TOPIC III: NERVOUS SYSTEM I – NEURONS, IMPULSE GENERATION & TRANSMISSION

Learning Outcomes: Upon completion of Topic III (3), you should be able to
   a) Define the resting membrane potential of a typical neuron.
   b) List the major ion channels of neurons and describe them as non-gated or voltage-gated channels, mechanically-gated channels, chemically-gated channels or thermally-gated channels, and identify where they are typically located on neurons.
   c) Explain the role of concentration gradients and membrane permeability to ions in establishing the resting membrane potential.
   d) Describe the physiological basis of the resting membrane potential (RMP) in a neuron, including the ions involved, the relative ion concentrations, and the electrochemical gradient.
   e) Describe the role of the Na^+/K^+-ATPase in maintaining the resting membrane potential.
   f) Describe the characteristics of a graded potential.
   g) Define and describe depolarization, repolarization, hyperpolarization and threshold.
   h) Compare and contrast graded potentials and action potentials, with particular attention to their locations in the neuron and the ions and ion channels involved in each.
   i) Label a voltage versus time diagram of an action potential with the ions involved in each phase, the direction of their movement across the membrane, and the terms depolarization, repolarization and hyperpolarization.
   j) Distinguish between absolute and relative refractory periods and compare the physiological basis of each.
   k) Explain the impact of absolute and relative refractory periods on the activity of a neuron.
   l) Explain the all-or-none principle of an action potential.
   m) Describe the physiological process involved in the propagation of an action potential, including the types and locations of the ion channels involved.
   n) Describe the importance of voltage-gated ion channels in the propagation of an action potential.
   o) Explain how axon diameter and myelination affect propagation velocity.
   p) Describe the classification of neurons based on their propagation velocity.
   q) Explain the role of myelin in saltatory conduction.
   r) Compare action potential propagation in myelinated versus unmyelinated axons.
   s) Define a chemical synapse.
   t) Describe the structures involved in a typical chemical neuronal synapse (e.g. axon terminal, synaptic end bulb, voltage-gated calcium channels, synaptic vesicles of presynaptic cell, synaptic cleft, neurotransmitter receptors on postsynaptic cell).

u) Define excitatory postsynaptic potential (EPSP), and inhibitory postsynaptic potential (IPSP), and interpret graphs showing the voltage-versus-time relationship of an EPSP and IPSP.

v) Explain why a single neurotransmitter can produce different responses at different postsynaptic cells.

w) List the most common neurotransmitters found at excitatory and inhibitory synapses.

x) Explain summation of postsynaptic potentials, and how it affects production of action potentials.

y) Compare and contrast a chemical neuronal synapse and the neuromuscular junction.

A) Neurons Review

- Neurons are excitable (responsive to stimuli)
    - when stimulated (usually on cell body or dendrites) an electrical impulse may be generated and propagated along the axon = nerve impulse

B) Electrical Properties of Cells:

- due to:
    1) ionic concentration differences across the cell membrane (gradients)
        a) important ions:
            - Na^+, K^+, Cl^-, Ca^{++}
            - large, negatively charged organic ions (org^-) – are non-diffusible proteins

Insert MyFigures Topic III #1 Na and K gradients across the cell membrane

        b) $[Na^+]$ & $[K^+]$ due to and maintained by activity of Na^+/K^+- ATPase (pump) in cell membrane
        c) $[Ca^{++}]$ due to various transporters in cell and ER membrane
        d) Cl^- repelled by org^-, so is higher outside the cell than inside
        e) org^- stay inside the cell

    2) permeability of cell membrane to ions
        - determined by ion channels - ions <u>diffuse</u> through them down their conc. gradients
        - ion channel types:
            a) non-gated
                - always open
                - more K^+ than Na^+ in a neuron $\therefore$ cell membrane more permeable to K^+ at rest (no stimulus)
                - *these channels (especially K^+ - more numerous) are important in establishing the resting membrane*

potential (RMP)

b) gated

- <u>NOT</u> involved at rest
- open in response to stimuli: e.g.
    - i) membrane voltage changes = voltage gates
    - ii) chemical e.g. binding of hormone or
        neurotransmitter (nt) = chemical gates
    - iii) temperature = thermal gates
    - iv) mechanical deformation = mechanical gates

C) <u>Neuronal Physiology</u>

1) <u>Resting Membrane Potential (RMP):</u>

- at rest (not simulated) a charge difference (potential difference) exists just across the
    cell membrane = **resting membrane potential**
- $\approx$ -70 mV - i.e. inside of cell = 70 mV more negative than outside
- factors establishing RMP:
    - a) Na^+/K^+-ATPase (Na^+/K^+ pump) - not a channel
        - breaks down 1 ATP and uses energy to pump **3 Na^+ out and 2 K^+
            in** $\rightarrow$ both ions are pumped against their concentration gradients
            $\therefore$ active transport
        - effects:
            - i) <u>maintains</u> concentration gradients of Na^+ and K^+
            - ii) contributes a little (a few mV) to RMP (pumping more
                positive (+ve) ions out than in)
    - b) org^- inside cell e.g. proteins - <u>cannot</u> cross membrane
    - c)) more non-gated K^+ channels than non-gated Na^+ channels (membrane
        more permeable to K^+ than Na^+ at rest $\therefore$ K^+ is <u>major</u> determinant
        of RMP)
        - i) K^+ diffuses out of cell down its concentration gradient $\therefore$ cell loses
            +ve charge (inside becomes more negative (–ve))
        - ii) unlike charges attract and K^+ diffusion slows as inside becomes
            increasingly –ve
        - iii) Na^+ diffusion <u>into cell</u> increases due to increasing attraction to
            –ve cell interior
        - iv) until – 70 mV reached, +ve moving out (K^+) is greater than +ve moving
            in (Na^+) – greater K^+ permeability
        - v) at -70 mV, the amount of +ve (K^+) moving out equals the
            amount of +ve (Na^+) moving in
        - vi) $\therefore$ The net movement of charge (ions) is 0 (equal in both
            directions): RMP = - 70 mV

2) <u>Electrically excitable cells</u>

- ONLY muscle and nerve cells

- capable of producing departures from RMP in response to stimuli (= changes in the external or internal environment)
- when a neuron is stimulated:
  a) gated ion channels open
  b) MP changes, producing a <u>graded potential</u>. If the <u>threshold potential</u> is reached…
  c) triggers an action potential

3) <u>Graded Potentials (GPs)</u>
- stimulus causes a small change in MP, usually on dendrite or cell body (no longer at rest) by opening gated channels (changes membrane permeability) = GP
- possible results:
  a) more +ve than RMP = depolarization
    e.g. -70 mV to -65 mV (closer to zero)
  b) more -ve than RMP = hyperpolarization
    e.g. from -70 mV to -75 mV
- characteristics:
  a) ions move passively (unlike charges attract (+, -)) = current flow, causing depol. or hyperpol. on adjacent membrane

Insert MyFigures Topic III #2 Passive charge movement during graded potential
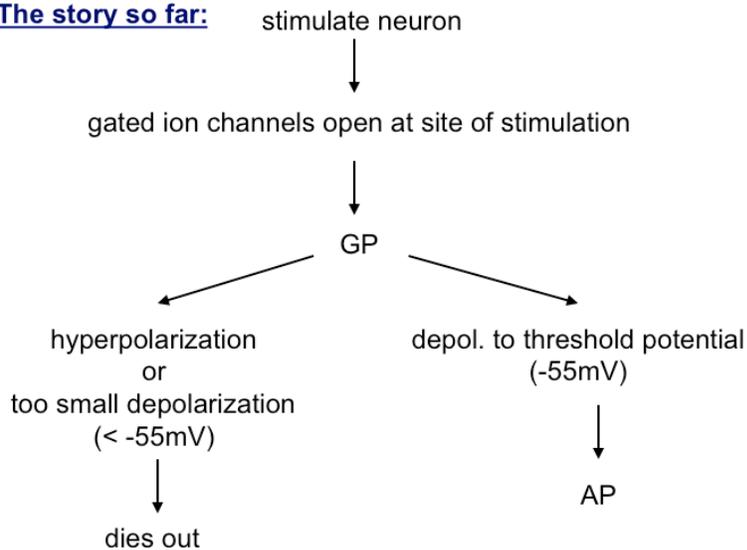 b) GPs are short distance signals – die away quickly (short-lived)
  c) magnitude and distance traveled by potential <u>varies directly with the   strength of the stimulus</u>
    - i.e. larger stimulus → larger graded potential that travels further across the membrane
  d) GPs can summate - 1st GP present when 2nd stim occurs → these add (sum) to create the resulting larger GP

Insert MyFigures Topic III #3 Summation of Graded Potentials

- after a GP:
  - repolarization = return to RMP after depolarization or hyperpolarization

4) GPs → Action Potential (AP)
- GPs are essential in initiating a nerve impulse (AP)
- <u>if</u> the GP causes depol. and <u>if</u> depol. is large enough or multiple GPs sum to be large enough (i.e. there is a critical stimulus) → leads to an action potential
- steps:
  a) critical stimulus (large GP or summation of multiple GPs)
      ↓
  b) GP reaches threshold
      ↓
  c) Action Potential

The story so far: stimulate neuron

↓

gated ion channels open at site of stimulation

↓

GP

↙ ↘

hyperpolarization
or
too small depolarization
(< -55mV)

depol. to threshold potential
(-55mV)

↓

↓

dies out

AP

5) Action Potential (AP):
- a nerve impulse (signal)
- large change in MP that propagates along an <u>axon</u> with <u>no change in intensity</u>
- initiates at trigger zone
> e.g. axon hillock of multipolar neurons and bipolar neurons; just past dendrites of unipolar neurons

Insert MYfigures Topic III #4 Trigger Zones
Insert MyFigures TOPIC III #5 Neuronal Action Potential

- events:
> a) = GP – membrane potential at the trigger zone reaches -55mV (threshold)
> b), c) and d) = action potential

- phases of the AP:
> b) depolarization phase
>> i) voltage-gated Na^+ channels respond to MP change (i.e. GP) and open – greatly increases Na^+ permeability
>> ii) as gates open more Na^+ diffuses in (further increasing MP) → causes even more Na^+ voltage gates to open (a +ve feedback mechanism)
>> iii) Na^+ diffuses in, causing depolarization to +30 mV (inside of membrane becomes +ve)

> c) repolarization phase
>> i) Na^+ channels close, become inactivated (decreased Na^+ permeability) → Na^+ movement returns to resting levels
>> ii) voltage-gated K^+ channels are open (increased permeability) ∴ K^+ diffuses out (+ve charges (K^+) move out – decreases MP)

> d) after-hyperpolarization phase (below RMP)
>> i) K^+ channels are slow to close

ii) Na$^+$ channels are reactivated (but closed) – can respond to stimuli
- once K$^+$ channels close → MP returns to RMP (e)
- Note: Na$^+$/K$^+$-ATPase always working to maintain gradients
- takes 10,000s of APs to cause a measurable change in [ion] in the cell

6) Refractory Periods of an ap:
    a) Absolute Refractory Period (prevents AP summation)
        - **NO** AP can be generated, regardless of stimulus size
        - results from either:
            i) all voltage-gated Na$^+$ channels are open (there are no more that can
                open) (region b) or
            ii) Na$^+$ channels are inactivated (cannot open until MP reaches RMP,
                end of region c)
    b) Relative Refractory Period (region d)
        - period when an ap can be generated but only by a greater than normal
            stimulus
        - Na$^+$ channels are reactivated when MP passes RMP ∴ they are closed but can
            be reopened if threshold reached
        - K$^+$ channels are open & membrane is hyperpolarized
        - further to go to get to threshold ∴ need larger stimulus

Insert MyFigures Topic III #6 Refractory Periods

7) All-or-None Principle of Aps:
    - **ALL:** if threshold reached, AP is produced - same every time (same max depol. etc)
    - **NONE:** below threshold → no AP

8) Action Potential Propagation:
    - to act as a communication mechanism, an AP must be propagated along the axon's
        entire length
    - depolarization during AP (Na$^+$ in) → +ve ions move toward more –ve charge on
        adjacent membrane → adjacent membrane depolarizes to reach threshold
        (voltage-gated Na$^+$ channels open) → get AP on adjacent membrane

Insert MyFigures #7 & 8: Action potential propagation

    - movement of charge occurs in both directions but APs move in 1 direction because
        preceding membrane is in refractory period
    - ∴ get sequence of APs along membrane, each one the same
    - AP propagates along axon's entire length to the axon terminal

    - rate of propagation depends on:
        a) fibre (axon) diameter
        - larger diam. = faster propagation because less resistance to ion flow (= current)
        b) myelination
            i) unmyelinated fibres - APs all along the fibre (Na$^+$ channels are adjacent

to each other) = <u>continuous conduction</u> = slower

ii) myelinated fibres - AP occurs at nodes of Ranvier (ion channels only present here) = <u>saltatory (leaping) conduction</u> → fast

- Fibre types range from:
 a) Type A
  - large diameter
  - myelinated
  - propagate APs at ~ 130 m/sec
  - most sensory neurons & motor neurons to skeletal muscles
to
 b) Type C
  - small diameter
  - unmyelinated
  - propagate APs at ~ 0.5 m/sec
  - found in Autonomic NS (ANS) ANS and some pain fibres

- <u>Comparison of GP and AP:</u>

Characteristic	Graded Potential (GP)	Action Potential (AP)
1. Location	dendrites / cell body	axon hillock / axon
2. Strength of MP	variable	all-or-none (+30mV)
3. Summation?	YES	NO
4. Repolarization	current dies away	Na+ gates close; K+ gates open
5. Type of Gates	chemical, mechanical, thermal (i.e. NOT voltage)	only voltage
6. Distance Travelled	short (1-2 mm) & dies away	produced anew on axon & propagates over long distances
7. Refractory Period	Absent	Present

9) <u>Synaptic Transmission (ST) at Neuronal Junction</u>
 - NS depends on chains of neurons connected by junctions called **synapses**
 - presynaptic neuron to postsynaptic neuron transmission
 - Steps:

a) AP arrives at axon terminal (synaptic end bulb)

b) Ca^{++} voltage gates open (due to AP) and Ca^{++} enters (higher $[Ca^{++}]$ outside)

c) rise in Ca^{++} triggers exocytosis of vesicles containing neurotransmitter (nt)

d) nt diffuses across synaptic cleft, binds to specific receptors on postsynaptic
  membrane
   - receptors are (or act on) chemically gated ion channels → open in
    response to nt

e) gated ion channels open – allowing movement of ions into (or out of)
  postsynaptic membrane
    - creates a graded potential (GP) called a **postsynaptic potential
    (PSP)**

10) <u>Postsynaptic Potentials (PSPs)</u>
 - PSPs may be:
  a) Excitatory PSPs (EPSPs) = GP → depolarization
   - due to opening of Na^+ (or Ca^{++}) channels, or closing of K^+ channels
   - nt is often acetylcholine (ACh) or glutamate
  b) Inhibitory PSPs (IPSPs) = GP → hyperpolarization
   - due to opening of K^+ or Cl^- channels
    - inhibits neuron from reaching threshold
   - nt is often glycine or GABA
 - PSPs occur on cell body or dendrites
  - many neurons can synapse onto one → if many EPSPs → summation → large
   area of membrane depolarized → spreads to axon hillock → if (sum of)
   EPSPs strong enough, get AP
  - <u>However</u>, some may be IPSPs → the sum of all EPSPs & IPSPs determines if AP
   will occur at axon hillock

11) <u>Synaptic Transmission (ST) at the Neuromuscular Junction</u>:
 - junction between axon terminal & an individual muscle fibre
 - Steps = similar to those for neuronal junction with the following modifications:
  a) neurotransmitter (nt) released = always ACh
  b) chemical gates on muscle motor end plate (= sarcolemma of muscle fibre)
   open and Na^+ enters
    - causes GP (= end plate potential (EPP)) on sarcolemma
  c) EPP triggers AP on sarcolemma
   - **lots** of ACh released in a) ∴ always get an AP from an EPP

Insert MyFigures Topic III # 9 Excitatory Pathway & # 10 Inhibitory Pathway