Lecture 6C

Physiology of Pain
Types of Pain
Physiologic Response to Pain
Treatment of Pain

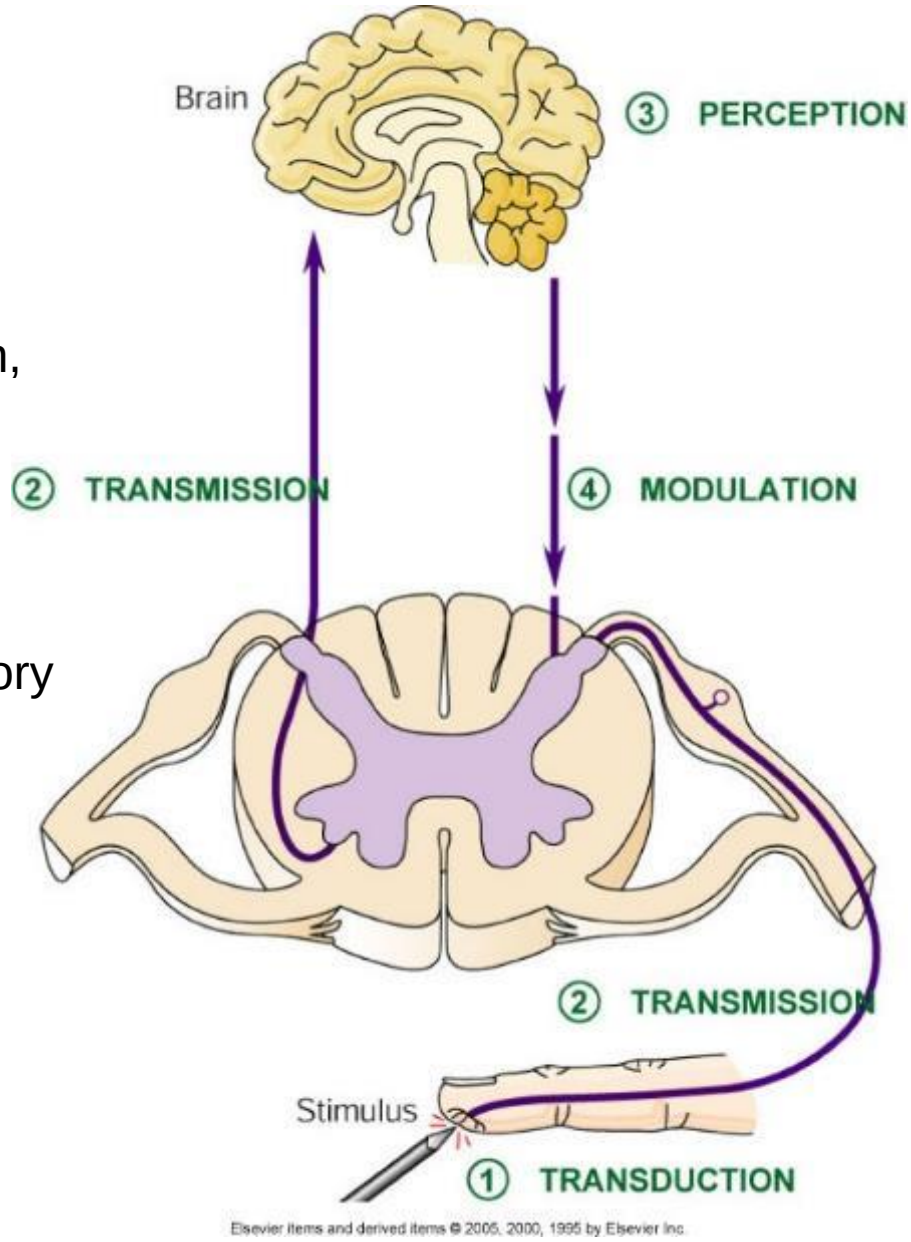
The Physiology of Pain

Pain Signaling (Nociception): Four Processes

- **Transduction:** Interaction between pain stimuli and pain receptors (nociceptors)
- **Transmission:** Pain impulses travel in sensory neurons to the dorsal horn of the spinal cord, cross to the opposite side of the spinal and climb to the brain.
- **Perception:** Impulses are integrated in the brain to produce the perception of pain.
- **Modulation:** The perception of pain generates impulse pathways from the brain back down to the dorsal horn of the spinal cord to modulate pain transmission.

1. Pain Transduction

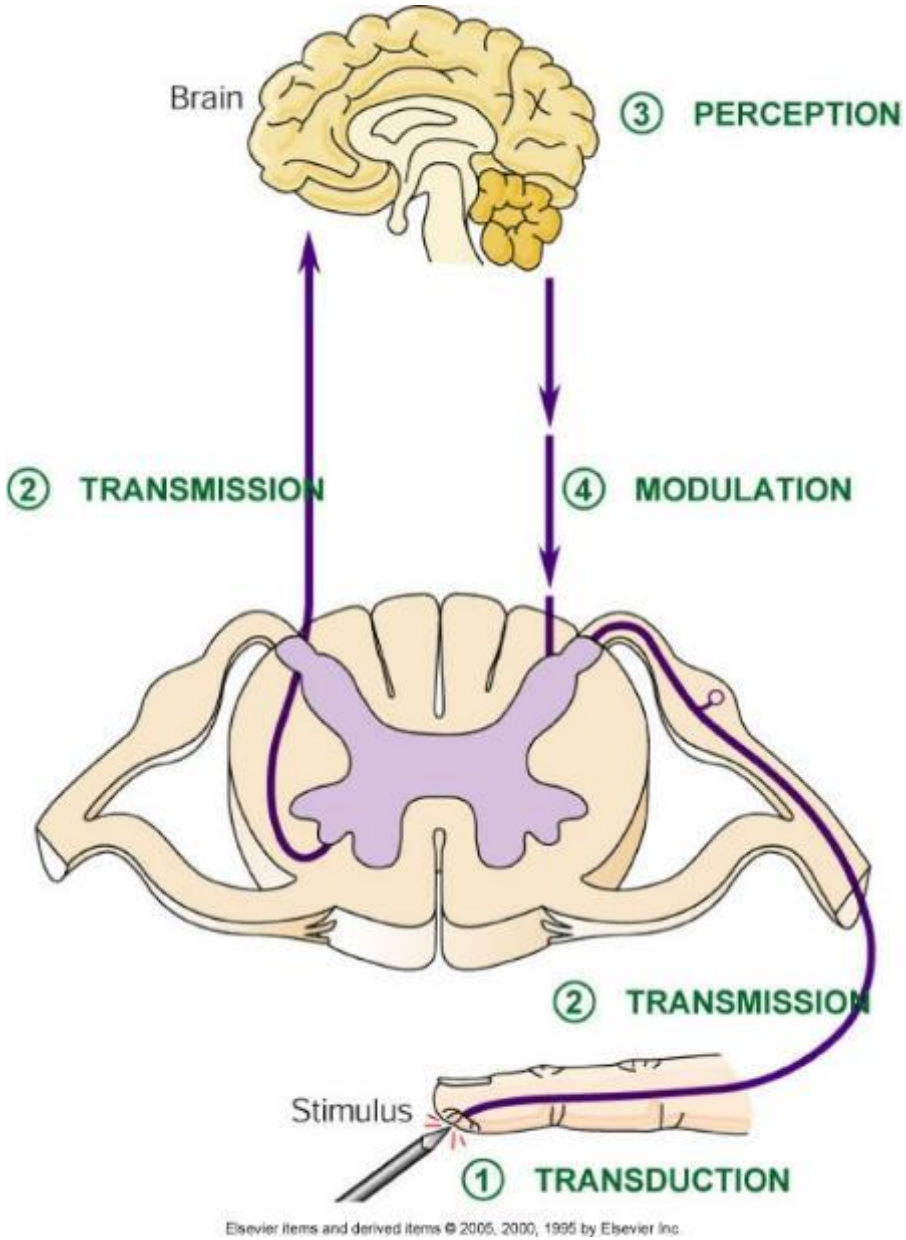
- Nociceptors convert painful stimuli into action potentials.
- Painful physical stimuli: Pressure, tension, heat, cold
- Painful chemical stimuli: K+, H+, lactate, histamine, serotonin, bradykinins, and prostaglandins. Note that many pain-stimulating chemicals are also inflammatory chemicals.



2. Pain **Transmission**

PNS to Spinal Cord

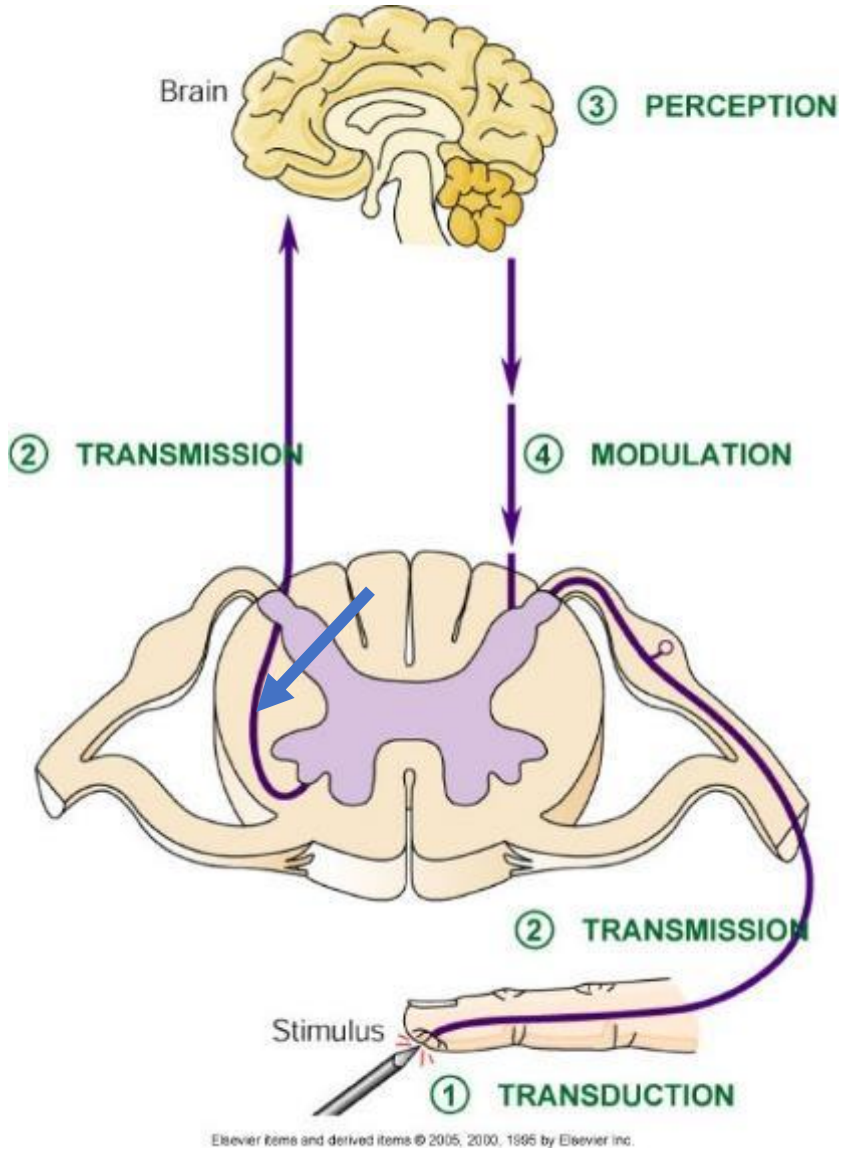
- Pain signals are transmitted to the spinal cord in two types of unipolar sensory neurons:
  - **Aδ (A delta) fibers**
  - **C fibers**
- Pain neurons have their cell bodies in the dorsal root ganglia of the spinal nerves.



2. **Pain Transmission**

Spinal Cord to Brain

- Aδ and C fibers synapse with and release the neurotransmitter, Substance P, to interneurons in the dorsal horn of the spinal cord.
- Those interneurons synapse with other interneurons that decussate (crossover) and climb to the brain in the anterolateral (spinothalamic) tracts of the spinal cord. See the blue arrow.

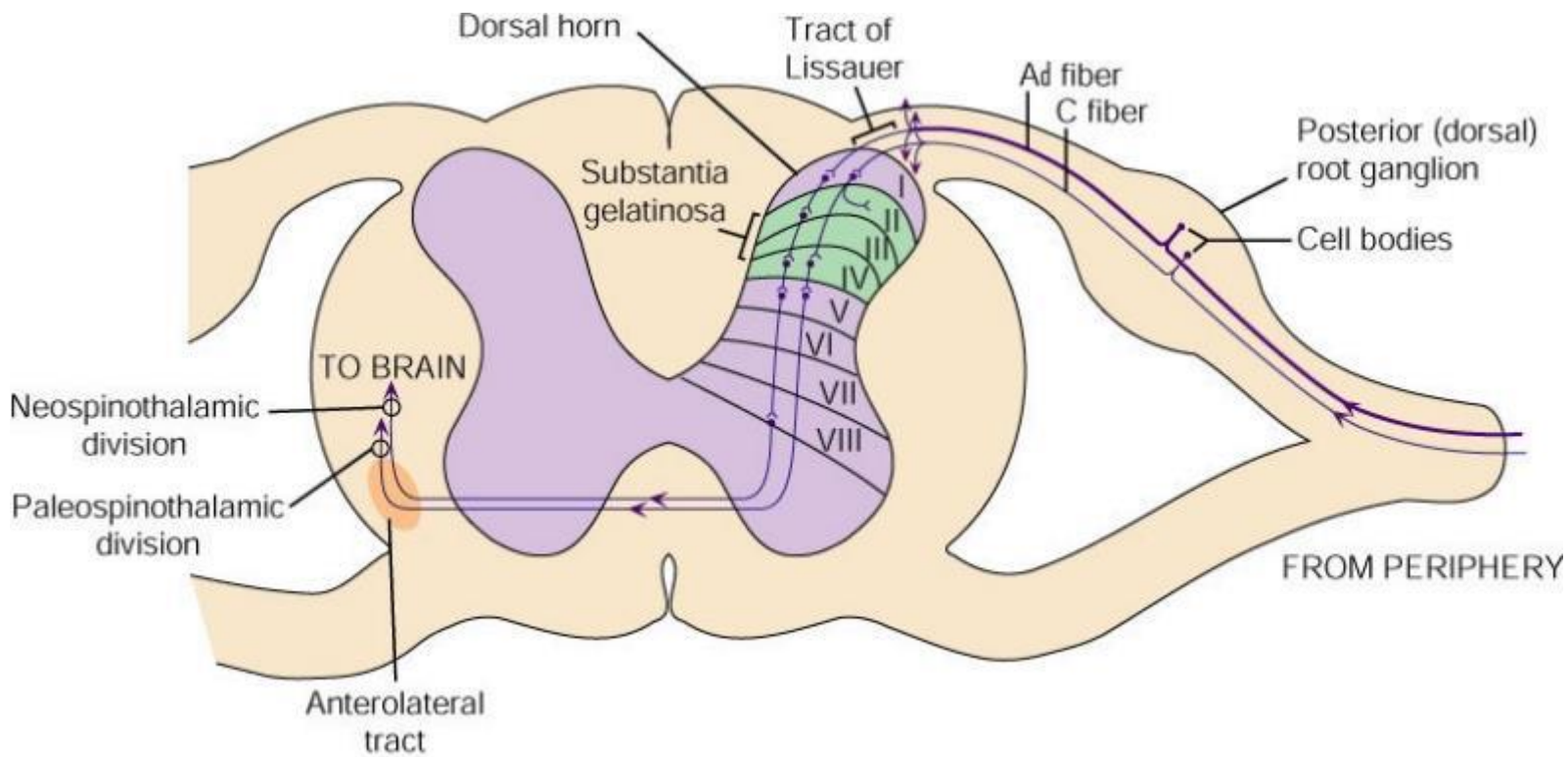


2. Pain Transmission by Sensory Neurons

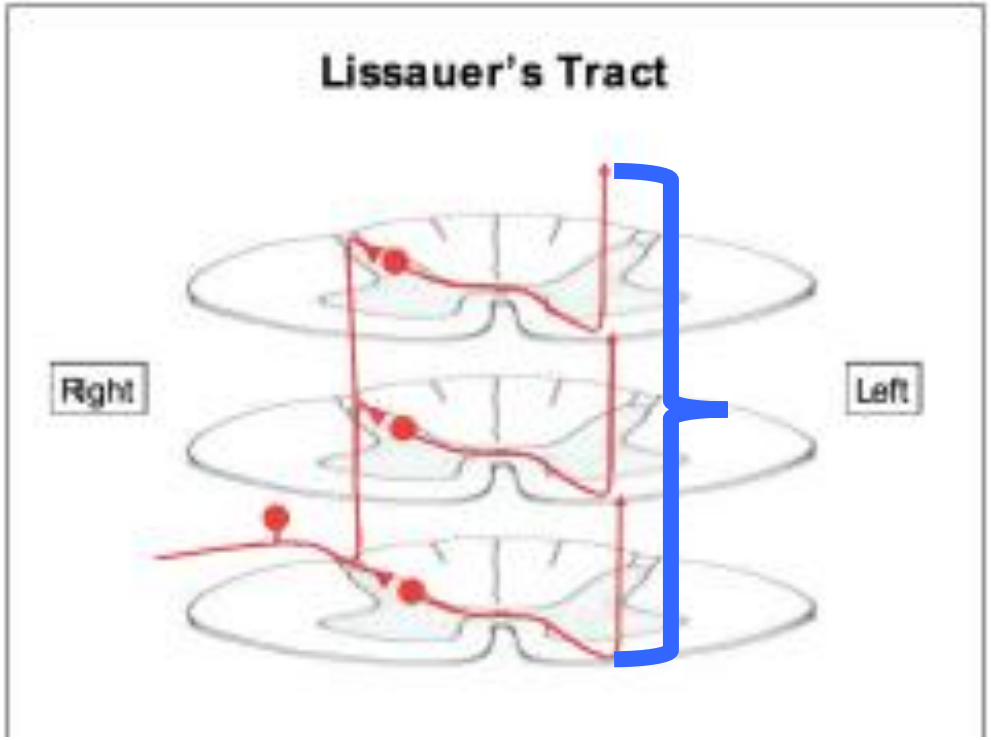
Feature	Aδ Fibers	C Fibers
Structure	Myelinated	Unmyelinated
Amount	10%	90%
Source	Mechanical	Mechanical, Chemical, Thermal
Speed	Fast, 5-10 m/sec Via Neospinothalamic Tract	Slower, 0.6-2 m/sec Via Paleospinothalamic Tract
Quality	Sharp, stinging, cutting, pinching, highly localized	Dull, burning, aching, poorly localized, evokes emotional response

2. Pain Transmission

As the afferent fibers of the sensory neurons approach the dorsal horn of the spinal cord, they branch to form collaterals that climb up or down the cord for two or three spinal segments within the Tract of Lissauer (white matter) before penetrating the dorsal horn.

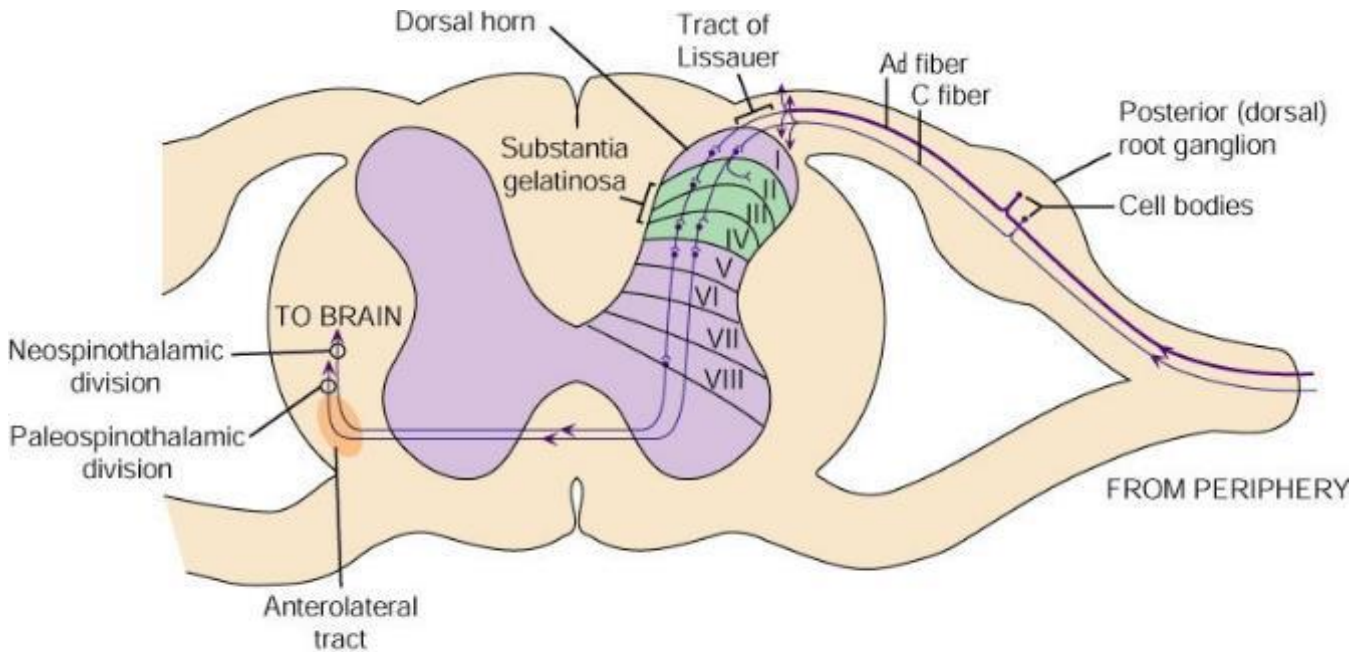


Tract of Lissauer: This diagram shows sensory input ascending two spinal sections in the Tract of Lissauer (blue bracket), but input can also descend a few segments.



2. Pain Transmission

As the afferent fibers of the sensory neurons enter the dorsal horn of the spinal cord they synapse with interneurons in the lamina (numbered I through VIII from dorsal to ventral) of the spinal cord. Post synaptic neurons carry impulses from the lamina across to the opposite side of the cord to the anterolateral tract.



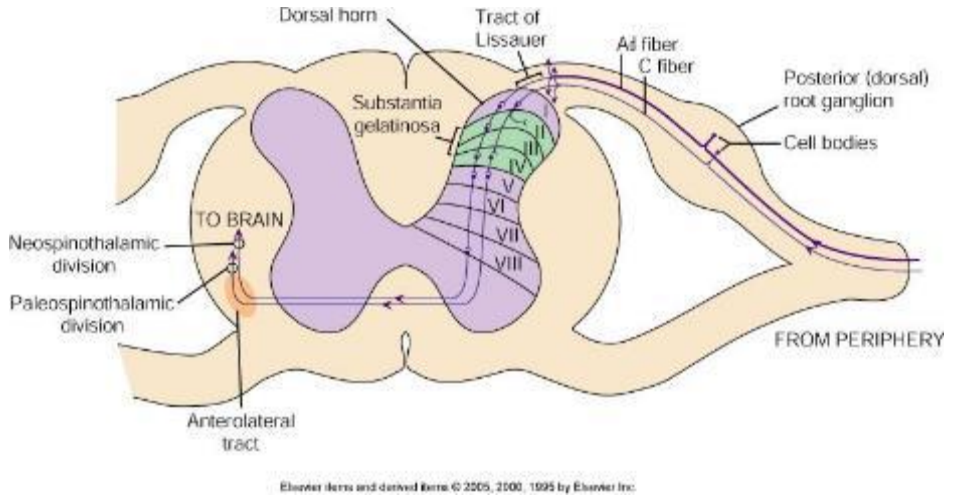
2. Pain Transmission

Aδ fibers synapse in lamina I and lamina V.

C fibers synapse in lamina I and lamina II.

The substantia gelatinosa is located in lamina II (which sends impulses into lamina III and IV). It is an important area for modulation of pain.

Lamina V is important as an area where inputs from visceral and peripheral fibers converge. This lamina is thus the site of referred pain generation.



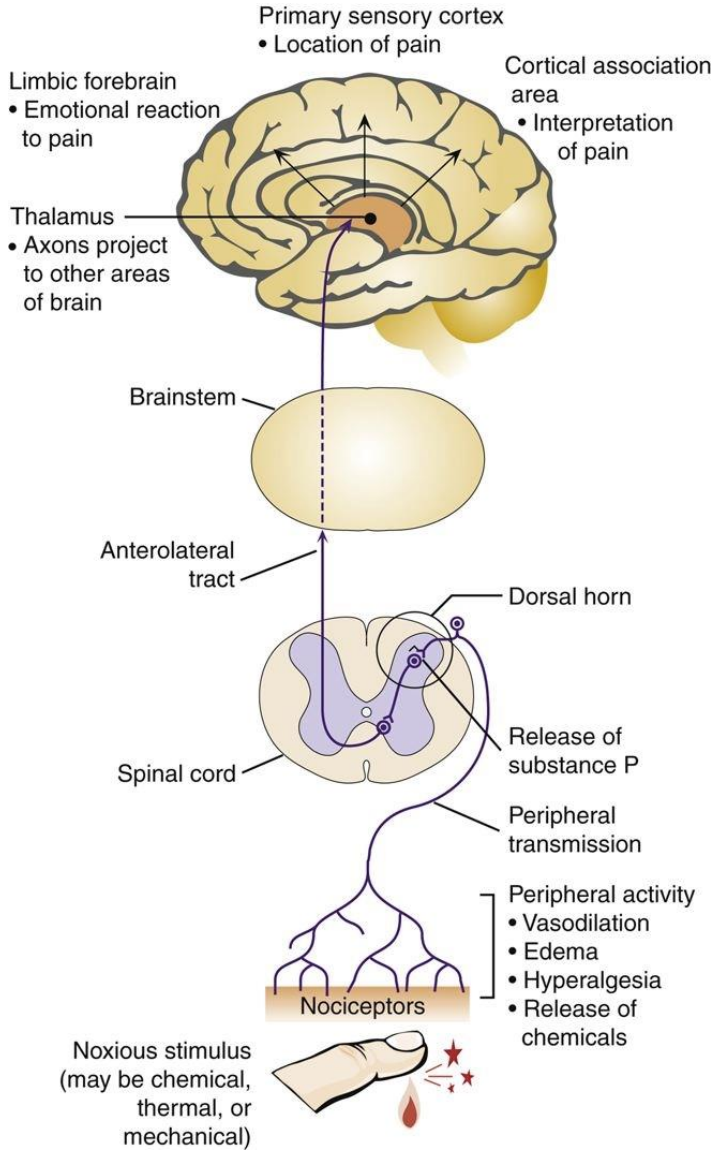
2. Pain Transmission

Pain signals originating in Aδ fibers ascend in the NEOSPINOTHALAMIC DIVISION of the anterolateral tract.

Rapid transmission to the thalamus (the “traffic director of sensory input) occurs. From the thalamus neurons carry pain impulses higher brain centers occurs.

Pain signals originating in C fibers ascend in the PALEOSPINOTHALAMIC DIVISION of the anterolateral tract.

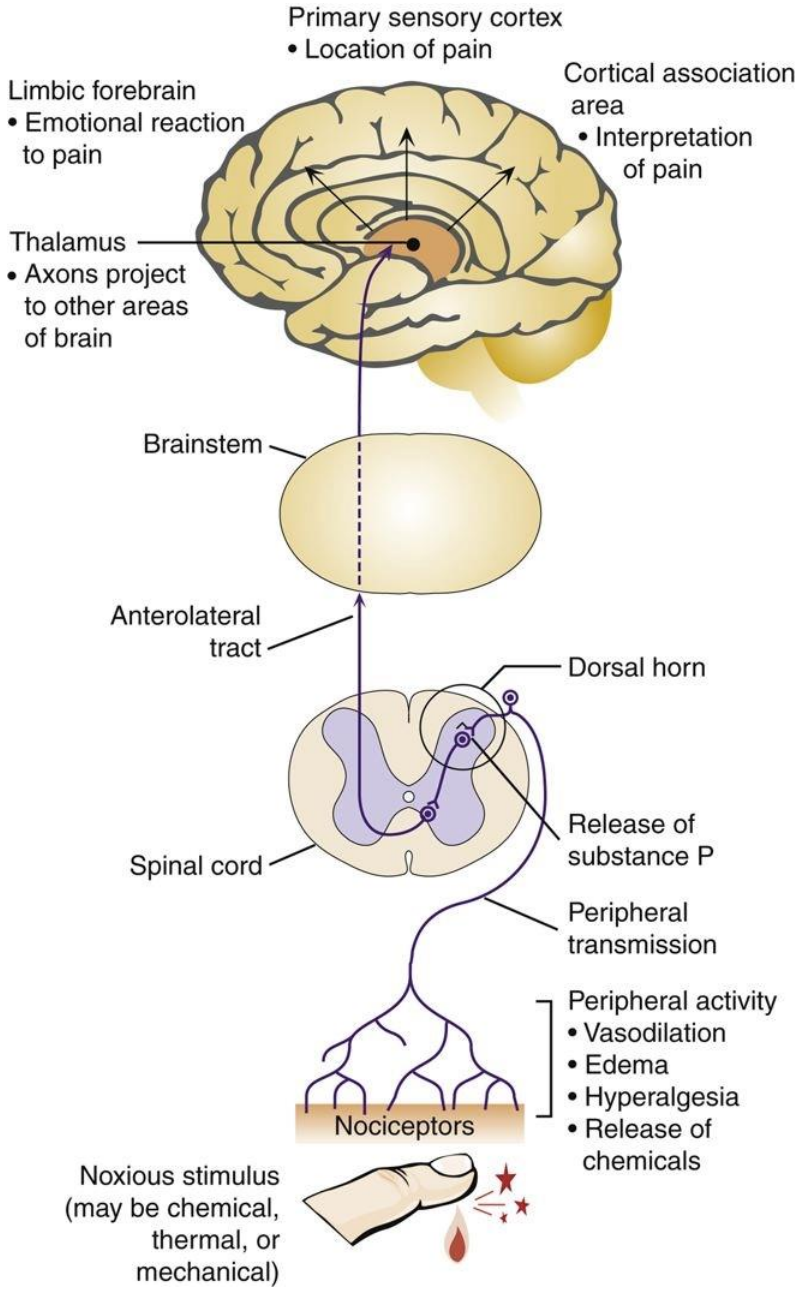
Slower transmission to the thalamus occurs. From the thalamus neurons carry pain impulses to higher brain centers occurs.



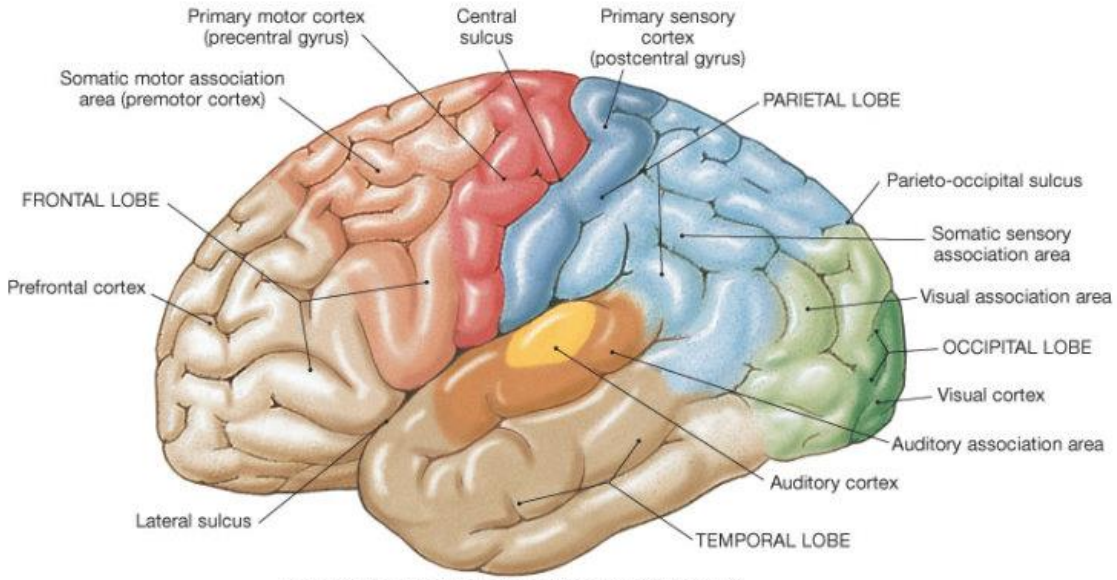
3. **Pain Perception**

From the thalamus neurons carry pain information to the:

- Limbic system which adds emotion to pain perception.
- Primary sensory cortex in the post central gyrus. It functions in in the perception of pain location.
- Somatic sensory association area of the cortex which integrates pain inputs with other sensory inputs relevant to the perception of pain quality (sharp vs dull, etc.).



- The **primary sensory cortex** is in the postcentral gyrus of the parietal lobe. Bright blue in the diagram.
- The somatic sensory association area is just posterior to the post central gyrus in the parietal lobe. Light blue in the diagram.



(a) Motor and sensory areas of the cerebral cortex

The locations of the limbic system structures are shown in red.

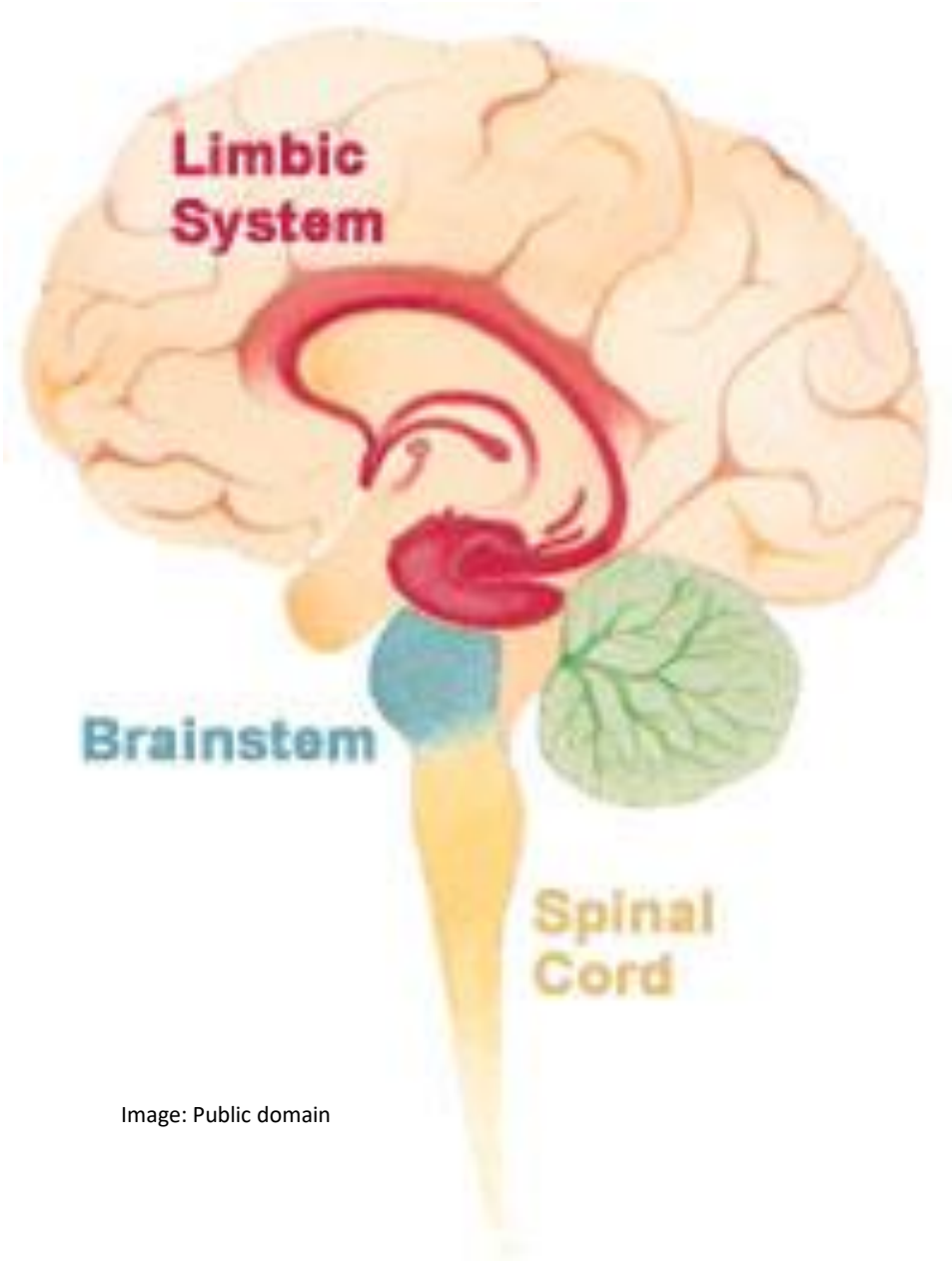
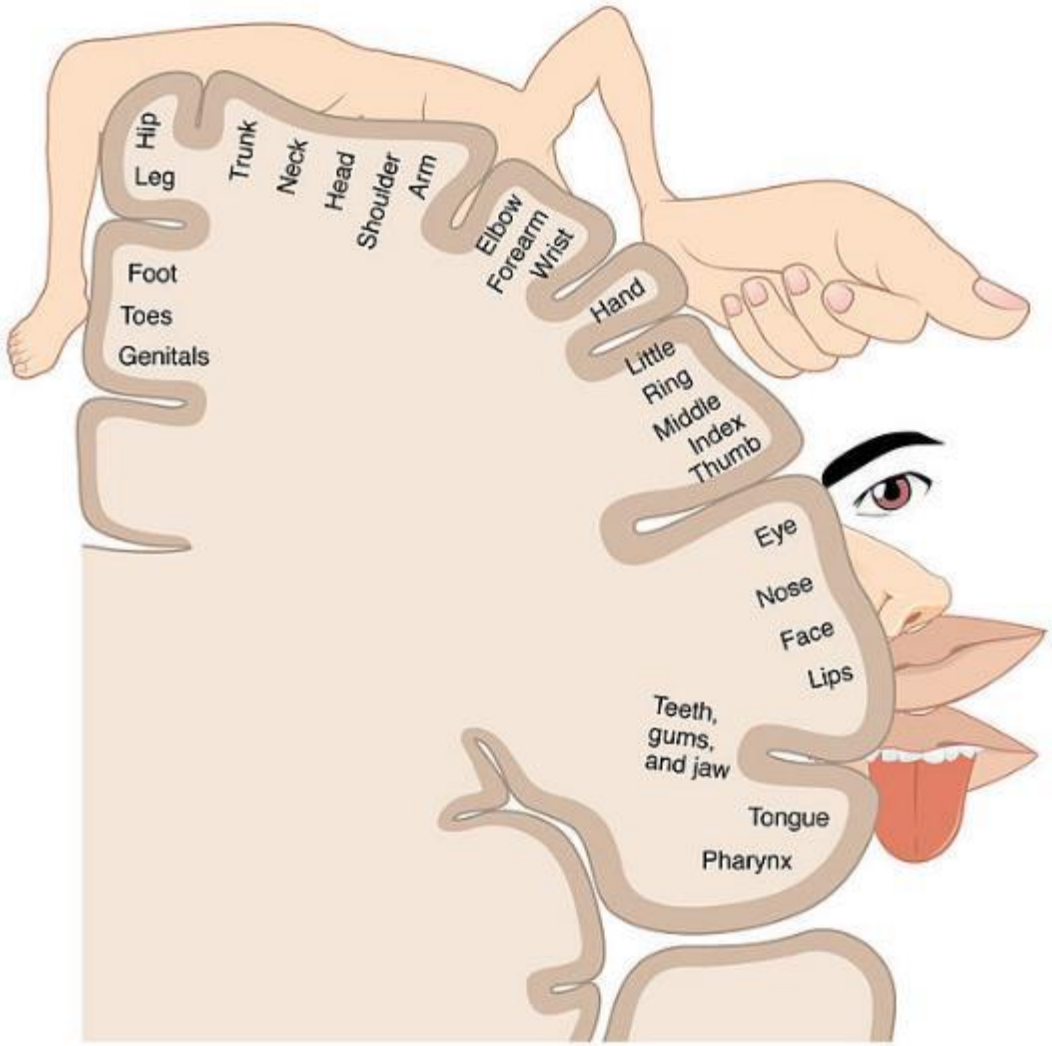


Image: Public domain

This is image is the **homunculus of the primary sensory cortex**. It depicts the area of the postcentral gyrus that receives sensory information from each of several body locations.



3. **Pain Perception**

- The primary sensory cortex allows **localization of pain** because nociceptor pathways are kept in strict anatomical order in both the spinal cord and in the primary sensory cortex of the post central gyrus.
- The term **radiculopathy** refers to pain perceived to be localized to a dermatome. A dermatome is the surface area of the body served by sensory neurons in a particular spinal nerve. Vertebral disc disease is the most common cause of radiculopathy. Shingles pain is also radicular in nature.
- The term **peripheral neuropathy** refers to pain (or other odd sensations) perceived at the surface of the body that does NOT follow a dermatomal pattern. Examples include carpal tunnel syndrome (wrist and part of the hand) and diabetic neuropathy (both legs and feet in a stocking-like pattern).

Radiculopathy and Peripheral Neuropathy

Dermatomes to add text

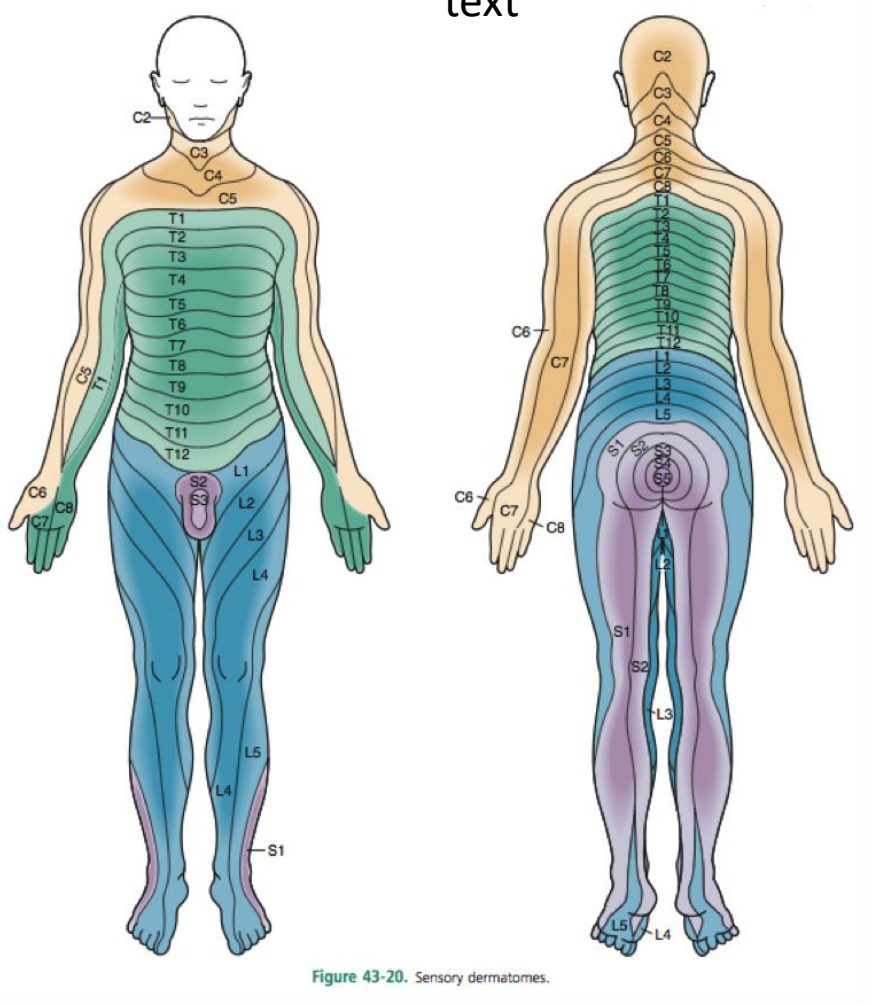
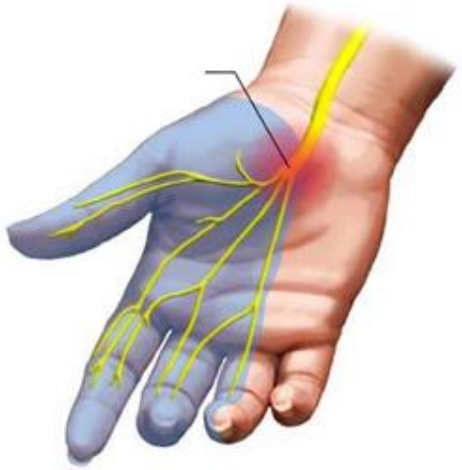
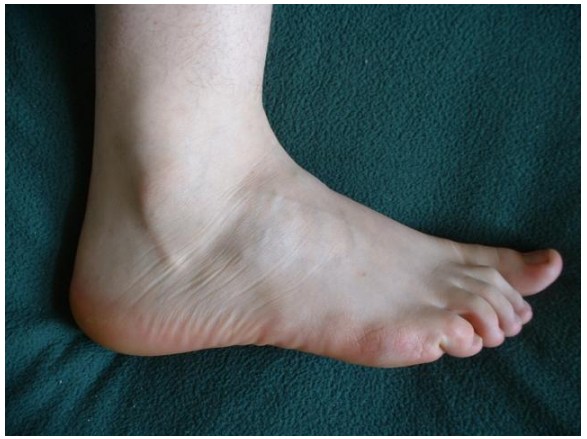


Figure 43-20. Sensory dermatomes.

Carpel Tunnel o t

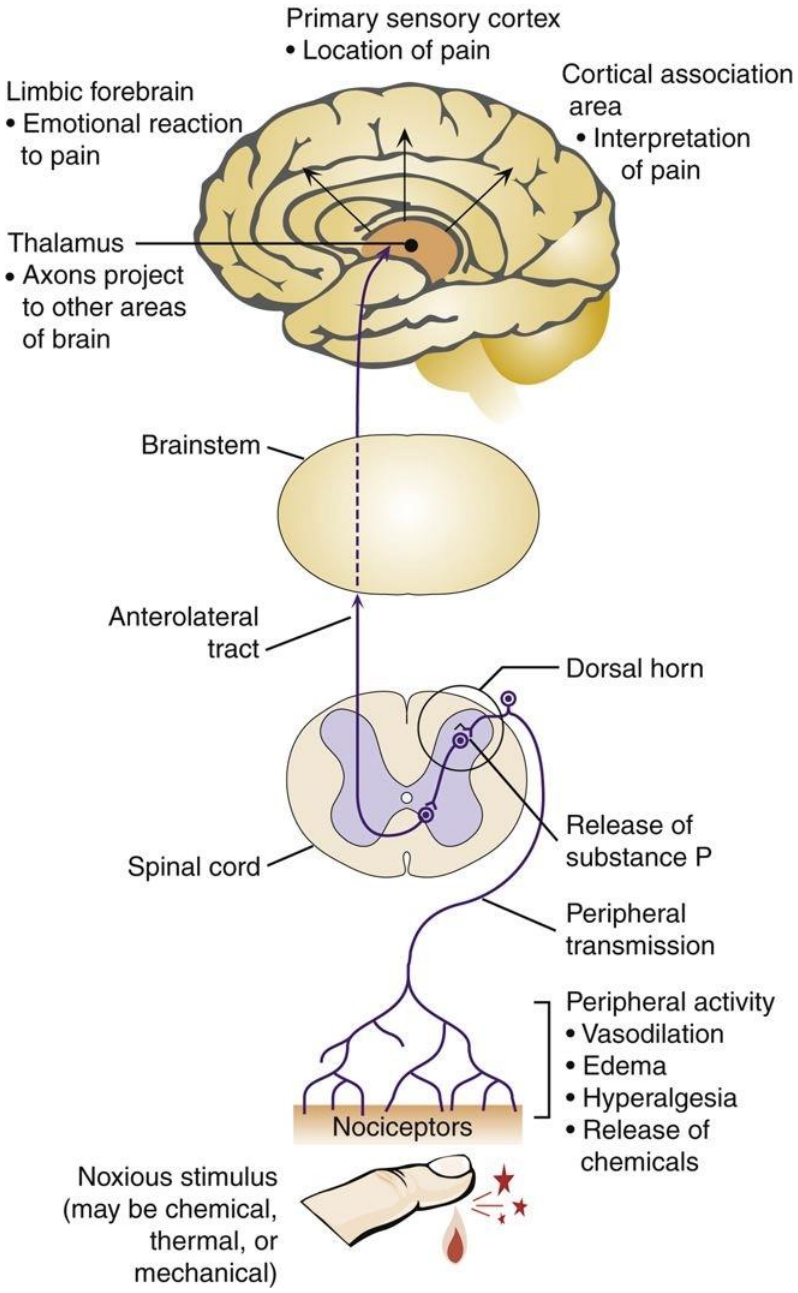


Diabetic Neuropathy



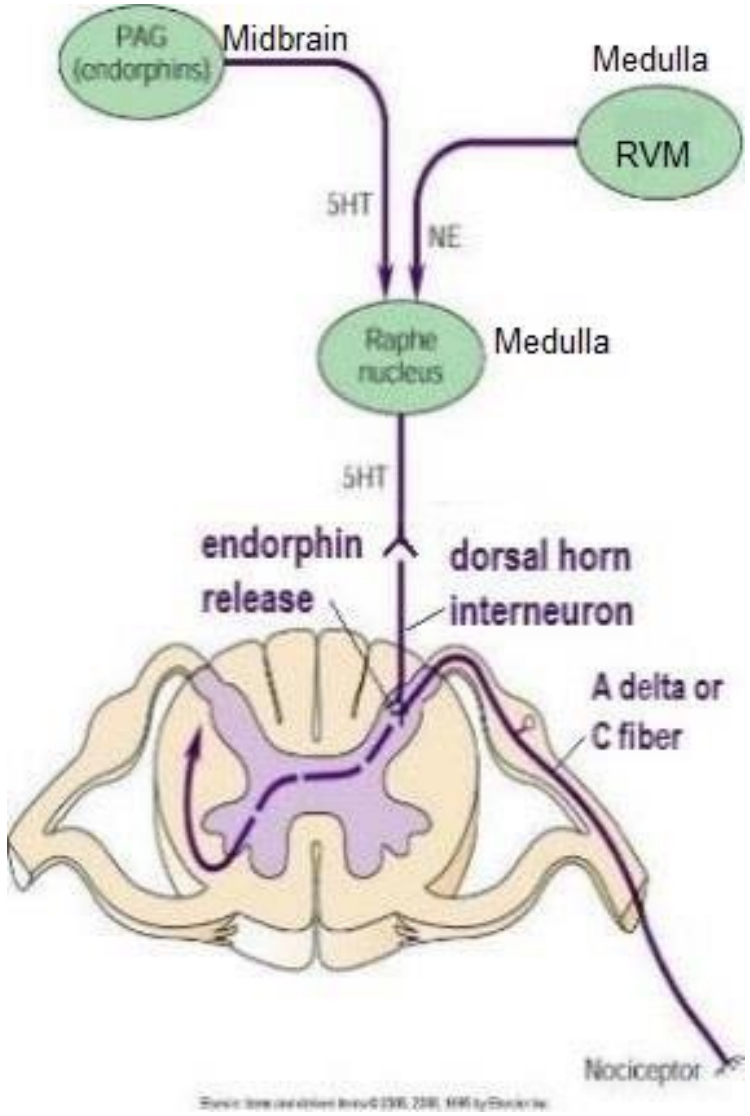
3. **Pain Perception**

- Pain perception is a combination of pain threshold and pain tolerance.
- Pain threshold is the level of stimulus required in order for pain to be perceived. It is very similar from person to person.
- Pain tolerance is the degree of pain sustained before seeking help. It varies widely person to person.



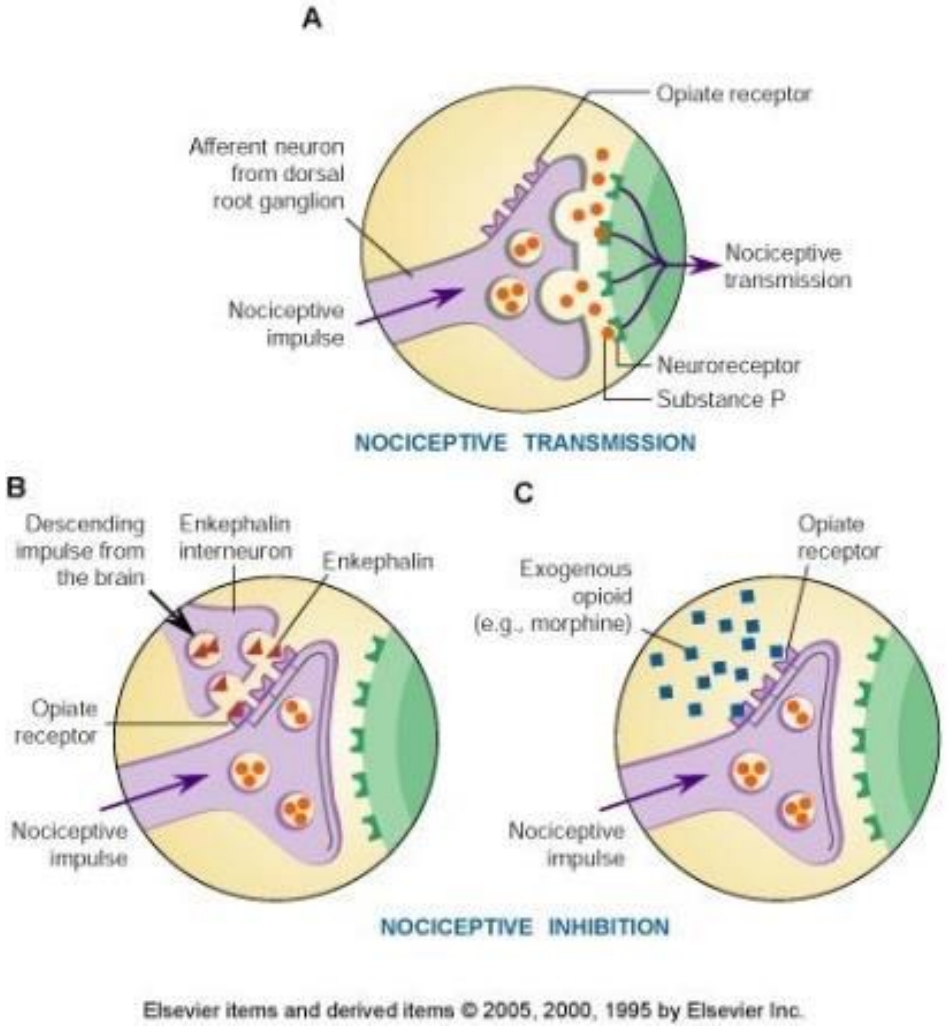
4. **Pain Modulation**

- As impulses in the ascending pain pathway travel through the brainstem, a descending pain modulating pathway is initiated.
  - Neurons of the **periaqueductal gray matter (PAG)** near the cerebral aqueduct in the midbrain, release **serotonin** (5HT) to the neurons of the **raphe nucleus** in the medulla. (The PAG also releases endorphins locally in the brain.)
  - Neurons of the **rostral ventral medulla (RVM)** release **norepinephrine (NE**) to neurons of the **raphe nucleus.**
- From the raphe nucleus, fibers project down to **interneurons in the dorsal horn** (substantia gelatinosa, lamina II and III) of the spinal cord where they release serotonin.
- The dorsal horn interneurons then release natural **opioids (endorphins)** to Aδ fiber and C fiber axon terminals.



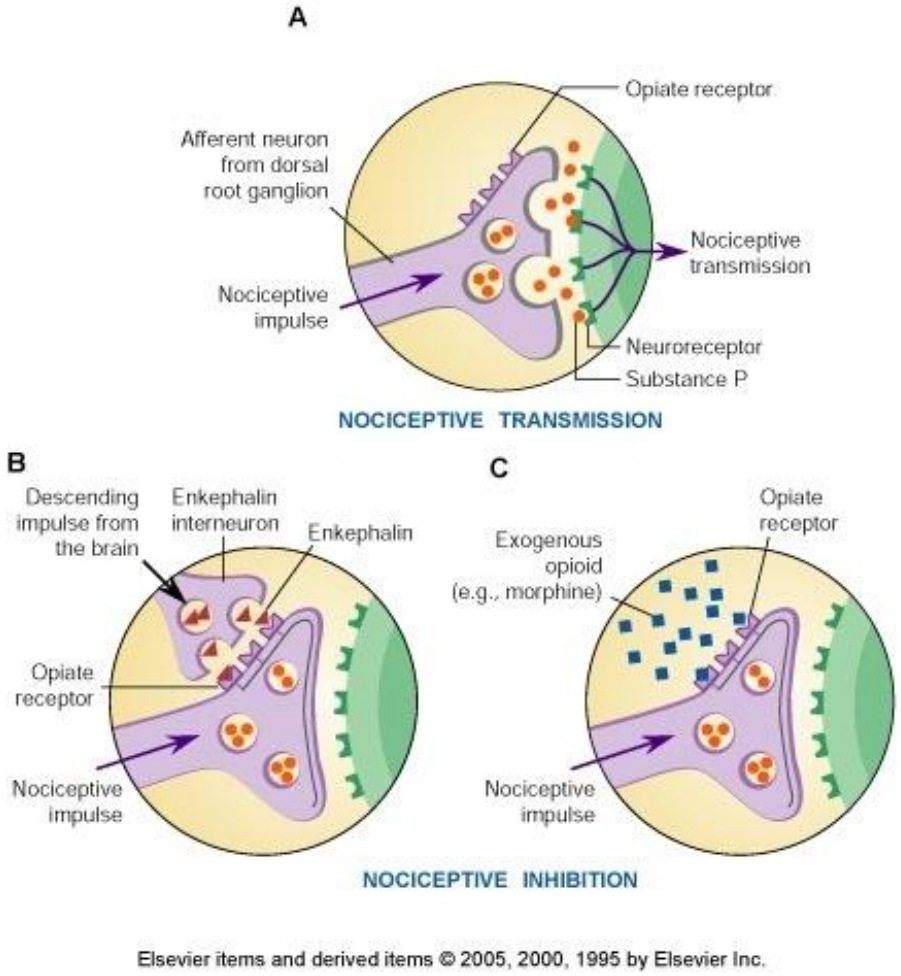
4. Pain Modulation

- Endorphins bind to **opioid receptors** on A delta and C fibers.
- That binding prevents the A delta and C fibers from releasing **Substance P** at synapses with dorsal horn interneurons.
- The pituitary and adrenal glands also release natural opioids in response stress, pain, and emotion. Pain modulation also occurs in the brain, but the mechanism is not clearly known.



4. Pain Modulation

- There are multiple types of opioid receptors. The **mu and kappa** receptors have **analgesic** properties. Mu receptors are located mostly in the brain, and kappa receptors are located mostly in the spinal cord.
- Both mu and kappa receptors have activities other than analgesia. Other activities may include sedation, respiratory rate depression, nausea, pruritis and pupil constriction. **Pinpoint pupils** are a sign of opiate overdose.



Types of Pain: Acute Pain

- Acute pain is related to tissue Injury and/or Inflammation. It elicits **sympathetic responses (fight or flight)**:
  - Increased heart rate, blood pressure, and respiratory rate
  - Perspiration, pallor, and dilated pupils
  - Blood shunting from skin to muscles and viscera
  - Bronchodilation
  - Increased blood glucose.
  - Inhibition of GI (gastrointestinal) mobility and secretion; increased GI sphincter tone (nausea and vomiting)
  - Urine retention (decreased urine volume)
  - Release of stress hormones (ADH, cortisol, aldosterone).
- Acute pain is accompanied by pain behaviors: grimacing, pacing, crying, moaning, etc.

Types of Pain: Acute Pain

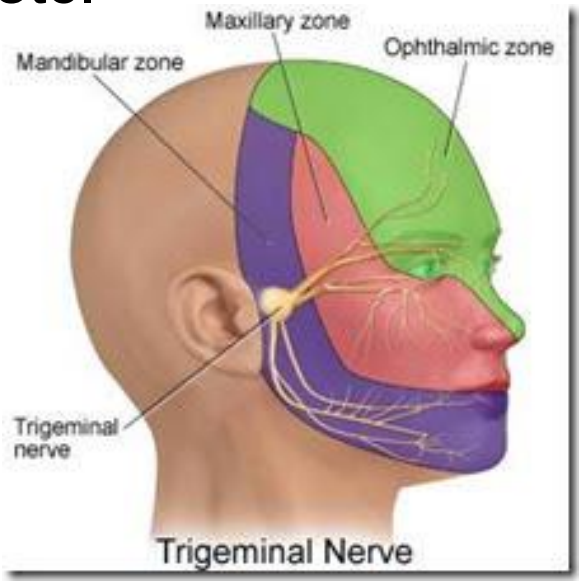
Migraine Headache

- Migraine headaches are a common example of acute pain. 10% of Americans suffer from migraines. There is a genetic predisposition.
- "Migraine triggers" vary from person to person, but they are believed to cause local inflammation and vasodilation in a cranial blood vessel or vessels. Afferent fibers from the blood vessel carry impulses to the brainstem resulting in the abnormal stimulation of the **trigeminal nucleus caudalis**. That nucleus is in neural contact with the trigeminal nerve and causes it to become hypersensitive to sensory inputs. In other words sensory inputs become pain inputs.
- The trigeminal nerve has **three branches: ophthalmic, mandibular and maxillary.** Any one of them, two of them or all three may generate migraine pain.

Types of Pain: Acute Pain

Migraine Headache

- **Clinical Manifestations**
  - Migraine pain is usually unilateral and throbbing. It is accompanied by nausea, vomiting, photosensitivity, phonosensitivity, lacrimation, etc.
  - The pain may last up to 72 hours.
  - Some migraines are preceded by an “aura”: visual disturbances, unilateral paresthesia, etc.



Types of Pain: Acute Pain

Migraine Headache

- **Prevention**
  - Avoidance of migraine triggers such as vasoactive foods (caffeine, chocolate, cheese and foods containing nitrates, nitrites or MSG).
  - Adherence to a regular sleep/wake pattern
  - Stress management
  - Various medications: antidepressants, beta/alpha blockers, calcium channel blockers, Botox injections in the scalp, hormones
- **Treatment**
  - Quiet, dark room, cold packs
  - Prompt administration of migraine medication, **Sumatriptan (Imitrex)**, for example. It is a **serotonin analog** that binds to serotonin receptors in cranial blood vessel walls to constrict them. It also decreases trigeminal nerve activity.

Types of Pain: Chronic Pain

- Chronic pain has a duration of **more than 6 months**, well beyond normal healing time.
- It is self-perpetuating and no longer protective.
- It is due to changes in pain transduction and/or transmission. There are two possible mechanisms.
  - **Peripheral sensitization:** Nociceptors become more sensitive to stimulation. Transduction of pain impulses increases.
  - **Central sensitization:** Neurons in the dorsal horn of the spinal cord have a reduced threshold for action potential generation or may generate action potentials spontaneously. Transmission of pain impulses increases.
- Chronic pain, unlike acute pain, is usually **not accompanied by sympathetic responses**. The sympathetic nervous system becomes desensitized due to the chronic nature of the pain.
- Chronic pain is associated with lack of sleep, depression, poor body image and job/family difficulties.

Types of Pain: Chronic Pain

Fibromyalgia Syndrome (FMS)

- Patients have a history of chronic widespread pain affecting all four extremities and various trigger points.
- Affects about 2% of Americans, women more than men
- Risk factors: physical/emotional trauma, viral infections, endocrine disorders, multiple surgeries, hypothyroidism, extreme stress
- FMS patients have a lower threshold for pain likely due to disordered pain mechanisms in the CNS. Pain modulation is likely disordered as well.
- Pain is exacerbated by physical exertion.
- Associated with fatigue, central sleep apnea, irritable bowel syndrome, depression, anxiety

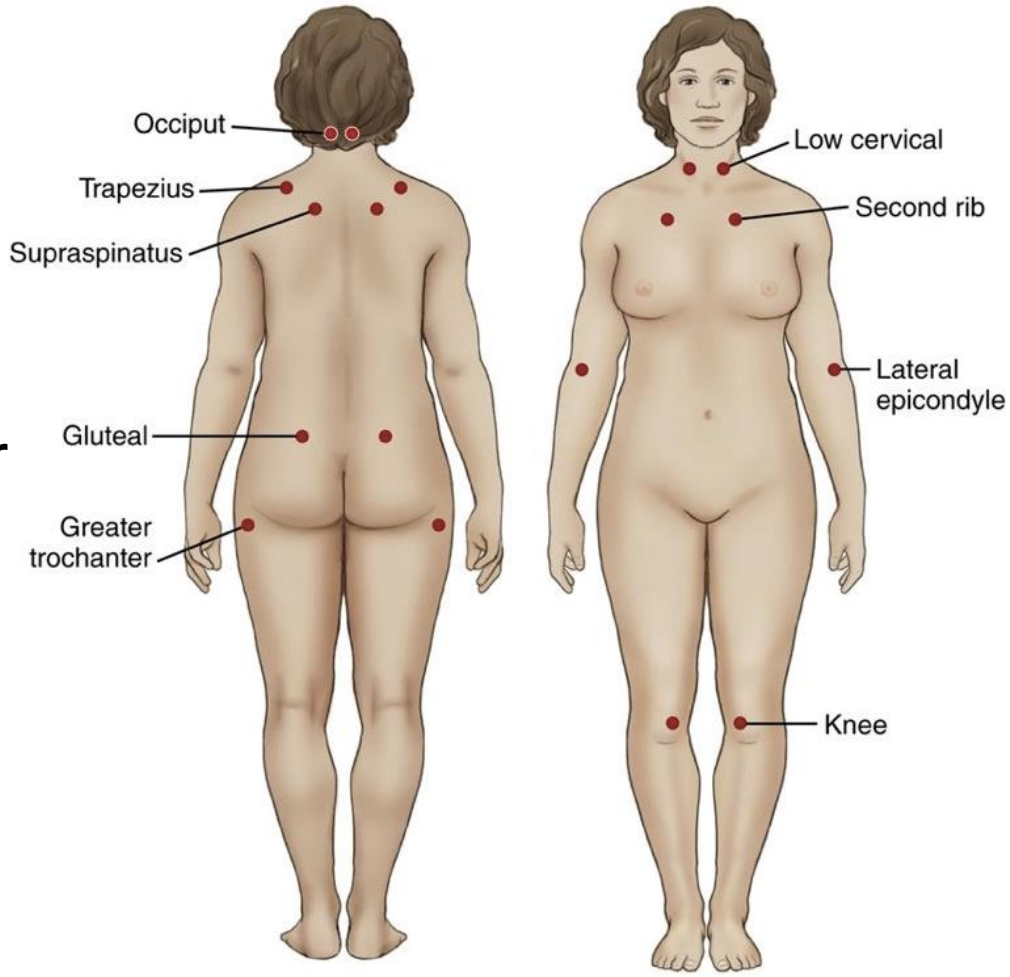
Types of Pain: Chronic Pain

Fibromyalgia Syndrome (FMS) Diagnosis

- Many other disorders must be ruled out.
- Criteria have been established by **American College of Rheumatology**: Widespr ead pain of at least 3 months duration and pain in 7 of 18 trigger points.

Treatment

- Three approved medications: Lyrica, Cymbalta, Savella



Types of Pain: Neuropathic Pain

Neuropathic Pain

- Neuropathic pain results from damaged or dysfunctional nerves (peripheral or central) rather than stimulation of nociceptors. Nerves may be damaged by trauma, surgery, infection, cancer therapy, diabetes, etc.
- Constant aching accompanied by bursts of burning or shock-like pain. **Allodynia** (pain from light touch) is common.
- Nerve injury causes depletion of **GABA-secreting interneurons in the dorsal horn** of the spinal cord. (GABA is an inhibitory neurotransmitter.)
- In some cases, central pain perception in the brain is generated in the absence of nociceptor input.
- **Examples** of neuropathic pain: sympathetically maintained pain, post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia, spinal cord or spinal nerve compression, phantom limb pain

Types of Pain: Neuropathic Pain

- **Neuropathic Pain: Sympathetically-maintained pain** is a type of neuropathic pain that can occur in the **absence of nerve injury**.
  - Release of norepinephrine sensitizes nociceptors to respond at a lower threshold.
  - Allodynia, hyperalgesia, atrophy of the affected extremity, coldness, hair loss, and shiny appearance of skin in the affected area are common manifestations.
- **Neuropathic Pain: Trigeminal Neuralgia (aka Tic Douloureaux)**
  - Momentary, excruciating unilateral pain along the second (maxillary) and third (mandibular) divisions of a trigeminal nerve .
  - Occurs more often in women and during or past middle age; affects about 1.7 million Americans
  - Compression of the trigeminal nerve by a blood vessel (causes demyelination) is suspected in most cases; may also occur as a result of brainstem lesion or tumor.

Types of Pain: Neuropathic Pain

- Treatment of trigeminal neuralgia includes anti-seizure medications, surgical decompression of the trigeminal nerve, gamma knife radiosurgery (the newest treatment)

- **Neuropathic Pain: Diabetic Neuropathy**
  - Affects about 60-70% of all diabetics
  - Thought to involve inflammation and demyelination of large peripheral nerves leaving many smaller myelinated fibers. Pain modulation at the spinal cord level is deficient allowing unopposed nociceptor transmission.
  - Patients complain of burning pain in the feet. Paresthesia also occurs. Pain is usually worse at night.

Types of Pain: Neuropathic Pain

- **Treatment** of diabetic neuropathy includes topical and systemic pain medications.
- To prevent complications diabetics must adhere to **daily foot care** to prevent developing sores or ingrown toenails. The combination of the numbness and impaired circulation sets the stage for undetectable injuries that fail to heal and easily become infected. **Amputation** is a common outcome.

- **Neuropathic Pain: Postherpetic Neuralgia**
  - Postherpetic neuralgia is persistent **pain along the dermatomal pathways (radiculopathy)** that lasts for more than eight weeks after the onset of shingles lesions. **10-15% of shingles patients** develop postherpetic neuralgia.
  - Risk factors include advanced age and history of immune compromise. The **shingles vaccine** lowers risk of PHN.
  - Treatment is topical and systemic pain medication.

Types of Pain: Neuropathic Pain

- **Neuropathic Pain: Phantom Limb Pain**
  - Phantom limb pain (PLP) is pain perceived to be in a region of the body that is no longer present.
  - It is most common in cases of amputated limbs, but phantom sensation and pain have also been reported in teeth, eyes, breast, penis and even bowel and bladder.
  - Phantom sensation and pain may begin immediately after amputation of the body part, or it may take years to develop.
  - **Females** tend to be more affected than males. **Upper limb** PLP is more common than lower limb PLP.
  - The most cited theory for the mechanism of PLP is **cortical reorganization**. Sensory information is normally received by the cerebral cortex in a very structured pattern. If a body part is removed that pattern becomes reorganized. Reorganization of the **somatic sensory cortex** is associated with the most intense phantom sensations and pain.

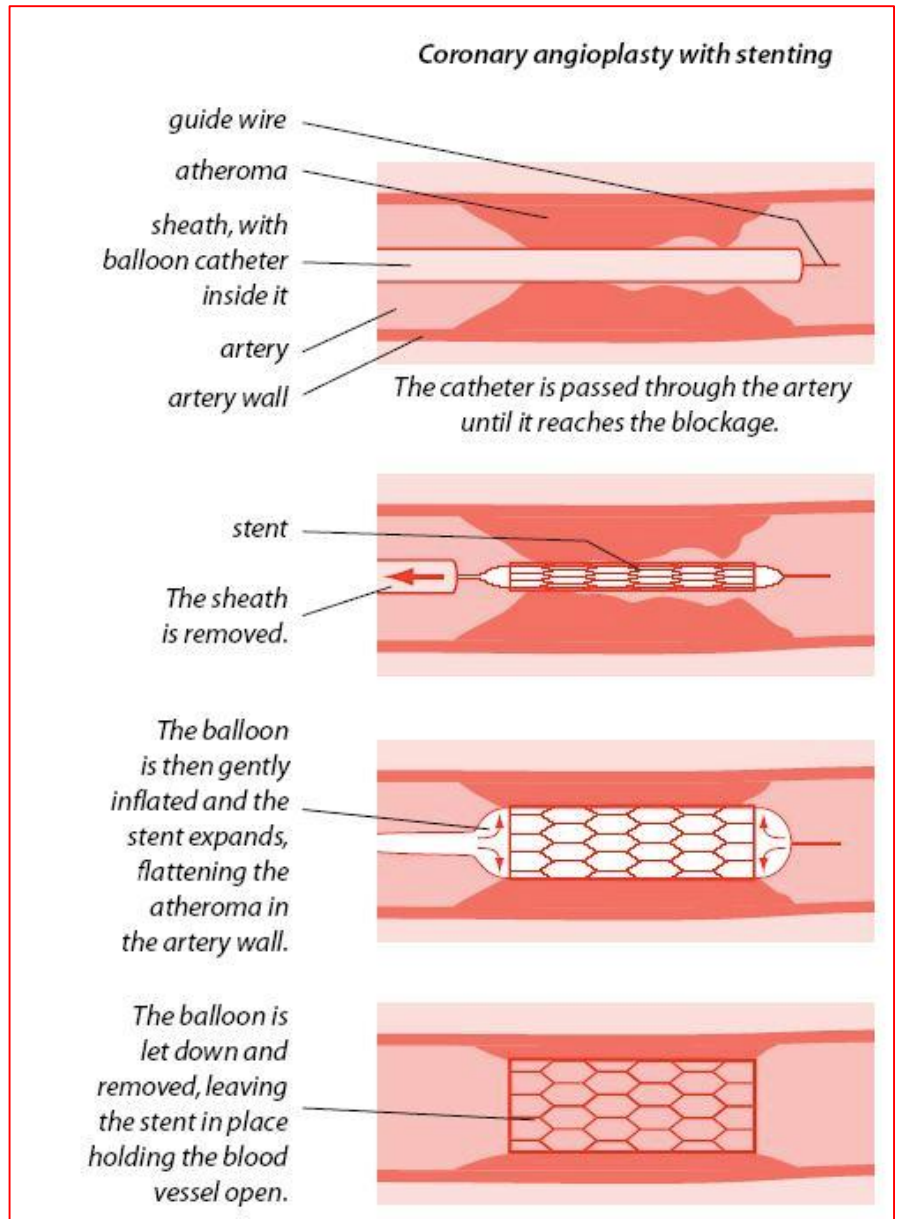
Types of Pain: Ischemic Pain

- **Ischemic Pain**
  - Due to a sudden or profound loss of blood flow to a tissue or body region (**hypoxic injury**) and the resultant release of inflammatory chemicals that evoke pain.
  - The pain is described as aching, burning or prickly (paresthesia).
  - If the pain is due to coronary artery occlusion **(angina)** it is described as deep, pressing and diffuse. It usually **radiates (refers)** to the lower jaw and/or left arm.
  - If the pain is due to occlusion of a **vein**, as in deep vein thrombosis, it is described as aching and deep, with a **gradual** onset.
  - If the pain is due to occlusion of an **artery**, it is described as aching or burning and deep, with a **sudden** onset.
  - **Chronic** ischemic pain in the lower extremities is associated with **atherosclerosis**. The pain, described as cramping, occurs with exercise, and is called **intermittent claudication**.

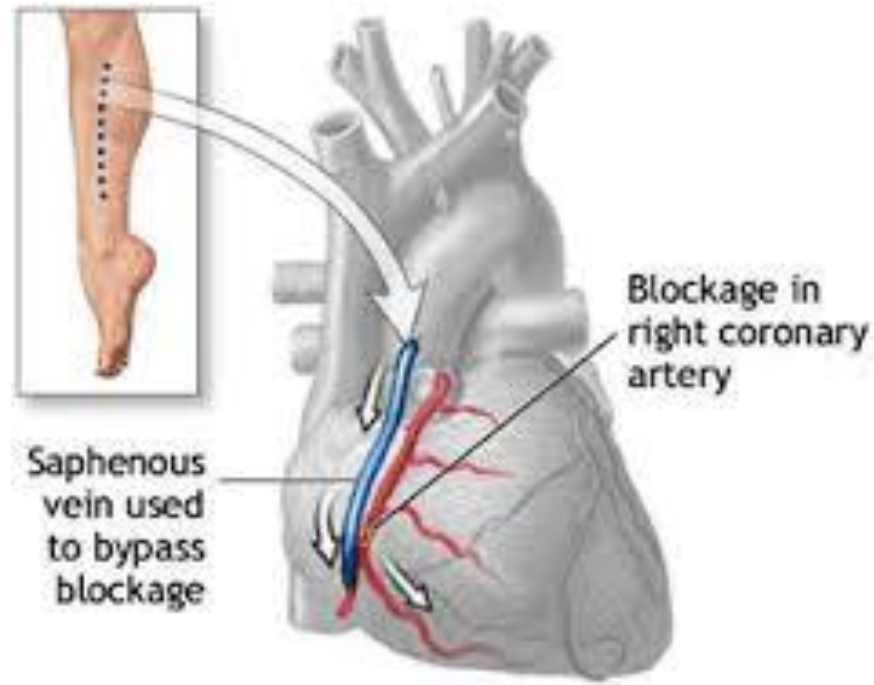
Types of Pain: Ischemic Pain

- **Ischemic Pain Management**
  - **Management** of ischemic pain is aimed at removing the occlusion. Acute ischemia is usually due to a thrombus or an embolus, and is managed by dissolving the clot with medication or by surgically removing it.
  - Coronary artery occlusion is managed by **coronary angioplasty** with **stenting** (a cardiac catheterization procedure) or **coronary artery bypass surgery** (requires opening the thoracic cavity). Similar procedures exist for peripheral vessels.
  - Chronic cardiac ischemia (angina) may be improved by lifestyle changes such as smoking cessation, regular exercise and improved diet.

Management of Coronary Artery Occlusion

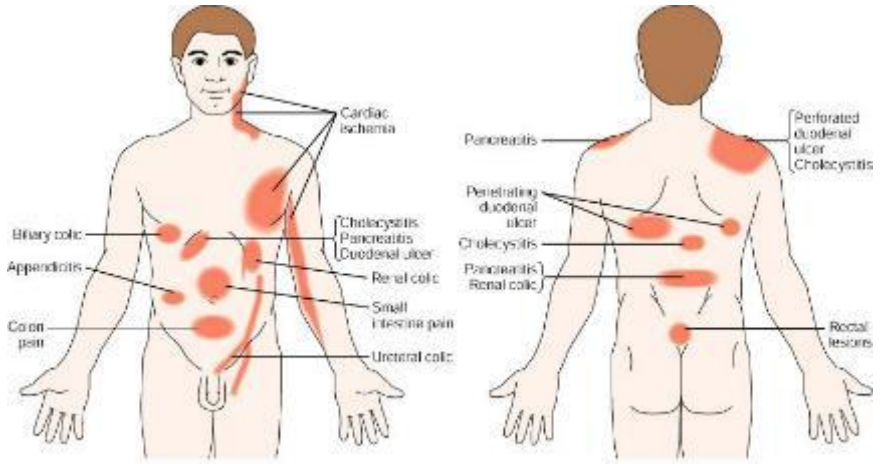


Coronary Bypass Surgery



Types of Pain: Referred Pain

- **Referred Pain**
  - **Referred pain** is perceived to be located elsewhere than the site of injury.
  - Afferent pain fibers from both somatic and visceral nociceptors converge in the dorsal horn. The brain cannot differentiate between the two sources of pain signals and tends to **attribute visceral pain to a body surface location**, sometimes along a **dermatome.**
  - Patterns of referred pain help to locate the source of visceral pathological processes.



Treatment of Pain

- **Three Strategies for Pain Management:**

1. **Interrupting Peripheral Transduction/Transmission of Pain**
   - NSAIDs/Steroids (block the arachidonic acid pathway production of prostaglandins)
   - Local anesthetics (lidocaine or novacaine) at the injury site (blocks sodium influx and action potential generation)
2. **Altering Pain Transmission/Modulation at the Spinal Cord**
   - Cutaneous stimulation: TENS, massage, acupuncture, therapeutic touch activates mechanoreceptors which stimulate interneurons to secrete opioids.
   - Spinal analgesia: epidural and intrathecal application (injection) of opioids, local anesthetics, and α-blockers (Clonidine blocks sympathetically mediated pain.)
   - Dorsal column stimulators: stimulate descending pain modulating impulses from the brainstem. Dorsal horn interneurons release natural opioid in response.

Treatment of Pain

- **Three Strategies for Pain Management:**

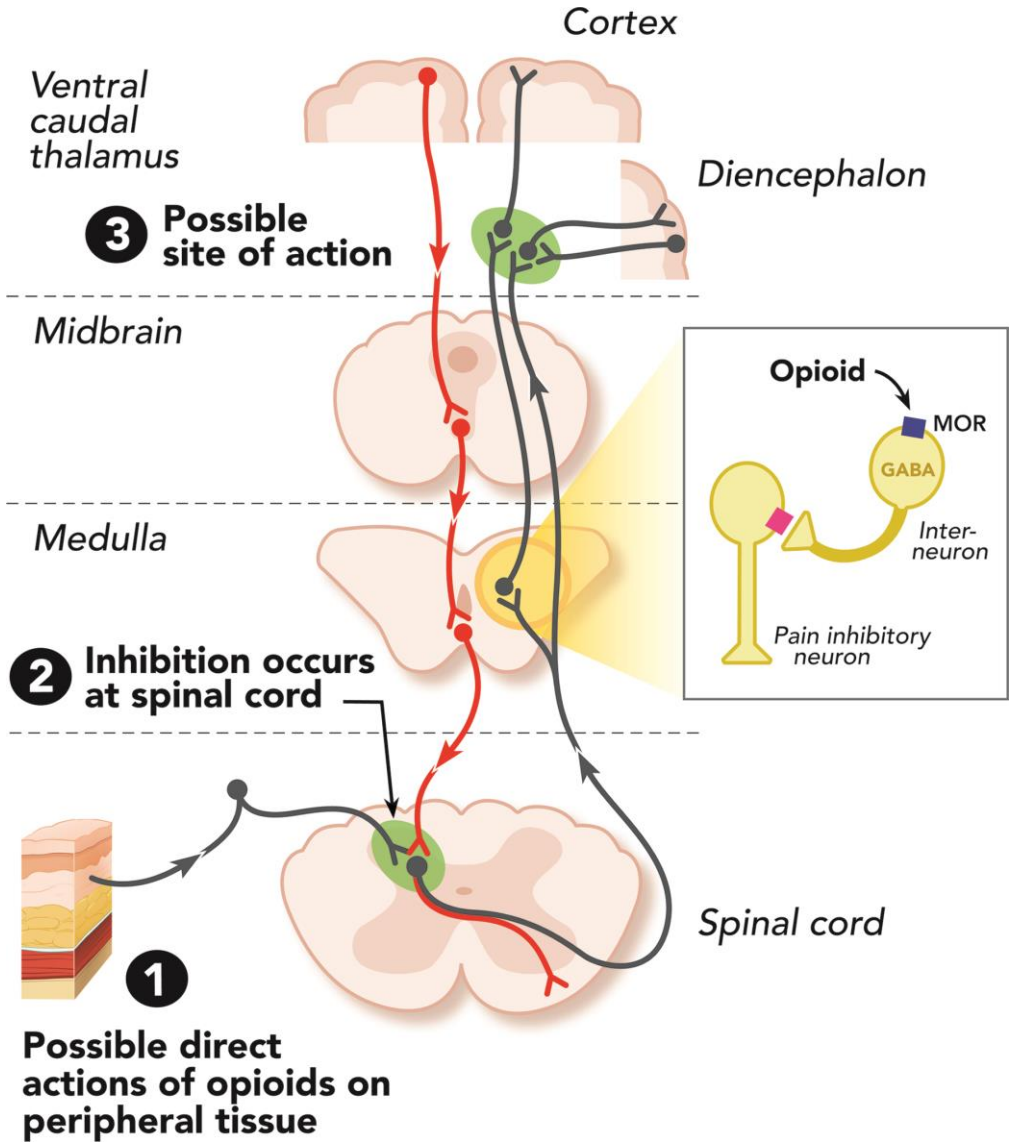
3. Altering Perception and Integration of Pain by the Brain

- Administration of systemic opioid medication. Opioid medications are theorized to interrupt the pain production pathway at multiple sites. They are known to enhance the descending pain modulating pathway described earlier.
- Distraction, imagery, hypnosis (cause the brain to attend to multiple stimuli, rather than just the pain).
- Relaxation and biofeedback to increase blood flow to affected area, diluting pain chemicals. Biofeedback may also increase endorphin release in the spinal cord.
- NOTE: Opioids (morphine, codeine, meperidine, methadone) act at multiple receptor types throughout the body. Thus they are associated with many side effects, including dependence (addiction) and tolerance (need for increasing dosage to achieve the same pain relief effect).

Treatment of Pain

The upward pain production pathway is shown in **black**.

The downward pain modulating pathway is shown in **red**.



Lecture 6D
Mechanisms of Brain Injury

Mechanisms of Brain Injury

Unique Features of Neuronal Injury

- **Neuronal Vulnerability to Ischemia**
  - Neurons have a strong preference for **aerobic cellular respiration** over anaerobic cellular respiration.
  - Neurons store **very little glycogen** (the major storage form of glucose), so, if blood supply is low they have a limited back-up supply of glucose fuel .
  - The brain only accounts for about **2%** of the body weight yet it receives 15% of the cardiac output and consumes **20% of the total body oxygen consumption**. Per tissue weight only the heart consumes more oxygen than the brain.
  - If neurons are forced to switch to anaerobic metabolism due to ischemia, the **lactic acid** produced rapidly causes damage to neurons due to their **high sensitivity to H+ toxicity (acidity).**
  - **Most of the ATP is used by neurons is consumed by the operation of ion pumps**. Therefore, under conditions of ischemia, neurons ion pumps are immediately affected by ischemia.

Mechanisms of Brain Injury

- Recall that ion pump failure causes K+ to leak out of the cell, and allows Ca2+, Na+ and Cl- to enter the cell.
  - Membrane ion gradients are disrupted. Neurons cannot function without membrane ion gradients.
  - **Elevated cytoplasmic Ca2+ activates damaging cytoplasmic enzymes.**
  - **Elevated cytoplasmic Na+ causes hydropic swelling.** In brain tissue hydropic swelling is also known as **cytotoxic cerebral edema.**
  - In neurons elevated cytoplasmic Ca2+ also causes the release of too much glutamate at the synapse. **Glutamate is the major excitatory neurotransmitter** for the neurons of the central nervous system.
  - When glutamate binds to its receptors, ion channels open to allow the influx of both Na+ and Ca2+. **The combination of ion pump failure and glutamate effects results in way too much cytoplasmic Na+ and Ca2+ in neurons!**

Mechanisms of Brain Injury

- **Glutamate Excitotoxicity**
  - **Glutamate** acts by binding to two types of receptors in the **postsynaptic** membrane, **AMPA receptors and NMDA receptors**.
    - AMPA receptors are **chemically-gated**. Glutamate binding opens Na+ ion channels to depolarize the postsynaptic membrane.
    - NMDA receptors are both **chemically-gated and voltage gated**. BOTH glutamate binding and AMPA-dependent membrane depolarization are required to activate them.
  - Activated NMDA receptors contain ion channels that allow BOTH **sodium ion and calcium ion** influx to occur.
  - **In healthy neurons**, the release of glutamate and the influx of Na+ and Ca2+ into the post synaptic neuron is **tightly regulated**.
  - Presynaptic neurons are responsible for **reuptake** of the neurotransmitter it releases. Injured presynaptic neurons, however, have a faulty glutamate reuptake mechanism.
  - Ischemic injury to neurons causes them to **release too much glutamate and to fail to reuptake glutamate from the synapse.**
  - Excessive synaptic glutamate causes additional injury and brain cell death.

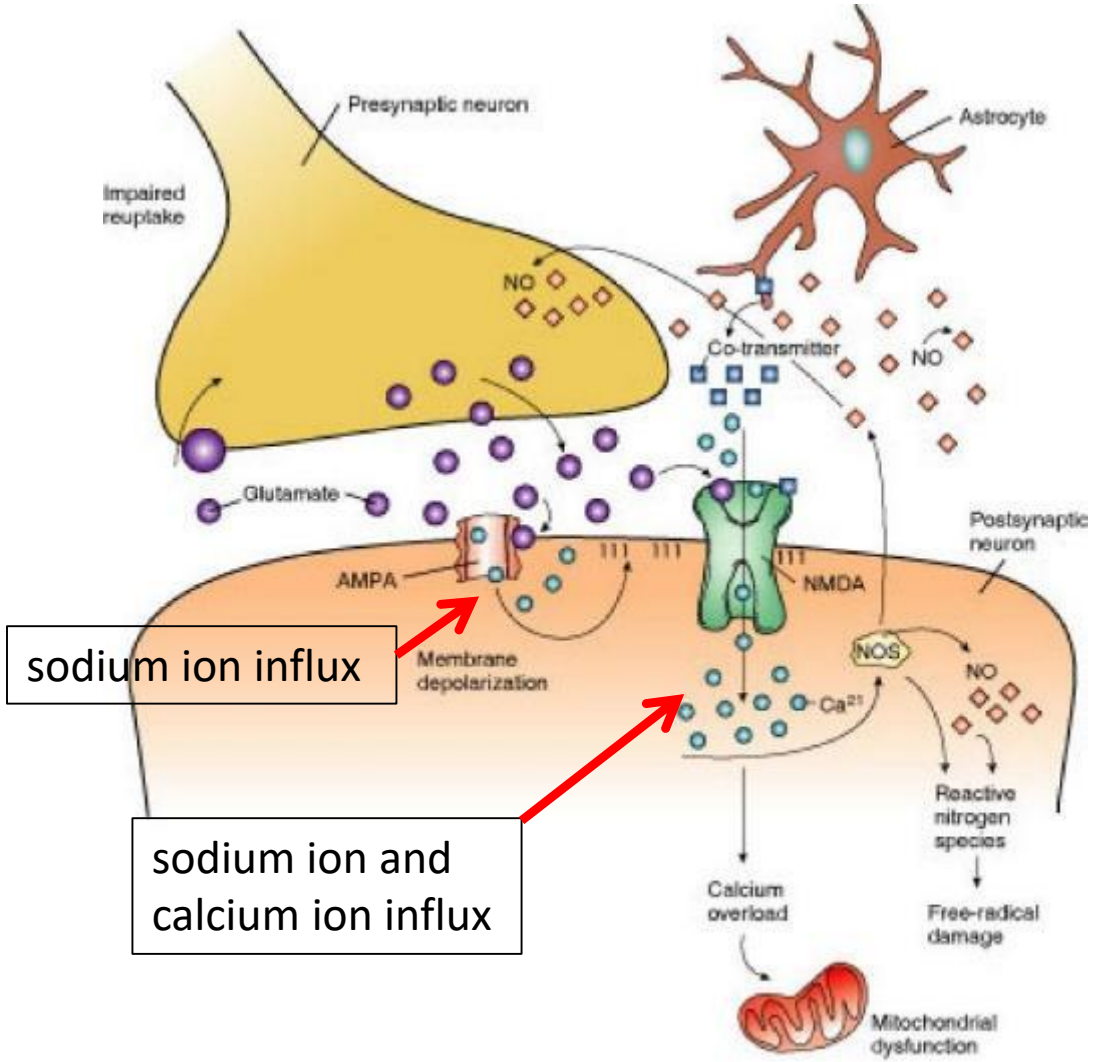
Mechanisms of Brain Injury

- During glutamate excitotoxicity NMDA receptors remain active for an abnormally extended period allowing the **influx of large amounts of Ca+2 and Na+** in the postsynaptic neuron**. Just what neurons do not need!**
- Neurons are subjected to further damaging effects of Ca2+ overload:
  - **Activation of more damaging enzymes: phospholipase, proteases, nucleases, etc.**
  - **Mitochondrial membrane damage leads to release of mitochondrial contents, including oxygen free radicals, into the cytoplasm**
  - **One of the enzymes that tends to be activated by calcium overload in neurons is nitric oxide synthase (NOS). It catalyzes the production of excessive nitric oxide (NO acts as a neurotransmitter in the brain.) which in turn leads to the production of nitrogen free radicals.**
- Glutamate excitotoxicity is a cause of **apoptosis** in neurons. It has been linked to several neurodegenerative disorders including **Alzheimer Disease and Parkinson Disease.**

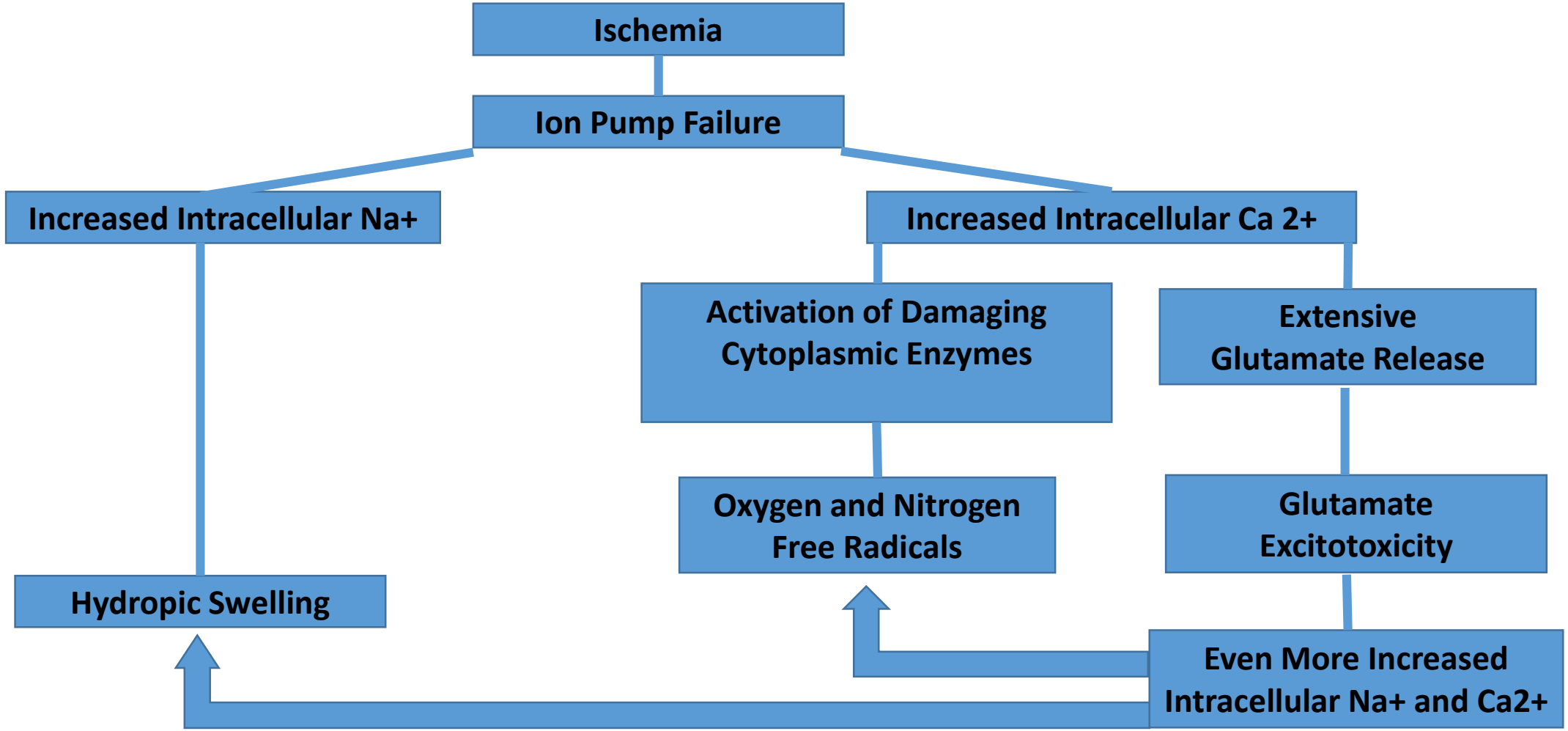
Mechanisms of Brain Injury

Mechanism of Glutamate-Mediated Excessive Sodium Ion and Calcium Ion Influx

(Glutamate Excitotoxicity)



Mechanisms of Brain Injury



Mechanisms of Brain Injury

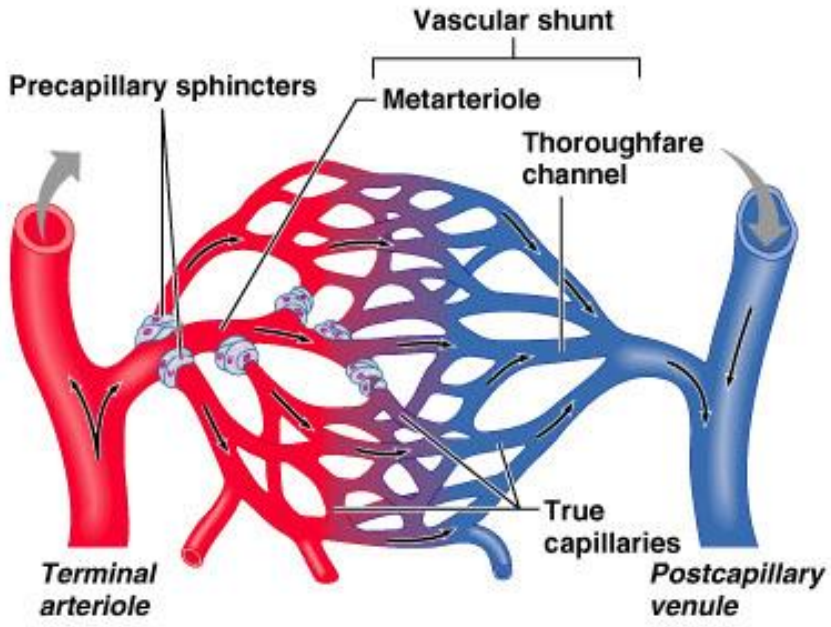
- **Reperfusion Injury in Neurons**
  - During the period of ischemia neurons accumulate substrates for oxidative phosphorylation including **xanthine and hypoxanthine** (metabolites of AMP=adenosine monophosphate) that are subject to **free radical formation** upon reperfusion.
  - The sudden increase in oxygen also causes production of **oxygen free radicals.**
  - Cell membrane lipids undergo peroxidation by free radicals causing membrane damage and release of **phospholipids,** including arachidonic acid. The **arachidonic acid pathway** begins.
  - The endothelial cells of the **BBB (blood brain barrier)** are injured by ischemia. Upon reperfusion IL-1, IL-6 and TNF are found in injured brain tissue. They attract neutrophils and platelets to the area.
  - The damaged BBB allows fluid to leak out of the capillaries and into the interstitial space, adding to intracranial pressure (ICP).

Mechanisms of Brain Injury

- **Abnormal Autoregulation of Capillary Bed Perfusion in Brain Tissue**
  - Terminal "feeder" arterioles and precapillary sphincters **normally** dilate in response to three signals in interstitial fluid: **increased pCO2, decreased pH, decreased pO2** (This type of autoregulation is **local** and is called the **metabolic response**.).
  - The metabolic response to **increased partial pressure of CO2** in the brain tissue is **very robust.** Increased pCO2 (as would occur in ischemia) **instantly** increases capillary bed perfusion.
  - **Cerebral perfusion pressure (CPP)** is the arterial blood pressure at the point where arteries enter the cranium. The normal range for CPP is **60 mm Hg to 160 mm Hg**. Above or below that range autoregulation of capillary perfusion of brain tissue is lost.
  - Remember, the brain is encased in bone, so **cerebral edema** can lead to dangerously elevated intracranial pressure (ICP). Elevated ICP **compresses cerebral blood vessels** leading to **decreased CPP** and further brain injury.
  - If CPP falls **below 60 mm Hg**, autoregulation is lost. CPP becomes totally dependent on systemic blood pressure.

Mechanisms of Brain Injury

Normal Autoregulation of Capillary Bed Perfusion by the Metabolic Mechanism



Strong metabolic signals:

Decrease pO2

Increased pCO2

Decreased pH

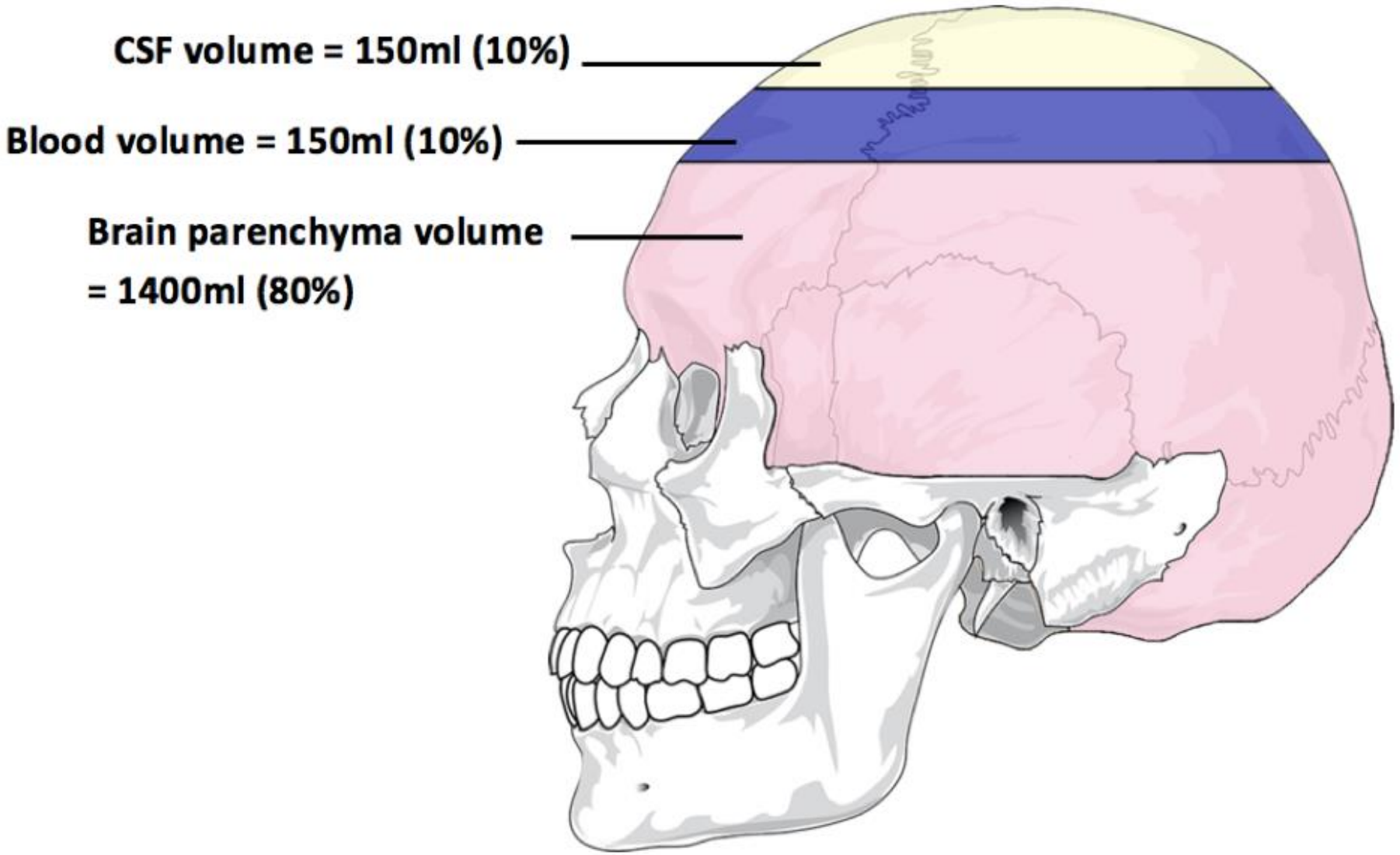
Weak metabolic signals

Mechanisms of Brain Injury

Increased Intracranial Pressure (ICP) in Brain Injury

- **Normal ICP is 0-15 mm Hg**. It increases sharply due to increased intracranial volume.
- **Compliance** is the ability to increase volume without increasing pressure. Because the brain is encased in bone, compliance is **low.** Even a small increase in volume leads to a steep increase in intracranial pressure.
- There are **three sources of intracranial volume:**
  - **80% Brain tissue (brain cells + interstitial fluid)** aka **brain parenchyma**
  - **10% CSF** (cerebral spinal fluid in ventricles)
  - **10% Blood** (in arterial and venous blood vessels)
- The **Monro-Kellie Hypothesis** states that a **slight increase** in one of the three sources can be compensated by reduction in the other two.
- Increases in blood volume or increased CSF volume are more **amenable to compensation** than increases in brain tissue volume. Increases in brain tissue volume readily lead to increased intracranial pressure (ICP).

3 Sources of Brain Volume



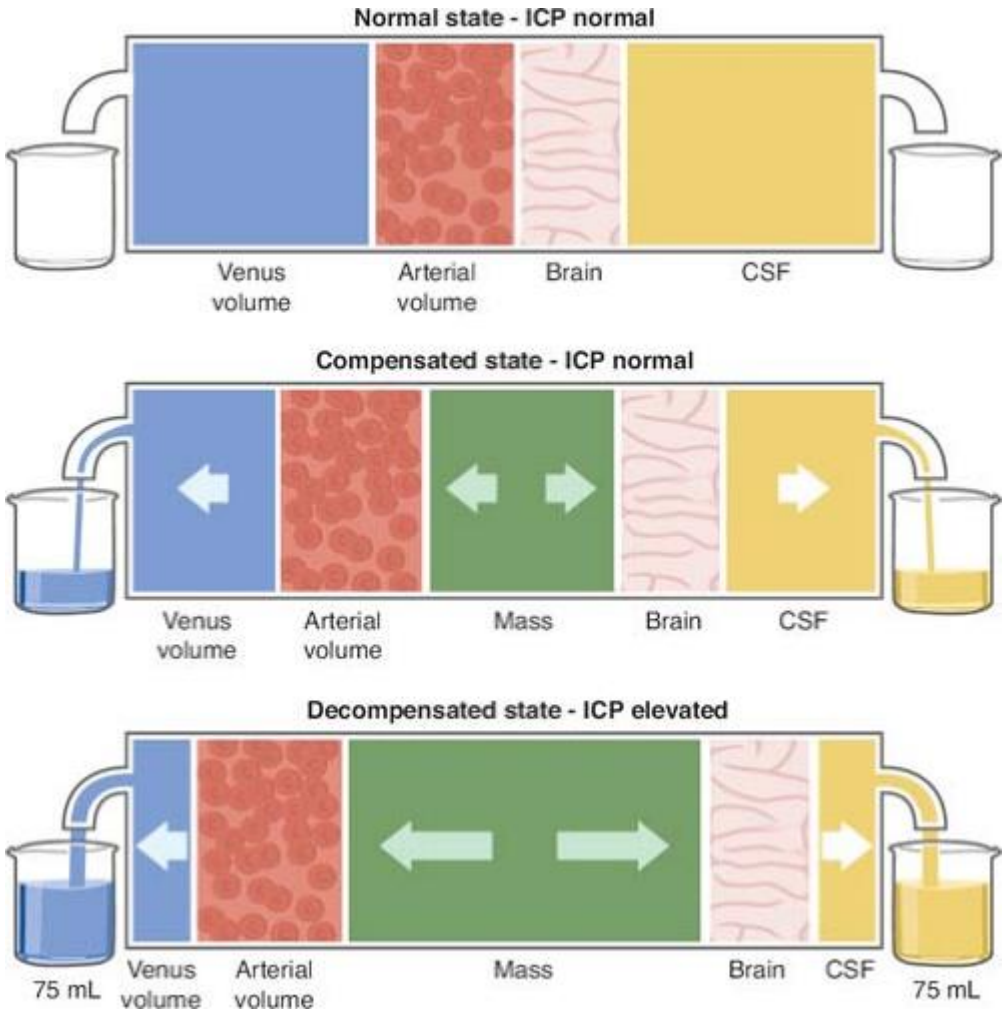
Monroe-Kellie Hypothesis

The body compensates for increases in brain volume by decreasing the **brain blood volume or cerebral spinal fluid (CSF) volume** in the brain.

Venous blood is drained out of the brain back to the heart.

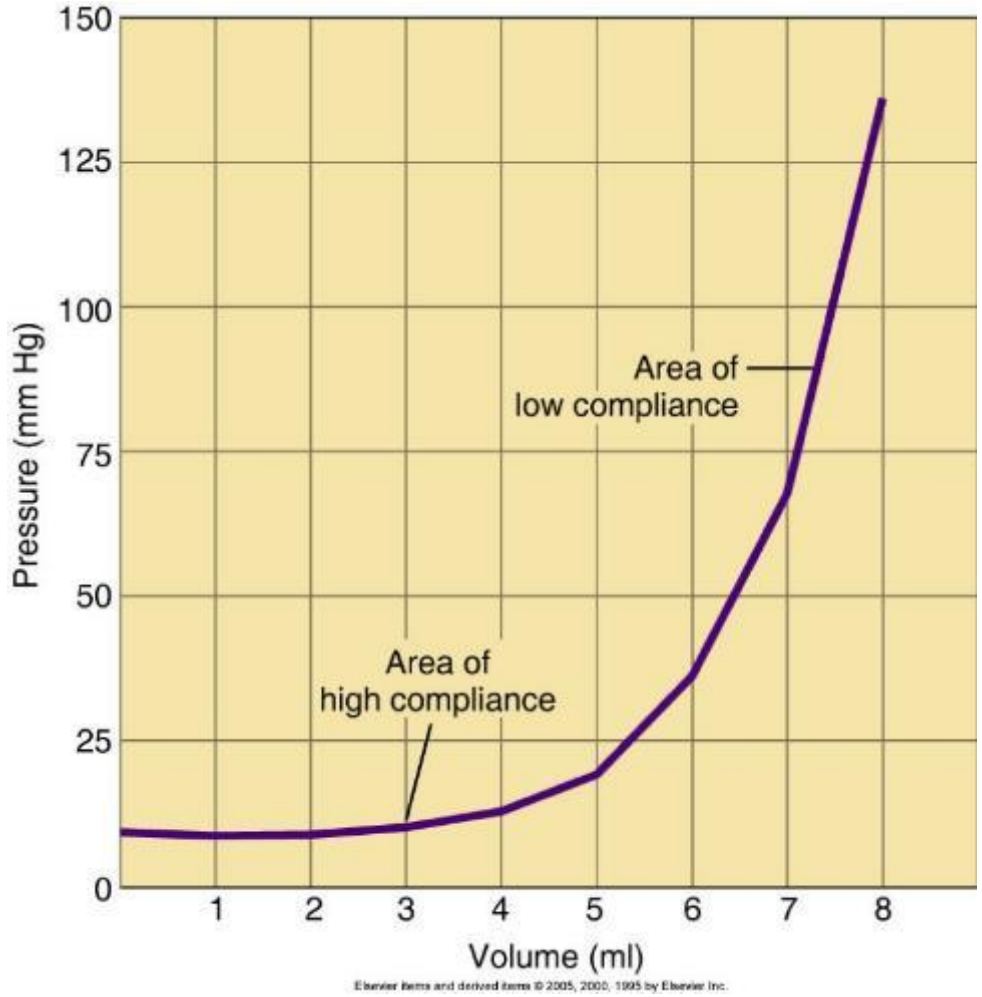
CSF is drained out the brain into the spinal cord.

But there is a **limit of about 75 ml** of drainage for both fluids. After that ICP climbs rapidly!



Mechanisms of Brain Injury

Only small increases in brain tissue volume can be compensated by slightly **decreasing cranial venous blood volume or CSF volume.** After that, intracranial pressure increases steeply.



Mechanisms of Brain Injury

- **Increased Brain Tissue Volume (Cerebral Edema): two sources**
  - **Vasogenic Cerebral Edema=Increased interstitial fluid** in brain tissue due to leaking of fluid and proteins out of capillary beds.
    - Recall that the capillaries of the brain are referred to as the **blood brain barrier (BBB)** because they have tight junctions between endothelial cells of the capillary wall and they are wrapped in glial cells (astrocytes).
    - The BBB may be damaged by ischemia, reperfusion injury or chemicals released by glutamate excitotoxicity. The damaged BBB is leaky.
  - **Cytotoxic Cerebral Edema= Increased brain cell (neuron or glial cell) volume** due to hydropic swelling.
    - Accumulation of **sodium ions** inside cells pulls water into the cells to cause hydropic swelling.
      - **Glutamate excitotoxicity** causes elevated Na+ ion influx.
      - **Stalling of sodium potassium pumps** due to ischemia and low ATP keeps sodium ions from being pumped out of cells.

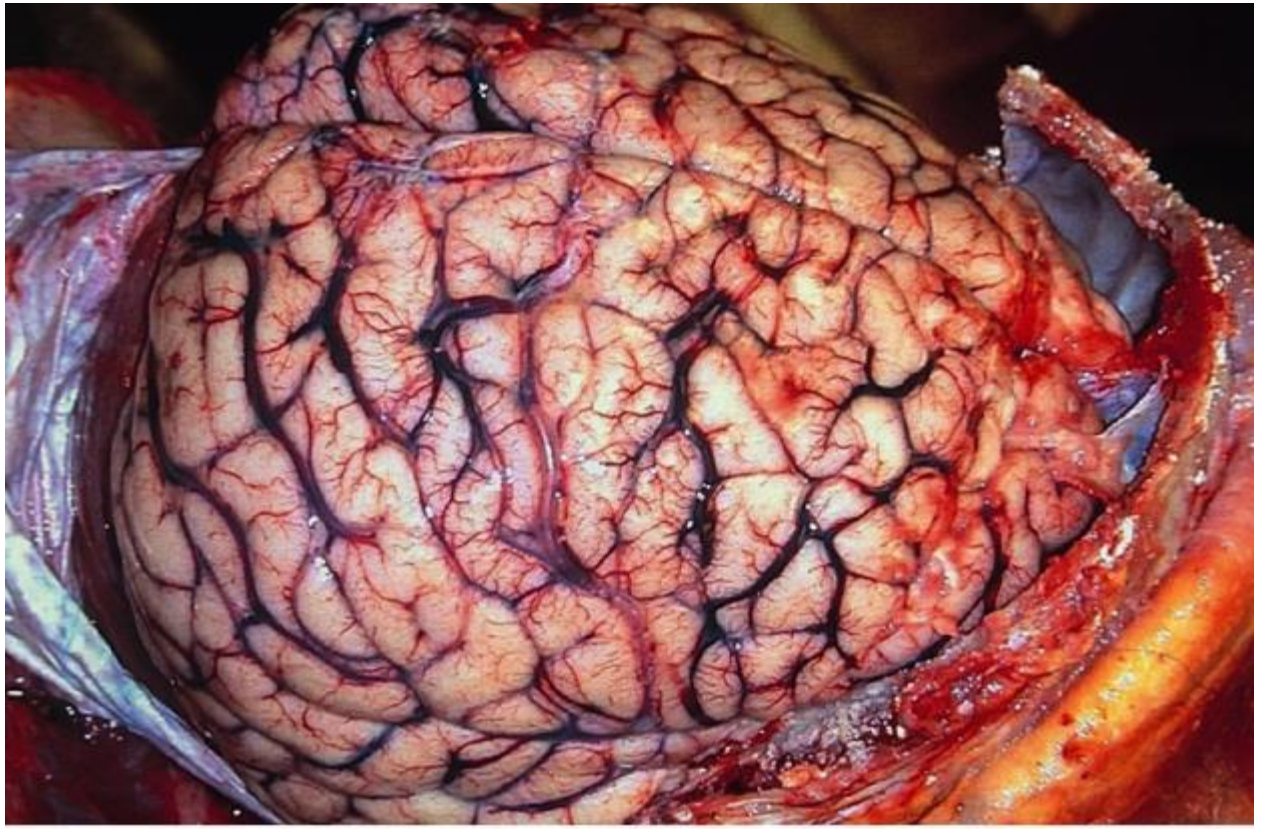
Mechanisms of Brain Injury

- Brain injury often involves **both** increased vasogenic brain tissue volume and increased cytotoxic brain tissue volume.
- The resulting elevated ICP starts a **cyclic process**—the increased ICP **compresses and occludes cranial blood vessels in the injured area. That prevents blood from traveling forward to serve healthy brain tissue** causing ischemic cell injury to previously healthy tissue.
- Inflammation leads to increased capillary bed perfusion and permeability and increased brain tissue volume from both **vasogenic** and **cytotoxic** sources.
- **In addition to vasogenic and cytotoxic sources, tumors, hematomas and abscesses** contribute to increased brain tissue volume and increased ICP.

Mechanisms of Brain Injury

Increased Brain Tissue Volume

Gyri are flattened with no space (sulci) between them.



From Kumar V, Cotran R, Robbins S: Robbins basic pathology, ed 7, Philadelphia, 2003, Saunders, p 812

Mechanisms of Brain Injury

Increased Cerebral Blood Volume

- Decreased drainage of venous blood from the brain into the jugular veins and back to the right atrium causes increased cerebral blood volume.
  - **Dural sinus thrombosis obstructs drainage of venous blood from the brain back to the heart.**
  - **Increased right atrial pressure** (as occurs in **pulmonary hypertension**) restricts drainage of venous blood from the brain back to the heart.

Images of Dural Sinus Thrombosis

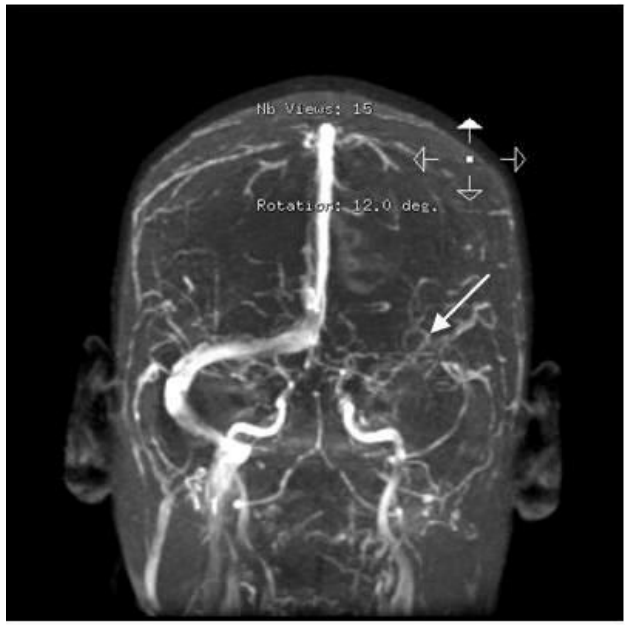


Figure 3

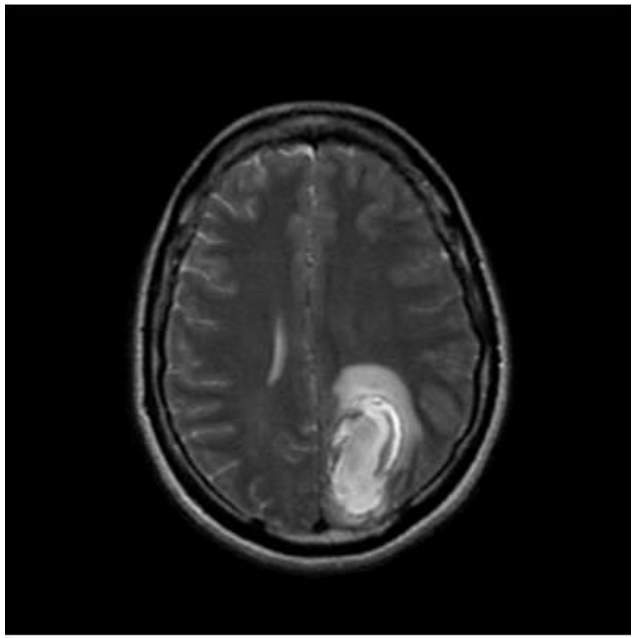
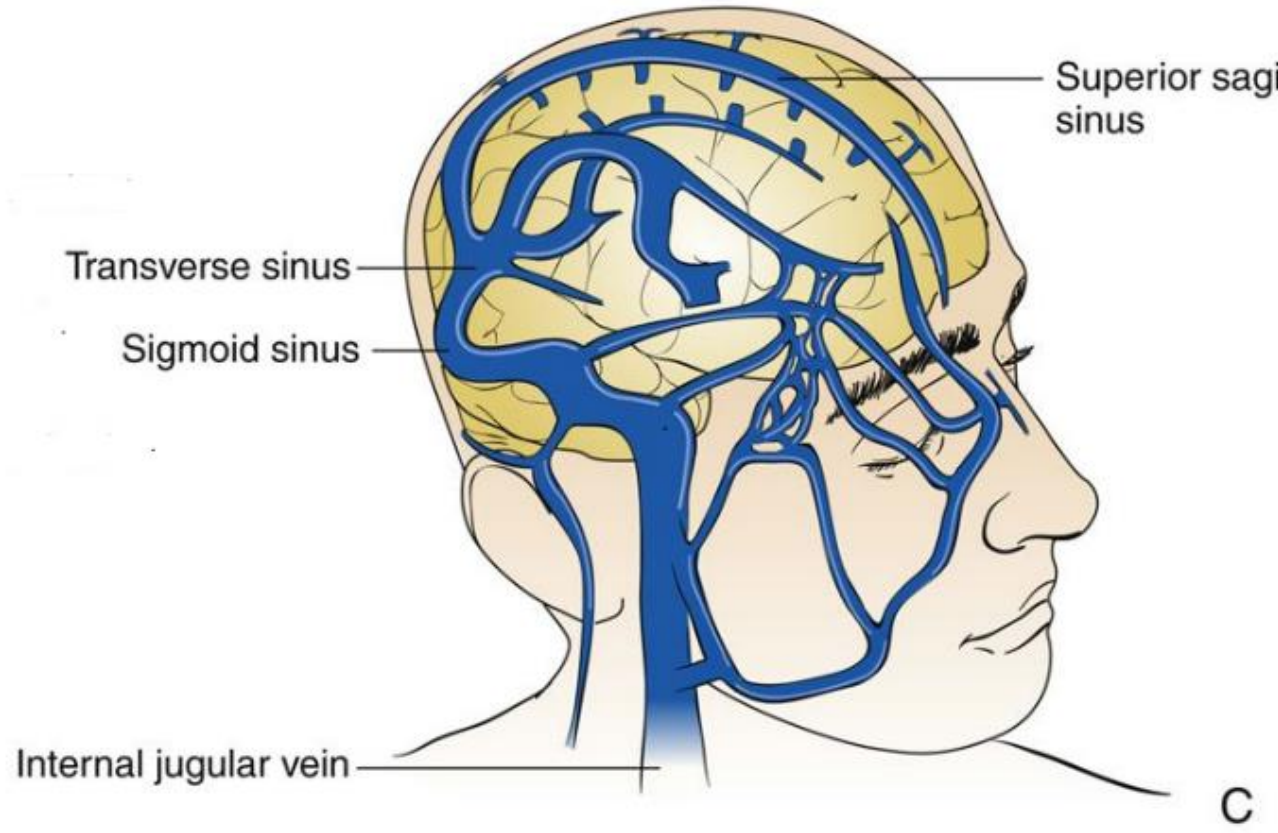


Figure 2

Mechanisms of Brain Injury

- Venous Structures of the Brain

Note that the dural sinuses drain venous blood into the jugular veins.

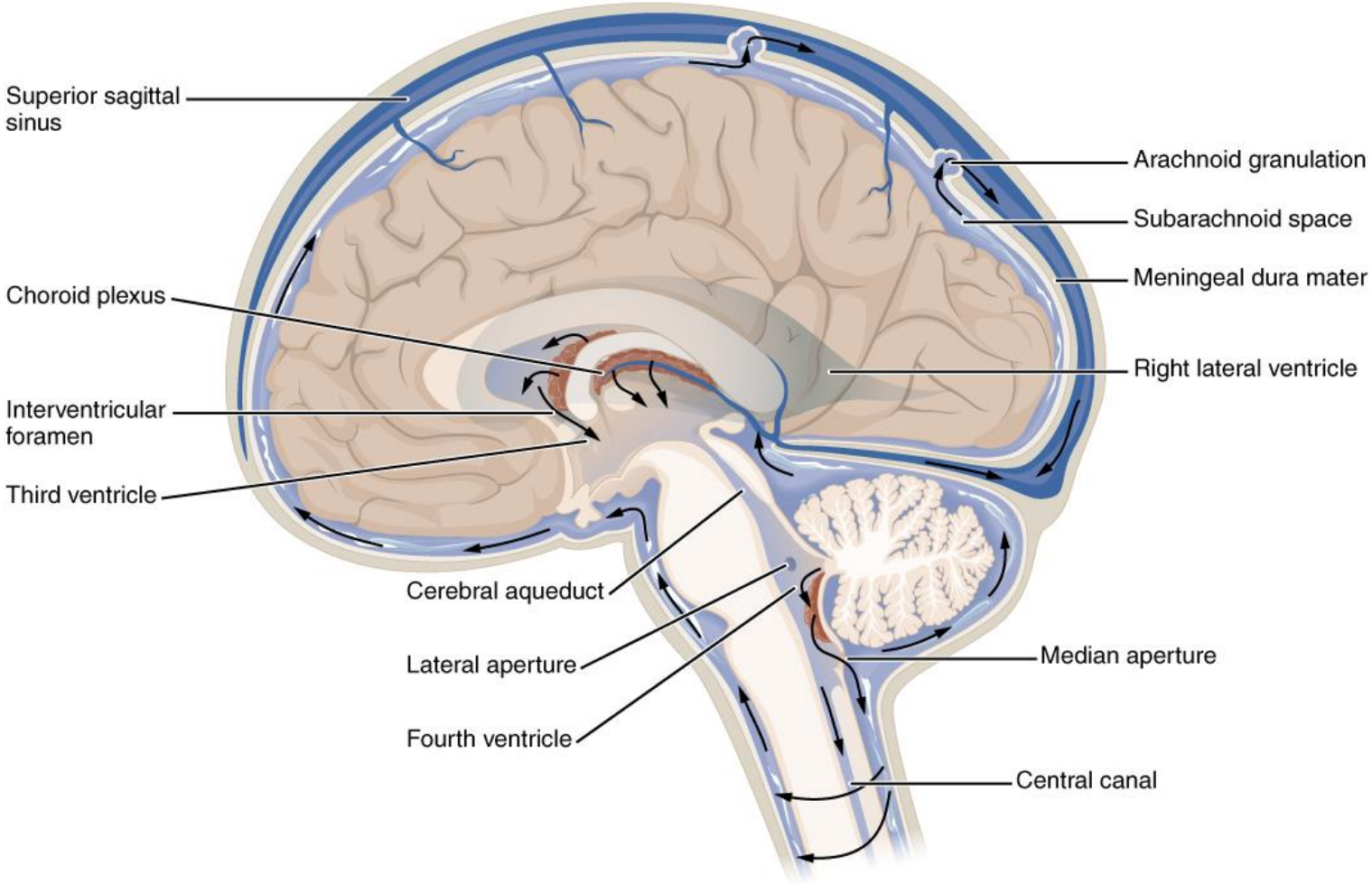


Mechanisms of Brain Injury

- **Increased CSF Volume (Hydrocephalus**)
  - **Non-Communicating Hydrocephalus** is due to obstruction somewhere in the pathway that connects the ventricles. The CSF is still able to flow through the **arachnoid granulation villi** into the dural sinus, but the communication between ventricles is lost.
    - The most common obstruction to CSF flow between the choroid plexus and the arachnoid villi is caused by stenosis of **the cerebral aqueduct.** It lies between the third ventricle and the fourth ventricle.
  - **Communicating Hydrocephalus** is due to obstruction of the arachnoid villi (granulations). CSF **can** communicate from ventricle to ventricle, but it **cannot flow through the villi in the arachnoid granulations** from the subarachnoid space into the dural sinus.
      - The most common etiology is damage to the arachnoid villi due to ischemia or infection (meningitis).

Mechanisms of Brain Injury

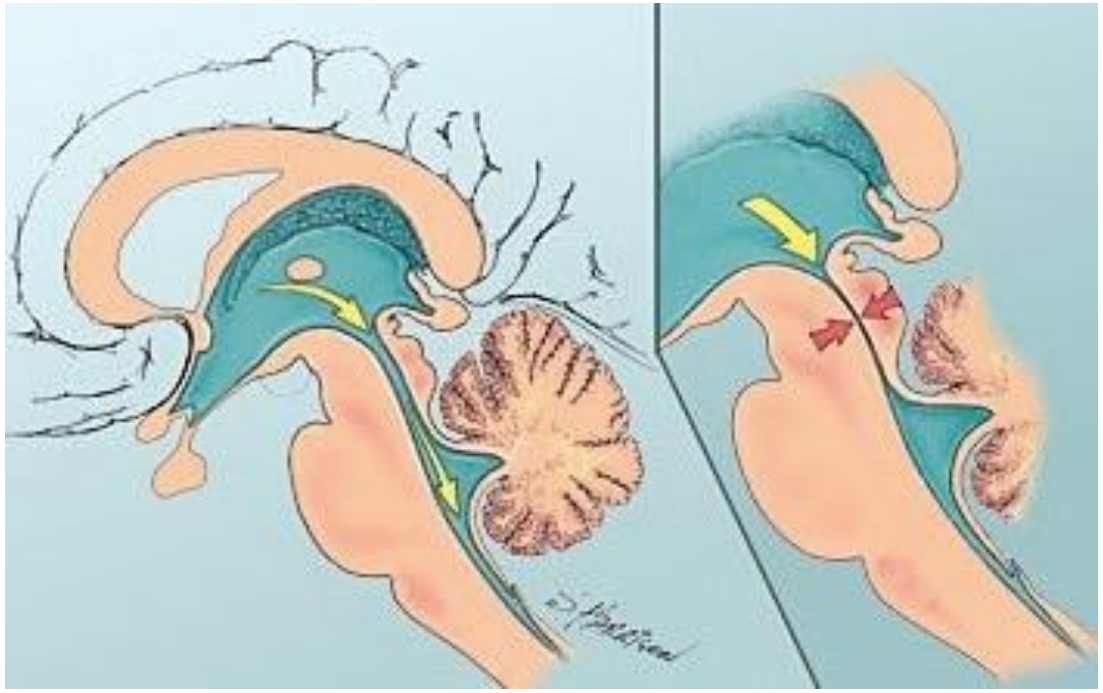
Normal Flow Pattern of CSF

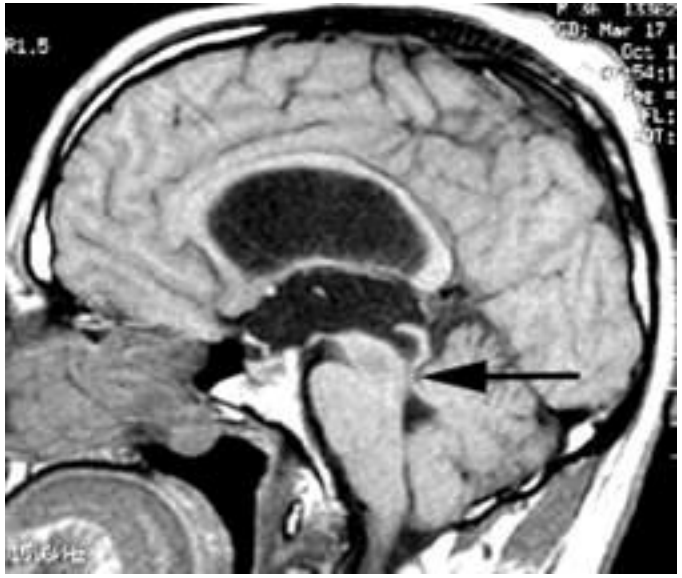


Mechanisms of Brain Injury

Non-Communicating Hydrocephalus

The most common cause is **stenosis of the cerebral aqueduct**. This causes the lateral and third ventricles to enlarge due to backup of CSF.

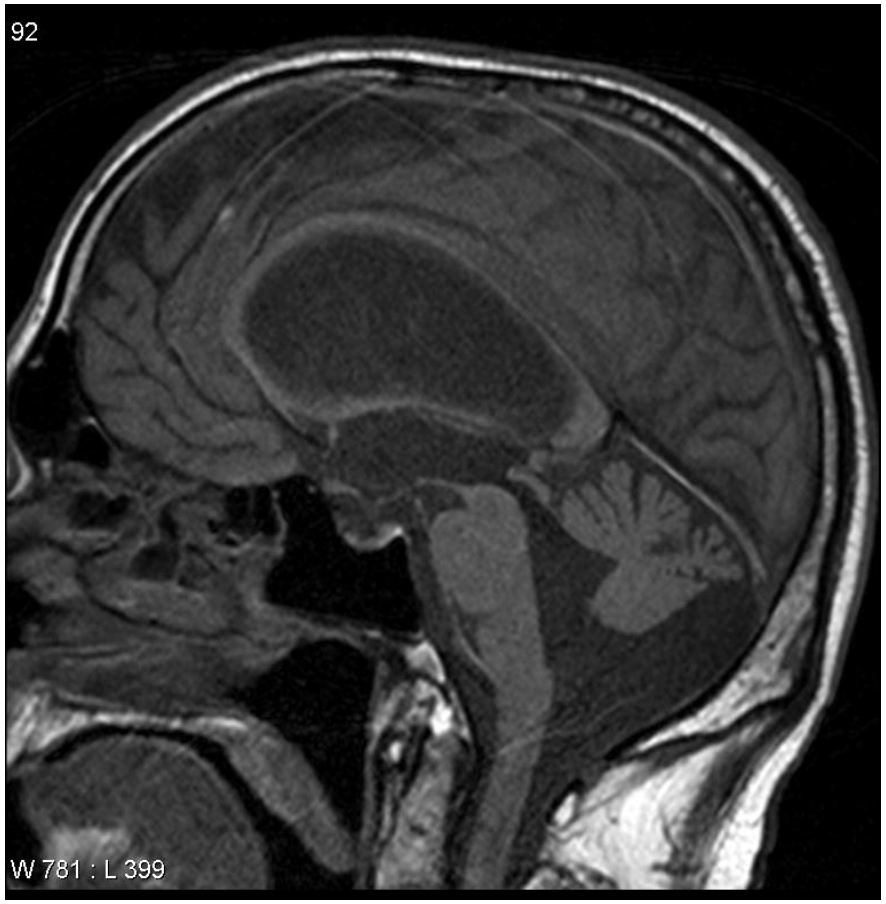




Mechanisms of Brain Injury

Communicating Hydrocephalus

CSF cannot flow from the subarachnoid space into the dural sinus, but it can flow from ventricle to ventricle. All of the ventricles (both laterals, third and fourth) as well as the subarachnoid space enlarge.



SUMMARY
Increased Intracranial Pressure(ICP)

Increased Brain Tissue Volume

Vasogenic Edema
Cytotoxic Edema

Causes:
Ischemic Injury
Trauma

Increased Brain Blood Volume

Causes:
Dural Sinus Obstruction
Elevated Right Atrial Pressure

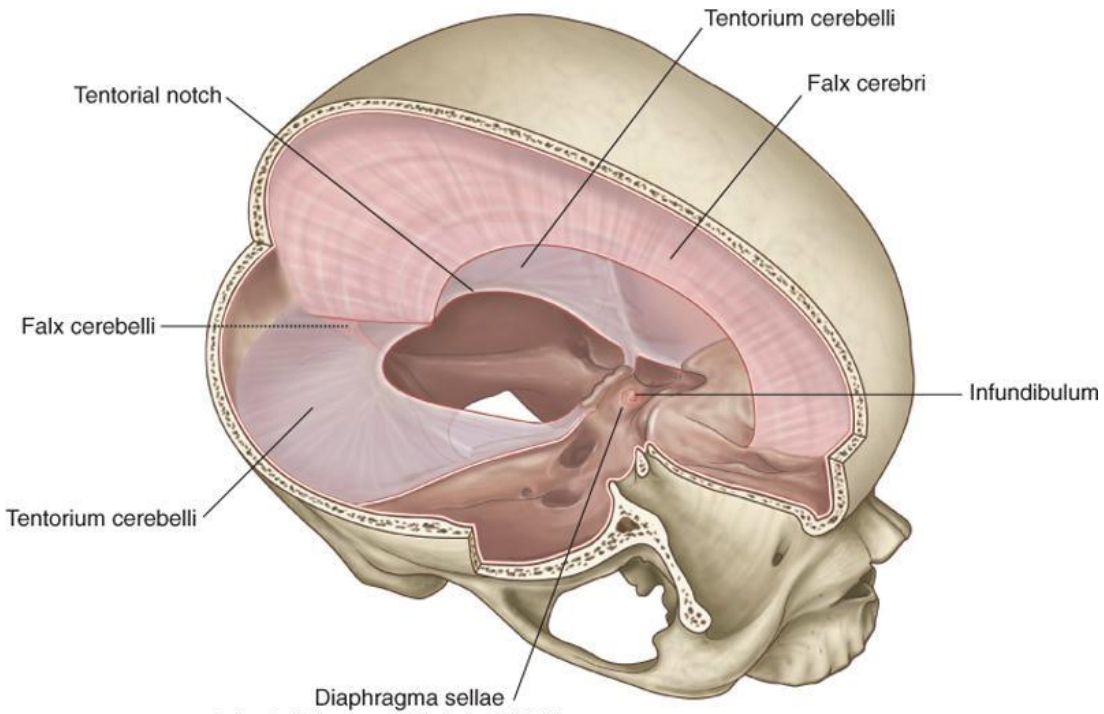
Increased Brain CSF Volume

Causes:
Hydrocephalus

Mechanisms of Brain Injury

Herniation of Brain Tissue

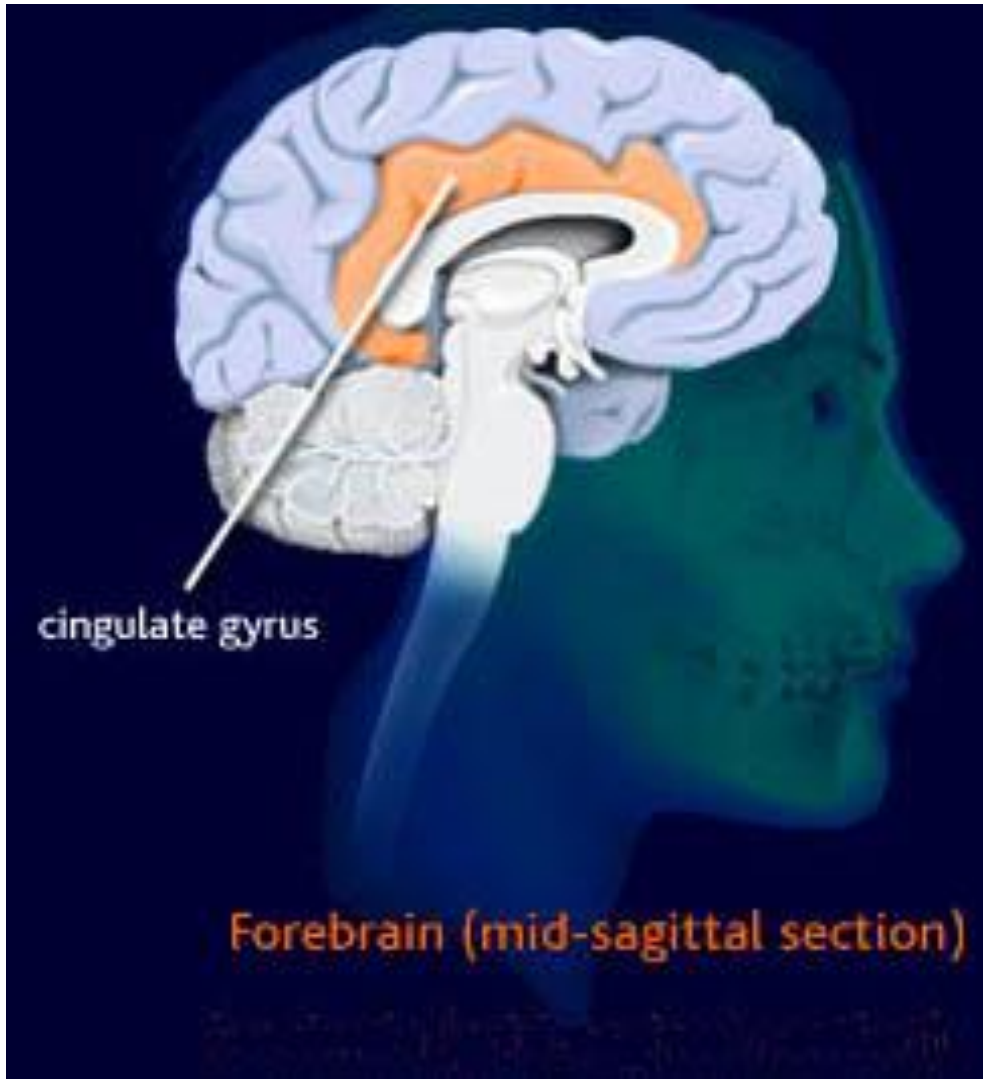
- Increased brain volume may lead to **herniation,** a protrusion of brain tissue. Herniation forces brain tissue against the sharp edges of dural structures. Dural structures are shown below in pink and blue.



Mechanisms of Brain Injury

- **Tonsillar herniation**-swelling of the cerebellum pushes the cerebellar tonsils into the foramen magnum compressing the medulla and upper cervical spinal cord. It is the least common and most serious herniation form.
  - Can cause death in a matter of minutes!
  - Cardiac, vasomotor, and respiratory centers lie within the medulla.
- **Subfalcine or cingulate herniation**-the cingulate gyrus (the gyrus just superior to the corpus callosum) protrudes under the edge of the falx cerebri (the part of the dura mater that extends into the longitudinal fissure). Least serious herniation type.
  - Compression of an **interventricular foramen** causes contralateral hydrocephalus due obstruction of flow of cerebral spinal fluid.
  - Compression of the **anterior cerebral artery** causes contralateral leg weakness. The anterior cerebral artery serves the primary motor cortex.
- **Tentorial or transtentorial herniation**-herniation under the inner edge (incisura or tentorial notch) of the tentorium cerebelli (the part of the dura mater that extends into the transverse fissure). There are two forms, central and uncal.

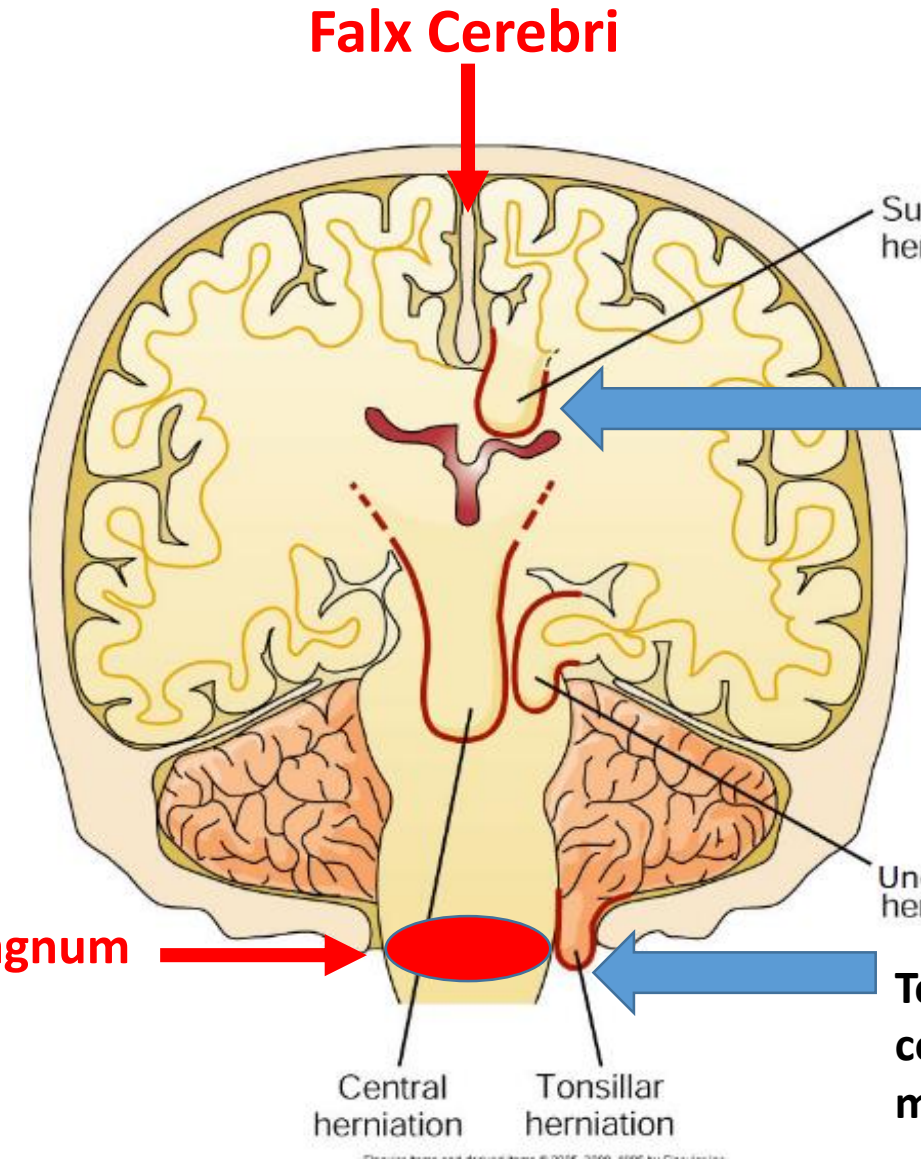
Mechanisms of Brain Injury



Subfalcine Herniation is due to swelling of the cingulate gyrus.

Mechanisms of Brain Injury

Subfalcine herniation



Subfalcine herniation may compress an intraventricular foramen or the anterior cerebral artery.

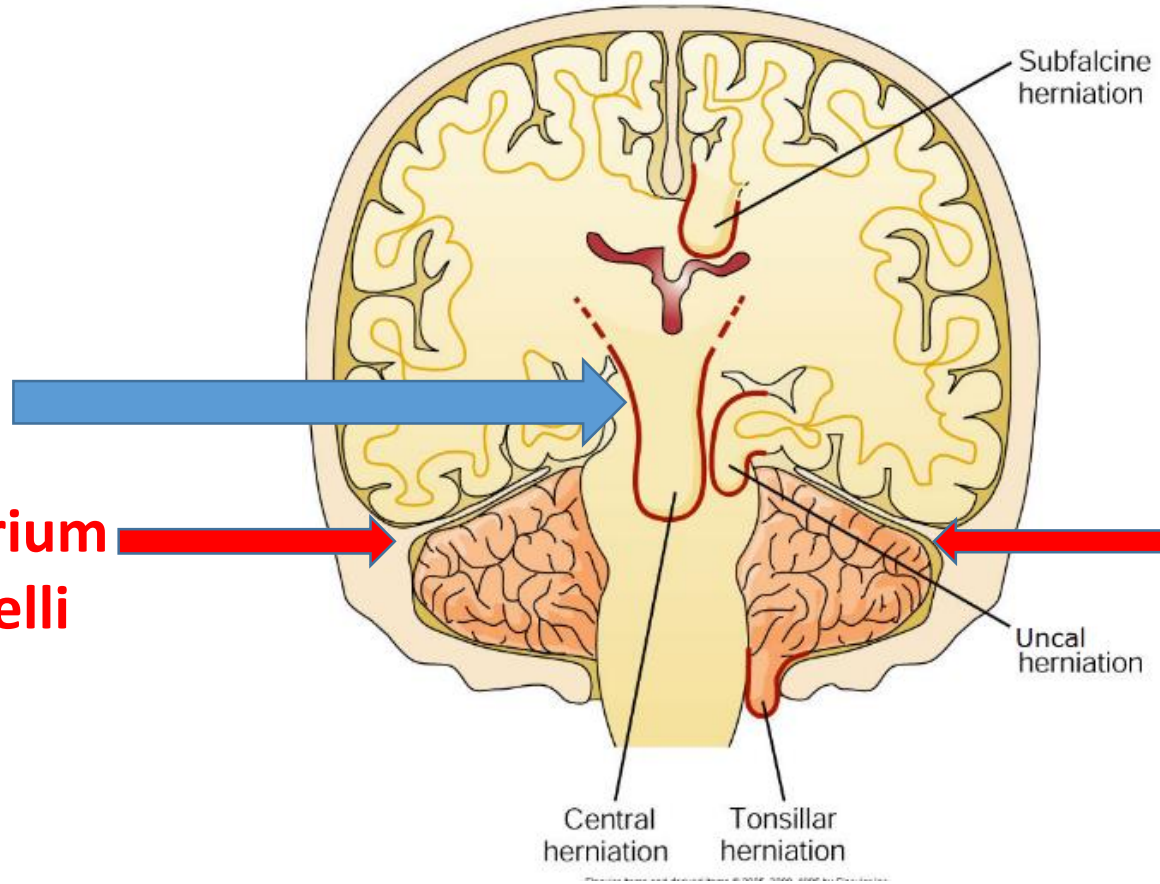
Tonsilar herniation compresses the medulla.

Mechanisms of Brain Injury

- **Central Tentorial Herniation**-symmetric swelling of the cerebral hemispheres causes a downward displacement of both cerebral hemispheres. The brainstem and the diencephalon are pushed against the **incisura (tentorial notch) of the tentorium cerebelli.**
    - Tearing of the **pontine arteries** (located in the pons) may cause a **Duret hemorrhage (usually fatal).**
    - Compression of the **dorsal midbrain** (causes **pinpoint pupils** and inhibits upward eyeball movement, a condition known as **"sunsetting eyes".** The dorsal midbrain is the location of the **cranial nerve nuclei** (cell bodies of the neurons in cranial nerves). Effects on the eyes are bilateral.
    - Compression of the anterior midbrain and **infundibulum (stalk of the pituitary gland)** obstructs the passage of **antidiuretic hormone (ADH)** from the hypothalamus to the posterior pituitary gland and into the blood.
        - ADH normally causes reabsorption of water from the renal filtrate into the blood.
        - Lack of serum ADH causes **diabetes insipidus**. A high volume of body fluid is then excreted in the urine.

Mechanisms of Brain Injury

Central tentorial herniation may compress the dorsal midbrain or the ventral midbrain. It may also tear the pontine arteries.

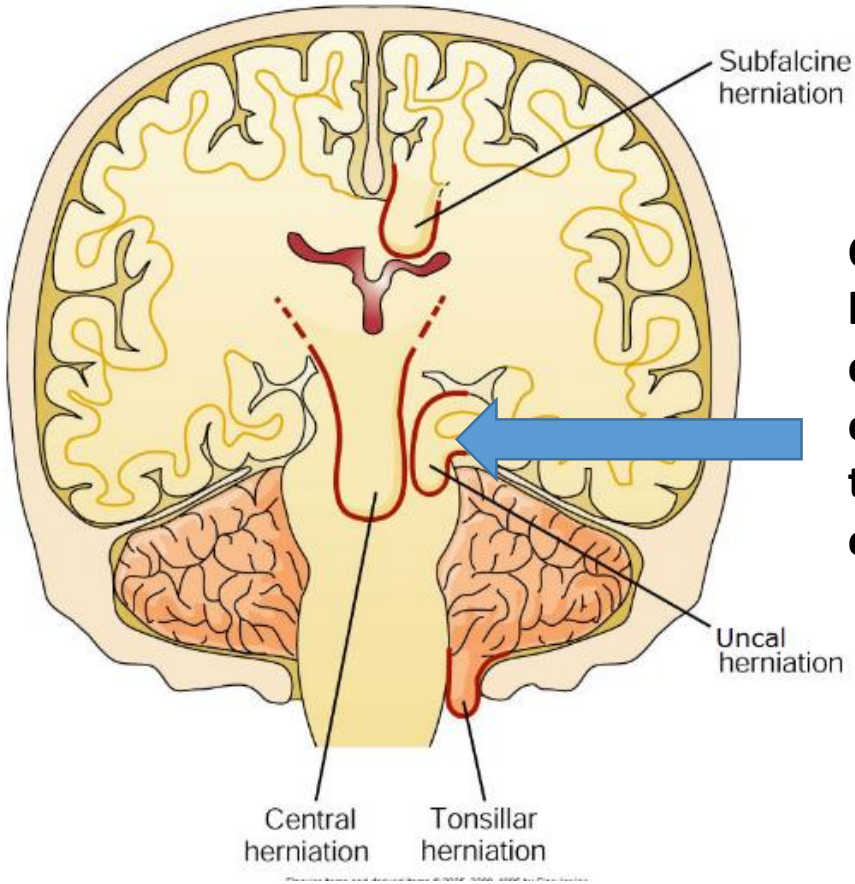


Mechanisms of Brain Injury

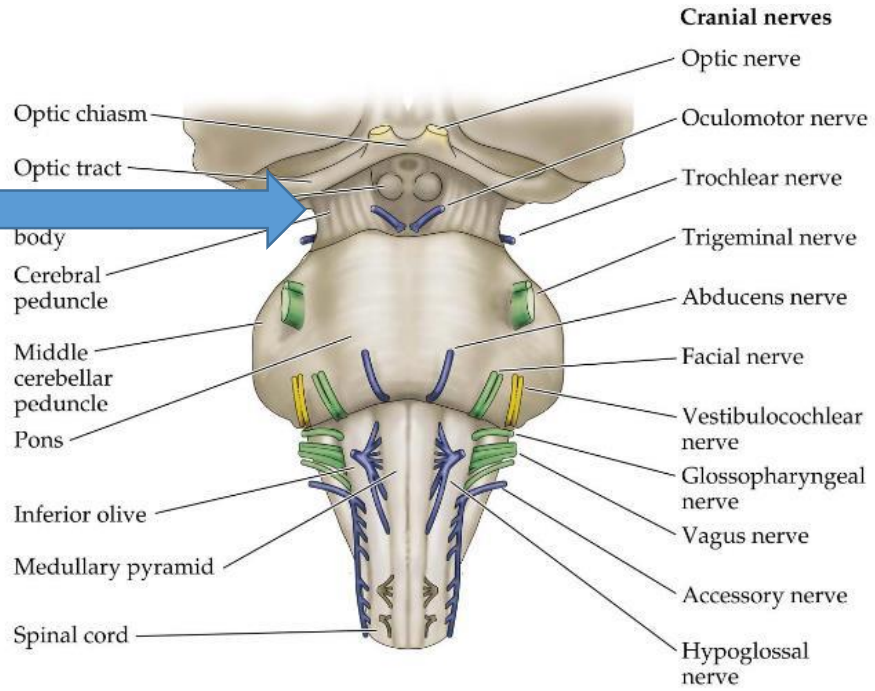
- **Uncal Tentorial Herniation**-swelling of **one uncus** region in the medial temporal lobe causes it to bulge over the edge of the incisura (tentorial notch) compressing the **oculomotor (III) nerve** and the **cerebral peduncle** on one side. Uncal is a common form of herniation with distinctive signs.
  - **Ipsalateral** (same side as the herniation) pupil becomes **fixed and dilated** due to compression of parasympathetic motor fibers in the **oculomotor nerve** (The fibers don't **decussate**—cross to the other side.). Increasing compression affects the deeper somatic motor fibers in the oculomotor nerve next. At that point **eyeball movement** is affected.
  - Compression of the cerebral peduncle has **contralateral** (opposite side as the herniation) effects on skeletal muscle function, because axons in the peduncles decussate.

Mechanisms of Brain Injury

Common Herniations



Central uncal herniation may compress the oculomotor nerve or the cerebral peduncle on one side.

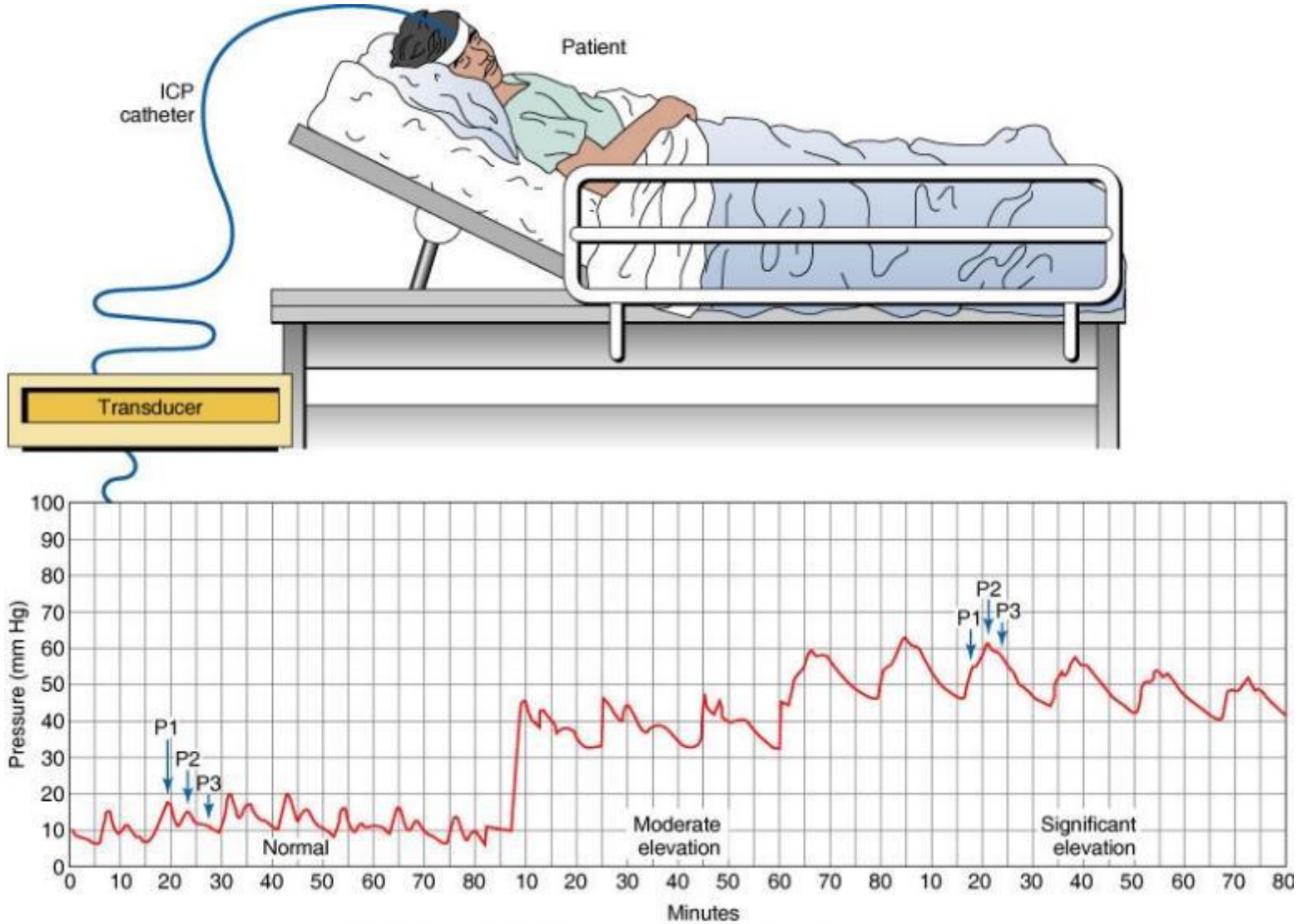


Mechanisms of Brain Injury

Manifestations of Increased ICP and Possible Herniation

- Headache, vomiting, altered consciousness, blurred vision
- Diminished pupillary response to light reflex
- Unresponsive to stimuli, inability to move, verbalize, open eyes
- Elevated ICP is monitored by inserting a pressure probe through a burr hole in the skull. See next slide.
- High ICP will compress blood vessels, impede blood flow and cause ischemia.
- Ischemia will lead to inflammation, further escape of fluid from the vascular bed, more extensive cerebral edema and even higher ICP.

ICP Monitor: Normal, Moderate and Significant Elevation



Mechanisms of Brain Injury

Management of Acute Brain Injury

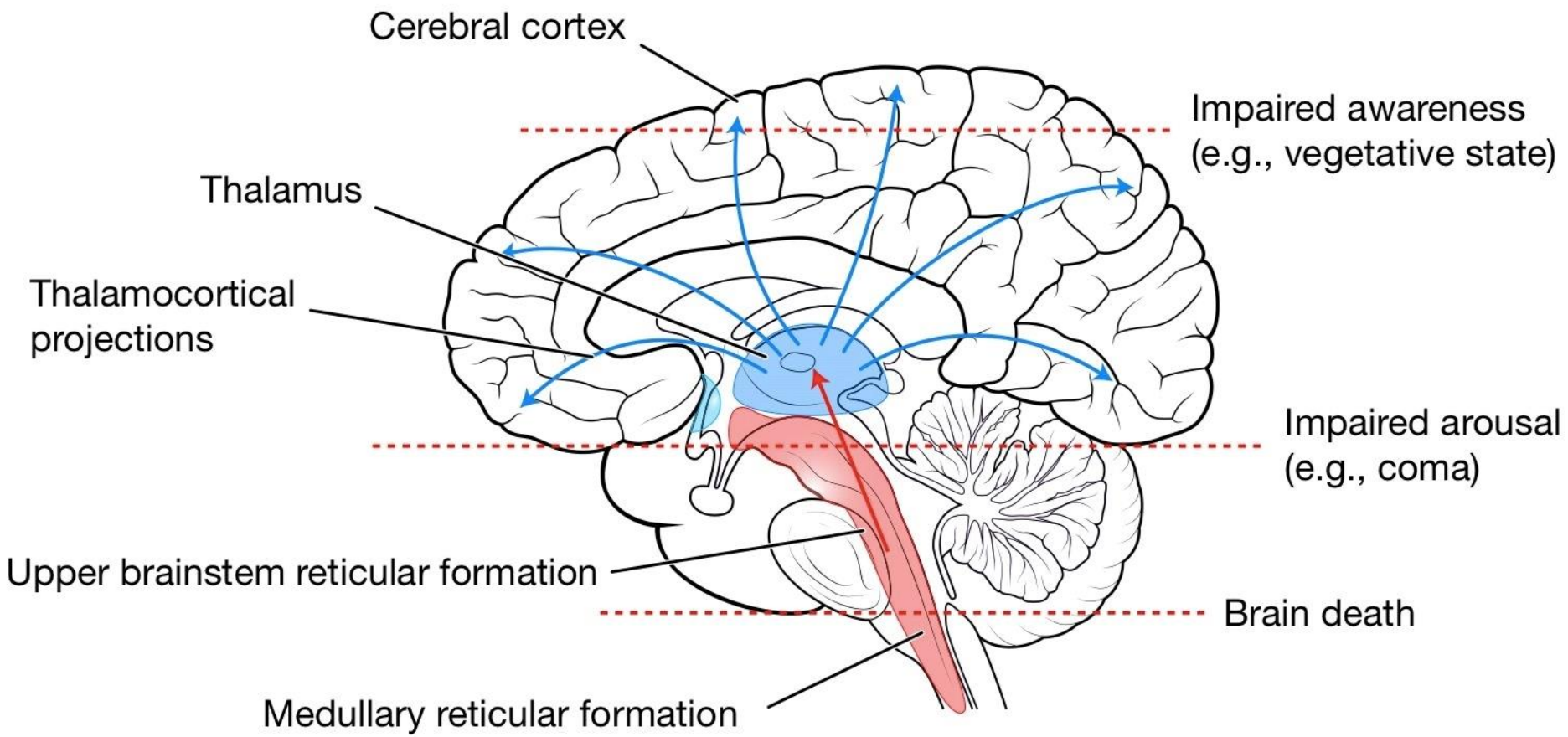
- Brain-injured patients may present with symptoms ranging from a mild headache or visual disturbances to loss of consciousness.
- Careful and frequent assessment of neurologic signs is crucial for detecting changes in conditions.
- Three areas of assessment provide important clues:
  - **Level of Consciousness**
  - **Cranial Nerve Reflexes**
  - **Brain Hemodynamics and Metabolism**

Mechanisms of Brain Injury

Management of Acute Brain Injury

- **Level of Consciousness**
  - Consciousness is dependent on a flow of neural signals from the **reticular activating system (RAS) (aka reticular formation)** in the brainstem to the **thalamus** and finally to the **cerebral cortex.**
  - Cortical functions, those that occur in the cerebral cortex, (cognition and memory, for example) are impaired early leading to confusion.
  - Delirium with hallucinations may follow.
  - As RAS function deteriorates the patient requires increasingly noxious stimuli to produce verbal or motor responses.
  - **Coma** is loss of consciousness. Neural signals fail to reach the thalamus.
  - **The Glasgow Coma Scale** is used to assess the level of consciousness. See next slide.
  - Note: Motor responses should be checked in each limb, because partial paralysis may have occurred. The score of the “best” limb is used.

Consciousness and the RAS



Glascow Coma Scale

Mild
Coma GCS >12

Moderate
Coma GCS 9-12

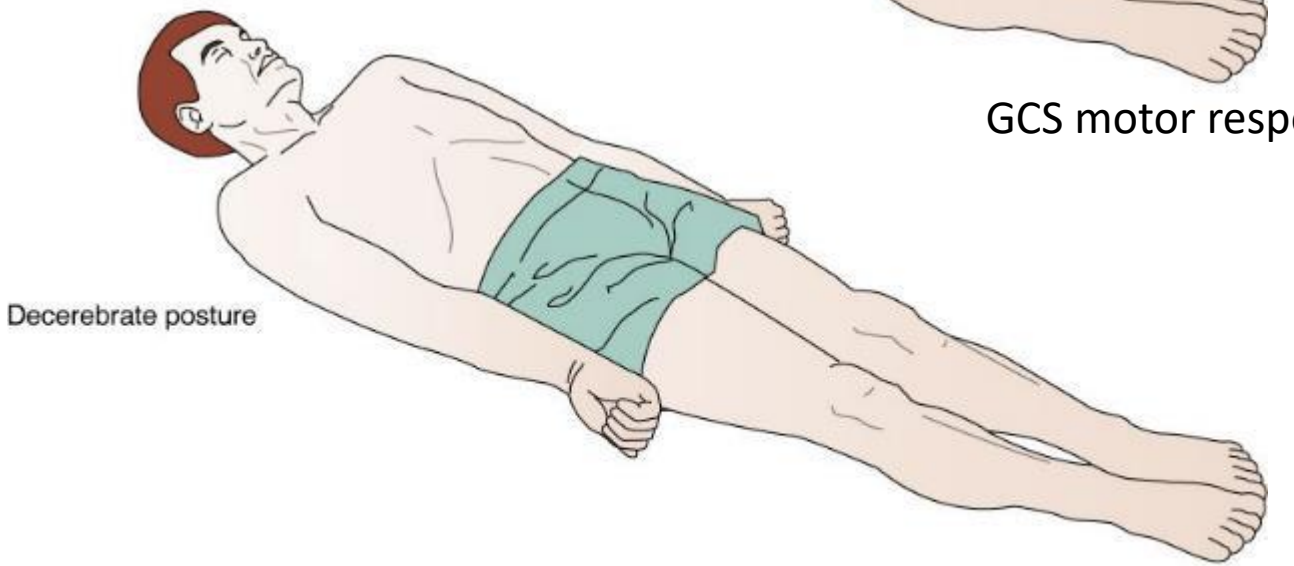
Severe
Coma GCS<8

Eye Opening
4. Spontaneously 3. To speech 2. To pain 1. Never
Verbal Response
5. Oriented to time, person, place 4. Confused speech 3. Inappropriate speech 2. Incomprehensible speech 1. None
Motor Response (each limb)
6. Obeys commands 5. Localizes pain 4. Withdrawal from pain 3. Abnormal flexion (*decorticate) 2. Abnormal extension (**decerebrate) 1. Flaccidity
*elbows and wrists flexed, legs and feet extended **elbows extended, wrists externally rotated, legs and feet extended

Abnormal Motor Activity with Coma

GCS motor response score of 3

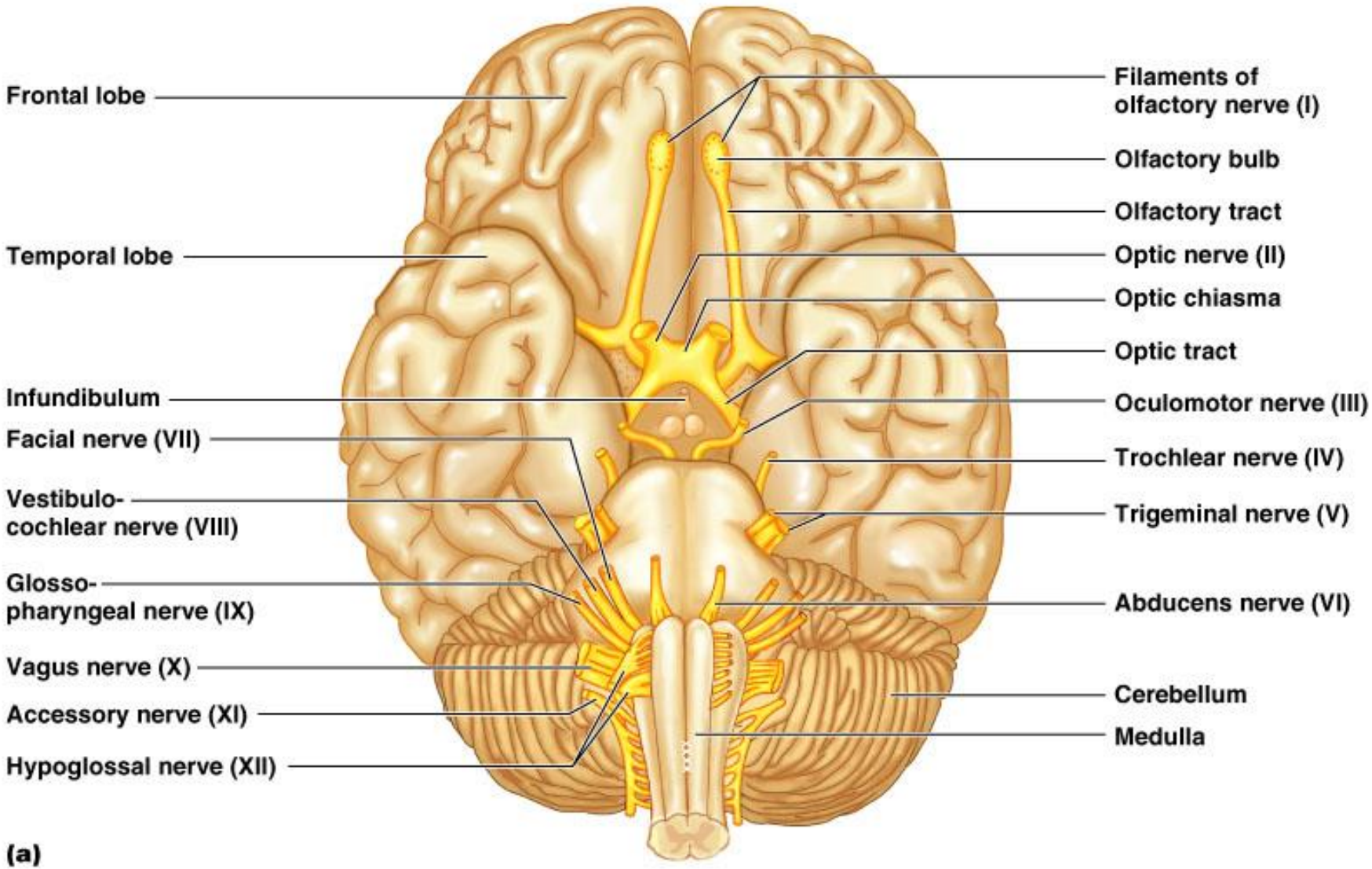
GCS motor response score of 2



Mechanisms of Brain Injury

- **Cranial Nerve Reflexes**
  - Brain swelling/herniation often causes pressure on some of the cranial nerve roots.
  - It is important to assess:
    - **Pupil Size, Shape and Response to Light**
    - **Eye Movements**
    - **Oculovestibular Reflex**
    - **Corneal Reflex**
  - **Note the location of the cranial nerve roots and the functions of the cranial nerves described in the next few slides.**

12 Cranial Nerves



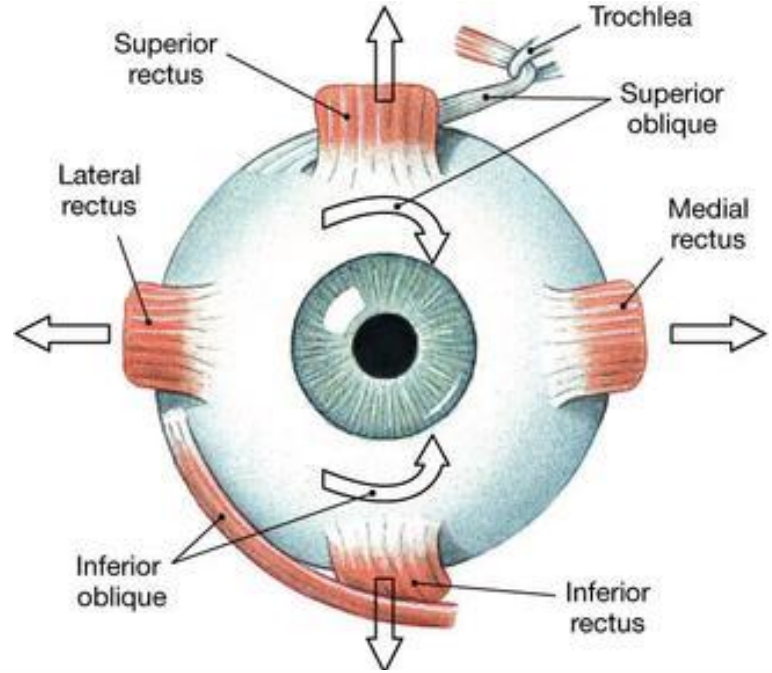
(a)

The Cranial Nerves

Nerve Number and Name		Composition	Some Functions
I	Olfactory	Sensory only	Olfaction (smell)
II	Optic	Sensory only	Vision
III	Oculomotor	Motor and sensory	Serves muscles of the eye
IV	Trochlear	Motor and sensory	Serves the superior oblique eye muscle
V	Trigeminal	Motor and sensory	Sensory from face and mouth; motor to muscles of mastication (chewing)
VI	Abducens	Motor and sensory	Serves the lateral rectus eye muscle
VII	Facial	Motor and sensory	Serves the muscles of facial expression, lacrimal glands, and salivary glands
VIII	Vestibulocochlear	Sensory only	Equilibrium and hearing
IX	Glossopharyngeal	Motor and sensory	Serves the pharynx (throat) for swallowing, posterior third of tongue, parotid salivary gland
X	Vagus	Motor and sensory	Sensations from visceral (internal) organs, and parasympathetic motor regulation of visceral organs
XI	Accessory	Motor and sensory	Serves muscles that move head, neck, and shoulders
XII	Hypoglossal	Motor and sensory	Serves muscles of the tongue

Extrinsic Eye Muscles

(skeletal muscles that move the eyeball)



Name	Action	Controlling cranial nerve
Lateral rectus	Moves eye laterally	VI (abducens)
Medial rectus	Moves eye medially	III (oculomotor)
Superior rectus	Elevates eye	III (oculomotor)
Inferior rectus	Depresses eye	III (oculomotor)
Inferior oblique	Elevates eye and turns it laterally	III (oculomotor)
Superior oblique	Depresses eye and turns it laterally	IV (trochlear)

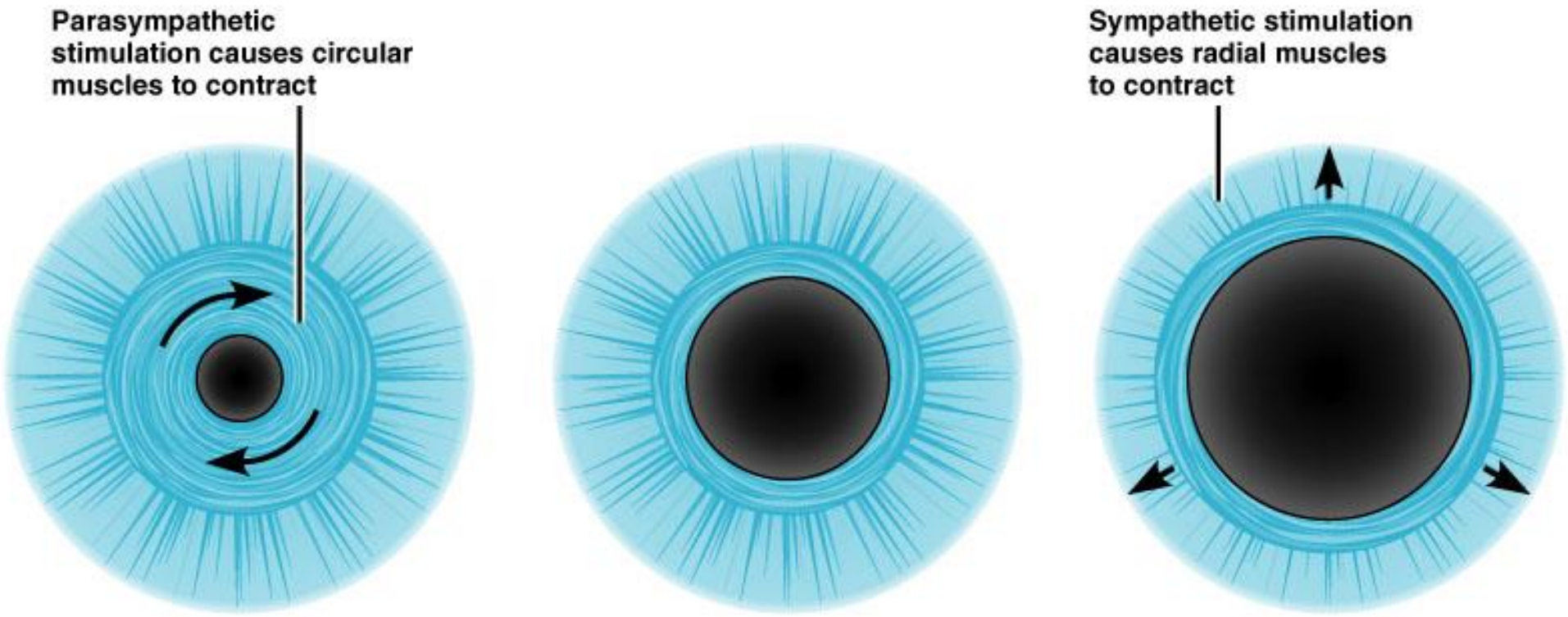
(c)

The Oculomotor Nerve and Pupil Diameter

(Smooth muscle fibers in the iris control pupil size.)

Pupil Constriction

Pupil Dilation



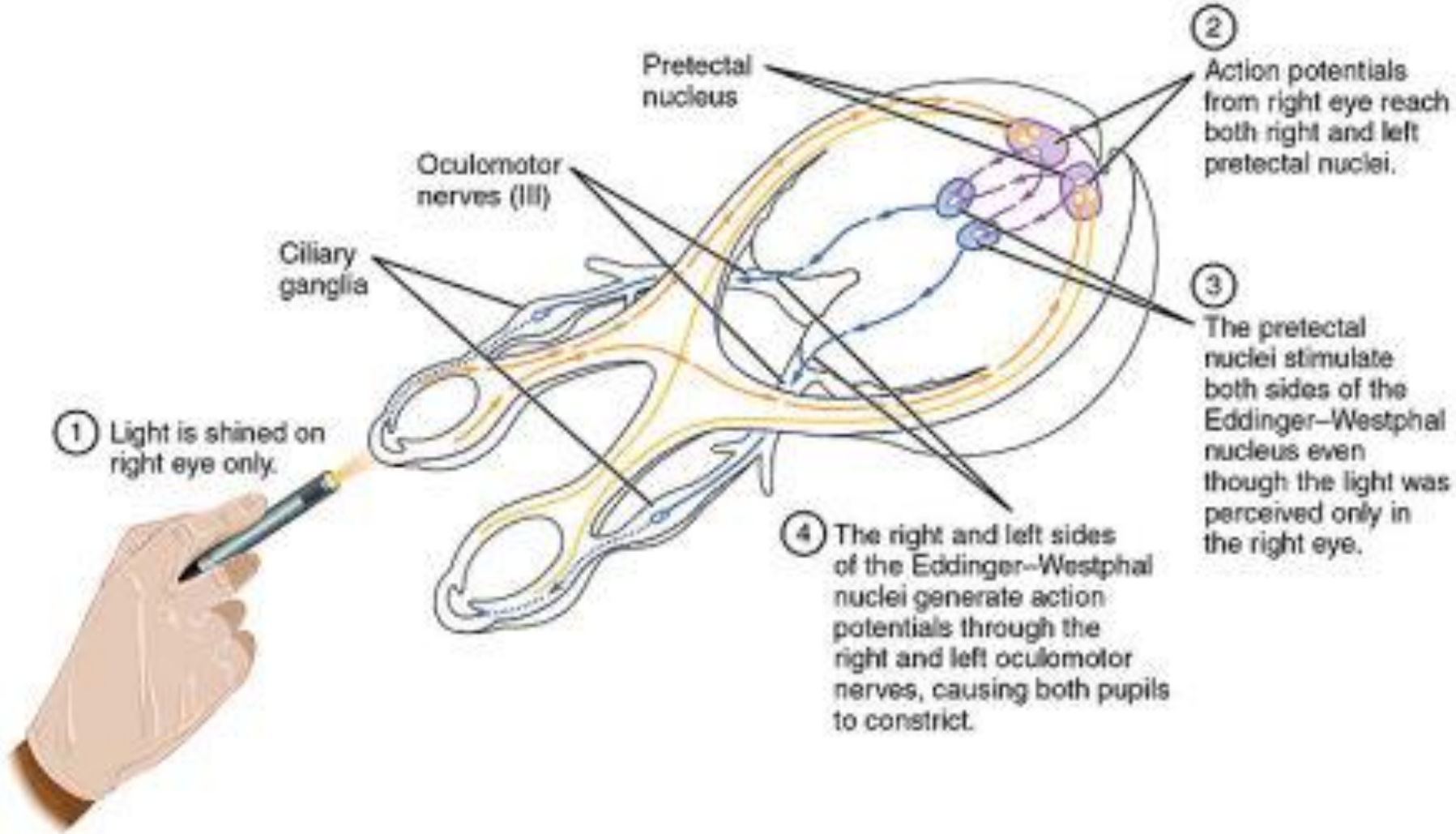
Mechanisms of Brain Injury

- **Pupillary assessment** provides information on **cranial nerves II (optic) and III (oculomotor).**
- **Pupillary assessment** includes the shape of the pupil, the diameter of the pupil (in mm) and the response of the pupil to light.
- **Pupil Size and Shape**
  - **Oval pupil**
    - An early indicator of elevated ICP and transtentorial herniation with **pressure on cranial nerve III** (oculomotor).
    - It is reversible if ICP is controlled.
  - **Bilaterally fixed and dilated pupils**
    - Suggests inadequate brain perfusion as would occur with elevated ICP or vascular hypotension.
    - Lack of activity in the **circular** smooth muscle of the iris and external eye muscles. **Nerve III damage.**

Mechanisms of Brain Injury

- **Bilaterally small (pinpoint) pupils**
  - Suggest a lesion in the pons region of the brain stem or the presence of certain drugs (opioids).
  - There is a lack of contractile activity in the **radial** smooth muscle fibers of the iris. Nerve III (oculomotor) damage.
- **Pupillary Response to Light Reflex**
  - Shining a light into one eye normally causes **both pupils** to **constrict** (consensual response). Failure of one or both pupils to constrict points to damage to **cranial II (optic) or III (oculomotor)**. Nerve II carries sensory impulses. Nerve III carries motor impulses.
  - The **afferent signal** is carried by **optic** nerve fibers from the eye into which the light is shone to the **midbrain** (pretectal nuclei) on both sides. This is because some of the fibers in the optic nerve **decussate**. See the gold pathway in the diagram below.

Normal Pupillary Response to Light Reflex



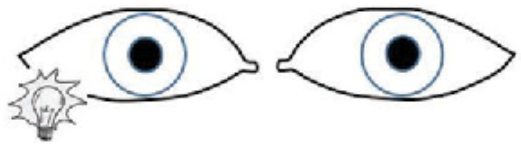
Mechanisms of Brain Injury

- Synapses are made with interneurons that carry the **impulse** to both the left and right **E-W (Edinger-Westphal) nuclei**. See the purple pathway in the diagram below.
- Parasympathetic motor fibers in both **oculomotor** nerves carry the **efferent impulses** from the E-W nuclei to the **circular** muscle fibers of both irises causing pupil **constriction.** See the blue pathway in the diagram below. (Those fibers do not decussate.)
- The **afferent pupillary defect (APD)** is detected by the "swinging light" test. As the examiner swings a light from the normal eye to the abnormal eye, the pupil of the abnormal eye responds with weak constriction followed by dilation. The **damaged optic nerve** of the abnormal eye doesn't carry a strong enough afferent (sensory) signal to maintain the constriction triggered by shining the light into the normal eye.

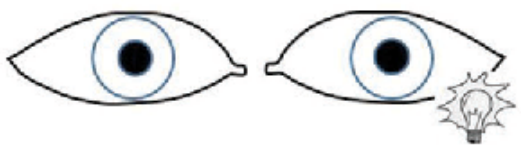
Normal swinging light test

1. Begin with dark room, bright pen light and patient fixated at distant object (to avoid a near pupil response).

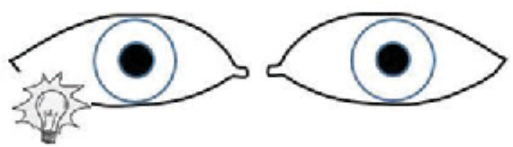
2. **Shine light into right (R) eye.** Both pupils should constrict.



3. **Swing light to left (L) eye.** Both pupils remain constricted.



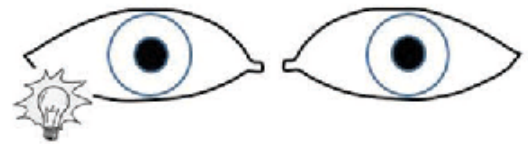
4. **Swing light back to right eye.** Both pupils remain constricted.



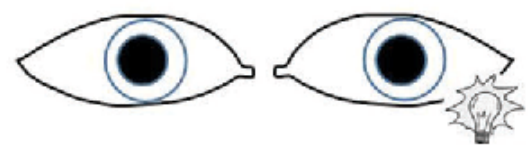
Left relative afferent pupillary defect* (RAPD)

1. Begin with dark room, bright pen light and patient fixated at distant object.

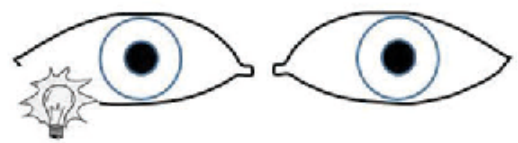
2. **Shine light into right (R) eye.** Both pupils should constrict.



3. **Swing light to left (L) affected eye.** Instead of pupil constriction, both pupils will *dilate*.



4. **Swing light back to right (normal) eye.** Both pupils constrict.



A RAPD indicates unilateral or asymmetric optic nerve pathology (e.g., asymmetric glaucoma) or retinal disease and should *always* be referred to an optometrist or an ophthalmologist.

*In a right RAPD, both pupils dilate when light is shone in the right eye during the swinging light test.

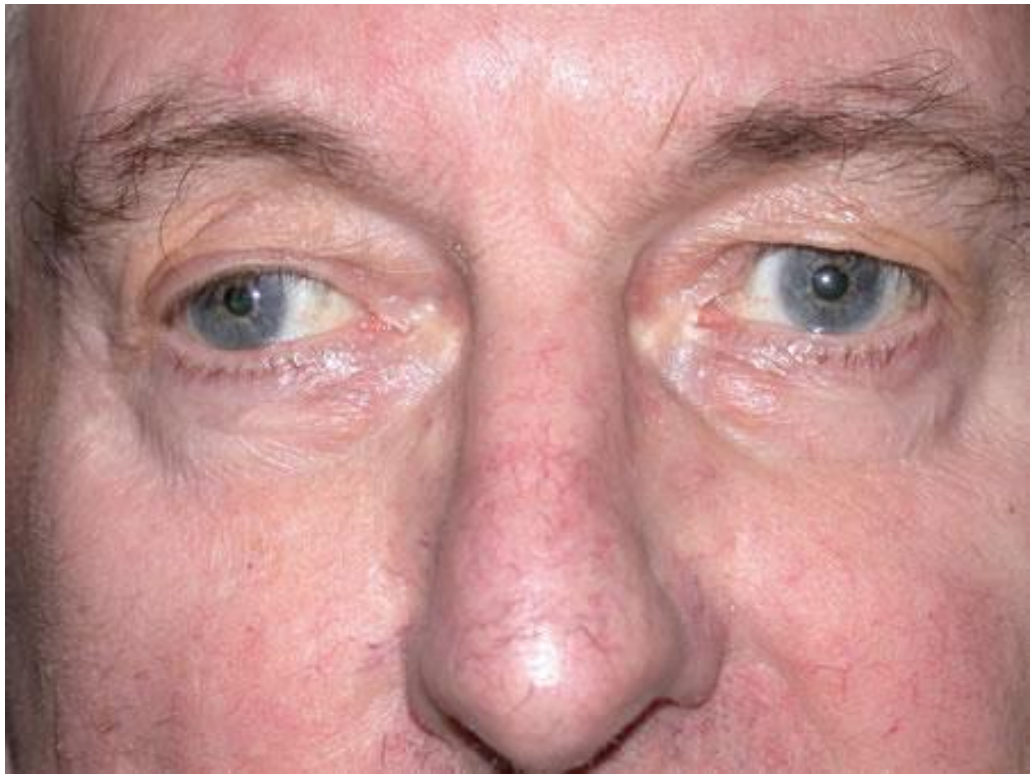
Mechanisms of Brain Injury

- **Eyeball movement assessment** evaluates cranial nerves III (oculomotor), IV (trochlear), and VI (abducens). These nerves control the **extrinsic eye muscles that move the eyeball**.
  - **Nystagmus** is persistent rhythmic or jerky movements in one or both eyes. The "fast component" of nystagmus is the jerky lateral movement. The "slow component" of nystagmus is the return to center.
  - **Dysconjugate movements** occur when the eyes do not move together in the same direction when tracking an object.
  - **Ocular palsies** occur when one or more of the cranial nerves are damaged such that paralysis of extrinsic eye muscles impairs eyeball movements in one or both directions.
    - For example, when the oculomotor nerve is damaged the eyeball on the affected side (ipsalateral side) points **"down and out"**. This effect is termed **third nerve palsy**. Note that the fibers of the oculomotor nerves do not decussate.

Mechanisms of Brain Injury

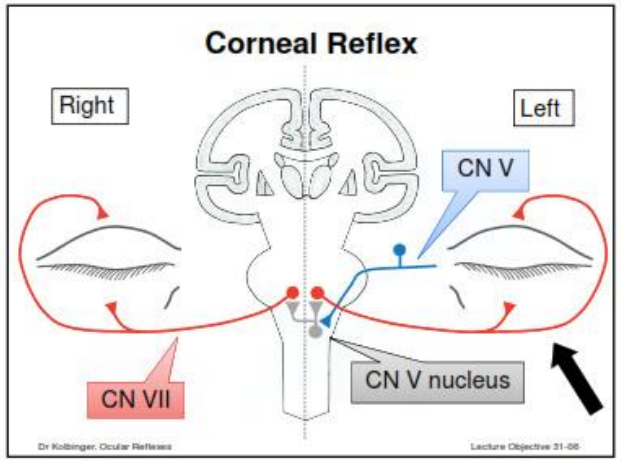
Third Nerve Palsy of the Right Eye
(Due to a damaged right oculomotor nerve the extrinsic eye muscles fail to hold the eyeball in the correct position.)

The right eye exhibits the “down and out” position due to damage to the right oculomotor (III) nerve.



Mechanisms of Brain Injury

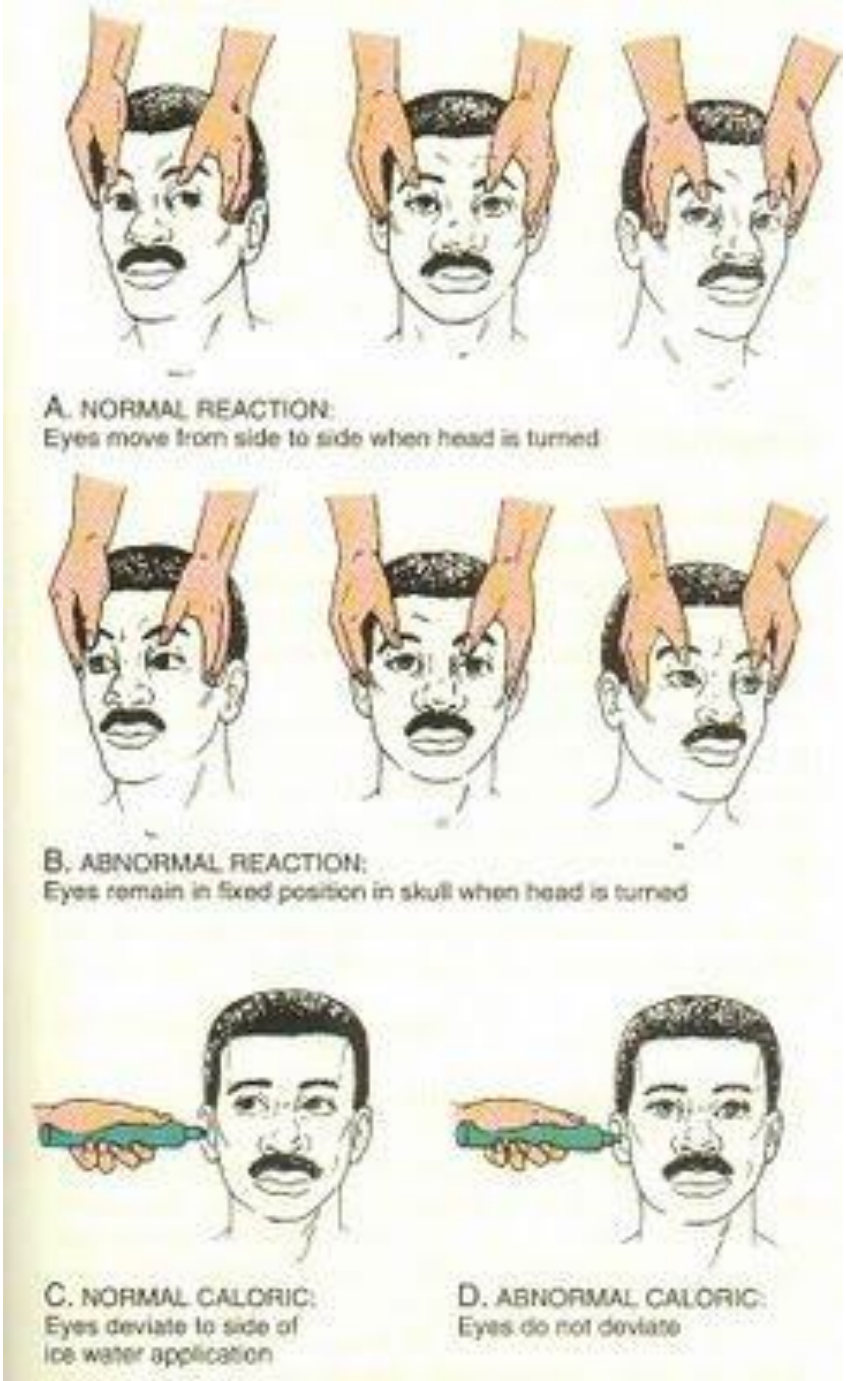
- **Corneal reflex assessment** evaluates the function of **cranial nerve V (ophthalmic branch of the trigeminal)** and **cranial nerve VII (facial)**.
  - When the left cornea is touched by a swab of cotton, the afferent (sensory) impulse travels in fibers of the left trigeminal nerve (V). These fibers synapse with interneurons that in turn synapse with efferent (motor) fibers in both left and right facial (VII) nerves.
  - The absence of a **blink response (closing both eyes)** to corneal contact on one eye (with a wisp of cotton) is an indicator of injury to nerve V or VII.



Mechanisms of Brain Injury

- **Oculovestibular reflex assessment** evaluates the function of the vestibular branch of **cranial nerves VIII (vestibulocochlear) and III (oculomotor).**
  - Sensory detection of head movements by the vestibular branch of nerve VIII (vestibulocochlear) causes motor adjustment of eye position by nerve III (oculomotor) so that the image of an object remains fixed on the retina even though the head is moving.
  - Impairment of this reflex is indicative of serious brainstem dysfunction.
  - Two tests can be performed to evaluate the reflex.
    - **The Doll's Eyes Test-**The eye lids are held open. When the head is moved to one side, the oculomotor nerves normally adjust the position of the eyes so they stay focused centrally. The irises appears to move in the direction opposite to the head turn. Cranial nerve damage prevents the reflex.
    - **The Cold Calorics Test** -Cold fluid in the ear canal on one side of the head normally causes nystagmus with a fast (jerky) component to the opposite side and a slow component back to center. In a negative test eyes remain central.
  - These tests are normally performed on unconscious patients and are **essential in determining brain death.**

Oculovestibular Reflex

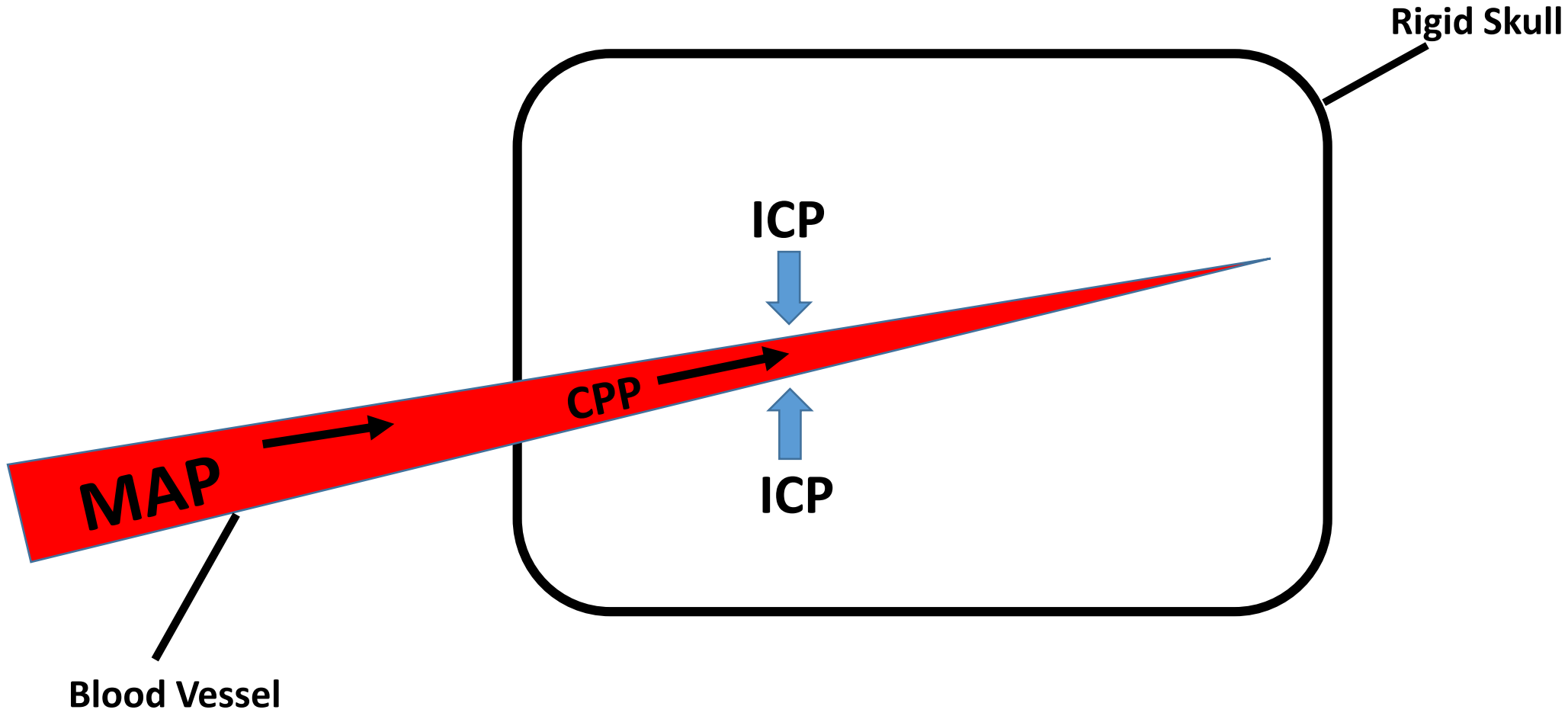


Mechanisms of Brain Injury

Brain Hemodynamics and Metabolism

- Low brain tissue perfusion is poorly tolerated and must be detected and managed promptly. Blood pressure (MAP) is monitored continuously by an indwelling **arterial** catheter.
  - **MAP mean arterial pressure** (diastolic pressure + one third of the pulse pressure) **should not fall below 70 mm Hg.**
  - **NOTE:** The pulse pressure is the difference between the systolic blood pressure and the diastolic blood pressure. For example, if the blood pressure is 120/80, the systolic pressure is 120 mm Hg and the diastolic pressure is 80 mm Hg. The pulse pressure is 40 mm Hg. The MAP is (80 + 1/3 of 40)= 93 mm Hg.
  - **CPP cerebral perfusion pressure** is the pressure of the arterial blood when it enters the brain. It is the pressure available to perfuse brain capillary beds. It is the difference between the mean arterial blood pressure and the intracranial pressure (MAP-ICP). **CPP should not fall below 60 mm Hg.**
  - **ICP opposes CPP. Elevated ICP must be managed in order to preserve CPP!**

ICP Opposes Perfusion of the Brain



Mechanisms of Brain Injury

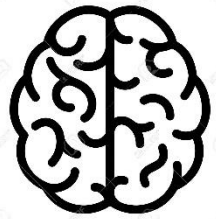
- Try this! If the systolic pressure is 140 mm Hg, the diastolic pressure is 90 mm Hg and ICP is 40 mm Hg, what is the cerebral perfusion pressure (CPP)?
- (Hint: calculate the MAP first.)
- Did you get MAP=106.6 mm Hg?
  - PP= 140 – 90 = 50 mm Hg
  - MAP = [90 + 1/3 (50)] = 90 + 16.6 = 106.6 mm Hg
- Now subtract the ICP from the MAP to find the CPP. According to the previous slide is this CPP high enough for adequate perfusion?
  - 106.6 – 40 = 66.6 mm Hg
  - Yes. CCP is above 60 mm Hg

Increased ICP is very dangerous! It compresses blood vessels and decreases CPP. Brain tissue becomes ischemic.

Conditions that increase ICP:

- **Intracranial Bleeding**
- **Tumors**
- **Hydrocephalus**
- **Ischemic Brain Tissue Injury (Cerebral Edema)**
  - **(Vasogenic Cerebral Edema)**
  - **(Cytotoxic Cerebral Edema)**

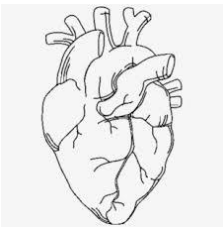
ICP=Intracranial Pressure
CPP=Cerebral Perfusion Pressure
MAP=Mean Arterial Pressure



ICP

CPP

MAP



MAP – ICP = CPP

80 mm Hg

70 mm Hg

60 mm Hg (target value)

50 mm Hg

40 mm Hg

If CPP is **too low,** ischemia occurs.

Mechanisms of Brain Injury

- **Treatments for Elevated Intracranial Pressure (ICP)**
  - **Hyperventilation** may be used in some cases to decrease (blow off) pCO2 and thus decrease capillary bed perfusion and intracranial pressure.
    - The downside of that treatment is that it can reduce the perfusion of capillary beds in areas of healthy brain tissue.
  - **Hypertension**-Mild hypertension (in hypertensive patients) helps keep CPP at an adequate level by increasing the MAP. **(MAP-ICP = CPP)**
  - **Induced hypothermia (decreasing body temperature)** has been shown delay and lessen ischemic brain injury. Possible mechanisms include:
    - inhibition of glutamate release (lower risk of excitotoxicity, elevated pCO2, hydropic swelling)
    - reduced IL-1 release (delays inflammation)
    - reduced neuronal metabolic rate (reduced CO2 production, reduced oxygen demand); optimal temperature for most enzymes is normal body temperature
    - On the downside hypothermia can cause:
      - platelet dysfunction and abnormal coagulation
      - shivering, which increases oxygen demand
  - **Drug-induced coma** is also used to reduce brain metabolism especially in the case of injuries that cause seizures. Seizures greatly increase neuron metabolism and oxygen demand.

Mechanisms of Brain Injury

Brain Death

- Completion of all therapeutic procedures
- Absence of motor and reflexive movement.
- No spontaneous respirations in the presence of pCO_2 >60 mmHg (Normal pCO_2 range is 40-45 mm Hg.)
- No ocular response to head turning (doll's eyes test) or cold calorics test with fixed, dilated pupils
- Flat EEG (electroencephalogram)
- (In brain death sensory impulses do not get past the medulla of the brain stem. They don't enter the upper brainstem reticular formation.)

QUIZ 6CD

- COMPLETE QUIZ 6CD.
- THEN PREPARE FOR EXAM 6.

EXAM 6

- COMPLETE EXAM 6.
- THEN GO ON TO MODULE 7AB PPT.