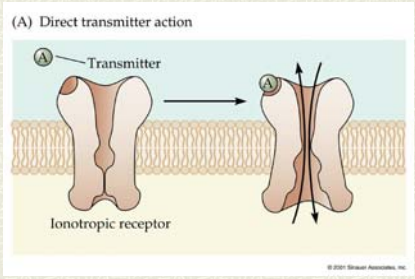
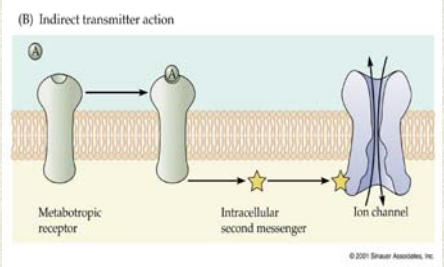
ZOO332H1S
Lecture 8 (AJE 2003)

Indirect Mechanisms of Synaptic Transmission

Fast transmitter-gated channel:
ionotropic receptor



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



Diverse cellular responses by 2nd messengers

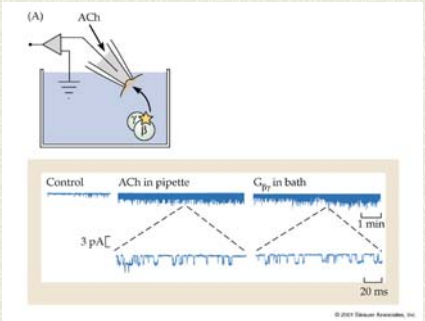
- Direct or indirect gating of channels by
  - G-proteins
  - cAMP, cGMP
- Phosphorylation of channels
  - increase open probability (activate)
  - decrease open probability (inactivate)
- Phosphorylation of receptors
  - increase sensitivity to NT
  - decrease sensitivity to NT
- Regulation of gene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

Example:
Direct action of G-protein on ion channel

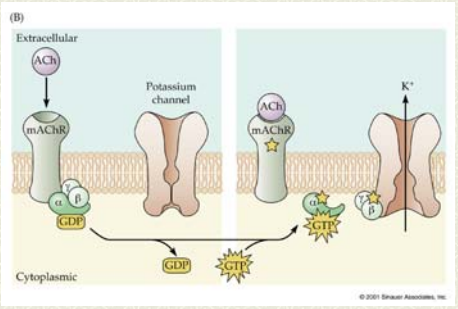
Parasympathetic (vagal) slowing of heart
(action on pacemaker)

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

cont…G-protein opens K^+ channels

Direct or membrane-delimited effects of G-protein

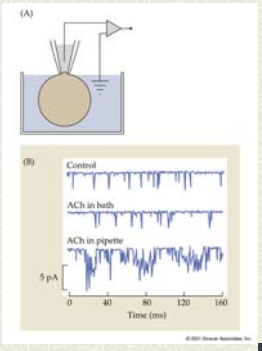


Fig. 10.5

G-protein closes Ca^{2+} channels

- Direct effect of G-protein subunits
- Sympathetic neurons
- α_2-adrenergic receptors

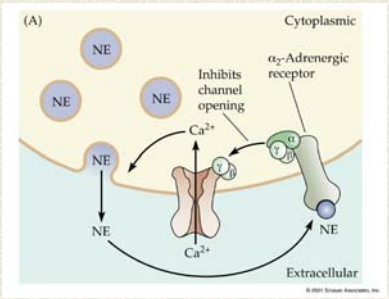
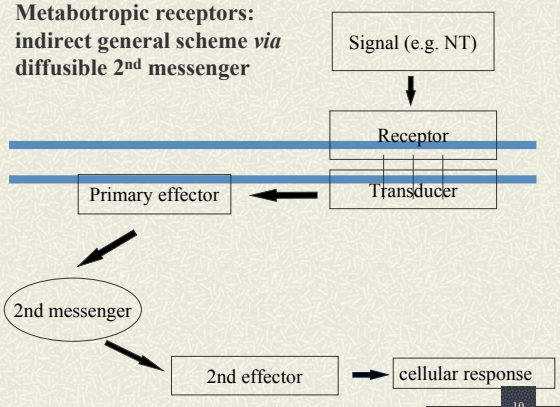


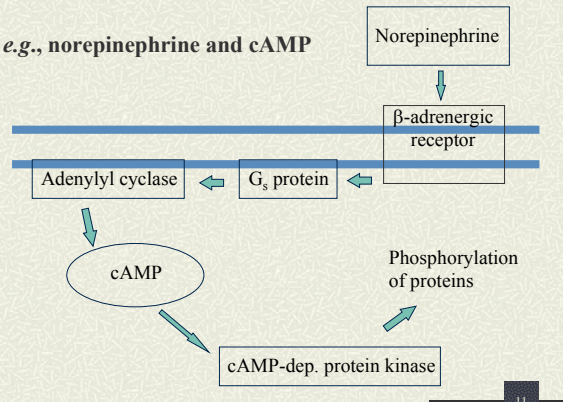
Fig. 10.5

Metabotropic receptors: indirect general scheme *via* diffusible 2nd messenger



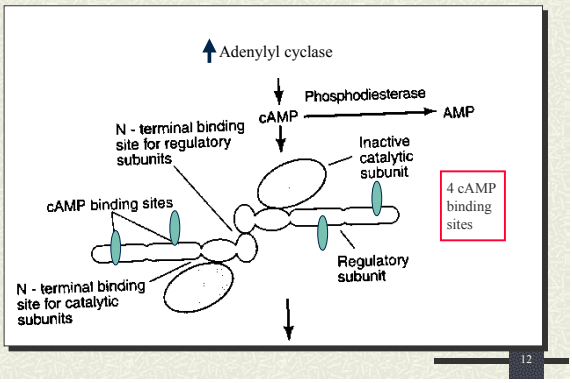
10

***e.g.*, norepinephrine and cAMP**



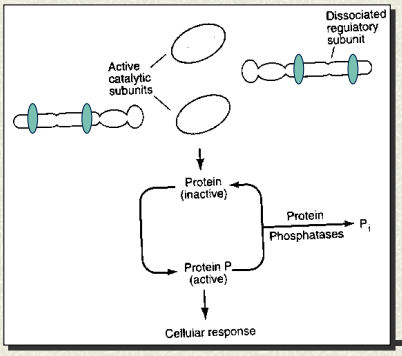
11

cAMP binds to cAMP-dependent protein kinase



12

Liberated catalytic subunits then phosphorylate substrate protein



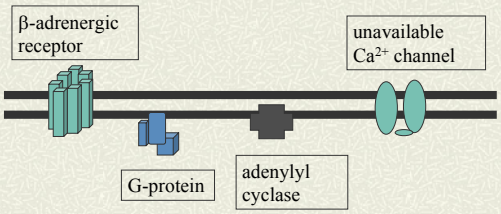
13

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

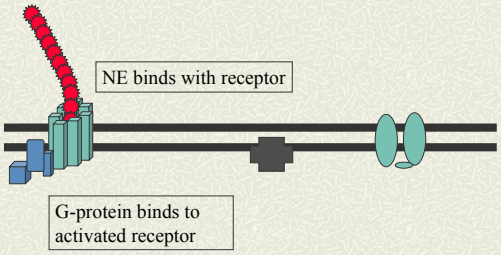
14

cont. Action of NE

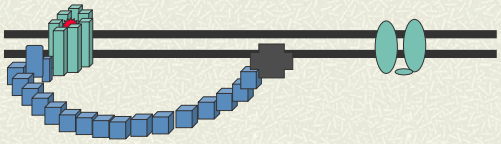


15

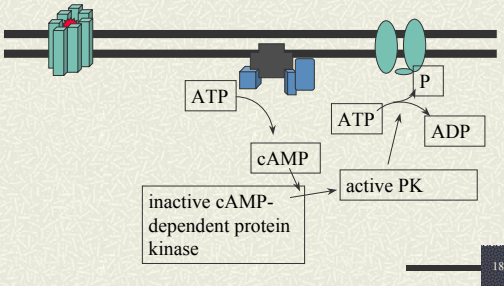
cont. Action of NE



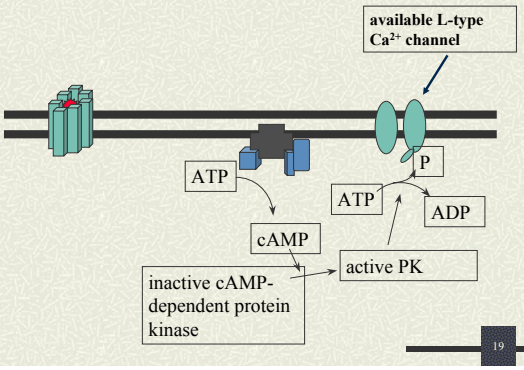
cont. Action of NE



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")

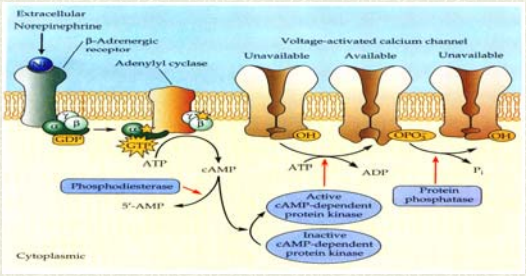
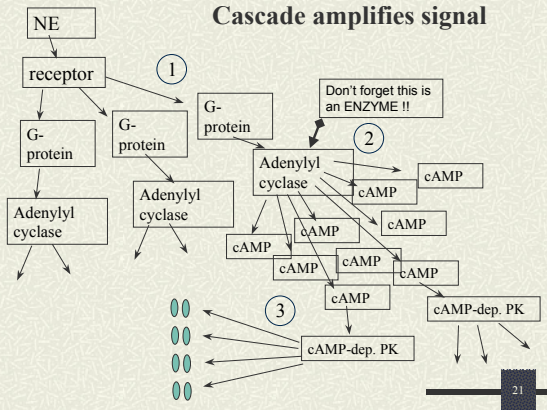
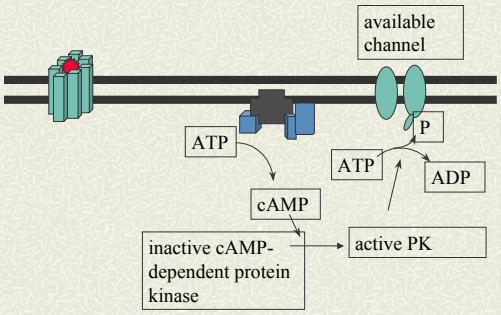


Fig. 10-10 *NOTE: mAChR – can activate G_i protein that inhibits adenylyl cyclase*

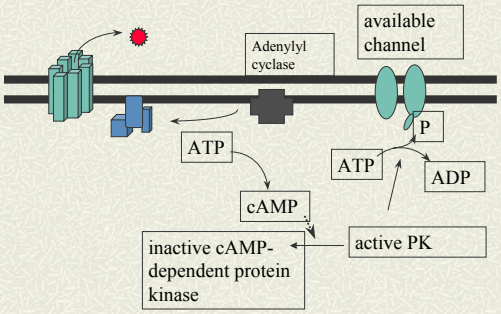
Cascade amplifies signal



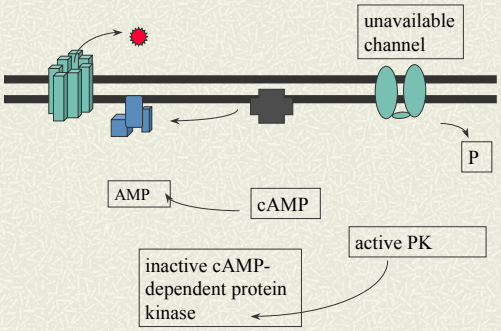
System is dynamic



Processes are reversible

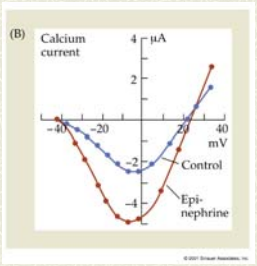


cont…Processes are reversible



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)

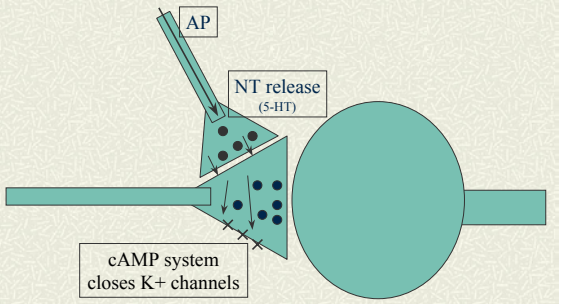
26

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)

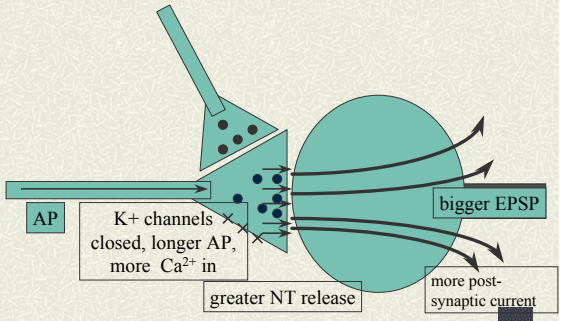
27

NT from facilitating neuron activates 2nd messengers



28

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



29

Important generalization

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

30

K^+ and Ca^{2+} channels

- Modifying K^+ channels alters resting potential/conductance:
  - excitability of cell to fast excitatory inputs
  - pacemaker rhythms
  - duration of APs presynaptically
- Modifying Ca^{2+} channels
  - changes Ca^{2+} APs
  - modifies Ca^{2+} influx and muscle contraction
  - leads to intracellular responses to Ca^{2+} (recall early slide showing broad range of Ca^{2+} responses)

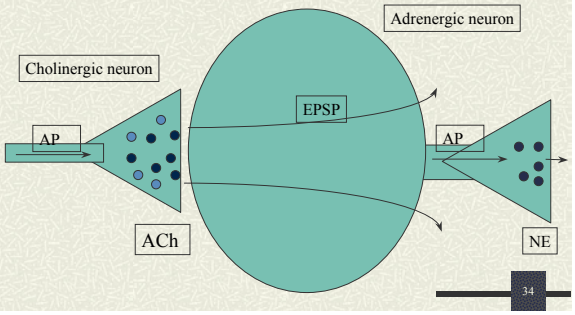
But also at a more fundamental level/beyond ion channels – an example of gene regulation

- 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

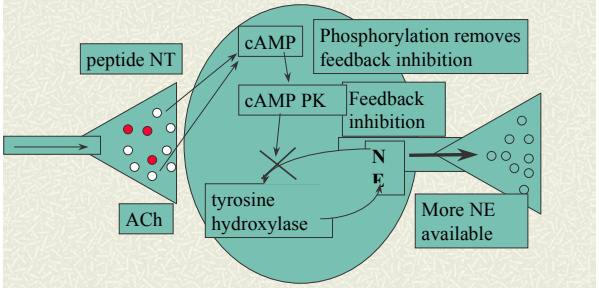
cont…Neurotransmitter regulating gene transcription/translation

- 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)

Controlling release of NE

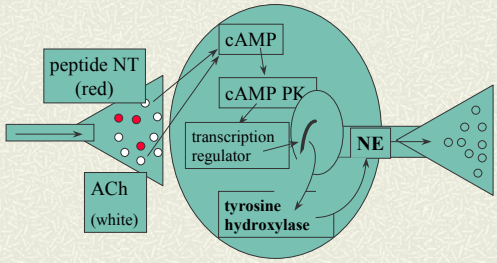


Peptide increases short-term NE production via cAMP



Short term: phosphorylation of TH blocks inhibition by NE

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



Long-term: CREB = CRE (**c**AMP **r**esponsive **e**lement) **B**inding protein – binds to regulatory region and promotes transcription

PART 2 – INDIRECT SYNAPTIC TRANSMISSION

- OTHER 2ND MESSENGER SYSTEM
- SPECIFIC EXAMPLES