Opposing effects of glucose on stroke and reperfusion injury: acidosis, oxidative stress, and energy metabolism

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Introduction

Reduced delivery of glucose and oxygen during brain ischemia can cause energy failure (ATP depletion), which can in turn trigger processes leading to cell death. Glucose can support glycolytic ATP production even in the absence of oxygen, and it would seem to follow that increased glucose in the residual blood flow to ischemic brain should increase cell survival. This was tested experimentally in a rat model of is ischemia-reperfusion by Pulsinelli and colleagues several decades ago [1]. Glucose had a striking effect, but in the direction opposite to what might be expected: rats in which circulating blood glucose was increased by intravenous infusion had far more extensive brain injury and mortality than normoglycemic rats. This experiment has subsequently been revisited dozens of times, using different animal species, stroke models, glucose concentrations, timing of glucose elevations, and permutations of these factors. The net result is one of the most robust in all of stroke research: hyperglycemia almost always exacerbates brain injury [2, 3]. Clinical experience mirrors the animal literature in these respects, as both retrospective studies and patient registries show a striking correlation between elevated admission glucose concentrations and poor outcomes [4]. Hyperglycemia is similarly associated with increased hemorrhage formation and poor outcome in patients treated with tPA [5–7].

Random blood glucose levels are roughly 4.4 to 6.1 mmol/L in both humans and rodents, with rodents being the species most commonly used for experimental stroke. The definition of hyperglycemia varies somewhat in stroke studies, ranging from 6.1 to greater than 10 mmol/L glucose. Using these definitions, hyperglycemia is found at presentation in 30–60% of all stroke patients [8, 9]. Some of these patients are diabetic, but in most the acute, post-stroke hyperglycemia is a sympathomimetic stress response.

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Despite the frequency of hyperglycemia in stroke, and 30-plus years of congruent experimental and clinical observations linking hyperglycemia to poor outcomes, it remains uncertain whether hyperglycemia should be corrected in acute stroke patients. This uncertainty stems in part from a concern that the hyperglycemic stress response is to some extent adaptive; that some regions of ischemic brain may require increased glucose delivery to survive ischemia. A related concern stems from the practical difficulty in preventing an overcorrection of hyperglycemia in acutely ill patients, and providers are understandably reticent to lower blood glucose when an overshoot could be catastrophic. Against this background, we aim to summarize what is now known about the mechanisms by which hyperglycemia can exacerbate ischemic brain injury in the acute stroke setting. These mechanisms are then placed in the context of relevant clinical observations and clinical trials that address this complex issue.

Dual roles of glucose in energy metabolism and oxidative stress

The central nervous system is unique in that it requires a continuous supply of glucose for normal function. All other tissues, including the heart, can readily metabolize fatty acids, amino acids, and ketone bodies in place of glucose substrate, but the blood brain barrier prevents rapid influx of these alternative substrates under most conditions [10]. Glucose is metabolized almost completely to CO_2 in normal brain. There can be transient local metabolism of glucose to lactate in response to local brain activity, but the lactate so produced is subsequently metabolized oxidatively, or else escapes into the venous system [11]. Blood glucose concentrations are normally 4 – 6 mmol/L, essentially all of which can be extracted by brain. Normal, fully oxygenated blood carries approximately 9 mmol/L O_2, of which only a portion can be extracted [10]. Since 6 moles of O_2 are required to oxidize each mole of glucose, this leaves a large molar excess of glucose available for anaerobic metabolism to lactate when blood delivery of oxygen falls short of demand (Fig. 1). Anaerobic glucose metabolism can rapidly generate ATP, as occurs normally in exercising muscle. However, this process also produces lactic acid, and under ischemic conditions the lactic acid accumulates and reduces tissue pH (Figs. 1, 2). This effect is magnified during hyperglycemia.

Independent of its function role in energy metabolism, glucose is also required for both the quenching and production of reactive oxygen species in the CNS. This stems from the fact that glucose is the exclusive substrate NADPH production through the hexose monophosphate shunt (Fig. 1). NADPH produced by this pathway is used by the enzyme glutathione reductase to convert oxidized glutathione (GSSG) back to reduced glutathione (GSH), the major thiol anti-oxidant in brain. GSH production is impaired during hypoglycemia, [12], and this may limit the capacity of brain to counter oxidative stress. It is unknown whether GSH production can be accelerated by hyperglycemia.

Somewhat paradoxically, NADPH is also used by cells to generate reactive oxygen species: NADPH used by nitric oxide synthase to generate nitric oxide (NO·), and by NADPH oxidase to generate superoxide ($O_2^·$) (Fig. 1). These reactive oxygen species are important mediators of ischemic brain injury. Glucose supply to the hexose monophosphate shunt can be rate-limiting for $O_2^·$ production, and $O_2^·$ production in brain can be accelerated by

hyperglycemia [13]. O_2. can also be generated from the electron transport chain of damaged mitochondria during ischemia-reperfusion [14]; however, this process is also ultimately glucose-dependent because glucose is the source of almost all reducing equivalents passing through the mirochondrial electron transport chain in CNS tissues (Fig. 1).

Effects of blood glucose concentrations on ischemic brain injury

These multiple roles for glucose in brain lead to multiple and sometimes opposing effects of glucose on ischemic brain injury (Fig. 1). On one hand, low blood glucose concentrations (hypoglycemia) may exacerbate ischemic injury by reducing glucose delivery and hastening energy failure, particularly when oxygen supply is compromised or mitochondria are damaged. Hypoglycemia does not ordinarily cause neuronal death unless blood levels fall very low, below 1 mmol/L, but given the increased reliance on ischemic tissue for anaerobic energy production; it likely that much smaller reductions in blood glucose may exacerbate injury in ischemic brain. However, the only published study directly addressing this issue examined retinal rather than brain pathology [15].

On the other hand, elevated blood glucose concentrations can exacerbate cell injury by multiple mechanisms. Acidosis has long been recognized as one such mechanism, but even acidosis has complex and competing effects on ischemic cell survival. Normal brain pH is approximately 7.2. During ischemia, anaerobic metabolism of glucose to lactic acid can reduce this to roughly 6.6 under normoglycemic conditions, and below 6.0 under hyperglycemic conditions [16]. Modest levels of acidosis, to roughly pH 6.7, inhibit the production of superoxide by NADPH oxidase and are robustly neuroprotective in ischemia [17, 18]. More severe reductions in pH are thought to be exacerbate ischemic brain injury by causing protein denaturation, activation of acid-sensing ion channels, and release of ferrous iron [19, 20]. It should be noted, however, that despite these potential injury mechanisms there has been no direct demonstration that acidosis has a causal role in hyperglycemic exacerbation of brain injury, as this would require evidence that the deleterious effects of hyperglycemia can be negated by normalizing brain pH.

The requisite role of glucose in the production of superoxide and nitric oxide provides an additional mechanism of glucose-mediated injury that may be particularly important during reperfusion [21]. The formation of these reactive oxygen species requires oxygen and therefore cannot occur under the anaerobic conditions of severe or complete ischemia. With reperfusion there is both an influx of oxygen and a normalization of pH, which releases acid-mediated inhibition of NADPH oxidase [17]. Superoxide production by NADPH oxidase during reperfusion is increased by hyperglycemia and decreased by reducing cellular glucose utilization, NADPH oxidase activity, or brain pH [13, 17, 22].

Hyperglycemia may also promote ischemic injury by other mechanisms, including enhanced glucose-sodium exchange and formation of abnormal protein glycosylation and advanced glycation products [23–25], but a definitive role for these processes in acute ischemic injury has not yet been established. Hyperglycemia is also strongly associated with an intensified post-ischemic inflammatory response, but it has been difficult to unravel whether the increased inflammation is a cause or result of increased ischemic brain injury. Interestingly,

it has also been suggested that glucose-induced cortisol elevations, rather than glucose per se, exacerbate ischemic brain injury in experimental stroke [26]. Cortisol can indeed potentiate neuronal death, but the magnitude of glucose-induced cortisol elevations has been disputed [24], and this explanation would not account for the effects of interventions that negate effects of hyperglycemia.

Metabolic heterogeneity in brain ischemia

The opposing effects of glucose on ischemic brain injury are further complicated by the metabolic heterogeneity of ischemic tissue. The classic concept of an ischemic core and penumbra has stood the test of time, with the "core" defined as tissue with zero or near-zero blood flow in which energy failure occurs within minutes. The term "ischemic penumbra" was originally introduced to describe regions with reduced blood flow that are electrically silent but viable if blood flow is restored [27], but the term is now applied more generally to ischemic brain regions that are metabolically compromised but potentially salvageable [28]. The flow thresholds at which these conditions occurs is somewhat variable between brain regions and with duration of ischemia.

The bioenergetic state and response to hyperglycemia in these regions is quite different (Fig. 2). At one extreme, a core region of focal ischemia may have no residual blood flow at all, in which case circulating blood glucose concentrations are of little consequence. This may occur in areas with poor collateral circulation, such as lacunar strokes affecting deep white matter regions, or in the core areas of very large cortical ischemic territories. Interestingly, this is the one setting in which hyperglycemia has repeatedly been shown *not* to exacerbate experimental ischemic brain injury, and may in fact have a beneficial effect [2, 29]. The beneficial effect may stem from the ability of glucose to fuel the very high energy demand imposed by spreading depression near ischemic core regions [30].

Where collateral circulation exists, as is more commonly the case, a "penumbral" region of reduced but non-zero blood flow is formed between non-ischemic tissue and an ischemic (or in the absence of a core). The molar excess of glucose over oxygen in arterial blood dictates that glucose delivery will continue to these ischemic regions even after all extractable oxygen removed, permitting ATP production by glucose metabolism to lactic acid. ATP consumption is slowed in these penumbral regions by cessation of electrical activity, but there remains a residual ATP demand for continued cell viability. Anaerobic metabolism of glucose to lactic acid produces only $1/16^{th}$ as much ATP per molecule of glucose as normal oxidative metabolism, and consequently tissue viability in these regions can be maintained only by increasing the rate of glucose utilization to values *higher* than in non-ischemic tissues [30, 31].

The ischemic penumbra is unstable and dynamic, with both regional and temporal fluctuations in blood flow [28, 31]. Hyperglycemia has complex effects on metabolism in the region. Where blood flow is only modestly reduced, lactic acid can be cleared and the additional ATP production fueled by augmented glucose delivery may prevent release of excitotoxic glutamate and other sequelae of energy failure [28]. Conversely, where (or when)

ischemia is more severe, lactic acid accumulates and pH falls in proportion to blood glucose levels [32].

Effects of hyperglycemia on vascular injury

Ischemic injury to the cerebral vasculature may be particularly dependent on circulating glucose concentrations. In animal models of ischemia-reperfusion, hyperglycemic has frequently been associated with a striking "no reflow" of blood into the microvasculature, along with evidence of increased blood-brain barrier disruption [33]. It is possible that these effects on vasculature are also a manifestation of increased parenchymal injury, but evidence also exists for direct effects of hyperglycemia on cerebrovascular tone and endothelium, resulting in increased edema formation, increasing hemorrhage, and reduced microvascular reflow. Several interrelated mechanisms have been identified by which glucose can induce these changes, including increased endothelial protein kinase C activation, amplified inflammatory responses, and increased superoxide generation [22, 34–36]. Hyperglycemia also increases the rate of tPA-induced hemorrhage in a model of ischemia-reperfusion, and the reversal of this effect by inhibitors of NADPH oxidase further suggest that glucose-fueled superoxide production contributes to vascular injury [22].

Correlations between experimental and clinical observations

Animal models of stroke differ in important ways from clinical stroke in that the subjects are almost young, healthy, male, and under general anesthesia. In addition, animal models of stress-induced hyperglycemia almost always employ exogenous glucose administration, which elevates insulin secretion, whereas stress-induced hyperglycemia results from an increase in circulating catecholamines, which *suppress* insulin secretion. These factors could in principle skew the experimental stroke literature, but despite these limitations there is a very strong agreement between experimental and clinical observations. Clinical studies show a robust association between elevated admission hyperglycemia and negative outcome measures such as infarct size, mortality, disability, and poor recovery. This association is observed in ischemic stroke with or without thrombolysis and in patients with intracerebral hemorrhage, and it remains significant in studies using logistic regression analysis to control for a number of confounding factors [4, 8, 37].

Recent clinical studies using imaging end points have further confirmed this relationship. A study using transcranial Doppler, MRI, and MRS showed that hyperglycemia is a strong predictor of infarct growth and poor outcome, even when statistically accounting for original infarct size, size of the perfusion mismatch deficit, NIHSS on admission, and time to vessel reperfusion [38]. A subsequent study similarly showed that, for patients with evidence of diffusion/perfusion mismatch, admission hyperglycemia is independently associated with infarct size, progression of the ischemic penumbra to infarct, and lactate peaks in the penumbra [39]. Interestingly, for those subjects with very little diffusion/perfusion mismatch (indicating a minimal penumbra), there was no relationship between hyperglycemia and lactate peaks or outcome measures [39], and in a separate study insulin treatment tended to increase rather than decrease ultimate infarct size in hyperglycemic patients with complete arterial occlusion. [40]. These results are consistent with studies in animal stroke models

showing little or no detrimental effect of hyperglycemia in complete ischemia [29]. They also agree with the clinical observations that hyperglycemia is not detrimental and may even be beneficial in lacunar strokes [41, 42], which occur most frequently in end-arterial vascular territories with poor collateral flow. Also in parallel with results of animal studies, evaluations of hemorrhagic risk after thrombolytic therapy identify hyperglycemia to be strongly associated with both hemorrhage and poor outcomes [6, 43], particularly in the setting of vessel recanalization [44].

Nevertheless, despite well-established injury mechanisms and a general agreement between the experimental and clinical literature, there remains some evidence against a causal role of hyperglycemia in exacerbating ischemic injury. One recent study suggests that diabetes and stroke severity may be more important factors than admission blood glucose levels per se, [45], and two studies that measured serum cortisol found that these levels predicted poor stroke outcomes better than blood glucose levels [46, 47].

Prospective trials

A Cochrane review of seven trials completed before June 2010 all concluded that treatment with intravenous insulin to maintain normoglycemia after ischemic stroke provides no benefit in terms of functional improvement, ultimate functional outcome, or death, [4]. Two subsequent studies arrived at similar conclusions [40, 48], but the concern remains that even the largest of these studies were underpowered. [7]. The prospective studies also noted a significant increase in the number of hypoglycemic episodes in insulin-treated patients. Although glucose levels rarely fell to levels normally considered dangerous, it is possible that even modest reductions in circulating glucose concentrations can have a negative impact on energy metabolism in ischemic brain for reasons discussed above. An ongoing multi-center clinical trial with targeted enrollment of 1400 patients will assess the effects of aggressive glucose control starting within 12 hours of stroke symptom onset [7].

Conclusions

The experimental literature identifies fundamental complexities in the role of glucose and ischemic injury. Hyperglycemia can enhance glucose delivery and preserve ATP levels in ischemic tissue, but at the cost of deleterious lactic acidosis and oxidative stress. In an individual case it currently not possible to predict which of these factors will prevail, and the heterogeneous and dynamic nature of ischemic brain lesions makes it likely that both negative and positive effects may occur within a given lesion over time. The preponderance of evidence suggests that the deleterious effects of hyperglycemia will dominate in most settings, but there is clinical and experimental evidence that lesions with complete ischemia are the least likely to be exacerbated by hyperglycemia, and may even be helped.

These opposing effects of hyperglycemia on ischemic brain likewise contribute to the difficulty in determining in any given patient whether aggressive glucose management will be helpful. Future advances in spectroscopic and other imaging modalities may provide information on collateral circulation and metabolic state of penumbral tissues that may help distinguish those patients who are at high risk from ongoing hyperglycemia from those in

whom reductions in blood glucose may be particularly hazardous. Perhaps the greatest promise lies in interventions targeting specific deleterious processes induced by hyperglycemia, as these could in principle obviate the need for normalizing blood glucose concentrations in acute stroke.

In contrast to this somewhat mixed effects of hyperglycemia on ischemic brain, the experimental literature indicates a univalently negative effect of hyperglycemia in the setting of reperfusion. The clinical experience likewise indicates a particularly negative effect of hyperglycemia in during reperfusion; nevertheless, hyperglycemia is not presently identified as a contraindication to thrombolytic therapy (except as a potential stroke mimic). This issue may warrant re-examination - not only because thrombolytic therapy could have a net negative effect in this patient group, but also because removing this group from treated cohorts may reveal a longer window of opportunity for treatment and/or lower hemorrhage rates in non-hyperglycemic patients.

Acknowledgments

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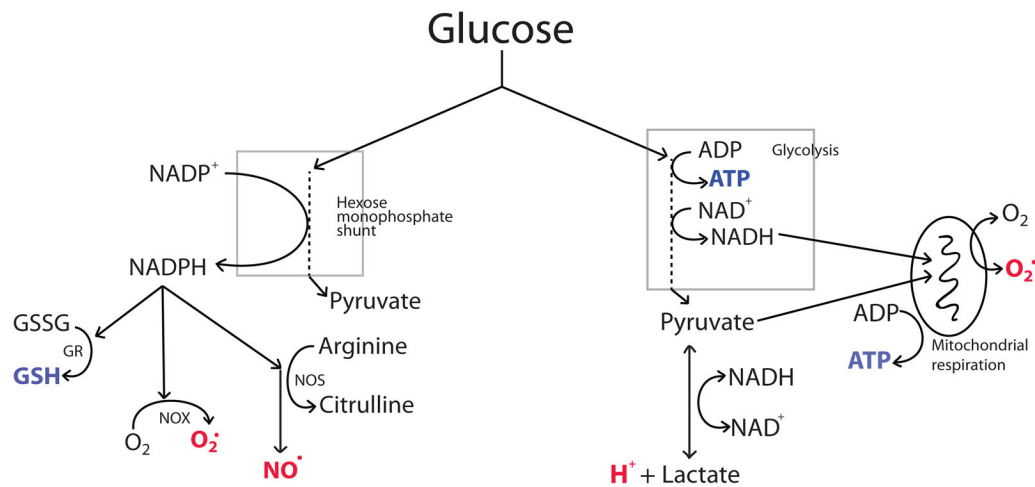
Figure 1.

Metabolic fates of glucose relevant to ischemic injury.

Products thought to have favorable effects on stroke outcome are shown in blue font, and products thought to have deleterious effects are in red font. Glucose metabolized by the hexose monophosphate provides reducing equivalents for producing NADPH. NADPH in turn can be used by glutathione reductase (GR) to regenerate glutathione (GSH) from glutathione disulfide (GSSG), and for the production of nitric oxide (NO·) by nitric oxide synthase or superoxide (O_2·) by NADPH oxidase (NOX). ATP is produced by glycolytic production of glucose to pyruvate and NADH. Pyruvate and NADH are normally oxidized to CO_2 and NAD^+ by mitochondrial respiration to generate additional ATP. Under ischemic conditions, oxidative metabolism cannot occur and NAD^+ is instead regenerated by the formation of lactic acid. During reperfusion, damaged mitochondria may produce superoxide by donating glucose-derived reducing equivalents to molecular oxygen.
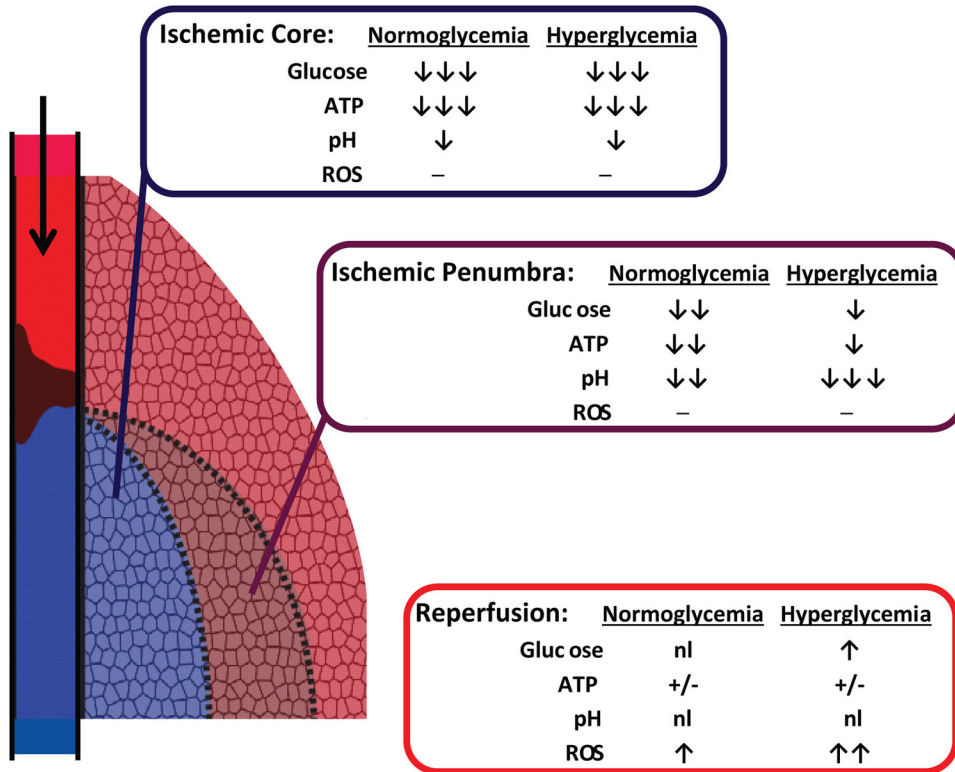
Figure 2.
Differing effects of hyperglycemia on ischemic core, penumbra, and reperfusion. Complete or near-complete ischemia in core regions with poor collateral circulation leads to glucose and oxygen depletion, accompanied by ATP depletion and mild acidosis.
Hyperglycemia supports metabolism and exacerbates the acidosis to only a minor degree in core regions, because only the glucose present at onset of ischemia is metabolized.
Penumbral regions with residual blood flow through collateral circulation receive continued glucose but not oxygen delivery, due to the molar excess of glucose in arterial blood.
Glycolysis fueled by the continued glucose delivery can attenuate ATP depletion, but also generates lactic acidosis in proportion to blood glucose levels. During reperfusion pH is normalized and ATP recovers where tissue is still viable, but with increased glucose delivery there is increased production of reactive oxygen species.