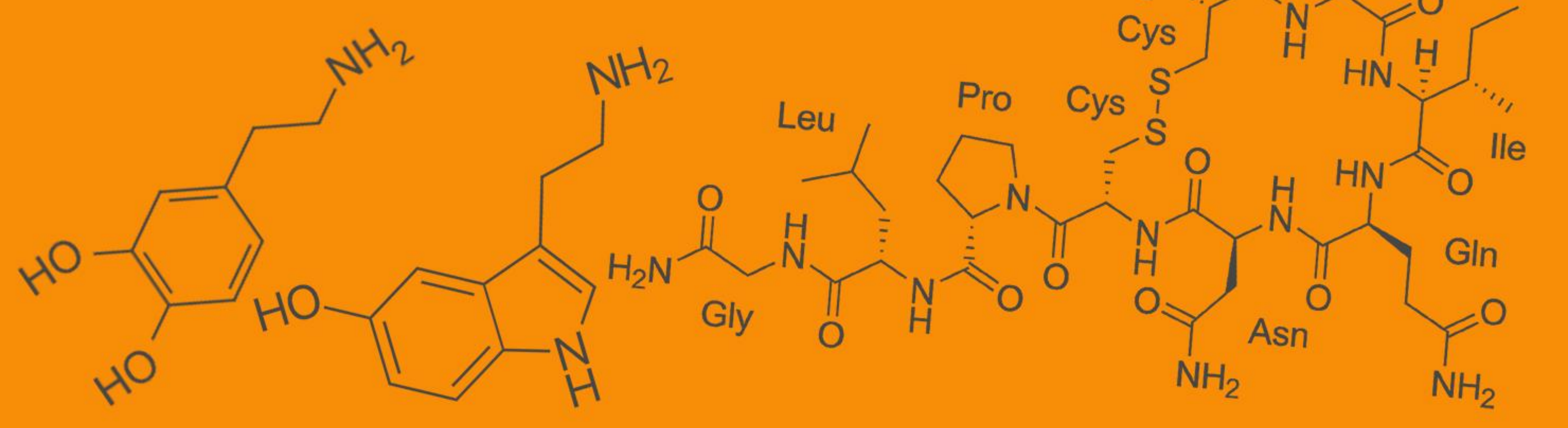
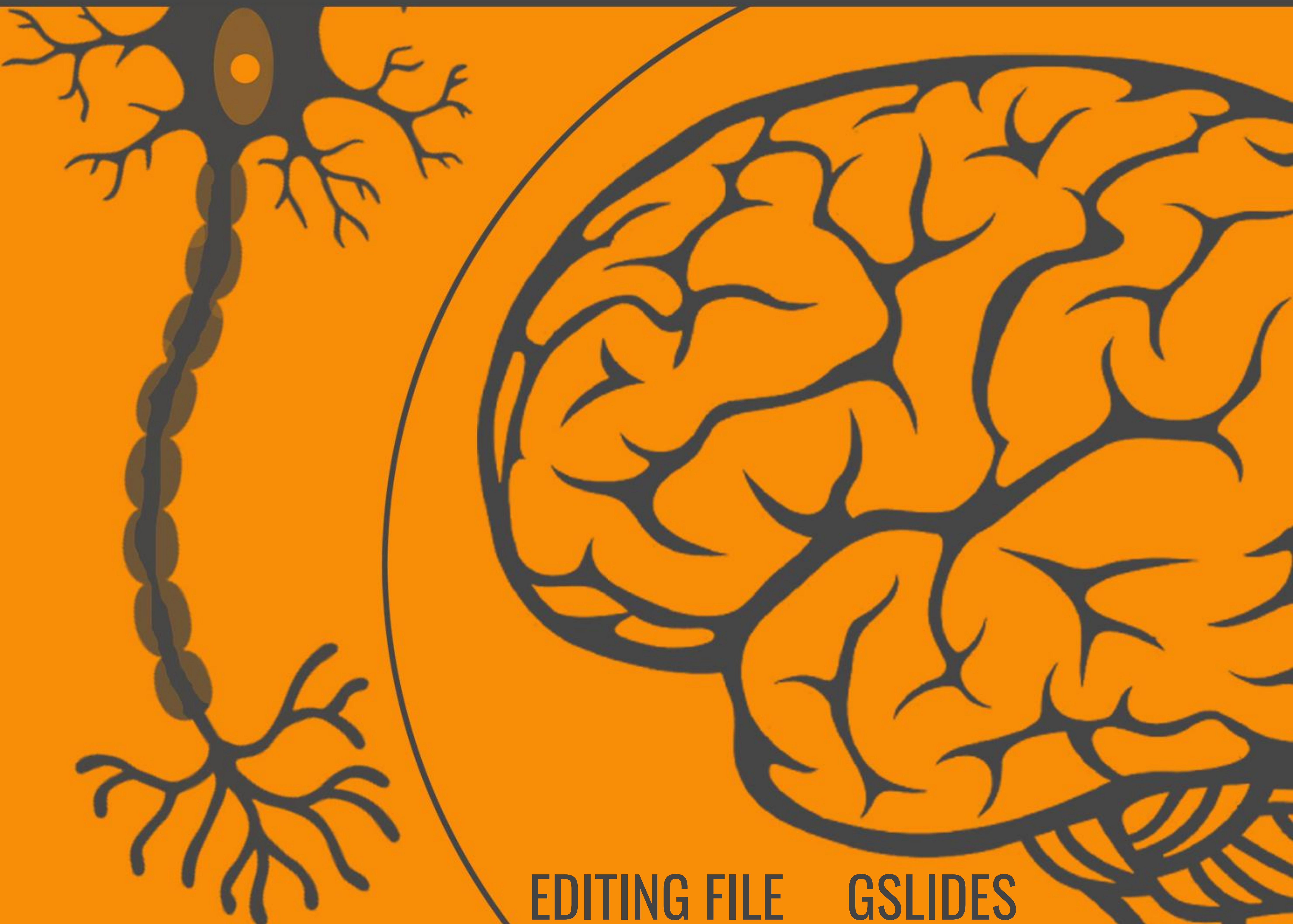



MEDICINE438's

# CNS PHYSIOLOGY

## LECTURE XXII: Autoregulation of Cerebral Blood Flow



EDITING FILE GSLIDES

IMPORTANT MALE SLIDES EXTRA FEMALE SLIDES LECTURER'S NOTES

## OBJECTIVES

- Describe cerebral circulation & circle of Willis
- Explain main arteries that supply blood to brain
- Normal Rate of Cerebral Blood Flow
- Explain auto-regulation of cerebral blood flow
- Explain the factors affecting the cerebral blood flow
- Effects of impaired cerebral blood circulation
- CSF formation, absorption & function

## Cerebral Crculation

- brain receive its blood supply from four main arteries & they form the circle of Willis (a group of arteries near the base)

### Circle of Wilis

1. R. Vertebral artery
2. L. Vertebral artery

(1 and 2) Unite & form → Basilar artery

3. R. Internal carotid artery
4. L. Internal carotid artery

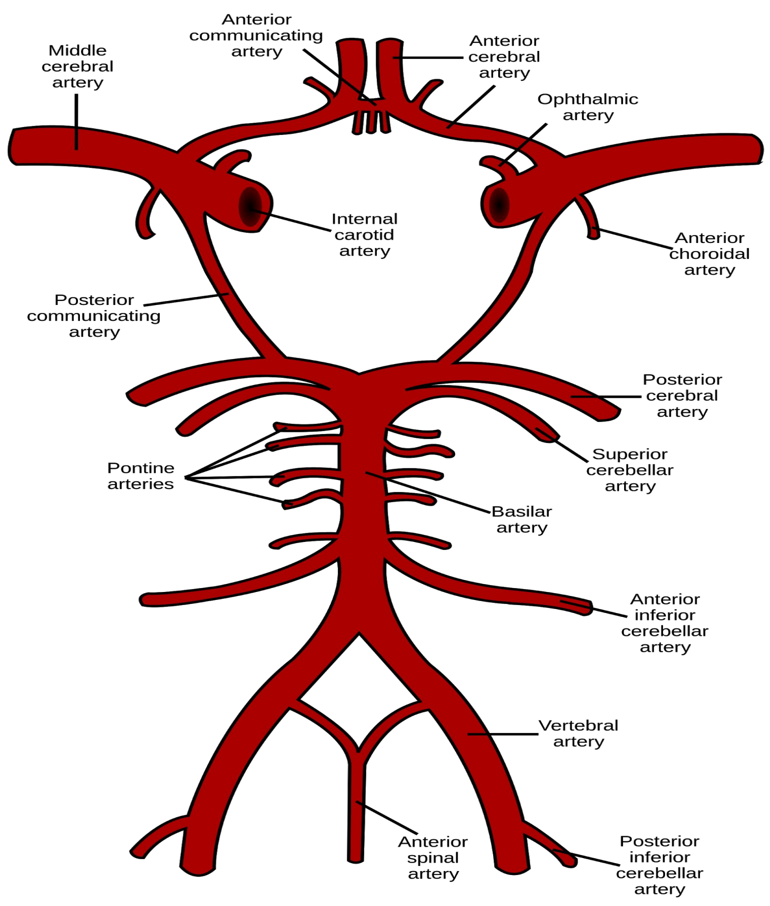



**Figure 22-1** Circle of Willis

- **The circle of Willis consists of six large Vessels:**

1. **Anterior cerebral artery** (left and right)
2. **Anterior communicating artery**
3. **Internal carotid artery** (left and right)
4. **Posterior cerebral artery** (left and right)
5. **Posterior communicating artery** (left and right),
6. **Basilar artery**

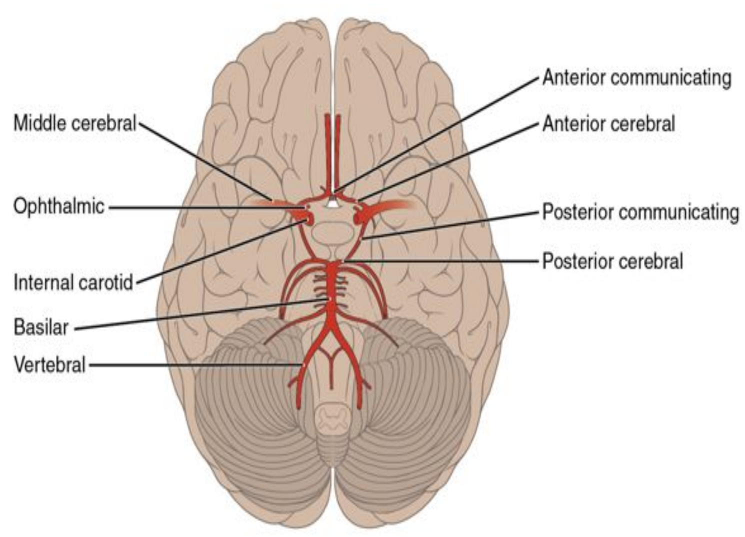
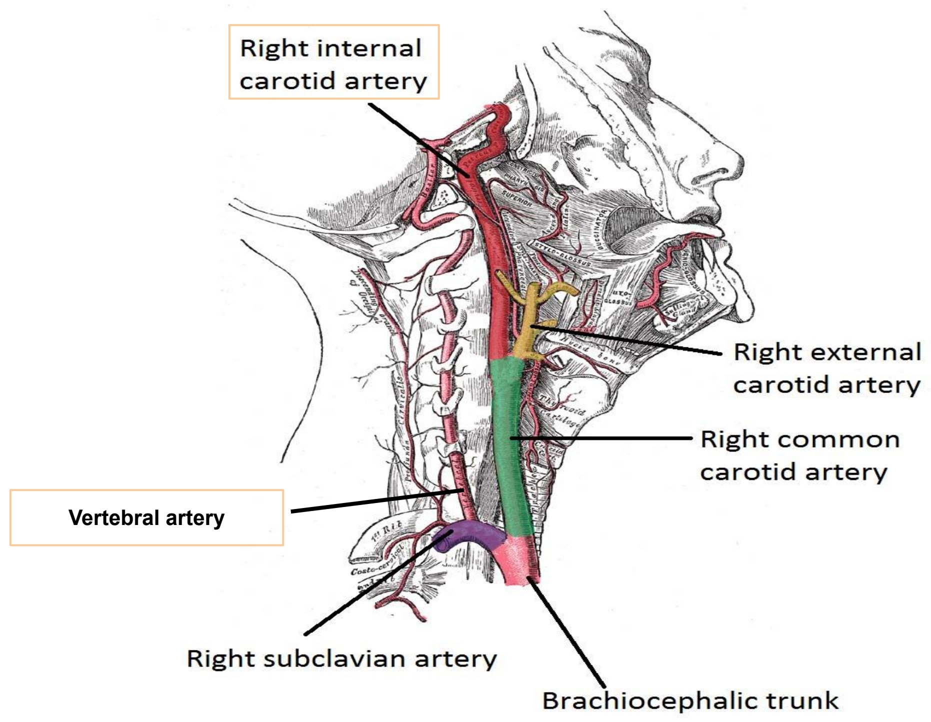



**Figure 22-2** Bottom view of the brain

N.B: The **middle cerebral arteries**, supplying the brain, are not considered part of the circle.

One of the most common types of stroke is blockage of the *middle cerebral artery.*



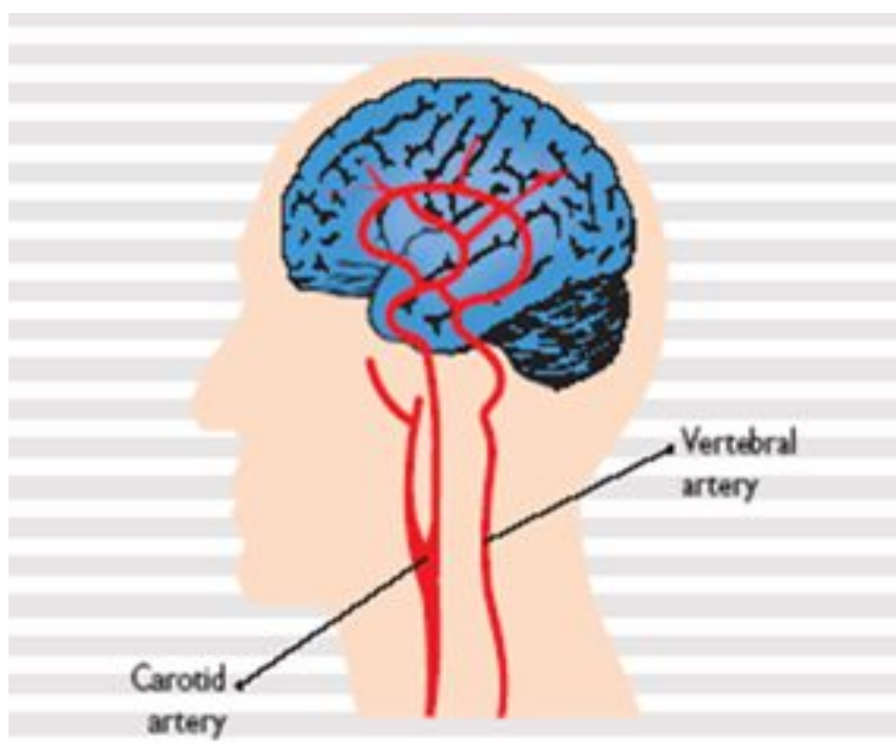




**Figure 22-3** Arteries forming the Circle of Willis

## Carotid Artery Injection

Substances injected into one carotid artery distributed completely to the cerebral hemisphere on that side. Normally **no crossing over** occurs <u>because of equal pressure on both sides</u>.

### CLINICAL SIGNIFICANCE

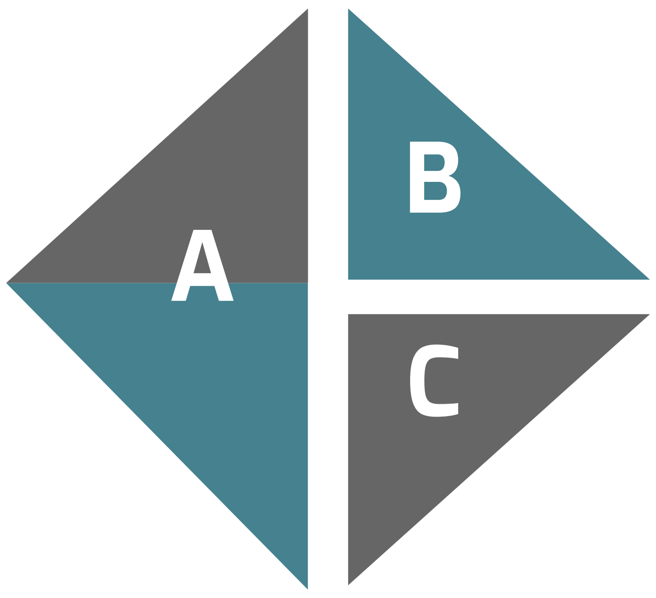
The clinical consequences of vascular disease in the cerebral circulation depend upon which vessels or combinations of vessels are involved.

## Innervation of the cerebral blood vessels

- **Three systems of nerves innervate the cerebral blood vessels:**

### Sympathatic

Postganglionic sympathetic neurons have their bodies in the **superior cervical ganglia**. During **acute hypertension** it <u>attenuates</u> the increase in CBF[1].




### Parasympathetic

Cholinergic neuron originate in **sphenopalatine ganglia** end on large arteries.

### Sensory nerves

## Blood Brain Barrier (BBB)

It is between **blood** & **CSF** & **brain tissue**
It is formed by the tight junctions between:
1. Choroid plexus epithelial cells (**astro & pericytes**)
2. At brain capillary membrane (**endothelial cells**)

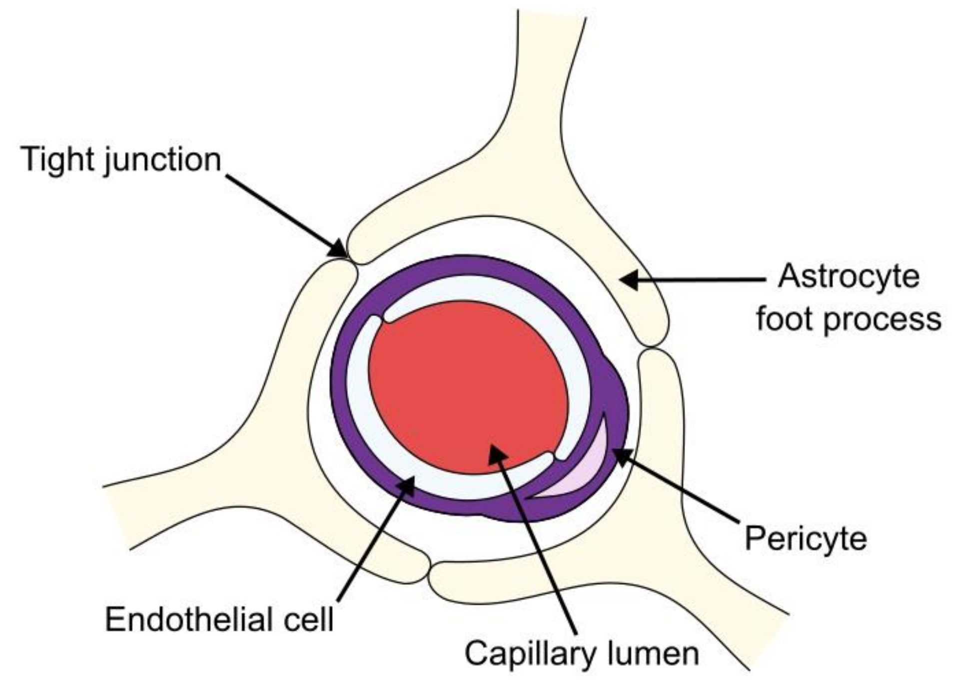



**Figure 22-4** Blood Brain Barrier

| Penetration Of Substances Into The Brain | | | |
|---|---|---|---|
| **Molecules pass easily[2]** | **Molecules do not pass** | **Slight penetration** | **Glucose[5]** |
| H2O, CO2, O2, lipid-soluble substances (as steroid hormones) | proteins[3], antibodies[4], non-lipid-soluble large molecules | $Cl^-$, $Na^+$, $K^+$ | its passive penetration is slow, but transported across brain capillaries by **GLUT1** |

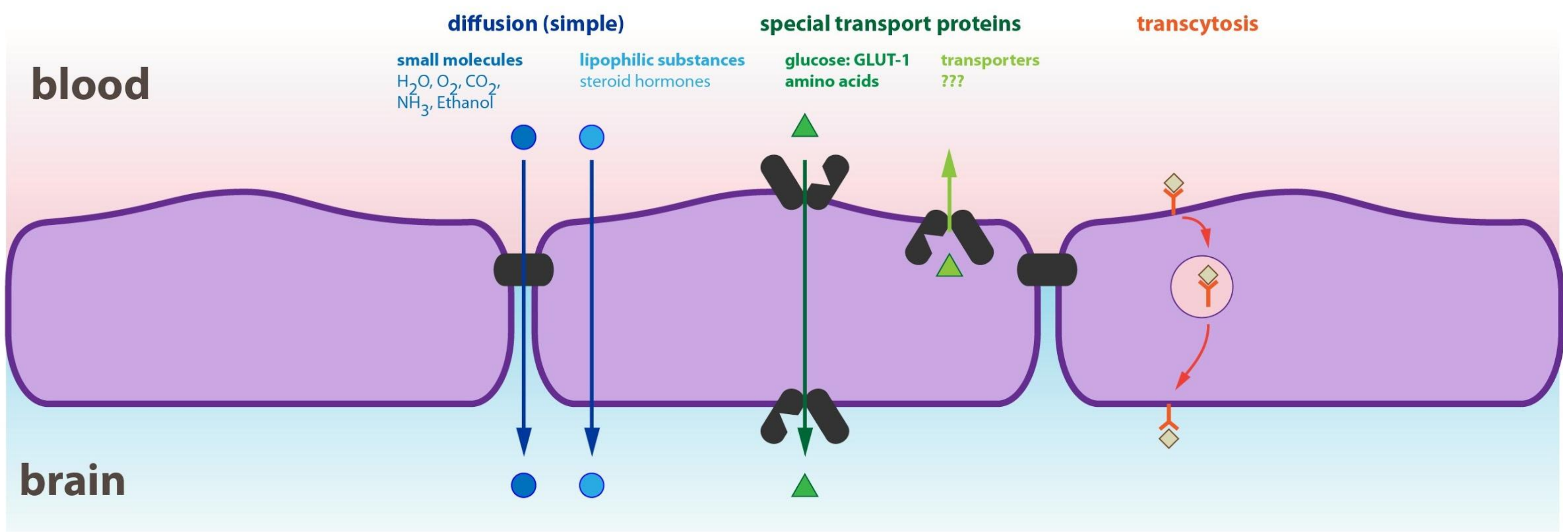



**Figure 22-5** Penetration of substances into the brain

1: By causing vasoconstriction of the blood vessels
2: Usually they're molecules that are already present in the brain
3: Could have a toxic effect on the brain
4: If they enter the brain they would cause neural reaction & damage the brain
5: Glucose enter the brain & get consumed without the need of insulin

# 3 Auto-regulation of Cerebral Blood Flow

## Functions of BBB

1. **Maintains** 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

### BOX 22-1: GUYTON AND HALL

An important structural characteristic of the brain capillaries is that most of them are much less "leaky" than the blood capillaries of the body. One reason for this phenomenon is that they are supported on all sides by "glial feet," which are small projections from the surrounding astroglial cells that abut against all surfaces of the capillaries and provide physical support to prevent overstretching of the capillaries in case of high capillary blood pressure.

## Cerebral blood flow (CBF)

**All Values in this lecture are very important. YOU HAVE TO MEMORIZE IT**

- CBF is tightly regulated to meet the brain's **metabolic demands**
- Normal Rate of Cerebral Blood Flow
  - Brain: 1350 gm; 2% of Total Body Weight
  - Normal blood flow through the brain of the adult person average 50 to 65 ml/100 grams of brain tissue per minute
  - For <u>entire brain</u>: 750 to 900 ml/min, 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

## Physiological considerations

- Brain accounts for 2% of body weight yet requires **20%** of resting oxygen consumption
- $O_2$ requirement of brain is 3-3.5 ml/100 gm/min in adults
- In children it goes higher up to 5 ml/100 gm/min

Brain has metabolic rate because:
- Requires more substrate
- Lacks of storage of energy

## Cerebral perfusion pressure (CPP)

- **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 **(MAP)** is the force that pushes blood <u>into the brain</u>

2-intracranial pressure **(ICP)** force that <u>pushes out</u>

- **CPP** is normally between 70 - 90 mmHg in an adult human
- Normal intracranial pressure **10 mmHg**
- Pressure > 20 mmHg is abnormal
- Increase in ICP → decreases CBF & cerebral perfusion

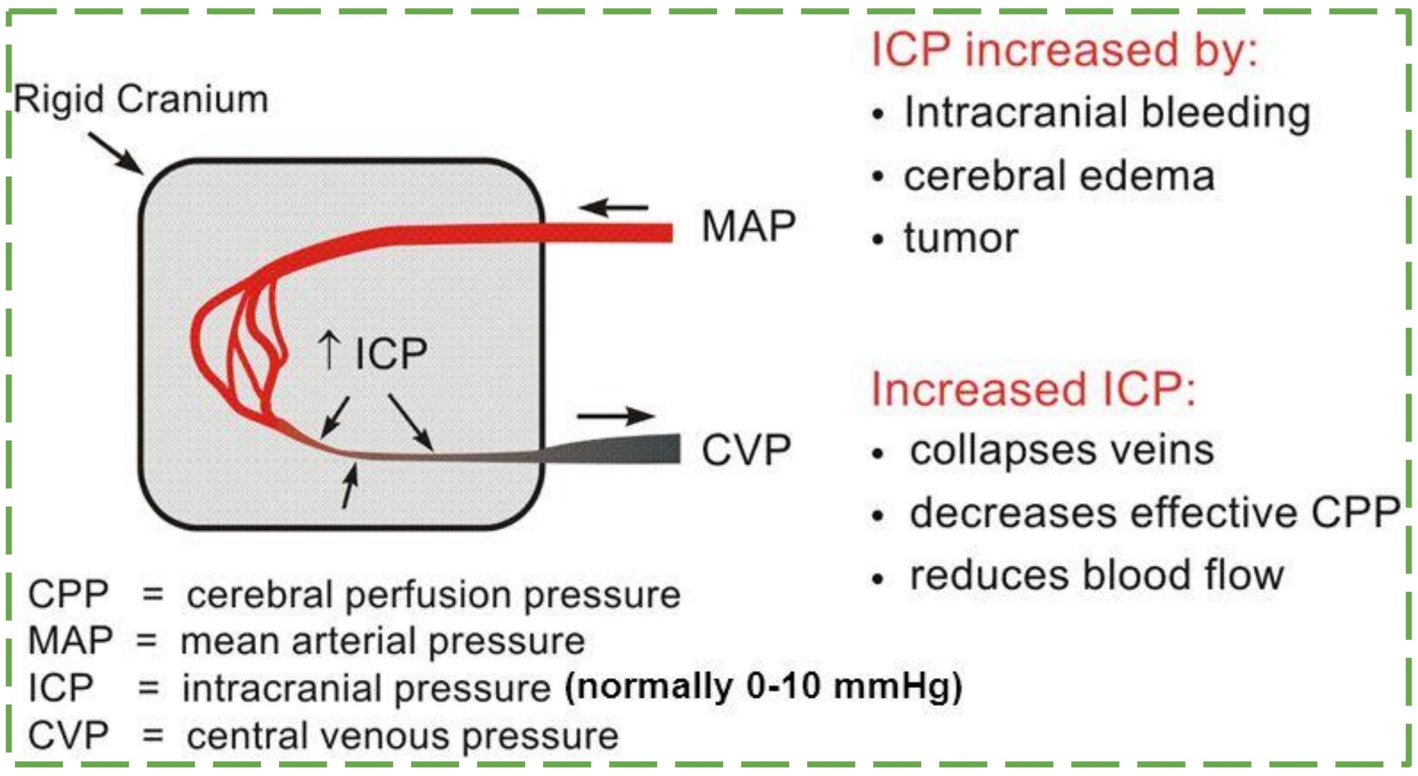
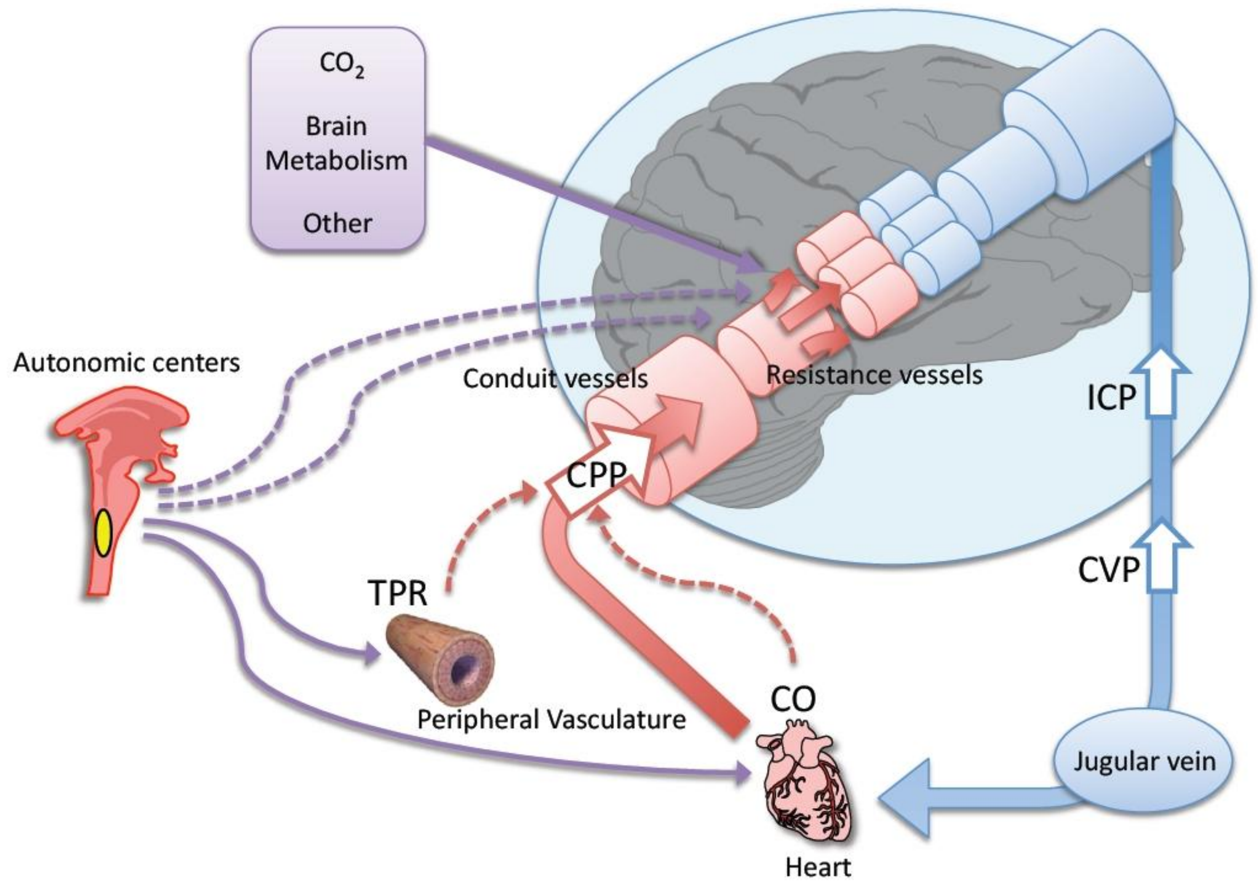



**Figure 22-6** Cerebral perfusion pressure

## 1- Myogenic/Pressure Autoregulation

- Arterioles **dilate** or **constrict** in response to changes in BP and ICP in order to maintain a constant CBF

- Myogenic theory: The vascular smooth muscles are highly responsive to changes in pressure, a process called **myogenic activity**, that contributes to auto-regulation of cerebral blood flow.




- Vascular smooth muscle within cerebral arterioles contract to stretch response, regulating pressure changes. **Autoregulation of CBF completely BP-dependent**

**Figure 22-7** Cardiac output (CO); Cerebral perfusion pressure (CPP); Total peripheral resistance (TPR); Carbon dioxide (CO2); Central venous pressure (CVP); Intracranial pressure (ICP)

- 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.

## CBF in relation to blood pressure

- **The brain maintains proper CPP through the process of autoregulation**
- **Cerebral blood flow is "auto-regulated" extremely well** between arterial pressure limits of 60 and 140 mmHg.
- Mean arterial pressure can be **decreased** acutely to as low as 60 mmHg or **increased** to as high as 140 mmHg **without significant change in cerebral blood flow.**
- Hypertension, auto-regulation of cerebral blood flow occurs even when the mean arterial pressure rises to as high as 160 to 180 mmHg. If arterial pressure falls **below** 60 mmHg, cerebral blood flow become severely decreased.
- At their most constricted condition, blood vessels create a pressure of 150 mmHg, and at their most dilated the pressure is about 60 mmHg.

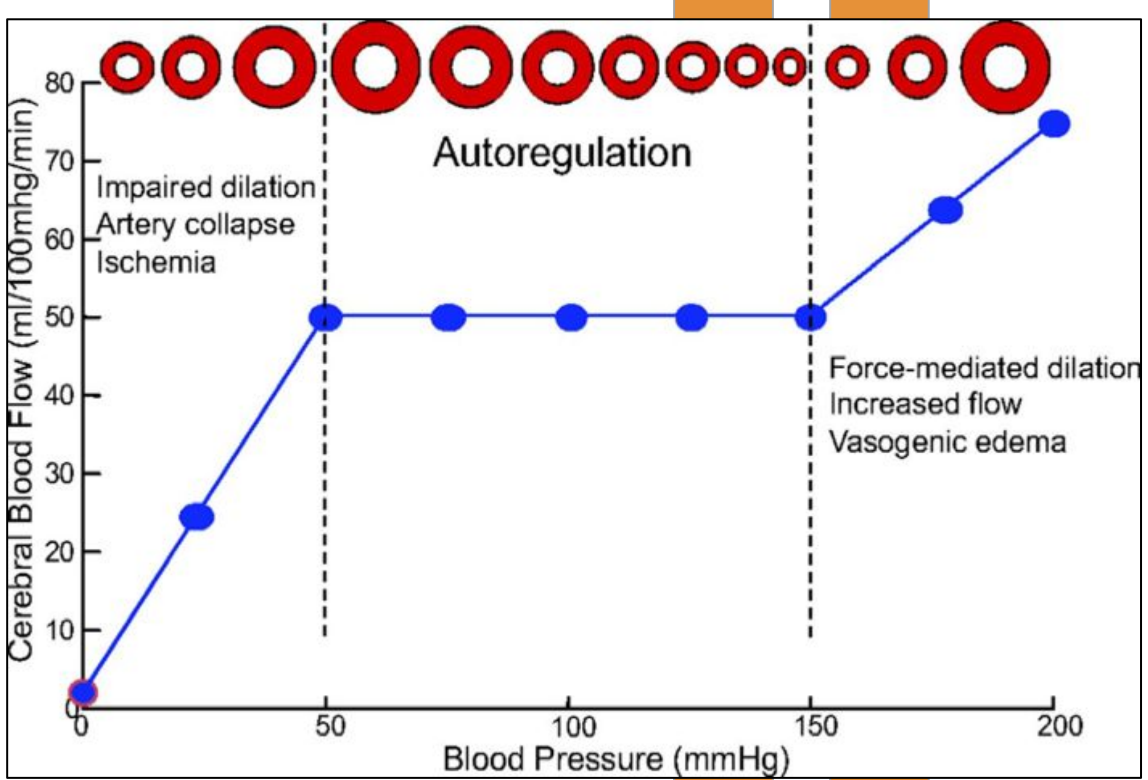



**Figure 22-8**

## CBF & MAP

- 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 <u>determined by blood pressure alone</u> without autoregulation.
- Thus, **<u>hypotension</u>** can result in **severe cerebral ischemia** & **<u>hypertension</u>** can result in **stroke or rupture.**

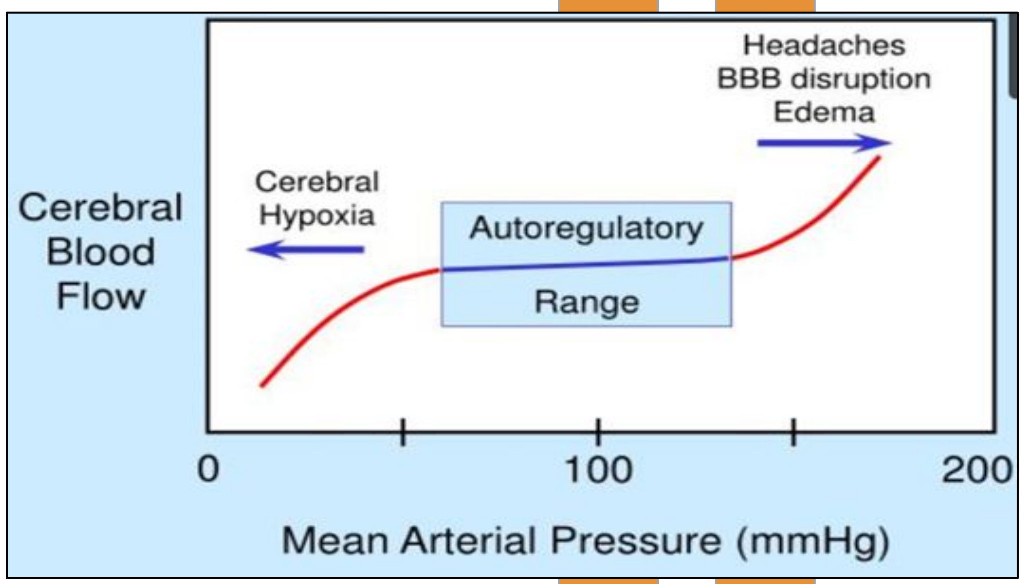



**Figure 22-9**

## 2- Metabolic Autoregulation

Cerebral blood flow is highly related to metabolism of the tissue. These **three** metabolic factors have potent effects in controlling the cerebral blood flow. Nitric oxide & adenosine are autoregulation mediators (both dilate).

(1) **Carbon dioxide** concentration

(2) **Hydrogen** ion concentration

(3) **Oxygen** concentration

## Hydrogen & Carbon dioxide

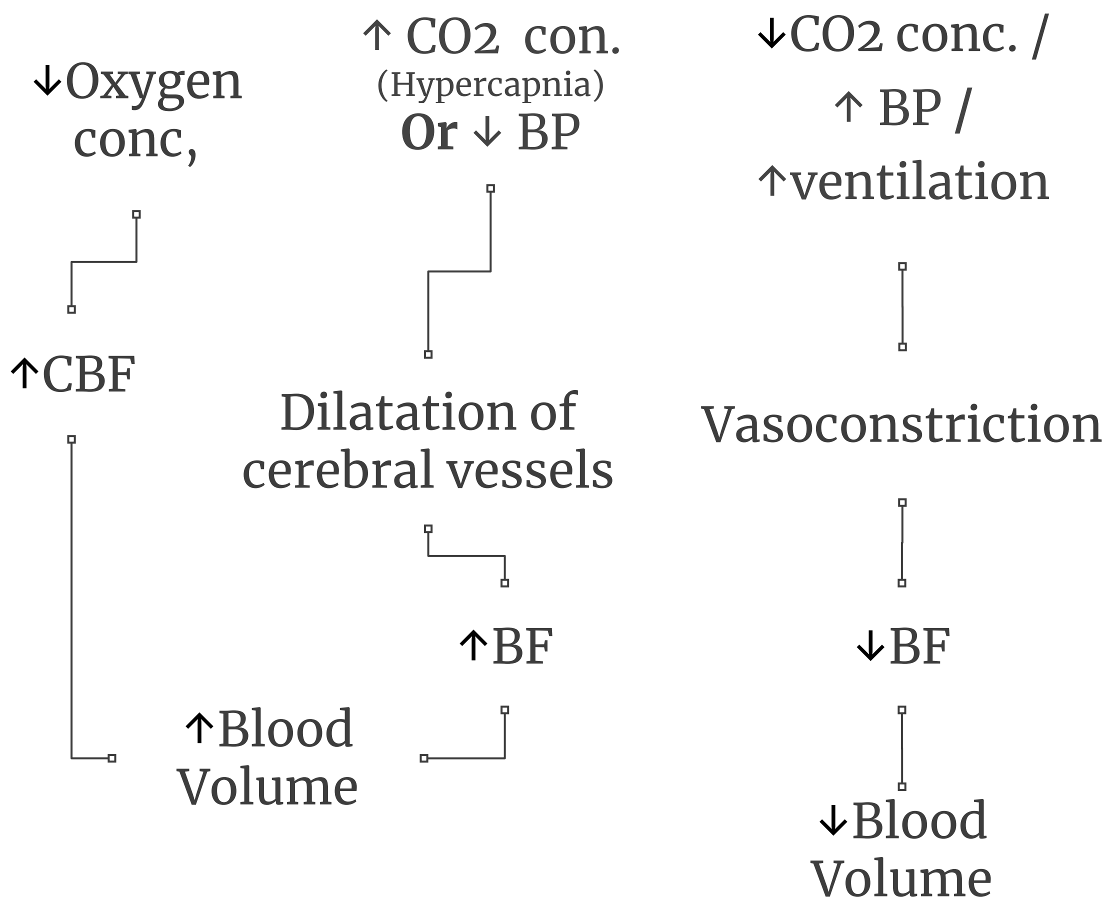
Arterioles dilate in response to potent chemicals that are by-products of tissue metabolism such as lactic acid, carbon dioxide and pyruvic acid. $CO_2$ is a potent **vasodilator**. **<u>A 70 % increase</u>** in arterial $PCO_2$ approximately **<u>doubles</u>** the cerebral blood flow.

- ↑ $CO_2$ (**hypercapnia**) causes **Vasodilation**, and vasoconstriction if it's decreased (during hyperventilation) leading to cerebral hypoxia (decreased blood flow).
- As the arterial tension of $CO_2$ rises, CBV and CBF increase.
- Carbon dioxide <u>increase</u> cerebral blood flow[1] by combining first with **water** in the body fluids to form **carbonic acid**, with subsequent dissociation of this acid to form **hydrogen ions**.
- ↑ [H+] *depresses* neuronal activity, and also causes an increase in blood flow (by vasodilation), which in turn carries hydrogen ions, carbon dioxide, and other acid forming substances (lactic Acid, Pyruvate) **away** from the brain tissues thereby maintaining a normal level of neuronal activity.
- The dilation is ***directly*** proportional to the increase in [H].
- Excess carbon dioxide can dilate blood vessels up to **<u>3.5 times</u>** their normal size. Blood vessels also dilate in response to low pH (acidity).

### BOX 22-2: FLASH BACK (LECTURE II)

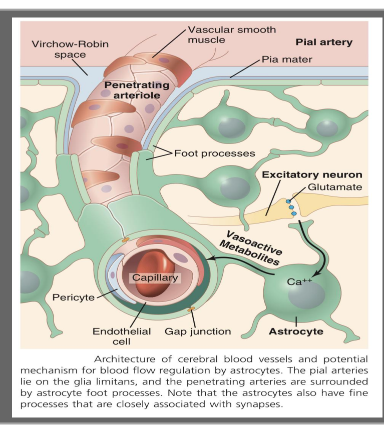
Alkalosis (↓$CO_2$) causes cerebral epileptic seizures. Over breathing in person with epilepsy blows of carbon dioxide and therefore elevates the pH of the blood momentarily leading to a seizure(Increased excitability of cerebral neurons).

While a pH of around 7 (leaning towards acidosis) usually causes come. For example in severe diabetics.




### BOX 22-3: GUYTON AND HALL

***Substances Released from Astrocytes Regulate Cerebral Blood Flow.***
We should emphasize on the importance of astrocytes in controlling blood flow, electrical stimulation of glutamate releasing neurons can open calcium channels within astrocytes, astrocytes, as we mentioned in BOX 22-1, have their foot processes on the capillaries, thereby participating in formation of BBB, these astrocytes can be stimulated to release variety of vasodilators that also help maintain blood flow.



### FOOTNOTES

1. $CO_2$ dissolves in water making carbonic Acid which then by the help of Carbonic anhydrase breaks into water and bicarbonate, water later on dissociate into two oxygen molecules and one hydrogen(potent vasodilator). So $CO_2$ has an indirect effect while Hydrogen itself has a direct effect of dilation.

## Oxygen

**When activity** in a given region of the brain is heightened, the **increase in $CO_2$ and H+ conc.** causes cerebral **vasodilatation**, and deliver more blood to the area to meet the increased demand.

- Hypoxia, or inadequate oxygen, also dilates blood vessels and increases blood flow. While **high levels** of oxygen **constrict** cerebral B.V. "opposite action to $CO_2$".

- Oxygen metabolism for local regulation of CBF is an important protective response against diminished cerebral neuronal activity and therefore, against derangement of mental capability.

### BOX 22-4: GUYTON AND HALL

Blood flow in each individual segment of the brain changes as much as 100 to 150 percent within seconds in response to changes in local neuronal activity.
For instance, simply making a fist of the hand causes an immediate increase in blood low in the motor cortex of the opposite side of the brain. Reading a book increases the blood low, especially in the visual areas of the occipital cortex and in the language perception areas of the temporal cortex. **Figure 22-10** demonstrates the effect of local neuronal activity on cerebral blood low by showing a typical increase in occipital blood flow recorded in a cat's brain when intense light is shined into its eyes for one-half minute.

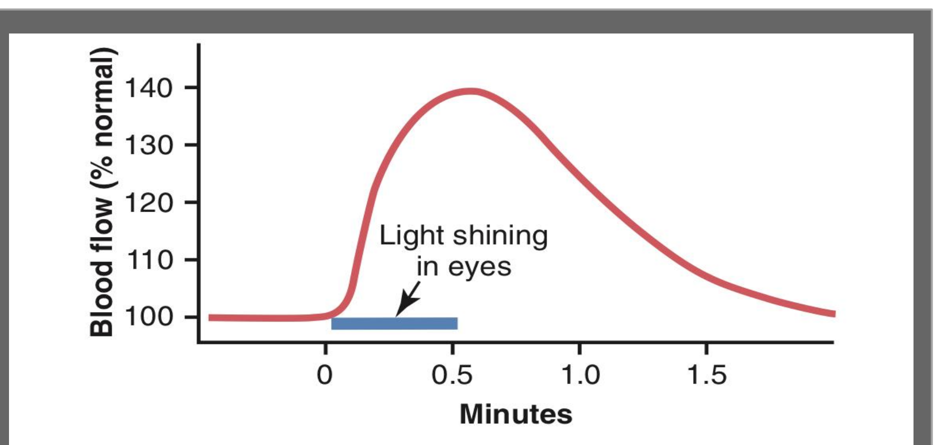



**Figure 22-10** Increase in blood flow to the occipital regions of a cat's brain when light is shined into its eyes.

- The rate of utilization of oxygen by the brain tissue remains within narrow limits—almost exactly 3.5 (± 0.2) ml of oxygen per 100 grams of brain tissue per minute.
- If blood flow to the brain insufficient to supply this needed amount of oxygen, 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 $PO_2$ below about 30 mm Hg (normal value is 35 to 40 mm Hg) immediately begins to **increase** cerebral blood flow.
- Brain function becomes unbalanced at lower values of $PO_2$, at $PO_2$ levels below 20 mm Hg.

Oxygen deficiency is a regulator of cerebral blood flow <u>**except**</u> during periods of intense Brain activity (at this time $CO_2$& H are more important). As they're faster to respond.

# 3- Neurogenic Autoregulation

## Sympathetic

The cerebral circulatory system has strong **sympathetic** innervation that passes upward from <u>the superior cervical sympathetic ganglia</u> in the neck and then into the brain along with the cerebral arteries.

- ANS and Neurochemical control has minor role, Pressure & Metabolic Autoregulation is <u>**most important.**</u>

During acute hypertension, sympathetic attenuates increase in CBF by vasoconstriction.

- The sympathetic nervous system normally **constricts** the large and intermediate-sized brain arteries enough to <u>prevent the high pressure</u> from reaching the smaller brain blood vessels.

This is important in preventing vascular hemorrhages, preventing the occurrence of "cerebral stroke."

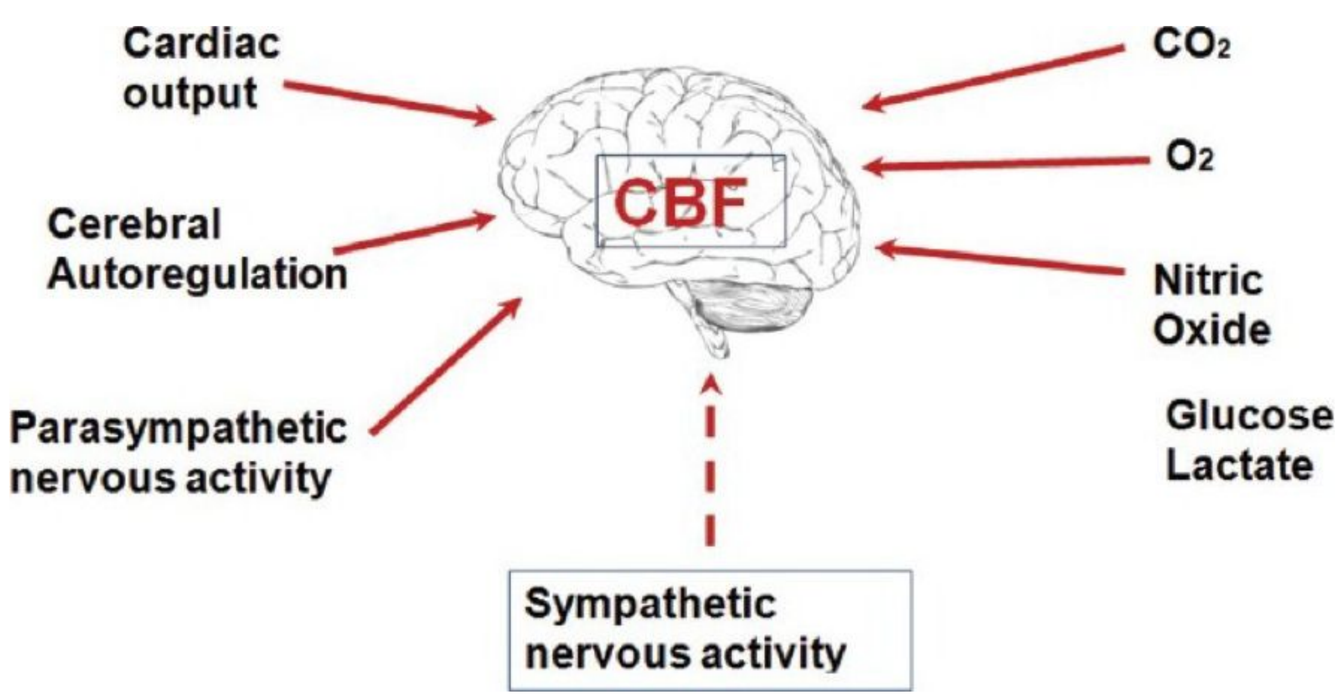



**Figure 22-11** Factors affecting cerebral blood flow

## Factors that result in the loss of normal CBF autoregulation

| | |
|---|---|
| **Noxious stimuli** | 1. Hypoxia due to cerebrovascular disease<br>2. Trauma from head injury[1]<br>3. Brain compression from tumors, hematoma, cerebral edema. |
| **Stroke** | Occurs when the blood supply to a part of the brain is **blocked** resulting in the death of an area.<br>If a large vessel is blocked the outcome may be rapidly fatal or may lead to very severe disability.<br>The most common types of disability are the loss of functions of one side of the body and speech problems |
| **Cerebral perfusion pressure** | - Normal intracranial pressure is 10 mmHg. if the pressure is over 20 mmHg it is abnormal.<br>- Increase in ICP will lead to a decrease in CBF and a decrease in cerebral perfusion |

## STROKES

Occur when the blood supply to a part of the brain is **blocked** resulting in the death of an area.

### TYPE 1: Thrombotic

- Stroke due to the blockage of an artery in the brain by a blood clot.
- Vasospasm (ET-1[2]) associated with subarachnoid hemorrhage

### TYPE 2: Hemorrhagic

- Ruptured aneurysm
- Vascular weakening due to chronic hypertension

### TYPE 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 in the brain.

- The thrombotic and hemorrhagic forms are common types of stroke.

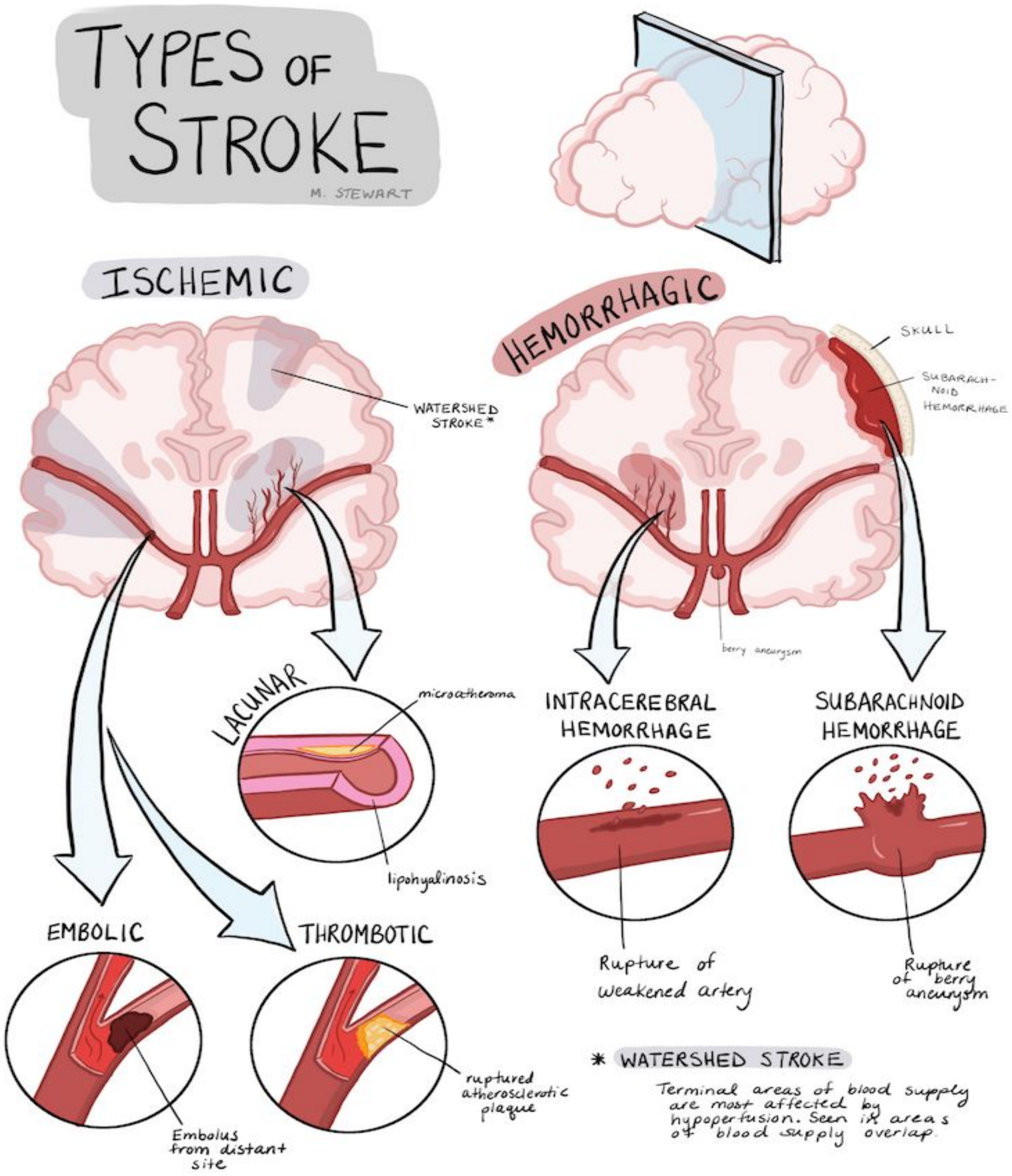



**Figure 22-12**

### BOX 22-5: CLINICAL RELEVANCE

Endothelin-1 receptor antagonists (Bosentan) are used in the treatment of pulmonary hypertension. Inhibition of these receptors prevents pulmonary vasculature constriction and thus decreases pulmonary vascular resistance.

## FOOTNOTES

1. "contrecoup phenomenon" When a blow to the head is extremely severe, it is likely to damage the opposite side. And that's due to the fluid shifting to the opposite side creating a vacuum of space in the cranial cavity (as the brain lags). And then as the acceleration stops, it collapses leaving the brain to *strike* the inner surface of the skull causing a bruises or an injury.
2. Endothelin 1 (ET-1) is a potent vasoconstrictor that is produced by vascular endothelial cells.

If the middle cerebral artery is blocked on the left side of the brain, the person is likely to become:

1. Totally demented because of lost function in Wernicke's speech comprehension area in the left cerebral hemisphere
2. Unable to speak words because of loss of Broca's motor area for word formation.
3. 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.
4. Blockage of a posterior cerebral artery will cause infarction of the occipital pole on the same side, which causes loss of vision as ( hemianopsia).

## INFARCTION

Tissue death (necrosis) due to inadequate blood supply to the affected area.

## DEMENTIA [1]

The main clinical feature is a gradual loss of memory and intellectual capacity. Loss of motor function in limbs & incontinence can also occur.

## FAINTING

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

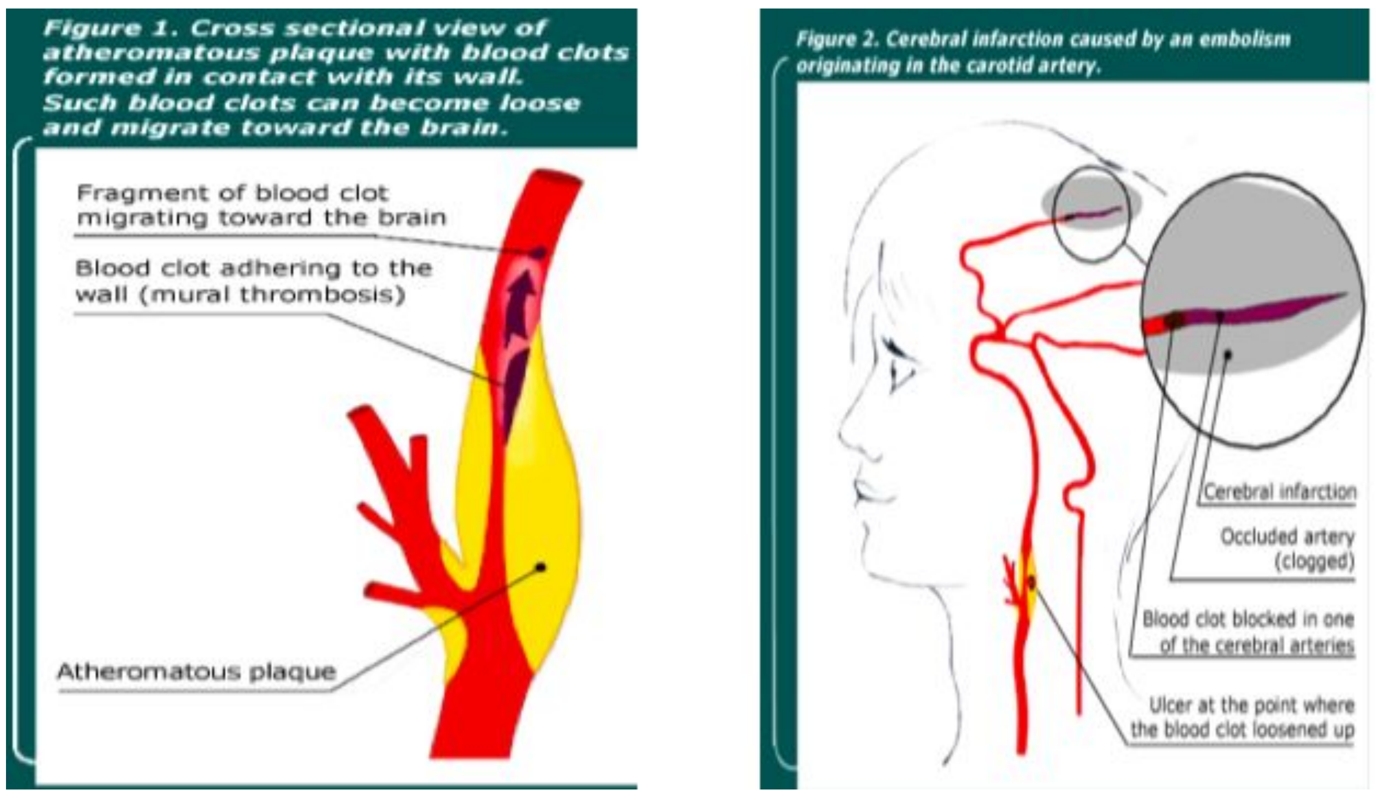



Figure 22-13

Effect of ICP changes on systemic blood pressure:

- Cushing reflex:'Normally, the ICP [Intracranial Pressure] ranges 1 - 15 mm Hg'. ( other sources: 8 - 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 causing **blood pressure rises (To overcome the ICP).**

## CEREBROSPINAL FLUID

This fluid is 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.

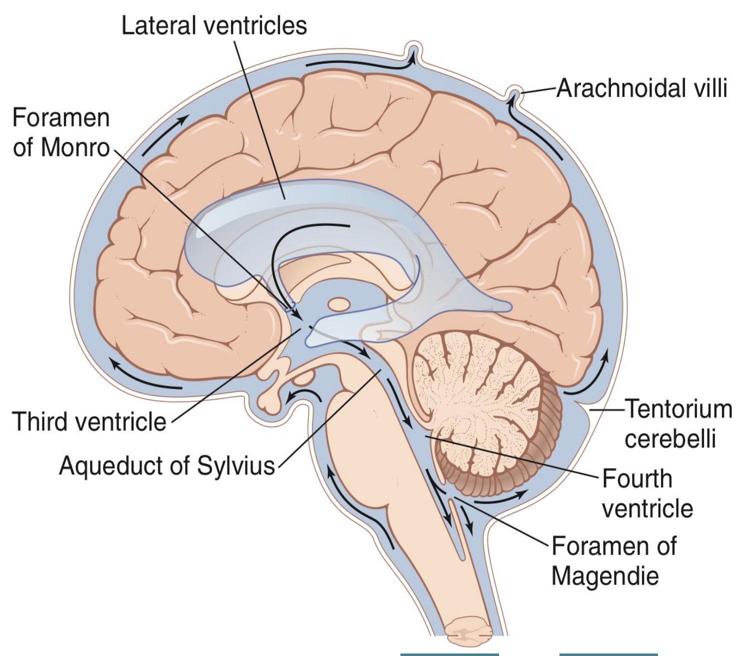



Figure 22-14

FOOTNOTES

1. **Dementia** can result from ***repeated episodes of small strokes*** produce progressive damage to the brain over a period of time.

## CSF

- Volume: **150 ml**
- Rate of production: **500 ml/day**[1]
- Lumbar CSF pressure: **70-180 mmhg**

Absorption of CSF 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.

## FUNCTION

1. Protective function (cushioning): In air brain weight =1400 gm, but in its water bath of CSF, brain weight = 50 gm, making it suspended and floated effectively.
2. Facilitation of pulsatile cerebral blood flow. So blood vessel don't get compressed by bones.
3. Distribution of peptides, hormones, neuroendocrine factors and other nutrients and essential substances to cells of the body
4. Wash away waste products.

## BOX 22-6: GUYTON AND HALL

**Regulation of Cerebrospinal Fluid Pressure by the Arachnoidal Villi.**
- The arachnoidal villi function like "valves" that allow cerebrospinal fluid and its contents to low readily into the blood of the venous sinuses while not allowing blood to flow backward in the opposite direction.
- In disease states, the villi sometimes become blocked by large particulate matter, by fibrosis, or by excesses of blood cells that have leaked into the cerebrospinal fluid.

## COMPOSITION

| Subc. | CSF | Plasma |
|---|---|---|
| Na+ | 147 | 150 |
| K+ | 2.9 | 4.6 |
| HCO3- | 25 | 24.8 |
| PCO2 | 50 | 39.5 |
| pH | 7.33 | 7.4 |
| Osm | 289 | 289 |
| Glu | 64 | 100 |

The composition of CSF is nearly the same as brain ECF:

- Osmotic pressure is ~ equal to that of plasma.
- Na ion concentration is ~ equal to that of plasma.
- Cl ion is about 15 % greater than in plasma.
- K ion is ~ 40 % less.
- glucose about 30 % less.

*The tables isn't important but these are highly important.*

## FOOTNOTES

1. 350ml get reabsorbed.

## SUMMARY

## REGULATION OF CEREBRAL BLOOD FLOW

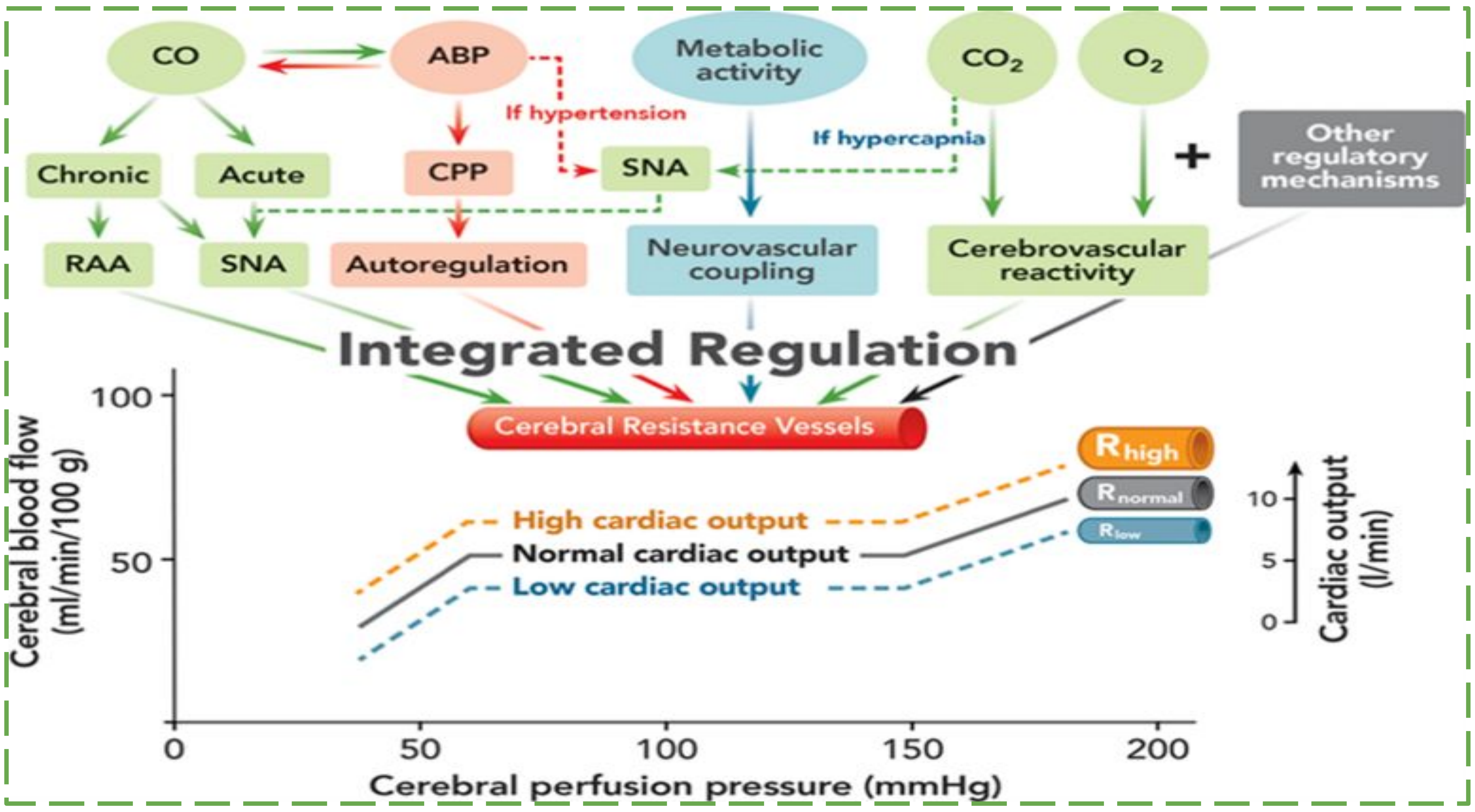



**Figure 22-15** Cardiac output (CO); Sympathetic nervous activity (SNA);Renin–angiotensin–aldosterone (RAA) system; Arterial blood pressure (ABP); Cerebral perfusion pressure (CPP); Carbon dioxide (CO2) and oxygen (O2) (R) Cerebral resistance vessels at high ($R_{high}$), normal ($R_{normal}$), and low ($R_{low}$)

**REGULATION OF CEREBRAL BLOOD FLOW**

### 1 Myogenic/Pressure Autoregulation

- ↓ BP → arteriolar dilation
- ↑ BP → arteriolar constriction
- Autoregulation is present from 60-150 mmHg
- 60 mmHg → most dilated condition
- 150 mmHg → most constructed condition
- below 60 mmHg → CBF become severely decreased

### 2 Metabolic Autoregulation

- ↑ $CO_2$ → vasodilation → ↑ CBF
- ↓ pH = ↑ H ions = ↑ acidity → vasodilation → ↑ CBF
- Hypoxia = low oxygen → vasodilation → ↑ CBF
- High levels of oxygen → vasoconstriction
- Nitric oxide & adenosine are autoregulation mediators

### 3 Neurogenic Autoregulation

- Sympathetic
  - Acute hypertension → constriction of large-intermediate arteries → ↑ CBF
  - Prevent vascular hemorrhages & cerebral stroke from occurrence

## Values

- ❖ Normal rate of CBF = 50-65 ml/100 grams of brain tissue/min
- ❖ Normal rate of CBF for entire brain = 750-900 ml/min = 15% of the resting cardiac output
- ❖ CBF = 18-20 ml/100 grams of brain tissue/min → Ischemia
- ❖ CBF < 8-10 ml/100 grams of brain tissue/min → Tissue death
- ❖ Cerebral perfusion pressure (CPP) = 70-90 mmHg
- ❖ Rate of oxygen utilization = 3.5 (+/- 0.2) ml of O2/100 grams of brain tissue/min
- ❖ Normal PO2 = 35-40 mmHg
- ❖ PO2 < 30 mmHg → autoregulation (↑ CBF)
- ❖ PO2 < 20 mmHg → brain function derangement
- ❖ ICP = 1-15 mmHg
- ❖ CSF volume = 150 ml
- ❖ Rate of CSF production = 500 ml/day
- ❖ Lumbar CSF pressure = 70-180 mmHg
- ❖ At pressure of 112 mmHg → filtration & absorption are equal
- ❖ < 68 mmHg → CSF absorption stops
- ❖ Air brain weight = 1400 gm, brain water bathed in CSF weight = 50 gm

# QUIZ

MEDICINE438's CNS PHYSIOLOGY

1. Cognitive stimuli such as reading, problem solving, and talking all result in significant increases in cerebral blood flow. Which set of changes in cerebral tissue concentrations is the most likely explanation for the increase in cerebral blood flow?

| | CO2 | pH | Adenosine |
|---|---|---|---|
| A) | ↑ | ↑ | ↑ |
| B) | ↑ | ↓ | ↑ |
| C) | ↑ | ↓ | ↓ |

ANSWER: **B,** Cognitive stimuli increase cerebral blood flow by decreasing cerebral vascular resistance. The diameter of cerebral vessels is decreased by various metabolic factors in response to cognitive stimuli. Metabolic factors that enhance cerebral blood flow include increases in carbon dioxide, hydrogen ion (decreased pH), and adenosine.

2. Which of the following would produce an increase in cerebral blood flow?

   A) Increase in carbon dioxide concentration
   B) Decrease in the activity of cerebral cortex neurons & Increase in oxygen concentration
   C) Decrease in carbon dioxide concentration
   D) Decrease in arterial blood pressure from 120 mm Hg to 90 mm Hg

**ANSWER: A,** The most potent stimulator of cerebral blood flow is a local increase in carbon dioxide concentration, followed in order by a decrease in oxygen concentration and an increase in local neuronal activity.

3. A left-side subdural hematoma develops in a 23-year-old man after an automobile accident. Physical examination shows papilledema 3 days after the accident. Which of the following is most likely to be increased in this patient?

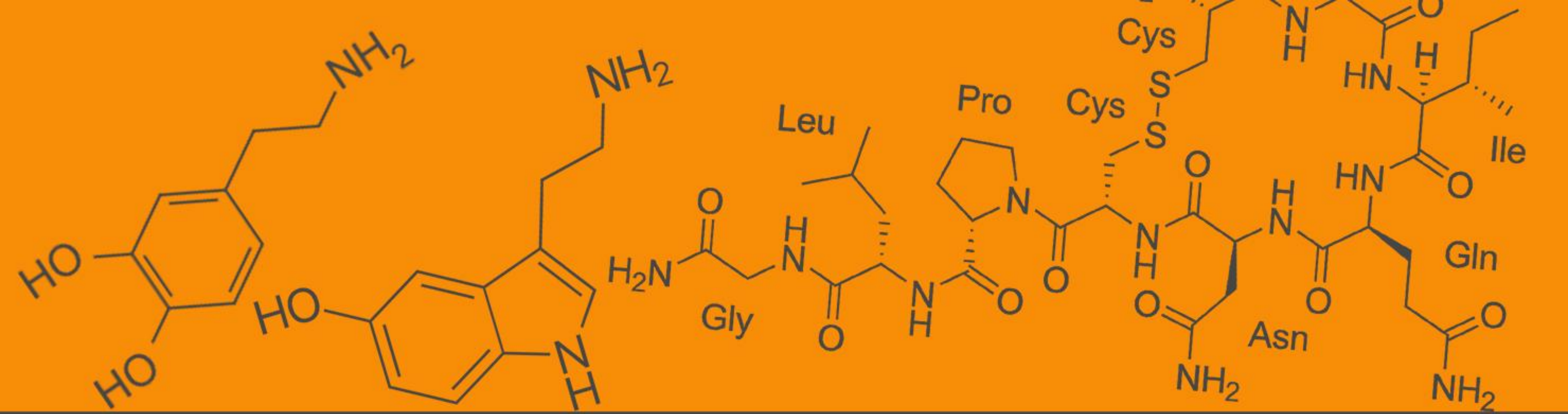
   A) Cerebral blood flow
   B) Cerebrospinal fluid production
   C) Cerebrospinal fluid volume
   D) Intracranial pressure

**ANSWER: D,** A subdural hematoma can lead to increased intracranial pressure because it takes up space in the cranium; papilledema (optic disc swelling) suggests an increase in intracranial pressure. The increase in intracranial pressure does not affect production of CSF, but it may cause decreased CSF volume because the high pressure pushes CSF into venous blood through the arachnoid villi and also compresses the volume of brain structures that contain CSF. Cerebral blood flow should remain normal with small increases in intracranial pressure, but larger increases can decrease cerebral blood flow.

## SHORT ANSWER QUESTIONS

1. What are the four main arteries that supply the brain?
2. Give 3 examples of molecules that can NOT penetrate into the brain?

1) Vertebral (left & right), internal carotid (left & right) arteries
2) Proteins, antibodies & non-lipid soluble large molecules

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## REFERENCES

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