*Nature Reviews Neurology* **7**, 418 (2011); published online 26 July 2011; doi:10.1038/nrneurol.2011.114

STROKE

# Antibody improves stroke outcomes and rtPA therapy

A therapeutic antibody targeting the interaction between tissue-type plasminogen activator (tPA) and the *N*-methyl-D-aspartate (NMDA) receptor in the brain could expand the time window for thrombolysis and improve outcomes in ischemic stroke, new research indicates.

Vascular tPA is an endogenous fibrinolytic, and a recombinant form of the enzyme (rtPA) is the only approved treatment for ischemic stroke. However, the narrow time window for administering the drug is a key limitation of the therapy. "When someone has a stroke, the first hours are critical to administer treatment that will help prevent hemorrhage and brain damage," explains Denis Vivien, a lead investigator of the study. "Later use of rtPA—for example, after 4 or 5 h—is advised against, as it tends to lead to worse outcomes overall."

The deleterious effects of tPA arise from its interaction with the brain parenchyma, and particularly with the amino-terminal domain of the NR1 subunit (ATD-NR1) of the NMDA receptor, leading to excitotoxic effects. The group therefore generated an ATD-NR1-specific antibody (αATD-NR1) in mice to block this interaction with tPA. Fluorescent staining showed that αATD-NR1 delivered intravenously crossed the blood–brain barrier and trafficked to the ipsilateral hemisphere of a middle cerebral artery occlusion (MCAO).

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A single dose of the antibody to mice 20 min or 4 h after MCAO reduced lesion volume by 44% and 41%, respectively, compared with saline-injected controls, "presumably by counteracting the endogenous activity of tPA," says Vivien.

What is the effect of the antibody on rtPA therapy? rtPA administered 20 min post ischemia reduced lesion volume by 31.5%, and this improvement was not further increased by αATD-NR1. However, administration of rtPA 4 h after MCAO increased lesion size by 33% and, in this situation, coadministration of a single dose of αATD-NR1 produced a markedly beneficial effect that was comparable to early administration of rtPA. Therefore, the antibody could "increase the 'therapeutic window' of rtPA for people who cannot get to hospital immediately," explains Vivien. Laser Doppler imaging showed that αATD-NR1 did not alter the ability of rtPA to improve cerebral blood flow, which underlies the beneficial effects of the fibrinolytic therapy.

The investigators carried out longitudinal MRI studies on mice at 24 h post MCAO to assess the long-term effects of antibody treatment. αATD-NR1 treatment alone at 4 h led to sustained reductions in lesion volume. Moreover, tests for neurological deficits, similar to those performed in a clinical setting, showed antibody-associated improvements at 3 months, suggesting the functional importance of αATD-NR1 treatment. "Evidence indicates the relevance of tPA's neurotoxicity to a number of other diseases, such as retinal occlusion, multiple sclerosis and hemorrhagic stroke," adds Vivien.

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**Original article** Macrez, R. *et al.* Antibodies preventing the interaction of tissue-type plasminogen activator with N-methyl-D-aspartate receptors reduce stroke damages and extend the therapeutic window of thrombolysis. *Stroke* doi:0.1161/STROKEAHA.110.606293