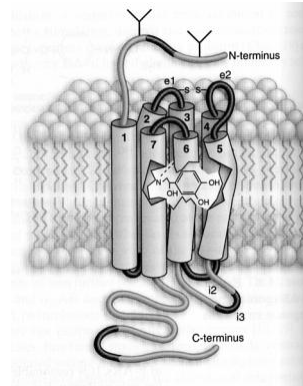
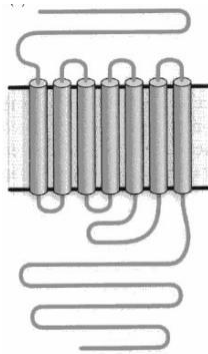
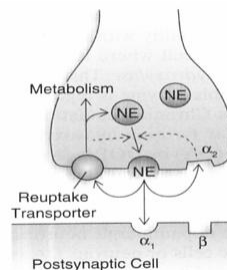


Continuation of Adrenoceptors

1. AR family
 - A. 9 distinct GPCRs (G-protein coupled receptor)
 - mediate agonist E & NE effects



- B. α -AR
 1. α_1 & α_2 ARs arterial vasoconstriction
 - a) 3 subtypes of α_1 AR
 - α_1 AR → neuroeffector junction (junctional receptors)
 - b) 3 subtypes of α_2 AR
 - α_2 AR → (extrajunctional) away from neuroeffector junction
 - c) α_1 & α_2 autoinhibition of NE



sympathetic: – **feedback mechanisms** for inhibition of sympathetic neuron secretion

C. β -AR1. β 1-AR

- a. adipose tissue \rightarrow lipolytic response
- b. cardiac tissue \rightarrow contraction

2. β 2-AR

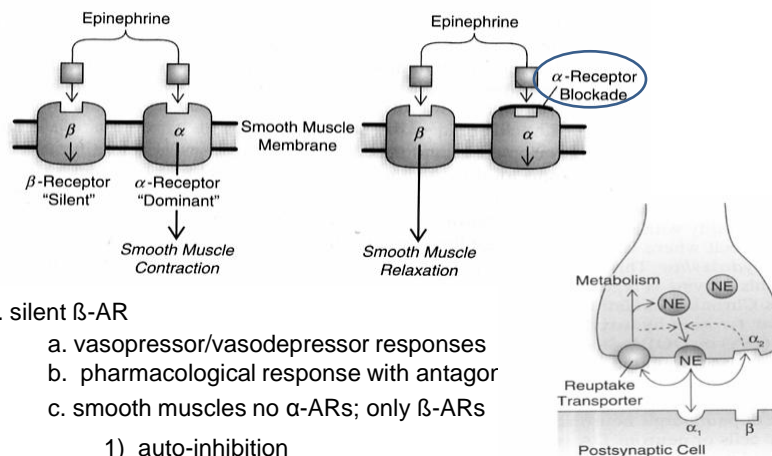
- a. vasodepression & bronchodilation

3. differences between two receptors \rightarrow sensitivity to NE

- a. ISO > E > NE
- b. β 1-AR respond to circulating E or to neural NE
- c. β 2-AR: E natural agonist
- d. β 1-AR neural
- e. β 2-AR hormonal

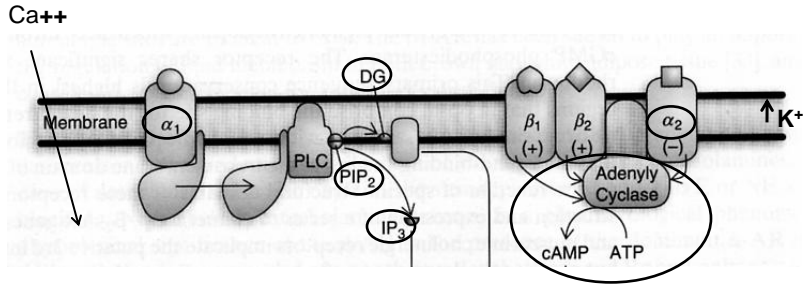
4. β 3-AR

- a. regulation of lipid metabolism brown & white adipose
- b. target by anti-obesity drugs

Ahlquist's dual adenoceptor hypothesis \rightarrow 5. silent β -AR

- a. vasopressor/vasodepressor responses
 - b. pharmacological response with antagonist
 - c. smooth muscles no α -ARs; only β -ARs
 - 1) auto-inhibition
 - 2) protection against continual vascular vasoconstriction
- \downarrow O_2 deprivation/gangrene

α-AR Signal Transduction



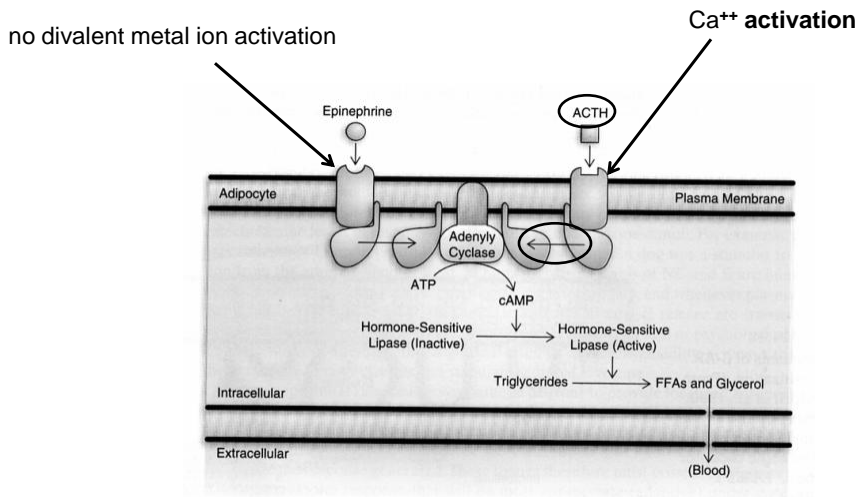
protein kinase C ← Ca²⁺ ← ER/SR

β-AR Signal Transduction

1962 Sutherland: cAMP

1971 Sutherland: Nobel Prize in Physiology or Medicine

- 1) hepatic glycogenolytic response
- 2) adipose lipolytic response



Adrenoceptor Autoinhibition

Isolated uterine myometrium

E: ↑ contraction

E stimulates adenylate cyclase activity
 blocked by α -AR antagonist
 inhibited by doses of E
 inhibition released by β -AR antagonist propranolol
 cAMP inhibitory action of E

2. dopamine (dopaminergic) receptors →

a. CNS → brain

b. PNS → autonomic nervous system

c. cardiovascular

d. effects

1) ↑ vasodilation blood vessels

2) ↑ diuresis & natriuresis

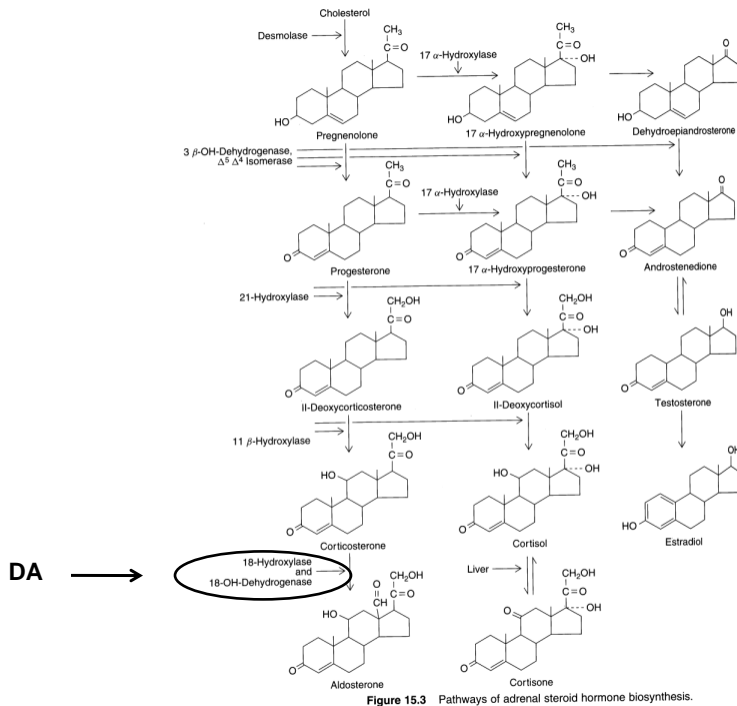
3) ↑ renin release

4) ↓ aldosterone release

5) Inhibitory of Nt release during neural stimulation

6) regulate **pituitary secretion of prolactin & α -melanotropin**

7) Inhibitory of **hypothalamic secretion of prolactin & α -melanotropin**



Other Factors Affecting AR



I. Gonadal

- A) modulate AR response to catecholamines
- 1) **estrogen & progesterone** → catecholamine metabolism
 - 2) oviduct & uterine smooth muscles response:
 - a) α -AR → contraction: ↑ estrogen → uterus
 - b) β -AR → relaxation: pregnancy/ ↑ progesterone → uterus

II. Adrenal Steroid Hormones

A) **glucocorticoid**

permissive role → cAMP mediated effects on liver/other organs
catecholamines in adrenalectomized rats?

↓ gluconeogenesis/glycogenesis & lipolytic response of adipose
~cardiovascular response

III. Thyroid Hormones (TH)

↑TH → catecholamine effect enhanced
↓TH → catecholamine effect depressed } → sympathetic neurons

Desensitization of β -AR Function

- 1) catecholamine stimulation of plasma membrane β -AR
- 2) \uparrow cAMP

- 1) catecholamine agonist stimulation of plasma membrane β -AR
- 2) \uparrow cAMP

- 1) removal of catecholamine agonist stimulation of plasma membrane β -AR
- 2) GTP_{ase} of $\text{G}\alpha_s$: **GTP (guanine triphosphate) \rightarrow GDP (guanine diphosphate)**

- 1) Continual agonist presence: cAMP
- 2) desensitization \rightarrow cAMP plateau or return to basal concentrations despite continuous exposure to stimulant

other hormone & neurotransmitter-receptor systems
especially activation of G protein & effector systems

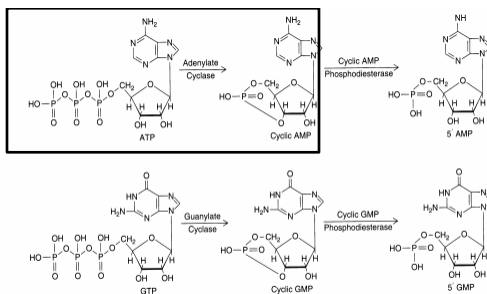
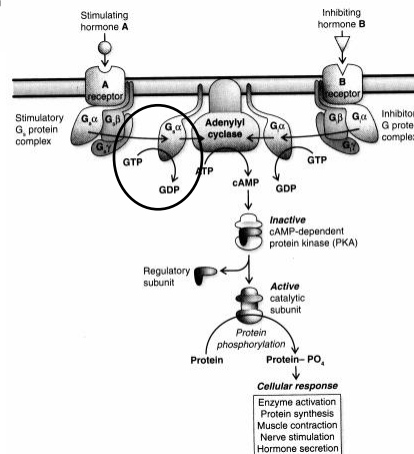
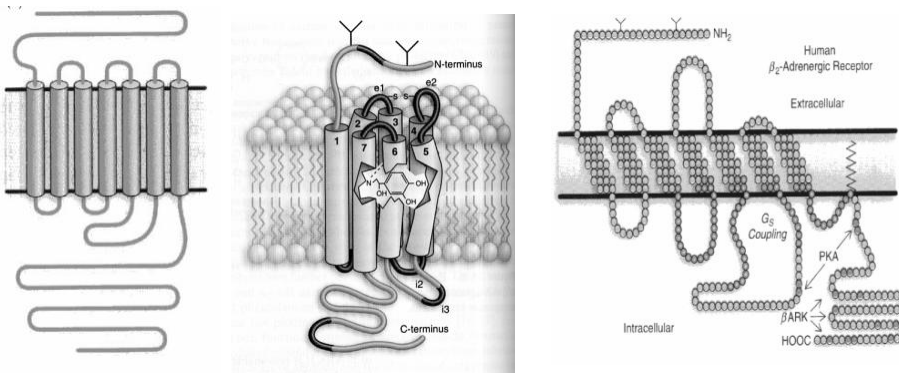


Figure 3.6 Cyclic nucleotide synthesis and inactivation.



- 1) desensitization of agonist induced β -AR
- 2) rapid attenuation stimulated cAMP production
 - a) not internalization of receptors
 - b) alteration in β -AR *uncoupling from G_{α_s}*
 - c) phosphorylation by protein kinase A (PKA) & β -AR kinase (β -ARK)



Tissue Density of AR

- 1) up-regulation
 - ↑ ARs absence of stimulation
- 2) down-regulation
 - ↓ ARs continuous stimulation
- 3) denervation of rat pineal & dog heart
 - ↑ catecholamines ↑ cAMP **denervation supersensitivity**
 - ↑ tissue β -ARs
- 4) ↓ tissue β -ARs ← continual presence of agonist (isoproterenol)