Exacerbation of thromboinflammation by hyperglycemia precipitates cerebral infarct growth and hemorrhagic transformation


Laboratory of Vascular Translational Science, Inserm 1148, Paris, France

BACKGROUND and OBJECTIVES
Acute ischemic stroke remains a leading cause of disability, cognitive impairment, and mortality worldwide, despite the development of revascularization therapies. Besides recanalization status, other prognostic factors in AIS patients are associated with clinical outcome. Among them, hyperglycemia has been found to be associated with hemorrhagic transformation (HT) and worsened neurological outcomes. Given that 40% to 50% of AIS patients present with hyperglycemia, understanding and reducing hyperglycemia-induced neurovascular injury constitute an important clinical stake. Nevertheless, the mechanisms by which preexisting hyperglycemia contributes to exacerbated neurovascular injury and poor outcomes are still not fully understood. We investigated how preexisting hyperglycemia increases ischemia/reperfusion cerebral injury.

METHODS

- Normoglycemic (NG) and streptozotocin-treated hyperglycemic (HG) rats were subjected to transient middle cerebral artery occlusion (MCAO).
- Infarct growth and brain perfusion were assessed by magnetic resonance imaging.
- Markers of platelet, coagulation, and neutrophil activation were measured in brain homogenates and plasma.
- Downstream microvascular thromboinflammation (DMT) was investigated by intravital microscopy (IVM).

Figure 1. Hyperglycemia increases infarct volume, blood–brain barrier disruption, and hemorrhagic transformation after MCAO. The higher magnification view of the squared area in A show petechial bleeding spots (*) in the infarct zone of a HG rat.

Figure 2. Hyperglycemia accelerates neurovascular damage during MCAO and is associated with incomplete reperfusion despite recanalization after tMCAO. D: Representative images of coronal slices of ASL and ADC (2nd column) sequences obtained during MCA occlusion and at 1 hour after recanalization with the corresponding 24-h coronal brain sections before and after TTC staining.

Figure 3. Hyperglycemia exacerabtes tMCAO–induced DMT. A. Rhodamine 6G-labeled platelets and leukocytes were observed by IVM in cortical microvessels downstream the MCA. B. Thrombosis during MCAO was evidenced by the accumulation of fibrinogen, neutrophils, and platelets and fibrinogen. C. Quantification MMP-9, MPO, and thrombin–antithrombin (TAT) complexes in homogenates of ischemic and nonischemic hemispheres obtained at 24 hours after tMCAO. D. Immunostaining of MPO in the infarct zone of HG rats showing the colocalization of neutrophils with microhemorrhage areas (*).

Figure 4. Priming of the thromboinflammatory cascade by hyperglycemia leads to increased and accelerated tMCAO–induced thromboinflammation. Plasma levels of MMP-9, MPO, serotonin, and thrombin–antithrombin complexes in NG and HG rats, as indicated. T0, baseline; T1, during ischemia (immediately before monofilament withdrawal); T2, 1 hour after recanalization, and T24, 24 hours after tMCAO.

Figure 5. Neutrophils from diabetic patients are primed for interactions with endothelial cells. Purified neutrophils were perfused for 5 min on HUVECs under venous flow conditions (1 dyn cm⁻²) for 5 min, and neutrophils adherent to endothelial cells were quantified after a 3-min rinse. A. Representative images of endothelial layers after perfusion with neutrophils from control donors or diabetic patients. B. Neutrophil adhesion was quantified as the number of adherent neutrophils in 10 fields of view. Results are expressed as percent of mean control values. n=18 to 21 runs out of 8 donors per group.

Conclusions

- Hyperglycemia primes the thromboinflammatory cascade, thus, amplifying tMCAO–induced DMT.
- DMT exacerbation in hyperglycemic rats impaired reperfusion and precipitated neurovascular damage, BBB disruption, and hemorrhagic transformation.
- Our results designate DMT as a possible target for reduction of the deleterious impact of hyperglycemia in acute ischemic stroke.