

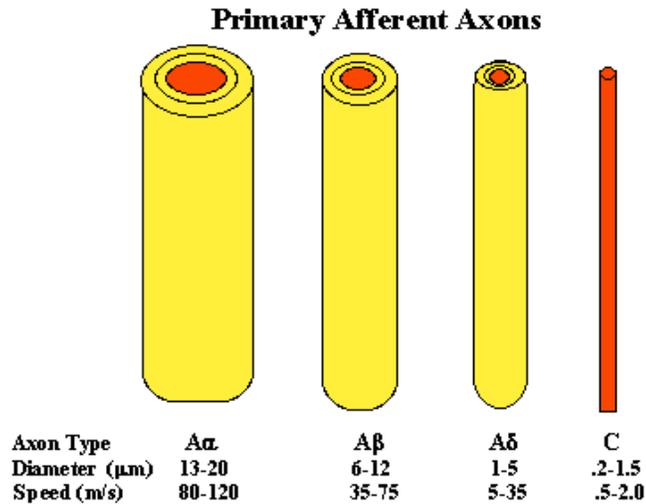
# NEUROPHYSIOLOGY

## ACTION POTENTIAL MEASUREMENT & NERVE-TRUNK PROPERTIES

EXTRACELLULAR RECORDING: Non-invasive recording of action potentials by placing electrodes outside the neuron, on the skin.

- **MONOPHASIC RECORDING:** Utilizes one electrode plus a ground electrode. The electrical potential outside the neuron is then recorded as action potentials pass through.
  - DEPOLARIZATION is represented as an upward peak on the graph, where up is *more negative* and down is *more positive*. As the action potential passes the electrode, the outside of the neuron becomes more negative, as  $\text{Na}^+$  flux in.
- **BIPHASIC RECORDING:** Utilizes two electrodes & measures the potential difference between them.
  - Depolarization passes the first electrode: The first electrode becomes negative with respect to the second electrode.
  - Depolarization passes the second electrode: The two electrodes are now both depolarized and therefore have the same volt-potential.
  - Depolarization then reaches second electrode while first depolarizes.
- **THRESHOLD POTENTIAL:** *With external stimulation, large axons are excited more easily (have a lower threshold potential) than small axons because they have a lower internal resistance.*

AXON DIAMETER: Many properties of nerves vary according to axon diameter:



- **CONDUCTION VELOCITY:** *There is a linear relationship between axon diameter and conduction velocity:*
  - Myelinated Axons: **CONDUCTION VELOCITY (m / sec) = 6 x Diameter (micron)**
  - Unmyelinated Axons: **CONDUCTION VELOCITY (m / sec) = 1.7 x Diameter (micron)**
- **EXTRACELLULAR EFFECTS:**
  - The amplitude of the *extracellular* action potential varies directly with cell diameter.
  - The threshold for *extracellular stimulation* varies inversely with axon diameter. The larger the axon, the lower the stimulus threshold.
- **LOCAL ANESTHETICS:** Small axons are blocked before large axons.
- **LARGE AXONS** are more sensitive to (blocked first by):
  - **Temperature change**
  - **Pressure change**
  - **Extracellular positive stimulation**
  - **Asphyxia, anoxia**

**COMPOUND ACTION POTENTIAL:** An *extracellularly stimulated* action potential that has graded stimulus intensity. It only occurs with artificial stimulation.

- **SUMMATION:** The potential shows summation of the individual axons contained within the nerve being stimulated.
  - At low stimulus intensity, only the largest axons will be stimulated.
  - At higher intensity, more axons will be stimulated, and a higher resultant stimulus intensity will be recorded.

## CLASSIFICATION OF NERVE TRUNKS

- **ELECTROPHYSIOLOGICAL CLASSIFICATION:** Use capital letters. Based on conduction velocities.
  - This scheme is used for all nerves but muscle spindle afferents.
  - *Cutaneous Afferents use this designation.*
  - CATEGORIES:
- **ANATOMICAL CLASSIFICATION:** Use roman numerals. Based on axon diameter.
  - *Only Muscle Spindle Afferents use this designation.*
  - CATEGORIES:

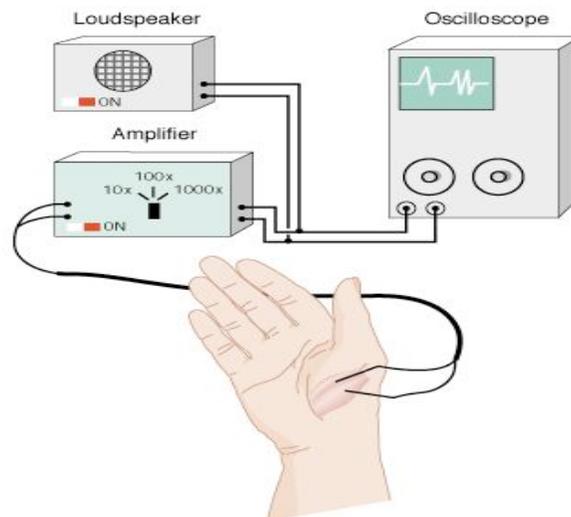
**BELL-MAGENDIE LAW:** Afferent nerves enter over the dorsal Root, and efferent nerves leave through the Ventral Root.

- **EXCEPTION:** Some **Pelvic Viscera** pain and temperature axons enter the spinal cord through the *Ventral Root*.
  - The Dorsal Root Ganglion is still in dorsal root, but the post-ganglionic axons bends around the Rami Communicans and actually enters the spinal cord through the Ventral Root.
  - **CLINICAL:** Thus, sectioning of dorsal roots will not completely alleviate pelvic pain.

**MEASURING CONDUCTION VELOCITY:** Conduction velocity of a motor axon cannot be measured directly, because it would include the time for the potential to cross neuromuscular junction and to conduct through the muscle membrane. If you want to just measure conduction through the nerve itself:

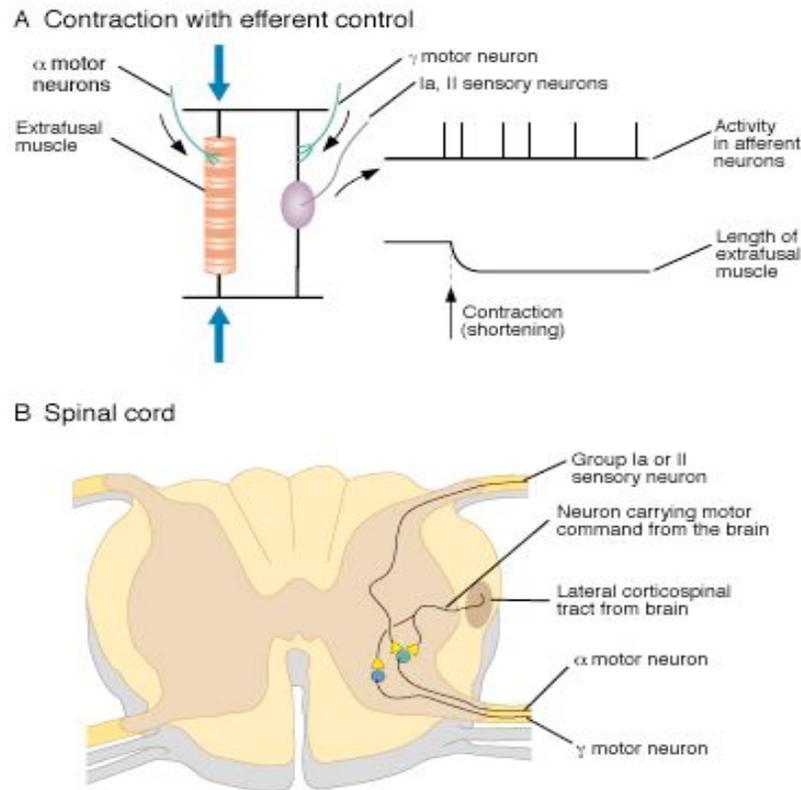
### PROCEDURE:

- Place two electrodes on the forearm, on two different parts of the Median Nerve.
- Stimulate the Abductor Pollicis muscle.
- On the graph, record the different in time (*latency period*) between stimulation and muscle flexion.
- Use equation above to get conduction velocity,  $m/sec$
- **PAIN FIBERS:** In measuring sensory nerves, *sharp pain fibers (pin prick) travel faster than temperature fibers*. So, a withdrawal reflex from sharp pain occurs faster than a withdrawal reflex from a hot stove.
- **LOCATING AXIAL NEUROPATHIES:** We can't directly, non-invasively stimulate nerves that aren't in the extremities, but we can determine conduction problems by using a REFLEX ARC.
  - **SEGMENTALLY** stimulate a sensory nerve going up the arm, and induce a reflex. If a local stimulation shows normal velocity, but the reflex took too long of a time, then you can deduce that there must be a conduction problem in the *proximal part of the reflex*.



- **ELECTROMYOGRAM (EMG):** Test to measure muscle contractility and stimulation of motor nerves.
  - The amplitude of the muscle response tends to drop off as you go from distal to proximal, by about 15%
  - **REPEATED STIMULATIONS:** The normal response should show the *same magnitude for each stimulation* with repeated stimulations of low frequency. With higher frequency (i.e. *tetanic stimulation*), normal response should be a tetanic graph (increasing tension with decreasing magnitude on each successive stimulus).
    - Low frequency stimulations (non-tetanic) are used to diagnose MG.
    - MG is an auto-immune disorder against the *post-synaptic neuron* (nerve terminal)
    - High frequency stimulations (Tetanic Stimulation), which hurts a lot, are used to diagnose Myasthenic Syndrome.
    - This syndrome is an auto-immune disorder against the *pre-synaptic neuron*.

## SPINAL CORD & SPINAL CORD REFLEXES



**MOTOR UNIT:** An  $\alpha$  Motor Neuron, plus all of the muscle cells it innervates.

- $\alpha$  Motor Neurons innervate extrafusal muscles.
- Final Common Pathway
- Any given muscle cell is innervated by only one  $\alpha$  Motor Neuron.
- **INNERVATION RATIO:** The number of  $\alpha$  neurons innervating a whole muscle (innervation density) depends on the amount of control over the muscle we need.
  - **Extraocular Muscles = 9 : 1** (9 muscle cells to 1 neuron) ratio, high innervation density.
  - **Postural Muscles = 2000 : 1** (2000 muscle cells to 1 neuron) ratio, low innervation density.
- **OBLIGATORY, NON-GRADED STIMULATION:** Every time an  $\alpha$  neuron is fired, it will cause an action potential in every muscle cell it innervates. There are no graded or partial potentials.
  - **MYASTHENIA GRAVIS** and other pathologies may prevent an action potential from happening with every neuron firing—but this is pathological and not the normal circumstance.
- **MOTOR NEURON POOL:** All of the motor neurons that innervate a single muscle. They are arranged close to each other in the ventral horn, according to somatotopic organization:
  - **SPINAL CORD ORIENTATION:** The more dorsolateral you go, the more you go distally away from the midline:
    - **FLEXORS:** Nerves going to flexors tend to lie dorsally.
    - **EXTENSORS:** Nerves going to extensors tend to lie ventrally.

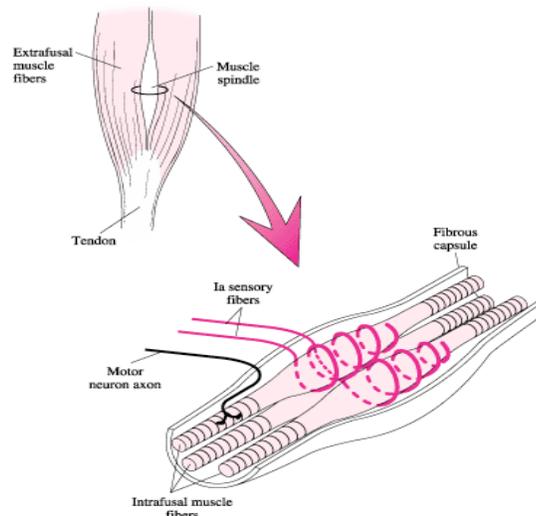
**FORCE TRANSDUCTION:** **Twitch Tension** in a muscle is increased by increasing the *frequency* with which  $\alpha$  motor neurons are fired.

- With high frequency firing, the muscle doesn't get a chance to completely relax before the next action potential.
  - **Tetanus** is maximal twitch tension.
- **PRINCIPLE OF ORDERLY RECRUITMENT ACCORDING TO SIZE:** INTRACELLULAR, physiological stimulation of nerves, the *smallest axons are stimulated first (have the lowest threshold), and largest axons are stimulated last.*
  - This is another way to increase the force with which a muscle contracts: "Recruit" more  $\alpha$  neurons to fire on the muscle. In this case, again, the smallest neurons will fire first (small twitch tension), and larger neurons will fire later (larger twitch tension).
  - **V = IR:** Small neurons have a higher resistance, which means they will show a *stronger depolarization (V) for the same current (I).*
  - In physiological stimulation, smaller neurons have a *smaller threshold potential* than larger neurons.

## SLOW vs. FAST TWITCH MUSCLE

	SLOW TWITCH	FAST TWITCH
$\alpha$ Motor Neuron Diameter	Small	Large
Conduction Velocity	Fast	Slow
Muscle Cells innervated (motor unit size)	Fewer cells innervated, and with a smaller diameter	More cells innervated, with a larger diameter
Twitch Tension	Small tension	Large tension
Contraction Speed	Slow speed of contraction	Rapid contraction
Extracellular spike size (magnitude)	Small	Large
Metabolism	Oxidative (lots of mitochondria)	Glycolytic (few mitochondria)
Capillary Supply	High	Low
Resistance to fatigue	High resistance to fatigue	Easily fatigued
Muscle Color	Red (from mitochondria)	White
Functional Adaptation	Generate small forces over a long period of time— <i>Endurance</i>	Generate large forces for a brief time— <i>Sprint</i>

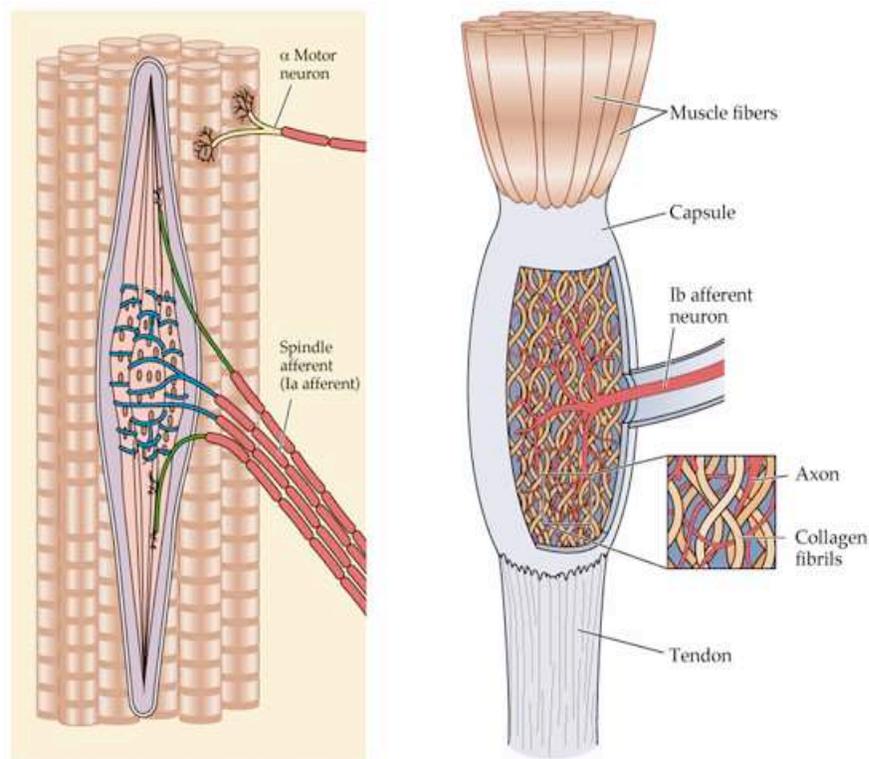
**MUSCLE SPINDLE:** Intrafusal muscle fibers are innervated by afferent nerves that send signals back to the CNS about the muscle's contractility. The muscle spindle is arranged in parallel with extrafusal muscle.



- Two different types of muscle fibers: They run parallel to each other in the muscle spindle. They both have respective equatorial and polar regions.
  - **BAG FIBERS:** The **velocity component** of the muscle spindle. These fibers convey how quickly the muscle spindle is changing length.
  - **CHAIN FIBERS:** The **length component** of the muscle spindle. These fibers convey the spindle length at any instant in time.
- Two different regions of the muscle spindle:
  - **EQUATORIAL REGION:** Contains muscle cell nuclei, and no actin or myosin. It behaves like a **spring**.
    - **Stretch Muscle** -----> **Increase Ia and II firing rate**
    - **Contract Muscle** -----> **Decrease Ia and II firing rate**
  - **POLAR REGION:** Contains striated muscle, actin, and myosin.
    - **Gamma Firing** -----> **Contract polar region** -----> **Stretch whole spindle** -----> **Increase IA Afferent firing rate**

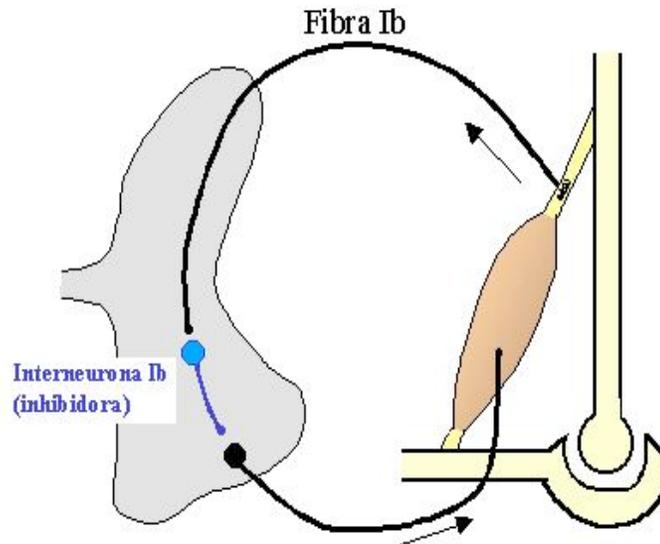
- **IA AFFERENT NERVES:** They synapse with  **$\alpha$  Motor Neurons** that go back to the same muscle.
  - **“Local Sign”:** The response is confined exclusively to the muscle cell from which the signal originated.
  - RAMP AND HOLD EXPT: Stretch a muscle and keep it stretched, and **IA** afferents will detect **both the velocity and length** of the muscle.
  - **ANNULOSPIRAL ENDINGS:** They form annulospiral endings, on both bag and chain fibers, on the equatorial region of the spindle.
- **IIA AFFERENT NERVES:** Their pathway is more complex. The connection is not monosynaptic but rather involves interneurons.
  - RAMP AND HOLD EXPT: Stretch a muscle and keep it stretched, and **IIA** Afferents will detect **only length** of muscle spindle.
  - **FLOWER SPRAY ENDINGS:** They form “flower spray” endings on the polar regions of the spindle, which help them detect the current muscle length.
- **STATIC GAMMA EFFERENT NERVES:** They increase the **length sensitivity** of the muscle spindle.
  - They innervate Chain fibers in the polar regions of muscle spindles.
  - They bring about strong contraction in the poles of the spindle.
  - FNXNS in the Muscle Spindle.
- **DYNAMIC GAMMA EFFERENT NERVES:** They increase the **velocity sensitivity** of the muscle spindle. That is, under the influence of Dynamic Gammas, the spindle will respond more quickly to a faster rate of change of spindle length.
  - They innervate Bag fibers.
  - They increase muscle tension but there is *no contraction* - i.e. spindle length doesn't change.
  - FNXN: They produce a large increase in the *velocity sensitivity of muscle spindle IA afferents*. *Dynamic Gammas do not affect IIA afferents*.

**GOLGI TENDON ORGAN:** The muscle receptor responsible for the Inverse Stretch Reflex.



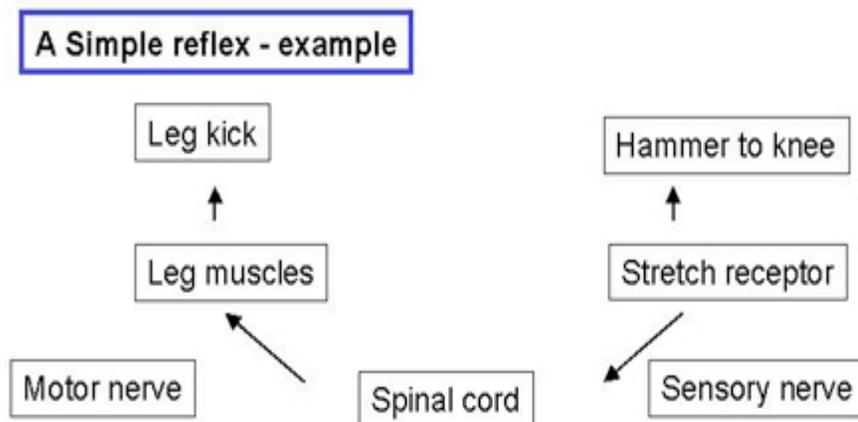
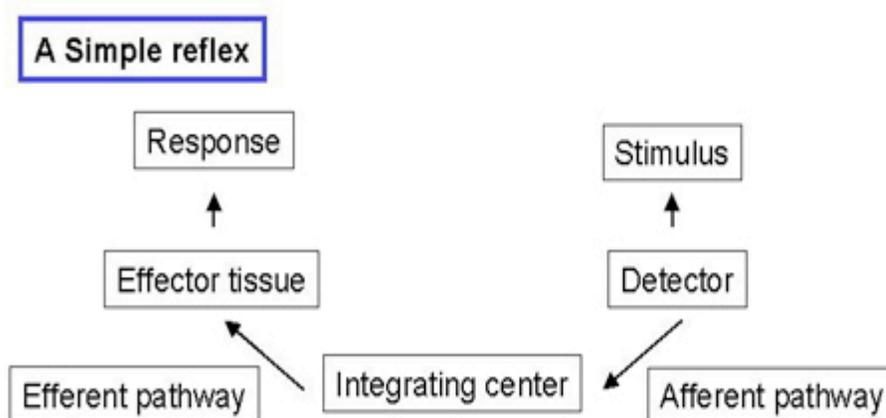
- **STRUCTURE:** It is a capsule of elastic fibers, *in series* with (i.e. attached to the end of) 1% of all extrafusal muscle fibers.
  - 99% of extrafusal fibers do not connect to the Golgi Tendon Organ.
- **FNXN:** When Golgi Tendon stretches, it will decrease  $\alpha$  Motor Neuron activity back to the same muscle, preventing further contraction and reducing muscle tension.
  - Also it will send muscle information back to cerebellum.
  - The GTO increases muscle **compliance**, as in muscles needing to “give” a little (by lengthening to absorb shock) when jumping off a roof and landing on feet.
  - Compensation for fatigue.

- **1B AFFERENT NERVES:** They innervate the Golgi Tendon Organ. Stretching of the Golgi Tendon fire these nerves.

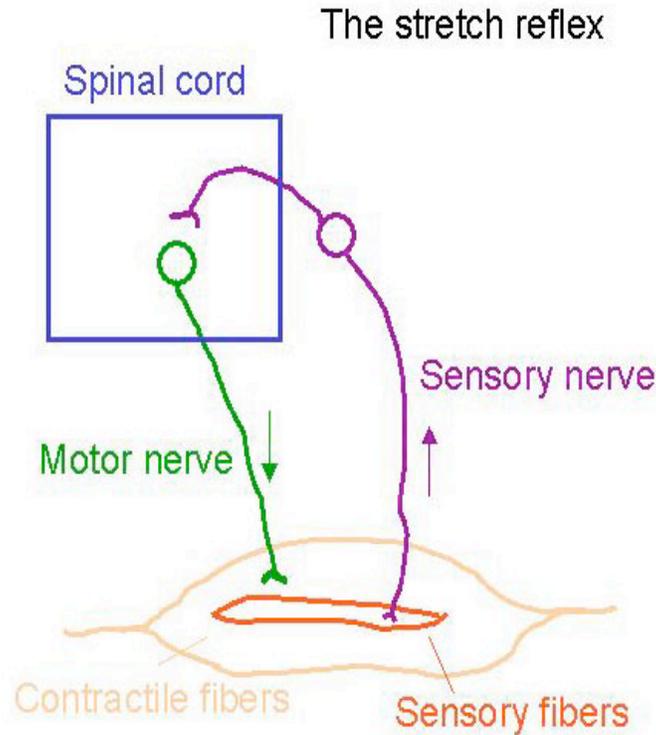


- They go to spinal cord -----> SYNAPSE with INHIBITORY INTERNEURON -----> INHIBIT  $\alpha$  Motor Neuron activity back to same muscle.

### SPINAL CORD REFLEXES



**STRETCH REFLEX:** Contraction of a muscle elicited by stretch of the muscle, such as the patellar tendon reflex.



- **AFFERENT LIMB:** Muscle spindle **IA** Afferents.
- **EFFERENT LIMB:**  $\alpha$  Motor Neurons.
- **PATHWAY:** Monosynaptic. *Stretch Muscle -----> Increase firing rate of IA Afferents -----> Fire  $\alpha$  Motor Neurons back to same muscle -----> increase muscle tension.*
- **EXPT:** Decerebrated Cat soleus muscle
  - Experimenter did a **Ramp-and-Hold** experiment, stretching the muscle. Muscle tension increased as he stretched the muscle, due to the Stretch Reflex. After a certain point the muscle tension stopped increasing.
  - **CUT DORSAL ROOTS** and the tension was even greater, due to lost inhibition by the *Vestibulospinal Tract*.

**INVERSE STRETCH REFLEX:** Once you stretch a muscle past a certain threshold, the rigidity will “melt away”, and the muscle will stretch easily. Past the threshold, the muscle is undergoing the inverse stretch reflex.

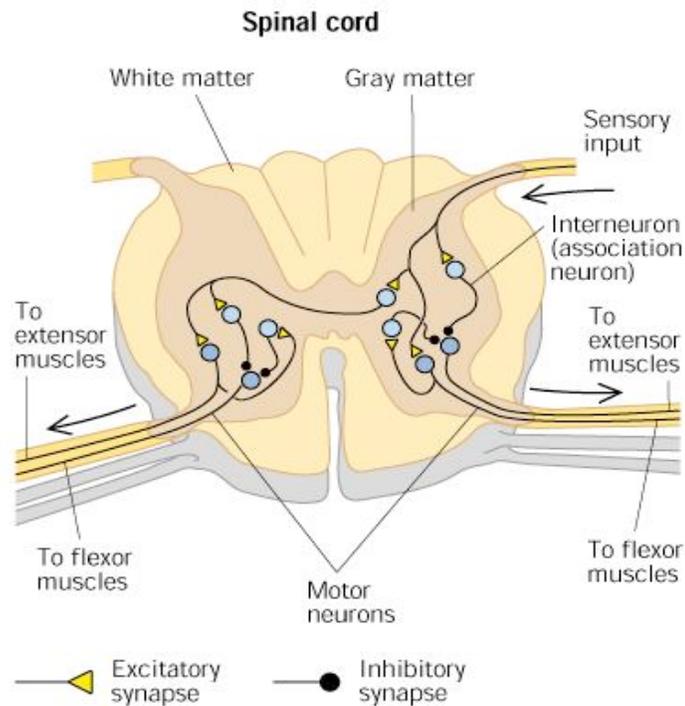
- **AFFERENT LIMB:** Golgi Tendon Organ, **IB** Afferents
- **EFFERENT LIMB:**  $\alpha$  Motor Neuron disinhibitory
- **PATHWAY:** The reflex is **disynaptic**. *Stretch Muscle past threshold -----> Golgi Tendon Organ stretches -----> IB Afferents fire -----> SYNAPSE with INHIBITORY interneuron in spinal cord -----> DECREASE  $\alpha$  Motor Neuron Activity back to same muscle -----> Decrease muscle tension -----> muscle lengthens easily*

**WITHDRAWAL (FLEXION) REFLEX:** Remove hand from a burning stove, for example.

- **Paraplegia / Quadriplegia:** It causes an increased Withdrawal Reflex, and it may also result in unintended autonomic responses such as defecation, urination.
- **C FIBERS:** Pain fibers initiate the reflex.
- **PATHWAY:** C Fibers activation -----> Dorsal Root -----> **Excitatory synapses to  $\alpha$  neuron and gamma neuron** -----> contraction of same muscle.
  - Activation of the gamma neuron will cause activation of **IA** Afferents, which will then initiate the stretch reflex -----> more  $\alpha$  activation.
  - The net result of this is that you get a *large, long lasting* reflex. **The reflex itself can easily outlast the original pain stimulus.**
  - There is also a **recurring excitatory circuit**, some excitatory interneurons will send fibers back to other excitatory interneurons, which potentiates the original signal in the spinal cord.

**RECIPROCAL INNERVATION: IA** Afferents from an extensor muscle will synapse with an interneuron that *inhibits the opposing (i.e. flexor) muscle*.

- **IA AFFERENTS** therefore have two monosynapses in the spinal cord:



- Excitatory (EPSP) to the  $\alpha$  Motor Neuron of the same muscle
- Excitatory interneuron -----> Inhibitory (IPSP) to the  $\alpha$  Motor Neuron of the opposing muscle.
- *The inhibitory arm of the reflex is disynaptic, while the excitatory arm is monosynaptic.*

**CROSSED EXTENSOR REFLEX:** The contralateral reflex for the withdrawal reflex. Step on a tack, and you withdraw one foot while extending the other.

- **PATHWAY:** Pain fibers synapse with two interneurons in spinal cord—one to ipsilateral side and one goes across ventral white commissure to contralateral side.
  - **IPSILATERAL** will then make two synapses, to cause **FLEXION** of the ipsilateral limb.
  - **CONTRALATERAL** will then make two synapses, to cause **EXTENSION** of the contralateral limb.

**MUSCLE TONE DISORDERS:** Hypotonia and Hypertonia arise from disorders in the sensitivity of  $\alpha$  Motor Neurons.

- **HYPOTONIA:** Decreased  $\alpha$  and gamma neuron excitability. Diminished reflexes and flaccid paralysis.
  - Examples: **Early phase of spinal cord transection**



- **HYPERTONIA:** Increase **tonic stretch reflex**, i.e. the response to muscle length when the muscle is not moving. Sustained contraction at rest, increased tonic stretch reflex, increased muscle stiffness
  - Examples: **Decerebrate Rigidity** (UMN Paralysis), **Parkinson's Disease**
- **SPASTICITY:** Increased **phasic stretch reflex**, i.e. the response to muscle velocity when it is stretching. The faster the stretch, the worse is the resistance to the stretch.
  - Examples: Late phase of spinal cord transection, Motor Cortex / SMA lesions.
  - **CLONUS:** Rhythmic series of contractions brought about by quick stretch of a spastic muscle. Clonus can occur with spastic muscles.

## SPINAL MUSCULAR ATROPHY (SMA):

- Types of Spinal Muscular Atrophy:
    - **ACUTE - SMA 1:** Onset at birth and death before age 2
    - **INTERMEDIATE (Werdnig-Hoffman) - SMA 2:** Survival beyond 4 years.
      - Scoliosis.
      - Death ultimately due to respiratory complications.
    - **CHRONIC (Kugelberg-Welander) - SMA 3**
  - GENETIC BASIS:
    - **SURVIVAL MOTOR NEURON (SMN):** The SMN gene is defective (duplication mutation) in virtually all cases of SMA.
    - **NEURONAL APOPTOSIS INHIBITORY PROTEIN (NAIP):** The NAIP gene is defective (duplication mutation) in many SMA cases, however this defect is not required for SMA.
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## NERVE SYNAPSES

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.
  - **Type II Synapse:** Found on Dendritic shaft or cell body.

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.
    - **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.

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**.

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

- Membrane Depolarizes.
- Voltage-Gated  $\text{Ca}^{+2}$  **Channels** open on pre-synaptic membrane.
- $\text{Ca}^{+2}$  comes flooding into the pre-synaptic axon.
- **$\text{Ca}^{+2}$ -Dependent Protein Kinases** become activated in the presence of  $\text{Ca}^{+2}$ . 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.

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)

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.

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

- Signal Transduction Pathways, for the 25<sup>th</sup> time:
  - $\beta$  Adrenergic: cAMP.
  - $\alpha$  Adrenergic:  $\text{IP}_3$  + DAG
  - **Arachidonic Acid**: It is released by the cell membrane **Phospholipase A<sub>2</sub>**. Arachidonic acid then leads to several short-lived metabolites:
- EFFECTS OF PROTEIN PHOSPHORYLATION:
  - Close  $\text{K}^+$  Channels: They can lead to closure of  $\text{K}^+$  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**: Some 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  $\text{Na}^+$ -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  $\text{Na}^+$ ,  $\text{Ca}^{+2}$ , and  $\text{K}^+$  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  $\text{K}^+$  Channels can also cause an IPSP (via  $\text{K}^+$  out -----> **hyperpolarization**).

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

- $\text{Na}^+$  and  $\text{Ca}^{+2}$  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  $\text{Na}^+$  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  $\text{K}^+$  Channel (which this might be) and counteracts the  $\text{Na}^+$  current, slowing down the rate of depolarization.
  - **STIMULUS SIGNIFICANTLY ABOVE RESTING:** The channel is **inactivated**, so that there is no countercurrent to the  $\text{Na}^+$  channels, so that depolarizations occur more rapidly.
- **$\text{Ca}^{+2}$ -Activated Potassium Channel:** *Spike Frequency Adaptation.*
  - In response to high  $\text{Ca}^{+2}$ , 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  $\text{Ca}^{+2}$  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.
  - 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  $\text{Na}^+$  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  $\text{Ca}^{+2}$  Channels** to open on the pre-synaptic membrane, and  $\text{Ca}^{+2}$  comes pouring into the *presynapse*.
  - The  $\text{Ca}^{+2}$  then triggers the mobilization of the synaptic vesicles and ultimate exocytosis of acetylcholine.
  - About 15-250 quanta of acetylcholine are released, in 1-2 millisecond.
- **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.
  - ION CHANNEL: The cation channel in the middle of the acetylcholine receptor, when open, is equally permeable to  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{+2}$
- 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.
  - This triggers the standard **Voltage-gated  $\text{Na}^+$  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  $\text{Ca}^{+2}$  channels** in the SR to open, leaking  $\text{Ca}^{+2}$  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: By **Acetylcholinesterase**.
  - **Neostigmine:** Blocks Acetylcholinesterase.
  - Some ACh is also removed by simple diffusion.

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## NEUROTRANSMITTERS

**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 in CNS.
  - SYNTHESIS:  $\alpha$ -Ketoglutarate -----> GABA, via a transamination and then decarboxylation.
  - **GABA<sub>A</sub> RECEPTOR:** Opens a **Cl<sup>-</sup> channel**, which hyperpolarizes the membrane.
  - **BENZODIAZEPINES:** facilitate GABA's action by increasing the **frequency** of **Cl<sup>-</sup> channel** opening.
  - **BARBITURATES:** Also, facilitate GABA's action by increasing the **duration** of **Cl<sup>-</sup> channel** opening.
  - **GABA<sub>B</sub> AUTORECEPTOR:** Thought to decrease inward  $\text{Ca}^{+2}$  flux on presynapse, thereby inhibiting further GABA release.
  - REMOVAL: The presynapse reuptake transporter is a **Na<sup>+</sup>/GABA Antiport ATPase**.

- **Glycine:** Also causes the opening of **Cl<sup>-</sup> channels** on the post-synaptic membrane.
  - DISTRIBUTION: Glycine is specific to certain regions of CNS.
  - SYNTHESIS: Serine -----> Glycine
  - GLYCINE RECEPTOR: *Ionotropic*.
  - **Strychnine** blocks Glycine receptors.
  - REMOVAL: The only known method of removal is **reuptake**. Degradation may also occur.
- **Glutamate and Aspartate:** Both are excitatory Neurotransmitter in the CNS. Generally they work by opening **Na<sup>+</sup> channels** and depolarizing post-synapse membrane.
  - SYNTHESIS: Brain tissue makes them *de novo*. They do **not** diffuse into CNS neurons from the general circulation.
  - **N-Methyl-D-Aspartate (NMDA) RECEPTOR:** A *Voltage-Gated and Ligand-Gated* receptor, which has *both metabotropic and ionotropic effects*.
    - VOLTAGE-ACTIVATION: Magnesium is driven out, and **Ca<sup>+2</sup> and Na<sup>+</sup>** 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.*
  - **Glutamate Toxicity:** High levels of glutamate are toxic.

**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 ----> L-Dopa ----> Dopamine
  - DISTRIBUTION: It is the most prominent catecholamine in the brain, found in the midbrain, through three neuronal tracts.
  - DOPAMINE RECEPTORS: Dopamine has *metabotropic receptors*.
  - DOPAMINERGIC DRUGS: Lots of them, both agonistic and antagonistic.
  - REMOVAL: Two compounds will degrade all catecholamines:
- **Norepinephrine:**
  - SYNTHESIS: *Dopamine beta-Hydroxylase*: Dopamine -----> Norepinephrine
  - 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**.
  - DISTRIBUTION: In CNS, the medulla, pons, and midbrain.
  - SEROTONIN RECEPTORS: *Metabotropic*.
  - DRUGS: Several, both antagonistic and agonistic.
  - REMOVAL: Reuptake, plus monoamine oxidase.
- **Histamine:** Involved in arousal, mental disease, cardiovascular control, to name a few.
  - SYNTHESIS: It is synthesized from **Histidine**
  - DISTRIBUTION: Only hypothalamus
  - HISTAMINE RECEPTORS: *Metabotropic*
  - 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 in **Neuro-Pharmacology**.
- **SYNTHESIS:** *Choline Acetyltransferase*: Choline -----> Acetylcholine
- **ACETYLCHOLINE RECEPTORS:** There are multiple types of both the muscarinic and nicotinic type receptors.
  - **MUSCARINIC RECEPTORS:** *Metabotropic Receptor*
    - **Muscarine** is an agonist to the receptor.
    - **Atropine** is an antagonist.
  - **NICOTINIC RECEPTORS:** *Iontropic Receptor*
    - **Nicotine** is an agonist to the receptor.
    - **Tubocurarine** is an antagonist.
- **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.

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## 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.

- **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.
  - **Chromatolysis:** The structural changes to the cell body resulting from axotomy.
  - 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.
- **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 (BDNF)**
- **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. BDNF, 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.

## SLEEP & WAKEFULNESS

**ELECTROENCEPHALOGRAPH (EEG):** Electrodes are placed in five general regions bilaterally, over the five cortices.

- The EEG measures only cortical activity—not subcortical activity.

Rhythm	Dominant Freq	Amplitude	State of Arousal
Beta	20 Hz <i>High Frequency</i>	<i>Low Amplitude</i>	Alertness REM Sleep
Alpha	10 Hz high frequency	High	Alertness but with eyes closed; Relaxed wakefulness
Theta	3 - 7 Hz	High	Slow-Wave Sleep
Delta	0.5 - 3 Hz <i>Low Frequency</i>	High	Slow-Wave Sleep

## SLEEP STAGES:

- **Stage 1:** Stage 1 and REM show the same patterns: **beta-waves**
- **SLOW-WAVE:** Low sympathetic tone, regular breathing, normal muscle tone.
  - **Stage 2:** Transitional sleep.
  - **Stage 3:** Deep sleep, **theta waves**
  - **Stage 4:** Deep sleep, **delta waves**
- **REM:** Rapid-Eye Movement.
  - Rapid eye movements, very low muscle tone (very still), high cortical activity (beta waves), **penile erection** is hallmark sign of REM sleep.
  - **Dreaming.** People aroused out of REM sleep remember their dreams vividly.
  - There is *active cortical inhibition of spinal muscles* thus resulting in low muscle tones. If it weren't for this active inhibition, then the subject would probably sleep walk or move during this period of sleep.
- Normal Sleep Progression: 1, 2, 3, 4, 3, 2, REM, 2, 3, 4, 3, 2, REM, 2, 3, 4 ... etc.
- *Sleep is an active process. It is not simply the absence of consciousness.*

**ALPHA WAVES:** Relaxed Wakefulness with the eyes closed.

- The recording is most pronounced over the parietal and occipital lobes, and is least prevalent over the frontal lobe.

## SYNCHRONIZED vs. DESYNCHRONIZED WAVES

- **Synchronized Waves** characterizes slow-wave sleep. Synchronous discharge of neurons.
  - **RETICULAR NUCLEUS of Thalamus** is one of the major source of synchrony in the brain. It projects neurons onto *itself* and releases **GABA** as an inhibitory neurotransmitter to cause synchronization of discharge.
- **Desynchronized Waves:** Neurons don't discharge at same time. Characteristic of arousal.

## DEFINITIONS

- **Sleep:** Normal, physiological alteration in consciousness and unconsciousness, which is freely reversible with appropriate stimulation.
- **Coma:** A state of irreversible unconsciousness. (May be reversible).
- **Concussion:** Brief loss of consciousness after a blow to the head, with no permanent ramifications.
- **Syncope (Fainting):** Massive, widespread anoxia of cortical neurons.
  - It happens from a hyperactive Vagus nerve that stops the heart from pumping enough blood to the brain. Fainting relieves the hyperactivity of the Vagus, and everything return to normal.

**CONSCIOUSNESS:** Awareness of environment and self. It involves two systems.

- **RETICULAR ACTIVATING SYSTEM (RAS):** It is responsible for the **arousal** aspect of Consciousness.
  - Activity of Reticular formation and some brainstem nuclei, which involve the **Reticular Formation** and **Diffuse Thalamic Nuclei**
- **CEREBRAL CORTEX:** It is responsible for the **content** aspect of consciousness.
- Anatomical Lesions that can produce coma:
  - **Posterior Fossa:** All of the subcortical structures, caudal to the Tentorium Cerebelli. A lesion to the posterior fossa will damage the Reticular Formation and can thus result in coma.
  - **Uncal Herniation** can press up against Tegmentum causing coma.
  - Metabolic Encephalopathy.
- TONIC vs. PHASIC Modes of Consciousness:
  - **TONIC MODE:** Characteristic of Wakefulness and REM sleep.
  - **PHASIC MODE:** Characteristic of Slow-Wave sleep.
- Neurohormonal Systems of Arousal and sleep:
  - **CHOLINERGIC SYSTEM:** Raises the resting potential of thalamic and cortical neurons by a few millivolts and is related to the RAS.
  - **NORADRENERGIC SYSTEM:** Raises the resting potential of thalamic and cortical neurons by a few millivolts and is related to the RAS.
  - **SEROTONERGIC SYSTEM:** Related to *sleep* and to the pain-control system.
    - (Pain Control Pathway): Periaqueductal Gray -----> **Nucleus Raphe Magnus** -----> Dorsal Horn of Spinal Cord to inhibit pain. This pathway is also involved in causing sleep.
    - **Preoptic Area (POA) of Hypothalamus:** It also releases Serotonin.

## SLEEP APNEA

- **SYMPTOMS:** Excessive daytime sleepiness, resulting from waking up many times during the night due to obstructed airways.
  - Hypercapnia, Hypoxia, Compensated Respiratory Acidosis, morning headaches.
  - Complications: Cor Pulmonale (Right-Heart Failure), Pulmonary Hypertension, Systemic Hypertension
  - Inordinately loud snoring

- Types:
  - **Obstructive Sleep Apnea:** Sleep Apnea due to obstructed or collapsed upper airways. Essentially a respiratory problem.
  - **Central Sleep Apnea:** Sleep Apnea due to a loss of the CNS drive to breathe - i.e. sleep somehow inhibits the Phrenic Nerve from firing on the diaphragm.
- Treatment:
  - **Continuous Positive Airway Pressure (CPAP):** Physically keep upper airways open, for obstructive apnea.
  - Tracheostomy, or procedures to surgically widen the space in the nasopharynx are also options.
  - **Medroxyprogesterone** can be given to *women* to stimulate breathing in the case of central apnea.

**EPILEPSY:** *Two or more unprovoked seizures.*

- **SEIZURE:** Abnormal behavior resulting large amplitude hypersynchronous neuronal discharge.
- **ETIOLOGIC CLASSIFICATION of SEIZURES:**
  - **Acute Symptomatic:** *Non-Epileptic* seizures caused by some explainable, reversible condition such as *hypernatremia* (high blood  $\text{Na}^+$ ).
  - **Remote Symptomatic:** Epileptic seizures caused by physical or metabolic trauma, such as an automobile accident, which resulted in incurable Epilepsy.
  - **Idiopathic:** Genetic or unexplained Epilepsy.
- **BEHAVIORAL CLASSIFICATIONS OF SEIZURES:**
  - **Generalized:** *At Onset*, a seizure that starts by virtually all neurons of the cortex synchronously discharging.
  - **Partial:** *At Onset*, a seizure that starts by a localized region of cortex discharging.
- **Dilantin** is a drug that is effective in treating partial seizures.

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