Hormones & Chemical Signaling

Lecture Outline

- Communication Basics
  - Communication Overview
  - Communication Methods
  - Signal pathways
    - Regulation (modulation) of signal pathways
  - Homeostasis . . . again
- Endocrine System
  - Hormones
    - what they are
    - How they work

Communication Basics: Overview

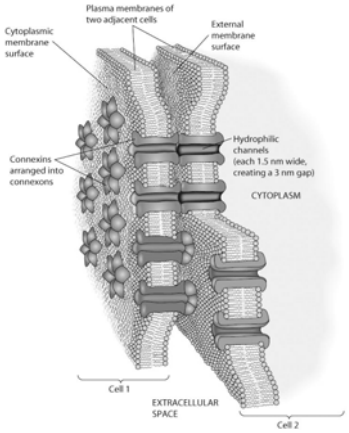
- Physiological Signaling (Communication) occurs via
  - Electrical signals
    - Changes in a cells membrane potential
  - Chemical signals
    - Molecules that are secreted into the ECF
    - Responsible for most communication
  - Target cells
    - Those cells that receive the message regardless of its chemical or electrical nature

Communication Basics: Methods

- Four methods of cell communication
  1. Gap junctions
  2. Contact – dependent signals
  3. Local communication
  4. Long distance communication

Communication: Gap Junctions

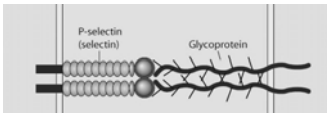
- Recall Structure…
- Function as a result:
  - Controllable
    - Open vs. closed states
  - Passage of small molecules:
    - Amino acids
    - ATP
    - cAMP/cGMP
    - Ions
  - Allows tissues to work as a syncytium



Communication: Contact Dependent Signals

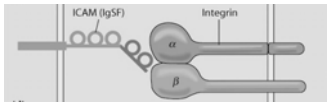
- Exactly what it sounds like:
  - Two cells contact each other and…
    - some types of immune responses can start
    - cells know where they are…
      - neurons during growth and development
    - platelets can do their thing
  - CAMs can act as receptors/signalers
    - Via linkage to intracellular components
      - Cytoskeletal structures
      - enzymes

Communication: Contact Dependent Signals



P-selectin – stored inside cells when not needed

When inserted into the cell membrane, contact by leukocytes causes their recruitment



Integrins – shown to be involved in contact signaling between platelets

Contact-dependent signaling events that promote thrombus formation

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Abstract

There is increasing evidence that formation of a stable hemostatic plug requires adhesive and signaling events that continue beyond the onset of platelet aggregation. These events are facilitated and, in some cases, made possible, by the persistent close contacts between platelets that can only occur when platelets begin to aggregate. Participants include integrins and other cell adhesion molecules, secreted agonists, receptor tyrosine kinases, and protein fragments that are shed from the surface of activated platelets. Collectively, these molecules promote the continued growth and stability of the hemostatic plug.

Communication: Autocrine Signaling

- Cell – to – Self Cell
  - Cell secretes chemical in response to stimulus
  - Chemical binds to receptor on its own membrane
  - Examples:

Chemical	Source	Target	Effect
IL-1	Macrophage	Macrophage	Inflammation
IL-1	B-cell	B-cell	Maturation & proliferation
IL-6	B-cell	B-cell	Differentiation into plasma cells

Communication: Paracrine Signaling

- Chemical Signals secreted and effect neighboring cells
  - Some signals act as paracrine & autocrine messengers
  - Include classes of chemicals such as cytokines & eicosanoids (prostaglandins, prostacyclins, thromboxane and leukotrienes)
  - Ex. Histamine – belongs to cytokine group
    - Acts on local area cells, they increase p-selectin membrane molecules which attract leukocytes.
    - Can cause phosphorylation of CAM molecules, which causes increased cellular separation… making them leaky!

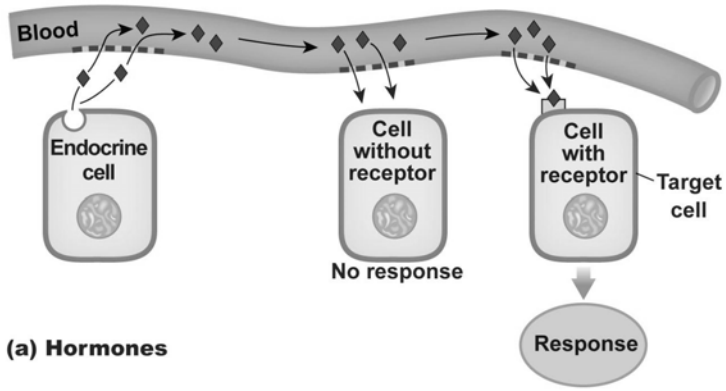
Communication: Cytokines

- Chemical messenger hybrids
  - Act as paracrine messengers as well as long distance messengers, but…
    - Not hormones because they work on many different cells
    - Not produced by an endocrine gland

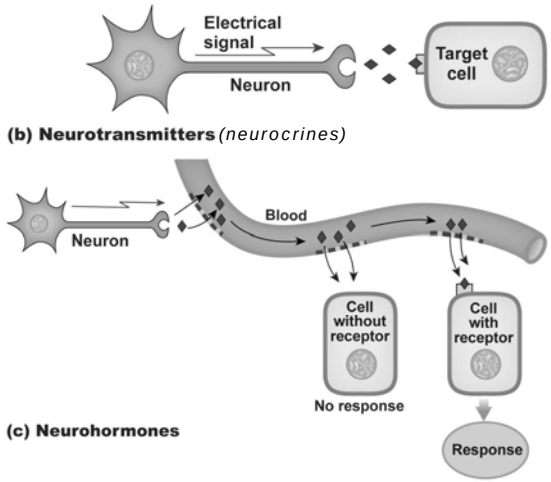
Communication: Long Distance

- Long Distance communication occurs by
  - Electrical signaling (action potentials)
  - Endocrine System – Hormones:
    - chemical messengers secreted by glands into the blood
    - not specific in where they go
    - specificity is due to the receptors!
  - Nervous System
    - Chemicals released due to electrical signal and becomes:
      - neurocrines – released and binds to target at the immediate area
        - » Ex. Acetylcholine, GABA
      - neurohormones – released into the blood
        - » Ex. Antidiuretic hormone & oxytocin

Communication: Long Distance

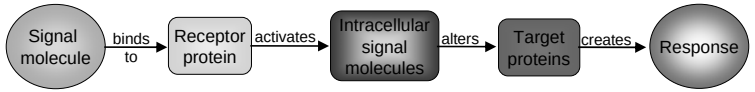


Communication: Long Distance



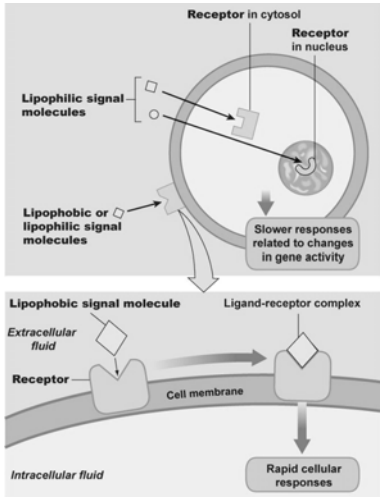
Communication: Signal Pathways

- How do hormones create a reaction in some cells and not others?
  - The receptor proteins
- If a receptor is present, the effect of binding always initiates a response through a signal pathway



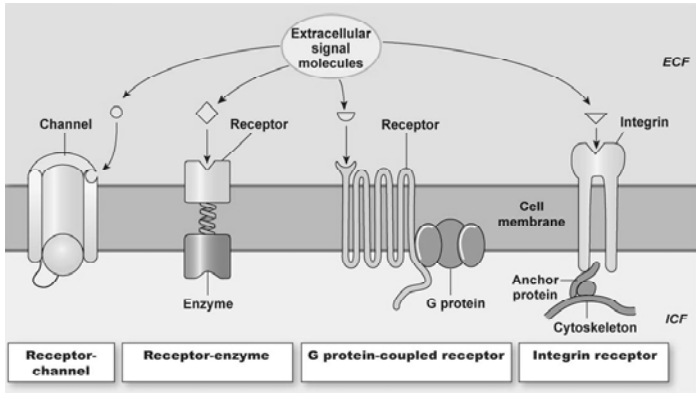
Communication: Signal Pathways

- Receptor Protein Location
  - Intracellular
    - Chemical messengers must be lipophilic
    - Bind to cytosolic receptors or nuclear receptors
      - Effect is to modulate gene activity (+ or -)
  - Cell Membrane
    - Lipophobic molecules bind to membrane receptor
    - Receptor transfers the signal to the ICF (signal transduction)



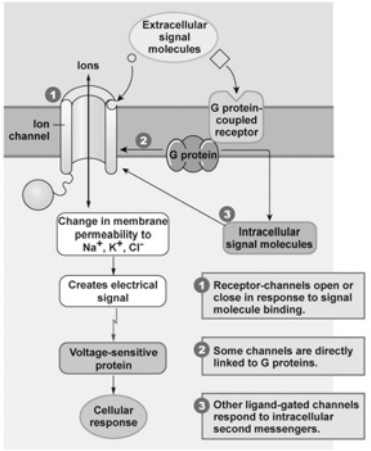
Communication: Signal Transduction

Available Options for Signal Transduction



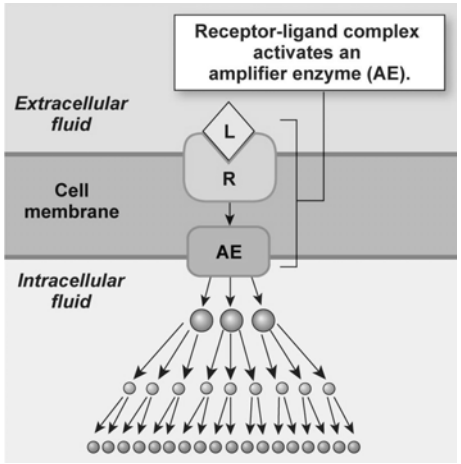
Communication: Signal Transduction

- Channel receptors
  - Ligand binds and electrical signal is formed
  - Creates a very fast intracellular response
  - May open via other pathways as well



Communication: Signal Transduction

- Why do we care about signal transduction
  - Another example of big payoff with little effort!
  - Amplification



Communication: Signal Transduction

- Signal Transduction & amplification relies on the following process:

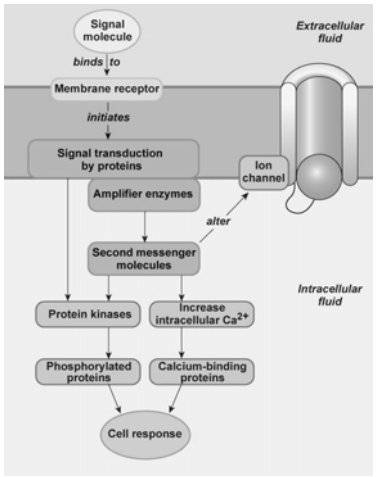
1 → 10 → 1000 → 100,000

1. Molecule (primary messenger) in ECF binds to membrane receptor and activates it
2. Membrane proteins are activated which may
   a. Activate protein kinases
   b. Activate enzymes that create secondary messengers
3. Secondary messengers
   a. Alter ion channel gating resulting in membrane potential change
   b. Increase intracellular calcium
   c. Alter enzyme activity of protein kinases (phosphatases)
4. Proteins modification (by Ca^{2+} or PO_4^-) affects
   a. Metabolic enzymes
   b. Motor proteins
   c. Gene expression (and therefore protein synthesis)
   d. Membrane transport & receptor proteins

Communication: Signal Transduction

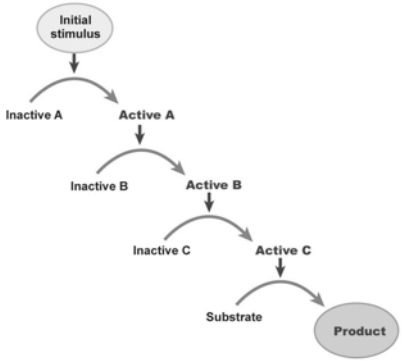
Same Steps (summary)

1. Molecule (primary messenger) in ECF binds to membrane receptor and activates it
2. Membrane proteins are activated which may
3. Secondary messengers
4. Proteins modification (by Ca^{2+} or PO_4^-) affects



Communication: Signal Transduction

- This pathway is a cascading event

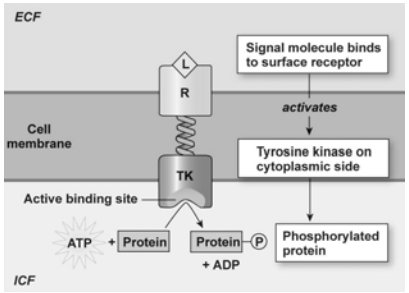


What kind of mechanism are cascading events?

MANY PRODUCTS!!

Communication: Signal Transduction

- Receptor-Enzyme and Signal Transduction
  - Binding of ligand causes activation of the active binding site on enzyme and are either
    - Protein kinases
      - transfer phosphates
    - Guanylyl cyclase
      - converts GTP to cGMP (2° messenger)
  - Insulin, cytokines and growth factors bind to receptor enzyme complexes

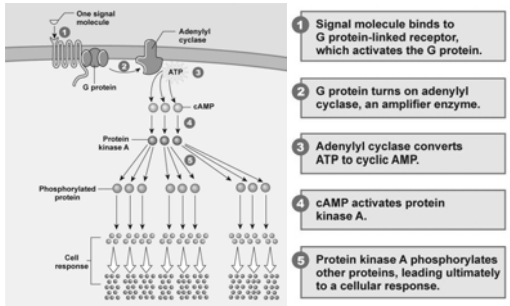


Communication: Signal Transduction

- G-Protein Activation *(G proteins on front cover)*
  - Most common signal transduction pathway
    - Receptor (G protein-coupled receptor) is linked to a G protein (ICF peripheral protein) transducer molecule
    - Activated by exchange reaction (GDP to GTP) and
      - Open ion channel OR
      - Activate amplifier enzyme (most common pathway)
        - » Adenylyl cyclase and phospholipase C are the most common amplifier enzymes

Communication: Signal Transduction

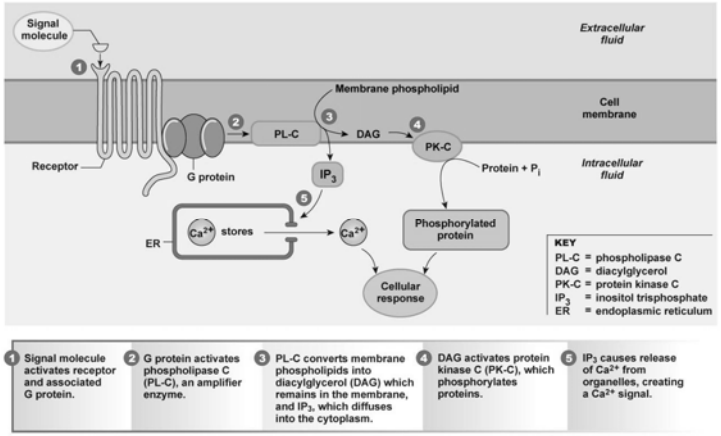
- G protein-coupled adenylyl cyclase-cAMP system
  - Process figured out in the 1950s by Earl Sutherland and subsequently won a Nobel prize for it!
  - Most commonly used for protein hormones



Communication: Signal Transduction

- G protein-coupled phospholipase C system
  - When activated G protein activated phospholipase C, it converts a membrane phospholipid (phosphatidyl inositol bisphosphate) into diacylglycerol (DAG) and inositol trisphosphate (IP_3)
  - DAG is non polar and remains in the phospholipid bilayer where it activates protein kinase C (PK-C)
    - PK-C phosphorylates cytosolic proteins and furthers the cascade effect
  - IP_3 is hydrophilic and enters into the cytosol where it binds to ER and opens Ca^{2+} channels and acts as a signaling molecule

Communication: Signal Transduction



Communication: Signal Transduction

TABLE 6-2 Second Messenger Pathways

SECOND MESSENGER	ACTION	EFFECTS
Ions		
Ca^{2+}	Binds to calmodulin Binds to other proteins	Alters enzyme activity Exocytosis, muscle contraction, cytoskeleton movement, channel opening
Nucleotides		
cAMP	Activates protein kinases, especially protein kinase A Binds to ion channels	Phosphorylates proteins Alters channel opening
cGMP	Activates protein kinases, especially protein kinase G Binds to ion channels	Phosphorylates proteins Alters channel opening
Lipid-derived		
IP_3	Releases Ca^{2+} from intracellular stores	See Ca^{2+} effects above
DAG	Activates protein kinase C	Phosphorylates proteins

Communication: Signal Transduction

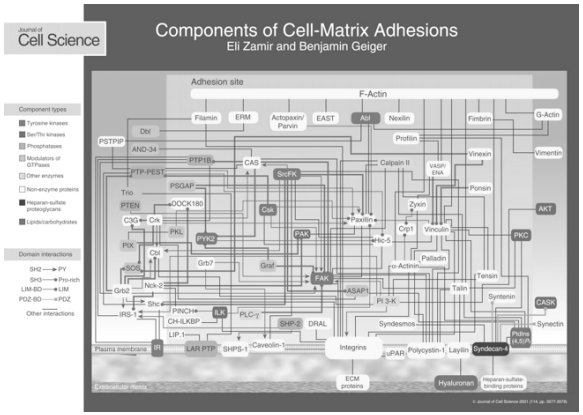
- Integrin Receptor Signal Transduction
  - Integrins are membrane spanning proteins involved in
    - Hemostasis
    - Tissue repair
    - Cell adhesion
    - Immune processes
    - Cell migration during development

Communication: Signal Transduction

- Integrin Receptor Signal Transduction
  - When ligand binds to integrin
    - Intracellular enzymes are activated and
    - Cytoskeletal organization is changed
    - Quite a few pathways figured out
    - One important one is when an integrin membrane receptor is missing and platelet activation does not occur = hemophilia

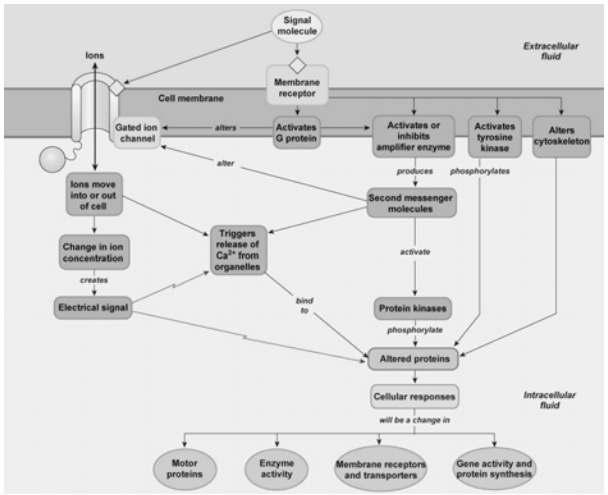
Communication: Signal Transduction

- LOL!



Communication: Signal Transduction

Over-view

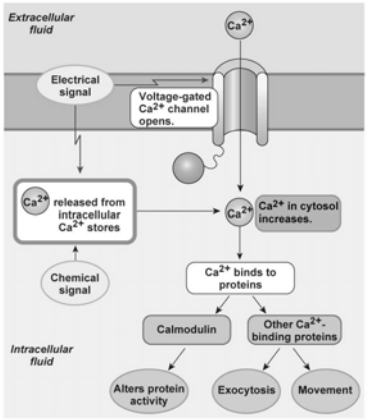


Communication: novel signal molecules

- Intracellular signal molecules
  - Ca^{2+}, NO, CO, H_2S and
  - Two important eicosanoids derived from arachadonic acid
    - Leukotrienes
    - Prostanoids (prostaglandins & thromboxanes)

Communication: novel signal molecules

- Effects of Ca^{2+} when intracellular levels increase



Communication: novel signal molecules

- NO, CO and H_2S
  - Short acting paracrine/autocrine signal molecules
  - NO acts as a vasodilator by diffusing from the cell that produced it into the surrounding tisse
    - Activates formation of cGMP which can block channels, causing muscle to relax
  - CO known for its affinity for hemoglobin (thus starving tissues of oxygen) it also
    - Activates formation of cGMP
  - H_2S also acts as a vasodilator
    - Garlic is a good supply of sulfur compounds…

Communication: novel signal molecules

- Lipids as paracrine signal molecules
  - Derived from arachidonic acid (precursor to eicosanoids)
  - Phospholipase A_2 is responsible for the production of arachidonic acid
    - Arachidonic acid can act as a secondary messenger by
      - Influencing ion channels & Intracellular enzymes
    - Arachidonic acid may also produce two other paracrine messengers
      - Leukotrienes
      - Prostanoids (prostaglandins and thromboxanes)

Communication: novel signal molecules

- Leukotrienes
  - Secreted by some leukocytes
  - Initiate smooth muscle spasms in bronchioles
  - Also involved in anaphylaxis
    - Death unless medical intervention
- Prostanoids
  - Produced as a result of cyclooxygenase (COX) action on arachidonic acid
    - Products are prostaglandins and thromboxanes
      - Influence sleep, inflammation, pain, fever
    - *Cox inhibitors (aspirin, ibuprofen)… stop the formation of prostaglandins = stop the pain!*
- *Sphingolipids – also be involved with G protein coupled receptors*

Communication: Modulation of Pathways

- How are these pathways controlled?
  - Receptors are proteins!
    - Subject to
      - Specificity of binding
      - Competition for binding site
        - » Agonists and antagonists
      - Saturation of ligand
        - » Up regulation and down regulation of receptors
  - Pathways are mechanisms under homeostasis guidelines

Communication: Modulation of Pathways