Neuroprotection Does Not Work!

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For more than 2 decades neurologists have searched for a drug that protects ischemic brain tissue from cell death—without success so far. The list of drugs tested in phase II and III trials is long. One of the first substances that showed a neuroprotective effect in experimental ischemia was the NMDA-antagonist MK-801, which protected hippocampal CA1 and CA2 pyramidal neurons. Besides NMDA-antagonists, other neuroprotective agents such as radical scavengers, calcium antagonists, sodium, or potassium channel blockers, cell membrane stabilizers, antiinflammatory agents, antiadhesion molecules, glycine-, AMPA-, and serotonin-receptor antagonists significantly reduced the infarct volume in animal models but were disappointing in clinical trials. Side effects, especially drowsiness and impaired consciousness, limited the clinical application in some agents. Surrogate markers such as stroke MRI was applied to support proof of principle that infarct growth was prevented or reduced. But neither the infarct volume nor clinical outcome was influenced persuasively.

Many arguments may be brought forward to explain why neuroprotective drugs work in experimental stroke, but not in stroke patients.

In some preclinical studies, drugs were given shortly after vessel occlusion or even before experimental stroke was induced, and therefore do not mimic the clinical situation. Most animal stroke models use young healthy rats, whereas stroke patients are often multimorbid and have macro- and microangiopathy. Whereas a reproducible ischemic lesion is induced in experimental stroke models, a heterogeneous stroke population with a wide range of stroke severity and etiology is included in clinical trials. The drug action in animal models is confined to the cerebral cortex, whereas the white matter is the major ischemic component in human stroke. Whereas many drugs apply the suture stroke model with reperfusion at a defined time point, recanalization is at chance in clinical trial patients.

It is unlikely that a neuroprotective drug acts on lacunar stroke the same as it does on embolic stroke. Stroke MRI offers a way to focus on patients with homogenous stroke etiologies and to select patients with target tissue for neuroprotection namely a salvageable penumbra. However, clinical trials using acute stroke MRI are recruiting very slow and the availability of the MRI scanner in the acute time frame is still a major obstacle.

The STAIR (Stroke Therapy Academic Industry Roundtable) conferences defined criteria for the development and improved clinical testing of neuroprotective drugs, and many of the above mentioned drawbacks were addressed in recent trials: Preclinical testing of new neuroprotective drugs used a variety of stroke models, focused on neuroprotective drugs that reduce the ischemic damage by at least 50% or better 80%, included dose-response studies, and demanded proof of penetration of the blood-brain-barrier. The ED95 was tested (95% of the maximum effect achieved with the minimum dose), and pharmacokinetic evaluation was performed.

New concepts were realized in clinical trial design and outcome assessment. The “adaptive design” with real-time assessment of the dose-response relationship was used in the ASTIN trial. The SAINT I trial deemed a perfect trial that implemented STAIR recommendations. A “shift design” was used where a responder analysis adjusts for baseline severity of stroke. The neuroprotective drug was applied within the first 6 hours after symptom onset, and combination therapy with rt-PA was allowed in the subgroup of patients treated within the first 3 hours. However, NXY-059 did not meet efficacy end points in a Phase III trial.

Other trials used stroke MRI to determine a difference in lesion volume change from baseline or aimed to stratify subgroups of patients to well characterized stroke etiologies such as moderate middle cerebral artery (MCA) occlusion with a diffusion/perfusion mismatch (some currently running trials).

No Tissue Salvage Without Reperfusion!
If there is nothing to blame on trial design and study conduct, the question arises, whether neuroprotection as a biological concept is too weak in human stroke or is counteracted by mechanisms not well understood. A recently described multidrug resistance transporter that prevents the penetration of drugs via the blood brain barrier might be one possible explanation for ineffectiveness and its inhibitor the solution for success.

Until innovative concepts teach better, neuroprotection must be considered ineffective in human stroke and tissue reperfusion is the sine qua non of recovery and the prerequisite for clinical improvement. Because it is unlikely that a neuroprotective drug reaches high enough pharmacological levels to prevent progression of tissue damage in the ischemic
penumbra, combination with thrombolytic treatment is mandatory. New thrombolytics such as desmoteplase are currently under study in phase III trials and may extend the opportunity of treatment without increasing bleeding rates. Whether an extended time window for thrombolysis opens new opportunities for neuroprotection remains to be seen.

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None.

References

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