

Nervous system : nervous tissue and nerve physiology

I. Introduction

- the nervous system (NS) is the master controlling and communicating system of the body; together with the endocrine system it is responsible for maintenance of homeostasis.

A. Functions of the nervous system:

1. monitors changes occurring inside/outside of the body - sensory input.
2. processes/interprets sensory input - integration.
3. causes a response in effector organs (muscles, glands) - motor output.

B. Organization of the nervous system.

- the NS is divided into two major parts:

- CNS: brain, spinal cord; integrative/control centers, interprets incoming information & dictates responses.

- PNS: spinal nerves, cranial nerves; it is divided into two parts, functionally:

- sensory division: conducts impulses from receptors to CNS.

- motor division: conducts impulses from CNS to effectors; has two major subdivisions:

- somatic division: conducts impulses from CNS to skeletal muscles; voluntary.

- autonomic division (ANS): conducts impulses from CNS to cardiac and smooth muscle, and glands; involuntary; has two final subdivisions:

- sympathetic division: fight or flight

- parasympathetic division: non emergency, vegetative body functions.

II. Histology of nervous tissue

- nervous tissue is highly cellular, cells densely packed/intertwined
- two major cell types, neurons (excitable cells) and supporting cell (smaller, wrap around neurons).

A. Supporting cells: six types total, 4/CNS, 2/PNS; provide protective scaffolding for neurons.

1. CNS supporting cells: neuroglia, branching processes with central body, outnumber neurons 9 : 1.

a. astrocytes: star shaped, most common; radial projections cling neurons to capillaries, role in making exchanges between neurons and capillaries.

b. microglia: the macrophages of the CNS

c. ependymal cells: range from squamous to columnar, line central cavities of brain/spinal cord

d. oligodendrocytes; wrap themselves around thicker neuron fibers of CNS forming insulating covering, myelin sheath.

2. PNS supporting cells: satellite cells & Schwann cell, similar structures, differ mostly in location.

a. satellite cells: surround neuron cell bodies in ganglia, role in chemical environment control.

b. Schwann cells: wrap themselves around thicker nerve fibers, form myelin sheaths.

B. Neurons: nerve cells, structural & functional units of NS; very specialized cells, conduct messages in form of electrical impulses.

- general characteristics: extreme longevity, amitotic, high metabolic rate.
- very diverse structurally, but "idealized neuron" contains a cell body from which one or more processes emerge.
- all neurons have three functional regions, a receptive region (input, receives information), a conducting component (generates and transmits nerve impulses or action potentials), and a secretory component (neurotransmitter release).

1. Neuron cell body (soma): biosynthetic center of cell, contains very well developed RER, also called Nissl bodies; well developed Golgi apparatus; numerous neurofilaments; part of receptive component.

2. Neuron processes: cytoplasmic extensions projecting from cell bodies; two major types, axons and dendrites

a. dendrites: short, diffuse branching processes, usually close to soma; receptive region - conducts electrical signals to cell body; these signals are not nerve impulses (action potentials), they are short lived electrical currents (graded potentials).

b. axon: single, large process; arises at axon hillock, can be short or very long; long axon called a nerve fiber; may give rise to axon collaterals and terminates in many numerous telodendria that have bulbous ending called axon terminals.

- are the conducting component of a neuron: generate nerve impulses (action potentials, AP) at the trigger zone and propagate them away from soma to axon terminals; also are the secretory component of neurons: AP reaches axon terminals, causes neurotransmitter (NT) release.

- contains same organelles as soma, except no Nissl bodies; hence depends on soma to renew necessary membrane/protein components and other enzymes; these substances are transported down axon by axonal transport (anterograde, retrograde), a function of MT, microfilaments, neurofilaments.

3. Myelin sheath: white, fatty material that covers large diameter axons in a segmented fashion; protects, insulates fibers from one another, increases conduction velocity.

a. Formation of myelin sheaths in PNS

-Schwann cells wrap plasma membranes around axon in successive layers; the cytoplasm is squeezed out of plasma membrane layers forming a structure consisting of many concentric layers of Schwann cell plasma membrane wrapped around a single axon.

- nucleus and cytoplasm of Schwann cell lie immediately below the outer leaflet of plasma membrane, outside concentric rings of empty membrane - neurilemma.

- one Schwann cell myelinates only a segment of one axon, thus various Schwann cells myelinate a single axon; gaps in myelin sheath produced by adjacent Schwann cells are called Nodes of Ranvier - axolemma exposed at these areas, basis of saltatory conduction.

- unmyelinated axons are also associated with Schwann cells; however, Schwann cell does not wrap its membrane around nerve fiber, just encloses it; in this case a single Schwann cell can enclose several axons.

b. Formation of myelin sheaths in CNS

- oligodendrocyte produces myelin sheath; a single oligodendrocyte can wrap its plasma membrane around several nerve fibers; cell extensions doing the coiling rather than whole cell itself.

4. Classification of neurons

a. Structural classification: based on number of processes extending from soma.

i. multipolar neurons: three or more processes, many dendrites, one axon.

ii. bipolar neurons: two processes, one axon/one dendrite extending from opposite sides of the soma; very rare, receptors in sense organs.

iii. unipolar neurons (pseudounipolar) : a single process emerges from soma, divides T-like into a peripheral process (usually associated with a sensory receptor) and a central process (enters CNS)

b. Functional classification: according to direction of impulse propagation relative to CNS.

i. sensory (afferent) neurons: conduct sensory input towards CNS; mostly unipolar; cell bodies in sensory ganglia outside CNS.

ii. motor (efferent) neurons: conduct nerve impulses away from CNS to effector organs; multipolar; cell bodies in CNS (except some ANS), axons bunched as nerves.

iii. interneurons (association): lie between sensory and motor neurons in neural pathways; multipolar usually confined to CNS.

III. Neurophysiology

- neurons are highly irritable - responsive to stimuli, that is; when a neuron is adequately stimulated, an electrical impulse will be generated at and conducted along the axon.
- AXON POTENTIAL = NERVE IMPULSE.

A. Electricity, basic principles

- the body is electrically neutral (total), however there are areas where opposite charges are separated - work must be done to keep them apart, energy (NRG) liberated when they come together.
- separated opposite charges have potential NRG, measured in volts; thus voltage is the difference in potential between two areas of opposite charge.
- the flow of electrical charge from one point to the other is current.
- Current (I) = Voltage (V)/Resistance (R)
- in body electrical currents are flow of ions across membranes; ions cross membranes through channels, ion channels, three types:
 - passive (leakage) channels: always open.
 - chemically-gated channels: open upon ligand binding.
 - voltage-gated channels: open/close in response to changes in membrane potential.

Keep in mind that ions diffuse in membrane through channels down both chemical and electrical gradients.

B. The resting membrane potential (RMP)

- plasma membrane delineates outside/inside of cell, ion distribution across plasma membrane is unique to inherent permeability properties of the membrane; generally:
 - $[Na^+]_o > [Na^+]_i$
 - $[K^+]_i > [K^+]_o$
 - $p [K^+] \gggg p [Na^+] \text{ ---- } K^+ \text{ leaks out a lot faster than } Na^+ \text{ leaks in -- a function of passive channels.}$
 - accumulation of positive charge outside membrane, a difference in potential across it, the resting membrane potential (RMP)
 - RMP would be dissipated eventually without Na^+ / K^+ ATPase -- latter maintains distinct distribution of ions across membrane.
 - what are electrochemical gradients for Na^+ and K^+ ?

C. Membrane potentials (MP) that act as signals

- cells use changes in membrane potential as communicating signals for receiving, integrating, sending information.
- changes in membrane potential are achieved by either changing the membrane permeability to a specific ion, or by any factor that affects the ion concentration on either side of the membrane.
- changes in MP greater than RMP (more negative than RMP) -- hyperpolarization.
- changes in MP less than RMP (less negative) -- depolarization.
- two types of signals can be produced by a change in RMP, graded potentials (signal over a short distances), and action potentials (signal over long distances).

1. Graded potentials: short-lived, local changes in RMP, depolarizations/hyperpolarizations

- local flows of current that decrease with distance traveled.
- "graded" in the sense that the magnitude of the RMP change varies directly with the magnitude of the stimulus.
- triggered by some change in a neuron's environment that causes gated ion channels to open (have different names depending on location, i.e., receptor potential, postsynaptic potential).
- mechanism of the graded potential:
 - stimulus, small depolarization.
 - generation of local current on both sides of the membrane between depolarized and polarized (resting) areas.
 - thus neighboring areas become less negative on the inside, less positive on the outside - a small depolarization.
 - thus, a change in potential (a voltage change) spreads to surrounding areas, change decreases with increasing distance from the area of stimulus application.

2. The action potential (AP): nerve impulse.

- only cells with excitable membranes can generate an action potential.
- AP is a brief reversal of MP with total amplitude (voltage change) of about 100 mV (from -70 mV to +30 mV); takes a few milliseconds, does not decrease in strength with distance.
- a neuron will generate and propagate a nerve impulse (AP) only when adequately stimulated; that is, a stimulus causes a graded potential in receptive portion of the neuron, spreads towards the axon along neuron membrane; if change in MP "strong" enough, opening of voltage-gated Na⁺ channels occurs at the axon hillock, leading to an AP.

a. Generation of an AP

- **resting state (phase 1):** voltage gated Na^+ and K^+ channels are close; some K^+ diffusing to cell exterior via passive channels; very small amount of Na^+ diffusing into the cell via passive channels

- **depolarizing phase (phase 2a):** axonal membrane depolarized by graded potentials; voltage-gated Na^+ channels begin to open, Na^+ permeability increases, membrane depolarized further (interior less negative).

- when depolarization reaches a critical level (-55 to -50 mV, when Na^+ entry equals or greater than outward K^+ leakage, threshold), **all** voltage-gated Na^+ channels open -- Na^+ permeability increased over 1000X! Na^+ rushes in down its electrochemical gradient, MP less and less negative, peaks at about +30 mV

- this portion of AP called foot and uplimb of the spike; note that after threshold the depolarization becomes self generating, driven by ionic currents created by Na^+ influx.

- **depolarizing phase (phase 2b):** as Na^+ rushes in and intracellular areas become more positive, further Na^+ entry is resisted - slows down (decreases slope of) upper part of uplimb of spike.

- also, voltage-gated Na^+ channels close - no more Na^+ passage, Na^+ permeability decreased dramatically.

- thus spike stops rising, begins to drop.

- **repolarization (phase 3):** caused by opening of voltage-gated K^+ channels - K^+ rushes out down electrochemical gradient, cell interior less and less positive, cell exterior more and more positive.

- MP moves towards resting level, a repolarization.

- **undershoot (after hyperpolarization):** K^+ gates remaining open cause excessive K^+ efflux, MP momentarily more negative than RMP - after hyperpolarization; it is quickly restored to RMP.

- note that while repolarization restores the original RMP, it does not restore original ionic distributions across the membrane -- a role for the Na^+/K^+ ATPase.

b. Propagation of an action potential (AP)

- AP propagated along the length of axon without loss of strength.

- a current flows on both sides of the membrane: positive ions in the interior move laterally from area of polarity reversal to area that is still polarized (negative); positive ions in the ECF move laterally from area that is polarized to area of polarity reversal -- causes depolarization in adjacent area, threshold is reached, voltage-gated Na^+ channels open, another AP occurs -- self propagation in the sense that an AP is generated anew at each membrane area.

- note that because area "behind" has just generated an AP, Na^+ are closed, and no AP can be generated there.

- following depolarization, each area of neuronal membrane undergoes repolarization - a wave of depolarization being followed by repolarization wave.

c. Threshold and All or None Law

- not all local depolarization events produce an AP; depolarization must hit a threshold to produce an AP

- threshold is that transmembrane potential that must be reached to produce an AP (all or none response).

- All or None Law: if a response occurs, response will be maximal for the physiological conditions existing at the time. That is if neuron fires an AP it fires it off -- same amplitude regardless of strength of stimulus; if it doesn't fire it doesn't regardless of how far or close the graded depolarizations got to threshold level.

d. Coding for stimulus intensity

- once generated AP independent of stimulus strength, all APs in one neuron have the same amplitude.

- how does CNS determine if stimulus was weak or intense?

- strong stimuli cause nerve impulses (APs) to be generated more often; thus increased stimulus intensity results in increased frequency of AP generation.

e. Absolute/relative refractory period

- absolute refractory period - period of AP during which excitability is zero, neuron incapable of responding to other stimulation.
- relative refractory period - period of AP when excitability is below normal, slowly rising; the neuron can respond to the stimulus, however has a much higher threshold (needs stronger stimulus).

f. Conduction velocities of axons

- conduction velocities vary widely
- rate of propagation of AP dependent on axon diameter and degree of myelination.

i. increasing diameter results in increasing conduction velocities

ii. influence of myelin sheath: increases conduction velocity due to saltatory conduction - local currents on either side of the membrane occur between nodes.

- nerve fibers classification:

- Group A fibers: somatic sensory and motor fibers serving skin, muscles, joints; largest diameter; thick myelin sheaths (15-150 m/sec).

- Group B fibers: lightly myelinated, intermediate diameter (3-15 m/sec)

- Group C fibers: smallest diameter, unmyelinated (1m/sec)

Note: Groups B and C fibers are ANS motor fibers serving visceral organs, visceral sensory fibers, smaller somatic sensory fibers transmitting impulses from skin.

IV. Synapses

- the operation of the NS depends on flow of information through networks of neurons functionally connected by synapses.
- synapse (def.): a unique junction that mediates transfer of information from one neuron to another or from a neuron to an effector cell; most synapses are axodendritic or axosomatic, a minority are axoaxonic, dendrodendritic, dendrosomatic.
- synapses formed by presynaptic and postsynaptic neurons.
- a synapse where postsynaptic cell is a muscle is called a neuromuscular junction; where it is a gland it is called a neuroglandular junction.
- there are two types of synapses, electrical and chemical synapses.

A. Electrical synapse

- relatively uncommon; a gap junction between two neurons, allows ions to move directly from one neuron to the next; thus neurons are electrically coupled.
- found in regions of the brain responsible for stereotyped movements, rapid movements of eyes; also common embryonically.

B. Chemical synapses

- specialized for release and reception of chemical neurotransmitters (NT); NTs function to open/close chemically-gated channels that influence membrane permeability and hence membrane potential.
- chemical synapse has two parts: a knob-like axon terminal full of synaptic vesicles containing NT molecules; and a region of membrane of postsynaptic neuron that contains NT receptors (receptor region).

C. Information transfer across chemical synapses

1. Nerve impulse reaches axon terminal, depolarization of membrane opens voltage-gated Ca^{++} channels; Ca^{++} rushes into axon terminal.
2. Surge in free Ca^{++} causes synaptic vesicles to fuse with axonal membrane, contents emptied into synaptic cleft via exocytosis; Ca^{++} in axonal terminal quickly removed from cytoplasm either into mitochondria or to exterior through active Ca^{++} membrane pump.
3. NT diffuses across synaptic cleft, binds to receptors on postsynaptic membrane.
4. This causes opening of chemically-gated ion channels which changes membrane permeability and produces changes in membrane potential - depolarizations or hyperpolarizations.

D. Termination of neurotransmitter effects can occur in three ways:

1. Degradation of NT by enzymes associated with postsynaptic membrane.
2. Removal from synapse by reuptake into presynaptic terminal.
3. Diffusion of NT away from synapse.

E. Synaptic delay

- the time required for NT release, diffusion across synaptic cleft, and binding to receptors, 0.3-0.5 msec.
- it is the rate-limiting event of synaptic transmission.

V. Postsynaptic potentials and synaptic integration

- receptors to which NTs bind are associated with voltage-gated channels -- they alter membrane permeability to certain ions; however they are **voltage-insensitive**, hence channel opening cannot become a self-generating event propelled by positive feedback as is the case for the trigger zone of the axon hillock.
- thus NTs cause changes in membrane potential that are **graded** according to the amount of NT released and the time it remains in the area; called postsynaptic potentials.
- chemical synapses are excitatory or inhibitory depending on how they affect RMP of postsynaptic membrane; excitatory postsynaptic potentials (EPSPs) occur at excitatory synapses; inhibitory postsynaptic potentials (IPSPs) occur at inhibitory synapses.

A. Excitatory synapses (ES) and EPSPs

- at ES, NT binding causes depolarization of postsynaptic membrane; it is a graded depolarization, dependent on amount of NT bound to receptors of postsynaptic membrane.
- NT binds to receptors associated with a specific kind of chemically-gated channels that allow Na^+ and K^+ ions to diffuse simultaneously down their respective electrochemical gradients; since the **electrochemical gradient for Na^+ is much greater than the electrochemical gradient for K^+** , Na^+ influx is greater than K^+ efflux and a depolarization (not an AP) occurs.
- again, **postsynaptic membrane (either of dendrites or cell body) cannot generate APs, only axons can.**
- however, if depolarization is "strong enough" it may spread along neuron body and eventually get to the trigger zone of the axon hillock before it dies out; here there are voltage-gated channels, the small depolarization causes opening of Na^+ voltage gated channels, membrane further depolarized, more voltage-gated channels open, more depolarized, etc., etc., a positive feedback system builds up, eventually depolarizations reach threshold level, **all** Na^+ voltage-gated channels open, an AP is generated and begins to propagate itself.

B. Inhibitory synapses (IS) and IPSPs

- at IS, NT binding causes hyperpolarization of postsynaptic membrane; again this is a graded hyperpolarization dependent on amount of NT bound to receptors of postsynaptic membrane.
- the hyperpolarization results from opening of chemically-gated K^+ channels (increase K^+ permeability, Na^+ permeability not affected).
- thus trigger zone of axon less likely to generate an AP.

C. Integration and modification of synaptic events

- neurons don't receive information from other neurons "one signal at a time"; at any point in space and time a single postsynaptic neuron can be receiving many signals from other neurons that result in production of many EPSPs and IPSPs -- the response of this postsynaptic neuron will depend on the additive effect (or summation) of all EPSPs and IPSPs.

- that is, EPSPs/IPSPs can add together or summate to influence activity of postsynaptic neuron; there are two types of summation, temporal summation and spatial summation.

1. Temporal summation: occurs when or more presynaptic fibers transmit impulses in rapid fire order -- waves of NT released in rapid succession and before the first EPSP dies out, a new one occurs -- additive effect, can get a large enough postsynaptic potential that influences the trigger zone.

- IPSPs also can summate temporally.

2. Spatial summation: occurs when a postsynaptic neuron is stimulated by a large number of terminals at the same time; large amount of NT released, various EPSPs formed at the same time, additive.

- IPSPs also can summate spatially.

3. Most synaptic neurons receive a mix of stimulatory and inhibitory inputs (depends on NT and NT receptors); EPSPs and IPSPs summate both temporally and spatially with one another to create a net effect.

- even if the net effect of all summation is a depolarization not strong enough to cause trigger zone to fire, still get a facilitation of neuron (closer to threshold).

4. Synaptic potentiation: repeated or continuous use of a synapse considerably enhances ability of presynaptic neuron to excite postsynaptic neuron, synaptic potentiation.

- due to the fact that presynaptic terminals contain a higher level of basal calcium concentration; hence more NT can be released to produce a greater EPSP.

- when enhancement occurs during repeated stimulation, called tetanic potentiation.

5. Presynaptic inhibition/neuromodulation

- presynaptic inhibition occurs when release of an excitatory NT by one neuron is inhibited by activity of another neuron via an axoaxonic synapse.

-neuromodulation occurs when activity of a neurotransmitter at a postsynaptic membrane is influenced by other chemicals -- may influence rate NT degradation, release, synthesis, reuptake.

VI. NTs and their receptors

- NTs transduce electrical signals at presynaptic membrane into chemical signals; latter are transduced back to electrical signals at postsynaptic membrane receptors.

A. Criteria for classification as a NT:

1. Must be present at presynaptic terminal and be discharged when a neuron is appropriately stimulated.

2. Mimics natural NT when applied in vitro.

3. Must be some means of removing it from synaptic junction.

B. Classification of NTs according to chemical structure

1. Acetylcholine: neuromuscular junction NT, excitatory; inhibitory to visceral effectors; CNS/PNS.

2. Biogenic amines

- includes catecholamines: dopamine, norepinephrine, epinephrine; all derivatives of amino acid (AA) tyrosine; also includes indolamines: serotonin (derivative of AA tryptophan), histamine (derivative of AA histidine).
- broadly distributed in brain, role in emotional behavior, biological clock regulation.
- catecholamines associated with motor neurons of ANS.

3. Neuropeptides: strings of AAs

- includes substance P, pain signals; and endorphins and enkephalins, natural opiates involved in reducing pain perception under stressful conditions.

4. Novel messengers: ATP, nitric oxide (NO), carbon monoxide (CO).

C. Classification of NT according to function

1. Excitatory vs. inhibitory: depends on NT, and NT receptor; EPSPs , IPSPs.

2. Mechanism of action

a. Direct: NT opens chemically-gated ion channels.

b. Indirect: NT promotes broader, long term effects.

- acts through a receptor not associated with a chemically-gated ion channel; receptor associated with protein in the membrane (G proteins) that in turn activate other proteins; results in formation of second messengers that lead to further enzyme activation/deactivation; usually associated with phosphorylation/dephosphorylation events.

- effects in cell metabolism, gene transcription.

VII. Basic concepts in neural integration

- up to this point have been concentrating on activities of individual neurons or pairs of neurons; however neurons exist in groups or pools and their activity needs to be integrated.

A. Organization of neurons: neuronal pools

- neurons are organized into neuronal pools, functional groups of neurons that process and integrate incoming information and forward it to other sources.

- simple neuronal pool: consists of one presynaptic fiber that branches profusely as it enters pool, synapses with several different neurons; when incoming fiber is excited postsynaptic neurons in the center of the pool are excited, those in the periphery are facilitated.

B. Organization of neurons: types of circuits

- organization of neurons within a neuronal pool is varied; the organization of synapses in neuronal pool determines functional capability of the pool.

1. Diverging circuits: one incoming fiber triggers responses in ever increasing numbers of neurons, amplifying circuit; can occur along a single pathway or along several pathways.

2. Converging circuits: pool receives input from several presynaptic neurons, circuit as a whole has funneling, concentrating effect.

3. Reverberating or oscillating circuit: impulse travels through chain of neurons each of which has collateral connections with neurons previous in the pathway; positive feedback set up, impulses reverberate.

4. Parallel after-discharge: incoming fiber stimulates several neurons arranged in parallel that stimulate common output cell; impulses reach output cell at different times creating an after discharge, a burst of impulses after original impulse has ended.

C. Reflexes

- example of serial processing; reflexes are rapid, automatic responses to stimuli in which a particular stimulus always causes the same motor response; inherent or learned.