Glycaemic control has been an area of active research over the past decade. To a large extent, this was kick-started by the seemingly impossible beneficial effects of tight glycaemic control demonstrated by van den Berghe et al in 2001. Subsequent to this, numerous trials were conducted which have not shown the same degree of benefit and, in addition, numerous concerns have been raised with regard to the potential harmful effects related to hypoglycaemic events.

Is glucose fuel or poison for the brain?

From the complexity of the issues at hand, the heterogeneity of patient population sub-groups and the lack of firm data, it is immediately apparent that this is not a simple case of “yes” or “no”.

The outline of this talk will explore the cerebral handling of glucose as a fuel, touching on the relevant physiological aspects. We will explore the correlations between blood glucose levels and brain glucose levels and will examine the latest evidence with regards to glycaemic control.

The evidence for this presentation has been drawn from a variety of sources, ranging from experimental trials published in physiology journals, to review articles from neuroendocrine and ICU literature. This reflects the fact that in many ways, we are still seeking to comprehend how exactly we utilise glucose at a cellular level, and at the same time are trying to draw up practice guidelines to implement at clinical level.

Is glucose a fuel for the brain? Most certainly, yes. Is it a poison? Yes. As with so many things in life, an excess of something that is beneficial can sometimes be detrimental.

A few fundamental questions need to be asked:

- How does blood glucose correlate with brain glucose and how does it enter the intracellular environment?
- How is intracerebral metabolic status measured?
- What are the effects of hyper- and hypoglycaemia?
- What blood glucose levels are optimal for cerebral metabolism?

How does blood glucose relate to brain glucose?

When talking of glucose levels, it is important to bear a few things in mind. The brain is entirely dependent upon a constant supply of glucose for cellular metabolism. During periods of energy deficits, it can utilise ketones, pyruvate and lactate, but these are most certainly not the preferred fuel sources. Firstly, we must look at the mechanisms by which blood glucose arrives within the protected sanctuary of astrocytes and neurons, lying behind the protective veil of the blood-brain barrier (BBB). The BBB, with its tight junctions between endothelial cells, requires a transport system to be in place to allow for the movement of glucose and other compounds into the intracerebral environment.

These transporters account for 95% of glucose transfer into the brain. They differ between organ systems within the body. Within the brain, they assume the form of facilitative transporters, and as their name suggests, they assist the flux of glucose down a concentration gradient. There are two major types of glucose transporters, namely GLUT1 and GLUT3. GLUT1 in turn exists in two isoforms, one on endothelial cells and one the perivascular end-feet of astrocytes. GLUT3
exists on neurons and has two important features. These are a low Michaelis-Menten constant and a high maximal transport velocity, both of which favour glucose transport into neurons.

The net result is that the neuronal environment has a much lower glucose concentration than blood. For example, a blood glucose concentration of 5-6 mmol/l experimentally correlates with a brain glucose of 1.5±0.5 mmol/l. While there appears to be a somewhat linear relationship between the two, this may not be the case with blood glucose extremes.

It is also important to understand that the ratio of GLUT1 and GLUT3 receptors may vary under certain pathophysiologic circumstances. Alterations in levels of pro-inflammatory cytokines, endothelin 1, transforming growth factor-β and tissue hypoxia, all result in upregulation in GLUT1 and GLUT3 expression, with the result that there is increased cellular glucose uptake, which may result in cellular hyperglycaemia through compromising the protective effects of the GLUT transporters.

**Measures of cellular metabolism**

In order to know what changes are occurring within the brain, it is necessary to look beyond measures of global metabolism. Exploration of measures that better reflect what is occurring within the cocoon of the blood-brain barrier is required. Various tools exist to allow better illumination of what is happening. Brain microdialysis allows measurement of parameters such as glucose, lactate, pyruvate and glutamate. Their relative concentrations to one another is hugely significant. In this context, the widely used lactate/pyruvate (L/P) ratio unmasks impaired mitochondrial function with sustained cytosolic glycolysis due to diminished or absent oxidative phosphorylation. The effect is seen as a reduction in pyruvate and an elevation in lactate, as pyruvate cannot enter the citric acid cycle and is converted into lactate to be used as a fuel source. Increased L/P ratio, while being a marker of cerebral metabolism, has also been shown to precede rises in intracranial pressure.

Hyperglycolysis, as seen in traumatic brain injury as a result of sustained hypoxia and ischaemia, will result in elevated lactate/glucose ratios.

As glutamate levels rise due to release from ischaemic neurons, it is converted to lactate within astrocytes, which is utilised as a fuel source. This probably represents an adaptive response and lactate/glutamate ratios have also been used as a marker of ischaemic injury.

This form of monitoring represents an advance on less accurate measures, such as jugular venous saturation and oxygen extraction ratios.

Functional imaging has also been utilised. These techniques include PET and SPECT, the details of which are beyond the scope of this discussion.

So what are the effects of cerebral hypo- and hyperglycaemia?

Plasma glucose levels less than 2.8 mmol/l have been used to define hypoglycaemia in adults. Experimentally, it would seem that brain glucose levels of < 1 reflect intracerebral hypoglycaemia. It is important to recognise that levels at which patients will become symptomatic will depend on various other physiologic parameters and patients with poor glycaemic control will often become symptomatic at much higher levels.

It appears that hypoglycaemia has three major sequelae within the brain:

- It induces a systemic stress response.
- It increases cerebral blood flow.
- It alters cerebral metabolism.

Let us address the issue of the stress response. Sudden reductions in systemic glucose levels result in a physiologic counter-regulatory response aimed at restoring normoglycaemia. This response involves increased production and release of adrenaline, noradrenaline, glucagon, cortisol and growth hormone. The cerebral manifestations of this are seen as slow waves on EEG, impaired cognitive function and seizures.

The alterations in cerebral blood flow are due to impairment in autoregulation, the magnitude of which is in part dependent upon mean arterial pressure. In other words, at low pressures, even mild hypoglycaemia will cause vasodilation and increased cerebral blood flow. Due to the loss of autoregulation, this vasodilation is not uniform and so certain areas may show a dramatic drop in flow. This effect is exacerbated by hypocapnia.

Metabolic derangements and their magnitude will depend on the duration and severity of hypoglycaemia. This results in alterations in protein synthesis, amino acid metabolism and neurotransmitter release. This can ultimately lead to changes in pH homeostasis and membrane stability. Increased levels of excitotoxins acting via
a calcium influx mechanism lead to neural death. Low blood glucose levels are also known to result in cortically spreading depolarisations. This may occur at blood levels as high as 6 mmol/l in the injured brain. This is described as a process of spontaneous mass neuronal depolarisation with resultant influx of both cations and water.

From a cerebral perspective, defining hyperglycaemia is less easily done. The threshold for harm appears to vary depending on the clinical setting. Blood glucose levels exceeding 9 mmol/l appear to be detrimental.

There seem to be several pathophysiologic mechanisms whereby this harm is triggered. There is upregulation of the hypothalamohypophyseal adrenal axis, inflammation, reduced perfusion, and increased levels of excitatory amino acids and intracellular calcium concentrations. The inflammation leads to increased superoxide production and microcirculatory disruption with associated alterations in the coagulation cascade and nitric oxide levels.

With this in mind, in the lecture I will present some literature that will hopefully help us to guide clinical practice. I cannot give absolute levels of blood glucose for which to aim in the neurocritical care setting, but it would seem that levels of between 6 and 8 mmol/l are ideal. The challenge is to implement protocols that will keep glucose at these levels in the face of the myriad physiologic and management alterations that occur on a regular basis within the ICU.

Bibliography

8. Meierhans R et al; Brain metabolism is significantly impaired at blood glucose below 6 mM and brain glucose below 1mM in patients with severe traumatic brain injury. Critical Care. 2010; 14.