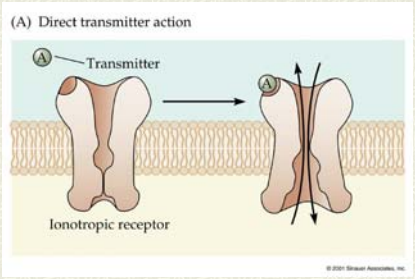
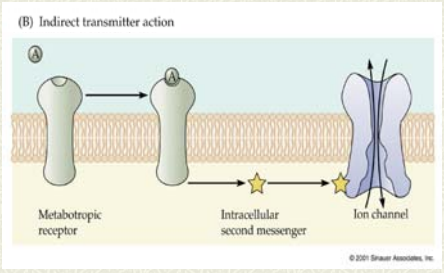
ZOO332H1S
Lecture 8 (AJE 2003)

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

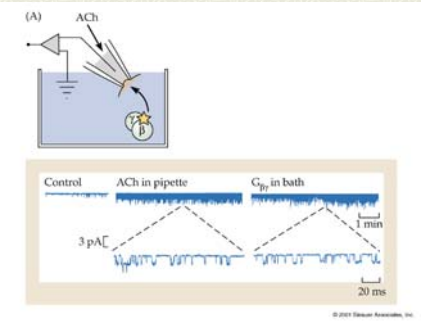
- Direct or indirect gating of channels by
  - G-proteins
  - cAMP, cGMP
- Phosphorylation of channels
  - increase open probability (activate)
  - decrease open probability (inactivate)
- Phosphorylation of receptors
  - increase sensitivity to NT
  - decrease sensitivity to NT
- Regulation of gene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

Example:
Direct action of G-protein on ion channel

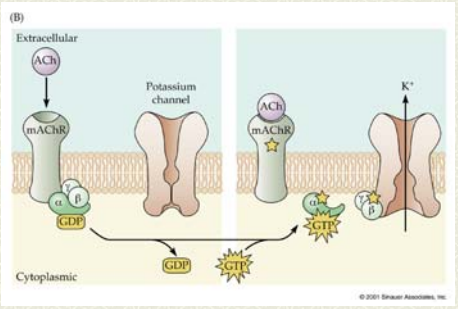
Parasympathetic (vagal) slowing of heart
(action on pacemaker)

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

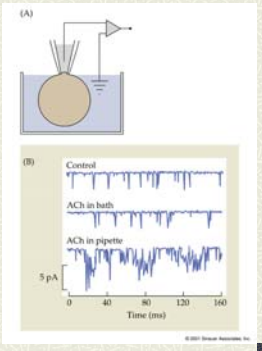


Fig. 10.5

G-protein closes Ca^{2+} channels

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

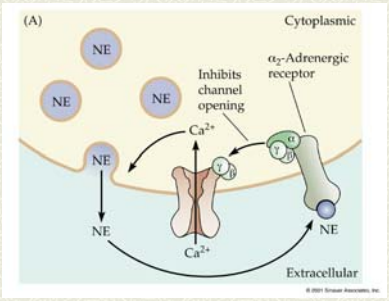
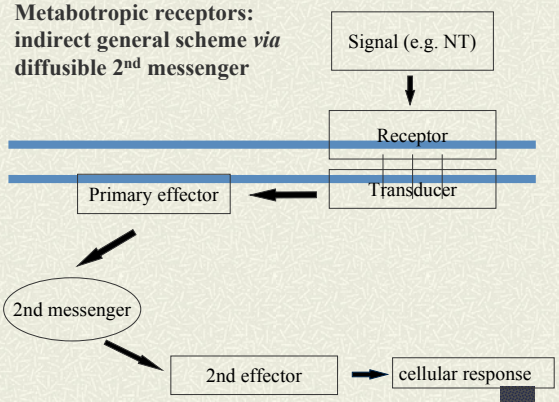
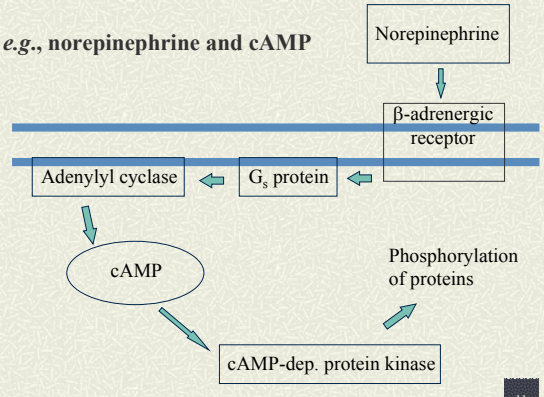


Fig. 10.5

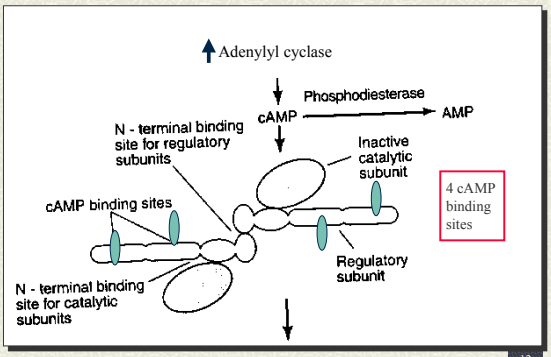
Metabotropic receptors: indirect general scheme *via* diffusible 2nd messenger



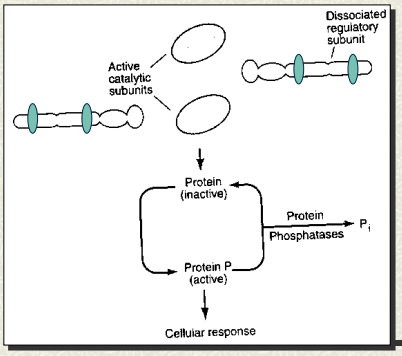
e.g., norepinephrine and cAMP



cAMP binds to cAMP-dependent protein kinase



Liberated catalytic subunits then phosphorylate substrate protein



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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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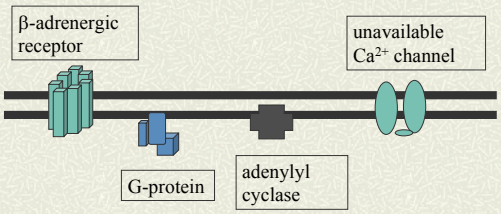
cont. Action of NE



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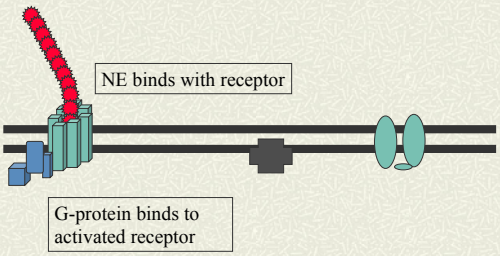
cont. Action of NE



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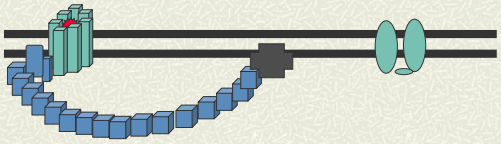
cont. Action of NE



Exchanging GTP for GDP, α- and βγ- subunit of G-protein dissociate and bind to adenylyl cyclase

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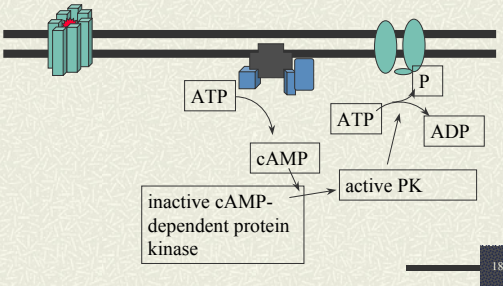
cont. Action of NE



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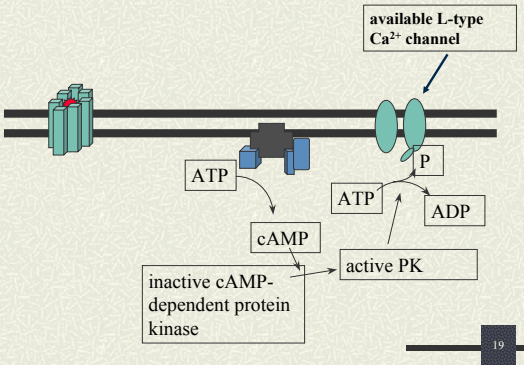
cont. Action of NE



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")

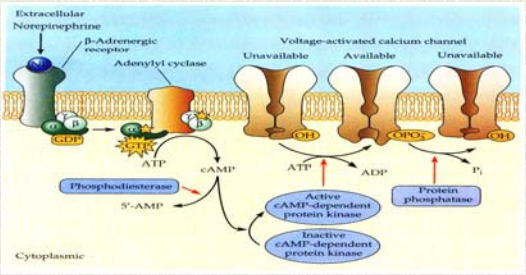
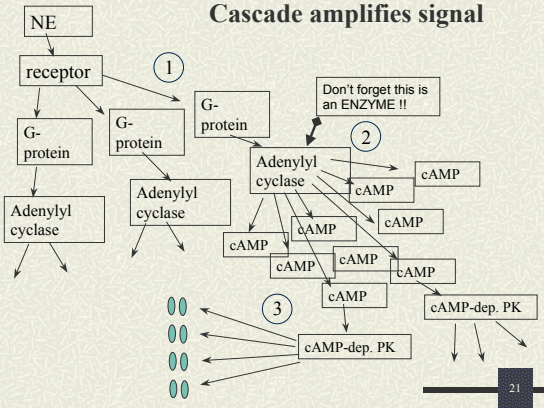


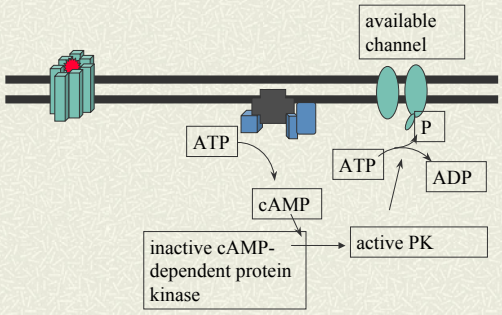
Fig. 10-10

NOTE: mAChR – can activate G_i protein that inhibits adenylyl cyclase

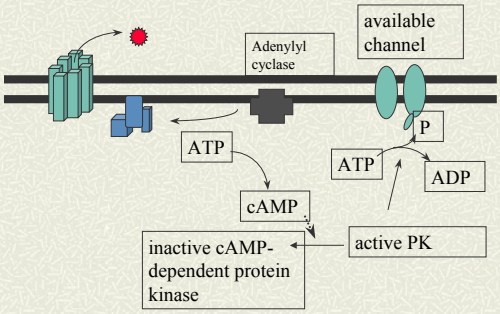
Cascade amplifies signal



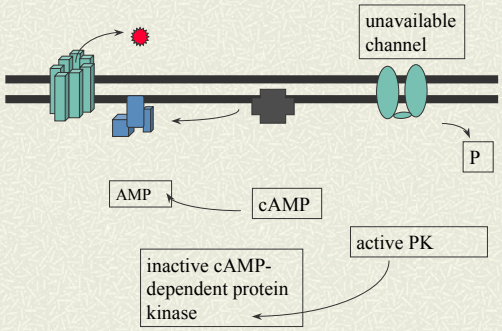
System is dynamic



Processes are reversible

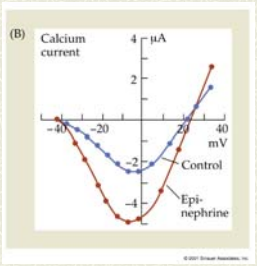


cont…Processes are reversible



Effect in cardiac muscle specific to calcium current

Adrenergic receptors – type specifies action



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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)

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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)

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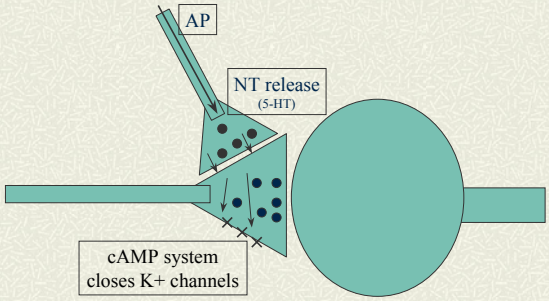
NT from facilitating neuron activates 2nd messengers



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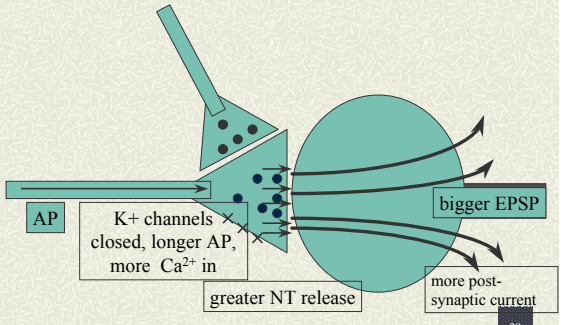
Lower G_{K+} means longer AP and enhanced transmission



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Important generalization

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

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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)

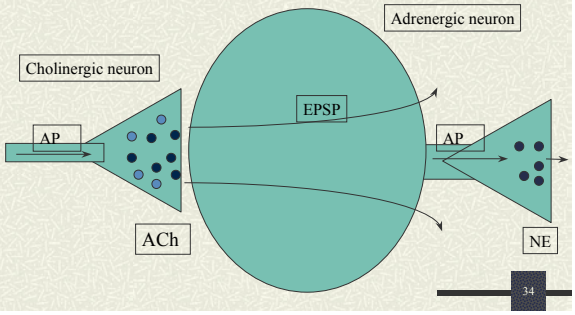
But also at a more fundamental level/beyond ion channels – an example of gene regulation

- 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

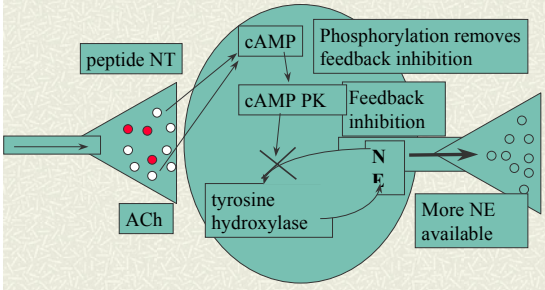
cont…Neurotransmitter regulating gene transcription/translation

- 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

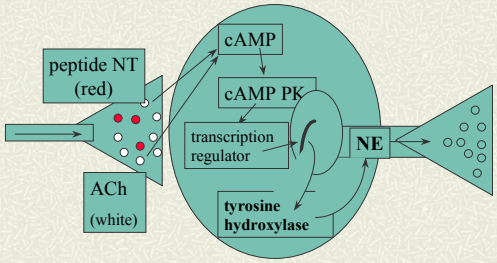


Peptide increases short-term NE production via cAMP



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