Commentary

Optimizing cerebral glucose in severe traumatic brain injury: still some way to go

Cameron Zahed and Arun K Gupta

Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 2QQ, UK

Corresponding author: Arun K Gupta, akg01@globalnet.co.uk

See related research by Holbein *et al*., http://ccforum.com/content/13/1/R13

Published: 6 April 2009
This article is online at http://ccforum.com/content/13/2/131

Critical Care 2009, **13:**131 (doi:10.1186/cc7753)

Abstract

This commentary considers some of the factors that affect cerebral glucose metabolism in patients with traumatic brain injury. A study recently reported in *Critical Care* suggested a blood glucose range that may optimize cerebral glucose utilization; the findings of this study are evaluated and discussed. Some of the mechanisms of cerebral glucose control are explored, including the impact of intensive insulin therapy on cerebral metabolism.

Although glycaemic control in intensive care patients has been fertile ground for research over many years, optimizing cerebral glucose in acute brain injury has more recently attracted the interest of physicians involved in neurocritical care. The key research themes that are emerging include determining the range of arterial blood glucose that optimizes brain glucose concentration; the threshold of extracellular glucose below which neuronal injury occurs; determining the pathophysiological changes in the brain caused by deranged glucose control; and elucidating the effects of insulin therapy on cerebral glucose metabolism.

Holbein and coworkers [1] have begun to address some of these questions by using arterial and jugular venous measurements to determine a range of plasma glucose between which cerebral metabolism is optimized in patients with traumatic brain injury (TBI). Their findings, albeit from retrospective data, suggest an optimal arterial blood glucose level of 6 to 8 mmol/l. On the face of it, this would seem a very useful clinical parameter, particularly because cerebral glucose levels were thought to be dependent on plasma glucose concentrations in a near linear relationship [2]. However, evidence demonstrating increased glucose utilization after head injury, coupled with data showing that low brain glucose levels measured by cerebral microdialysis is related to poor outcome after TBI, suggest that plasma glucose concentration may not be a good reflection of extracellular cerebral glucose concentrations [3,4]. This is supported by Schlenk and coworkers [5], who found that cerebral glucose levels varied independently of plasma glucose in patients with subarachnoid haemorrhage. This clearly makes control of cerebral glucose based on plasma glucose much more difficult to achieve, particularly when significant metabolic heterogeneity exists after TBI, as reported by Abate and colleagues [6]. This heterogeneity implies that techniques to detect regional changes in glucose and oxygen metabolism such as microdialysis and positron emission tomography may be preferable to jugular bulb measurements - an issue eluded to in the discussion by Holbein and colleagues [1].

Using arterial-jugular differences in oxygen and glucose, both Holbein [1] and Vespa [7] and their colleagues demonstrated that higher arterial blood glucose levels may be associated with a lower oxygen extraction ratio (OER). However, Abate and coworkers [6] - using positron emission tomography - demonstrated that in some cases a higher glucose metabolism is associated with a higher OER. The mechanisms underlying these changes are unclear. Although high glucose metabolism with a high OER could be attributed to ischaemic hyperglycolysis, other mechanisms that may represent a compensatory response to injury could be responsible. For example, upregulation in the neuronal cell glucose transporter (GLUT)-3, which occurs after severe TBI, facilitates increased neuronal uptake of glucose and may therefore offer some explanation for the findings of Abate and coworkers [6,8]. However, as Holbein and colleagues [1] pointed out in their discussion, downregulation of the GLUT1 transporter in the blood-brain barrier after severe TBI decreases endothelial flux

GLUT = glucose transporter; IIT = intensive insulin therapy; OER = oxygen extraction ratio; TBI = traumatic brain injury.

of glucose even at higher arterial blood glucose levels, thereby leading to reduced cerebral glucose availability despite an adequate arterial supply. This would increase lactate production, decrease intracellular pH and cause cellular distress, which results in impaired metabolic activity and possibly adverse outcome [1,7,9].

The complexity of this subject is further compounded by the concept of cerebral spreading depression, which is a phenomenon of cortical depolarizations that can spread across the cerebral cortex in patients with severe TBI. Repolarization after cerebral spreading depression causes vasoconstriction that may reduce perfusion and glucose supply. As Strong and coworkers pointed out, spontaneous cortical depolarizations primarily occur at plasma glucose levels below 5 mmol/l, and levels of 7 to 9 mmol/l appear to be beneficial in improving metabolic stability [10-12].

Clearly, further work needs to be undertaken to confirm or reject these theories, but while this is ongoing we should approach interventions to control blood glucose with caution. Van den Berghe and coworkers [13,14] demonstrated that tightly controlling blood glucose levels with intensive insulin therapy (IIT) improved outcome in intensive care patients and that this may confer some benefit in head injured patients. However, low arterial blood glucose levels during IIT may be associated with lower cerebral glucose levels, possibly below the level required to meet cerebral metabolic demands. In an observational study, Vespa and colleagues [7] found that IIT was associated with lower cerebral extracellular glucose concentrations and increased markers of cerebral metabolic distress, while also demonstrating a higher OER in more patients with IIT than in those with loose glucose control.

Although hyperglycaemia in TBI is known to be associated with a higher incidence of poor outcome, the mechanisms of glucose handling by the brain after TBI remain unclear. Is it, as Donnan and Levi [15] imply, that hyperglycaemia is 'too much of a good thing'? Perhaps the risk of low brain tissue glucose is greater than hyperglycaemia, particularly if IIT is commenced. This brings us back to the key issue of the optimal plasma glucose range that should be sought in TBI patients. The results reported by Holbein and coworkers [1] provide an excellent platform from which larger prospective studies can be undertaken, not only to help unravel the complex mechanisms involved in cerebral glucose metabolism but also to provide data to help in the clinical management of the TBI patient.

Competing interests

The authors declare that they have no competing interests.

References

1. Holbein M, Béchir M, Ludwig S, Sommerfeld J, Cottini SR, Keel M, Stocker R, Stover JF: **Differential influence of arterial blood glucose on cerebral metabolism following severe traumatic brain injury.** *Crit Care* 2009, **13:**R13.
2. Choi IY, Lee SP, Kim SG, Gruetter R: **In vivo measurements of brain glucose transport using the reversible Michaelis-Menten model and simultaneous measurements of cerebral blood flow changes during hypoglycemia.** *J Cereb Blood Flow Metab* 2001, **21:**653-663.
3. Bergsneider M, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, Phelps ME, McArthur DL, Caron MJ, Kraus JF, Becker DP: **Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study.** *J Neurosurg* 1997, **86:**241-251.
4. Vespa PM, McArthur D, O'Phelan K, Glenn T, Etchepare M, Kelly D, Bergsneider M, Martin NA, Hovda DA: **Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study.** *J Cereb Blood Flow Metab* 2003, **23:**865-877.
5. Schlenk F, Nagel A, Graetz D, Sarafzadeh AS: **Hyperglycemia and cerebral glucose in aneurysmal subarachnoid hemorrhage.** *Intensive Care Med* 2008, **34:**1200-1207.
6. Abate MG, Trivedi M, Fryer TD, Smielewski P, Chatfield DA, Williams GB, Aigbirhio F, Carpenter TA, Pickard JD, Menon DK, Coles JP: **Early derangements in oxygen and glucose metabolism following head injury: the ischemic penumbra and pathophysiological heterogeneity.** *Neurocrit Care* 2008, **9:**319-325.
7. Vespa P, Boonyaputthikul R, McArthur DL, Miller C, Etchepare M, Bergsneider M, Glenn T, Martin N, Hovda D: **Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving lactate/pyruvate ratio after traumatic brain injury.** *Crit Care Med* 2006, **34:**850-856.
8. Hamlin GP, Cernak I, Wixey JA, Vink R: **Increased expression of neuronal glucose transporter 3 but not glial glucose transporter 1 following severe diffuse traumatic brain injury in rats.** *J Neurotrauma* 2001, **18:**1011-1018.
9. Zygun DA, Steiner LA, Johnston AJ, Hutchinson PJ, Al-Rawi PG, Chatfield D, Kirkpatrick PJ, Menon DK, Gupta AK: **Hyperglycemia and brain tissue pH after traumatic brain injury.** *Neurosurgery* 2004, **55:**877-881.
10. Strong AJ, Fabricius M, Boutelle MG, Hibbins SJ, Hopwood SE, Jones R, Parkin MC, Lauritzen M: **Spreading and synchronous depressions of cortical activity in acutely injured human brain.** *Stroke* 2002, **33:**2738-2743.
11. Strong AJ: **The Management of plasma glucose in acute cerebral ischemia and traumatic brain injury: more research needed.** *Intensive Care Med* 2008, **34:**1168-1172.
12. Shin HK, Dunn AK, Jones PB, Boas DA, Moskowitz MA, Ayata C: **Vasoconstrictive neurovascular coupling during focal ischemic depolarizations.** *J Cereb Blood Flow Metab* 2006, **26:**1018-1030.
13. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasserlaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in the critically ill patients.** *N Engl J Med* 2001, **345:**1359-1367.
14. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ: **Insulin therapy protects the central and peripheral nervous system of intensive care patients.** *Neurology* 2005, **64:**1348-1353.
15. Donnan GA, Levi C: **Glucose and the ischemic brain: too much of a good thing?** *Lancet Neurol* 2007, **6:**380-381.