SUMMARY AND CONCLUSIONS

Neuroinflammation, oxidative stress and mitochondrial dysfunction are the key factors responsible for the degeneration of dopaminergic neurons in the nigro-striatal pathway resulting in the development of PD. Various epidemiological and experimental studies have demonstrated the beneficial role of anti-inflammatory agents’ especially non-steroidal anti-inflammatory agents (NSAIDs) in the attenuation of the progression of PD. Experimental and post-mortem studies reveal the presence of activated microglia in the substantianigra of the Parkinsonian brain. During neuroinflammation, increased activation of microglia is there which further induces the expression of proinflammatory enzymes (COX and iNOS). It is well known that COX and LOX enzymes catalyze the biosynthesis of arachidonic acid derived lipid mediators involved in the inflammatory cascades. Since MPTP is a potent inhibitor of mitochondrial function, it further leads to the inhibition of electron transport chain and result in energy depletion. During mitochondrial inhibition, the production of ROS (such as superoxide anions) increases with the subsequent damage to the cellular proteins, leads to up regulation and transcription of proinflammatory markers such as NF-κB and induction of apoptotic proteins such as caspase-3. All these processes induce a cascade of events that ultimately lead to the neuronal cell death.

With this background, the present study was designed to elucidate the neuroinflammatory mechanisms involved in the pathogenesis of PD. Moreover, study also focused to understand the potential role of anti-inflammatory drugs in the therapeutic management of PD.

Chapter – 1:To elucidate the role of COX-inhibitors in drug-induced catatonia and MPTP-induced neurotoxicity in rodents

The present study explored the involvement of COX in the pathophysiology of PD. Further, the protective effect of COX-inhibitors against perphenazine-induced catatonia and 1-methyl-4-phenyl-1, 2, 3, 6-terahydropyridine (MPTP)-induced neurotoxicity in animals was evaluated. Administration of perphenazine produced severe catatonia (rigid behavior) in
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rats; the maximum score reached at 4 h (estimated as 100% AUC) and declined within 24 h. Systemic administration of MPTP produced hypolocomotion in mice. Both perphenazine and MPTP produced oxidative stress as demonstrated by increased levels of lipid peroxides, nitrite and decreased antioxidant defense system in the whole brain and striatal region, in particular. Pretreatment with various COX-inhibitors viz. rofecoxib, celecoxib, nimesulide or naproxen offered protection against perphenazine-induced catatonia, the effect was more pronounced with rofecoxib. Further, treatment with selective COX-2 inhibitors rofecoxib, valdecoxib and NS-398, reversed both the behavioral and biochemical changes induced by MPTP. The results suggest that COX isoenzyme particularly, COX-2 plays a crucial role in the pathophysiology of PD and selective inhibition of COX-2 may offer protection against drug-induced catatonia and MPTP-induced neurotoxicity possibly by modulating dopaminergic neurotransmission and/or oxidative stress.

Chapter 2 – To elucidate the role of COX and LOX enzymes in the pathophysiology of PD and its attenuation by LOX-inhibitor, dual COX/LOX-inhibitor and LT receptor antagonist

Neuroinflammation and oxidative stress play a critical role in the pathophysiology of neurodegenerative diseases including Parkinson’s disease (PD). Recent reports indicate the beneficial effect of anti-inflammatory drugs in attenuating the progression of PD. Therefore, the present study is aimed to evaluate the possible role of caffeic acid (a 5-LOX-inhibitor), licofelone (a dual COX/LOX-inhibitor) and montelukast (a LT receptor antagonist) against MPTP-induced neurotoxicity in mice. Administration of MPTP significantly induces behavioral and biochemical alteration in experimental animals. Treatment with caffeic acid, licofelone or montelukast significantly improved the MPTP induced abnormalities in mice. The findings of the present study suggest that COX and LOX plays a crucial role in the pathophysiology of PD. Either inhibition of LOX, dual inhibitor of COX/LOX or inhibiting the effects of leukotrienes on its receptors represents a new class of anti-inflammatory agent which may provide a novel therapeutic alternative for the treatment and management of PD.
Chapter 3 - To elucidate the role of peroxisome proliferator-activated receptor-γ (PPARγ) in attenuating neuroinflammatory cascade in experimental model PD

Neuroinflammation has been well suggested in the pathophysiology of neurodegenerative diseases including PD. However, role of PPARs in the neuroinflammatory cascades of neurodegenerative diseases is poorly understood. The present study was been designed to investigate the possible role of pioglitazone, a PPARγ agonist in experimental model of PD where MPTP was used to induce Parkinson-like symptoms in mice. Various behavioral observations (locomotor activity and catatonia), followed by biochemical (lipid peroxidation, glutathione, nitrite concentrations), mitochondrial enzymes (Complex-I, MTT assay), proinflammatory (NF-κB/p65) and apoptotic markers (caspase-3) were assessed in the striatum region of brain. Challenge with MPTP significantly impaired motor behavior, oxidative defense, mitochondrial function, increased expression of proinflammatory and apoptotic markers as compared vehicle group. Pioglitazone (10, 20 and 40 mg/kg, p.o.) treatment significantly improved motor behavior, decreased the oxidative damage, restored mitochondrial enzyme complex activity and attenuated proinflammatory and apoptotic biomarkers in MPTP challenged animals. Further, Bisphenol A diglycidyl ether (BADGE) (15 mg/kg, p.o.), a PPARγ antagonist significantly reversed the protective effect of pioglitazone. Present study provides evidence for the involvement of PPARγ in the neurodegeneration and highlights the importance of drugs modulating this pathway in the management of neurodegenerative disease.

Chapter 4 - To study the role of natural antioxidants and nutritional supplements against MPTP induced neurotoxicity

Various reports have established the role of mitochondrial dysfunction and resultant oxidative insult in experimental models of PD. Thus, there is a robust scientific rationale for testing suitable antioxidants and nutritional supplements for potential neuroprotective therapy in such disorders. With this background, the present study investigated the modulatory effect of tocotrienol (an isoform of Vitamin E) and lycopene (nutritional supplement and natural antioxidant)
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against MPTP-induced behavioral, biochemical and cellular alterations in mice. Pretreatment with tocotrienolor lycopene significantly attenuated the behavioral deficits, oxidative and cellular damage as well as molecular alterations in mice. Present study suggests a strong correlation between oxidative stress and up regulation of neuroinflammatory cascade in MPTP-induced PD like symptoms in mice. Study further demonstrates the effectiveness of natural antioxidants and nutritional supplements in the management of PD.

Though the role of neuroinflammation in PD is established in various experimental studies; very few studies have explored its role clinically. Based on the literature reports, it can be understood that, neuroinflammation is a key player in the development and pathogenesis of PD. Anti-inflammatory drugs especially COX-inhibitors or dual (COX/LOX)-inhibitors with more safety-to-risk ratio could be developed and tested in suitably designed experimental studies to explore their role in PD. Furthermore, clinical studies should be conducted to ascertain their better therapeutic potential and efficacy in PD as a single entity or in adjunct with the regular L-DOPA therapy. 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/ cholinergic pathway or by virtue of their antioxidant effects, has yet to be established.

Collectively, the current observations lead to the conclusion that in the pathogenesis of PD, neuroinflammation is a vital player and anti-inflammatory drugs could be useful as protective therapy in PD. However, proper clinical correlations are warranted before anti-inflammatory drugs are therapeutically used in PD.