Neurons, Glia & the Action Potential

OBJECTIVES:
1. Classify neurons according to their morphology.
2. Recognize unique structural and functional characteristics of neurons.
3. Understand the process behind generating an action potential.
4. Describe the types of axonal transport and the mechanisms associated with each type.
5. List the various types of neuroglia and describe their function.
6. Describe the processes of nerve cell degeneration & regeneration.

NEURONS:

Neurons respond to stimuli (e.g., environmental changes) by rapidly altering the cell membrane ionic gradient (‘excitable’); the spreading (propagating) of this change along the cell membrane is called a nerve impulse or action potential. The vast majority of neurons in the adult CNS do not divide.

Components: Cell body and Processes

Cell Body:
- Large nucleus (euchromatic), with a prominent nucleolus
- Large amounts of Nissl substance (rER)
- Other typical organelles, such as Golgi body, mitochondria, etc.
- Neuropil – fibrous intercellular network surrounding cells of the CNS consisting of processes of neurons and glial cells

Staining Techniques:
- The large size and complex morphology of neurons, the extreme elongation of axons, and the need to study neuronal interconnections have resulted in an extensive range of techniques being employed in neurohistology.
- Methods which demonstrate nuclei, cell bodies and their cytoplasmic contents include routine stains such as H&E and more specific techniques for demonstrating particular cytoplasmic elements such as the Nissl method for RNA; however, these methods are of limited use in the study of axons and dendrites.
- Heavy metal impregnation techniques with gold and silver are valuable in the study of neuron morphology, including axons and dendrites, and were widely employed by the pioneers of neuroanatomy such as Cajal and Golgi from whom they take their names. Thick sections are often used with such methods as there is then a much greater chance of whole cells being included in the plane of section. Likewise, spread preparations often permit the examination of complete neurons and their cytoplasmic processes. Heavy metals are also deposited in the neuronal micro tubules thus permitting study of the cytoskeleton.
- Immunohistochemistry can also be used to identify neuron-specific proteins, e.g., neurofilament protein, and γγ enolase (neuron-specific enolase).

Processes:

Dendrites:
- Main signal reception and processing sites
- Increase receptor surface area; some have short “dendritic spines”
- Short and divided branches; highly complex in some cells (ie. Purkinje cells)
- Contents similar to cell body

Axons:
- Conducts action potential to presynaptic terminal
- Axolemma (plasma membrane)
- Axoplasm (contents)
- Axon hillock – region of cell body where the axons originate
- Initial segment – just past the hillock; where excitatory and inhibitory stimuli are summed
- Terminal arborization and boutons at the presynaptic terminal
- Axonal transport – anterograde and retrograde

**ACTION POTENTIAL:**
Conductance of the membrane to ions increases during the action potential due to the opening of voltage-gated channels permeable to Na⁺, which allow Na⁺ ions to enter the cell due to its strong electro-chemical gradient. This cycle is regenerative; and is responsible for the rising phase of the action potential. The falling phase of the AP is the result of inactivation of these voltage-gated Na⁺ channels AND the delayed opening of voltage-sensitive K⁺ channels.

**Specialized Na⁺ Channels:**

Na⁺ channels actually exist in one of 3 states: resting (closed), activated (open), and inactivated (blocked). If the depolarization is brief (<0.5ms), then the channel can return to its resting state. If the depolarization is maintained (>0.5ms), then the channels inactivate, and MUST be reset by a strong hyperpolarization before they can be activated again.

**Duration of the Action Potential:**

Two important factors control the duration of the action potential:

1. Inactivation of the Na⁺ channels.
2. Delayed activation of the voltage-gated K⁺ channels.

**Refractory Period:**

- ABSOLUTE - immediately following the AP; NO amount of stimulation will elicit another AP due to the inactivation of the Na⁺ channels.
- RELATIVE - follows the absolute period; increased stimulus strength can elicit a second AP due to the resetting of some of the inactivation gates; the amount of current necessary to produce the second AP decreases as the number of Na⁺ channels reset increases.
**Intracellular Transport:**
In neurons cellular components are continuously synthesized in the soma and moved into the axon and dendrites by a process of **anterograde transport**. At the same time, worn-out materials are returned to the soma by **retrograde transport** for degradation in lysosomes. **Microtubules** are the structures which support neuronal transport.

**Anterograde transport** is of two kinds: **rapid** and **slow**. Included in **rapid transport** (at a speed of 300-400 mm/day) are free elements such as synaptic vesicles, transmitter substances (or their precursor molecules), and mitochondria. Also included are lipid and protein molecules (including receptor proteins) for insertion into the plasma membrane. Included in **slow transport** (at 5-10 mm/day) are the skeletal elements and soluble proteins, including some of those involved in transmitter release at nerve endings.

**Retrograde transport** of worn-out mitochondria, SER, and plasma membrane (including receptors therein) is fairly rapid (150-200 mm/day). In addition to its function in waste disposal, retrograde transport is involved in **target cell recognition**. At synaptic contacts, axons constantly 'nibble' the plasma membrane of target neurons by means of endocytotic uptake of protein-containing **signalling endosomes**. These proteins are known as **neurotrophins**. They are brought to the soma and incorporated into Golgi complexes there. In addition, the uptake of target cell 'marker' molecules is important for cell recognition during development. It may also be necessary for viability later on because adult neurons shrink and may even die if their axons are severed proximal to their first branches.

**Microtubules** are the supporting structures for neuronal transport. Microtubule-binding proteins, in the form of ATPases, propel organelles and molecules along the outer surface of the microtubules. Distinct ATPases are used for anterograde and retrograde work. Retrograde transport of signalling endosomes is performed by the **dynein ATPase**. Failure of dynein performance has been found in motor neuron disease.

**SYNAPSES:**
- **Types:** axosomatic, axodendritic, axoaxonic
- **Formed by:**
  - Presynaptic terminal (active zone)
  - Synaptic cleft (space between neurons)
  - Postsynaptic terminal (receptors)
- **Chemical messengers (neurotransmitter) released**

**Synaptic Transmission (covered Thursday):**
1. Action potential opens voltage-gated Ca\(^{2+}\) channel
2. Calcium entry into presynaptic membrane
3. Neurotransmitter released from vesicles
4. Neurotransmitter diffuses to postsynaptic membrane
5. Neurotransmitter binds to receptors on cell membrane
6. Cell membrane permeability altered
7. Excitation/depolarization or Inhibition/hyperpolarization
**Types of Neurons:**

**Classified by Structure:**
- Multipolar
- Bipolar
- Pseudounipolar
  - Peripheral process
  - Central process

**Classified by Function:**
- Sensory (afferent)
- Motor (efferent)
- Interneuron

**Glia:**

**Peripheral Glia: Schwann Cells & Satellite Cells**

- Schwann cell (neurommocyte) - myelinates axons
  - Myelination process
  - Node of Ranvier
  - Neurilemma (sheath of Schwann)

- Satellite cell – found in ganglia; support ganglion cell bodies

**Neuroglia – found in the CNS; 4 basic types:**

**Oligodendrocyte**
- myelinate CNS axons (may myelinate more than one axon)
- predominate glial cell in white matter;
- small cell with rounded condensed nuclei and unstained cytoplasm

**Astrocyte**
- most numerous glial cell;
- have radiating processes;
- supportive role, necessary for proper development of CNS;
- control ionic environment of neurons, contribute to blood-brain barrier via perivascular feet;
- form scar tissue;
- functions are necessary for neuronal survival

**Microglia**
- Phagocytic; immune system

**Ependymal cells**
- line CNS cavities (ventricles):
• columnar or cuboidal

Lymphatics – evidence is growing for a “glymphatic pathway” for the removal of potentially toxic metabolites from the brain. Dysfunction of this flow has been linked to several brain disorders.

**PERIPHERAL NERVOUS SYSTEM:**

**Cranial and Spinal nerves:**

- **Peripheral nerve**: (bundles of fascicles) Surrounded by epineurium
  - Fascicle: (bundle of nerve fibers) Surrounded by perineurium
  - Nerve fiber: Surrounded by endoneurium
- Blood vessels travel in epineurium and branches penetrate into the perineurium;
- The anastomosis of these branches forms an unbroken intraneural net called the vasa nervosum;
- It allows for the diffusion of nutrients and wastes to & from nerve fibers

**Vasa nervosa** can be compromised by:

- Stretch of nerve tissue (more than 5% of resting length);
  - Flattening/folding of lumen of arterioles or venules
  - Can lead to ischemia which, if prolonged, can cause transient or permanent nerve injury
- Compression (direct);
  - May reduce local blood flow
- Ischemia;
  - Transient nerve dysfunction from short, temporary episodes
  - Severe ischemia, axon damaged and may degenerate
  - If trauma involved, axons are permanently damaged

**Regeneration of Nerve Axons:**

Neuroregeneration in the peripheral nervous system (PNS) occurs to some degree if certain conditions are met. After injury, the proximal end of the nerve swells and experiences some retrograde degeneration, but once the debris is cleared, it begins to sprout axons, and the presence of growth cones can be detected. The proximal axons are able to regrow as long as the cell body is intact, and they have functional contact in the endoneurial channel or tube. Human axon growth rates can reach 1 mm/day in small nerves and 5 mm/day in large nerves. The distal segment experiences Wallerian degeneration within hours of the injury; the axons and myelin degenerate, but the endoneurium remains. In the later stages of regeneration, the remaining endoneurial tube directs axon growth back to the correct targets. During Wallerian degeneration, Schwann cells grow in ordered columns along the endoneurial tube, creating a band of Büngner (boB) that protects and preserves the endoneurial channel, while macrophages and Schwann cells release neurotrophic factors that enhance regrowth. After a nerve is repaired, the regenerating nerve endings must grow all the way to their target. The return of function decreases with increased distance over which a nerve must grow.

**Regeneration of CNS Axons:**

Unlike peripheral nervous system injury, injury to the central nervous system (CNS) is not followed by extensive regeneration. It is limited by the inhibitory influences of the glial and extracellular environment. The non-permissive growth environment is created by the migration of myelin-associated inhibitors, astrocytes, oligodendrocytes, oligodendrocyte precursors, and microglia. The environment within the CNS, especially following trauma, counteracts the repair of myelin and neurons. Growth factors are not expressed or re-expressed; for instance, the extracellular matrix is lacking laminins. Glial scars rapidly form, and the glia actually produce factors that inhibit remyelination and axon repair (NOGO and N1-35). The axons themselves also lose the potential for growth with age, due to a decrease in GAP43 expression.