Physiology
Unit 2

NEUROTRANSMITTERS and RECEPTORS
Axonal Transport

- Movement of organelles, other materials from one part of the cell to another
- Microtubule “rails” that run the length of an axon
- Motor proteins
  - Kinesins
    - Antegrade movement
  - Dyniensi
    - Retrograde movement
Release of Neurotransmitter

- AP arrives at the terminal end bulb of pre-synaptic neuron
- Voltage-gated Ca\(^{2+}\) channels open
- Ca\(^{2+}\) influx activates calmodulin
- Activated calmodulin activates a protein kinase
- Series of events lead to a conformational change in SNARE proteins
- SNARE proteins dock vesicles, vesicles fuse with the pre-synaptic membrane and release neurotransmitter
- NT binds to receptors on postsynaptic membrane
Neurotransmitter Release

(a) Action potential reaches terminal

1. Action potential reaches terminal
2. Voltage-gated Ca\(^{2+}\) channels open
3. Calcium enters axon terminal
4. Neurotransmitter binds to postsynaptic receptors
5. Neurotransmitter release and diffusion
6. Neurotransmitter removed from synaptic cleft

(b) Synaptotagmin

1. Synaptotagmin
2. +Ca\(^{2+}\)
3. SNAREs
Activation of the Postsynaptic Cell

(a) Excitatory synapse

(b) Inhibitory synapse
Neurotransmitter Clearance

- NT binding to the receptor is a transient event
- Unbound neurotransmitter in the synaptic cleft is removed from the synaptic cleft
  1. Reuptake
     - Secondary active transport back into the presynaptic terminal
  2. Active transport into astrocytes
  3. Diffuse away from the receptor type
  4. Inactivated by an enzyme
     - Some of the inactive products are transported back into the presynaptic neuron to be recycled
What is a Neurotransmitter?

1. The chemical exists in the presynaptic terminal
2. The enzymes for synthesing the transmitter exist in the presynaptic terminals or, in the case of peptides, in the cell body
3. The transmitter is released when nerve impulses reach the terminals, and in sufficient quantities to produce normal changes in postsynaptic potentials
4. Specific receptors exist on the postsynaptic membrane for the released transmitter
5. Blocking release of the transmitter prevents presynaptic nerve impulses from altering the activity of the postsynaptic cell
Neurotransmitters and Neuromodulators

• **Neurotransmitter**
  – A chemical messenger released by a neuron
  – Elicits an EPSP or IPSP

• **Neuromodulators**
  – Elicit complex responses
  – Sometimes synthesized and co-released with the NT
  – Can also be hormones, paracrine agents and cytokines
  – Modify the cell’s response
Receptors

• A membrane protein that has a binding site for a NT

• 2 kinds of receptors
  – Ionotopic
    • The receptor is the ion channel
  – Metabotropic
    • Indirectly regulates ion channel activity by activating a G-protein 2\textsuperscript{nd} messenger system
Neurotransmitters

- Quaternary Amine
  - Acetylcholine (ACh)

- Monoamines
  - Catecholamines
    - Dopamine (DA)
    - Norepinephrine (NE)
    - Epinephrine (Epi)
  - Serotonin
  - Histamine

- Amino acids
  - GABA
    - Inhibitory
  - Glutamate
    - Excitatory
Peripheral Nervous System Control

SOMATIC NS
- CNS
- ACh
- N-AChR
- Skeletal muscles

AUTONOMIC NS
- Parasympathetic division
  - CNS
  - Ganglion
  - N-AChR
  - ACh
  - Smooth or cardiac muscles, glands, or GI neurons.

- Sympathetic division
  - CNS
  - Ganglion
  - N-AChR
  - ACh
  - Adrenergic receptors
  - Adrenal medulla
  - Epi
Acetylcholine

- Neurotransmitter of the CNS and PNS
- Cholinergic neurons release ACh
- Synthesized from choline and acetyl-CoA
- Degraded by acetylcholinesterase (AChE)
  - Located on the pre and post-synaptic membranes
  - Degrades unbound ACh
- 2 types of receptors
  - Nicotinic (N-AChr)
  - Muscarinic (M-AChr)
Actions of Acetylcholine

• Somatic Nervous System
  – Somatic motor neurons
  – Stimulates contraction of skeletal muscle (N)

• Parasympathetic Nervous System
  – Rest and digest
  – Released from pre and postganglionic neurons
  – Vasodilation (M)

• Sympathetic Nervous System
  – Fight or flight
  – Released from preganglionic neurons
  – Sweat gland secretion (M)
  – Widespread in the brain (cognitive function, behavior, memory, emotion, arousal state (N,M))
Nicotinic ACh Receptors

• N-ACh receptors
  – Ionotropic receptor
  – Binding of ACh opens Na⁺ channel
  – results in an EPSP

• Locations
  – Autonomic ganglia
  – Skeletal muscle fibers
Muscarinic ACh Receptors

- **M-ACh receptors**
  - Metabotropic receptor
  - G-protein opens $K^+$ channel
  - Results in an IPSP

- **Locations**
  - Smooth muscle
  - Cardiac muscle
  - Glands
Catecholamine Biosynthesis Pathway

Tyrosine → L-Dopa → Dopamine → Norepinephrine → Epinephrine
Catecholamines

- Adrenergic neurons release NE (Epi ***)
- Nerve cell bodies in brainstem and hypothalamus
  - Heavily branched axons
  - Go to all parts of the brain and spinal cord
- All metabotropic receptors
- Bind to NE and Epi
  - Alpha adrenergic receptors
    - (a1) = postsynaptically stimulates or inhibits K⁺ channels
    - (a2) = presynaptically inhibit release of NE
  - Beta adrenergic receptors
    - cAMP as second messenger
Actions of Catecholamines

• Involved in:
  – States of consciousness
  – Mood
  – Motivation
  – Directional attention (focusing)
  – Movement
  – Blood pressure regulation
  – Hormone release
Adrenergic Receptors

Alpha Adrenergic Receptors
- $\alpha_1$ Receptors
- $\alpha_2$ Receptors
- Smooth muscle contraction
- Inhibition of transmitter release
- Heart muscle contraction, smooth muscle relaxation, glycogenolysis

Beta Adrenergic Receptors
- $\beta_1$ Receptors
- $\beta_2$ Receptors
- Inhibitory subunit Protein kinase (inactive)
- Protein kinase (active)
- Phosphorylation of proteins
- Activation of specific enzymes
- Inactivation of specific enzymes

Adrenaline, Noradrenaline

Adenylyl cyclase
- cAMP
- cAMP + PPi
- ATP

Hormone
- Receptor protein
- Plasma membrane

G-proteins
Norepinephrine

• Found as NT in both PNS and CNS
• NT released by postganglionic neurons of sympathetic nervous system
• Effectors
  – Smooth muscle
  – Cardiac muscle
  – Glands
Dopamine

• Found as NT only in the CNS
• Dopaminergic neurons release DA
• Involved in:
  – Behavior and Cognition
  – Motor Activity
  – Motivation and Reward
  – Sleep
  – Mood
  – Attention
  – Learning

• Parkinson’s Disease
  – Death of dopaminergic neurons in the midbrain
  – Basal ganglia located in the midbrain
Actions of Dopamine

• Mesolimbic dopamine system
  – Neurons originate in midbrain, send axons to limbic system
  – Involved in modulating *reward behavior* such as
    • Food
    • Sex
    • Drugs

• Addictive drugs
  – Cocaine, nicotine, amphetamines
  – Inhibit re-uptake of dopamine

• Also involved in
  – Laughter
  – Pleasure
  – Addiction
  – Aggregation
  – Fear
Dopamine Receptor

- Dopamine receptors are g-protein coupled receptors that (+) or (-) the production of cAMP
- Can be inhibitory or excitatory
Degradation of Catecholamines

1. Presynaptic
   - Reuptake
     - via autoreceptors
   - Degradation by an enzyme
   - MAO (monoamine oxidase)

2. Postsynaptic or Cleft
   - Degradation by an enzyme
   - COMT (catechol-o-methyl transferase)
Serotonin

• Tryptophan precursor (essential a.a.)
• Neuromodulator
  – Modulate the release of glutamate, GABA, DA, NE, Epi, ACh
  – Modulate the release of oxytocin, prolactin, ADH, cortisol, corticotropin, substance P
• Receptors are mostly g-protein coupled receptors that (+) or (-) cAMP
• Degraded in presynaptic neuron by oxidative deamination
Actions of Serotonin

• Under circadian control
  – Secreted by cells of the stomach, CNS and platelets
  – Activity of serotonergic neurons is
    • lowest or absent during sleep
    • highest during states of alert wakefulness

• Involved in regulating: digestion, aggression, appetite, addiction, blood pressure, impulsiveness, memory, nausea, erection, orgasm, sleep, sociability, thermoregulation

• May control mood
  – Low levels associated with depression
  – SSRI’s = medications which inhibit the reuptake of serotonin (Prozac, Paxil, Zoloft)
Histamine

• Histidine Precursor (essential a.a.)
• Actions
  – Triggers the inflammatory response *(immune response)*
  – Regulates digestive physiology *(smooth muscle contraction)*
  – Motion sickness
  – Regulate sleep
  – Appetite suppression
• Histamine receptors are g-protein coupled receptors that open Cl⁻ channels
• Inhibitory
• Degraded by enzymes
GABA
Gamma-aminobutyric acid

• Glutamate precursor
• GABAergic neurons release GABA
• GABA neurons are small interneurons
• Neurons of the
  – Basal ganglia
  – Hypothalamus
  – Central gray matter
  – Hippocampus
Actions of GABA

• Involved in muscle tone
• Dampens skeletal muscle contraction
• GABA receptors also have binding sites for other chemicals
  – Steroids, barbituates, benzodiazepines (Xanax, Valium)
  – Enhances the effect of GABA
    • Sedatives
    • Muscle relaxers
    • Anti-anxiety medications
GABA Receptor

• Ionotropic receptors
  – Cl⁻ channels
  – Major inhibitory NT produced in CNS

• Degredation
  – Active transport into astrocytes
Glutamate

- **Glutamate**
  - Most common excitatory NT in CNS
  - 90% of synapses
  - NMDA receptors
    - Ionotropic receptors
      - Non-selective to cations
      - Activate Ca\(^{2+}\) 2\(^{nd}\) messenger system
  - AMPA receptors
    - Receptor is a Na\(^{+}\) channel
    - Fast, common
  - Neurons of the cortex
    - Hypocampus
    - Basal ganglia
    - Amygdala
  - Long-term potentiation
    - Involved in learning and memory
  - NT clearance
    1. Reuptake via secondary active transport with Na\(^{+}\)/K\(^{+}\)/ATPase pump
    2. Active transport into astrocytes
Neuropeptides

- 2 or more amino acids bound together
- Neuromodulators
  - Released in small amounts
  - Co-released with other NTs
- Mediate sensory (pain) and emotional responses
- Examples
  - CCK = satiety
  - Substance P
  - Endogenous opioids
    - Beta-endorphins
    - Oxytocin
    - Receptors bind opiates (morphine, codeine)
Nitric Oxide (NO)

• Precursor: L-arginine

• Roles
  – Relaxation of smooth muscle in blood vessels
  – Kills bacteria in macrophage
  – NT using cGMP as second messenger
    • PNS = smooth muscle relaxation
    • CNS = memory and learning