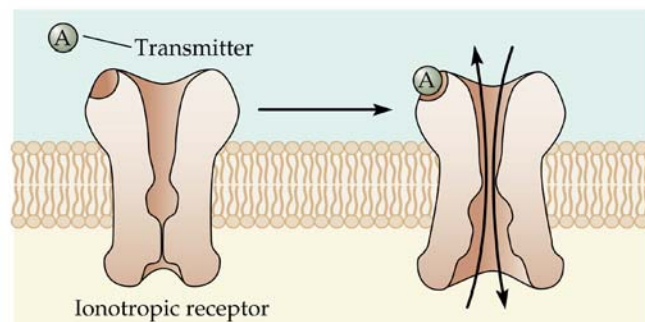

ZOO332H1S
Lecture 8 (AJE 2003)

**Indirect Mechanisms of Synaptic
Transmission**

1

**Fast transmitter-gated channel:
*ionotropic receptor***

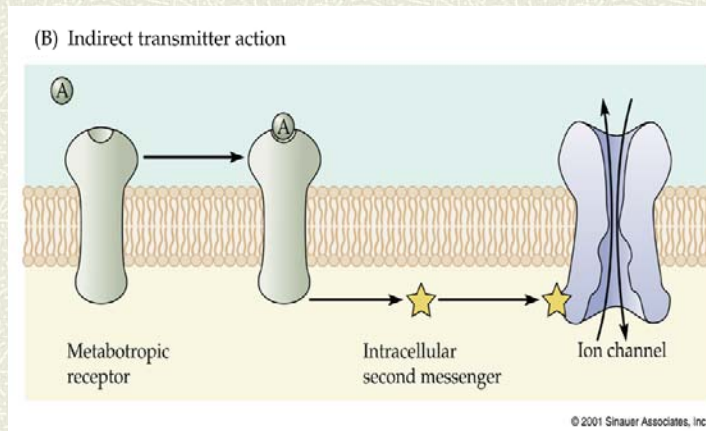
(A) Direct transmitter action



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2

Metabotropic receptors are indirectly coupled to channels – “slow” action, often G-Protein Coupled



3

Diverse cellular responses by 2nd messengers

- # Direct or indirect gating of channels by
 - G-proteins
 - cAMP, cGMP
- # Phosphorylation of channels
 - increase open probability (activate)
 - decrease open probability (inactivate)
- # Phosphorylation of receptors
 - increase sensitivity to NT
 - decrease sensitivity to NT
- # Regulation of gene activity

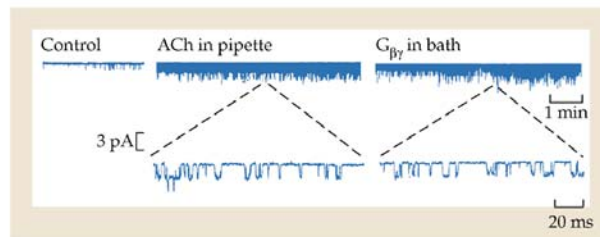
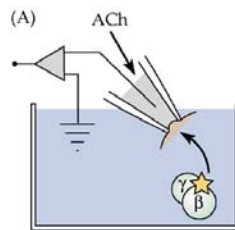
4

**Example:
Direct action of G-protein on ion channel**

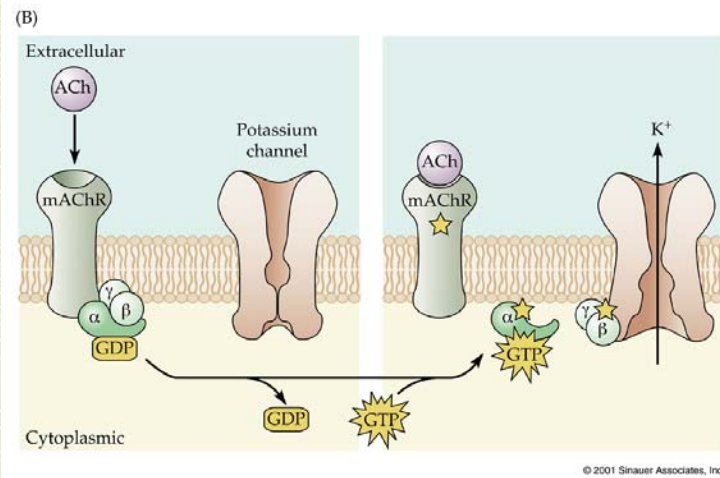
Parasympathetic (vagal) slowing of heart
(action on pacemaker)

ACh (parasympathetic transmitter) acts on muscarinic receptor of heart

mAChR



G-protein opens K^+ channels



Greater G_k delays depolarization and increases beat interval, *i.e.*, slows heart rate

Fig. 10.4

7

cont...G-protein opens K^+ channels

Direct or membrane-delimited effects of G-protein

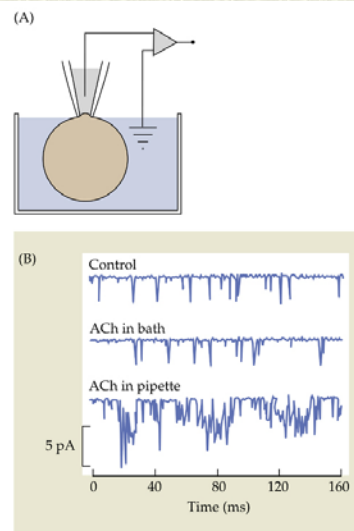
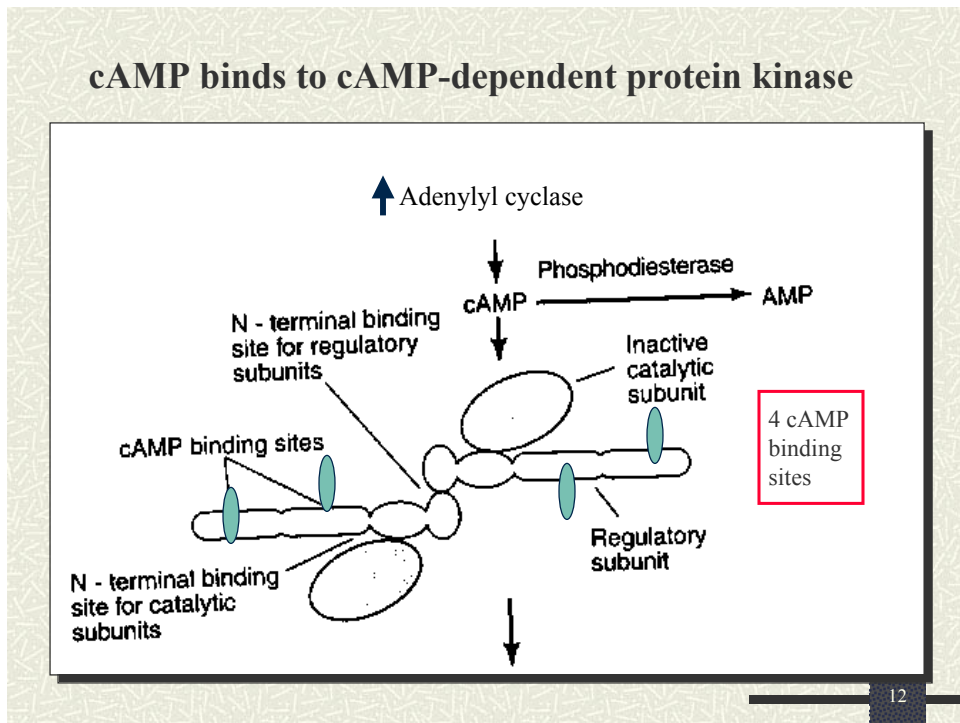
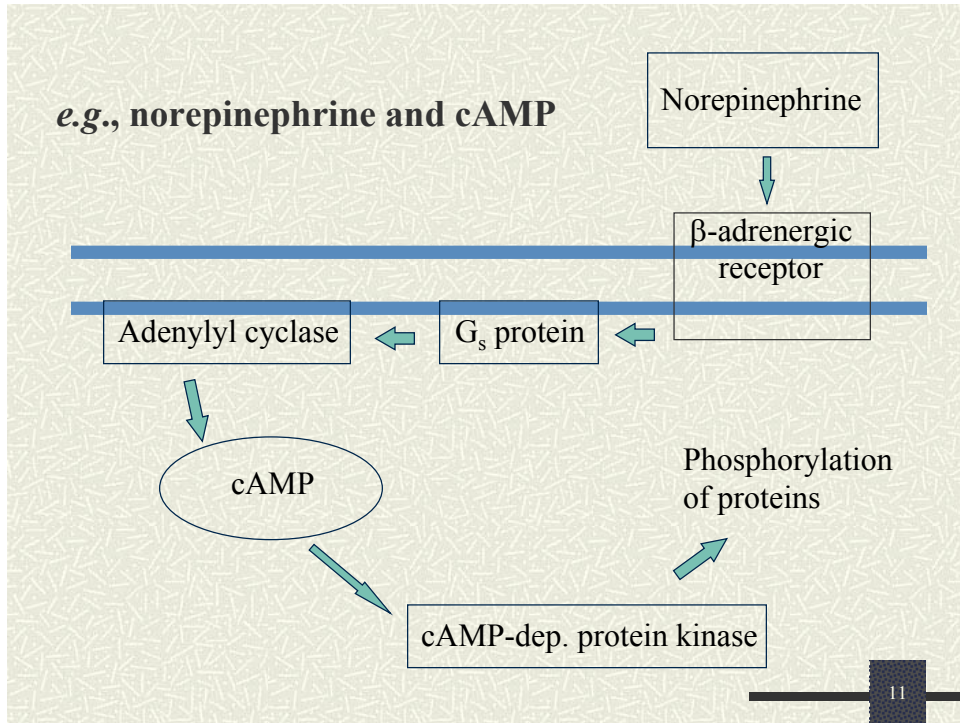
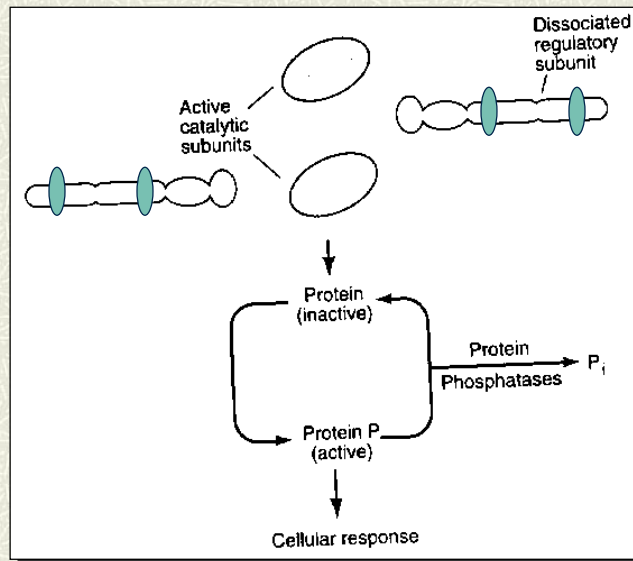


Fig. 10.5

8



Liberated catalytic subunits then phosphorylate substrate protein



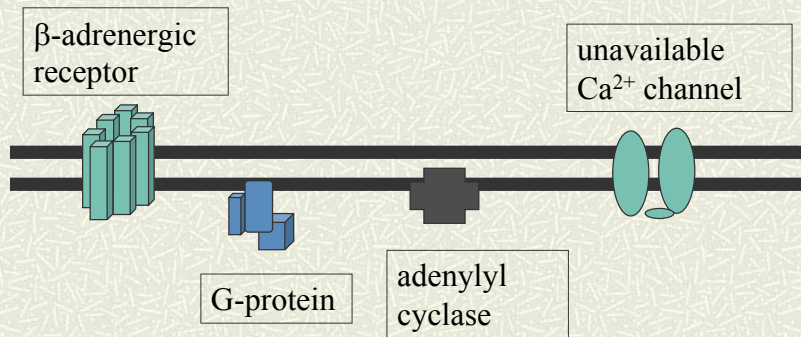
13

Example: increasing heart contractility

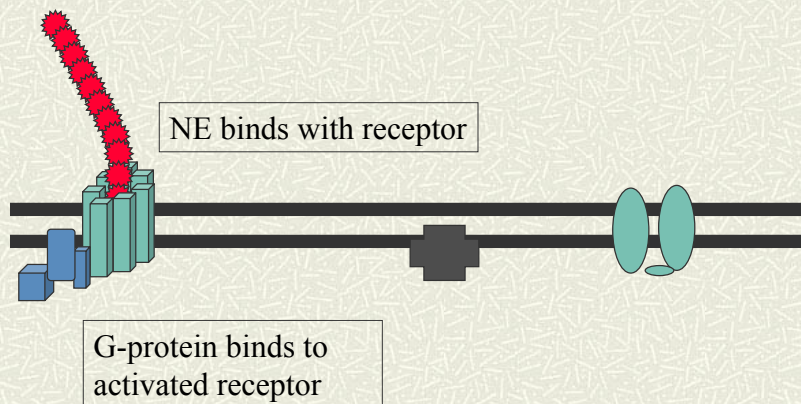
- # Noradrenalin (same as norepinephrine, NE) is NT from sympathetic neurons
- # NE causes stronger contractions of heart
- # Cardiac APs use Na^+ & Ca^{2+} (heart muscle cells)
- # NE increases number of available voltage-gated Ca^{2+} channels
- # This increases Ca^{2+} conductance, Ca^{2+} influx during AP, strength and rate of contraction

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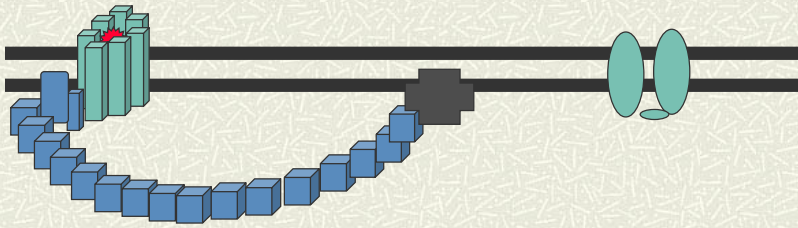
cont. Action of NE



cont. Action of NE

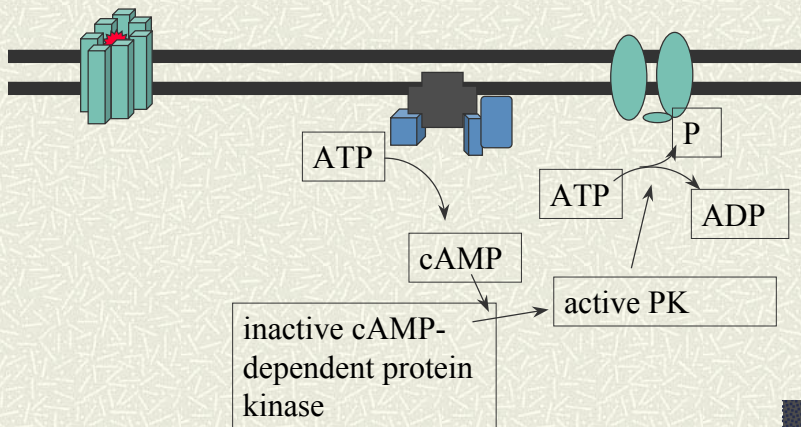


cont. Action of NE

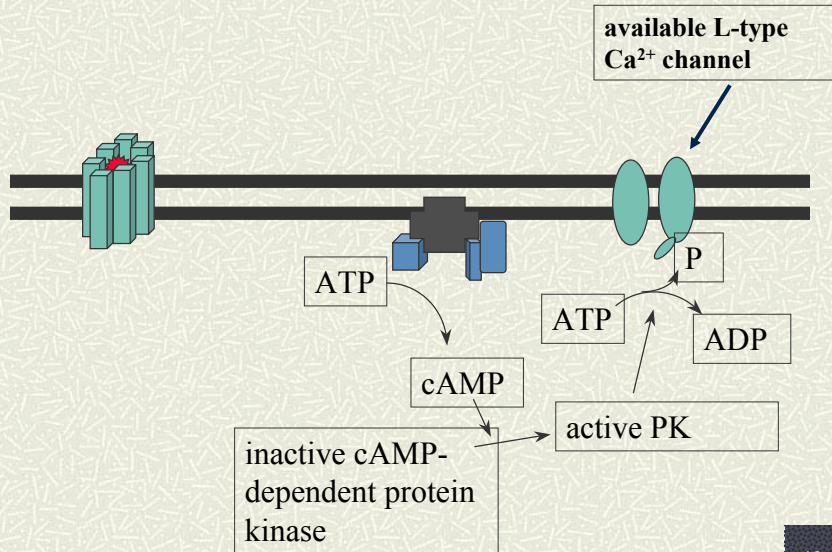


Exchanging GTP for GDP,
 α - and $\beta\gamma$ - subunit of G-
protein dissociate and bind to
adenylyl cyclase

cont. Action of NE



cont. Action of NE



Summary - NE effects on L-type Ca^{2+} channel activity in heart muscle

- Importance of site, receptor, G-protein mediating effect
- NE > G_s > AC > cAMP > PK > PO_4 on Ser/Thr of Ca-channels > alters Ca-channel (makes "available")

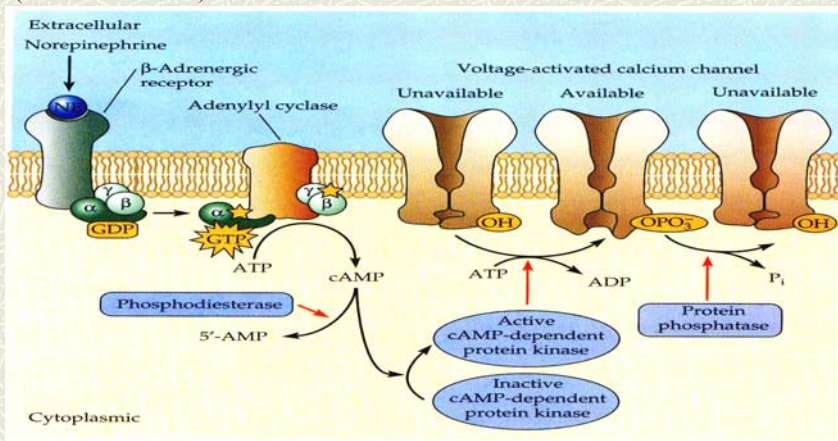
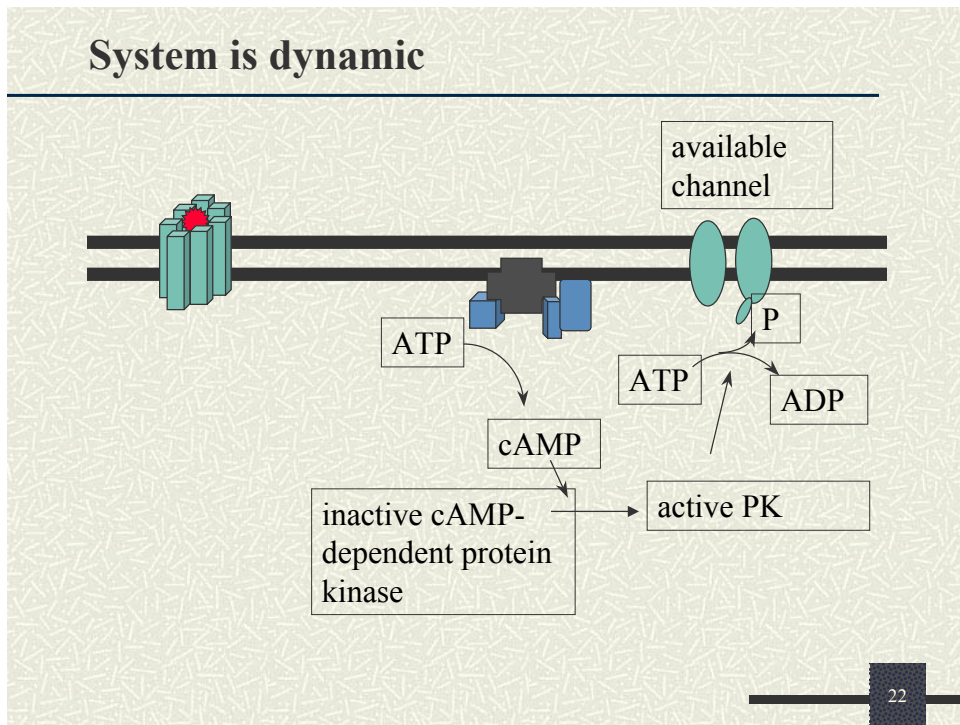
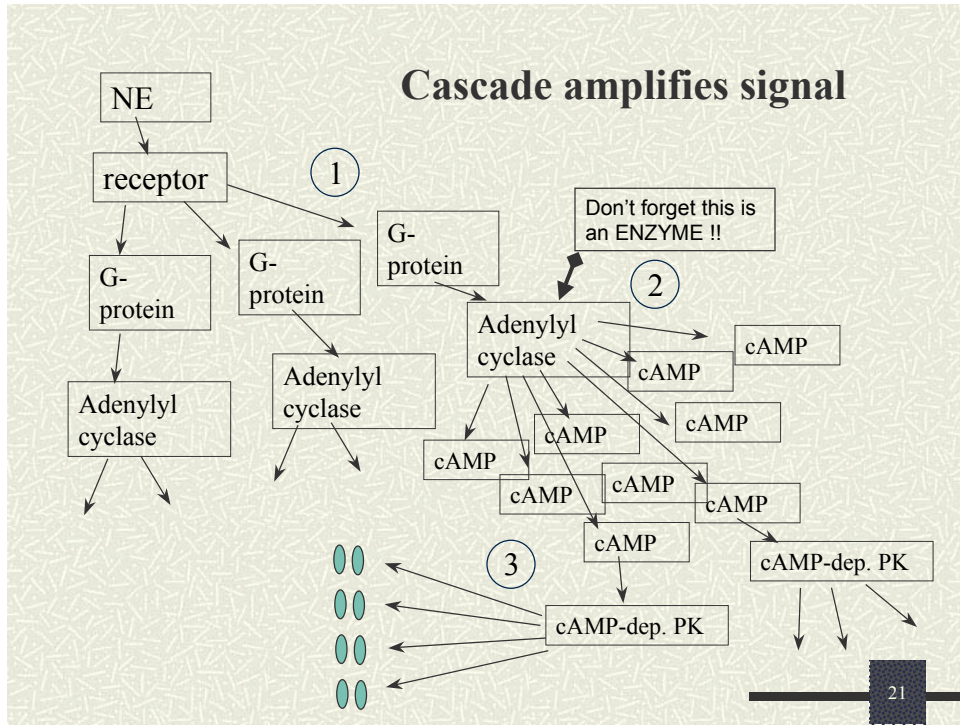
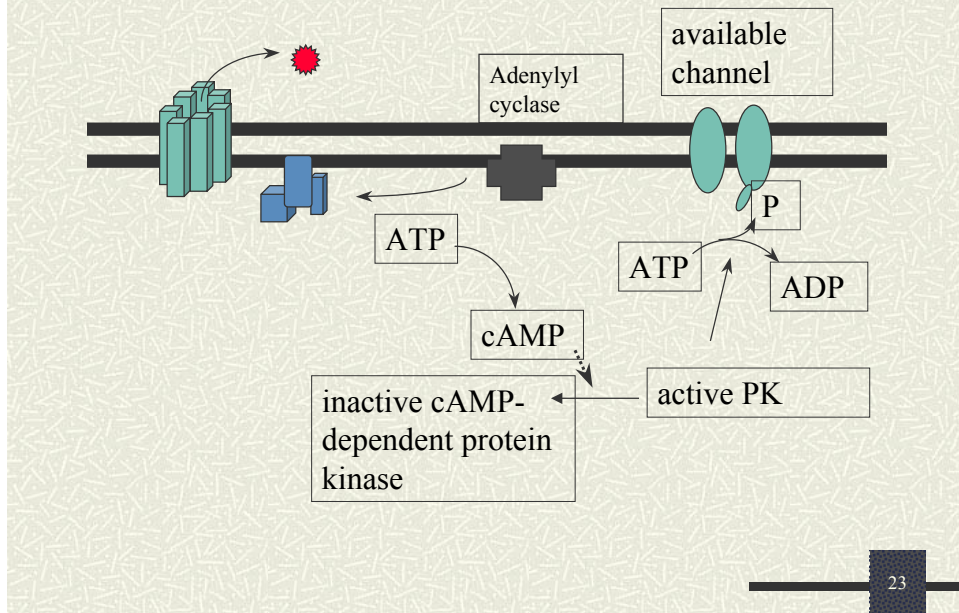


Fig. 10-10 NOTE: mAChR – can activate G_i protein that inhibits adenylyl cyclase

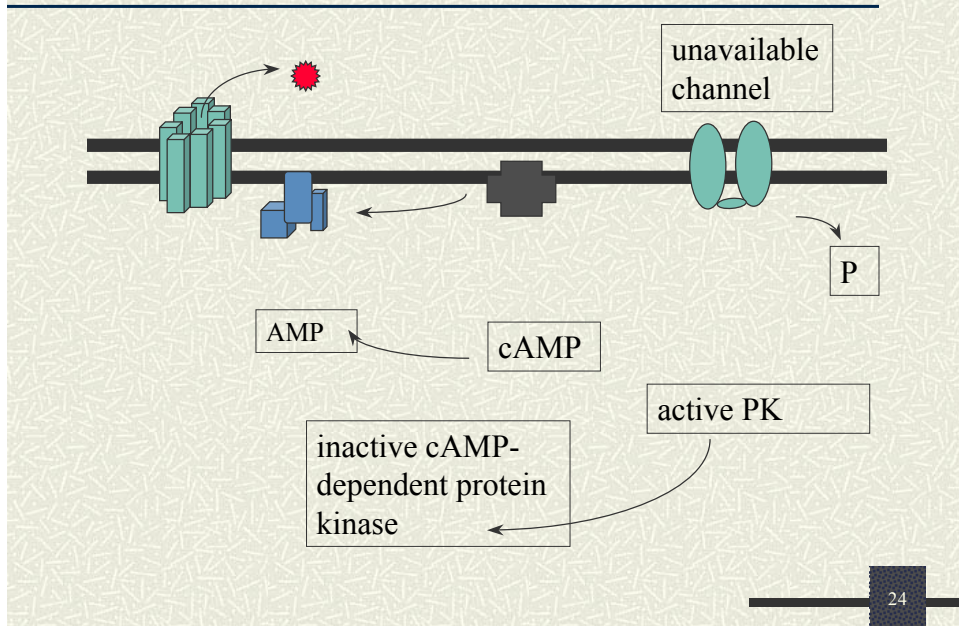


Processes are reversible



23

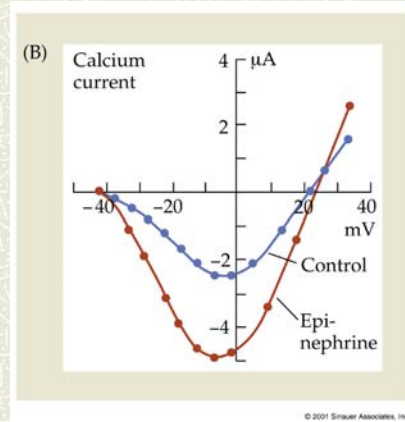
cont...Processes are reversible



24

Effect in cardiac muscle specific to calcium current

Adrenergic receptors – type specifies action



25

Further on specificity conferred by receptor, NOT neurotransmitter

AChR – nicotinic vs. muscarinic

Adrenergic receptors – type specifies action

Action of noradrenalin on heart (β -adrenergic receptor)

G-protein, 2nd messenger (cAMP)

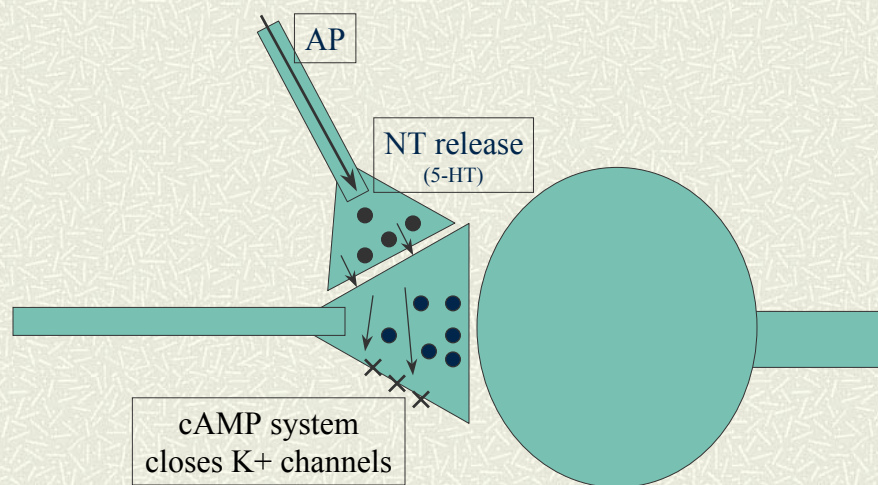
26

Phosphorylation of ion channel

- ▣ Sympathetic action of noradrenalin increasing heart contractions: activating voltage-gated Ca^{2+} channels
- ▣ Action of 5-HT (serotonin) presynaptically in facilitating neurons: closing K^{+} channels (in *Aplysia* withdrawal response)

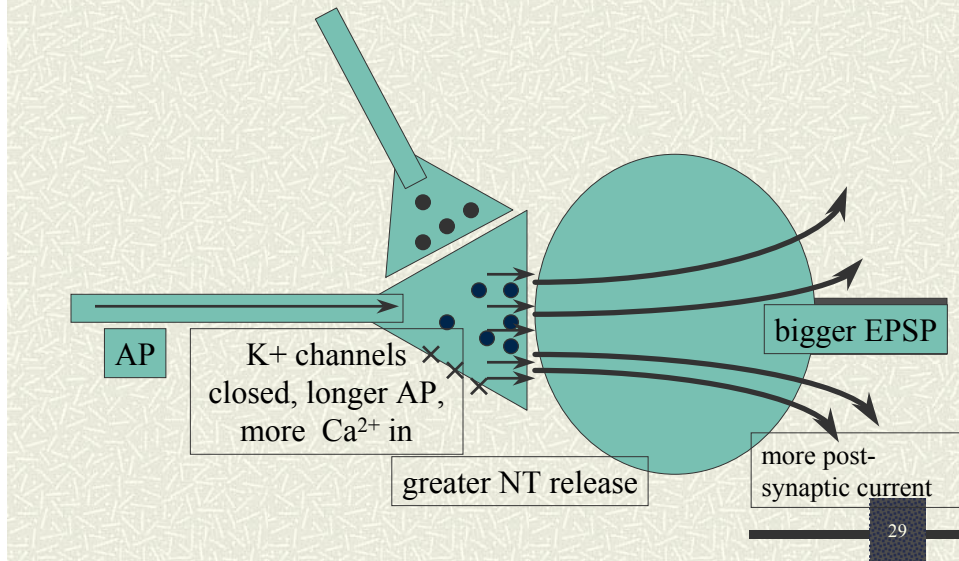
27

NT from facilitating neuron activates 2nd messengers



28

Lower G_{K^+} means longer AP and enhanced transmission



Important generalization

Targets of many indirectly-coupled synaptic systems are K^+ and Ca^{2+} channels

K⁺ and Ca²⁺ channels

- # Modifying K⁺ channels alters resting potential/conductance:
 - excitability of cell to fast excitatory inputs
 - pacemaker rhythms
 - duration of APs presynaptically
- # Modifying Ca²⁺ channels
 - changes Ca²⁺ APs
 - modifies Ca²⁺ influx and muscle contraction
 - leads to intracellular responses to Ca²⁺ (recall early slide showing broad range of Ca²⁺ responses)

But also at a more fundamental level/beyond ion channels – an example of gene regulation

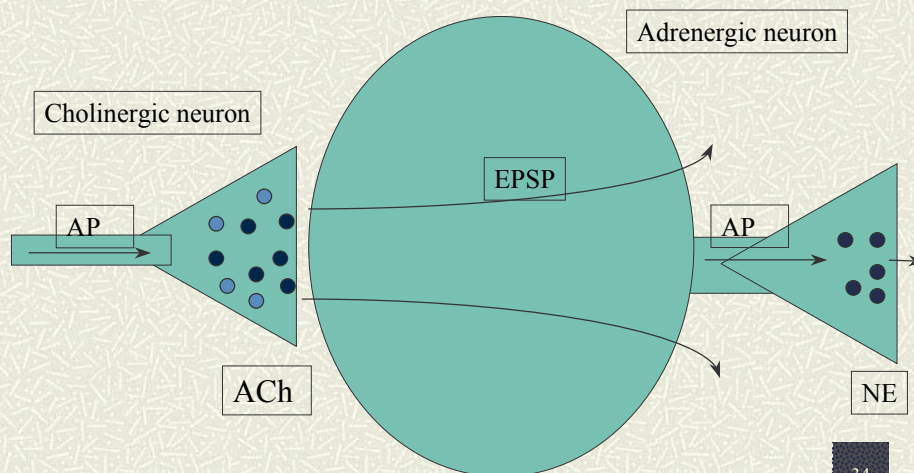
- # Adrenergic neurons release noradrenalin (NE): part of stress response
- # Adrenergic neurons activated by preganglionic cholinergic neurons, → fast depolarization by ACh
- # Presynaptic ACh neurons may also release peptide co-transmitter
- # Peptide produces short-term and long-term increases in NE production

cont...Neurotransmitter regulating gene transcription/translation

- synthesis of NE tightly regulated
- activity of presynaptic neuron N.B. in regulating level of NE in postsynaptic cell
- feedback inhibition – TH can be inhibited by NE (and DA)
- stress results in excessive cholinergic/peptidergic input to the adrenergic neuron
- high rate of release of NT by presynaptic neuron causes upregulation of tyrosine hydroxylase (R8 limiting; tyrosine dependent)
- Peptide – activates 2nd messenger cAMP
- large increase in cAMP >> kinase activity >> phosphorylation of TH AND transcriptional regulator (CREB – CRE binding protein)

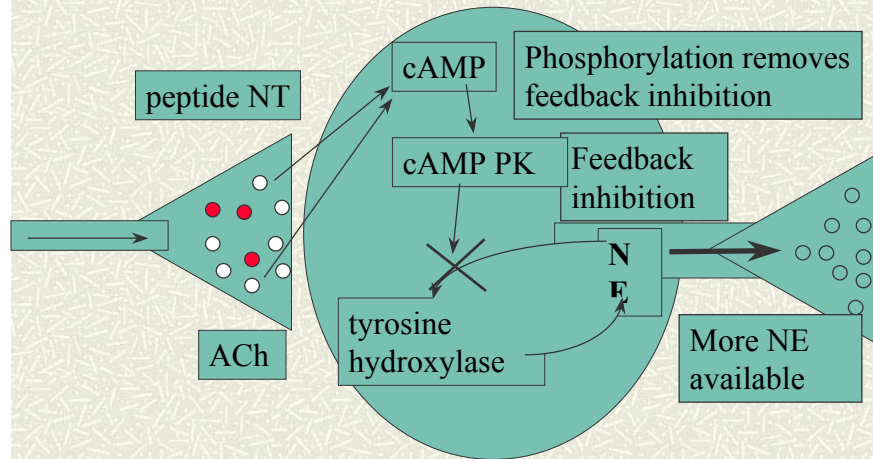
33

Controlling release of NE



34

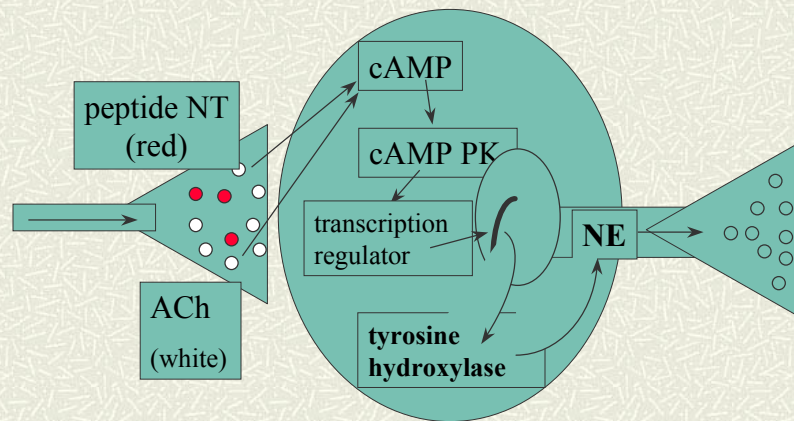
Peptide increases short-term NE production via cAMP



Short term: phosphorylation of TH blocks inhibition by NE

35

Peptide increases long-term NE production *via* gene regulation



Long-term: CREB = CRE (cAMP responsive element) Binding protein – binds to regulatory region and promotes transcription

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PART 2 – INDIRECT SYNAPTIC TRANSMISSION

- OTHER 2ND MESSENGER SYSTEM
- SPECIFIC EXAMPLES