Synaptic Transmission

Introduction

- For information from action potentials to be processed by the rest of the nervous system it is necessary for this information to be passed on to other neurons.
- Transfer of information from one neuron to the next occurs at specialized sites of contact.
- Charles Sherrington named these sites Synapses.
- The existence of electrical synapses was proven in 1959 (Edwin Furshpan and David Potter).
- Strong evidence for chemical synapses in the heart was provided in 1921 (Otto Loewi).
- Evidence for chemical synapses in the neuromuscular junction was provided by Bernard Katz (1938-1950).
- Evidence for chemical synapses in the central nervous system was provided by John Eccles (1951).

Types of Synapses

Elecrical Synapses

- Occur at specialized sites called gap junctions (3nm).
    - Composed of connexin proteins making a channel called a connexon.
    - Two connexons form a gap junction channel.
    - Allow ionic currents to pass between cells.
- Found in invertebrate and vertebrate nervous systems, especially during early embryonic stages.
- Also prominent in the heart.

Chemical Synapses

- Most synaptic transmission in mature human nervous system is chemical.
- Consist of presynaptic and postsynaptic membranes separated by a synaptic cleft (20-50 nm).
    - Axon terminal (synaptic bulb) contains synaptic vesicles and or secretory granules that store neurotransmitter.
    - On the presynaptic side many proteins jut into the cytoplasm.
    - On the post synaptic side many proteins are found in and just under the membrane and include the neurotransmitter receptor.

CNS Synapses

- Axodendritic
- Axosomatic
- Axoaxonic

Neuromuscular Junction

- These chemical synapses are between axons of somatic or autonomic neurons and skeletal or smooth and cardiac muscle.
- The post synaptic membrane is called the motor end plate.
- One of the largest synapses in the body.

Principles of Chemical Synaptic Transmission

- Mechanism for synthesizing neurotransmitter and packing it into synaptic vesicles.
- Mechanism for causing the vesicles to empty into the synaptic cleft in response to action potential.
- Mechanism for producing an electrical or chemical response to the neurotransmitter in the postsynaptic neuron.
- Mechanism for removing neurotransmitter from synaptic cleft.

Neurotransmitters

Amino Acids and Amines

- Amino acids and amines are stored in and released from synaptic vesicles.
- Amino Acids
    - Gamma Amino Butyric Acid (GABA)
    - Glutamate (Glu)
    - Glycine (Gly)
- Amines
    - Acetylcholine (Ach)
    - Dopamine (DA)
    - Epinephrine (E)
    - Histamine
    - Norepinephrine (NE)
    - Serotonin (5-HT)

Peptides

- Peptides are stored in and released from secretory granules (vesicles).
- Peptides
    - Cholecyctokinin (CCK)
    - Dynorphin
    - Enkephalins (Enk)
    - N-acetylaspartylglutamate (NAAG)
    - Neuropeptide-Y (NP-Y)
    - Somatostatin
    - Substance P
    - Thyrotropin releasing hormone (TRH)
    - Vasoactive intestinal peptide (VIP)

Fast Synaptic Transmission

- Fast synaptic transmission at most CNS synapses is mediated by the amino acids glutamate, GABA, and glycine.
- Fast synaptic transmission at all neuromuscular junctions is mediated by the amine acetylcholine.

Slow Synaptic Transmission

- Slow synaptic transmission is mediated by the amino acid, amine and peptide neurotransmitters.

Neurotransmitter Synthesis and Storage

- Glutamate and Glycine are abundant in all cells of the body; GABA and the amines are made only by the neurons that release them.
    - The synthesizing enzymes for both amino acid and amine neurotransmitters are transported to the axon terminal.
    - Once synthesized the neurotransmitter must be taken up by the synaptic vesicles using transporter proteins in the synaptic vesicles.
- Peptides are formed from amino acids by ribosomes of the cell body involving the rough ER. (This process of course involves genes, DNA and RNA.)
    - A long peptide synthesized in the rough ER is split in the Golgi apparatus and one of the peptide fragments is the active neurotransmitter.
    - Secretory granules (vesicles) containing the peptide bud off from the Golgi apparatus and are carried to the axon terminal by axoplasmic transport.

Neurotransmitter Release

Release of Amino Acids and Amines

- Depolarization of the axon terminal opens voltage gated Ca^{2+} channels.
- Ca^{2+} rushes into the cytoplasm of the axon terminal.
- Ca^{2+} changes the conformation of proteins holding vesicles onto the presynaptic membrane.
- The membranes of the vesicle and the axon terminal fuse, forming a pore through which the neurotransmitter diffuses out.
- Exocytosis take about 0.2 ms
- Vesicles are recovered by endocytosis and refilled with neurotransmitter.

Release of Peptides

- Secretory granules also release peptide neurotransmitter by exocytosis triggered by Ca^{2+} entry into the cytoplasm of the axon terminal.
- However, granule exocytosis occurs at a distance from the site of Ca^{2+} entry.
- Therefore more Ca^{2+} must enter and generally requires trains of action potentials
- Exocytosis takes 50 ms or more

Neurotransmitter Receptor

Neurotransmitters bind to specific receptor proteins in the postsynaptic membranes and cause conformation changes in the proteins.

Transmitter Gated Ion Channels

Amino acid or amine neurotransmitters acting on gated ion channels cause rapid, short lasting responses.

- A neurotransmitter binds to a channel permeable to Na^+, opens the channel, and allows Na^+ to rush into the postsynaptic cell which causes depolarization.
    - The depolarization is called an excitatory postsynaptic potential (EPSP).
    - Activation of acetylcholine gated ion channels or activation of glutamate gated ion channels cause EPSPs.
- A neurotransmitter binds to a channel permeable to Cl^-, opens the channel, and allows Cl^- to rush into the postsynaptic cell which causes hyperpolarization.
    - The hyperpolarization is called an inhibitory postsynaptic potential (IPSP).
    - Activation of glycine gated ion channels or activation of GABA gated ion channels cause IPSPs.

G-Protein Coupled Receptors (GPCRs)

Amino acid, amine, or peptide neurotransmitters acting on G-protein couples receptors cause slow, long lasting, and more diverse responses.

1. A neurotransmitter binds to a receptor protein embedded in the postsynaptic membrane.
2. The receptor proteins activate small proteins (G-proteins) that can move along the intracellular face of the postsynaptic membrane.
3. The activated G-proteins activate other 'effector" proteins.
    - The effector proteins can be G-protein gated ion channels.
    - Enzymes that synthesize other molecules (second messengers) that in turn:
        - Activate additional enzymes that regulate ion channels.
        - Activate additional enzymes that regulate cellular metabolism.

Response Diversity

The same neurotransmitter can have (and usually does have) different postsynaptic actions depending on what receptor it binds to.

Autoreceptors

In addition to postsynaptic receptors there are also presynaptic receptors, often called autoreceptors.

- Presynaptic receptors are sensitive to neurotransmitter released by the presynaptic terminal.
- Presynaptic receptors are involved in feedback control of neurotransmitter release and/or synthesis.

Neurotransmitter Recovery and Degradation

Neurotransmitter may be cleared from the synaptic cleft by several mechanisms:

- Diffusion
- Reuptake into the presynaptic axon terminal via transporter proteins in the presynaptic membrane.
    - The neurotransmitter is subsequently destroyed or reloaded into synaptic vesicles (especially for amino acid and amine neurotransmitters)
- Uptake into glial cells (astrocytes) via transporter proteins.
- Destruction in synaptic cleft by enzymes
    - For example acetylcholine in the neuromuscular junction is cleaved by acetylcholinesterase.

Neuropharmacology

Each step of synaptic transmission is chemical and therefore can be affected by specific drugs. For example by:

- Inhibitors that interfere with normal function of specific proteins.
- Receptor antagonists that bind to and "block" a receptor.
- Receptor agonists that bind to a receptor and mimic the action of a neurotransmitter.

Synaptic Integration

Most CNS neurons receive thousands of synaptic inputs that activate different combinations of neurotransmitter gated ion channels and G-protein coupled receptors. The signals are integrated together to give rise to and output. This process is often called neural computation.

Integration of EPSPs

The content of 1synaptic vesicle = 1 quantum of EPSP

- At the neuromuscular junction an action potential causes the exocytosis of about 200 synaptic vesicles which will cause an EPSP of about 40 mV
- At a CNS synapse an action potential causes the exocytosis of as few as 1 synaptic vesicle which will cause an EPSP of about 0.2 mV.

Neurons in the CNS perform sophisticated computations requiring that many EPSPs are added together.

- Spatial summation occurs when EPSPs generated simultaneously at many different synapses on a dendrite are added together.
- Temporal summation occurs when EPSPs generated at the same synapse in rapid succession (1-15 ms) are added together.

Inhibition

The neurotransmitter gated channels of most inhibitory synapses are permeable to only Cl^-.

- If the membrane potential is less negative than -65 mV, opening of Cl^- channels will cause a hyperpolarizing IPSP.
- If the membrane potential is already -65 mV, opening of Cl^- channels will not cause hyperpolarization but an inward movement of Cl^-.
- Opening of Cl^- channels will reduce the magnitude of EPSPs.

Other inhibitory synapses utilize neurotransmitter gated channels that are permeable to K^+.

- Opening of K^+ channels allows K^+ ions to leave the cell and will cause an IPSP.
- Opening of K^+ channels will reduce the magnitude of EPSPs.

Modulation

Modulation modifies the effectiveness of EPSPs generated by other synapses.

- Closing K^+ channels prevents the movement of K^+ ions out of the cell and will cause an EPSP.
- In dendrites closing K^+ channels make the cell more excitable.