Paramedic Care, V1

Cholinergic Agonists

*Cholinergic agents
cause SLUDGE!*

HINT!

*These effects are
predictable by knowing
PNS physiology (table 9-4)*

Salivation

Lacrimation

Urination

Defecation

Gastric motility

Emesis

Direct Acting Cholinergics

- bethanechol (Urecholine) prototype
 - Direct stimulation of ACh receptors
 - Used for urinary hesitancy and constipation

Indirect Acting Cholinergics

- Inhibit ChE (cholinesterase) to prolong the duration of ACh stimulation in synapse
- Reversible
- Irreversible

Reversible ChE Inhibitors

- neostigmine (Prostigmine[®])
 - Myasthenia Gravis at nicotinic_M receptors
 - Can reverse nondepolarizing neuromuscular blockade
- physostigmine (Antilirium[®])
 - Shorter onset of action
 - Used for iatrogenic atropine overdoses @ muscarinic receptors

Irreversible ChE Inhibitors

- Very rarely used clinically
- Very common in insecticides & chemical weapons
 - VX and Sarin gas
 - Cause SLUDGE dammit and paralysis
- Tx: atropine and pralidoxime (2-PAM[®])
 - Anticholinergics

Anticholinergics

- Muscarinic antagonists
 - Atropine
- Ganglionic antagonists
 - block nicotinic_N receptors
 - *Turns off the ANS!*
 - trimethaphan (Arfonad®)
 - Hypertensive crisis

- Atropine Overdose
 - Dry mouth, blurred vision, anhidrosis

Hot as Hell
Blind as a Bat
Dry as a Bone
Red as a Beet
Mad as a Hatter

Neuromuscular Blockers

- Nicotinic Cholinergic Antagonists
 - Given to induce paralysis
- Depolarizing
 - succinylcholine (Anectin[®])
- Nondepolarizing
 - tubocurarine from *curare*
 - rocuronium (Zemuron[®])
 - vecuronium (Norcuron[®])

Warning!

- Paralysis without loss of consciousness!
 - MUST also give sedative-hypnotic
 - Common agents:
 - fentanyl (Sublimaze®)
 - midazolam (Versed®)

SNS Drugs

- Predictable response based on knowledge of affects of adrenergic receptor stimulation
- HINT: Know table 9-5, page 321
- Each receptor may be:
 - Stimulated (sympathomimetic)
 - Inhibited (sympatholytic)

Alpha₁ Agonists

- Profound vasoconstriction
 - Increases afterload & blood pressure when given systemically
 - Decreases drug absorption & bleeding when given topically

Alpha₁ Antagonism

- Inhibits peripheral vasoconstriction
 - Used for hypertension
 - prazosin (Minipress[®])
 - doxazosin (Cardura[®])
 - phentolamine (Regitine[®])
 - Blocks alpha_{1&2} receptors

Beta₁ Agonists

- Increases heart rate, contractility, and conductivity

Beta Antagonists (β Blockers)

- Frequently used
- Lower Blood Pressure
- Negative chronotropes & inotropes









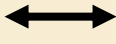
Beta₁ Selective Blockade

- atenolol (Tenormin[®])
- esmolol (Brevibloc[®])
- metoprolol (Lopressor[®])

Nonselective

- propranolol (Inderal[®])
- labetalol (Normodyne[®], Trandate[®])
- sotalol (Betapace[®])

Adrenergic Receptor Specificity

Drug	α_1	α_2	β_1	β_2	Dopaminergic
Epinephrine					
Ephedrine					
Norepinephrine					
Phenylephrine					
Isoproterenol					
Dopamine					
Dobutamine					
terbutaline					

Web Resources

- Web based synaptic transmission project
 - <http://www.williams.edu/imput/index.html>

Thank You!

- To Temple College EMS Professions for permission to use their materials

