NERVE SYNAPSES

ELECTRICAL SYNAPSES: A signal is passed from one neuron to another by the passive diffusion of electrical charge.

- General properties
    - They are only excitatory.
    - They are less common than chemical synapses.
    - Electrical synapses have cytoplasmic continuity between cells, formed by gap junctions.
    - Electrical synapses can conduct action potentials in both directions.
    - Electrical conduction of a signal is virtually instantaneous, while a chemical synapse has a delay time.
- Development: Electrical synapses are prevalent during development.
- **Gap Junction:** Structure is six cylindrical proteins, one each cell membrane, aligned in a circle such that they form a hole between the two cells.
    - Gap Junctions can exist in the open or closed state. The state of the junction is influenced by Ca^{+2}, neurotransmitters, etc.

THE PRESYNAPSE:

- **Bouton:** The bulb-like structure formed at the axon terminal.
- **Quantal Unit:** The constant number of neurotransmitter molecules found in a single **synaptic vesicle**.
- **Active Zone:** The electron-dense end of an axon terminal, that extends from the plasma membrane to the synaptic vesicles.
- Three Proteins control the release of neurotransmitters in synaptic vesicles
    - Actin + Spectrin: Form the active zone cytoskeleton, and hold the synaptic vesicles in place.
    - **Synapsin**: Cross-links synaptic vesicles with the cytoskeleton of the active zone.
        - STRUCTURE: Phosphoprotein with globular head and fan-like tail.
            - **Head:** Binds other synapsin heads or actin filaments.
            - **Tail:** Binds the synaptic vesicles.
    - **Dense Projections** helps guide released synaptic vesicles to the right part of the plasma membrane.
- Synaptic Vesicles: *They are acidic*. Protons are pumped into the vesicle by an ATPase.
    - The acid pH creates a gradient so that neurotransmitter can get imported into the vesicles.
    - It is thought the acid pH protonates neurotransmitters once they get in the vesicle, so they can't get back out.
- Fusion of Synaptic Vesicle with Pre-Synaptic Membrane:
    - Synaptobrevin and Syntaxin: May be essential for targeting and docking of vesicles.

    - Synaptotagmin: Calcium-dependent releasing protein, that facilitates fusion in presence of calcium, and prevents it in absence of calcium.

NEUROTRANSMISSION: The process of releasing neurotransmitter is calcium-mediated.

- Membrane Depolarizes.
- Voltage-Gated **Ca^{+2} Channels** open on pre-synaptic membrane.
- Ca^{+2} comes flooding into the pre-synaptic axon.
- **Ca^{+2}-Dependent Protein Kinases** become activated in the presence of Ca^{+2}. They phosphorylate targets to cause neurotransmitter release.
- **Synapsin** gets phosphorylated, which causes it to release the synaptic vesicle and let go of the actin filament.
- **Synaptotagmin** and other Vesicle-Releasing Proteins also get phosphorylated, which causes them to facilitate the fusion of the synaptic vesicles with the pre-synaptic membrane.

RECYCLING: Synaptic vesicles are recycled following their fusion with the plasma membrane, by continual **pinocytosis**.

THE SYNAPTIC CLEFT: 10-20 nm wide in the central nervous system.

- It contains filamentous materials that link the pre and post synapse together, and that may help prevent extracellular diffusion of the neurotransmitter.
- NEUROTRANSMISSION Across the Synaptic Cleft: Occurs by **simple diffusion**.

NEUROTRANSMITTER CLEARANCE: After affecting the post-synapse, the neurotransmitter is disposed of by one of three mechanisms.

- Degradation (as in Acetylcholinesterase)
- Diffusion
- Reuptake (as in Norepinephrine)

TYPES OF SYNAPSES: Synapses can be categorized by various means.

- Categorization by the types of cells synapsing:
    - **Axo-Dendritic:** An axon synapsing on a dendrite.
    - **Axo-Somatic:** An axon synapsing on the cell soma.
    - **Axo-Axonal:** An axon synapsing on another axon.
- Synapses based on synapse morphology: This is actually a continuum.
    - **Type I Synapse:** Found on Dendritic Spine and the smooth parts of neurons.
        - Prominent dense bodies and synaptic vesicles
        - Synapse contain a basement membrane.
    - **Type II Synapse:** Found on Dendritic shaft or cell body.

        - Dense bodies and synaptic vesicles less prominent.
        - Synapse does not contain a basement membrane.

Criteria for being a "Classical Neurotransmitter":

- The presynaptic neuron must synthesize it, or its precursor.
- It must be found in the nerve terminal
- The terminal should release the compound.
- Compound should bind with high affinity to post-synaptic membrane.
- The compound should cause the effects expected of neurotransmission at the post-synaptic membrane.
- The effects should be susceptible to antagonistic and/or agonistic drugs.
- The compound should be removed from post-synaptic membrane.

RECEPTORS: There are several sets of criteria that define a neurotransmitter receptor.

- Kinetic Criteria:
    - High affinity binding of the ligand
    - Saturable binding at low concentrations
    - First order kinetics
    - No other molecules should be involved
- Pharmacological Criteria:
    - Agonistic and antagonistic pharmacological effects
    - Binding is stereospecific
    - The pharmacological effect should be coupled temporally (in time) with the effect.
- Anatomical Criteria:
    - An organ tissue that shows no response to the neurotransmitter should not have the receptor.
    - Concentration of receptors should be appropriate for the concentration of neurotransmitters found in that region.
- Chemical Criteria:
    - Chemical structure
    - Antibodies can be made to it, and it should be able to be localized by immunocytochemistry
    - In Situ hybridization to isolate and localize the mRNA's that encode the receptor.

AMINO ACID NEUROTRANSMITTERS: These neurotransmitters function in the CNS and exhibit ionotropic effects. They all exhibit *ionotropic* effects on the post-synapse.

- **GABA (gamma-Amino Butyric Acid):** Inhibitory Neurotransmitter
    - SYNTHESIS: alpha-Ketoglutarate ------> GABA, via a transamination and then decarboxylation.
    - **$GABA_A$ RECEPTOR:** Opens a **Cl^--Channel** which hyperpolarizes the membrane.

        - **alpha-Domain:** Principle site to which GABA Itself binds.
        - **beta-Domain: Barbiturates** bind to the beta-domain and have agonistic effects.
        - **gamma-Domain: Benzodiazepine** binds to the gamma-domain and ultimately has agonistic effects.
    - **VALIUM:** Benzodiazepine
        - It *only* will bind to the gamma-domain of the $GABA_A$ receptor.
        - It is thought to *facilitate the binding of GABA to its receptor*, as opposed to having straight agonistic effects in itself.
    - **$GABA_B$ AUTORECEPTOR:** Thought to decrease inward Ca^{+2} flux on presynapse, thereby inhibiting further GABA release.
    - REMOVAL:
        - GABA **Reuptake** is done by the presynapse and glial cells.
            - The presynapse reuptake transporter is a Na^+/GABA Antiport ATPase.
        - GABA **Degradation** can occur by GABA alpha-Oxoglutarate Transaminase. Some drugs can block this degradation, thus enhancing GABA's effects.
- **Glycine:** Also causes the opening of Cl^- channels on the post-synaptic membrane.
    - DISTRIBUTION: Glycine is a specific to certain regions of CNS:
        - Cerebellum
        - Retina
        - Brain Stem
        - Spinal Chord
    - SYNTHESIS: Serine ------> Glycine
    - GLYCINE RECEPTOR
        - Appear to be homologous with both nicotinic Ach receptor and $GABA_A$ Receptor.
    - **Strychnine** blocks Glycine receptors.
    - REMOVAL: The only known method of removal is **reuptake**. Degradation may also occur but details are not known.
- **Glutamate** and **Aspartate:** Both are excitatory Neurotransmitter in the CNS. Generally they work by opening Na^+-Channels and depolarizing post-synapse membrane.
    - SYNTHESIS: Brain tissue makes them *de novo*. They do **not** diffuse into CNS neurons from the general circulation.
        - *Glutaminase* can make Glutamate in brain, via Glutamine ------> Glutamate
    - **N-Methyl-D-Aspartate (NMDA) RECEPTOR:** A *Voltage-Gated and Ligand-Gated* receptor, which has *both metabotropic and ionotropic effects*.
        - RESTING STATE: **Magnesium** is bound to the inside of the receptor, blocking current flow through it.
        - ACTIVATED: The effects of voltage-gating and ligand-gating are additive in the NMDA receptor.

            - VOLTAGE-ACTIVATION: Magnesium is driven out, and **Ca^{+2} and Na^{+}** can come in. These are the ionotropic effects, as this further depolarizes the membrane.
            - **LIGAND-ACTIVATION:** *Binding of aspartate or glutamate facilitates even higher current flow and more calcium coming into the cell.*
        - METABOTROPIC EFFECTS: **Calcium**, once inside, activates **Ca^{+2}-Dependent (calmodulin) Kinases**
    - **Glutamate Toxicity:** High levels of glutamate are toxic.
        - Overstimulation of NMDA Receptor ------> Too much in Ca^{+2} in cell ------> Ca^{+2}-dependent proteaases will produce **free radicals** and cause neuron death.
        - Aspartate would be similarly toxic, but it isn't present in high enough levels to ever be a threat.

Long-Term Potentiation: An enhanced response to a neurotransmitter, via a higher EPSP.

- Potentiation plays a role in learning.
- The enhanced response is thought to be mediated by NMDA-Receptors and Nitric Oxide.

AMINE NEUROTRANSMITTERS: **CATECHOLAMINES** (Generally Metabotropic)

- **Dopamine:**
    - SYNTHESIS:
        - *Tyrosine Hydroxylase*: Tyrosine ------> L-DOPA (Dihydroxyphenylalanine)
        - *DOPA-Decarboxylase:* L-DOPA ------> Dopamine
    - DISTRIBUTION: It is the most prominent catecholamine in the brain, found in the midbrain, through three neuronal tracts.
        - Nigrostriatal Tract: Initiation and execution of movement. Implicated in **Parkinson's Disease**
        - Mesolimbic-Mesocortical Tract: Emotions, thought organizations. Implicated in **Schizophrenia**.
        - **Tuberoinfundibular System:** Couples the hypothalamus to the pituitary. Dopamine gets put into portal circulation in this system.
    - DOPAMINE RECEPTORS: Dopamine has *metabotropic receptors*.
        - **D1 RECEPTOR:** Coupled to a **G-Stimulatory Protein** that stimulates adenylate cyclase ------> higher cAMP levels.
        - **D2 RECEPTOR:** Coupled to a **G-Inhibitory Protein** that inhibits adenylate cyclase ------> lower cAMP levels.
    - DOPAMINERGIC DRUGS: Lots of them, both agonistic and antagonistic.
    - REMOVAL: Two compounds will degrade all catecholamines:

        - **Monoamine Oxidase (MAO):** Several drugs inhibit this compound ------> higher catecholamine levels.
        - **Catechol-O-Methyltransferase**
- **Norepinephrine:**
    - SYNTHESIS: *Dopamine beta-Hydroxylase*: Dopamine ------> Norepinephrine
    - DISTRIBUTION:
        - In the CNS, Norepinephrine is more concentrated than dopamine in other parts of the brain (other than midbrain)
        - Norepinephrine is the main sympathetic neurotransmitter in the PNS.
    - REMOVAL: Norepinephrine is primarily removed by **reuptake**, although degradation also occurs.
- **Epinephrine:**
    - SYNTHESIS: Norepinephrine ------> Epinephrine via a *methyltransferase*.
    - DISTRIBUTION: Primarily secreted by adrenal medulla into bloodstream, but it is also found as a neurotransmitter in medulla, and maybe hypothalamus + retina.

AMINE NEUROTRANSMITTERS: OTHER AMINES (Generally Metabotropic)

- **Serotonin (5-Hydroxytryptamine):** Involved with appetite, thermoregulation, sleep, pain perception.
    - SYNTHESIS: It is synthesized from **Tryptophan**.
        - Tryptophan ------> 5-Hydroxytryptophan ------> Serotonin
    - DISTRIBUTION: In CNS, the medulla, pons, and midbrain.
    - SEROTONIN RECEPTORS: *Metabotropic*.
        - **5HT1-RECEPTOR:** beta-Adrenergic Receptor, linked to adenylate cyclase.
        - **5HT2-RECEPTOR:** alpha-Adrenergic Receptor, linked to Inositol Triphosphate (IP_3) and Diacylglycerol (DAG).
    - DRUGS: Several, both antagonistic and agonistic.
        - Antidepressant **Prozac** = inhibit Serotonin reuptake.
        - LSD is a serotonin antagonist.
    - REMOVAL: Reuptake, plus monoamine oxidase.
- **Histamine:** Involved in arousal, mental disease, cardiovascular control, to name a few.
    - SYNTHESIS: It is synthesized from **Histidine**
        - *L-Histidine Decarboxylase:* Histidine ------> Histamine
    - DISTRIBUTION: Only hypothalamus
    - RECEPTORS:
        - **H1 + H2 RECEPTORS:** Metabotropic
        - **H3 RECEPTOR:** An Autoreceptor.
    - REMOVAL: Via monoamine oxidase.

NEUROPEPTIDES: Also called **Cotransmitters** or **Neurohormones**.

- How they differ from Amino Acid and Amine Neurotransmitters:
    - They are present in very low concentration
    - They are made from amino acids 3-100 residues long
    - They are found in association with other transmitters (i.e. not acting by themselves)
    - They may act at a distance (i.e. through a microcirculation)
    - They are degraded by **peptidases**. There is no reuptake.
    - They are **propeptides,** and they are generated by cleave of the precursors.
- HYPOTHALAMUS: A rich source for neuropeptides in the brain.
- RECEPTORS: The same neuropeptide can have multiple receptors (like hormones), and they are generally metabotropic.

ACETYLCHOLINE:

- DISTRIBUTION:
    - In the PNS, primary neurotransmitter in the Parasympathetic nervous system and at the skeletal neuromuscular junction.
    - In the brain there are five discrete functions, to be learned later.
- SYNTHESIS: *Choline Acetyltransferase:* Choline ------> Acetylcholine
- ACETYLCHOLINE RECEPTORS: There are multiple types of both the muscarinic and nicotinic type receptors.
    - **MUSCARINIC RECEPTORS:** *Metabotropic Receptor*
        - DRUGS:
            - **Muscarine** is an agonist to the receptor.
            - **Atropine** is an antagonist.
        - Activation of this receptor has slow excitatory onset.
        - **Thalamus:** Muscarinic receptors have slow inhibitory onset.
        - Effects are stimulatory or inhibitory, depending on the type of G-Protein attached.
    - **NICOTINIC RECEPTORS:** *Ionotropic Receptor*
        - DRUGS:
            - **Nicotine** is an agonist to the receptor.
            - **Tubocurarine** is an antagonist.
        - Activation of this receptor has rapid excitatory onset.
        - STRUCTURE: There are five separate subunits comprised of four different chains: 2 alpha, 1 beta, 1 gamma, 1 delta. The subunits form a **Na^+-Channel** that opens which Acetylcholine binds.
- REMOVAL: **Acetylcholinesterase**. Reuptake is not significant.

NITRIC OXIDE: Important in communication between cells.

- SYNTHESIS: *Nitric Oxide Synthetase*
    - L-Arginine ------> Nitric Oxide + Citrulline
    - NADPH and Ca^{+2} are cofactors.
- FUNCTIONS:
    - Relaxation of smooth muscle vascular walls.

    - Contraction of GI Tract
    - Penile erection
    - A neurotransmitter
- Unique Properties:
    - It is not stored in vesicles.
    - It is used once synthesized, and it passes through cell membrane to reach target.
    - It binds to **iron** to modulate enzymatic activity.
- **Long-Term Potentiation:** NO is synthesized at the *post-synapses* and then diffuses backward to the presynapse, or so they think.

CARBON MONOXIDE: Synthesized by *Heme Oxygenase*. Little else is known.

METABOTROPIC RESPONSES: Response via a signal transduction pathway that ultimately changes metabolic behavior.

- Signal Transduction Pathways, for the 25th time:
    - beta-Adrenergic: cAMP.
        - Adenylate Cyclase ------> cAMP ------> Protein Kinase A ------> Target
    - alpha-Adrenergic: IP_3 + DAG
        - Phospholipase C cuts Phosphatidylinositol-4,5-biphosphate into Inositol Triphosphate (IP_3) and Diacylglycerol
        - IP_3 then goes to ER where it opens Ca^{+2} Channels ------> influx of Ca^{+2} into cytoplasm.
        - IP_3 activates Calcium-Dependent Protein Kinase C which then phosphorylates targets.
        - **Lithium** blocks the degradation of inositol phosphates.
    - **Arachidonic Acid:** It is released by the cell membrane **Phospholipase A_2**. Arachidonic acid then leads to several short-lived metabolites:
        - **Prostaglandins** via cyclooxygenase
        - **Leukotrienes** via 5-lipoxygenase
        - These hydrophobic compounds interact with neighboring cells without going through a receptor.
- EFFECTS OF PROTEIN PHOSPHORYLATION:
    - Close K^+ Channels: They can lead to closure of K^+ channels ------> membrane depolarization and hence an excitatory effect.
    - Altered gene expression
    - **Short Term Sensitization**: Make the post-synapse more sensitive to certain neurotransmitters, such as Serotonin, for short-term.
    - **Long Term Memory:** Come genes that are up regulated by phosphorylation are believed to play an important role in long-term memory.

IONOTROPIC RESPONSES:

- **Ligand-Gated Channels:** They open Na^+-Channels in response to binding ligand (such as ACh).
    - *They are not voltage-sensitive and therefore cannot spread an action potential, but only initiate it at the post-synaptic membrane.*
    - Voltage-gated channels are required to spread the AP.
    - **Excitatory Ligand Gated Channels:** Unlike voltage-gated channels, most of them are **non-specific**. They let Na^+, Ca^{+2}, and K^+ through equally.
- In the CNS, about **10 signals** (+1 mV each) are required to generate a post-synaptic action potential.
    - CNS resting potential is around -65mV and threshold is generally -55mV.
    - Summation of signals is required to accomplish this. One signal is insufficient.

INHIBITORY POST-SYNAPTIC POTENTIAL (IPSP): Hyperpolarization of the post-synaptic membrane in response to a neurotransmitter.

- Ligand-Gated **Cl^- Channels** can be triggered open.
- A second messenger (metabotropic) that opens K^+ Channels can also cause an IPSP (via K^+ out ------> hyperpolarization).

EXCITATORY POST-SYNAPTIC POTENTIAL (EPSP): Depolarization of the post-synaptic membrane in response to a neurotransmitter.

- Na^+ and Ca^{+2} ligand-gated channels will lead to EPSP.

GRAND POSTSYNAPTIC POTENTIAL and SUMMATION: The sum of all EPSP's and IPSP's generated in the *soma,* from multiple simultaneous in-coming signals.

- **Spatial Summation:** Summation of signals in space, due to juxtaposed or closely placed synapses on the same post-neuron.
- **Temporal Summation:** Summation of signal in time.
- It is the job of the cell body, at the axon hillock, to process and interpret the summation of positive and negative signals.
- FREQUENCY: *The larger (more positive) the incoming signal is at the Axon Hillock, the **faster** it will fire action potentials.* A larger incoming signal does not generate a stronger action potential -- only more action potentials in a faster time.

AXON HILLOCK: It has five different ion channels to achieve the function of encoding incoming signals and converting them into a firing frequency.

- **"Delayed Rectifier" Voltage-Gated Potassium-Channel**: Functions to repolarize the membrane.
    - It open in response to depolarization, but it does so more slowly than the Na^+ channels.

- **"Early" Voltage-Gated Potassium-Channel:** *Modulates the frequency of depolarization according to the strength of the stimulus.*
    - STIMULUS SLIGHTLY ABOVE RESTING: The channel is **open**. It thus behaves like an A-Type K^+ Channel (which this might be) and counteracts the Na^+ current, slowing down the rate of depolarization.
    - STIMULUS SIGNIFICANTLY ABOVE RESTING: The channel is **inactivated**, so that there is no countercurrent to the Na^+ channels, so that depolarizations occur more rapidly.
- **Ca^{+2}-Activated Potassium Channel:** *Spike Frequency Adaptation.*
    - In response to high Ca^{+2}, these channels are just plain open, hyperpolarizing the membrane and making it difficult (or impossible) to fire an action potential.
- **Voltage-Gated Calcium Channel:** A brief influx of Ca^{+2} occurs through these channels at each action potential.
    - This calcium contributes to spike frequency adaptation, when the level is high enough.
- **Voltage-Gated Sodium Channel:** Standard depolarizing kinda channel.

THE NEUROMUSCULAR JUNCTION

Somatic Efferent Motoneurons: Myelinated peripheral neurons that target skeletal muscle.

- Neuronal Cell-Type = **Polygonal, Multipolar**.
- Cell bodies in the **ventral horn** of the grey matter of the spinal column.

Visceral Efferent Motoneurons: Unmyelinated

- Cell bodies in various autonomy ganglia.

MOTOR UNIT: A single somatic motor neuron, plus all of the muscle fibers it supplies.

- Small motor units: Fine, precision control and less strength
- Large motor units: Gross motor control and greater strength

SYNAPSE MORPHOLOGY:

- **Pre-Synaptic Boutons:** As the nerve approaches the muscle, the myelin disappears and the nerve divides into multiple boutons.
    - The boutons generally lie along the middle of the muscle fiber.
    - They contain synaptic vesicles and numerous mitochondria.
        - **Synaptic Vesicles** are near the Active Zone
        - **Mitochondria** are *away from* the Active Zone.
    - The muscle cells have **troughs** (infoldings), and the presynaptic boutons of the motoneurons lie in those troughs.
- Acetylcholine Synthesis in Boutons:

    - Acetylcholine Synthesis occurs in the pre-synaptic boutons themselves.
    - Choline-Acetyltransferase is synthesized in the cell body and transported down the axon.
    - Choline is taken in from the ECF via an energy dependent Na^{+} cotransport mechanism, in the nerve terminals.
- Acetylcholine Receptors: They are present at the *mouths* of the **junctional folds** on the muscle membrane -- that portion closest to the presynaptic boutons.
    - They are present in very high concentration.

MINIATURE ENDPLATE POTENTIAL (MEPP): The potential created by a single quantum of acetylcholine, or one synaptic vesicle.

- One MEPP results in a muscle membrane depolarization of about 0.4mV
- A quantum contains about 5000 ACh-Molecules, and about 2000 ACh-Receptors are activated per MEPP.
    - 2 molecules of Ach bind to each receptor, so about 4000 Ach molecules contribute to each MEPP.
- Multiple MEPP's are required to depolarize a muscle membrane.

PROCESS OF MUSCLE STIMULATION:

- PRESYNAPSE
    - Action potential causes depolarization of pre-synaptic bouton.
    - This causes **Voltage-Gated Ca^{+2} Channels** to open on the pre-synaptic membrane, and Ca^{+2} comes pouring into the *presynapse*.
    - The Ca^{+2} then triggers the mobilization of the synaptic vesicles and ultimate exocytosis of acetylcholine.
        - **Botulinum Toxin** blocks release of acetylcholine from presynapse.0
    - About 15-250 quanta of acetylcholine are released, in 1-2 millisec.
- **ACETYLCHOLINE RECEPTOR:** Again -- five subunits, 2alpha,beta,gamma,delta
    - The two **alpha-subunits** both contain ACh-binding sites -- so ***two acetylcholine*** bind to each ACh-Receptor.
        - **alpha-Bungarotoxin** binds the alpha-subunits and blocks ACh from binding.
        - *Both of the alpha-subunits must bind a molecule in order to effect the conformational change in the molecule*.
    - ION CHANNEL: The cation channel in the middle of the acetylcholine receptor, when open, is equally permeable to Na^{+}, K^{+}, and Ca^{+2}
- POSTSYNAPSE: Muscle Activation
    - 2 Acetylcholine molecules per receptor bind to the post-synaptic membrane.
    - The receptor changes conformation for a brief time and then changes back. This allows cations to flow through, depolarizing the membrane slightly.

        - Na^{+} contributes the most to the depolarization, because of its concentration gradient, although Ca^{+2} contributes too.
    - This triggers the standard **Voltage-gated Na^{+} Channels** on the muscle membrane. They finish the depolarization, creating an action potential in the muscle membrane.
    - The depolarization spreads throughout the Sarcolemma and triggers **voltage-gated Ca^{+2} channels** in the SR to open, leaking Ca^{+2} into the muscle fibers and effecting muscle contraction.
- SUMMATION: *Muscles are not affected by summation*. A single motoneuron action potential ------> a single muscle contraction.
- Acetylcholine REMOVAL: Acetylcholinesterase.
    - **Neostigmine:** It blocks acetylcholinesterase.
    - Some ACh is also removed by simple diffusion.

TROPHIC FACTORS

ANTEROGRADE TROPHIC EFFECTS: A cell secreting substances onto a target cell, thereby effecting a change in the target cell. This is basically a hormonal paracrine (cell to neighboring cell) interaction.

- Mediated primarily by classical neurotransmitters.
- **Atrophy** and **Hypertrophy** of muscles (where the muscle is subjected a trophic effect) is an example, although this may be due to electrical stimulation rather than to a substance.
    - Working the muscle plays a role, but electrical stimulation of a muscle alone, without the contraction, can prevent a muscle from undergoing atrophy.
- Regulating the levels of substances in the target cells (such as neurotransmitter in the target cell) is a primary function of anterograde trophism.

RETROGRADE TROPHIC EFFECTS: All other important effects are retrograde -- the target cell secreting some substance onto the axonal process. Then the axonal process takes it back to the soma, via retrograde transport, where it elicits some response in the cell body.

- **Neurotrophins** is the catch-term for all compounds that elicit retrograde trophic effects.

NERVE GROWTH FACTOR (NGF): The one and only coolest retrograde neurotrophin.

- DEVELOPMENT: As nerves grow, the final number of neurons that will ultimately innervate a target is determined by the target. This determination is mediated by NGF.
    - NGF by itself is all that is necessary for a neuron to survive. If a target substance secretes NGF, then the neuron adjacent to it will survive.

    - Antibodies to NGF will cause *neuronal developmental death*, as NGF is unavailable.
    - Neuronal Morphology: Trophic Factors affect neuronal shape and size during development -- especially the complexity of the dendritic tree.

        - The larger the target mass, the higher the **dendritic complexity**. Supplementing a neuron with extra NGF can also increase dendritic complexity.
- **WALLERIAN DEGENERATION:** Death of a nerve axon *distal to* the point of lesion. Loss of NGF from target is the central cause of this neuronal death.
    - **Axotomy:** Cutting a nerve is known as axotomy. It will make the segment of axon distal to the lesion die.
        - Axotomy also makes the cell body swell, and Rough ER is lost, a process called **Chromatolysis** because of the RER staining properties.
    - **Chromatolysis:** The structural changes to the cell body resulting from axotomy.
        - ***NGF prevents Chromatolysis***.
        - **Chromatolysis is caused by an absence of NGF.** This can be from a *loss of axonal transport* or loss of contact with the target.
        - So, the nerve, now severed from its target, no longer as the effects of NGF acting on its cell soma.
    - The loss of NGF can be trans-synaptic and spread to neighboring neurons.
    - **SUPPORT CELLS:** With a nerve injury, Schwann Cells dramatically increase NGF production.
        - They are stimulated to do that by interleukins released from macrophages at the point of injury.
        - This can help explain how cell death is prevented, in cases when it is prevented.
        - Because of the role of Schwann cells, lesions *closest to the cell body* of a neuron are most likely to result in the neurons death.
- INNERVATION DENSITY: NGF also correlates with sympathetic innervation density, i.e. the number of neuroeffectors innervating a target organ or muscle.
- **COLLATERAL SPROUTING:** NGF mediates recovery from limited nerve damage, by adjacent neurons extending processes to the denervated area.
    - This appears to be mediated by NGF and other neurotrophins.
    - This is an important in **Polio** where many muscles are partially denervated.

OTHER NEUROTROPHINS OF THE NGF FAMILY: These molecules have similar sequences as and bind the same receptors as NGF.

- **Brain Derived Neurotrophic Factor (BNDF)**
- **Neurotrophin 3 (NT3)**

NGF RECEPTORS: There are two NGF-type receptors. Both are required on the nerve-membrane for high affinity binding of NGF.

- **Low-Affinity NGF Receptor (LNGFR)**:
- **Tyrosine Kinase NGF Receptor:** Autophosphorylating tyrosine kinase cascade.
    - This receptor has three genetic isoforms. BNDF, NT3, and NGF differ in which forms they are receptive to.
    - The genes are protooncogenes.

CILIARY NEUROTROPHIC FACTOR (CNTF): Another neurotrophin that does not belong to the NGF family.

- FNXN: It mediates the switch from noradrenergic to cholinergic innervation of sympathetic neurons on **eccrine sweat glands**.
- Nearly all sympathetic neurons secrete NorE, except those innervating eccrine sweat glands, which secrete Acetylcholine.
- *The nerves that innervate these glands originally secreted NorE,* and it wasn't until they contacted the target glands that they switched to Cholinergic.

Amyotrophic Lateral Sclerosis (ALS): A loss of *anterograde* trophic effects to skeletal muscles, from lower motor neurons.

- Lateral Sclerosis = hardening and gliosis of corticospinal tracts along lateral spinal cord.
- Recombinant CNTF is currently being tried as a potential therapy.