Hyperglycemia in Acute Stroke

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Elevated blood glucose is common in the early phase of stroke. The prevalence of hyperglycemia, defined as blood glucose level >6.0 mmol/L (108 mg/dL), has been observed in two thirds of all ischemic stroke subtypes on admission and in at least 50% in each subtype including lacunar strokes. Extensive experimental evidence in stroke models supports that hyperglycemia has adverse effects on tissue outcome, and an association between blood glucose and functional outcome has been found in an increasing number of clinical studies. Although no interventional stroke studies have addressed the acute reversal of hyperglycemia, active lowering of elevated blood glucose by rapidly acting insulin is recommended in most published guidelines, even in nondiabetic patients (European Stroke Initiative [EUSI] guidelines >10 mmol/L, American Stroke Association [ASA] guidelines >300 mg/dL).

Causes of Acute Hyperglycemia

Although up to one third of acute stroke patients have either diagnosed or newly diagnosed diabetes, probably a major proportion of patients have stress hyperglycemia mediated partly by the release of cortisol and norepinephrine. It is also a manifestation of relative insulin deficiency, which is associated with increased lipolysis. Even in nondiabetic patients, stress hyperglycemia may be a marker of deficient glucose regulation in individuals with insulin resistance and developing diabetes mellitus.

How Elevated Glucose Injures the Ischemic Brain

By provoking anaerobic metabolism, lactic acidosis, and free radical production, hyperglycemia may exert direct membrane lipid peroxidation and cell lysis in metabolically challenged tissue. Moderately and severely increased blood glucose has been found to further the metabolic state and mitochondrial function in the area of ischemic penumbra. Insulin resistance is a known risk factor for the onset of stroke acting through a number of intermediate vascular disease risk factors (ie, thrombophilia, endothelial dysfunction, and inflammation). The evolution of an acute infarction may be expedited by the very same vascular factors, explaining why ischemia time seems to fly faster with patients with diabetes or grave hyperglycemia. Relative insulin deficiency liberates circulating free fatty acids, which, together with hyperglycemia, reportedly diminishes vascular reactivity. Furthermore, lowering glucose with insulin has been reported to reduce ischemic brain damage in an animal model.

The evolution of an infarction is accompanied by glutamate release mediating repeated waves of spreading depression (SD), another mechanism believed to propagate the necrosis of the penumbral tissue. Although hyperglycemia alone did not trigger early-response genes in the cortical tissue of rats, in conjunction with induced SD, the expression of c-fos and cyclooxygenase-2 were substantially increased. This suggests that elevated glucose may trigger untoward intracellular biochemical cascades also by altering early gene expression in metabolically challenged neurons.

The blood-brain barrier is well known to be vulnerable to hyperglycemia, presumably through the liberation of lactic acid and free radicals. The recent experimental study by Song et al in a rat model of collagenase-induced intracerebral hemorrhage (ICH) adds that hyperglycemia aggravates edema formation in a zone surrounding cerebral hemorrhages. The study also documented increased cell death measured by the TUNEL staining. It is conceivable that hemorrhages are surrounded by a zone of similarly challenged tissue as infarctions are, where the availability of glucose influences the metabolic state.

Clinical Correlation of Hyperglycemia and Infarct Progression

Although experimental studies have clarified several mechanisms by which hyperglycemia influences the destiny of ischemic brain tissue, studies bridging the gap between clinical stroke and experimental models have been scarce. Recent advances in MRI techniques have permitted correlation of loss of penumbral tissue with elevated blood glucose, which was linked to increased brain lactate production. Using a subcutaneous glucose sensor for continuous monitoring up to 72 hours, the same group could reproduce the finding that the infarcts expanded more in hyperglycemic patients, and that hyperglycemia was independently associated with the infarct volume change. This suggests that elevated glucose not only reflects the initial volume of infarcted tissue in the acute stage but is one of the true determinants of early infarct progression in man.

Prognosis and Hyperglycemia

Already ample literature has demonstrated that hyperglycemia on admission is associated with worsened clinical outcome, as reviewed in a systematic overview of 33 studies. Glycemic control may be indicated also in nondiabetic patients, in which stress hyperglycemia was associated with a 3-fold risk of fatal 30-day outcome and 1.4-fold risk of poor functional outcome, as compared with normoglycemic patients. Good glycemic control seems warranted also in hemorrhagic stroke, although more clinical information is needed in this area. At least 2 clinical trials have recently been
Summary of Evidence Supporting a Detrimental Role for Elevated Glucose in Stroke

1. Experimental ischemic damage is worsened by hyperglycemia.
2. Experimental ischemic damage is reduced by glucose reduction.
3. Early hyperglycemia is associated with clinical infarct progression in brain imaging.
4. Early hyperglycemia is associated with hemorrhagic conversion in stroke.
5. Early hyperglycemia is associated with poor clinical outcome.
6. Early hyperglycemia may reduce the benefit from recanalization.
7. Immediate insulin therapy reported beneficial in acute myocardial infarction and surgical critical illness.

Conclusions

This recent evidence supports that acutely elevated, predominantly stress-related hyperglycemia is associated with poor outcomes such as dependent state or intracerebral hemorrhage. Through several different biochemical mechanisms, elevated glucose in the setting of cerebrovascular insults probably accelerates the course of ischemic injury, also in the boundary regions with milder perfusion deficit. Although admission hyperglycemia has been clearly demonstrated to be a risk factor for symptomatic hemorrhage and worsened outcome after thrombolytic therapy, there is perhaps not enough evidence to withhold thrombolysis from hyperglycemic patients within the 3-hour time window. However, restoration of normoglycemia as soon as possible should be encouraged, although conclusive evidence of decreased risk with this approach is lacking. Especially the nondiabetic patients may be at risk of further brain damage if hyperglycemia prevails. The recent evidence summarized above and in the Table urges corroboration in randomized controlled trials of the efficacy of immediate glycemic control, and determination of where the level of target glucose concentrations of the relatively different current target values in the published guidelines (EUSID: <10 mmol/L, ASA: <300 mg/dL = 16.63 mmol/L) should be set. In the interim, we should fare well with adhering to good general stroke management, including control of blood glucose, normalization of body temperature, fluid balance and hemodynamics, or we may otherwise risk the favorable outcome even in the patient with early recanalization.

References

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