▶ NEUROLOGICAL DISORDERS

Making steps in stroke therapy

Agents currently used in the treatment of stroke have a narrow window of time for therapeutic application and dose-limiting adverse effects. Unfortunately, the development of new therapies has been hampered by a lack of adequate models of blood vessel dysfunction that mimic the vascular disruptions occurring in human stroke. However, two new potential therapeutic strategies for the treatment of stroke and three new models of stroke have recently been reported.

Rupture or blockage of a blood vessel in the brain causes rapid cell death in the core of the injured region, and triggers mechanisms in the surrounding area — the penumbra — that lead, for example, to increases in the concentrations of intracellular Ca^{2+} and reactive oxygen species (ROS), which initiate cell death. Targeting these mechanisms provides a promising route for the development of therapies for the treatment of stroke.

One such strategy, reported by Jiang and colleagues, involved using the metal chelator PAN-811 (also known as Triapine) to 'mop up' intracellular Ca^{2+} ions. PAN-811 was also shown to scavenge ROS, and so protects neurons from the degenerative effects of both chemical species. In a rat model of ischaemic stroke, intracerebroventricular administration of PAN-811 1 hour after occlusion of the middle cerebral artery (MCA) led to a 59% reduction in infarct volume. In addition, PAN-811 has been shown to have a favourable safety and pharmacodynamic profile in the range required for neuroprotection.

In a different approach, Kawano and colleagues focused on enzymes implicated in the neurotoxicity that occurs after stroke, specifically the cascade involving cyclooxygenase 2 (COX2). Long-term treatment with COX2 inhibitors is thought to increase the risk of cardiovascular complications, and so Kawano and colleagues sought to identify molecules downstream of COX2 that are associated with COX2 neurotoxicity. One such receptor in this pathway is the prostaglandin E_2 receptor EP1. In mice, administration of the EP1 receptor inhibitor SC51089 6 hours after occlusion of the MCA reduced brain injury. This receptor could therefore be an alternative target to COX2 in stroke.

Current models of stroke involve invasive intravascular injections, and the location and size of the occlusion produced can vary. Nishimura and colleagues have found a way to occlude a single microvessel deep below the surface of the brain. After selecting a vessel using two-photon microscopy, ultrashort-laser pulses were applied to disrupt the vessel. By varying the energy of the pulse, the authors were able to produce three models of stroke: haemorrhage (high energies); extravasations with continued blood flow (low energies); and clots with full vessel occlusion (multiple irradiation with increasing energy). These models and the strategies described above will be important in the continued progress in the development of new therapies for stroke.

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