PRESENTING OUR

GKTEACH

STAGE 1 SERIES

MSA Education

~~FMS – CELL BIOLOGY AND SIGNALLING~~	~~MONDAY 13TH NOV 6PM~~
~~FMS – MOLECULAR AND CELL GENETICS~~	~~THURSDAY 16TH NOV 6PM~~
~~FMS – NUTRITION AND METABOLISM~~	~~TUESDAY 21ST NOV 6PM~~
~~ANATOMY OF RESPIRATORY AND CARDIOVASCULAR SYSTEMS~~	~~WEDNESDAY 29TH NOV 13:30PM~~
~~PHYSIOLOGY OF RESPIRATORY AND CARDIOVASCULAR SYSTEMS~~	~~WEDNESDAY 29TH NOV 4PM~~
FPP – PHARMACOLOGY	MONDAY 4TH DEC 6PM
RESPIRATORY PHYSIOLOGY	MONDAY 11TH DEC 6PM
RESPIRATORY ANATOMY	THURSDAY 14TH DEC 6PM

MAKE SURE TO COME ALONG!

FPP Pharmacology

GKTeach 23/24
Noor Amir Khan Y2

Lectures Covered

- The ANS - a pharmacological perspective
- Pharmacology of the Sympathetic Nervous System

Key Points

- You do **not** need to know all the drugs mentioned in lectures
  - Learn about the drugs in context – tried to only name relevant drugs in this teaching session!
- Focus on **understanding rather than memorising**. This applies to:
  - Sympathetic vs parasympathetic effects
  - Receptor classes
  - Drug classes vs memorising individual drug names
  - As much of medicine as you can!
- Feel free to interrupt + ask questions throughout the session!

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Basics

Section 1

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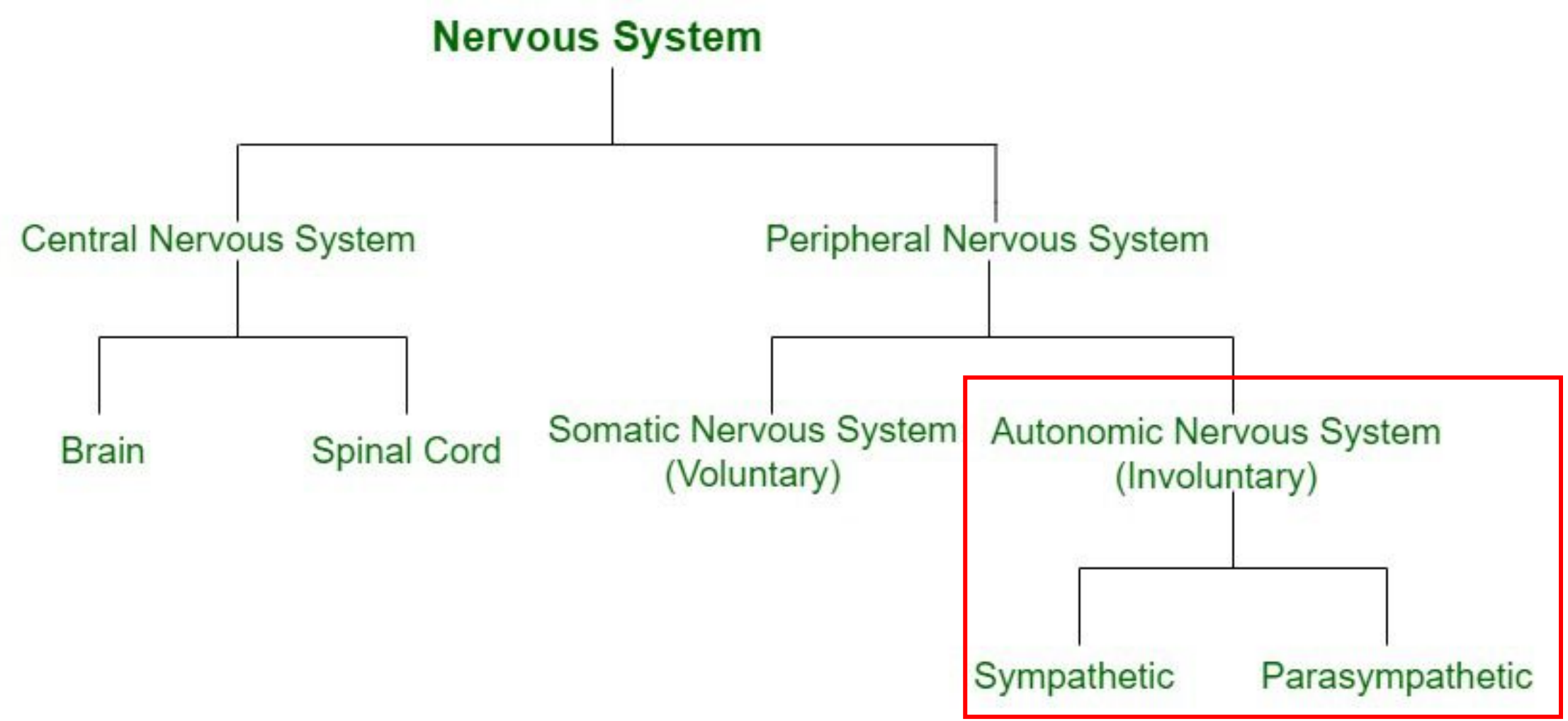
What are the divisions of the nervous system?



Sympathetic vs Parasympathetic Effects

Sympathetic = fight/flight

Parasympathetic = rest + digest

Smooth muscle: GI tract, bronchioles, detrusor muscle, (vascular)

Sympathetic and parasympathetic nerves cause opposite effects in some organs but not others

Function	Sympathetic effect	Parasympathetic effect
Heart rate		
Pupil diameter		
GI tract activity		
Detrusor muscle contraction		
Arterial tone		
Exocrine gland secretion		
Metabolism		
Renin secretion		
Bronchioles		
Erection/Ejaculation?		

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‘Exceptions’ – Exocrine Gland Secretion

Function	Sympathetic Effect	Parasympathetic Effect
General exocrine gland secretion		
Salivary glands		
Sweat glands		

Sympathetic = fight/flight

Parasympathetic = rest + digest

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How are afferent neurones generally structured in the ANS? SBA 1

A. Effector □ postganglionic neurone □ autonomic ganglion □ preganglionic neurone □ CNS

B. CNS □ preganglionic neurone □ postganglionic neurone □ autonomic ganglion □ effector

C. CNS □ preganglionic neurone □ autonomic ganglion □ postganglionic neurone □ effector

D. CNS □ postganglionic neurone □ autonomic ganglion □ preganglionic neurone □ effector

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C. CNS □ preganglionic neurone □ autonomic ganglion □ postganglionic neurone □ effector

D. CNS □ postganglionic neurone □ autonomic ganglion □ preganglionic neurone □ effector

- **Answer = C**

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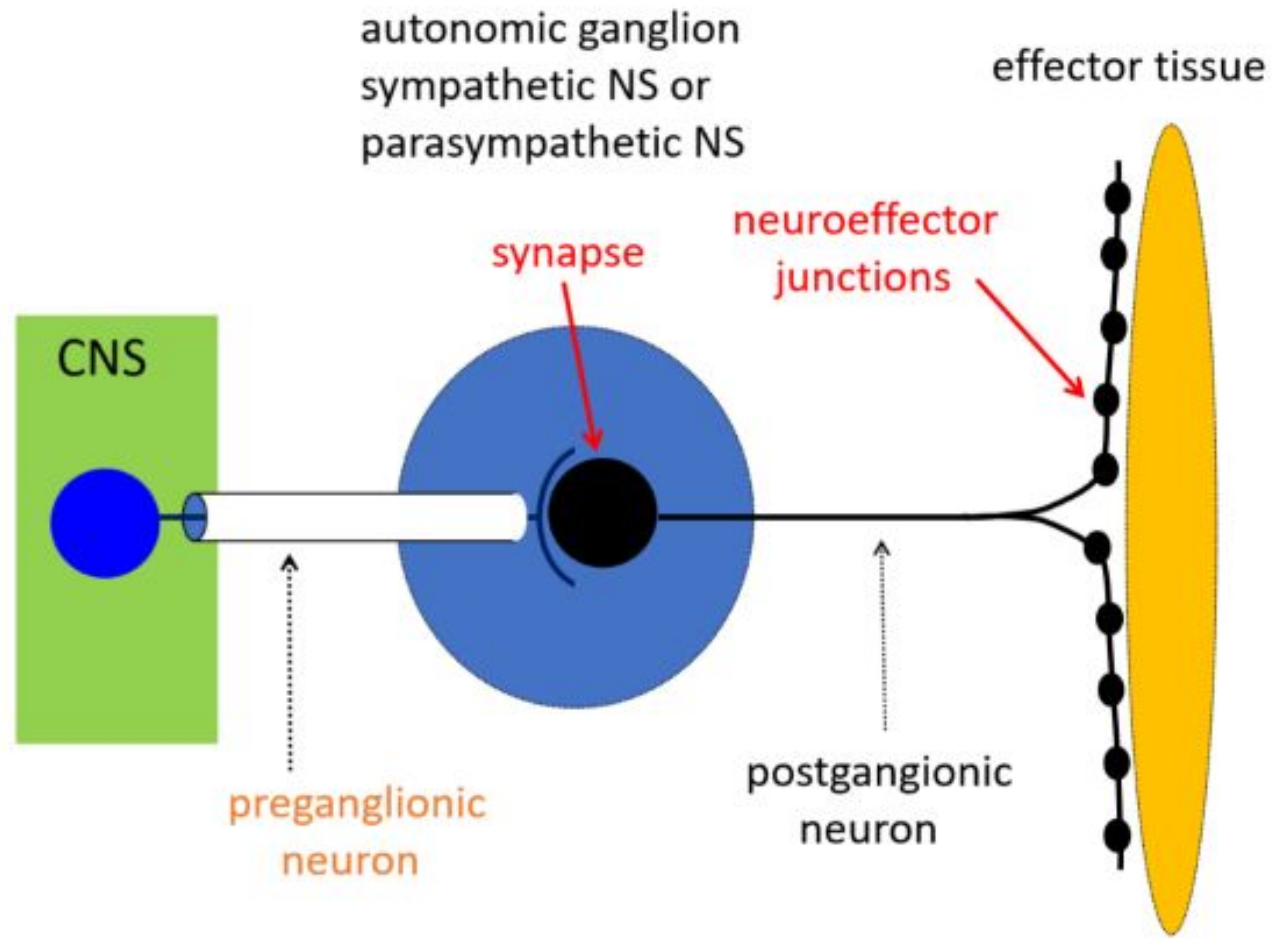
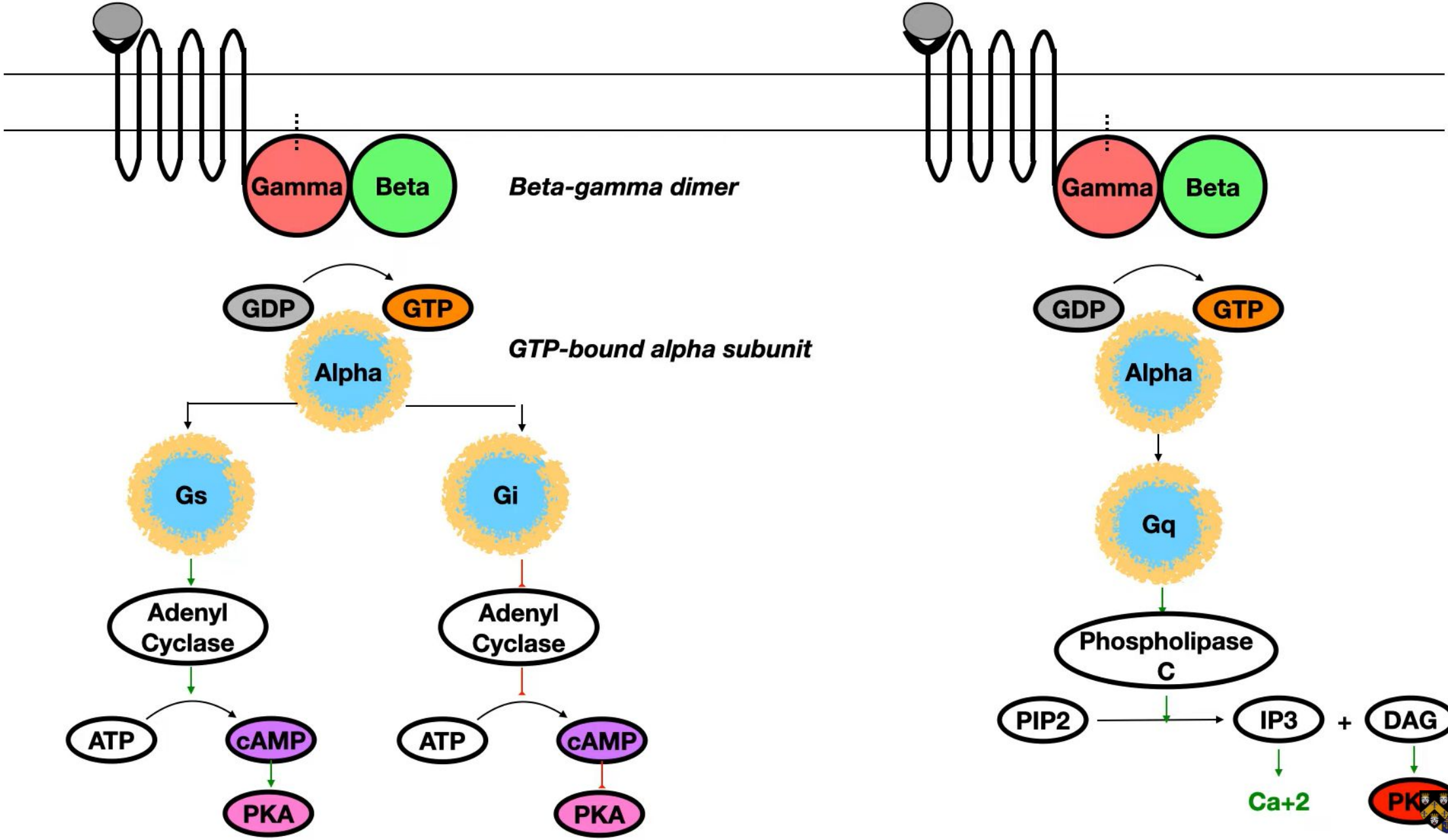
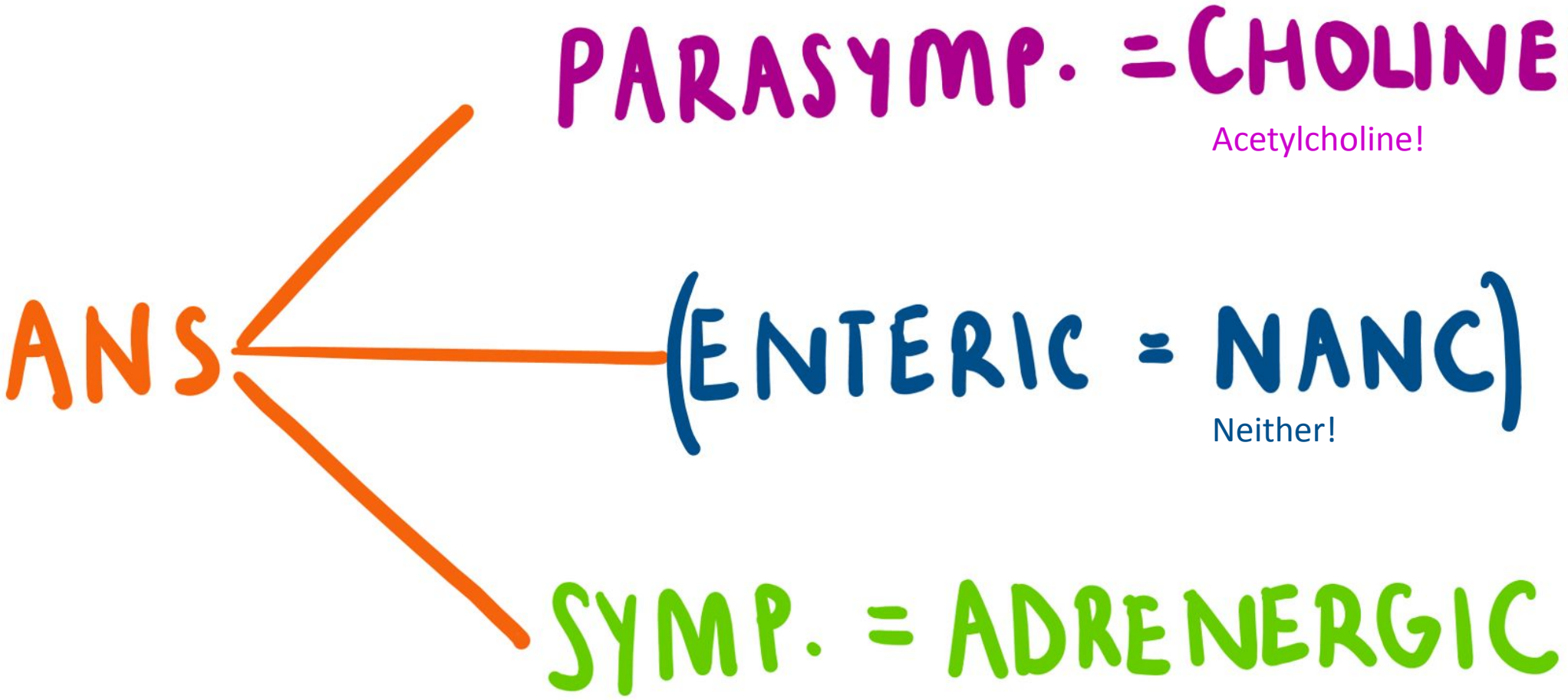
General afferent neurone structure ANS




Gamma
Beta
Beta-gamma dimer
GDP
GTP
Alpha
GTP-bound alpha subunit
Gs
Gi
Adenyl Cyclase
Adenyl Cyclase
ATP
cAMP
ATP
cAMP
PKA
PKA
Gamma
Beta
GDP
GTP
Alpha
Gq
Phospholipase C
PIP2
IP3
+
DAG
Ca+2
PK

ANS Receptor Types



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Smooth muscle = detrusor muscle, bronchioles, GI tract

Cholinergic = generally parasympathetic

CHOLINERGIC

NICOTINIC

Non-selective cation channel
= DEPOLARISATION

↳ muscle (skeletal)

↳ ganglionic

MUSCARINIC

G protein coupled
= 2° messengers

↳ M2 = ♡
Gi = ↓ aden. cyclase
↓ cAMP

↳ M3 = SMOOTH MUSCLE
Gq = IP_3 + DAG

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Smooth muscle = detrusor muscle, bronchioles, GI tract, (vascular)

Adrenergic = generally sympathetic

ADRENERGIC

Noradrenaline!

α

↳ α_1 = Gq = ↑IP_3 + DAG
= ↑Ca^{2+} ↑PKC

vascular SM vasoconstriction

↳ α_2 = Gi = ↓adenyl. cyc.
= ↓cAMP

autoreceptors on presynaptic membrane

β

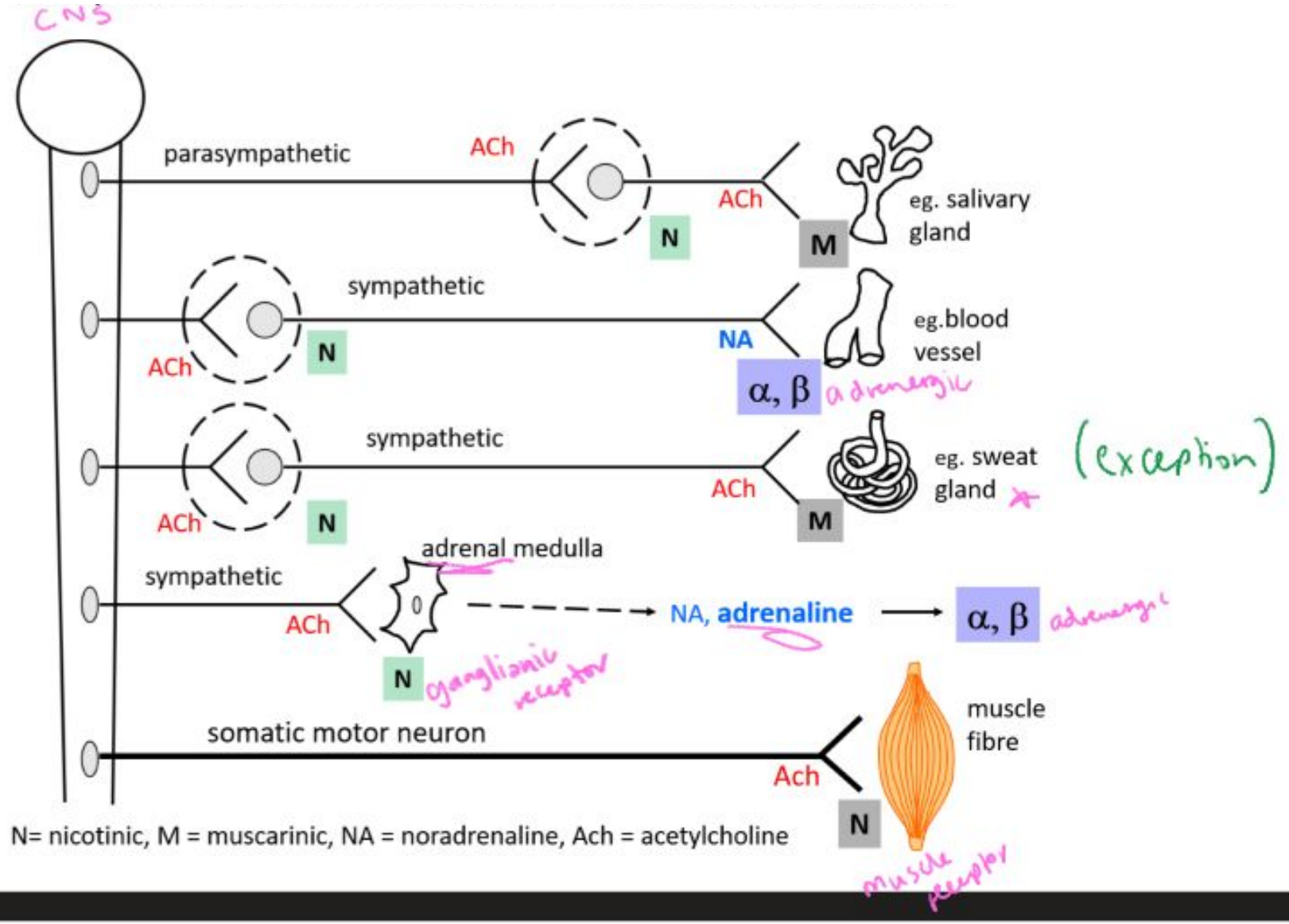
★ All Gs = ↑aden cyc
= ↑cAMP ★

↳ β_1 = ♡ (1x)
+ kidneys ↑RAAS

↳ β_2 = LUNGS (x2)
vascular + airway

↳ β_3 = adipose/bladder
β3 stops your pee!

Afferent Neurones, Receptors, Neurotransmitters



All **preganglionic** neurones and ganglia are **cholinergic**, specifically nicotinic receptors as they allow fast transmission across ganglion.

The **second receptor** + neurotransmitter is determined by the **effector**

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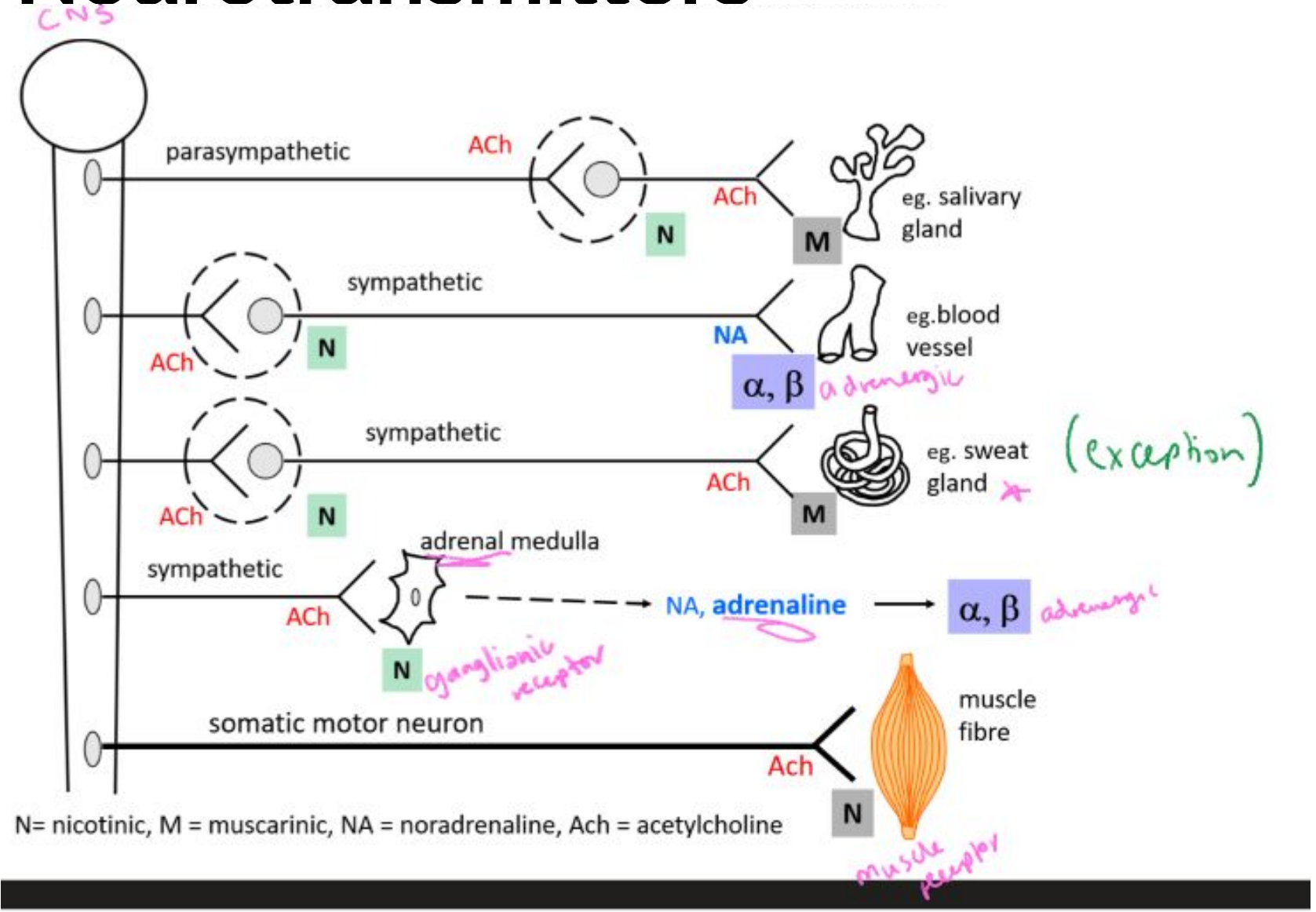
Afferent Neurones, Receptors, Neurotransmitters



- Parasympathetic has _____ preganglionic neurones and ____ postganglionic neurones? (length)
  - LONG preganglionic
  - SHORT postganglionic
- Sympathetic has _____ preganglionic neurones and ____ postganglionic neurones?
  - SHORT preganglionic
  - LONG postganglionic
  - Except adrenal medulla = DIRECT
- Somatic neurones are for ___ muscle?
  - Skeletal muscle (PNS)
  - DIRECT

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Quick Quiz!

- Which receptor is responsible for relaxing the detrusor muscle?
  - B3 stops your pee! (**s**ympathetic = **s**torage)
- Which part of the nervous system is responsible for increasing peristalsis?
  - Parasympathetic
- Which G-protein coupled receptor is responsible for M2?
  - Gi = inhibitory. M2 = decreasing HR, contractility and CO of cardiac muscle (parasympathetic)
- Is changing the composition of saliva parasympathetic or sympathetic?
  - Sympathetic – changing saliva composition
  - Parasympathetic – increasing saliva production

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Specific Parasympathetic Effects + Managing Conditions

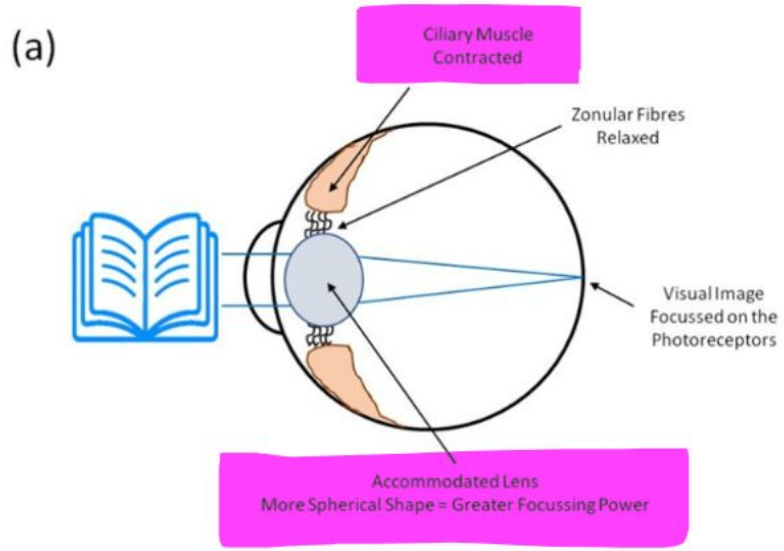
Section 2

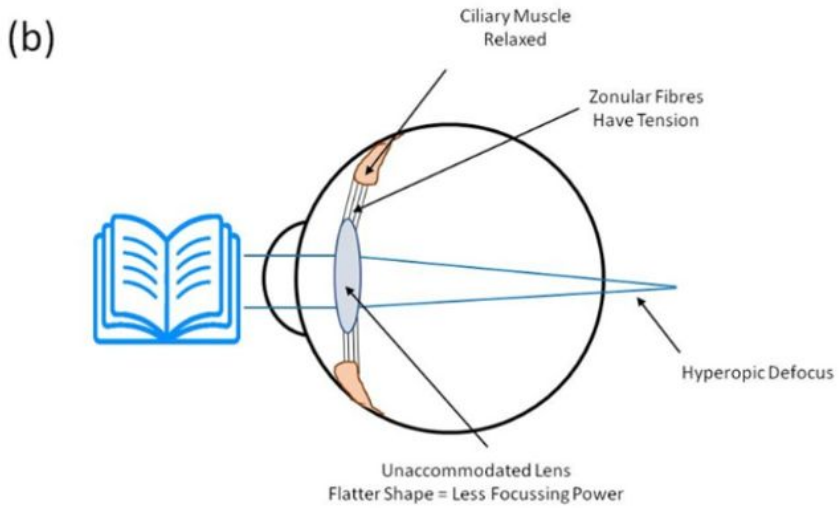
The Eye

Sympathetic	Parasympathetic
Pupil dilatation	Pupil constriction/pupillary light reflex
	Visual accommodation = focusing

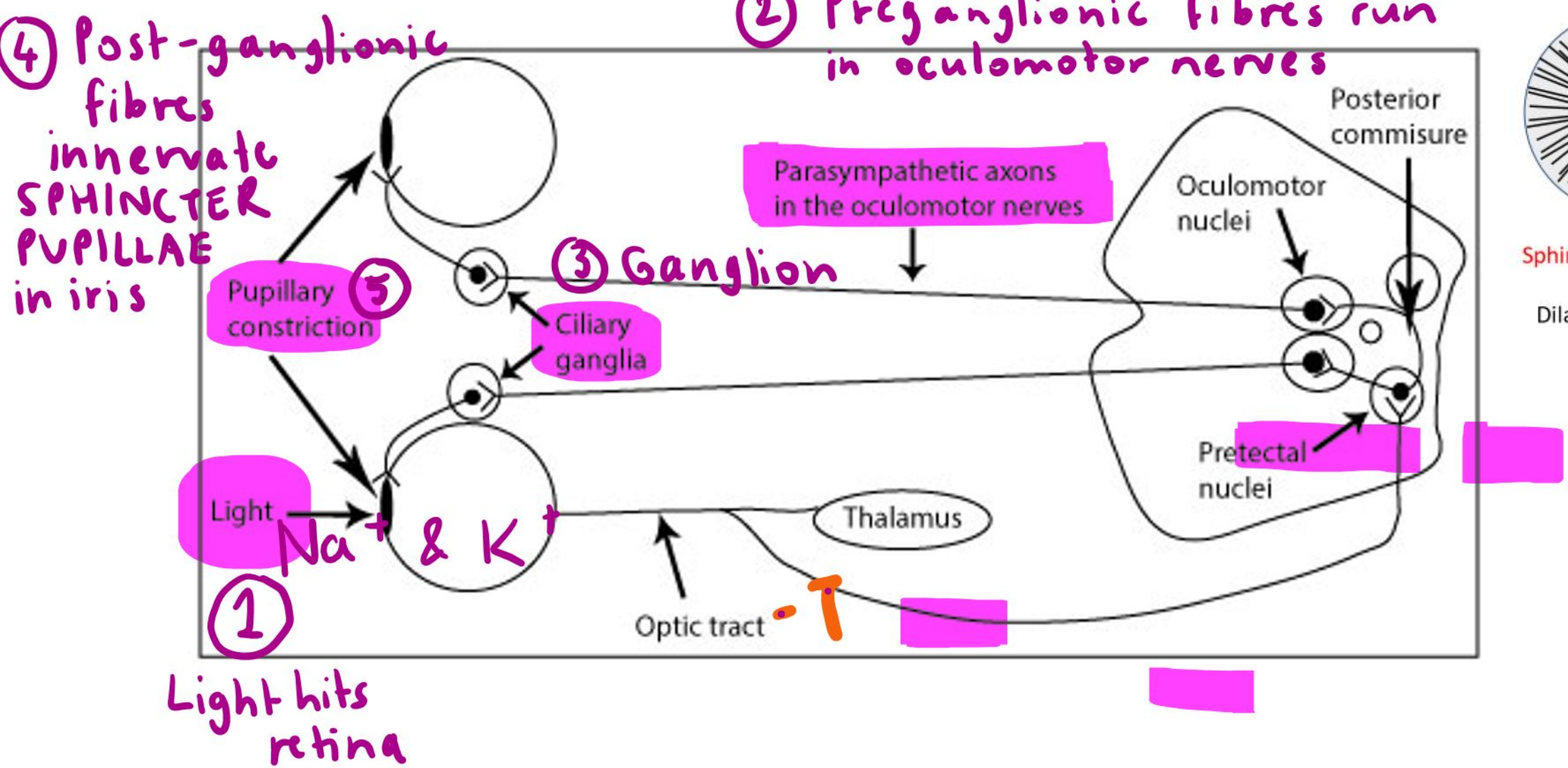
<u>Visual Accommodation: PARASYMPATHETIC (eg reading = relaxing)</u>

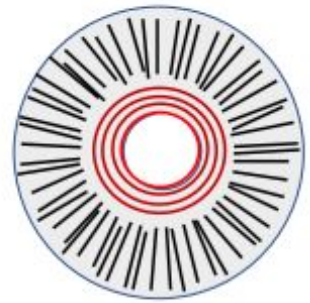
- Ciliary muscle contracts = thick
- Lens relaxes = thin
- Therefore, focus on objects that are near





Pupillary Light Reflex = PARASYMPATHETIC





Sphincter pupillae

Dilator pupillae

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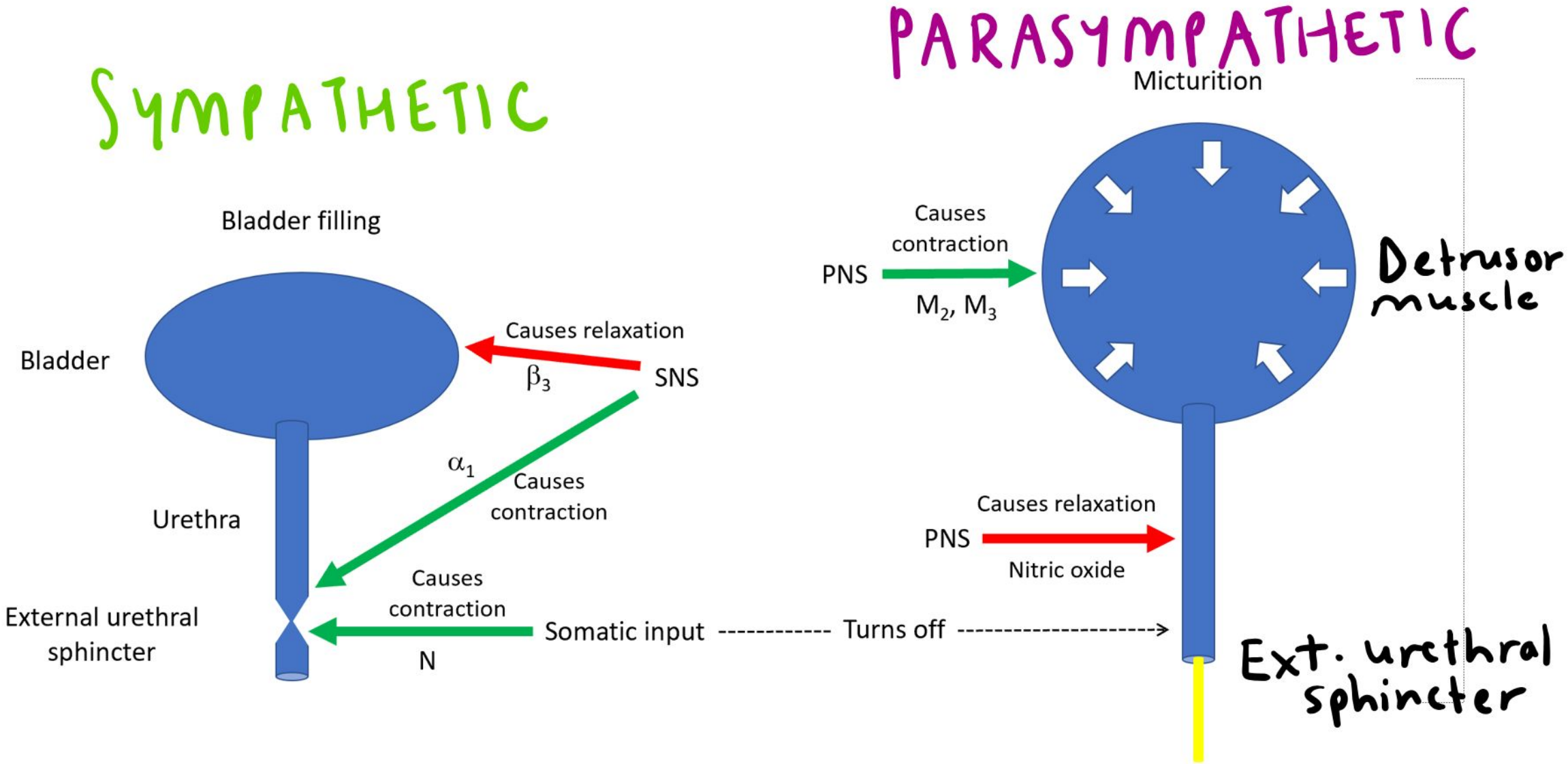
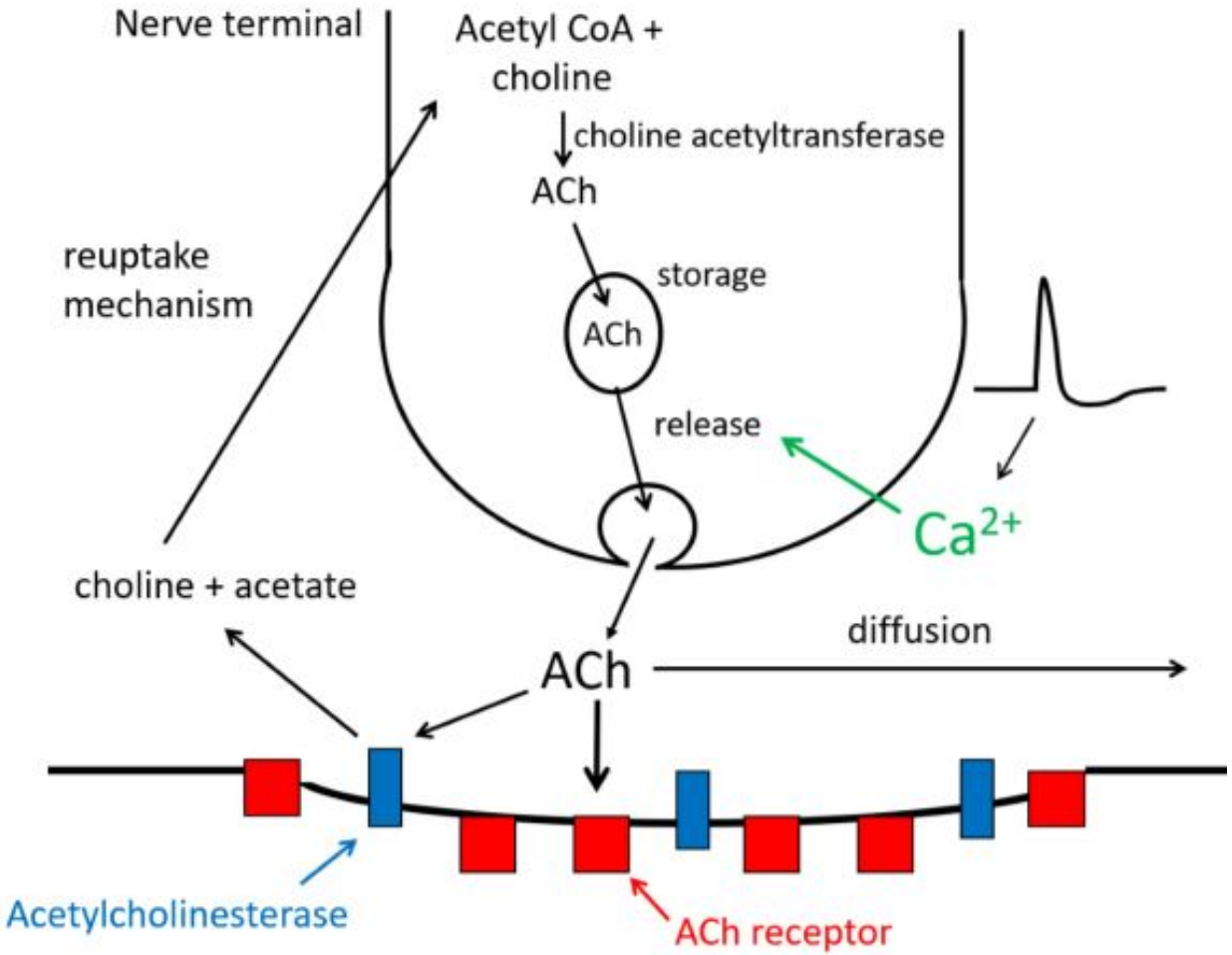
Control of Micturition



Cholinergic Neurotransmission



Drugs Affecting Cholinergic Neurotransmission?

Smooth muscle = detrusor muscle, bronchioles, GI tract

Cholinergic = generally parasympathetic

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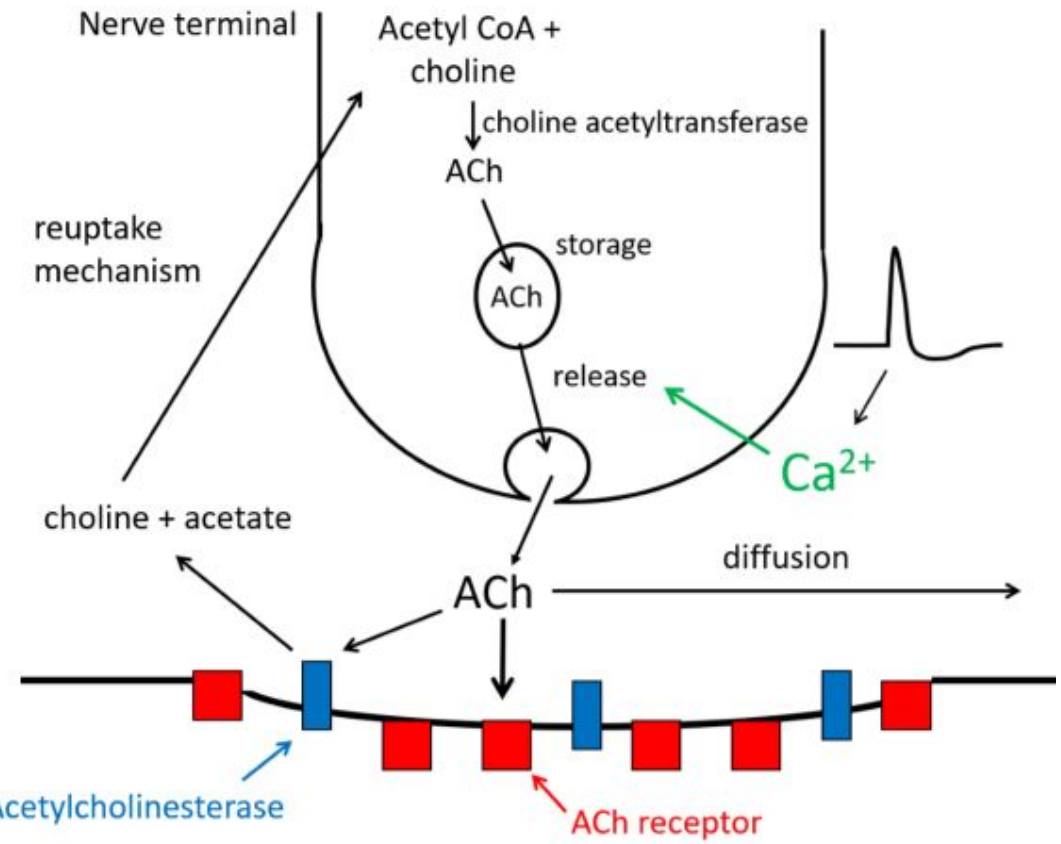

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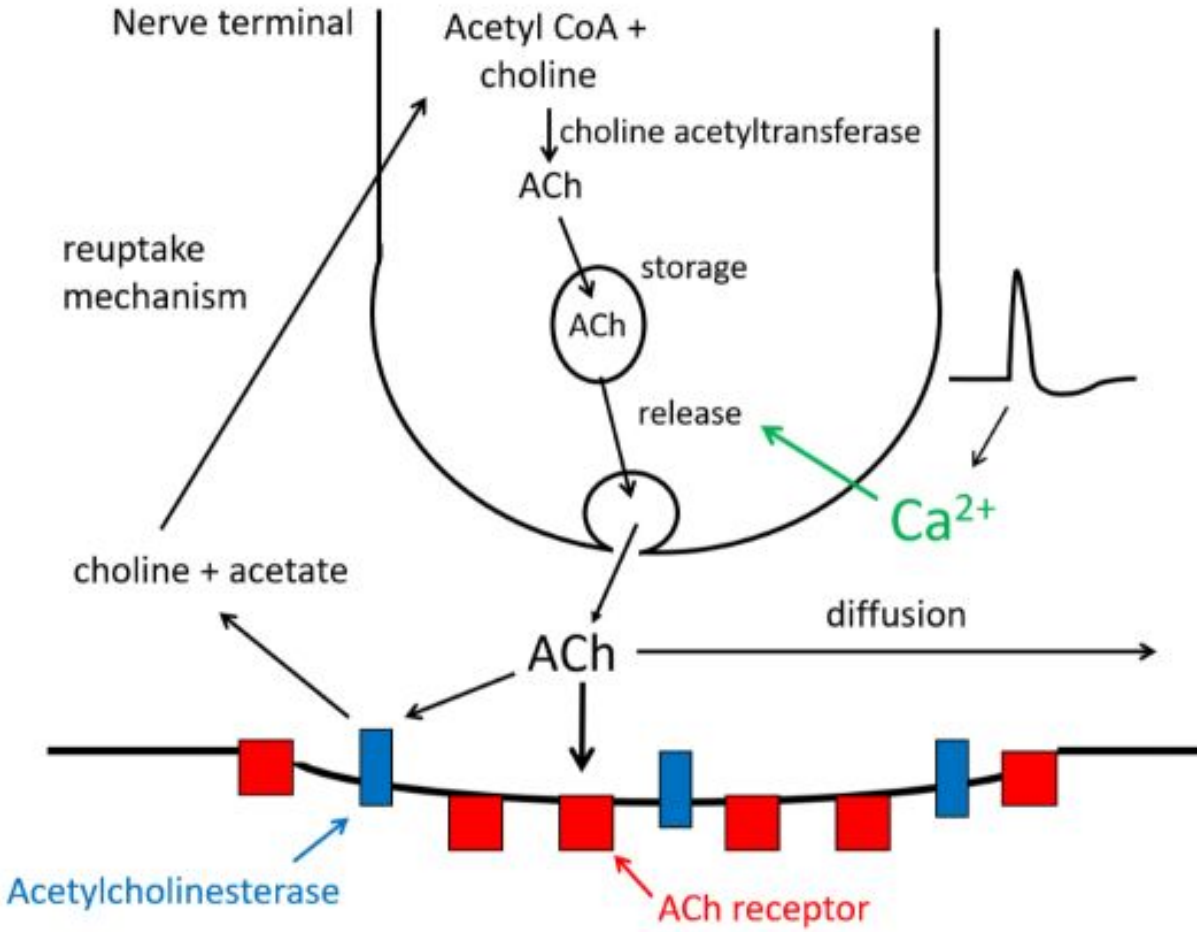
Drugs Affecting Cholinergic Neurotransmission



M2, M3, N (muscle), N (ganglion)

<u>Decrease effects: ie decrease parasympathetic</u>

- RECEPTOR ANTAGONISTS (muscarinic, nicotinic ganglionic/neuromuscular)
- Neurotransmission step = stop Ach from being released from vesicle (botulinum toxin)

<u>Exacerbate effects: ie increase parasympathetic</u>

- RECEPTOR AGONISTS (Nicotine, Muscarinic agonist)
- Neurotransmission step = cholinesterase inhibitor stops Ach breakdown

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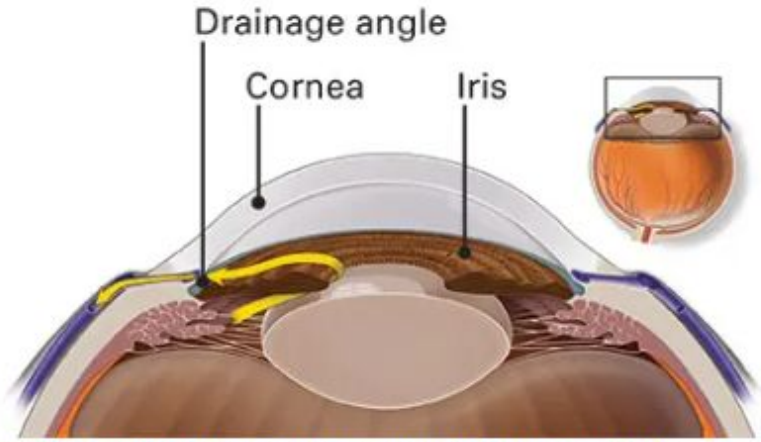
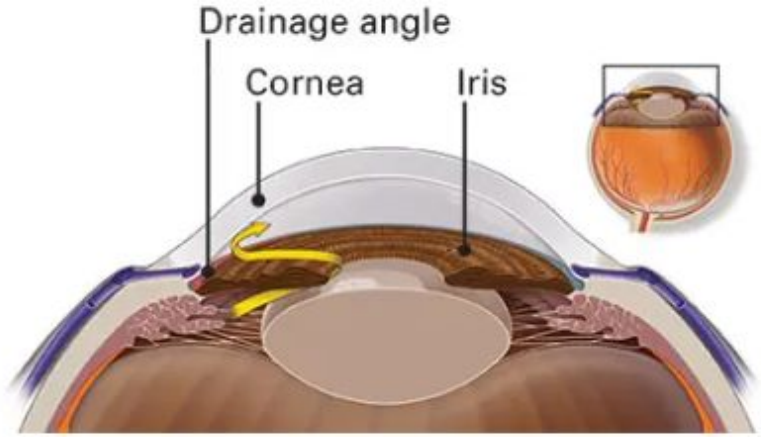
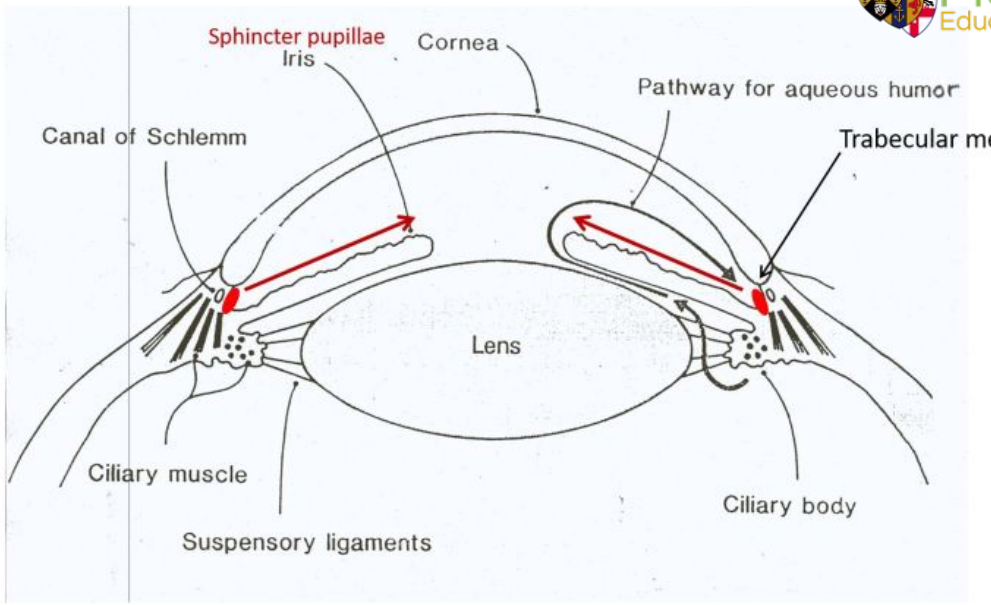
Closed Angle Glaucoma



In a healthy eye, fluid leaves the eye through the drainage angle, keeping pressure stable.



With angle-closure glaucoma, the drainage angle becomes blocked by the iris.



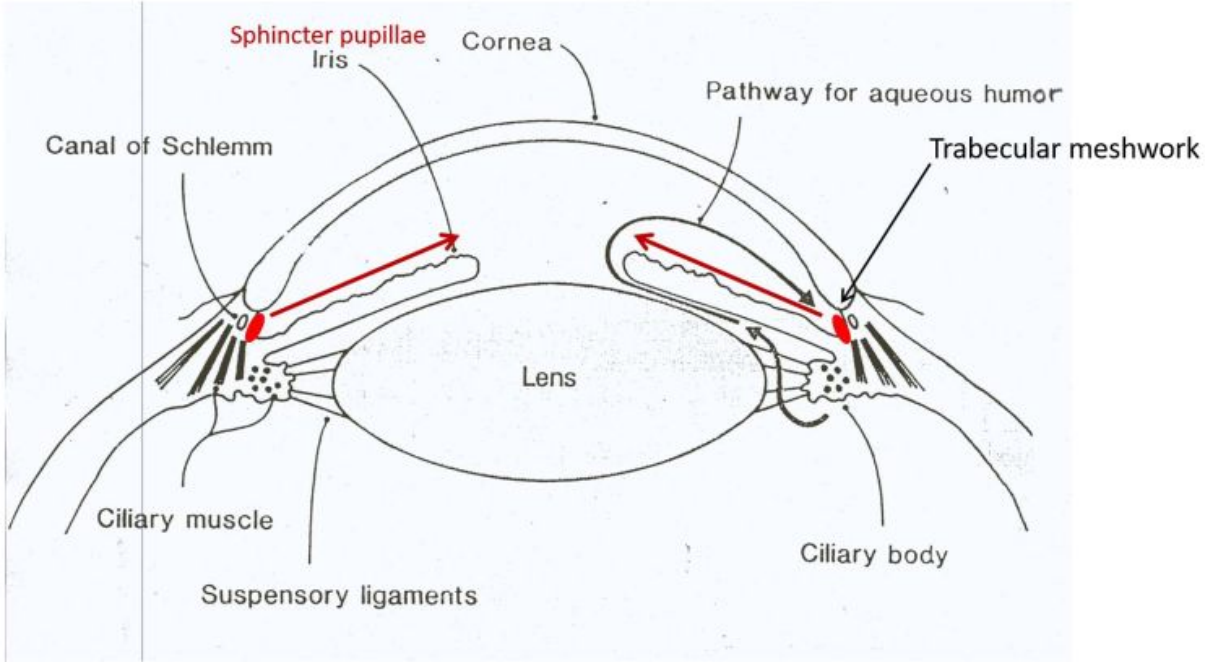
- Lack of ACh in the sphincter pupillae of iris
- Sphincter pupillae in iris relaxes
- Pupil is relaxed

- Aqueous humour can't leave through the Canal of Schlemm
- This increases intraocular pressure

How could we treat this?

Treating Closed Angle Glaucoma

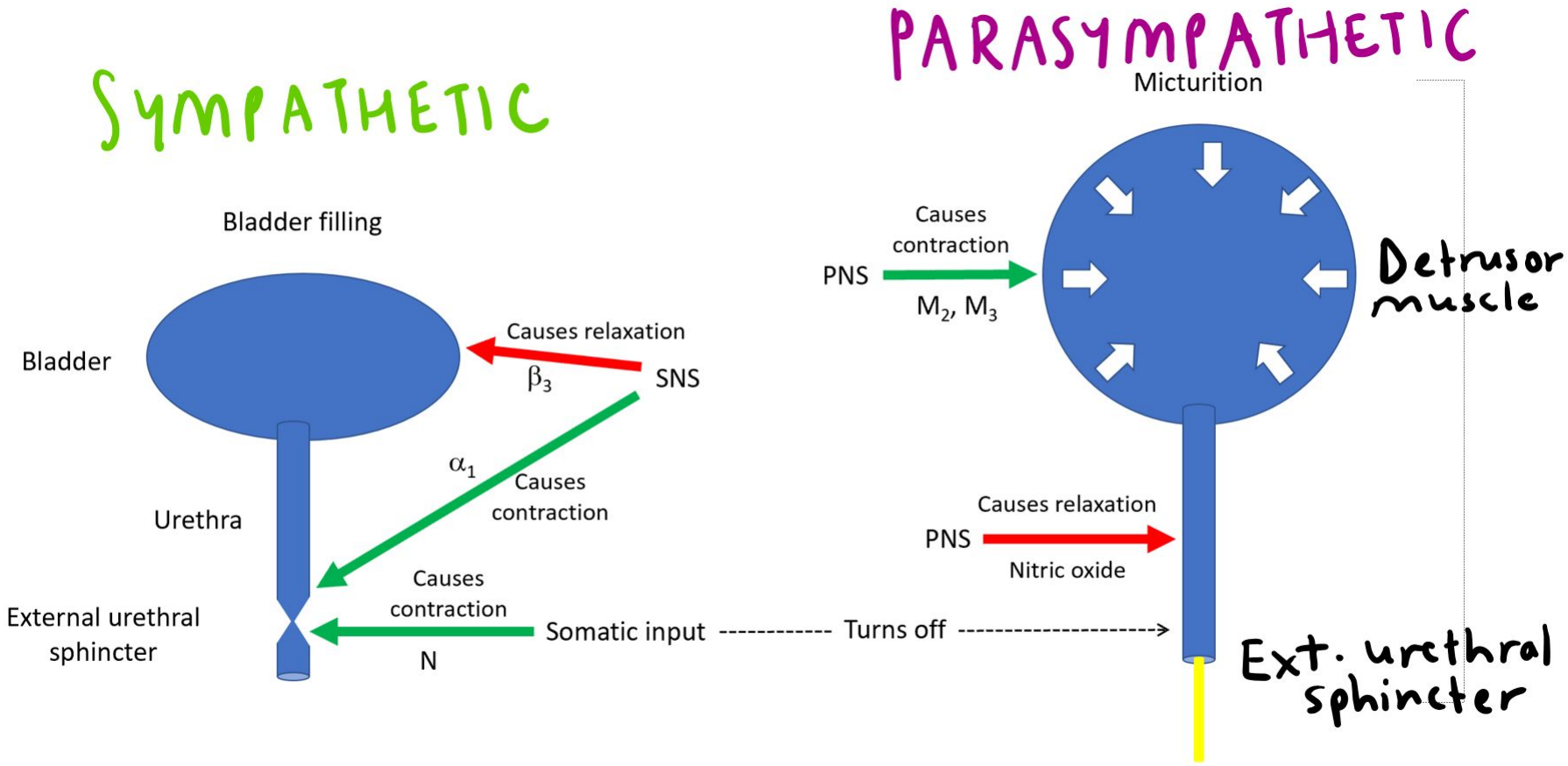
- PROBLEM: too little ACh
- SOLUTION: prevent ACh breakdown through cholinesterase inhibitors = ecothiopate eye drops
- ACh causes sphincter pupillae in iris to contract, pupil constricts
- Space for the aqueous humour to flow i canal of Schlemm
- Intraocular pressure decreases



- We could also use an M agonist!

How can we treat bladder incontinence?

- Wall of bladder inflamed **bladder starts contracting inappropriately = bladder hyperreactivity** incontinence



Treating Bladder Incontinence

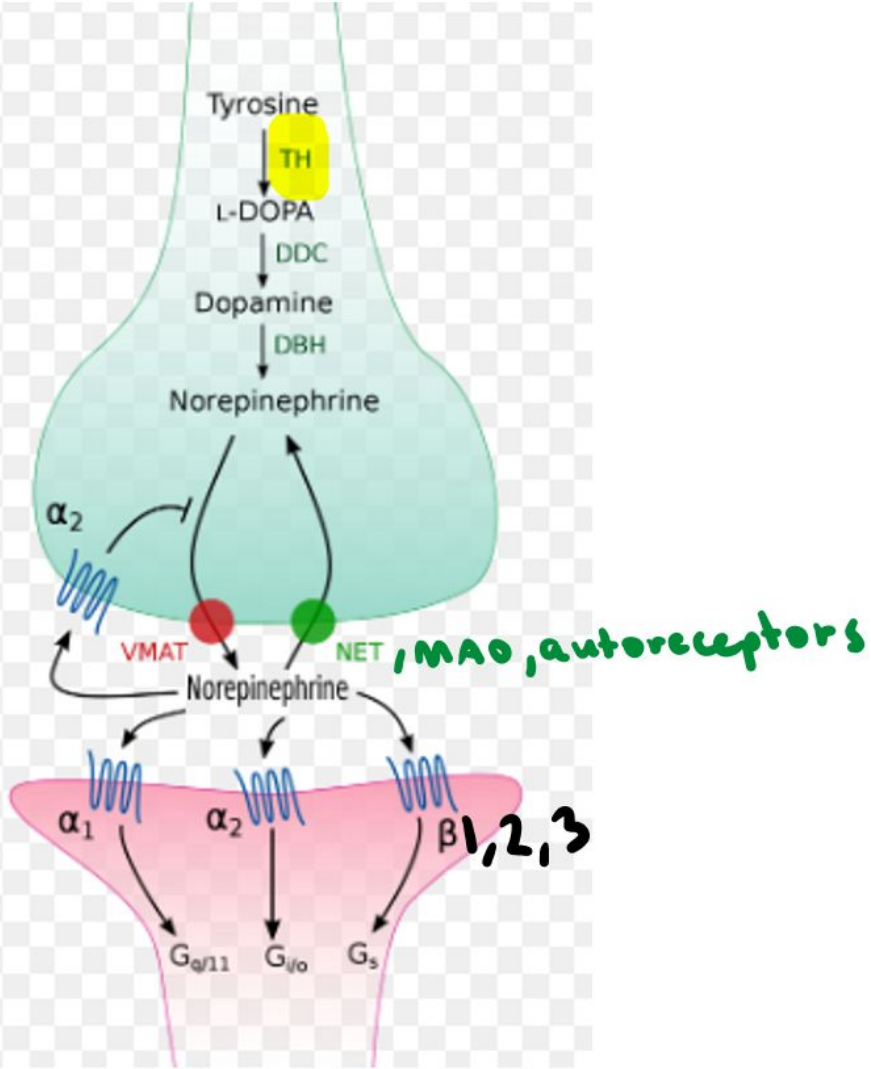
- Too much parasympathetic action (ACh) decrease ACh release = botulinum toxin A/botox
- Too much parasympathetic action (Ach) block M3 receptors (smooth muscle)
- Not enough sympathetic action activate B3 (B3 stops your pee!)

BOTOX = skin wrinkles, relax muscle spasms too!

Specific Sympathetic Effects + Managing Conditions

Section 3

Noradrenergic Synapse Transmission



, MAO, autoreceptors

- Synthesis and storage of noradrenaline in Vesicles
- Depolarisation of Presynaptic Terminal
- Activation of Voltage-Gated Ca^{2+} channels
- Vesicle fusion with nerve terminal membrane and exocytosis
- Diffusion of noradrenaline across synaptic cleft
- Activation of post-synaptic adrenergic receptors
- Generation of post-synaptic signal
  - *Activation of Second messenger cascades (neuroeffector junction)*
- Signal termination

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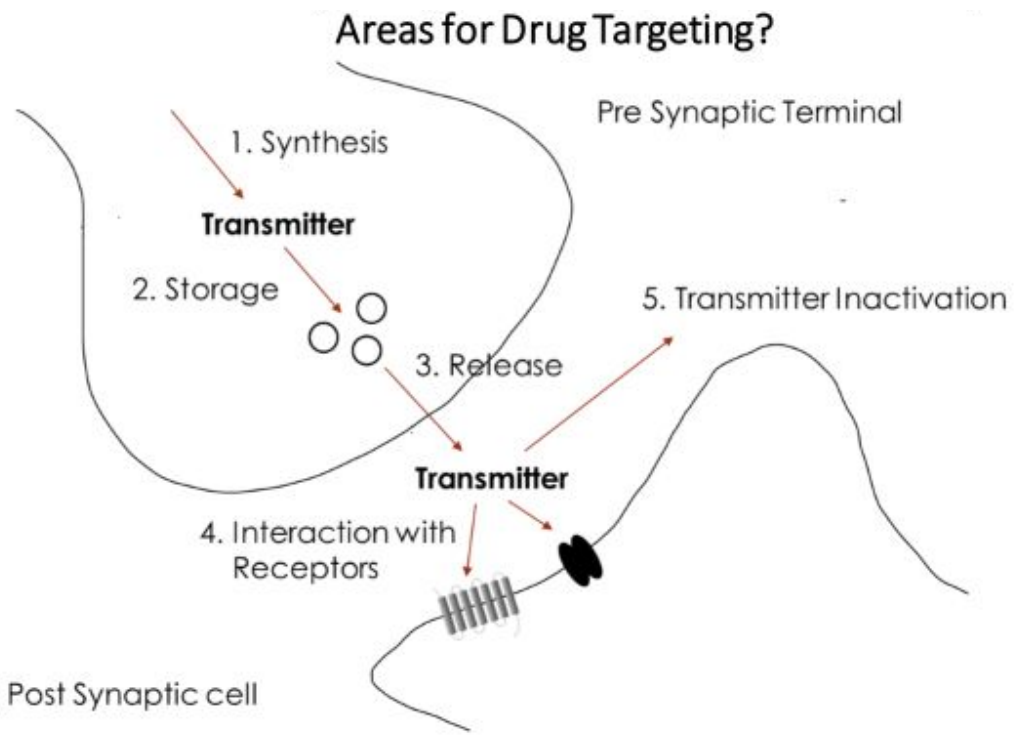
How is NA formed



tyrosine

↓ tyrosine hydroxylase

DOPA

↓

dopamine

↓

NA → adrenaline

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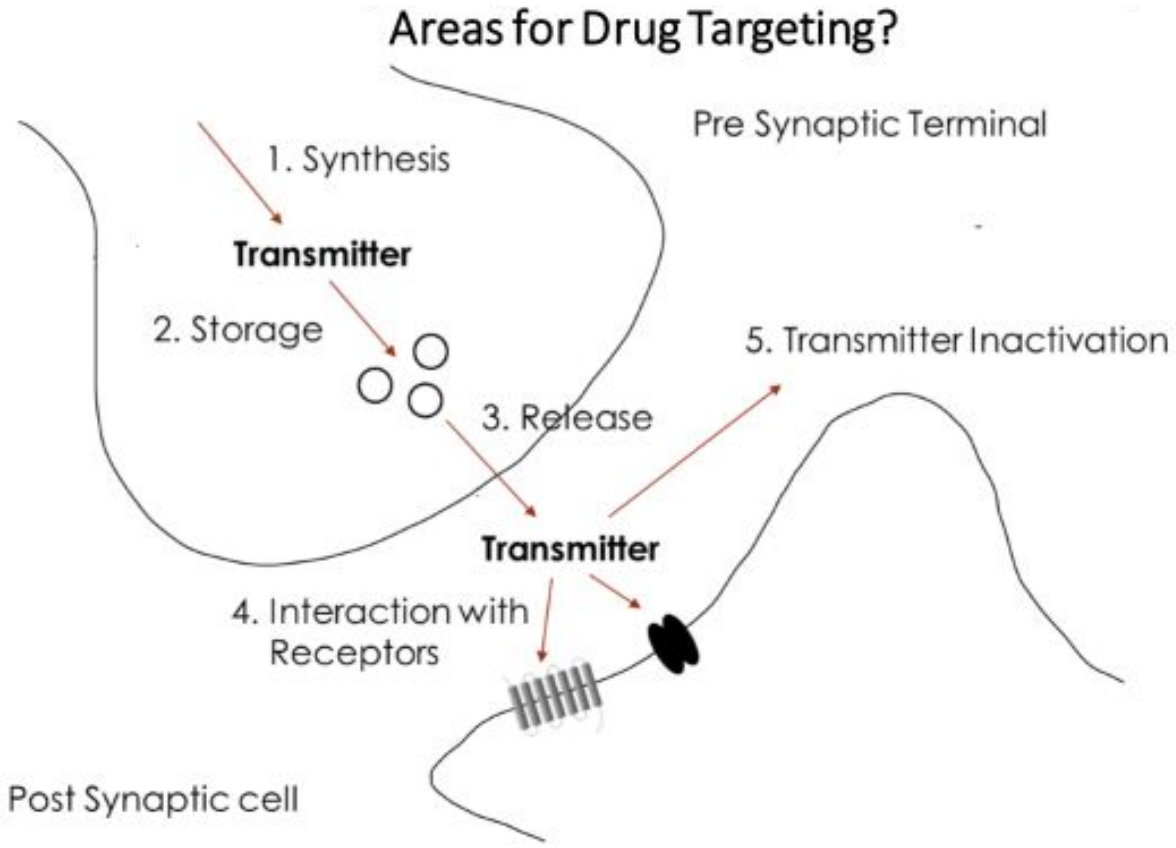
Why is NA stored + how?

- Noradrenaline is an unprotected monoamine
- Unprotected monoamines are broken down by MAO
- Therefore loaded into vesicles via VMAT for protection



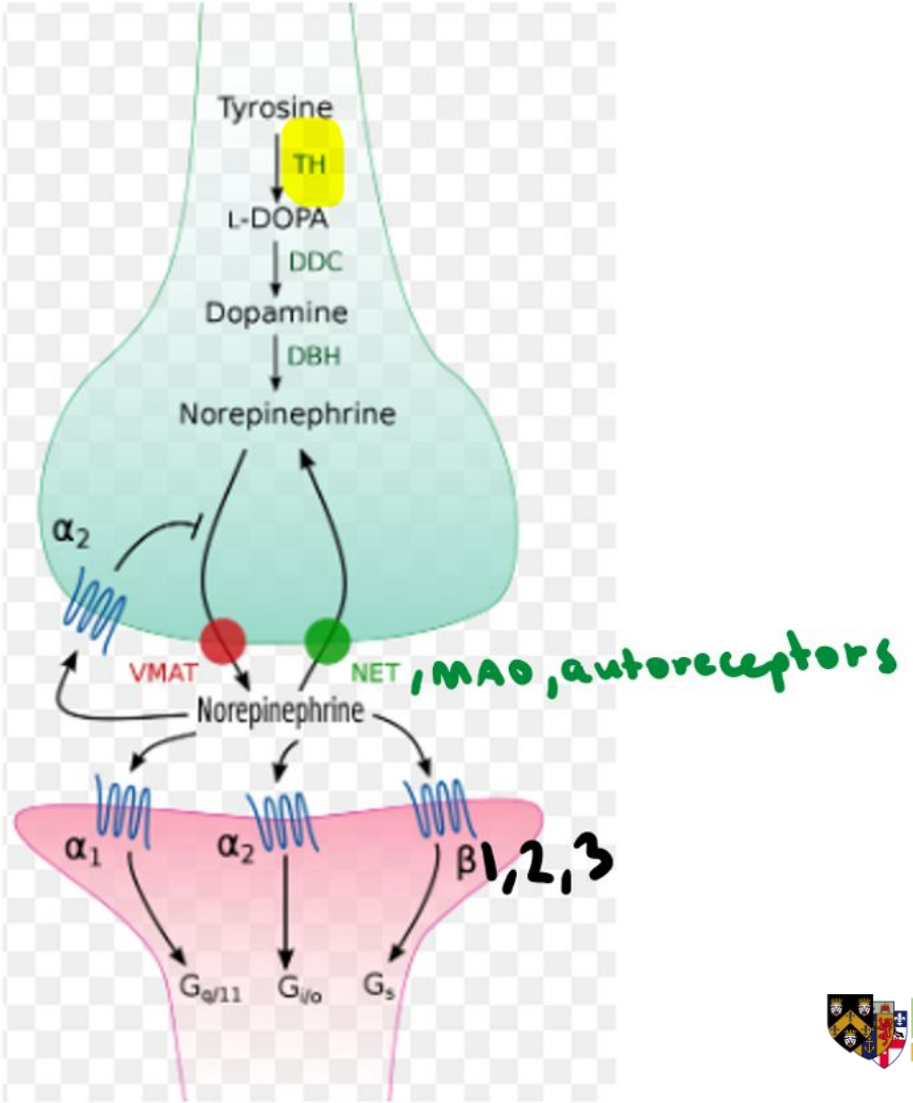
How is excess NA production prevented?

1) Simple Diffusion away from the synapse

2) Uptake of neurotransmitter into the presynaptic terminal or by other cells e.g. **Uptake of NA through the norepinephrine transporter (NET)/Uptake 1**

3) Enzymatic degradation e.g. **MAO_A**

- 'negative feedback' – autoreceptors/NET (alpha 2) on presynaptic membrane
- When bound to, alpha 2 = Gi = inhibitory effect, stops exocytosis of NA



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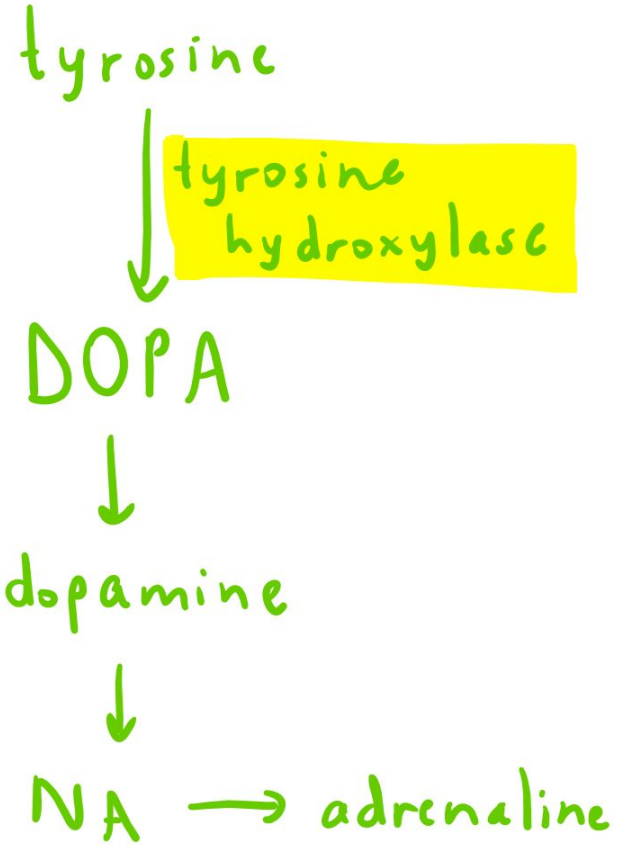
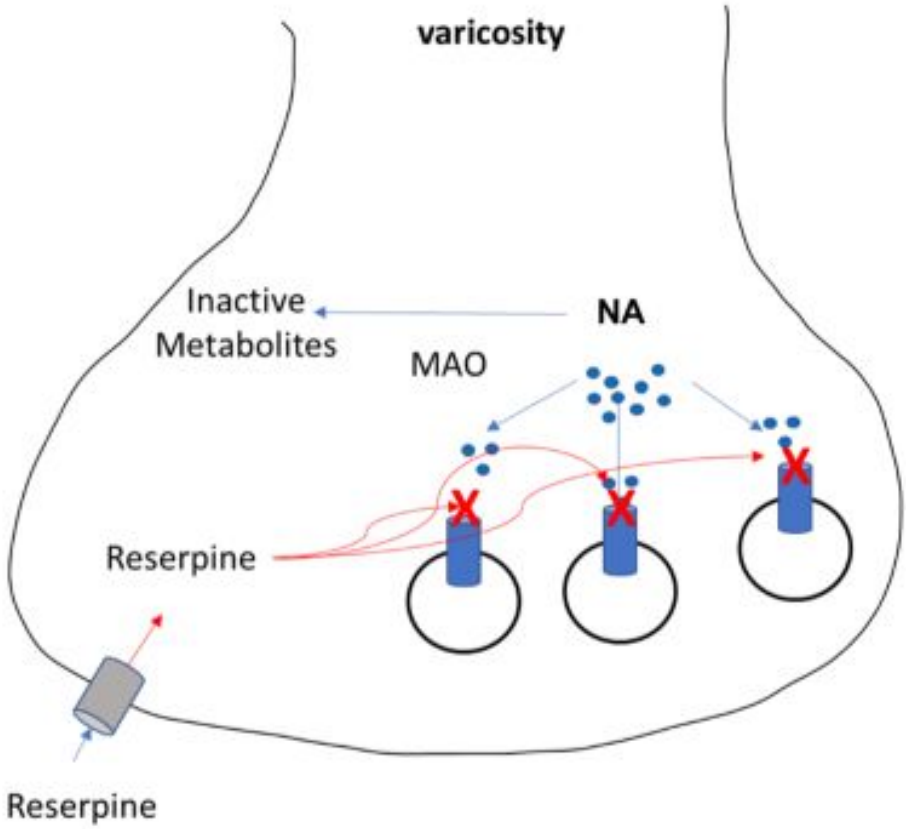
α methyl tyrosine

- α methyl tyrosine blocks the action of tyrosine hydroxylase? What effect will it have on blood pressure?
  - Tyrosine isn't converted to DOPA… less NA
  - This **decreases** BP
  - Side effects: decreased sympathetic/increased para. =
  - Sedation
  - Parkinsonism
  - Diarrhoea (increase gastric motility)



Reserpine

- Reserpine stops the packaging of NA into vesicles to prevent depletion of functional neurotransmitter.
- Reserpine is acting against the action of _ _ _ _?
  - VMAT
- Will this cause an increase or decrease of NA?
  - As NA isn't protected, MAO breaks it down, NA decreases
  - This can lead to CNS depression = side effect



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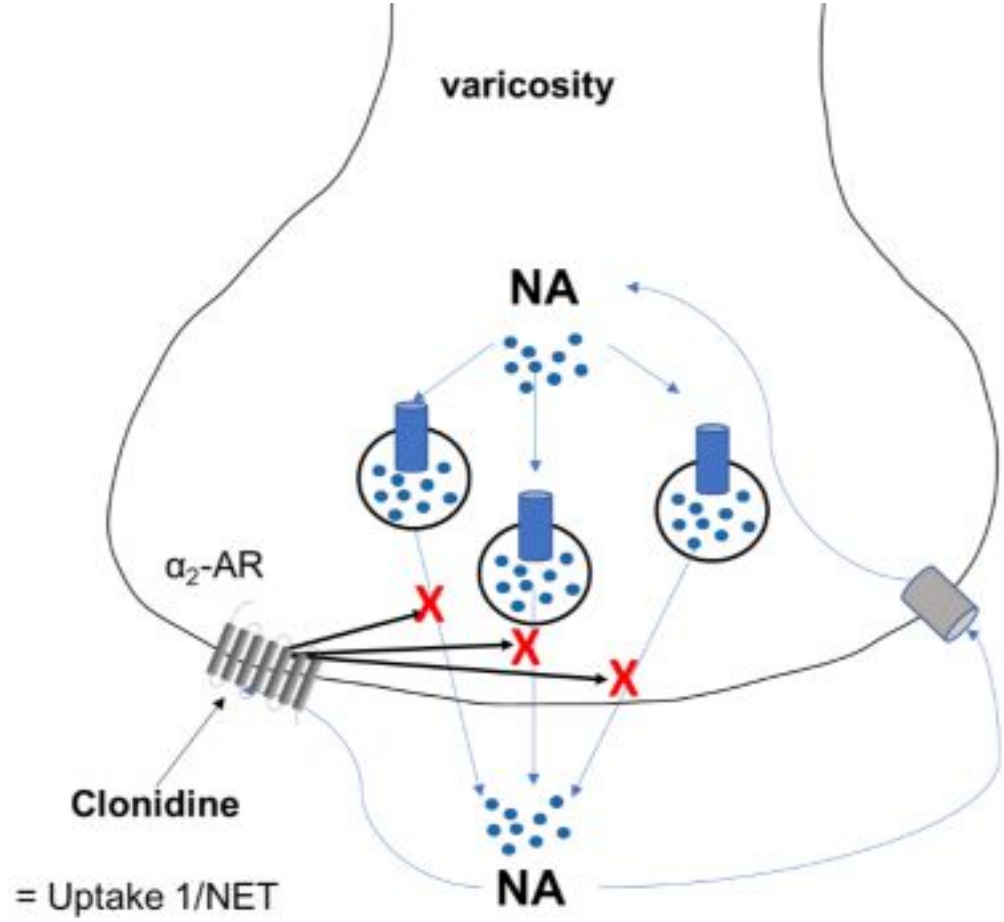
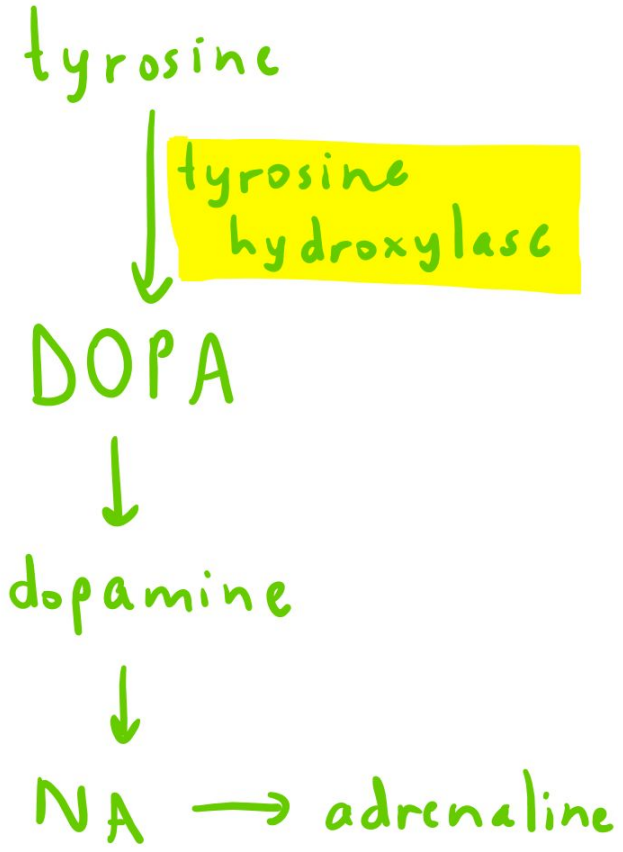
Clonidine

- Clonidine causes stimulation of NET/autoreceptors. What effect will this have on the levels of NA in the synaptic cleft?
  - NET/Autoreceptors = Gi = inhibitory action
  - Therefore prevent neurotransmitter release from vesicles
  - Low conc of NA in synaptic cleft



The Cheese Effect/ MAO Inhibitors

- Tyrosine is found in cheese, wine and yoghurt. It is normally degraded by MAO. A patient takes a MAO inhibitor. How will this affect the patient's blood pressure if they eat a lot of cheese and yoghurt?
  - MAO inhibitor = tyrosine not metabolised
  - Tyrosine builds up
  - This leads to formation of NA
  - Blood pressure **increases** (hypertensive crisis!)



A Note on Selectivity

- The more selective a drug is (ie acts on a specific receptor) = fewer side effects

Anti-hypertensives

- We don't like using non-selective alpha blockers severe reflex tachycardia

Other options for hypertension:

- **Doxasosin** = selective a1 antagonist (stops vasoconstriction)
- **Labetalol** = non-selective a/b antagonist
- **Propranolol** = b-selective (b1/2)
- **Atenolol** = selective b-1 antagonist (decreases HR + contractility – good for angina too!)

Salbutamol and Asthma

- In asthma the airways are constricted so there isn't enough air going to the lungs
- **SALBUTAMOL = B2 agonist**
- (2 lungs) = bronchodilation - lets more air inside = **ASTHMA**

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SBAs

Nearly at the end, keep going!

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SBA 2

Which receptor could you block to treat **hypertension or heart attack**?

A. B1
B. B2
C. Nicotinic for muscle
D. M2

SBA 2

Which receptor could you block to treat **hypertension or heart attack**?

A. B1
B. B2
C. Nicotinic for muscle
D. M2

Answer: A

SBA 3

- An anaesthetist injects adrenaline at the site of injection. Which statement is correct?

A. This will encourage bleeding from the site of injection, therefore decreasing the chance of acquiring an infection from the needle tip

B. The adrenaline will act on alpha 2 receptors

C. This will prolong the action of the anaesthetic

D. This will act on M3 receptors

E. This will speed up dilution of the anaesthetic

SBA 3

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B. The adrenaline will act on alpha 2 receptors

C. This will prolong the action of the anaesthetic

D. This will act on M3 receptors

E. This will speed up dilution of the anaesthetic

Answer : C

SBA 4

- **Ipratroprium** is a muscarinic receptor antagonist. Which of the following is true?

A. This is a cholinergic drug

B. This can cause dry mouth

C. This can cause bronchoconstriction

D. This can cause bradycardia

SBA 4

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A. This is a cholinergic drug

B. This can cause dry mouth

C. This can cause bronchoconstriction

D. This can cause bradycardia

Answer: B

SBA 5

Which medication would you give a patient with closed-angle glaucoma?

A. Salbutamol
B. Acetylcholinesterase agonist
C. M agonist
D. Propranolol

SBA 5

Which medication would you give a patient with closed-angle glaucoma?

A. Salbutamol
B. Acetylcholinesterase agonist
C. M agonist
D. Propranolol

Answer: C

MSA Education

Thank you for attending the session -

Please fill in the feedback form:
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