1 Cerebral Blood Flow Physiology and Metabolism

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The brain comprises only 2% of total body weight; however, under normal conditions, it receives 15–20% of the cardiac output and accounts for 20% of total body oxygen consumption.[1] Because energy reserves within the brain are negligible, adequate blood flow is essential for the provision of a continuous supply of energy-producing substrates and for the removal of the byproducts of cellular metabolism.[1]

NORMAL PHYSIOLOGY OF CEREBRAL BLOOD FLOW

Cerebral blood flow (CBF) is normally approximately 50 mL/100 g per minute.[2] Regionally it is greater for gray matter than for white matter, 70 mL/100 g per minute versus 20 mL/100 g per minute, respectively. This rate is slightly increased in youth, and decreases with age.[3–5]

- CBF less than 30 mL/100 g per minute can produce neurologic symptoms.[2,3]
- CBF between 15 and 20 mL/100 g per minute will cause reversible damage or "electrical failure"[1,6,7]
- CBF rates of 10–15 mL/100 g per minute cause irreversible neuronal damage.[6,7]

CBF is determined by blood viscosity, cerebral perfusion pressure (CPP), and vessel radius. This relationship is expressed with the Hagen–Poiselle formula:

$$Q = P * P_i * r^4 / 8 * n * L$$

where P is CPP, r is the cumulative radii of cerebral regulatory resistance vessels, n is whole blood viscosity, L is cerebral vessel length, and Q is CBF. Vessel length is not a physiologic variable that changes or can be manipulated. The brain has no significant storage capacity, so metabolism and CBF are tightly coupled, and this is called metabolic-flow coupling. This relationship can be expressed with Fick's equation:

$$CMRo_2 = CBF * AVDo_2.$$

- $AVDo_2$ is the arteriovenous difference in oxygen and $CMRo_2$ is the central nervous system metabolic rate of oxygen consumption.
- Under normal conditions the brain maintains normal $AVDo_2$ by responding to changes in metabolism, CPP, and blood viscosity with changes in cerebral vessel caliber, that is, autoregulation.[2,8,9]
- As demonstrated with the Hagen–Poiselle formula, vessel radius is the largest determinant of CBF.

AUTOREGULATION

- The differentiation between the terms cerebral autoregulation and regulation of CBF is often confusing. The latter term broadly encompasses a variety of vasomotor regulatory mechanisms, of which cerebral autoregulation is one type.[10] Cerebral autoregulation describes the intrinsic ability of the cerebral circulation to maintain a constant blood flow in the face of changing perfusion pressure.[11] This is purely a pressure-related phenomenon. The changes are subserved mainly by precapillary resistance vessels.[12] Arteries dilate in response to

decreased perfusion and constrict in response to increased perfusion. The exact mechanism of autoregulation is unknown. Proposed mechanisms include the myogenic hypothesis, the endothelial hypothesis, and the neurogenic hypothesis. The myogenic theory is the most widely accepted explanation for the mechanism of autoregulation.

- A metabolic hypothesis has also been described, but is better suited as a description of metabolic-flow coupling rather than autoregulation.

Bayliss first proposed the myogenic theory in 1902 after he observed the direct constriction and relaxation of canine arteries in response to changes in intravascular pressure. The myogenic theory assumes that there is a basal tone of vascular smooth muscle, which is affected by changes in transmural pressure.[1,13] This results in constriction of precapillary arterioles to rising intravascular pressure and dilatation to falling intravascular pressure.[8,11] Studies suggest that there may be two myogenic mechanisms involved in cerebral autoregulation: a rapid fast reaction to pressure pulsations and a slower reaction to change in mean arterial pressure (MAP).[14]

Important evidence supporting the myogenic theory is the existence of stretch-activated cation channels (SACCs) in myocytes.[10,15] SACC activation is associated with an influx of cations, especially calcium and sodium, leading to cellular depolarization. This, in turn, results in the opening of membrane voltage-gated calcium channels (VGCCs) with the end result of smooth muscle contraction.[10,16] The neurogenic hypothesis states that alterations in transmural pressure trigger changes in neurotransmitter release from perivascular nerve fibers.[10] The hypothesis is supported by several facts:

- First, both intracranial and extracranial arteries are endowed with a rich and active network of nerves located throughout the adventitial space as demonstrated by anatomic studies.[10,17] There is innervation from both extrinsic (remote) and intrinsic (local) neurons. Origins of the extrinsic neurons supplying blood vessels are the sympathetics from the superior cervical ganglion, parasympathetics from the pterygopalatine, sphenopalatine, and otic ganglion, trigeminal connections from the gasserian ganglion, and serotonergic neurons from the raphe nuclei.[18] There are also intrinsic peptidergic neurons from local adventitial neurons.[18]
- Second, the presence of specific neurotransmitter receptors has been demonstrated on vascular endothelial and smooth muscle cells.[10,18]
- Third, nerve stimulation studies demonstrated a correlation between altered vasomotor tone after electrical stimulation of deendothelialized arteries.[10]

Current literature suggests that some neurogenic control comes into play only under conditions of cerebrovascular stress.[18–20] It may be that neurogenic mechanisms lead to very fine-tuned modulation or that they protect cerebral vessels during acute, severe stress.[20]

The endothelial hypothesis suggests that the cerebral arterial endothelial cells may act as a mechanoreceptor that senses and transduces variations in mechanical factors such as stretch and flow velocity into altered vascular tone.[10,21,22] It is known that the endothelium releases substances that are vasoactive such as endothelium-derived relaxing factors, nitric oxide, endothelium-derived hyperpolarizing factor, thromboxane, and endothelin-1.[22,23] Observations that increasing flow rate and shear stress without increasing transmural pressure can induce endothelial vasodilatation suggest endothelial dependence of vasomotor activity.[10,23] It is thought that the changes in vasomotor tone are brought about by a change in the endothelium's liberation of relaxing or contracting factors.[22,23] This is corroborated by an experiment wherein changes in vascular smooth muscle tone were observed after smooth muscle cells were exposed to perfusate from normal endothelium that had been exposed to changes in transmural pressure.[23]

The metabolic theory argues that autoregulation is determined by the release of vasoactive substances that regulate the resistance of the cerebral vessels keeping CBF constant. This assumes that the primary determinant of regional blood flow is local cerebral metabolic activity, that is, metabolic-flow coupling. Although no specific agent has been identified as the primary determinant of flow adenosine, potassium, prostaglandins, and nitric oxide have been proposed as metabolic coupling agents.

- Adenosine is of particular interest, as it is known to be a potent vasodilator. It is formed by the

breakdown of ATP, and is abundant when oxygen supply is not sufficient to meet metabolic demands, that is, anaerobic metabolism.[14]

- Adenosine binds to A1 and A2 receptors located on neurons and vascular smooth muscle cells respectively.
  - The A1 receptors inhibit neuronal activity, and the A2 receptors activate a second messenger cascade mediated by adenylate cyclase. These events together are considered protective when there is a flow-metabolism mismatch.

Potassium (K) is released during neuronal excitation. During periods of hypoxia, electrical stimulation, and seizures, increases in perivascular K coincide with increases in CBF.[13] In the range of 2–10 mM, extracellular K causes vasodilatation due to hyperpolarization of the vascular smooth muscle cells and decreased cytosolic calcium ion levels.[10] At concentrations above 10 mM, K acts as a vasoconstrictor.

Arachidonic acid metabolites, or eicosanoids, affect cerebral arterial vasomotor tone, and likely play a role in modulating CBF.[10] Eicosanoids are generated from three major enzyme systems: cyclooxygenase (COX), lipoxygenase (LOX), and epoxygenase (EPOX). Some are vasodilators such as prostacyclin (PGI_2) and others are vasoconstrictors such as thromboxane (TXA_2). Also suggesting the importance of prostaglandins is the fact that the use of the nonsteroidal anti-inflammatory drug (NSAID) indomethacin can block the ability of the brain to maintain constant cerebral perfusion during arterial hypotension.[13]

Nitric oxide (NO) is a freely diffusible molecule that regulates CBF. NO has a short half-life of approximately 6 seconds, and is produced from L-arginine by a group of enzymes designated NO synthases (NOS). NO usually works via a second messenger pathway to stimulate vascular smooth muscle relaxation. Two constitutive forms of NOS, nNOS and eNOS, and one inducible form, iNOS, are present in the brain. The constitutive forms have a role in physiologic regulation of blood flow.

- nNos is found in glia and neurons near the vasculature, and eNOS in the endothelial layers of large vessels and astrocytes in contact with blood vessels.[10,24]
- nNOS has an important role in the regulation of CBF in response to metabolism, hypercapnia, and ischemia.[13]
- eNOS is believed to play a role in blood flow during ischemia. This is supported by the observation that elevated levels of eNOS were detected 4–6 hours after global ischemic insult.[13]

Limits of Autoregulation

In a normotensive individual, the brain is able to keep CBF stable between MAPs of 60–150 mm Hg. This is sometimes called the autoregulatory plateau. Below this level, vasodilation becomes insufficient, and ischemia results. Above this level, increased intraluminal pressure forcefully dilates the arterioles, causing luxury perfusion.[2] This breakthrough of autoregulation is accompanied by damage to the endothelium, and disruption of the blood–brain barrier. This results in extravasation of plasma proteins into the brain, neuronal dysfunction and damage, and development of edema.[2,23]

Autoregulation can be impaired by many pathologic insults including hypoxia, ischemia, head injury, and aneurysmal subarachnoid hemorrhage. Then CBF passively follows changes in arterial pressure. Loss of autoregulation can be a global, focal, or multifocal process.

CO_2 Regulation of CBF

Carbon dioxide has long been known to have an effect on CBF. Between a $PaCO_2$ range of 25–60 mm Hg, a 1 mm Hg change in $PaCO_2$ changes CBF by 3–4%.[1,2,5] Decreases in $PaCO_2$ cause increased in vasoconstriction, and increases in $PaCO_2$ cause vasodilatation. CO_2 is a rapidly diffusible gas that readily crosses the blood–brain barrier into the perivascular space and to the cerebral vascular smooth muscle cells.[14] CO_2 is then broken down by carbonic anhydrase into bicarbonate and hydrogen ions. The change in CBF is not mediated by a direct effect of carbon dioxide. Instead, the change is mediated through one of two different mechanisms: either pH changes in the extracellular fluid around microvessels or the H^+ ions affect vessels directly. Effects occur within seconds after $PaCO_2$ is changed, and complete equilibration occurs within 2 minutes.[14] Decreased responsiveness to $PaCO_2$ variability is seen in severe carotid stenosis, head injury, subarachnoid hemorrhage, cardiac failure, or where vascular response is already exhausted. Carbon

dioxide–dependent vasoconstriction of arterioles is also impaired at reduced hematocrit.[25,26]

Oxygen

In the normal physiologic range for PaO_2, 60–100 mm Hg, fluctuations in PaO_2 do not affect CBF. However, CBF does dramatically increase when PaO_2 drops below 50 mm Hg. Important mediators for this enhanced blood flow may be increases in adenosine concentration and/or developing extracellular acidosis related to the anaerobic metabolism of glucose.[27] Molecular oxygen has been shown to directly affect vascular smooth muscle tone, and may be a mediator of the flow response to changes in PaO_2.[1,28]

Shifts in CBF

Chronic hypertension shifts the limits of autoregulation toward higher MAPs, that is, the lowest and highest blood pressures tolerated are higher. This inhibits the ability of chronically hypertensive patients to maintain CBF and $CMRO_2$ during acute hypotensive stimuli. Pressures that would be tolerated in a nonhypertensive individual can be symptomatic in a hypertensive individual.[29,30] Thickening of the tunica media of arterial walls has been seen in chronically hypertensive rats.[31] Hypertrophy of the vessel wall results in a decreased ability of the vasculature to dilate in response to a lower perfusion pressure, and an increased ability to vasoconstrict at higher perfusion pressures. These changes are thought to protect the vascular tissue from increased perfusion pressure.[30–32] Experimental evidence suggests that these adaptive changes are reversible, and that with effective treatment of the hypertension one can shift the autoregulatory limits back toward normal.[30,33]

BLOOD RHEOLOGY

The viscosity of blood refers to its consistency or "thickness," and determines its internal frictional resistance. This constitutes a determinant of flow. The Hagen–Poiselle equation demonstrates that blood flow is inversely related to blood viscosity. Under normal conditions viscosity has little effect on CBF, but in areas of the brain where autoregulation is depressed or completely lost it assumes a greater role.[34,35] Factors that affect whole blood viscosity are erythrocyte aggregation, deformability, shear rate, plasma viscosity, and hematocrit.[34]

Hematocrit is the most important element influencing whole blood viscosity.[36] Increases in CBF are known to occur during anemia. The increase is attributable to both reduced arterial oxygen content and blood viscosity.[25]

- Studies in animals and humans have demonstrated an increase in CBF between 19% and 50% when hematocrit was reduced by 7–14%.[36] The mechanism by which decreased hematocrit changes CBF is not completely clear.
- Studies evaluating changes in CBF under conditions of low CPP show no change in CBF. This suggests that decreasing the hematocrit has a direct vasodilatory effect, likely from the decreased availability of oxygen.[36,37] This implies that in areas of decreased oxygen availability, that is, ischemia, hemodilution would have no effect in increasing blood flow.
- Plasma viscosity has also been shown to affect CBF, and under conditions of increased CBF this role is increased.[38] Changes in CBF due to hemodilution are attributed to both improved rheology of the blood as well as a compensatory response to decreased oxygen delivery.[14,25,38]

Intracranial Pressure

The intracranial space contains three incompressible elements: brain (80%), blood (10%), and CSF (10%). The Monro–Kellie doctrine states that if one changes the volume of any of those three elements there must be a compensatory change in the other spaces to keep intracranial pressure (ICP) the same. In pathologic states, when ICP increases there is initially little change due to small volumes of CSF shifting into distensible spinal subarachnoid spaces. However, the exhaustion of this compensatory mechanism causes increases in ICP. The cerebral perfusion pressure (CPP) is defined as mean arterial pressure (MAP) – ICP, and is maintained in healthy individuals. However, as ICP rises, CPP will decrease if MAP is not changed. Thus, changes in ICP can have tremendous effects on CBF through changes in CPP.

TECHNIQUES FOR MEASUREMENT

KETY–SCHMIDT METHOD. Kety and Schmidt first described their method in 1945.[39] This process assumes that the quantity of any inert substance taken up by brain tissue is equal to the amount of substance carried to the brain in the arteries minus the amount removed by the venous system: the Fick principle. This method requires the inhalation of a highly diffusable inert gas, nitrous oxide. Jugular and arterial concentrations are then monitored to determine the quantity taken up by brain tissue.[39]

- This method has the advantage of proven reliability and easy repeatability. The Kety–Schmidt method also allows measurement of arteriovenous differences in oxygen, glucose, and lactate useful for determining cerebral metabolic rate.
- Disadvantages include invasiveness, inability to provide regional information, and the variability of venous drainage.[1]

NONINVASIVE XENON-133. The noninvasive xenon-133 clearance technique is also predicated upon the Fick principle utilizing xenon-133 as the inert substance. Xenon-133 is administrated either intravenously or via inhalation. Detectors positioned against the head monitor clearance of the isotope, and arterial concentrations are estimated from the analysis of end-tidal expired air. The elimination of isotope can be divided into a fast compartment, representing flow to the gray matter, and a slow compartment, representing flow to the white matter.

- This method has the advantage of not being invasive, and may be performed at the bedside.
- The disadvantages of this method are the inability to obtain information about deep structures, such as cerebellum or brain stem, and because the method assumes a normal blood–brain barrier.[1,40]

STABLE XENON COMPUTED TOMOGRAPHY. Stable xenon computed tomography relies on the fact that xenon is a radiodense, lipid-soluble gas that acts as a contrast agent during computed tomography. The patient breathes a mixture of oxygen and 30–35% stable xenon. Arterial levels of xenon can be calculated from end-tidal expiratory concentrations. The relatively slow diffusion rate of xenon allows high-resolution imaging from serial tomograms separated by approximately 1 minute.

- The advantage of this technique is that it provides excellent anatomic resolution and the blood–brain barrier partition coefficient can be determined for discrete regions.
- The disadvantages are that the patient must remain still for the full study, 20–30 minutes and must inhale high concentrations of xenon. Xenon has been shown to function as a mild anesthetic agent, and has been shown to directly increase CBF.[1,41]

POSITRON EMISSION TOMOGRAPHY. Positron emission tomography requires the intravenous or inhalation administration of positron-emitting isotopes of carbon, fluorine, or oxygen. In the body, the positrons combine with electrons, thus emitting γ photons that are recorded by detectors surrounding the body. The detectors are able to precisely locate the source of the γ-ray emission with very good resolution.

- This technique allows for ascertainment of the metabolic rate of glucose, oxygen, protein synthesis, and CBF. ^{15}O-labeled water is the most common tracer, and is used because it is inert, stable, has a short half-life, and has few physiologic side effects.
- The major drawback to this technique is cost.[42]

TRANSCRANIAL DOPPLER ULTRASOUND. Transcranial Doppler ultrasound (TCD) is a relatively inexpensive and noninvasive method that allows repeated measurements and continuous monitoring of CBF. It has a high temporal resolution, making it ideal to study rapid changes in cerebral hemodynamics.[43] Estimates of global CBF can be made using TCD if the amount of flow through all vessels is measured simultaneously. It has more common applications for estimating regional CBF by analyzing the CBF velocity, resistance index, or pulsatility index of intracranial or extracranial arteries such as the middle cerebral artery. Increased flow velocities in both the contralateral and ipsilateral middle cerebral arteries during motor tasks have been demonstrated.[24] Other uses of this tool include monitoring the development of vasospasm after subarachnoid

hemorrhage; pattern of collateral flow through the circle of Willis; and state of artery patency before, during, or after thrombolytic therapy.

CEREBRAL METABOLISM

Cerebral metabolism is a term used to denote the multitude of biochemical pathways in the brain collectively geared toward enzyme-mediated use of substrate to carry out cellular work.[10] Because there is no significant source of energy storage, the brain is highly dependent on a continuous supply of energy. As noted previously, the brain receives 15–20% of the total cardiac output, and CBF is meticulously maintained across a wide variety of pressures. This ensures adequate substrate delivery. The main energy substrates are high-energy triphosphates, that is, adenosine triphosphate (ATP). The central nervous system has small stores of glycogen, and is almost entirely dependent on the glucose for production of energy.[3,12] As in other tissues, glucose can be either anaerobically degraded to lactic acid through glycolysis, or oxidized, aerobically degraded, to CO_2 and water via oxidative phosphorylation.[12] Because the energy yield of glycolysis is small compared to that with oxidative phosphorylation, the brain relies for its continuing function on oxidative metabolism.[12] Oxygen is delivered to the tissue where it is involved in a variety of reactions in the cell, but the majority of oxygen is used in the generation of energy by the aerobic metabolism of glucose. In view of the fact that the need for energy is dependent on oxygen, it is not surprising that the brain's metabolic rate of oxygen ($CMRO_2$) in a normal conscious human is approximately 150–160 μmol/100 g per minute or approximately 20% of the resting body oxygen consumption.[13] The global rate of glucose utilization, also known as the cerebral metabolic rate of glucose (CMRGlu), is 35–30 μmol/100 g per minute. If one assumes normal CBF, then the extraction fraction (i.e., the proportion of substance extracted by the brain relative to the amount delivered to it in arterial blood) is 50% for oxygen and 10% for glucose.[3,34] Most of the brain's energy is used for the maintenance and restoration of ion gradients across the cell membrane. However, rapid synthesis, degradation, molecular transport, and synaptic transmission are also significant energy-consuming processes.[1,3,12]

Oxidative Phosphorylation

Glucose is transported into the cells of the central nervous system through two different glucose transports, GLUT-1 and 3. GLUT-1 is located on glia and endothelial cells and GLUT-3, on neuronal surfaces.

- Glucose is brought into the cell, and then phosphorylated by the enzyme hexokinase into glucose-6-phosphate. Through the initial steps of the glycolytic pathway, the glucose is metabolized into pyruvate.
- Another critical enzyme and site of regulation is phosphofructokinase (PFK). This enzyme is inhibited in high-energy states, that is, excess ATP, and activated in low-energy states. In the presence of oxygen, the newly generated pyruvate then enters the citric acid cycle, or Krebs cycle. The pyruvate is completely oxidized, with the products being the reduced forms of nicotinamide-adenine dinucleotide (NADH), guanosine triphosphate (GTP), and flavin adenine dinucleotide ($FADH_2$).
- For pyruvate to enter the Krebs cycle it is irreversibly decarboxylated into acetyl-coenzyme A (acetyl-CoA) by the enzyme pyruvate dehydrogenase (PDH). This is another major regulation point. The PDH is inhibited by NADH and ATP, both indicators of a high-energy state.
- The reduced NADH and $FADH_2$ then act as electron donors within the mitochondria to a series of proton pump complexes designated the electron transport chain. The final electron donor is oxygen, which is converted to water. The proton gradient that is made by the electron transport chain is used to generate ATP. This final step is termed oxidative phosphorylation.
- This entire process is summarized by the equation: Glucose + 6 O_2 + 38 ADP + 38 P_i yields 6 CO_2 + 44 H_2O + 38 ATP. In conclusion, 1 mole of glucose yields 38 moles of ATP though oxidative metabolism.

Glycolysis

In the absence of oxygen, anaerobic glycolysis occurs. During periods of ischemic stress, experimental evidence shows the upregulation of the GLUT glucose transporters so that more glucose is imported into the cell for energy production.[3,34,44] Glucose is metabolized into pyruvate, as occurs in the steps before entry into the citric acid cycle.

- In a low oxygen state, there is depletion of NADH, and the enzyme PDH is inhibited, impairing the ability of pyruvate to enter the Krebs cycle. Pyruvate is then transformed into lactate through a reversible reaction catalyzed by lactate dehydrogenase.
- The end result of glycolysis is the production of lactate and ATP summarized by this equation: Glucose + 2 ADP + 2 P_i yields 2 lactate + 2 ATP. In summary, through glycolysis 1 mole of glucose yields 2 moles of ATP. The accumulation of lactate is potentially neurotoxic from lactic acidosis.

Pentose Shunt Pathway

The main role of the pentose shunt pathway is to maintain the production of ribose 5-phosphate and reduced nicotinamide adenine dinucleotide phosphate. This is achieved through the use of phosphorylated glucose. The ribose 5-phosphate and its derivatives are incorporated into many biomolecules including ATP, NAD, FAD, RNA, and DNA. This metabolic shunt pathway is critical for maintaining their synthesis. Of the total amount of glucose entering the glycolytic pathway under normal conditions, about 85% enters the Krebs cycle, 5–10% is converted to lactate through anaerobic glycolysis, and the last 5% is metabolized in the pentose shunt pathway.

Ketosis

Metabolism utilizing ketone bodies occurs in circumstances such as starvation or diabetes when glucose is not available for use by the cell. Adipose tissue is catabolized, and the products are brought to the liver. There β-hydroxybutyrate and acetoacetate are generated and transported in the plasma to the brain. In the brain they are metabolized into 2 molecules of acetyl-CoA, which are able to enter the citric acid cycle. Under conditions of hypoglycemia, oxidation of ketone bodies may provide up to 75% of the total cerebral energy supply.[45]

Metabolic Contributions

NEURONS

Gray matter has a metabolic rate that is 3–4 times greater than that of white matter, and is closely linked to the functional activity of neurons.[3] Most of the brain's energy is used for the maintenance and restoration of ion gradients across cell membrane.[1,12] Neurons are the major site of ATP utilization mainly for maintenance of large numbers of Na^+, K^+-ATPase pumps located on axonal membranes as noted above. ATP production is also used for neurotransmitter metabolism and biosynthetic work such as protein chaperoning and axonal transport. Neurons are also involved in ATP production through oxidative metabolism of glucose, and under certain conditions through ketone body metabolism. Byproducts of neuronal metabolism are responsible for the flow-metabolic coupling between brain metabolism and CBF.

ASTROCYTES

Glial cells occupy almost half of the volume of the brain, and there are 20–50 times as many glial cells as neurons.[3,12] However, they consume less than 10% of total cerebral energy due to low metabolic demands.[12] They are instrumental in regulating the composition of the perineuronal fluid environment. This occurs in three important ways:

1. Buffering extracellular potassium concentrations
2. The glutamate-glutamine cycle
3. The lactate shuttle.

After neuronal activity the extracellular fluid (ECF) has an increased concentration of potassium ions (K^+). The K^+ enters astrocytes through both passive and active means. The K^+ continues to spread along osmotic gradients within the astrocytes through gap junctions. This is called K spatial buffering, and is important because excessive accumulation of K^+ in the ECF can affect membrane polarity.

Glutamate can also accumulate in the ECF after neuronal activity. In addition to reuptake by neurons, glutamate is also sequestered by astrocytes. The glutamate is enzymatically changed to glutamine through glutamine synthase, and is subsequently released into the ECF, where it can be taken up by neurons. This is important for limiting the action of this excitatory neurotransmitter through decreasing its presence in the synaptic cleft, and the transfer of glutamine across the ECF from astrocytes to neurons has the advantage of being a non-neuroexcitatory process.[46] This is termed the glutamate-glutamine cycle.

Glucose is also taken up by astrocytes, and can be shunted into one of two pathways:

1. It may enter anaerobic glycolysis, and is metabolized into lactate.
2. It may be converted into glycogen.[47]

Lactate produced by astrocytes can then be transported to neurons, where it enters the Krebs cycle and subsequent oxidative phosphorylation. Energy production from oxidative metabolism of lactate is about half as effective when compared with glucose.[47]

BLOOD–BRAIN BARRIER

The blood–brain barrier (BBB) isolates the brain from variations in body fluid composition, thereby providing a stable environment for neural–neural and neural–glial interactions.[10] It does this by first acting as an ionic and molecular sieve through its involvement in ionic transport and selective transport of small molecules and proteins.[26] Large molecules, polar molecules are generally excluded by the BBB except for metabolically important molecules such as glucose, amino acids, lactate, and neurotransmitter precursors. The movement of these molecules into the CBF depends on special transport mechanisms.[10,26] For example, the movement of glucose depends on the transporter GLUT-1. During times of stress, such as hypoglycemia, the BBB has been shown to have adaptive responses to a changing metabolic environment by increasing the transport of lactate and ketone bodies into the CBF.[48] Second, the endothelial cells contain a host of enzymes that protect the brain from circulating neurochemicals and toxins. For example, amino acid decarboxylase (MAO), pseudocholinesterase, γ-aminobutyric acid (GABA) transaminase, aminopeptidases, and alkaline phosphatase are present in the brain capillaries.[10] This prevents the unrestricted entry of potential toxins into the brain.

Effects of Temperature on Metabolism

In hypothermic conditions, the flux of glucose going through glycolysis and the Krebs cycle declines. The energy state of the brain, as measured by the ATP/P_i ratio, increases, suggesting that energy-consuming reactions are reduced more than ATP synthesis.[49] Measurements of the brain's metabolic rate, for example, $CMRO_2$, is reduced 2-to 4-fold by a 10-degree decrease in temperature.[49] On the other hand, in the setting of hyperthermia several studies using different animal models have observed a rise in $CMRO_2$, supporting the idea that hyperthermia itself leads to a rise in whole brain energy turnover.[50]

SUGGESTED READINGS

Bryan RM. Cerebral blood flow and metabolism during stress. *Am J Physiol Heart Circ Physiol* 1990; **259**: H269–80.

Chillon JM, Baumbach GL. Autoregulation of cerebral blood flow. In Welch KMA, Caplan LR, Reis DJ, et al. (eds), *Primer on Cerebrovascular Diseases*. San Diego: Academic Press, 1997, pp 51–4.

Gonzalez C, Estrada C. Nitric oxide mediates the neurogenic vasodilation of bovine cerebral arteries. *J Cereb Blood Flow Metab* 1991; **11**(3): 366–70.

Harrison MJ, Pollock S, Thomas D, Marshall J. Haematocrit, hypertension and smoking in patients with transient ischaemic attacks and in age and sex matched controls. *J Neurol Neurosurg Psychiatry* 1982; **45**(6): 550–1.

Khurana VG, Smith LA, Weiler DA, et al. Adenovirus-mediated gene transfer to human cerebral arteries. *J Cereb Blood Flow Metab* 2000; **20**(9): 1360–71.

Rebel A, Ulatowski JA, Kwansa H, Bucci E, Koehler RC. Cerebrovascular response to decreased hematocrit: effect of cell-free hemoglobin, plasma viscosity, and CO_2. *Am J Physiol Heart Circ Physiol* 2003; **285**(4): H1600–8.

Symon L, Branston NM, Strong AJ. Autoregulation in acute focal ischemia. An experimental study. *Stroke* 1976; **7**(6): 547–54.

Wade JP, Taylor DW, Barnett HJ, Hachinski VC. Hemoglobin concentration and prognosis in symptomatic obstructive cerebrovascular disease. *Stroke* 1987; **18**(1): 68–71.

Winn HR. Adenosine and its receptors: Influence on cerebral blood flow. In Welch KMA, Caplan LR, Reis DJ, et al. (eds), *Primer on Cerebrovascular Diseases*. San Diego: Academic Press 1997, pp 77–70.

REFERENCES

1. Torbey M, Bhardwaj A. Cerebral blood flow physiology and monitoring. In Suarez JI, (ed.), *Critical Care Neurology and Neurosurgery*. Totowa, NJ: Humana Press, 2004, pp 23–36.
2. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. *J Neurosurg*. 1984;**61**(2):241–53.
3. Meyer CH, Lowe D, Meyer M, Richardson PL, Neil-Dwyer G. Progressive change in cerebral blood flow during the first three weeks after subarachnoid hemorrhage. *Neurosurgery*. 1983;**12**(1):58–76.
4. Melamed E, Lavy S, Bentin S, Cooper G, Rinot Y. Reduction in regional cerebral blood flow during normal aging in man. *Stroke*. 1980;**11**(1):31–5.

5. Davis SM, Ackerman RH, Correia JA, et al. Cerebral blood flow and cerebrovascular CO2 reactivity in stroke-age normal controls. *Neurology*. 1983;**33**(4): 391–9.
6. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke*. 1981;**12**(6): 723–5.
7. Hossmann KA. Viability thresholds and the penumbra of focal ischemia. *Ann Neurol*. 1994;**36**(4):557–65.
8. Fog M. Cerebral circulation. The reaction of the pial arteries to a fall in blood pressure. *Arch Neurol Psychiatry*. 1937;**37**:351–64.
9. Lassen N. Cerebral blood flow and oxygen consumption in man. *Physiol Rev.* 1959;**39**:183–238.
10. Khurana VG, Benarroch EE, Katusic ZS, Meyer FB. Cerebral blood flow and metabolism, 1467–94.
11. Symon L, Held K, Dorsch NW. A study of regional autoregulation in the cerebral circulation to increased perfusion pressure in normocapnia and hypercapnia. *Stroke*. 1973;**4**(2):139–47.
12. Siesjö BK. Cerebral circulation and metabolism. *J Neurosurg*. 1984;**60**(5):883–908.
13. Zauner A, Daugherty WP, Bullock MR, Warner DS. Brain oxygenation and energy metabolism: Part I – biological function and pathophysiology. *Neurosurgery*. **51**(2):289–301.
14. Vavilala MS, Lee LA, Lam AM. Cerebral blood flow and vascular physiology. *Anesthesiol Clin North Am*. 2002;**20**(2):247–64, v.
15. Sachs F. Stretch-sensitive ion channels: An update. *Soc Gen Physiol Ser.* 1992;**47**:241–60.
16. Davis MJ, Donovitz JA, Hood JD. Stretch-activated single-channel and whole cell currents in vascular smooth muscle cells. *Am J Physiol*. 1992;**262**(4 Pt 1):C1083–8.
17. Obrist WD, Thompson HK Jr, Wang HS, Wilkinson WE. Regional cerebral blood flow estimated by 133-xenon inhalation. *Stroke*. 1975;**6**(3):245–56.
18. Branston NM. Neurogenic control of the cerebral circulation. *Cereb Brain Metab Rev.* 1995;**7**(4):338–49.
19. Gross PM, Heistad DD, Strait MR, Marcus ML, Brody MJ. Cerebral vascular responses to physiological stimulation of sympathetic pathways in cats. *Circ Res*. 1979;**44**(2):288–94.
20. Heistad DD. Protection of cerebral vessels by sympathetic nerves. *Physiologist*. 1980;**23**(5):44–9.
21. Toda N, Okamura T. Nitroxidergic nerve: Regulation of vascular tone and blood flow in the brain. *J Hypertens*. 1996;**14**(4):423–34.
22. Katusic ZS, Shepherd JT, Vanhoutte PM. Endothelium-dependent contraction to stretch in canine basilar arteries. *Am J Physiol*. 1987;**252**(3 Pt 2):H671–3.
23. Rubanyi GM, Freay AD, Kauser K, Johns A, Harder DR. Mechanoreception by the endothelium: Mediators and mechanisms of pressure- and flow-induced vascular responses. *Blood Vessels*. 1990;**27**(2–5):246–57.
24. Hennerici MG, Meairs SP. Cerebrovascular ultrasound. *Curr Opin Neurol*. 1999;**12**(1):57–63.
25. Rebel A, Ulatowski JA, Kwansa H, Bucci E, Koehler RC. Cerebrovascular response to decreased hematocrit: effect of cell-free hemoglobin, plasma viscosity, and CO2. *Am J Physiol Heart Circ Physiol*. 2003;**285**(4):H1600–8.
26. Partridge WM. Blood brain barrier transport mechanisms. In Welch KMA, Caplan LR, Reis DJ, et al. (eds), *Primer on Cerebrovascular Diseases*. San Diego: Academic Press, 1997, pp 21–5.
27. Edvinsson L, MacKenzie E, McCulloch J. *Cerebral Blood Flow and Metabolism*. New York: Raven Press, 1993, pp 524–52.
28. Carrier O, Walker J, Guton A. Role of oxygen in autoregulation of blood flow in isolated vessels. *Am J Physiol.* 1964;**206**:951.
29. Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. The modifying influence of prolonged antihypertensive treatment on the tolerance to acute, drug-induced hypotension. *Circulation*. 1976;**53**(4):720–7.
30. Hoffman WE, Miletich DJ, Albrecht RF. The influence of antihypertensive therapy on cerebral autoregulation in aged hypertensive rats. *Stroke*. 1982;**13**(5):701–4.
31. Nordborg C, Johansson BB. Morphometric study on cerebral vessels in spontaneously hypertensive rats. *Stroke*. 1980;**11**(3):266–70.
32. Strandgaard S, Jones JV, MacKenzie ET, Harper AM. Upper limit of cerebral blood flow autoregulation in experimental renovascular hypertension in the baboon. *Circ Res*. 1975;**37**(2):164–7.
33. Barry DI. Cerebrovascular aspects of antihypertensive treatment. *Am J Cardiol*. 1989;**63**(6):14C–18C.
34. Sakuta S. Blood filtrability in cerebrovascular disorders, with special reference to erythrocyte deformability and ATP content. *Stroke*. 1981;**12**(6):824–8.
35. Grotta J, Ackerman R, Correia J, Fallick G, Chang J. Whole blood viscosity parameters and cerebral blood flow. *Stroke*. 1982;**13**(3):296–301.
36. von Kummer R, Scharf J, Back T, Reich H, Machens HG, Wildemann B. Autoregulatory capacity and the effect of isovolemic hemodilution on local cerebral blood flow. *Stroke*. 1988;**19**(5):594–7.
37. Brown MM, Marshall J. Regulation of cerebral blood flow in response to changes in blood viscosity. *Lancet*. 1985;**1**(8429):604–9.
38. Tomiyama Y, Brian JE Jr, Todd MM. Plasma viscosity and cerebral blood flow. *Am J Physiol Heart Circ Physiol*. 2000;**279**(4):H1949–54.
39. Kety S, Scmidt C. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure, and normal values. *J Clin Invest*. 1948;**27**:476–83.
40. Obrist WD, Thompson HK, King CH, et al. Determination of regional cerebral blood flow by inhalation of 133-xenon. *Circ Res*. 1967;**20**:124–35.
41. Winkler S, Sacketr JF, Holsten J, et al. Xenon inhalation as an adjunct to computerized tomography of the brain: Preliminary study. *Invest Radiol*. 1977;**12**: 15–18.
42. Leenders KL, Perani D, Lammertsma AA, et al. Cerebral blood flow, flood volume and oxygen utilization. Normal values and effect of age. *Brain*. 1990;**113**(Pt1):27–47.

43. Markdus HS. Transcranial Doppler ultrasound. *J Neurol Neurosurg Psychiatry*. 1999;**67**(2):135–7.
44. Vannucci SJ, Maher F, Simpson IA. Glucose transporter proteins in brain: Delivery of glucose to neurons and glia. *Glia*. 1997;**21**:2–21.
45. Owen OE, Morgan AP, Kemp HG, et al. Brain metabolism during fasting. *J Clin Invest*. 1967;**46**:1589–95.
46. Rebel A, Lenz C, Krieter H, Waschke KF, Van Ackern K, Kuschinsky W. Oxygen delivery at high blood viscosity and decreased arterial oxygen content to brains of conscious rats. *Am J Physiol Heart Circ Physiol*. 2001;**280**(6):H2591–7.
47. Magistretti PJ Coupling of cerebral blood flow and metabolism. In Welch KMA, Caplan LR, Reis DJ, et al. (eds), *Primer on Cerebrovascular Diseases*. San Diego: Academic Press, 1997, pp 70–5.
48. Nehlig A. Cerebral energy metabolism, glucose transport and blood flow: Changes with maturation and adaption to hypoglycemia. *Diab Metab*. 1997;**23**:18–29.
49. Erecinska M, Thoreson M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. *J Cereb Blood Flow Metab*. 2003;**23**:513–30.
50. Carlsson C, Hågerdal H, Siesjö BK. The effect of hyperthermia upon oxygen consumption and upon organic phosphate, glycolytic metabolites, citric acid cycle intermediates and associated amino acids in rat cerebral cortex. *J Neurochem*. 1976;**26**:1001–6.