Applied cerebral physiology

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Abstract
The brain uses large amounts of glucose for its basal energy requirements, and these are further increased during cerebral activation. In order that glucose can provide this energy, a plentiful and uninterrupted supply of oxygen is necessary. Cerebral blood flow is therefore critical for normal cerebral function. Its control is dictated by local intrinsic metabolic needs as well as extraneous factors such as arterial blood pressure, arterial carbon dioxide and oxygen tension, temperature and neural factors. This article reviews cerebral metabolism and cerebral blood flow and techniques by which both can be monitored.

Keywords cerebral autoregulation; cerebral blood flow; cerebral metabolism; intracranial pressure

Cerebral metabolism and blood flow

The primary function of the brain is the generation of nerve action potentials in response to stimulation, and this function is affected by the movement of ions against electrical gradients and the release and regeneration of neurotransmitters at synapses. These functions require a large amount of energy in the form of ATP. Under normal conditions, the metabolic fuel is almost exclusively glucose and an appropriate supply of oxygen is needed for the oxidative processes involved. This article outlines the mechanisms by which the brain receives its vital supply of glucose and oxygen and balances these against its demands (Table 1).

Cerebral energy metabolism: mass for mass, the brain consumes more energy than any other tissue in the body. Under basal conditions, about 60% of this energy is used to fuel the Na^+/K^+-ATPase ion pumps, which maintain the ionic gradients across neuronal membranes. During increased neuronal activity, this demand is further increased. Glucose is the major source of this energy. It enters the brain by active transport across the blood–brain barrier via the transporter GLUT 1 in cerebral capillaries and is then distributed to the cells of the CNS by various transporter molecules (i.e. GLUT 1 to astrocytes, GLUT 3 to neurones and GLUT 5 to microglial cells). These glucose transporters are up-regulated in hypoxic conditions. Glucose uptake is high in brain tissue and the cerebral metabolic rate for glucose (CMRGl) is about 30 μg/100 g/min, which represents approximately 25% of the body's total glucose consumption. Whilst the level of the brain's glucose requirement is impressive, its reserves are not. Hypoglycaemia soon results in cerebral cellular dysfunction, manifested as anxiety and confusion, which soon progresses to convulsions and coma. The symptoms seen reflect the greater susceptibility of cortical structures to hypoglycaemia compared with the brainstem. Whilst cerebral cells do contain glycogen, this (and all available glucose) is exhausted within 2 minutes if cerebral blood flow (CBF) is completely stopped.

Following uptake into cerebral cells, glucose is oxidized to carbon dioxide and water in the glycolytic and tricarboxylic acid (TCA) pathways, and together with oxidative phosphorylation within mitochondria, provides the ATP necessary for energy supplies.

Under hypoxic conditions astrocytes metabolize glucose anaerobically by glycolysis to form lactate, generating enough ATP to allow glutamate uptake. The lactate released into the extracellular space is actively taken up by neurones and converted to pyruvate, which then enters the TCA cycle to generate more energy aerobically. This lactate is thought to be a vital energy substrate during neuronal activation and for recovery of synaptic function following hypoxic injury; it has a monocarboxylate transporter (similar to glucose), which allows active transport across the blood–brain barrier.

During prolonged fasting the brain uses ketone bodies (end products of fatty acid metabolism in the liver) as an alternative fuel. They are exported from the liver and actively taken up by the brain. There, they are broken down to acetyl coenzyme A (acetyl-CoA), which is oxidized via the TCA cycle to yield energy. Under such conditions the brain is capable of regenerating glucose (gluconeogenesis) from alternative substrates such as glycerol, glutamine and glycine.

Cerebral blood flow: normal aerobic cerebral metabolism requires a plentiful and uninterrupted supply of oxygen. Blood

Normal cerebral physiological values

CBF	750 ml/min or 15% of cardiac output
CBF (Global)	50 ml/100 g/min
Grey matter	90 ml/100 g/min
White matter	20 ml/100 g/min
$CRMO_2$ (Grey matter)	3 ml/100 g/min
$CRMO_2$ (White matter)	1 ml/100 g/min
CMRGl (Global)	30 μg/100 g/min or 25% of total body consumption

CBF, cerebral blood flow; $CRMO_2$, cerebral metabolic rate for oxygen; CRMGl, cerebral metabolic rate for glucose

Table 1

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is supplied to the brain from the anterior paired internal carotid arteries and posterior paired vertebral arteries. These anterior and posterior circulations are joined at the circle of Willis in the base of the brain but it is important to note that this anastomosis is incomplete in 50% of individuals.

Although the brain constitutes only 2% of the total body mass, it receives 15% of the cardiac output (750 ml/min in adults). Resting CBF is approximately 50 ml/100 g/min. The flow is not evenly distributed. Grey matter, which is metabolically more active, receives approximately 90 ml/100 g/min and in these regions the rate of oxygen consumption, termed the cerebral metabolic rate for oxygen ($CMRO_2$), is about 3 ml/100 g/min. White matter receives about 20 ml/100 g/min and its $CMRO_2$ is approximately 1 ml/100 g/min. The level of CBF is critical. Complete interruption of CBF produces loss of consciousness within seconds as does a reduction of CBF to approximately 20 ml/100 g/min. Neuronal conversion to anaerobic metabolism occurs below 18 ml/100 g/min and the electroencephalogram becomes flat. Brain cell death (infarction) takes place at about 3 hours with flows of 10 ml/100 g/min and after 30 minutes at flows of 5 ml/100 g/min.

Cerebral perfusion pressure (CPP): the perfusion pressure (i.e. the arteriovenous pressure gradient) in the brain is more complex than that of other organs because it is confined within an incompressible vault. It is dependent on the pressure difference between the mean arterial pressure (MAP) or the driving pressure (measured at brain level) and the intracranial pressure (ICP) or the pressure that needs to be overcome to supply adequate blood to the brain. This pressure difference is known as the CPP. A normal CPP is 70–80 mm Hg; the threshold for critical ischaemia is 30–40 mm Hg. As can be seen from the equation below, even at normal levels of MAP an elevated ICP of more than 20 mm Hg will compromise CPP, and therefore reduce cerebral blood flow. This emphasizes the importance of maintaining an adequate MAP in circumstances such as head injury to ensure adequate perfusion.

Cerebral perfusion pressure = mean arterial pressure − intracranial pressure

Intracranial pressure: the contents of the skull are brain parenchyma (80%), blood (9%), CSF (6%) and interstitial fluid (5%). After fusion of the cranial sutures, the brain becomes contained within a rigid bone box. Normal intracranial pressure is 7–12 mm Hg and is determined by the balance between the rate of CSF formation and absorption (the latter depending on the venous sinus pressure and the resistance of the arachnoid villi). ICP is a dynamic pressure and fluctuations occur with arterial pulsations, position, respiration, coughing and straining (Figure 1).

As mentioned on page 413 the Monro–Kellie doctrine states that because intracranial volume is fixed, an increase in volume of one of the components contained within the skull, unless accompanied by a reduction in volume of the other components, will lead to a rise in ICP. Initially, as the brain volume increases, compensation occurs by movement of CSF into the spinal compartment, accompanied by an increase in absorption, a decrease in CSF production and a reduction in cerebral blood volume; this limits the rise in ICP. However, as these compensatory processes

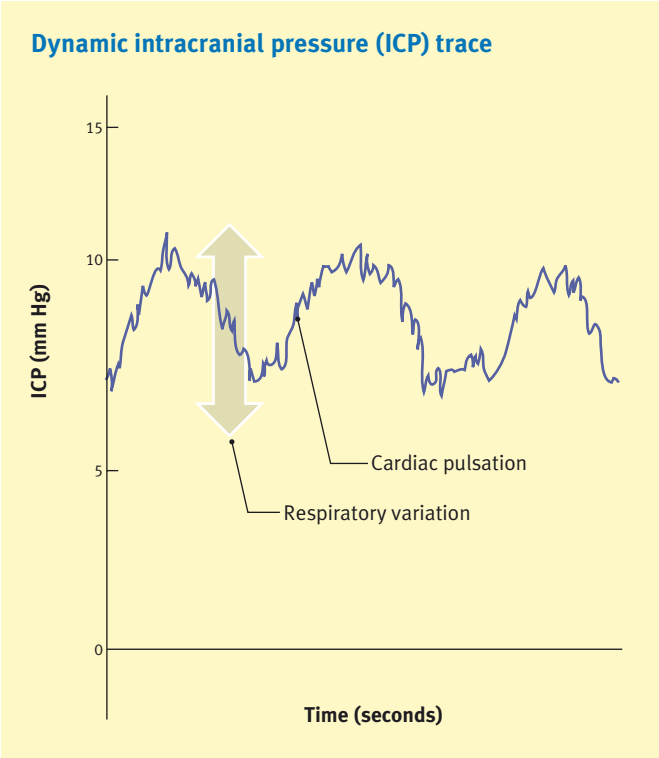

Figure 1

are overwhelmed, intracranial compliance falls, and ICP rises dramatically with further small increases in intracranial volume (Figure 2). Eventually, if unchecked, rises in ICP will cause brainstem compression with hypertension, bradycardia and irregular respiration (Cushing's reflex).

Anaesthetists institute various methods to reduce ICP acutely in high-risk patients with critically high ICPs. With the exception of surgical CSF drainage or decompression, methods for the control of ICP depend on either reducing intracranial blood volume or reducing interstitial fluid volume. Reduction of intracranial blood volume can be achieved by reducing arterial carbon dioxide tension ($PaCO_2$), which promotes cerebral vessel vasoconstriction, or by increasing venous drainage with a head-up position and providing adequate sedation and muscular relaxation, which reduces intrathoracic pressure. Interstitial fluid volume reduction can be achieved by fluid restriction or by the administration of diuretics (e.g. mannitol and furosemide) or corticosteroids. Conversely, poor anaesthetic technique may result in a dramatic rise in ICP in patients with existing raised ICP.

CSF is an ultrafiltrate of plasma that circulates freely throughout the cerebral ventricles and the central canal of the spinal cord. It is formed (and reabsorbed) at the rate of about 500 ml/day by energy-dependent and perfusion-related processes in the choroid plexuses and the cerebral ventricles. CSF then flows through the foramen of Monro to the third ventricle, into the fourth ventricle via the aqueduct of Sylvius and then into the cisterna magna and subarachnoid spaces via the medial foramen of Magendie and the lateral foramen of Luschka. Ultimately CSF is reabsorbed through the subarachnoid villi into the cerebral venous sinuses as a result of the pressure gradient between CSF and sinus. If the