CHOLINERGIC NERVOUS SYSTEM // SITES OF DRUG ACTION

SITE 1 // BIOSYNTHESIS OF ACh
Acetyl CoA + Choline ---ChAT--- > ACh
Goal: inhibit the enzyme ChAT
Inhibitor: NVP
4° >> 3° NH3 because much stronger bond = much stronger reaction
Ortho methyl causes steric hindrance → inactive

SITE 2 // UPTAKE of ACh & CHOLINE
Uptake of choline: rate limiting step
CHOLINE
• After degraded by AChE, needs to be actively transported back in
• Problem: charged, water soluble: can’t cross lipid membrane
• Solution: Carrier Protein A: crosses via Na+ lipid-like transporter

INHIBITORS
1. Competitive: HC-3
   • Structurally similar to choline
   • Has 2 choline like moieties
   • Transporter can only handle 1 choline moiety at a time, so not transported in
2. False neurotransmitter: TEC
   • Does everything choline does:
     o Binds to Carrier Protein A
     o Binds to ChAT to get acetylated → TE-ACh
     o Encapsulated into vesicle
   • But when released into synapse, doesn’t bind to receptors because triethyl group too bulky
3. Inhibitor of vesicular ACh uptake: L-Vesamicol
   • Noncompetitively inhibits VACHt to stop encapsulation
   • Binds to α- and α-receptors

SITE 3 // RELEASE OF ACh
(−) Blocking vesicular release into the synaptic cleft
• Remove Ca2+, which is needed for vesicles to fuse with the cell membrane
• Botox: cleaving SNAP-25, which is needed for docking/release of ACh from vesicles

(+ Promoting vesicular release into the synaptic cleft
• Black widow spider venom: β-bungarotoxin
• Delecit: treats ADD and Alzheimer’s
  o Delecit = phosphate ester of choline
  o 1. Phosphatases cleave the phosphate ester off leaving choline, which is actively taken up by the brain
  o 2. Lipases in the intestine acylate it into lecithin, which is lipoidal and crosses the BBB → once inside brain, gets hydrolyzed to give choline

SITE 4 // POSTSYNAPTIC RECEPTORS
Agonists or antagonists
Nicotinic receptors
• Transmitter gated ion channel → change in ion concentration
• ACh binds to 2 α subunits of this heterodimer
• Model antagonist: α-bungarotoxin
  o Basic: 5 Arg + 5 Lys + 5 disulfide S-S bonds
  o Binds to α/β subunits → blocks ACh binding site and ionic channel
• Agonists: only moiety needed is a 4° NH3 ion
Muscarinic receptors
• G-protein coupled → cascade of chemical reactions
• 7TM helical structure
• Odds M1, M3, M5: stimulatory (+)
  o Gs → (+)PLC → ↑Ca2+
• Evens M2, M4: inhibitory (−)
  o Gi → (−)AC → ↓cAMP
MUSCARINIC AGONISTS // Pharmacology

Muscarinic agonists are not as widely used as antagonists. Most muscarinic drugs are not specific and affect all subtypes.

INDIRECT acting agonists: require ACh presence
- Includes reversible and irreversible cholinesterase inhibitors
- Muscarinic & nicotinic

DIRECT acting agonists: don’t require ACh presence
- Directly stimulates receptors like ACh
- Muscarinic
- Choline esters & cholinomimetic alkaloids:

CHOLINE ESTERS
- Mostly useless: quickly degraded and no selectivity (both N & M receptors)
- Somewhat useful (compared to ACh): AChE doesn’t like it as much, muscarinic receptors like it more, doesn’t cross BBB
- Given po, sc, or topically in eye (but absorbed systemically)
- SE: parasympathomimetic effects
- Tx of toxicity: atropine (muscarinic antagonist)

METHACHOLINE
- Structure: adds β-methyl group to ACh
- Compared to ACh: more resistant to hydrolysis, more selective
- PO: not effective, short duration of action
- Problem: strong CV effects strong
- Diagnostic agent: tests for belladonna poisoning
- Treats emergency narrow-angle glaucoma

CARBACHOL
- Stability: not hydrolyzed by AChE
- PO: effective
- Problem: nicotinic action
- Used in ophthalmology to produce miosis, treats wide-angle glaucoma

BETHANECHOL
- Structure: put β-methyl + carbamoyl group on choline
- Stability: hydrolysis resistant
- PO: effective
- GI tract: treats GI stasis disorders (paralytic ileus, gastric stasis)
- Urinary bladder: treats urinary retention w/o obstruction
- Doesn’t cross BBB

CHOLINOMIMETIC ALKALOIDS
- PILOCARPINE
  - Useful diagnostically: sweat glands particularly sensitive
  - Parasympathetic (+): treats xerostomia/dry mouth
  - Ophthalmic use: miosis (pinpoint pupil), spasm of accommodation (lens are fixed for near vision, hard to focus on distant sights), treats glaucoma (↓ intraocular pressure)
- MUSCARINE
  - Stimulates PNS
  - Cause of some mushroom poisoning

PHARMACOLOGY OF MUSCARINIC AGONISTS
- EYE
  - Contract ciliary muscle → accommodation for near vision
  - Contract iris sphincter muscle → miosis (pinpoint pupil), better drainage to treat glaucoma
- HEART
  - Bradycardia: slows HR
  - ↓SA node rate, ↓atria contractile strength, ↓AV node conduction velocity, and ↓ventricular strength
  - Metacholine: most potent
- BLOOD VESSELS
  - Have only sympathetic innervation
  - Vasodilation with rebound tachycardia (due to baroreceptor reflex)

PHARMACOLOGY OF CHOLINE ESTERS
- GI SYSTEM
  - ↑peristalsis, ↑secretion, sphincter relaxation
  - N&V, intestinal cramping, belching, defecation
  - Effective: all choline esters
- URINARY TRACT
  - ↑ureteral peristalsis, detrusor muscle contraction (bladder voiding)
  - Effective: bethanechol, carbachol
- RESPIRATORY
  - Bronchoconstriction, ↑secretions
  - Contraindicated in asthmatic patients
- GLANDS
  - ↑sweating, ↑salivation, ↑lacrimation
**NEWMAN PROJECTIONS**

- Most stable: syn
- Receptor-bound: (+)ac $\rightarrow$ unstable, high energy reversible binding
- Receptors are stereospecific

**MOD THE ACETYL**
- Carbamoyl: oral activity, ↑stability against hydrolysis by gastric acid
- Phenolic: partial agonist/antagonist
- Benzylic: muscarinic antagonist

**MOD THE BRIDGE**
- CH$_3$ on β ➔ muscarinic
- β stereochemistry: S > R
- CH$_3$ on α ➔ nicotinic

**MOD THE QUAT**
- Needs a pos charged moiety (N$^+$, S$^+$, P$^+$)
- Needs at least 2 methyl groups on charged moiety

**CLOTHIA’S MODEL // Receptor-Drug Interaction**

- Positively (+) charged NH$_3$ group with 2 methyls
- OH or O function pointing upward
- Conformation of ACh showing the methyl-side (i.e., the C$_7$) for muscarinic receptor binding and carbonyl-side (i.e., O$_2$) for nicotinic receptor binding (Chlothia Receptor Model)
MUSCARINIC ANTAGONISTS // Pharmacology

Most antimuscarinics end in “-ine”

THERAPEUTIC AGENTS with ANTIMUSCARINIC ACTIVITY

- Antihistamines
- Tricyclic antidepressants (TCAs)
- Antipsychotics
- Drugs of abuse

Drugs that cross the BBB have CNS ACTIVITY (along with peripheral activity)

DOSE-DEPENDENT EFFECTS: different organs respond at different doses

1. GLANDS: ↓ salivation (dry mouth)
2. BLADDER: ↓ micturition/urination
3. EYES: ↓ accommodation (blurry vision)
4. HEART: ↑ heart rate (tachycardia)
5. GI TRACT: ↓ GI acid

CNS ACTIVE
- Atropine
- Scopolamine
- Benztropine

CNS INACTIVE
- Methscopolamine
- Propantheline
- (synthetics, 4°NH₃)

Quaternary antimuscarinics can’t cross BBB and are devoid of CNS activity

PERIPHERAL PHARMACOLOGY

EYES
- MYDRIASIS
  o Inhibits sphincter muscle from contracting
  o Short acting synthetics
  o Ophthalmic exams
  o SE: photophobia
- CYCLOPLEGIA
  o Inhibits ciliary muscle of lens → paralyzes accommodation
  o Short acting synthetics
  o Ophthalmic exams
  o SE: blurry vision, micropsia
- GLAUCOMA: may worsen it

RESPIRATORY
- Bronchodilation
- ↓ Secretions

HEART
- Inhibit SA and AV nodes
- ↑ HR: tachycardia
- Possible atrial arrhythmias

BLOOD VESSELS
- Eh

GI TRACT
- Dose dependent sensitivity: ↓ salivary glands > ↓ smooth muscle propulsive activity > ↓ gastric acid secretion

URINARY TRACT
- Inhibit detrusor muscle → ↓ bladder tone → urinary retention
- ↓ Ureteral contractions: antispasmodic effect

BODY TEMP
- Hypothalamus → hyperthermia
- Sweat glands → ↓ sweating

THERAPEUTIC USES

Ophthalmic exams: Mydriasis & cycloplegia → Mydriacyl, Cyclogel
Pulmonary disorders: Treats bronchitis & emphysema via bronchodilation & dry resp. secretions → Atrovent, Spiriva
Common cold: OTC preps in combo with antihistamines to dry respiratory secretions (counterproductive in long run)
GI disorders: Treats diarrhea, ulcers, functional GI disorders → not so great
Urinary tract: Treats overactive bladder and some infections → Detrol, Ditran, Enablex, Vesicare, Sanctura
Motion sickness: Nausea & vomiting → AntiVert, Bonine, Transdermal Scopolamine
Parkinson’s Disease: DA neurons under tonic inhibition by ACh → Cogentin, Artane

ADVERSE REACTIONS: dry mouth, mydriasis, cycloplegia, cardiac arrhythmias, coma
CONTRAINDICATIONS: narrow angle glaucoma, gastric retention, urinary retention
MUSCARINIC ANTAGONISTS // Chemistry

Bind to muscarinic receptors → but causes NO ACTION

Lead compounds: Tropine Alkaloids: jimson weed, deadly nightshade, black henbane
Tropane: nitrogenous bicyclic compound
Tropine: hydroxylated tropane
(−)-hyoscyamine → base catalyzed racemization → ATROPINE
Important: benzylic carbon
Stereochemistry: S>R

ACh receptor site: ester binding subsite + anionic subsite [+hydrophobic area + H-bonding subsite]

ESTERS
Compounds that have an ester group have shorter durations of action because it is easily hydrolyzed by esterase

4° AMMONIUM
Compounds that have a quaternary ammonium group have localized action, not easily absorbed (usually as inhalers)

Acrivastine
Non-sedating antihistamine

Although both R1 and R2 can either be phenyl or carbocyclic rings, this formation is IDEAL

Stereochemistry: R > S
R: clockwise, S: counterclockwise

Can only have an F substituent at para position

Carbocyclic
H, OH, CH₃, or CH₃OH,

Can't cross BBB
ANTICHOLINESTERASES // Indirect cholinomimetic effects w/o receptor binding

**ANTICHOLINESTERASES**
- Occur naturally as venoms and poisons
- Are used as weapons in the form of nerve agents
- Are used to treat myasthenia gravis, Alzheimer’s disease, and Lewy Body dementia
- Are used as an antidote to anticholinergic poisoning

**REVERSIBLE inhibitors have therapeutic use**
**IRREVERSIBLE inhibitors are used as weapons & pesticides**

Enzyme intermediates that are
- **ACETYLATED** → physiological (i.e. ACh)
- **CARBAMOYLATED** → reversible
- **PHOSPHORYLATED** → irreversible

**CARBAMATE** ester-type reversible AChE inhibitors
- Are all aryl carbamates
- Aryl carbamates > alkyl carbamates
- **Physostigmine**: treats glaucoma & CNS anticholinergic overdoses (e.g. atropine, tricyclic antidepressants)
- **Neostigmine**: ionized, has no CNS activity; prophylaxis for post-op, urinary retention, myasthenia gravis
- **Pyridostigmine**: ionized, has no CNS activity; po effective; myasthenia gravis, prophylaxis of nerve gas exposure in battle
- **Rivastigmine**: CNS activity, pseudo-irreversible (slow dissociation of carbamylated enzyme), treats Alzheimer’s Disease

**ORGANOPHOSPHATES**
- Irreversible AChE inhibitors
- Doesn’t undergo nucleophilic attack by antidotes
- Renders AChE inactive
- Therapeutic use: DFP & Echotiophate → treat glaucoma, long duration of action
- Chemical warfare: Tabun, Sarin, Paraoxon
- Insecticides: Parathion, Malathion, Dimethylphosphoramide, Schradan
  - Agents are more toxic to insects than humans: is it dealkylated in humans but rearranged in insects
  - Thiophosphates (prodrug) are activated by CYP450 → phosphate esters (toxic metabolite)
  - In humans, CYP450 metabolizes it into an inactive metabolite
  - Insects have a lower esterase activity: malathion is the least toxic since it has an ester function

**ANTIDOTES**
- Agents that catalyze phosphate ester cleavage to regenerate active AChE
- For organophosphate poisoning: **2-PAM** → reactivates AChE by correctly positioning the OH group for nucleophilic attack
**NICOTINIC // AGONISTS & ANTAGONISTS**

**LOCATION**
- Autonomic ganglia
- Neuromuscular junction
- CNS

**STRUCTURE**
- Heteromeric, 5 subunits
- 2 α subunits: ACh binding sites
- Transmitter-gated ion channel

**AGONISTS: CENTRALLY ACTING**
- Treats Alzheimer’s Disease
- Mechanism:
  - ACh binds to nAChRs
  - ↑ presynaptic Ca\(^{2+}\) influx
  - Stimulates release of ACh at postsynaptic mAChRs
  - Influx of Ca\(^{2+}\) needed for vesicles to release ACh

**ANTAGONISTS**

**Competitive antagonists**

**Block at ganglionic nAChRs**
- Most end in “-onium” or “-curium”
- Competitive and reversible
- No intrinsic activity → no Ca\(^{2+}\) ion channel opening
- Bind tightly to ACh binding site (α) → overstimulation → depolarization
- Initially mimetic, then after awhile become blocking
- Structure: long carbon chain is important
- Hexamethonium (C\(_8\))
- Decamethonium (C\(_{10}\))

- d-Tubocurarine
- Pancuronium: longer acting, more potent than d-tubocurarine; causes tachycardia

- Atracurium, Cisatracurium
  - Base catalyzed Hofmann elimination yields laudanosine → responsible for CV effects
  - Clearance: ester hydrolysis by esterases

- Doxacurium
  - Non-depolarizing NM blocker
  - Minimal CV effects
  - Longer duration of action than atracurium because resistant to hydrolysis by plasma cholinesterases