Physiology 435 team

AUTOREGULATION OF CEREBRAL BLOOD FLOW

Objectives:

- Describe cerebral circulation & circle of Willis.
- Explain main arteries that supply blood to brain.
- Normal Rate of Cerebral Blood Flow.
- Explain autoregulation of cerebral blood flow.
- Explain the factors affecting the cerebral blood flow.
- Effects of impaired cerebral blood circulation.

(Girls Slides Version)

We advise you to study the anatomy lecture first.

Done by:

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★ References:

- 435 girls slides and notes.
- Ganong's Review of Medical Physiology, Twenty-Third Edition, Chapter 34, pages: 569 - 577

Color index: Important - Further explanation - Doctors Notes - Numbers.

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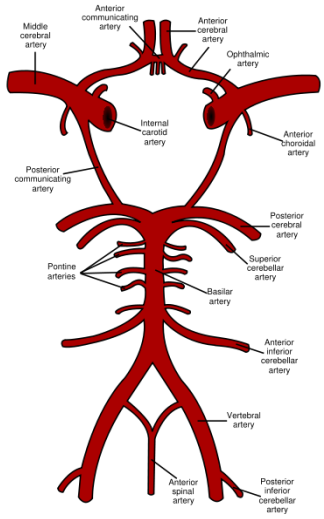
*Please check out this link before viewing the file to know if there are any additions or changes.

Cerebral blood flow

❖ Brain receives its blood supply by four main arteries:



- ◇ **Two internal carotid arteries.**
- ◇ **Two vertebral arteries.** (form the basilar artery)
  - ■ The four form the **circle of willis**.

- **Circle of Willis:** A group of arteries near the base of the brain

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❖ Cerebral circulation:

- The vertebral arteries unite to form basilar artery. The basilar artery and the carotids form the circle of willis.
- The circle of Willis consists of **six large vessels.** Substances injected into one carotid artery distributed almost completely to the **ipsilateral** cerebral hemisphere . Normally no crossing over occurs probably because **the pressure is equal on both sides.**

❖ Cerebral artery areas:

1. anterior cerebral artery | 2. middle cerebral artery | 3. penetrating branches of middle cerebral. | 4. anterior choroidal | 5- posterior cerebral

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❖ Innervation:

➔ Three systems of nerves innervate the cerebral blood vessels:

- ◆ **Sympathetic:**
  - Type: **Post**ganglionic sympathetic neurons.
  - Location: have their **bodies** in the **superior cervical ganglia.**
  - During **acute hypertension** attenuate **increase** in CBF.
- ◆ **Parasympathetic:**
  - Type: **Cholinergic** neuron.
  - Location: originate in **sphenopalatine ganglia** end on large arteries.
- ◆ **Sensory nerves:** autoregulation for the blood vessels.

❖ Cerebral blood flow(CBF): The numbers are important here:

- CBF is tightly regulated to meet the brain's metabolic demands

❖ Normal Rate of Cerebral Blood Flow

- ➢ Normal blood flow through the brain of the adult person averages 50 to 65 ml /100 grams of brain tissue / minute.
- ➢ For entire brain: 750 to 900 ml/min, or 15% of the resting **cardiac output**.

- ➢ It is important to maintain CBF within narrow limits because too much blood can raise intracranial pressure(ICP) which can compress and damage delicate brain tissue.
- ➢ **Too little blood flow causes ischemia.**
  - **Ischemia results** if blood flow to the brain is below 18 to 20 ml / 100 g / minute
  - **Tissue death** occurs if flow drops below 8 to 10 ml / 100 g / minute.

❖ Cerebral perfusion pressure (CPP):

- **Definition:** The net pressure of blood flow to the brain.
- CPP is normally between 70 - 90 mmHg in an adult human.
- CPP can be defined as: **CPP = MAP – ICP**
- CPP is regulated by two balanced, **opposing**(معاكسة) forces:
  - **Mean arterial pressure(MAP)**: It is the force that pushes **blood into the brain**
  - **IntraCranial Pressure (ICP):** It is force that pushes **out**.

Regulation of Cerebral Blood Flow

❖ Three metabolic factors have potent effects in controlling the cerebral blood flow:

Carbon dioxide concentration	Hydrogen ion concentration	Oxygen concentration. • Neural factors • Other mediators

- **Increase Cerebral Blood Flow in Response to Excess Carbon Dioxide or Excess Hydrogen Ion Concentration.**

- 70 % increase in arterial PCO2 approximately **doubles** the cerebral blood flow(meaning the more acidic co2 and hydrogen the more blood flow).
- Carbon dioxide 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 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 increases hydrogen ion concentration, will **increase cerebral blood flow**. Such substances include lactic acid, pyruvic acid. Any acidic substance will increase the blood flow

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❖ Hypoxia and Hypercapnia

- **Excess carbon dioxide (CO2)** can **dilate** blood vessels up to 3.5 times their normal size
- Blood vessels also **dilate** in response to **low pH (when acidic)**.
- when activity in a given region of the brain is heightened, the increase in CO2 and H+ concentrations causes cerebral **vasodilatation**, and deliver **more blood** to the area to meet the increased demand.
- **Hypoxia** also **dilates** blood vessels and **increases blood flow** (vasodilates to get oxygen going into the brain). While high levels of oxygen constrict cerebral blood vessels.

vasodilatation	vasoconstriction
Hypoxia and hypercapnia: Low oxygen and high co2 concentrations	High concentration of oxygen

❖ Neural stimuli:

- Under normal conditions sympathetic has little effect, because the blood flow auto-regulation mechanism can override the nervous effects.
- During **acute hypertension**, **sympathetic** attenuates increase in CBF.
- 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—for preventing the occurrence of "cerebral stroke."**
- Nitric oxide and adenosine are mediators(the exact function is unknown but it said that it aids in autoregulation of blood vessels).
- **Increased hydrogen** ion concentration:
  - Greatly **depresses** neuronal activity(can cause coma).
  - **increases** blood flow, which in turn carries hydrogen ions, carbon dioxide.
- Loss of carbon dioxide removes carbonic acid and other acid forming substances away from the brain tissues ,this **reduces** the hydrogen ion concentration back toward normal to maintain a constant hydrogen ion concentration in the cerebral fluids and thereby helps to maintain a normal neuronal activity.

❖ Oxygen Deficiency as a Regulator of Cerebral Blood Flow.

- The rate of utilization of oxygen by the brain tissue is almost exactly 3.5 (± 0.2) ml of oxygen / 100 grams of brain tissue/minute.
- If blood flow to the brain **insufficient** , the oxygen deficiency mechanism causing **vasodilation**, returning the brain blood flow and transport of oxygen to the cerebral tissues to normal.
- Decrease in cerebral tissue **PO2** below about 30 mmHg (normal value is 35 to 40 mm Hg) immediately begins to **increase** cerebral blood flow.
- Brain function becomes deranged at lower values of PO2, especially at PO2 levels below 20 mmHg.
- Oxygen deficiency is a regulator of cerebral blood flow except during periods of intense Brain activity (at this time Co2& H are more important)

Autoregulation of CBF

The brain maintains proper CPP[1] through the process of Autoregulation:

[1] CPP= Cerebral perfusion pressure

• At limits of 60 and 140 mm Hg. • 150 mmHg • 60 mmHg	Cerebral blood flow is "autoregulated" extremely well between arterial pressure limits of 60 and 140 mm Hg. The response to **lower pressure is arteriolar dilation** in the brain, while **when blood pressure rises they constrict**. Thus, changes in the body's overall blood pressure do not normally alter cerebral perfusion pressure drastically. At their most constricted condition, blood vessels create a pressure of 150 mmHg, and at their most dilated, the pressure is about 60 mmHg. *Autoregulation is very fast and occur in Minutes
• Outside the range of 60 to 150 mmHg	When pressures are outside the range of 60 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 without autoregulation. Thus, hypotension can result in severe cerebral ischemia.

❖ Effect of ICP[2] changes on systemic blood pressure:

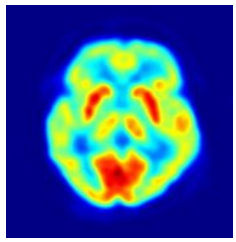
- Cushing reflex: 'Normally, the ICP ranges from 1 to 15 mm Hg' (but other sources give ranges like 8 to 18 mm Hg). If ICP > 33 mmHg over a short period of time, CBF will drop markedly, leading to hypoxia and hypercapnia of vasomotor area, which leads to activation of vasomotor centre that affects tone of blood vessels, causing blood pressure to **rise**.
- Cushing reflex is not related to cushing's syndrome (an endocrine disorder)

Remember: ↑ ICP = ↓ CBF = Cushing reflex = ↑ blood pressure

Cushing's Reflex | Physiology
Excellent, please watch it (Duration 3:09)

Measuring cerebral blood flow

❖ Measuring cerebral blood flow:



- **Both** methods mentioned can be used to measure CBF as well as regional CBF (rCBF) within a specific brain region.

1. **Functional imaging resonance.**
2. **Positron emission tomography:**
   - Radioactive xenon injection into carotid artery -which pass into brain tissues- will show increase radioactivity in areas of increased blood flow that is due to local neuronal activity (e.g. blood flow increase in left motor area by movement of right hand).

EXTRA - Ganong, page 576:
Functional magnetic resonance imaging (fMRI) measures the amount of blood in a tissue area. When neurons become active, their increased discharge alters the local field potential. A still unsettled mechanism triggers an increase in local blood flow and oxygen. The increase in oxygenated blood is detected by fMRI.

[2] ICP= intracranial pressure, which is the force that pushes blood out from the brain

PET scanning can be used to measure not only blood flow but the concentration of molecules, such as dopamine, in various regions of the living brain. On the other hand, fMRI does not involve the use of radioactivity. Consequently, it can be used at frequent intervals to measure changes in regional blood flow in a single individual.

Stroke

- Stroke occurs when the blood supply to a part of the brain is blocked resulting in the death of an area. Blockage can either be by hemorrhage or ischemia (obstruction by thrombus/embolus).

- **Blockage of the middle cerebral artery:**

- if the middle cerebral artery is blocked on the **left** side of the brain, the person is likely to become almost totally demented because of lost function in Wernicke's speech comprehension area in the **left** cerebral hemisphere, and becomes unable to speak words because of loss of Broca's motor area for word formation. In addition, loss of function of neural motor control areas of the **left** hemisphere can create spastic paralysis of most muscles on the **opposite side of the body**.

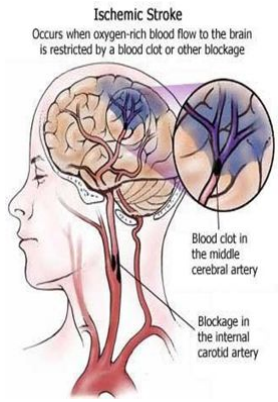
- **Blockage of a posterior cerebral artery:**

- This will cause infarction of the occipital pole on the **same side**, which causes loss of vision as (hemianopsia[3]). Total blindness may also occur.

- **Blockage of blood supply to the midbrain:**

- Strokes that involve the blood supply to the midbrain can block nerve conduction in major ascending & descending pathways between the brain and spinal cord, causing both sensory and motor abnormalities.

❖ Principal types of stroke:



1. **Thrombotic:** Stroke due to the blockage of an artery leading **to or in** the brain by a **blood clot**.
2. **Haemorrhagic:** Stroke due to bleeding from a ruptured blood vessel, usually a consequence of hypertension.
3. **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. E.g. air/fat thrombus.

(The thrombotic and haemorrhagic forms are common.)

**We recommend studying the pathology lectures of cerebrovascular accidents after finishing this lecture for more information on stroke. **

Cerebral Microcirculation

- **Definition:** The metabolic rate of the brain **gray matter** where the neuronal cell bodies lie is about four times as great as that of **white matter**; so, the number of capillaries and rate of blood flow are also about four times as great in the **gray matter**.

[3] Helpful graph: visual field defects.

❖ Structural characteristic of the brain capillaries:

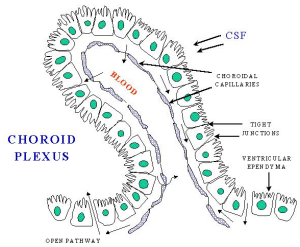
- ➢ Brain capillaries are mostly **much less "leaky"** than other blood capillaries, because they have tight junctions and are also supported on all sides **by "glial feet,"**[4] which are small projections from glial cells that provide physical support to prevent overstretching of the capillaries in case of high capillary blood pressure.
- ➢ The walls of the small arterioles leading to the brain capillaries are **greatly thickened** in people who develop high blood pressure, and these arterioles remain significantly constricted all the time to prevent transmission of the high pressure to the capillaries.

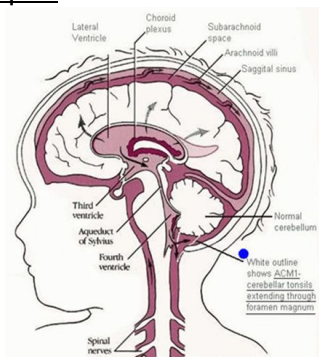
Cerebrospinal fluid

Formation	Absorption	Distribution
CSF is formed in the Choroid plexus in the 4 ventricles.	Absorbed by Arachnoid villi into venous circulation.	Present in the ventricles of the brain, cisterna around brain and in the subarachnoid space around both the brain and the spinal cord. All these chambers are connected with one another, and the pressure of the fluid is maintained at a constant level.

Volume	Rate of production	Lumbar CSF pressure
150 ml	500 ml/d	70-180 mm hg

- **Absorption** of CSF is proportionate to CSF **pressure**.[5]
- At CSF **pressure** of 112 mm (normal average): **filtration** and **absorption** are equal.[6]
- CSF pressure below 68 mm, **absorption** stops. مهم معرفة القيم (الأرقام) هذي ^





Hydrocephalus

External hydrocephalus	Internal hydrocephalus
Large amount of CSF accumulates when the reabsorptive capacity of **arachnoid villi** decreases.	Occurs when **certain foramina** are blocked or obstruction **within ventricular system**, resulting in distention of the ventricles.

Composition of the cerebrospinal fluid

[4] In the picture on the right side of the page: Glial cells are in green, endothelial cells are in red.

[5] كل الكمية اللي بتتكون يجب أن تُمتَص يعني الضغط (pressure) لازم يكون ثابت بين 70-180.

[6] Medial level 112 mm it is between 70-180 mm hg.

البروف ما تكلمت عن الجدول

1. The composition of CSF is nearly the same as brain ECF.
2. **Osmotic pressure**, approximately equal to that of plasma.
3. **Sodium ion concentration**, approximately equal to that of plasma.
4. **Chloride ion**, about 15 percent greater than in plasma.
5. **Potassium ion**, approximately 40 percent less than in plasma.
   النسب مهمة
6. **Glucose**, about 30 percent less than in plasma.

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	289	289
Glucose	64	100

❖ Functions of the cerebrospinal fluid

➔ **Protective function (cushioning[7]):**

- In air brain weight =1400 gm, but in its water bath of CSF, brain weight =50gm, making it suspended and floated effectively.[8]
- When the head receives a blow, the arachnoid slides on the dura and the brain moves, but its motion is gently absorbed by the CSF cushion and by the arachnoid trabeculae.

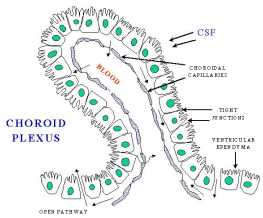
➔ **Facilitation** of pulsatile cerebral blood flow.[9]

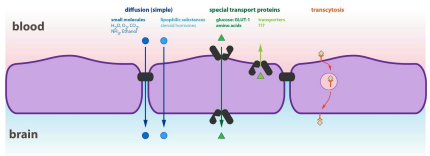
➔ **Distribution** of peptides, hormones, neuroendocrine factors and other nutrients and essential substances to cells of the body.[10]

➔ **Wash away** waste products.

Features of cerebral vessels

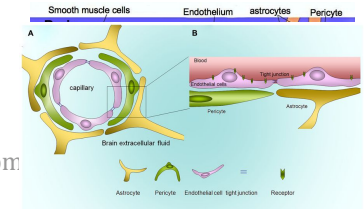
Choroid plexus		Capillaries in the brain substance
There are gaps between **endothelial cells**[11] of the capillary wall allow CSF flow	No gaps between **epithelial cells**[12] which is in direct contact with blood	Are non-fenestrated and there are tight junctions between **endothelial cells** to limit passage of substances through the junctions and supported by **glial feets**





Blood brain barrier

- **Location:**[13] It is between blood and cerebrospinal fluid and brain tissue.[14] [15]



[7] The CSF is contained within the meninges and acts as a cushion(وسادة) to protect the brain from movement.

[8] CSF decrease the weight of the brain.

[9] يحافظ لي على الcerebral blood flow constant ثابت

[10] بيوزعها بالتساوي على مخي

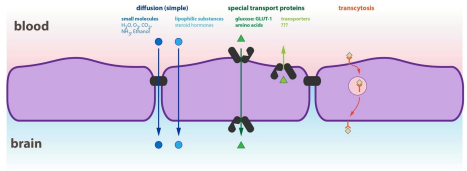
[11] الendothelial ناحية الbrain tissue.

[12] الepithelial ناحية الblood تمنع دخول الدم للCSF.

[13] Testes, brain, placenta: have barriers

[14] يمنع مرور المواد من الدم إلى أنسجة الدماغ ومن الCSF إلى أنسجة الدماغ ما عدا المواد المسموح فيها فقط.

- **formed at:**
    1. **Choroid plexus** by the tight junctions between epithelial cells[16] of the choroid plexus.
    2. **Brain tissue capillary membrane** by the tight junctions between capillary endothelial cells of the brain capillaries.



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

❖ Penetration of substances into the brain[17]

Molecules pass easily	Molecules not pass[18]	Slight penetration	Glucose
H2O, CO2, O2, lipid-soluble substances (as steroid hormones)	Proteins, antibodies, non-lipid-soluble, large molecules	Cl, Na, K	Its passive penetration is slow, but is transported across brain capillaries by **GLUT1**[19]

❖ Functions of blood brain barrier:

1. **Maintains** the constancy of the environment of the neurons in the CNS.[20]
2. **Protection** of the brain from endogenous and exogenous toxins.[21]
3. **Prevent** escape of the neurotransmitters into the general circulation.[22]

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[15] Capillaries, Endothelial tight junction, Pericyte of the capillaries and choroid plexus, Glial feet :عن عبارة الBBB
Glial feet protect the blood vessels from outside from being over stretched and ruptured

[16] Epithelial cells prevent blood from entering the choroid plexus.

[17] BBB have selective permeability.

[18] Not all the antibiotic pass through BBB so if someone has brain abscess or brain infection the doctor should not give him any kind of antibiotic he should give him antibiotic that can pass the BBB.

[19] الجلوكوز يحتاج transporter اسمه GLUT1 يشيل الجلوكوز ويدخله جوا الخلايا عشان تستهلكه, ايضا هذا الترانزبورتر موجود في خلايا البنكرياس.

[20] يحافظ لي على المواد اللي بمخي أو اللي يحتاجها مثل الجلوكوز والبوتاسيوم والكلورايد وغيرها ما يحصل لهم فقد في الvenous drainage.

[21] مواد سامة ماخذها او جسمك مكونها مثل الurea والfree radicals يمنعها من الدخول للدماغ.

[22] لو ما كان موجود الBBB الneurotransmitter بتروح للGeneral circulation عن طريق الvenous drainage وتطلع من جسمنا تماما فتسبب مصيبة لأن مخنا معتمد على الNT.