Pharmacology of the Neuron, Essentials

MEMBRANE TRANSPORT PROTEINS

All known membrane transport proteins are multipass transmembrane proteins. There are two distinct classes:

- carrier proteins
- bind the specific solute and undergo conformational changes to transfer the solute, 10^5 solutes/s
- active transport allows the transport of solutes against their electrochemical gradient and is therefore tightly coupled to a source of metabolic energy
- passive transport

- channel proteins
their transport occurs at a much faster rate than transport mediated by carrier proteins

CHANNEL PROTEINS

- simple aqueous pores
- non-gated, non-selective, 10^8 solutes/s

- gap junctions
- relatively large (max size: 1kD) and permissive pores between two cells (distance: 2-4nm), gated
- channels made of 2 connexons, each being an assembly of 6 connexins
- in bacteria, mitochondria and chloroplasts, porins form similar channels

- ion channels
- narrow, highly selective, gated pores, 10^7 ions/s
- ions must lose their bound water molecules to pass, the energy required is supplied by non-covalent bindings between the ion and the selectivity filter of the channel
- primarily for Na^+, K^+, Ca^{2+} and Cl^- to diffuse rapidly down their electrochemical gradients

- subtypes of ion channels are
  - voltage-gated channels
  - mechanically gated channels
  - ligand-gated channels
    - transmitter-gated channels (extracellular mediator, e.g. neurotransmitter)
    - ion-gated channels (intracellular mediator)
    - nucleotide-gated channels (intracellular mediator)

SPECIAL CHANNELS

- K^+ leak channels
- selective to K^+, always open, have a crucial role in determining the resting membrane potential across the plasma membrane

- Na^+-K^+-ATPase
- pumps out 3 Na^+ for every 2 K^+ that it pumps in

THE 3 MAJOR CLASSES OF CELL-SURFACE RECEPTOR PROTEINS

- ion-channel-linked receptors (transmitter gated ion channels)
- immediate, simple, brief
- belong to a large family of homologous, multipass transmembrane proteins

- g-protein-linked receptors (GPCR = g-protein-coupled receptors)
- metabotropic receptor
- signalling mediated by ligands binding to ~ is slow, complex and long lasting
- ~ act indirectly to regulate the activity of a separate plasma-membrane-bound target protein (effector), which can be either an enzyme or an ion channel. The interaction is mediated by a third protein, called a trimeric GTP-binding protein
- ~ belong to a large family of homologous, seven-pass transmembrane proteins

- enzyme-linked receptors
- metabotropic receptor
- signalling mediated by ligands binding to ~ is slow, complex and long lasting
- two distinct subtypes exist
  - enzyme-inked receptors with intrinsic enzyme activity
  - ~ relaying on associated enzymes
- are formed by single-pass transmembrane proteins that have their ligand-binding site outside the cell and their catalytic or enzyme-binding site inside
- the great majority are protein kinases, or are associated with protein kinases

NEURONS

- carry their signals in form of action potential sequences of different frequencies

- action potentials
- are a direct consequence of the properties of voltage-gated cation (Na^+, K^+) channels
- propagate through saltatory conduction
- are initiated at the axon hillock
- normal human resting membrane potential: -70mV; after depolarisation: ca +20mV

- myelin sheath
- insulation formed by specialized supporting cells, called glia cells
  - Schwann cells myelinate axons in peripheral nerves, one Schwann cell per each axon
  - oligodendrocytes do so in the central nervous system, but one oligodendrocyt can myelinate up to 50 axons
- the myelin sheath is interrupted at regularly spaced nodes of Ranvier

- ion concentration of skeletal muscle cells from homoiotherms

	inside	outside
K^+	*high*	*low*
Na^+	*low*	*high*
Ca^{2+}	*very low*	*low*
Cl^-	*low*	*high*

GLIA CELLS

- 10% of the brain is neuron, the rest is glia
- glia cells, which form a supporting tissue, are divided in three classe
  - astrocytes
    - have an additional function as space buffers in adult cells and as support in growing axons
    - form part of the blood-brain-barrier
  - microglia
  - oligodendrocytes, that serve as insulation

NEUROTRANSMITTERS

- Many of the signalling molecules that are secreted by nerve terminals, including a large variety of neuropeptides, bind to receptors that regulate ion channels only indirectly.
- agonist: natural ligand, excitatory ligand
- antagonist: inhibitory ligand, inhibits effects of the agonist

- excitatory neurotransmitters

- open cation channels, causing an influx of Na^+ that depolarises the postsynaptic membrane toward the threshold potential for firing an action potential
- glutamate, predominant neurotransmitter in vertebrate brains
- serotonin
- mostly acetylcholine

- inhibitory neurotransmitters

- open either Cl^- channels or K^+ channels, thereby suppressing firing by making it harder for excitatory influences to depolarise the postsynaptic membrane
- γ-aminobutyric acid (GABA)
- glycine
- sometimes acetylcholine

- vesicles

- vesicle fusion, that leads to the release of neurotransmitters at the presynaptic membrane, is regulated by voltage-gated Ca^{2+} channels; there are two distinct types of vesicles

- synaptic vesicles
  - small neurotransmitter-filled secretory vesicle formed at the axon terminals of nerve cell and whose contents are released into the synaptic cleft by exocytosis when an action potential reaches the axon terminal
  - activate GPCRs and ion channels, diameter: 50nm
  - fuse only with the presynaptic membrane after a local increase of Ca^{2+} concentration

- secretory vesicles (secretory granule)
  - membrane-bounded organelle in which molecules destined for secretion are stored prior to release
  - in neurons, secretory vesicles are filled with neuropeptides and amines
  - activate GPCRs, Kinases, diameter: 90-250nm
  - fuse with non-specialized sites of the nerve terminal after high increase of Ca^{2+} concentration

DESENSITISATION OF RECEPTORS

- ion channel-linked receptors

- after long exposition (~ 20ms - 1s) of a transmitter-gated channel to neurotransmitters, the receptor will no more be sensitive
- after minutes of exposition the receptors will be internalised; however, a few internalised receptors will still be active because their ligands remain bound despite the acid pH 5 found inside the lysosome
- some internalised receptors can be reactivated
- degradation of the ligand and receptor follows after hours

- metabotropic receptors

- heterologe desensitisation is initiated by the second messenger product (e.g. cAMP, IP_3, Ca^{2+}) of the signalling pathway and can be manifested as a decrease of activity of receptor, G-protein, or effector
- homologous desensitisation usually is some direct modification (covalent or conformational) of the agonist-liganded receptor