AIMS AND OBJECTIVES

Neuroinflammation is a common feature in most of the neurodegenerative diseases. The course of the PD progression is still unknown. However, the foremost hypothesis for the degeneration of dopaminergic neurons includes protein aggregation, mitochondrial dysfunction, oxidative stress and up regulation of proinflammatory cascade could be the major events that act synergistically causing this debilitating disease. Since experimental and clinical studies have demonstrated the presence of activated microglia and elevated levels of inflammatory cytokines in the SN, an emerging area of interest involves developing strategies to inhibit the glial activation/reaction or targeting inflammatory pathway, which promotes apoptosis of dopaminergic neurons and sustains the levels of oxidative stress induced by microglial activation. There is need to explore the exact mechanism of the antiparkinson effect of these anti-inflammatory drugs i.e. may be by modulation of dopaminergic or cholinergic pathway, has to be established.

Therefore, one of the main objectives of this thesis was to mimic this neuroinflammatory cascade in the rodent model, in order to recapitulate the behavioral, biochemical and cellular deficits that are prevalent in PD. Also, the present work further aimed to understand the neuroinflammatory mechanisms involved in the experimental paradigm of PD by targeting novel cellular mediators such as COX, LOX, LTs and PPARs apart from oxidative stress.

Chapter 1 deals with elucidation of the role of COX-inhibitors in drug-induced catatonia and MPTP-induced neurotoxicity in rodents. This chapter has been subdivided into two parts. First part investigates the role of selective (rofecoxib, celecoxib), preferential (nimesulide) and non-selective (naproxen) COX-2 inhibitors in modulating the effect of levodopa against perphenazine induced catatonia in rats. Second part of this explores the neuromodulatory potential of selective COX-2 inhibitors (rofecoixib, valdecoxib and NS-398) against systemic administration of MPTP in mice. Since neuroinflammation is the primary response to external stimuli, COX represents a novel target in halting the progression of PD.

Chapter 2 elucidates the role of LOX and COX enzymes in the pathophysiology of PD and describes the modulatory potential of 5-LOX...
inhibitor (caffeic acid), dual COX/LOX inhibitor (licofelone) and CysLT receptor antagonist (montelukast) against MPTP induced neurotoxicity in mice. The first part of this chapter deals with the possible neuroprotective effect of caffeic acid and its combination with rofecoxib (a selective COX-2 inhibitor) against MPTP-induced Parkinson-like symptoms in mice. Second part of this chapter deals with the neuromodulatory potential of licofelone, a dual COX/LOX inhibitor in attenuating neuroinflammatory signaling cascade in experimental paradigm of PD induced by MPTP. Third part of this chapter investigates the effect of montelukast against MPTP-induced Parkinson-like symptoms in mice. These signaling pathways have been chosen for the proper understanding of their putative role in the therapeutic management of PD.

Chapter 3 brings into account the possible involvement of PPARγ in the pathophysiology of PD and the neuroprotective potential of pioglitazone, a PPARγ agonist in ameliorating neuroinflammatory cascade in mouse model of PD, where in MPTP was used to induce PD-like symptoms in animals. Furthermore, the chapter also describes the modification of the neuromodulatory property of PPARγ agonist by a PPARγ antagonist. Since recent reports focus on the neuroprotective effect of PPARγ agonists, it therefore, represents a novel drug target in the management of PD.

Chapter 4 explores the neuroprotective effect of nutritional supplements and antioxidants in the management of experimental paradigm of PD. First part of this chapter deals with the comparative study of two isoforms of Vitamin E (tocopherol and tocotrienol) in mitigating the behavioral, biochemical and cellular deficits induced by MPTP. Second part of the chapter illustrates the beneficial effect of antioxidant (lycopene) in modulating the dopaminergic neurodegeneration induced by MPTP in mice.

The extensive studies reported in the above chapters are expected to enhance our understanding of the various neuroinflammatory mediators involved in the pathophysiology of PD. These studies also substantiate the neuroprotective role of anti-inflammatory drugs and nutritional supplements in halting the progression of secondary mediators in PD.