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Hyperglycemia, diabetes and stroke: Focus on the cerebrovasculature

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Abstract

Acute ischemic stroke (AIS) results from the occlusion of an artery and causes vascular and neuronal damage, both of which affect the extent of ischemic injury and stroke outcome. Despite extensive efforts, there is only one effective treatment for AIS. Given that up to 40% of the AIS patients present with admission hyperglycemia either as a result of diabetes or acute stress response, targets for neuronal and vascular protection under hyperglycemic conditions need to be better defined. Here, we review the impact of diabetes and acute hyperglycemia on experimental stroke with an emphasis on cerebrovasculature structure and function. The relevance to clinical evidence is also discussed.

Keywords

Ischemia reperfusion injury; Stroke; Diabetes; Hyperglycemia

1. Introduction

Given the sheer number of 700,000 victims per year and the availability of only one effective treatment, acute ischemic stroke (AIS) remains to be one of the most under-treated serious diseases in the United States. A major challenge in the study of AIS is that most treatments effective in experimental animals have failed in humans. One plausible explanation is that strategies for protection and intervention have been developed in healthy and young experimental models upon which focal cerebral ischemia has been imposed. While it is known that the ischemia reperfusion-induced vascular damage in AIS propagates a series of events that lead to neuronal damage, targets to protect the vasculature from ischemic injury in the presence of preexisting vascular disease are far from clear.

Approximately 30–40% of AIS patients present with admission hyperglycemia either as a result of diabetes or acute stress response (Baird et al., 2003; Gray et al., 2007). Type 2 diabetes, a disease that affects more than 24 million Americans with an alarming number of new cases, holds a 2–6 fold increased risk for cerebrovascular disease and stroke (Capes et al., 2001; Gray et al., 2007; Martini and Kent, 2007). Moreover, hyperglycemia is associated

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with poor outcome in AIS (Capes et al., 2001; Gray et al., 2007) Thus, in recent years there is growing interest in how to manage hyperglycemia in AIS culminating in several clinical trials including The Glucose Insulin in Stroke Trial (GIST), The Treatment of Hyperglycemia in Ischemic Stroke (THIS) and The Glucose Regulation in Acute Stroke Patients (GRASP) Trial. Despite extensive research, our understanding of the mechanisms of poor stroke outcome in hyperglycemia is very limited. It also remains unclear whether chronic hyperglycemia as is the case in diabetes and acute hyperglycemia at the time of stroke affect ischemia/reperfusion injury in similar or different pathways. This is important to identify therapeutic targets and strategies.

Cerebrovascular protection is not limited to prevention of diabetes-induced detrimental changes in vascular structure/function before the occurrence of an ischemic insult but can also be implemented acutely by preventing vascular dysfunction and disruption of vascular integrity leading to edema and hemorrhage following acute ischemic stroke. In this article, impact of diabetes and acute hyperglycemia on cerebrovascular function and structure which may influence the degree of ischemic injury in experimental models are reviewed. In addition, the relevance of experimental models to clinical evidence with respect to the effect of preexisting hyperglycemia (acute or chronic elevations in blood glucose) is briefly discussed.

2. Experimental Models

2.1 Ischemic injury in acute hyperglycemia versus diabetes

The extent of cerebral ischemic injury in experimental models has been traditionally evaluated by measuring infarct size which is an indicator of neuronal damage. On the other hand, edema formation and hemorrhagic transformation (HT) which develops secondary to prolonged ischemia followed by reperfusion injury are measures that reflect the vascular damage mediated by ischemia. Thus in this section both neuronal and vascular damage under hyperglycemic and diabetic conditions will be reviewed. The discussion of relevant papers is organized by the methods used to induce ischemia.

Myers and Yamaguchi (Myers and Yamaguchi, 1977) were the first to report that acute hyperglycemia augmented neuronal injury after cardiac arrest-induced global ischemia in monkeys. They demonstrated mild edema and widespread necrosis of cortex and basal ganglia in the brain of glucose infused monkeys. In the following years, the deleterious effect of acute hyperglycemia on brain injury after global ischemia was confirmed in other studies (Kalimo et al., 1981; Pulsinelli et al., 1982; Warner et al., 1995). Natale et al. (Natale et al., 1990) demonstrated increased mortality in dogs with moderate hyperglycemia (18 ± 0.9 mmol/L) following global ischemia and this was associated with increased lactate levels in the cortex. Interestingly, Sieber et al. (Sieber et al., 1994) observed a similar drop but faster recovery of cerebral pH values in diabetic animals (3 months of diabetes duration) compared to that observed in acute hyperglycemia without diabetes following incomplete global ischemia. Dietrich and colleagues reported worsening of the degree of BBB breakdown in moderate hyperglycemia achieved by intraperitoneal injection of 50% dextrose 15 min prior to global ischemia (Dietrich et al., 1993). In contrast, an earlier study reported that there is no difference in the extent of BBB damage in normoglycemic and hyperglycemic rats when exposed to 10 min cerebral ischemia suggesting that duration of ischemia is critical for BBB breakdown (Siemkowicz, 1981).

In permanent focal ischemia models, most authors indicate that hyperglycemia increases ischemic damage. de Courten-Myers et al. (de Courten-Myers et al., 1988) reported increased infarct size in both brief and prolonged hyperglycemia states after permanent middle cerebral artery occlusion (MCAO) in cats where acute hyperglycemia was induced

by glucose infusion. The same group also found that acutely hyperglycemic cats showed a wide spectrum of outcomes after 8 hr permanent ischemia, ranging from small infarcts to hemispheric edema deaths (de Courten-Myers et al., 1992). Compared to normoglycemia, the acutely hyperglycemic cats had a 3-fold increase in hemispheric infarct volume. Anderson et al. (Anderson et al., 1999) demonstrated, under both normoxia and mild hypoxia, that acute severe hyperglycemia (> 28 mmol/L) led to a more pronounced intracellular acidosis and retardation of NADH regeneration than in acute hypoglycemia (≈ 2.8 mmol/L). However, there are also other studies which showed contrary results. Nedergaard et al. (Nedergaard and Diemer, 1987) reported that compared with normoglycemia, the infarct volume was decreased in hypoglycemic rats, unaltered in acute diabetes induced by single streptozotocin (STZ) injection 2 days before MCAO, and increased in chronic diabetes induced by STZ injection 4 months before MCAO. The same group also found that the cortical glucose metabolism remained normal and there was no neuronal loss in the penumbra in hyperglycemic rats after MCAO. These indicated that hyperglycemia might protect against neuronal injury in the areas next to the infarct. In a study with photochemically induced permanent cerebral ischemia, acute severe hyperglycemia induced by dextrose infusion (range 15–34 mmol/L) was reported to result in smaller infarct volume compared with normoglycemic (range 4–10 mmol/L) rats (Ginsberg et al., 1987). Similar results have been reported in rabbits (Kraft et al., 1990) and cats (Zasslow et al., 1989).

The results from reversible focal ischemia models are also variable. Most studies reported increased brain injury in hyperglycemic animals after reperfusion (de Courten-Myers et al., 1992; Gisselsson et al., 1999; Liu et al., 2007). When hyperglycemia was induced acutely in spontaneously hypertensive rats, there was no effect of hyperglycemia on infarct volume (Slivka, 1991). By using the magnetic resonance imaging (MRI) techniques, Quast et al. (Quast et al., 1997) determined the effect of preexisting hyperglycemia on the ischemia/reperfusion injury in acute hyperglycemia induced by STZ injection 2 days prior to induction of stroke. The larger lesion size and lower hemispheric blood volume was found in hyperglycemic animals after temporary, but not permanent, ischemia. de Courten-Myers et al. (de Courten-Myers et al., 1992) demonstrated that acutely hyperglycemic cats had a 7-fold increased death rate due to hemispheric edema after transient MCAO, whereas there was no difference in infarct volume between control and acutely hyperglycemic animals.

As discussed above, ischemia/reperfusion injury not only results in neuronal damage but also vascular damage resulting in HT. This phenomenon is distinct from primary intracerebral hemorrhage and develops secondary to prolonged brain ischemia. Hyperglycemia causes increased HT in ischemia/reperfusion models indicating that reperfusion injury contributes to the development of this complication (de Courten-Myers et al., 1992; de Courten-Myers et al., 1989). Even the acute hyperglycemia induced by anesthesia worsens HT and induces larger infarct size after reperfusion (Kawai et al., 1997). In recent studies, Ennis and Keep (Ennis and Keep, 2007) have reported marked blood-brain barrier disruption in intraperitoneal glucose injection-induced mild (5.5–11 mmol/L) and transient severe (>20 mmol/L) hyperglycemia after temporary and permanent occlusion. They also found that compared with prolonged hyperglycemia for 90 minutes after ischemia, transient severe hyperglycemia shortly (5–30 min) after occlusion caused more severe blood-brain barrier disruption. Similar results were shown in the recent study by Kamada et al. (Kamada et al., 2007). In STZ induced acute hyperglycemia, they reported increased edema volume and Evans blue leakage after 60 min MCAO. While there are few studies that report otherwise, as summarized above most of these past studies point to a greater ischemic damage in animals made hyperglycemic acutely by glucose infusion or STZ injection 2–3 days prior to ischemic injury emphasizing the need for additional studies focusing on mechanisms of HT development in diabetic stroke.

Data on the effect of diabetes resulting in longer term hyperglycemia on ischemic damage are scarce. With the well established type 2 diabetes model, db/db mice, Vannucci et al. (Vannucci et al., 2001) have reported increased edema and infarct size after hypoxic-ischemic injury compared to non-diabetic animals. Interestingly, in contrast to diabetic males, diabetic female mice achieved a higher blood glucose level but less edema and reduced infarct size. In this model, blood glucose levels were >22 mmol/L and hypoxia-ischemia was induced by first ligating the carotid artery and 3 h later exposing the animals to 8% oxygen/92% nitrogen gas mixture for 15–30 min. It also has to be mentioned that leptin is neuroprotective and lack of leptin receptor might have contributed to the severity of ischemic damage in this model. Interestingly, an earlier study by Warner et al reported that acutely hyperglycemic but not diabetic rats are more vulnerable to global ischemia despite similar levels of glycemia suggesting some degree of protection in diabetes (Warner et al., 1992). Again, in this study blood glucose levels were higher than normally seen in type 2 diabetic patients and the study employed a global ischemia method. Recently we reported a smaller volume and characteristic subcortical localization of infarcts after temporary MCAO in Goto-Kakizaki (GK) rats, a lean and moderate model of type 2 diabetes (Ergul et al., 2007). In our studies, the duration of diabetes was 4–6 weeks and average blood glucose was 10–12 mmol/L. Moreover, in all diabetic animals there was HT and increased edema after transient (Ergul et al., 2007) but not permanent ischemia (unpublished results).

As discussed above, there are contrasting reports on the extent of ischemic damage in hyperglycemia and diabetes. Different techniques to induce ischemia and/or increase blood glucose in these models may have contributed to a wide array of outcomes emphasizing the complexity of stroke pathophysiology as well as the need for a more systemic approach to delineate relative roles of hyperglycemia and diabetes. Another important point of discussion is the diabetic models used in these past studies which mainly employed STZ-induced type 1 model diabetes. Given that a vast majority of diabetic stroke patients have type 2 diabetes, we need to incorporate relevant diabetic models to stroke research.

2.2 Cerebrovascular structure in acute hyperglycemia vs. diabetes

Diabetes is not only a metabolic disease but also considered as a vascular disease because of its effect on macro and microcirculation of many vascular beds, including the cerebral circulation. Generally, diabetes or chronic hyperglycemia contributes to proliferation of vascular smooth muscle cells (Li et al., 2004; Srivastava, 2002), degeneration of endothelial cells and pericytes (Chen et al., 2006; Lorenzi et al., 1985; Lorenzi et al., 1986), thickening of the capillary basement membrane (Jakobsen et al., 1987; Junker et al., 1985; McCall et al., 1982), and an increase in aggregation and adhesion of platelets to the endothelium (Dunbar et al., 1990; Stratmann and Tschoepe, 2005).

Kikano et al. (Kikano et al., 1989) demonstrated that acute hyperglycemia induced by glucose injection or STZ-induced chronic hyperglycemia has no effect on cerebral intravascular volume and the anatomic density of brain capillaries. An earlier study showed that acute hyperglycemia does not alter overall vessel diameter but causes significant endothelial swelling and thus impairing reperfusion (Paljarvi et al., 1983).

At the early stage of diabetes, smooth muscle cells of cerebral arterioles endure changes in shape and intercellular elements which are confirmed by swollen mitochondria and cisternae of the endoplasmic reticulum and reduced cytoplasmic staining (Moore et al., 1985). In this study, necrosis of arteriolar endothelial cells was evident in virtually every vessel section. These results indicated that the degeneration of endothelial cells and smooth muscle cells in cerebral cortical arterioles begins in the very early stages in the STZ model of diabetes (Moore et al., 1985). Increased capillary basement membrane thickening and decreased cortical capillary density have been observed in STZ induced chronic diabetes (Jakobsen et

al., 1987; Junker et al., 1985). However, one study reported unchanged regional density of perfused cerebral capillaries and cerebral blood flow (CBF) in STZ-induced diabetes 3 or 20 weeks after the onset (Knudsen et al., 1991).

Another study looked at temporal changes in cerebrovascular structure in STZ diabetic rats. After one month, the pial vessels of diabetic animals were dilated and tortuous, and increased arterio-venous shunting was observed (McCuskey and McCuskey, 1984). After 5 months of diabetes, there were focal changes in vascular basement membrane thickness and density. It was demonstrated that astrocytic end feet were greatly swollen. In addition, there were nodules on the basement membrane invading the space occupied by degenerating smooth muscle cells, pericytes and astrocytes. By 11 months, greatly widened basement membranes which varied in density and content were observed. Interestingly, the ultrastructure of endothelial cells was not noticeably altered and interendothelial tight junctions appeared to be intact (McCuskey and McCuskey, 1984). However, recent studies have demonstrated that cerebral tight junction proteins, occludin and zona occludens-1, were decreased in STZ induced diabetes (Chehade et al., 2002; Hawkins et al., 2007). This decrease may be mediated through increased matrix metalloproteinase (MMP) activity induced by diabetes (Hawkins et al., 2007). We have also shown that a short term of diabetes (4 weeks) is associated with increased tortuosity of pial vessels (Ergul et al., 2007). At this point, there is no change in MCA wall and lumen thickness but MMP activity is already increased. 12 weeks of diabetes in the same rat model induces MCA remodeling characterized by an increased wall to lumen ratio associated with augmented MMP activity (Harris et al., 2005).

While the above mentioned studies provide strong evidence of diabetes-induced structural changes in the cerebrovasculature, our understanding of the impact of preexisting vascular disease on cerebral ischemic injury is still incomplete. Changes in vascular structure may influence vascular tone and integrity which ultimately affect CBF and the magnitude of ischemia/reperfusion injury. As discussed above our recent findings demonstrated that animals that display increased tortuosity and MMP activity after a short duration of diabetes present with smaller infarcts but greater HT providing compelling evidence that preexisting vascular disease may have a differential effect on hyperglycemic ischemic injury (Ergul et al., 2007).

2.3 Cerebrovascular function in acute hyperglycemia vs. diabetes

Cerebral blood vessels develop a state of partial constriction or tone that allows an artery to increase or decrease its diameter to regulate blood flow. This basal tone is mainly determined by the myogenic reactivity of vascular smooth muscle cells to changes in perfusion pressure and hence referred as myogenic tone. Since blood flow is related to the fourth power of vessel radius, even a small increase in basal myogenic tone would lead to significant reductions in lumen diameter and may complicate perfusion under normal conditions and more so in ischemia/reperfusion injury. Cipolla et al. (Cipolla et al., 1997) reported that the myogenic tone of posterior cerebral arteries was decreased with increasing glucose concentration in the perfusate buffer using isolated vessels in a pressurized arteriograph. However, Zimmermann et al. (Zimmermann et al., 1997) demonstrated greater membrane potential depolarization and tone of MCAs from diabetic female Sprague-Dawley rats compared with controls. In this study, the duration of diabetes was 4–8 weeks. It has been shown that ischemic injury increases the stiffness of MCAs of control Wistar rats (Coulson et al., 2002). In addition to myogenic regulation of vascular tone, vasoreactivity to endocrine and biochemical factors is also a determinant of vessel caliber and function. A recent study showed impaired vasodilation of the internal carotid artery, MCA, and perforating artery of six-month-old diabetic GK rats under hypercapnia conditions (Oizumi et al., 2006). Didion et al (Didion et al., 2007) reported decreased dilation of cerebral

arterioles in response to acetylcholine in transgenic type 2 diabetic mice. In BBZDR/Wor rats, a recently described obese model of type 2 diabetes, the myogenic tone of posterior cerebral arteries steadily increased with disease progression. Moreover, there was increased sensitivity to vasoconstrictors and endothelium-dependent dilation was reduced (Jarajapu et al., 2008). An earlier study reported that one month after the onset of STZ-induced diabetes, the vasoreactivity of arterioles to changes in partial oxygen pressure was reduced and blood flow was slower (McCuskey and McCuskey, 1984). Although our knowledge of the acute hyperglycemia-induced changes in cerebrovascular function is quite limited, there appears to be differences in acute hyperglycemia versus diabetes-induced cerebrovascular dysfunction.

All of these changes in cerebral vascular function induced by either acute or chronic hyperglycemia/diabetes may be coordinated by multiple mechanisms including increased oxidative stress, PKC and Rho kinase activity, all of which also contribute to ischemia/reperfusion injury as recently reviewed (Brownlee, 2001; Chrissobolis and Sobey, 2006; Johansen et al., 2005; Sachidanandam et al., 2005). It is well established that hyperglycemia causes a robust increase in mitochondrial free radical generation which then triggers downstream mediators such as NADPH oxidase and PKC to cause further increases in the formation of reactive oxygen species (Brownlee, 2001). Increased oxidative stress not only reduces the bioavailability of nitric oxide (NO), which plays very important roles in relaxation of blood vessels and regulation of platelet adhesion, but also leads to generation of peroxynitrite, an important reactive nitrogen species. Peroxynitrite alters the function of biomolecules by protein nitration as well as causing lipid peroxidation (Turko et al., 2001). For example, potassium channels, which regulate the vasorelaxation response, are inhibited by nitration not only in the cerebral vasculature (Elliott et al., 1998) but also in the coronary circulation (Liu and Gutterman, 2002; Liu et al., 2002). A recent study showed that peroxynitrite diminishes myogenic reactivity of cerebral arterioles via disruption of actin cytoskeleton organization (Maneen et al., 2006). Given that ischemia/reperfusion injury itself causes significant increases in oxidative stress (Fagan et al., 2004), regulation of cerebral vascular tone and thus CBF may be further impaired in acute hyperglycemia and/or diabetes.

Another elementary mechanism of diabetic complications, increased protein kinase C (PKC) activity, contributes to cerebral microvascular dysfunction (Atochin et al., 2007). PKC is a widely expressed serine/threonine kinase (Brownlee, 2001). It has been recognized that PKC plays a key role in mediating arterial tone and vascular function via stimulation of free radical formation as well as inhibiting NOS activity (Hamilton et al., 2007). In a recent study, Bright et al. has reported that a δ PKC inhibitor treatment improved cerebrovascular pathology, increased the number of patent microvessels, and increased CBF after MCAO. In hypertensive rats, the δ PKC inhibitor even decreased infarct size (Bright et al., 2007). Therefore, PKC might be an important therapeutic target for protection of cerebral microvascular function. Another emerging signaling pathway in both diabetes and stroke is the activation of Rho kinase (Chrissobolis and Sobey, 2006; Didion et al., 2005; Miao et al., 2002a; Miao et al., 2002b; Shin et al., 2007). Similar to the PKC pathway, Rho kinase is also involved in the regulation of endothelial NOS activity and increases smooth muscle contractility by attenuating NO synthesis. Since Rho kinase is important for actin cytoskeleton organization, dysregulation of Rho kinase may contribute to acute and chronic hyperglycemia-induced regulation of cerebrovascular tone. However, the effect of acute hyperglycemia on Rho kinase activity is less clear and warrants further studies. Together, diabetes and acute hyperglycemia have significant and important effects on cerebral vascular function. Efforts have been focused on the macrovessels but our knowledge on smaller caliber vessels which also contribute to cerebrovascular resistance is limited. Contributions are needed to disclose the key therapeutic targets for hyperglycemia-associated ischemic cerebral diseases.

3. Clinical Studies

From a clinical stand point, it is extremely difficult to prove a cause-effect relationship between worsened outcomes of stroke and acute hyperglycemia, with or without diabetes presence, as the AIS patient population presents with multiple confounding factors. Our knowledge heavily relies on observational studies. There is a clear correlation between admission hyperglycemia and much worse outcomes (Alvarez-Sabin et al., 2003; Bruno et al., 1999; Bruno et al., 2002; Capes et al., 2001; Martini and Kent, 2007; Parsons et al., 2002). Importantly, there is a higher incidence of hemorrhage following early reperfusion with t-PA in hyperglycemic patients (Alvarez-Sabin et al., 2003). In addition, persistent elevation in blood glucose after stroke is independently associated with expansion of the infarct and thus worse clinical outcome (Baird et al., 2003).

Due to the nature of these studies, the hyperglycemic patient group included diabetic patients as well as patients that did not have a history of diabetes. In the NINDS rt-TPA stroke trial, even after adjusting for diabetes as a confounding factor, higher admission blood glucose levels were associated with worse outcomes (Bruno et al., 2002). In order to provide further insight into the effect of high admission blood glucose levels on both short term mortality and functional recovery after stroke in patients with and without a history of diabetes, Capes et al (Capes et al., 2001) conducted a meta-analysis of thirty one studies. They reported that after stroke (ischemic and hemorrhagic stroke combined) relative risk of in-hospital and 30-day mortality was higher in nondiabetic patients with hyperglycemia (3.07, 95%CI, 2.5–3.79) than in diabetic patients (1.30, 95%CI, 0.49–4.43). When only ischemic stroke patients were analyzed, the relative risk of in-hospital and 30-day mortality was higher only in hyperglycemic nondiabetic patients (3.28, 95%CI, 2.32–4.64). Moreover, nondiabetic stroke survivors had a greater risk of poor functional recovery. These observations suggest that acute elevations in blood glucose may be more detrimental in stroke pathophysiology than chronic hyperglycemia and warrant further research.

Given the fact that hyperglycemia is present in about 30–40% of AIS patients with or without diabetes and this independent risk factor is modifiable, clinical trials testing the efficacy and safety of aggressive glycemic control on improving acute ischemic stroke outcomes were recently initiated. A search of the clinicaltrials.gov database using the keywords stroke, hyperglycemia and diabetes, resulted in a list of clinical trials in progress (GRASP, NICE, SUGAR, IRIS, INSULINFARCT, SELESTIAL). A literature search revealed 2 recent publications including THIS (Treatment of Hyperglycemia in Ischemic Stroke) where most of the study subjects were diabetics (Bruno et al., 2008) and GIST-UK (Glucose-potassium-insulin infusion in the management of post-stroke hyperglycemia in UK) study which mostly included hyperglycemic patients without a diabetes history (Gray et al., 2007). GIST-UK was a multi-center, randomized controlled trial to test the feasibility and effectiveness of glucose-potassium-insulin infusion in correcting hyperglycemia and maintaining euglycemia during the initial 24 hrs of stroke onset. The main eligibility criterion was admission blood glucose of 6.0–17.0 mmol/L and the population was mostly hyperglycemic patients with no history of diabetes. Results showed euglycemia was achieved and maintained during the first 16 hrs. 90 day mortality was the primary outcome and it was not significantly different between study groups. However, the authors acknowledged that the study was terminated early due to recruitment issues and there was not enough statistical power to make outcome conclusions.

THIS was a blinded, randomized, multi-center pilot trial to explore the safety, feasibility and effectiveness of aggressive versus usual hyperglycemia treatment in diabetic patients with AIS. The main hypothesis was that early aggressive intervention within 12 hours of AIS onset would be optimal when the cells of the cerebral penumbra were still viable. Blood

glucose monitoring was performed every 2 h and blinded assessment of outcomes at 90 days were obtained. 73% of the subjects were diabetic and 100% of the diabetic patients received aggressive treatment. The usual care group showed controlled levels of 24 hour blood glucose measurements (10.5 mmol/L) whereas the aggressive treatment group showed lower levels (7.3 mmol/L). These results demonstrated the effectiveness and tolerability of aggressive glycemic control in this population. The functional assessment of clinical outcomes at 90 days was not significantly different among groups even after adjusting for confounders.

It has to be recognized that these studies were not powered to determine efficacy. Nevertheless, they are important studies to highlight the impact of blood glucose on acute ischemic stroke outcomes. Questions regarding the effect of glycemic control on both short and long-term stroke outcomes and whether there is a subpopulation that would benefit more from glycemic control remain to be answered.

4. Conclusion

There is no question that the structural and functional integrity of the cerebrovasculature is very important for regulation of CBF to meet the oxygen and glucose demand for proper brain function. Our knowledge of the functional and structural effects of hyperglycemia and diabetes on different caliber cerebral vessels and how these vascular changes could influence the pathophysiology and severity of ischemic brain injury is far from clear. Most of the data in this field come from animal studies done in acute hyperglycemia which causes greater infarcts and increases the risk of hemorrhagic transformation. Clinical evidence also suggests that acute elevations in blood glucose worsen stroke outcomes to a greater extent than diabetes. On the other hand, fewer studies addressed the role of diabetes on ischemic injury and yielded conflicting results. It is highly possible that duration and degree of hyperglycemia in diabetes is critical for the severity of ischemic injury. We speculate that early in the disease process, moderate diabetes promotes a “latent” neuroprotective state via regulation of cerebrovascular tone, remodeling and neovascularization which limits infarct expansion but causes greater occurrence of HT upon reperfusion injury (Figure). Exposure to acute hyperglycemia does not allow sufficient time to promote this compensating preconditioning effect resulting in larger infarcts. Studies focusing on the effects of duration and severity of hyperglycemia on cerebrovascular function and structure and ultimately on the extent and severity of ischemic damage and functional outcome are long overdue. These studies will enable us to develop acute and chronic vascular protection strategies.

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Figure. Consequences of chronic and acute hyperglycemia-mediated changes in cerebral resistance artery structure and function on ischemic brain injury

Moderate diabetes promotes neovascularization, remodeling and increases in vascular tone limiting cerebral perfusion. Resulting hypoxia and/or metabolic changes mediate ischemic tolerance via neuronal preconditioning but decreases vascular ischemic tolerance leading to increased and accelerated HT development and edema in the event of an ischemic event. Acute hyperglycemia also increases vascular tone and disrupts vascular integrity but in the absence of sufficient time to stimulate adaptive protective mechanisms, the magnitude of neuronal damage is greater.