MEDS 370 – Modulation of Synaptic Transmission

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Reading: Kandel, Schwartz, and Jessell (2000) Principles of Neural Science, 4th Edition, Chapter 13.

Modulators: Are defined as substances or synaptic actions that are insufficient to cause a cell to fire an action potential. However, modulation can greatly influence the properties of a neuron resulting in changes in the resting membrane potential, threshold, input resistance, length and time constants, action potential duration and receptor function. Hence these modulatory functions change cell excitability.

I. Modulatory Synaptic Actions

1) **Presynaptic Modulation**: alterations in transmitter release in presynaptic terminal
   a) Autoreceptors (ionotropic and metabotropic)
   b) Heteroreceptors (mainly metabotropic)
   c) Retrograde signaling

2) **Postsynaptic Modulation**: direct/indirect changes in transmitter-gated channels
   a) Alterations in receptor activity
   b) Change in agonist affinity
   c) Change in the number of active receptors

3) **Modulation in Cell body:** change in electrical excitability via alteration of resting and voltage-gated channels

II. Mechanisms of Modulation:

1) Ionotropic Receptors (gate ion channels directly) minority of presynaptic receptors but most common receptor modulated postsynaptically

Conveys signals by altering the cells membrane potential or ionic composition

2) Metabotropic Receptors: (gate ion channels indirectly) majority of presynaptic and postsynaptic modulatory receptors

a.) G protein coupled receptors: (at least 30 types)

i) Single largest gene family
ii) Mediate responsiveness to neurotransmitters, hormones, peptides, oderants, light
iii) 7 transmembrane domain structure
iv) interact with G protein at the cytoplasmic surface of plasma membrane

G protein = guanine nucleotide binding protein

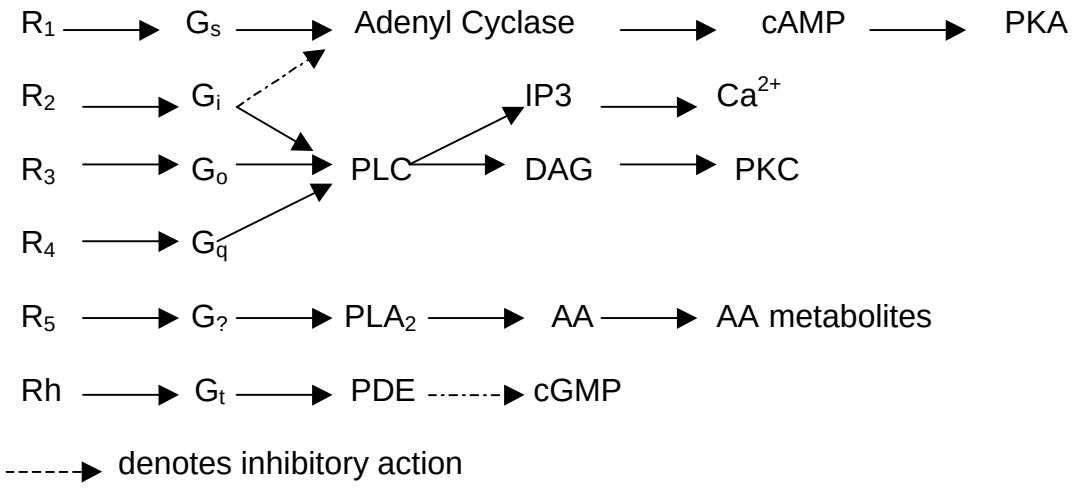
i) heterotrimer made up of $\alpha\beta\gamma$ subunits

α subunit: loosely associated with membrane usually the coupling agent between receptor and effector

$\beta\gamma$ subunits are more tightly fixed to membrane
originally thought that this dimer did not play a role in cell signaling, now there is evidence to the contrary (e.g. GIRKs).

Actions mediated via second messengers or via the G protein subunits directly

Second Messengers: (response takes 5-30 sec)



R= receptor (intergral membrane protein); R_h = rhodopsin ; PLA_2 = phospholipase A_2; PDE = phosphodiesterase; IP_3 = inositol triphosphate; DAG = diacylglycerol; AA = arachidonic acid; PKC = protein kinase C. G = G protein (membrane associated protein)

Some G-protein-Coupled Receptors:

Small NT and mediators	norepinephrine; dopamine; 5HT; histamine; acetylcholine; $GABA_{B;}$ glutamate; ATP; adenosine; prostaglandins; endocannabanoids
Peptides	opiods; tachykinins; bradykinins; VIP; NPY; TSH; LH; FSH; ACTH; CCK; gastrin; glucagon; somatostatin; endothelin; vasopressin; oxytoxin
Sensory receptors	rhodopsin; odorant receptors

GPCR Transduction:

1) Transmitter binds to its integral membrane receptor resulting in a confirmational change that allow G-protein to bind
2) G-protein in its inactive state (G-GDP) diffuses in the lipid bilayer and binds receptor. Binding to the receptor activates GTP exchange
3) Exchange of GDP for GTP (G-GTP) activates G-protein--α and $\beta\gamma$ separate and this exposes a binding site for effector (Adenyl Cyclase; PLC etc) on α subunit
4) Activated G-GTPα slides to Effector and activates enzyme
5) α subunit has intrinsic GTPase acitvity, thus hydrolyzing GTP to GDP. The Gα-GDP falls off the enzyme and reassociates with its $\beta\gamma$ (inactive).

NB: G proteins outnumber the receptor #!! This means that a single ligand receptor can activate many G-proteins thus serving to amplify the response.

Examples:

1) mgluR (G_s; G_o/G_q); Dopamine (D1 receptor--G_s) increases the phosphorylation of NR1 subunit of the NMDA receptor in a PKA dependent manner. Increases the activity of the receptor.

2) At NMJ; PKA/PKC-dependent phosphorylation of the nAChR occurs via synaptically released CGRP which enhances the desensitization of the receptor

3) In spinal cord; D_1 receptor activation results in PKA-dependent phosphorylation of AMPA and kainate receptors resulting in enhanced kainate response and the prevention of the desensitization of AMPA receptor in the motor neurons.

4) In hippocampus; CB1 receptors(G_i/$_o$) proteins in the presynaptic terminal and suppress the release of GABA and/or glutamate by inhibiting VGCC

"Membrane Delimited" Modulation

a) uses no second messenger
b) can be mimicked by exposing the cytoplasmic face of membrane to activated $G_{i\alpha}GTP\gamma S$ subunits
c) can be found in perforated patches—no cytosol--- no second messengers

Examples:

1) GIRKs (G-protein coupled inwardly rectifying potassium current) found in heart. ACh acting on mAChR activates G_i. In this case $\beta\gamma$ subunit bind and open this channel which results in movement of K^+ out of the cell-hyperpolarization-slowing of the heart. [Interstingly, study done in excised patches from xenopus oocytes expressing GIRK1 showed that $G_{\alpha i1}$ (but not splice variants 2 or 3) can antagonize this effect].

2) N, P/Q type Ca^{2+} channels inhibition by $\beta\gamma$ sub units

3) M-type K^+ current: of autonomic ganglia : closed by ACh ($G\alpha$) decreases K^+ conductance. May be responsible for repetitive burst firing in these cells.

4) N-type Ca^{2+} channels: 30% reduction in current by 5HT; of m2/m4 ACh receptor activation

5) L-type Ca $^{2+}$ channels: stimulation by V1 vasopressin receptor

b) Receptor Tyrosine Kinase:

i) cytoplasmic domain of receptor is tyrosine kinase
ii) binding of ligand (EGF; NGF; BDNF; FGF; insulin) to receptor results in autophosphorylation and activation of the kinase domain and allows for tyrosine phosphorylation of other proteins

Example:

BDNF enhances phosphorylation of NR1 and NR2B subunits of the NMDA receptor resulting in increased channel open probability (i.e increased activity). Could be important for the modulation of Long Term Potentiation (LTP)

3) Retrograde Signaling: transcellular modulator of presynaptic terminal

???????? Modulators of LTP and LTD?????

Properties:

i) freely diffusible and membrane permeable
ii) affect nearby cells without activating a surface receptor
ii) short lived

a) Arachidonic Acid
b) Nitric Oxide
c) Carbon Monoxide
d) Endocannabanoids

Evidence For:

a) Arachidonic acid

b) Arachidonic acid is produced by activation of ionotropic glutamate receptors and is released into the extracellular space
c) AA increased K^+-stimulated Ca^{2+} influx into and release of glutamate from brain synaptosomes
d) Exogenous application of AA elicits a long lasting potentiation of Ca1 region of hippocampus
e) LTP is blocked by inhibition of PLA_2 (the enzyme which liberates AA from cellular membranes)
f) LTP induction is impaired in aged rats and this is correlated with loss of arachidonic acid from membranes
g) The ability of aged rats to sustain long-term potentiation is restored when the age-related decrease in membrane arachidonic acid concentration is reversed via diet supplementation.

2) Nitric Oxide:

a) gaseous free radical formed from Ca^{2+}-dependent form of nitric oxide synthase (NOS) subsequent to NMDA receptor activation
b) NO is known to enhance presynaptic release of neurotransmitter directly via advancing synaptic vesicle interactions leading to vesicle fusion.
c) Inhibitors of NOS block LTP. Most strikingly injection of NOS inhibitor into the Ca_1 pyramidal neuron blocked presynaptic LTP.
d) Hemoglobin (membrane impermeant scavenger of NO) also blocked LTP.
e) May be involved in the induction phase as delayed administration of NOS inhibitors don't alter already established LTP
f) ? role of cGMP?

3) Carbon Monoxide

a) gas formed via activation of the enzyme heme oxygenase (HO-2)

b) enzyme colocalized with guanylate cyclase and CO can activate GC.
c) Inhibitors of GC block LTP; activators produce enhancement in activity-dependent manner (??? Selectivity???)
d) Inhibitors of HO blocked LTP induction and reversed already established LTP
e) Inhibition of HO blocks presynaptic glutamate release.

4) Endocannabinoids

a) Anandamide and 2-archidonylglycerol (2-AG) are synthesized from membrane phospholipids in an activity- and Ca^{2+}-dependent manner and released into the extracellular environment
b) Agonists via presynaptic CB1 receptors suppress the release of neurotransmitters, such as glutamate, GABA, ACh and NE via inhibition of presynaptic Ca^{2+} channels.
c) Believed to mediate depolarization-induced suppression of inhibition (DIS) in hippocampus (when activation of postsynaptic receptor inhibits inhibitory input to that cell)
    i) agonist mimic DSI at synapses which show DSI
    ii) DSI is eliminated by cannabanoid receptor antagonist