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Parkinson's Disease, the Inflammatory Pathway and Anti-Inflammatory Drugs: An Overview

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The exploration of the role of inflammation and its components and also the role of inflammation inhibition on neurodegenerative brain disorder Parkinson's disease (PD) were chosen as the base aim and interest of this review. PD is known to be a chronic/progressive neurodegenerative disease caused by a specific degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) region of the striatum. A large number of experimental evidence indicates that the factors involved in the pathogenesis of this disease are several, occurring inside and outside the dopaminergic neuron. Recently, the role of the inflammatory process, in particular, has been the object of research interest by the scientific community. This assumes to represent a new therapeutic approach opportunity for this neurological disorder. Indeed, it has been demonstrated that the cyclooxygenase type 2 (COX-2) is over expressed in SNc Dopaminergic neurons in both PD patients and PD animal models and, furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) and Steroidal anti-inflammatory drugs (SAIDs) pre-treatment protect against 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) or 6 hydroxydopamine (6-OHDA)-induced nigrostriatal dopamine degeneration. Moreover, recent epidemiological studies have revealed that the risk of developing PD is reduced in humans who make therapeutical use of NSAIDs or SAIDs. Consequently, it is hypothesized that the onset of the disease might be delayed or prevented by the rational prescription of SAIDs or NSAIDs.

Key words: NSAIDs, SAIDs, COX-2, neurodegenerative disease

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INTRODUCTION

Parkinson's disease (PD) is a chronic/progressive neurodegenerative disorder of largely unknown etiology. Its prevalence/incidence rates increase with age and more than 2% of the population aged over 65 years and ~5-20/100,000 individuals per year are affected by the disease (Marttila and Rinne, 1981; Zhang and Roman, 1993; Lang and Lozano, 1998; De Rijk *et al*., 2000; Hughes *et al*., 2001; Van Den Eeden *et al*., 2003; Twelves *et al*., 2003), with variations being due to environmental/genetic factors (Van Den Eeden *et al*., 2003; Von Campenhausen *et al*., 2005). The social and or financial burdens of PD are important and projected to rise in the future (Esposito *et al* 2007; Huse *et al*., 2005). Today, UK health economics study reported the annual cost of care per patient with PD to be £5993 (US$ 9554) (Findley *et al*., 2003; Hernán *et al*., 2004) and in the USA, the annual total cost for PD is estimated to be US$ 23 billion (Huse *et al*., 2005). The importance of social burden has been also reported in a French cohort (LePen *et al*., 1999). The diagnosis of PD is based on medical history and a neurological examination and can be difficult to be proven accurately (Tolosa and Wenning, 2006). The majority of PD motor manifestations (resting tremor, bradykinesia, rigidity) result principally from a striking loss of dopamine (DA) producing neurons in the Substantia Nigra (SN) (Calne and Langston, 1983; Fearnley and Lees, 1991; Masliah *et al*., 2000; Jankovic and Kapadia, 2001; Fahn, 2003), associated with the presence of intraneuronal Lewy bodies and Lewy neuritis (Forno, 1987, 1996; Hughes *et al*., 2001; Fahn and Sulzer, 2004). This neurodegeneration leads to a decrease in DA content in both SN and striatum, which has been ascertained by several neuroimaging studies. The reduction of ^{18} F-fluoro-L- Dopa and DA presynaptic transporter radioligand ^{18} F-CIT/ FCCIT in the striatum has been demonstrated using positronemission tomography (PET) and Single Photon Emission Computed Tomography (SPECT) scanning (Innis *et al*., 1999; Benamer *et al*., 2000; Staffen *et al*., 2000; Parkinson's Study Group, 2002; Forsback *et al*., 2004; Eidelberg *et al*., 1995; Hilker *et al*., 2005). In addition, much work has shown the substantial effect of PD on the person's quality of life (Kuopio *et al*., 2000; Schrag *et al*., 2000). PD is not curable at present. Medications currently available such asL-Dopa and DA agonists have shown a clearly efficient improvement of motor dysfunction symptoms during the early phase of the disease (Esposito *et al*., 2007; Watts, 1997; Weiner, 1999; Singh *et al*., 2007). However, as the disease progresses, symptoms respond less and less well toL-Dopa requiring higher doses that, in long term, are often associated with serious motor complications (motor fluctuations, dyskinesia, stooped posture, freezing, loss of postural reflexes) and extra-motor manifestations (sleep disorders, fatigue, depression, autonomic dysfunction, apathy and decline of cognitive functions) (Hurtig, 1997; Jankovic, 2005; Chaudhuri *et al*., 2006). Moreover, symptomatic treatments cannot alleviate the inevitable pathophysiological processes leading to progressive death of SN dopaminergic cells. Therefore, the development of drugs capable of slowing, arresting or reversing this selective dopaminergic neuronal death during the early phases of the disease is a major urgent pharmacological challenge. Increasing knowledge of the disease and of the biological processes underlying neuronal cell death as well as modified methods for demonstrating proof of humans effect (Akwa *et al*., 2005) has led to the concept of pharmacological neuro-protection (Baudry *et al*., 2005).

However, the sequential neuroapoptotic and specifics events in associated with premature/ progressive SNc neuronal atrophy remain undefined. Thus far, throughout the various accepted experimental models of PD, neurotoxins still represent the most popular tools to produce selective death of Dopaminergic neurons both in *in vitro* and *in vitro* systems. Even though recent genetic discoveries have lead to a number of different genetic models of PD, none of these shows the typical degeneration of Dopaminergic neurons (Fleming *et al*., 2005). Among the neurotoxins, 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP), a synthetic meperidine derivative and 6-hydroxydopamine (6-OHDA), hydroxylated dopamine derivatives are the most utilized for inducing parkinsonian features in cells and animal species (Esposito *et al*., 2007). MPTP is metabolized to the 1-methyl-4-phenylpyridinium ion (MPP^+) by monoamine oxidase-B (MAO-B). This highly toxic metabolite is selectively taken up into Dopaminergic neurons, via the dopamine (DA) transporter (Snyder and D'Amato, 1986), where it provokes an intracellular accumulation of Ca^{2+}, interfering with the function of nerve terminals in the striatum and inhibiting complex 1 (NADH-ubiquinone oxidoreductase) of the respiratory chain causing progressive cell death (Cleeter *et al*., 1992). On the other hand, the neurotoxic effects of 6-OHDA are mediated by the generation of hydroxyl radicals, pro-inflammatory mediators or pro-apoptotic agents. The results of the administration of each neurotoxin, albeit by different mechanisms, is DA depletion in the nigrostriatal pathway of laboratory animals and molecular alterations comparable to those seen in PD's patients. Recently, it has been shown that 6-OHDA and MPTP like the bacterial

lipopolysaccharide (LPS) induce the death of DA cells activating an immune response (Vijitruth *et al*., 2006). These animal models have been crucial in the study of PD and have allowed the formulation of different hypotheses about its etiopathogenesis and recently, they have been utilized to evaluate the role of DA- inflammation mediated neuronal death. Moreover, toxin-based models have been useful in developing neuroprotective and neurorestorative strategies and in examining new drugs for the treatment of this disorder (Esposito *et al*., 2007). The present review, experimental data regarding the role of neuroinflammation in the PD etiology, the effect anti-inflammatory agents such as NSAIDs or SAIDs and the possibility for their use as a new therapeutic approach for this neurodegenerative disease will be elaborately discussed.

Inflammation and parkinson's disease: Plenty of research on PD etiology has resulted in much information, but little has been also gained in establishing the events causing the initiation and progression of the disease. Up date, the involvements of neuroinflammation and microglial activation in the pathogenesis of PD have been emphasized.

Normally, very few microglial cells are detected in the vicinity of Dopaminergic neurons and when present, they appear to be resting with fine, long processes. Neuronal damage, aggregated proteins with abnormal conformations present in Lewy bodies and other unknown factors increase the number and change the shape of glial cells, to such an extent that they can be found in proximity to DA cells with short cellular processes (Zhang *et al*., 2005; Esposito *et al*., 2007). Activated microglia are recruited to the SNc from various structures and finally stuck to DA neurons. It has been shown that glial cells once activated become phagocytes that ingest degenerating DA neurons pieceby- piece. This occurs early in neuronal degeneration, starting at the extending fibres, such as the dendrite which extends into the SN reticulata. Hence, activated glial cells release detrimental compounds such as, interleukin (IL)-1β, IL6, tumor necrosis factor-α (TNF-α) and interferon γ (IFN- γ), which may act by stimulating inducible nitric oxide synthase (iNOS), or which may exert a more direct deleterious effect on Dopaminergic neurons by activating receptors that contain intracytoplasmic death domains involved in apoptosis. Microglia can also induce neuritic beading or synaptic stripping along dendrites leading to synaptic disconnection and loss of trophic support and cell death (Jiang *et al*., 2006). Given that glial cells are potent activators in lymphocyte invasion, animal studies using MPTP have clearly shown that the immune reaction might evolve, ultimately leading to the infiltration of lymphocytic CD^{4+} and CD^{8+} T cells into the injured SN and striatum. Moreover, activated lymphocytes have been shown in the SN of patients with PD and they could be responsible for the immune reaction-associated inflammatory process seen in the PD brain (Baba *et al*., 2005). Such activation of microglia is, nevertheless, not only disadvantageous to neurons. Indeed, some researches indicate that microglial cells activation and macrophages tend to synthesize and neurotrophic factors produce (brain-derived neurotrophic factor, BDNF and glia-derived neurotrophic factor, GDNF) through certain compensatory mechanisms following neuronal injury and induce sprouting surrounding the wound in the striatal DA terminals (Minghetti *et al*., 2005). Furthermore, activated glia play a role in gradually removing the dead DA neurons as a defence mechanism, although some healthy DA neurons might also be phagocytosed during the process (Cho *et al*., 2006). As a consequence, inflammation has been rightly defined as a double-edged sword. It normally starts as a defence reaction but, for the failure of its control mechanism, can lead to an uncontrolled and continuous extremely damaging immune response. Moreover, brief pathogenic insult can induce an ongoing inflammatory response and the toxic substances released by the glial cells may be involved in the propagation and perpetuation of neuronal degeneration (Esposito *et al*., 2007). This theory is plausible, corroborated by the evidence that several years after exposure to MPTP, increased levels of factors such as, TNF-α, IL-6 and IL-1β have been also found in the basal ganglia and Cerebral Spinal Fluid (CSF) of patients with toxin-induced PD. A prominent factor in neuroinflammatory reactions in PD seems to be the activation of the complement system (Bonifati and Kishore, 2007) a major mediator of immune/inflammation reactions. Indeed, increased mRNA levels of complement components have been found in affected brain regions (McGeer and McGeer, 2004). The complement components presence, including all constituents of the Membrane Attack Complex (MAC), has been shown intracellularly on Lewy bodies and on oligodendroglia in the SN of PD patients. Lewy bodies accumulation can apparently cause the activation of complement, the initiation of reactive changes in microglia and the release of potentially neurotoxic products such as the MAC, hydroxyl radicals and excess glutamate (GLU) (McGeer and McGeer, 1998). So far, among the plethora of toxic factors released by the reactive glia it is not clear which one of them is responsible for the Dopaminergic neuronal death? Reactive Oxygen Species (ROS), hydroxyl radicals, NO and its peroxinitrite ($ONOO^-$), are the likely candidates.

From this evidence it appears clear that the inflammatory process and oxidative stress derived from DA metabolism constitute a vicious cycle that lead to the final demise of nigral DA cells. Furthermore, experimental evidence has also shown that inflammatory loss of DA nigro-striatal neurons might be mediated by apoptosis (Ruano *et al*., 2006). Indeed, inflammation induced by intranigral injection of LPS could be mediated, at least in part, by the mitogen-activated protein kinase p38 (MAPK p38) signal pathway leading to activation of inducible nitric oxide synthase (iNOS) and cysteine protease caspase-11 (Ruano *et al*., 2006). Consistent with this evidence, it has been recently shown that LPS-induced inflammation causes apoptosis in the SNc due to increased proinflammatory cytokine levels of mRNA for TNF-α, IL-1α, IL1 β and IL-6 and the apoptosis-related genes Fas and Bax and caspase-3 immunoreactivity. These data have also been confirmed in a MPTP mouse model, neurotoxic effect seems to be mediated via activation of the caspase-11 cascade and inflammatory cascade, as well as the mitochondrial apoptotic cascade (Furuya *et al*., 2004). The relation between inflammation and apoptotic signalling cascade might follow other pathways. In fact, in a chronic MPTP model of PD, activation of the nuclear transcription factor NF-κB, which is well known for its role in preventing apoptotic cell death, has been elaborately revealed. NF-κB, among other effects, promotes the synthesis of cyclooxygenase types 2 (COX-2) (Dehmer *et al*., 2004). Cyclooxygenase (COX) is the first enzyme in the prostaglandin/ prostacyclin/thromboxane pathway. It converts arachidonic acid to prostaglandins and thromboxanes, which are collectively known as its metabolites. Three COX isoforms, COX- 1, COX-2 and COX-3 have been identified. COX-1 is the constitutive form of COX and performs a housekeeping function to synthesize prostaglandins, which are involved regulating normal cellular activities. In contrast, COX-2 is the inducible form of COX, as its expression can be induced by inflammatory stimuli or mutagens, tumor necrosis factor alpha (TNF-α) and the transcription factor CCAAT enhancer binding protein (c/EBP) beta. The brain possesses both COX-1 and COX-2 isoforms, also COX-2 up regulation during the stressful conditions such as cerebral ischemia and up regulated by neuronal apoptosis and neurobehavioral defect (McGeer and McGeer, 2004).

In addition, the steroidal anti-inflammatory drugs such as Dexamethasone can inhibit COX-2 gene expression; the glucocorticoids have widespread effects because they influence in the function of most cells in the body. Glucocorticoids dramatically reduce the manifestations of inflammation. This is because of their profound effects on the concentrations, distribution and function of peripheral leukocytes and to their suppressive effects on the inflammatory cytokines such as TNF-α or Interleukin-6 (IL-6) and chemokines on other glucolipid and/ or lipid elements of inflammation. In addition to their effects, glucocorticoids influence the inflammatory response by reducing the prostaglandin synthesis that results from activation of phospholipase A_2 (Katzung, 2004).

COX-2 appears to be expressed in dendrites and cell bodies of neurons in several areas of the brain such as nigrostriatal pathway, CA-1 hippocampus, amygdala nucleus. Among the COX isoenzymes just COX-2 corresponds to inflammatory and degenerative brain disease (McGeer *et al*., 2001).COX-2 induction/effect, in turn increases inflammatory response with the formation of different types of free radicals, a tyrosyl one and two different carbon- centred free radicals as well (Fig. 1), capable of causing phospholipid peroxidation (Jiang *et al*., 2004). The release of arachidonic acid (AA) also inhibits GLU uptake contributing to the neurodegenerative processes seen in PD (Dugan and Choi, 1999). COX-2 could also be induced by pro-inflammatory cytokines such as TNF-α via the c-Jun Nterminal kinase (JNK) pathway (Teismann *et al*., 2004; Esposito *et al*., 2007). Nonetheless, it is with underlining that the interactions between apoptotic neurons and microglia don't always have detrimental effects but they can lead microglia to acquire an anti-inflammatory phenotype. Indeed, recent studies from Minghetti's group have provided evidence that under chronic stimulation the interaction with apoptotic cells contributes to glial pro-inflammatory molecule expression progressive down-regulation and or a sustained release of immunoregulatory substances, such as PGE2 and TGF-β1, while promoting the synthesis of other products with potential immunoregulatory and protective activities (Minghetti *et al*., 2005).

COX-2, prostaglandins and parkinson's disease: The strong correlations found between COX-2 and PGE2levels, microglial activation and dopaminergic neurodegeneration suggest that COX-2 may mediate microglial activation and may play a key role in amplifying the inflammatory response and other toxic effects in a vicious circle, which ultimately exacerbates dopaminergic neuronal loss (Fig. 1) (Vijitruth *et al*., 2006). The detrimental effects have been also discussed above, however, within the brain, PGE2 production, depending on its level, has also been associated with protective effects on neurons and glial cells behaving as an anti-inflammatory molecule (Minghetti *et al*., 2005). Indeed, in spite of its classic role as a pro-inflammatory molecule,

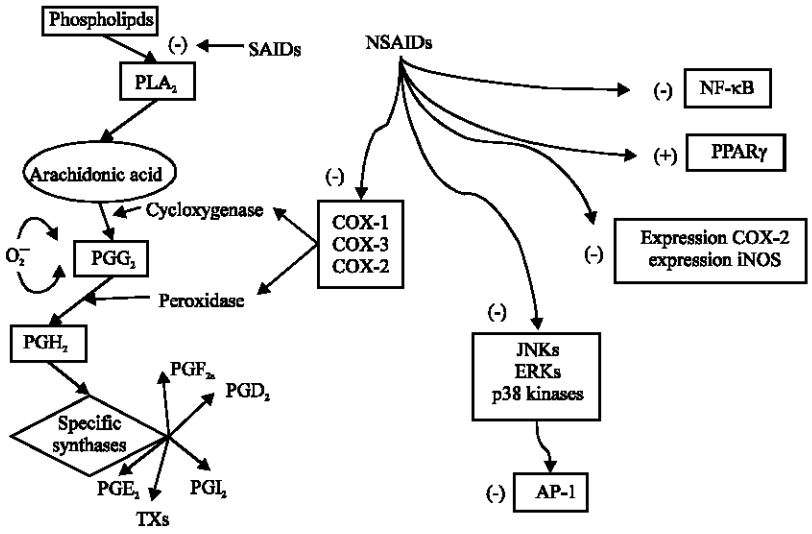

Fig. 1: Classical versus non-classical effects of NSAIDs and SAIDs. COX: Cyclooxygenase; PLA_2: phospholipase A_2; PGG_2: Prostaglandin G_2; PGH_2: Prostaglandin H_2: Prostaglandin F2alha, PGF2α: Prostaglandin D_2, PGD_2: Prostaglandin I2, PGI2: Prostaglandin E_2, PGE_2: Thromboxanes, TXs: Nuclear Factor kappa B, NF-κB: Peroxisome proliferator-activated receptor gamma, PPARγ: Inducible nitric oxide synthase, iNOS; c-Jun N-terminal kinases, JNKs: Extracellular signalregulated kinases, ERKs: P38 mitogen-activated protein kinases, p38 kinases; factor activator protein 1, AP-1. 298 Esposito *et al.* (2007)/Experimental Neurology 205 295-312 with some modification

several recent *in vitro* observations indicate that prostaglandin E2 can inhibit microglial activation. At lower (nanomolar) concentrations, PGE2 protects hippocampal and cortical neuronal cultures against excitotoxic injury or LPS-induced cytotoxicity (McCullough *et al*., 2004). The protective effect of EP2 receptor activity has been confirmed *in vitro*, in a model of transient forebrain ischemia, in which the genetic deletion of this PGE2receptor exacerbates the extent of neuronal damage (McCullough *et al*., 2004). PGE2 has also been shown to down-regulate microglial activation and expression of pro- inflammatory genes, including TNF-α, both *in vitro* and *in vivo*. Minghetti's group found that the interaction of microglial cells with apoptotic neurons promotes the synthesis of PGE2 along with neuroprotective and immunoregulatory molecules such as TGF-β and NGF (De Simone *et al*., 2004). Additionally, they have recently given further clear evidence for the anti-inflammatory PGE2 effect, showing that it is involved in the brain cholinergic anti-inflammatory pathway. In fact, glial α7 nicotinic receptor stimulation reduces the LPS-induced release of TNF-α and enhances the expression of COX-2 and the synthesis of PGE2 (De Simone *et al*., 2005). COX-2 activation, moreover, might result in direct Dopaminergic cell demise by producing the neurotoxic oxidant species DAquinone (Asanuma and Miyazaki, 2006) and by increasing DNA damage inducing the formation of Table 1.

Anti-inflammatory agents and PD affiliated disorders: It has been shown that acute and chronic use of NSAIDs or SAIDs can improve the PD affiliated disorders such as rigidity or locomotion activity impairment. These evidences were clearly and respectively investigated by M S Ardestani and his coworkers in the several studies. They showed that COX-2 selective inhibition can improve the rigidity or locomotion impairments of parkinsonian rats as well as the COX-2 gene expression inhibition. In contrast using NSAIDs or SAIDs have not shown any significant effects on the movement activities of normal rats (Ardestani *et al*., 2007, 2008a; Moghaddam *et al*., 2007).

The effects of subacute and chronic anti-inflammatory agents' prescription on MPTP/PD animal models or PD patients: The best treatment results (clinically/basically) while the anti-inflammatory agents used chronically and then after subchronically. For instance histological studies demonstrate a disability for the COX inhibition which had not found any improving effects on damaged SNc neurons. The same result for COX-2 gene expression inhibition has been also reported as well

Table 1: Biological, pharmacokinetic and chemical subdivision of NSAIDs Cox-2/Cox-1 ratio Inhibition kinetics Chemical structure Nonselective COX inhibitors (e.g., ketorolac or piroxicam, with ratio ˜1); simple, competitive (e.g., ibuprofen and Naproxen) Carboxylic acids (e.g., Aspirin and Ibuprofen) Selective COX-1 inhibitors (e.g., Dexketoprofene and SC 560 with ratio <0.01) competitive, time-dependent, reversible (e.g., Indomethacin and DuP 697) Pyrazoles (e.g., Phenilbutazone and Kebuzone) Preferential COX-2 inhibitors (e.g., ibuprofen and indomethacin, with ratio 15-60) competitive, time- dependent, irreversible (e.g., Aspirin and Valeryl salicylate) Oxicams (e.g., Piroxicam and Isoxicam) Selective COX-2 inhibitors (e.g., coxibs, selective COX-2, with ratio >1000) Sulphonamides (e.g., Valdecoxib and Celecoxib) Methylsulphones (e.g., Rofecoxib and Etoricoxib) Arylacetic acid (e.g., Lumiracoxib) 300 (Esposito *et al*., 2007) / Experimental Neurology 205 (2007) 295-312

COX2/COX1 ratio	Inhibition kinetics	Chemical structure
Non selective COX inhibitors	Simple, competitive	Carboxylic acid
Selective COX-1 inhibitors	Competitive, time-dependent, reversible	Pyrazoles
Preferential COX-2 inhibitors	Competitive, time-dependent, Irreversible	Oxicams
Selective COX-2 inhibitors	Mix of the above	Methylsulphones/Arylacetic acid

(Ardestani *et al*., 2008b; Shafiee *et al*., 2008; Shafiee and Fathi-Moghaddam, 2008; Moghaddam *et al*., 2008).

Anti-inflammatory agents and Brain neurotransmissions: Recently scientists investigated the effect of COX-2 or COX-2 gene expression inhibition on striatum neurotransmission as the region mainly affiliated to the PD signs.

By the administration of the selective COX-2 and COX-1 inhibitors to normal and parkinsonian rats, followed by the analysis of the striatal dopamine, GABA and glutamate concentrations using the microdialysis technique and the simultaneous catalepsy measurement, it has been observed that only selective COX-2 inhibition showed improving effects on the catalepsy resulting from a significant decrease the striatum glutamatergic-GABAergic and enhancing the dopaminergic neurotransmission. However, histological studies demonstrate a disability for the COX inhibition which had not found any improving effects on damaged SNc neurons. The same result for COX-2 gene expression inhibition has been also reported as well (Ardestani *et al*., 2008b; Shafiee *et al*., 2008; Shafiee and Fathi-Moghaddam, 2008; Moghaddam *et al*., 2008).

The effect of COX-2 inhibition on the brain neurotransmission needs to be further investigated, needs more experimental data because the diversity presents in the literature and it would be desirable as the novel area of research interest for the neuroscientists.

From the large amount of literature here reviewed it appears evident that inflammatory processes are involved in the pathophysiology of PD. Neuroinflammation, a processes orchestrated by activated resident microglia cells and sustained by them and other immune cells, might be contributing to the demise of nigral DA cells, perpetuating the neurodegenerative phenomenon. A large body of information on the molecular and cellular mechanisms whereby inflammation might induce neuronal death has been generated in the past few years by investigators in the neuroscience community. Nevertheless, further clarification of the role of inflammation in the pathophysiology of basal ganglia disorders is required, since the overall picture is still confusing. Complicating the situation is the fact that inflammation is a double-edged sword and probably begins as a beneficial defense mechanism that at some point evolves into a destructive and uncontrollable chronic reaction. Thus, the ideal approach would be to inhibit the deleterious effects associated with neuroinflammation while preserving the inflammatory pathways that lead to neuroprotection. From the above discussion it seems clear that drugs inhibiting inflammation and microglial activation might be an important feature of the treatment of PD and also the dementia, often associated with the disease (McGeer and McGeer, 2004; McCarty, 2006). Consequently, rational use of NSAIDs or SAIDs might be useful as a therapeutic intervention in PD and in other major neurological diseases with similar etiopathology, such as AD, ASL and MS. Despite the fact that experimental and epidemiological evidence has been provided for future use of antiinflammation agents, they have not been rigorously corroborated in trial studies for the treatment of motor disorders as yet and most of the data have yielded contradictory results. This may be a result of the peculiar characteristics of the drugs, so different both at the chemical and action level. In fact, NSAIDs might exert their neuroprotective actions not only inhibiting COX enzymes but also by acting on NF-κB, iNOS, PPARã, suppressing the formation of DA quinones, scavenging ROS and RNS activity and probably by other unknown mechanisms. Indeed, recently it has also been proposed that anti-inflammatory compounds might act inhibiting microglial proliferation, modulating the cell cycle progression and apoptosis (Elsisi *et al*., 2005). NSAIDs are sui generis and the further anti-inflammatory agents research progresses, the greater the number of indications that are discovered. NSAIDs have carved out a unique career in such diverse fields as the treatment of pain, migraine, prevention of cardiovascular disorders and the chemoprophylaxis of various types of cancer (Hernán *et al*., 2004). Probably, we are on the threshold of a new promising career for NSAIDs or SAIDs especially in prevention or treatment of neurodegenerative disease

rather than for their treatment. Indeed, it is quite possible that NSAIDs are ineffective once the pathological process has started, the pharmacological intervention should start very early in the pre-symptomatic period, based on some experimental epidemiologic document. Compounds inhibiting neuroinflammation such as NSAIDs or SAIDs represent an important starting point that could, for the first time, lead us to the identification of disease-modifying agents for this devastating disease. Overall, according to the mentioned documents anti-inflammatory compounds may be provided a new framework/benefit in treat/prevention the PD affiliated disorders.

SAIDs clinical prescription: SAIDs are clinically administrated in several neurological choices such as Acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury. However, the evidence for the clinical administration in PD is rare and seems to be under current investigation.

Interesting clinical reports by The Annals of Pharmacotherapy: Vol. 24, No. 7, pp. 707-708 and Neurosci Behav Physiol. 2000 Nov; 30(6):717-21 or Neurol Neurochir Pol. 2001; 35 Suppl 3:65-8 demonstrates a good potency of patient PD sign recovery for SAIDs.

SAIDs or NSAIDs side effects: A very important fact here is necessarily to be explored is dedicating a review part to mention NSAIDs or SAIDs adverse effects. NSAIDs cause ulcers in some people. Some of those who have ulcers also have symptoms, which include bleeding. In some of those who have bleeding ulcers, the bleeding is sufficiently severe to result in hospital admission and may cause death. This is a fairly simplified version of events and many of the papers in this field have as many as 10 different classifications of upper gastrointestinal complaints from which to classify an event. Clearly, the important issue is the overall incidence of severe adverse events, including hospital admission and death, however much we might like information about the risk of any particular event happening to any particular patient. The variables are drug and dose, duration of exposure and patient characteristics. Most of the publications referenced in this focus have reams about the scale of the problem of NSAID-related GI problems. About the use of SAIDs it could be also stated that SAIDs are more showing side effects including bradycardia, cardiac arrest, cardiac arrhythmias, dermatological disorders, Fluid and electrolyte disturbances and Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients (Esposito *et al*., 2007; Ardestani *et al*., 2008b; Shafiee *et al*., 2008; Shafiee and Fathi-Moghaddam, 2008; Moghaddam *et al*., 2008).

The above occurrence is very rarely low and body dependent and usually is happening in chronic high dose prescription. Overall, the caution is urgently required.

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