Physiology Team

LECTURE 27

Cerebral Circulation and CSF Formation

Done By: Thekra Alolayan
Reviewed By: Naif Al-Ajji and Fatma Alshihri

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OBJECTIVES

At the end of this lecture, student should be able to describe:

- Innervations of cerebral blood vessels.
- Cerebral blood flow and factors affecting;
- Autoregulation/metabolic .
- Blood pressure.
- Intracranial pressure (ICP)
- Factors affecting cerebral blood flow: Blood gases, Neural stimuli, -Humoral stimuli
- CSF formation / absorption.
- CSF functions.
- Blood brain barrier (BBB).

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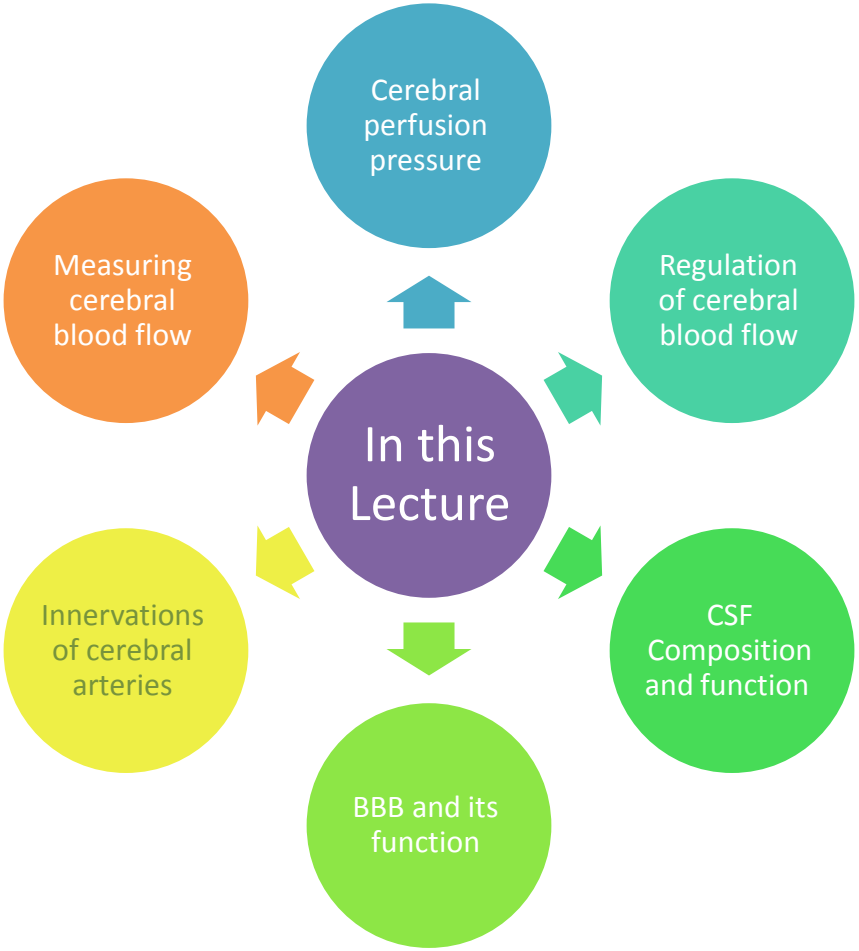
MIND MAP



Slides | Important | Doctor's Notes | Explanation | Boy's Slides

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Notes from Dr.Eman

Difference between Cerebral Circulation and Systemic Circulation

1- Cerebral circulation has circle of Willis.

2- Veins drain in Dural sinuses.

3- Supply oxygen and nutrition to the brain(like any circulation).

4- Pulmonary, cerebral and hepatic circulation are special circulations.

5- The unique thing about pulmonary circulation is pressure.

- The average pressure of systemic circulation is about 35 mmHg, but in pulmonary circulation it is lower than that.
- If the pressure in pulmonary circulation increase more than 25 mmHg, that's will lead to pulmonary edema.
- Capillary pressure in kidney = 60 mmHg (the highest) **(why)** because the function of the kidney is filtration .

6- The brain is one of the low capillary pressure if it gets higher it will also cause brain edema.

Cerebral Circulation

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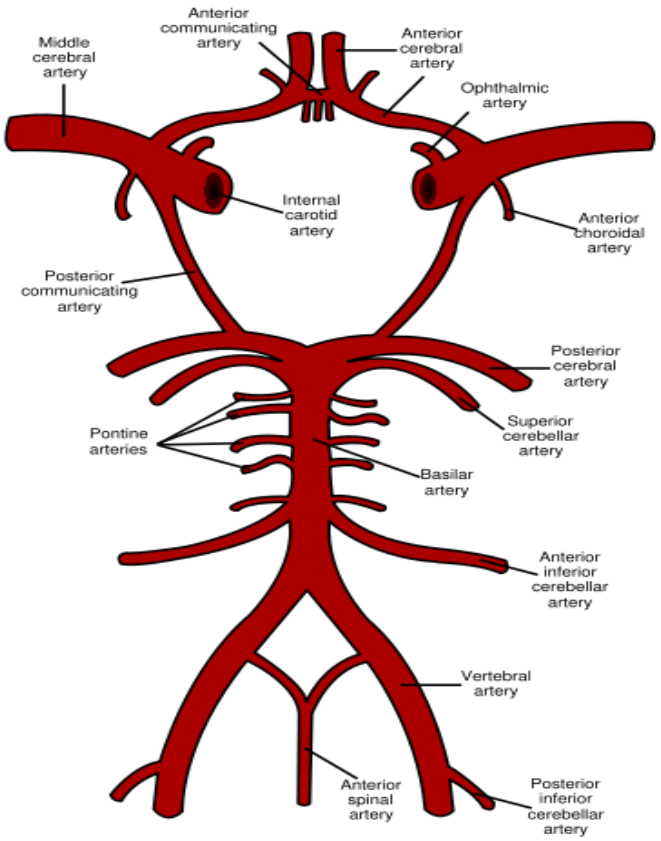
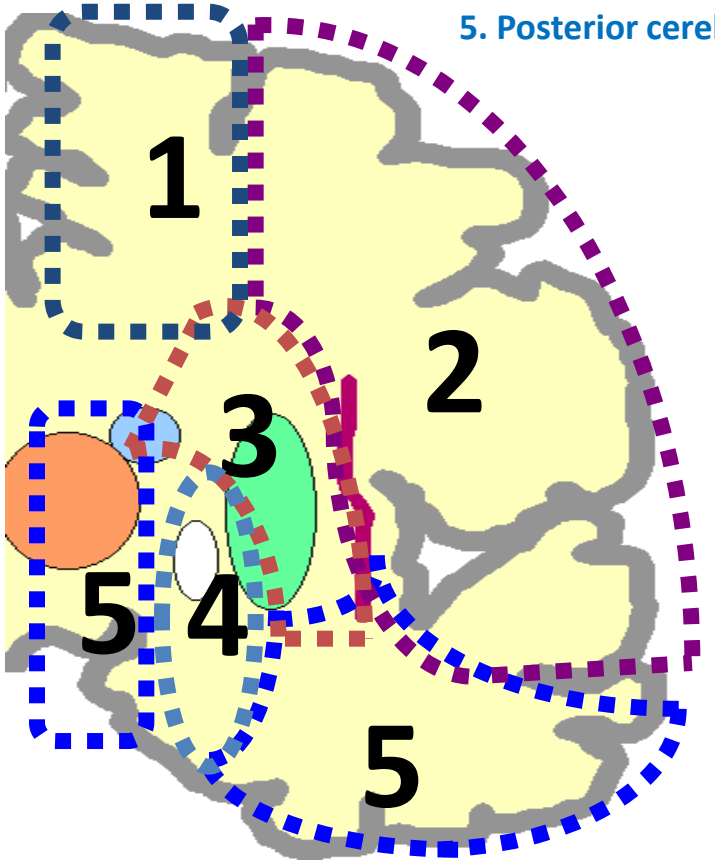


Important for patient who do positron emission tomography or what we call functional tomography. E.g. if there is a change in area 1 the anterior cerebral artery has hypoperfusion and so on..

Cerebral Artery Areas

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



Notes

- Sometimes we do models in animal to study what happen in the brain, So, if we block an artery it will cause ***focal ischemia***. If we put a clip in carotid or vertebral arteries it will cause ***global ischemia*** >> there will be no blood flow to all brain.

- ***if I occluded an artery in the cerebral circulation what are the consequences ?***

  It depends on which artery is occluded so it will be focal or global ischemia.

- The occlusion of an artery Should not be more than ***4 min***
- Patients who have shock or break down of an artery for any reason either (hypotensive or cardiogenic), if they get on coma because hypotension or defect in perfusion of the brain and then they recover , their recovery **depends on how long they stayed in this hypoperfusion** . if it is less than 4 min it is okay, but if it is more than that it will effect areas of brain such as hippocampus and areas responsible for memories.

That's why till now brain transplantation is not possible because there will be a lot of changes in it and it wont be Efficient.

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VD=vasodilatation
VC=vasoconstriction
VIP= Vasoactive Intestinal Peptide also found in GIT
CBF=cerebral blood flow

Innervations

In cases of migraine strong VC of cerebral blood vessels followed by extensive VD cause headache.
Sensory nerves are mainly responsible for the VC &VD.

Sympathetic

VC and hypertension

Postganglionic sympathetic neurons have their bodies in the superior cervical ganglia
(NE & neuropeptide Y).
During acute hypertension attenuate increase in CBF

Parasympathetic

VD

Cholinergic neuron originate in sphenopalatine ganglia (Ach, VIP).End on large Arteries

Sensory nerves

Contain mediators at the terminals such as

- Substance P, VIP*, cause VD*,
- neuropeptide Y causes VC*.
- Contribute to increase in CBF during meningitis.

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Cerebral blood flow

- CBF is tightly regulated to meet the *brain's metabolic demands.*
- **(when you study you need blood to flow more to your brain in areas of memory , attention and vision).**
- 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.

- ***If the brain weights 2 kilos, how much the CBF?***

2 kilos=2000 gram

2000x50\100=1000 milliliters per minute.

- It is important to maintain CBF within narrow limits because *too much* blood can raise *ICP,* which can *compress and damage delicate brain tissue*.

  Too little blood flow causes ***ischemia*** and if it lasts more than 4 min → infarction + brain damage + no regeneration
- 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 drops below 8 to 10 ml per 100 g per minute.

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Cont.

- *Therefore it is important to maintain proper CBF in patients with conditions like shock , stroke and traumatic brain injury (first aid is to maintain normal cerebral blood flow).*
- *Cerebral blood flow in excess of 55 to 60 ml per 100 g per minute, called hyperemia (1), is more than the brain needs and can contribute to an increase in intracranial pressure.*

***(ICP)** =difference between mean arterial blood pressure **(MAP)** and cerebral blood flow **(CBF)**.*

**** MAP** should be higher than **CBF***

- *If ICP increased >> patient has space occupying lesion or hypertension (hypertensive encephalopathy) it will cause compression and herniation.*

(1) Hyperemia: an abnormally large amount of blood in any part of the body.

Cerebral perfusion pressure

- ***Cerebral perfusion pressure (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:*
  1. *Mean arterial pressure (takes the upper hand), is the force that pushes blood into the brain*
  2. *ICP, force that pushes out.*
- *Thus raising MAP raises CPP, and raising ICP lowers it.*
- *(this is one reason that increasing ICP in traumatic brain injury is potentially deadly).*
- *CPP, or MAP minus ICP, 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.*

Slides | Important | Doctor's Notes | Explanation | Boy's Slides

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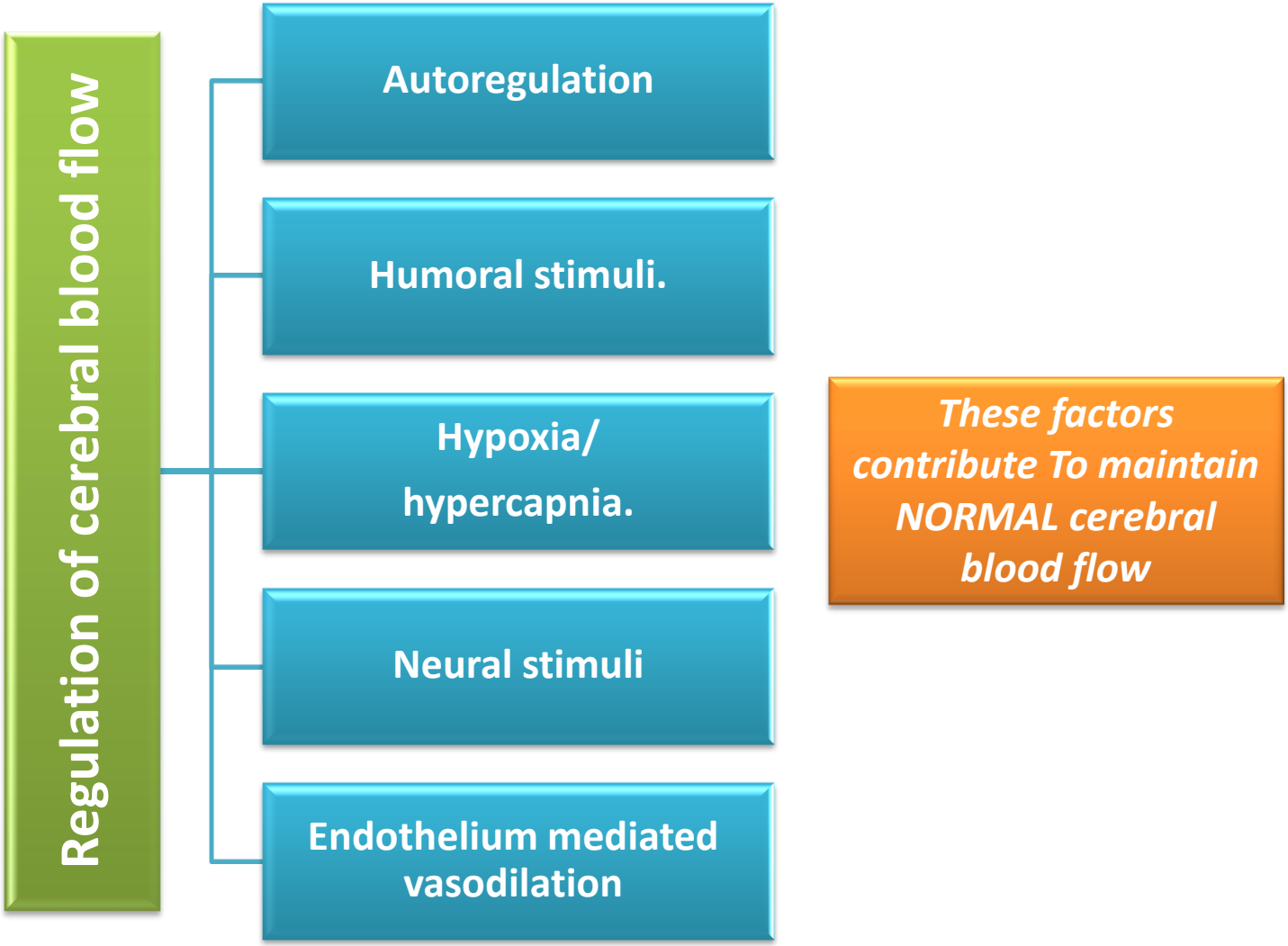

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Autoregulation

ability of the tissue to regulate their own blood flow according to it's metabolic needs

- *The brain maintains proper CPP through the process of autoregulation:*
- *(studies show that there is an increase blood flow in certain areas while studying or solving a problem by using petrosin emission tomography)*
- *The response to lower pressure, there is arteriolar dilation caused by the release of vasodilator mediators in the brain creating more room for the blood, while when blood pressure rises within limits, they constrict, or narrow to prevent the excess increased in the blood flow to the cerebral blood vessels.*
- ***if you're relaxed and there is an increased in arterial blood pressure within limits, will it directly increase your cerebral blood flow?***

  No ,because the metabolic needs is not increased, brain will autoregulate by closure of precapilliries filter to maintain the blood flow within normal levels, and if there is a drop in ABP the precapillaries will OPEN.
- *Thus, changes within ranges in the body's overall blood pressure do not normally alter cerebral perfusion pressure drastically. BUT if there is extreme change in ABP for example hypertension(200 and above) it will effect CPP because THIS is beyond the autoregulation of the brain.*

Autoregulation Cont.

- *At their most constricted condition, 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. 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 Normal range which Autoregulation work on is between (50-150). So, If the pressure is less than 50 or higher than 150 there will be NO autoregulation.*
- *Brain changes its blood flow according to its metabolic activities.*
- *Nitric oxide & adenosine are mediators.*

Hypoxia & Hypercapnia

normal O2 tension in arterial blood pressure is 95 mmHg. If it drops to 60 or less there will be ***hypoxemia*** which lead to increase in CBF.

- Alterations in blood gas content.
- Amounts of carbon dioxide and oxygen in the blood affect constriction and dilation even in the absence of autoregulation:
- excess carbon dioxide **(like in respiratory failure and anesthetic over dose)** can dilate blood vessels up to 3.5 times their normal size, while high levels of oxygen constrict them. Hypoxia, or inadequate oxygen, also dilates blood vessels and increases blood flow.
- Blood vessels also dilate in response to low pH. **(Can be *local* at the level of the brain or *systemic* in conditions of metabolic ketoacidosis) 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.

↑ CO2	↑ O2	↓ Hypoxia	↑ PH = acidosis = H+
Dilatation	Constriction	Dilatation	Dilatation

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Neural stimuli

Under normal conditions sympathetic has little effect. During acute hypertension, a decrease in CBF occurs. Sympathetic stimuli can be strong enough to cause increasing pressure of cerebral blood vessels and it occurs usually with severe pain *agony pain*or terminal pain in patient with cancer.

-Different neural stimuli can cause VC or VD,

-Vasovagal attack cause VD in cerebral blood vessels

Endothelium-mediated dilation

depends on vasoconstrictor and vasodilator mediators present in the endothelium.

most important vasodilatror is nitric oxide and most vasoconstrictor is thromboxilin.

is impaired by hypertension.

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- ***EFFECT OF ICP CHANGES ON SYSTEMIC BLOOD PRESSURE***

Example: significant drop in arterial blood pressure will cause the CNS Ischemic response →strong vasoconstriction of cerebral blood vessels →try to raise cerebral blood flow

Differ from cushing syndrom which we will take it insha'a Allah in the endocrine block (:

Cushing reflex ***it is the effect of increased ICP on CBF***

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

If it raise above 33mmHg it will compress the blood vessels → decrease in the blood flow → ischemia of the brain → CNS ischemic response → strong sympathetic VC of systemic blood vessels → increase in arterial blood pressure → over come the increase in ICP → finally increase in the cerebral blood flow

This happen in patients with intracranial tumors and children with obstructive type of hydrocephalus.

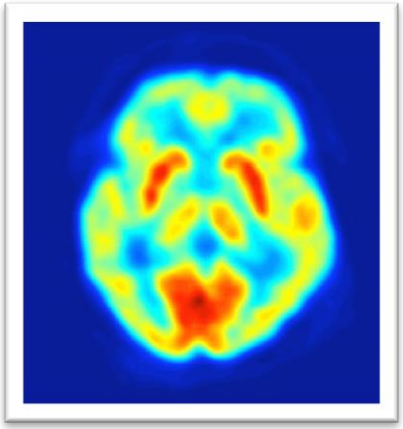
Measuring cerebral blood flow

Average cerebral blood flow = 756 ml/min (1\9 or 1\10 of cardiac output)

-Functional imaging resonance.

-Positron emission tomography.

-Both be used to measure CBF. These techniques are also used to measure regional CBF (rCBF) within a specific brain region.



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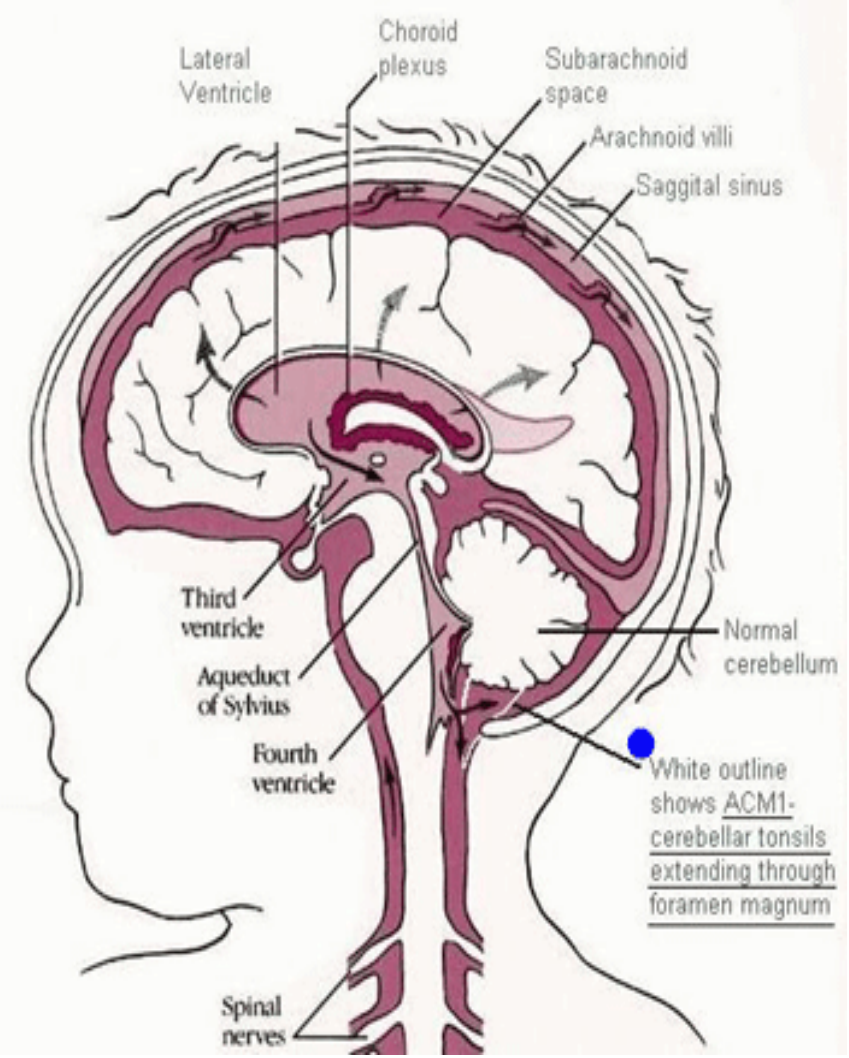
Cerebrospinal fluid

- This is an illustration (midline view) showing the anatomical structures involved in the production and flow of cerebrospinal fluid through the ventricular system, brain and spinal cord, and finally absorption into the bloodstream. You'll also see the difference between a "normal" cerebellum and the cerebellum of an ACM patient with the cerebellar tonsils protruding through the foramen magnum

Cerebrospinal fluid provide a cushion effect around the brain to protect it from traumas . .



Cerebrospinal Fluid (CSF)

CSF fills ventricles and subarachnoid space.

-Volume = 150 ml and it is in a narrow space so if it increased the pressure will increase .

-Rate of production =550 ml/d but due to absorption its volume is constant = 150 ml. , so it turns 3.7 times/day.

-Lumbar CSF pressure = 70-180 *mm CSF*

-Absorption of CSF occurs by bulk flow **(fluid mechanism)** 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 it is a protective mechanism otherwise CSF pressure will severely drop and cause brain herniation which is a serious condition may lead to death

Clinically, sever drop in CSF pressure may happen to child affected by meningococcal meningitis and the physician decided to do a lumbar puncture. A huge amount of CSF will come out because these condition of inflammation will lead to increased CSF production and then increased CSF pressure. This sever drop in the pressure cause brain herniation "fatal condition"

-Hydrocephalus: happens if the CSF pressure increased.

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

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

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Composition of the CSF

COMPARING WITH COMPONANTS OF PLASMA

Substance	CSF	Plasma	Info
Na+	147	150	Almost same
K+	2.9	4.6	Half of it (K+ is more important in muscles and brain doesn't contain ms we only need k+ for neurotransmitters
HCO3-	25	24.8	Almost same more imp in buffer system and respiratory center
PCO2	50	39.5	---
pH	7.33	7.4	Slightly acidic ***compared to plasma*** because the CSF is representing as an extracellular fluids and it is equal to its pH.
Osmolality	**289**	**289**	If the osmolality different it may cause 1-brain edema 2-brain dehydration Factors can affect it: Na+ , glucose and urea
Glucose	64	100	----

The composition of CSF is essentially the same as brain ECF

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CSF is formed in

- Choroid plexus.
- Around blood vessels.
- Along ventricular walls.

CSF is absorbed by

- Arachnoid villi

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Functions of the CSF

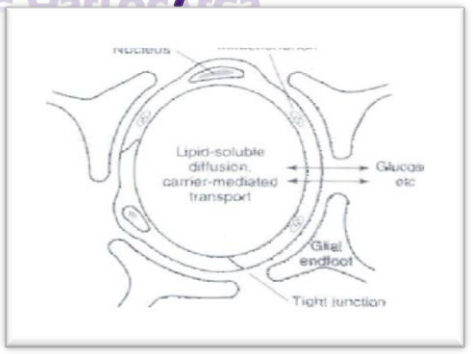
1. **Protective function:** The brain is supported within the arachnoid by the blood vessels , nerve roots and the arcahnoid trabiculae. In air brain weight =1400 g, but in its water bath of CSF , brain weight = 50 g **(brain weight is lighter with CSF),** making it suspended effectively. When the head 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
2. **Facilitation** of pulsatile cerebral blood flow
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

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.
- **CAPILLARIES** in the brain substance are **Non-fenestrated** and there are **Tight Junctions** between endothelial cells to limit passage of substances through the junctions .

-Few Vesicles in endothelial cytoplasm and so little vesicular transport.

-Brain capillaries are **Surrounded By The End-feet Of The Astrocytes**. There are gaps of 20 nm between the end-feet.



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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*

***Example: Dopamine** is one of the neurotransmitter and it is secreted by the dopminergic neurons and acts locally and affect muscles tone, if there is a patient who needs dopamine we cannot give him dopamine as such because it can not cross the BBB and reach the brain so we give him for example*

L-dopa which is dopamine precursor.

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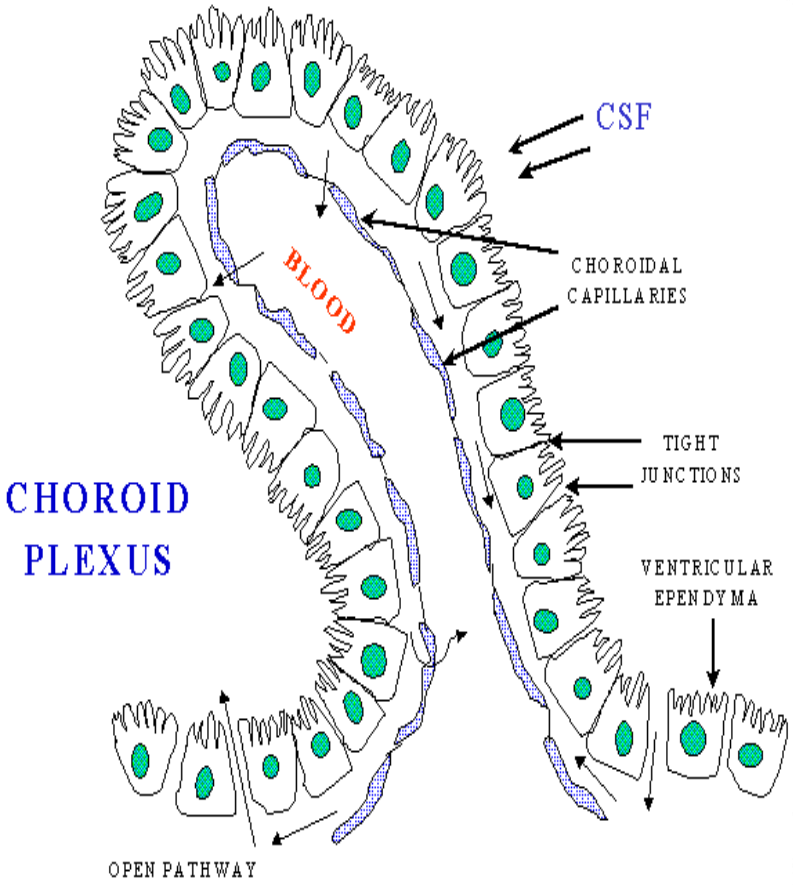
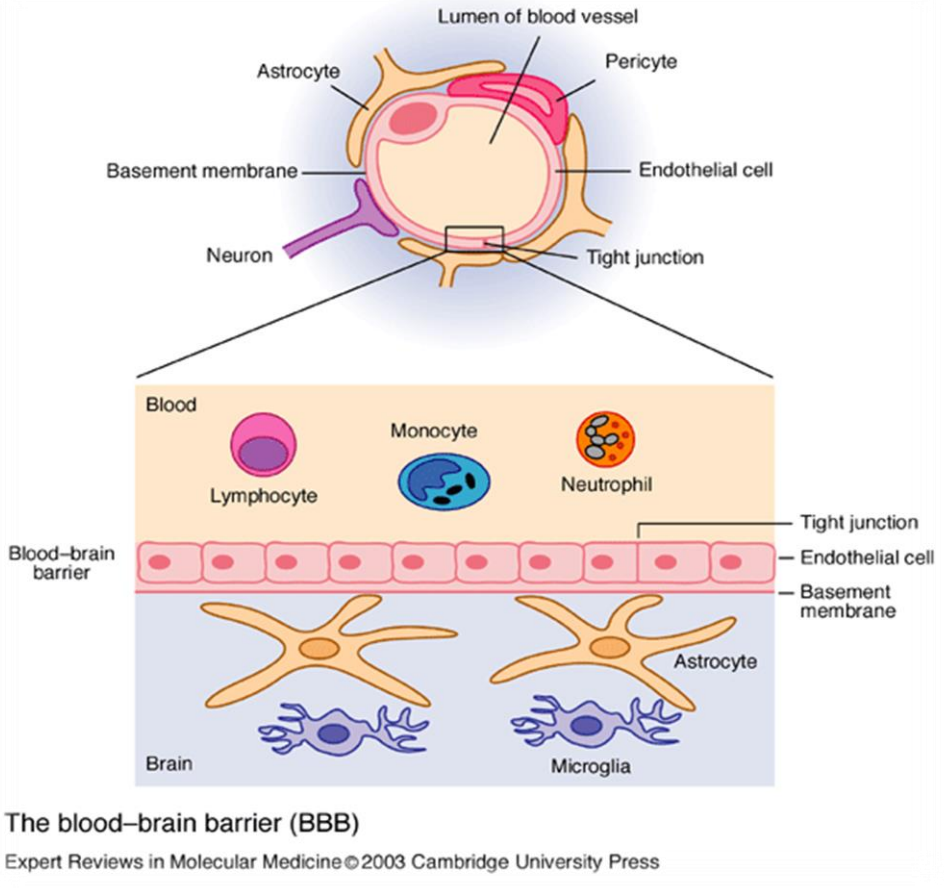
This diagrams just for more understanding, if you see it will stalk in your mind (:





The blood–brain barrier (BBB)

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Penetration of substances into the brain

- Molecules pass easily: H_2O, CO_2, O_2, lipid-soluble free forms of steroid hormones. Anesthetic drugs and volatile anesthesia can cross BBB because they are fat soluble.
- Molecules not pass: proteins(**if pass can cause immune response**) ,polypeptides.
- Slow penetration: H^+, HCO_3^- **(If H+ concentration increased *locally at respiratory center* it will increase the rate of respiration, but if metabolic acidosis happens H+ will not pass through BBB easily and the hyperventilation is caused by the effect of H+ on *peripheral chemoreceptors* rather than the central chemoreceptor)**
- Glucose : its passive penetration is slow, but is transported across brain capillaries by GLUT1

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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.

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Development of BBB

Premature infants with hyperbilirubinemia (congenital jaundice), free bilirubin pass BBB (because BBB not yet developed), and may stain basal ganglia causing damage (Kernicterus)

If jaundice happens in adults bilirubin wont pass BBB.

Clinical implications

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

***Anesthetic drugs can pass BBB.**

- 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.

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SUMMARY

- **CBF** is tightly regulated to meet the brain's **metabolic demands**
- **THE RESPONSE TO LOWER PRESSURE**, there is arteriolar dilation in the brain creating more room for the blood, while when blood pressure rises, they constrict, or narrow.
- **CSF FILLS** ventricles and subarachnoid space
- **VOLUME** of CSF= 150 ml
- **THE COMPOSITION OF CSF** is essentially the same as brain ECF
- **BBB** Protect the brain from endogenous and exogenous toxins.

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QUESTIONS

1- Why are the Capillaries in the brain substance are non-fenestrated ?

A- to allow more substance to pass

B- limit passage of substances through the junctions

2- Which of the following molecules cannot pass through BBB?

A- Glucose

B- proteins

3- The most important function of CSF is?

A- Cushion for the brain

B- transmission of the neurotransmitter

Q1-B
Q2-B
Q3-A

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THE END

If there are any Problems or Suggestions,
Feel free to contact:

Physiology Team Leaders

Mohammed Jameel & Shaimaa Al-Refaie

432100187@student.ksu.edu.sa
432200643@student.ksu.edu.sa

THANK YOU