CHAPTER 4
DISCUSSION

Our experimental data provided evidence for the significant inflammatory reaction in CNS after peripheral LPS administration. Furthermore, our results provided evidence for the anti-inflammatory and neuroprotective efficacies of COX inhibitors in LPS treated rats.

4.1 OPTIMIZATION OF LPS IN RAT DOSE

The present investigation demonstrated that peripheral administration of LPS (1, 3 and 10µg/kg) elicited profound effects on rat behavior activity such as body weight, rectal temperature, locomotion, anxiety and depression. Decrease in food intake and increased thermogenesis would leads to weight loss. Intraperitoneal administration of LPS caused a reduction in body weight dose dependently. This finding can be explained considering the rats sickness behavior. The higher dose of LPS would have decreased the energy levels in rats during the recovery period when compared to control rats, as well as animals exposed to a lesser dose of LPS. This effect is in part in agreement with previous reports showing that IL-1β and LPS treatment resulted in reduced food intake and increased loss of body weight (Bluthe et al 2000). Similarly at high dose, LPS induced weight loss at both 4hr and 24hr but not at LPS (1µg/kg) in rats (Bison et al 2009). An elevation in body temperature during fever is due to growth of pathogens and also stimulates the activation and proliferation of immune cells. LPS did not produce a reliable effect in body temperature it varied between time intervals; initially it
produced hypothermia followed by hyperthermia in later stage. In particular a hypothermic effect was observed at the earlier time point of 2 h for the 10μg/kg LPS dose; whereas the sole hyperthermic effect was displayed at 24 h after 10μg/kg LPS challenge (Bison et al 2009).

In the present study, LPS (10μg/kg) produced significant hyperthemic effect at 4hr after LPS treatment as compared to control rats but not exhibited hyperthermic effect at the low doses (LPS 1 and 3μg/kg). LPS produced either hypothermic or hyperthermic response depending on the timing and dose administered to the rats. Findings from our study have shown that LPS produced hyperthermic effect for aversion to water intake due to inhibitory effect of LPS on thirst. The inconsistencies between the results on LPS thermal response in our present experiments and many literature data could be explained by various factors involved: the serotype and/or doses of LPS. LPS also impaired the locomotor activity at all doses tested except 1 μg/kg. This finding compliment from previous work low doses of LPS (1 μg/kg) did not affect the locomotion after 24hr LPS treatment (Bison et al 2009).

Previous studies have shown that peripheral administration of LPS severely depresses locomotor activity in the rats (Yirmiya 1996). LPS treated rats have shown increased immobility period in the forced swim test (FST) and decreased line crossing and head dipping in the hole board test. Dunn & Swiergiel (2005) previously reported similar effect is the FST and open field after LPS administration (1-5 μg). The symptoms induced by LPS treatment resembles many clinical and animal studies generally called as sickness behavior. In the present investigation LPS doses (1, 3, 10μg/kg) are used to assess the sickness behavior in rats. LPS (10 μg/kg) have shown better sickness behavior effective to induce neuroinflammation among the other doses used in rats and this dose of LPS was finalized for our further study.
4.2 COMPARATIVE STUDY OF PRE AND POST TREATMENT OF ASPIRIN WITH LPS TO FINALIZE THE METHOD OF TREATMENT

Epidemiological evidence has identified a possible prophylactic action or at least an ameliorative effect of non steroidal anti inflammatory drugs (NSAID) use on the incidence and expression of neurodegenerative diseases like Alzheimer’s disease (AD) (Breitner 1996). AD is a progressive inflammation and degenerative disease of the brain that is characterized by deterioration of memory and higher cognitive function. It may be caused by genetic or bacterial / viral and environmental toxins. LPS is a non infectious component of gram negative cell walls and can potently stimulate immune system. Peripheral or central administration of this bacterial endotoxin characteristically leads to behavioral alterations such as reduced body weight, food and water intake, decreased exploration and anxiety (Gasparotto et al 2007). In our present study pretreatment of aspirin (100mg/kg) for seven days followed by single dose of LPS (10µg/kg) significantly increased the body weight and locomotion in the actophotometer, line crossing as well as head dipping in the hole board test and decreased the rectal temperature and immobility period in the forced swim test when compared to LPS treated rats. Post treatment of aspirin (100mg/kg) failed to reverse the LPS induced behavioral changes in rats. In many ways, the history of neuroinflammation in Parkinson’s disease (PD) appears to be taking a similar course to that in AD. The prior and/or concurrent administration of anti-inflammatory drugs, for example, results in significantly less severe DA depletion and PD symptomatology in rodents exposed to MPTP (Kurkowska-Jastrzebska et al 2004) or 6-OHDA (Sanchez-Pernaute et al 2004). Several studies proved pretreatment were effective to attenuate LPS induced behavioral changes in rats. In our present study pretreatment of aspirin (100mg/kg) was effective and based on literature reports pretreatment protocol was finalized for further studies.
4.3 EFFECT OF COX INHIBITORS ON LPS INDUCED BEHAVIORAL CHANGES IN RATS

The present study confirms the previous observation that, acute administration of LPS induces depressive behavior and reduction in exploratory behavior in rats (Teeling et al 2010). These behavioral changes are believed to be largely triggered by proinflammatory mediators or by COX-2 mediated prostaglandins production in immune cells. Indomethacin which can interfere with the COX pathway attenuated IL-1β induced behavioral alterations in rats (Plata-Salaman 1991). Ample evidence suggests that prostaglandin synthesis contributes to the development of depressive and exploratory behavior in rats as COX inhibitors abolish this response and LPS induced depressive behavior (de Paiva et al 2010).

Communication between the peripheral immune system and the brain is well known phenomenon. Despite numerous studies, the biological mechanisms underlying these behavioral changes are not known. To further study the mechanism underlying these observations, we pretreated anti-inflammatory drugs including, aspirin (non selective COX inhibitor), resveratrol (selective COX-1 inhibitor) and celecoxib (selective COX-2 inhibitor) for seven days followed by single dose of LPS (10µg/kg) and evaluated the behavioral assessments in rats. Our study showed that pretreatment with COX inhibitors attenuated the behavioral changes induced by LPS. Behavioral responses are associated with neuroimmune and neuroendocrine activation with non specific inflammatory processes in animals (Larson & Dunn 2001). Recent evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs) attenuated neuroimmune and neuroendocrine activation. Non-steroidal anti-inflammatory drug (NSAID) (indomethacin and nimesulide) have attenuated the behavioral changes induced by LPS (de Paiva et al 2010). Currently our study suggests that the
LPS induced behavioral alterations were better attenuated with nonselective and selective COX 2 inhibitor than selective COX 1 inhibitor. This conclusion is in consistent with the recent study, COX 2 was more important than COX 1 in various behavioral assessments following LPS administration (Johnson et al 2002). COX play a pivotal role in depressive pathology mediates many of the central effects of psychologically relevant stressors (Madrigal et al 2003; Malvar et al 2010) and that peripheral application of LPS serves as a model for major depression (Pitychoutis et al 2009). It has been reported that chronic treatment with celecoxib, a selective COX-2 inhibitor, reverses chronic unpredictable stress induced depressive like behavior by reducing COX-2 expression in the rat brain (Guo et al 2009).

Intraperitoneal administration of LPS (10µg/kg) produced loss of body weight significantly greater in saline treated rats than COX inhibitors treated rats. Previous reports showed that NSAID zaltoprofen attenuated decreased body weight and sickness behavior induced by concanavalin-A (an activator of T-cells and cytokines) in rats (Okamoto 2002).

Fever and thermogenesis in response to bacterial endotoxin involve elevation of prostaglandins and activation of macrophages. Prostaglandin E2, that is produced by the effect of exogenous (like lipopolysaccharide) and endogenous pyrogens (like IL-1, IL-6, TNF-α) on this center, elevates the thermoregulatory threshold value and causes fever (Murahovsch 2003; Thompson et al 2003) which was reversed by COX inhibitors. Zhang et al (2003) found a differential role for COX-1 and COX-2 enzymes in inducing fever and c-Fos expression, a marker for neuronal activity. In present study, LPS (10µg/kg) induced hyperthermic response attenuated by non selective (aspirin) and selective COX-2 inhibitor (celecoxib) is more effective than selective COX-1 inhibitor (resveratrol). COX-1-/- mice showed typical fevers during the first 2 hours after administration of low dose LPS, but COX-2-/-
mice developed hypothermia (Li et al 1999). Previous report supports our present study, pretreatment with selective COX-1 inhibitor (SC-560) did not reduce hyperthermic response induced by low dose of LPS, but a COX-2 inhibitor (nimesulide or meloxicam) attenuated the fever in guinea pigs (Steiner et al 2001; Roth et al 2002). Selective COX inhibitors and knockout mice shown febrile response and behavioral changes with administered and IL-1β mediate through COX-2 pathway (Blatteis 2007). In agreement with the involvement of COX-2 enzymes in fever the selective COX-2 inhibitors NS-398, DFU, rofecoxib, celecoxib or lumiracoxib inhibit the febrile response induced by LPS (Fabricio et al 2005). It is possible that COX-2 mediated production of the febrigenic mediator, possibly PGE₂ in this condition.

**4.4 EFFECT OF COX INHIBITORS ON LPS INDUCED COGNITIVE IMPAIRMENT IN RATS**

Many reports have demonstrated that LPS may produce cognitive alterations both learning and memory (Sparkman et al 2005). In the present study, LPS (10µg/kg) impaired emotional learning in the passive avoidance test, and spatial learning and memory in the elevated plus maze and Morris water maze when compared to control rats. Several research data suggest that COX inhibitors ameliorated memory impairment both in vivo and in vitro induced by LPS.

The passive avoidance test memory is amygdala dependent and measures emotional memory. It has been related to ‘long-term’ or reference memory. NMDA receptors are involved in the formation of post-training memory in the amygdala and hippocampus. The passive avoidance paradigm has been used to study learning and memory for a stressful stimulus. The procedure is based on the innate preference of rat model for the dark chamber of the instrument and the suppression of the innate preference following inescapable shock that is passive avoidance performance is an adaptive
response to a stressful experience that acts as a measure of learning and memory (Tsuji et al 2003). The elevated plus maze test is a spatial learning and memory test. The animal should remember the open and closed arm and should escape from unsafe open arm to safe closed arm more rapidly on the second trail. Shortened transfer latency on the second day trial is used as a parameter for retention or consolidation of memory while treatment with drugs prior to the first day affects task acquisition (Sharma & Kulkarni et al 1992). Morris water maze test evaluates spatial reference memory (Morris 1989) which is dependent on the hippocampus (Broadbent et al 2004) and long-term potentiation (LTP) of learning. In the Morris water maze task, two main components are to be considered, first the rodent to develop the necessary behavioral strategies to cope with the stressful, aversive situation, learning to swim and recognizing and reaching the platform is the only means of escape. These behavioral strategies require the animal to have spatial information about the surrounding cues and the location of the escape platform. The second component is the spatial learning component, the animal has to learn the position of the platform and create swimming strategies to move from one of the randomly chosen starting points toward the platform. The swimming efficiency during the probe trial is the best parameter with which to measure real spatial acuity.

Administration of non-selective (Choi et al 2010; Sunget al 2004; McKee et al 2008) and selective (Choi et al 2010; Choi et al 2013) COX inhibitors in various murine AD models resulted in significant reduction in neuroinflammation, as well as improved performance of cognitive function. Present study demonstrates that chronic administration of COX inhibitors reversed the LPS induced cognitive performance including passive avoidance test, elevated plus maze and Morris water maze in rats. Considering the fact that cognitive impairment was associated with increased level of prostaglandins due to LPS administration. Chronic treatment of COX
inhibitors resveratrol (COX 1 inhibitor), celecoxib (COX 2 inhibitor) and aspirin (non selective COX inhibitor) significantly attenuated the LPS induced cognitive impairment in these tests. Pretreatment with resveratrol significantly improved motor and cognitive impairment, and ameliorated oxidative stress damage (Kumar et al 2006). Previous report suggests that selective COX 2 inhibitor nimesulide improved memory and motor performance after trauma (Cernak et al 2001, 2002). Very little information about aspirin use in cognitive function in animal studies was available. Indeed, behavioral experiments have focused aspirin only in the control of pain mechanisms (e.g., LaBuda and Fuchs 2001), although its ability to target the arachidonic acid cascade has prompted further use (Yamaguchi et al 2001). Rogers et al (1993) conducted a short-term double-blind placebo-controlled clinical trial using the non-steroidal anti-inflammatory drug (NSAID) indomethacin, and reported reduced cognitive impairment in patients received NSAID after six months of treatment compared to controls. LPS induced impairment of active avoidance learning and interferon 6 induced increases PGE₂ release in rats suppressed by non selective COX inhibitor (Ma & Zhu et al 1997).

In the present study selective and non selective COX inhibitors protected LPS induced cognitive impairment; however marked effect was observed with nonselective COX inhibitor. A compliment finding from recent study supports our present results, the report suggest that possible involvement of arachidonic acid cascade in memory acquisition and retention. Further, bilateral intra-hippocampal injection of PGE₂, endotoxin or interleukin-1β, significantly impaired memory that resemble Alzheimer’s dementia, which was attenuated by pretreatment of nonselective COX inhibitors (Matsumoto et al 2004). Furthermore, selective inhibition of COX-2 but not COX-1 reduced postsynaptic membrane excitability and LTP induction in hippocampal dentate granule neurons. This reduction, as well as
the reduction in downstream signaling mechanisms (extracellular signaling-regulated kinase (ERK) phosphorylation and c-FOS expression) could be completely rescued by exogenous application of PGE₂ (Chen et al 2002; Cowley et al 2008). These findings indicate that endogenous basal levels of PGE₂ resulting from COX-2 but not COX-1 activity are critical for long-term hippocampal synaptic plasticity. The memory retention deficit that was induced by sub-chronic immobilization stress in the elevated plus maze was found to be reversed by treatment with either a non-selective COX inhibitor or a selective COX-2 inhibitor (Dhir et al 2006). The impairments in contextual fear conditioning and in working memory, which were induced by intrahippocampal IL-1β administration, were found to be blocked by co-administration of the non-specific COX inhibitors naproxen and diclofenac, respectively (Hein et al 2007; Matsumoto et al 2004).

4.5 EFFECT OF COX INHIBITORS ON LPS INDUCED OXIDATIVE DAMAGE IN RATS

LPS induces production of reactive oxygen species (ROS), peroxides and cytokines (Cadenas and Cadenas 2002) results in neuroinflammation. Free radical generation has been implicated as one of the important mechanism in neurodegenerative diseases such as AD and PD. LPS activates microglia and astrocytes in brain and releases inflammatory cytokines. Microglia releases inflammatory cytokines such as IL-1β and TNF-α and also produces oxygen and nitrogen centered free radicals that can play a pivotal role in neurodegenerative processes (Tanaka et al 2006). The biochemical alterations indicate significant increase in TBARS levels and marked decrease in the activity of reduced glutathione, superoxide dismutase and catalase levels in cerebral cortex, striatum and hippocampus regions of LPS treated rats when compared to saline treated rats (Yoshikawa et al 1994; Sewerynek et al 1995). COX inhibitors reduced the oxidative stress
Therefore, inhibition of COX isoforms could prevent the LPS induced oxidative stress. Further pretreatment of COX inhibitors (resveratrol, celecoxib and aspirin) significantly protected the LPS induced biochemical alterations suggesting the involvement of the COX pathway. The COX pathways are involved in ROS generation and responsible for neuronal cell death both \textit{in vivo} and \textit{in vitro} (Pepicelli et al 2002). Recent study has shown the protective role of COX inhibitor against 3-NP induced biochemical alterations in rats (Kumar et al 2006).

The present study suggests that LPS induced biochemical alterations in rats attenuated by non selective (aspirin) and selective COX 1 (resveratrol) inhibitors are better than selective COX 2 inhibitor (celecoxib). Previous reports support our present study COX 1 deficient mice had a decreased oxidative stress after injection of LPS (Choi et al 2008; Choi & Bosetti 2009).

\subsection*{4.6 EFFECT OF COX INHIBITORS ON LPS INDUCED INCREASED PROINFLAMMATORY CYTOKINES}

The administration of LPS can induce a large amount of proinflammatory mediator’s expression such as COX-1, COX-2, IL-6, iNOS, TNF-\(\alpha\) levels. Elevated expression levels of COX-2 and iNOS can play an important role in the process of inflammation and also correlate with many neuroinflammatory disorders (Choi et al 2003). Furthermore, peripheral infection can stimulate the release of cytokines in the brain which includes tumor necrosis factor-alpha (TNF-\(\alpha\)), interleukin-1beta (IL-1\(\beta\)) and interleukin-6 (IL-6). In addition, many research papers have suggested that the production of several proinflammatory cytokine is associated with the activation of transcriptional factor of nuclear factor kappa B (NF-\(\kappa\)B) by LPS and are involved in the pathological conditions in the brain (Munhoz et al 2006). These inflammatory cytokine may produce sickness behavior
syndrome and affect the normal brain function. Collectively suppressing the proinflammatory cytokine induced by LPS is an important approach to prevent neuroinflammatory diseases. The important mechanisms associated with the toxic effects of enhanced COX activity during neuroinflammation include production of PGE$_2$.

However, the present study demonstrated that chronic treatment with selective COX-1 and COX-2 inhibitor (resveratrol and celecoxib) and non-selective COX inhibitor (aspirin) significantly attenuated the LPS induced increased expressions of proinflammatory cytokines TNF-$\alpha$, IL-6, iNOS, COX-1 and COX-2 in rat brain. Many of the genes under study (TNF-$\alpha$, IL-6, iNOS, COX-1 and COX-2) are under the transcriptional control of the inflammation-related nuclear factor-kappa B (NF-$\kappa$B). Earlier studies showed COX 2 inhibition reduces proinflammatory COX 2 expression in the cortex and hippocampus after 72hr traumatic brain injury (Gopez et al 2005). Pretreatment with COX inhibitors attenuated NFkB dependent anti-inflammatory pathway stimulated through LPS. The present study suggests that LPS induced proinflammatory cytokines release was attenuated with non-selective COX inhibitor is better than selective COX 1 and COX 2 inhibitor.

To further explore the mechanisms underlying the inhibitory effect of COX inhibitors on the expression of elevated levels of proinflammatory cytokines, the phosphorylation of NFkB p65 was also analyzed by Western blot. Among the several transcriptional factors activated by viral and bacterial infections, NFkB is upregulated (Ghosh & Karin 2002). When cells unstimulated, NFkB are bound to I kB retained in the cytoplasm. LPS stimulated the cells, I kB are rapidly phosphorylated and degraded and the free NFkB is translocated to nucleus and it can induce the proinflammatory mediators release (Li & Verma 2002). Present study strongly suggests that non-selective COX inhibitor (aspirin) significantly decreased the expressions of NFkB than selective COX inhibitors induced by LPS. Similarly other study
indicates that aspirin did inhibit LPS and/or cytokines-induced NF-κB activation and iNOS mRNA expression at the therapeutic concentration, and consequently reduce NO production (Sanchez de Miguel et al 1999).

4.7 EFFECT OF COX INHIBITOR ON LPS INDUCED NEUROCHEMICAL ALTERATIONS

Patients affected with neurodegenerative diseases such as Alzheimer’s disease, had poor memory because of decreased neuronal transmission including glutaminergic, cholinergic, noradrenergic and serotonergic transmitter systems. (Francis et al 1999). Excitatory amino acid neurotransmitters (EAA) such as glutamate and asparate play an important physiological function in synaptic plasticity and memory but excessive release, or impaired reuptake of EAA's leads to neuronal damage and ultimate neuronal death. Inhibiting the central glutaminergic neurotransmission might provide a potential strategy for treating the neurodegenerative diseases. Long term potentiation (LTP) has been demonstrated as one of the important parameters for learning and memory (Brown et al 1999). LTP dependent on glutamatergic receptors (Bekkers & Stevens 1989) as well as GABA receptors. Administration of GABAergic antagonist resulted in facilitation of LTP induction (Mott & Lewis 1991). The involvement of GABA in the pathogenesis of depression is consistent with several clinical and preclinical findings. In depressed patients, GABA level was found to be decreased in plasma and in the cerebral cortex; GABA receptor changes also been reported. These findings have prompted scientists to formulate a GABAergic hypothesis of depression. Therefore, glutamate and GABA dependent activity occurs predominantly in the memory system of the temporal region (Eichenbaum & Cohen 2001). Glutamate and GABA have both been linked to associative activity and LTP (Bellinger et al 1993). LPS or IL1β administration leads to enhanced hypothalamic pituitary adrenal axis (HPA)
and modulation of long term potentiation (LTP) (Bellinger et al 1993; Murray & Lynch 1998).

In the current report, LPS (10μg/kg, ip) administration decreased GABA levels and increased glutamate and aspartate levels in the brain regions such as cortex, hippocampus and striatum and these neurochemicals were significantly attenuated in rats pretreated with COX inhibitors. These results are partially in accordance with previous report which showed that LPS stimulated the release of GABA from hypothalamic fragments (Feleder et al 1996). Mascarucci et al (1998) showed that LPS (10 µg/rat ip or iv) increased apparent glutamate release from the nucleus tractus solitaries (NTS). LPS is a potent stimulator of IL-1 production, therefore IL-1 is the mediator of the response to LPS. Studies have shown that peripheral activation of cytokines can lead to release of various central neurotransmitters. Specifically, IL-1 administration may promote release of norepinephrine, serotonin, dopamine, glutamate, and GABA in CNS. With enhanced turnover of these neurotransmitters, significant neurological and behavioral alterations transpire.

In the central nervous system COX 1 and COX 2 are enzymes constitutively expressed. COX 2 has been implicated in important physiological function such as synaptic transmission and neurotransmitter release. Ample evidence supports the action of COX products as mediators of some of the changes that are observed following either endotoxin or IL-1 administration (Revhaug et al 1988). The present study demonstrated that chronic treatment with selective COX-1 and COX-2 inhibitor (resveratrol and celecoxib) and non selective COX inhibitor (aspirin) significantly attenuated the LPS induced neurochemical alterations (GABA, glutamate and aspartate) in the brain regions such as cortex, striatum and hippocampus. Among the COX inhibitors non selective COX inhibitor (aspirin) is much effective than
selective COX 1 and COX 2 inhibitor (resveratrol and celecoxib). Previous report indicates that non selective COX inhibitor (indomethacin) pretreatment more or less completely blocked the IL-1 induced increase in neurotransmitters levels and corticosterone levels was slightly reduced (Wieczorek & Dunn 2006).

4.8 EFFECT OF COX INHIBITORS ON LPS INDUCED NEURONAL DAMAGE IN DIFFERENT BRAIN REGIONS

LPS induced neuronal damage in cortex, striatum and hippocampus attenuated by chronic treatment with COX inhibitors. LPS treatment resulted in increase of necrotic cells, chromatolysis and pyknotic nuclei in the cortex, striatum and hippocampus regions when compared to saline treated rats. If the initial stimulus that elicited microglia activation is not been controlled leads to chronic inflammatory response to elicit neuronal damage and death of neuronal population. Short-term systemic inflammation produced by administration of LPS can result in neuronal damage (Qin et al 2007) or exacerbates damage in an existing cerebral pathological state (Spencer et al 2007). Previous report suggested that neuronal damage was observed in the brain 24hr after LPS treatment measured with Fluoro Jade stain (FJB) (Schmued & Hopkins 2000). Many researchers have concluded that neuroinflammation contributes to neuronal damage in brain (Akiyama et al 2000), the use of anti inflammatory drugs as a possible treatment has been widely investigated in neurodegenerative conditions (in’t Veld et al 2001). Although there are many aspects to neuroinflammation and neuronal damage, the pathways involving the cyclooxygenases (COX) enzyme and subsequent generation of prostaglandins clearly play an important role. Thus, NSAIDs actions to inhibit COX-mediated production of apoptotic factors by neurons could be one of the mechanisms by which these drugs seem to exert beneficialeffects in neurodegenerative disease. In physiological condition
COX-1 is mainly expressed in microglia and majority of COX-2 appears to be made in neurons, COX-2 was also seen in rat astrocytes and microglia (Hirst et al 1999).

The Present study suggests that chronic treatment with selective and non selective COX inhibitors attenuated LPS induced neuronal damage in different brain regions including cortex, striatum and hippocampus. Previous study has shown neuroprotection with resveratrol against global cerebral ischemic model in gerbils, suggesting glial cell activation inhibition and decreased neuronal cell death (Wang et al 2002), which support our present study. Another report indicates that resveratrol reduces the frequency of seizures and improves pathological damage in the hippocampus CA1 and CA3 neurons after kainic acid-induced temporal lobe seizures (Wu et al 2009). Neuroprotective action of celecoxib has been observed in the LPS-induced nigrostriatal neurodegeneration (Hunter et al 2007) and 6-hydroxydopamine (6-OHDA)-induced progressive dopamine neuron degeneration in a rat model of Parkinson’s disease (Sanchez-Pernaute et al2004). COX-2 has been shown to be a key player in the evolution of neurodegenerative disease in animal model (Nakayama et al 1998). Increase in the expression of COX-2 but not COX-1, has been observed in the models of ischemic brain damage (Nogawa et al 1997; Iadecola et al 2001). In both invitro and invivo models COX-2 inhibitors play a potent role in neuroinflammatory diseases. Inhibition of COX2 enzyme protected neurons in mixed cultures against NMDA excitotoxicity (Hewett et al 2000). Significantly, COX-2 specific inhibition (NS398, 3–30 lM) blocked neuronal cell death, whereas COX-1 specific inhibition (valeryl salicylate, 10–100 lM) did not (Hewett et al 2000). From the present study it can be concluded that pretreatment with non selective COX (aspirin) and selective COX 2
(celecoxib) showed better efficacy than selective COX-1 inhibitor (resveratrol) on LPS induced neuronal damage in different brain regions.

The effect of COX inhibitors has preferential activity. Among the three drugs studied, non selective COX inhibitor was found to have a significant neuroprotective role than selective COX-2 though COX-2 inhibitors have been indicated as anti inflammatory drug. The resveratrol selective COX-1 found to be best in controlling oxidative stress. Hence, we can say COX inhibitor had differential effect in controlling neuroinflammation among the studied drug aspirin and was found to be a better medicine in controlling neuroinflammation induced by peripheral administration of LPS.