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The Cerebral metabolic requirements under normal conditions.

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Cerebral metabolic demand

In contrast to most other tissues, which exhibit considerable flexibility with respect to the nature of the foodstuffs extracted and consumed from the blood, the normal brain is restricted almost exclusively to glucose as the substrate for its energy metabolism. Despite long and intensive efforts, the only incontrovertible and consistently positive arteriovenous differences demonstrated for the human brain under normal conditions have been for glucose and oxygen (1). The human brain comprises only 2% of body weight, yet consumes more than 20% of oxygen and glucose at rest, with almost all adenosine triphosphate in the brain being produced by oxidative metabolism of glucose.

Normally, the substrates are glucose and oxygen and the products are carbon dioxide and water (1,2) In physiology textbooks, a consistent generalization appears - that the human brain demands high octane fuel in the form of oxygen and glucose (1).

Negative arteriovenous differences, significantly different from zero, have been found consistently only for CO_2, although water, which has never been measured, also is produced. Pyruvate and lactate production have been observed occasionally, certainly in aged subjects with cerebral vascular insufficiency but also irregularly in subjects with normal oxygenation of the brain (1).

In the normal in vivo state, glucose is the only significant substrate for energy metabolism in the brain. Under normal circumstances, no other potential energy-yielding substance has been found to be extracted from the blood in more than trivial amounts (1).

Some oxygen is used for oxidation of substances not derived from glucose, for example, in the synthesis and metabolic degradation of monoamine neurotransmitters, as mentioned above. The amount of O_2 used for these processes is, however, extremely small and is undetectable in the presence of the enormous O_2 consumption used for carbohydrate oxidation (1,2).

The brain normally derives almost all of its energy from the aerobic oxidation of glucose, but this does not distinguish between preferential and obligatory utilization of glucose. Most tissues are largely facultative in their choice of substrates and can use them interchangeably more or less in proportion to their availability (1). The brain, under most normal circumstances, will preferentially use aerobic glucose metabolism and nothing else. Approximately 156 μmol of oxygen (or about 3.8ml) is consumed per 100 g brain tissue per minute. At the same time, those 100g of brain tissue require about 31 mmol per minute of glucose (1,3). The result is the production of 156 μmol of carbon dioxide, supposedly giving a respiratory ratio of 1.0 (1).

The dependence on glucose is fairly inflexible. Unlike many other tissues, the brain is unable to quickly switch its metabolism to other substrates in a scenario where glucose is deficient. This is easily observed in the complete neurological collapse which is seen with profound hypoglycaemia. This does not appear to be so in the brain (1,3).

Except in some unusual and very special circumstances, only the aerobic utilization of glucose is capable of providing the brain with sufficient energy to maintain normal function and structure. The brain appears to have almost no flexibility in its choice of substrates in vivo. This conclusion is derived from the following evidence (1).

For example: During convulsions, cerebral metabolism increases and the brain's need for oxygen and substrate rises. At the same time, respiration ceases and this plus the intense muscle activity of the convulsion results in arterial blood hypoxia. To meet the increased metabolic demands of cerebral seizures, cerebral vessels dilate, systemic blood pressure increases, and cerebral blood flow rises (3).

However, these compensating mechanisms cannot prevent brain hypoxia if the arterial blood is desaturated and, as a result, during a generalized convulsion cerebral venous and cortical oxygen tension decrease, cerebral energy stores are depleted, and brain lactate rises (3).

For example: Administration of anesthetic agents fundamentally shifts the responsibility for maintenance of homeostasis from the patient and their intrinsic physiological regulatory mechanisms to the anesthesiologist (4,5).

Continuous delivery of oxygen and nutrients to the brain is necessary to prevent irreversible injury and arises from a complex series of regulatory mechanisms that ensure uninterrupted cerebral blood flow (6). Our understanding of these regulatory mechanisms and the effects of anesthetics on them has been driven by the tireless work of pioneers in the field. While no single agent has yet been identified as being the “silver bullet” for neuroprotection, there is cause for hope (4,6).

As the brain has relatively little capacity for energy storage, a continuous supply of oxygen and nutrients must be delivered by uninterrupted cerebral blood flow (CBF) (6). Prior to an examination of the effects of anesthetics on CBF, we will review the physiological mechanisms that define flow. Under conditions of normothermia and normoxia, CBF must remain at 50–60 ml/100 g/min to meet the metabolic demands of the functioning brain, with women having slightly higher flow rates (5). Reserve blood flow exists to a point, but ischemic injury generally occurs once CBF drops below 22 ml/100 g/min, although concurrent pathology such as traumatic brain injury (TBI) or hypothermia can change this threshold (6).

The energy requirements of the brain are very high, and tight regulatory mechanisms operate to ensure adequate spatial and temporal delivery of energy substrates in register with neuronal activity. Astrocytes-a type of glial cell-have emerged as active players in brain energy delivery, production, utilization, and storage. Our understanding of neuroenergetics is rapidly evolving from a "neurocentric" view to a more integrated picture involving an intense cooperativity between astrocytes and neurons (7).

Since the work of Cushing over 100 years ago, the existence of brain baroreceptors capable of eliciting increases in sympathetic outflow and blood pressure has been hypothesized. In the clinic, this response has generally been thought to occur only in extremis, to perfuse the severely ischemia brain as cerebral autoregulation fails. We review evidence that pressor responses may also occur with smaller, physiologically relevant increases in ICP (8).

The incoming brain oxygen supply is closely monitored by the carotid chemoreceptors; however, hypoxia and other markers of ischaemia are also sensed intrinsically by astrocytes or other support cells within brain tissue itself and elicit reactive hyperaemia (8). Recent studies suggest that astrocytic oxygen signalling within the brainstem may directly affect sympathetic nerve activity and blood pressure (7,8).

Intracranial pressure (ICP) is the pressure exerted by fluids such as cerebrospinal fluid (CSF) inside the skull and on the brain tissue (8). ICP is measured in millimeters of mercury (mmHg) and at rest, is normally 7–15 mmHg for a supine adult. Symptoms of increased ICP: Headache, Blurred vision, Confusion, High blood pressure, Shallow breathing, Vomiting, Changes in your behavior and Weakness or problems with moving or talking (7,8).

Considering that the main energy substrates of the brain are oxygen and glucose, one should be able to determine the rate of metabolism by measuring the amount of blood oxygen used up during its transit through the brain. This can be accomplished by measuring the oxygen saturation of the venous blood exiting the brain through the jugular vein (9,10).

Additionally, increases in cerebral blood flow (CBF) induced by evoked neural activation are accompanied by arterial vasodilation and also by increases in arteriolar oxygenation. Increases in neural activity evoke increases in both CBF and CMRO2: Cerebral Metabolic Rate of Oxygen (9,11).

The increase in cerebral blood flow is produced at least in part by the dilation of feeding arteries, and hence, increases in cerebral blood volume (CBV) have also been observed (9).

Increases in neural activity evoke increases in both cerebral blood flow and CMRO2 (9): Cerebral Metabolic Rate of Oxygen. These increases have been thought to reflect the metabolic demands of tissue. However, in terms of oxidative metabolism, the delivery of oxygen largely exceeds the consumption of oxygen in tissue (11).

The delivery of oxygen is driven by the increases in cerebral blood flow and its associated increases in cerebral blood volume, but additional mechanisms are necessary to describe observations of tissue oxygen delivery (9). Arterial blood is highly saturated with oxygen and measurements of the vascular oxygen tension have shown that a relatively large amount of oxygen diffuses out of arteries prior to capillaries (10). This oxygen gradient along the arterial vasculature allows the mechanisms regulating cerebral blood flow to also regulate the delivery of oxygen to sub-serving areas (9,12). In addition, neurally-evoked increases in CBF are also accompanied by increases in the arteriolar oxygen tension.

This increase in arterial oxygenation contributes not only to the down-stream delivery of oxygen to tissue, but also to delivery of additional oxygen to extra-vascular spaces surrounding the arterioles. The supply of arterial oxygen to tissue has been hypothesized as necessary to homogenize the distribution of tissue oxygen (9,11).

Nonetheless, other mechanisms beyond the increase in cerebral blood flow and upstream oxygenation are necessary to fully describe the delivery of oxygen to tissue during evoked neural activity (13). While measurements of the tissue oxygen tension with increases in neural activity indicate that the role of cerebral blood flow is not to maintain a constant average tissue oxygen tension, it is possible that the transient increases in tissue oxygen are necessary to maintain a minimum intra-cellular oxygen tension (9,13).

Conclusions

Understanding of the mechanisms by which the brain deals with energy shortage is of utmost importance in shedding light on the fundamentals of brain disorders and their potential treatment. To achieve such understanding, accurate measurement of brain energy metabolic rates is necessary (14).

Cerebral Energy Metabolism, the various techniques used to measure cerebral metabolic rates of oxygen (CMRO2) and glucose (CMRglucose), and elaborates on the potential of measuring the cerebral metabolic rate of lactate (CMRlactate) to improve our understanding of brain energy metabolism (14).

At the basis of each technology designed to measure the rate of brain energy metabolism is the idea that measuring the consumption rate of the main two substrates of glycolysis and mitochondrial respiration, glucose and oxygen (O2), should provide a complete picture of the brain's energy use. Theoretically, under normal conditions, each glucose molecule that enters the glycolytic pathway requires six molecules of oxygen to be fully oxidized via the mitochondrial TCA cycle and the electron transport chain (14).

Thus, simultaneous measurements of glucose and oxygen consumption during rest or activation supposedly produces accurate estimate of the energy needs for the brain region under observation. However, the ratio CMRO2/CMRglucose values calculated are often significantly smaller than the expected 6/1. Such discrepancies have attributed to other glucose-consuming reactions not accompanies with oxygen consumption. Consequently, it has been a common understanding that a value of CMRO2/CMRglucose < 6 indicates that a partial non-oxidative glucose consumption. The smaller the value of CMRO2/CMRglucose, the greater is the non-oxidative consumption of glucose.

This understanding makes sense when one assumes that a fully coupled glycolytic-mitochondrial respiratory apparatus should produce a CMRO2/CMRglucose value of 6 and an uncoupled apparatus (non-oxidative) should produce a CMRO2/CMRglucose value of ~0.

As indicated above, myriad techniques and technologies have been developed during the past six decades to measure both CMRO2 and CMRglucose. To measure cerebral energy metabolism in vivo one can analyze chemical changes in the blood entering and exiting the brain and/or in the cerebrospinal fluid.

Of course, brain tissue samples can also be taken for analysis before and after physiological activity, although this approach would lend itself only to experimental animals. The introduction of radioisotopes to the analytical techniques of brain metabolic activity has greatly improved their speed and accuracy.

Radioisotopes allow not only the tracing of end-products of cerebral metabolism, but also the detection of intermediates of that metabolism. Nevertheless, these techniques have their own drawbacks, including the need to sacrifice the animal under study only to receive a single measurement which provides mainly a qualitative value. A quantitative measurement is frequently confounded by compartmentation and its misinterpretation thereof.

One of the most reliable techniques to measure oxygen consumption is the polarographic technique, which allows the determination of oxygen concentration via the measurement of the partial oxygen pressure (PO_2) locally. Continuous measurements over a period of time when brain activity (EEG) is monitored, demonstrated a correlation between increased activity and decreased tissue oxygen level. The development of oxygen microelectrodes has afforded a more accurate localization of such measurements.

In principle, CMR can be expressed as: $CMR = CBF (A - V)$.

NORMAL VALUES FOR CEREBRAL METABOLIC SUPPLY AND DEMAND:	CEREBRAL BLOOD FLOW:
*Cerebral blood flow: 50ml per 100g of tissue, per minute. *Cerebral DO2: 150-300ml/min (Hb of 150) *CMRO2: Cerebral Metabolic Rate of Oxygen: 3.8ml/100g/min *Cerebral oxygen extraction ratio (CO2ER): 35-25% *Jugular bulb venous saturation (SjvO2): 55-75% *Cerebral glucose consumption: 6.3mg glucose per 100g per minute	Blood flow to the brain is about 50ml per 100g of tissue, per minute. The original study found the mean value to be 65ml/100g (in a range of 50 - 102, or 750-1530ml/minute for a 1.5kg brain). This is about 14% of normal cardiac output. The details of what cerebral blood flow can do are discussed elsewhere, and here it will suffice to say that this range is maintained by autoregulatory mechanisms, even if other hemodynamic conditions are fluctuating.
SYMPTOMS OF POOR BLOOD FLOW TO THE BRAIN *Slurred speech. *Sudden weakness in the limbs. *Difficulty swallowing. *Loss of balance or feeling unbalanced. *Partial or complete loss of vision or double vision. *Dizziness or a spinning sensation. *Numbness or a tingling feeling. *Confusion.	**THE FACTORS THAT DETERMINE CEREBRAL PERFUSION PRESSURE** Blood flow to the brain is called cerebral perfusion pressure. Blood pressure and intracranial pressure affect the cerebral perfusion pressure. If the blood pressure is low and/or the intracranial pressure is high, the blood flow to the brain may be limited. This causes decreased cerebral perfusion pressure.
METABOLIC SUBSTRATE *The brain normally consumes glucose and oxygen, and its RQ is 1.0 *Alternative substrates include ketones, lactate, mannose, and others	
**Cerebral metabolic rate of oxygen CMRO2: Cerebral metabolic rate of oxygen (CMRO2) decreases to approximately one third of normal and is maintained at that level for the duration of coma. **Cerebral oxygen utilization: Cerebral metabolic rate of oxygen consumption (CMRO2) is a measurable index of oxygen utilization in the brain. It is defined as the amount of oxygen consumed per unit mass tissue and per unit time, and reflects oxygen demand in the brain. Regulation of oxygen metabolism is vital for normal neuronal functioning. **The metabolic rate of the brain: It has been estimated that the human brain accounts for between 44% and 87% of resting metabolic rate (RMR) during infancy, childhood, and adolescence (23⇓–25), suggesting strong trade-offs with other functions. **The normal rate of cerebral blood flow to the brain: The normal average cerebral blood flow (CBF) in adult humans is about 50 ml / (100 g min), with lower values in the white matter [~ 20 ml / (100 g min)] and greater values in the gray matter [~ 80 ml / (100 g min)]. ** Cerebral blood flow (CBF), defined as the volume of blood (mL)/100 g of brain tissue/min, is primarily determined by autoregulation, cerebral perfusion pressure (CPP), CO2 reactivity, O2 reactivity, cerebral metabolic rate of O2 (CMRO2) coupling, temperature, viscosity, and some autonomic influences.	

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FACTORS WHICH INCREASE CEREBRAL METABOLIC RATE

Seizures
Hyperthermia
Amphetamines

FACTORS WHICH DECREASE CEREBRAL METABOLIC RATE:	**DECREASE IN CEREBRAL BLOOD FLOW:**
*Sleep *Anaesthesia (eg. propofol or thiopentone) *Hypothermia *Stroke *Encephalitis *Uraemia *Myxoedema	Carbon dioxide (CO2) has a profound and reversible effect on cerebral blood flow, such that hypercapnia causes marked dilation of cerebral arteries and arterioles and increased blood flow, whereas hypocapnia causes constriction and decreased blood flow.

EFFECTS OF HYPOTHERMIA ON ENERGY METABOLISM

Results of studies on the effect of lowered temperatures on cerebral energy metabolism in animals under normal conditions and in some selected pathologic situations. In sedated and paralyzed mammals, acute uncomplicated 0.5- to 3-h hypothermia decreases the global cerebral metabolic rate for glucose (CMRglc) and oxygen (CMRO2) but maintains a slightly better energy level, which indicates that ATP breakdown is reduced more than its synthesis. Intracellular alkalinization stimulates glycolysis and independently enhances energy generation.

Lowering of temperature during hypoxia–ischemia slows the rate of glucose, phosphocreatine, and ATP breakdown and lactate and inorganic phosphate formation, and improves recovery of energetic parameters during reperfusion. Mild hypothermia of 12 to 24-h duration after normothermic hypoxic–ischemic insults seems to prevent or ameliorate secondary failures in energy parameters.

FACTORS WHICH INFLUENCE CEREBRAL METABOLISM

FACTORS	**INCREASE**	**DECREASE**
Neoplasia	Glioma	Paraneoplastic cerebellar degeneration
Drugs	Ketamine Amphetamine	General anaesthetics
Neurological disorders	Seizure	Post-ictal state Eclampsia
Physiological phenomena	Stress Anxiety Hyperventilation	Normal sleep

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GLUCOSE CONSUMPTION BY BRAIN TISSUE
*The brain uses 6.3mg glucose per 100g (in a range of 3.9 to 9,5, or 58.5 - 142.5mg/minute for a 1.5kg brain). Thus, at a blood glucose level of 5.5mmol/L (1g/L), or 50mg/100g brain tissue, the brain receives well over ten times its normal requirement of glucose. FACTORS *That's a lot of redundancy. However, the whole liver is only producing it at a rate of about 100-200mg per minute. Thus, the brain actually consumes around 70% of the total hepatic glucose output. *The brain lacks fuel stores and hence requires a continuous supply of glucose. *It consumes about 120 g daily, which corresponds to an energy input of about 420 kcal (1760 kJ), accounting for some 60% of the utilization of glucose by the whole body in the resting state. *Because the brain is so rich in nerve cells, or neurons, it is the most energy-demanding organ, using one-half of all the sugar energy in the body. *Brain functions such as thinking, memory, and learning are closely linked to glucose levels and how efficiently the brain uses this fuel source. At its most severe, insufficient glucose flow to the brain can cause confusion, seizures, and loss of consciousness (coma). *First, the numbers. “Post-meal blood sugars of 140 mg/dl [milligrams per deciliter] and higher, and fasting blood sugars over 100 mg/dl [can] cause permanent organ damage and cause diabetes to progress. *What's sometimes called "diabetic rage" can be dangerous, because it may involve behaviors a person isn't consciously aware of. *Physiologically, when someone's blood sugar fluctuates, spikes, or drops, it can produce feelings of anger, anxiety, or depression that are out of the control of the person experiencing them.
JUGULAR VENOUS OXYGEN SATURATION (SjvO2)
The normal range of jugular venous oxygenation is 55-75%. This value changes under the following circumstances: SjvO2 increases when: Jugular venous oxygen saturation (SjvO2) measures the balance between cerebral oxygen delivery and cerebral oxygen consumption.
*Cerebral metabolic rate is decreased *Cerebral oxygen delivery is excessive (eg. hypercapnia or hypertension) *SjvO2 decreases when *Oxygen delivery to the brain is reduced (eg. hypotension, hypoxia), or: *Cerebral metabolic rate is increased: *As oxygen delivery to the brain decreases, the oxygen extraction of the brain increases, and the SjvO2 decreases.

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Conflict of interest statement
The authors declare no conflicts of interest.

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