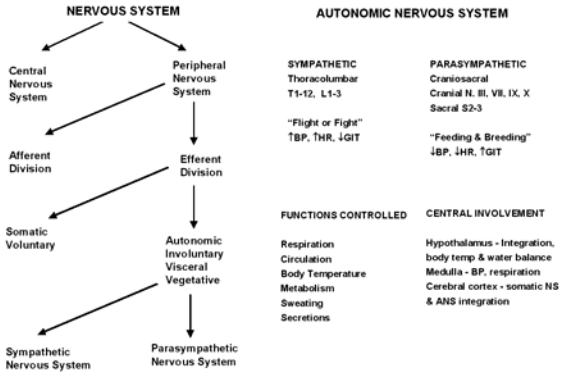
Parasympathetic Nervous System Part I

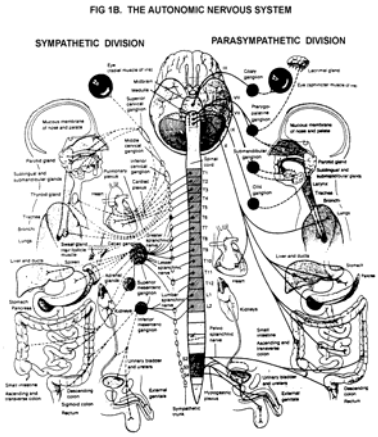
Edward JN Ishac

Smith Building, Room 742
eishac@hsc.vcu.edu
8-2127 8-2126

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Autonomic Nervous System





ANS Diagram

Key Points

Division – Anatomical

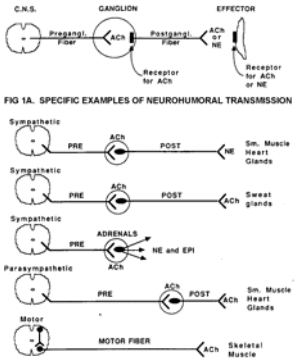
Usually dual innervation

Usually antagonistic

Usually one dominates

Usually some ANS "tone"

Neurons of the ANS



Key Points

Preganglionic fibers – mylinated

Postganglionic fibers – non mylinated

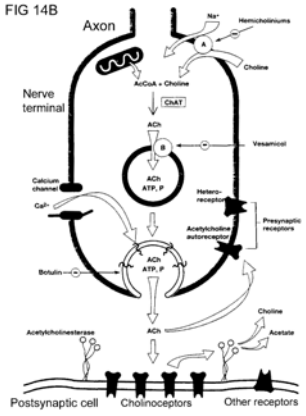
SNS pre : post 1:20

PNS pre : post 1:1 (exception 1:10,000 Auerbachs plexus)

Key role of Ach

Motor fiber not part of ANS

Cholinoceptors



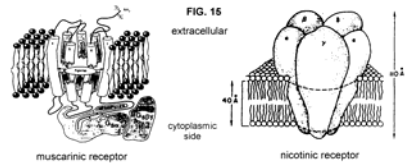
Cholinergic Neurotransmission

Rate limiting step
Uptake of choline into nerve terminal

Synthesis
Choline Acetyltransferase

Termination
Enzymatic by acetylcholinesterase (AchE)

Cholinergic Receptors

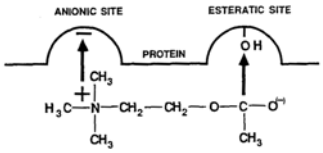


Na+ - in
K+ - out

- **Muscarinic** (7 transmembrane)
  - M_1 -autonomic ganglia, CNS
  - M_2 -heart
  - M_3 -smooth muscle, glands
  - M_4, M_5
  - M_{135} ↑PLC, M_{24} ↓AC
  - G-protein coupled
- **Nicotinic** (ion channel)
  - pentamer, 5 subunits
  - N_N or N_1 -ganglia, adrenal medulla ($\alpha_2\beta_3$, $\alpha_3\beta_2$)
  - N_M or N_2 -skeletal muscle (infant $\alpha 2\beta\delta\varepsilon$, adult $\alpha 2\beta\delta\gamma$)
  - α subunit, Ach binding (2)

True Acetylcholinesterase (AchE)

(Other: Pseudocholinesterase, circulating, plasma, butylcholinesterase)



Quaternary group **Acyl carbon**

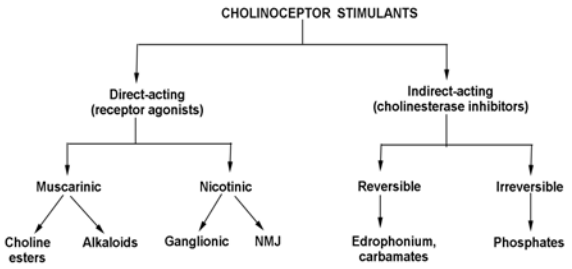
	AchE	BuChE
Nerves	Yes	Little
NMJ	Yes	Little
Circul^n	Little	Yes

AchE: 300,000 Ach / enzyme / min (0.15 msec/cycle)

Muscarinic effects on organ systems

- **Heart (M2)**
  - ↓ HR, ↓ contractility, ↓conduction velocity
- **Vasculature** (not innervated)
  - vasodilation: nitric oxide (NO)
- **Other smooth muscle**
- **- Eye:** pinpoint pupil (miosis), focus for near vision
- **- GI-tract:** ↑tone to intestine, bladder, ↓ tone to sphincters
- **- Lung:** contract bronchial SM. → ↑resistance, ↑ secretions
- **- Exocrine glands:**
  - ↑ sweating (cholinergic sympathetic)
  - ↑ salivation, ↑ gastric acid secretion (M1)

Cholinergic Stimulants

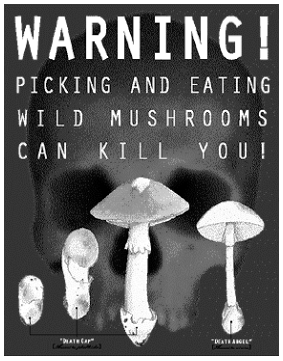


Ach	Ach	Physostigmine	Malathion
Pilocarpine	Nicotine	Neostigmine	DFP
Muscarine		Edrophonium	Nerve gas

Muscarinic receptor agonists

- **Choline esters**
  - ACH (muscarinic & nicotinic action)
  - bethanechol (oral or sc, never iv or im → cardiac arrest)
  - methacholine (not common)
  - carbachol (direct/indirect; muscarinic & nicotinic)
- **Alkaloids:**
  - muscarine (mushrooms)
  - pilocarpine (DOC, used in glaucoma emergency)
  - oxotremorine (synthetic) CNS action (basal ganglia)
- **Uses:**
  - ophthalmic (Ach, brief miosis)
  - diagnostic for belladonna poisoning (methacholine)
  - urinary retention (bethanechol)
  - reverse GIT depression (bethanechol)

Wild Mushrooms - Amanita



10,000 cases per year

Muscarine poisoning
5,000 mushroom species
100 “bad”, 10 “deadly”

Adverse Reactions - Cholinergics

- **Adverse reactions:** (SLUDE)

  - **S**alivation
  - **L**acrimation
  - **U**rination
  - **D**iarrhea
  - **E**mesis (vomiting)

  - cardiac slowing (arrest, esp. bethanechol)
  - nausea, cramps
  - bronchoconstriction, can precipitate asthma
  - involuntary defecation, urination
  - tremor, CNS induced convulsions

Nicotinic receptor agonists

Ganglionic stimulants

- Clinically not important

- Acetylcholine (natural transmitter)
- DMPP (experimental)
- Nicotine (alkaloid, tobacco)
- Lobeline (tobacco)

Indirectly-Acting Parasympathomimetics

- **Interact with acetylcholinesterase**
  True and/or pseudocholinesterase (serum)

- **Two sites:**
  - anionic site that binds the quaternary amine and positions the Ach molecule

  - esteratic site which attacks the acyl carbon

- **Inhibitors of cholinesterase:**

  - Reversible inhibitors (eg. physostigmine)
  - Irreversible inhibitors (eg. organophosphates)

Reversible inhibitors

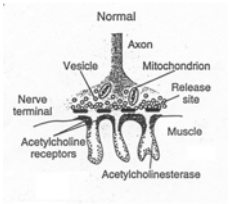
- **Quarternary ammonium compounds**
  - Edrophonium (synthetic, water stable, 5-10 min)
    Tensilon test – Myasthenia gravis
  - Ambenonium (synthetic, 4-8 hr)

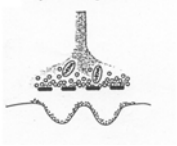
- **Carbamates**

  - Physostigmine (0.5-2 hr)
    (tertiary amine, well absorbed, cns activity, can give topically)

  - Neostigmine (0.5-2 hr)
    (quaternary amine, no cns activity, synthetic, some direct action)

Myasthenia gravis
Autoimmune disease





1:10,000 (250,000 USA)

- **antibodies to NMJ nicotinic receptors leads to degradation**
- **simplified synaptic folds**
- **normal nerve terminal and transmitter**
- **wider synaptic junction**

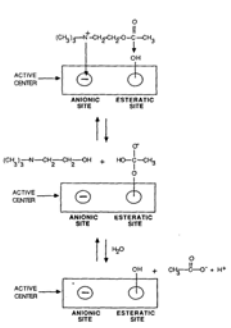
- **Diagnosis: Edrophonium (Tensilon, short acting) is used for diagnosis and determination of maintenance dose**

- **Treatment: Neostigmine has direct (stimulates receptor) and indirect actions (inhibition of AchE). No cns activity.**

Acetylcholinesterase and Reversible inhibitors

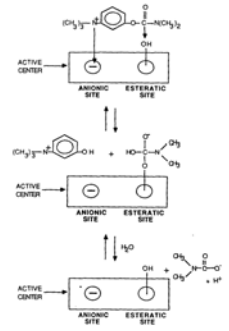
ACH

FIG. 17A Interaction of Acetylcholine and Acetylcholinesterase



Neostigmine

FIG. 17B Reversible Acetylcholinesterase Inhibitor



Ach very fast 0.15msec

Neostigmine undergoes metabolism 0.5 – 6 hr

Enzyme becomes operational again

Irreversible inhibitors

- **Organophosphates**
  (highly lipid soluble, >50,000 compounds)

  - Diisopropyl-fluorophosphate (DFP)

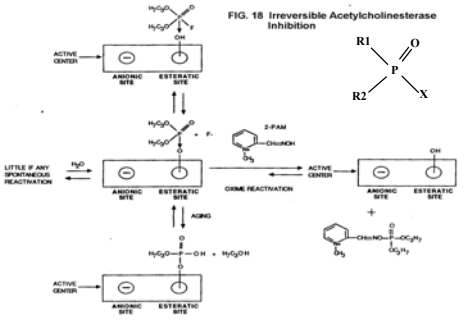
  - Echothiophate (low lipid solubility, no CNS)

  - Sarin, Suman (nerve gases)

  - Malathion, Parathion (more toxic)
    Inactive, converted to active compound in body (S → O)
    pesticides, very lipid soluble

Acetylcholinesterase & Irreversible Inhibition

DFP, Isoflurophate



2-PAM
Pralidoxime
No cns action

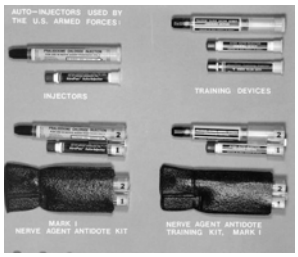
DFP Aging
30-40 min

Nerve gas
secs / min

Malathion
4 – 6 hr

US Military 2-PAM / Atropine Injector

2.5 mg Atropine, 600mg 2-PAM



Clinical use: Acetylcholinesterase Inhibitors

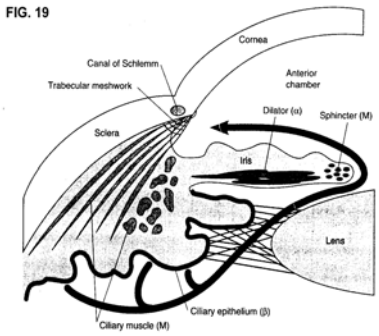
- **Eye:** miosis (sphincter contraction), accommodation block (ciliary muscle contraction)
  Use: Glaucoma (wide-angle or secondary glaucoma)
  Physostigmine or echothiophate (long acting)

- **GI tract:** ↑motility in paralytic ileus (post-op) or atony of urinary bladder. Neostigmine (bethanechol better)

- **Neuromuscular junction:**
  - Neostigmine in Myasthenia gravis
  - Edrophonium as diagnostic Myasthenia gravis
  - Reverse NMJ block after surgery, Neostigmine

- **Reverse toxicity by anticholinergic agents:**
  - ie. atropine, tricyclic antidepressants (high doses)
  - Physostigmine is preferred (CNS action)

Actions on the Eye



Glaucoma treatment

1. α-Agonist
↑Outflow

2. M-Agonists
↑Outflow

3. β-Blocker
↓Secretion

4. α2-Agonist
↓Secretion

5. PGs: ↑Outflow

6. Carbonic acid inhibitors ↓Secretion

Acetylcholinesterase Inhibitors

	Uses	Approximate Duration of Action
Alcohols		
Carbamates and related agents		
Organophosphates		

Toxicity & Treatment of AchE Inhibitors

- **Adverse reactions:** (SLUDE)
  - **S**alivation (muscarinic)
  - **L**acrimation (muscarinic)
  - **U**rination (muscarinic)
  - **D**iarrhea (muscarinic)
  - **E**mesis (vomiting) (muscarinic)
  - cardiac slowing (muscarinic)
  - hypertension / hypotension (nicotinic)
  - NMJ paralysis (nicotinic)
  - cramps (muscarinic)
  - bronchoconstriction (muscarinic)
  - tremor, nausea, CNS induced convulsions
- **Treatment:** Muscarinic antagonist ie. Atropine
  AchE reactivator (Pralidoxime, 2-PAM)
  mechanical respiration

Symptoms of Parasympathetic Toxicity

SLUDGE

S - Salivation
L - Lacrimation
U - Urination
D - Diarrhea
G - Gastric upset
E - Emesis

DUMBBELS

D - Diarrhea
U - Urination
M - Miosis/muscle weakness
B - Bronchorrea (↑mucus)
B - Bradycardia
E - Emesis
L - Lacrimation
S - Salivation/sweating