THE ROOTS OF CURRENT CLINICAL LIMITATIONS IN NEUROPROTECTION

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There are posited to be substances ("neuroprotectants") and strategies ("neuroprotection" that render the brain relatively resistant, at least for some time, to the deleterious effect of lack of oxygen and energy delivery, keeping brain cells alive despite poor perfusion. Trials of putative neuroprotectants, when used alone without measures to enhance reperfusion, have all resulted in failure. Effective agents in experimental animal models of acute ischemia have had no or little benefit in humans with brain ischemia. Many failures are due to suboptimal trial design and testing.

Armchair ideas and theories abound and far outweigh data, but this field of investigation still may prove fruitful in the future. Trials in human stroke patients have been poorly designed to show effectiveness of the various therapies. They have customarily been given to all patients with acute stroke, and in most studies full brain and vascular imaging have not been mandated at entry or follow-up.

Among all patients with acute brain ischemia:

1) Many already have large infarcts. These could be identified by DWI MRI scans or full CT protocols. Dead brain cannot respond to neuroprotection.
2) In many patients the blood vessels supplying the ischemic brain are occluded. The neuroprotective agents might not reach the ischemic neurons because the entry main road is blocked. Giving the agents to patients who have open arteries or are undergoing thrombolysis or other reperfusion techniques would be most effective.
3) White matter infarcts especially lacunes might not respond to neuroprotective agents that are cytoprotective since the white matter consists of tracts and not neurons.

If a neuroprotective agent proves effective among patients investigated thoroughly using modern neuroimaging who have small or no brain infarcts, open arteries (or are undergoing reperfusion), and non-lacunar mechanisms, and the agent is safe, it will become widely used. Because cerebral cortex is the main aim of protection, cognitive and behavioral testing is needed to show benefit. The presently pursued strategy of treating all acute stroke patients provides a very difficult barrier for any neuroprotective agent to hurdle. Small studies of fully evaluated patients, after thorough animal and pharmacokinetic data, might identify suitable neuroprotective agents for larger trials of well evaluated patients.