ANS DRUGS

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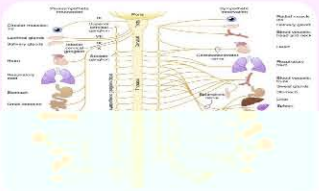
Learning Objectives

1. มีความรู้ความเข้าใจในเรื่อง ANS FUNCTIONAL ANATOMY และ AUTONOMIC DYSFUNCTION
2. อธิบายกระบวนการการสังเคราะห์ การเก็บ การหลั่ง การทำงาน และการหมดฤทธิ์ของสารสื่อประสาท ที่เกิดขึ้นภายในส่วนปลายประสาทของระบบประสาทอัตโนมัติ
3. จำแนกและอธิบายชนิดและการทำงานของ Autonomic receptors
4. อธิบายความหมายและกลไกการออกฤทธิ์ของ ANS DRUGS เช่น Adrenergic & Cholinergic drugs, Anticholinergic drugs

Overview for ANS



I. FUNCTIONAL ANATOMY

II. ADRENERGIC & CHOLINERGIC

I.FUNCTIONAL ANATOMY

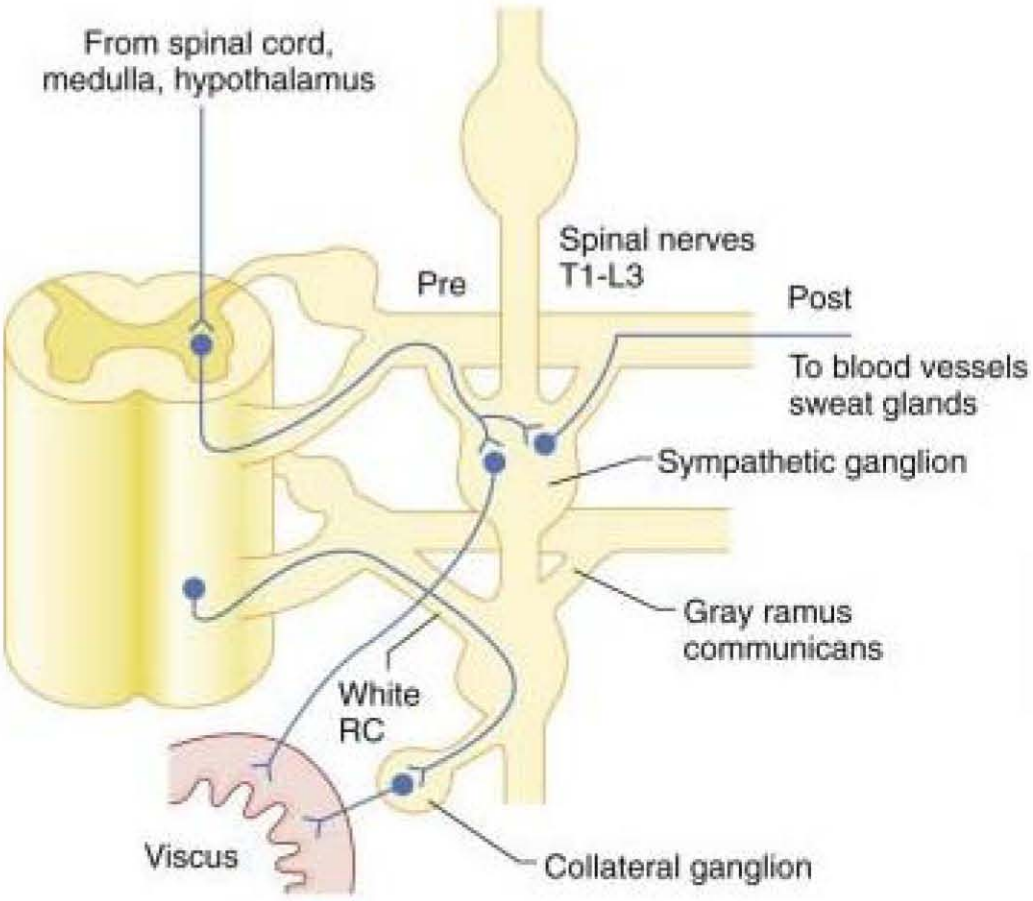
SYMPATHETIC NERVOUS SYSTEM

PARASYMPATHETIC NERVOUS SYSTEM

ENTERIC NERVOUS SYSTEM

- Walls of GI tract, Pancrease, Gallbladder
- Local autonomy : Digestion & Peristalsis

Sympathetic division



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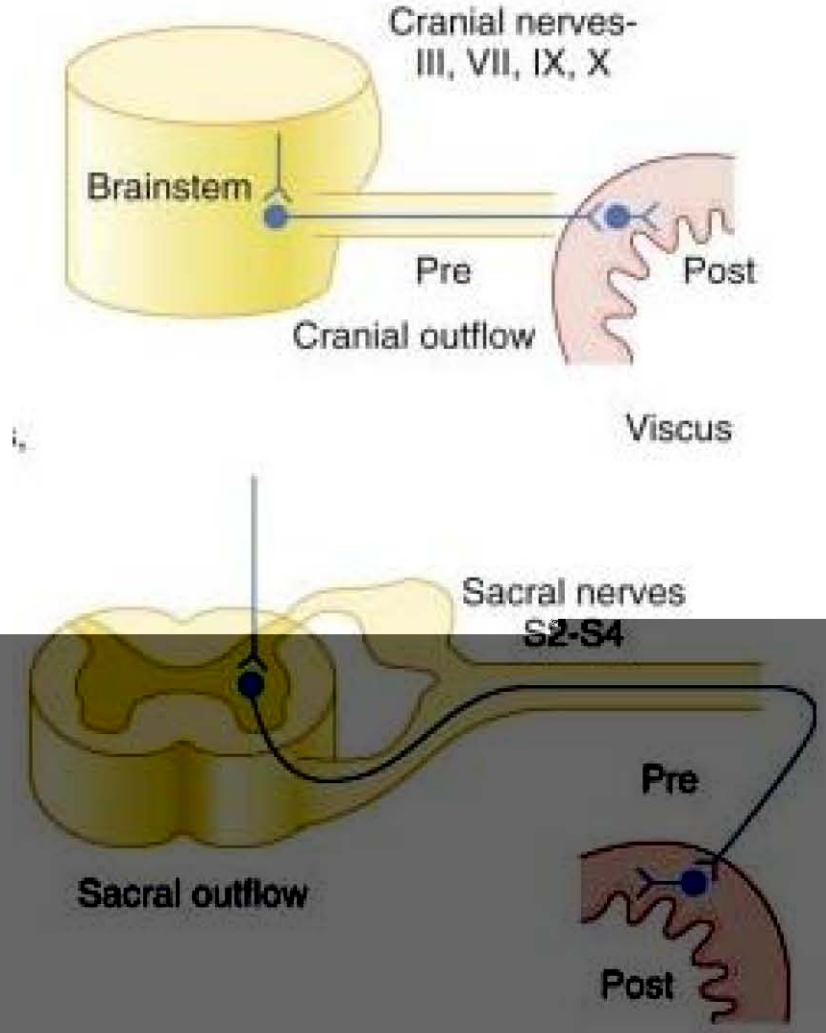
Parasympathetic division



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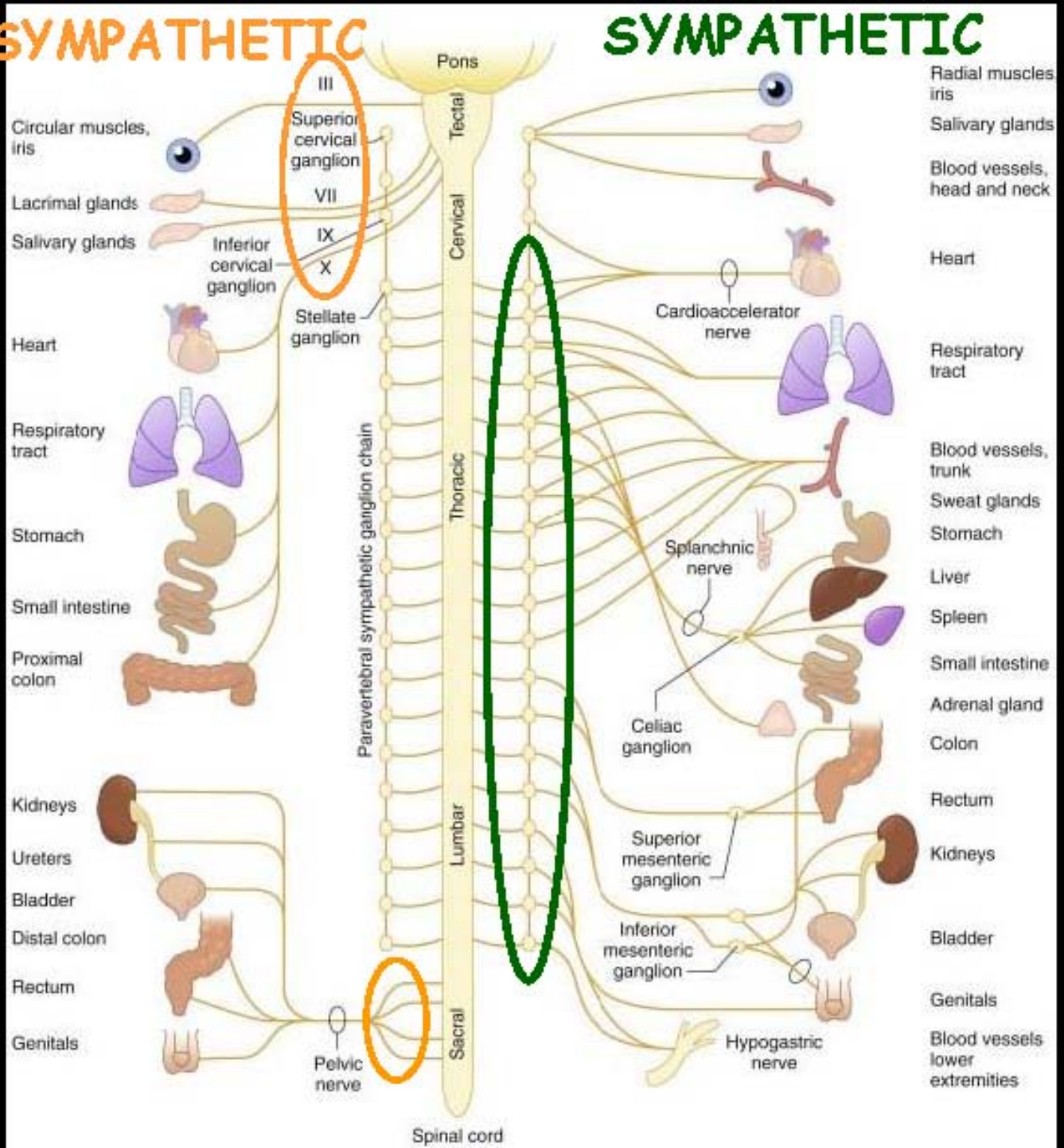
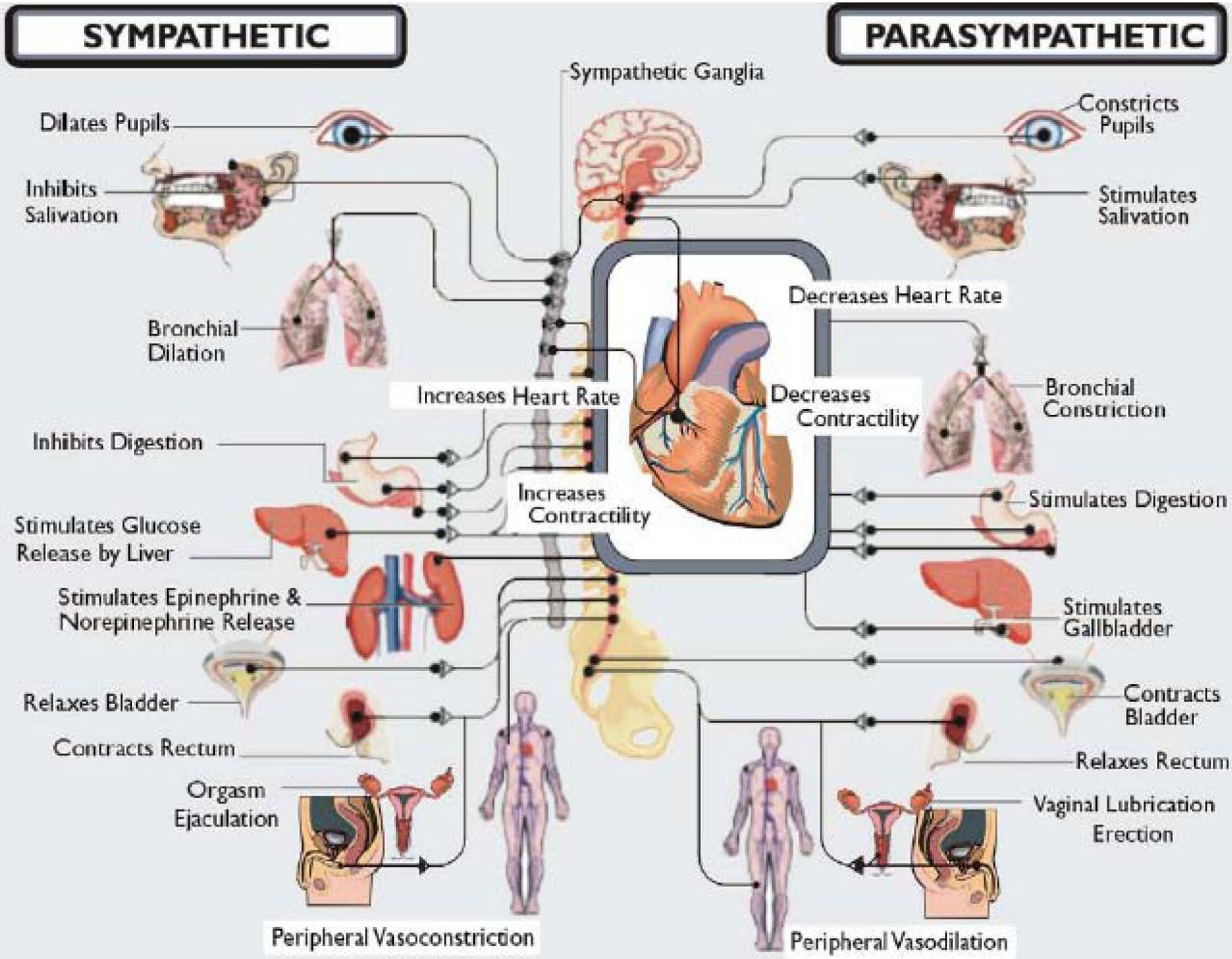
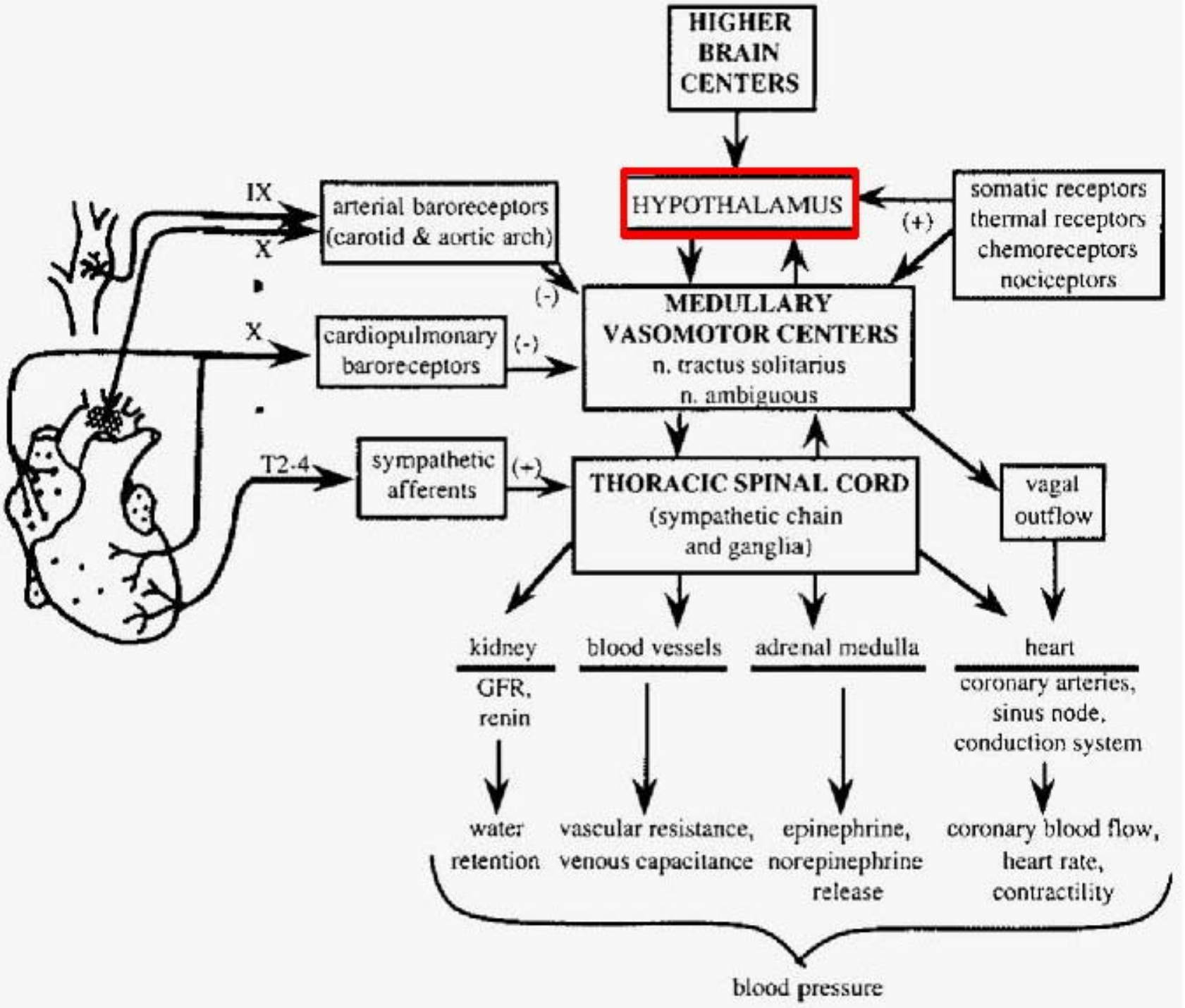
PARASYMPATHETIC

SYMPATHETIC



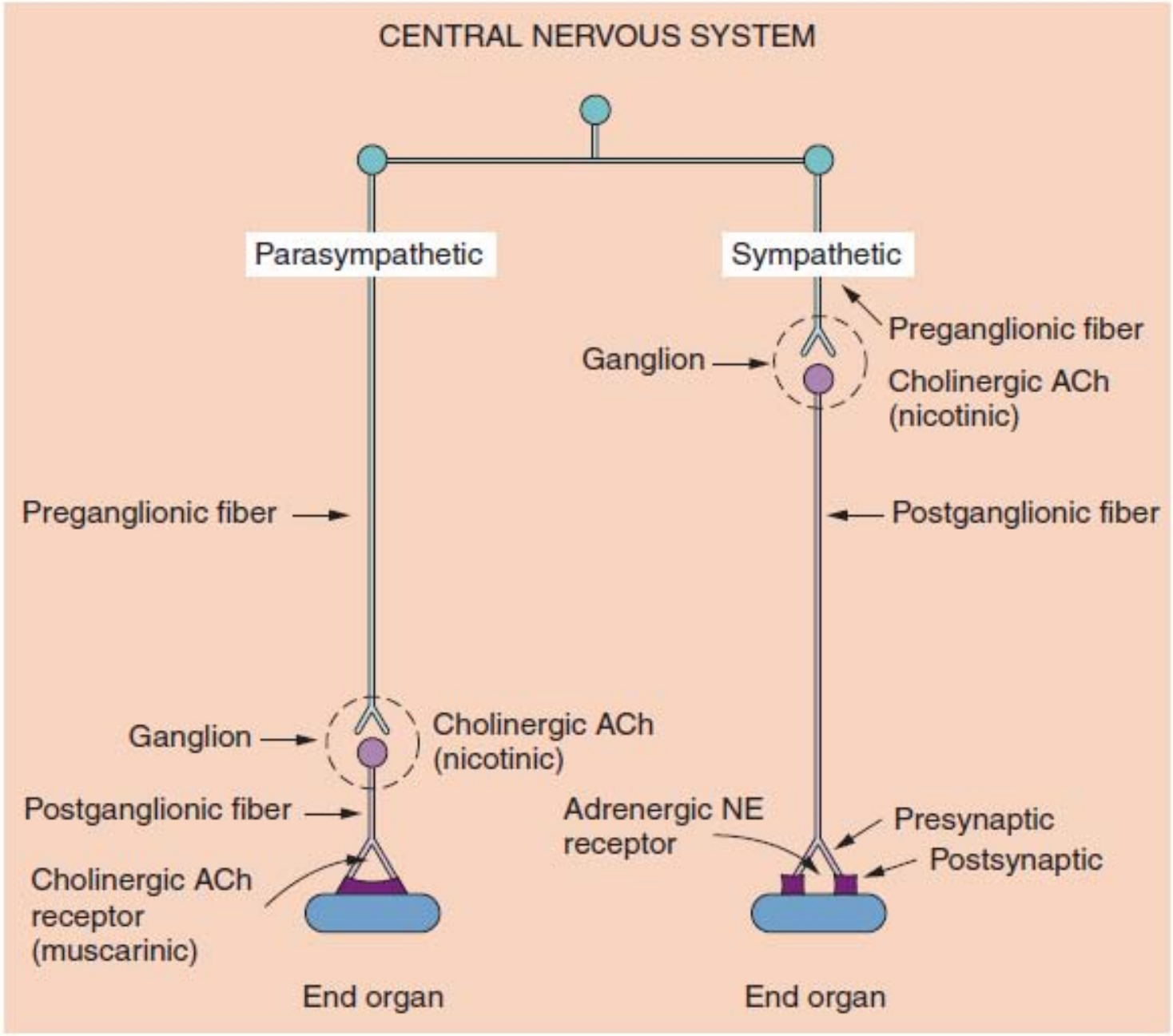

SYMPATHETIC
PARASYMPATHETIC
Sympathetic Ganglia
Dilates Pupils
Constricts Pupils
Inhibits Salivation
Stimulates Salivation
Bronchial Dilation
Decreases Heart Rate
Increases Heart Rate
Decreases Contractility
Bronchial Constriction
Inhibits Digestion
Increases Contractility
Stimulates Digestion
Stimulates Glucose Release by Liver
Stimulates Epinephrine & Norepinephrine Release
Stimulates Gallbladder
Relaxes Bladder
Contracts Bladder
Contracts Rectum
Relaxes Rectum
Orgasm Ejaculation
Vaginal Lubrication Erection
Peripheral Vasoconstriction
Peripheral Vasodilation


HIGHER BRAIN CENTERS
HYPOTHALAMUS
somatic receptors
thermal receptors
chemoreceptors
nociceptors
(+)
IX
X
arterial baroreceptors (carotid & aortic arch)
(-)
X
cardiopulmonary baroreceptors
(-)
MEDULLARY VASOMOTOR CENTERS
n. tractus solitarius
n. ambiguous
T2-4
sympathetic afferents
(+)
THORACIC SPINAL CORD
(sympathetic chain and ganglia)
vagal outflow
kidney
blood vessels
adrenal medulla
heart
GFR, renin
coronary arteries, sinus node, conduction system
water retention
vascular resistance, venous capacitance
epinephrine, norepinephrine release
coronary blood flow, heart rate, contractility
blood pressure

Neurotransmitter in ANS

II. ADRENERGIC & CHOLINERGIC PHARMACOLOGY

- CHOLINERGIC RECEPTORS ; Ach
  - MUSCARINIC : visceral organ; myocardium, coronary vessels, and peripheral vasculature
  - NICOTINIC : NMJ, SYMPATHETIC & PARASYMPATHETIC
- ADRENERGIC RECEPTORS ; NE,E
  - ALPHA : a_1 , a_2
  - BETA : b_1 , b_2
  - DAPOMINE : DA_1 , DA_2



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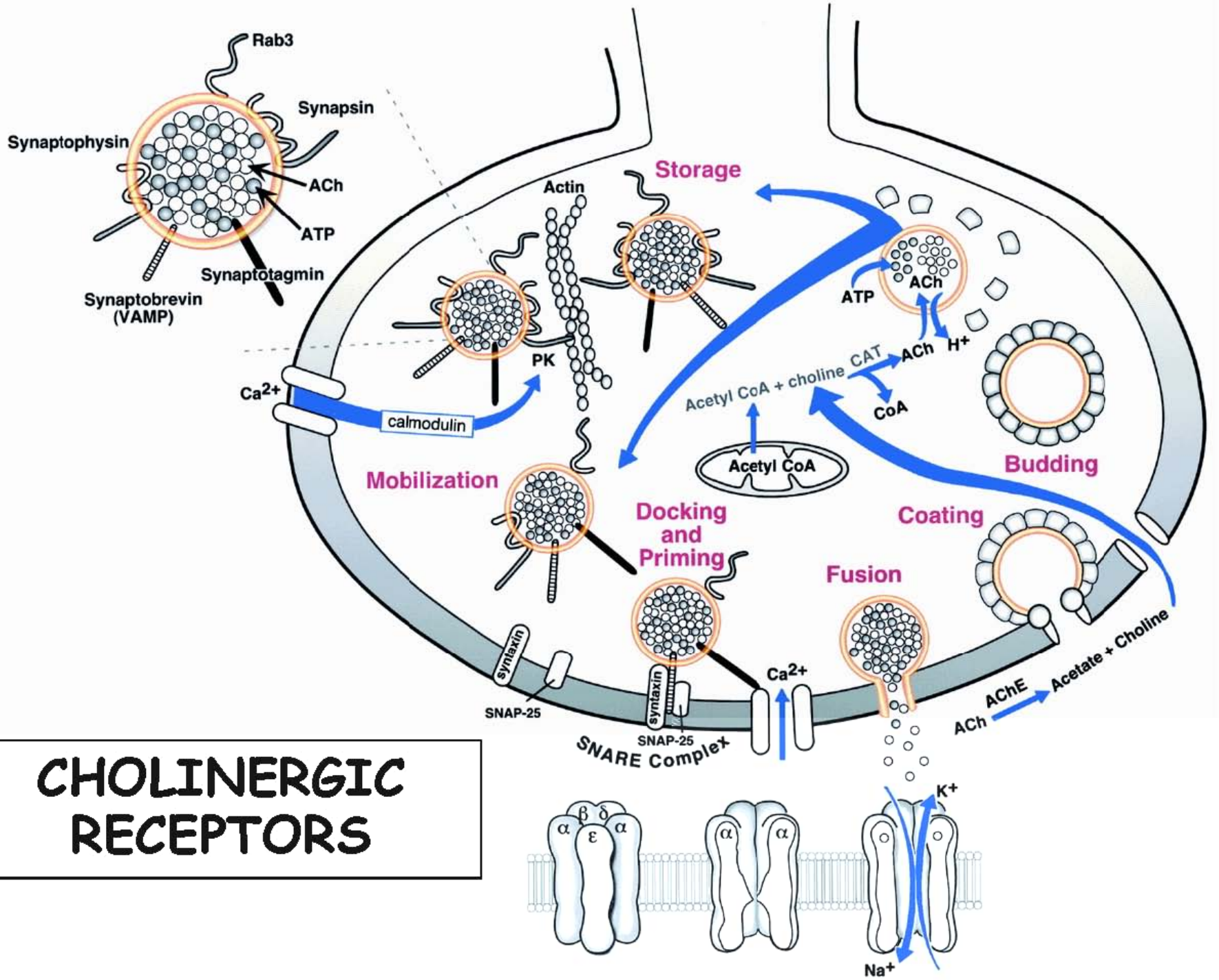
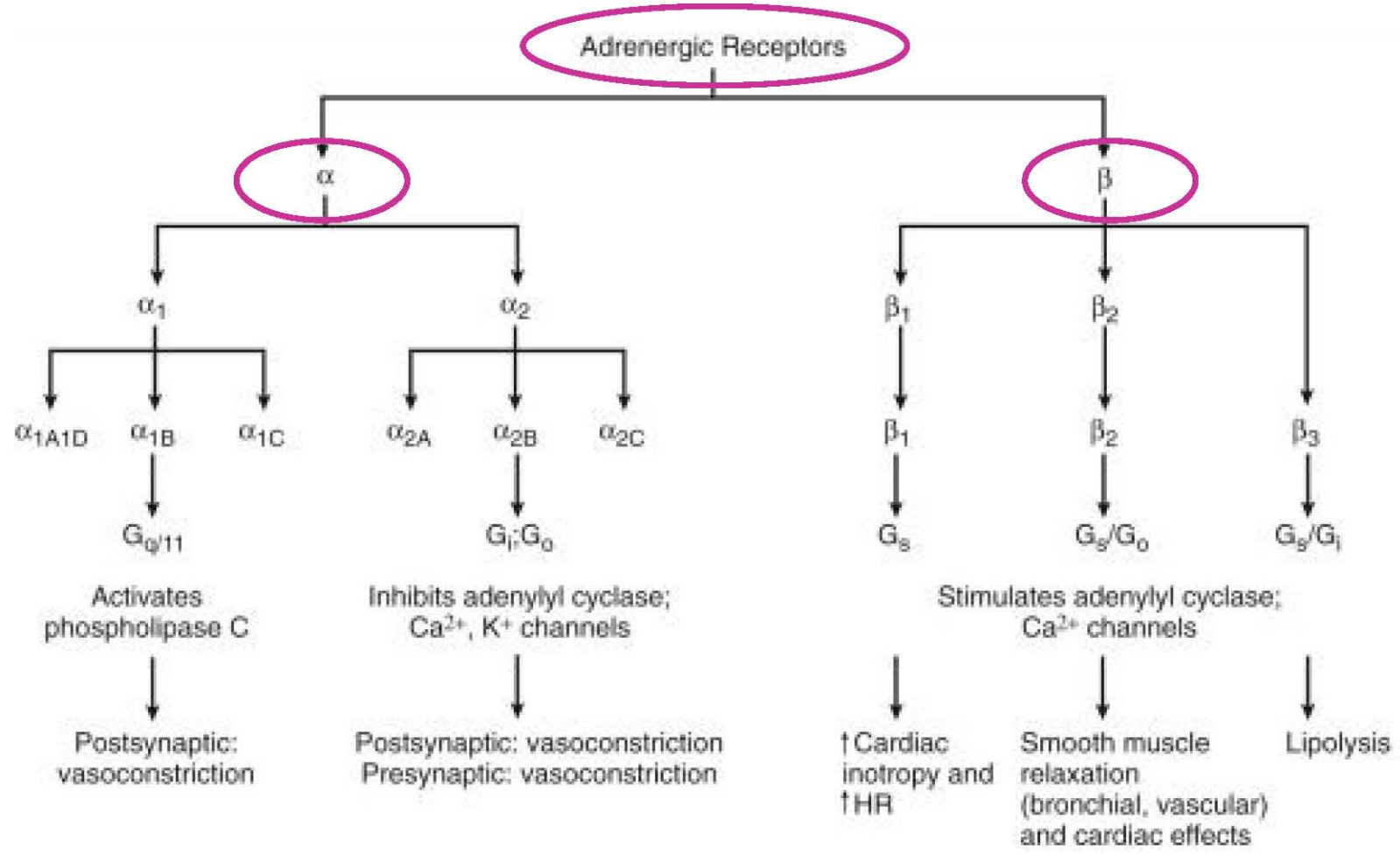


CHOLINERGIC RECEPTORS


Adrenergic Receptors
α
β
α1
α2
β1
β2
α1A1D
α1B
α1C
α2A
α2B
α2C
β1
β2
β3
Gq/11
Gi;Go
Gs
Gs/Go
Gs/Gi
Activates phospholipase C
Inhibits adenylyl cyclase; Ca2+, K+ channels
Stimulates adenylyl cyclase; Ca2+ channels
Postsynaptic: vasoconstriction
Postsynaptic: vasoconstriction
Presynaptic: vasoconstriction
↑Cardiac inotropy and ↑HR
Smooth muscle relaxation (bronchial, vascular) and cardiac effects
Lipolysis
Ahlquist (original definition)
"Classic" pharmacology
Molecular pharmacology
Signal transduction
Effectors

Distribution of a-, b- and DA-Receptors

RECEPTOR	DISTRIBUTION	RESPONSE	AGONIST	ANTAGONIST
a_1	Smooth muscle	Constriction	Methoxamine Phenylephrine	Prazosin
a_2	Presynaptic	Inhibit NE release	Clonidine Dexmedetomidine	Yohimbine
b_1	Heart	Inotropy Chronotropy	Dobutamine	Metoprolol
b_2	Smooth muscle	Dilation Relaxation	Terbutaline	
DA_1	Postsynaptic	Vasodilatation	Dopamine	
DA_2	Presynaptic Central	NE,A N/V ch		Droperidol

Effects of Activation of the Sympathetic Nervous System

Site of Action	Stimulation	Inhibition
Heart	Rate, conduction, contractility	
Blood vessels	Vasoconstriction (skin, gut, liver, heart, kidney)	Vasodilation (skeletal muscle, heart, brain)
Respiration	Respiratory center Bronchodilation	
Gastrointestinal tract	Sphincters	Smooth muscle
Genitourinary tract	Sphincters	Ureteral & uterine muscle
Metabolic & endocrine effects	Glycogenolysis (muscle, liver)	Insulin release (α stimulation or β_1 antagonism)
	Gluconeogenesis	Lipolysis
	Insulin release (β_1)	
	Renin release	
	ADH release	

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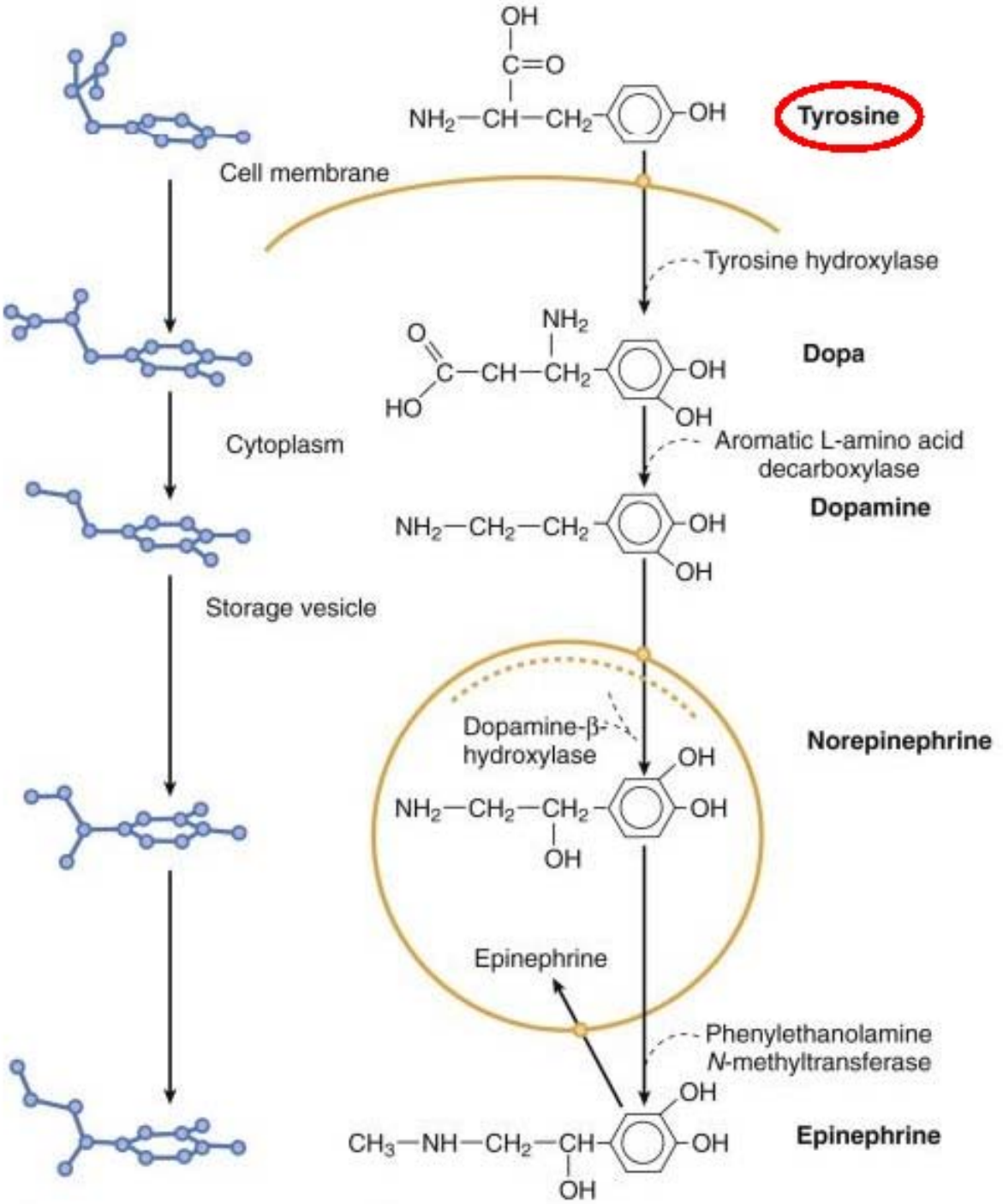
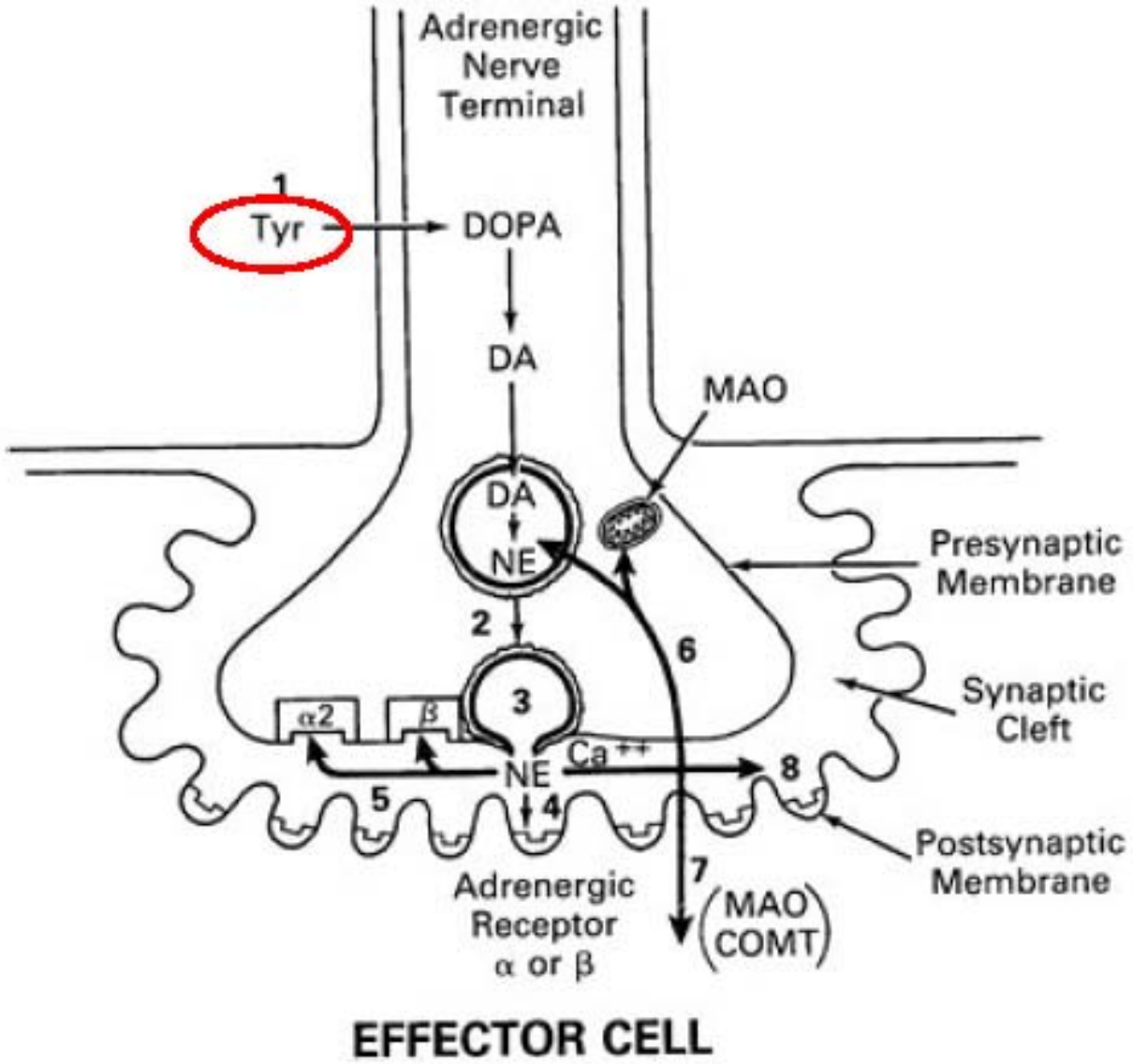
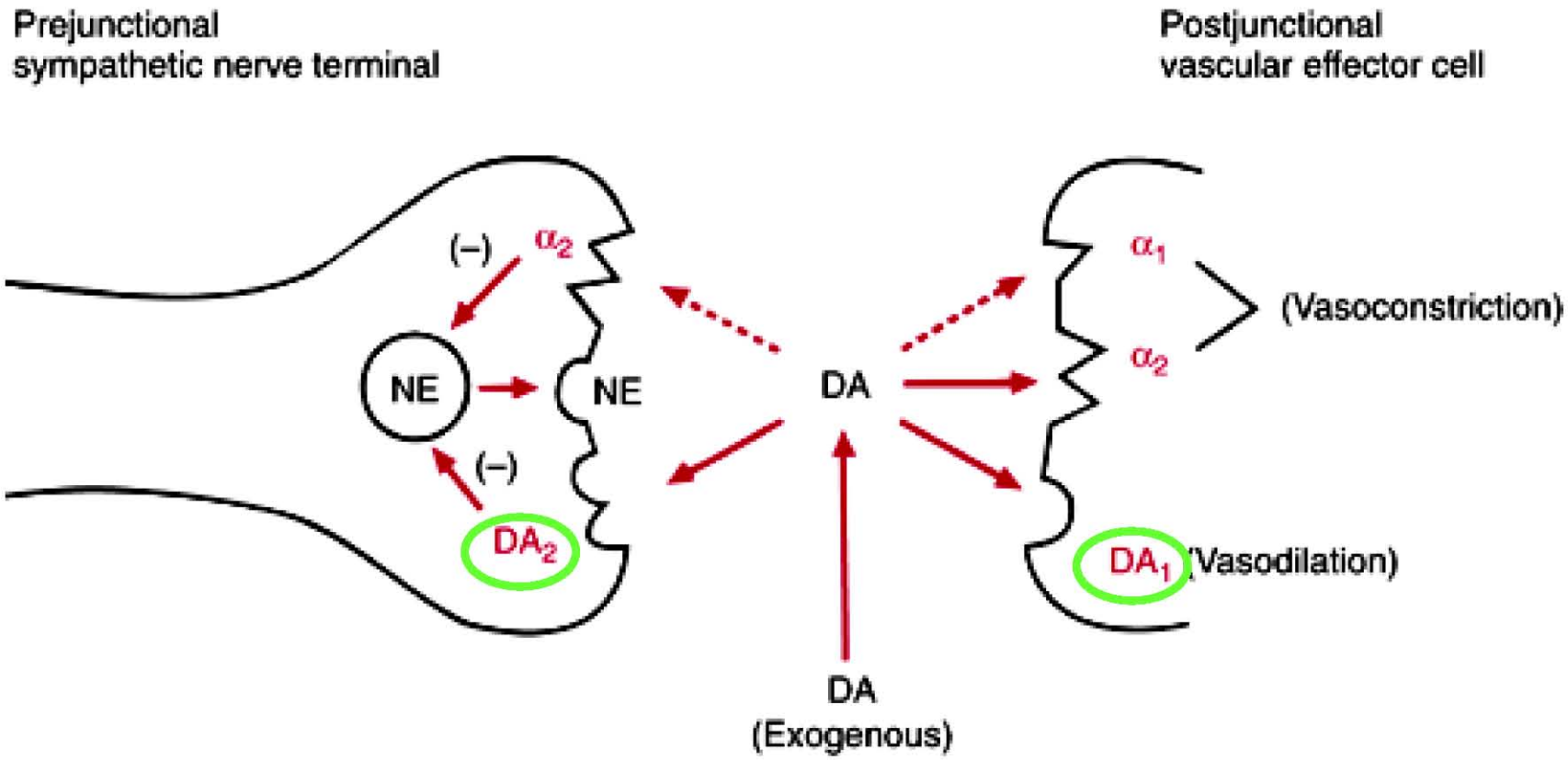

Tyrosine
Cell membrane
Tyrosine hydroxylase
Dopa
Cytoplasm
Aromatic L-amino acid decarboxylase
Dopamine
Storage vesicle
Dopamine-β-hydroxylase
Norepinephrine
Epinephrine
Phenylethanolamine N-methyltransferase
Epinephrine

Synthesis and disposition of NE



Dopaminergic receptors



Conditions Associated with Up- and Down-regulation of Acetylcholine Receptors

nAChR Up-regulation	nAChR Down-regulation
Spinal cord injury	Myasthenia gravis
Stroke	Anticholinesterase poisoning
Burns	Organophosphate poisoning
Prolonged immobility	
Prolonged exposure to neuromuscular blockers	
Multiple sclerosis	
Guillain-Barré syndrome	

nAChR = nicotinic acetylcholine receptor.

Adrenergic-Receptor Differentiation

ALPHA Receptor	STIMULATION	INHIBITION
Heart		
Blood vessels	Vasoconstriction (skin, gut, kidney, liver, heart)	
Gastrointestinal tract	Sphincters	
Genitourinary tract	Sphincters	
Metabolic&endocrine effects		Insulin release

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Responses in Effector Organs by Stimulation of Sympathetic & Parasympathetic Nerves

EFFECTOR ORGAN	ADRENERGIC RESPONSE	RECEPTOR INVOLVED	CHOLINERGIC RESPONSE	DOMINANT RESPONSE(A-C)
Heart				
-Rate of contraction	Increase	b_1	Decrease	C
-Force of contraction	Increase	b_1	Decrease	C
Blood vessels				
-Arteries (most)	Vasoconstriction	a_1		A
-Skeletal muscle	Vasodilation	b_2		A
-Veins	Vasoconstriction	a_2		A

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Responses in Effector Organs by Stimulation of Sympathetic & Parasympathetic Nerves (cont)

EFFECTOR ORGAN	ADRENERGIC RESPONSE	RECEPTOR INVOLVED	CHOLINERGIC RESPONSE	DOMINANT RESPONSE(A-C)
Bronchial tree	Bronchodilation	b_2	Bronchoconstriction	C
Splenic capsule	Contraction	a_1		A
Uterus	Contraction	a_1	Variable	A
Vas deferens	Contraction	a_1		A
Prostatic capsule	Contraction	a_1		A
Gastrointestinal tract	Relaxation	a_2	Contraction	C
Insulin	Decrease	a_2		A
Fat cells	Lipolysis	b_1		A

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Responses in Effector Organs by Stimulation of Sympathetic & Parasympathetic Nerves (cont)

EFFECTOR ORGAN	ADRENERGIC RESPONSE	RECEPTOR INVOLVED	CHOLINERGIC RESPONSE	DOMINANT RESPONSE(A-C)
Eye				
-Radial muscle, iris	Contraction (mydriasis)	a_1		A
-Circular muscle, iris			Contraction (miosis)	C
-Ciliary muscle	Relaxation	b	Contraction (accommodation)	C
Kidney	Renin secretion	b_1		A
Urinary bladder				
-Detrusor	Relaxation	b	Contraction	C
-Trigone&sphincter	Contraction	a_1	Relaxation	A, C
Ureter	Contraction	a_1	Relaxation	A

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Responses in Effector Organs by Stimulation of Sympathetic & Parasympathetic Nerves (cont)

EFFECTOR ORGAN	ADRENERGIC RESPONSE	RECEPTOR INVOLVED	CHOLINERGIC RESPONSE	DOMINANT RESPONSE(A-C)
Liver glycogenolysis	Increase	α_1		A
Hair follicles	Contraction (piloerection)	α_1		A
Nasal secretion	Increase			C
Salivary glands	Increase	α_1	Increase	C
Sweat glands	Increase	α_1	Increase	C

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Usual Sympathetic or Parasympathetic Dominance at Specific Effector Sites

SITE	PREDOMINANT TONE
Ciliary muscle	Parasympathetic
Iris	Parasympathetic
Sinoatrial node	Parasympathetic
Arterioles	**Sympathetic**
Veins	**Sympathetic**
Gastrointestinal tract	Parasympathetic
Uterus	Parasympathetic
Urinary bladder	Parasympathetic
Salivary glands	Parasympathetic
Sweat glands	**Sympathetic** (cholinergic)

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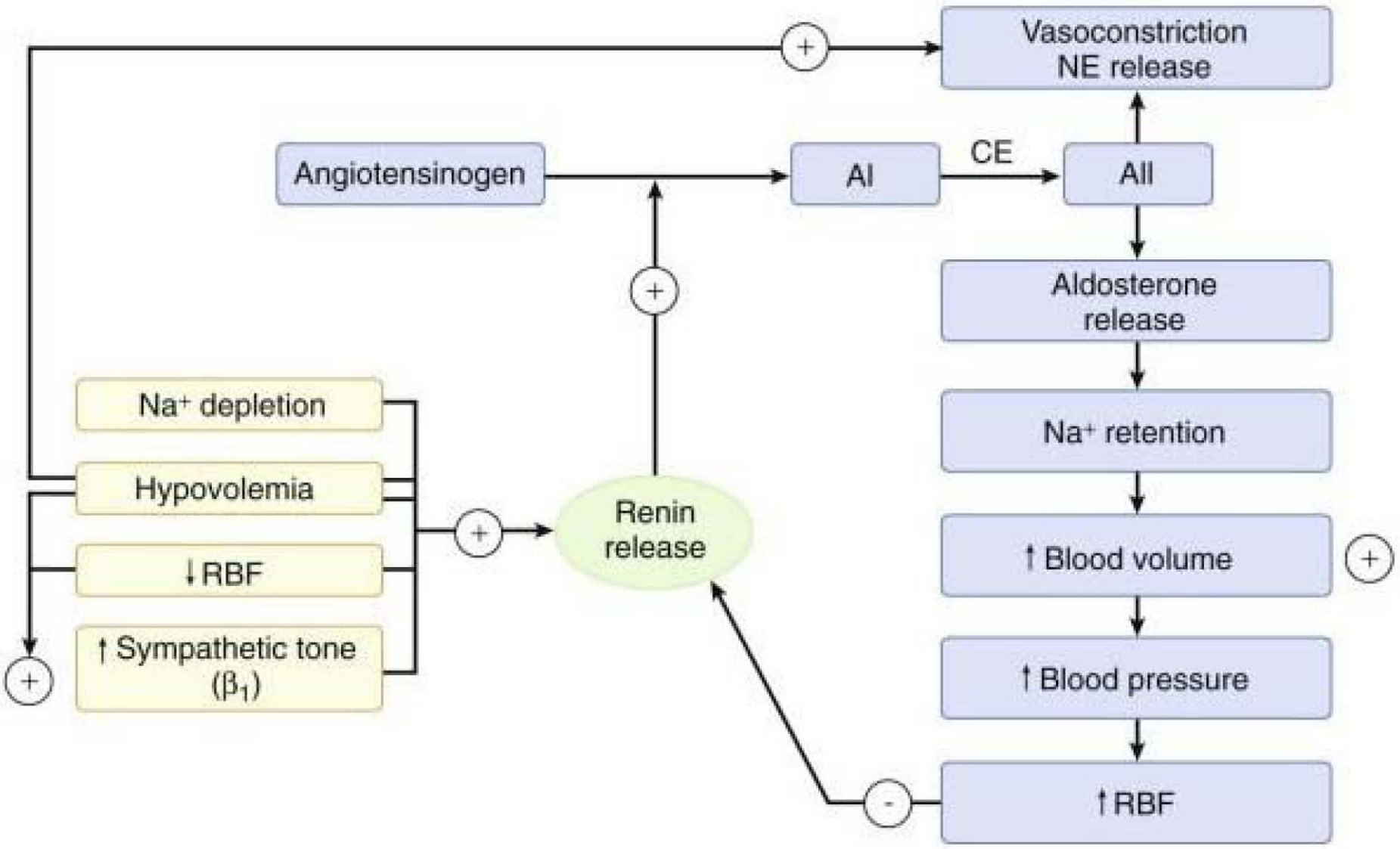
Interactions of the renin-angiotensin-aldosterone & sympathetic nervous systems in maintaining blood pressure & volume



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Causes of Systemic Hypotension

Hypovolaemia

- Dehydration/inadequate fluid intake
- Haemorrhage
- Severe vomiting/diarrhoea
- Burns
- Abnormal fluid losses into the gut
- High output fistula of the small bowel

Cardiogenic causes

- Acute myocardial ischaemia/infarction
- Severe valvular heart disease
- Cardiomyopathy
- Acute myocarditis
- Constrictive pericarditis

Sepsis

- Any cause of systemic sepsis

Neurogenic

- High spinal cord injury

Anaphylaxis

III.ANS DRUGS

- **Adrenergic drugs**
  - Agonist – Antagonist
  - Alpha – Beta
  - Catecholamine – Noncatecholamine
- **Anticholinergics drugs**

- Anticholinesterase drugs; Neostigmine
- Ganglionic blockade ; Trimethaphan
- Neuromuscular blockade ; DR , NMDR

Infusion formula

$$1 \text{ mcg/kg/min} = X \text{ ml/hr} = \frac{6\ W}{100\ C}$$

W = Body weight (kgs.)

C = Concentration (mg/ml)

SELECTIVE α-ADRENERGIC RECEPTOR AGONISTS

- α1-Adrenergic Agonists
  - Phenylephrine
- α2-Adrenergic Agonists
  - Clonidine
  - Dexmedetomidine

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α-ADRENERGIC RECEPTOR ANTAGONISTS

- Phenoxybenzamine
- Prazosin
- Yohimbine

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β2-ADRENERGIC RECEPTOR AGONISTS

- Metaproterenol
- Terbutaline
- Albuterol
- Ritodrine

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- Beta agonists
  - Terbutaline ; B_2,SQ 0.25 mg q 15-30 mins.
- Beta antagonists
  - Propanolol ; CNS,$T_{1/2}$ 4 hrs.,0.25-0.5 mg IV
  - Esmolol ; $T_{1/2}$ 10 mins.,0.5mg/kg IV
  - Labetalol ; B>A 5-10 เท่า,5-10 mg IV q 5 mins
    or 2 mg/min Infusion

Comparative Pharmacology of Selective β_2-Adrenergic Agonist Bronchodilators

	β_2 Selectivity	Peak Effect (min)	Duration of Action (h)	Concentration (μg per puff)	Method of Administration
Albuterol	High	30–60	4	90	MDI, oral
Metaproterenol	Moderate	30–60	3–4	200	Oral, subcutaneous
Terbutaline	High	60	4	200	MDI, oral, subcutaneous

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β -ADRENERGIC ANTAGONISTS

available as intravenous drug ;

- Propranolol
- Metoprolol
- Labetalol
- Esmolol

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Pharmacokinetics and Pharmacology of Selected β-Adrenoceptor Blockers

Characteristic	Atenolol	Metoprolol	Propranolol HCl	Labetalol	Esmolol	Carvedilol
Proprietary name	Tenormin	Lopressor	Inderal Ipran	Trandate Normodyne	Brevibloc	Coreg
Relative β sensitivity	+	+	0	0	+	0
Intrinsic sympathetic activity	0	0	0	+	0	0
Membrane-stabilizing activity	0	0	++	0	0	— *
Lipophilicity [†]	Low	Moderate	High	Low	Low	High
Predominant route of elimination	RE (mostly unchanged)	HM	HM	HM	Hydrolysis by RBC esterase	HM
Drug accumulation in renal disease	Yes	No	No	No	No	No
Elimination half-life (hr)	6 to 9	3 to 4	3 to 4	≈6	9 min	2 to 8
Usual oral maintenance dose	50-100 mg qd	50-100 mg qid	60 mg qid	100-600 mg bid	N/A	25-50 mg bid
Usual intravenous dose (caution)		5 mg q5min × 3	0.1 mg/kg (maximum)	1-2 mg/kg	50 to 300 μg/kg/min infusion	15 mg

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Comparative Characteristics of β-Adrenergic Receptor Antagonists

	Propranolol	Nadolol	Pindolol	Timolol	Metoprolol
Cardiac selectivity	No	No	No	No	Yes
Partial agonist activity	No	No	Yes	No	No
Protein binding (%)	90–95	30	40–60	10	10
Clearance	Hepatic	Renal	Hepatic/ Renal	Hepatic	Hepatic
Active metabolites	Yes	No	No	No	No
Elimination half-time (h)	2–3	20–24	3–4	3–4	3–4
First-pass hepatic metabolism (estimate) (%)	75	Minimal	10–15	50	60
Blood level variability	+ + + +	+	+ +	+ + +	+ + + +
Adult oral dose (mg)	40–360	40–320	5–20	10–30	50–400
Adult intravenous dose (mg)	1–10		0.4–2	0.4–1	1–15

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Comparative Characteristics of β-Adrenergic Receptor Antagonists *(continued)*

	Atenolol	Acebutolol	Betaxolol	Esmolol
Cardiac selectivity	Yes	Yes	Yes	Yes
Partial agonist activity	No	Yes	No	No
Protein binding (%)	5	25		55
Clearance	Renal	Hepatic/Renal	Hepatic/Renal	Plasma hydrolysis
Active metabolites	No	Yes		No
Elimination half-time (h)	6–7	3–4	11–22	0.15
First-pass hepatic metabolism (estimate) (%)	10	60		
Blood level variability	+	+ +		
Adult oral dose (mg)	50–200	200–800	10–20	
Adult intravenous dose (mg)	5–10	12.5–50		10–80 IV 50–300 μg/kg/min

+, minimal; + +, modest; + + +, moderate; + + + +, marked.

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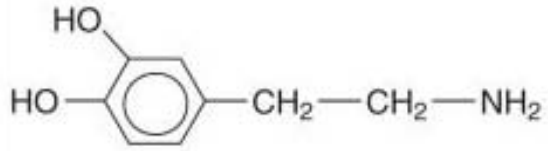
- PDE III inhibitor
  - Milrinone ; ↑ Contractility,Arterial dilatation, Loading = 50 mcg/kg then 0.5-0.75 mcg/kg/min

Adrenergic drugs

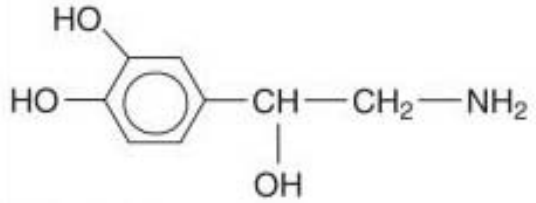
- Catecholamine Sympathomimetics
  - Epinephrine
  - Norepinephrine
  - Dopamine
  - Dobutamine
  - Isoproterenol
- Noncatecholamine Sympathomimetics
  - Ephedrine
  - Metaraminol (Aramine)

Endogenous Catecholamines

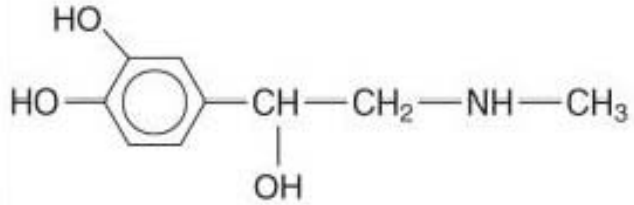
Dopamine



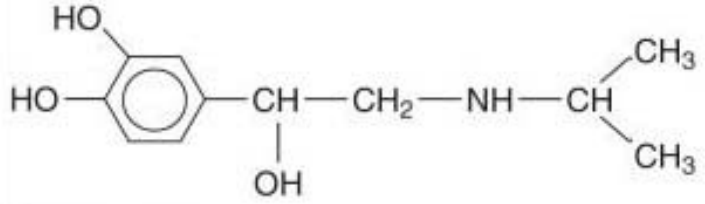
Norepinephrine



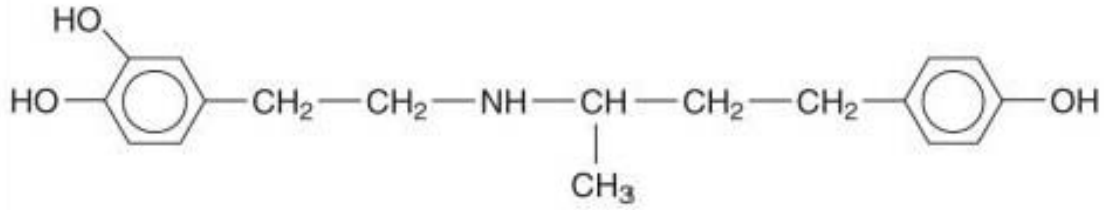
Epinephrine



Isoproterenol



Dobutamine



Epinephrine

- Adrenal medulla
- B & A agonists
  - β_2 infusion rate 1-2 mcg/kg/min
  - β_1 β_2 " 2-10 mcg/kg/min
  - α_1 " > 10 mcg/kg/min
- Indications :
  - Cardiac arrest 0.01 mg/kg or 1 mg
  - Asthma 0.01 mg/kg SQ
  - Anaphylaxis 1:10,000 = 1-2 ml
  - Pediatric with shock or CHF 0.05-3mcg/kg/min
  - Adult 2-16 mcg/min

Norepinephrine

- Postganglionic sympathetic fibers
- NE ⟶ E
- A & B receptors(usually A1)
- short half-life = 2.5 minutes
- Indications : Increase BP by increase SVR
- Dose : Bolus 0.1 mcg/Kg
  Infusion 3-20 mcg/Kg/min
- Side effect : Extravasation → Tissue necrosis
  Rx: by LA with Phentolamine

Dopamine

- NE ⟶ E ⟶ Dopamine
- Indications :
  - Dopaminergic1 0 – 3 mcg/kg/min
  - Beta 1 3 - 10 mcg/kg/min
  - Alpha1 > 10 mcg/kg/min
- half-life of 1 minute

Dobutamine

- $B_1 > B_2 > A$
- increasing myocardial contractility via B_1
- causing arteriolar vasodilatation in skeletal muscle reducing afterload via B_2 adrenoceptors
- Indications :
  - Low CO
  - CHF
- Dose = 1-10 mcg/kg/min

Doses < 20 mg/kg/min usually do not produce tachycardia

- Prolonged Rx > 3 days → down regulation b-receptors

Isoproterenol

- B_1 > B_2 receptors
- Indications :
  - 2nd - 3rd degree AV block
  - Chronotropic agent after heart transplant
  - Reverse – excessive B blocker
    - atropine resistance bradycardia
- Doses = 0.01-0.1 mcg/kg/min titrate to HR

Usual infusion rate 2.5-10 mcg/min

Dose-Dependent of Inotropes & Chronotropes

DRUG	RECEPTORS	USUAL INFUSION RATE
Epinephrine (bolus: 2–10 mcg)	b_2	1–2 mcg/min
	$b_1 + b_2$	2–10 mcg/min
	a_1	≥10 mcg/min
Norepinephrine	a_1, b_1, >>b_2	4–12 mcg/min
Dopamine	Dopaminergic	0–3 mcg/kg/min
	b	3–10 mcg/kg/min
	a	>10 mcg/kg/min
Dobutamine	b_1 >> b_2, a	2.5–10 mcg/kg/min
Isoproterenol	b_1 > b_2	0.5–10 mcg/min
Amrinone	Increase cyclic adenosine monophosphate through phosphodiesterase inhibition	0.75 mg/kg load 5–10 mcg/kg/min infusion over ~ min

Ephedrine

- A & B1 receptors
- No effect on UBF
- Indirect agonist, Tachyphylaxis
- Indications :
  - Hypotension
  - Topical
- Doses = 2.5-25 mg IV or 25-50 mg IM
  0.1 mg/Kg in Children

Pharmacologic Effects and Therapeutic Doses of Catecholamines

Catecholamine	Mean Arterial Pressure	Heart Rate	Cardiac Output	Systemic Vascular Resistance	Renal Blood Flow	Cardiac Dysrhythmias	Preparation (mg/250 mL)	Intravenous Dose (μg/kg/min)
Dopamine	+	+	+ + +	+	+ + +	+	200 (800 μg/mL)	2-20
Norepinephrine	+++	–	–	+++	---	+	4 (16 μg/mL)	0.01-0.1
Epinephrine	+	++	++	+ +	--	+++	1 (4 μg/mL)	0.03-0.15
Isoproterenol	–	+++	+++	--	–	+++	1 (4 μg/mL)	0.03-0.15
Dobutamine	+	+	+++	–	++	–	250 (1000 μg/mL)	2-20

Ronald D. Miller, Chapter 7-The Autonomic Nervous System, Basic of Anesthesia, 6th ed., 2011.

Classification and Comparative Pharmacology of Sympathomimetics

	Receptors Stimulated			Mechanism of Action	Cardiac Effects			Peripheral Vascular Resistance
	α	β_1	β_2		Cardiac Output	Heart Rate	Dysrhythmias	
Nature catecholamines								
Epinephrine	+	++	++	Direct	++	++	+++	±
Norepinephrine	+++	++	0	Direct	−	−	+	+++
Dopamine	++	++	++	Direct	+++	+	+	+
tic catecholamines								
erenol	0	+++	+++	Direct	+++	+++	+++	−−
mine	0	+++	+	Direct	+++	+	±	NC
tic noncatecholamines								
ine	++	+	+	Direct and Indirect	++	++	++	+
ephrine	+++	0	0	Direct	−	−	NC	+++

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Classification and Comparative Pharmacology of Sympathomimetics *(continued)*

	Renal Blood Flow	Mean Arterial Pressure	Airway Resistance	Central Nervous System Stimulation	Single Intravenous Dose (70-kg Adult)	Continuous Infusion Dose (70-kg Adult)
Nature catecholamines						
Epinephrine	−−	+	−−	Yes	2–8 μg	1–20 μg/min
Norepinephrine	−−−	+++	NC	No	Not used	4–16 μg/min
Dopamine	+++	+	NC	No	Not used	2–20 μg/kg/mi
Synthetic catecholamines						
Isoproterenol	−	±	−−−	Yes	1–4 μg	1–5 μg/min
Dobutamine	++	+	NC		Not used	2–10 μg/kg/mi
Synthetic noncatecholamines						
Ephedrine	−−	++	−−	Yes	10–25 μg	Not used
Phenylephrine	−−−	+++	NC	No	50–100 μg	20–50 μg/min

0, none; +, minimal increase; ++, moderate increase; +++, marked increase; −, minimal decrease; −−, moderate decrease; −−−, marked decrease; NC, no change.

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Phenylephrine

- A & B receptors (dominant A1) ⟶

(increases venous constriction & arterial constriction in a dose-related)

  - not change CO & not produce dysrhythmias
- Indications :
  - Hypotension in AS
  - Rx Tet spell
  - nasal decongestant
- Dose : Bolus 50-100 mcg/Kg IV or
  25-50 mg IM
  Infusion 0.25-1 mcg/Kg/min
- rapid onset & short duration (5-10 mins)

Metaraminol (Aramine)

- A_1 receptors
- Tolerance or Tachyphylaxis
- Reflex bradycardia
- Indications :
  - Hypotension
- Doses = 100 mcg IV

Clonidine

- Sympatholytic
- A receptors(usually A2)
- Indications :
  - Rebound HT from Clonidine withdrawal
  - Anesthetic effect → Oral,Transdermal
- Dose : 250-1,000 mg IV over 30 mins q 6 hrs
  Oral 3-5 mcg/Kg, Transdermal 0.1-0.3 mg/d
- Side effect : Positive direct Coomb test, Bradycardia, Hypotension, Sedation, Dry mouth

Dexmeditomidine

- Highly selective A2 receptors
- half-life= 2.3 hrs & distribution half-life < 5 mins
- Indications :
  - sedation, analgesia, amnesia
  - Anesthetic effect
- Dose : 1 mcg/Kg IV over 10 mins then infusion
  0.3-0.7 mcg/Kg/hr
- Side effect : Bradycardia

- Anticholinergics drugs
  - Atropine : 0.02 mg/kg or 0.4-0.6 mg IV
  - Scopolamine : 0.2-0.6 mg IV
  - Glycopyrrolate : 0.1-0.2 mg IV

Anticholinergics	Duration
Atropine	Short
Glycopyrrolate	Long
Scopolamine	Short

Comparative Effects of Anticholinergics Administered Intramuscularly as Pharmacologic Premedication

Effect	Atropine	Scopolamine	Glycopyrrolate
Antisialogogue effect	+	+++	++
Sedative and amnesic effects	+	+++	0
Increased gastric fluid pH	0	0	0/+
Central nervous system toxicity	+	++	0
Relaxation of lower esophageal sphincter	++	++	++
Mydriasis and cycloplegia	+	+++	0
Heart rate	++	0/+	+

Ronald D. Miller, Chapter 7-The Autonomic Nervous System, Basic of Anesthesia, 6th ed., 2011.

Clinical Pharmacology of Anticholinergics

- only muscarinic receptors are blocked

- General Pharmacological Characteristics
  - **Cardiovascular**; Blockade of muscarinic receptors in the SA node → tachycardia
  - **Respiratory**; inhibit the secretions of the respiratory tract mucosa
  - **Cerebral**; ranging from stimulation to depression
  - **Gastrointestinal**; Decreased intestinal motility & secretion

Clinical Pharmacology of Anticholinergics (cont)

- General Pharmacological Characteristics
  - **Ophthalmic;** mydriasis, cycloplegia (inability to accommodate to near vision)
  - **Genitourinary;** smooth muscle relaxation →lead to urinary retention
  - **Thermoregulation;** Inhibition of sweat glands → lead to a rise in body temperature → fever (atropine)
  - **Immune-Mediated Hypersensitivity;** little efficacy

Central Anticholinergic Syndrome

- **Belladonna alkaloids** → undesirable side effects ranging from stupor (scopolamine) to delirium (atropine)
- "postoperative delirium & atropine toxicity"
- High doses of atropinic alkaloids rapidly produce
  - dryness of the mouth
  - blurred vision with photophobia (mydriasis)
  - hot and dry skin (flushed) → fever
  - Mental symptoms range from sedation, stupor, coma →anxiety, restlessness, disorientation, hallucinations, delirium
- Convulsions & ventilatory arrest from lethal poisoning
- Intoxication is usually short lived and followed by amnesia
- controlled by intravenous (iv) physostigmine (1 mg or 2 mg)

- Anticholinesterase drugs
  - Neostigmine
- Ganglionic blockade ; Trimethaphan
- Neuromuscular blockade ; DR , NMDR

Some Drugs & Toxins That Affect Autonomic Activity

SITE OF ACTION	COMPOUNDS THAT AUGMENT ACTIVITY	COMPOUNDS THAT DEPRESS ACTIVITY
Sympathetic & Parasym. ganglia	**Inhibit AchE** Neostigmine (Prostigmine) Physostigmine	**Block conduction** Trimethaphan
Endings of postganglionic noradrenergic neurons	**Release NE** Ephedrine Tyramine, Amphetamine	**Block NE synthesis** Guanethidine, Reserpine Methyldopa (Aldomet)
a-Receptors	**Stimulate a_1-receptors** Phenylephrine	**Block a-receptors** Prazosin (blocks a_1)
	Stimulate a_2-receptors Clonidine	Yohimbine (blocks a_2)
B-Receptors	**Stimulate b-receptors** Isoproterenol (Isuprel) Dobutamine (Dobutrex	**Block b-receptors** Propranolol (Inderal) Atenolol (Tenormin)

IV AUTONOMIC DYSFUNCTION

- Clinical Syndromes
  - Surgical Stress Response
  - Diabetes Mellitus
- Autonomic Changes with Aging
- Autonomic Changes in Spinal Cord Transsection

Surgical Stress Response

- profound metabolic and endocrine responses → combination of autonomic, hormonal and catabolic changes
- use of continuous thoracic epidural infusions of local anesthetics minimized the rise in plasma catecholamines, cortisol, and glucagon and improved outcomes

Diabetic autonomic neuropathy

- occurs in 20-40% of all insulin-dependent diabetic pts
- Common manifestations;
  - impotence, diarrhea, sweating abnormalities → little effect on survival
  - postural hypotension, gastroparesis → 5-year mortality rates > 50%

- **greater decline in BP** with induction & greater need for vasopressors
- **gastroparesis** → awake or rapid-sequence intubation
- **postural hypotension** increases the risk for hemodynamic instability & cardiovascular collapse
- **Compromised Baroreceptors** in the carotid sinus & aortic arch

Autonomic Changes with Aging

- **primary autonomic defect** in aging → impairment in reuptake of NE
- **Blunted end-organ responsiveness** by compensatory down regulation of β_1-receptors
- **loss of adrenergic control** through the reduction of α2- & β-receptor → decrease in sympathetic nervous system's ability to maintain CVS homeostasis
- **Orthostatic hypotension** ~ 20%
- **Blunted HR responses** to changes in BP, the Valsalva maneuver, respiratory cycle

Autonomic Changes in Spinal Cord Transsection

- affects motor & sensory function → profound changes in autonomic activity depending on site, extent, timing of the lesion

- cervical spinal cord transection → profound abnormalities that alter CVS, thermoregulatory, gastrointestinal, urinary systems
- spinal shock (immediately last days to weeks)→ peripheral atony & dilated blood vessels

- chronic high spinal lesions → fail to respond to hypovolemia exhibit bradycardia

- **Autonomic dysreflexia** can occur with stimulation below lesion
  - Bladder or bowel distention can elicit mass reflex

- hypothermia result from cutaneous vasodilation & inability to shiver

- hyperthermia → impaired normal sweating mechanism

Noninvasive Tests for Assessing the Autonomic Nervous System

Clinical Examination	Normal Value
Parasympathetic	
HR response to a Valsalva maneuver	Ratio of >1.21
HR response to standing	Ratio of >1.04
HR response to deep breathing	Mean difference >15 beats/min
Sympathetic	
BP response to standing	Difference <10 mm Hg
BP response to sustained handgrip	Difference >16 mm Hg

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