Pathomechanism of ischemic stroke and Neuroprotective therapy

Koji Abe
Department of Neurology, Okayama University Medical School, Japan

Among neural cells, neurons are particularly sensitive to various injuries such as ischemia, oxidative stress, hypoxia, hypoglycemia, infection, degeneration, and trauma. These vulnerabilities of neurons make it difficult to cure patients suffered from the above injuries in clinical situations. Normal differentiation of neuronal and glial cells and their maintenance are under control of neurotrophic factors (NTFs). As well as blood flow restoration, neuroprotection is essential for therapy in acute stage of stroke. Both NTFs and free radical scavenger can be such neuroprotective reagents with inhibiting death signals and potentiating survival signals under cerebral ischemia.

A free radical scavenger Edaravone is the first clinical drug for neuroprotection in the world which has been used from 2001 in most ischemic stroke patients in Japan. Edaravone scavenges hydroxyl radicals both in hydrophilic and hydrophobic conditions, and is especially useful in thrombolytic therapy with tissue plasminogen activator (tPA). Combination therapy of Edaravone with tPA greatly reduced hemorrhagic transformation accompanied by tPA treatment, and may also extend therapeutic time window with tPA therapy for more than 4.5 hr in human stroke patients for preserving neurovascular unit (NVU). An intensive Edaravone therapy for 3 days now showed a favorite recovery in 3 European countries. Stem cell therapies with MSC (mesenchymal stromal cell), iPS cell, and Muse cell are also be a strong therapeutic candidate for human stroke patients.

A recent multicenter prospective double-blind placebo-control clinical trial with edaravone for ALS patients conducted in Japan showed a positive effect for delaying the clinical score (ALS FRS-R) during the 24 weeks of examination. Of particular was that this clinical benefit of edaravone was shown as an add-on therapy after anti-glutamatergic riluzole. These data strongly suggest a potential underlying mechanism of oxidative stress in ALS and a clinical delay by a free radical scavenger. These translational studies on a free radical scavenger Edaravone allowed governmental permissions both for acute ischemic stroke after 2001 and for ALS after 2015. Edaravone was now widely used in the world both for stroke and ALS.

(1) Abe K et al., A strong attenuation of ischemic and postischemic brain edema by a novel free radical scavenger. Stroke 1988; 19: 480-485.
(2) Abe K et al., Stem cell therapy for cerebral ischemia: from basic science to clinical applications. J Cereb Blood Flow Metab. 2012; 32: 1317-1331.
(3) Abe K et al., Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurology 2017; 16: 505-512.