



Review

Ischemia-induced hyperglycemia: Consequences, neuroendocrine regulation, and a role for RAGE

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ABSTRACT

This article is part of a Special Issue “Neuroendocrine-Immune Axis in Health and Disease.”

Many patients that present with cerebral ischemia exhibit moderate to severe hyperglycemia. Although many hyperglycemic patients suffer from diagnosed or previously undiagnosed diabetes a further subset of individuals is hyperglycemic without diabetes. Hyperglycemia during cerebral ischemia is associated with high levels of mortality and morbidity and limits the effective treatment interventions available. Controlling hyperglycemia with insulin treatment in critical care situations improves overall outcomes, although it is not without risk. Therefore it is critically important to understand the basic mechanisms that underlie both the induction of hyperglycemia and the consequences of it for ischemic outcomes. In this manuscript, the neuroendocrine mediators, and mechanisms of hyperglycemia exacerbated inflammation, glucose dysregulation and ischemic outcomes are discussed. The possibility that the advanced glycation end product (AGE) and receptor for AGE (RAGE) axis mediates the deleterious effects of hyperglycemia on inflammation and neuronal damage is discussed.

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Introduction

Many patients that suffer an acute ischemic injury to the central nervous system present with moderate to severe hyperglycemia (Capes et al., 2001; Melamed, 1976). Importantly, diabetes is a major risk factor for ischemic cerebrovascular disease and so many of the patients in this population had been previously diagnosed with diabetes (Gisselsson et al., 1999; Heuschmann et al., 2004; Kannel and McGee, 1979; Mortel et al., 1990). Further, a subset of these patients probably exhibited some dysfunction of glucose metabolism that was either sub-clinical or not detected previously (Murros et al., 1992). However, there is a third group of patients that exhibit hyperglycemia with no record or evidence of previous metabolic disease. Hyperglycemia following a

variety of types of injury to the CNS is an independent risk factor for poorer outcomes and substantial clinical evidence has demonstrated that controlling hyperglycemia with insulin treatment in critical care situations improves overall outcomes although it is not without risk (Weir et al., 1997). The goals of this review therefore are to discuss the proximate and ultimate causes of injury induced glucose dysregulation and to discuss the consequences of hyperglycemia for inflammatory responses and overall recovery.

There is a strong negative correlation between admission hyperglycemia and mortality and morbidity in CNS-injured patients. Individuals that present with blood glucose only mildly elevated (e.g. 110 to 126 mg/dl) were over 3 times more likely to die within 30 days after ischemic stroke (Capes et al., 2001). Additionally, poorer functional outcomes were also more likely in stroke survivors that presented with moderate hyperglycemia (Bruno et al., 1999). Further, hyperglycemia limits the interventional tools available to clinicians since the only FDA approved treatment for ischemic stroke is tissue plasminogen

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activator an enzyme that can reduce the size of clots and allow for increased blood flow to the infarcted tissue (Hacke et al., 1995). Unfortunately tPA must be used sparingly because it greatly increases the possibility that ischemic strokes will become devastating hemorrhagic strokes (Kase et al., 1990; Lansberg et al., 2007). Hyperglycemic patients are much more likely to experience hemorrhagic transformation after tPA treatment than are patients that present with normoglycemia (Demchuk et al., 1999; Poppe et al., 2009). Finally, in patients that do experience intracranial hemorrhage hyperglycemia is associated with larger bleeds and poorer outcomes (Fogelholm et al., 2005; Kimura et al., 2007).

Further, evidence for the negative consequences of ischemia-induced hyperglycemia is provided by the large body of evidence demonstrating that insulin-induced reductions in blood glucose are potentially neuroprotective and greatly improve overall outcomes. Controlling even moderate hyperglycemia with intensive insulin therapy has been shown to improve outcomes in a large variety of chronically ill patients in addition to those with CNS damage. This is an approach that has been adopted in most neurocritical care settings (Johnston et al., 2009). However, insulin therapy is not without consequences. First, if insulin concentrations are not closely monitored and patients become even moderately hypoglycemic this can have profound consequences for recovery of the damaged tissue. In a large clinical trial of critically ill patients that received intensive glucose control, a protocol that maintains blood glucose at a markedly reduced level (81–108 mg/dl) and was also associated with transient hypoglycemia, had poorer outcomes than patients on standard glucose management that maintained glucose below 180 mg/dl (Finfer et al., 2009). Secondly, the possibility exists that insulin is neuroprotective independent of its effects on glucose metabolism as evidenced by a recent report that both insulin and glucagon despite having opposite effects on blood glucose both produce neuroprotection apparently by reducing glutamate efflux indicating that insulin may exert neuroprotective effects both via glucose-dependent and independent mechanisms.

Taken together, it seems important to understand the mediators of glucose dysregulation following injury, the mechanisms that link hyperglycemia to poorer outcomes and therefore to be able to manipulate these processes independently without further impairing recovery.

Mechanisms of hyperglycemia-induced exacerbation of ischemic outcomes

The first major and persistent hypothesis to explain the relationship between hyperglycemia and poor ischemic outcomes was that anaerobic metabolism of glucose through the lactic acid cycle was responsible. That is, in the absence of oxygenated blood neurons and other CNS cell types would metabolize glucose anaerobically and produce lactic acid which would acidify cells and the extracellular environment. Acidosis in neuronal cells is potentially damaging and can lead to free radical production, deficits in calcium metabolism and mitochondrial dysfunction (Anderson et al., 1999; OuYang et al., 1994; Rehnroona et al., 1989; Siesjo et al., 1985) all of which would be particularly damaging in the face of ischemia. Indeed, experimental studies have confirmed that hyperglycemia prior to ischemia does result in increased lactic acid accumulation and there is a general correlation between lactic acid concentrations and extent of neuronal damage (Anderson et al., 1999; LaManna et al., 1992). However, as with all correlational data this must be considered critically (Schurr, 2002). More recent data have shown that lactic acid accumulation cannot be the only mediator of hyperglycemic exacerbation of injury 1) lactic acid metabolism has been shown to be a part of CNS metabolism in uninjured tissue, 2) inhibitors of lactic acid production in ischemia exacerbate rather than ameliorate glucose potentiated injury and 3) lactic acid metabolism is essentially the only metabolic pathway capable of maintaining ATP production during ischemia

(Cassady et al., 2001; Pellerin and Magistretti, 1994; Schurr, 2002; Welsh et al., 1983).

Another possibility is that glucose stimulated glucocorticoids are responsible for the enhanced ischemic injury in hyperglycemic patients. As discussed above hyperglycemia (and CNS injury) increases circulating glucocorticoids (Harris et al., 1994; Schurr et al., 2001). Dexamethasone a powerful synthetic glucocorticoid was also a past standard of care for comatose and ischemic patients with the presumption that the powerful steroid would inhibit damaging central inflammatory responses. However, this approach has fallen out of favor given the glycemic consequences of glucocorticoid signaling and the myriad negative effects that glucocorticoids can have on ischemic outcome. Although the acute stress response increases blood flow and thus energy availability to the CNS, over time glucocorticoids inhibit the uptake of glucose into CNS cells and generally reduce the energy available and increase the rate of ischemic energy depletion (Lawrence and Sapolsky, 1994; Virgin et al., 1991; Yusim et al., 2000). Glucocorticoids hormones also influence ischemic outcomes by promoting apoptotic signaling and enhancing central inflammatory responses (Craft et al., 2006; DeVries et al., 2001; Dinkel et al., 2003; Lawrence and Sapolsky, 1994; Sapolsky and Pulsinelli, 1985; Yusim et al., 2000). In experimental animals blocking glucocorticoid synthesis with metyrapone prevents hyperglycemic exacerbation of global cerebral ischemic outcomes (Payne et al., 2003; Schurr et al., 2001) but not focal ischemia (Martin et al., 2006). Clinical studies have generally reported higher glucocorticoid concentrations in patients with poorer ischemic outcomes though it is difficult to distinguish cause from consequence in this relationship (Christensen et al., 2004; Fassbender et al., 1994; Marklund et al., 2004). Taken together, it seems that glucocorticoids contribute to but are not the sole mediators of hyperglycemic effects on cerebral ischemia.

A role for RAGE?

In this section the role of advanced glycation end products and their receptor RAGE will be discussed and an argument presented that this system is responsible for, at least in part, mediating hyperglycemic exacerbation of ischemic outcome. This system was originally described in the context of vascular injury and atherosclerosis in chronic diabetes and serves as a link between chronic hyperglycemia and oxidative stress, inflammation and tissue damage in that population. RAGE has previously been linked to the pathophysiology of stroke in experimental animals but has not been shown to be the mediator of hyperglycemia-induced exacerbation of ischemic injury (Muhammad et al., 2008; Ramasamy et al., 2005).

Advanced glycation end products are the result of nonenzymatic oxidation and glycation of proteins and lipids and accumulate in the context of prolonged hyperglycemia (Thornalley, 1998). A receptor has been identified for AGEs in tissue and called RAGE (Neeper et al., 1992; Schmidt et al., 1992). This protein RAGE is expressed in a variety of cell types involved in the complications from diabetes including endothelial cells but has also been localized to neurons and microglia in the CNS (Kamide et al., 2012; Muhammad et al., 2008). RAGE is a multiligand member of the immunoglobulin superfamily and has been shown to bind other molecules in addition to AGEs including amphoterin (also known as high mobility group box 1 (HMGB1)) S100 proteins, amyloid beta and recently the macrophage cell surface antigen MAC-1 (Chavakis et al., 2003; Hofmann et al., 1999; Hori et al., 1995; Schmidt et al., 1996). RAGE expression itself is upregulated by inflammatory conditions and prolonged hyperglycemia (Hofmann et al., 1999; Li and Schmidt, 1997). Activation of RAGE by AGEs or other ligands leads to the induction of proinflammatory cytokines in large part through the NF κ B pathway although elements of MAP kinase and JNK signaling are also activated (Hofmann et al., 1999; Huang et al., 2001; Yan et al., 1994). Additionally, AGE production is enhanced by oxidative stress and AGE–RAGE interactions

increase oxidative stress in part by activation of NADPH oxidase indicating that a vicious cycle can be established with RAGE in the center of reactive oxygen species and AGEs (Yang et al., 2009). Further, RAGE can serve to maintain the insulin resistance of type 2 diabetes by mediating inflammatory and oxidative responses to hyperglycemia that in turn feed back to inhibit insulin sensitivity in other target tissues.

RAGE activation likely amplifies inflammatory signals by inducing both proinflammatory cytokines and other RAGE ligands including S100s and HMGB1 from nearby leukocytes (Hagiwara et al., 2008). Certainly, RAGE activation by AGEs and other ligands is central to the pathophysiology of various inflammatory diseases as blockade of RAGE signaling with a decoy receptor soluble RAGE (sRAGE) or in transgenic RAGE null mice prevents the development of collagen arthritis, experimental autoimmune encephalomyelitis, atherosclerosis and diabetic neuropathies (Hofmann et al., 2002; Soro-Paavonen et al., 2008; Toth et al., 2008; Yan et al., 2003). Further, in normoglycemic tissue ischemia outside of the CNS including the liver, heart and lungs RAGE inhibition improves outcomes (Bucciarelli et al., 2006; Sternberg et al., 2008; Zeng et al., 2009).

RAGE clearly plays a role in the basic pathophysiology of cerebral ischemia. Human stroke patients have elevated HMGB1, a key RAGE ligand, concentrations (Goldstein et al., 2006; Muhammad et al., 2008). Transgenic mice lacking the RAGE gene are significantly protected from both focal (Hassid et al., 2009; Muhammad et al., 2008) and global cerebral ischemia (Kamide et al., 2012). There are several pathophysiological links between RAGE signaling and poor ischemic outcomes in experimental animals. First, RAGE activation appears to occur very early (within 12 h) in vascular endothelial cells following global ischemia (Kamide et al., 2012). Importantly, AGE administration to vascular endothelial cells inhibits both the production and activity of the endothelial form of nitric oxide synthase (eNOS) (Rojas et al., 2000; Xu et al., 2003) and that eNOS deficiency exacerbates ischemic cell death (Atochin et al., 2007; Huang et al., 1996). Taken together these data would seem to indicate that RAGE activation may in part exacerbate ischemic injury by inhibiting eNOS activity in vascular endothelial cells.

Resident and peripheral immune cells in the brain appear to mediate many of the neurotoxic consequences of RAGE signaling in the injured nervous system. Transgenic mice lacking RAGE signaling also exhibit significantly less astrocyte activation and microglial activation that is accompanied by reduced proinflammatory cytokine gene expression (Kamide et al., 2012). Further, neurotoxic effects of RAGE appear to be mediated by microglia. HMGB1 is toxic to cultured neurons; however, the toxic effects are markedly amplified by addition of microglial cells to the neuronal culture (Kamide et al., 2012). Finally, chimeric mice that lacked RAGE only in bone marrow-derived cells also exhibit reduced infarct size in a mouse model of focal cerebral ischemia (Muhammad et al., 2008). These data taken together suggest strongly that RAGE potentiates both the activation of microglia and other leukocytes thereby increasing the expression and release of cytokines, proteolytic enzymes and other inflammatory and oxidative mediators.

Soluble RAGE is also produced endogenously and apparently acts as a decoy receptor that binds endogenous RAGE ligands and prevents activation of membrane-bound RAGE (Hanford et al., 2004; Schmidt et al., 2001). There appears to be at least two types of soluble RAGEs including an endogenous secretory form (esRAGE) that results from alternative splicing of the RAGE gene and a cleaved form of the full length membrane bound protein called sRAGE (Raucci et al., 2008). Inflammation in both human and experimental animals is associated with elevated sRAGE concentrations (Raman et al., 2006; Soop et al., 2009). Mice over-expressing the esRAGE gene and RAGE knockout animals were both significantly protected from vascular injury and neuronal insult following global cerebral ischemia (Kamide et al., 2012) additionally activation of microglia and astrocytes were also inhibited by esRAGE overexpression (Kamide et al., 2012). It is not clear whether sRAGE is produced

and released as part of a negative feedback loop to inhibit membrane-bound RAGE activity or if it is passive shedding of upregulated receptors from the cell surface (Arabi et al., 2011). In either case, it appears that concentrations of circulating sRAGE reflect membrane-bound RAGE signaling (Bopp et al., 2008; Ramasamy et al., 2012).

The AGE–RAGE axis plays an important role in a variety of metabolic, inflammatory and neurodegenerative diseases. However, most of the research into AGE accumulation has occurred in cases of chronically elevated blood glucose, aging or inflammatory diseases. That is over a much longer time scale than that associated with acute ischemia-induced hyperglycemia. Further, RAGE can be activated by a variety of inflammatory molecules including HMGB1 that have been already been implicated in ischemic pathophysiology (Hagiwara et al., 2008). Therefore it remains undetermined whether hyperglycemia induced AGE production is at least partially responsible for RAGE activation and poorer ischemic outcomes. Still, AGE production has been documented with acute glucose exposure. Healthy non-diabetic adults were maintained on either a euglycemic or hyperglycemic glucose infusion protocol for 2 h. Immediately following the glycemic clamp peripheral blood mononuclear cells were collected and exhibited increased content of carboxymethyl lysine a key AGE component as well as marked activation of both NF κ B and P42/44 MAP kinase signaling (Schiekofer et al., 2003). Similarly ex vivo PBMCs cultured with high levels of glucose exhibited similar patterns of AGE accumulation and the activation of inflammatory signaling cascades (Schiekofer et al., 2003). While this is a single study it is apparent that increased AGE content can result from even short term hyperglycemia in healthy adults. These data fit nicely into the broader finding that acute hyperglycemia is proinflammatory (Aljada et al., 2006). When combined with the marked inflammatory milieu associated with an ischemic injury to the CNS it seems likely that this effect would be of an even greater magnitude. Very recently, Lapar and colleagues reported that hyperglycemia exacerbated lung injury in WT but not RAGE knockout mice though the transgenic animals were relatively protected from injury even under normoglycemic conditions (Lapar et al., 2011). Taken together it seems likely that activation of RAGE signaling by both rapidly induced AGEs and other inflammatory ligands like members of the S100 family and HMGB1 that are induced by hyperglycemia mediates at least part of the deleterious effects of injury induced hyperglycemia.

Further, it remains possible that the RAGE-mediated inflammatory responses associated with CNS injury could serve to both initiate and amplify the glucose dysregulation. RAGE activation by various alarm-associated cues can potentiate cytokine release with downstream consequences for glucose regulation. Acutely the release of catecholamines stimulates glucagon release from the pancreas and rapidly increases blood glucose by stimulating hepatic gluconeogenesis and glycogenolysis, and inhibiting glucose uptake and utilization in the periphery. However, slower acting glucocorticoid hormones potentiate the rapid glycemic effects of the sympathetic nervous system and could potentially be linked to RAGE as proinflammatory cytokines also serve to drive activity of the HPA axis and therefore can serve to prolong both the inflammatory and metabolic effects of the injury response (Turnbull and Rivier, 1995). Additionally, injuries produce both increased insulin expression and a decrease in the ability of insulin to stimulate glucose uptake into skeletal muscle and inhibit hepatic gluconeogenesis (Desouza et al., 2001; Kendall and Harmel, 2002).

The peripheral insulin resistance is mediated by a combination of sympathetic, inflammatory and glucocorticoid pathways. For instance blocking glucocorticoid signaling with either metyrapone or RU-486 injury prevents the development of skeletal muscle insulin resistance but is ineffective at restoring insulin sensitivity to the liver (Li et al., 2009). Additionally, inflammatory signaling also inhibits insulin sensitivity and promotes glucose release in part by reducing the molecular machinery necessary for insulin signaling. For instance, TNF α activates the JNK and NF κ B pathways which both increase serine phosphorylation levels of

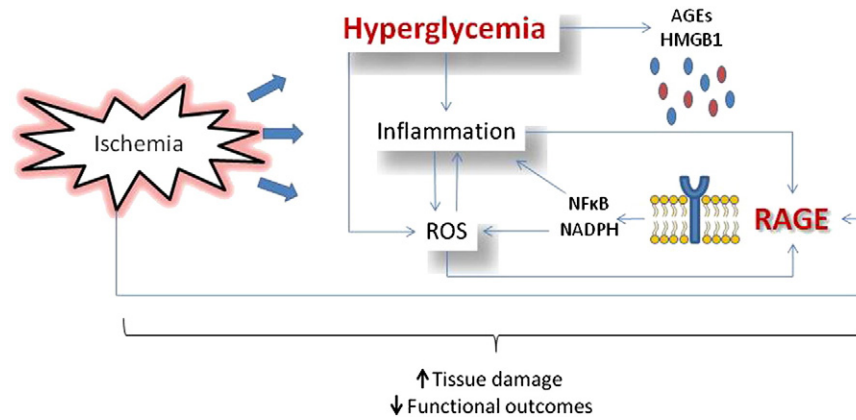


Fig. 1. A schematic representation of the role of RAGE signaling in hyperglycemia-potentiated ischemic injury and the multidirectional relationship among inflammation, reactive oxidant species, glucose dysregulation and neuronal damage. AGE, advanced glycation end-product, HMGB1, high mobility group box protein, ROS, reactive oxygen species.

the insulin receptor substrate protein IRS-1 thereby inhibiting downstream insulin signaling (Feinstein et al., 1993; Hotamisligil et al., 1993; Li and Messina, 2009).

Finally, the increase in blood glucose concentrations associated with ischemia is proinflammatory (in part through production of RAGE ligands) which in turn increases overall inflammation and further dysregulates glucose metabolism. One potential model linking hyperglycemia, ischemic pathophysiology and the RAGE system is described in Fig. 1. Specifically, this model suggests that RAGE is involved both in the activation and perpetuation of inflammatory responses and involved in perpetuating the hyperglycemia via inflammation-mediated down regulation of insulin and leptin sensitivity. Further, this system is self sustaining as inflammatory and oxidative events associated with hyperglycemia increase the production of RAGE ligands that can lead to further glucose dysregulation.

Conclusion

The role of acute hyperglycemia in the pathophysiology of cerebral ischemia is still developing but it seems clear that the inflammatory-metabolic consequences are not fully understood. Further, it seems likely that the AGE-RAGE axis already a popular pharmaceutical target in multiple degenerative and chronic conditions, associated with peripheral and neuro-inflammation, will also be a central target in the treatment of ischemia and metabolic disease. Manipulation of RAGE signaling appears likely to be a fruitful experimental and clinical tool for altering injury-induced derangement of metabolic systems and inflammation.

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