physiology team 429

Cerebral Circulation & CSF formation

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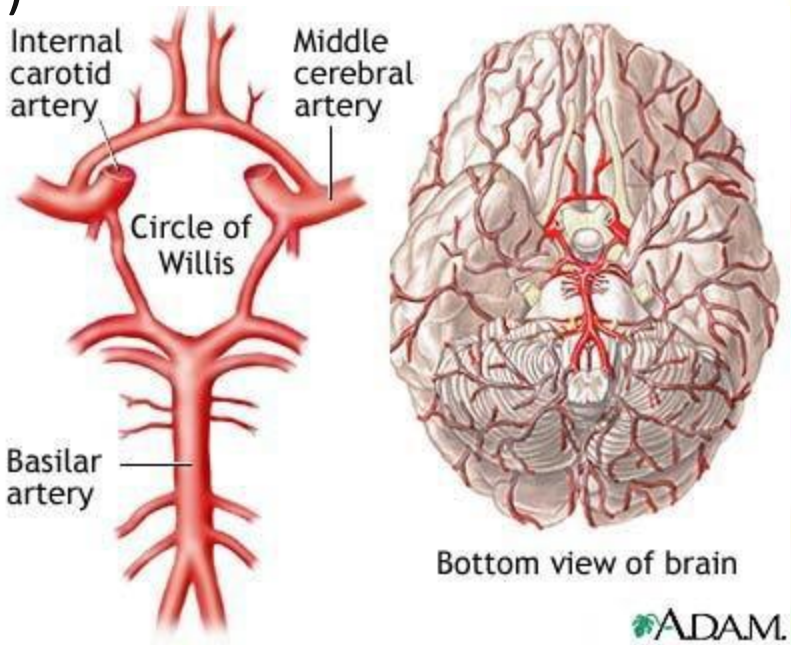
Cerebral Circulation

- The Circle of Willisis the joining area of several arteries at the bottom (inferior) side of the brain.
- At the Circle of Willis,the internal carotid arteries branch into smaller arteries that supply oxygenated blood over 80% of the cerebrum.



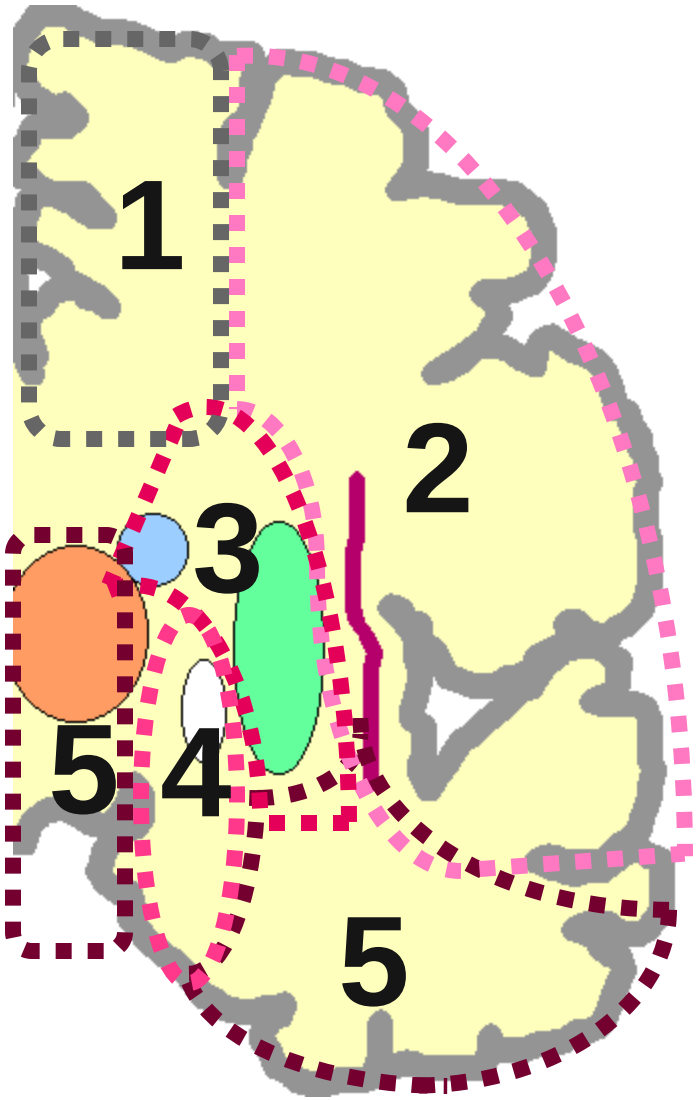
- The brain receives its blood supply from four main arteries:

  Two internalcarotid arteries

  Two vertebral arteries

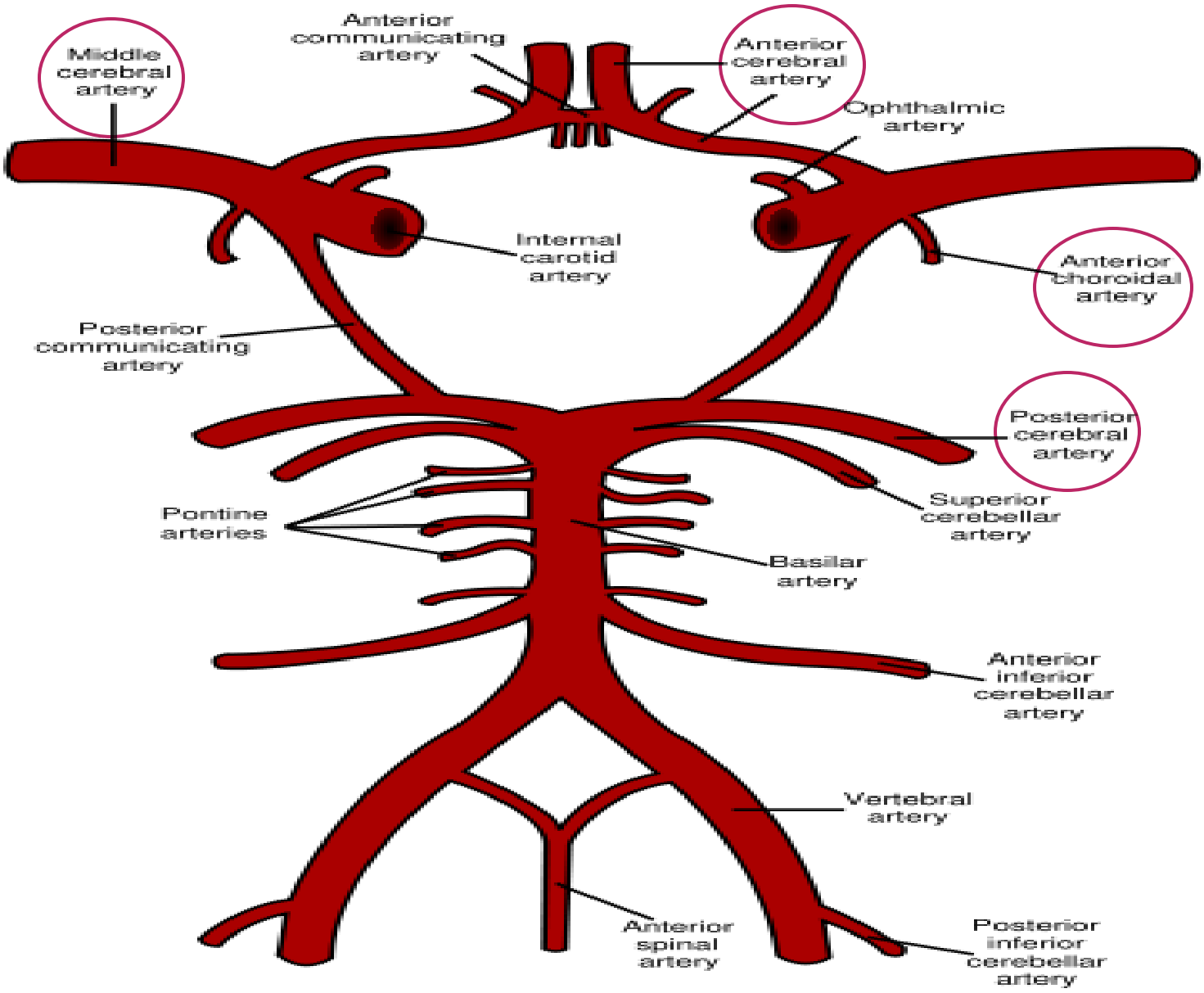
- The vertebral arteries unite to form Basilar artery
- The basilar artery and the carotids form the circle of Willis below the hypothalamus
- The circle of Willis is **origin** of six large vessels supplying the cerebral cortex
- Substances injected into one carotid artery distributed almost completely to the cerebral hemisphere on that side.
  Normally **no crossing over occurs** probably because the pressure is equal on both sides

Cerebral Artery Areas



1. anterior cerebral
2. Middle cerebral
3. Penetrating branches of middle cerebral
4. anterior choroidal
5. Posterior cerebral

You should know each area supplied by what



Features of cerebral vessels

- **Choroid plexus;**

- Gaps are present between endothelial cells of the capillary wall, while choroid epithelial cells that separate them from CSF are connected by tight junctions.

> The endothelial face capillary lumen
> The epithelial cell face the ventricle
> CSF is like extracellular fluid

- ***Capillaries in the brain*** :
  - non-fenestrated and there are tight junctions between endothelial cells → to limit passage of substances through the junctions.

  - **Bulk flow** : the flow of molecules **from capillary to brain** tissue according to **pressure diffrences**
  - Few vesicles in endothelial cytoplasm and little vesicular transport.
  - Brain capillaries are surrounded by the endfeets of the **astrocytes**.
    (There are gaps of 20 nm between the endfeet and the capillaries).

What gaured against cerebral edema

1. **Thight junction** prevent large molecules “like water” to cross into brain tissue → so, it prevent cerebral edema

2. **Pressure in cerebral capillaries** :
   it is one of the lowest pressure in the circulation “ 5-8 mmHg”→ if there is severe high pressure →“ normal bult flow is interuppted”

3. **Blood brain barrier** :
   prevent microrganism and hydrophilic molecule

Innervation

Three systems of nerves innervate the cerebral blood vessels:

1. **Postganglionic sympathetic neurons** have their bodies in the *superior cervical ganglia* (NorEpinephrine & neuropeptide Y) → cause vasoconstriction
2. **Cholinergic neuron** originate in *sphenopalatine ganglia* (Acetyl choline, VIP).End on large arteries → cause vasodilatation
3. **Sensory nerves** (Substance P, VIP →cause VasoDilatation, neuropeptide Y→ causes Vasoconstrictor).

Like migrain : first it will constrict then it will dilate , causing severe headache → sensory nerve sense this changes

Measuring cerebral blood flow

1. Functional imaging resonance.
2. Positron emission tomography.

- Both be used to measure CBF.

These techniques are also used to measure **regional CBF (rCBF)** within a specific brain region → **i.e : for detection of tumer**

Cerebral blood flow

For the entire brain

- 750 to 900ml/min, or 15 percent of the resting cardiac output.
- Can be calculated by the equation:

  Q/(A*V)

  Q= amount of given substance.

  A = arterial conc of the substance.

  V= venous concentration of the substance

  Nitrous oxide is used.

EX :

- We inject nitrous oxide , then we measure its concentration in vein and artery
- So, we can know if the nitrous oxide spread freely in both artery and vein or there is slowness in blood flow !

Cerebral Blood Flow

- CBF is tightly regulated to meet the brain's **metabolic demands**, and on the average must be maintained at a flow of 50 milliliters of blood per 100 grams of brain tissue per minute in adult humans.

- It is important to maintain CBF within narrow limits because:

  - Too much blood can **raise Intra Cranial Pressure**, which can compress and damage delicate brain tissue

  Cerebral blood flow in excess of 55 to 60 ml per 100 g per minute, called hyperemia, is more than the brain needs and can contribute to an increase in intracranial pressure.

  - Too little blood causes **ischemia,** or inadequate blood supply. **Ischemia results** if blood flow to the brain is below 18 to 20 ml per 100 g per minute, and **tissue death occurs** if flow dips below 8 to 10 ml per 100 g per minute.

- Therefore it is important to maintain proper CBF in patients with conditions like shock , stroke and traumatic brain injury.

- Normal CBF = 50ml \ 100 gm \ min
- Hyperemia = 60ml \ 100 gm \ min
- Ischemia = 20ml \ 100 gm \ min
- Cell death = 10 ml \ 100 gm \ min
- Normal CPP = 70 – 90 mmHg (CPP = cerebral perfusion pressure)

100 gm of brain tissue

- When there is increase in CBF → pressure inside capillary will increase → more molecules cross to CSF → lead to high intracranial pressure →

1. compress on capillaries " that supply brain " → ISCHEMIA !!!
2. Compress on brain tissue !!

- In SHOCK state → "low blood flow in cerebrum " → we need more CBF !!
- traumatic brain injury → substances released → lead to vasodilatation → low blood flow → need more CBF

Cerebral perfusion pressure

- **Cerebral perfusion pressure**, or **CPP**, is the net pressure of blood flow to the brain.
- CPP can be defined as:

  CPP = MAP – ICP
- CPP is regulated by **two balanced, opposing forces**:

  Mean arterial pressure, is the force that pushes blood into the brain

  Intracranial pressure is the force that keeps it out.

- Thus raising MAP **raises** CPP
- raising ICP **lowers** CPP (this is one reason that increasing ICP in traumatic brain injury is potentially deadly).

- CPP is normally between 70 and 90 mmHg in an adult human, and cannot go below 70 mmHg for a sustained period without causing ischemic brain damage. Children require pressures of at least 60 mmHg.

•High MAP→push more blood to brain → high CPP → high CBF
•High ICP → compress on vessels → low CPP → low CBF

Autoregulation

- The brain maintains proper CPP through the process of autoregulation.
  The response to lower pressure, is **arteriolar dilation** in the brain creating more room for the blood,
  while when blood pressure rises, **they constrict**, or narrow.

- Thus, changes in the body's overall blood pressure do not normally alter cerebral perfusion pressure dramatically.

- At their most constricted, blood vessels create a pressure of 150 mmHg, and at their most dilated the pressure is about 60 mmHg.

- When pressures are outside the range of 50 to 150 mmHg, the blood vessels' ability to autoregulate pressure through dilation and constriction is **lost,** *and cerebral perfusion is determined by* ***blood pressure alone***,

- a situation called pressure-passive flow. Thus, hypotension can result in severe cerebral ischemia in patients with conditions like brain injury, leading to a damaging process called the ischemic cascade.

The brain has autoregulatory mechanism when there is :

- **Vasoconstriction** → inhibit vasomotor center in medulla → vasodilatation
- **Vasodilation** → stimulate vasomotor center → vasoconstriction

- **Factors disturb the autoregulation**
  - hypoxia due to occlusive cerebrovascular disease
  - trauma from head injury or surgery
  - brain compression from tumors, hematomas or cerebral edema

All results in the loss of normal cerebral blood flow(CBF) autoregulation

Regulation of Cerebral Blood Flow

As in most other vascular areas of the body, cerebral blood flow is highly related to metabolism of the tissue. At least three metabolic factors have potent effects in controlling cerebral blood flow :

(1)carbon dioxide & hydrogen ion concentration

(2) oxygen concentration

- Sympathatic nervous system has an important effect on the regulation of CBF

Carbon Dioxide &Hydrogen Ion Concentration

Excess CO_2 + H ion → increase in CBF

- **Carbon dioxide is believed to increase cerebral blood flow by combining first with water in the body fluids to form carbonic acid, with subsequent dissociation of this acid to form hydrogen ions.**

- **The hydrogen ions then cause vasodilation of the cerebral vessels , the dilation being almost directly proportional to the increase in hydrogen ion concentration up to a blood flow limit of about twice normal.**

- **Any other substance that increases the acidity of the brain tissue, and there fore increases hydrogen ion concentration, will likewise increase cerebral blood flow.**

- **Such substances include lactic acid, pyruvic acid, and any other acidic material formed during the course of tissue metabolism**

- Increased hydrogen ion concentration greatly depresses neuronal activity. Therefore, it is fortunate that an increase in hydrogen ion concentration also causes an increase in blood flow, which in turn carries hydrogen ions, carbondioxide and other acid forming substances away from the brain tissues.

- Loss of carbon dioxide removes carbonic acid from the tissues; this, along with removal of other acids, reduces the hydrogen ion concentration back toward normal.

- Thus, this mechanism helps maintain a constant hydrogen ion concentration in the cerebral fluids and thereby helps to maintain a normal, constant level of neuronal activity

Thus, when activity in a given region of the brain is heightened, the increase in CO_2 and H^+ concentrations causes cerebral blood vessels to dilate and deliver more blood to the area to meet the increased demand.

Oxygen Concentration

High O_2 → vasoconstriction **Low O_2 (hypoxia) → vasodilatation**

- **Oxygen Deficiency is a Regulator of Cerebral Blood Flow except during periods of intense Brain activity.**

- **The rate of utilization of oxygen by the brain tissue remains within narrow limits—almost exactly 3.5 (±0.2) milliliters of oxygen per 100 grams of brain tissue per minute.**

- **Decrease in cerebral tissue PO2 below about 30 mmHg (normal value is 35 to 40 mmHg) the oxygen deficiency mechanism cause vasodilation immediately , returning the brain blood flow and transport of oxygen to the cerebral tissues to near normal**

- **This is fortuitous because brain function becomes deranged at not much lower values of PO2, especially at PO2 levels below 20 mmHg. Thus, the oxygen mechanism for local regulation of cerebral blood flow is a very important protective response against diminished cerebral neuronal activy and,there fore, against derangement of mental capability**

Effect of the Sympathatic Nervous System

- The innervation of the Sym NS supplies both the large brain arteries and the arteries that penetrate into the substance of the brain.

- However, transection of the sympathetic nerves or mild to moderate stimulation of them usually causes very little change in cerebral blood flow because the blood flow autoregulation mechanism can over ride the nervous effects

- The sympathetic nervous system normally constricts the large-and intermediate –sized brain arteries enough to prevent the high pressure from reaching the smaller brain blood vessels. This is important in preventing vascular hemorrhages into the brain

- That is, for preventing the occurrence of “cerebral stroke.”

Effect of ICP changes on systemic blood pressure;

Cushing reflex:

If ICP > 33 mmHg over a short period of time, CBF will drop markedly, leading to ischemia of vasomotor area. Then blood pressure rises.

Problems of Cerebral Circulation

❖ Fainting

- Temporary loss of consciousness, weakness of muscles, and inability to stand up, caused by sudden loss of blood flow to the brain.

- Fainting is a relatively common symptom caused by a variety of problems relating to changes in blood pressure.

- The American Heart Association reports that fainting is responsible for 3% of all visits to emergency rooms and 6% of all admissions to hospitals.

❖ Stroke

- Stroke occurs when the blood supply to a part of the brain is blocked resulting in the death of an area within the brain.

- If a large vessel is blocked the outcome may be rapidly fatal or may lead to very severe disability.

- If smaller blood vessels are blocked the outcome is less severe and recovery may be good.

- The most common types of disability are the loss of functions of one side of the body and speech problems.

types of stroke:

- **Thrombotic Stroke** due to the blockage of an artery leading to or in the brain by a blood clot.

- **Haemorrhagic Stroke** due to bleeding from a ruptured blood vessel, usually a consequence of hypertension.

- **Embolic Stroke** due to the formation of a blood clot in a vessel away from the brain. The clot is carried in the bloodstream until it lodges in an artery leading to or in the brain.

The thrombotic and haemorrhagic forms are common,

Transient ischaemic attack:

When blood supply to a part of the brain is temporarily interrupted without producing permanent damage.

- Recovery may occurs within 24 hours.
- Usually result from small blood clots or clumps from plaques of atheroma which get carried into the blood circulation producing transient blockages.
- Occasionally these clots may get carried from the heart or arteries leading to the brain (e.g. carotid arteries), rather than from within the cerebral circulation itself.

Dementia:

- This may result from repeated episodes of small strokes which produce progressive damage to the brain over a period of time.
- The main clinical feature of dementia is a gradual loss of memory and intellectual capacity.
- Loss of motor function in the limbs and incontinence can also occur.

Cerebrospinal Fluid (CSF)

CSF is a fluid that fills the ventricles and subarachnoid space.

- **Volume = 150 ml**
- **Rate of production =550 ml/d, so it turns 3.7 times/day.**
- **Lumbar CSF pressure = 70-180 mm CSF**
- **Absorption of CSF occurs by bulk flow and it is proportionate to CSF pressure.:**
- **At pressure of 112 mm (normal average): filtration and absorption are equal.**
- **Below pressure of 68 mm → CSF absorption stops.**

When CSF pressure is low the absorption stop , trying to keep more CSF so , the pressure increase

- **Hydrocephallus:**

1. **External hydrocephallus:**

   Large amounts of CSF accumulates when the reabsorptive capacity of arachnoid villi decreases.

2. **Internal hydrocephallus:**

   occurs when foramina of Luschka & Magendie are blocked or obstruction within ventricular system, resulting in distention of the ventricles.

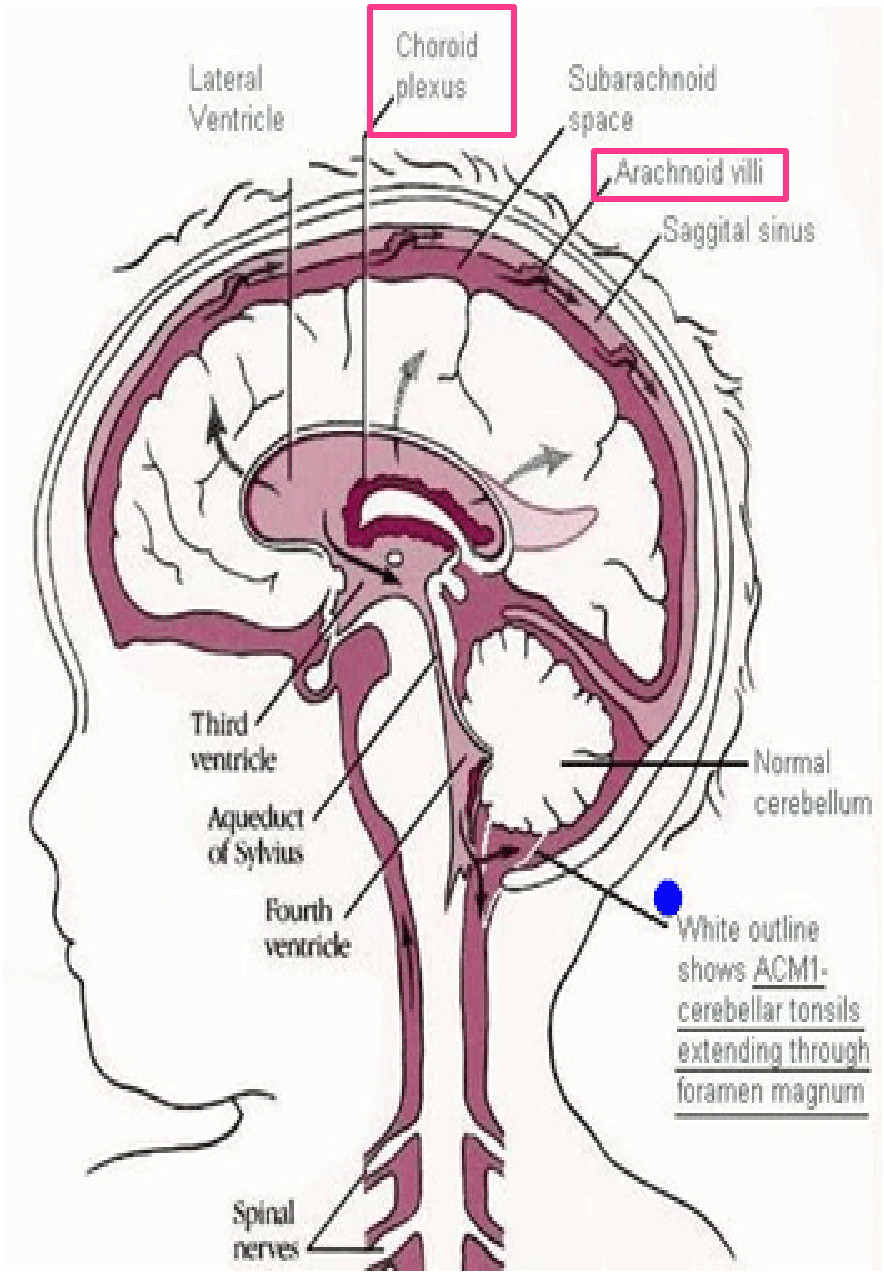
- **CSF is formed in**:

Choroid plexus.

- around blood vessels.
- along ventricular walls.

- **CSF is absorbed by**:

Arachnoid villi



Composition of the CSF

Substance	CSF	Plasma
Na+	147	150
K+	2.9	4.6
HCO_3^-	25	24.8
PCO_2	**50**	**39.5**
pH	7.33	7.4
Osmolality Glucose	289 64	289 100

- The composition of CSF is essentially the same as brain ECF

High CO2 → low PH

PCO2 is high in CSF because :
CO2 cross BBB easily ,
- it stimulate central chemoreceptor in respiratory center , so there is breathing !
- If it is low due to hyperventilation → respiration will decrease.

Functions of the CSF

1- The CSF has a protective function

- The brain is supported within the arachnoid by the blood vessels , nerve roots and the arcahnoid trabiculae.

- In air brain weight =1400 g, but in its water bath of CSF , brain weight = 50 g, making it suspended effectively.

- When the head receives a blow, the arachnoid slides on the dura and the brain moves, but its motion is gently checked by the CSF cushion and by the arachnoid trabiculae.

- Removal of CSF during lumbar puncture can cause severe headache

" the CSF is decresing so the brain will increase in its wight "
(more than 50) → So it will move down suddenly and cause sever headache !!

- When there is High pressure of CSF and we do a lumbar punctur → lead to brain herniation

Functions of the CSF continue ….

2. **Facilitation of pulsatile cerebral blood flow,**

→ High systole → need it for perfusion of brain tissue !!

3. **Distribution of peptides, hormones, neuroendocrine factors and other nutrients and essential substances to cells of the body,**

4. **Wash away waste products.**

5. **Cardiovascular dynamics are also affected by CSF pressure, as the flow of blood must be tightly regulated within the brain to assure consistent brain oxygenation .**

Blood brain Barrier (BBB)

It is formed by the tight junctions between capillary endothelial cells of the brain and between epithelial cells in the choroid plexus.

This effectively prevents proteins from entering the brain in adults and slow the penetration of smaller molecules.

Mechanisms of transport through the BBB:

- Bulk flow.
- Carrier mediated transfer
- Vesicular transport.

Penetration of substances into the brain

- **Molecules pass easily**

  H_2O, CO_2, O_2, lipid-soluble free forms of steroid hormones.

- **Molecules not pass**

  proteins “e.g:bacterial”, polypeptides.

- **Slow penetration**

  H^+, HCO_3^-

- **Glucose**

  its passive penetration is slow, but it is transported across brain capillaries by **GLUT1**

Functions of BBB

1- Maintanins the constancy of the environment of the neurons in the CNS.

2- Protection of the brain from endogenous and exogenous toxins.

3- Prevent escape of the neurotransmitters into the general circulation.

Development of BBB

- The BBB is not well developed in the first two months after birth
- Premature infants with hyperbilirubinemia → free bilirubin pass BBB → may stain basal ganglia causing damage (Kernicterus).

Kernicterus is a form of brain damage caused by **excessive jaundice**.
The substance which causes jaundice, bilirubin, is so high that it can move out of the blood into brain tissue.

Clinical implications

- Some drugs penetrate BBB with difficulty e.g. antibiotics and dopamine.

- BBB breaks down in areas of infection, injury, tumors, sudden increase in blood pressure, and I.V injection of hypertonic fluids.

- Injection of radiolabeled materials help diagnose tumors as BBB is broken down at tumor site because of increased vascularity by abnormal vessels.

- Radiolabeled materials are made of **Proteins**
- They usally cant penetrate to the brain bacause of the BBB

Circumventricular organs

These areas are outside the blood brain barrier.
They have fenestrated capillaries

They are

1. Posterior pituitary
2. Area postrema.
3. Organum vasculosum of the lamina terminalis (OVLT).
4. Subfornical organ (SFO).

Functions:

- Chemoreceptor trigger zone. As area postrema is the trigger of vomiting & cardiovascular control.
- Ang II acts on SFO and OVLT to increase H_2O intake (thirst).
- IL2 induce fever by (+) circumventricular organs.