Studies on neuroprotective role of RIP kinase inhibitors and their interaction with omega-3 fatty acid in MPTP induced Parkinson disease

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Parkinson disease (PD) characterized by inflammation of dopaminergic neurons leading to cell death. Programmed cell death (PCD) is a mechanism of cell demises includes apoptosis, autophagy or necroptosis. Signal transaction pathways involved in cell death mediated through inflammation of dopaminergic neurons is not well understood. Therefore, there is an urgent need for dopaminergic neurons protection by restricted PCD, necroptosis and oxidative stress in brain. Protective role of RIP kinase inhibitor and omega-3 fatty acid is not well known in PD. Therefore, present study was designed to explore neuroprotective role of RIP kinase inhibitor and its interactions with omega-3 fatty acid in MPTP induced PD in rats. PD was induced in mice (n=6, per group) by administration of MPTP (20 mg/kg, i.p) 4 times in one day at an interval of 2 hr. Simultaneously RIP kinase inhibitor (NEC-1) 2-10 mg/kg and omega-3 fatty acid 50-200 mg/kg were administered i.p. once daily for one week. Control group received only tween 20. After one week animals were observed for EPM and OF test for behavioral analysis, grip strength test, brain pathology and oxidative stress markers (MDA, SOD, CAT) in brain. Nec-1 (5-10 mg/kg) inhibits RIPK1 mediated necroptosis pathway which is evidenced by pathological analysis of treated brains in a dose dependent manner. We also observed that MPTP induced changes in behavioral and locomotor activities were significantly reversed by NEC-1. Omega-3 fatty acid alone and in combination with NEC-1 shown synergistic protective effect on pathological and biochemical (MDA, SOD & CAT) markers also substantiate these results. Nec-1 and omega-3 fatty acid shown significantly ($P<0.05$) ameliorating MPTP-induced changes in behavioral, biochemical and pathological changes as compared to controls. These results suggests that signal transaction pathways involved in PD pathogenesis may be mediated through RIP kinase and poor antioxidant defense mechanisms. RIP kinase inhibitors and omega-3 fatty acid may plays protective roles in PD. Further, studies are needed to confirm and understand mechanism of neuroprotection made by RIP kinase inhibitor and omega-3 fatty acid at molecular level in PD. It may focus light on designing of newer and better pharmacotherapeutics for non-curable PD patients.