Calcium Channel Blockers Can Reduce Iron-induced Apoptosis in Neural Stem Cells

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Excessive iron accumulation in the brain with oxidative damage has commonly been observed in haemorrhagic stroke as well as neurodegenerative disorders. It is partly mediated via extracellular signal–regulated kinases (ERK) signalling cascades that regulate a diverse neuronal functional processes including cell death. Since L-type calcium channels are key passages responsible for the iron entry into neuronal cells and therefore we postulated its blocker, nimodipine and flunarizine, could potentially protect against iron-induced neurotoxicity in neural stem cells (NSCs). In-vitro studies of iron overload on murine-derived multipotent neural stem cell line C17.2 cells and rat embryonic (E13.5) hippocampal neural stem cells (hNSCs) were performed. The cytotoxic effect of various forms of iron compound (ferrous ammonium sulfate, ferric chloride, and ferric ammonium citrate) on NSCs and the salvaging potential of calcium channel blockers (nimodipine and flunarizine) under such iron overloaded circumstances were studied. Cell viability was measured by XTT assay. Apoptotic cell death was assessed by annexin V/PI staining, activated caspase-3 and mitochondrial membrane potential (JC-1) using flow cytometry. The effect of iron overload on ERK activation as well as the rescuing effect of calcium channel blockers and MEK inhibitor (U0126) on ERK phosphorylation of iron-injured NSCs was also studied by flow cytometry. Our results showed that iron overload significantly decreased cell viability via inducing mitochondrial damage and caspase-3 activity in a dose- and time-dependent manner (0.15-1.8 mM, 24 and 48 hours). Clinically relevant doses of iron (0.6-0.9 mM) also induced ERK activation of NSCs. Under such conditions, calcium channel blockers could significantly improve cell viability by partially ameliorated iron induced apoptosis via preventing mitochondrial damage. Calcium channel blockers and U0126 also prevented ERK activation in iron-overloaded NSCs. In summary, iron-induced apoptosis of NSCs underwent mitochondria-mediated apoptotic pathway and it involved ERK activation. Calcium channel blockers could potentially protect iron-induced neurotoxicity in NSCs by inhibiting these processes.

Clinical Course of Patients with Myasthenia Gravis in Hong Kong

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Background: With advances in treatment, the prognosis of patients with myasthenia gravis has much improved in western countries over the past decades. However there is a scarcity of local data.
Methods: We conducted a retrospective review of the patients with myasthenia gravis who had disease onset after 2000 and under our care. Patients were identified using keyword search for "myasthenia gravis" in the Clinical Data Analysis and Reporting System (CDARS). The demographic data, clinical characteristics and outcome were obtained from written medical records and the records in the Clinical Management System.
Results: A total of 88 patients were identified and included. Patients' mean age at onset was 54.2 years; 58 was female and 42 was male. Fifty-five (63%) had pure ocular symptoms, 23 (27%) with generalised myasthenia at onset, nine (10%) with ocular onset followed by secondary generalisation. A thymic abnormality was diagnosed by CT in 10 patients (9 thymoma, 1 hyperplasia). Thymectomy was performed in nine patients (5 for thymoma, 1 for hyperplasia, 3 for normal thymus). Prednisolone and azathioprine was used in 38.6% and 28% respectively, predominantly in generalised cases. Two refractory cases were treated with mycophenolate. Twenty-three patients experienced significant deterioration in myasthenic symptoms requiring hospitalisation, cumulating to 671 days of hospitalisation. Fourteen patients developed myasthenic crisis, and a total of 21 courses of intravenous immunoglobulin was given to them. Two patients did not respond to IVIg and required a total of seven courses of plasmapheresis. All-cause mortality was 9% (8/88) after an average follow-up of 5 years, with four deaths from each group. None were disease-related in the ocular group. Among the generalised group, two died of respiratory failure, one from severe sepsis. Overall disease-related mortality was 3.4%.
Conclusion: The outcomes of local myasthenia gravis patients are good and comparable with western countries.