Electrical & Chemical Signaling

Part 2

Lecture Outline

- Graded Potentials
- Other electrical signaling
  - Gap junctions
- The Process of Synaptic Transmission
  - Events releasing Neurotransmitters
  - Neurotransmitters
- Modulation & Stopping Transmission

Graded Potentials

- **Characteristics**
  - NOT all-or-none
  - Graded
    - May increase or decrease in size
  - Decremental
  - Summable / cancelable
  - Local
  - May be excitatory or inhibitory

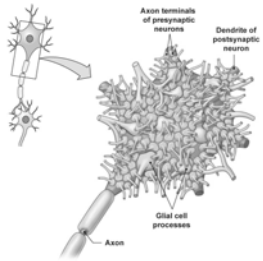
Graded Potentials

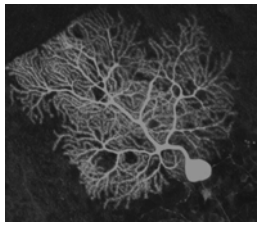
- **Function**
  - Integration
    - Decision making a the cellular level (neurons)
    - Called **post-synaptic potentials**
  - Transduction
    - Conversion of stimulus into action potential
    - Called **receptor potentials**
      - Stimulus modality may be:
        - Chemical
        - Mechanical
        - Light (photons)
        - Heat/cold
        - Pain
      - Receptors may be:
        - Chemoreceptors
        - Mechanoreceptors
        - photoreceptors\
        - Thermoreceptors
        - Nociceptors

Graded Potentials & Integration

- Location
  - Neuronal cell bodies & dendrites
- Creation of post-synaptic potentials
  - Binding of neurotransmitter to neurotransmitter receptor (chemically gated channel)
  - Chemically gated channel opens allowing
    - Na^+ or Ca^{2+} influx creates excitatory post-synaptic potentials (EPSPs)

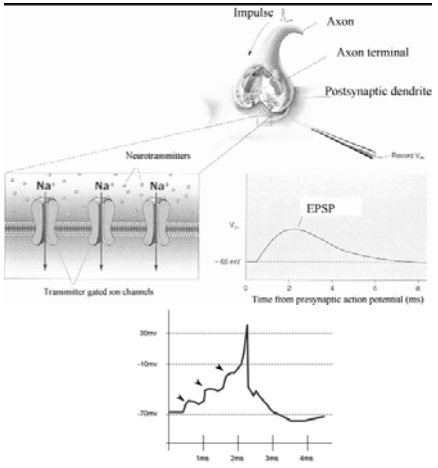
      OR
    - K^+ efflux or Cl^- influx creates inhibitory post-synaptic potentials (IPSPs)

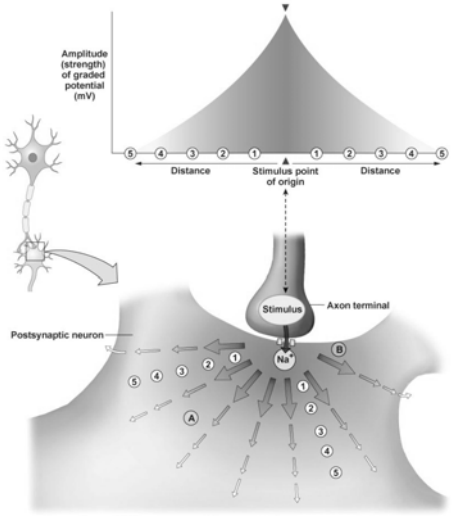




Graded Potentials & Integration

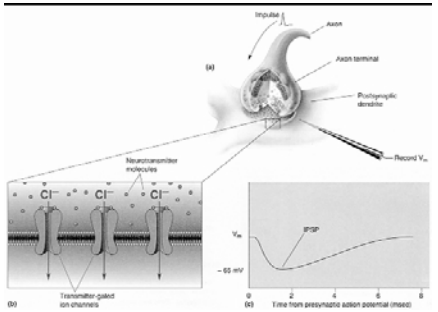
- EPSPs
  - Cause localized depolarization events
    - Due to influx of Na^+ or Ca^{2+} ions
  - individually, unless they occur very close to the axon hillock, nothing will happen
  - May be summed





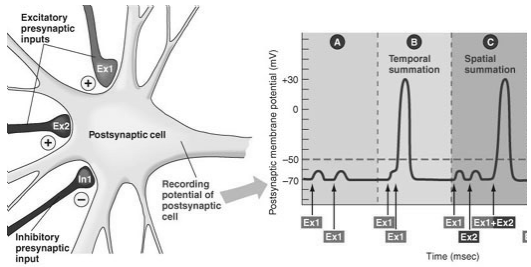
Graded Potentials & Integration

- IPSPs
  - Cause localized hyperpolarization events
    - Due to influx of Cl^- or efflux of K^+ ions
  - May be summed to create greater hyperpolarization



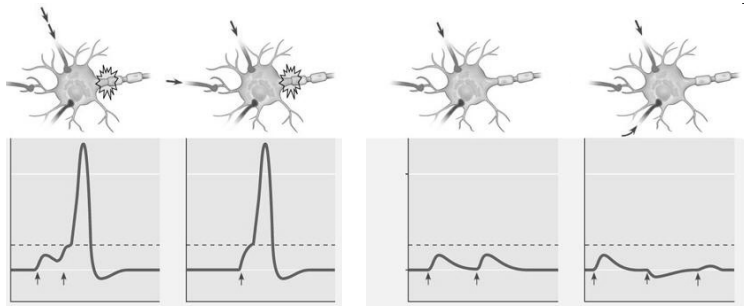
Graded Potentials & Integration

- Summation may be
  - Temporal
  - Spatial



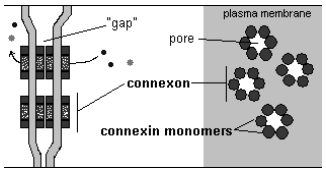
Post Synaptic Potentials

- May be EPSPs or IPSPs
- The sum of all post-snaptic events is called the Grand Post Synaptic Potential (GPSP)
  - If GPSP allows axon hillock to reach threshold an action potential occurs
  - If GPSP is not great enough to reach threshold, or moves axon hillock membrane potential away from threshold – no action potential



Gap Junction (Electrical Synapse)

- Direct flow between cells
  - Ions
  - cAMP
- Found to some extent in most cells of body
  - Exceptions: freely mobile cells (RBC's, sperm…)



- Connexons (formed by connexins) create a connection between cell membranes of adjacent cells
  - Rate of flow depends on density of gap junctions
- Useful
  - For creating a unified response in
    - Cardiac tissue
    - Smooth muscle
  - For modulating neuron activity in retina
  - Communication between glial cells (in CNS)

Chemical Synapses

- Transfers the action potential to the target cell/membrane via neurocrines or neurotransmitters
- Neuron secreting the chemical signals are the presynaptic neurons
- Cells receiving (with the receptors on the postsynaptic membrane) the chemicals are the postsynaptic cell
- The small space that the neurotransmitters diffuse is the synaptic cleft

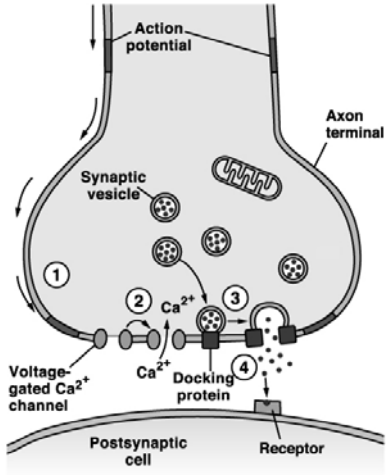
http://outreach.mcb.harvard.edu/animations/synaptic.swf

Chemical Synapses

- Physiologically, it is
  - The process of converting the action potential (*electrical*) at the synaptic bulb to a *mechanical* event that causes the release of neurotransmitter (*chemical*) that then creates a membrane potential (*electrical*) event on the post synaptic membrane
- Things to consider
  - Process
  - Influences on the process

The Process of Synaptic Transmission

1. action potential depolarizes the axon terminal
2. Voltage gated Ca^{2+} channels are activated by the depolarization, allowing a Ca^{2+} influx into the synaptic bulb
3. Ca^{2+} triggers secondary messenger system that causes
   a. Motor proteins to attach to vesicles and move along cytoskeletal "tracks" to the docking proteins in the presynaptic membrane
   b. Vesicle binds and releases neurotransmitters into synaptic cleft
4. Neurotransmitter binds to receptors on the postsynaptic membrane
   a. Initiating a response (EPSP or IPSP)



The Process of Synaptic Transmission

- The neurocrines (neurotransmitters and neuromodulators)
- Classes:
  - Acetylcholine
  - Amines
  - Amino acids
  - Peptides
  - Purines
  - Gases
  - Lipids

The Neurotransmitters

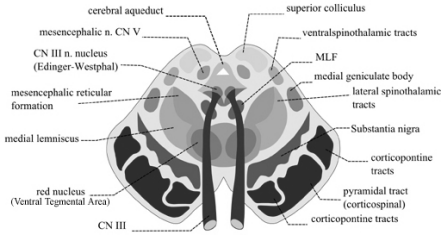
- Acetylcholine
  - Derived from choline & acetyl CoA
  - binds to cholinergic class of receptor which may be
    - Nicotinic
      - Ion channel receptor (Na^+/K^+)
      - Skeletal muscle, CNS and ANS
      - Agonist = nicotine
      - Antagonist = curare & α-bungarotoxin
    - Muscarinic
      - GPCR
      - Mainly in smooth muscle and cardiac muscle
      - Receptors also in CNS and glands (both exo & endocrine)
      - Agonist = muscarine, Antagonist = atropine
  - Used widely
    - By all preganglionic neurons in autonomic nervous system (ANS)
    - By all postganglionic neurons of the parasympathetic system of the ANS

Bungarus multicinctus

The Neurotransmitters

- **Amines**
  - Derived from single amino acid tyrosine
  - Function as neurohormones:
    1. Dopamine produced in the brain (substantia nigra, ventral tegmental area [VTA] & hypothalamus (where it inhibits release of prolactin)
       - Binds to dopamine receptors (at least 5)
       - GPCR
       - Targets the CNS
         - » In the substania nigra it is involved in reward, cognition as well as a major player in muscle control (death of dopamine producing neurons in the substantia nigra is responsible for Parkinson's Disease)
         - » In the VTA it is implcated in reward, cognition, motivation & addiction

however given orally, dopamine will act as a sympathomimetic, increasing heart rate and blood pressure, but will not affect CNS as it does not cross the BBB



The Neurotransmitters

Amines, cont…

2. Norepinephrine
3. Epinephrine

} Produced in the adrenal medulla

- Bind to adrenergic receptors (α,β)
- GPCR
- Affects smooth & cardiac muscle tissue as well as exo and endocrine glands

4. Seratonin – from tryptophan (aa)
   - Binds to serotonergic recetors (at least 20 different ones so far)
   - Activates ICR that regulate Na^+/K^+
     - LSD is an antagonist
   - In CNS Functions in various functions, including the regulation of mood, appetite, sleep, muscle contraction, and some cognitive functions including memory and learning
   - Most of serotonin is produced by the enteroendocrine system (gut) in regulation of digestive function
5. Histamine – from histidine (aa)
   - Binds to histamine receptors (GPCRs) in the CNS, PNS and system wide
     - In CNS modulate sleep
   - 4 receptors to date (H_1-H_4)
   - Antagonists in CNS will induce sleepiness (antihistamines)

The Neurotransmitters

- Amino Acids
  Four major amino acids functioning as NT's in the CNS
  1. Glutamate
     - Most abundant excitatory NT in the CNS
     - Involved in long term potentiation or synaptic plasticity
     - Binds to Glutaminergic ionotropic (iGluR) class of receptors
       - AMPA (α-amino-3-hydroxy-5methyl-4-isoxazole proprionic acid) which is a ICR that controls Na^+ and K^+
       - NMDA (N-methyl-D-aspartate) which is an ICR that controls Na^+, K^+, Ca^{2+} movement)
     - Long Term Potentiation (LTP)
       - Binding to NMDA receptors causes the cell to increase the density of AMPA receptors
  2. Aspartate binds to NMDA receptors, but can also be an excitotoxin!

The Neurotransmitters

- Amino Acids
  3. GABA
     - Main inhibitory NT of the brain
     - Binds to GABA receptors which are ICRs, that control Cl^-
       - antagonist = picrotoxin (Indian Berry)
         - » It is non-competitive
         - » Strong convulsive effects
       - Potentiators = alcohol, benzodiazapene & and barbituates (also block the AMPA receptors for glutamate!)

  4. Glycine
     - Main inhibitory NT of the spinal cord, brain stem and retina
     - A co-agonist with glutamate on NMDA receptors (in an excitatory role)
     - An antagonist is strychnine – causing convulsions, and possibly death due to asphyxiation

Benzodiazapenes - Cause we all need to relax a little more!

- Over 80 different drugs that utilize it with most being antianxiety, anticonvulsive, hypnotic in effect!

1,4-Benzodiazepines	Bromazepam • Camazepam • Chlordiazepoxide • Cinolazepam • Clonazepam • Clorazepate • Cyprazepam • Delorazepam • Diazepam • Doxefazepam • Elfazepam • Ethyl carfluzepate • Ethyl dirazepate • Ethyl loflazepate •Fletazepam • Fludiazepam • Flunitrazepam • Flurazepam • Flutemazepam • Flutoprazepam • Fosazepam • Gidazepam • Halazepam • Iclazepam • Lopirazepam • Lorazepam • Lormetazepam • Meclonazepam • Medazepam •Menitrazepam • Metaclazepam • Nimetazepam • Nitrazepam • Nitrazepate • Nordazepam • Oxazepam • Phenazepam • Pinazepam • Pivoxazepam • Prazepam • Proflazepam • Quazepam • QH-II-66 • Reclazepam •Sulazepam • Temazepam • Tetrazepam • Utidazepam
1,5-Benzodiazepines	Arfendazam • Clobazam • Lofendazam • Triflubazam
2,3-Benzodiazepines	Girisopam • GYKI-52466 • GYKI-52895 • Nerisopam • Tofisopam
Triazolobenzodiazepines	Adinazolam • Alprazolam • Estazolam • Triazolam
Imidazobenzodiazepines	Bretazenil • Climazolam • Flumazenil • Imidazenil • L-655,708 • Loprazolam • Midazolam • PWZ-029 • Ro15-4513 • Ro48-6791 • Sarmazenil • SH-053-R-CH3-2'F
Oxazolobenzodiazepines	Cloxazolam • Flutazolam • Haloxazolam • Mexazolam • Oxazolam
Thienodiazepines	Brotizolam • Ciclotizolam • Clotiazepam • Etizolam
Pyridodiazepines	Zapizolam • Lopirazepam
Pyrazolodiazepines	Ripazepam • Zolazepam • Zomebazam
Pyrrolodiazepines	Premazepam
Benzodiazepine Prodrugs	Avizafone • Rilmazafone
Others	Bentazepam • Devazepide • Ketazolam • Razobazam • Tifluadom

The Neurotransmitters

- Peptides
  - Usually two amino acids such as
  - May function as NT's as well as neurohormones
    - CCK (cholecystokinin)
    - Vasopressin
    - Atrial Natriuretic Peptide (ANP)
  - May also be involved with neuromodulation in pain/analgesic pathways
    - Substance P - pain
    - Enkephalins } Pain remediation – runner's high
    - Endorphins }

The Neurotransmitters

- Purines (adenosine, AMP, ATP)
  - All bind to purinergic receptors
  - Adenosine
    - Involved in sleep
      - Levels of adenosine rise continuously after awaking, eventually shutting you down
    - Bind to adenosine receptors which are GPCRs and modulate the activity of adenylyl cyclase
      - 2 adenosine receptors inhibit adenylyl cyclase activity
      - 2 adenosine receptors increase adenylyl cyclase activity
  - AMP & ATP
    - Bind to receptor (GPCRs) and modulate intracellular levels of Ca^{2+} and cAMP
    - As adenosine depending on receptor, may have + or - effect

The Neurotransmitters

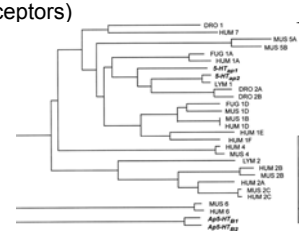
- Gases
  - NO, CO and H_2S
  - There is relatively little known about these as neurotransmitters
  - NO was named "molecule of the year" in 1992 as realization regarding it's very widespread effects in immunology, physiology, & neuroscience
  - What is known about NO is
    - It was found that NO acts through the stimulation of guanylate cyclase with subsequent formation of cyclic GMP.
    - Cyclic GMP activates protein kinase G
    - which caused phosphorylation of myosin light chain phosphatase which then inactivates myosin light-chain kinase
    - causing smooth muscle relaxation

The Neurotransmitters

- Lipids
  - Eiconsoid neurocrines that bind to cannabinoid receptors (so called because….)
    - There are two receptors
      - CB_1 which are in the brain & are linked to the psychoactive nature of marijuana
      - CB_2 which are mostly peripheral and associated with the immune system
        - » These may mediate inflammation and pain
        - » CB_2 Don't cause any psychoactive issues

The Process of Synaptic Transmission

- Receptor types
  - Determine effect on postsynaptic membrane
  - There are multiple subtypes (isoforms) of receptors for each neurotransmitter (except gases)
  - Two basic types of receptors
    - Ionotropic (ion channel-receptors)
    - Metabotropic (G-protein coupled receptors)
  - Why?
    - Allows for one NT to have multiple effects
      - Handy when you have only one autonomic nervous system!
      - Serotonin has over 20 different receptor types identified!

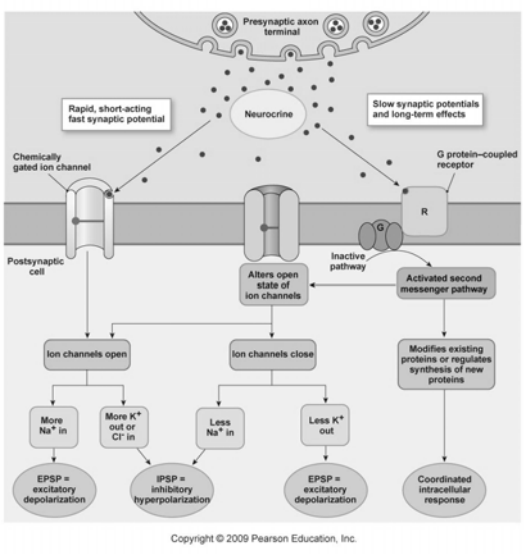


The Process of Synaptic Transmission

- Physiology of the Cholinergic & Adrenergic receptors
  - Cholinergic may be nicotinic or muscarinic
    - Both bind acetylcholine
    - Binding events differ vastly!
      - Nicotinic receptors are ICR (Na^+ / K^+) and are found mainly in skeletal muscle, Autonomic Division (aka ANS) of the PNS and in the CNS
        - » Excitatory as depolarization occurs upon binding
      - Cholinergic receptors are GPCR and are found in the CNS and ANS
        - » Reaction varies with receptor subtype and effect secondary messenger pathways

The Process of Synaptic Transmission

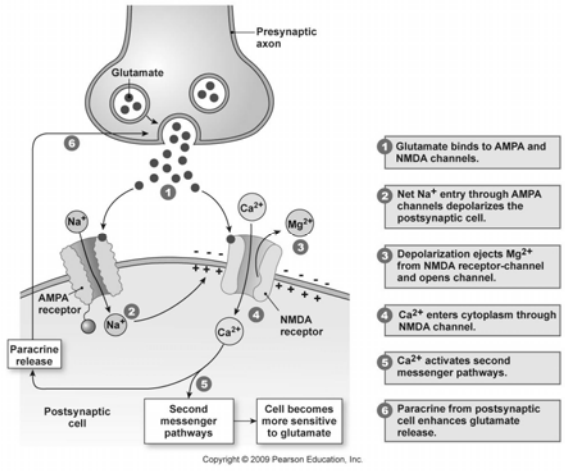
- The glutaminergic receptors
  - AMPA
    - ICR that cause depolarization (Na^+ influx =excitatory) upon binding of glutamate
  - NMDA
    - ICR channels that are trivalent cation channels
      - Na^+, K^+ and Ca^{2+} can pass through BUT
        - » Co activation by glutamate and a depolarizing event are required
        - » Glutamate partially opens channel
        - » Depolarization causes Mg^{2+} to be removed, opening the channel completely
        - » Aspartate can also bind to the NMDA receptors



The Process of Synaptic Transmission

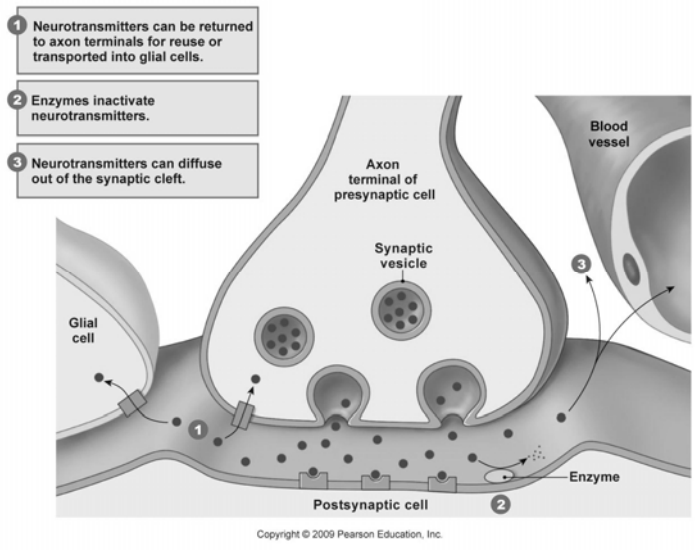
- Rate of Responses
  - With ICRs, Ion flow is typically fast
    - Ligand binds, channel opens
    - Typical EPSPs and IPSPs
  - With GPCRs
    - The intracellular change is slower
      - If the change is an electrical change, it is a slow synaptic potential
      - can be used for long term changes in potentiation

Long Term Potentiation



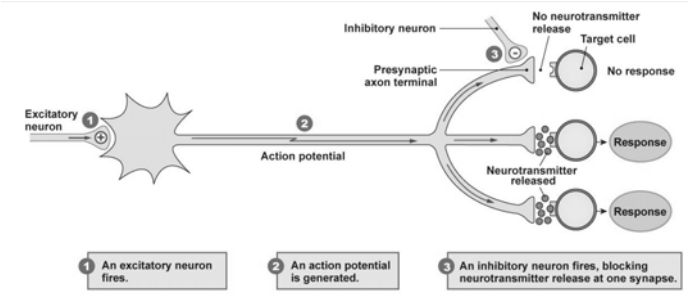
Stopping the Process of Synaptic Transmission

- Forever is bad when it comes to NT binding!
  - Thankfully, binding follows rules
    - Reversible
    - Equilibrium
      - Meaning if the presynaptic neuron “re-uptakes” it’s NT, the NT bound to the receptor has to leave to maintain equilibrium
  - Removal can be
    - Diffusion
    - Enzymatic activity in synaptic cleft
  - Removal of receptors will limit the effect as well



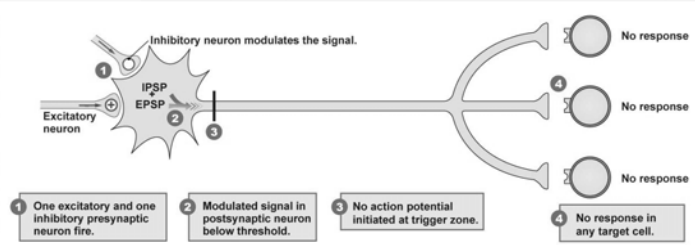
Presynaptic vs Postsynaptic Modulation of Activity

- Presynaptic modulation take place at the axon terminal near the synaptic bulb
  - Allows for local or specific control of that synaptic bulb and associated post-synaptic receptors
    - May be inhibitory or excitatory



Presynaptic vs Postsynaptic Modulation of Activity

- Post-synaptic modulation takes place at the cell and controls the axon hillock and is therefore
  - Less specific
    - If excitatory all synapses are effected
    - If inhibitory all synapses are effected



Next Time

- Nervous System