blood advances

A sweet deal: blocking NMDAR for safer t-PA in diabetes

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Comment on Lebrun et al, page 1330

In this issue of *Blood Advances*, Lebrun et al[1] elegantly provide preclinical proof of concept for improving thrombolysis in patients who have had a diabetic stroke. Combining tissue-type plasminogen activator (t-PA) with an antibody blocking the N-methyl-D-aspartate receptor (NMDAR) enhanced thrombolysis while reducing cerebral bleeding in diabetic mice. This seemingly counterintuitive finding builds on an extensive body of work by this group and others on the role of extravascular t-PA in the brain.[2]

Diabetes and stroke form a detrimental combination. Individuals with diabetes are at an increased risk of stroke, often experience more severe stroke-related complications, and typically respond less to treatment with t-PA.[3,4] Although diabetes is not an outright contraindication for t-PA, it does correlate with a heightened risk of hemorrhagic transformations.[4] Notably, these adverse effects are primarily attributed to hyperglycemia, which is found in ~40% of all patients who have had a stroke. Efforts to enhance stroke outcomes have led to numerous trials focusing on the acute management of glucose levels in patients who have had a stroke. However, to date, these trials have not yielded positive results.[5] This lack of benefit is likely due to the prolonged impact of hyperglycemia on the brain and the hemostatic system, creating changes that are not reversible through an acute reduction of blood glucose levels.

To improve safety and efficacy of t-PA in the setting of diabetes, the authors focused on targeting NMDAR in a clinically relevant ischemic stroke model. Ischemic stroke was induced by thrombin microinjection directly into the brain vasculature. This results in the formation of a fibrin-rich clot that successfully occludes local blood flow, resulting in brain damage and neurological deficit. In young and healthy mice, these thrombi are susceptible to t-PA–induced thrombolysis in a time-dependent manner. Similarly, as with patients who have had an ischemic stroke, early t-PA administration results in safe and effective recanalization, whereas delayed treatment reduces efficacy and increases the risk of hemorrhagic transformation.[6] In this study, the authors add a comorbidity to the equation and use a model of streptozotocin-induced type 1 diabetes. This is a straightforward model that results in severe hyperglycemia and greatly affects stroke outcomes. Diabetic mice exhibit poorer stroke outcomes, primarily due to heightened thrombosis, amplified inflammation, and a compromised blood-brain barrier.[7] Furthermore, the authors report that under diabetic conditions, t-PA does not improve stroke outcomes; rather, it leads to hemorrhagic transformations, closely mirroring clinical observations.

t-PA is mainly known for its role in fibrinolysis and its use as a thrombolytic drug; however, it also has an important role in the brain as a neuromodulator by signaling through NMDAR. In fact, many of t-PA's detrimental effects in the brain have been attributed to its activation of NMDAR.[2] NMDARs are glutamate receptors that play a crucial role in the excitatory neurotransmission. In the injured brain, excessive glutamate is released, stimulating NMDAR and causing an influx of calcium ions into neurons. This subsequently triggers a cascade of events leading to neuronal death.[2] In addition, endothelial NMDAR is involved in the maintenance of blood-brain barrier integrity and subsequent neuroinflammation. This makes targeting NMDAR an attractive therapeutic target for hemorrhagic and ischemic stroke.[8] Previously, the authors of this study generated a monoclonal antibody (Glunomab) that specifically blocks the interaction between t-PA and NMDAR and prevents subsequent NMDAR signaling and neurotoxicity.[9] Here, the authors provided strong evidence for Glunomab as an ischemic stroke drug either alone or in combination with t-PA. The results were most promising under diabetic conditions, in which Glunomab improved reperfusion and reduced hemorrhaging compared with t-PA alone.

In recent years, targeting NMDARs has been pivotal in rejuvenating neuroprotective strategies for ischemic stroke. However, the multifaceted roles of NMDARs in the brain complicates the design of therapeutic strategies blocking NMDARs. The strength of Glunomab lies in the specific inhibition of t-PA–NMDAR interactions while not affecting t-PA–induced fibrinolysis. This aspect is vital because fibrinolysis

using t-PA or tenecteplase, both of which interact with NMDAR,[10] often represents the sole acute therapeutic option for patients who have had an ischemic stroke. Despite the encouraging results of this study, several aspects warrant further investigation. The authors focused on acute stroke outcomes; however, given the role of NMDAR in learning and memory, it will be important to investigate the effects of Glunomab on long-term neurological recovery. Another open question is whether Glunomab's benefits are specifically due to blocking t-PA–NMDAR interactions in endothelial or neuronal cells. Because Glunomab was administered shortly after the onset of stroke in this study, it is challenging to ascertain whether its effects are primarily in reducing neurotoxicity, thereby mitigating neuroinflammation and the risk of hemorrhagic transformation, or whether it potentially has other impacts. Future research should validate Glunomab's protective efficacy in delayed treatment scenarios, in which more extensive brain damage has already occurred. This is particularly crucial for clinical application because it is uncommon for patients who have had a stroke to receive treatment within the first hour of symptom onset.

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