NEUROTRANSMITTERS and RECEPTORS
In Physiology Today

(a) Excitatory synapse

(b) Inhibitory synapse
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
  - Dyniens
    - 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

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 released and diffusion
6. Neurotransmitter removed from synaptic cleft

(a) Phases of neurotransmitter release

(b) Role of Synaptotagmin and SNAREs in calcium-induced neurotransmitter release
Activation of the Postsynaptic Cell

(a) Excitatory synapse

(b) Inhibitory synapse
Synaptic Integration

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Membrane potential (mV)

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Temporal summation
Spatial summation
Threshold
Neurotransmitter Clearance

• NT binding to the receptor is a transient event

• Unbound neurotransmitter in the synaptic cleft is cleared very quickly
  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
  – Ionotropic
    • The receptor is the ion channel
  – Metabotropic
    • Indirectly regulates ion channel activity by activating a G-protein 2nd messenger system
Neurotransmitters

• Quaternary Amine
  – Acetylcholine (ACh)

• Monoamines
  – Catecholamines
    • Dopamine (DA)
    • Norepinephrine (NE)
    • Epinephrine (Epi)
  – Serotonin (5-HT)
    • Derived from tryptophan
  – Histamine
    • Derived from histadine

• Amino acids
  – GABA
    • Inhibitory
  – Glutamate
    • Excitatory
Acetylcholine (ACh)

- Cholinergic neurons release ACh
- Synthesized from choline and acetyl-CoA
- ACh is a neurotransmitter found in both CNS and PNS
- Effectors
  - CNS: neurons
  - PNS: muscle
Actions of Acetylcholine

• Central Nervous System (CNS)
  – Widespread in the brain (neurons of the pons, thalamus, forebrain)
  – Neuromodulator
    • Plasticity, arousal, reward
  – Sustaining attention
  – Decision making

• Peripheral Nervous System (PNS)
  – Somatic Nervous System
  – Parasympathetic Nervous System
    • Released from pre and postganglionic neurons
  – Sympathetic Nervous System
    • Released from preganglionic neurons
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
Clearance of Acetylcholine

- Degraded by acetylcholinesterase (AChE)
- Degrades unbound ACh
- Reuptake of choline
- Acetate cleared by diffusion
Catecholamines

• Dopamine, Norepinephrine and Epinephrine (*)

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

Tyrosine → Tyrosine hydroxylase → L-Dopa → Dopa decarboxylase → Dopamine → Dopamine β-hydroxylase → Norepinephrine → Phenylethanolamine N-methyltransferase → Epinephrine
Norepinephrine (NE)

- Noradrenergic neurons release NE
- NE is a neurotransmitter found in both CNS and PNS
  - CNS
    - Adrenergic neurons have their nerve cell bodies in brainstem and hypothalamus
    - Heavily branched axons
    - Project to the cerebral cortex, limbic system, thalamus, cerebellum and spinal cord
  - PNS
    - Postganglionic neurons of sympathetic nervous system
Actions of Norepinephrine (NE)

• Responsible for concentration
• Fight or flight response
  – Heart rate
  – Respiratory rate
  – Free up glucose reserves
  – Increase in oxygen flow to the brain
  – Increase blood flow to skeletal muscle
• Increases vascular tone
Receptors for Norepinephrine (NE)

- Adrenergic Receptors
  - Metabotropic (both sub types)
    1. Alpha adrenergic receptors
    2. Beta adrenergic receptors
- Adrenergic receptors can bind to both NE and Epi
- Effectors
  - Smooth muscle
  - Cardiac muscle
  - Glands
Adrenergic Receptors

- Alpha Adrenergic Receptors
- 2 subtypes
- $\alpha_1$
  - Use DAG and $IP_3$ as 2$^{nd}$ messengers
  - Increase cytoplasmic $Ca^{2+}$ levels
- $\alpha_2$
  - Inhibits cAMP as 2$^{nd}$ messenger
Adrenergic Receptors

- Beta Adrenergic Receptors
- 3 subtypes
  - All activate cAMP as a 2nd messenger
  - $\beta_1$
  - $\beta_2$
  - $\beta_3$
Clearance of Norepinephrine

Catecholamines

- Presynaptic
  - Reuptake
  - Degradation by MAO
    - monoamine oxidase
- Postsynaptic or Cleft
  - Degradation by COMT
    - Catechol-O-methyl transferase
Dopamine (DA)

• Dopaminergic neurons release DA
• DA is a neurotransmitter found in the CNS/PNS (digestion)
• Dopamine is released by neurons of the midbrain and hypothalamus
Actions of DA

• Responsible for alertness
• Also involved in:
  – Cognition (thinking)
  – Behavior (laughter, pleasure, aggression, fear)
  – Motor Activity
  – Motivation and Reward
  – Sleep
  – Mood
  – Attention
  – Learning

• *Mesolimbic Dopamine System*
  – Neurons originate in midbrain, send axons to limbic system
  – Involved in modulating reward behavior such as
    • Eating, sex, drugs
Diseases and Disorders of DA

- Parkinson’s Disease
  - Death of dopaminergic neurons in the midbrain
    - *Basal ganglia located in the midbrain*
    - Basal ganglia involved in initiating motor programs
    - Low levels of DA result in stiffness and greatly reduced movement

- Addictive drugs
  - Cocaine, nicotine, amphetamines
    - High levels of DA result in high levels of motor activity and impulsive behavior
  - Adderall (ADD, ADHD medication)
  - Inhibit re-uptake of dopamine
Dopamine Receptor

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

- Presynaptic
  - Reuptake
  - Degradation by MAO
    - monoamine oxidase
- Postsynaptic or Cleft
  - Degradation by COMT
    - Catechol-O-methyl transferase
Serotonin (5-HT)

• Serotonergic neurons release serotonin
  – Also secreted by cells outside of the nervous system as a hormone

• Derived from L-tryptophan (essential a.a.)

• Serotonin is a neurotransmitter found in both CNS and PNS
Actions of Serotonin

• Direct Actions
  – Cognition
  – Aggression
  – Anxiety
  – Mood
  – Appetite
  – Sleep
  – Memory
  – Learning
  – Thermoregulation

• Neuromodulator Actions
  – Modulate the release of neurotransmitters
    • Glutamate, GABA, DA, NE, ACh
  – Modulate the release of hormones
    • Epi, oxytocin, prolactin, ADH, cortisol, corticotropin, substance P
Actions of Serotonin

• Under circadian control
  – 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
Disorders of Serotonin

• Depression
  – Low levels associated with depression
  – SSRI’s: selective serotonin reuptake inhibitor
    • medications which inhibit the reuptake of serotonin (Prozac, Paxil, Zoloft)
  – MAOI’s: monoamine oxidase inhibitor
    • Medications that inhibit the reuptake of monoamines presynaptically
      – Includes NE and DA

• Also implicated in migranes, psychosis, overeating, problems with gastrointestinal motility
Serotonin Receptors

- Serotonin receptors are called 5-HT receptors
  - *mostly* g-protein coupled receptors that (+) or (-) cAMP
  - Can be excitatory or inhibitory
- 14 known subtypes of 5-HT receptors
- Effectors
  - Neurons of CNS, PNS
  - Smooth muscle (GI tract, blood vessels)
  - Platelets
Clearance of Serotonin

• Clearance of serotonin is by reuptake
  – Monoamine transporter specific for serotonin (5-HT) called SERT (serotonin reuptake transporter)
  – SERT transporters are present in the presynaptic membrane

❖ Various chemicals can inhibit 5-HT reuptake
  – MDMA (ecstasy)
  – Amphetamines
  – Cocaine
Histamine

- Histaminergic neurons release Histamine
- Derived from histidine (essential a.a.)
- Histamine released by neurons of the hypothalamus and project to the cortex
  - Modulates sleep
- Have the greatest firing pattern while awake than any other NT measured
Actions of Histamine

• Actions (*Many, many, many*)
  – Motion sickness
  – Regulate sleep
  – Appetite suppression
  – Involved in forgetting memories and things learned
  – Also has many immune and digestive actions
Histamine Receptors

• Histamine receptors are called HT Receptors
  – 4 subtypes
• Histamine receptors in the brain are mostly of the following 2 types:
  – g-protein coupled receptors that activate or inhibit DAG and IP$_3$ as 2$^{nd}$ messengers
  – g-protein coupled receptors that inhibit K$^+$ channels
• Inhibitory or excitatory effects
Clearance of Histamine

- Active transport into astrocytes
GABA

gamma-Aminobutyric acid

• GABAergic neurons release GABA
• Derived from glutamate
• GABA is released from small interneurons
  – Almost all parts of the brain
  – “fine-tunes” neurotransmission
• GABA is released by neurons of the:
  – Basal ganglia (midbrain)
  – Hypothalamus
  – Central gray matter
  – Hippocampus
Actions of GABA

• Regulates muscle tone
• Dampens skeletal muscle contraction
• Other chemicals/drugs can bind to GABA receptors
  – Enhances the effect of GABA
    • Sedatives (barbiturates)
    • Muscle relaxers
    • Anti-anxiety medications (benzodiazepines: Xanax, Valium)
GABA Receptor

- GABA receptors
  - Ionotropic receptors
  - Cl⁻ channels
- Major inhibitory NT produced in CNS
Clearance of GABA

- GABA is cleared by active transport into astrocytes
Glutamate

- Glutamergic neurons release glutamate
  - Most common excitatory NT in CNS
  - 90% of synapses
- Glutamate is released by neurons of the:
  - Cortex
  - Hippocampus
  - Basal ganglia
  - Amygdala
Glutamate Receptors

- **NMDA receptors**
  - $\text{Ca}^{2+}$ channel
  - Activates $\text{Ca}^{2+}$ 2nd messenger system
- **AMPA receptors**
  - Receptor is a $\text{Na}^+$ channel
  - Fast, common
  - Long-term potentiation
- **Ionotropic receptors**
- Involved in memory and learning
Clearance of Glutamate

• Diffusion

• Cleared by active transport into astrocytes
Nitric Oxide (NO)

• Precursor: L-arginine

• Roles in the nervous system
  – NT using cGMP as second messenger
    • PNS = smooth muscle relaxation
    • CNS = memory and learning
**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)