STROKE

Widening the therapeutic window?

Ischaemic stroke can lead to permanent neurological damage and often death if not diagnosed and treated promptly. There is therefore an urgent need for novel treatment approaches. Now, writing in *Nature Medicine*, Su and colleagues identify platelet-derived growth factor (PDGF) signalling as a novel central pathway that is active during stroke, suggesting potential new therapeutic strategies.

The thrombolytic agent tissue plasminogen-activating factor (tPA) is the only drug that is specifically approved for the treatment of ischaemic stroke at present. It is a serine protease that converts the zymogen plasminogen into the fibrinolytic enzyme plasmin, which is capable of inducing thrombolysis in the occluded blood vessel to rescue ischaemia. However, tPA can only be safely administered within 3 hours following stroke onset, as beyond this, the integrity of the blood–brain barrier (BBB) is compromised, and haemorrhagic complications may ensue.

The role of tPA in the CNS is not well characterized, but previous studies have suggested that tPA may directly affect the permeability of the BBB. Recently, a new substrate that is activated by tPA was identified — PDGF-CC — which triggers PDGF receptor-α (PDGFR-α) signalling within the CNS. The authors therefore proposed that the tPA–PDGFR-α system regulates BBB integrity during stroke.

To test their theory, Su and colleagues first injected tPA or active PDGF-CC into the cerebrospinal fluid of non-ischaemic mice and found that both agents rapidly increased cerebrovascular permeability. Importantly, the effect of tPA was blocked when injected in conjunction with PDGF-CC neutralizing antibodies, indicating that PDGF-CC is a downstream substrate of tPA.

Next, the authors investigated PDGFR-α activation during stroke. In mice, middle cerebral artery occlusion (MCAO; a stroke model) resulted in a twofold increase in PDGFR-α phosphorylation in the ischaemic hemisphere of the brain, an effect that was not observed in tPA-deficient mice. Furthermore, mice treated with a PDGFR-α inhibitor — the anticancer agent, imatinib mesylate — 1 hour following MCAO, had a 33% reduction in cerebrovascular permeability at 24 hours, and a 34% reduced infarct volume at 72 hours in comparison with control mice. The effects of a PDGF-CC neutralizing antibody administered before MCAO were comparable to those of imatinib.

Finally, to assess the potential for imatinib to reduce haemorrhage associated with late administration of tPA following stroke, mice were given imatinib 1 hour after MCAO, and treated with tPA 4 hours later. The amount of haemoglobin in the ischaemic hemisphere was reduced by 50% in imatinib-treated mice, suggesting that imatinib may restore neuroprotection, thus extending the therapeutic window for tPA.

The authors propose that endogenous tPA–PDGFR-α signalling may therefore be responsible for the deterioration of the BBB during stroke, which may be worsened by late administration of therapeutic tPA, leading to haemorrhagic complications. Clinical trials are currently planned to evaluate the safety and efficacy of imatinib alone or in combination with tPA following the onset of stroke.

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ORIGINAL RESEARCH PAPER Su, E. J. *et al.* Activation of PDGF-CC by tissue plasminogen activator impairs blood–brain integrity during ischemic stroke. *Nature Med.* 14, 731–737 (2008)