Chemical messengers

- **Paracrines:** chemicals that communicate w/ neighboring cells → close enough that when paracrine is secreted into ECF, it can reach target cell by simple diffusion
  - growth factors: proteins that stimulate proliferation + differentiation of cells, clotting factors, cytokines: peptides (usually from immune cells) to coordinate body's defense against infections
  - histamine: secreted by mast cells, important in allergic reactions + inflammation
  - autocrines: act on the same cell that secreted them (secretory cell = target cell)
- **Neurotransmitters:** chemicals released into interstitial fluid by neurons → presynaptic neuron releases messanger from axon terminal over synapse to postsynaptic cell
- **Hormones:** chemicals released from endocrine glands into the interstitial fluid + diffuse into the bloodstream until they reach target cells
  - ↳ neurohormones: released by neurosecretory cells
- **Chemical Classification of messengers**
  - lipophilic (hydrophobic) molecules are lipid soluble and can cross the plasma membrane w/out dissolving
  - lipophobic (hydrophilic): water soluble, dissolve in plasma, can't cross the plasma membrane
  - ↳ **Amino acid messengers:** function as neurotransmitters in the brain + spinal chord, lipophobic
    - glutamate, asparate, (synthesized from glucose), glycine (synthesized from glycolyic intermediate), gamma-aminobutyric acid → GABA (synthesized from glutamate
      - ↳ following synthesis in cytosol, amino acid neurotransmitters are transported
  - ↳ **Amine messengers:** derived from amino acids, includes amine group ($-NH_2$) and catecholamines contain catechol (6-carbon ring), hydrophilic
    - dopamine, norepinephrine, epinephrine, serotonin → all synthesized in the secretory cell by a series of enzyme-catalyzed reactions
  - ↳ **Peptide/Protein messengers:** chains of 2 or more amino acids linked by peptide bonds → hydrophilic

- synthesized in the same way as other proteins (chapter 2) → mRNA is the template for coding, translation begins in the ribosomes in cytosol → prepropeptide is formed (lumen of rough ER) → proteolytic enzymes yield propeptide → packaged into transport vesicles (smooth ER) → active messenger is packaged in secretory vesicle (Golgi apparatus)

↳ **Steroid messengers**: compounds derived from cholesterol → function as hormones, hydrophobic

- synthesized from cholesterol in smooth ER or mitochondria. Cannot be stored → diffuse into interstitial fluid as they are synthesized

↳ **Eicosanoid Messengers**: includes variety of paracrines, hydrophobic

- synthesized on demand. Phospholipase A_2 catalyzes membrane phospholipid → arachidonic acid, then converted into eicosanoid

Transport of Messangers

- Paracrines + neurotransmitters: released near target cell → reach by simple diffusion
- Peptides + amines: transported in dissolved form by hydrophilic messenger
- Hormones: transported in the blood → either dissolved or bind to carrier proteins
  - half-life: time it takes for half of the hormone in the blood to be degraded

Signal Transduction Mechanisms

- **Magnitude of a target cells response** to a chemical messenger depends on
  - concentration ∝ response by binding reversibly to targets receptors $M + R \rightleftharpoons MR \rightarrow$ response
  - number of receptors present ∝ response
    - up-regulation: increase in # of receptors → occurs when cells are exposed to low messenger concentrations for a prolonged period (down-regulation → vice versa)
  - affinity ∝ response
- Antagonists → bind to receptors to block responses, agonist → produces a biological response
- **Lipophilic hormones**: hormone diffuses into the nucleus to bind to the receptor (or binds in the

cytosol then enters nucleus) → binds to hormone response element (HER) (region of DNA) → either activates / deactivates the gene → increases / decreases protein synthesis → mRNA moves to cytosol → translated into proteins

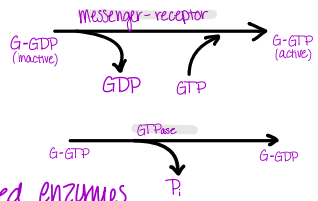
- Steroid hormones: bind to receptors in cytosol (nuclear receptors) → must bind to HRE in dimerization

- Lipophobic messengers: cannot permeate PM → their receptors are on PM facing ECF

↳ channel-linked receptors: fast ligand-gated channels → proteins that function as receptors + ion channels, open channels allow ions to move across PM down its electrochemical gradient. Slow channels → receptor and channel are separate proteins coupled together by a G protein

↳ Enzyme-linked receptors: receptor side faces interstitial fluid, enzyme side faces cytosol. messenger binds to receptor → changes confirmation + activates tyrosine kinase → TK catalyzes phosphorylation of intercellular protein → changes its activity by covelent regulation → brings response in target cell

↳ G Protein-linked receptors: located on intracellular side, link between receptor + effectors in PM →



- Stimulatory + inhibitory G proteins are associated w/ amplifier enzymes (catalyze production of second messengers

- major second messengers → communication through G-protein-regulated enzymes

  - cAMP (cyclic adenosine monophosphate): activates G_s protein → releases alpha subunit → binds to adenylate cyclase (ATP → cAMP) → activates protein kinase → catalyzes (ATP → protein) → altered protein activity through covelent regulation causes a response in the cell

  - cGMP: similar to cAMP, activates protein kinase G (cGMP-dependent protein kinase)

  - Phosphatidylinositol: membrane phospholipid undergoes enzyme-catalyzed reaction to produce two second messengers DAG (diacylglycerol) + IP_3 (inositol triphosphate)