Review

Hyperglycemia in acute ischemic stroke: physiopathological and therapeutic complexity

https://doi.org/10.4103/1673-5374.317959

Date of submission: November 13, 2020

Date of decision: December 31, 2020

Date of acceptance: February 26, 2021

Date of web publication: July 8, 2021

Federica Ferrari, Antonio Moretti, Roberto Federico Villa*

Abstract

Diabetes mellitus and associated chronic hyperglycemia enhance the risk of acute ischemic stroke and lead to worsened clinical outcome and increased mortality. However, post-stroke hyperglycemia is also present in a number of non-diabetic patients after acute ischemic stroke, presumably as a stress response. The aim of this review is to summarize the main effects of hyperglycemia when associated to ischemic injury in acute stroke patients, highlighting the clinical and neurological outcomes in these conditions and after the administration of the currently approved pharmacological treatment, i.e. insulin. The disappointing results of the clinical trials on insulin (including the hypoglycemic events) demand a change of strategy based on more focused therapies. Starting from the comprehensive evaluation of the physiopathological alterations occurring in the ischemic brain during hyperglycemic conditions, the effects of various classes of glucose-lowering drugs are reviewed, such as glucose-like peptide-1 receptor agonists, DPP-4 inhibitors and sodium glucose cotransporter 2 inhibitors, in the perspective of overcoming the up-to-date limitations and of evaluating the effectiveness of new potential therapeutic strategies.

Key Words: acute ischemic stroke; diabetes mellitus; DPP-4 inhibitor; glucose-like peptide-1 receptor agonist; hyperglycemia; hypoglycemia; insulin; physiopathology; sodium glucose cotransporter 2 inhibitor

Introduction

One of the conditions adversely affecting acute ischemic stroke (AIS) patients' outcome is hyperglycemia. In this review, we firstly consider the clinical studies highlighting the detrimental relationships between high blood glucose levels at admission and patients' functional outcome and mortality, both in diabetic and in non-diabetic patients. These studies support the observation that prompt management of hyperglycemia is mandatory.

Therefore, we subsequently discuss the pharmacological treatment with insulin, at present the only therapeutic strategy available according to international guidelines to control glycemic levels. However, both several randomized clinical trials, of which one of the more recent is the Stroke Hyperglycemia Insulin Network Effort trial (Johnston et al., 2019), and meta-analyses (Fuentes et al., 2018; Klingbeil et al., 2020) show that intensive insulin i.v. treatment does not improve the functional outcome and does not reduce the mortality of AIS patients. On the contrary, the tight glycemic control increases the risk of hypoglycemia.

Given these premises, because several pieces of evidence exist that novel therapeutic strategies are needed to overcome these limitations and complications in the clinical settings, we finally consider the molecular, cellular and metabolic mechanisms of injury triggered by hyperglycemia and hypoglycemia in the ischemic brain, in the perspective of evaluating the effectiveness of new potential drug classes.

Search Strategy and Selection Criteria

The studies cited in this review were published from 1980 and 2020, and they were searched on Pubmed Database using the following keywords: "stroke", "brain ischemia", "hyperglycemia", "hypoglycemia", "diabetes mellitus", "insulin", "DPP-4 inhibitors", "glucose-like peptide-1 receptor agonists", "sodium glucose cotransporter 2 inhibitors".

Hyperglycemia and Stroke

Hyperglycemia is frequently found in patients admitted to hospital for acute ischemic stroke. Hyperglycemia can result from diabetes mellitus (more frequently the type 2, T2DM) through chronic hyperglycemia due the relative deficiency of insulin (Mitsios et al., 2018); T2DM has been positively associated with the enhanced risk of AIS, which is a well-documented and modifiable risk factor for cerebral ischemia and for other co-morbidities such as hypertension (O'Donnell et al., 2010). However, hyperglycemia is also common in non-diabetic patients because of the acute stress responses involving the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in reaction to extensive brain injury (Christensen et al., 2004).

Hyperglycemia at hospital admission is an independent marker of larger ischemia, reduced functional and cognitive outcomes and increased risk of mortality (Tsivgoulis et al., 2019). In particular, persistent hyperglycemia both at 6 and 24 hours after stroke onset was correlated with increased risk of mortality within 30 days [odds ratio (OR) 24.0; 95%

Department of Biology and Biotechnology, Laboratory of Pharmacology and Molecular Medicine of Central Nervous System, University of Pavia, Via Ferrata, Pavia, Italy

*Correspondence to: Roberto Federico Villa, MD, DSc, Emeritus ACCP, FRSM, rfvilla@unipv.it.

https://orcid.org/0000-0002-9868-5997 (Federica Ferrari); https://orcid.org/0000-0001-6513-3531 (Roberto Federico Villa)

Funding: *This work was supported by a grant from Catholic Universitary Center (Centro Universitario Cattolico) - Conferenza Episcopale Italiana, Rome, Italy (to FF).*

How to cite this article: *Ferrari F, Moretti A, Villa RF (2022) Hyperglycemia in acute ischemic stroke: physiopathological and therapeutic complexity. Neural Regen Res 17(2):292-299.*

confidence interval (CI): 2.8–199.3] and it was also correlated with hemorrhagic transformation (OR = 13.3; 95% CI: 2.7–66.1) (Mi et al., 2017). Bevers et al. (2017) demonstrated that hyperglycemia was associated with lower apparent diffusion coefficient (ADC, $r = –0.32$, $P < 0.001$), a magnetic resonance sequence predictive of swelling on subsequent imaging; moreover, both hyperglycemia and lower *ADC* signal were associated with worse patients' outcome (OR = 0.239, $P = 0.017$; OR = 1.11, $P < 0.0001$, respectively).

Higher admission glucose levels affected functional outcome also in patients after thrombolysis and early reperfusion (Rosso et al., 2018). Coherently, Suissa et al. (2020) reported that hyperglycemia at admission had deleterious effects on the ischemic penumbra of patients with good recanalization scores, as confirmed by the fact that this condition was a predictor of functional outcome only in patients with National Institutes of Health Stroke Scale score ≥ 10, Alberta Stroke Program Early CT Score ≥ 6 and recanalization after mechanical thrombectomy (modified Treatment In Cerebral Ischemia - mTICI score 2b/3). In fact, higher glucose levels were reported to reduce the likelihood of good outcome among patients with good collaterals, while its effects were less significant when collaterals were poor (Kim et al., 2018).

Distinguishing between chronic and stress hyperglycemia, Tsivgoulis et al. (2019) did not report any difference in diabetic and non-diabetic AIS patients presenting hyperglycemia at admission. In particular, diabetic patients had lower rates of 3-month favorable functional outcome (modified Rankin Scale – mRS scores 0–1, 34.1% *vs*. 39.3%, $P < 0.001$) and higher 3-month mortality rates (23.7% *vs*. 19.9%, $P < 0.001$) respect to patients without hyperglycemia, and non-diabetic ones had lower 3-month functional independence rates (53.3% *vs*. 57.9%, $P < 0.001$) and higher 3-month mortality rates (19.2% *vs*. 16.0%, $P < 0.001$) (Tsivgoulis et al., 2019). On the other hand, Tziomalos et al. (2017) demonstrated that patients presenting stress hyperglycemia at the second day after admission had more severe stroke than diabetic patients.

Given the different physiopathological background of chronic and stress hyperglycemia, a reliable method to measure the degree of stress hyperglycemia is the stress hyperglycemia ratio (SHR), expressed as the glucose concentration at admission divided by the estimated average glucose concentration resulting from glycosylated hemoglobin levels (Roberts et al., 2015), in this way controlling for background glucose concentrations.

The association between SHR and outcome at 3 months after mechanical thrombectomy was studied by Chen et al. (2019), showing that increased SHR was a strong predictor of poor clinical outcome (mRS score 3–6), with high predictive power (≥ 0.96) only in non-diabetic patients. The Authors hypothesized that this result was probably due to the chronic adaptations to hyperglycemia occurring in diabetic patients, who are more tolerant to varying glycemic levels, as will be discussed later in this review as well.

Finally, it should be reported that hyperglycemia at admission is correlated with post-stroke infections, a deleterious complication which seems to further affect particularly non-diabetic patients' prognosis: Zonneveld et al. (2017) observed that admission hyperglycemia was not associated with post-stroke infection in diabetic patients (adjusted OR = 0.49, 95% CI: 0.15–1.58), while in non-diabetic ones the adjusted *OR* was 2.31 (95% CI: 1.31–4.07), also associated with worse 3-month functional outcome (adjusted OR = 1.40, 95% CI: 1.12–1.73) and 3-month mortality (adjusted OR = 2.11, 95% CI: 1.40–3.19). Moreover, fasting hyperglycemia is an independent risk factor for predicting stroke-associated pneumonia and combining its presence with the A_2DS_2 score (considering age ≥ 75 years, atrial fibrillation, dysphagia, male sex and stroke severity) is more effective in predicting the risk of stroke-associated pneumonia than A_2DS_2 score alone (Li et al., 2019).

Status of Pharmacological Treatment with Insulin

Hyperglycemia is pharmacologically treated with insulin paying attention to the risk of hypoglycemia (blood glucose level < 60 mg/dL); subcutaneous (s.c.) or intensive intravenous (i.v.) infusion should normalize glycemia and improve functional outcome (Palaiodimou et al., 2019).

Ad hoc guidelines of American Heart and American Stroke Association (Jauch et al., 2013) and of the European Stroke Organisation (Fuentes et al., 2018) recommend keeping glucose levels in the range of 7.7–10 mM (140–189 mg/dL), but the American Diabetes Association (2016) also recommends 6.1–7.7 mM (110–140 mg/dL) for critically ill patients. However, randomized and open cohorts did not confirm these results (Piironen et al., 2012), and the randomized Glucose Insulin in Stroke Trial (GIST-UK) did not demonstrate any benefit of post-ischemic intensive insulin infusion for 24 hours in stroke patients (Gray et al., 2007).

Comparing intravenous insulin treatment *vs*. the subcutaneous one, the Intensive versus Subcutaneous Insulin in Patients with Hyperacute Stroke (INSULINFARCT) trial demonstrated that in the intensive insulin therapy group the overall glucose control within the first 24 hours of stroke was improved, but this was associated with larger infarct growths at magnetic resonance imaging (MRI) controls [median, 27.9 cm^3 (95% CI: 14.6–40.7) *vs*. 10.8 cm^3 (95% CI: 6.5–22.4); 60% of increase, $P = 0.04$] (Rosso et al., 2012). Coherently, also some meta-analyses indicated that the glycemic control with insulin i.v. *vs*. no treatment/insulin s.c. did not improve either functional outcome [relative risk (RR) = 1.09; 95% CI: 0.87–1.37] or survival (RR = 0.99; 95% CI: 0.94–1.05) (Fuentes et al., 2018). These observations were confirmed by a further meta-analysis by Cerecedo-Lopez et al. (2020), considering the results of the Stroke Hyperglycemia Insulin Network Effort trial, which was stopped for futility because interim analyses revealed that intensive i.v. insulin was not superior respect to s.c. insulin in attaining a favorable outcome at 90 days (adjusted RR = 0.97, 95% CI: 0.87–1.08, $P = 0.55$) (Johnston et al., 2019).

Moreover, maintaining a glycemic range < 6.1 mM is associated with 4-fold to 9-fold increased risk of hypoglycemia (Yatabe et al., 2017), which after i.v. insulin occurs with a relative risk of 4.75 (95% CI: 1.52–14.85) *vs*. no treatment/s.c. insulin (Fuentes et al., 2018). As well as hyperglycemia, hypoglycemia leads to several molecular and metabolic changes in the ischemic brain (see later), which further affect patients' outcome, as recently reviewed by Klingbeil et al. (2020).

Physiopathological Mechanisms of Hyperglycemic Brain Injury

The reproducible association between T2DM, acute hyperglycemia and poor outcomes in acute ischemic patients suggests a potential causal relationship. Nevertheless, the etiological and clinical complexity of hyperglycemia effects is mirrored in the multiplicity of their potential mechanisms which have been postulated and discussed below.

Brain energy metabolism

Ischemia is characterized by anaerobic glycolysis which in the absence of O_2 continues to produce adenosine triphosphate (ATP), albeit inefficiently, from glucose and glycogen stores, leading to deficient cell functions. Hyperglycemia exacerbates this situation through the enhancement of anaerobic metabolism and the resulting accumulation of lactate and

tissue acidosis in proportion to blood glucose level (**Table 1**).

In normoglycemic situations, there is a rapid recovery of high-energy phosphate metabolites (mainly ATP) in accordance with the metabolic and functional resistance of mitochondria, as demonstrated during post-ischemic recovery up to 96 hours in adult and aged rats (Villa et al., 2013a; Ferrari et al., 2018). On the other hand, hyperglycemia worsens cortical acidosis and mitochondrial function, thus delaying the recovery of high-energy phosphates and pH. Moreover, experimental evidence showed the increased production of reactive oxygen species (ROS) by ischemia-damaged mitochondria, in particular of superoxide, by transfer of glucose-derived reducing equivalents to O_2. Additionally, ROS may be produced by the NADPH oxidase pathway through the glucose-sustained hexose monophosphate shunt (animal studies by Wagner et al., 1992; Widmer et al., 1992; MRI study in patients by Parsons et al., 2002).

Penumbra is the under-perfused part of the ischemic region that surrounds the irreversible infarct core and can potentially be salvaged thanks to a less severe blood flow reduction. Penumbra may still receive residual flow (through collateral circulation) and glucose supply. As mentioned before, this can attenuate energy failure through glycolysis, but it also aggravates acidosis, thus making penumbra particularly susceptible to hyperglycemia, less liable to be salvaged and more likely prone to infarction (Anderson et al, 1999; Rosso et al, 2011). Incidentally, this observation might explain the lower susceptibility of lacunar stroke in which penumbra is not present.

Cellular factors

Acidosis may induce cytotoxicity and cell death: this result was reported by Back et al. (1994) by measuring the reduction of ADC in rats and reproduced in diabetic and non-diabetic AIS patients, also in association with worse outcome (90-day mRS), as previously stated (Bevers et al., 2017). In turn, cytotoxicity can increase brain edema (Song et al., 2003).

Moreover, the oxidative stress may promote the disruption of the blood-brain barrier (BBB) (experimental studies by Dietrich et al., 1993; Zhang et al., 2016; clinical study by Venkat et al., 2017). The increased permeability of BBB might further worsen edema and raise the rate of hemorrhagic transformation of infarcts (clinical studies by Paciaroni et al., 2009; experimental studies by Won et al., 2011; McBride et al., 2016).

Not unexpectedly in the context of cerebral ischemia, hyperglycemia raised extracellular glutamate accumulation in neocortex and elevated intracellular Ca^{2+}. In turn, this promoted the release of cytochrome c into the cytoplasm and the activation of caspase-3, thereby worsening neuronal ischemic death (Li et al., 2001).

Neurovascular factors

Neurovascular injury (**Table 2**) is shown by the relationships between many factors, as outlined as follows:

(i) Impaired re-canalization related to increased coagulation and reduced fibrinolytic activity (Lemkes et al., 2010). Compared to euglycemia, both hyperglycemia and hyperinsulinemia enhanced plasminogen activator inhibitor and significantly reduced the tissue Plasminogen Activator, thus affecting thrombolytic therapy (Pandolfi et al., 2001). Notably, in the study by Rosso et al. (2011), hyperglycemia was deleterious in both recanalized and non-recanalized patients, but in the latter group the ischemic transformation was 2.8 times larger than in the former. Ribo et al. (2005) also reported that hyperglycemia had a major impact on the speed of infarct growth in non-recanalized patients;

(ii) Decreased perfusion as shown by reduced hemispheric relative cerebral blood flow and cerebral blood volume measured by MRI in rats (Quast et al., 1997). Penumbral blood flow is particularly affected (Venables et al., 1985). This was associated with the lowering of endothelium-dependent vasodilatation mediated by oxidative stress (Tsuruta et al., 2010) and with the decline of endothelium-derived nitric oxide synthesis by endothelium nitric oxide synthase

Table 1 | **Metabolic mechanisms of hyperglycemia effects in acute ischemic stroke: studies in hyperglycemic animals**

Species	Glucose/energy metabolism	Oxidative stress	Glutamate/Ca^{2+}	Brain injury	References
Monkey	↓pH				Marsh et al., 1986
Rabbit	↓pH ↑NADH (ischemic penumbra)			↑Infarct volume	Anderson et al., 1999
Rat	↑Lactate; pH < 6 *vs.* 6.45				Widmer et al., 1992
Rat	↓CBF; ↑lactate; hypermetabolism (a) of glucose mainly in ischemic penumbra; increased glycolysis both in anaerobic and aerobic conditions			BBB disruption; apoptosis	Arnberg et al., 2015
Cat	↓CBF; ↑lactate, time dissociation with ↓pH; ↓PCr (but not ATP) related to ↓pH;			↑Infarct size correlated with lactate post-occlusion	Wagner et al., 1992
Rat		↑•O_2^- during ischemia; ↑↑ during reperfusion			Weir et al., 1997; Li et al., 1999
Rat	•OH formation via NO mechanism		↑GLU release	↑Cytotoxic lesion	Wei and Quast, 1998
Rat			↑•O_2^- during ischemia; ↑↑during reperfusion		Tsuruta et al., 2010
Cat	↓Pi/PCr ratio (b), ↑lactate			↑Lesion in occluded area	Chew et al., 1991
Rat			↑extracellular GLU in neocortex		Li et al., 2000
Cat			↑Ca^{2+} during reperfusion		Araki et al., 1992
Rat				BBB: severe protein extravasation	Dietrich et al., 1993
Rat				↑Infarct volume, brain swelling, HT	McBride et al., 2016
Rat (c)				↑caspase-3, ↑BACE1	Zhang et al., 2009
Rat				↑caspase-3, cyt c release	Li et al., 2001

(a) 2-DG: uptake of [2-^{18}F]-2-fluoro-2-deoxy-D-glucose (PET scans); (b) 31P NMR spectroscopy; (c) diabetic rat BACE1: β-site amyloid precursor protein-cleaving enzyme; GLU: glutamate; HT: hemorrhagic transformation; NO: nitric oxide; •O_2^-: superoxide anion radical; •OH: hydroxyl radical; ROS: reactive oxygen species.

Table 2 | **Neurovascular and neuroinflammatory mechanisms of hyperglycemia effects in acute ischemic stroke: studies in hyperglycemic animals**

Species	Neurovascular factors	Neuroinflammation	Neurological outcome	Brain injury	References
Cat	↓CBF in ischemic penumbra during reperfusion				Venables et al., 1985
Rat	↓CBF, CBV; ↑edema; ↑HT				Kawai et al., 1997
Rat				↑Neocortical (but not striatal) infarction; strong correlation with increasing glucose level; collaterally-perfused areas more susceptible	Prado et al., 1988
Rat	↓CBF, CBV			Cellular injury (MRI) during reperfusion correlated with ↓CBV, CBF	Quast et al., 1997
Rat	BBB disruption, ↑HT, ↑edema			No worsened effects *vs*. normoglycemia	Xing et al., 2011
HG in control and diabetic GK rat					Elgebaly et al., 2011
STZ mice	↑HT during reperfusion (see mechanism in brain injury)			*In vitro*: in human endothelial cells exposed to high concentration of glucose→mitochondrial functional and morphological alterations leading to ↑apoptotic cell death (caspase-3);	Mishiro et al., 2014
GK rat	↑Edema; ↑HT		↓sensory motor	Infarct volume ↓24 h; ↑7 d	Li et al., 2013
Rat		MPO 24 h post-stroke in pial, parenchima vessels and parenchima			Lin et al., 2000
db/db mice	↑Edema	↑inflammatory markers, extravasated macrophages/neutrophils, ↑proinflammatory gene expression	↑severity of neurological score	↑Infarct volume	Tureyen et al., 2011
STZ rat	BBB disruption, ↑HT, ↑edema; cerebral hypoperfusion	↑DMT: early platelet and leukocyte adhesion to endothelial cells in cortical microvessels, leukocytes extravasation, postcapillary microthrombosis; ↑plasma MMP-9, 5-HT, TAT	↑severity of neurological score	↑Infarct volume	Desilles et al., 2017
STZ rat	↑Oxidative stress; BBB disruption, ↑edema	↑MMP-9			Kamada et al., 2007

5-HT: 5-Hydroxytryptamine, serotonin (platelet activation); BBB: blood brain barrier; CBF: cerebral blood flow; CBV: cerebral blood volume; DMT: thrombo-inflammatory response to occlusion; GK: GOTO-KAKIZAKI (a spontaneous model of T2DM); HG: hyperglycemia; HT: hemorrhagic transformation; MMP-9: metalloproteinease-9 (indicator of neutrophil activation); MPO: myeloperoxidase (polymorphonuclear leukocytes); MRI: magnetic resonance imaging; STZ: streptozotocin; TAT: thrombin-antithrombin complex (coagulation activator).

(Srinivasan et al., 2004);

(iii) Increased reperfusion injury developing when revascularization is delayed, so that the prompt restoration of oxygenated blood results in increased ischemic damage and raised risk of hemorrhagic transformation. Hyperglycemia exacerbates this condition by acting through oxidative stress (Won et al., 2011) and inflammation (Zhou et al., 2015).

Neuroinflammation

Hyperglycemia triggered massive neutrophil infiltration in post-ischemic rat brain (Lin et al., 2000) and increased the expression of cyclo-oxygenase-2 and interleukin-1β in a rat model of focal cerebral ischemia (Bémeur et al., 2005), pointing to enhanced inflammatory response to ischemia/reperfusion. Moreover, hyperglycemia raised mRNA expression of pro-inflammatory cytokine interleukin-1β and tumor necrosis factor α after ischemia (Bémeur et al., 2007). Neuroinflammation also plays a key role in worsening the cerebral ischemic damage in diabetics (Shukla et al., 2017).

Experimentally (**Table 2**), hyperglycemia exacerbated the downstream microvascular events secondary to proximal arterial occlusion, as well as the thrombo-inflammatory response (plasma levels of metalloproteinase-9, serotonin and thrombin-anti-thrombin complex) to middle cerebral artery occlusion in diabetic rats. Impairment of reperfusion, neurovascular damage, BBB disruption and hemorrhagic transformation were also reported (Desilles et al., 2017).

To sum up, hyperglycemia aggravates the molecular and metabolic changes triggered by cerebral ischemia. The main goal of future experimental studies should be to identify the most meaningful affected pathways by hyperglycemia during acute ischemic stroke in the perspective of identifying accurate pharmacological targets. Therefore, the observed association between hyperglycemia and outcome in patients affected by ischemia emphasizes the crucial issue of glucose-lowering treatment and its impact on clinical outcome.

Hypoglycemic Brain Injury: the Other Side of the Coin

Clinical studies have highlighted that intensive glucose lowering strategies are linked to the increased risk of hypoglycemia, a condition that should be avoided because it further affects AIS patients' recovery. In fact, several molecular and cellular mechanisms of injury are activated by low blood glucose levels.

First of all, it is long known that the autonomic nervous system triggers the release of catecholamines so to restore normal glucose concentrations by increasing glucose hepatic production and glycogen breakdown (Exton, 1987).

Nevertheless, this adaptive stress response is accompanied by detrimental effects, such as tachycardia, increased systolic blood pressure, enhanced myocardial contractility and decreased central venous pressure (Hanefeld et al., 2013). As suggested by Klingbeil et al. (2020), the hypertensive response to hypoglycemia could add up to post-ischemic hypertension and increasing the risk of hemorrhagic transformation.

On the other hand, hypoglycemia has been associated with alterations in fibrinolytic balance: Dalsgaard-Nielsen et al. (1982) observed that serum fibrinogen and coagulation factor VIII were increased in acute hypoglycemic episodes, while the total platelet count was reduced, because of the enhanced platelet aggregation. The resulting pro-coagulant state is furtherly supported by the increase of von Willebrand factor (Fisher et al., 1991) and of thrombin formation (Ibbotson et al., 1995). Moreover, several inflammatory and adhesion molecules are produced upon hypoglycemia, i.e. interleukin-6, tumor necrosis factor α, C-reactive protein, endothelin-1 and P-selectin (Galloway et al., 2000; Wright et al., 2010), leading to eventual secondary ischemic episodes due to vasoconstriction and to the formation of new thrombi, but also to BBB disruption and consequent vasogenic edema and hemorrhagic events.

Finally, Agardh et al. (1981) observed in a seminal study that acute severe hypoglycemia was linked to the decrease of brain energy metabolites, such as phosphocreatine, ATP and adenosine monophosphate. More recently, a metabolomic analysis through magnetic resonance spectroscopy confirmed that insulin-induced hypoglycemia led to various metabolic variations (Ennis et al., 2017), as also extensively reviewed by Rehni and Dave (2018).

Modifications in brain energy metabolism is one of the key events in the ischemic brain injury (Villa et al., 2013a; Ferrari et al., 2018) and therefore hypoglycemia may worsen the bioenergetic deficit occurring in the ischemic brain. In fact, mitochondrial ROS are increased by hypoglycemia in both *in vitro* and *in vivo* studies, together with the decrease in the mitochondrial membrane potential (Dave et al., 2011). Moreover, Shukla et al. (2019) recently demonstrated that recurrent hypoglycemia in a model of cerebral ischemia in insulin-treated rats increased post-ischemic damage enhancing mitochondrial dysfunction, particularly through the decrease of complex I activity in CA1 hippocampus, that is the more vulnerable area to the ischemic injury also from a bioenergetic point of view (Villa et al., 2013b; Ferrari et al., 2015).

Novel Therapeutic Strategies

Given the several disappointing results and drawbacks in clinical trials evaluating insulin treatment of hyperglycemia in AIS patients, novel therapeutic strategies are emerging in an attempt to treat more effectively this detrimental condition, taking into account not only the glucose lowering effects, but also the several physiopathological mechanisms linked to the hyperglycemic brain injury in ischemic conditions previously discussed.

A first alternative approach to insulin could consist in the use of glucose-like peptide-1 (GLP-1) receptor agonists, i.e. albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide (Aroda et al., 2018). GLP-1 is a peptide hormone devoid of hypoglycemic effect and better maintains normoglycemia in the ischemic brain. GLP-1 plays a crucial role in glucose homeostasis and in the pathophysiology of T2DM: GLP-1 stimulates the expression and secretion of insulin, while it inhibits that of glucagon. The complex effects are exerted through the cell-membrane glucagon-like peptide receptor (GLP-1R), whose activation enhances the glucose-dependent insulin secretion through the up-regulation of cyclic adenosine monophosphate and subsequent activation of PKA and Epac2 (Mayo et al., 2003). Because GLP-1 is rapidly degraded by the endoprotease dipeptidyl-peptidase-4 (DPP-4) resulting in a half-life of about 2 minutes, the possibility to employ a series of analogs resistant to DPP-4 degradation has prompted further studies in clinical settings, considering that these drugs rarely cause hypoglycemia (Meloni et al., 2013) and their main disadvantages are the mild to moderate gastrointestinal adverse effects. Several studies have highlighted the neuroprotective effects exerted by this drug class, like the anti-apoptotic and anti-edema actions, and the support to microcirculation and to BBB integrity (Zhu et al., 2016). Clinical trials confirmed as well the beneficial role of GLP-1 receptor agonists in treating hyperglycemia in AIS patients: exenatide (5 μg s.c.) started after 9 hours following stroke onset and continued for six days reduced glycemic variability (Daly et al., 2013). Moreover, some pilot trials have been undertaken about the effects of GLP-1 receptor agonists on hyperglycemic AIS patients with or without T2DM, but results have not been published yet (review in Ferrari et al., 2020).

Another strategy is to block the activity of GLP-1 degrading enzyme through DPP-4 inhibitors, i.e. alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin. DPP-4 has exopeptidase activity through its membrane-tethered form (Mulvihill and Drucker, 2014) and GLP-1 is an ideal substrate. In fact, DPP-4 inhibitors mainly act through the enhancement of GLP-1 levels (Andersen et al., 2018). However, DPP-4 inhibitors are involved also in the regulation of blood pressure and cerebral perfusion, inflammation, oxidative stress and immune system (Ahrén, 2007). These actions are due to the fact that several other oligopeptides may serve as substrates to DPP-4 (Mentlein, 1999). At present, clinical trials failed to show any effect of DPP-4 inhibitors on preventing cardiovascular events, including stroke (Barkas et al., 2018); nevertheless, failure to prevent stroke does not imply that these drugs are ineffective in reducing ischemic injury and in improving functional outcome. Therefore, further studies are recommended, particularly because several neuroprotective effects exerted by DPP-4 inhibitors have been observed in many experimental studies (Darsalia et al., 2018; El-Marasy et al., 2018).

Even if GLP-1 receptor agonists and DPP-4 inhibitors have been the most studied drug classes as novel therapeutic strategies to lower blood glucose levels in AIS patients, other drugs are under evaluation. For example, the sodium glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin was shown to have several neuroprotective effects in a cerebral ischemia/reperfusion model in hyperglycemic rats when administered intraperitoneally at 1 and 24 hours after reperfusion, decreasing oxidative stress, inflammation and apoptotic markers, along with the improvement of neurological functions and histopathological alterations (Amin et al., 2020). Moreover, this drug slowed down the progression of atherosclerotic plaques in streptozotocin-diabetic mice (Pennig et al., 2019). At present, clinical evidence is however scarce and so far contradicting to draw significant conclusions regarding the beneficial effects of SGLT-2 inhibitors after stroke (review in Al Hamed and Elewa, 2020): for example, in the EMPA-REG OUTCOME trial, a trend towards increased stroke risk was observed in the empagliflozin-treated group, likely because of hematocrit elevation in these patients (Imprialos et al., 2017). These latter disappointing results were not confirmed in the CANVAS trial (Neal et al., 2017), where a non-significant trend was observed towards the reduction of stroke risk.

On the other hand, anti-diabetic treatment with sulfonylurea class has been hypothesized to define a potential additive risk factor for stroke (Szeto et al., 2018); even if these drugs are now third-line agents for T2DM patients for their side

effects and hypoglycemic risk, they are widely used above all in Third World countries. In fact, sulfonylureas act by blocking K+ATP channels, which are activated when glucose enters the cells and it is metabolized by glucokinase, increasing the ATP/ADP ratio; ATP triggers the channel closure and β-cell depolarization, the voltage-gated Ca^{2+} channel activation and finally the calcium-dependent insulin release. During brain ischemia, ATP is lacking and the rise of ADP/ATP ratio activates this type of channel, which was shown to exert several neuroprotective effects (Sun and Feng, 2013), on the contrary respect to sulfonylurea mechanism of action. Moreover, repaglinide, a drug acting on the same sulfonylurea receptor, increased the risk of hypoglycemic events in AIS patients concomitantly under treatment with clopidogrel, whose main metabolite exerts a pharmacometabolic interaction towards repaglinide metabolism through cytochrome P450 2C8 (Akagi et al., 2020).

Conclusions and Future Perspectives

Several clinical and experimental studies have highlighted that diabetes mellitus and post-stroke hyperglycemia worsen AIS clinical conditions, increasing infarct extension, hemorrhagic risk and death rate, overall impairing functional recovery. Moreover, hyperglycemia also affects the efficacy of thrombolysis and thrombectomy, likely because this condition leads to increased coagulative state and reduced fibrinolytic activity.

Given the lack of convincing results of i.v. insulin treatment in clinical trials evaluating functional outcomes, neurological sequelae and mortality rate, together with the concomitant increase of hypoglycemia, new strategies are needed. The most promising roadmap to be followed is to start from the complex pathophysiological mechanisms of brain hyperglycemic injury in ischemic conditions, in the attempt to boost neuroprotective pathways. In this perspective, the most promising drug classes are firstly GLP-1 receptor agonists and DPP-4 inhibitors, which have been proven effective in several experimental studies and in some clinical observations (for GLP-1 receptor agonists); secondarily, preliminary evidence is available also for the SGLT-2 inhibitors. Therefore, the feasibility of these new therapeutic strategies requires thorough experimental and clinical studies, taking into consideration also the pharmacokinetic and pharmacometabolic profiles of these drugs, which could be modified in ischemic hyperglycemic conditions respect to the hyperglycemic alone ones, with important consequences also for their safety aspects.

Acknowledgments: *The authors are grateful to Dr. Martina Vitelli for language editing of the article.*
Author contributions: *FF, AM and RFV reviewed the literature and wrote each a part of the manuscript, which has been subsequently merged and synthesized. All authors approved the final version of the manuscript.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Financial support: *This work was supported by a grant from Catholic Universitary Center (Centro Universitario Cattolico) - Conferenza Episcopale Italiana, Rome, Italy (to FF).*

Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Michel Desjarlais, University of Montréal, Canada.*

References

Agardh CD, Kalimo H, Olsson Y, Siesjö BK (1981) Hypoglycemic brain injury: metabolic and structural findings in rat cerebellar cortex during profound insulin-induced hypoglycemia and in the recovery period following glucose administration. J Cereb Blood Flow Metab 1:71-84.

Ahrén B (2007) DPP-4 inhibitors. Best Pract Res Clin Endocrinol Metab 21:517-533.

Akagi Y, Iketaki A, Kimura H, Matsudaira Y, Yoshida T, Nishimura T, Kawano Y, Mano Y, Shigematsu E, Ujihara M (2020) Risk of hypoglycemia associated with repaglinide combined with clopidogrel, a retrospective cohort study. J Pharm Health Care Sci 18:6:5.

Al Hamed FA, Elewa H (2020) Potential therapeutic effects of sodium glucose-linked cotransporter 2 inhibitors in stroke. Clin Ther 42:e242-249.

American Diabetes Association (2016) Diabetes care in the hospital: standards of medical care in diabetes-2016. Diabetes Care 39:S99-S104.

Amin EF, Rifaai RA, Abdel-Latif RG (2020) Empagliflozin attenuates transient cerebral ischemia/reperfusion injury in hyperglycemic rats via repressing oxidative-inflammatory-apoptotic pathway. Fundam Clin Pharmacol 34:548-558.

Andersen ES, Lund A, Bagger JI, Andreasen C, Grøndahl MF, Deacon CF, Hartmann B, Holst JJ, Knop FK, Vilsbøll T (2018) Is glucagon-like peptide-1 fully protected by the dipeptidyl peptidase 4 inhibitor sitagliptin when administered to patients with type 2 diabetes? Diabetes Obes Metab 20:1937-1943.

Anderson RE, Tan WK, Martin HS, Meyer FB (1999) Effects of glucose and PaO2 modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. Stroke 30:160-170.

Araki N, Greenberg JH, Sladky JT, Uematsu D, Karp A, Reivich M (1992) The effect of hyperglycemia on intracellular calcium in stroke. J Cereb Blood Flow Metab 12:469-476.

Arnberg F, Grafström J, Lundberg J, Nikkhou-Aski S, Little P, Damberg P, Mitsios N, Mulder J, Lu L, Söderman M, Stone-Elander S, Holmin S (2015) Imaging of a clinically relevant stroke model: glucose hypermetabolism revisited. Stroke 46:835-842.

Aroda VR (2018) A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomised controlled trials. Diabetes Obes Metab 20:S1:22-33.

Back T, Hoehn-Berlage M, Kohno K, Hossmann KA (1994) Diffusion nuclear magnetic resonance imaging in experimental stroke. Correlation with cerebral metabolites. Stroke 25:494-500.

Barkas F, Elisaf M, Milionis H (2018) Protection against stroke with glucagon-like peptide 1 receptor agonists: a systematic review and meta-analysis. Eur J Neurol 26:559-565.

Bémeur C, Ste-Marie L, Desjardins P, Vachon L, Butterworth RF, Hazell AS, Montgomery J (2005) Deydroascorbic acid normalizes several markers of oxidative stress and inflammation in acute hyperglycemic focal cerebral ischemia in the rat. Neurochem Int 46:399-407.

Bémeur C, Ste-Marie L, Montgomery J (2007) Increased oxidative stress during hyperglycemic cerebral ischemia. Neurochem Int 50:890-904.

Bevers MB, Vaishnav NH, Pham L, Battey TW, Kimberly WT (2017) Hyperglycemia is associated with more severe cytotoxic injury after stroke. J Cereb Blood Flow Metab 37:2577-2583.

Cerecedo-Lopez CD, Cantu-Aldana A, Patel NJ, Aziz-Sultan MA, Frerichs KU, Du R (2020) Insulin in the management of acute ischemic stroke: a systematic review and meta-analysis. World Neurosurg 136:e514-e534.

Chen X, Liu Z, Miao J, Zheng W, Yang Q, Ye X, Zhuang X, Peng F (2019) High stress hyperglycemia ratio predicts poor outcome after mechanical thrombectomy for ischemic stroke. J Stroke Cerebrovasc Dis 28:1668-1673.

Chew W, Kucharczyk J, Moseley M, Derugin N, Norman D (1991) Hyperglycemia augments ischemic brain injury: in vivo MR imaging/spectroscopic study with nicardipine in cats with occluded middle cerebral arteries. AJNR Am J Neuroradiol. 12:603-609.

Christensen H, Boysen G, Johannesen HH (2004) Serum-cortisol reflects severity and mortality in acute stroke. J Neurol Sci 217:175-180.

Dalsgaard-Nielsen J, Madsbad S, Hilsted J (1982) Changes in platelet function, blood coagulation and fibrinolysis during insulin-induced hypoglycaemia in juvenile diabetics and normal subjects. Thromb Haemost 47:254-258.

Daly SC, Chemmanam T, Loh PS, Gilligan A, Dear AE, Simpson RW, Bladin CF (2013) Exenatide in acute ischemic stroke. Int J Stroke 8:E44.

Darsalia V, Larsson M, Klein T, Patrone C (2018) The high need for trials assessing functional outcome after stroke rather than stroke prevention with GLP-1 agonists and DPP-4 inhibitors. Cardiovasc Diabetol 17:32.

Dave KR, Tamariz J, Desai KM, Brand FJ, Liu A, Saul I, Bhattacharya SK, Pileggi A (2011) Recurrent hypoglycemia exacerbates cerebral ischemic damage in streptozotocin-induced diabetic rats. Stroke 42:1404-1411.

Desilles J-P, Syvannarath V, Ollivier V, Journé C, Delbosc S, Ducroux C, Boisseau W, Louedec L, Di Meglio L, Loyau S, Jandrot-Perrus M, Potier L, Michel JB, Mazighi M, Ho-Tin-Noé B (2017) Exacerbation of thromboinflammation by hyperglycemia precipitates cerebral infarct growth and hemorrhagic transformation. Stroke 48:1932-1940.

Dietrich WD, Alonso O, Busto R (1993) Moderate hyperglycemia worsens acute blood-brain barrier injury after forebrain ischemia in rats. Stroke 24:111-116.

El-Marasy SA, Abdel-Rahman RF, Abd-Elsalam RM (2018) Neuroprotective effect of vildagliptin against cerebral ischemia in rats. Naunyn Schmiedebergs Arch Pharmacol 39:1133-1145.

Elgebaly MM, Ogbi S, Li W, Mezzetti EM, Prakash R, Johnson MH, Bruno A, Fagan SC, Ergul A (2011) Neurovascular injury in acute hyperglycemia and diabetes: a comparative analysis in experimental stroke. Transl Stroke Res 2:391-398.

Ennis K, Lusczek E, Rao R (2017) Characterization of the concurrent metabolic changes in brain and plasma during insulin- induced moderate hypoglycemia using 1H NMR spectroscopy in juvenile rats. Neurosci Lett 653:370-375.

Exton JH (1987) Mechanisms of hormonal regulation of hepatic glucose metabolism. Diabetes Metab Rev 3:163-183.

Ferrari F, Gorini A, Villa RF (2015) Functional proteomics of synaptic plasma membrane ATP-ases of rat hippocampus: effect of l-acetylcarnitine and relationships with dementia and depression pathophysiology. Eur J Pharmacol 756:67-74.

Ferrari F, Gorini A, Hoyer S, Villa RF (2018) Glutamate metabolism in cerebral mitochondria after ischemia and post-ischemic recovery during aging: relationships with brain energy metabolism. J Neurochem 146:416-428.

Ferrari F, Moretti A, Villa RF (2020) The treament of hyperglycemia in acute ischemic stroke with incretin-based drugs. Pharmacol Res 160:105018.

Fisher BM, Quin JD, Rumley A, Lennie SE, Small M, MacCuish AC, Lowe GD (1991) Effects of acute insulin-induced hypoglycaemia on haemostasis, fibrinolysis and haemorheology in insulin-dependent diabetic patients and control subjects. Clin Sci (Lond) 80:525-531.

Fuentes B, Ntaios G, Putaala J, Thomas B, Turc G, Díez-Tejedor E; European Stroke Organisation (2018) European Stroke Organisation (ESO) guidelines on glycaemia management in acute stroke. Eur Stroke J 3:5-21

Galloway PJ, Thomson GA, Fisher BM, Semple CG (2000) Insulin-induced hypoglycemia induces a rise in C-reactive protein. Diab Care 23:861-862.

Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG; GIST Trialists Collaboration (2007) Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol 6:397-406.

Hanefeld M, Duetting E, Bramlage P (2013) Cardiac implications of hypoglycaemia in patients with diabetes- a systematic review. Cardiovasc Diabetol 12:135.

Ibbotson SH, Catto A, Davies JA, Grant PJ (1995) The effect of insulin-induced hypoglycaemia on factor VIII:C concentrations and thrombin activity in subjects with type 1 (insulin-dependent) diabetes. Thromb Haemost 73:243-246.

Imprialos KP, Boutari C, Stavropoulos K, Doumas M, Karagiannis AI (2017) Stroke paradox with SGLT-2 inhibitors: a play of chance or a viscosity-mediated reality? J Neurol Neurosurg Psychiatry 88:249-53.

Jauch EC, Saver JL, Adams HP, Bruno A, Conners JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology (2013) Guidelines for the early management of patients with acute ischemic stroke. Stroke 44:870-947.

Johnston KC, Bruno A, Pauls Q, Hall CE, Barrett KM, Barsan W, Fansler A, Van de Bruinhorst K, Janis S, Durkalski-Mauldin VL; Neurological Emergencies Treatment Trials Network and the SHINE Trial Investigators (2019) Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. JAMA 322:326-335.

Kamada H, Yu F, Nito C, Chan PH (2007) Influence of hyperglycemia on oxidative stress and matrix metalloproteinase-9 activation after focal cerebral ischemia/reperfusion in rats: relation to blood-brain barrier dysfunction. Stroke 38:1044-1049.

Kawai N, Keep RF, Betz AL (1997) Effects of hyperglycemia on cerebral blood flow and edema formation after carotid artery occlusion in Fischer 344 rats. Acta Neurochir Suppl 70:34-36.

Kim JT, Liebeskind DS, Jahan R, Menon BK, Goyal M, Nogueira RG, Pereira VM, Gralla J, Saver JL (2018) Impact of hyperglycemia according to the collateral status on outcomes in mechanical thrombectomy stroke. Stroke 49:2706-2714.

Klingbeil KD, Koch S, Dave KR (2020) Potential link between post-acute ischemic stroke exposure to hypoglycemia and hemorrhagic transformation. Int J Stroke 15:477-483.

Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB (2010) Hyperglycemia: a prothrombotic factor? J Thromb Haemost 8:1663-1669.

Li P, He QP, Ouyang YB, Liu CL, Hu Br, Siesjö BK (2001) Early release of cytochrome C and activation of caspase-3 in hyperglycemic rats subjected to transient forebrain ischemia. Brain Res 896:69-76.

Li PA, He QP, Miyashita H, Howllet W, Siesjö BK, Shuaib A (1999) Hypothermia ameliorates ischemic brain damage and suppresses the release of extracellular amino acids in both normo- and hyperglycemic subjects. Exp Neurol 158:242-253.

Li PA, Shuaib A, Miyashita H, He QP, Siesjö BK, Warner DS (2000) Hyperglycemia enhances extracellular glutamate accumulation in rats subjected to forebrain ischemia. Stroke 31:183-192.

Li WA, Moore-Langston S, Chakraborty T, Rafols JA, Conti AC, Ding Y (2013) Hyperglycemia in stroke and possible treatments. Neurol Res 35:479-491.

Li Y, Zhang Y, Ma L, Niu X, Chang J (2019) Risk of stroke-associated pneumonia during hospitalization: predictive ability of combined A2DS2 score and hyperglycemia. BMC Neurol 19:298.

Lin B, Ginsberg MD, Busto T, Li L (2000) Hyperglycemia triggers massive neutrophil deposition in brain following transient ischemia in rats. Neurosci Lett 278:1-4.

Marsh WR, Anderson RE, Sundt TM Jr (1986) Effect of hyperglycemia on brain pH levels in areas of focal incomplete cerebral ischemia in monkeys. J Neurosurg 65:693-396.

Mayo KE, Miller LJ, Bataille D, Dalle S, Göke B Thorens B, Drucker DJ (2003) International Union of Pharmacology. XXXV. The glucagon receptor family. Pharmacol Rev 55:167-194.

McBride DW, Legrand J, Krafft PR, Flores J, Klebe D, Tang J, Zhang JH (2016) Acute hyperglycemia is associated with immediate brain swelling and hemorrhagic transformation after middle cerebral artery occlusion in rats. Acta Neurochir Suppl 121:237-241.

Meloni AR, DeYoung MB, Lowe C, Parkes DG (2013) GLP-1 receptor activated insulin secretion from pancreatic β-cells: mechanism and glucose dependence. Diabetes Obes Metab 15:15-27.

Mentlein R (1999) Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. Regul Pept 85:9-24.

Mi D, Wang P, Yang B, Pu Y, Yang Z, Liu L (2017) Correlation of hyperglycemia with mortality after acute ischemic stroke. Ther Adv Neurol Disord 11:1756285617731686.

Mishiro K, Imai T, Sugitani S, Kitashoji A, Suzuki Y, Takagi T, Chen H, Oumi Y, Tsuruma K, Shimazawa M, Hara H (2014) Diabetes mellitus aggravates hemorrhagic transformation after ischemic stroke via mitochondrial defects leading to endothelial apoptosis. PLoS One 9:e103818.

Mitsios JP, Ekinci EI, Mitsios GP, Churilov L, Thijs V (2018) Relationship between glycated hemoglobin and stroke risk: a systematic review and meta-analysis. J Am Heart Assoc 7:e007858.

Mulvihill EE, Drucker DJ (2014) Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocr Rev 35:992-1019.

Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377:644-657.

O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, et al (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 376:112-123.

Paciaroni M, Agnelli G, CasoV, Corea F, Ageno W, Alberti A, Lanari A, Micheli S, Bertolani L, Venti M, Palmerini F, Billeci AM, Comi G, Previdi P, Silvestrelli G (2009) Acute hyperglycemia and early hemorrhagic transformation in ischemic stroke. Cerebrovasc Dis 28:119-123.

Palaiodimou L, Lioutas VA, Lambadiari V, Paraskevas GP, Voumvourakis K, Tsivgoulis G (2019) Glycemia management in acute ischemic stroke: current concepts and novel therapeutic targets. Postgrad Med 131:423-437.
Pandolfi A, Giaccari A, Cilli C, Alberta MM, Morviducci L, De Filippis EA, Buongiorno A, Pellegrini G, Capani F, Consoli A (2001) Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. Acta Diabetol 38:71-76.
Parsons MW, Barber A, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM (2002) Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy. Ann Neurol 52:20-28.
Pennig J, Scherrer P, Gissler MC, Anto-Michel N, Hoppe N, Füner L, Härdtner C, Stachon P, Wolf D, Hilgendorf I, Mullick A, Bode C, Zirlik A, Goldberg IJ, Willecke F (2019) Glucose lowering by SGLT2-inhibitor empagliflozin accelerates atherosclerosis regression in hyperglycemic STZ-diabetic mice. Sci Rep 9:17937.
Piironen K, Putaala J, Rosso C, Samson Y (2012) Glucose and acute stroke. Evidence for an interlude. Stroke 43:898-902.
Prado R, Ginsberg MD, Dietrich WD, Watson BD, Busto R (1988) Hyperglycemia increases infarct size in collaterally perfused but not end-arterial vascular territories J Cereb Blood Flow Metab 8:186-192.
Quast MJ, Wei J, Huang NC, Brunder DG, Sell SL, Gonzalez JM, Hillman GR, Kent TA (1997) Perfusion deficit parallels exacerbation of cerebral ischemia/reperfusion injury in hyperglycermic rats. J Cereb Blood Flow Metab 17:553-559.
Rehni AK, Dave KR (2018) Impact of hypoglycemia on brain metabolism during diabetes. Mol Neurobiol 55:9075-9088.
Ribo M, Molina C, Montaner J, Rubiera M, Delgado-Mederos R, Arenillas JF, Quintana M, Alvarez-Sabín J (2005) Acute hyperglycemia state is associated with lower tPA-induced recanalization rates in stroke patients. Stroke 36:1705-1709.
Roberts GW, Quinn SJ, Valentine N, Alhawassi T, O'Dea H, Stranks SN, Burt MG, Doogue MP (2015) Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab 100:4490-4497.
Rosso C, Attal Y, Deltour S, Hevia-Montiel N, Lehéricy S, Crozier S, Dormont D, Baillet S, Samson Y (2011) Hyperglycemia and the fate of apparent diffusion coefficient-defined penumbra. AJNR Am J Neuroradiol 32:852-856.
Rosso C, Baronnet F, Diaz B, Le Bouc R, Frasca Polara G (2018) The silver effect of admission glucose level on excellent outcome in thrombolysed stroke patients. J Neurol 265:1684-1689.
Rosso C, Corvol JC, Pires C, Crozier S, Attal Y, Jacqueminet S, Deltour S, Multlu G, Leger A, Meresse I, Payan C, Dormont D, Samson Y (2012) Intensive versus subcutaneous insulin in patients with hyperacute stroke: results from the randomized INSULINFARCT trial. Stroke 43:2343-2349.
Shukla V, Shakya AK, Perez-Pinzon MA, Dave, KR (2017) Cerebral ischemic damage in diabetes: an inflammatory perspective. J Neuroinflammation 14:21.
Shukla V, Fuchs P, Liu A, Cohan CH, Dong C, Wright CB, Perez-Pinzon MA, Dave KR (2019) Recurrent hypoglycemia exacerbates cerebral ischemic damage in diabetic rats via enhanced post-ischemic mitochondrial dysfunction. Transl Stroke Res 10:78-90.
Song EC, Chu K, Jeong SW, Jung KH, Kim SH, Kim M, Yoon BW (2003) Hyperglycemia exacerbates brain edema and perihematomal cell death after intracerebral hemorrhage. Stroke 34:2215-2220.
Srinivasan S, Hatley ME, Bolick DT, Palmer LA, Edelstein D, Brownlee M, Hedrick CC (2004) Hyperglycemia-induced superoxide production decreases eNOS expression via AP-1 activation in aortic endothelial cells. Diabetologia 47:1727-1734.
Suissa L, Panicucci E, Perot C, Romero G, Gazzola S, Laksiri N, Rey C, Doche E, Mahagne MH, Pelletier J, Faivre A, Robinet-Borgomano E (2020) Effect of hyperglycemia on stroke outcome is not homogeneous to all patients treated with mechanical thrombectomy. Clin Neurol Neurosurg 194:105750.
Sun HS, Feng ZP (2013) Neuroprotective role of ATP-sensitive potassium channels in cerebral ischemia Acta Pharmacol Sin 34:24-32.
Szeto V, Chen NH, Sun HS, Feng ZP (2018) The role of K ATP channels in cerebral ischemic stroke and diabetes. Acta Pharmacol Sin 39:683-694.
Tsivgoulis G, Katsanos AH, Mavridis D, Lambadiari V, Roffe C, Macleod MJ, Sevcik P, Cappellari M, Nevšímalová M, Toni D, Ahmed N (2019) Association of baseline hyperglycemia with outcomes of patients with and without diabetes with acute ischemic stroke treated with intravenous thrombolysis: a propensity score-matched analysis from the SITS-ISTR registry. Diabetes 68:1861-1869.
Tsuruta R, Fujita M, Ono T, Koda Y, Koga Y, Yamamoto T, Nanba M, Shitara M, Kasaoka S, Maruyama I, Yuasa M, Maekawa T (2010) Hyperglycemia enhances excessive superoxide anion radical generation, oxidative stress, early inflammation, and endothelial injury in forebrain ischemia/reperfusion rats. Brain Res 1309:155-163.
Tureyen K, Bowen K, Liang J, Dempsey RJ, Vemuganti R (2011) Exacerbated brain damage, edema and inflammation in type-2 diabetic mice subjected to focal ischemia. J Neurochem 116:499-507.
Tziomalos K, Dimitriou P, Bouziana SD, Spanou M, Kostaki S, Angelopoulou SM, Papadopoulou M, Giampatzis V, Savopoulos C, Hatzitolios AI (2017) Stress hyperglycemia and acute ischemic stroke in-hospital outcome. Metabolism 67:99-105.
Venables GS, Miller SA, Gibson G, Hardy JA, Strong AJ (1985) The effects of hyperglycaemia on changes during reperfusion following focal cerebral ischaemia in the cat. J Neurol Neurosurg Psychiatry 48:663-669.
Venkat P, Chopp M, Chen J (2017) Blood-brain barrier disruption, vascular impairment, and ischemia/reperfusion damage in diabetic stroke. J Am Heart Assoc 6:e005819.
Villa RF, Gorini A, Ferrari F, Hoyer S (2013a) Energy metabolism of cerebral mitochondria during aging, ischemia and post-ischemic recovery assessed by functional proteomics of enzymes. Neurochem Int 63:765-81.
Villa RF, Ferrari F, Gorini A (2013b) Functional proteomics related to energy metabolism of synaptosomes from different neuronal systems of rat hippocampus during aging. J Proteome Res 12:5422-5435.
Wagner KR, Kleinholz M, de Courten-Myers GM, Myers RE (1992) Hyperglycemic versus normoglycemic stroke: topography of brain metabolites, intracellular pH, and infarct size. J Cereb Blood Flow Metab 12:213-222.
Wei J, Quast MJ (1998) Effect of nitric oxide synthase inhibitor on a hyperglycemic rat model of reversible focal ischemia: detection of excitatory amino acids release and hydroxyl radical formation. Brain Res Apr 791:146-156.
Weir CJ, Murray GD, Dyker AG, Lees KR (1997) Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. BMJ 314:1303-1306.
Widmer H, Abiko H, Faden AI, James TL, Weinstein PR (1992) Effects of hyperglycemia on the time course of changes in energy metabolism and pH during global cerebral ischemia and reperfusion in rats: correlation of 1H and 31P NMR spectroscopy with fatty acid and excitatory amino acids levels. J Cereb Blood Flow Metab 12:456-468.
Won SJ, Tang XN, Suh SW, Yenari MA, Swanson RA (2011) Hyperglycemia promotes tPA-induced hemorrhage by promoting superoxide production. Acta Neurol 70:583-590.
Wright RJ, Newby DE, Stirling D, Ludlam CA, Macdonald IA and Frier BM (2010) Effects of acute insulin- induced hypoglycemia on indices of inflammation: putative mechanism for aggravating vascular disease in diabetes. Diab Care 33:1591-1597.
Xing Y, Jiang X, Yang Y, Xi G (2011) Hemorrhagic transformation induced by acute hyperglycemia in a rat model of transient focal ischemia Acta Neurochir Suppl 111:49-54.
Yatabe T, Inoue S, Sagaguchi M, Egi M (2017) The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. Intensive Care Med 43:16-28.
Zhang T, Pan B-S, Zhao B, Zhang L.M, Huang Y-L, Sun, F-Y (2009) Exacerbation of poststroke dementia by type 2 diabetes is associated with synergistic increases of beta-secretase activation and beta-amyloid generation in rat brains. Neuroscience 161:1045-1056.
Zhang Z, Yan J, Shi H (2016) Role of hypoxia inducible factor 1 in hyperglycemia-exacerbated brain barrier disruption in ischemic stroke. Neurobiol Dis 95:82-92.
Zhou J, Wu, J, Zhang J, Xu T, Zhang H, Zhang Y, Zhang S (2015) Association of stroke clinical outcomes with coexistence of hyperglycemia and biomarkers of inflammation. J Stroke Cerebrovasc Dis 24:1250-1255.
Zhu H, Zhang Y, Shi Z, Lu D, Li T, Ding Y, Ruan Y, Xu A (2016) The neuroprotection of liraglutide against ischaemia-induced apoptosis through the activation of the PI3K/AKT and MAPK pathways. Sci Rep 6:26859.
Zonneveld TP, Nederkoorn PJ, Westendorp WF, Brouwer MC, van de Beek D, Kruyt ND; PASS Investigators (2017) Hyperglycemia predicts poststroke infections in acute ischemic stroke. Neurology 88:1415-1421.

P-Reviewer: Desjarlais M; C-Editors: Zhao M, Qiu Y; T-Editor: Jia Y