Physiological Dynamics in Animals & Plants – Lecture 9 – Basics of signal transduction – receptors and integration

I. There are two types of cellular receptors: membrane receptors and intracellular receptors.

II. Phosphorylation of proteins by kinases and their de-phosphorylation by phosphatases is a major mechanism of signal transduction in all cells.

III. The largest family of cell surface (plasma membrane) receptors is the G-protein-linked receptors.

A. Respond to very diverse signaling molecules

B. Regulate a very wide variety of processes

C. All span the membrane seven times; belong to a family of proteins called seven-pass transmembrane receptor proteins

D. Binding of ligand to receptor changes shape of receptor, allowing it to bind to a G-protein.

1. A ligand is a smaller molecule that binds very specifically to a larger molecule.

2. A protein's 3-D shape is called its conformation.

E. Receptors span the membrane; G-proteins are on the intracellular side of the membrane.

F. There are two general types of G-proteins – monomeric and trimeric (trimeric = heteromeric = heterotrimeric G-proteins).

G. The most common G-proteins are trimeric.

1. Three subunits = α, β, γ; there are subclasses of $G\alpha$ subunits.

H. In its "unstimulated" state, α subunit has GDP (guanosine diphosphate) bound and G protein is "quiet".

I. When extracellular ligand binds to a G-protein-linked receptor, the receptor binds to the G-protein, causing it to eject the bound GDP from its α subunit.

1. GDP is replaced with GTP

2. G-protein breaks up into a "switched-on" α subunit and a β,γ complex, either or both of which may diffuse freely along the membrane and interact with "targets" (other proteins) on the membrane which can relay the signal to other destinations.

3. Duration of the signal is determined by how long the α subunit is bound to GTP

a. α subunit has GTPase activity and after a certain time hydrolyzes GTP to GDP and Pi; hydrolysis leads to reassociation of α subunit and β,γ complex, shutting off the signal

J. Targets of G-proteins

1. Ion channels

a. Acetylcholine inhibits contraction of heart muscle through G-protein-linked-receptor that regulates activity of potassium ion channels.

2. Enzymes that lead to production or release of second messengers

a. Adenylyl cyclase catalyzes formation of 3',5' cyclic AMP which in turn can activate cyclic-AMP-dependent kinase (A-kinase).

1. A-kinase can catalyze phosphorylation of other proteins; effects may be fast or slow; response is tissue-specific

b. Phospholipase C catalyzes hydrolysis of inositol phopholipid of plasma membrane to inositol 1,4,5, triphosphate (IP_3) and diacylglycerol (DAG).

1. IP_3 opens calcium ion channels on ER; binding of calcium to proteins such as calmodulin and CaM-kinases can affect many processes.

2. DAG activate protein kinase C = C-kinase

IV. Enzyme-linked receptors are transmembrane proteins with extracellular ligand binding domains and cytoplasmic domains with enzymatic activity.

A. Largest class is the receptor tyrosine kinases (RTK)

1. Binding of extracellular ligand causes dimerization, activating kinase activity

a. Each monomer of the dimer phosphorylates the other = autophosphorylation

2. Many types of intracellular signaling proteins can bind to phosphorylated domains of tyrosine kinase

3. Protein phosphatases remove phosphates to end signaling

4. Signaling proteins activated in response to autophosphorylation of RTK

a. A phospholipase equivalent to phospholipase C

b. Ras through an “adaptor” protein

5. Characteristics of Ras

a. Binds GTP, but unlike G-protein, is monomeric

b. Activates phosphorylation of several kinases in sequence; among those are:

Raf – a serine/threonine kinase

MAP kinase (microtubule-associated protein or mitogen-activated protein kinase; serine & threonine kinase)

MEK – a threonine/tyrosine kinase (MEK stands for "M"AP and "E"R"K", ERK being another acronym for MAP)

6. Signal molecules and processes connected to Ras activation

a. Platelet-derived growth factor (PDGF) promotes cell proliferation at healing wound

b. Nerve growth factor (NGF) prevents death of certain neurons in developing nervous system

c. Mutations in Ras are thought to account for about 30% of human cancers because they lead to "constituitive" cell division; many other cancers have mutations in other signaling proteins of the Ras signaling pathway.

1. Mutated genes that promote cancer = oncogenes; non-mutated forms = proto-oncogenes.

V. Ion-channel linked receptors = transmitter-gated ion channels found in membranes

A. Used for rapid transmission of nerve impulse in nervous system but may be used for other rapid responses (e.g., altering enzyme activity in cells.

B. Transduce chemical signals to electrical signals

1. Neurotransmitter at outside of cell causes change in membrane electric potential by changing permeability of membrane to certain ions

C. Most studied ion-channel-linked receptor is nicotinic acetylcholine recpetor of muscle cells

1. Binding of acetylcholine to receptor permeabilizes muscle plasma membrane to sodium and potassium ions when acetylcholine triggers opening of channel

a. Channels open within a few microseconds of binding acetylcholine

b. Nicotine is an agonist (has same effect as acetylcholine)

VI. Intracellular receptors are exemplified by those for the steroid hormones of animals.

VII. Multiple signal transduction pathways operate simultaneously in each cell, and thus their effects on cells are interactive and integrated.