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Multi-drug treatment for stroke with granule-colony stimulating factor (G-CSF), DETC-MeSO and sulindac- Therapy and mechanism

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Recently we have developed several novel drugs including granulocyte-colony stimulating factor (G-CSF), a stem cell enhancer and facilitator and a neuroprotector, S-methyl-N,N-diethylthiolcarbamate sulfoxide (DETC-MeSO), a NMDA receptor partial antagonist and sulindac, a potent catalytic anti-oxidant and anti-inflammatory agent and it was shown that each of them is quite effective in protecting and repairing ischemia-induced neuronal injury in MCAO stroke animal model as well as in hypoxia culture model. In addition, we found thatsimilar protection could be achieved by the multi-drug treatment with a combination of G-CSF, DETC-MeSO, and sulindac at 1/10 of the dose of the individual drug as mentioned above. The major findings are summarized as follows: 1. The brain infract size is reduced by 50-60% by the multi-drug treatment either administered prior to or post MCAO surgery; 2. The anti-apoptotic protein markers such as Bcl-2 are markedly up-regulated whereas the pro-apoptotic protein markers such as Bax, Bak, Bim, caspase 3 etc are markedly down-regulated; 3. The stress markers for endoplasmic reticulum (ER), such as GRP78 and CHOP are greatly down-regulated. In summary, these results indicate that the multi-drug treatment with G-CSF, DETC-MeSO and sulindac is effective in protecting and restoring the neuronal function in MCAO stroke model and represents a new approach for clinical intervention for stroke.

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Neuroprotectoin and neuroregenerative therapy for ischemic stroke

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Neuroprotection is essential for therapy in acute stage of stroke. Edaravone, a free radical scavenger 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 increased survival of stroke animals, reduced infarct size and inhibited molecular markers of oxidative damage in lipid, protein and DNA. Use of Edaravone 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. An intensive Edaravine therapy for 3 days now showed a favorite recovery in 3 EU countries (Finland, UK, and Holland). It is important for regenerative therapy that the neural stem cells which are intrinsically activated or exogenously transplanted. To support stem cell migration, an artificial scaffold can be implanted to injured brain for promoting ischemic brain repair. In vivo optical imaging is a recent technology to detect ischemic and other neurologic disorders without killing subjects which make able time-dependent monitoring of the disease conditions such as MMP9 activation and macro autophagy after ischemic stroke. We report a cell therapy for both ischemic stroke models. As a translational stroke research, we are currently conducting a clinical trial with G-CSF for ischemic stroke patients together with Professor Shunya Takizawa at Tokai University.

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