Studies on the treatment of acute ischemic stroke : development of new neuroprotective therapies

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Ischemic stroke often kills or permanently incapacitates its victims. The thrombolytic agent recombinant tissue plasminogen activator (rtPA) is sometimes given to restore blood flow to the ischemic tissue after acute ischemic stroke. Yet strict eligibility criteria have limited the patients who receive the agent to only 2-5%. The remainder of patients who suffer acute cerebral ischemia therefore require neuroprotective agents to salvage the ischemic penumbra.

Investigators have developed neuroprotective compounds such as glutamate antagonists, calcium channel blockers, anti-inflammatories, antioxidant, GABA agonist, and growth factors over the last few decades. Regretfully, few of the neuroprotective agents used to treat ischemic insults bring about desired effects after acute stroke.

Over the last four decades we have investigated the following neuroprotective agents and therapies for acute ischemic stroke including hyperosmotic agents, glyceol®, free radical scavengers, edaravone, immunosuppressants, FK506 (tacrolimus), unsaturated fatty acids, EPA (eicosapentaenoic acid), statin (atorvastatin), macrolide antibiotics, and cell transplantation.

In this paper we introduce our clinical and experimental studies on some of the neuroprotective compounds used.

Edaravone reduced the MRI T_2 relaxation time, decreased brain edema, suppressed the elevation of serum S100β, and reduced brain damage in patients with acute cerebral infarction. Edaravone also reduced infarct and edema volumes, ameliorated neurological symptoms, and suppressed apoptosis in a rat model of focal ischemia.

FK506 significantly reduced the infarct and edema volumes, ameliorated neurological symptoms, and suppressed the expression of oxidative stress (4HNE, 8OHdG) and inflammation (Iba-1, TNF-α). FK506 at a 0.3mg/kg dose had a therapeutic time window of between 60 and 120 min in transient focal ischemia.

EPA administration for 7 days before cerebral ischemia reduced infarct and edema volumes, ameliorated neurological symptoms, and suppressed markers of

oxidative stress (4HNE, 8OHdG).

Pretreatment with the macrolide antibiotics erythromycin (EM), clarithromycin (CAM), roxithromycin (RXM), azithromycin (AZM) or kitasamycin (INN) for 7 days before cerebral ischemia reduced infarct and edema volumes and improved functional recovery without affecting the CBF in transient focal ischemia.

Post-ischemic treatment with EM reduced infarct and edema volumes and improved neurological symptoms in the same ischemic model. EM also suppressed markers of oxidative stress (4HNE, 8OHdG) and inflammation (Iba-1, TNF-α). In a study of oxygen-glucose deprivation (OGD) in cultured neuronal cells, EM reduced cell death after the OGD.

These findings suggest that macrolide antibiotics, especially EM, may hold promise as neuroprotective agents for acute ischemic stroke.