Veterinary Bioscience: Cells to Systems

VETS70003 / VETS30015

THE UNIVERSITY OF MELBOURNE

FACULTY OF VETERINARY SCIENCE

Using drugs to modify sympathetic nervous system function

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At the end of this lecture, you should be able to:

- **Describe the synthesis, storage, uptake and metabolism of the major natural catecholamines and how certain drugs are able to modulate sympathetic NS activity through alteration of these processes**

- Describe, in a more detailed way, how adrenoceptors are divided into subtypes and the pharmacological basis for this division and how they are responsible for the major physiological roles of the sympathetic NS and circulating adrenaline

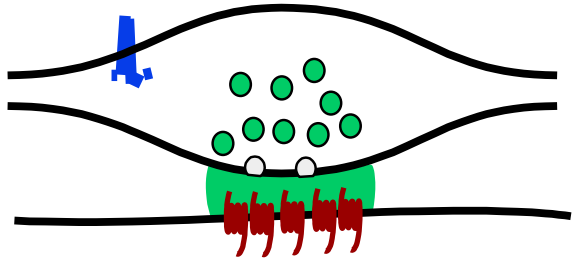
- Describe the basic signal transduction mechanisms that adrenoceptors employ to produce their functional effects

Drug targets in process of chemical transmission

Peripheral nervous system

Autonomic and Skeletal motor

Cholinergic & noradrenergic transmission



Nerve → **Target** → **Response**

Transmitter

Drugs can influence amount of transmitter reaching the receptors

Synthesis, Storage, Release & Inactivation

Receptor

Drugs can mimic, or inhibit, the actions of transmitters

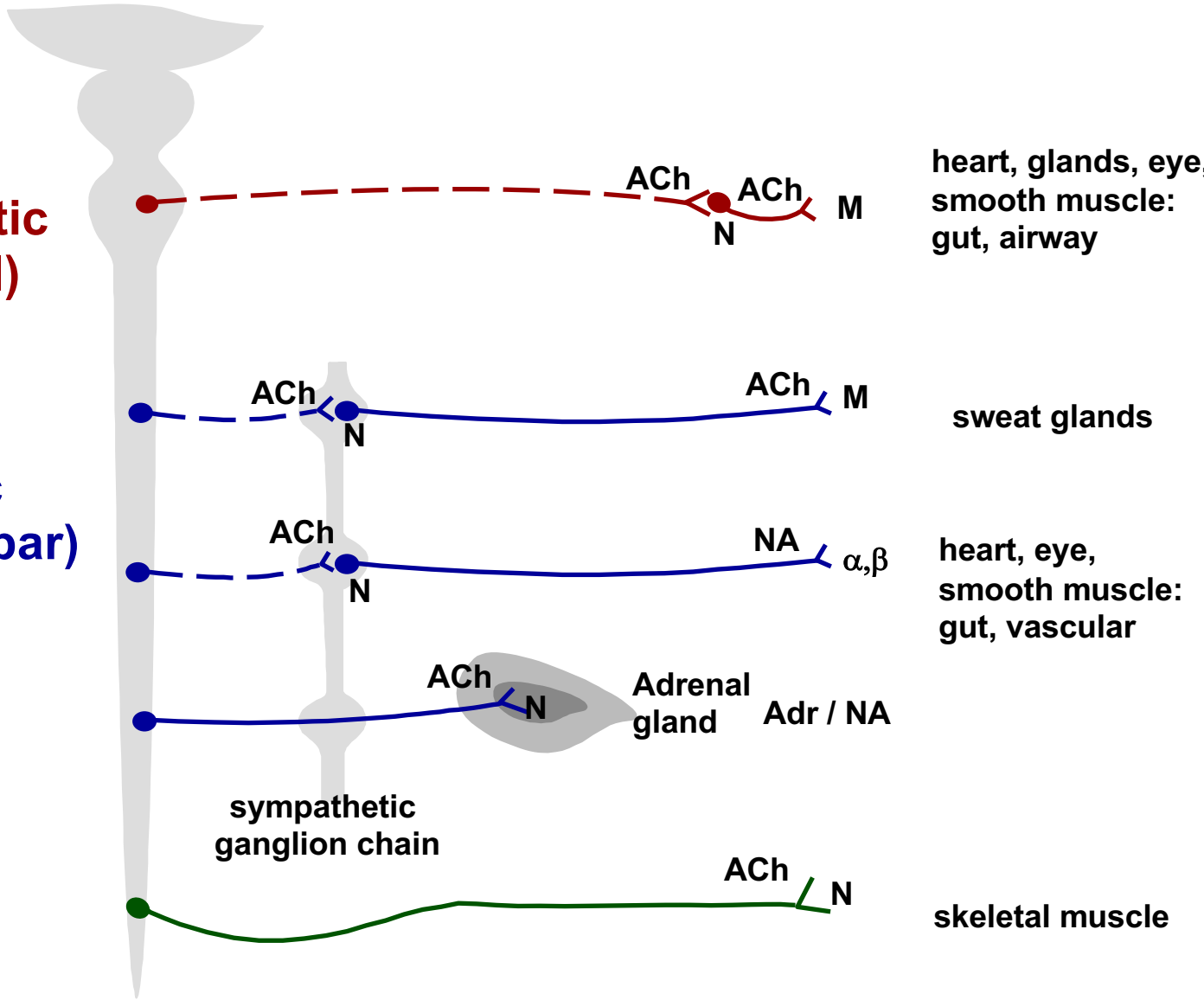
Agonists
Antagonists

Coupling

Drugs can influence receptor signalling

Ligand-gated
G protein-coupled

Peripheral Nervous System – Anatomy, Physiology & Pharmacology

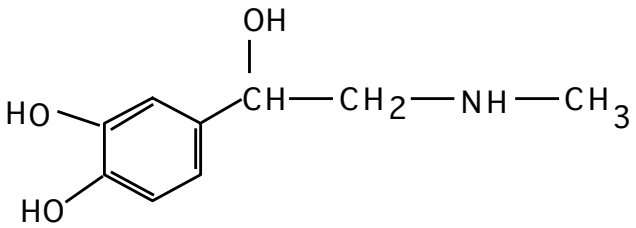


Adapted from Golan et al (3rd Ed); Ch 8

Identification of sympathetic transmitter

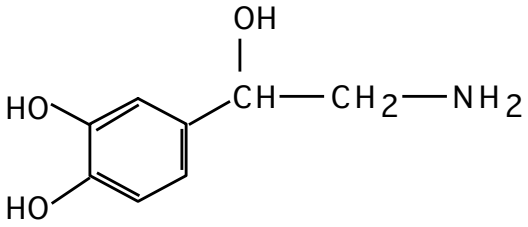
Adrenaline vs noradrenaline (Catecholamines)

Adrenaline (Adrenergic)



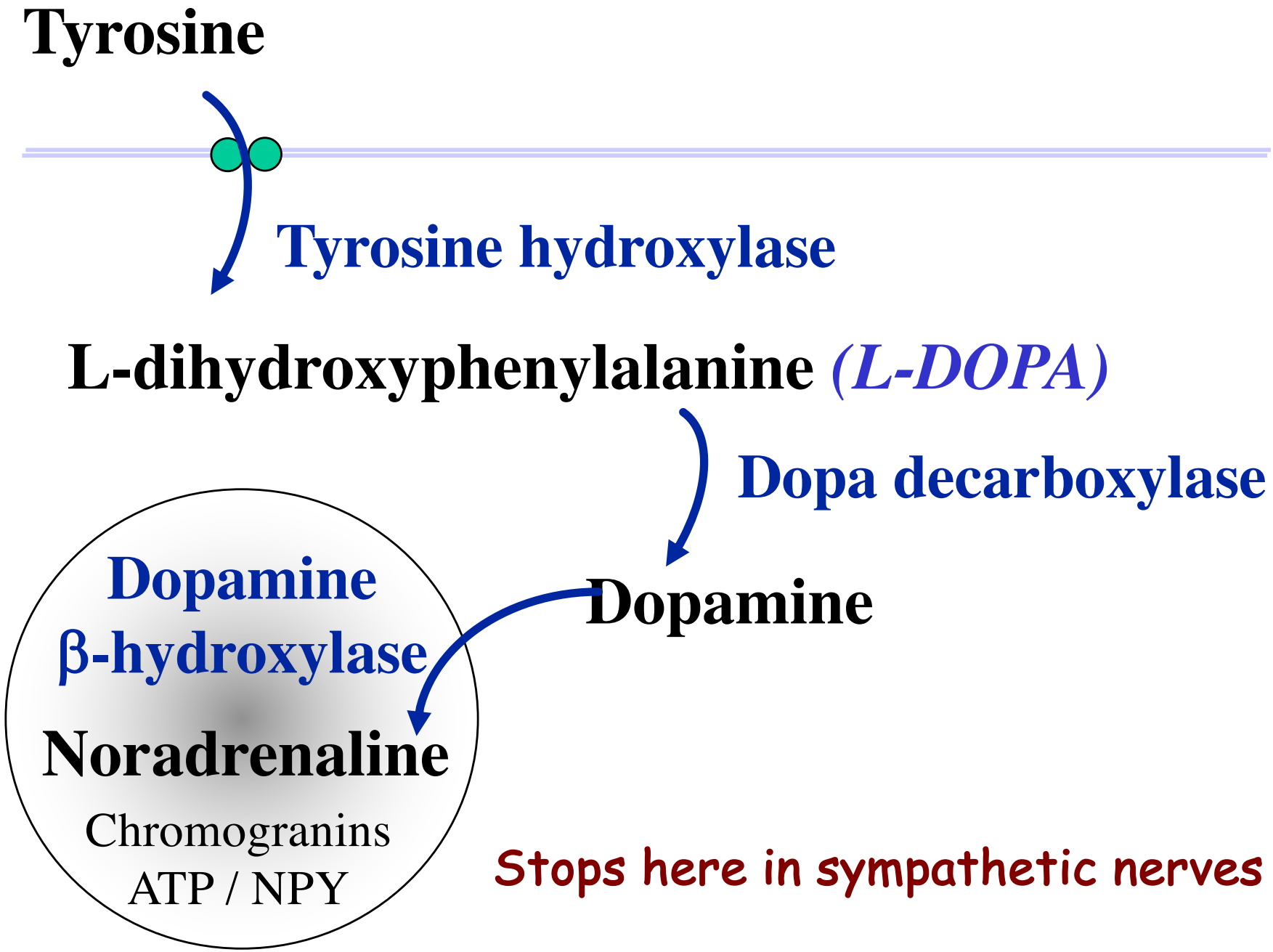
- found in blood
- mimicked sympathetic nerves
- isolated from adrenal extracts
- hormone released by SNS

Noradrenaline (Noradrenergic)

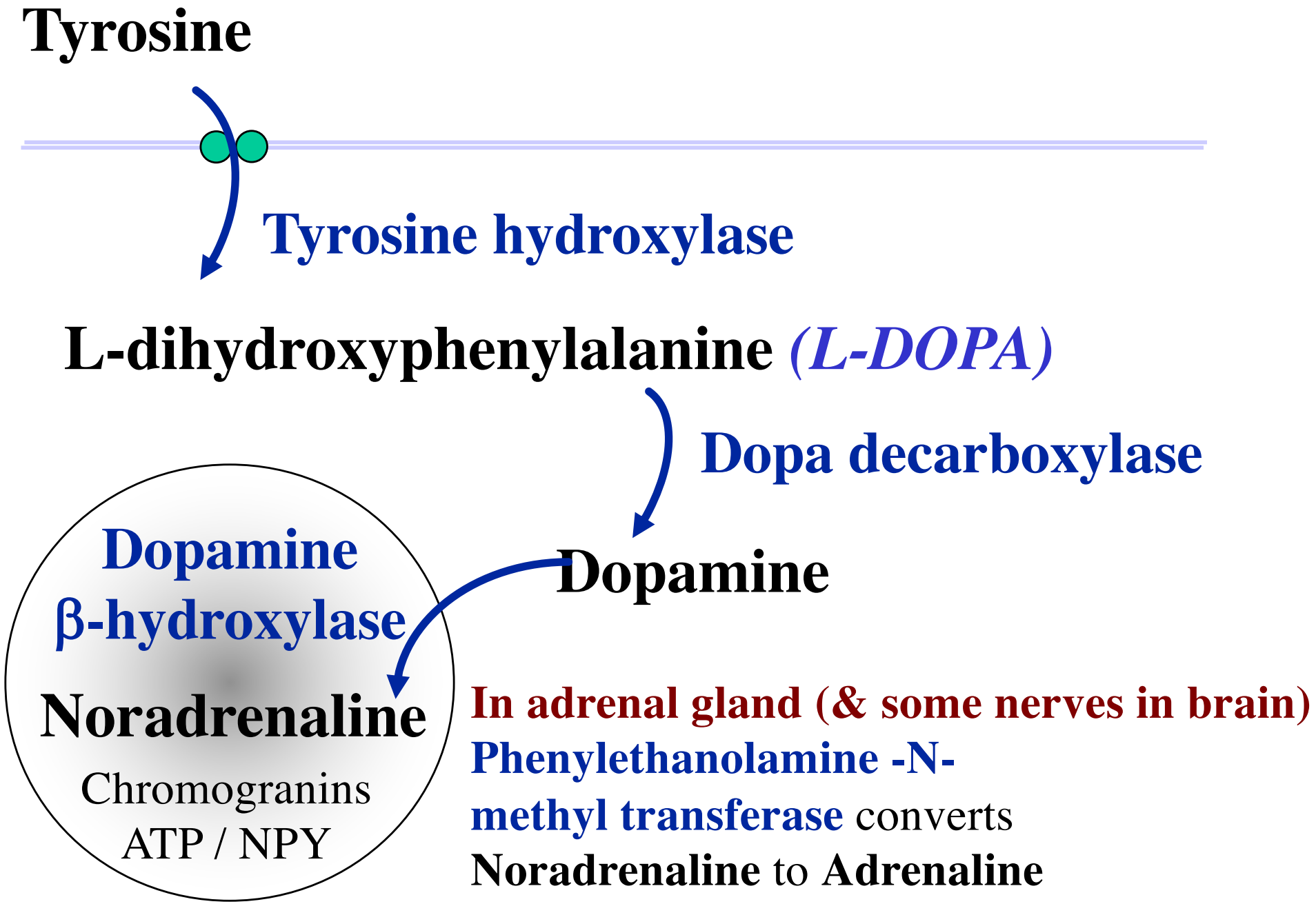


- not as abundant in blood
- mimicked sympathetic nerves
- synthesised in most postganglionic sympathetic nerves

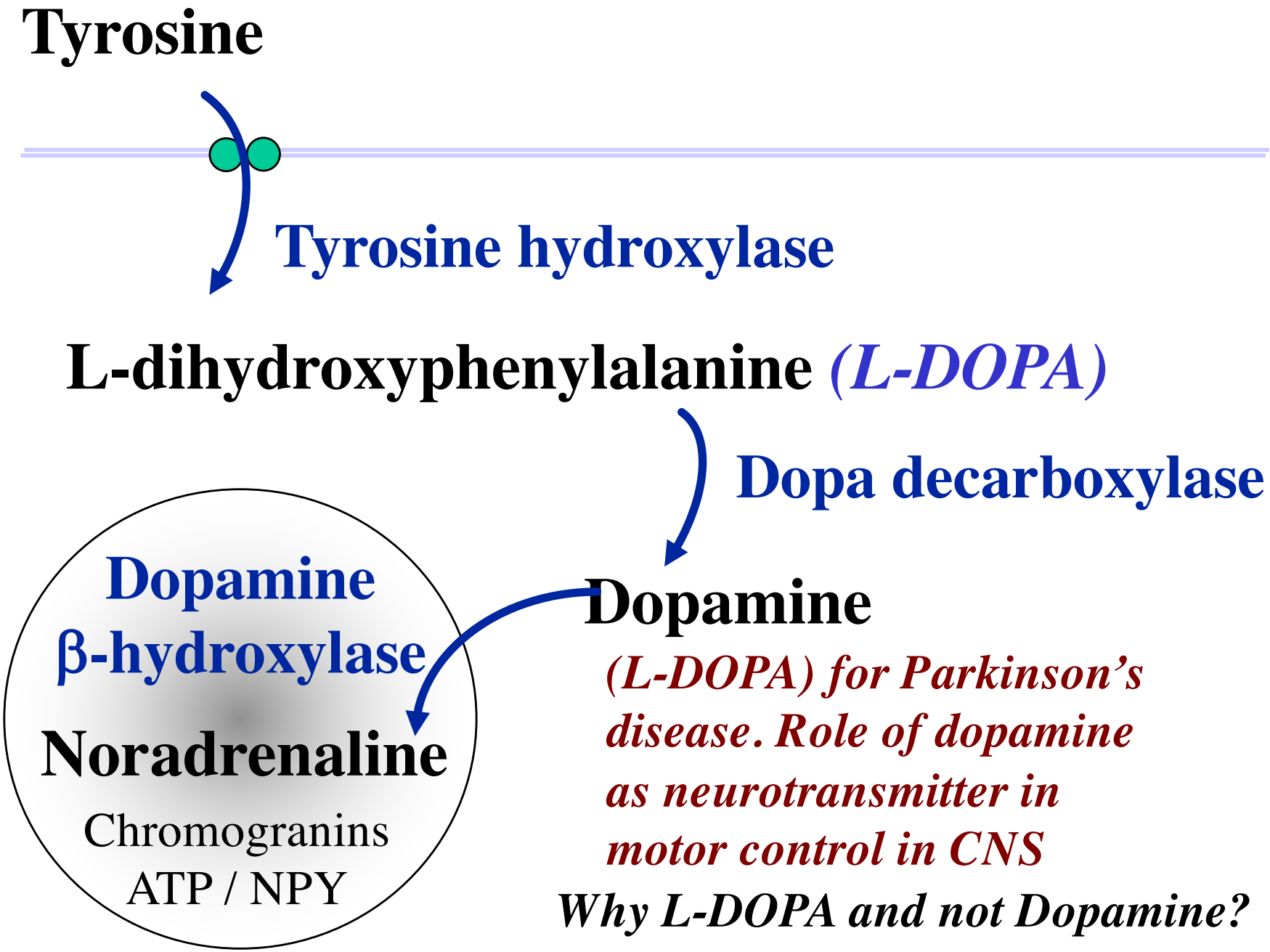
Catecholamine synthesis



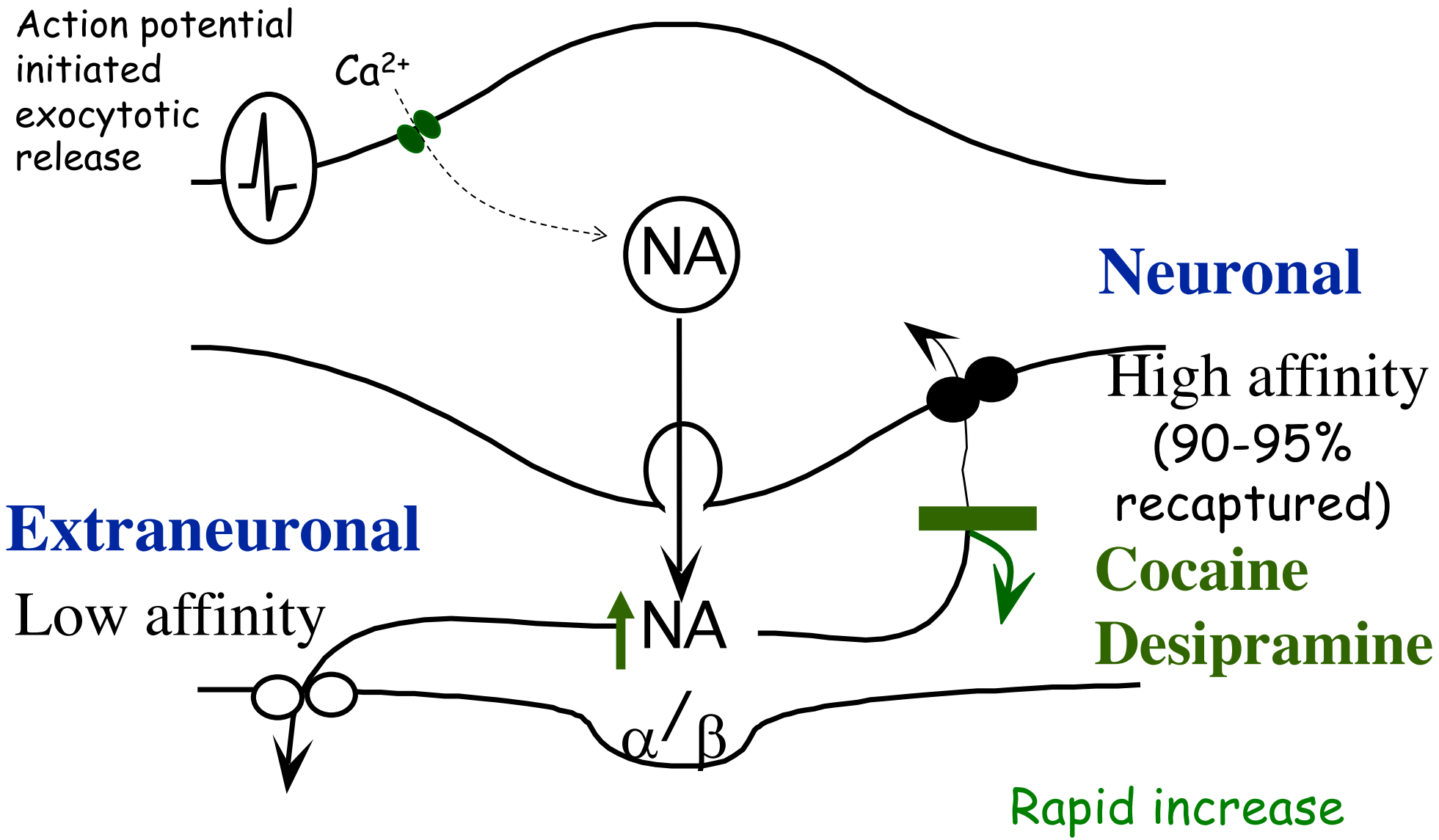
Catecholamine synthesis



Catecholamine synthesis: Therapeutic targets

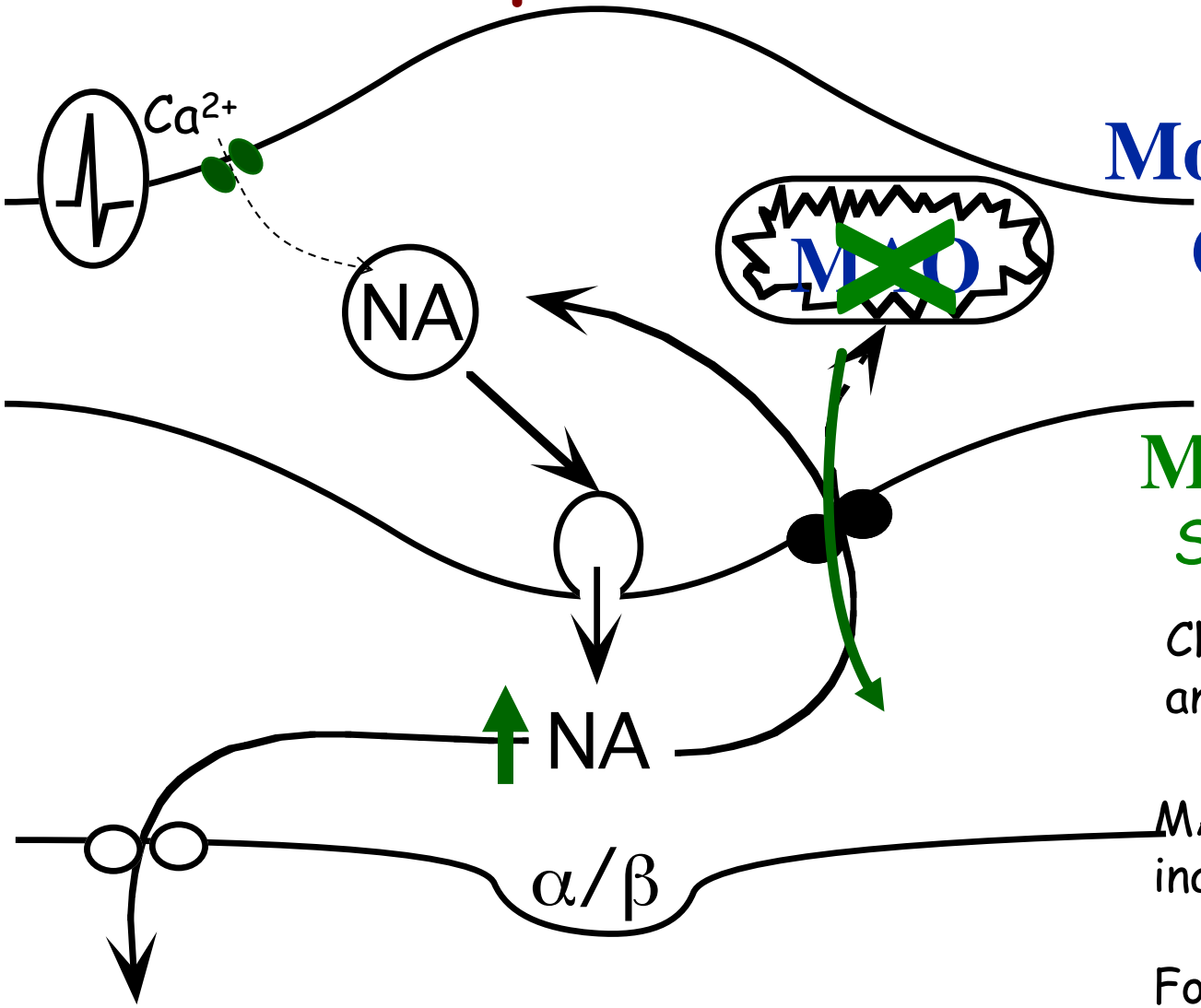


Inactivation - uptake



CNS actions: mood elevation, addiction, antidepressant drugs, but also effects on cardiovascular system

Inactivation - uptake & metabolism



Mono Amine Oxidase

Moclobemide
Slow increase

CNS actions:
antidepressant drugs

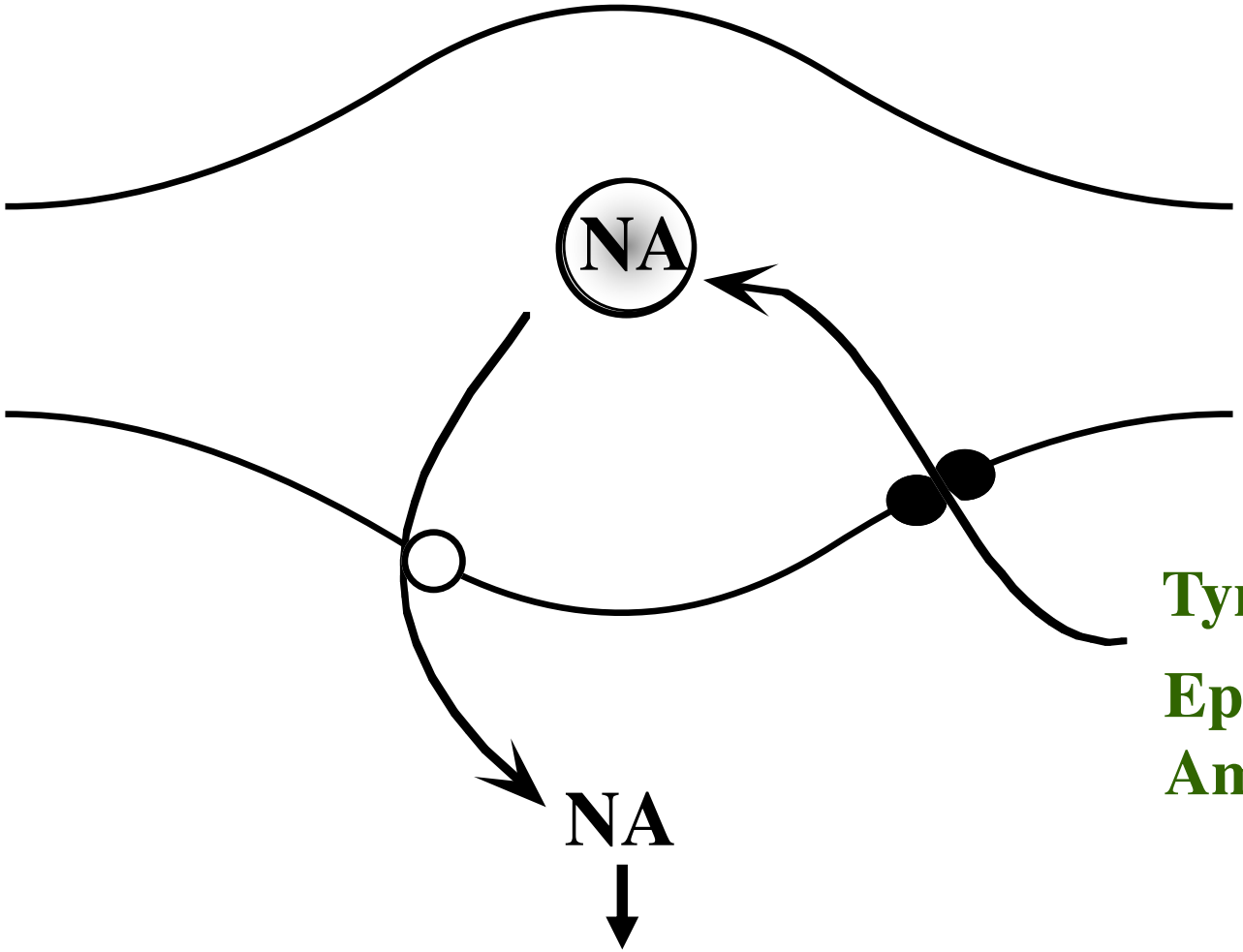
MAO in gut role of inactivating amines:

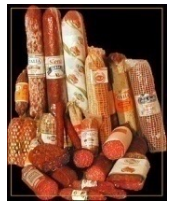
Food / drug interactions:
"cheese reaction"
profound effects on blood pressure

Catechol-O-methyl transferase
Monoamine oxidase

Indirectly acting sympathomimetics

Non-exocytotic release





Tyramine

Ephedrine

Amphetamine

α- or β-adrenoceptor ⟶ Response

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- Describe the basic signal transduction mechanisms that adrenoceptors employ to produce their functional effects

Adrenoceptor localisation & action

Comparison of the actions of noradrenaline and adrenaline

α-adrenoceptors:	**Agonist - phenyleprine**
	Antagonist - phentolamine
Blood vessels	- constrict
Pupil (dilates)	- constrict radial muscle
GIT	- constrict sphincters
β-adrenoceptors	**Agonist - isoprenaline**
	Antagonist - propranolol
Heart	- increase rate & force
Kidney	- renin secretion
Skeletal BV's	- dilate } (circulating Adr)
Bronchi	- dilate } (circulating Adr)

Golan et al (Ed); Ch 10, p132

α- and β- adrenoceptor selectivity of noradrenaline and adrenaline

For smooth muscle contraction

(α-adrenoceptors):- NA ≥ Adr

For smooth muscle relaxation & heart rate increase (β-adrenoceptors) :- Adr ≥ NA

- on closer inspection:

  Smooth muscle relaxation :- Adr > NA

  Heart rate increase :- Adr = NA

  - Subtypes of β-adrenoceptors have been identified
    - selective synthetic agonists and antagonists
    - gene sequencing

Adrenoceptor localisation & responses

Golan et al (Ed); Ch 10, p132

α-adrenoceptors

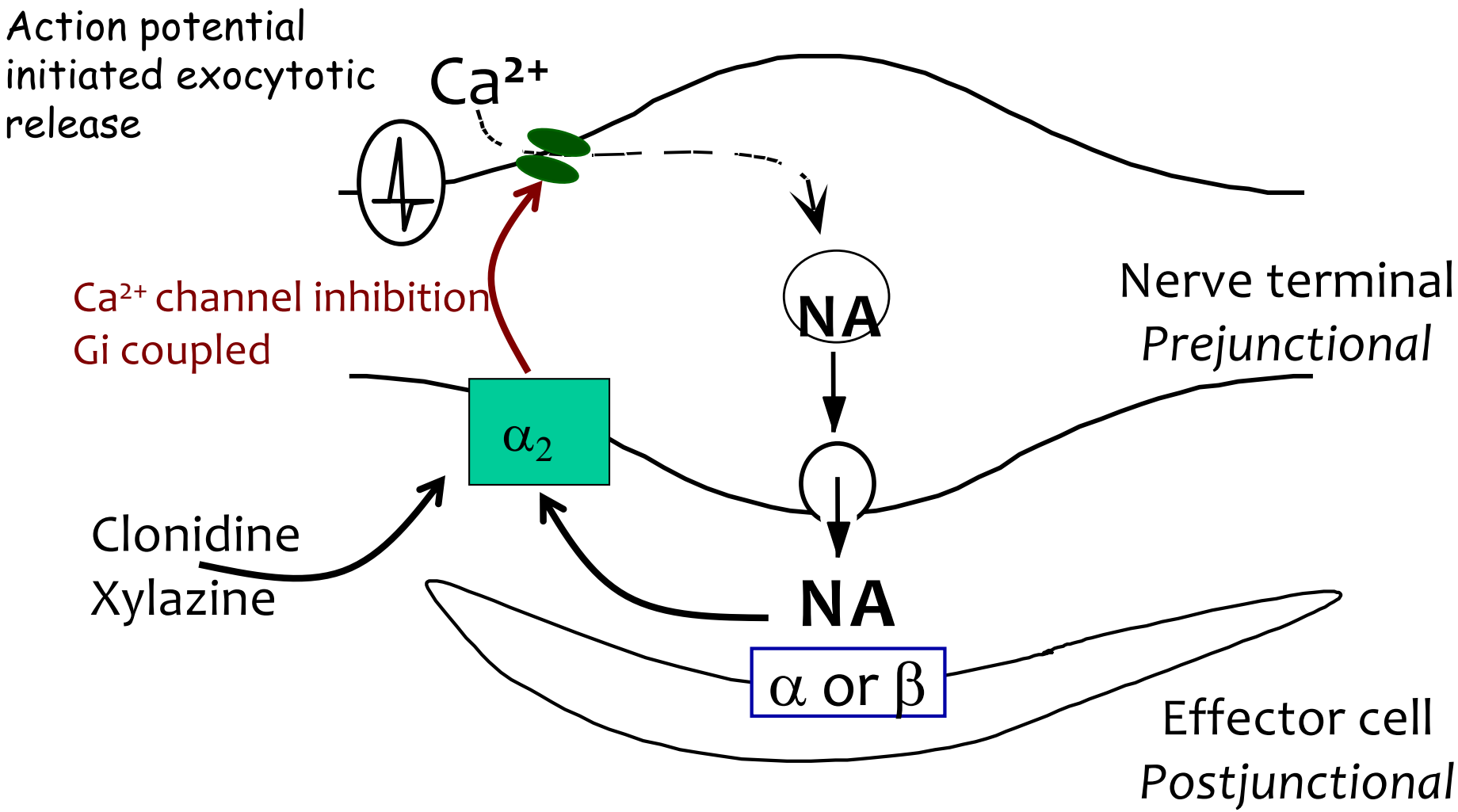
α_1	Blood vessels	- constrict
	Pupil (dilates)	- constrict radial muscle
	GIT	- constrict sphincters
α_2	Nerves	- inhibit transmitter release

β-adrenoceptors

β_1	Heart	- increase rate & force
	Kidney	- renin secretion
β_2	*Skeletal BV's*	- dilate } (circulating Adr)
	Bronchi	- dilate } (circulating Adr)

All couple through G protein-coupled receptors

Prejunctional α_2-adrenoreceptors inhibit transmitter noradrenaline release



"Autoinhibition" by noradrenaline

Selective α_2-adrenoceptor drugs in veterinary medicine

Agonist: Xylazine
- veterinary sedative

Antagonist: Yohimbine
- Xylazine reversal

Drugs with selectivity for α-adrenoceptor subtypes as therapeutics

α_1-adrenoceptor selective (vascular smooth muscle):

Agonists: phenylephrine

- nasal decongestant
- raise blood pressure (iv emergency)
  - reflex bradycardia

Antagonists: prazosin

- hypertension

α_2-adrenoceptor selective: (nerve terminal)

Agonists: Clonidine

- hypertension, CNS action
- sedation

Antagonists: *Yohimbine*

Drugs with selectivity for β-adrenoceptor subtypes as therapeutics

β_1-adrenoceptor selective (heart, kidney)

Agonists: dobutamine

- partial agonist
- heart failure (acute)

Antagonists: metoprolol

- hypertension, angina, anxiety
- heart failure (chronic)

β_2-adrenoceptor selective (smooth muscle):

Agonists: salbutamol

- asthma but cardiac palpitations

$\beta1$:$\beta2$ ratio in heart

Antagonists: None in therapeutic use.

Selectivity not everything!

Noradrenaline:

$$\alpha_1 > \beta_1 \sim \alpha_2 >> \beta_2$$

In nerves to perform specific task when required

Great transmitter but not a great "drug"

Adrenaline:

$$\beta_2 \sim \beta_1 \sim \alpha_1 > \alpha_2$$

Emergency hormone - improves airway function, promotes blood flow, stimulates metabolism.
ie. All the features of the fight or flight response

Life saving drug - severe allergic reactions
Also added to local anaesthetic solutions

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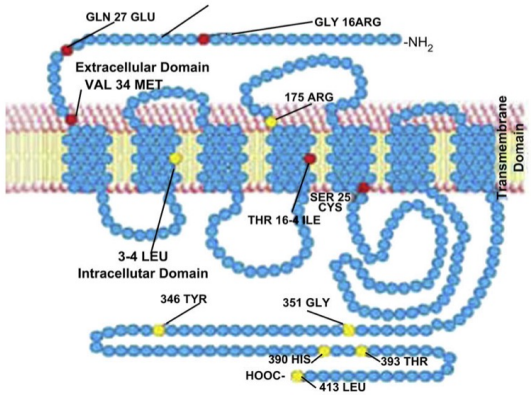
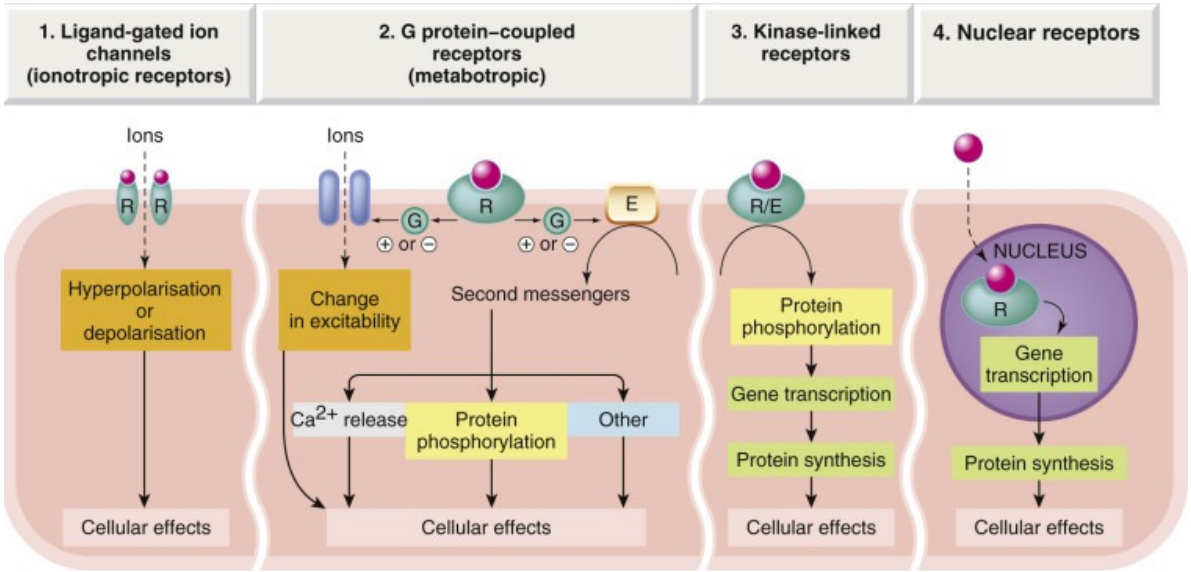
Molecular Aspects of Adrenergic Receptors

- Different gene for each receptor subtype
  - Unique amino acid sequence
  - 7 transmembrane spanning regions

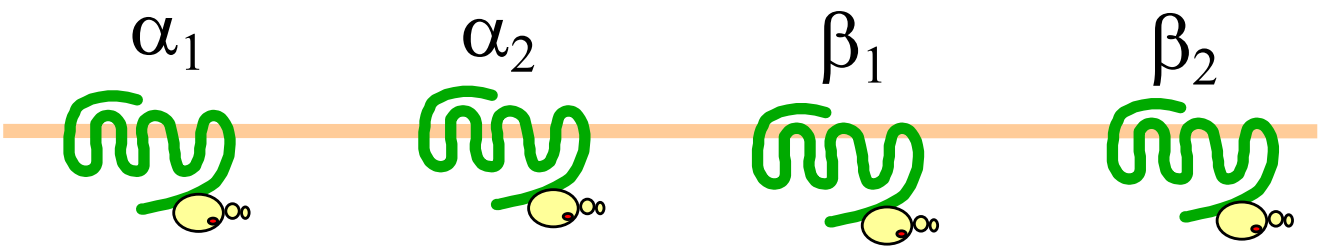


I. Yu, Bonny L. Bukaveckas, Clinics in laboratory medicine 2008

- All G protein-coupled receptors
  - specific 2nd messenger pathways



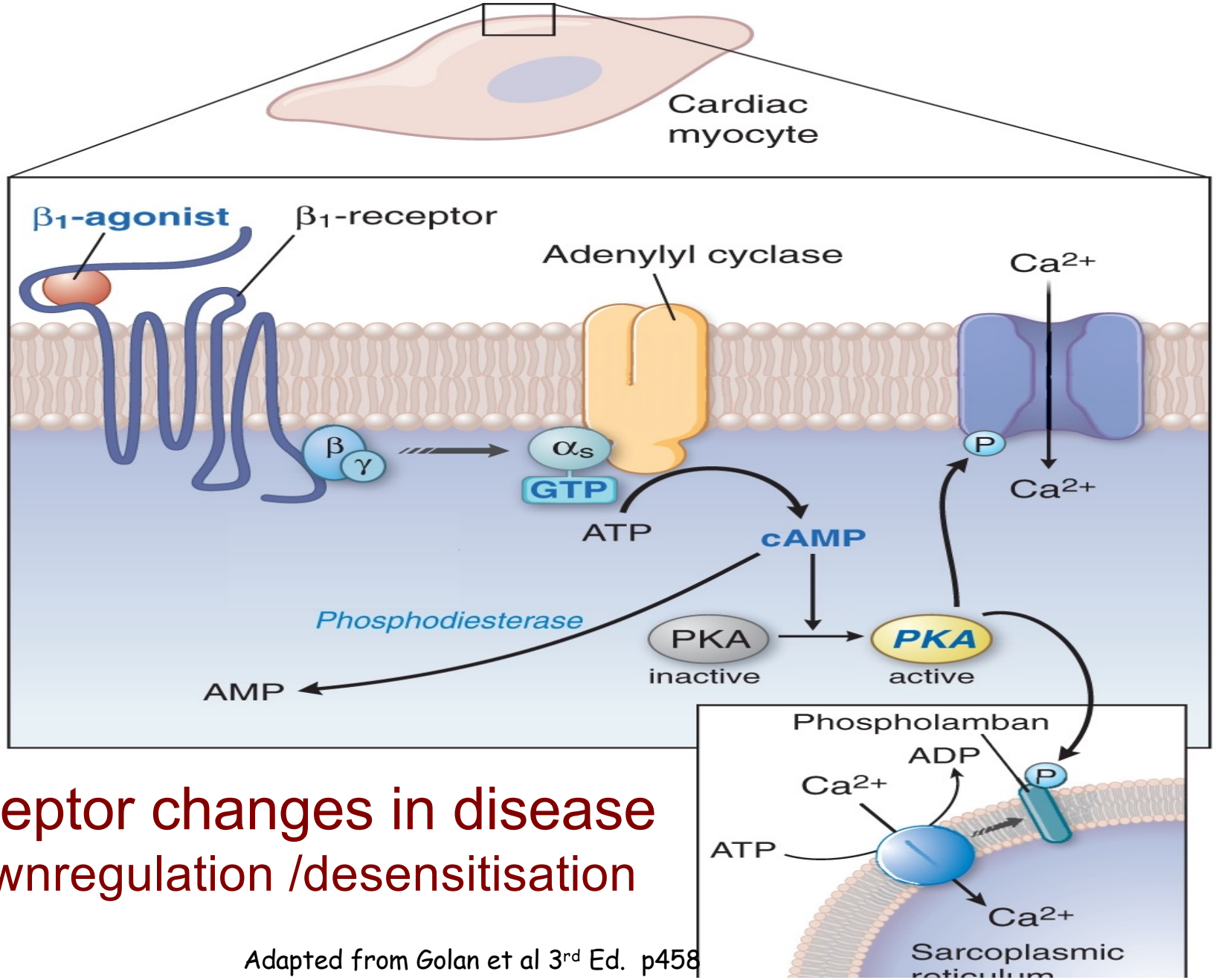
Adrenoceptor drugs & signalling mechanisms



	α_1	α_2	β_1	β_2
G protein	G_q	G_i	G_s	G_s
Enzyme	Phospho-lipase	Adenylyl cyclase	Adenylyl cyclase	Adenylyl cyclase
2nd Messenger	IP_3, DAG	↓cAMP	↑cAMP	↑cAMP
Selective agonist	Phenylephrine	Xylazine	Dobutamine	Salbutamol
Selective antagonist	Prazosin	Yohimbine	Atenolol	xxxxx

2nd messengers as drug targets

Beta$_1$-adrenoceptor signalling

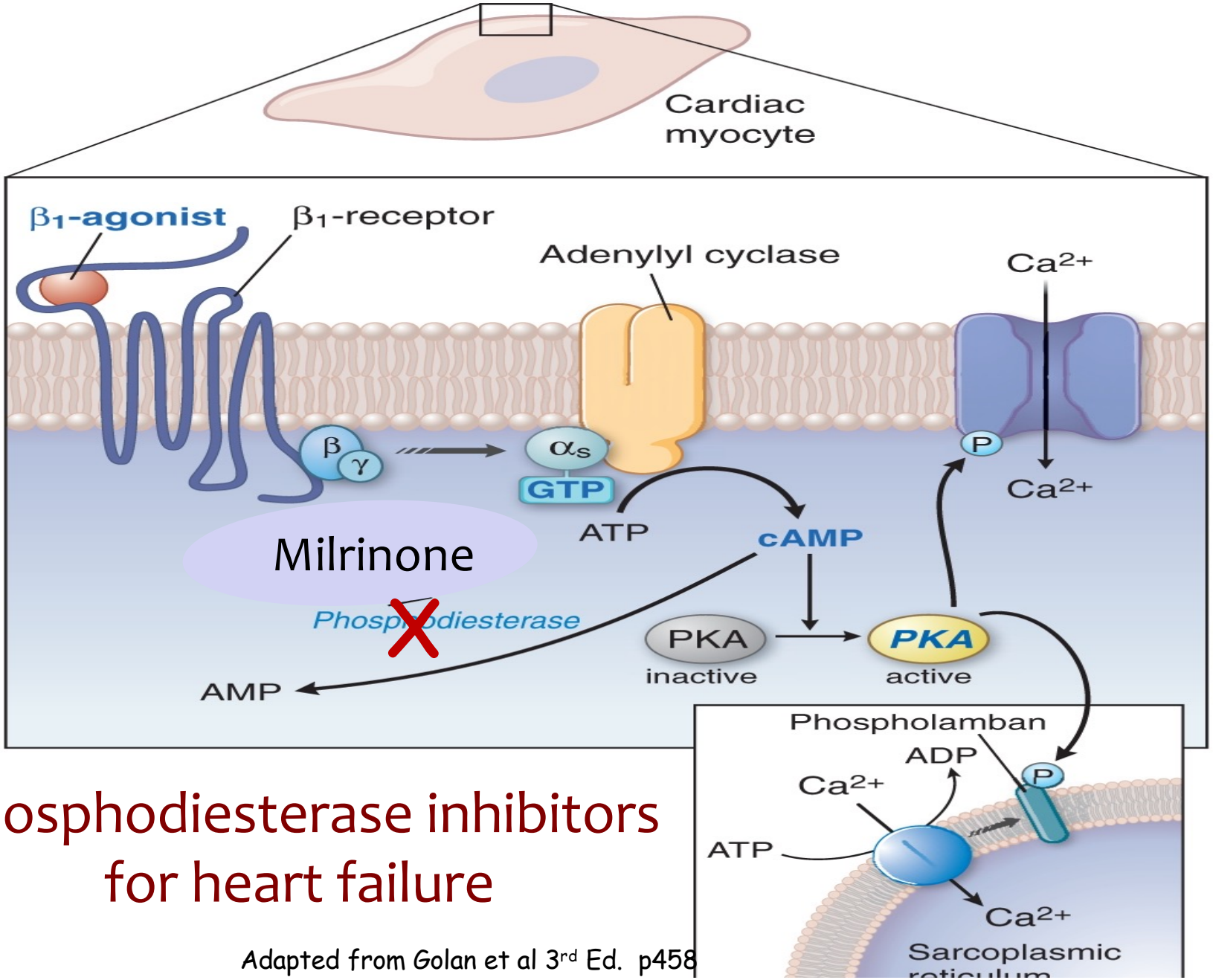


Receptor changes in disease

- downregulation /desensitisation

Adapted from Golan et al 3rd Ed. p458

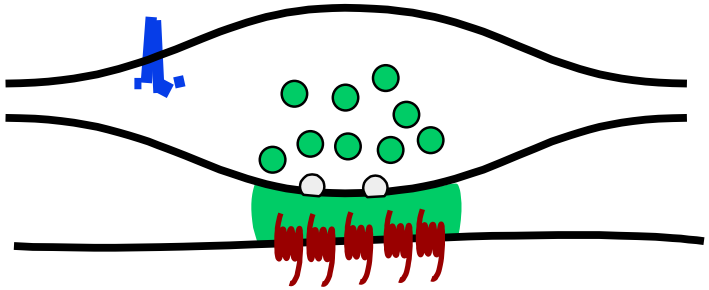
Beta$_1$-adrenoceptor signalling



Phosphodiesterase inhibitors for heart failure

Adapted from Golan et al 3rd Ed. p458

Drug targets in sympathetic transmission



Noradrenaline - neurotransmitter

(Adrenaline – hormone)

Nerve → **Target** → **Response**

Transmitter

Drugs can influence amount of transmitter reaching the receptors

Synthesis, Storage, Release & Inactivation

Precursors as drugs
Exocytotic release
Non-exocytotic release
Neuronal uptake & metabolism

Receptor

Drugs can mimic, or inhibit, the actions of transmitters

Agonists
Antagonists

α- & β- adrenoceptors

α_1 α_2 β_1 β_2

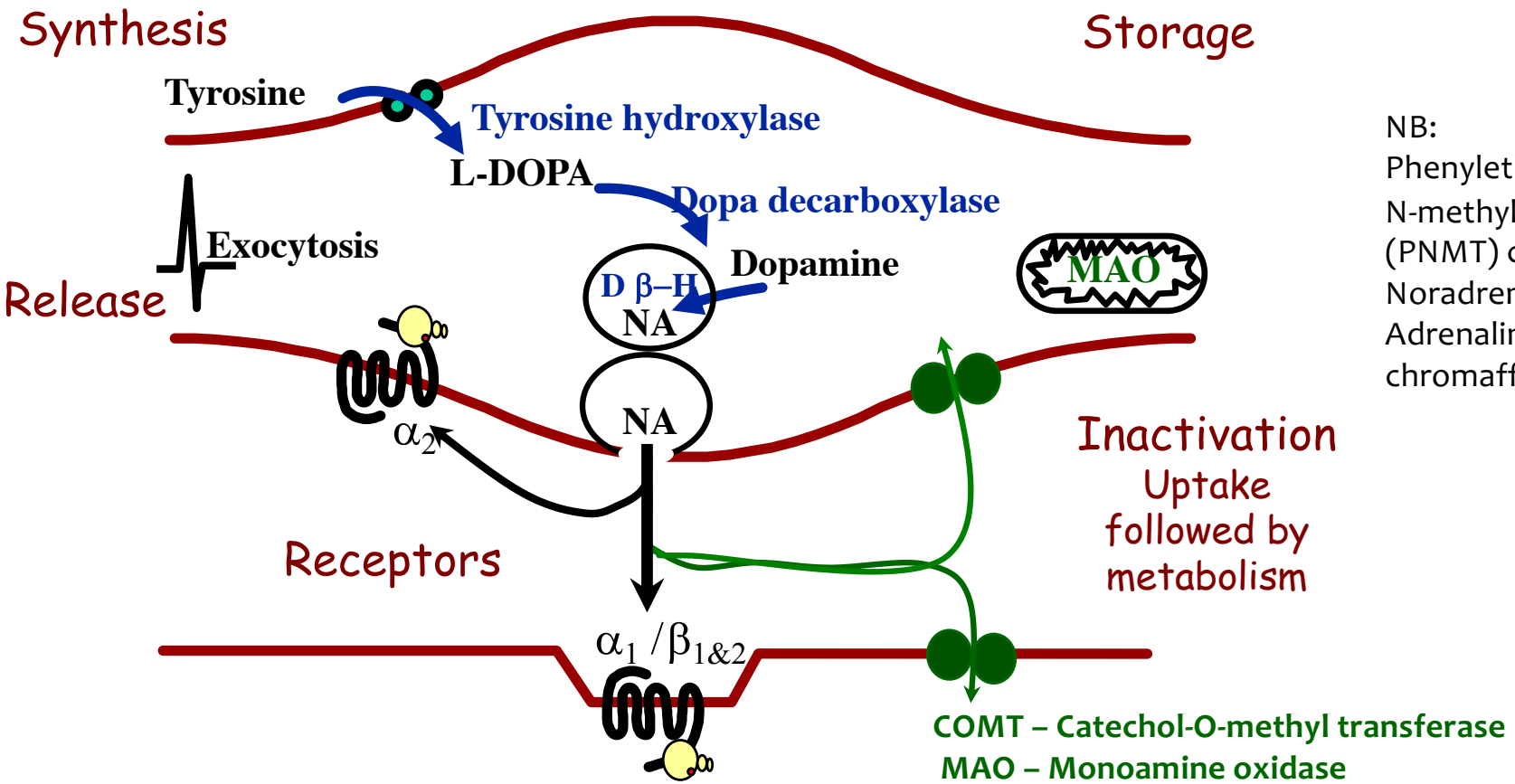
Coupling

Drugs can influence receptor downstream signalling

G protein-coupled

Phosphodiesterase

Noradrenergic transmission: Summary



NB:
Phenylethanolamine-N-methyl transferase (PNMT) converts Noradrenaline to Adrenaline in Adrenal chromaffin cells

Many drugs with diverse peripheral and central actions