Physiology of Synapse

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SYNAPSE

- A region where communication occurs between two neurons, or between a neuron and a target cell
- NMJ – between a motor neuron and a skeletal muscle fiber
Physiologic Anatomy

[Diagram of neuron structure and neurotransmission process]

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Types of Synapses

- **Chemical synapse**
  - The first neuron secretes a chemical substance (neurotransmitter) at the synapse
  - Transmitter acts on receptor proteins in the membrane of the next neuron
  - To excite, inhibit, or modify its sensitivity
  - Signal is transmitted in one direction

- **Electrical synapse**
  - Characterized by direct channels that conduct electricity from one cell to the next
  - Mostly consist of small protein tubular structure (gap junctions) that allow free movements of ions from the interior of one cell to the next
Pre-synaptic terminals

- **Excitatory**
  - They secrete a substance that excites the post synaptic neuron

- **Inhibitory**
  - They secrete a substance that inhibits the post synaptic neuron

Pre-synaptic terminal

- Separated from the post-synaptic neuronal soma by a synaptic cleft
- Has 2 internal structures important to the excitatory or inhibitory functions of the synapse:
  1. Transmitter vesicles – contain transmitter substance (excitatory or inhibitory)
  2. Mitochondria – supplies ATP to synthesize neurotransmitter substance
• AP spreads over pre synaptic terminal →
  emptying of vesicles into the cleft → NT
  causes immediate change in permeability of
  post-synaptic neuronal membrane →
  excitation or inhibition depending on receptor
  characteristics

Role of Calcium Ions

• Voltage-gated calcium channels – found in
  pre-synaptic membrane
• The quantity of transmitter substance that is
  released into the synaptic cleft is directly
  related to the number of calcium ions that
  enter the terminal
Post-synaptic terminal

- Receptor proteins – found at the membrane
  - 2 important components:
    1. Binding component
       - protrudes outward from the membrane into the synaptic cleft
       - binds with the NT from the pre-synaptic terminal
    2. Ionophore component
       - passes all the way through the membrane to the interior of the post-synaptic neuron
       - Has 2 types
         - Ion channel
         - “second messenger” activator
Ion channel

- Allows passage of specified types of ions through the channel
- 2 types:
  1. Cation channels – most often allow Na+ to pass, sometimes K+ or Ca++
  2. Anion channels – allow mainly Chloride ions to pass, minute quantities of other anions

- Opening of sodium channels excite the postsynaptic neuron
  A transmitter substance that opens sodium channels is called an excitatory transmitter
- Opening of chloride channels inhibit the neuron
  A transmitter substance that opens these are called inhibitory transmitter
“Second Messenger” system

- Protrudes into the cell cytoplasm and activates one or more substances inside the postsynaptic neuron
- Substances change specific cellular functions
Molecular and Membrane Mechanisms used by excitatory and inhibitory receptors

- **Excitation**
  1. Opening of Na+ channels to allow large numbers of positive electrical charges to flow to the interior of the post-synaptic cell.
  2. Depressed conduction chloride or K+ channels or both
  3. Various changes in the internal metabolism of the cell to excite cell activity

- **Inhibition**
  1. Opening of chloride ion channels through the receptor molecule
  2. Increase in the conductance of K+ ions through the receptor
  3. Activation of receptor enzymes that inhibit cellular metabolic functions
Chemical substances that function as synaptic transmitters

- Small-molecule, rapidly acting transmitters:
  - Acetylcholine
  - Norepinephrine
  - Epinephrine
  - Dopamine
  - Serotonin
  - Histamine
  - GABA
  - Glycine
  - Glutamate
  - Aspartate
  - Nitric oxide

- Cause most acute responses
- Synthesized in the cytosol of the pre-synaptic terminal, absorbed by active transport into the vesicles
- Vesicles are continually recycled
- Removed by:
  - Diffusion out of the synaptic cleft into surrounding fluids
  - Enzymatic destruction
  - Transmitter re-uptake
Vesicle Cycle in Presynaptic Terminal

Neuropeptide, Slowly acting transmitters

- A. Hypothalamic releasing hormones
  - Thyrotropin-releasing hormone
  - LHRH
  - Somatostatin
- B. Pituitary peptides
  - ACTH
  - β-endorphin
  - MSH
  - Prolactin
  - Thyrotropin
  - GH
  - ADH
  - oxytocin
Neuropeptides

- Cause more prolonged actions; small quantities are released but are more potent
- Synthesized as integral parts of large-protein molecules by the ribosomes in the neuronal cell body
- The vesicles are autolyzed
- Removed by diffusion into the surrounding tissue, followed by enzymatic destruction

EPSP/IPSP

A

Ratining Neuron

B

Excitatory

Na⁺ influx

-45 mV

Spread of action potential

C

Inhibitory

Cl⁻ influx

K⁺ efflux

70 mV

Inhibited Neuron
The RMP increased from -65 to -45mv
EPSP = 20mv, if this rises high enough it will elicit an AP in the neuron thus exciting it
An increase in neuronal potential of this magnitude requires the simultaneous discharge of many terminals (40-80) at the same time or in rapid succession (summation)

• Begins in the initial segment of the axon leaving the soma
• The membrane of the initial segment has 7x as great concentration of voltage-gated sodium channels, can generate AP with much greater ease
• EPSP that will elicit an AP at the initial segment is between +10 and +20mv
IPSP

• EMF (mv) = +/- 61 x log (Ci/Co)
• Nernst potential for Na+ is +61mv
  • Net quantities of Na+ normally diffuse inward through the sodium channels
• Nernst potential for K+ is -86mv (more negative than -65)
  • There is a net tendency of K+ to diffuse to the outside of the neuron, but this is opposed by the continual pumping of K+ back to the interior
• Nernst potential for Chloride is -70mv
  • Chloride ions tend to normally leak to the interior of the neuron
  • Opening of chloride channels will allow chloride ions to move to the interior
  • Opening of K+ channels will allow K+ to move to the exterior
  • Increase in degree of negativity – hyperpolarization
  • The MP is further away from the threshold for excitation
    → inhibition
• IPSP = -5mv
Mechanism of Excitatory transmission

- The propagated AP reaches the nerve ending
- The nerve ending is depolarized
- Permeability of membrane to calcium is increased
- Calcium influx
- Release of chemical transmitter from vesicles at nerve ending, into the synaptic cleft

- Chemical action on the membrane of postsynaptic element increases permeability to ions
- Depolarization; the voltage change is called the EPSP
- If firing level is reached, an AP is produced and subsequently propagated through the axon
Mechanism of Inhibitory transmission

- Propagated AP depolarizes the ending
- Release of inhibitory transmitters
- Chemical effects on post-synaptic membrane increase permeability to potassium and chloride ions

- Hyperpolarization; voltage variation is called the IPSP
- Reduced membrane excitability
- No AP develops (inhibitory)
Characteristics of synaptic transmission

- Summation – the simultaneous discharge of many pre-synaptic terminal at the same time or in rapid succession to produce an action potential
  - a) Temporal – the same terminal
  - b) Spatial – many terminals
• Inhibition
  a) Development of IPSP
  b) Pre-synaptic inhibition
    • Occurs in the pre-synaptic terminals before the signal even reaches the synapse
    • The inhibition is caused by discharge of inhibitory synapses that lie on the pre-synaptic terminal nerve fibrils
    • Opening anion channels
    • AP in terminal fibril is greatly reduced, reducing also the degree of excitation of post-synaptic neuron

• C. “short-circuiting” of the membrane
  • Another method for inhibiting neurons without causing IPSP
  • Caused by the tendency of the chloride ions to maintain the RMP near the resting value when the inhibitory channels are wide open, making the sodium current caused by excitatory synapses ineffective in exciting the cell
• Convergence
  • Pre-synaptic nerve endings from different neurons may make synaptic connections with a single post-synaptic element

• Divergence
  • Pre-synaptic nerve ending from one neuron may make synaptic connections with post-synaptic elements of other neurons
• Facilitation
  • Successive stimulation of the efferent neuron may build up an EPSP which reaches firing level
  • Neuron is said to be “facilitated” when its membrane potential is nearer the threshold from firing than normal but not yet at the firing level

• Occlusion
  • Simultaneous stimulation of efferent neurons produces a reflex response lesser than the sum of the responses produced when the two nerves are stimulated separately
  • Unidirectional transmission
    • orthodromic
• Repetitive discharge
  • A single volley of impulses through the pre-synaptic path may evoke a train of spikes in the post-synaptic neuron
• Transmission is depressed by hypoxia
• Fatigue
  • When excitatory synapses are repetitively stimulated at a rapid rate, the number of discharges by the post-synaptic neuron is at first very great, but becomes progressively less in succeeding msec
  • Mechanism: exhaustion of stores of NT in the pre-synaptic terminal

• Synaptic delay in the passage of a nerve impulse is accounted for by the time it takes for:
  a) Release of transmitter at pre-synaptic ending
  b) Diffusion of transmitter
  c) Change in membrane permeability of post-synaptic element
  d) Depolarization (EPSP)