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Cerebral blood flow, metabolism, cerebrospinal fluid & intracranial pressure

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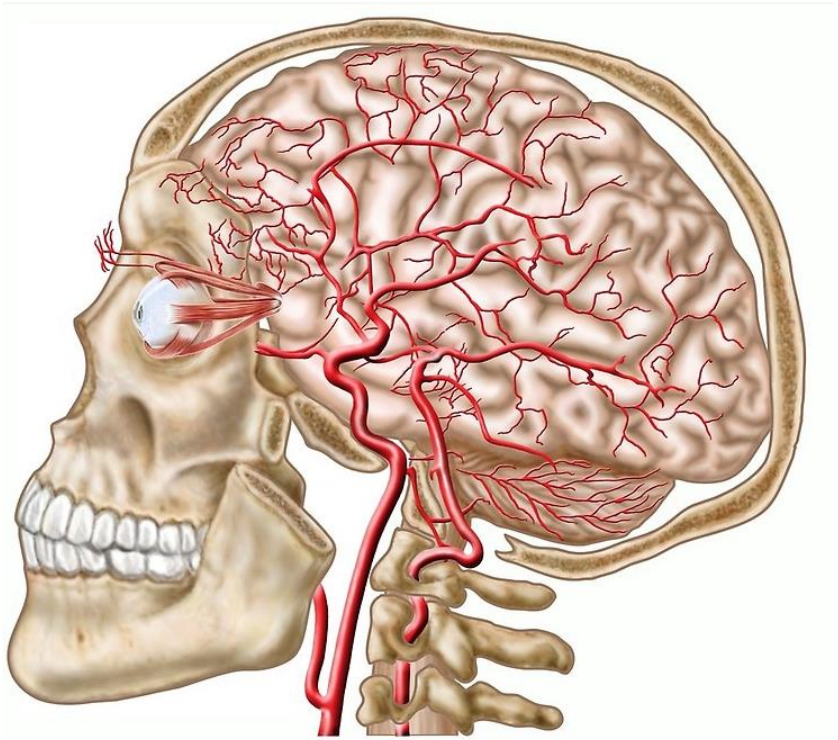
Brain energy demands

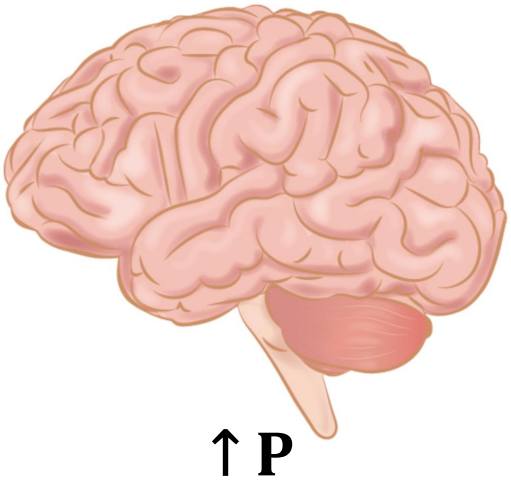
- 15% of total body metabolism (only 2% of body mass)
- Brain metabolism is in resting condition ~7.5 times the average metabolism of non-nervous tissue
- The brain is not capable of much anaerobic metabolism
- Sudden cessation of blood flow to the brain or sudden total lack of oxygen in the blood cause unconsciousness within 5 to 10 seconds
- **C**erebral **M**etabolic **R**ate for **O**xygen ($CMRO_2$) is ~ 3 – 3.5ml/100g/min

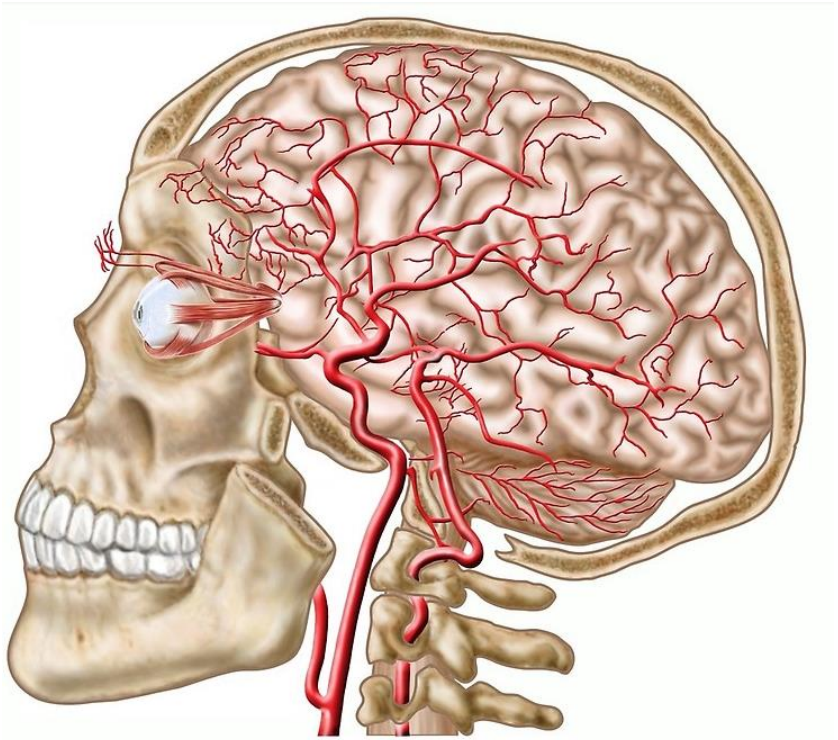
- Therefore brain receives 12 – 15% of cardiac output
- Cerebral blood flow ~50ml/100g/min
- **Why cerebral blood flow requires special lecture ?**

Viscoelastic body in rigid cavity

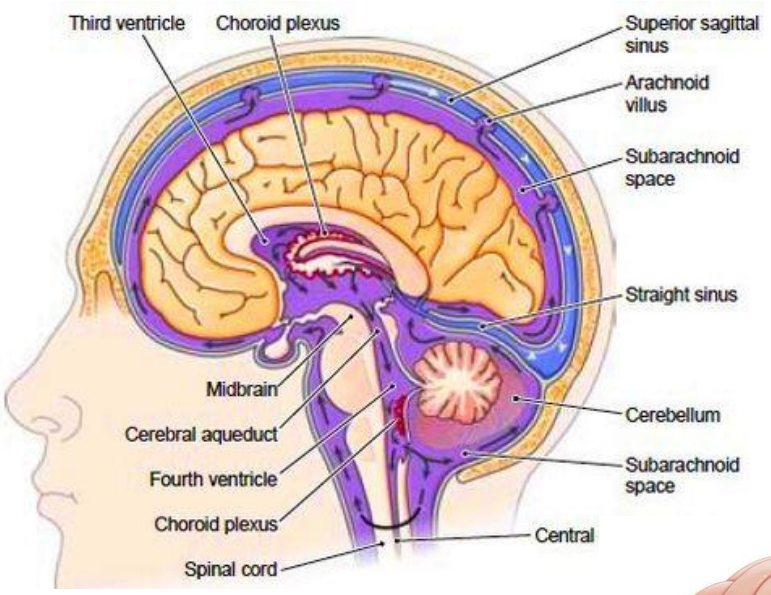


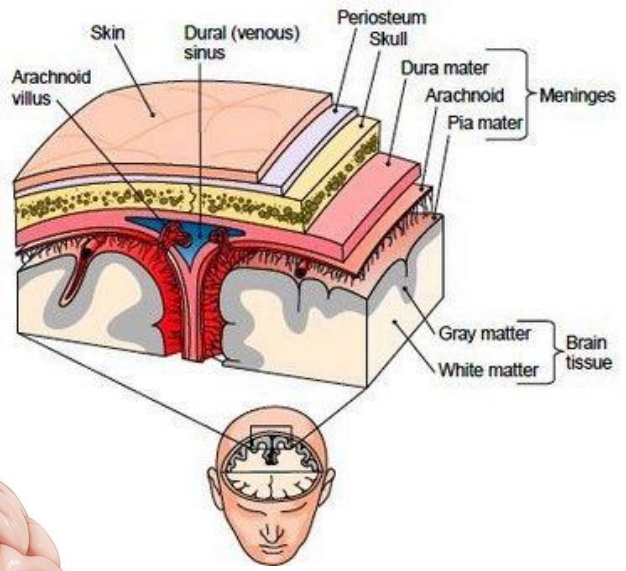
Viscoelastic body increases volume when pressure increases

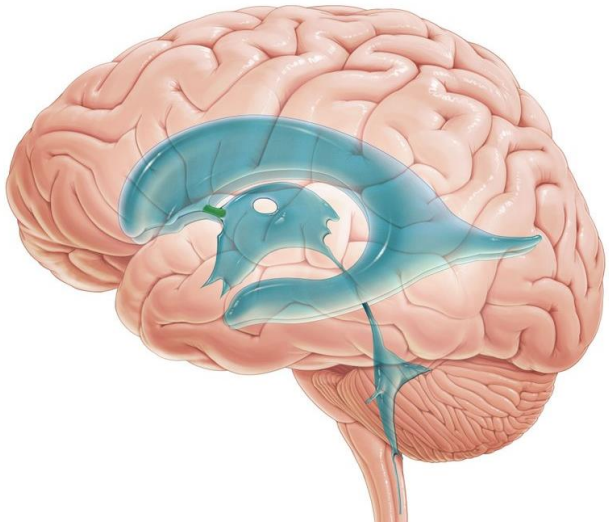




Intracranium contains fluid – cerebrospinal fluid – in subarachnoidal space and cerebral ventricles

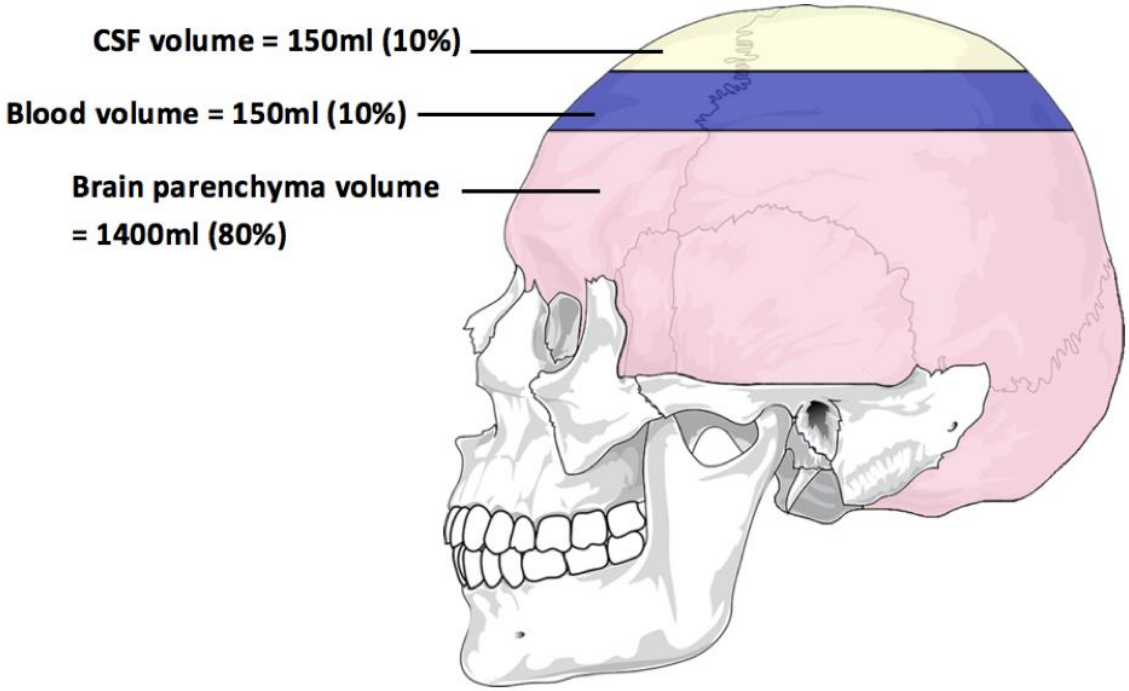






Monroe – Killie doctrine

Rigid skull can not extend = has constant volume

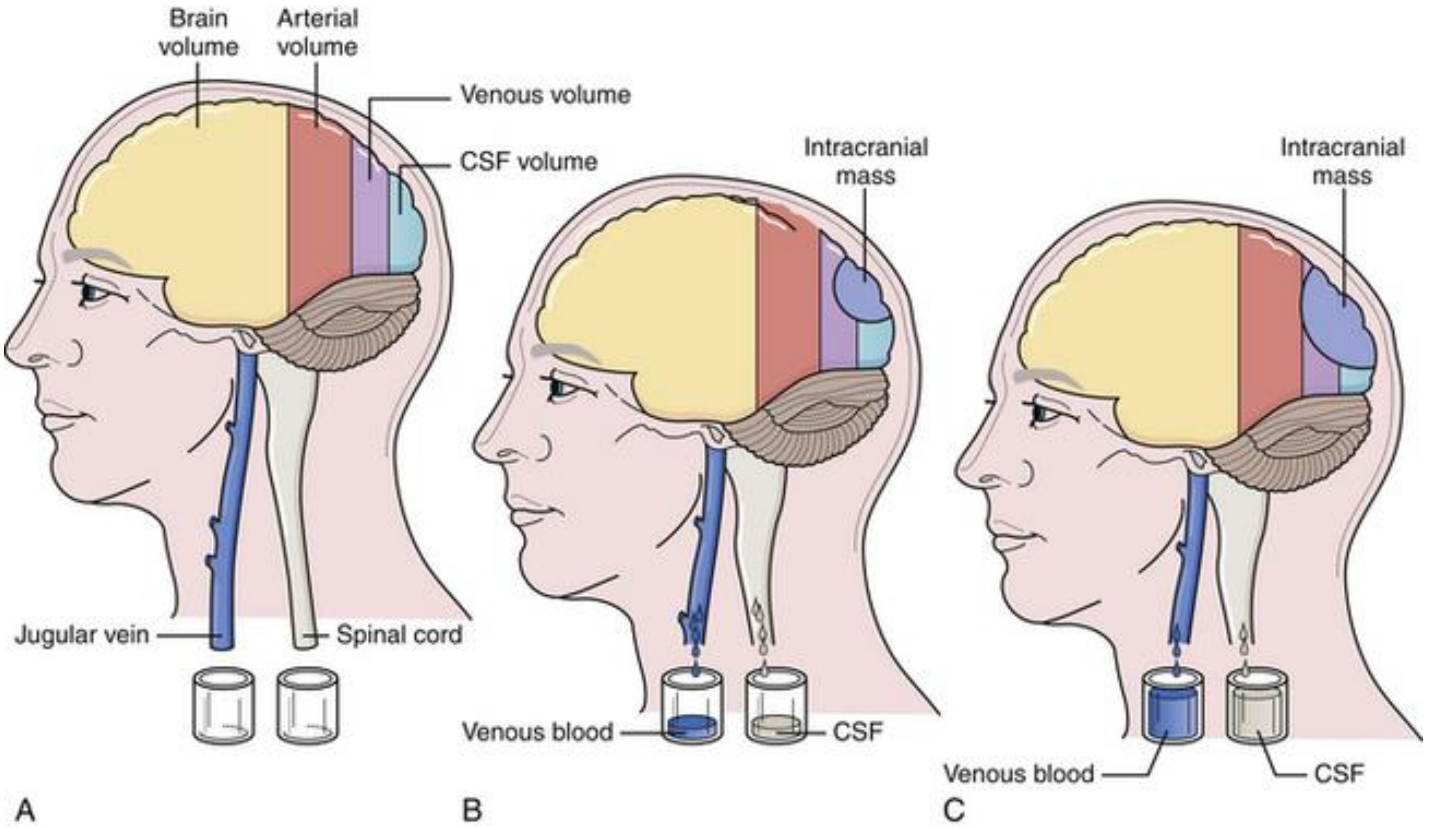


- Due to rigid skull the intracranial volume is constant

$$V_{ic} = V_{blood} + V_{CSF} + V_{brain}$$

Law of conservation of mass

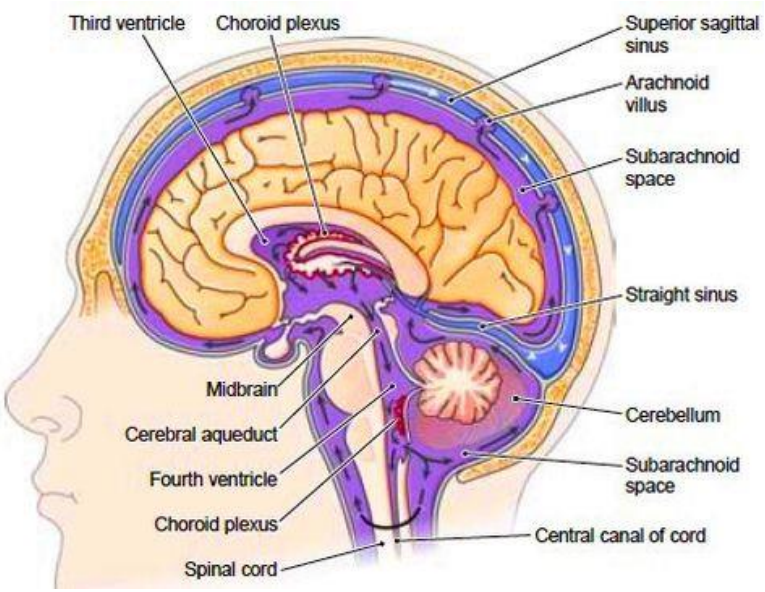
Monroe-Killie doctrine

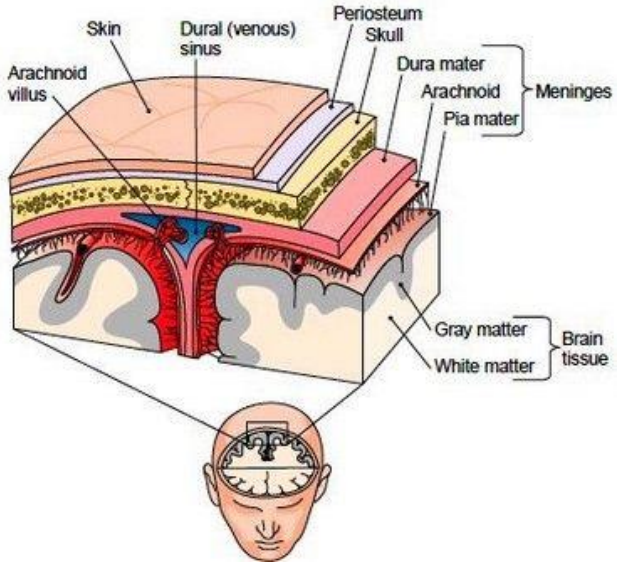


- Change in one compartment has to be compensated by change of remaining

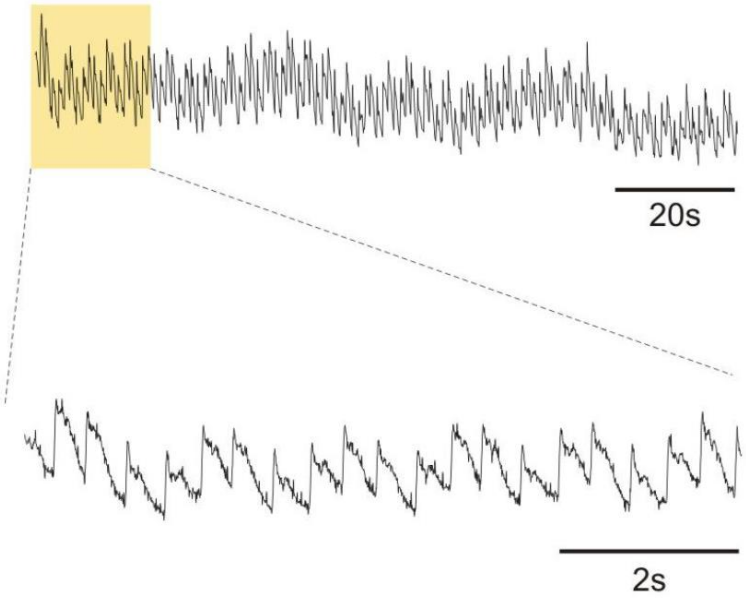
Cerebrospinal fluid volume

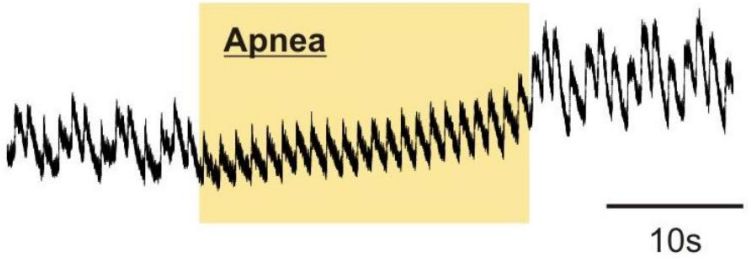
- Volume ~125ml
- 500ml daily production in choroid plexuses
- Blood – CSF barrier (tight junctions of epithelium, active transport)
- Pressure 7 – 15 mmHg
- Resorption – arachnoidal granulations
- Resistance is “constant”



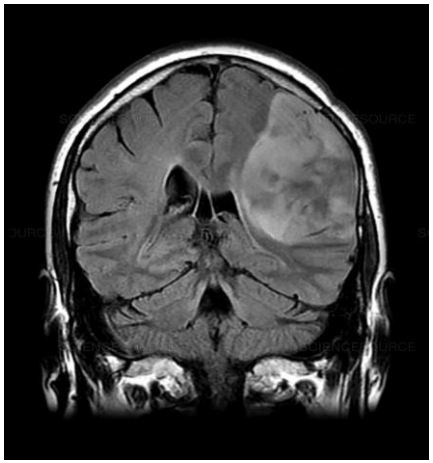


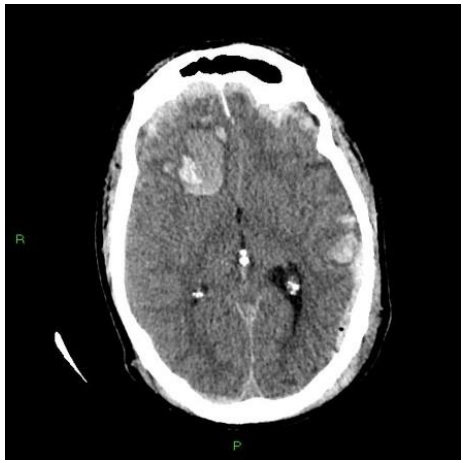
Pressure oscillations and flow of CSF

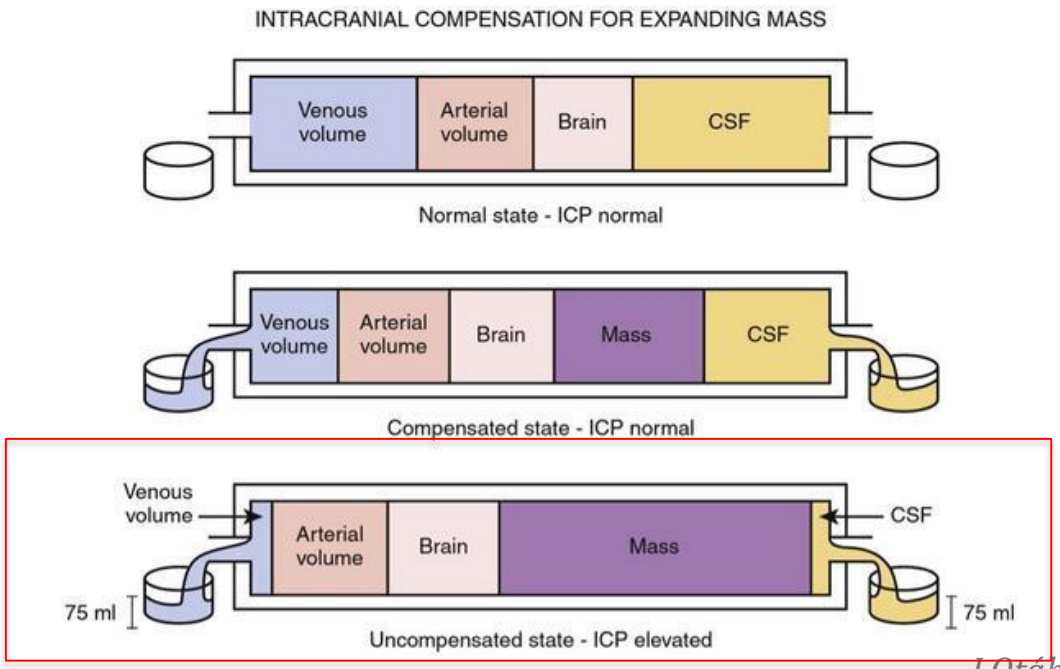




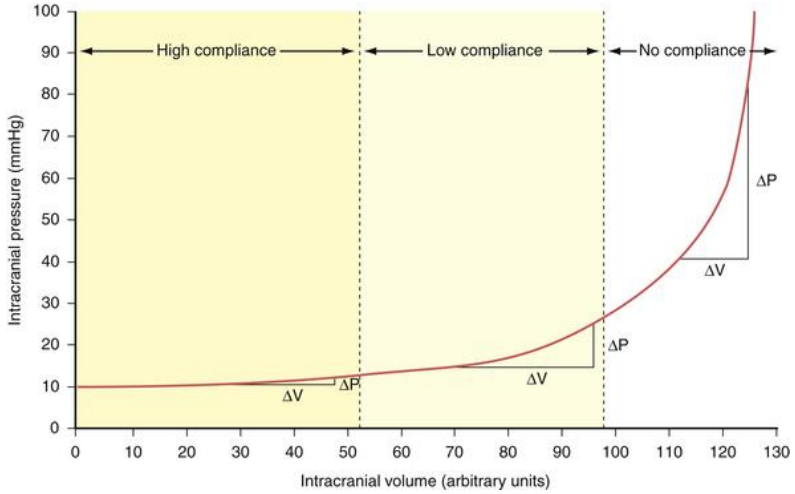
Brain volume

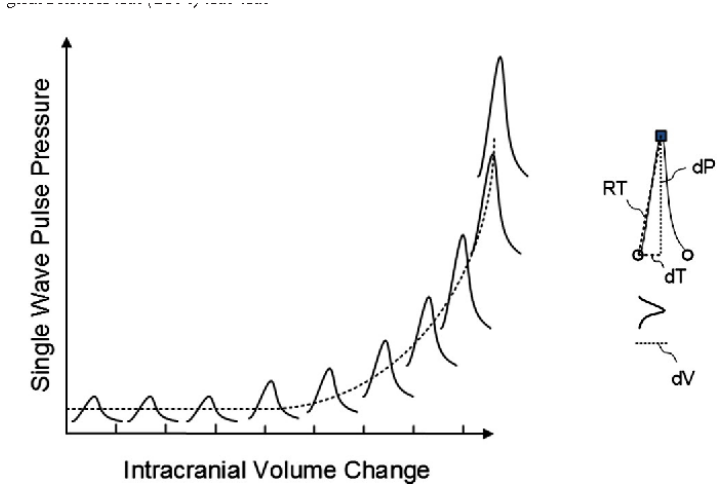


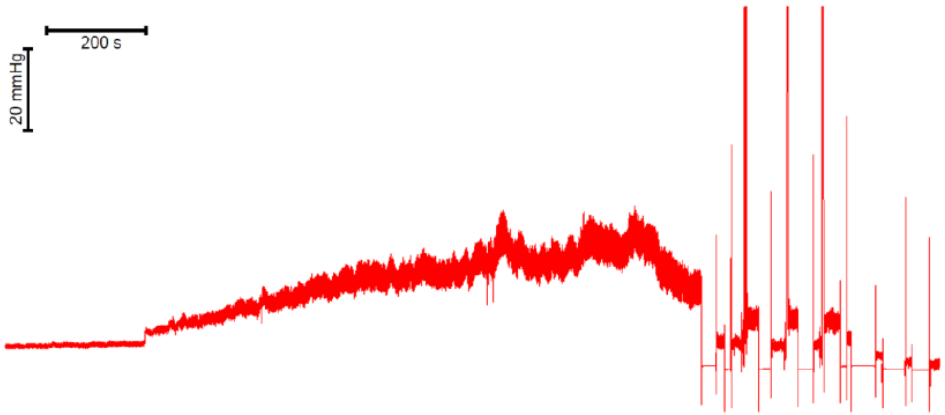




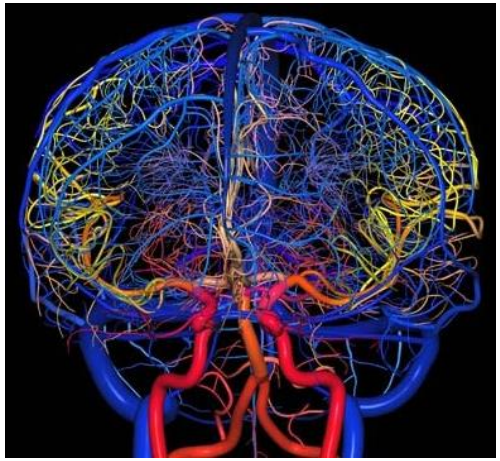
Compliance of cranio-spinal system

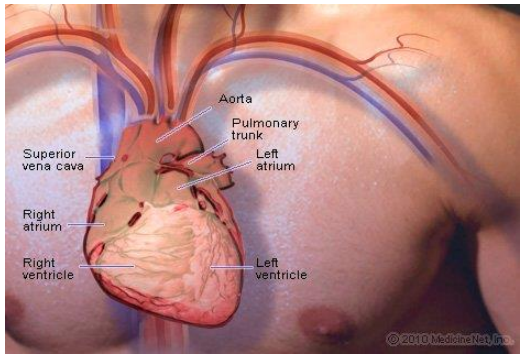






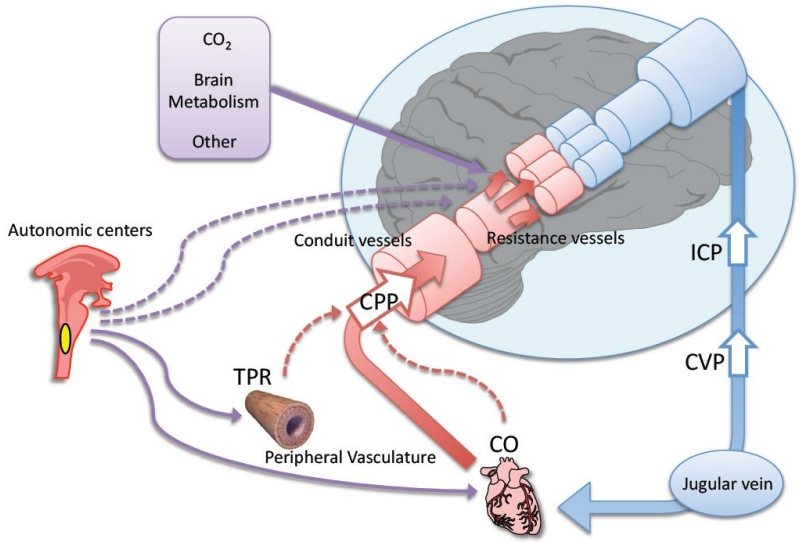
Blood volume



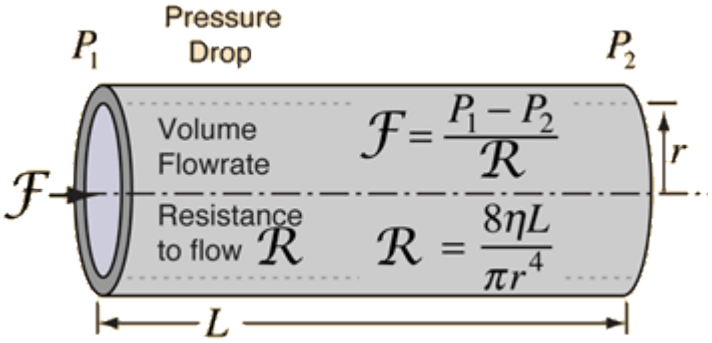


- Cerebral blood flow dependent on perfusion pressure and resistence
- Conservation of mass = Ohm's law I = U/R
- Q = P/R

- Perfusion pressure is in brain dependent on MAP and ICP. CPP = MAP - ICP



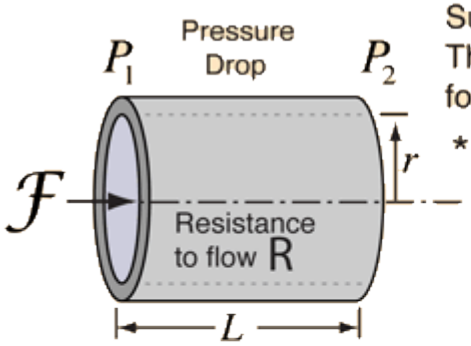
Hagen – Poiseuille law



Q	Flow rate
P	Pressure
r	Radius
η	Fluid viscosity
l	Length of tubing

$$Q = \frac{\pi \mathrm{Pr}^4}{8\eta l}$$

Hagen – Poiseuille law



Suppose the original flowrate is 100 cm^3/sec. The effect of changes in the parameters is as follows:

* Double length	⇒	50	cm^3/sec
Double viscosity	⇒	50	cm^3/sec
Double pressure	⇒	200	cm^3/sec
Double radius	➡	1600	cm^3/sec

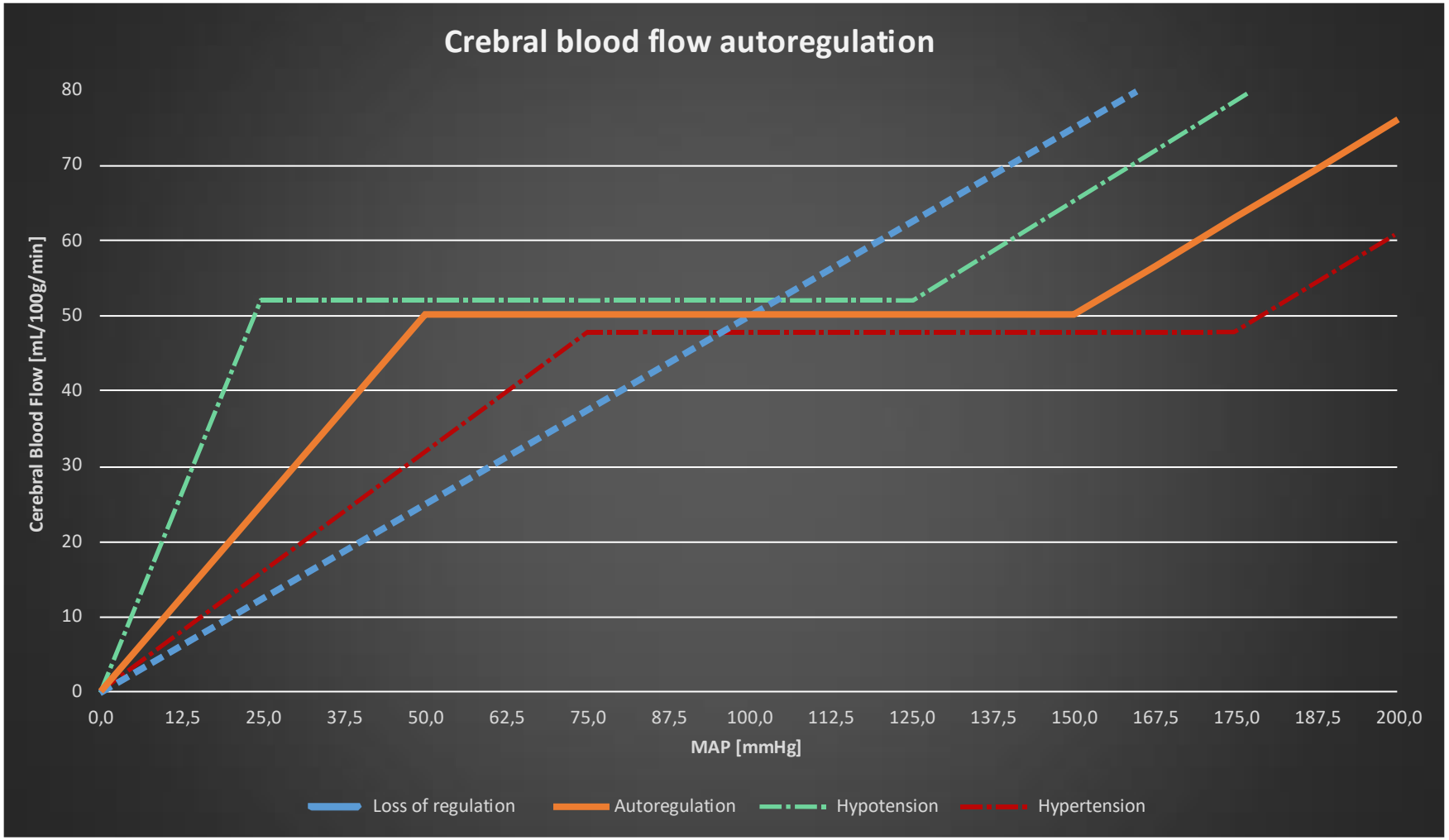
$$\mathcal{R} = \frac{8\eta L}{\pi r^4}$$ where η = viscosity

* With other parameters held at original values

$$\text{Volume Flowrate} = \mathcal{F} = \frac{P_1 - P_2}{\mathcal{R}} = \frac{\pi(\text{Pressure difference})(\text{radius})^4}{8(\text{viscosity})(\text{length})}$$

A 19% increase in radius will double the volume flowrate!

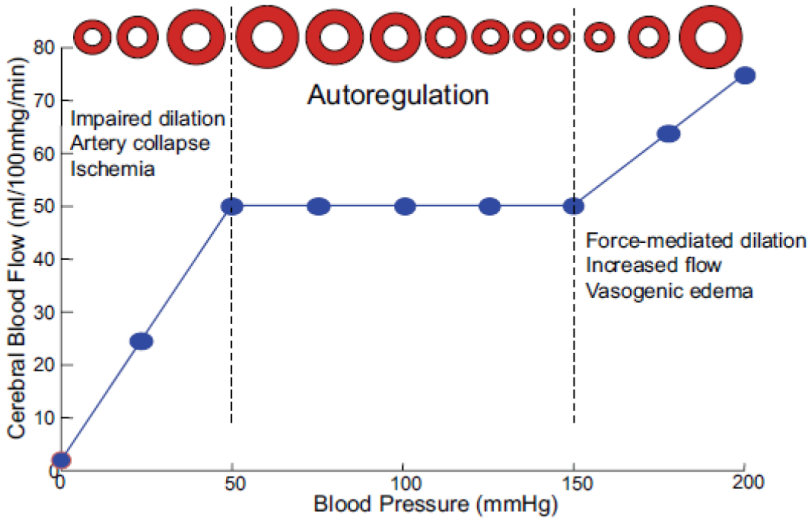
Cerebral autoregulation



Cerebral autoregulation

- Maintnance of CBF over a range of mean arterial pressure (MAP)
- Conservation of mass = Ohm's law I = U/R, Q = P/R

  CBF = CPP / CVR
- Cerebral vascular resistence (CVR) varies with MAP to maintain flow – response is typically taking 60 – 120s

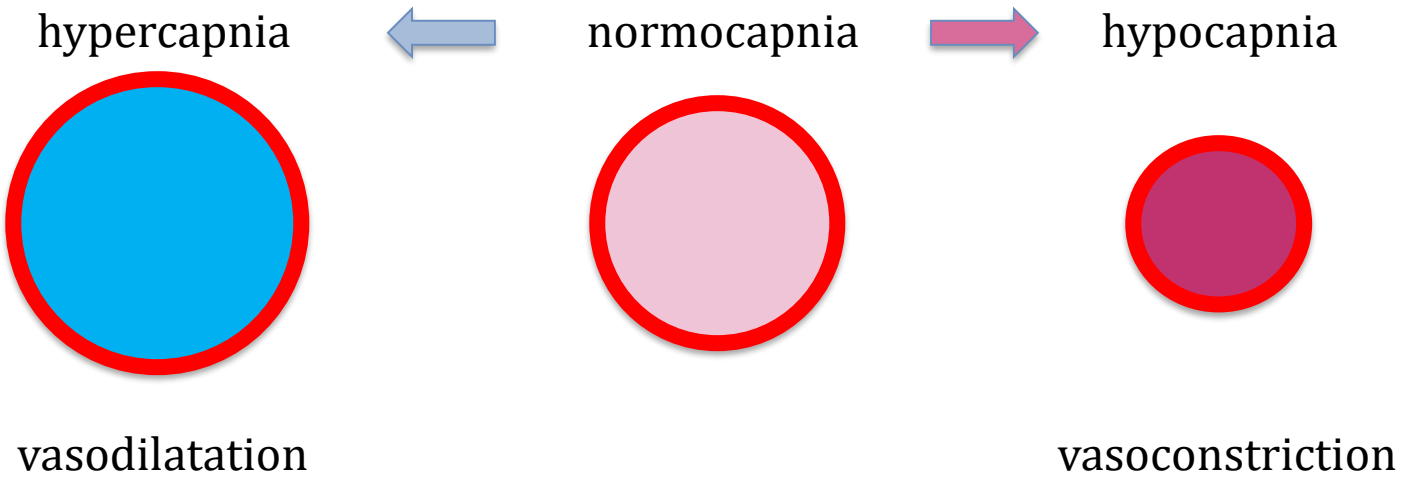


Mechanisms of autoregulation

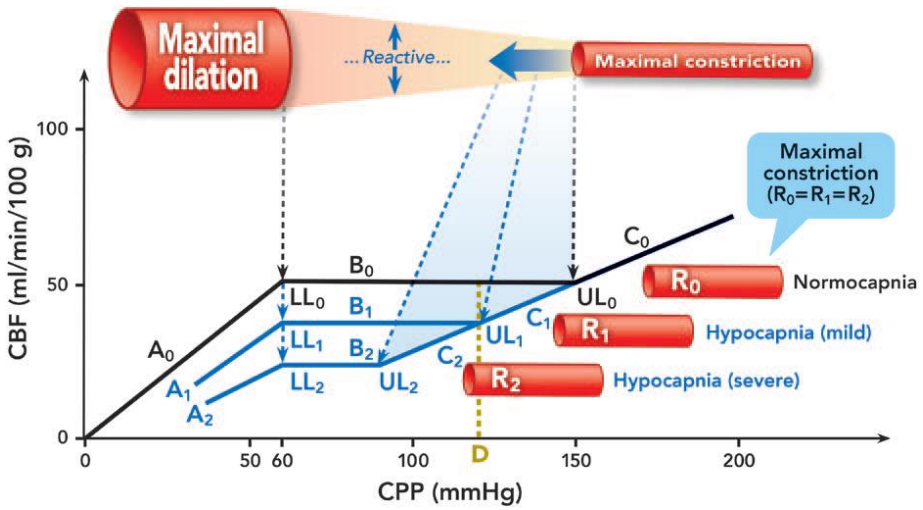
- **Neurogenic (Autonomic)**
  - vascular smooth muscle are controlled via autonomic mainly sympathetic innervation. Its role in cerebral autoregulation is speculative.
- **Myogenic**
  - transmural blood pressure is directly detected by the vascular smooth muscle in arterioles, probably via a stress sensing mechanism. Then, the calibers are adjusted accordingly to keep blood flow constant. Role of endothelial factors (NO, prostacyclin…)
- **Metabolic**
  - metabolic regulation is driven by the difference between cerebral metabolism and oxygen delivery through cerebral blood flow and acts by means of a vasoactive substance. These include CO_2, H^+, O_2, adenosine and adenosine nucleotides, K^+, Ca^{2+} and prostanoids.

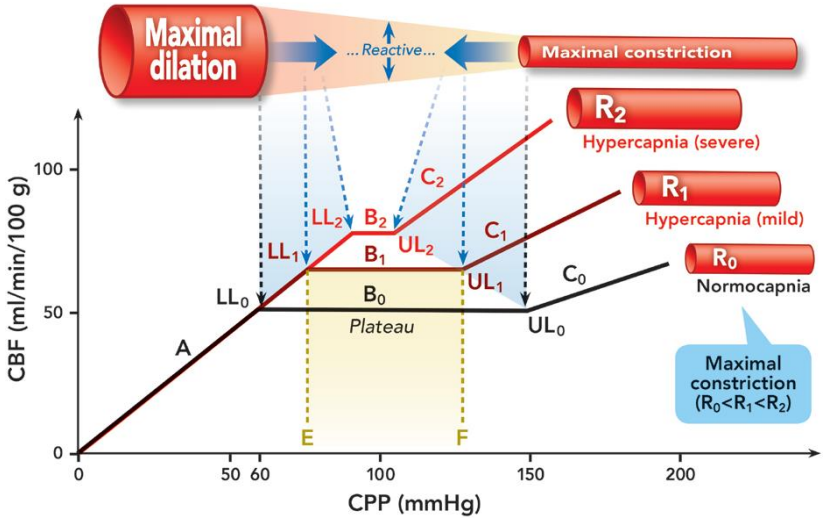
Regulation of Cerebral Autoregulation by Carbon Dioxide

- **<u>Carbon dioxide</u>** is a known **powerful modulator of cerebral vasomotor tone**, and change in arterial blood carbon dioxide partial pressure ($PaCO_2$) is frequently encountered in clinical care

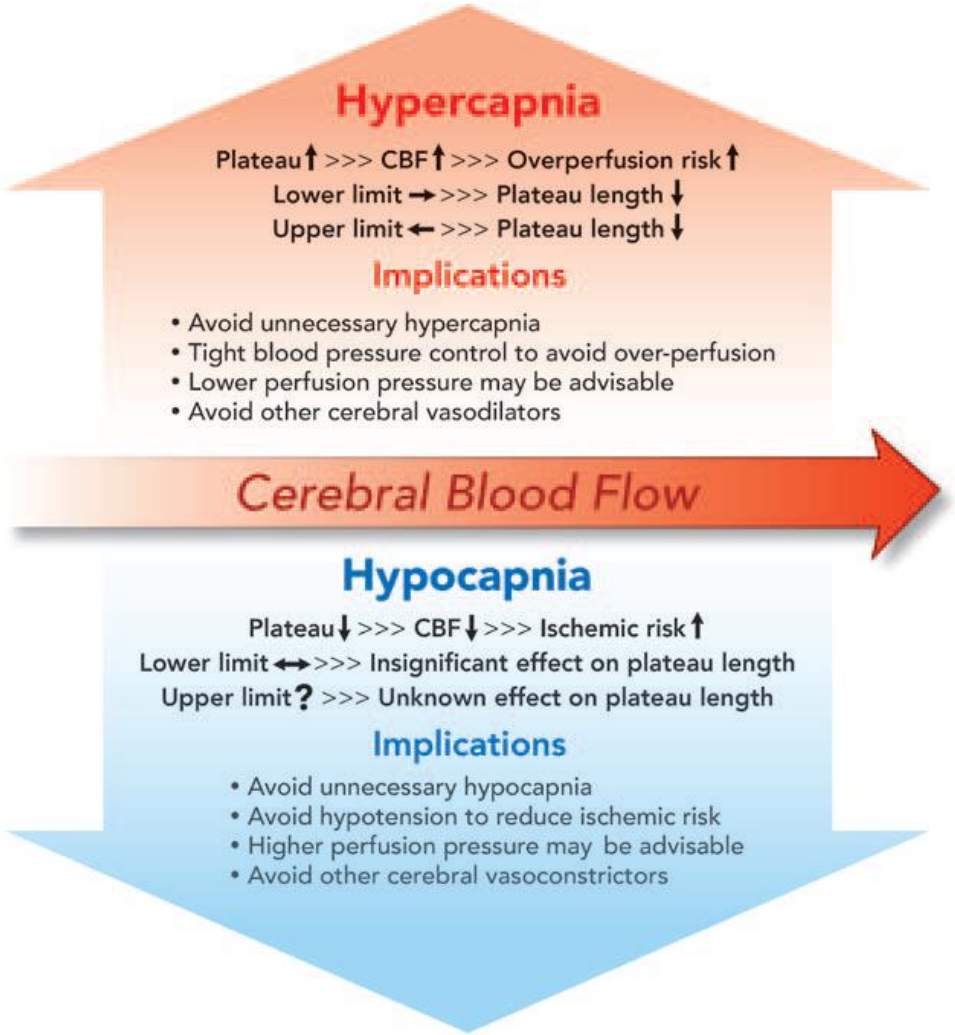


Regulation of Cerebral Autoregulation by Carbon Dioxide



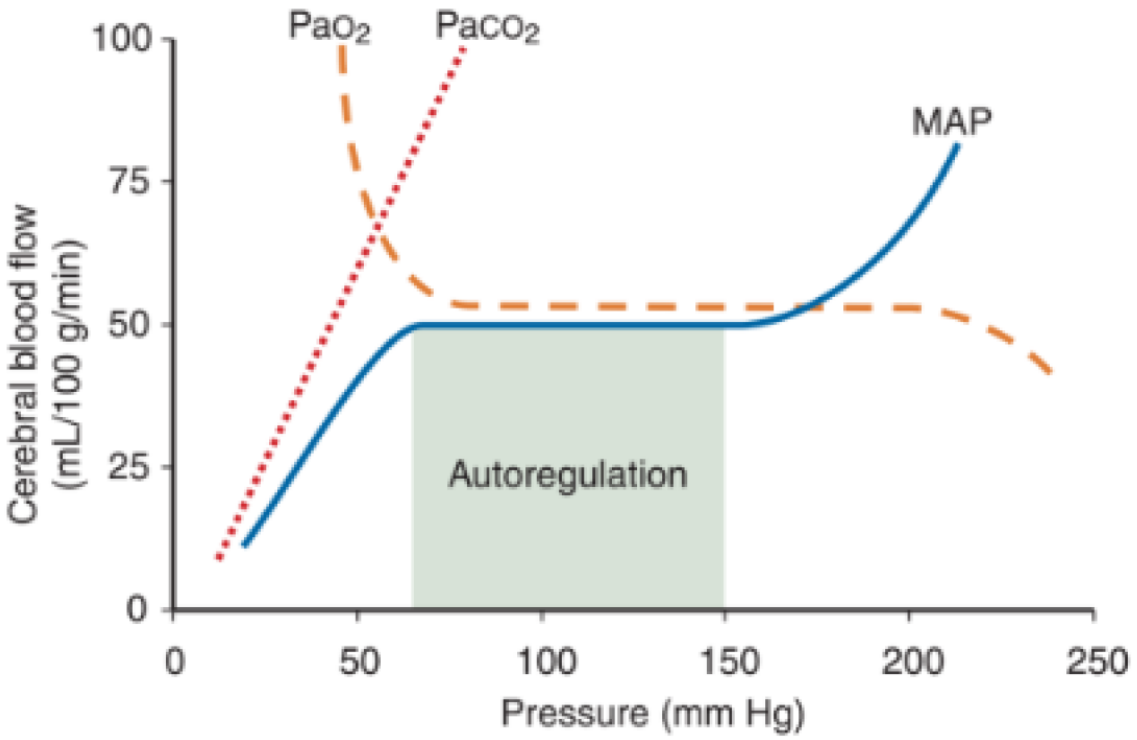


Regulation of Cerebral Autoregulation by Carbon Dioxide - overview

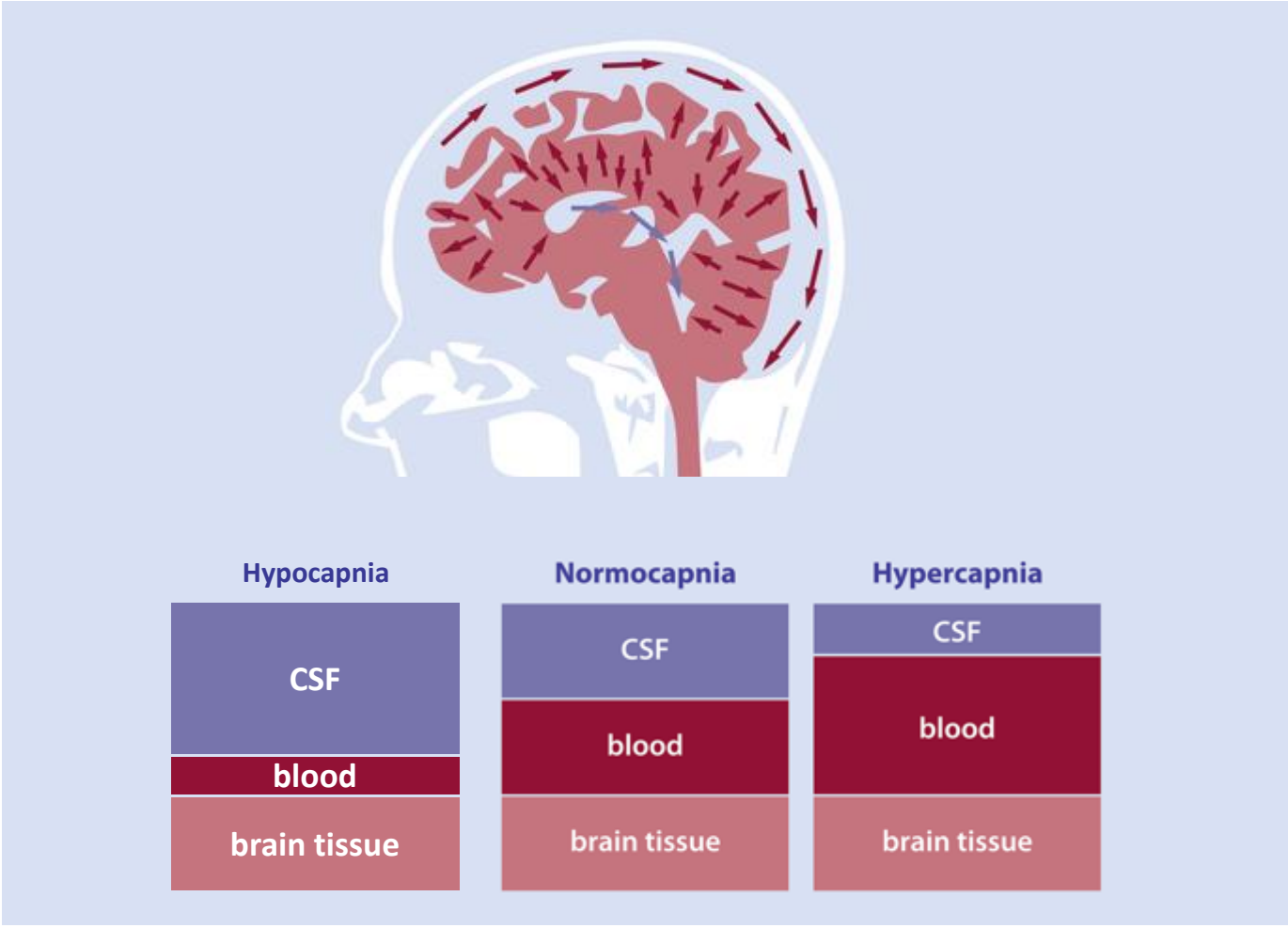


Regulation of Cerebral Autoregulation by Oxygen

- PaO_2 has little effect on CBF at values 60 – 300 mmHg.
- PaO_2 below 60 mmHg increases CBF if CPP is maintained

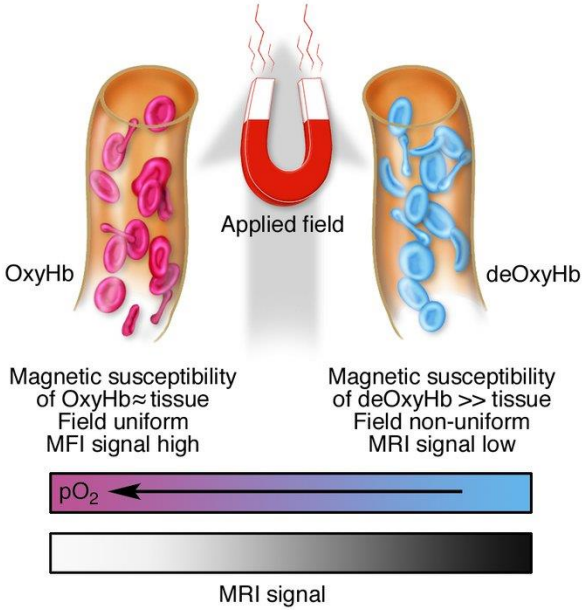


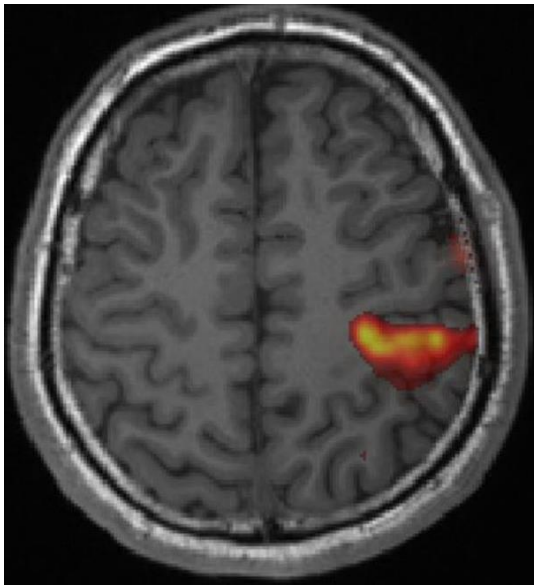
Effect of Carbon Dioxide on Cerebral Blood Volume



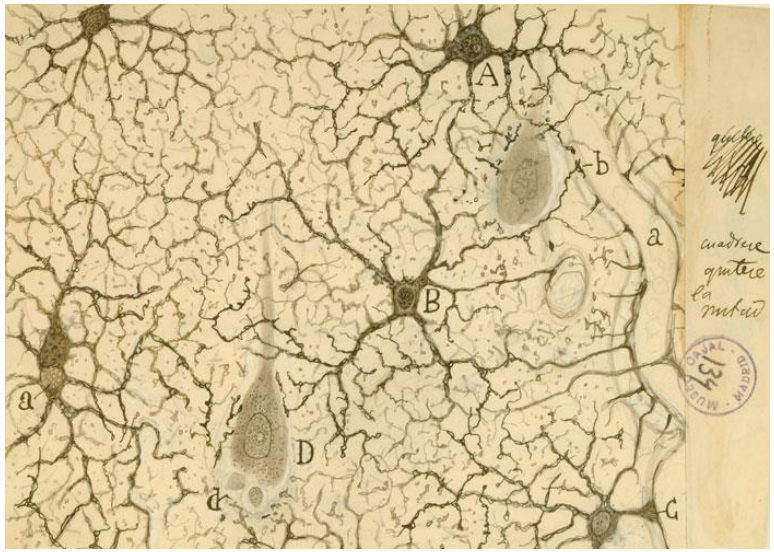
Regulation of rCBF on micro level = neurovascular coupling

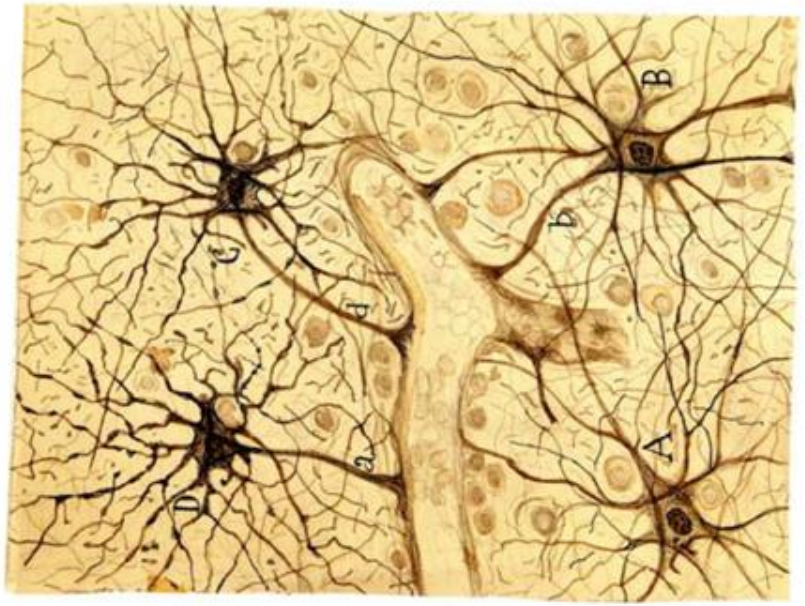
- Event related CBF transients = hemodynamic response
- During activity = increase in CBF
- fMRI = BOLD (blood oxygen level dependent)
- Oxyhemoglobin - Diamagnetic
- Deoxyhemoglobin - Paramagnetic

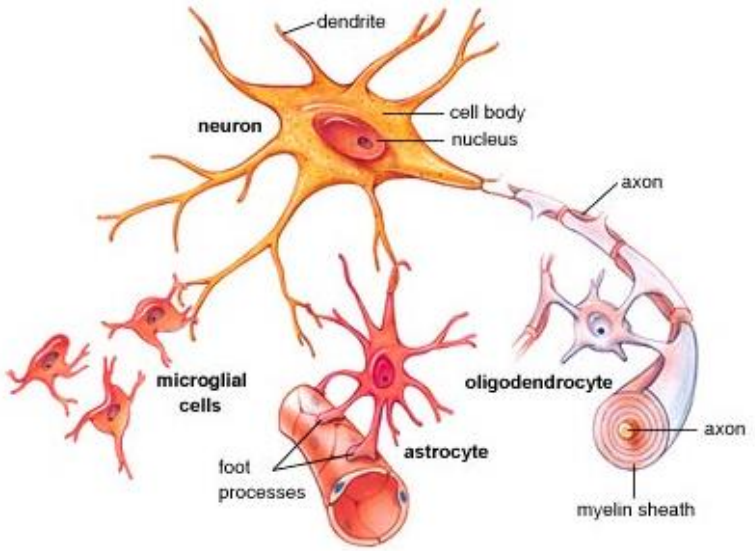




Neurons need appropriate supply = neurovascular unit

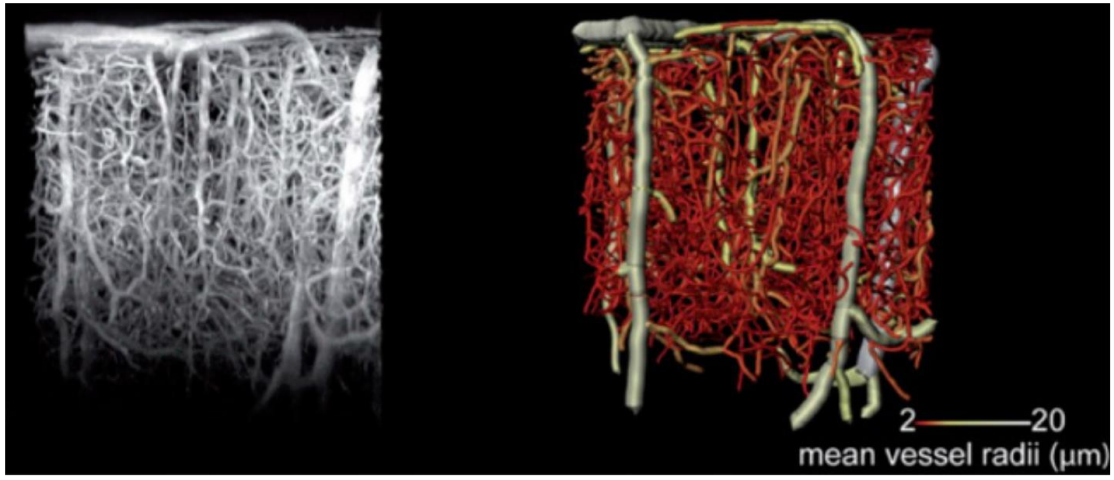


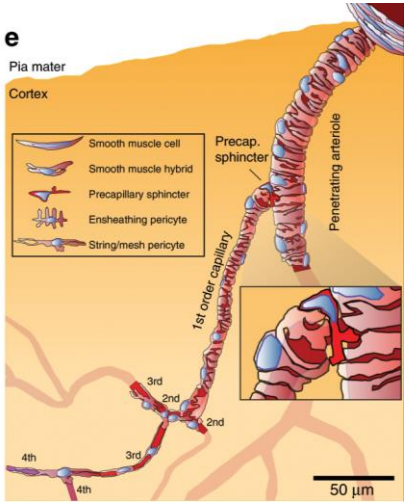


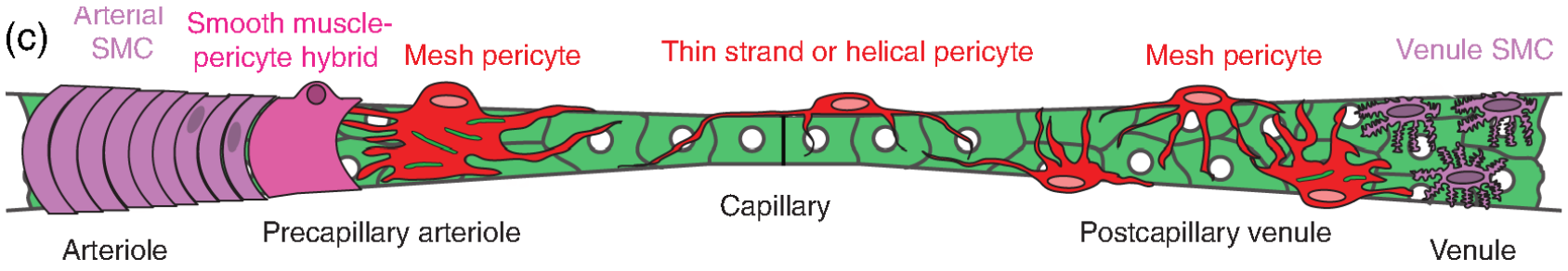


Which elements alters vascular resistance in micro level

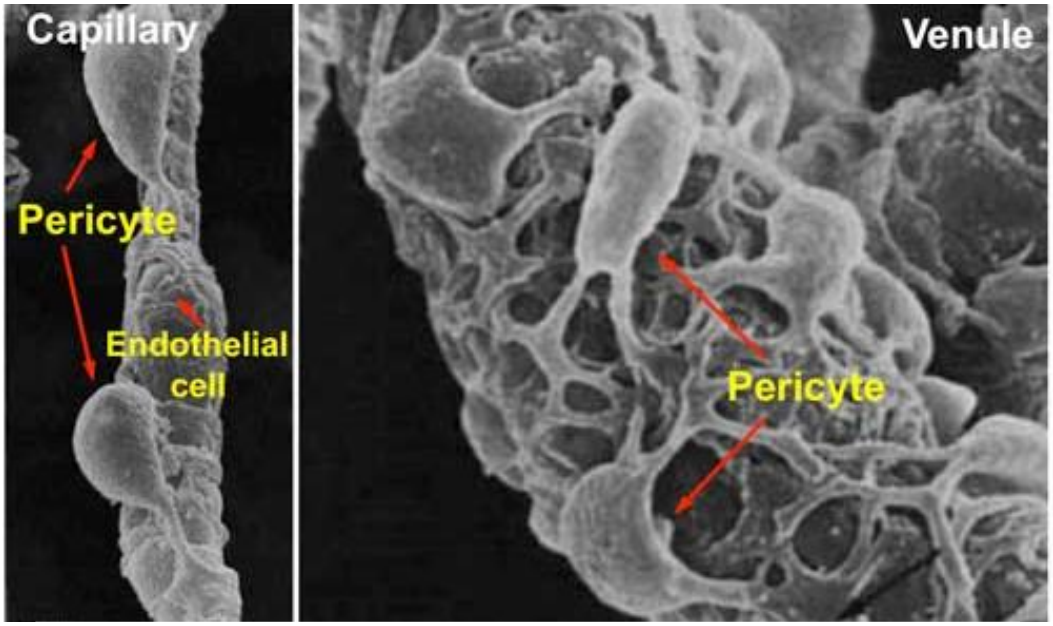
- Brain microvasculature components possessing contractility
  - precapillary sphincters
  - contractile pericytes

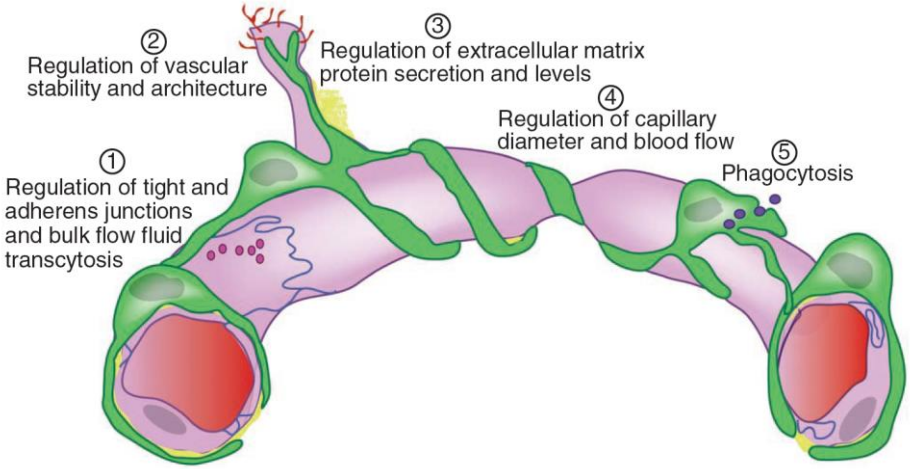






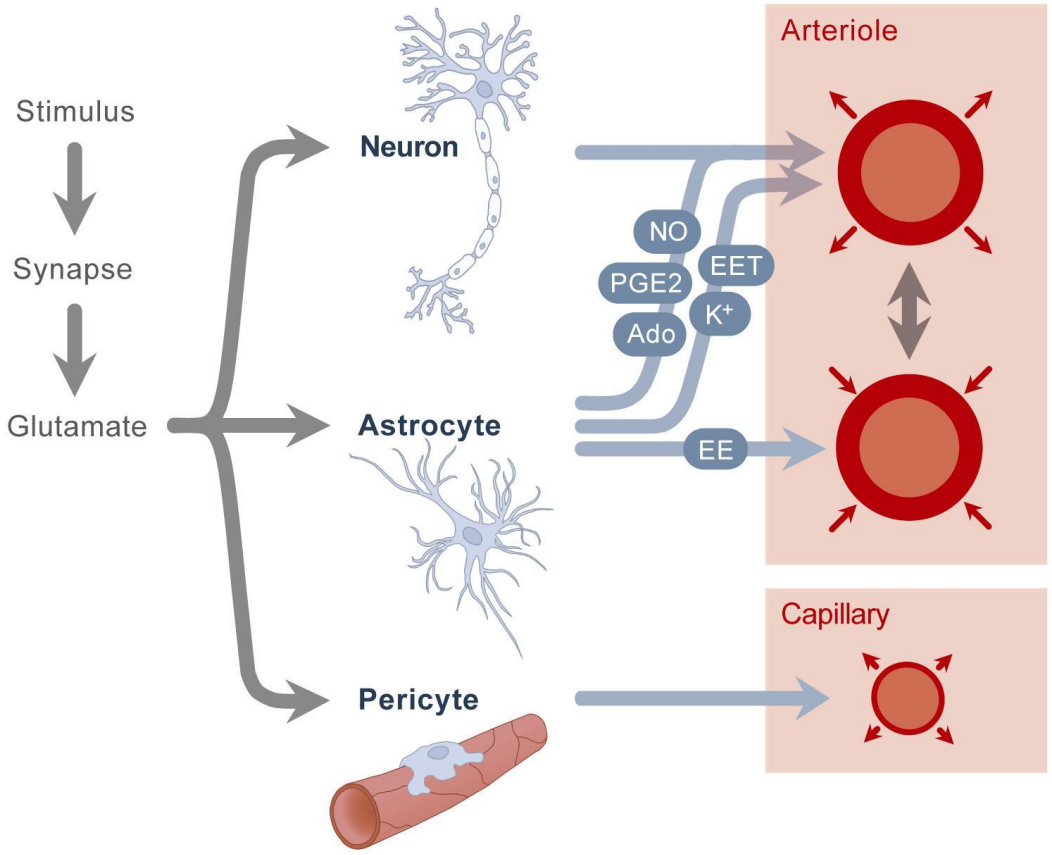
Pericytes


Capillary
Venule
Pericyte
Endothelial cell
Pericyte


② Regulation of vascular stability and architecture
③ Regulation of extracellular matrix protein secretion and levels
④ Regulation of capillary diameter and blood flow
⑤ Phagocytosis
① Regulation of tight and adherens junctions and bulk flow fluid transcytosis

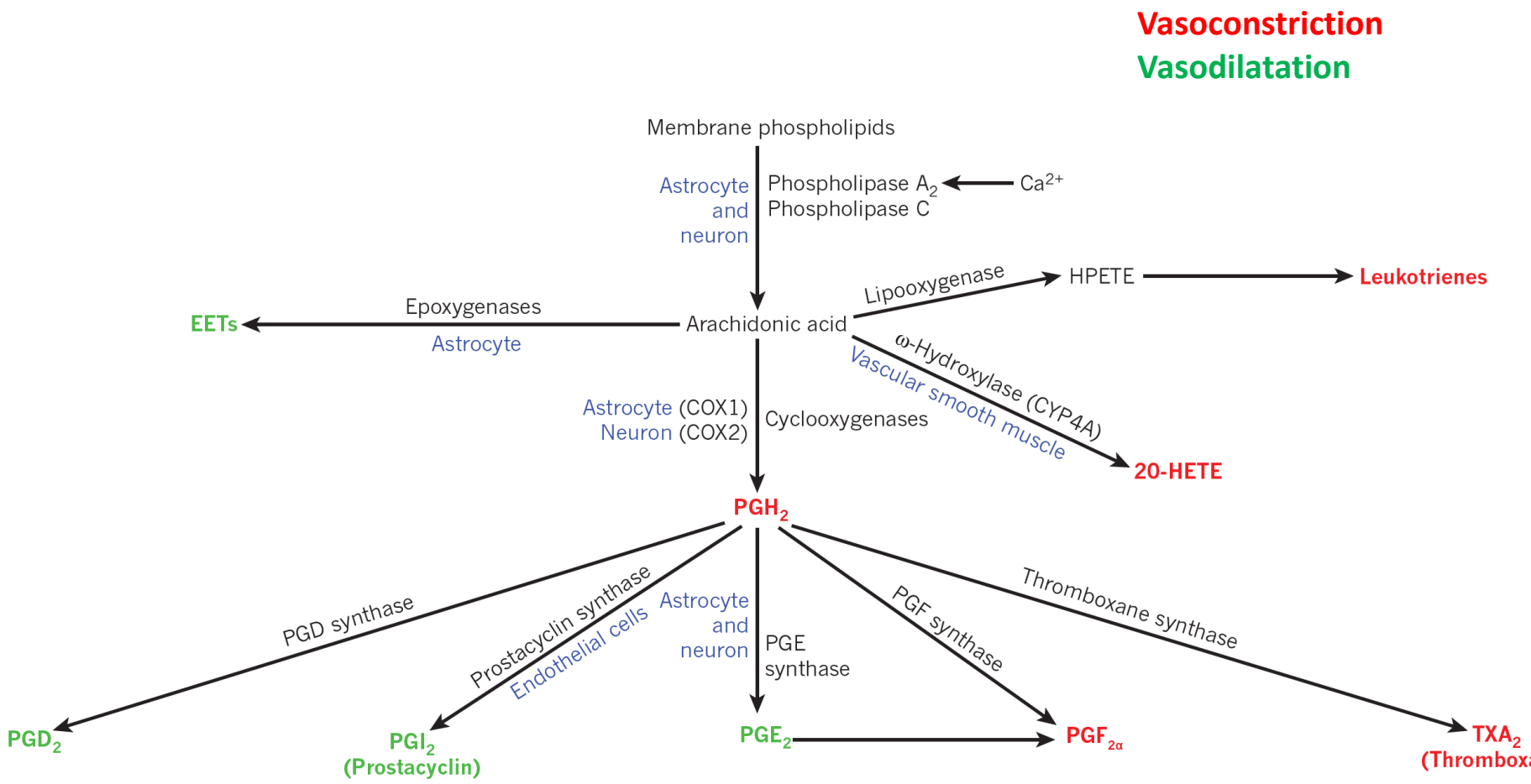
How is rCBF set to actual needs?

- Brain tissue set regional blood flow by **feedforward regulation** of tension of precapillary sphincters and pericytes



NO - nitric oxide
K+ - potassium
Ado - adenosine
EET - epoxyeicosa-trienoic acids
PGE2 - prostaglandins
AA - arachidonic acid
EE - 20-Hydroxyeicosa-tetraenoic acid

Prostanoids in rCBF regulation



Neurovascular coupling, unit, blood brain barrier

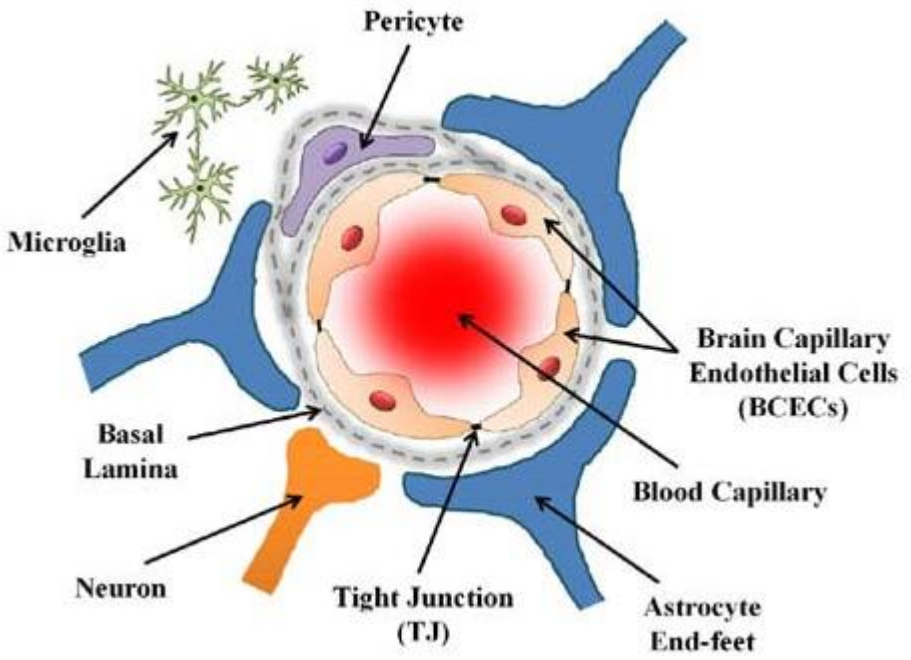
- Neurovascular unit set appropriate vessel diameter to follow current metabolic needs of surrounding tissue
- Increased blood flow brings higher availability of nutrients

- **How nutrients enters brain?**

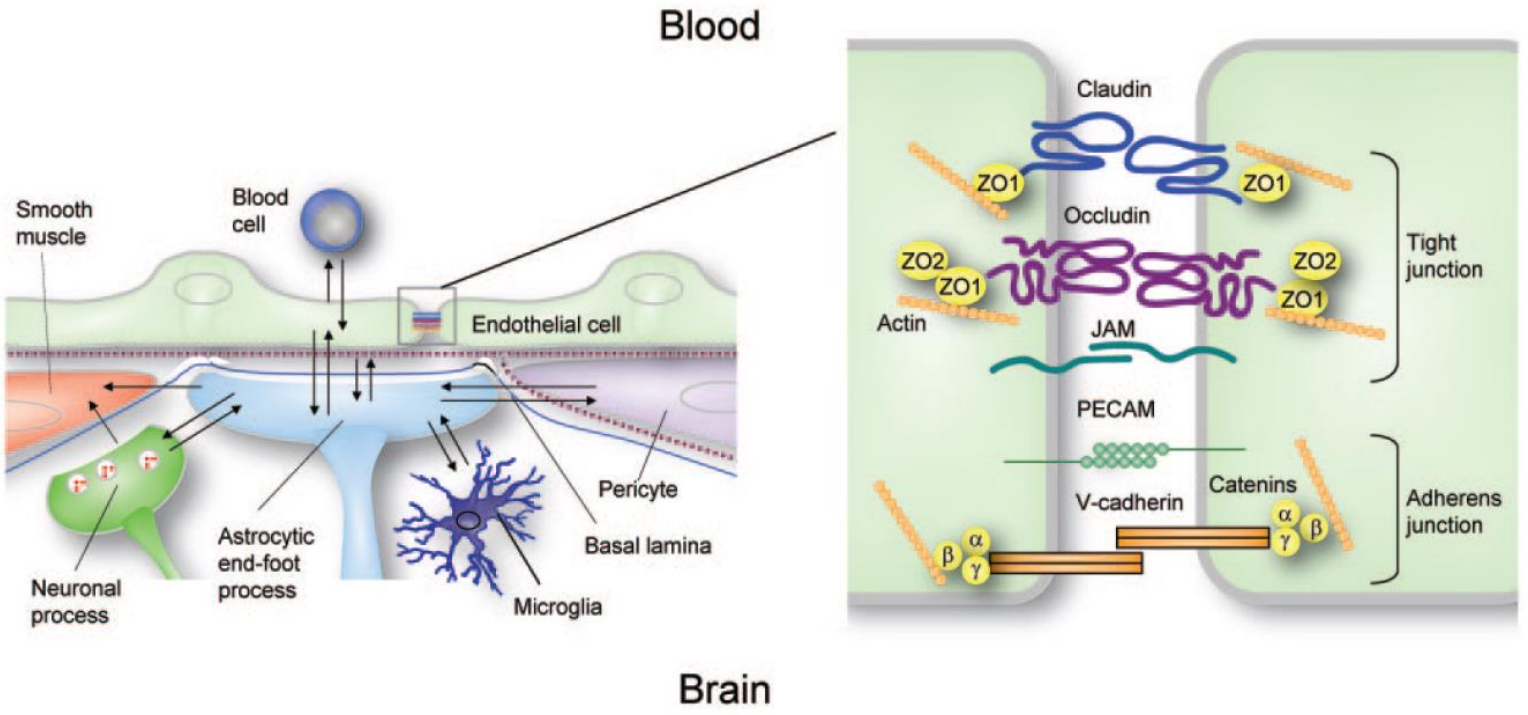
- Oxygen and other gases follow easily pressure gradient
- Other complex (larger or polar) substances cross capillary wall through so called Blood-brain barrier

Neurovascular unit, blood brain barrier

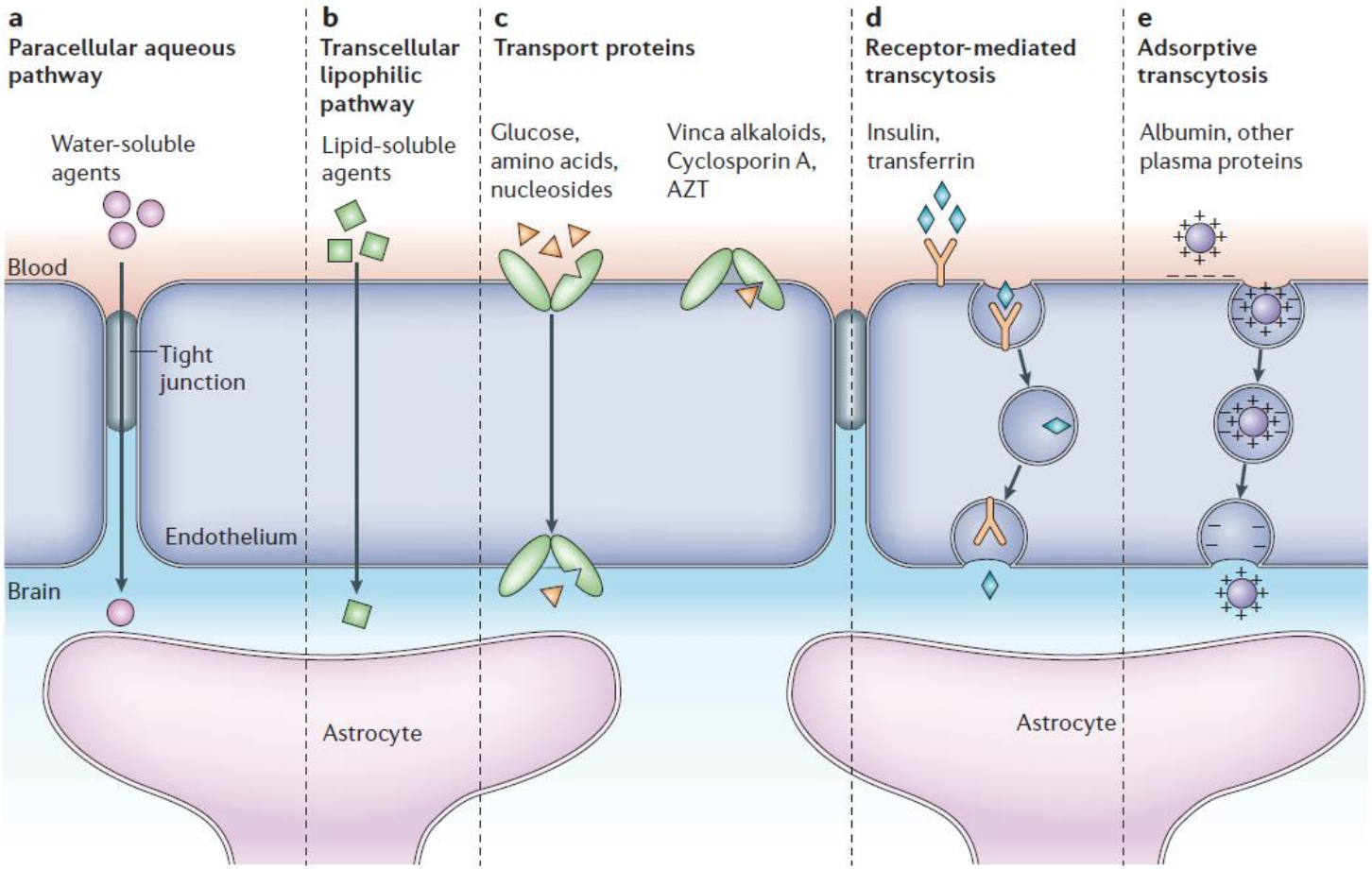
- Blood brain barrier
  - keeps stable environment of the brain
  - Protect brain against harmful substances
  - is composed of non-fenestrated capilary, basal lamina, endothelial tight jusnctions, astrocytic endfeet and pericytes



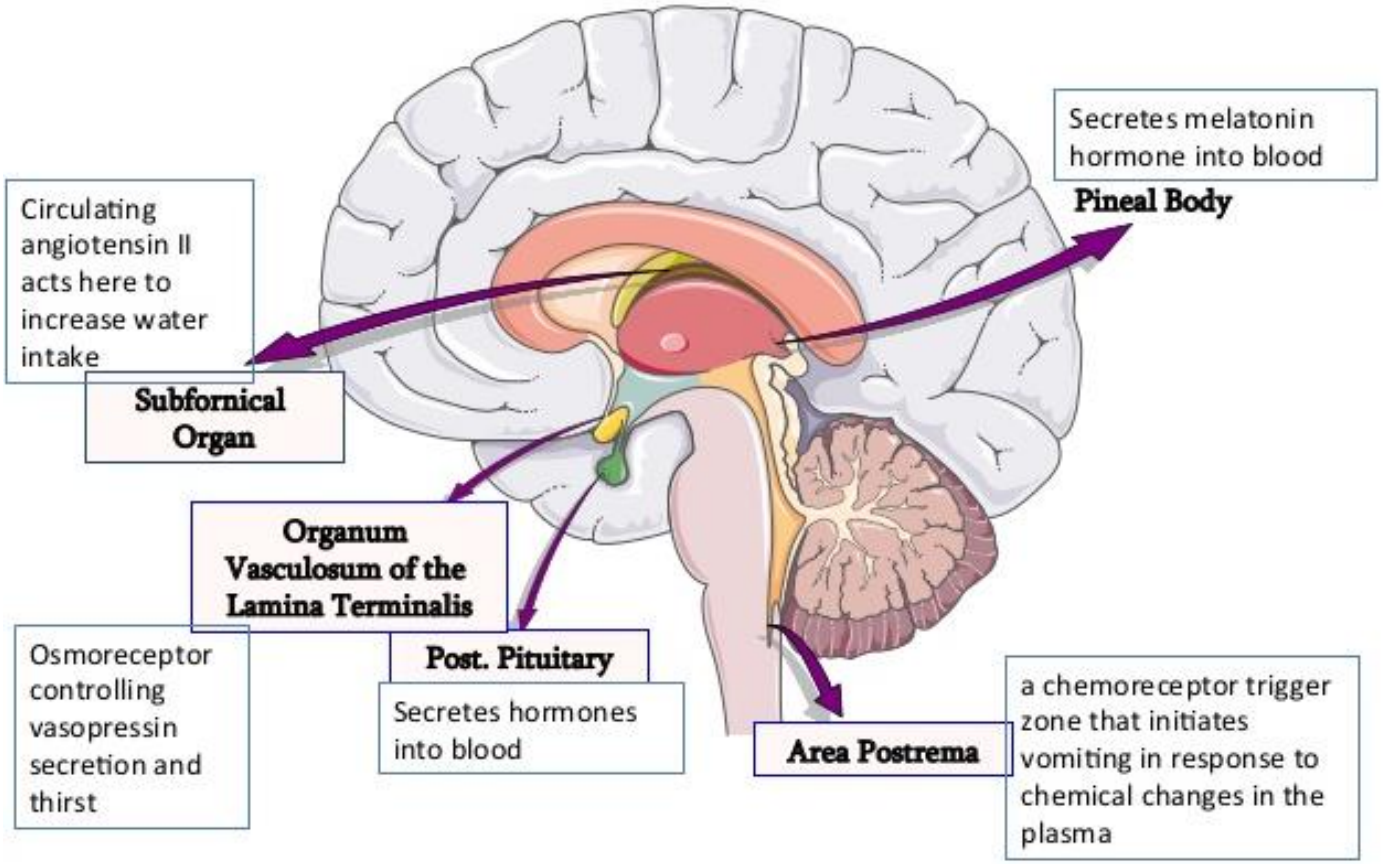
Blood brain barrier



Transport across blood brain barrier

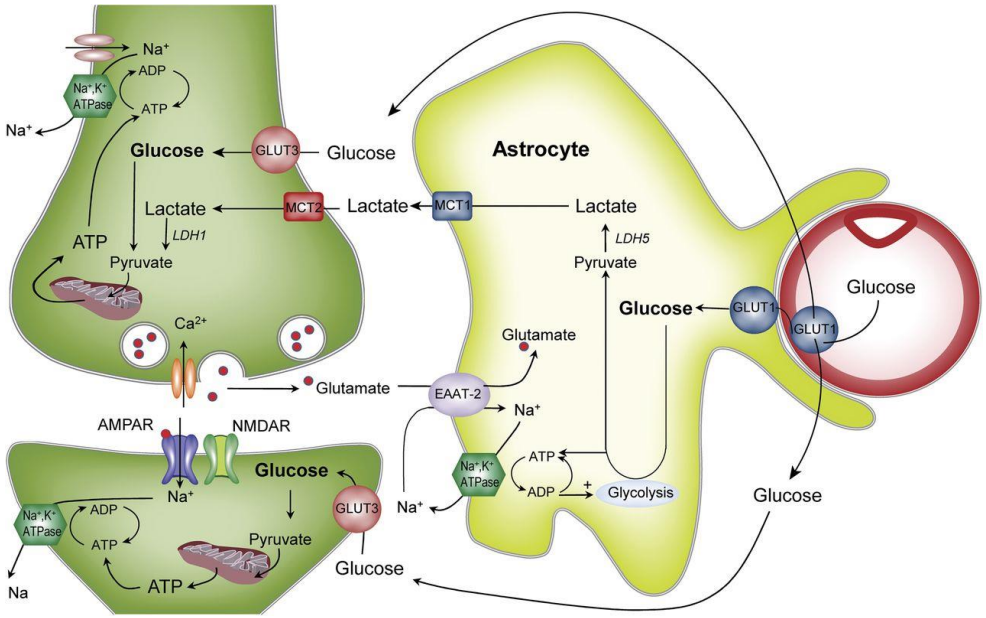


Places without blood brain barrier – the circumventrilcular organs



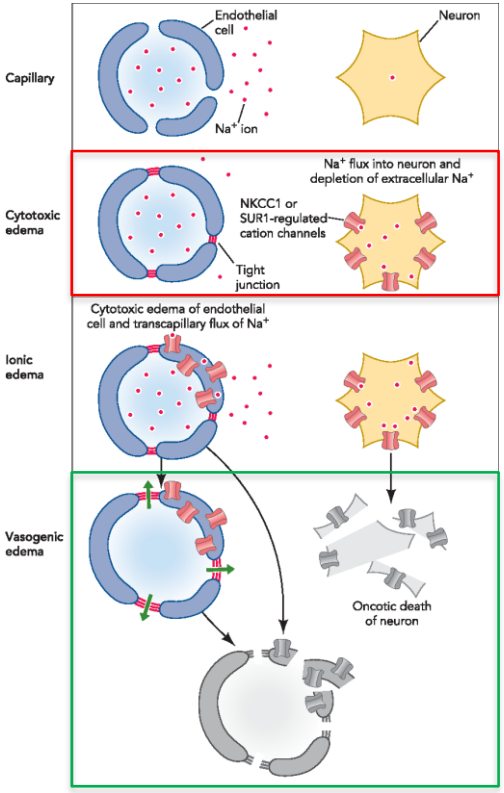
What is a fuel for brain ?

- Glucose cross BBB through insulin independent GLUT1
- Part is metabolized in astrocytes remaining directly in neurons
- Lactate from astrocytes moves to neurons through MCTs and enters mitochondrial TCA
- Metabolism is aerobic – glycolysis and phosphorylation



Clinical insight

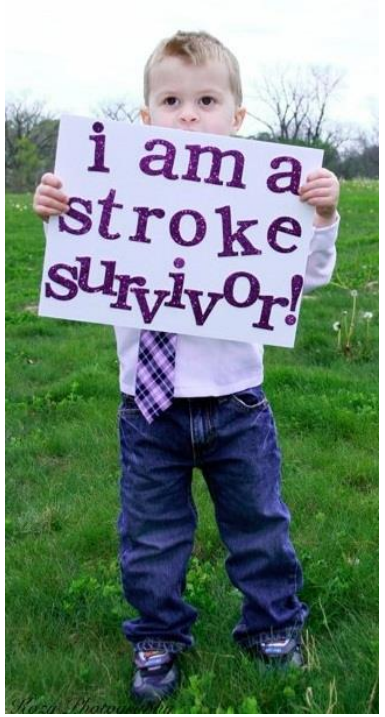
- What happens when blood supply is interrupted?
- Ischemia -> tissue damage -> vascular damage



Treatment? Fibrinolysis, Mannitol (hyperosmolar = reduction of edema = decrease ICP), Hyperventilation (hypocapnia = decrease CBV = decrease ICP)

Homework

- Blood brain barrier development in neonates.
- Regulation of cerebral blood flow in neonates.



Thank you for your attention….