CEREBRAL METABOLISM

CEREBRAL BLOOD FLOW

INTRACRANIAL PRESSURE

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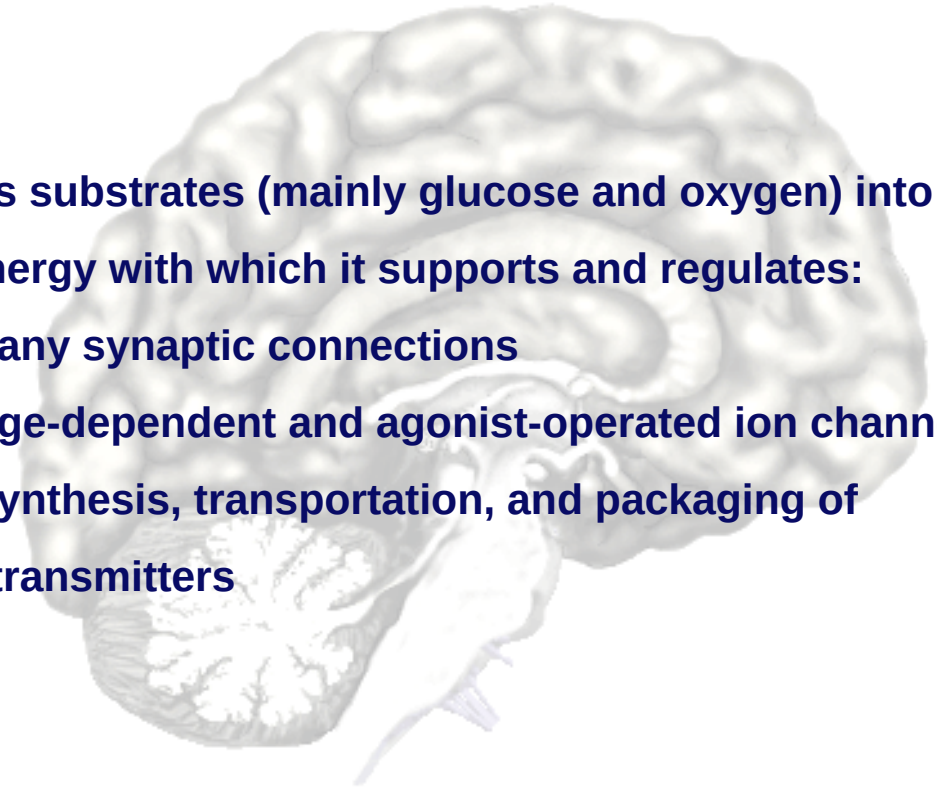
CEREBRAL METABOLISM

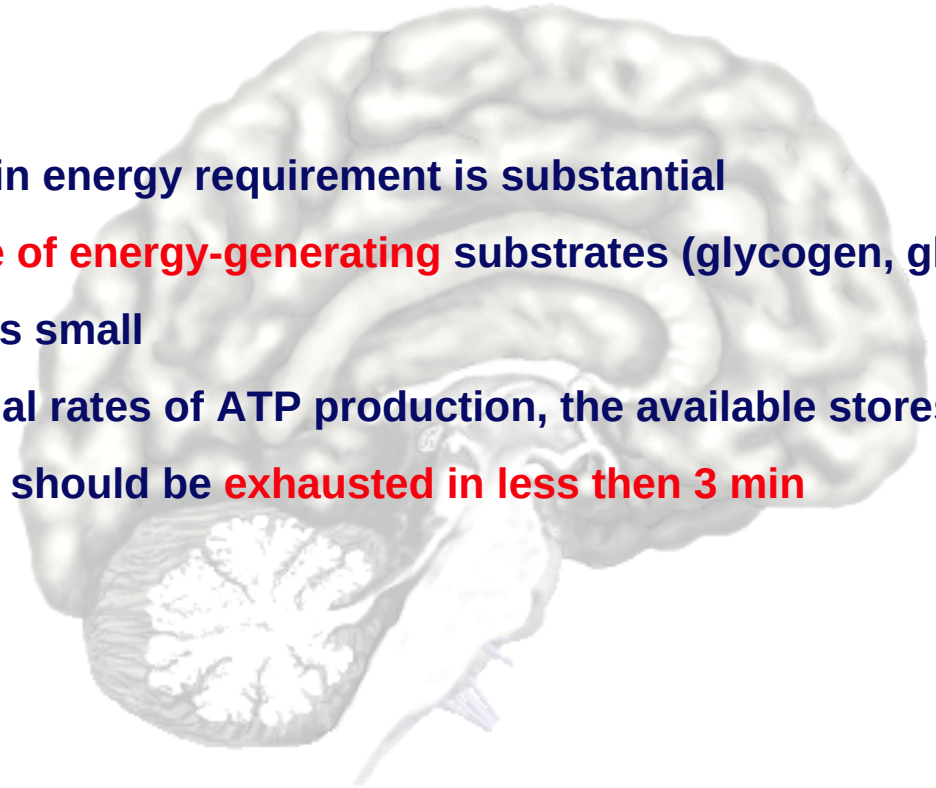
THE BRAIN AS A CONVERTER OF ENERGY



• It converts substrates (mainly glucose and oxygen) into the usable forms of energy with which it supports and regulates:

- **its many synaptic connections**
- **voltage-dependent and agonist-operated ion channels**
- **the synthesis, transportation, and packaging of neurotransmitters**

CEREBRAL METABOLISM



- **The brain energy requirement is substantial**
- **Its store of energy-generating substrates (glycogen, glucose, oxygen) is small**
- **At normal rates of ATP production, the available stores of glycogen should be exhausted in less then 3 min**

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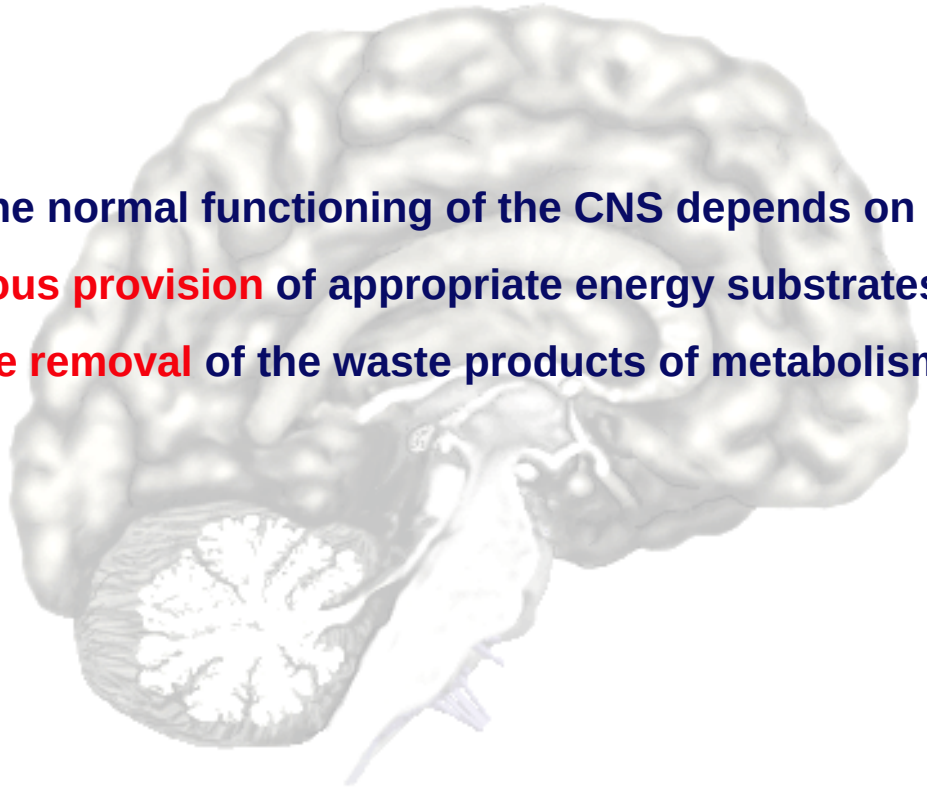

• **Thus the normal functioning of the CNS depends on the continuous provision of appropriate energy substrates and the adequate removal of the waste products of metabolism**

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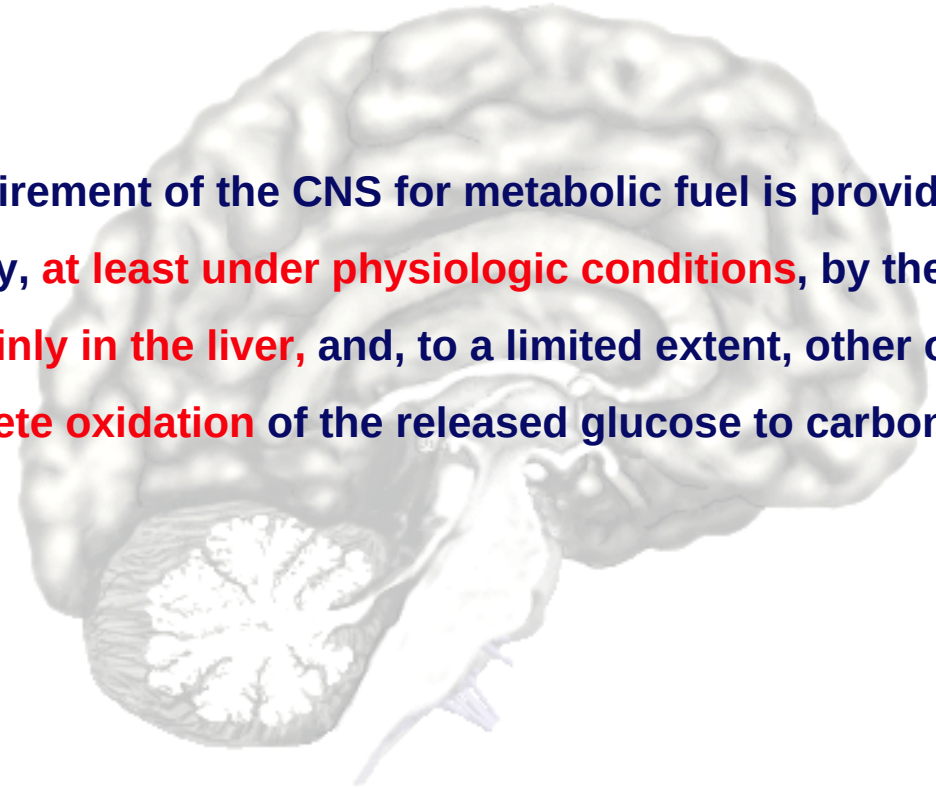

• **The requirement of the CNS for metabolic fuel is provided almost exclusively, at least under physiologic conditions, by the glycogen stored mainly in the liver, and, to a limited extent, other organs and the complete oxidation of the released glucose to carbon dioxide and water**

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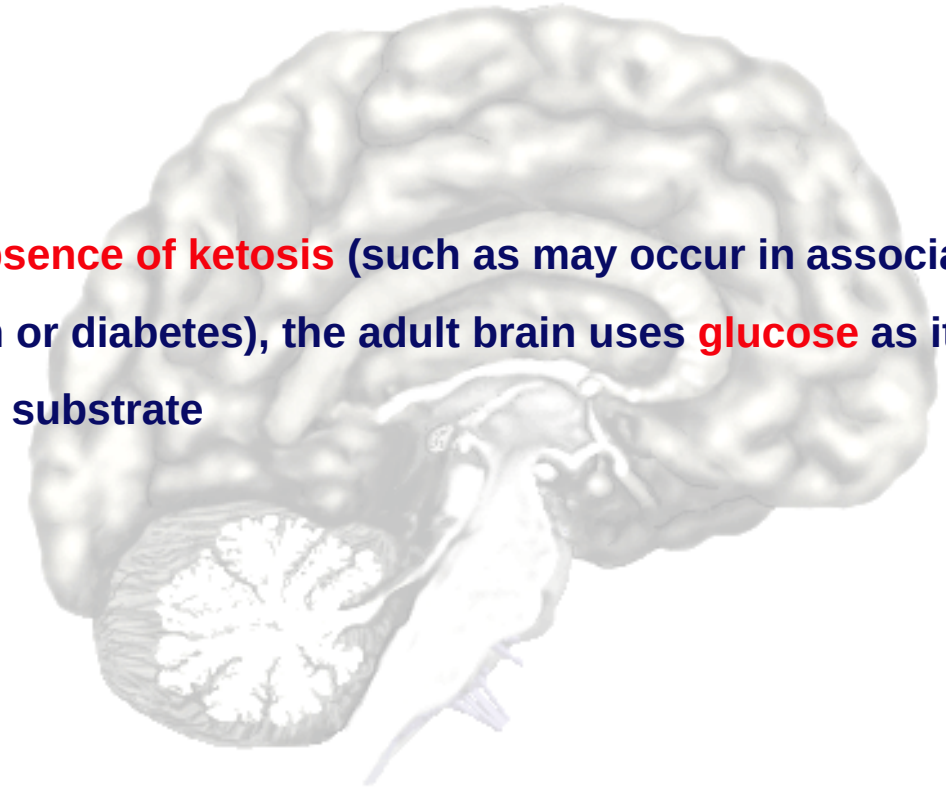

• In the absence of ketosis (such as may occur in association with starvation or diabetes), the adult brain uses glucose as its sole metabolic substrate

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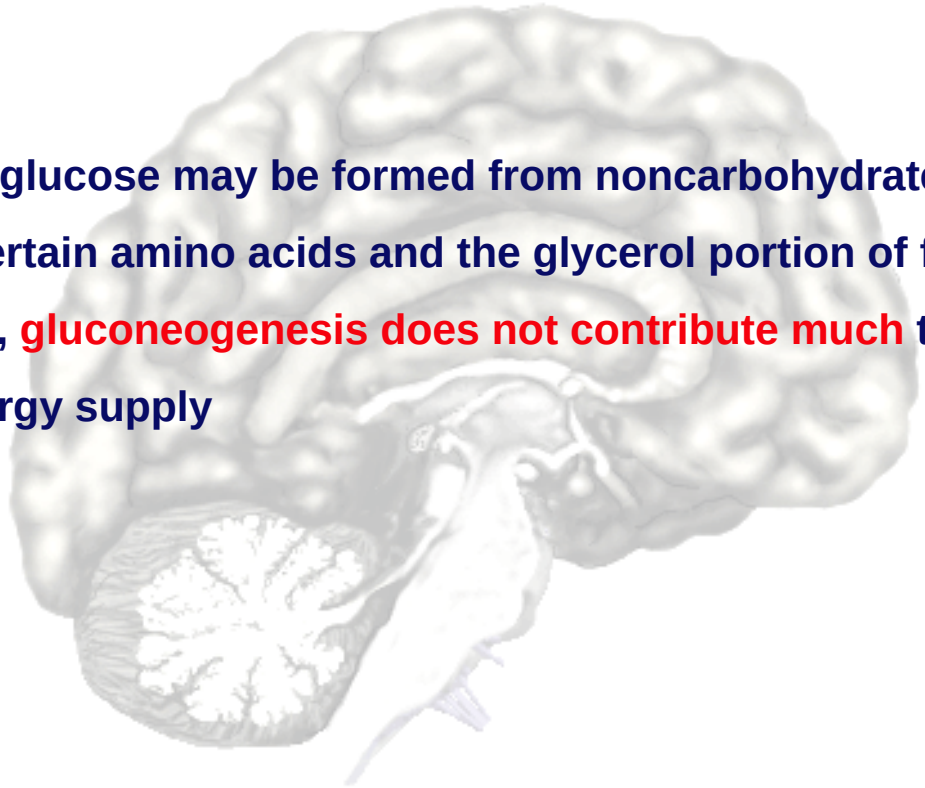

- **Although glucose may be formed from noncarbohydrate sources (such as certain amino acids and the glycerol portion of fat molecules), gluconeogenesis does not contribute much to the brain's energy supply**

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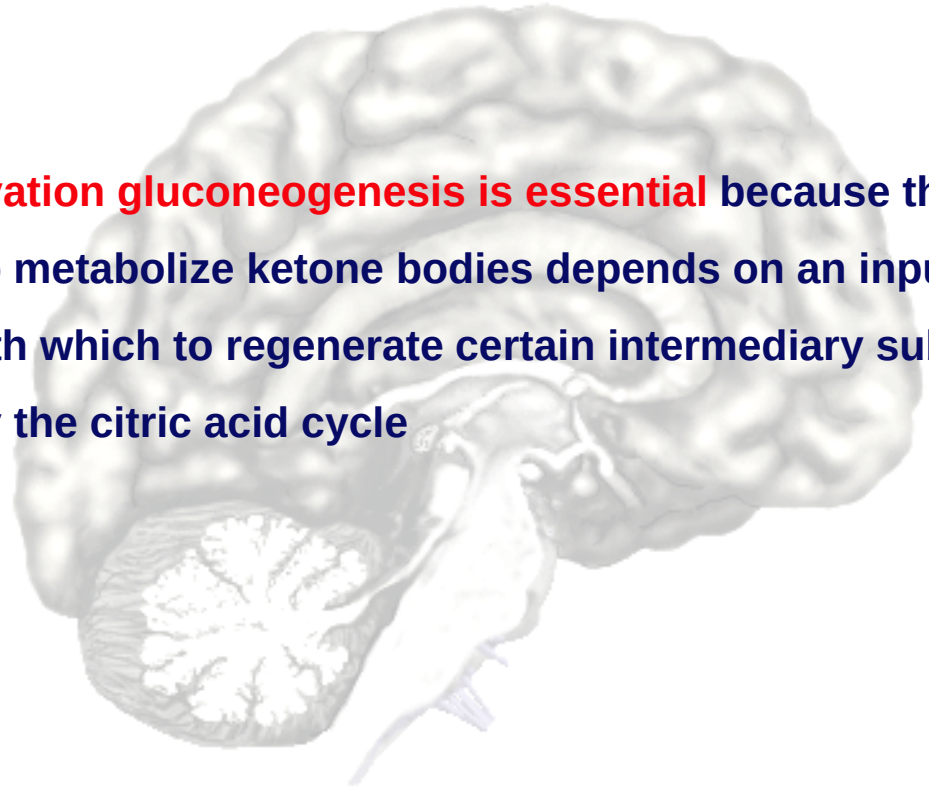

• **With starvation gluconeogenesis is essential because the ability of the brain to metabolize ketone bodies depends on an input of glucose with which to regenerate certain intermediary substrates required by the citric acid cycle**

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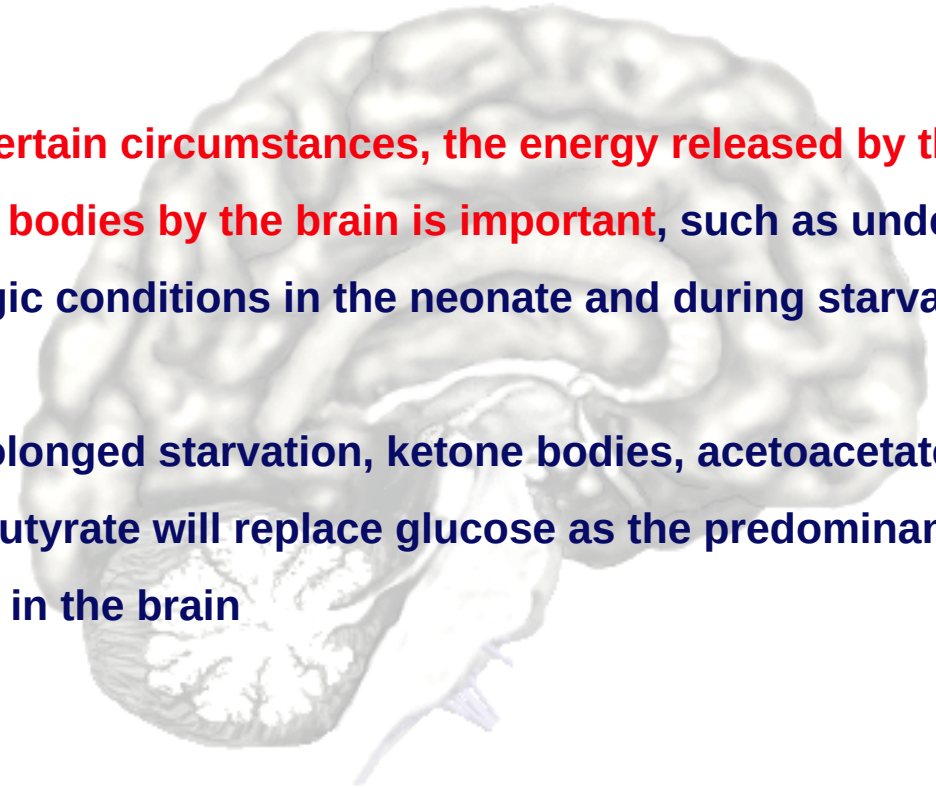

- **Under certain circumstances, the energy released by the oxidation of ketone bodies by the brain is important, such as under physiologic conditions in the neonate and during starvation in the adult**
- **With prolonged starvation, ketone bodies, acetoacetate, and beta-hydroxybutyrate will replace glucose as the predominant metabolic substrate in the brain**

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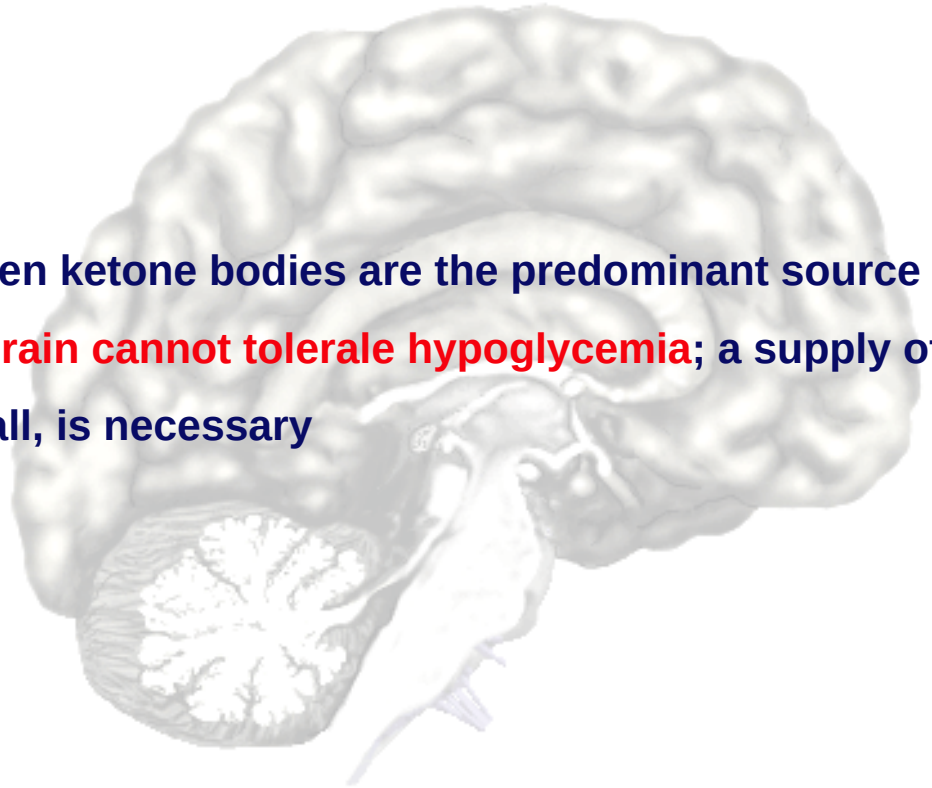

- **Even when ketone bodies are the predominant source of metabolic fuel, the brain cannot tolerale hypoglycemia; a supply of glucose, albeit small, is necessary**

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GLYCOLYSIS

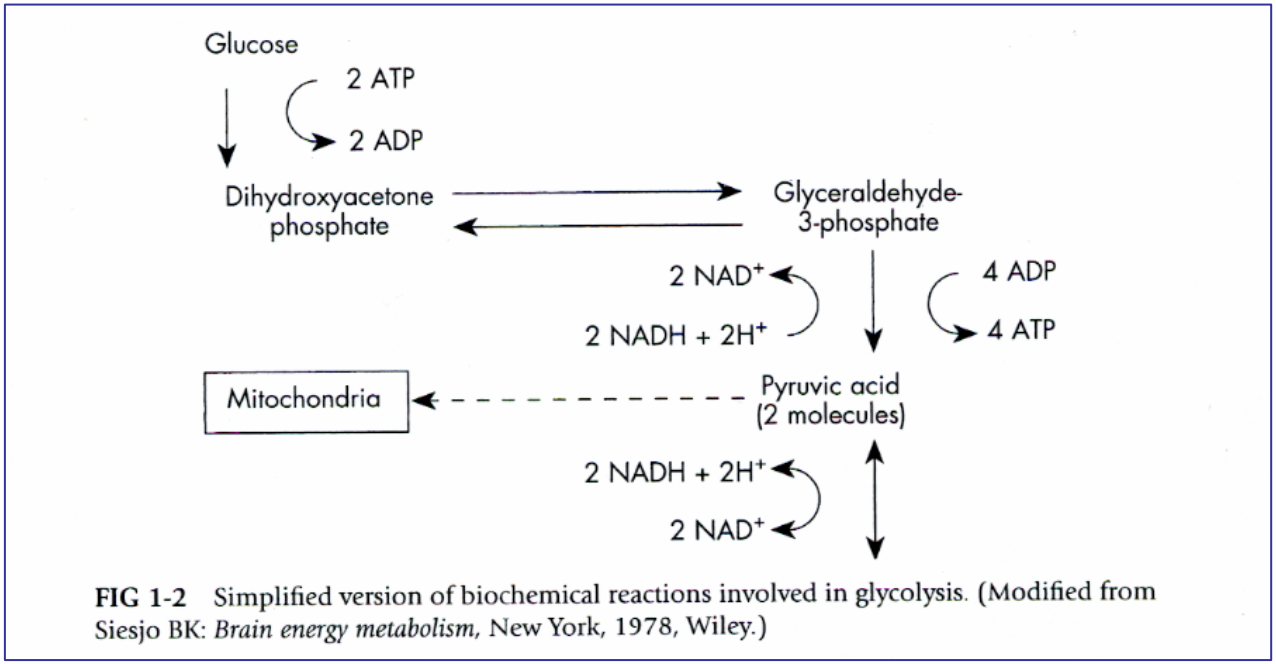

FIG 1-2 Simplified version of biochemical reactions involved in glycolysis. (Modified from Siesjo BK: *Brain energy metabolism*, New York, 1978, Wiley.)

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CITRIC ACID CYCLE

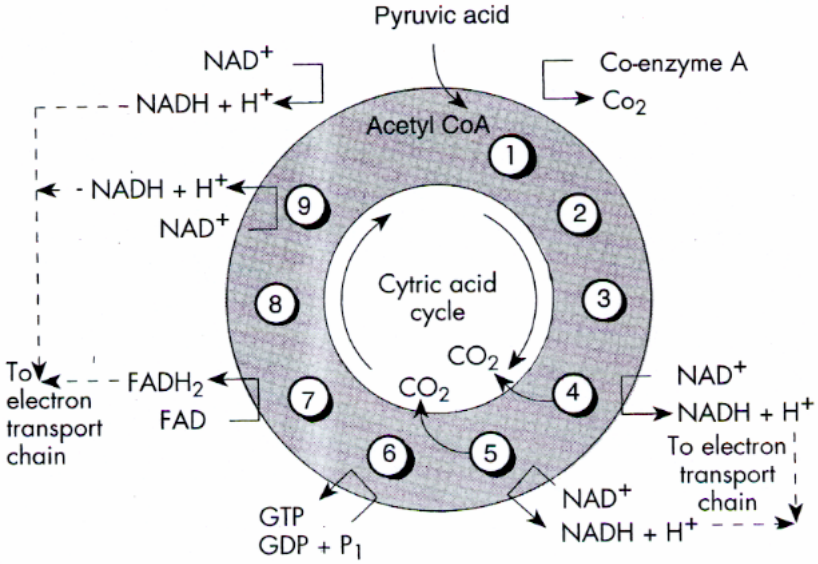

FIG. 1-3 Simplified version of biochemical reactions involved in citric acid cycle. (Modified from Siesjo BK: *Brain energy metabolism*, New York, 1978, Wiley.)

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ELECTRON TRANSPORT CHAIN

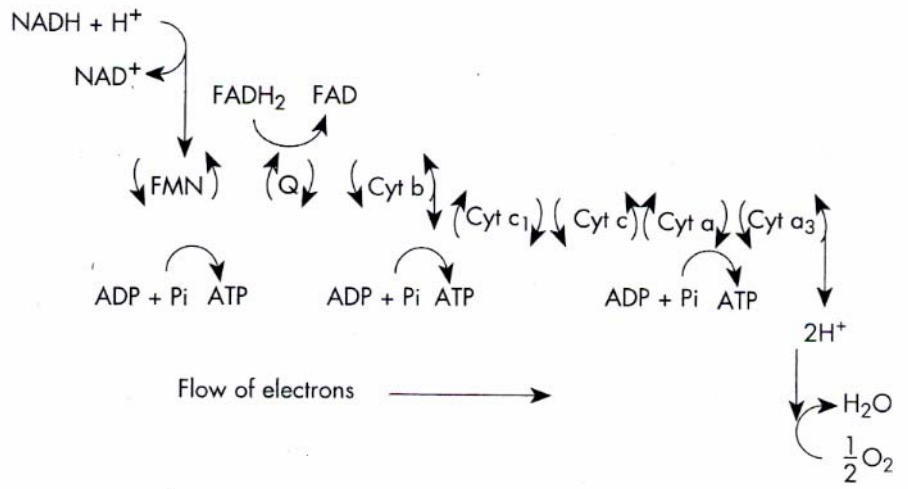

FIG. 1-4 Simplified version of reactions involved in electron transport chain. (Modified from Siesjo BK: *Brain energy metabolism*, New York, 1978, Wiley; Siesjo BK: Cerebral circulation and metabolism, *J Neurosurg* 60:883-908, 1984.)

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TABLE 1-1
Summary of ATP Production (Aerobic Metabolism) from One Molecule of Glucose

Source	Yield of ATP
Glycolysis	
Oxidation of glucose to pyruvic acid	2
Krebs cycle	
Oxidation of succinyl CoA to succinic acid	2 (GTP)
Electron transport chain	
1. 2 Nicotinamide adenine dinucleotide (NADH) + 2 H^+ (glycolysis)	6
2. 2 NADH + 2 H^+ (acetyl CoA)	6
3. 6 NADH + 6 H^+ (Krebs cycle)	18
4. 2 Flavin adenine dinucleotide ($FADH_2$)	4
TOTAL	38

Because the citric acid cycle, and the electron transport chain are *aerobic* processes (and yield 17 to 18 times as much ATP as glycolysis alone), *anaerobic* metabolism clearly cannot satisfy the energy requirements of the brain

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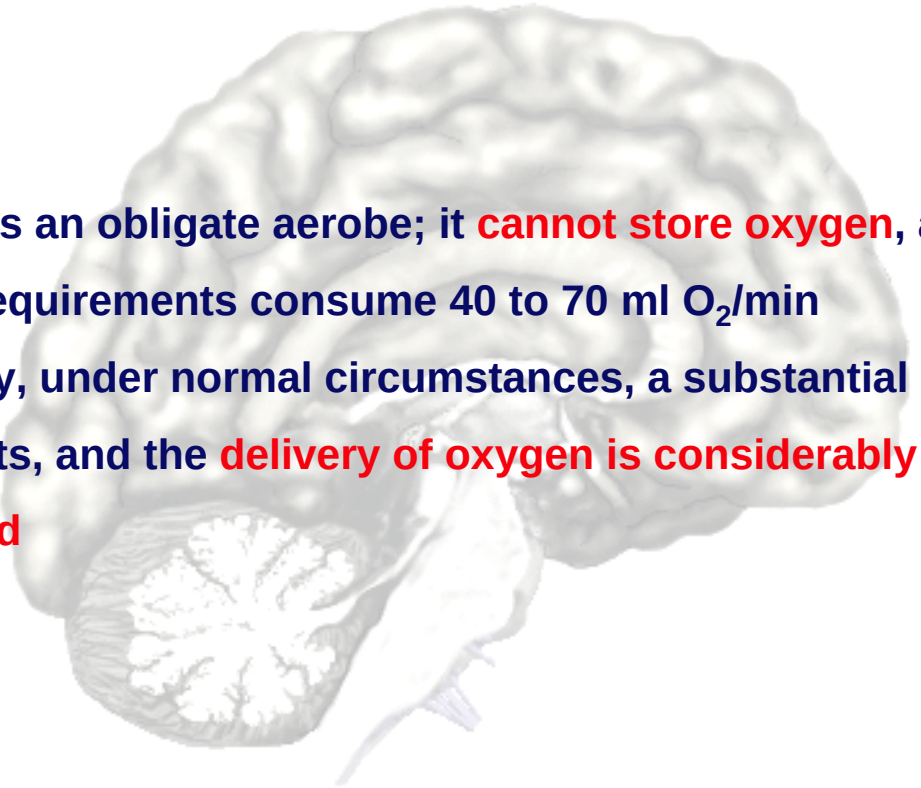

- **The brain is an obligate aerobe; it cannot store oxygen, and its high metabolic requirements consume 40 to 70 ml O_2/min**
- **Fortunately, under normal circumstances, a substantial safe margin exists, and the delivery of oxygen is considerably greater than demand**

CEREBRAL METABOLISM

BOX 1-1
SUMMARY OF BALANCE BETWEEN DEMAND FOR AND DELIVERY OF OXYGEN UNDER PHYSIOLOGIC CONDITIONS

Demand for Oxygen

3-5 ml per 100 g brain tissue per minute
(i.e., 40-70 ml/min)

Delivery of Oxygen

20 ml per 100 ml blood
50 ml blood per 100 g brain tissue per minute
(i.e., 150 ml/min)

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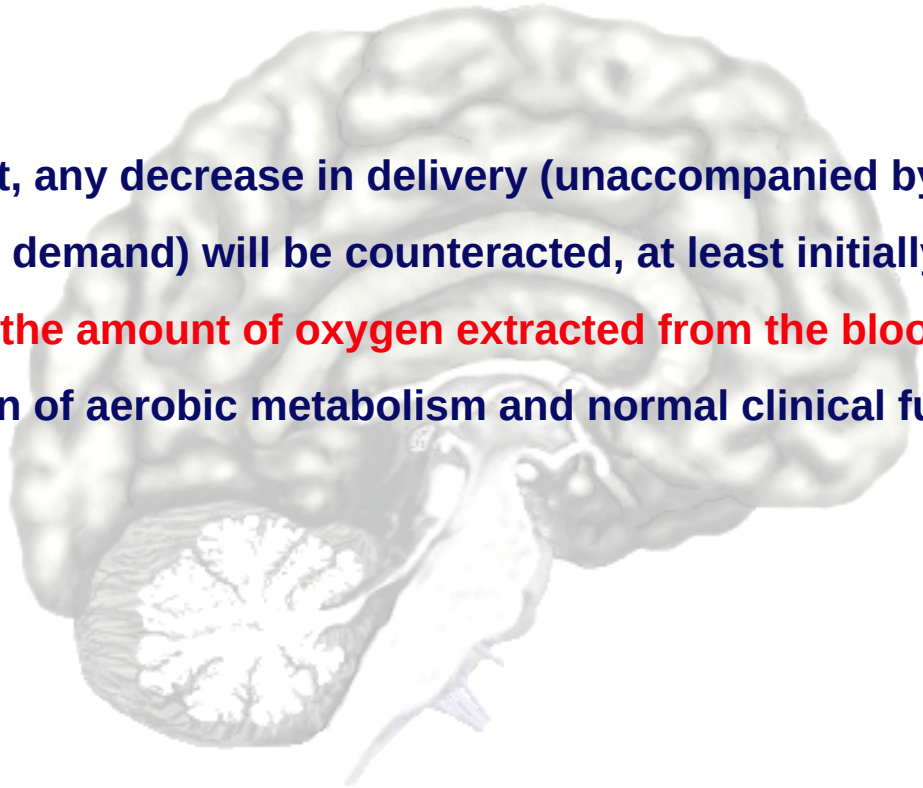
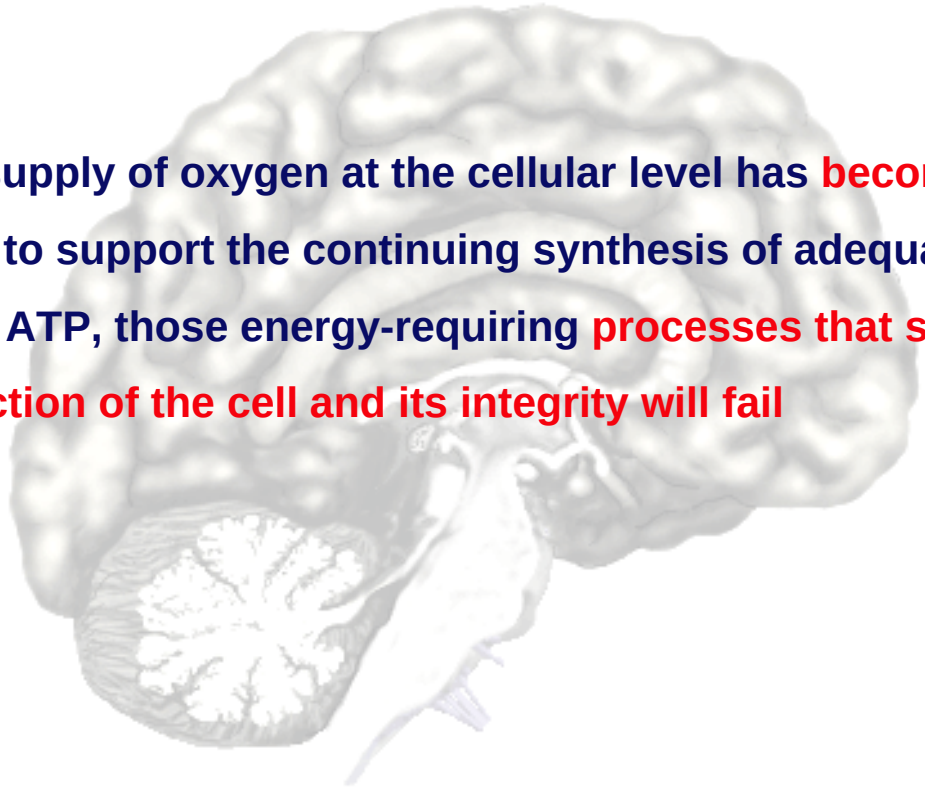


- **As a result, any decrease in delivery (unaccompanied by any decrease in demand) will be counteracted, at least initially, by an increase in the amount of oxygen extracted from the blood, with the preservation of aerobic metabolism and normal clinical function**

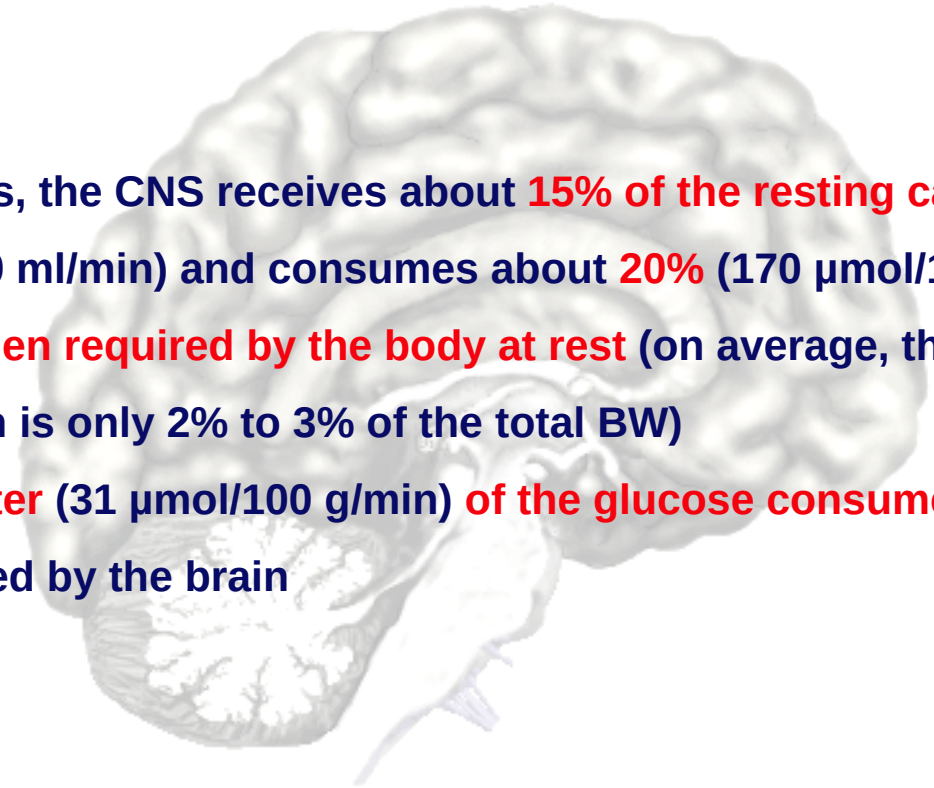
CEREBRAL METABOLISM



- **After the supply of oxygen at the cellular level has become insufficient to support the continuing synthesis of adequate amounts of ATP, those energy-requiring processes that sustain the normal function of the cell and its integrity will fail**

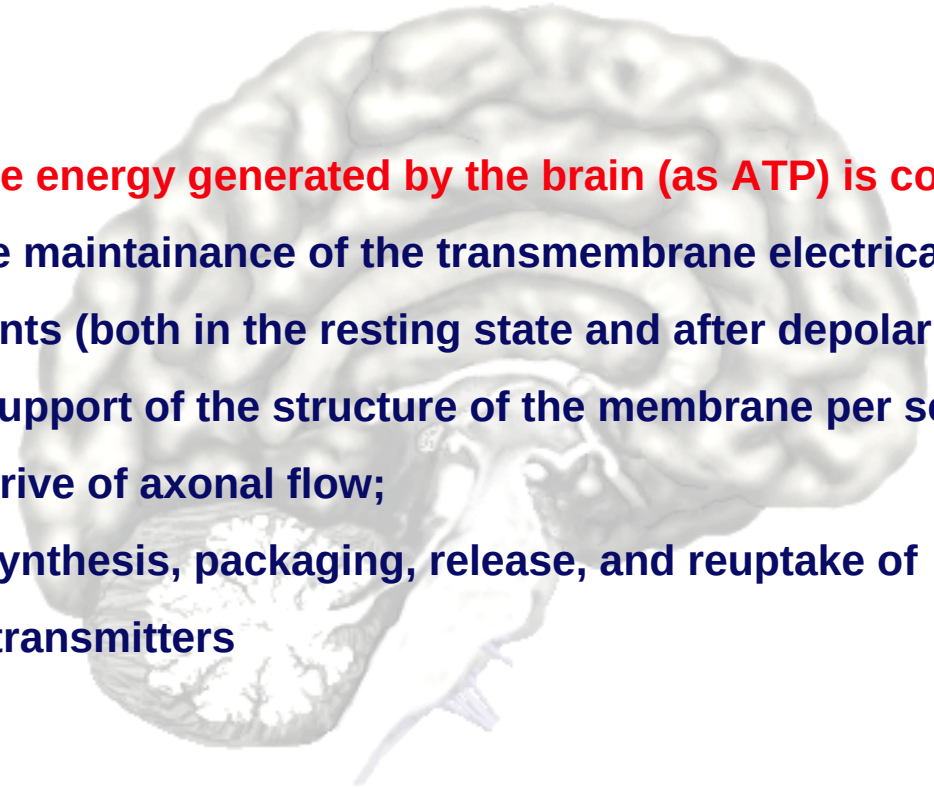
CEREBRAL METABOLISM

THE BRAIN AS A CONSUMER OF ENERGY



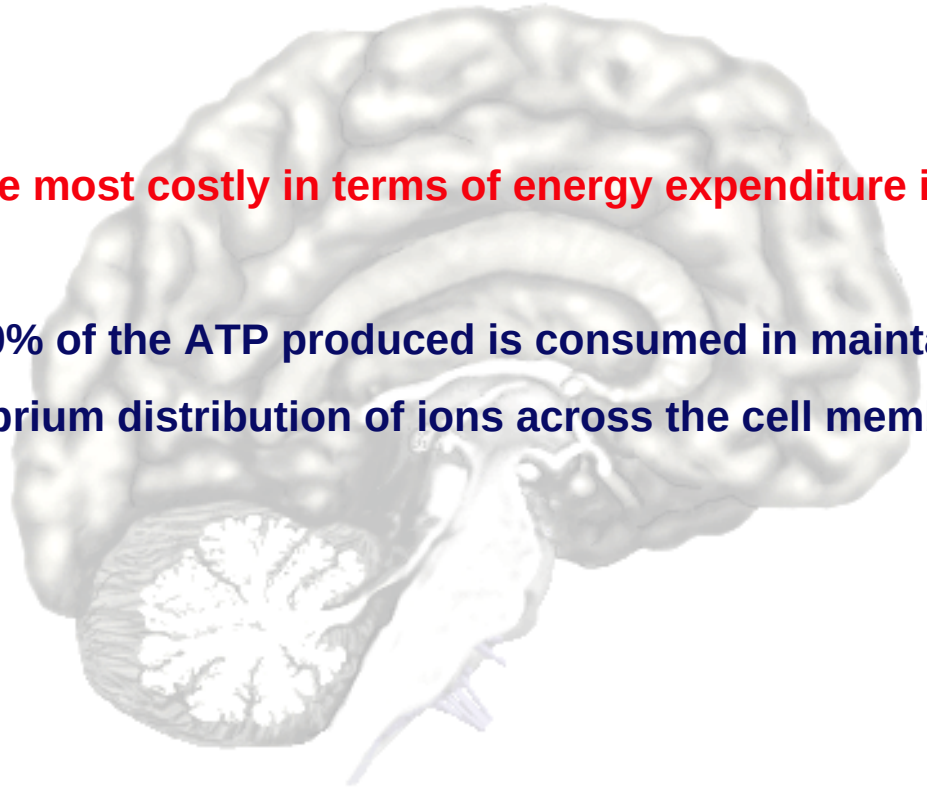
- **In humans, the CNS receives about 15% of the resting cardiac output (750 ml/min) and consumes about 20% (170 µmol/100 g/min) of the oxygen required by the body at rest (on average, the weight of the brain is only 2% to 3% of the total BW)**
- **One quarter (31 µmol/100 g/min) of the glucose consumed by the body is used by the brain**

CEREBRAL METABOLISM



- **The usable energy generated by the brain (as ATP) is consumed**
  - **in the maintainance of the transmembrane electrical and ionic gradients (both in the resting state and after depolarization);**
  - **the support of the structure of the membrane per se;**
  - **the drive of axonal flow;**
  - **the synthesis, packaging, release, and reuptake of neurotransmitters**

CEREBRAL METABOLISM



- **By far the most costly in terms of energy expenditure is ion transport**
- **About 70% of the ATP produced is consumed in maintaining the nonequilibrium distribution of ions across the cell membrane**

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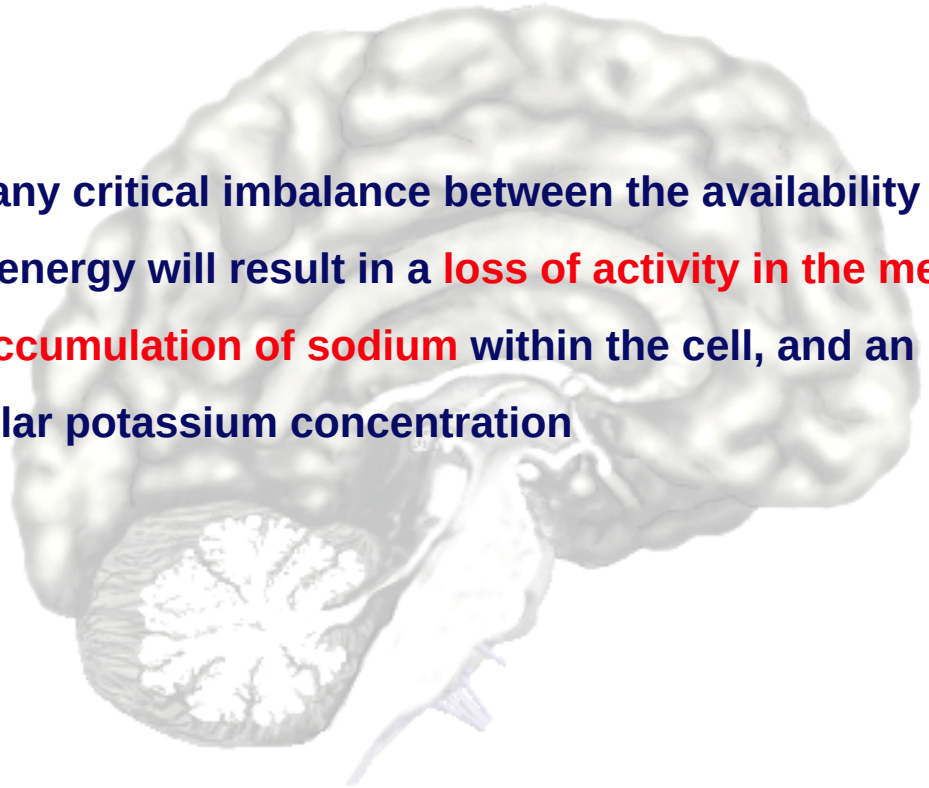

- **Therefore any critical imbalance between the availability of and the demand for energy will result in a loss of activity in the membrane pump, the accumulation of sodium within the cell, and an increase in extracellular potassium concentration**

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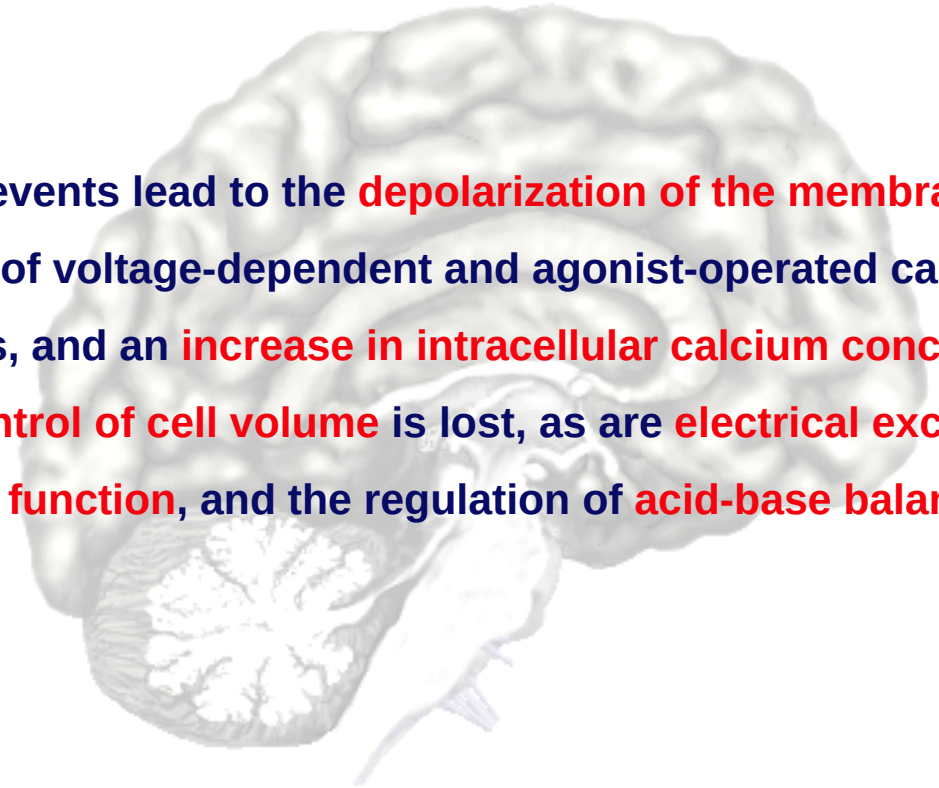
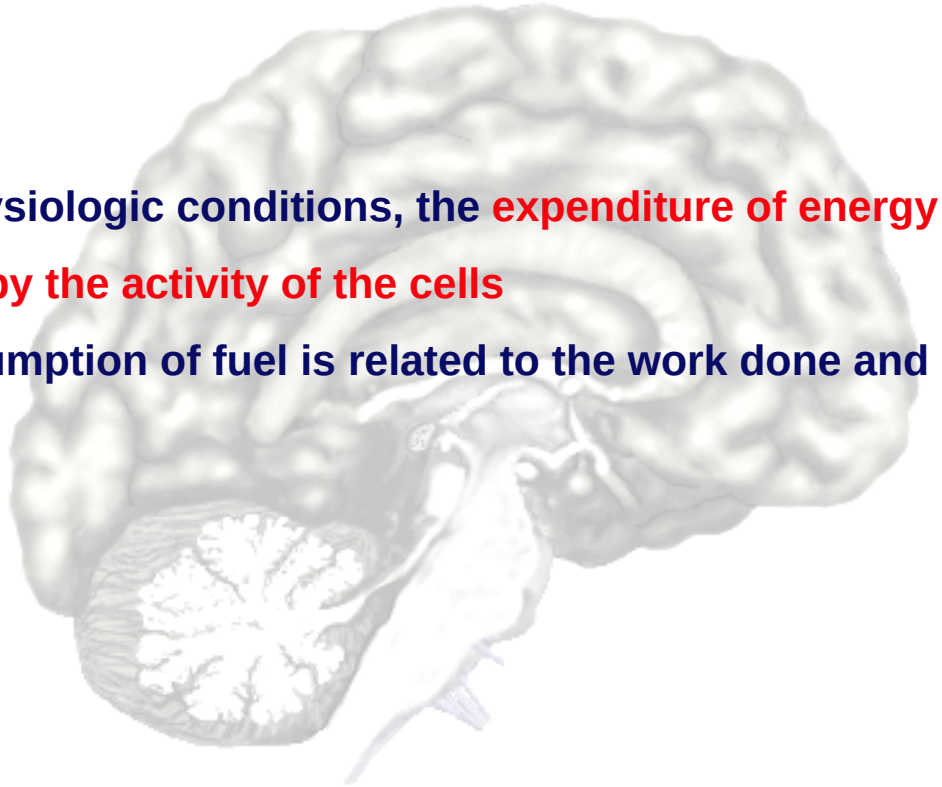


- These events lead to the depolarization of the membrane, the opening of voltage-dependent and agonist-operated calcium channels, and an increase in intracellular calcium concentration
- The control of cell volume is lost, as are electrical excitability, synaptic function, and the regulation of acid-base balance

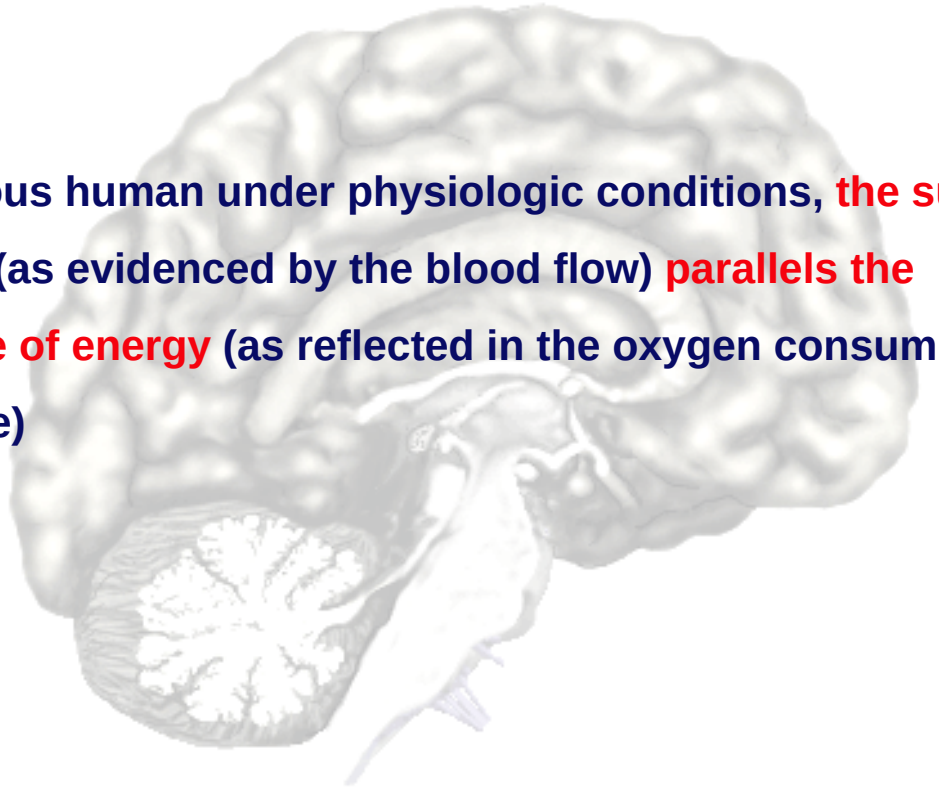
CEREBRAL METABOLISM

THE BRAIN AS A CONSERVER OF ENERGY



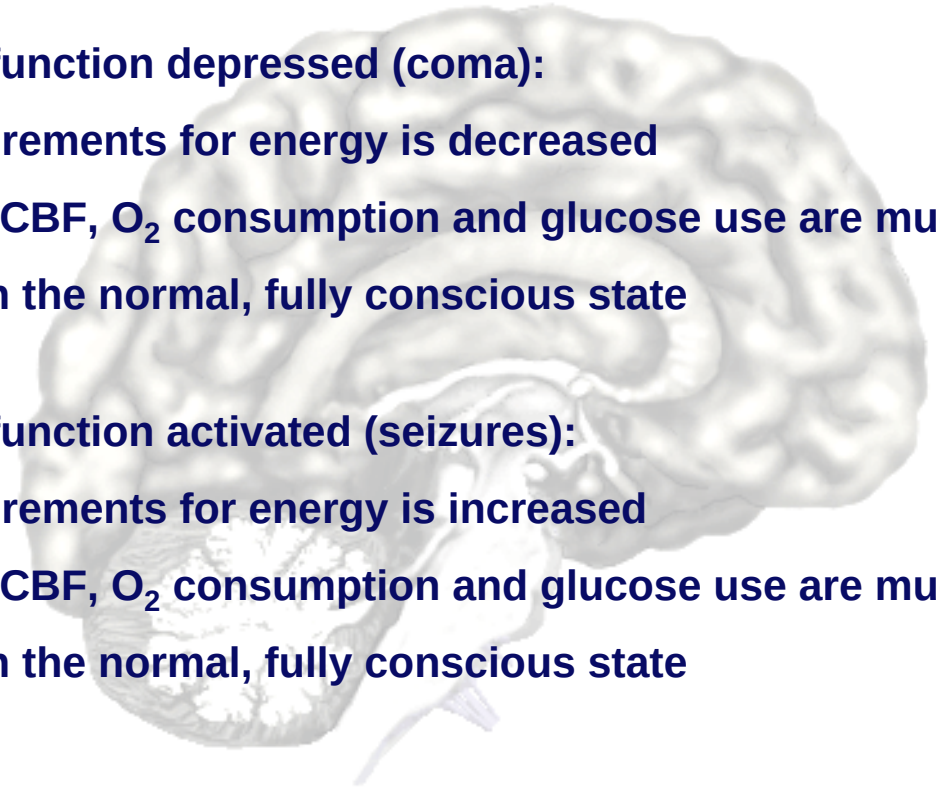
- **Under physiologic conditions, the expenditure of energy is controlled by the activity of the cells**
- **The consumption of fuel is related to the work done and not the reverse**

CEREBRAL METABOLISM



• **In conscious human under physiologic conditions, the supply of substrates (as evidenced by the blood flow) parallels the expenditure of energy (as reflected in the oxygen consumption and glucose use)**

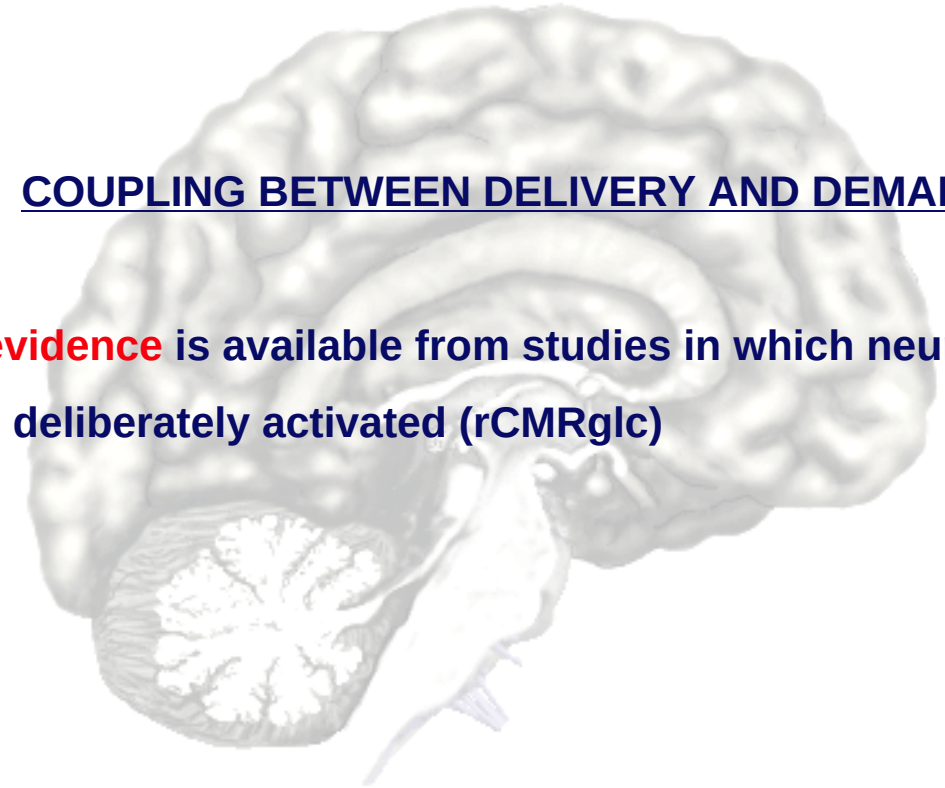
CEREBRAL METABOLISM



- **Cerebral function depressed (coma):**
  - **requirements for energy is decreased**
  - **total CBF, O_2 consumption and glucose use are much lower than in the normal, fully conscious state**

- **Cerebral function activated (seizures):**
  - **requirements for energy is increased**
  - **total CBF, O_2 consumption and glucose use are much higher than in the normal, fully conscious state**

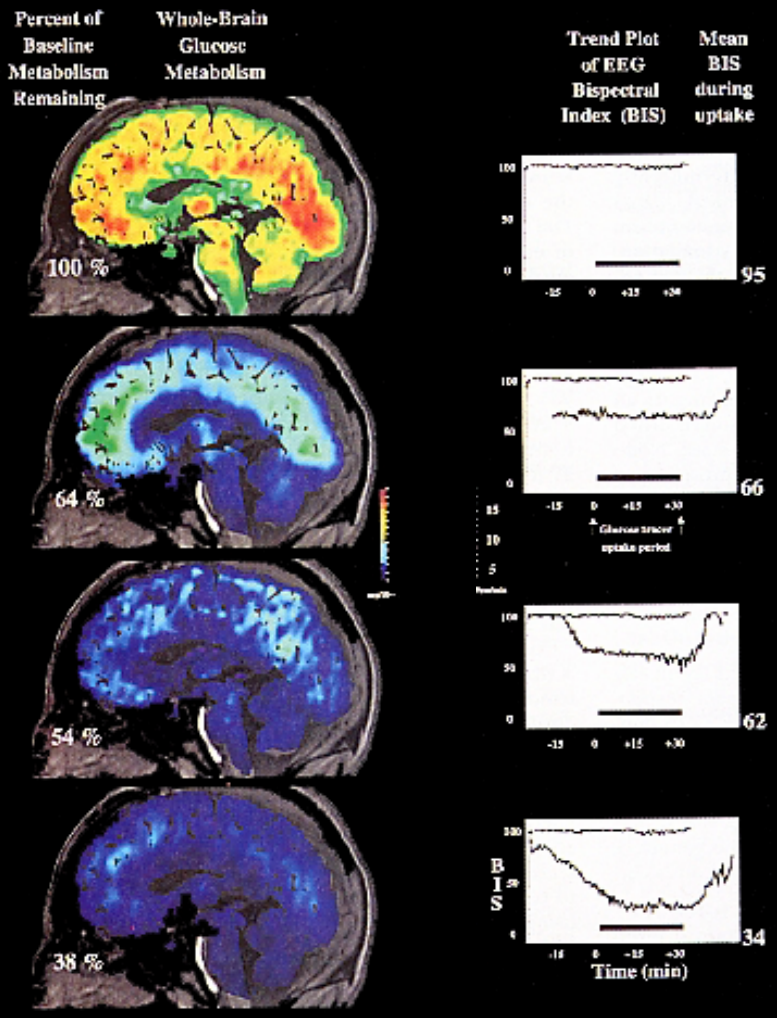
CEREBRAL METABOLISM

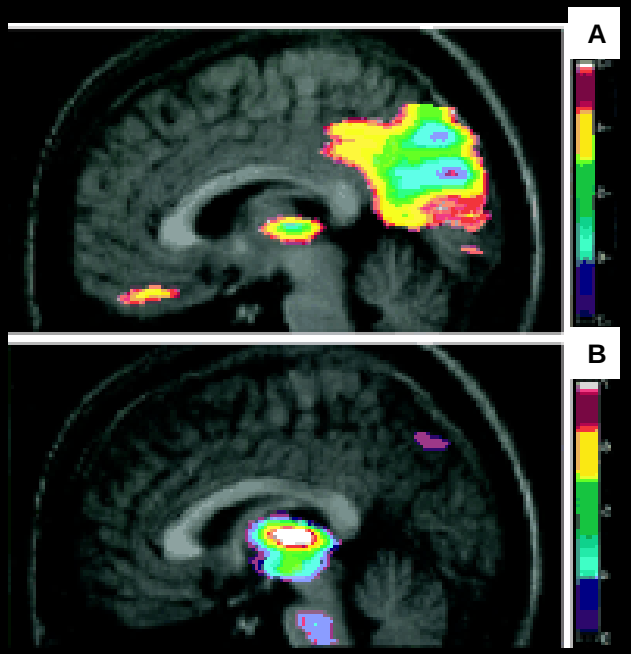


COUPLING BETWEEN DELIVERY AND DEMAND

- **Further evidence is available from studies in which neural pathways have been deliberately activated (rCMRglc)**

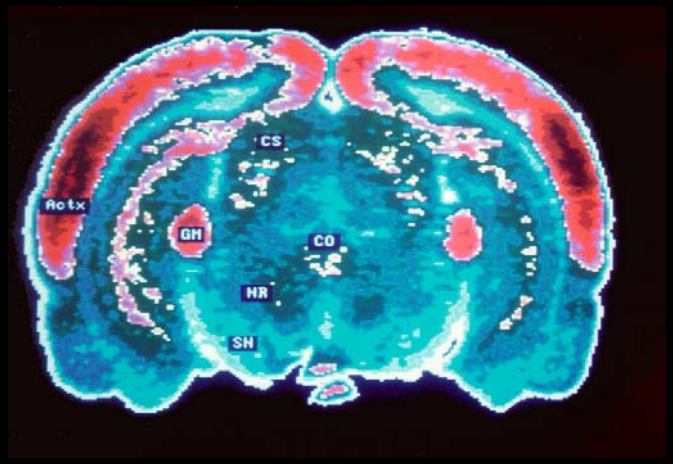
PROPOFOL



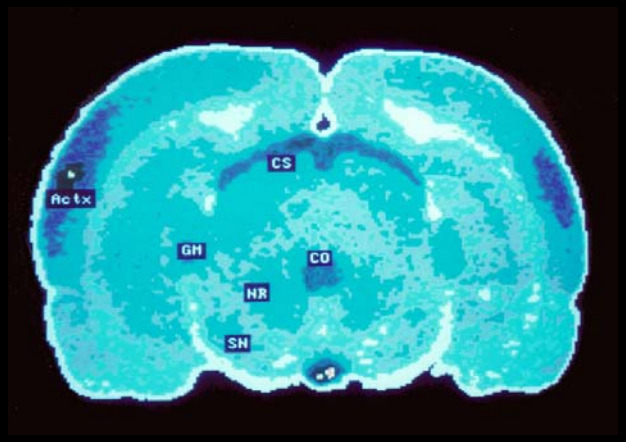


Alkire. Anesthesiology 89: 323, 1998
Fiset, Paus, Daloze, et al. J Neurosci 19: 5506, 1999

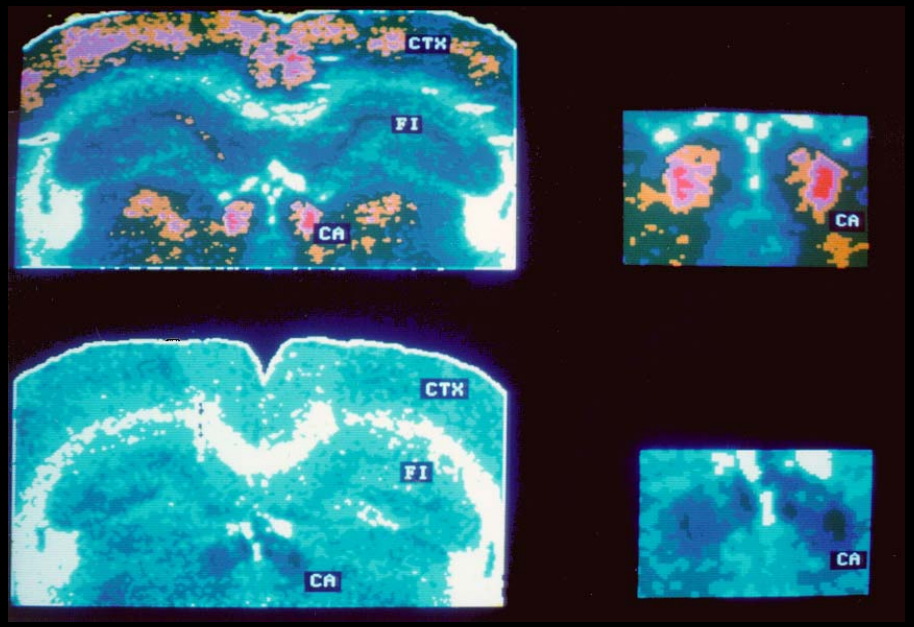
PROPOFOL



Control



Propofol



Dam, Ori, Pizzolato, et al. Anesthesiology 73: 499, 1990

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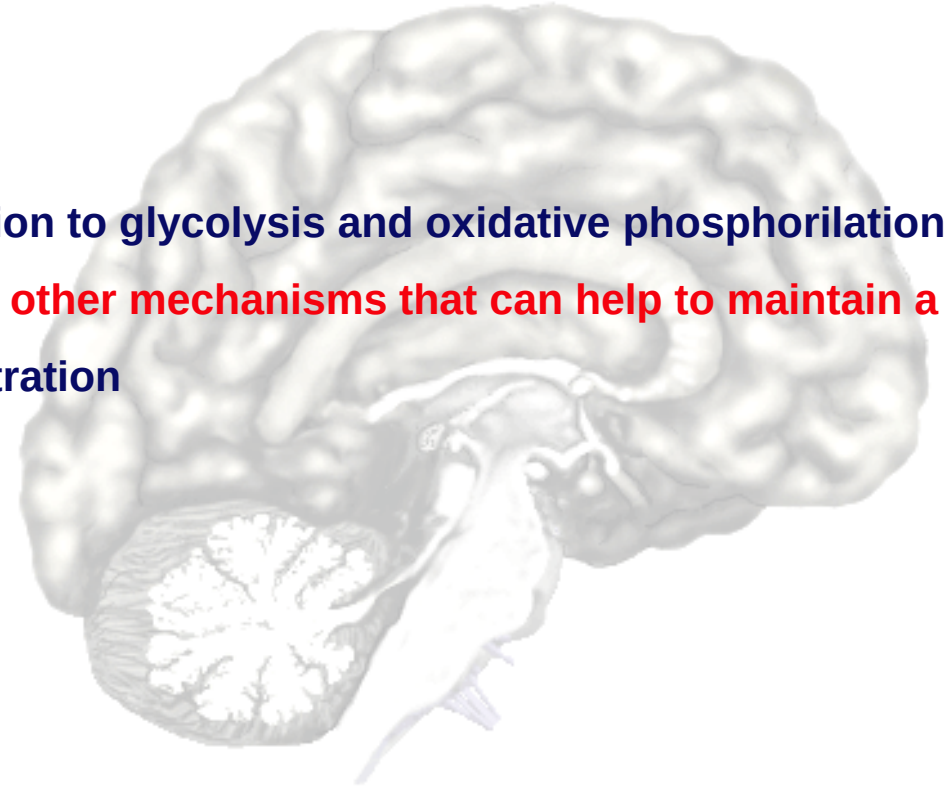
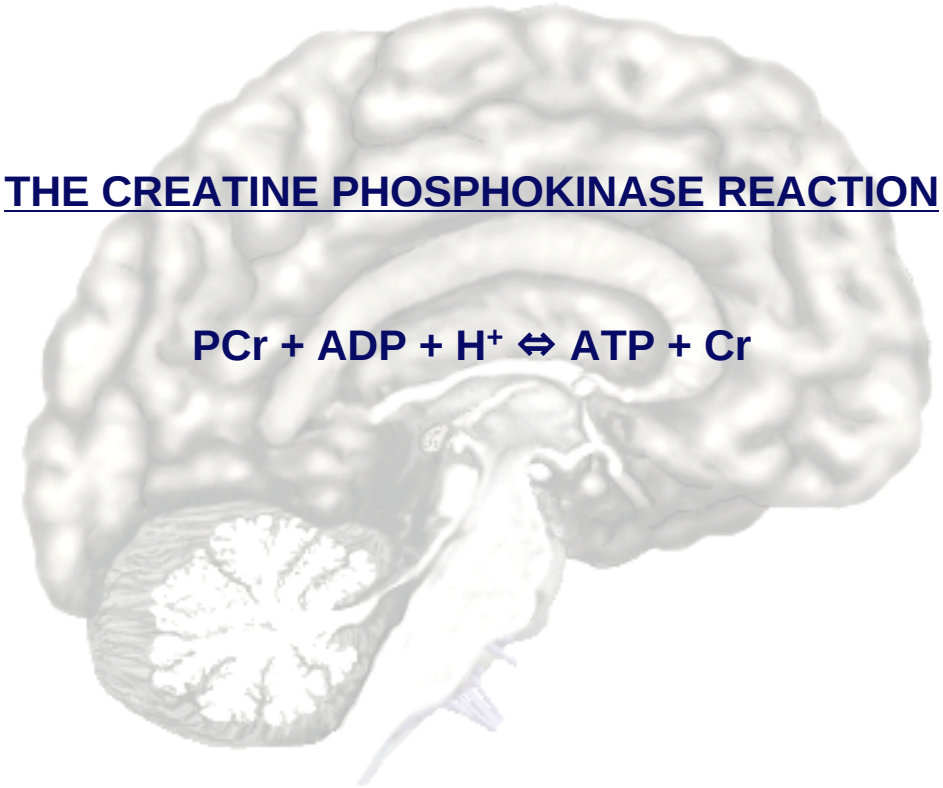


In addition to glycolysis and oxidative phosphorilation, the brain has two other mechanisms that can help to maintain a stable ATP concentration

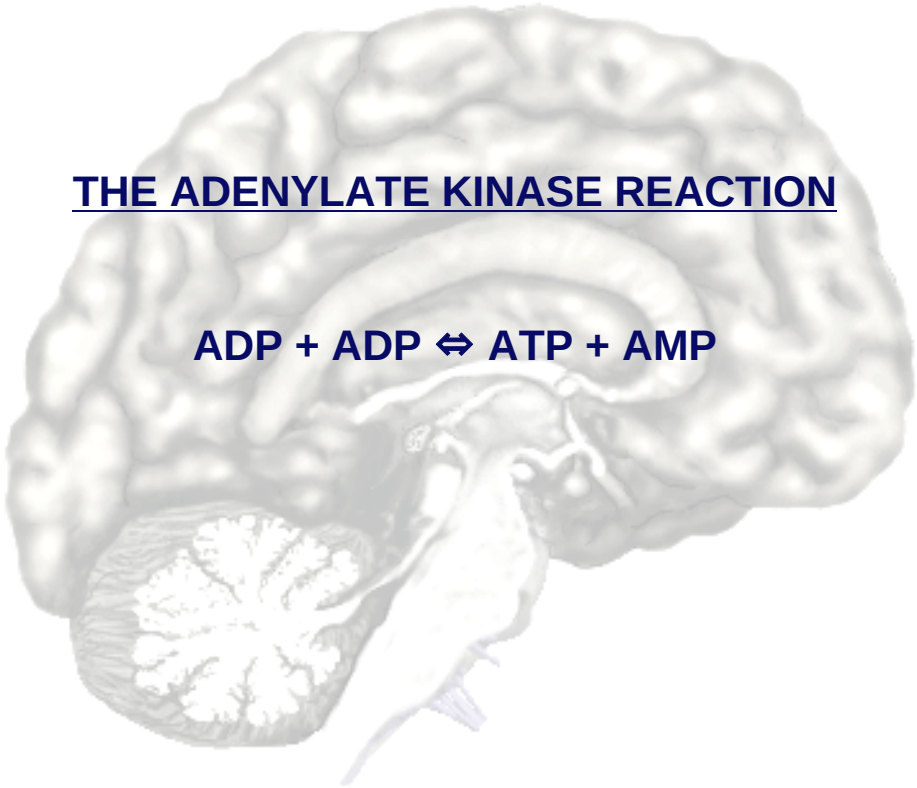
CEREBRAL METABOLISM



THE CREATINE PHOSPHOKINASE REACTION

$PCr + ADP + H^+ \Leftrightarrow ATP + Cr$

CEREBRAL METABOLISM



THE ADENYLATE KINASE REACTION

ADP + ADP ⇔ ATP + AMP

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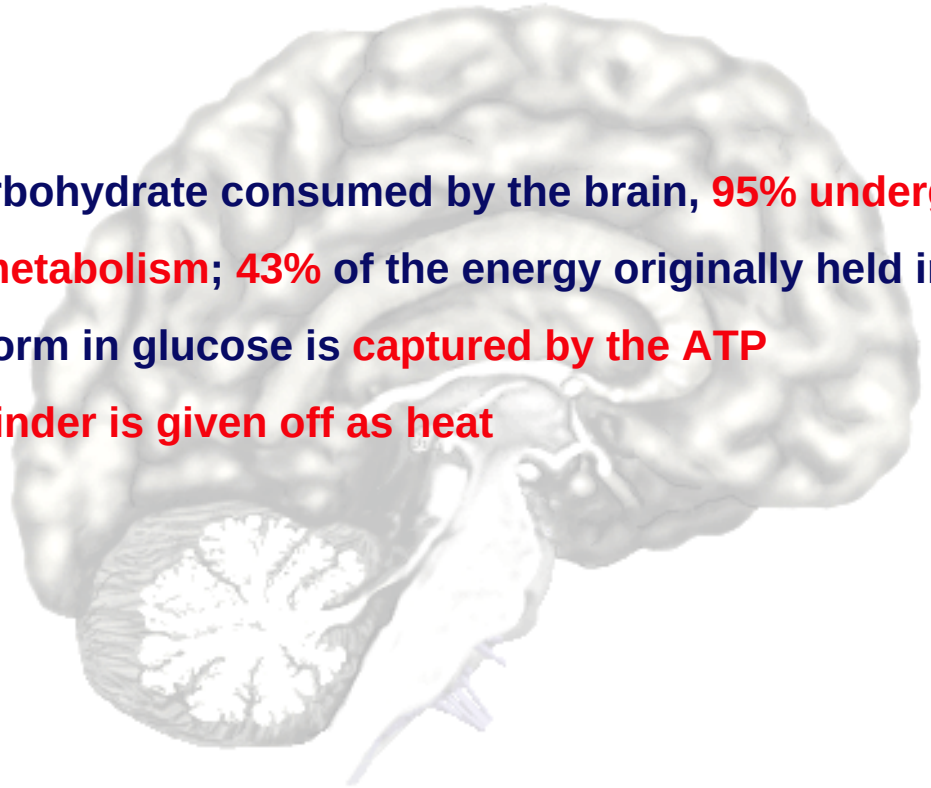
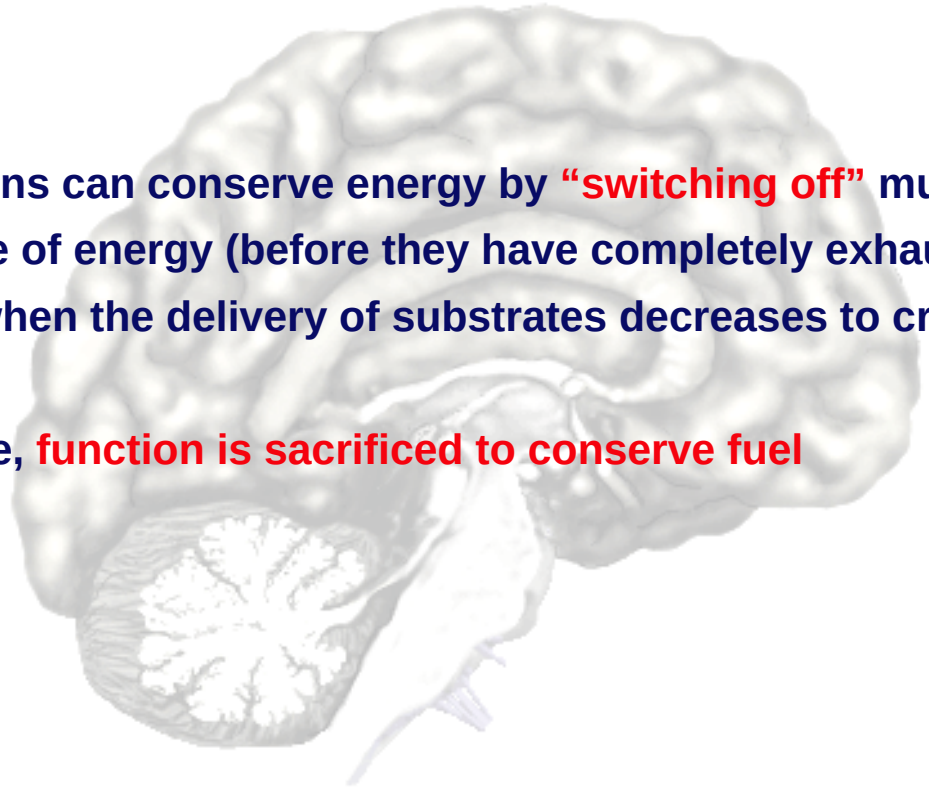


- **Of the carbohydrate consumed by the brain, 95% undergoes oxidative metabolism; 43% of the energy originally held in an unusable form in glucose is captured by the ATP**
- **The remainder is given off as heat**

CEREBRAL METABOLISM



- **The neurons can conserve energy by “switching off” much of their expenditure of energy (before they have completely exhausted their reserves) when the delivery of substrates decreases to critical levels**
- **In essence, function is sacrificed to conserve fuel**

CEREBRAL METABOLISM

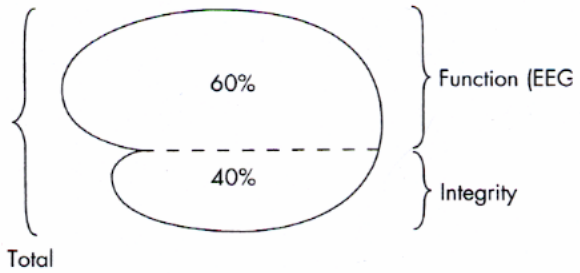


FIG. 1-5 Oxygen requirements of the normal brain. Values are those obtained in the canine. *$CMRO_2$*, Cerebral metabolic rate for oxygen; *EEG*, electroencephalogram. (From Michenfelder JD: The hypothermic brain. In *Anesthesia and the brain*, New York, 1988, Churchill Livingstone.)

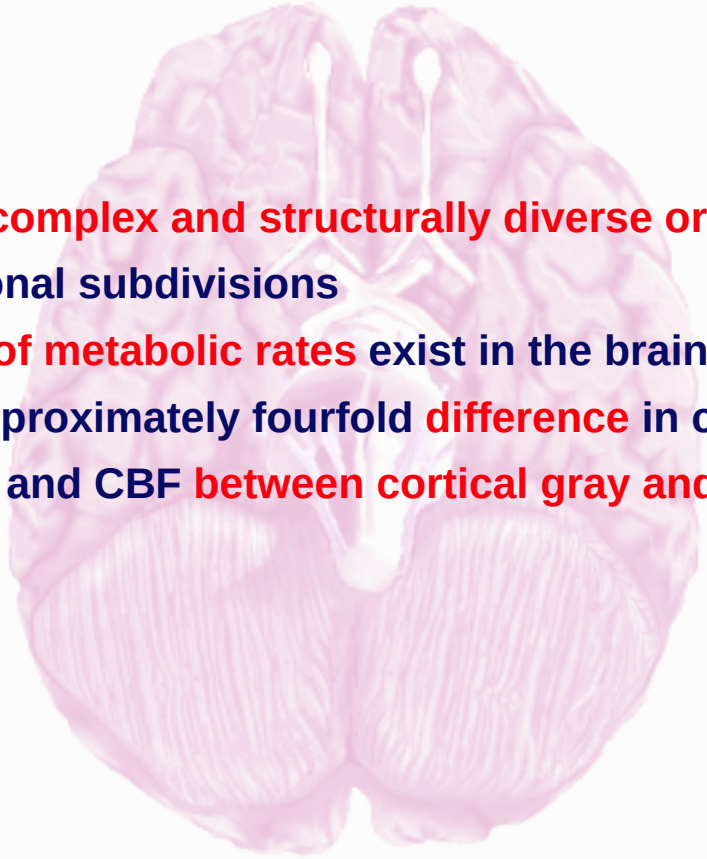
- **The brain has the capacity to "idle" and use less fuel**
- **As long as damage has not been done to the "engine" of the cell itself, function can be restored when more fuel becomes available**

CEREBRAL METABOLISM

CEREBRAL BLOOD FLOW

INTRACRANIAL PRESSURE

CEREBRAL BLOOD FLOW



- **The CNS is a complex and structurally diverse organ and comprises multiple functional subdivisions**
- **A wide range of metabolic rates exist in the brain**
- **There is an approximately fourfold difference in cerebral metabolic rate for oxygen and CBF between cortical gray and white matter**

CEREBRAL BLOOD FLOW

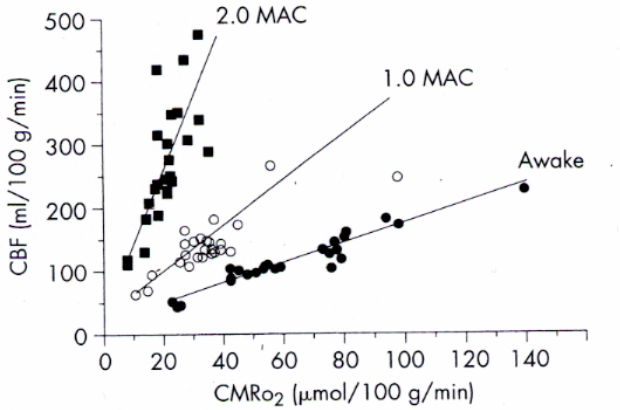
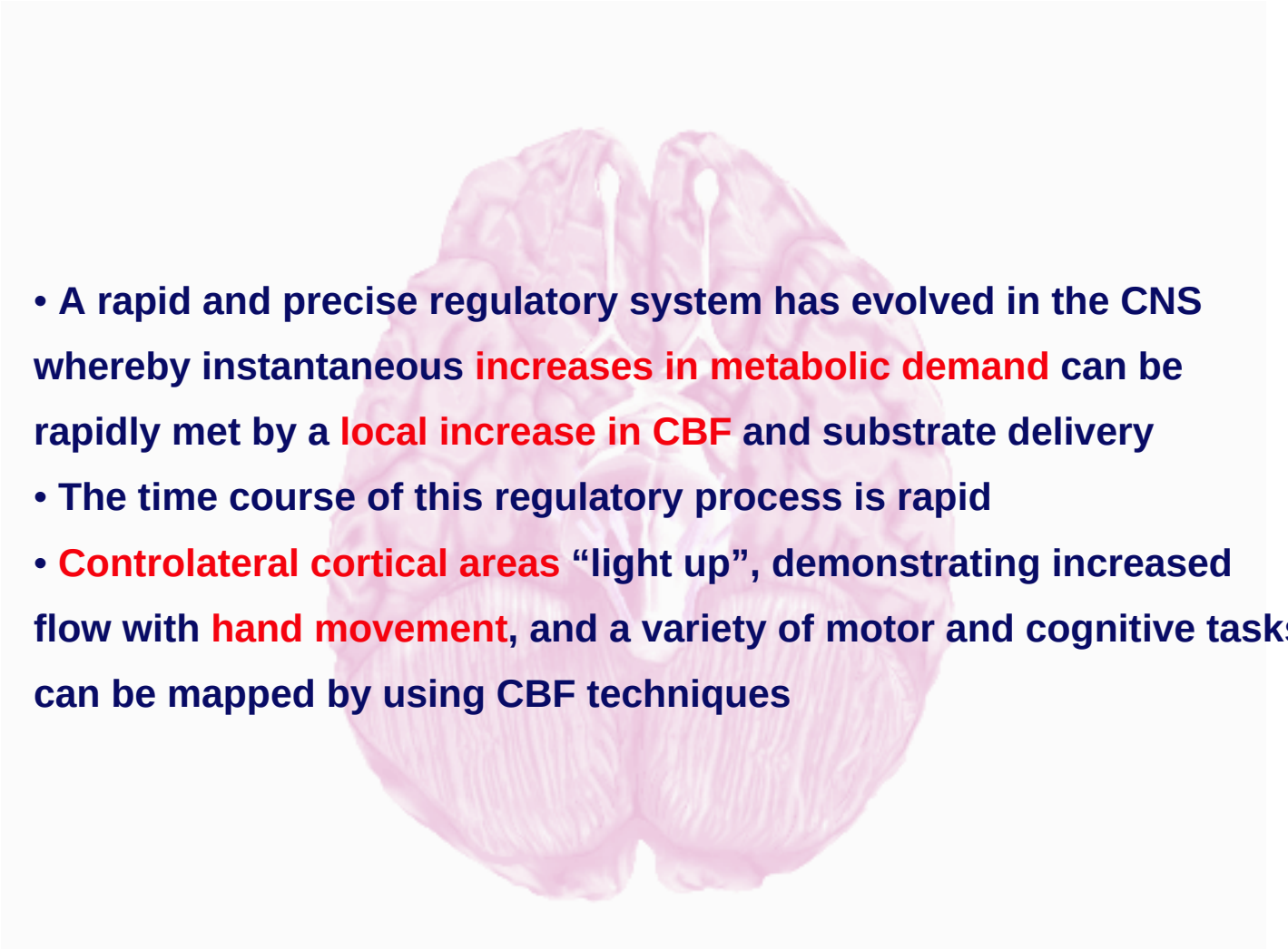


FIG. 2-1 CBF as a function of $CMRO_2$ in different brain regions of the rat, determined by autoradiography during isoflurane anesthesia. Three groups are included: awake, 1.0 MAC, and 2.0 MAC. Note that the volatile anesthetic does not uncouple flow and metabolism; rather it is "reset" along a different line. (Modified from Maekawa T, Tommasino C, Shapiro HM, et al: *Anesthesiology* 65:144, 1986. Figure courtesy Dr. David S. Warner, University of Iowa.)

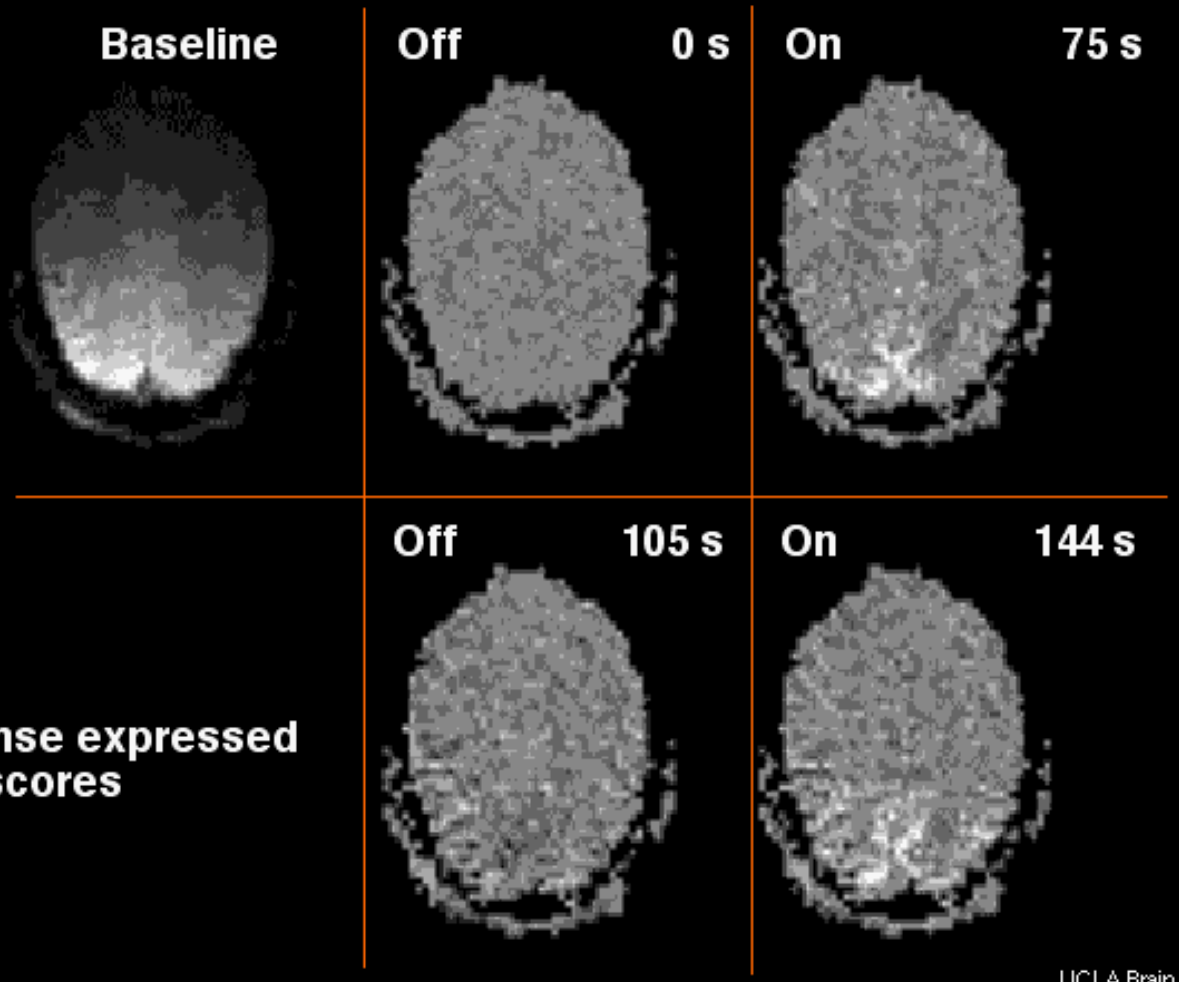
- **Flow and metabolism are said to be coupled, and under physiologic circumstances, including sedation and general anesthesia, this coupling is preserved**

CEREBRAL BLOOD FLOW



- **A rapid and precise regulatory system has evolved in the CNS whereby instantaneous increases in metabolic demand can be rapidly met by a local increase in CBF and substrate delivery**
- **The time course of this regulatory process is rapid**
- **Controlateral cortical areas "light up", demonstrating increased flow with hand movement, and a variety of motor and cognitive tasks can be mapped by using CBF techniques**

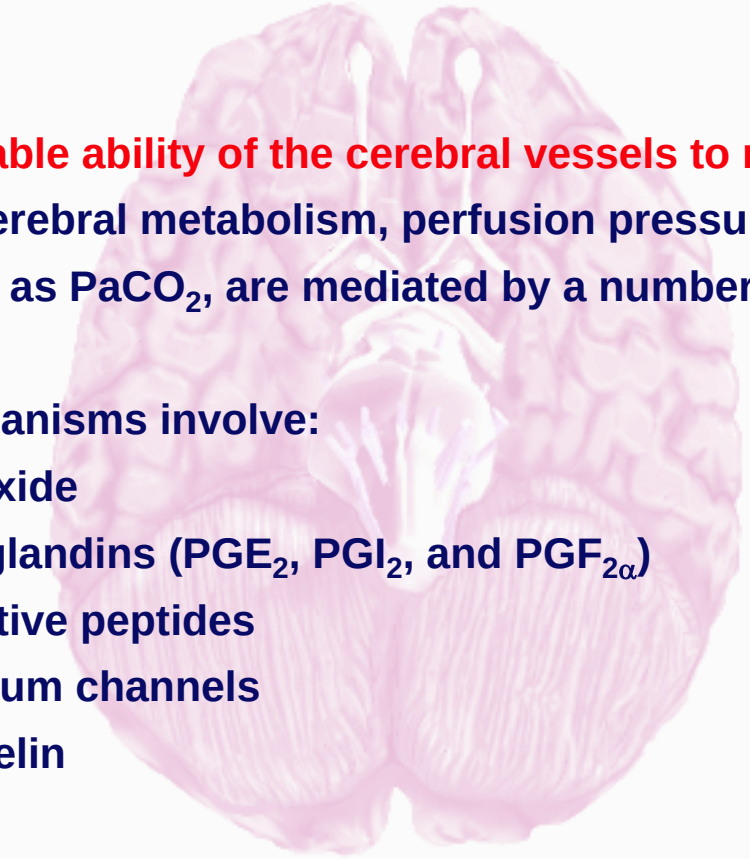
8 Hz Patterned Flash Stimulation



Visual stimulation results in almost immediate increases in flow velocity through the posterior cerebral arteries

CEREBRAL BLOOD FLOW

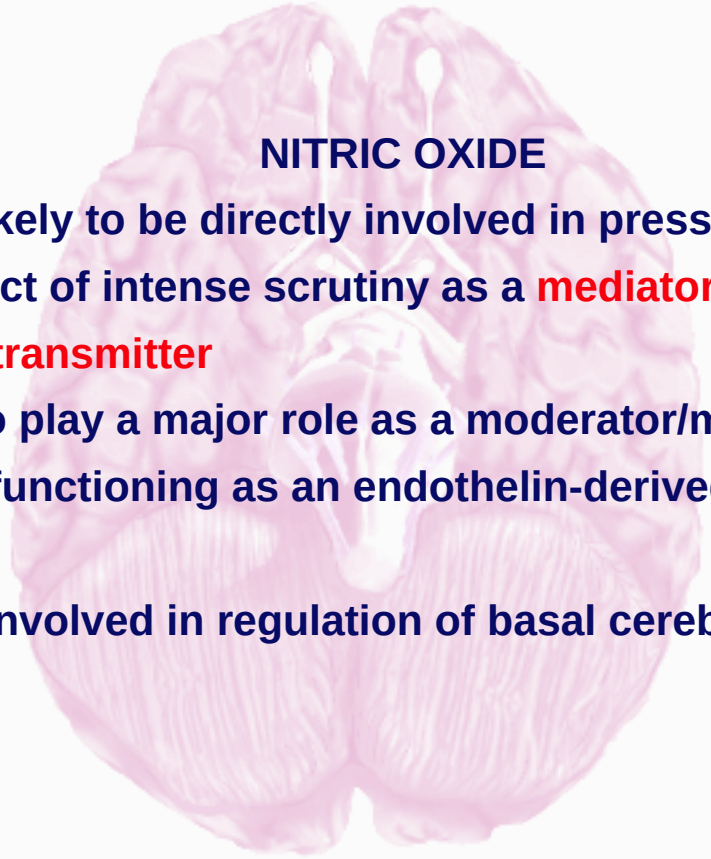
REGULATION OF CEREBRAL BLOOD FLOW



- **The remarkable ability of the cerebral vessels to respond to changes in cerebral metabolism, perfusion pressure, and milieu interior, such as $PaCO_2$, are mediated by a number of cellular mechanisms**
- **These mechanisms involve:**
  - **nitric oxide**
  - **prostaglandins (PGE_2, PGI_2, and $PGF_{2\alpha}$)**
  - **vasoactive peptides**
  - **potassium channels**
  - **endothelin**

CEREBRAL BLOOD FLOW

CELLULAR MECHANISMS OF CEREBRAL VASOMOTION

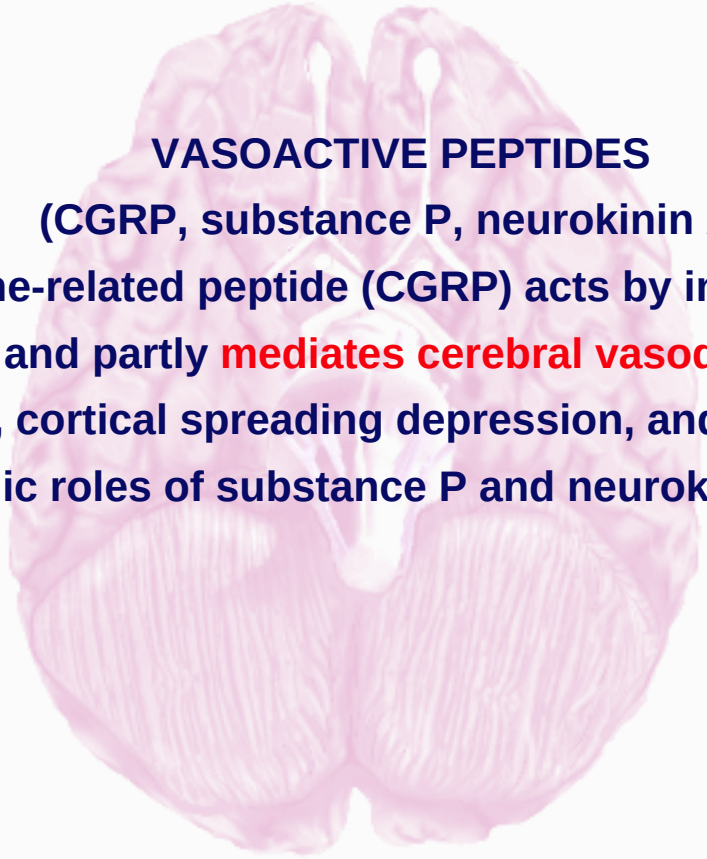


NITRIC OXIDE

- **Although unlikely to be directly involved in pressure autoregulation, NO is the subject of intense scrutiny as a mediator of vascular tone and as a neurotransmitter**
- **NO appears to play a major role as a moderator/mediator of vascular tone, functioning as an endothelin-derived relaxing factor (ERDF)**
- **NO might be involved in regulation of basal cerebrovascular tone**

CEREBRAL BLOOD FLOW

CELLULAR MECHANISMS OF CEREBRAL VASOMOTION



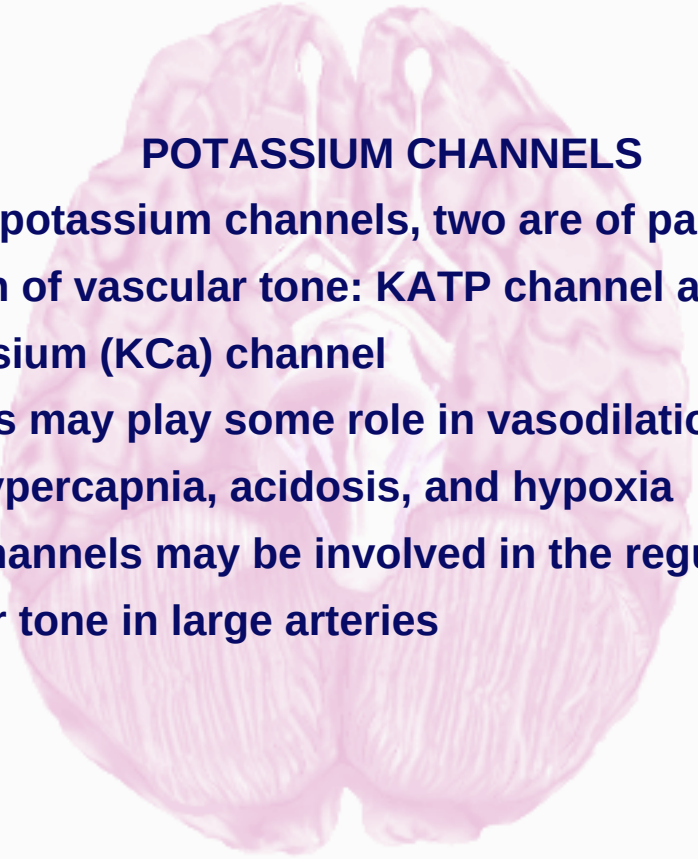
VASOACTIVE PEPTIDES

(CGRP, substance P, neurokinin A)

- **Calcitonin gene-related peptide (CGRP) acts by increasing cAMP concentrations and partly mediates cerebral vasodilation in response to hypotension, cortical spreading depression, and cerebral ischemia**
- **The physiologic roles of substance P and neurokinin A are not yet understood**

CEREBRAL BLOOD FLOW

CELLULAR MECHANISMS OF CEREBRAL VASOMOTION

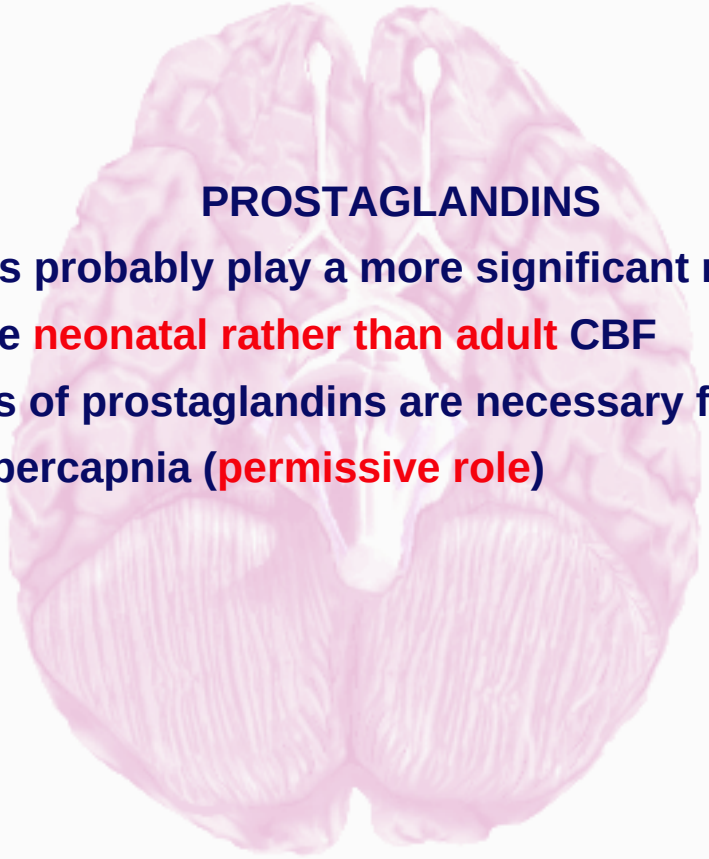


POTASSIUM CHANNELS

- **Of the several potassium channels, two are of particular importance in the regulation of vascular tone: KATP channel and calcium-activated potassium (KCa) channel**
- **KATP channels may play some role in vasodilation during hypotension, hypercapnia, acidosis, and hypoxia**
- **KCa (BKCa) channels may be involved in the regulation of the basal cerebrovascular tone in large arteries**

CEREBRAL BLOOD FLOW

CELLULAR MECHANISMS OF CEREBRAL VASOMOTION



PROSTAGLANDINS

- **Prostaglandins probably play a more significant role in the regulation of the neonatal rather than adult CBF**
- **Small amounts of prostaglandins are necessary for permitting CO_2 response to hypercapnia (permissive role)**

CEREBRAL BLOOD FLOW

HEMODYNAMIC FACTORS: PRESSURE REGULATION

Conceptually, a convenient way to model the cerebral circulation is to envision a parallel system of rigid pipes in which Ohm's law would apply

CPP

$$F = \frac{P_i - P_0}{R}$$

Circulatory resistance can be modeled in terms of the Hagen-Poiseuille's relationship

$$R = \frac{8l\mu}{r^4} = \frac{P_i - P_0}{F}$$

When these equations are applied to an intact vascular system, a number of critical assumptions are not met:

- **the equations apply to Newton fluids during nonturbulent flow through rigid tubes**
- **circulation, in contrast, is pulsatile with capacitance and the potential for turbulence**

CEREBRAL BLOOD FLOW

HEMODYNAMIC FACTORS: PRESSURE REGULATION

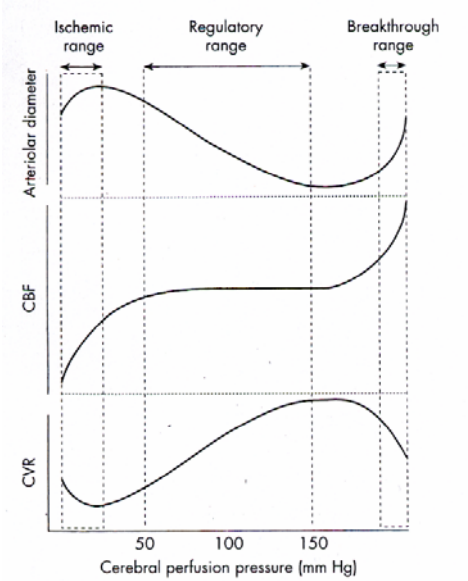
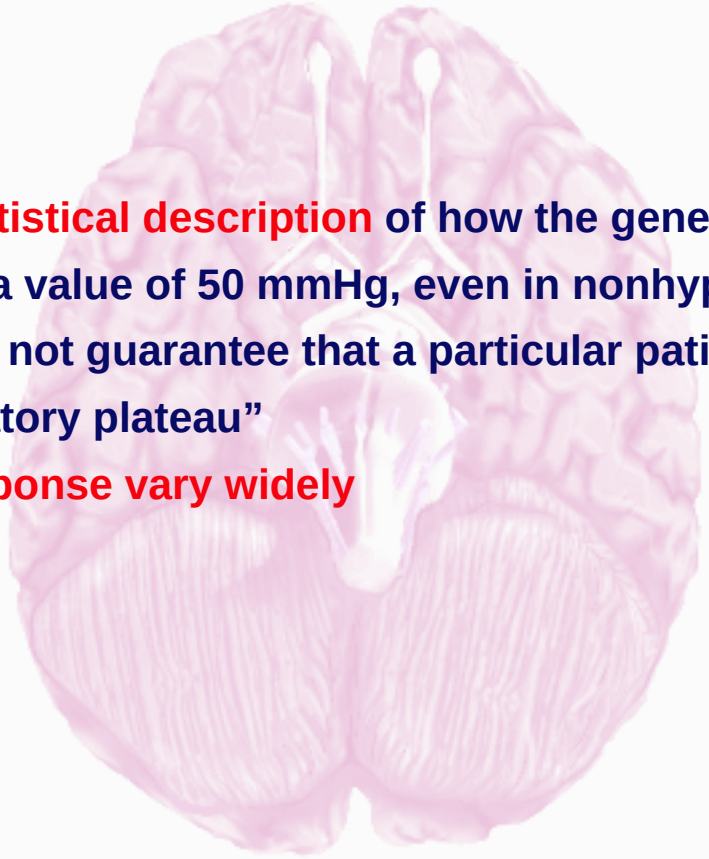


FIG. 2-4 Idealized depiction of pressure autoregulation in terms of cerebral blood flow *(CBF)*, cerebrovascular resistance *(CVR)*, and arteriolar diameter. See text for further explanation. (From Young W: *Clinical neuroscience lectures*, Munster, 1999, Cathenart Publishing.)

- **In normal individuals, CBF is constant at a CPP of approximately 50 to 150 mmHg**
- **As the ability of the cerebral vasculature to respond to changes in pressure is exhausted, CBF passively follows changes in CPP**

CEREBRAL BLOOD FLOW

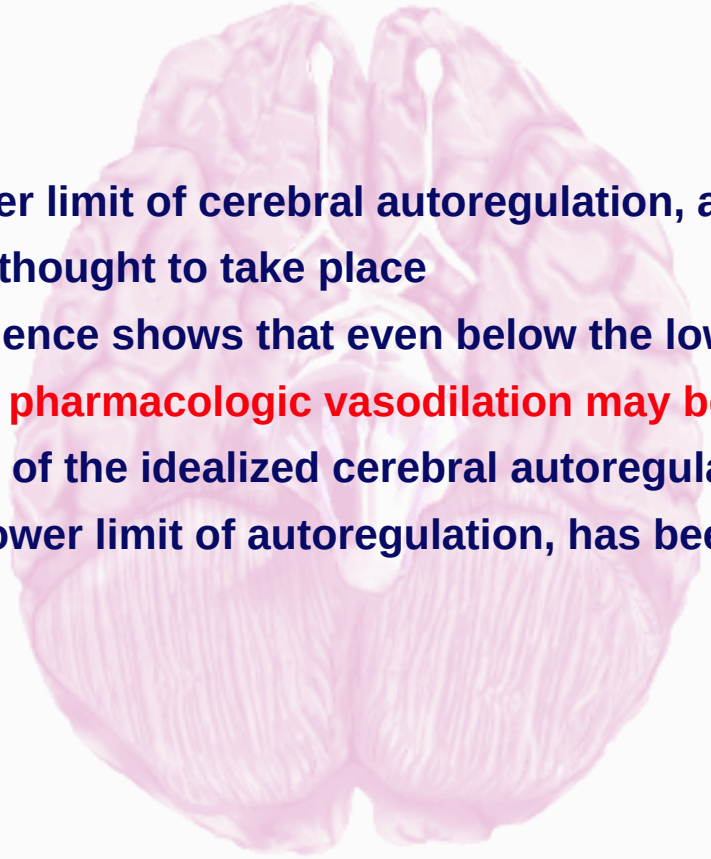
HEMODYNAMIC FACTORS: PRESSURE REGULATION



- **It is only a statistical description of how the general population responds, and a value of 50 mmHg, even in nonhypertensive individual does not guarantee that a particular patient remains within the “autoregolatory plateau”**
- **Individual response vary widely**

CEREBRAL BLOOD FLOW

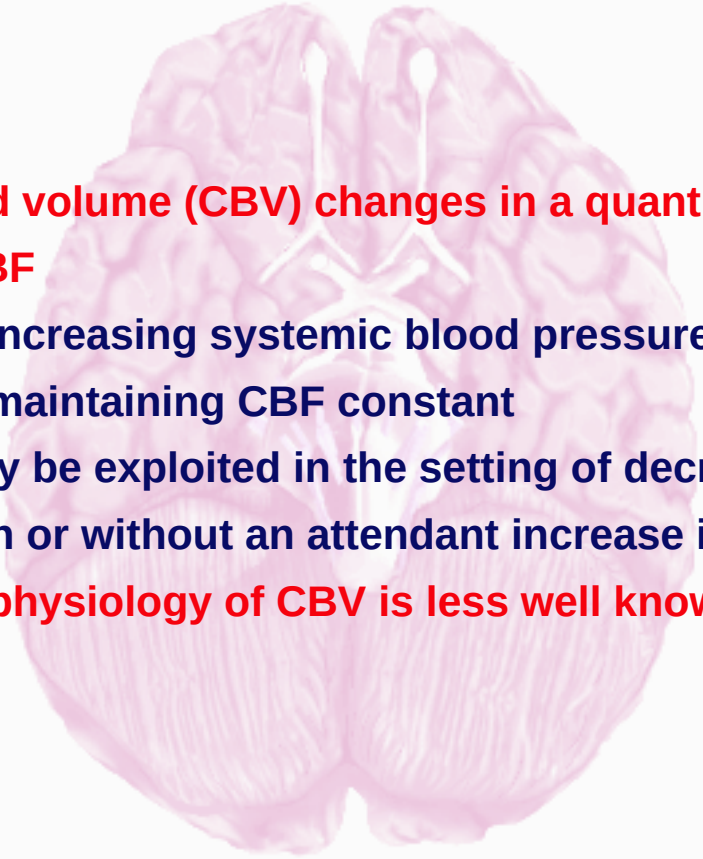
HEMODYNAMIC FACTORS: PRESSURE REGULATION



- **Ideally, at lower limit of cerebral autoregulation, a near maximal vasodilation is thought to take place**
- **However, evidence shows that even below the lower limit of autoregulation, pharmacologic vasodilation may be possible**
- **The relevance of the idealized cerebral autoregulation curve, in particular the lower limit of autoregulation, has been questioned by some authors**

CEREBRAL BLOOD FLOW

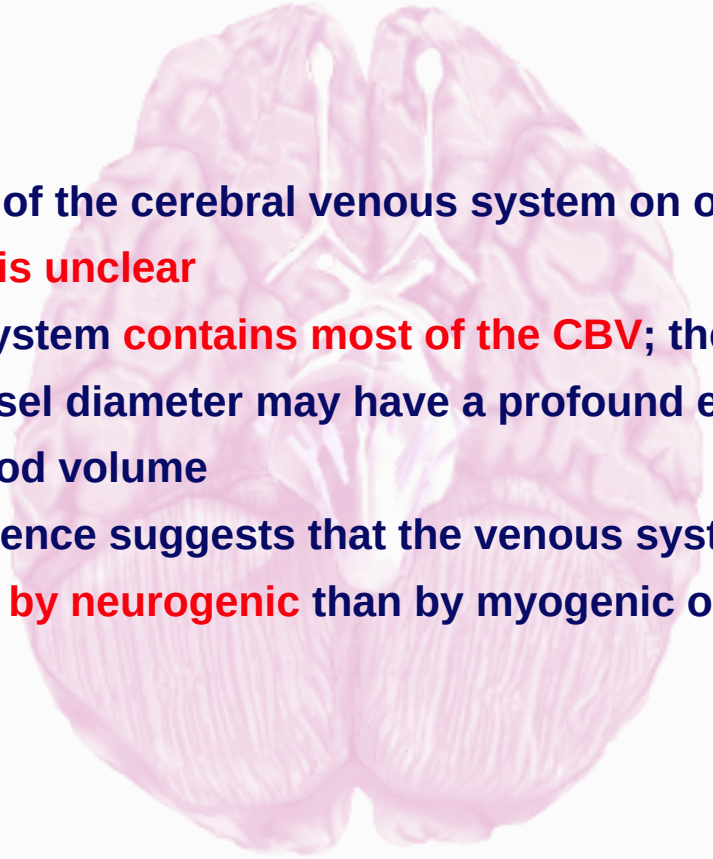
HEMODYNAMIC FACTORS: PRESSURE REGULATION



- **Cerebral blood volume (CBV) changes in a quantitatively different fashion than CBF**
- **For example, increasing systemic blood pressure decreases CBV in the process of maintaining CBF constant**
- **This effect may be exploited in the setting of decreased intracranial compliance with or without an attendant increase in ICP**
- **However, the physiology of CBV is less well known than that of CBF**

CEREBRAL BLOOD FLOW

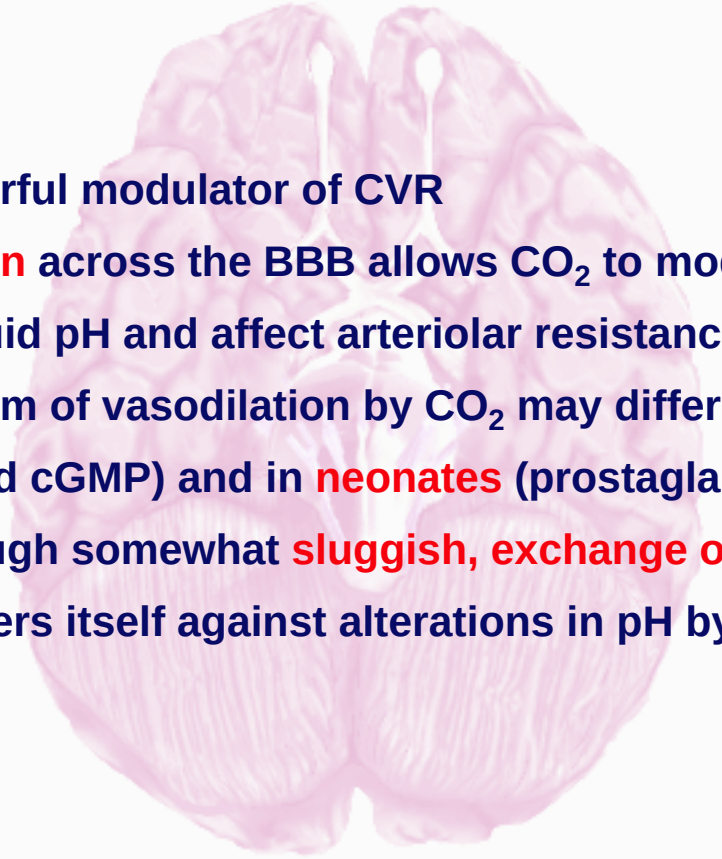
HEMODYNAMIC FACTORS: VENOUS PHYSIOLOGY



- **The influence of the cerebral venous system on overall autoregulation is unclear**
- **The venous system contains most of the CBV; therefore slight changes in vessel diameter may have a profound effect on intracranial blood volume**
- **Available evidence suggests that the venous system may be regulated more by neurogenic than by myogenic or metabolic factors**

CEREBRAL BLOOD FLOW

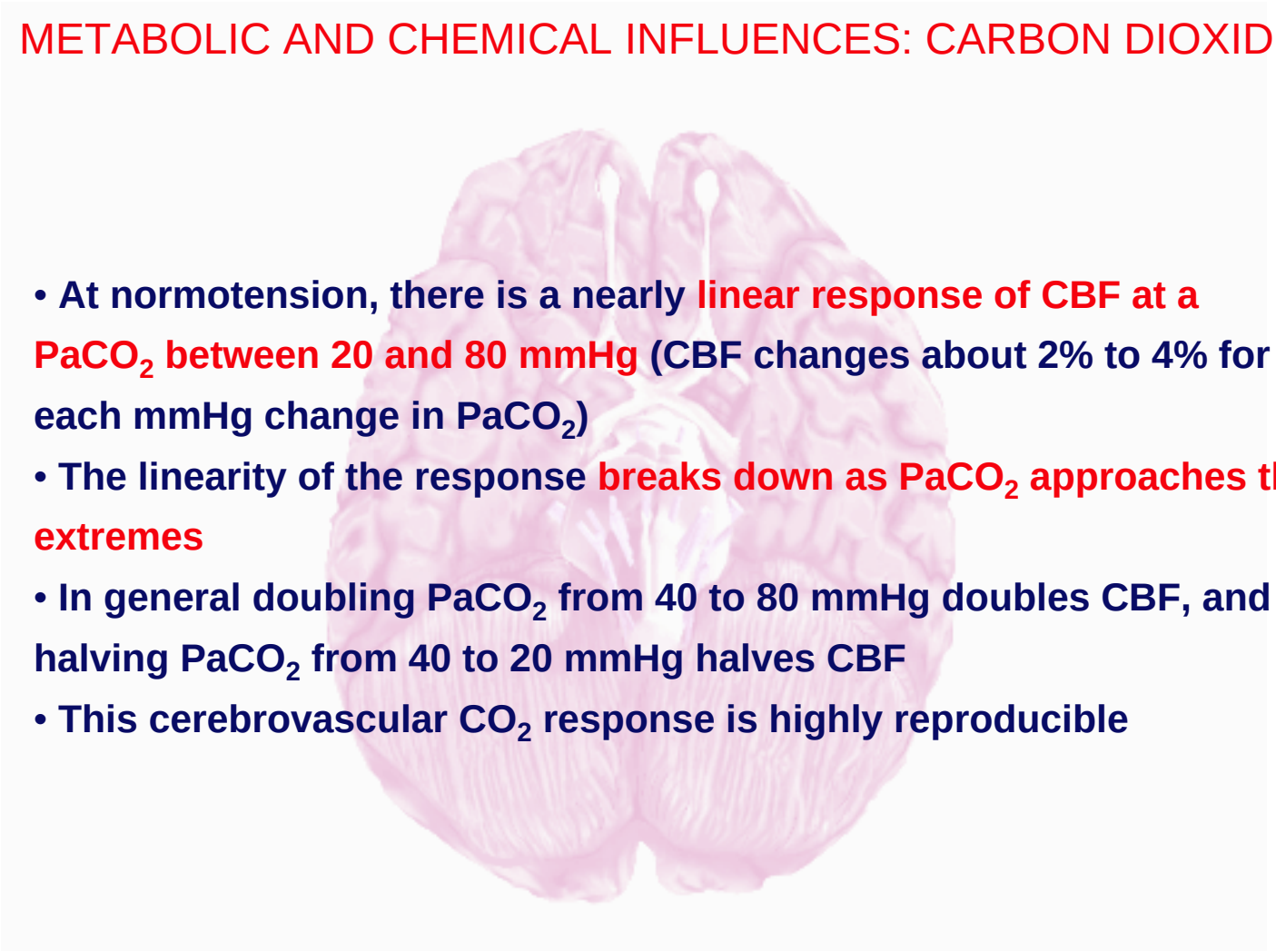
METABOLIC AND CHEMICAL INFLUENCES: CARBON DIOXIDE



- **CO_2 is a powerful modulator of CVR**
- **Rapid diffusion across the BBB allows CO_2 to modulate extracellular fluid pH and affect arteriolar resistance**
- **The mechanism of vasodilation by CO_2 may differ between adults (nitric oxide and cGMP) and in neonates (prostaglandins and cAMP)**
- **By active, though somewhat sluggish, exchange of HCO_3^-, the CSF eventually buffers itself against alterations in pH by CO_2 diffusion**

CEREBRAL BLOOD FLOW

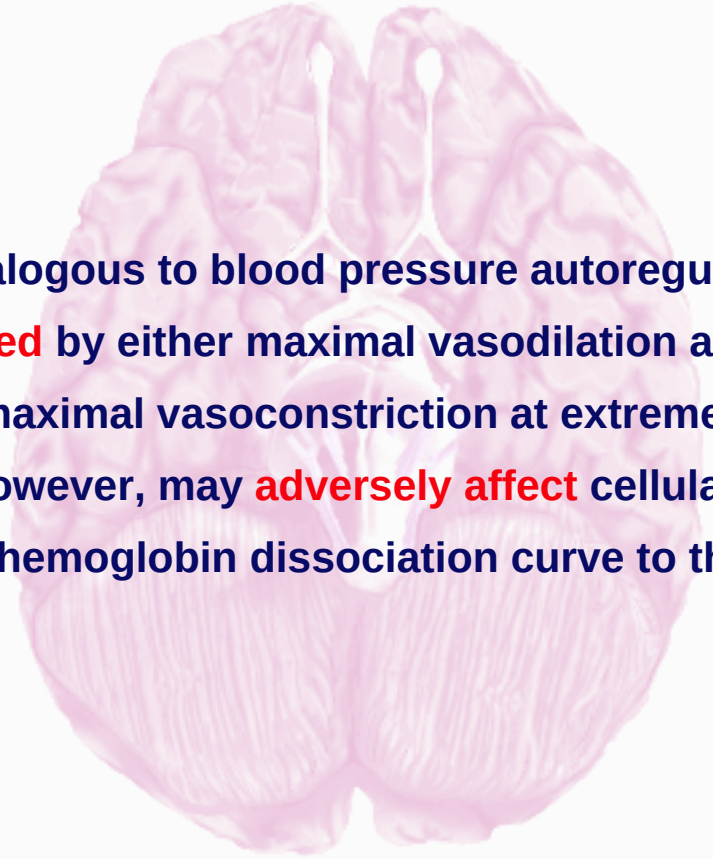
METABOLIC AND CHEMICAL INFLUENCES: CARBON DIOXIDE



- **At normotension, there is a nearly linear response of CBF at a $PaCO_2$ between 20 and 80 mmHg (CBF changes about 2% to 4% for each mmHg change in $PaCO_2$)**
- **The linearity of the response breaks down as $PaCO_2$ approaches the extremes**
- **In general doubling $PaCO_2$ from 40 to 80 mmHg doubles CBF, and halving $PaCO_2$ from 40 to 20 mmHg halves CBF**
- **This cerebrovascular CO_2 response is highly reproducible**

CEREBRAL BLOOD FLOW

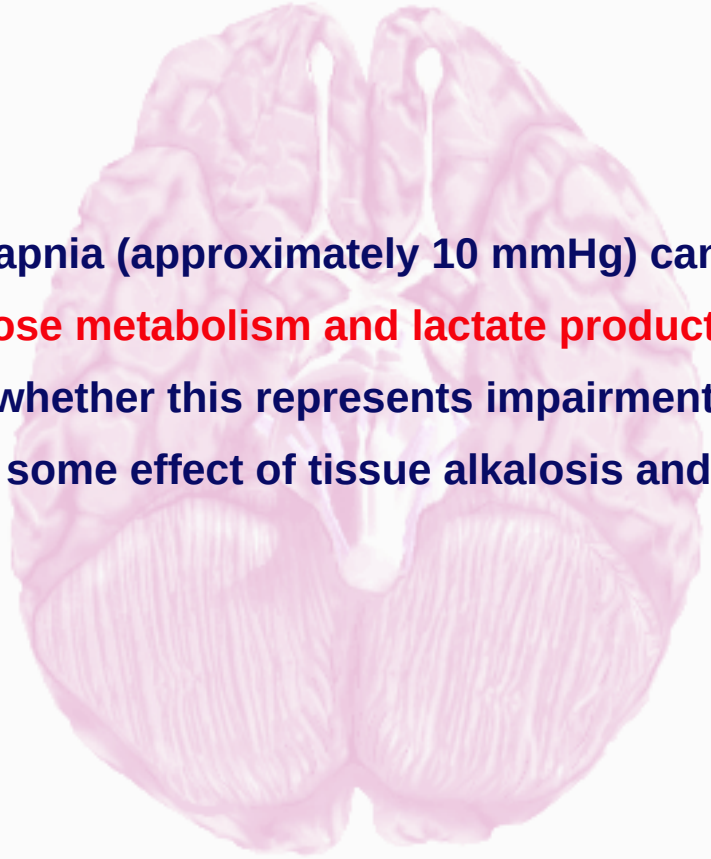
METABOLIC AND CHEMICAL INFLUENCES: CARBON DIOXIDE



- **In a fashion analogous to blood pressure autoregulation, the CO_2 response is limited by either maximal vasodilation at extreme hypercapnia or maximal vasoconstriction at extreme hypocapnia**
- **Hypocapnia, however, may adversely affect cellular metabolism and shift the oxyhemoglobin dissociation curve to the left**

CEREBRAL BLOOD FLOW

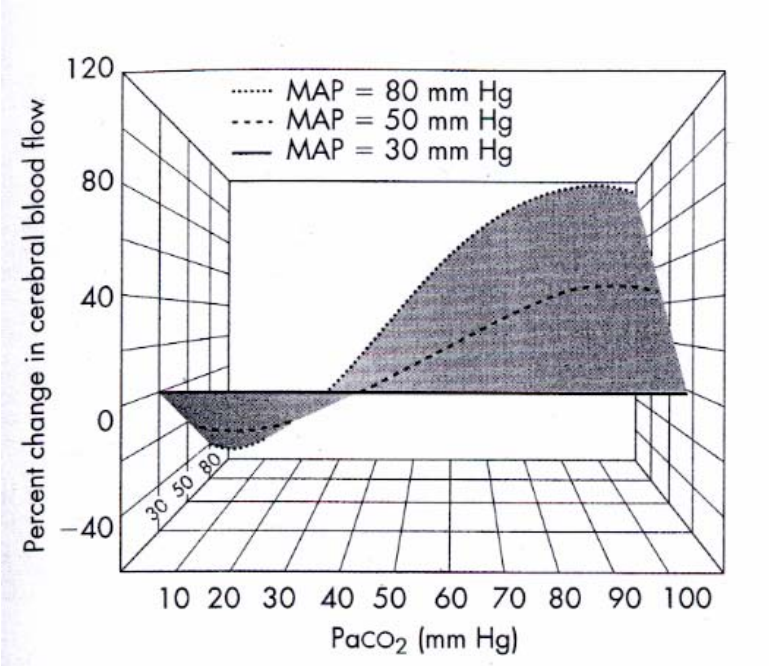
METABOLIC AND CHEMICAL INFLUENCES: CARBON DIOXIDE



- **Severe hypocapnia (approximately 10 mmHg) can result in anaerobic glucose metabolism and lactate production**
- **It is not clear whether this represents impairment of tissue oxygenation or some effect of tissue alkalosis and transcellular ionic shift**

CEREBRAL BLOOD FLOW

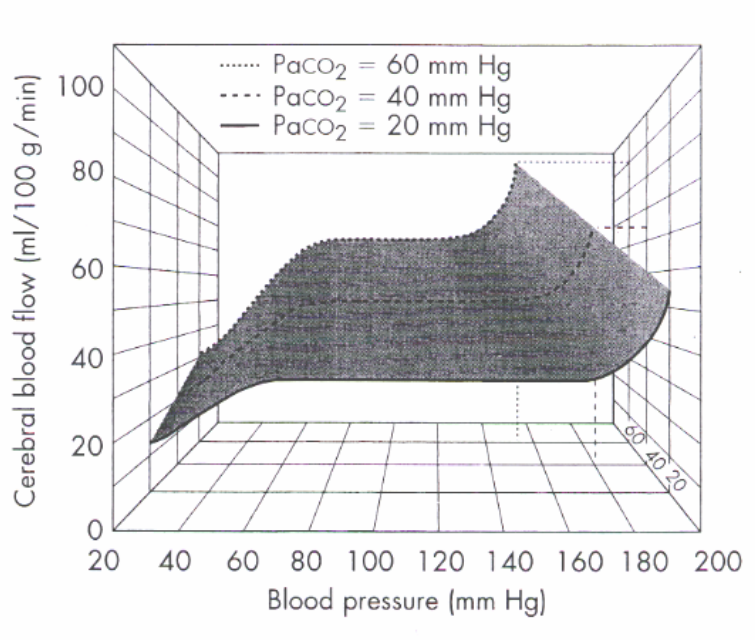
METABOLIC AND CHEMICAL INFLUENCES: CARBON DIOXIDE



- **Arteriolar tone, set by the systemic arterial blood pressure, modulates the effect of $PaCO_2$ on CBF**
- **Moderate hypotension blunts the ability of the cerebral circulation to respond to changes in $PaCO_2$, and severe hypotension abolishes it altogether**

CEREBRAL BLOOD FLOW

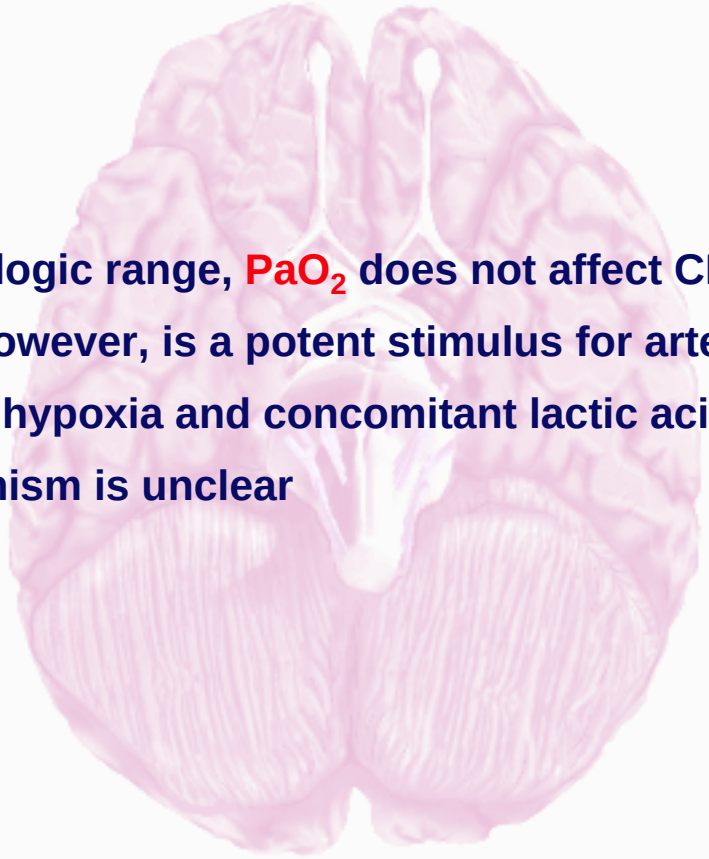
METABOLIC AND CHEMICAL INFLUENCES: CARBON DIOXIDE



- **Conversely, $PaCO_2$ modifies pressure autoregulation, and from hypercapnia to hypocapnia there is a widening of the "autoregulatory plateau"**

CEREBRAL BLOOD FLOW

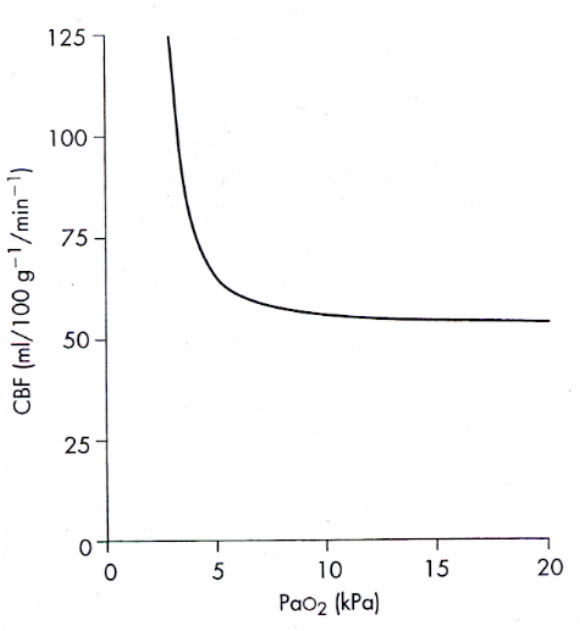
METABOLIC AND CHEMICAL INFLUENCES: OXYGEN



- **Within physiologic range, PaO_2 does not affect CBF**
- **Hypoxemia, however, is a potent stimulus for arterial dilation, as a result of tissue hypoxia and concomitant lactic acidosis, although the precise mechanism is unclear**

CEREBRAL BLOOD FLOW

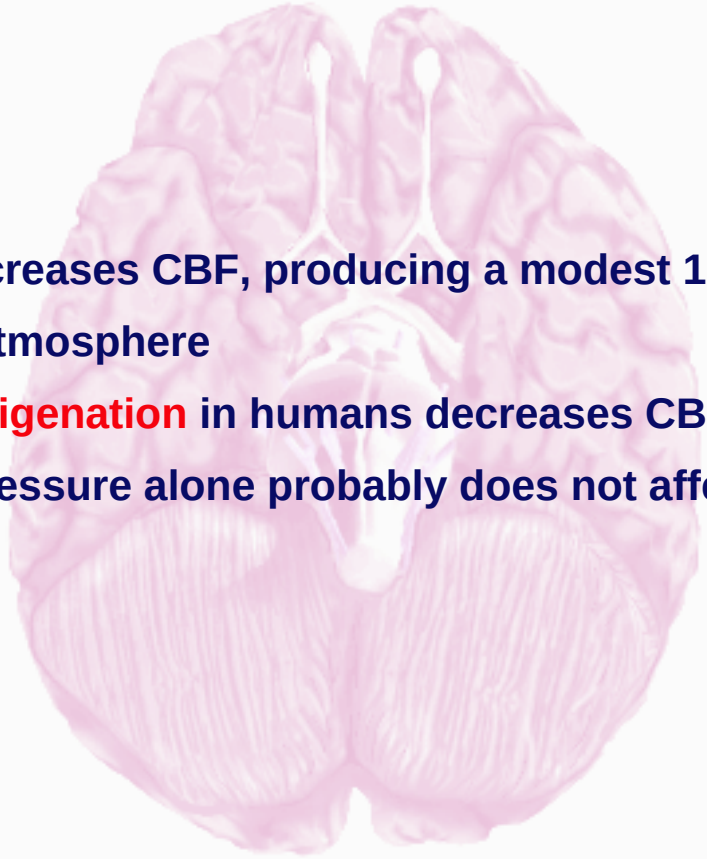
METABOLIC AND CHEMICAL INFLUENCES: OXYGEN



- **CBF begins to increase at a PaO_2 of about 50 mmHg and roughly doubles at a PaO_2 of 30 mmHg**

CEREBRAL BLOOD FLOW

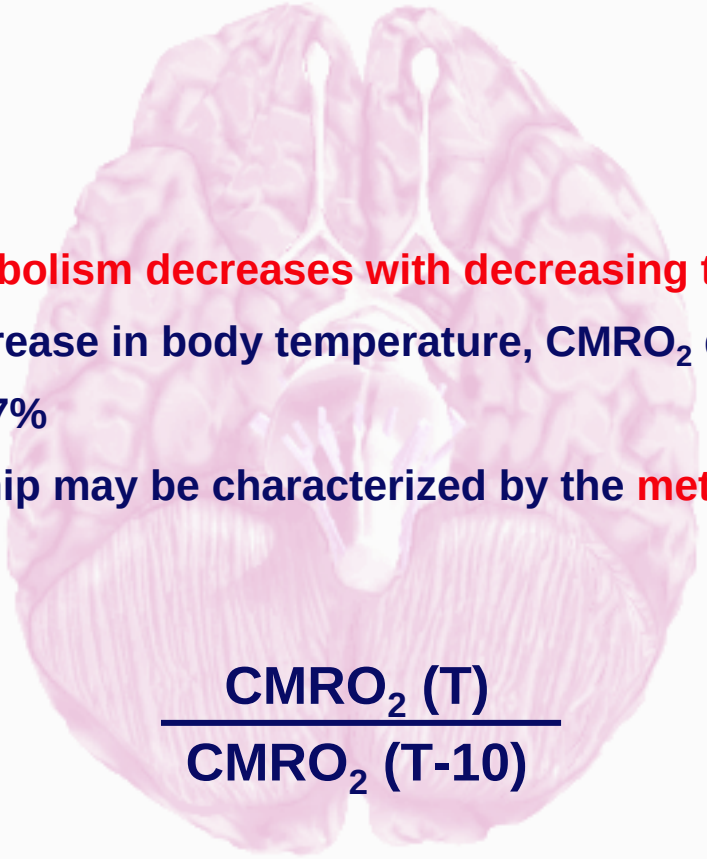
METABOLIC AND CHEMICAL INFLUENCES: OXYGEN



- **Hyperoxia decreases CBF, producing a modest 10% to 15% decrease at 1 atmosphere**
- **Hyperbaric oxigenation in humans decreases CBF, but high atmospheric pressure alone probably does not affect CBF**

CEREBRAL BLOOD FLOW

METABOLIC AND CHEMICAL INFLUENCES: TEMPERATURE

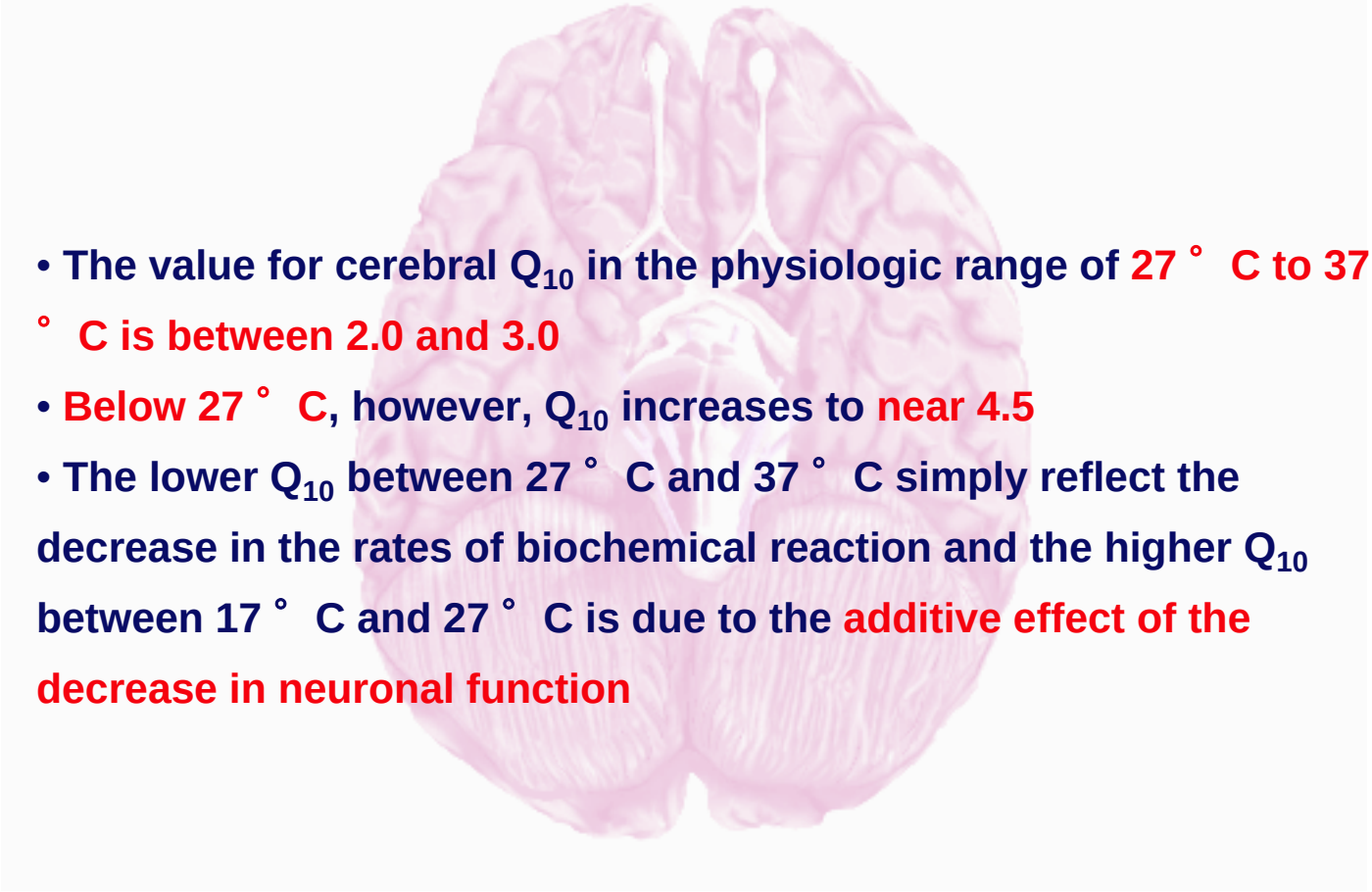


- **Cerebral metabolism decreases with decreasing temperature. For each 1 ° C decrease in body temperature, $CMRO_2$ decreases by approximately 7%**
- **The relationship may be characterized by the metabolic temperature coefficient Q_{10}**

$$\frac{CMRO_2\ (T)}{CMRO_2\ (T\text{-}10)}$$

CEREBRAL BLOOD FLOW

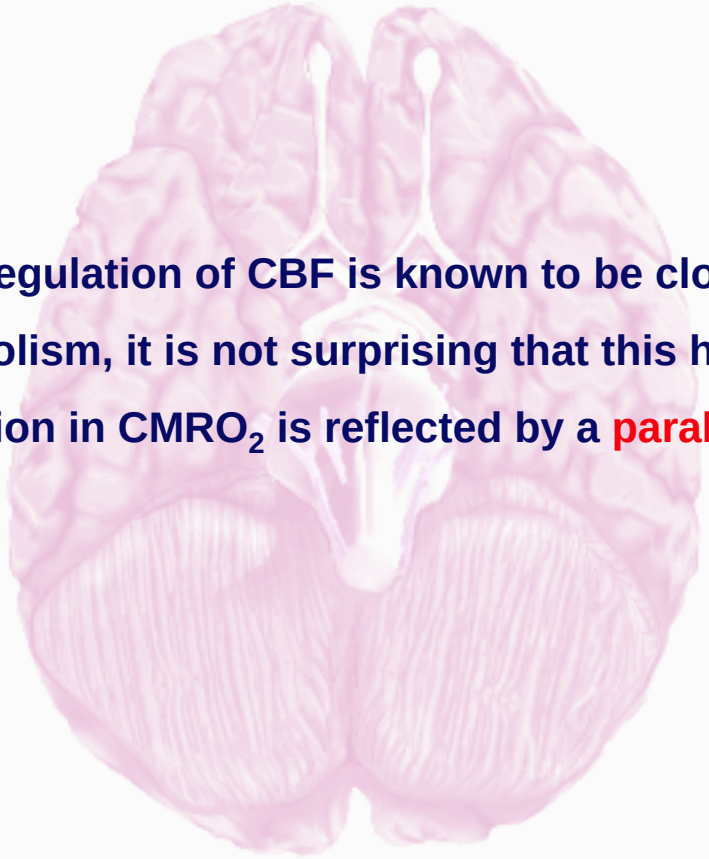
METABOLIC AND CHEMICAL INFLUENCES: TEMPERATURE



- **The value for cerebral Q_{10} in the physiologic range of 27 ° C to 37 ° C is between 2.0 and 3.0**
- **Below 27 ° C, however, Q_{10} increases to near 4.5**
- **The lower Q_{10} between 27 ° C and 37 ° C simply reflect the decrease in the rates of biochemical reaction and the higher Q_{10} between 17 ° C and 27 ° C is due to the additive effect of the decrease in neuronal function**

CEREBRAL BLOOD FLOW

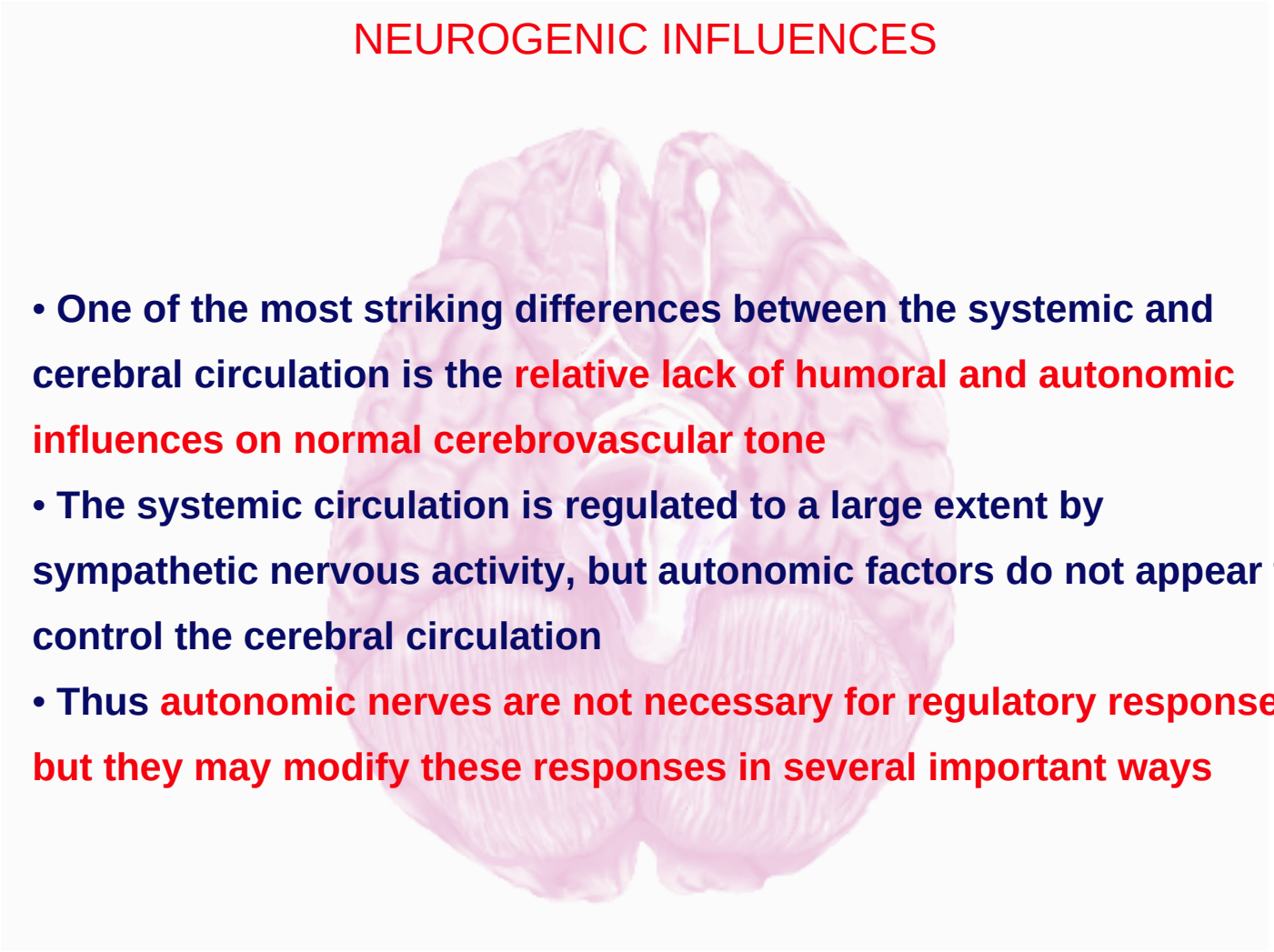
METABOLIC AND CHEMICAL INFLUENCES: TEMPERATURE



- **Because the regulation of CBF is known to be closely coupled to cerebral metabolism, it is not surprising that this hypothermia-induced reduction in $CMRO_2$ is reflected by a parallel decrease in CBF**

CEREBRAL BLOOD FLOW

NEUROGENIC INFLUENCES



- **One of the most striking differences between the systemic and cerebral circulation is the relative lack of humoral and autonomic influences on normal cerebrovascular tone**
- **The systemic circulation is regulated to a large extent by sympathetic nervous activity, but autonomic factors do not appear to control the cerebral circulation**
- **Thus autonomic nerves are not necessary for regulatory responses, but they may modify these responses in several important ways**

CEREBRAL BLOOD FLOW

NEUROGENIC INFLUENCES

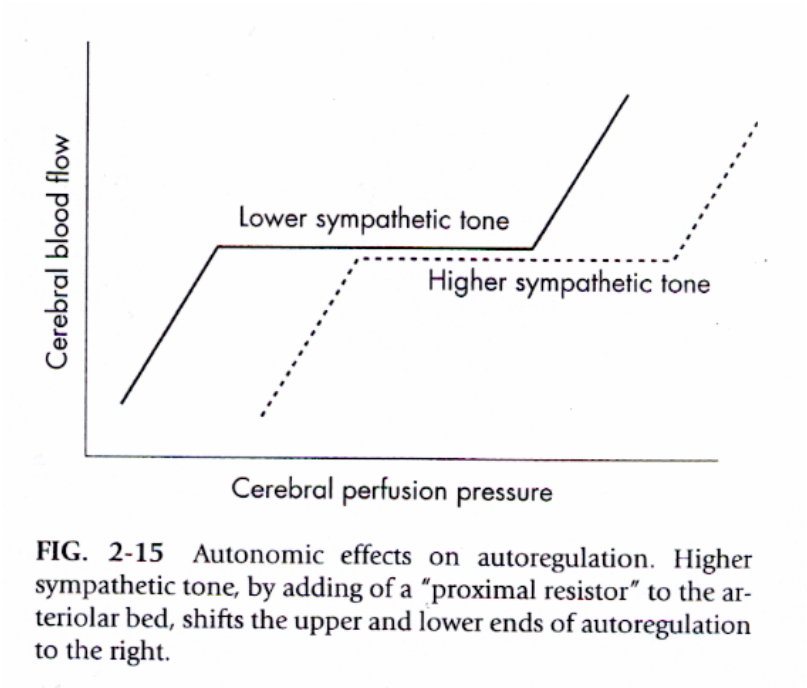
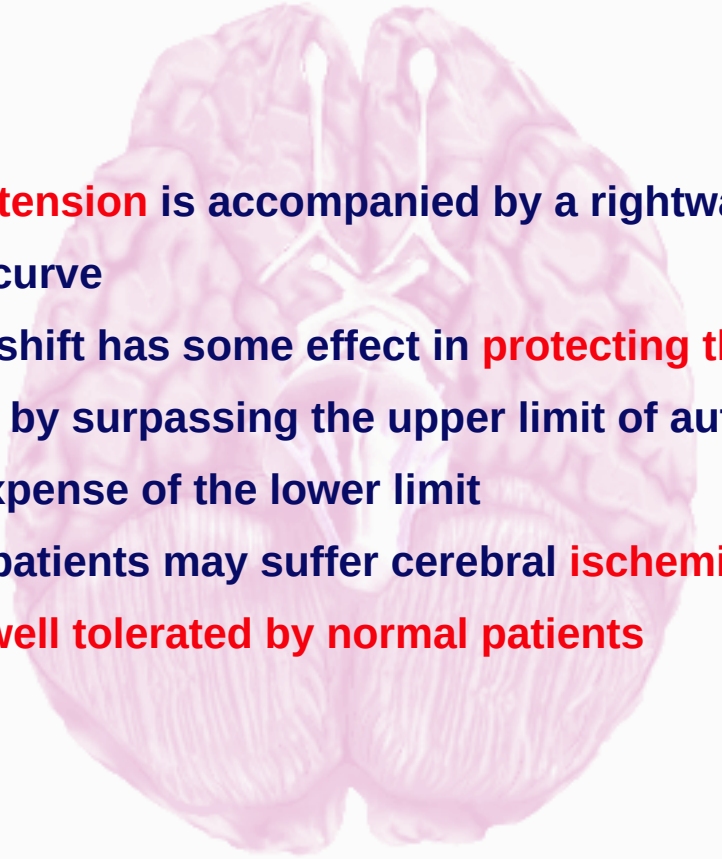


FIG. 2-15 Autonomic effects on autoregulation. Higher sympathetic tone, by adding of a "proximal resistor" to the arteriolar bed, shifts the upper and lower ends of autoregulation to the right.

CEREBRAL BLOOD FLOW

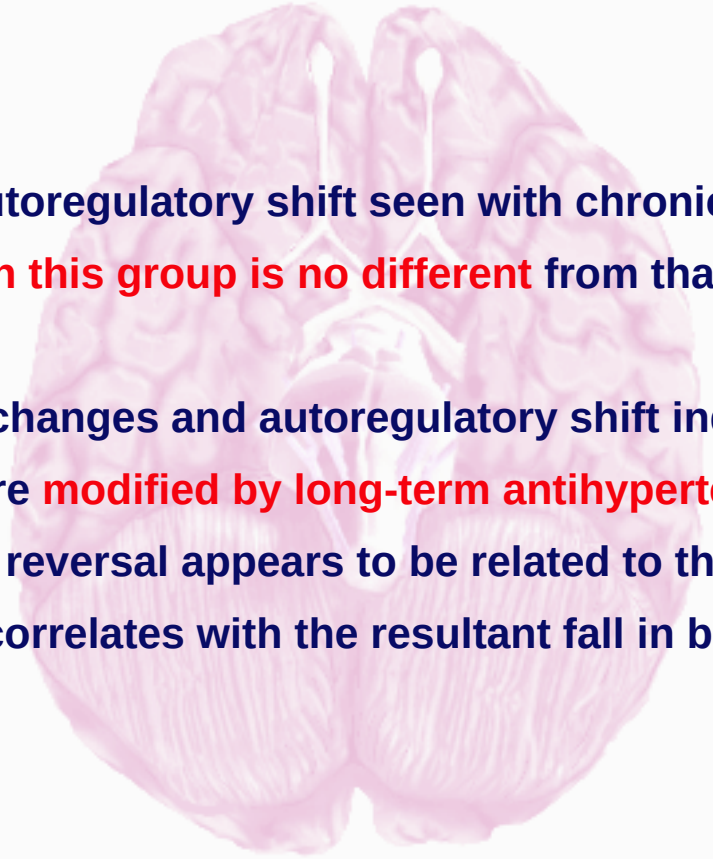
THE HYPERTENSIVE PATIENT



- **Chronic hypertension is accompanied by a rightward shift of the autoregulation curve**
- **Although this shift has some effect in protecting the brain against "breakthrough" by surpassing the upper limit of autoregulation, it occurs at the expense of the lower limit**
- **Hypertensive patients may suffer cerebral ischemia at blood pressure level well tolerated by normal patients**

CEREBRAL BLOOD FLOW

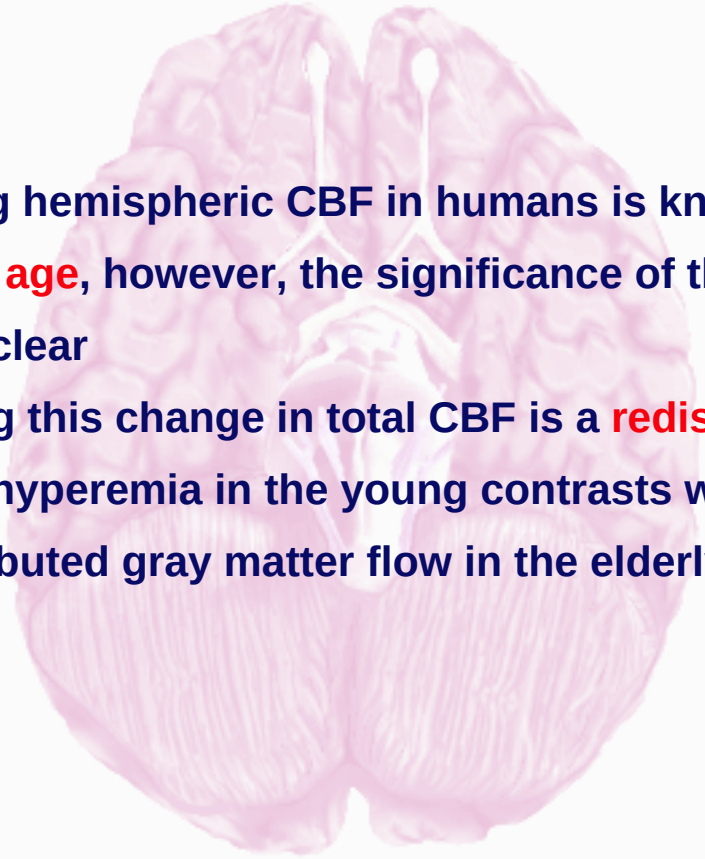
THE HYPERTENSIVE PATIENT



- **Despite the autoregulatory shift seen with chronic hypertension, CO_2 reactivity in this group is no different from that in normotensive population**
- **The vascular changes and autoregulatory shift induced by chronic hypertension are modified by long-term antihypertensive therapy**
- **The degree of reversal appears to be related to the length of treatment and correlates with the resultant fall in blood pressure**

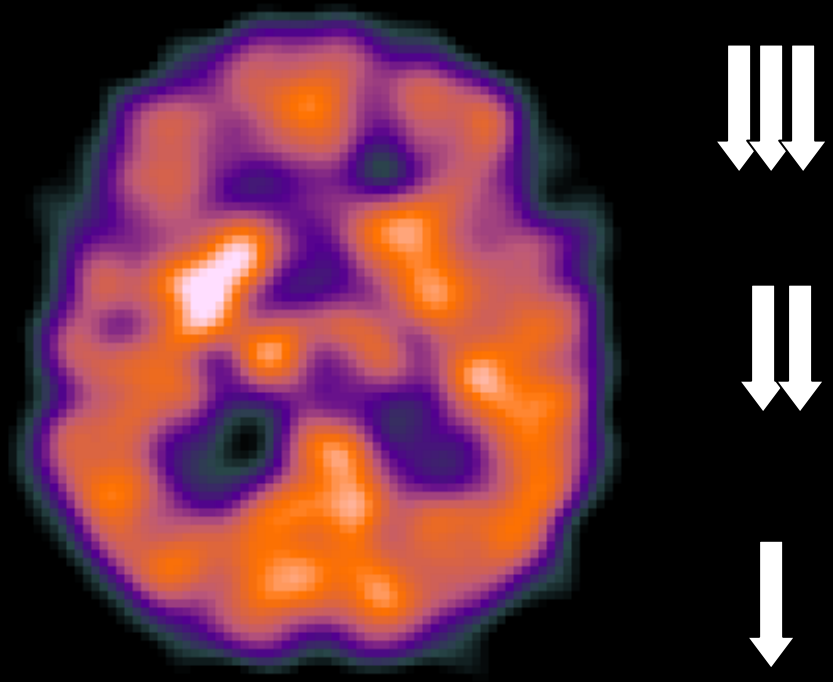
CEREBRAL BLOOD FLOW

THE ELDERLY PATIENT



- **Normal resting hemispheric CBF in humans is known to decrease with increasing age, however, the significance of this decreased perfusion is unclear**
- **Accompanying this change in total CBF is a redistribution of rCBF: relative frontal hyperemia in the young contrasts with a more uniformly distributed gray matter flow in the elderly**

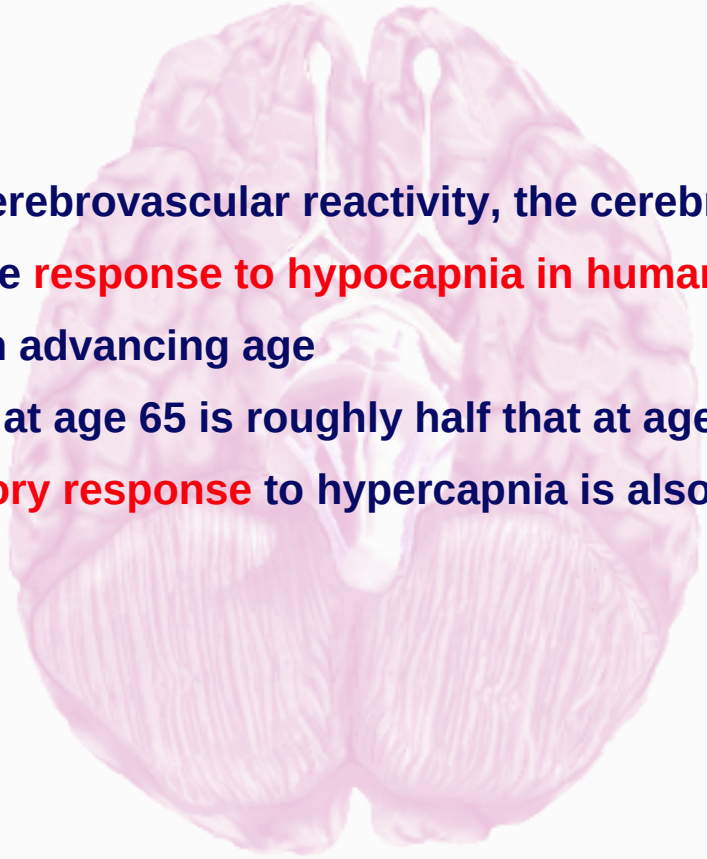
CBF IN THE ELDERLY PATIENT



SPECT

CEREBRAL BLOOD FLOW

THE ELDERLY PATIENT

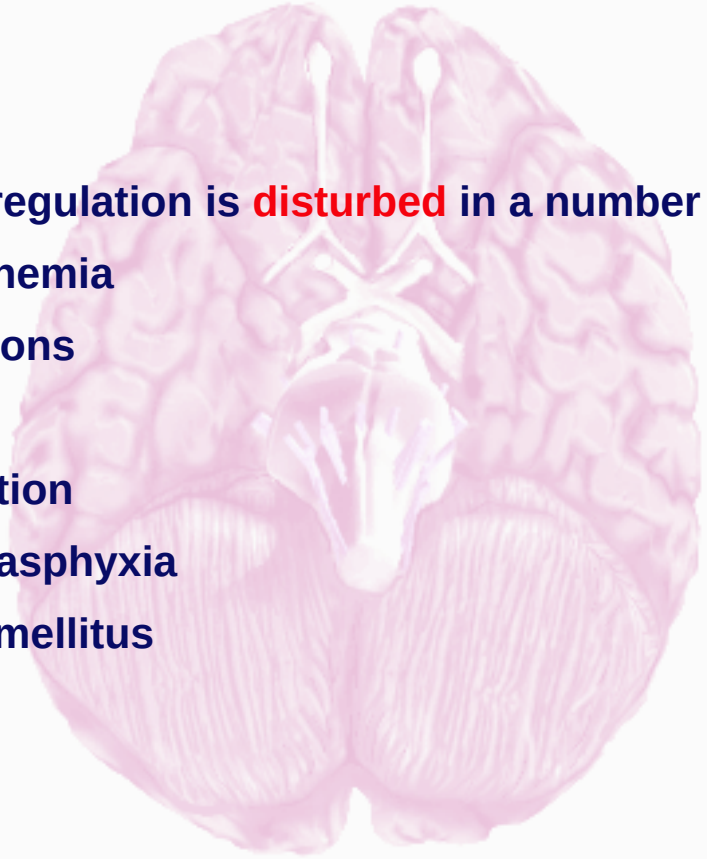


- **Concerning cerebrovascular reactivity, the cerebral vasoconstrictive response to hypocapnia in humans becomes diminished with advancing age**
- **CO_2 reactivity at age 65 is roughly half that at age of 20**
- **The vasodilatory response to hypercapnia is also altered in the elderly**

ALTHOUGH MOST STUDIES HAVE SHOWN A DECREASE CBF, AS WELL AS A DETERIORATION IN THE REGULATION OF CBF WITH ADVANCING AGE, THIS PREMISE IS NOT UNIVERSALLY ACCEPTED BECAUSE ISOLATING AGE AS AN INDEPENDENT FACTOR IS OFTEN DIFFICULT

CEREBRAL BLOOD FLOW

AUTOREGULATORY FAILURE



- **Cerebral autoregulation is disturbed in a number of disease states:**
  - **acute ischemia**
  - **mass lesions**
  - **trauma**
  - **inflammation**
  - **neonatal asphyxia**
  - **diabetes mellitus**

CEREBRAL BLOOD FLOW

AUTOREGULATORY FAILURE

- **Despite a wide range of causes, the final common pathway of dysfunction, in its most extreme state, may be termed *vasomotor paralysis***

CEREBRAL BLOOD FLOW

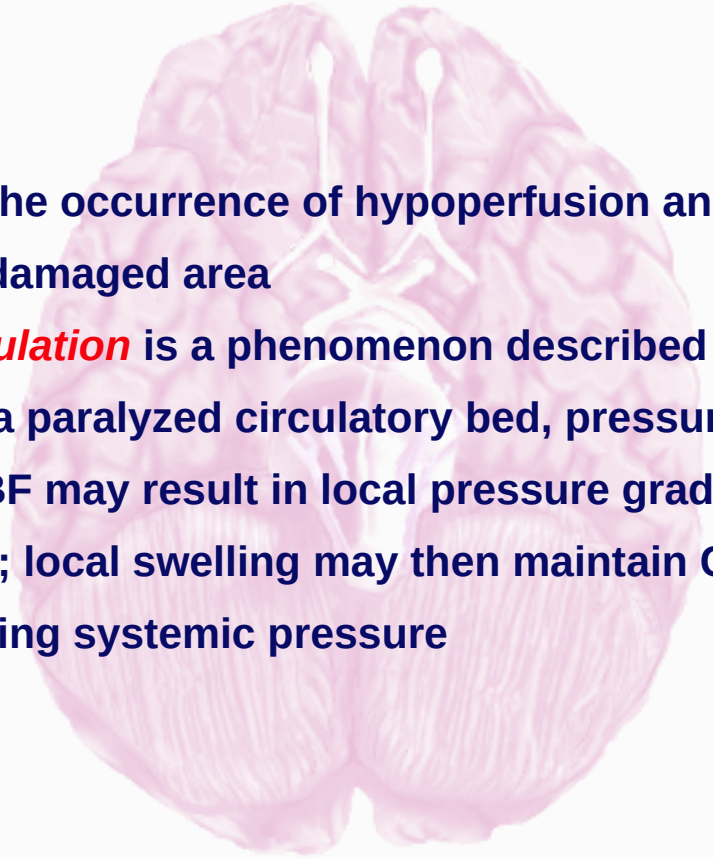
AUTOREGULATORY FAILURE

- **The term *dissociated vasoparalysis* describes retained CO_2 responsiveness with loss of autoregulatory capacity to changes in blood pressure**
- **This response can be observed in regions contralateral to tumor or infarction or during hyperperfusion after AVM resection**

- **PRESSURE REGULATION IS MUCH MORE VULNERABLE THAN IS LOSS OF CO_2 REACTIVITY OR POSSIBLY OTHER METABOLIC INFLUENCES ON REGULATORY MECHANISMS**
- **TOTAL LOSS OF CO_2 RESPONSIVENESS IS PROBABLY A PRETERMINAL EVENT**

CEREBRAL BLOOD FLOW

AUTOREGULATORY FAILURE



- ***Diaschisis*** **is the occurrence of hypoperfusion and hypometabolism remote from a damaged area**
- ***False autoregulation*** **is a phenomenon described in the setting of head injury: in a paralyzed circulatory bed, pressure-passive increases in CBF may result in local pressure gradients in the most damaged areas; local swelling may then maintain CBF constant despite increasing systemic pressure**

HYPOPERFUSION AND ISCHEMIA

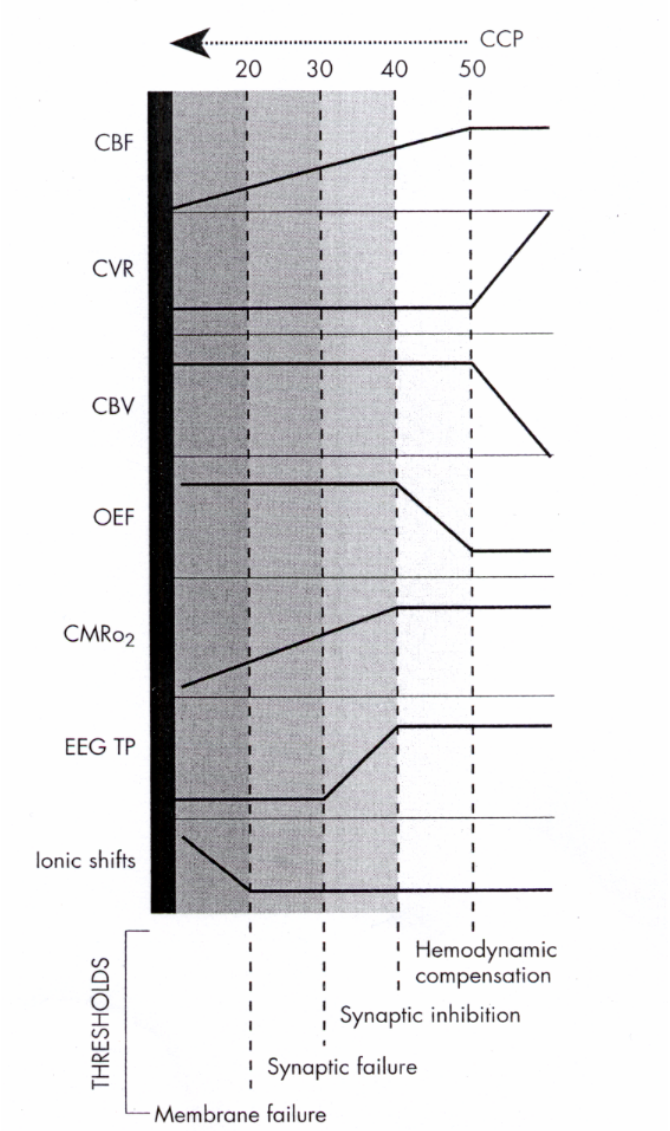
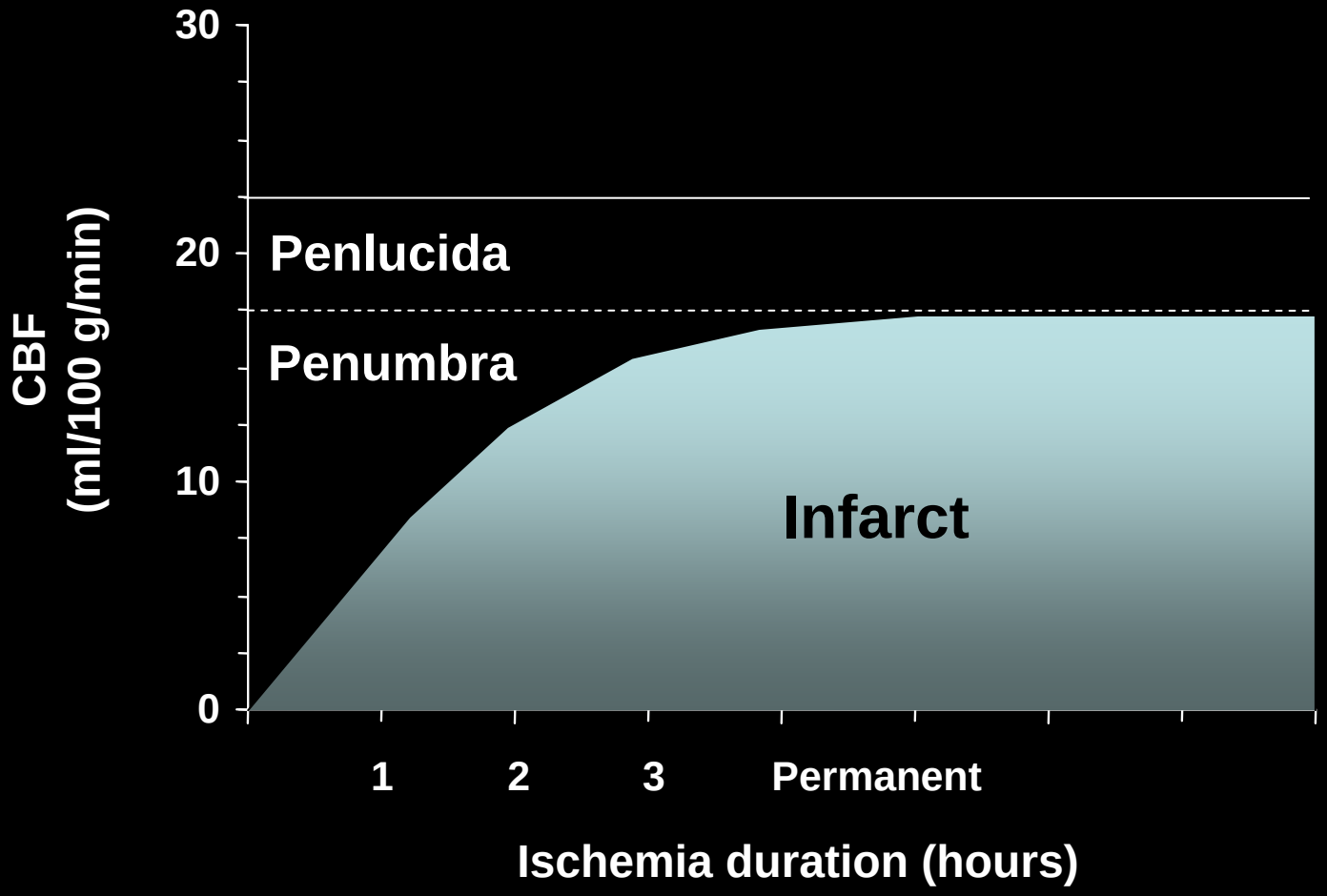


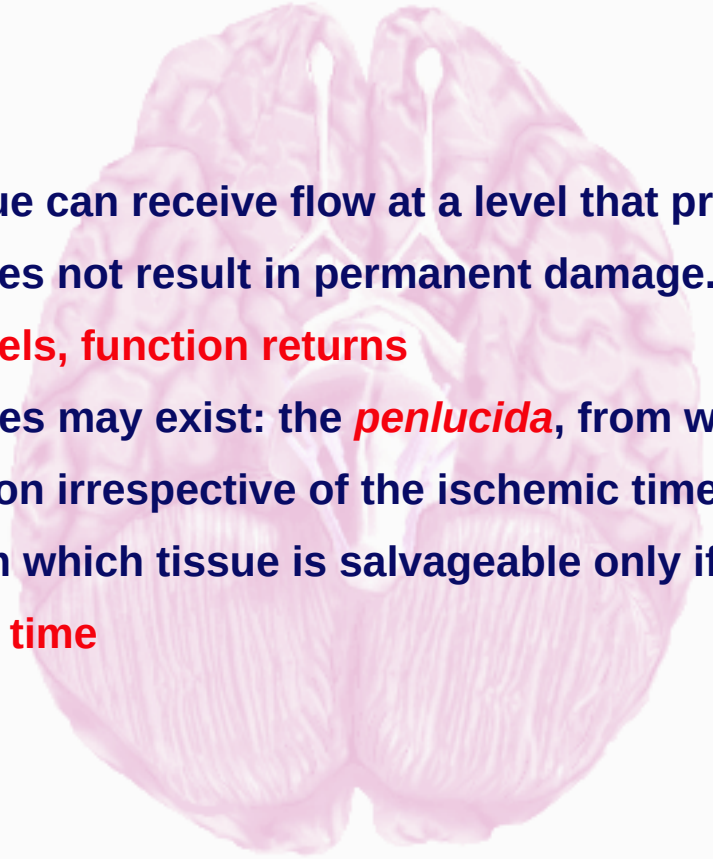
FIG. 2-16 Autoregulatory failure. The left side of Fig. 2-4 is expanded here to show idealized changes in various physiologic functions (some of the pathophysiologic events indicated overlap). The values for CPP are only approximate, and many of the changes in the various covariates may overlap. They are stylized here for the sake of clarity. *CBF* (cerebral blood flow), *CVR* (cerebrovascular resistance), *CBV* (cerebral blood volume), *OEF* (oxygen extraction fraction), $CMRo_2$ (cerebral metabolic rate for oxygen), *EEG TP* (total power of the cortical EEG signal), and *ionic shift* (e.g., water and Na^+ into the cells and K^+ out of the cells) are shown along the left of the figure. The various CBF thresholds are indicated by the broken lines and labeled at the bottom of the figure. The functional state between each threshold is shown along the abscissa. In this figure the loss of EEG power is still above the line for membrane failure. Clinically, any event that results in EEG signs of ischemia should be assumed to represent the potential for irreversible damage and should be treated accordingly. (From Young W: *Clinical neuroscience lectures*, Munster, 1999, Cathenart Publishing.)

INTERACTION OF DEGREE AND DURATION OF FLOW REDUCTION ON NEUROLOGIC FUNCTION



CEREBRAL BLOOD FLOW

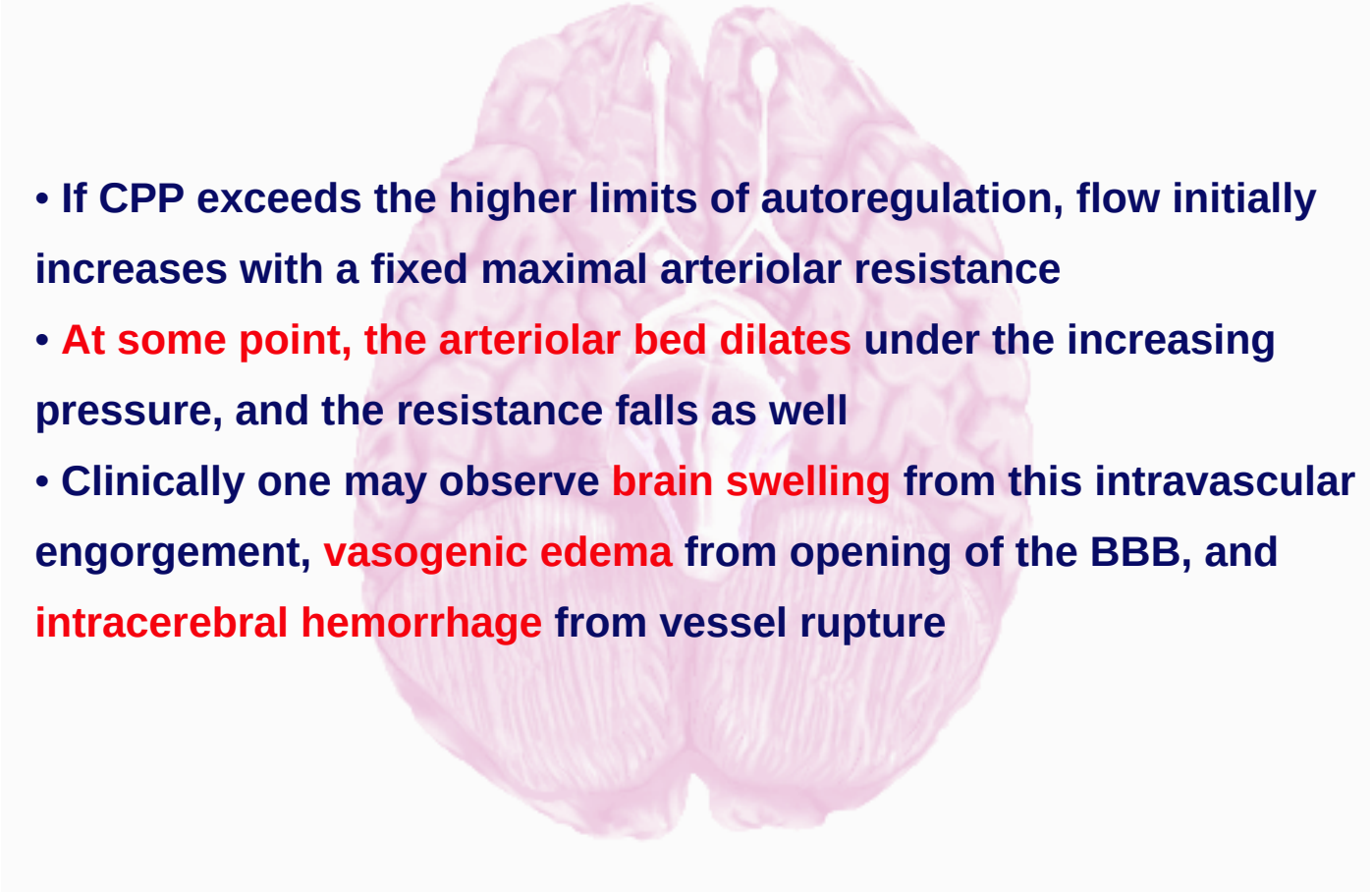
HYPOPERFUSION AND ISCHEMIA



- **Neuronal tissue can receive flow at a level that prevents normal function but does not result in permanent damage. If flow is returned to adequate levels, function returns**
- **Two such states may exist: the *penlucida*, from which tissue recovers function irrespective of the ischemic time, and the *penumbra*, from which tissue is salvageable only if flow is restored within a certain time**

CEREBRAL BLOOD FLOW

HYPERPERFUSION AND CIRCULATORY BREAKTHROUGH



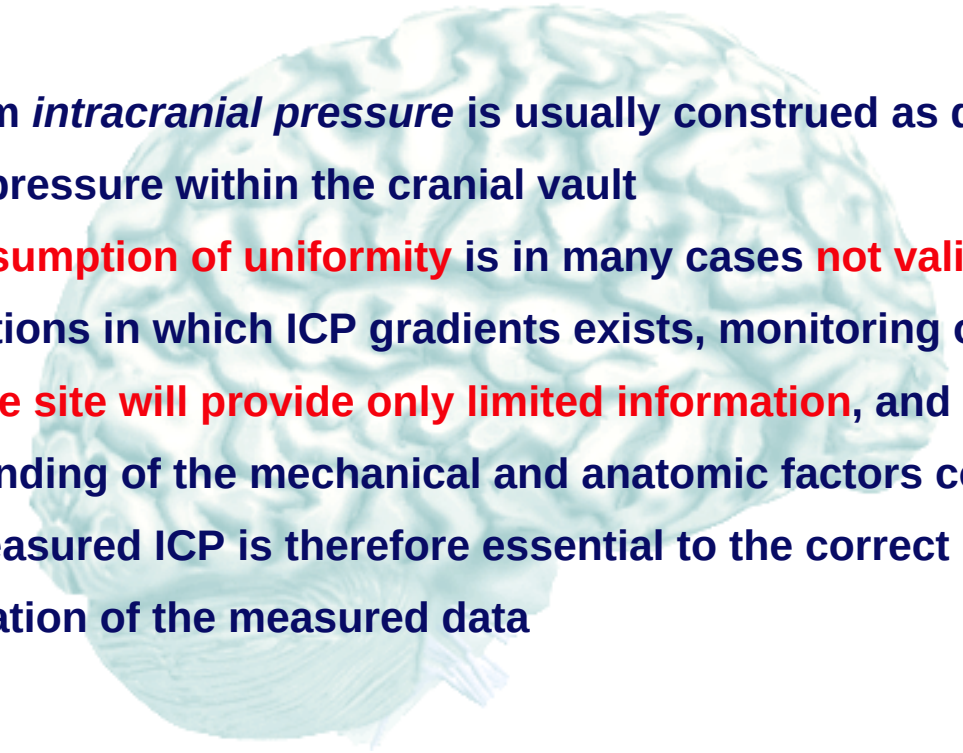
- **If CPP exceeds the higher limits of autoregulation, flow initially increases with a fixed maximal arteriolar resistance**
- **At some point, the arteriolar bed dilates under the increasing pressure, and the resistance falls as well**
- **Clinically one may observe brain swelling from this intravascular engorgement, vasogenic edema from opening of the BBB, and intracerebral hemorrhage from vessel rupture**

CEREBRAL METABOLISM

CEREBRAL BLOOD FLOW

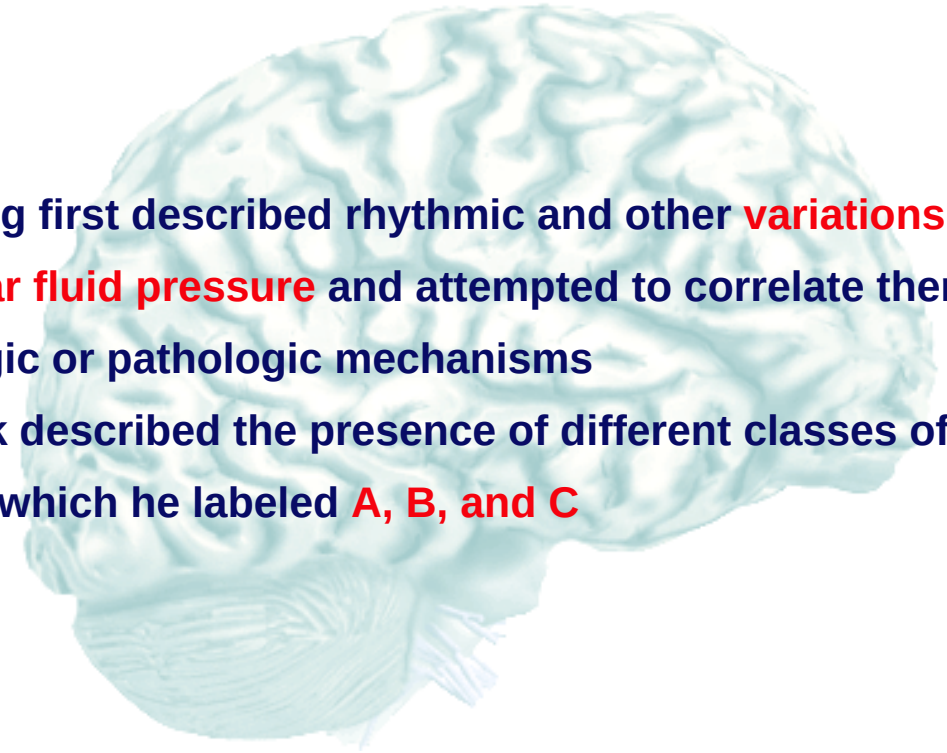
INTRACRANIAL PRESSURE

INTRACRANIAL PRESSURE



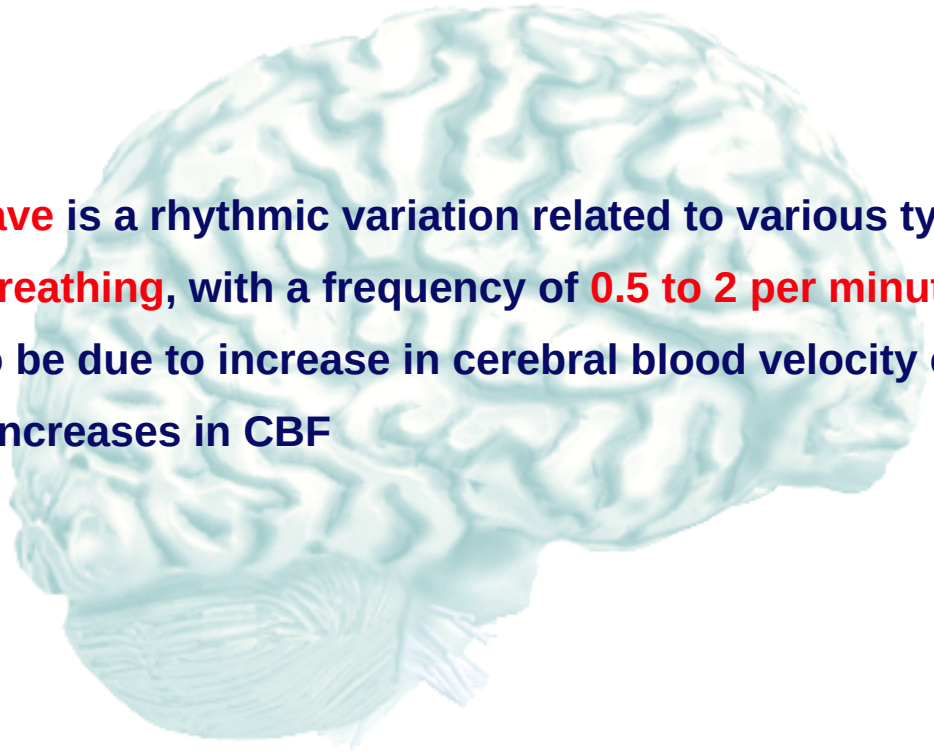
- **The term *intracranial pressure* is usually construed as defining a uniform pressure within the cranial vault**
- **This assumption of uniformity is in many cases not valid**
- **In situations in which ICP gradients exists, monitoring of pressure at a single site will provide only limited information, and an understanding of the mechanical and anatomic factors contributing to the measured ICP is therefore essential to the correct interpretation of the measured data**

INTRACRANIAL PRESSURE



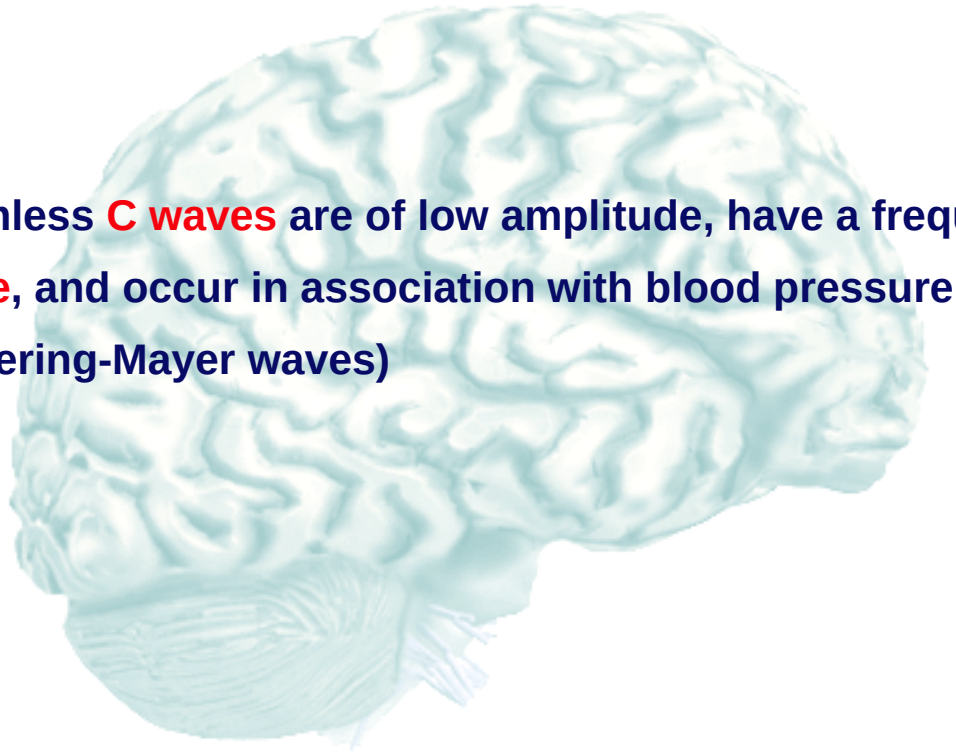
- **Lundberg first described rhythmic and other variations in ventricular fluid pressure and attempted to correlate them with their physiologic or pathologic mechanisms**
- **His work described the presence of different classes of pressure "waves", which he labeled A, B, and C**

INTRACRANIAL PRESSURE



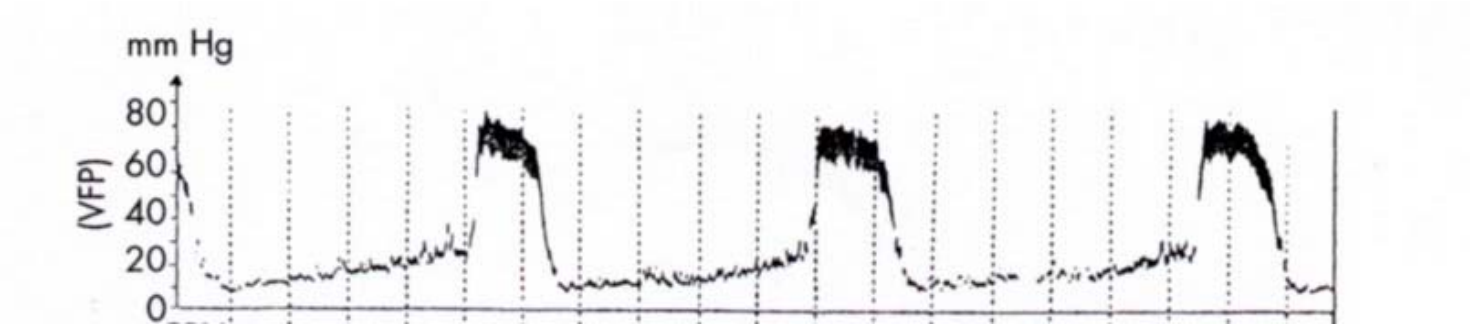
- **The B wave is a rhythmic variation related to various types of periodic breathing, with a frequency of 0.5 to 2 per minute. It is thought to be due to increase in cerebral blood velocity causing transient increases in CBF**

INTRACRANIAL PRESSURE



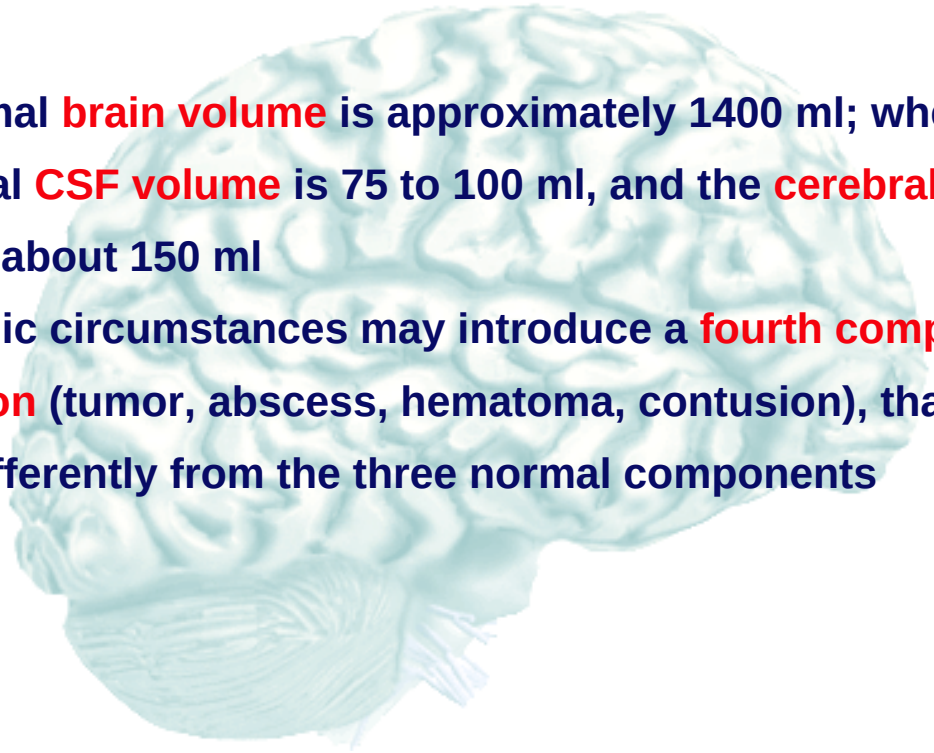
- **The harmless C waves are of low amplitude, have a frequency of 6 per minute, and occur in association with blood pressure phenomena (Traube-Hering-Mayer waves)**

INTRACRANIAL PRESSURE



- **A waves (plateau waves) were often associated with significant neurologic manifestations**
- **An A wave is tipically an acute elevation in ICP lasting from 5 to 20 minutes followed by a rapid fall to the former baseline level**
- **The amplitude of the plateau wave is generally 20 mmHg, although it may reach levels of 100 mmHg**

INTRACRANIAL PRESSURE



- **The normal brain volume is approximately 1400 ml; whereas the intracranial CSF volume is 75 to 100 ml, and the cerebral vascular volume is about 150 ml**
- **Pathologic circumstances may introduce a fourth component, the mass lesion (tumor, abscess, hematoma, contusion), that may behave differently from the three normal components**

INTRACRANIAL PRESSURE

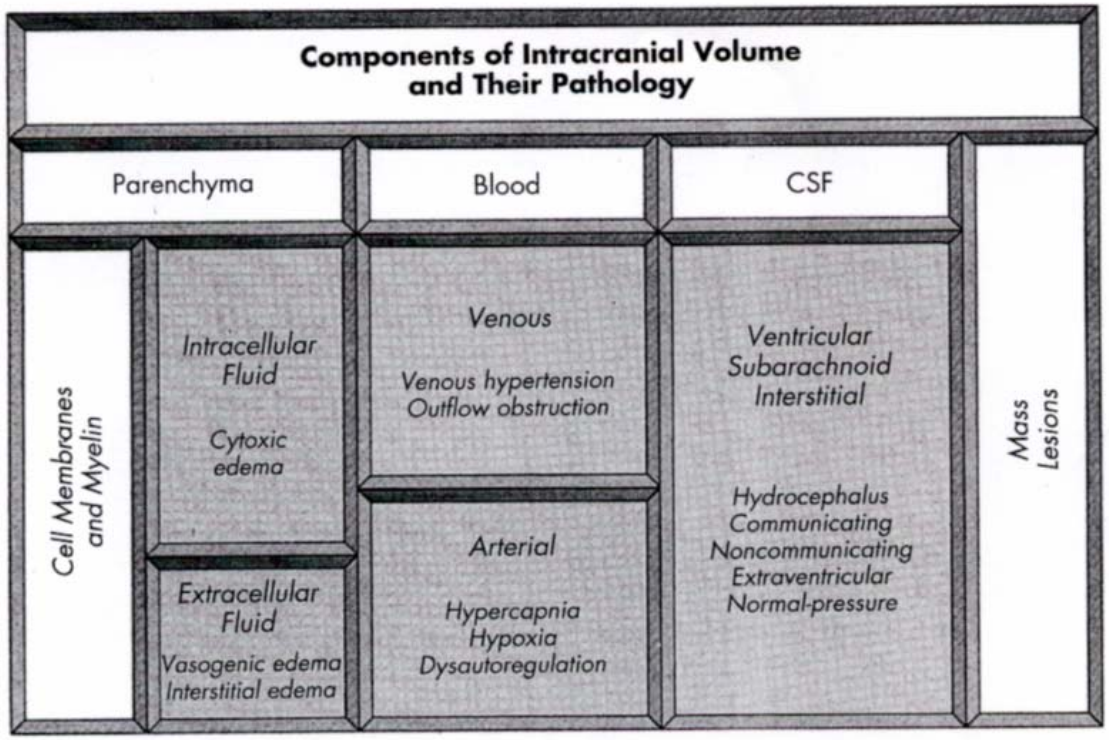
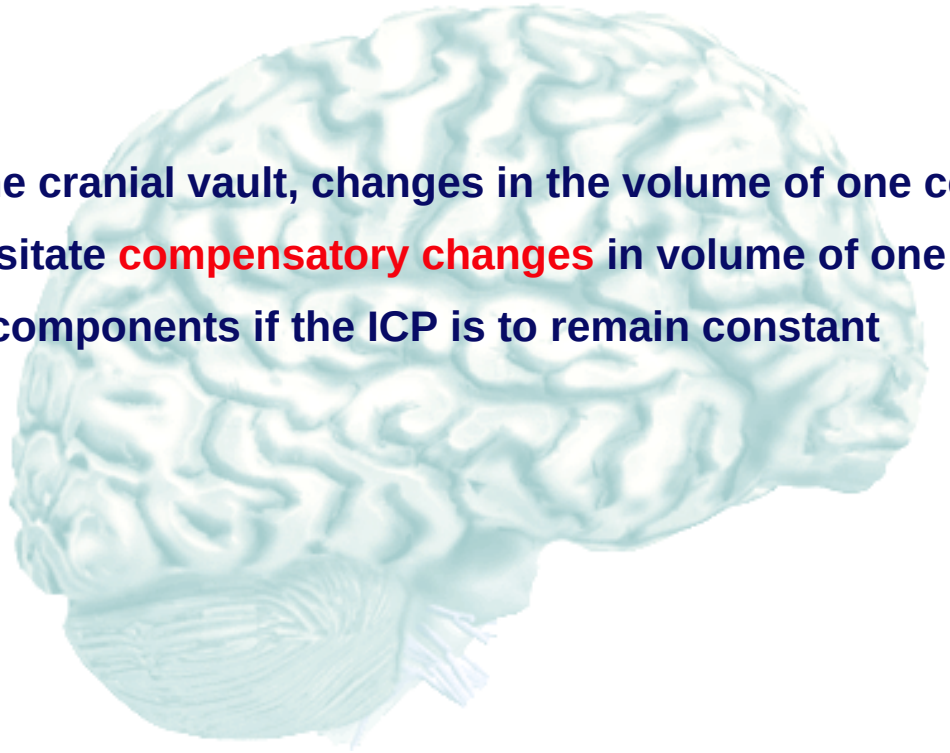


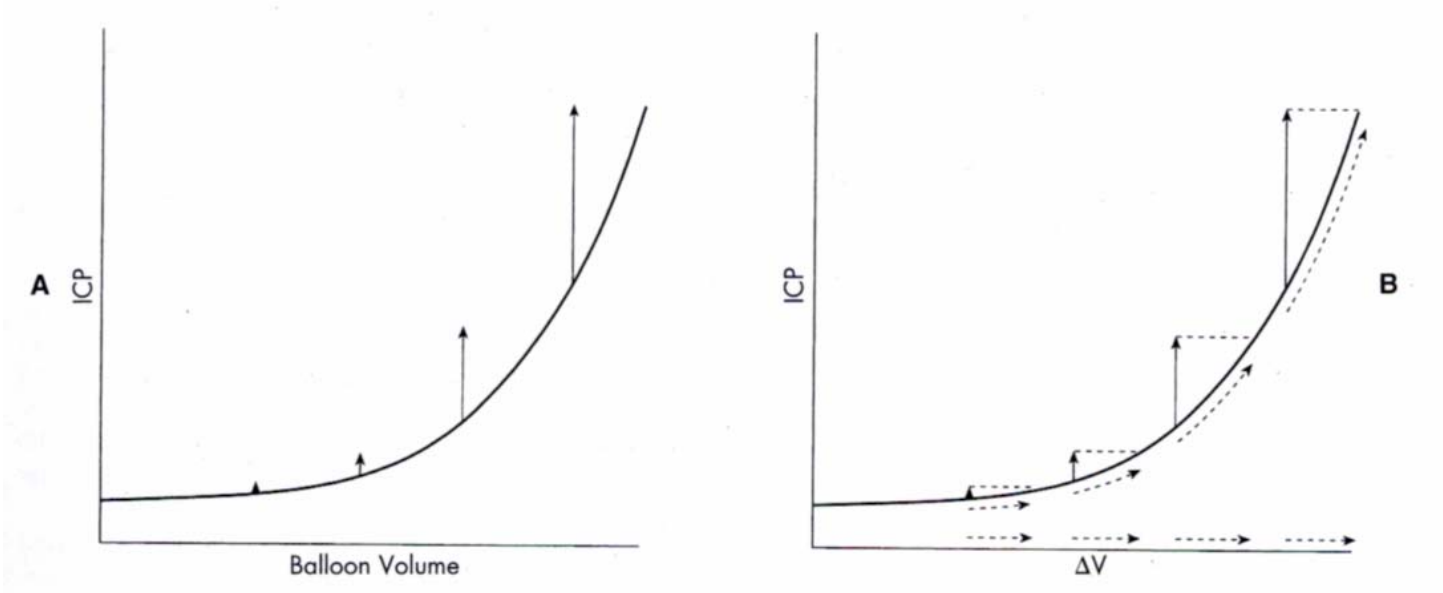
FIG. 5-2 Components of intracranial volume. Shaded portions indicate those elements that undergo volume changes in pathologic states; examples of such conditions are given for each component.

INTRACRANIAL PRESSURE



- **Within the cranial vault, changes in the volume of one component will necessitate compensatory changes in volume of one or more of the other components if the ICP is to remain constant**

INTRACRANIAL PRESSURE



- **The relative proportion and arrangements of brain parenchyma, CSF, and blood volume - together with mass lesion when present - may play an important role in determining ICP**
- **The putative relationship between volume and pressure in the intracranial space has been expressed as the so-called *pressure-volume curve***

INTRACRANIAL PRESSURE

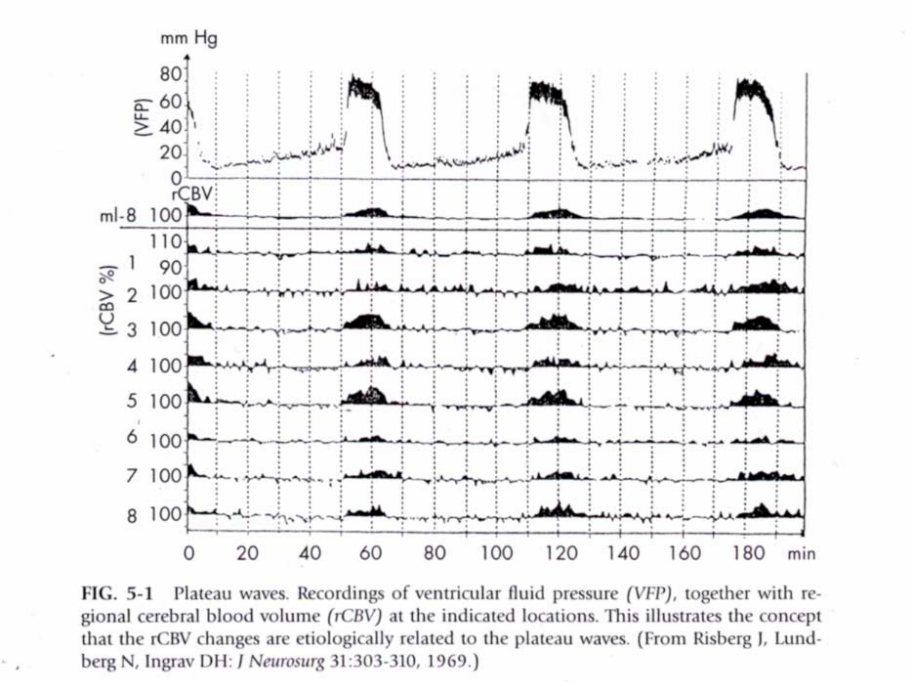
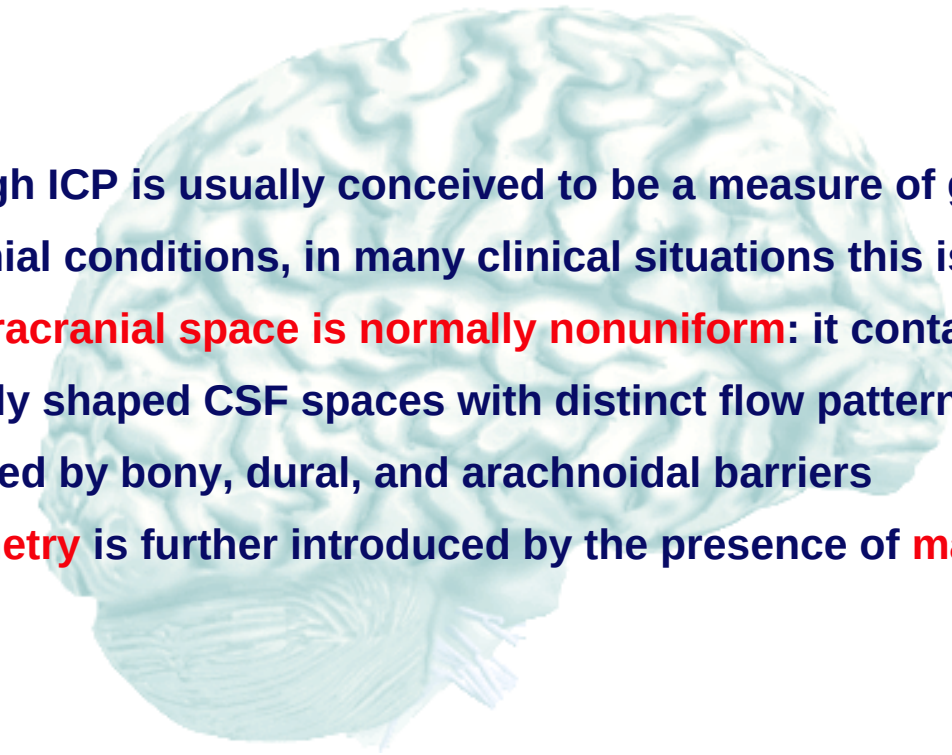


FIG. 5-1 Plateau waves. Recordings of ventricular fluid pressure *(VFP)*, together with regional cerebral blood volume *(rCBV)* at the indicated locations. This illustrates the concept that the rCBV changes are etiologically related to the plateau waves. (From Risberg J, Lundberg N, Ingrav DH: *J Neurosurg* 31:303-310, 1969.)

- **The relationship between cerebral blood volume and compliance is more complex**
- **The pathologic plateau waves occurred in association with regional increases in cerebral blood volume during a presumably low compliance state**
- **It has been proposed that vasodilation causes a rapid rise in ICP with concomitant obstruction of cerebral venous drainage, thus resulting in the increased rCBV and decreased CBF**

INTRACRANIAL PRESSURE

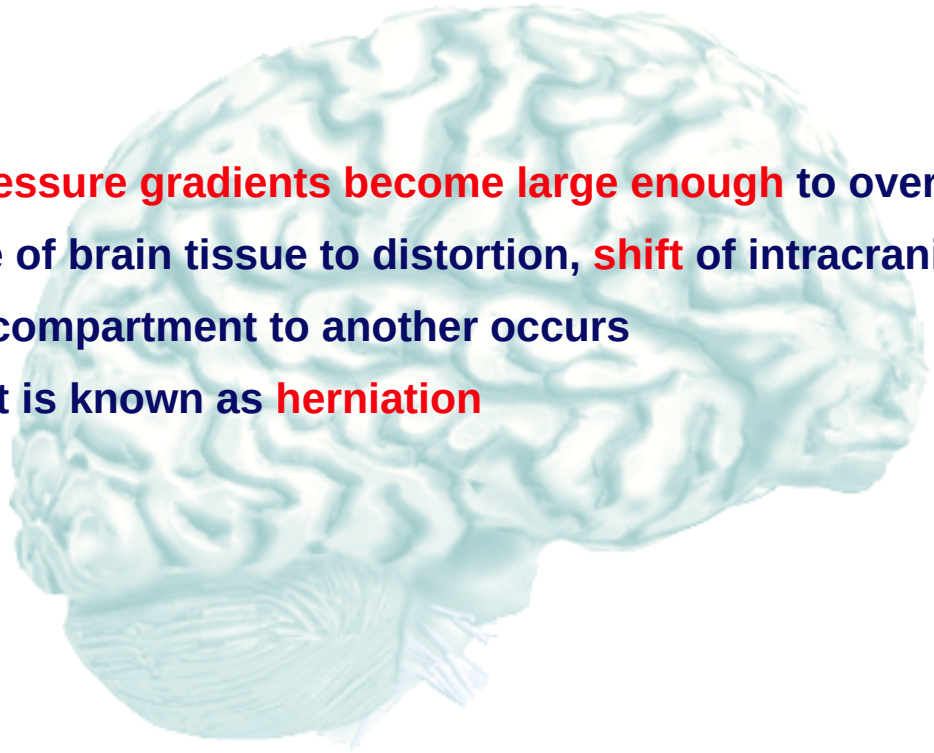


- **Although ICP is usually conceived to be a measure of global intracranial conditions, in many clinical situations this is untrue**
- **The intracranial space is normally nonuniform: it contains irregularly shaped CSF spaces with distinct flow patterns and is subdivided by bony, dural, and arachnoidal barriers**
- **Asymmetry is further introduced by the presence of mass lesions**

INTRACRANIAL PRESSURE

- **Under normal conditions, the various compartments communicate via the CSF channels, both within and outside the brain substance**
- **Focal pathologic lesions may cause obstruction of CSF flow and blockage of CSF egress from one portion of the ventricular system but not from another**
- **Under these circumstances, a catheter placed in one ventricular space may not accurately reflect pressure in another**
- **In addition, focal brain pathologic conditions alter the viscoelastic properties of the injured brain**

INTRACRANIAL PRESSURE



- **When pressure gradients become large enough to overcome the resistance of brain tissue to distortion, shift of intracranial contents from one compartment to another occurs**
- **This shift is known as herniation**

INTRACRANIAL PRESSURE

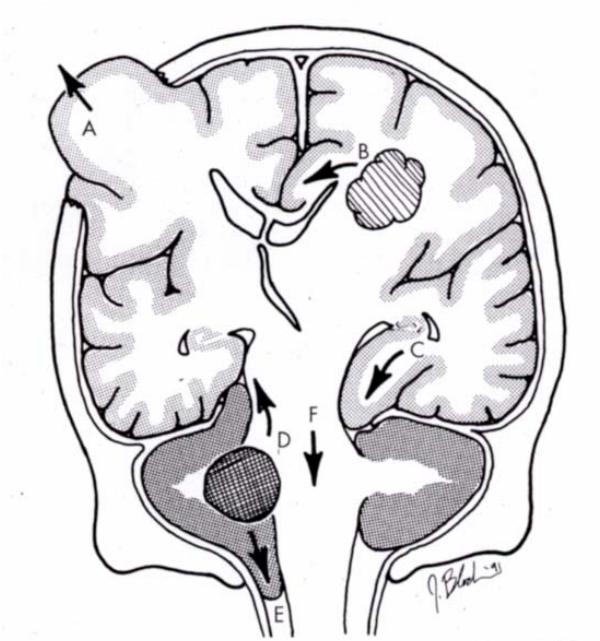


FIG. 5-5 Herniation syndromes. *A*, Transcalvarial; *B*, subfalcine; *C*, transtentorial (uncal); *D*, transtentorial ("upward"); *E*, tonsillar; *F*, transtentorial (central, or "coning").

• The hemispheres may herniate under the falx (subfalcine herniation), the supratentorial contents may herniate through the tentorial notch (transtentorial herniation), or the cerebellar tonsils may herniate through the foramen magnum

INTRACRANIAL PRESSURE

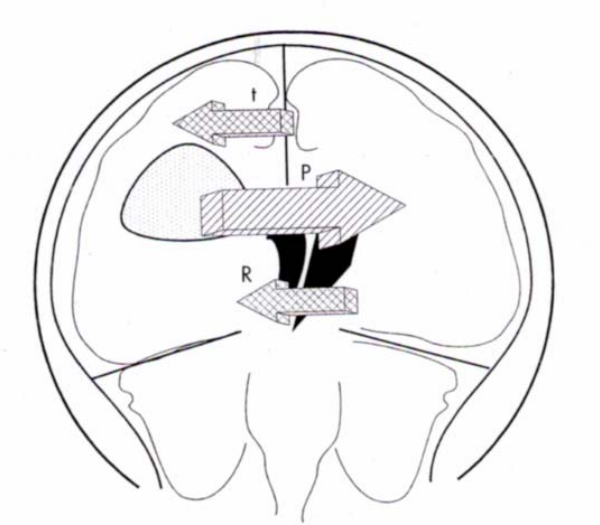
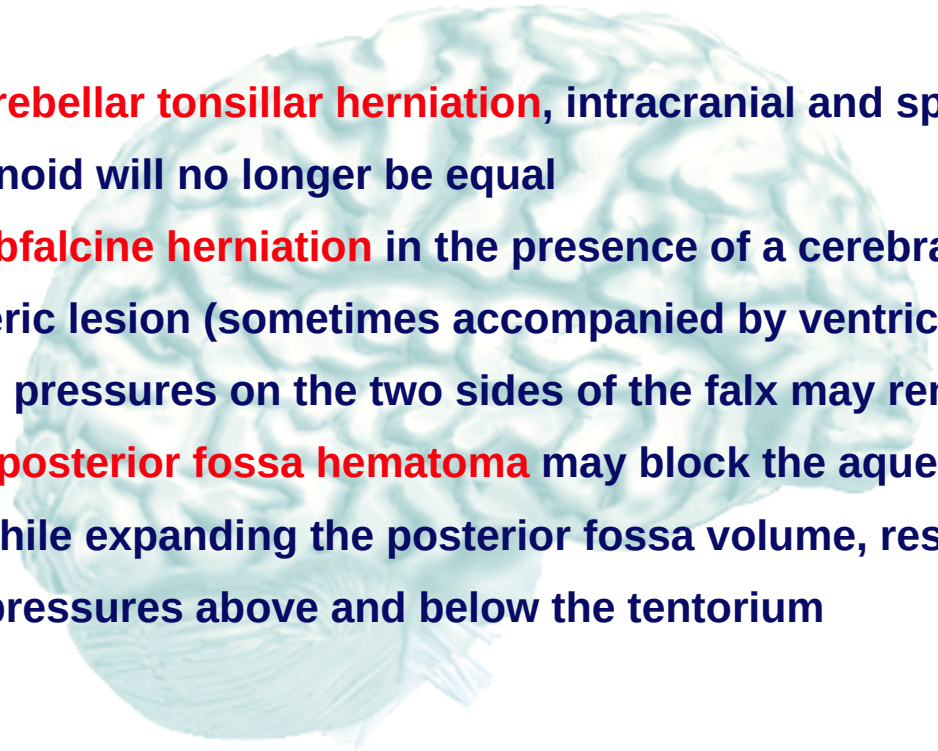


FIG. 5-6 Schematic diagram of intracranial forces in the presence of a mass lesion. *P*, Pressure gradient resulting from the presence of a hemispheric mass lesion; *t*, tentorial resistance force normal to this pressure gradient; *R*, composite force representing the sum of elastic, tangential, and other forces acting in various directions with components normal to the pressure gradient and opposite in sign. The system will be in equilibrium when $P = t + R$. This illustrates why a pressure gradient may be measured between the two hemispheres, even when equilibrium is reached.

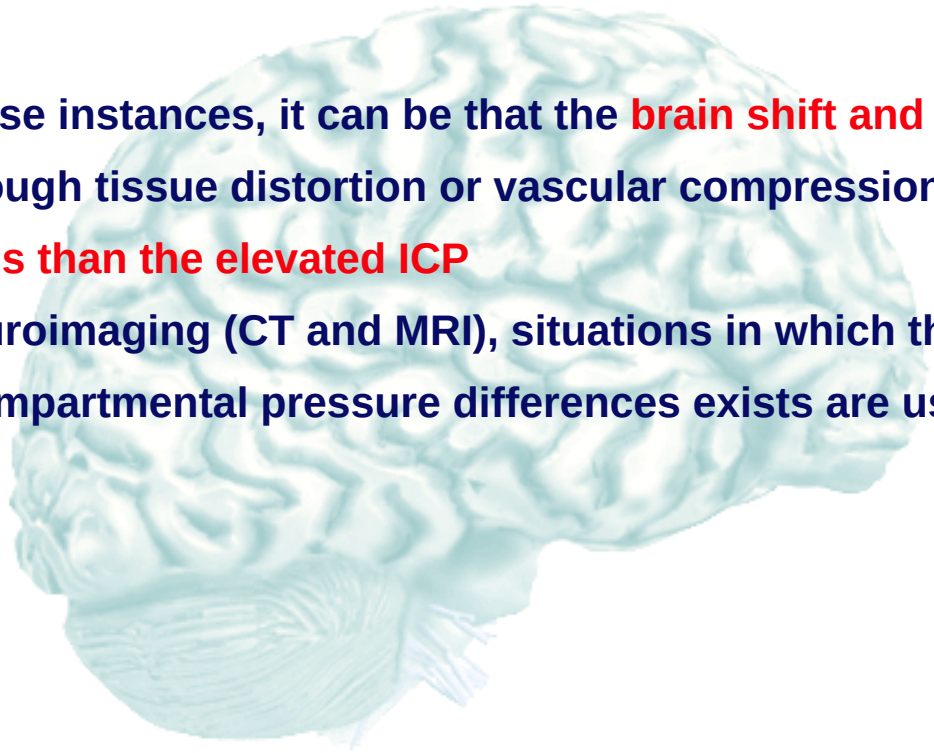
- **Movement will continue until the pressure gradient is eliminated or until the physical properties of the herniating tissue prevent further movement, even though a pressure gradient remains**

INTRACRANIAL PRESSURE



- **After cerebellar tonsillar herniation, intracranial and spinal subarachnoid will no longer be equal**
- **After subfalcine herniation in the presence of a cerebral hemispheric lesion (sometimes accompanied by ventricular trapping), pressures on the two sides of the falx may remain unequal**
- **A small posterior fossa hematoma may block the aqueduct of Sylvius while expanding the posterior fossa volume, resulting in unequal pressures above and below the tentorium**

INTRACRANIAL PRESSURE



- **In all these instances, it can be that the brain shift and movement itself, through tissue distortion or vascular compression, are more deleterious than the elevated ICP**
- **With neuroimaging (CT and MRI), situations in which the possibility of intercompartmental pressure differences exists are usually apparent**