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REVIEW

Neuroinflammatory responses in Parkinson's disease: relevance of Ibuprofen in therapeutics

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Abstract

Parkinson's disease (PD) pathogenesis inevitably involves neuroinflammatory responses attained through contribution of both neuron and glial cells. Investigation done in both experimental models of PD and in samples of PD patients suggested the involvement of both central and peripheral inflammatory responses during PD pathogenesis. Such neuroinflammatory responses could be regulated by neuron-glia interaction which is one of the recently focused areas in the field of disease diagnosis, pathogenesis and therapeutics. Such aggravated neuroinflammatory responses during PD are very well associated with augmented levels of cyclooxygenase (COX). An increased expression of cyclooxygenase (COX) with a concomitant increase in the prostaglandin E2 (PGE2) levels has been observed during PD pathology. Ibuprofen is one of the non-steroidal anti-inflammatory drugs (NSAID) and clinically being used for PD patients. This review focuses on the neuroinflammatory responses during PD pathology as well as the effect of ibuprofen on various disease related signaling factors and mechanisms involving nitrosative stress, neurotransmission, neuronal communication and peroxisome proliferator-activated receptor-γ. Such mechanistic effect of ibuprofen has been mostly reported in experimental models of PD and clinical investigations are still required. Since oxidative neuronal death is one of the major neurodegenerative mechanisms in PD, the antioxidant capacity of ibuprofen along with its antidepressant effects have also been discussed. This review will direct the readers towards fulfilling the existing gaps in the mechanistic aspect of ibuprofen and enhance its clinical relevance in PD therapeutics and probably in other age-related neurodegenerative diseases.

Keywords Parkinsons · Disease · Non-steroidal anti-inflammatory drug · COX · Neuroprotection

Introduction

Parkinson's disease (PD) is a chronic neurological disorder, phenotypically, biochemically and anatomically identified through motor dysfunction, dopamine depletion and progressive loss of dopaminergic terminals and neurons in the striatum and substantia nigra, respectively (Srivastava et al. 2012; Yadav et al. 2012; Singh et al. 2012). The cardinal symptoms of PD are resting tremor, bradykinesia, rigidity and postural instability (Singh et al. 2012; Dixit et al. 2013). In PD patients of advanced disease stage the aggregates of fibrillar α-synuclein are found to be deposited at multiple brain regions (Stefanis 2012; Giráldez-Pérez et al. 2014; Recasens and Dehay 2014; Longhena et al. 2017). Studies have suggested the various etiologies of disease but whereby it starts and progresses are yet difficult to understand (Srivastava et al. 2012; Carvalho et al. 2015). Factors such as aging, genetic factors, environmental toxins, neuronal metabolic disturbances and inflammation are considered to be major contributors in PD pathogenesis (Dias et al. 2013). However, the studies indicated that the persistent inflammatory responses along with activated microglia are the plebeian features of PD pathology as observed in both experimental models and PD patients (Esposito et al. 2007; Glass et al. 2010). Such aggravated inflammatory response significantly bestowed in propagation of disease related adverse signaling mechanisms which could be regulated by utilization of anti-inflammatory agent. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) which has a significant anti-inflammatory effect exerted through the inhibition of

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cyclooxygenase (COX), a precursor for the prostaglandin synthesis (Esposito et al. 2007; Ajmone-Cat et al. 2010). Elevated levels of COX and prostaglandins have been found to be involved in neurodegenerative disease pathogenesis including PD (Bartels and Leenders 2010; Corwin et al. 2018). COX level in the brain is very well associated with the pro-inflammatory activities which could be instrumental in the neurodegenerative signaling and drugs affecting such consociation of signaling mechanism may be relevant in therapeutics. Ibuprofen has antiinflammtory effects and is considered as the safest conventional NSAID that could be safe for chronic utilization during PD pathogenesis (Bushra and Aslam 2010). In this review we will discuss about the neuroinflammatory responses and microglial activation during PD pathogenesis, preclinical findings in support of utilization of ibuprofen in PD therapeutics and reported mechanistic interference of ibuprofen in PD-related neurodegenerative signaling mechanisms.

Neuroinflammation and Parkinsonism

Inflammation is the first line of defense in the body against any foreign invaders or injuries however, the excessive inflammatory responses could be harmful and initiate deleterious signaling (Kim and Joh 2006). Since neurons are post-mitotic these could not have the ability to recover from any injury and are susceptible to adverse signaling or auto destructive immune responses (Colafrancesco and Villoslada 2011). Abundant information has been reported regarding the etiology of PD but it is not clear how the disease initiates and how it progresses (Ardestani 2010). Research of the last decades has grabbed attention towards evaluation of role of glial cells in disease pathology as both experimental models and studies in patient's have suggested the activation of glial cells which is closely associated with inflammatory responses and neuron-glia crosstalk may play significant role in this mechanism (McGeer and McGeer 2004; Esposito et al. 2007; Tansey and Goldberg 2010; Perry 2012; More et al. 2013; Yan et al. 2014; Bruck et al. 2016; Wang et al. 2015; Booth et al. 2017). PD could not solely characterized by the neuroinflammation as it shares various other pathological mechanisms which are also detected in other neurodegenerative diseases. Neuroinflammatory responses during disease could play primary role in exacerbating the disease mechanisms and further investigations are required to understand their colligated mechanisms (Minghetti 2004; Chen et al. 2016). Studies in postmortem brain of PD patients revealed that substantia nigra region is enriched in microglia therefore more prone for the microglia mediated inflammatory reactions (McGeeret al. 2001; Hartmann 2004; Tufekci et al. 2011). Disease related microglia activation follow the release of interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α) and interferon- γ (IFN-γ) that may ultimately result in the death of neurons through activation of inducible nitric oxide (iNOS) or the apoptotic receptor and signaling (Saha and Pahan 2006; Förstermann and Sessa 2012; Peferoen et al. 2014). Interestingly some other factors like high content of iron and low content of glutathione in the dopaminergic neurons makes the substantia nigra more prone for inflammation related injury (Dias et al. 2013). These inflammatory responses involve the increased selective activity of COX-2 thus increased level of PGE2 and this augmented level could be further aggravated during neuronal apoptosis and microglial activation and worsen the conditions (Minghetti 2004; Bartels and Leenders 2010).

Microglial activation and Parkinson's Disease

Microglia cells are the phagocytic cells of the brain, act as immune sentinel and capable in instrumentation of various neuroinflammatory reactions during disease pathology (Farooqui et al. 2007; Graeber et al. 2011; Perry and Teeling 2013). Activated microglia are considered as hallmark of disease as well as neuroinflammation which act as scavenger and engulf the cellular debris of the brain (Fu et al. 2014; Sochocka et al. 2017). It has been reported that microglia are the major source of prostaglandins (PGs) which synthesized through membrane phospholipids mediated release of arachidonic acid (AA) (Ajmone-Cat et al. 2010; Ricciotti and FitzGerald 2011). Studies in postmortem brain of PD patients and in experimental models of PD have suggested the inescapable role of microglia during disease and suggested that these activated microglia play pathological role in disease pathogenesis however this still unexplored whether these activated microglia are the cause or consequence of the degenerating dopaminergic neurons (Su et al. 2008; Theodore et al. 2008; Griffiths et al. 2010; Chao et al. 2014). It has also been reported that with age the microglia numbers increased in substantia nigra which may be contributory in disease pathogenesis but require further investigations (Croisier et al. 2005; Bartels and Leenders 2010). It has also been reported that microglial cells induced chronic inflammatory responses play significantly in the death of dopaminergic neurons (Lull and Block 2010; Singh et al 2011). Under physiological conditions the microglial response remains tightly regulated however PD pathology involves their unregulated responses and consequent neurodegeneration involving chronic neuroinflammation as one of the culprit responsible for the progressive loss of dopaminergic neurons (Tansey and Goldberg 2010). The experimental data from PD patients also showed the increased level of pro-inflammatory cytokines, eicosanoids and oxidative stress in the brain and peripheral system which evidently support the pathological role of activated microglia in PD patients (Quian et al. 2010; Wang et al. 2015). Positron emission tomography in drug-naive PD patients utilizing

radiotracer [(11)C](R)-PK11195, for activated microglia showed its significantly higher level in comparison to control subjects reflecting close association of activated microglia during disease onset (Ouchi et al. 2005). Since early diagnosis of PD in patients is not very well established and human brain tissue cannot be utilized for estimations, therefore the investigations have been done in brain tissue of experimental rodent models. It has been observed that various neurotoxin like lipopolysaccharide (LPS), aggregated or nitrated form of α-synuclein could directly induce the microgliosis (Glass et al. 2010). Several other neurotoxins like 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA) and rotenone may directly induce the neurotoxicity with the assistance of microglial activation. In comparison to glial cells the neurons have weaker antioxidant capacity, as these are dependent on glial cells for GSH replenishment, therefore more susceptible for injury and degeneration during microglial induced inflammatory responses (Dringen et al. 1999; Bove et al. 2005; Bozyczko-Coyne 2007; Hernandez-Baltazar et al. 2017).

Ibuprofen: mechanistic aspects

Ibuprofen, a first derivative of propionic acid, is one of the most popular commonly used safest conventional NSAID (Bushra and Aslam 2010). Chemically, ibuprofen is a diastereoisomeric chiral drug with equal ratio of R (+) ibuprofen and S (+) ibuprofen. Pharmacokinetic studies have shown the presence of enantiomers of ibuprofen in plasma as determined by direct stereo selective high performance liquid chromatography (Menzel-Soglowek et al. 1990). Majority of pharmacologically active form of drug is contributed by its S-enantiomer as it prohibits the prostaglandin synthesis (Jamali and Brocks 2015). In the early to mid-1970s (R) -ibuprofen was first reported for unidirectional enzymatic conversion of inactive R enantiomer to the active S enantiomer. This is so because approximately 40–60% metabolism of R (−) enantiomer takes place into the S (+) form in liver (Rainsford 2012). Its anti-inflammatory effect is due to its inhibitory activity on cyclooxygenases (COX) that are responsible for the prostaglandins synthesis and play an important role in exacerbation of inflammatory responses mediated neuronal death (Simmons et al. 2004; Bartels and Leenders 2010; Teismann 2012). Ibuprofen also inhibits COX, reduces the nitric oxide (NO) production and activates the peroxisome proliferator-activated receptor-γ (PPAR-γ) (Esplugues 2002; Asanuma and Miyazaki 2007; Chaturvedi and Beal, 2008; Tsuji et al. 2009). As we and others have reviewed earlier that NO critically involve in the neuronal damage during PD pathology (Tuteja et al. 2004; Calabrese et al. 2007; Knott and Bossy-Wetzel 2009) thus the ibuprofen mediated inhibition of disease related augmented level of NO could offer neuroprotective responses. PPAR is a signaling receptor that takes part in the inhibition of the apoptotic pathway and thus plays an important role in providing protection against PD (Wu 2010; Wnuk and Kajta 2017). Several experimental and epidemiological studies have shown the neuroprotective effects of ibuprofen (Asanuma and Miyazaki 2007; Gao et al. 2011). Inflammation is an inescapable event in the PD pathogenesis therefore it is worth to review the mechanistic aspect of ibuprofen and its clinical utilization. Various pre-clinical studies have been performed in experimental animal models which have shown the protective effects of ibuprofen on dopaminergic cell loss (Casper et al. 2000; Hsieh et al. 2011; Singh et al. 2016; Tripathi et al. 2018). In the following sections the therapeutic application of ibuprofen has been discussed.

Effect of Ibuprofen on various PD models

Age related physiological and morphological alterations are contributory factors in most of the neurodegenerative diseases involving PD. Such alterations include the neuroinflammatory responses among which most are glial cell mediated as reviewed previously (Singh et al. 2011; Asanuma and Miyazaki 2007; Radtke et al. 2017; Heneka 2019) (Table 1). To evaluate the dopaminergic neuronal death related neuroinflammatory responses the LPS induced experimental models is being frequently utilized by researchers and readers may refer the article by Jeong et al. (2010). Studies have also been conducted with other neurotoxins like, MPTP, 1-methyl-4-phenylpyridinium (MPP^+) and 6-hydroxydopamine (6-OHDA) (Zawada et al. 2011). The data obtained from the studies on neurotoxins induced experimental models showed the increased density of microglial activation demonstrating the critical role of microgliosis during disease pathogenesis (Bove et al. 2005; Bozyczko-Coyne 2007; Glass et al. 2010; Hernandez-Baltazar et al. 2017). Along with microgliosis the experimental models also showed the significant depletion of PD related pathological markers like decreased TH immunoreactivity along with augmented level of COX-2 (Singh et al. 2016; Tripathi et al. 2018). Since the reports have suggested that microglia remain higher in population in substantia nigra thus dopaminergic neurons of this region are more susceptible for neuroinflammatory responses related neuronal death (Esposito et al. 2007; Bartels and Leenders 2010). With such observations the utilization of NSAID has been suggested in PD therapeutics specifically on ibuprofen (Gao et al. 2011; Casper et al. 2000). The neuroprotective efficacy of NSAIDs depends on their dose regime and duration and also on the stage of disease (Chen et al. 2003, 2005; Esposito et al. 2007). Epidemiological studies have also supported the role of ibuprofen as an anti-PD as it reduces the disease related augmented activity of COX (Chen et al. 2003, 2005; Gao et al. 2011). Studies in experimental in vitro and rodent models have suggested

Table 1 Ibuprofen as a neuroprotective agent in different PD models

SN	Animal	Neurotoxic compound/regimen	Ibuprofen	Effect of Ibuprofen	References
1	Male Wistar rats	Cypermethrin 1.5 mg/kg, i.p. for 5–19 days pre- and 15 mg/kg, i.p. for 12 weeks postnatal	20 mg/kg, i.p. for 12 weeks	Restored the normal morphology such as number of spines and dendrites of dopaminergic neurons	Tripathi et al., 2018
2	Male Wistar rats	Cypermethrin 1.5 mg/kg, i.p. for 5–19 days pre- and 15 mg/kg, i.p. for 12 weeks postnatal	20 mg/kg, i.p. for 12 weeks	Reduced the process of inflammation by COX-2 inhibition and protected the dopaminergic neurons	
3	Male Wistar rats	Rotenone(2.5 mg/kg, i.p., for 10 days)	15 mg/kg, p.o., for 22 days	Restored the decreased level of rotenone-induced glutathione and improved the antioxidant status in the striatum. Catalase activity recovered by ibuprofen	Zaminelli et al., 2014
4	Male C57Bl mice	MPTP i.p. in four doses of 10 mg/kg each, at one hour intervals, to a total dose of 40 mg/kg	10, 30 or50 mg/kg for 7 consecutive days	Recovered the MPTPinduced injury in striatal neurons	
5	1-methyl-4-phenylpyridinium (MPP+)-induced toxicity in primary ventral mesencephalic (VM) neurons	1-methyl-4-phenylpyridinium (MPP+)-MPP+ (20 µM;	Ibuprofen (25 and 250 µM)	However, inhibition of Selective inhibition of COX-2 by COX-2 inhibitor (DFU) or ibuprofen significantly reduced MPP+-induced VM cell toxicity and VM dopaminergic cell apoptosis, and also decreased ROS production in VM dopaminergic neurons	Hsieh et al., 2011
6	C57Bl/6 female mice	Mn 100 mg/kg by a single subcutaneous (s.c.) injection	140 µg/ml continuously for 2 weeks	Aattenuated the Mn-induced increase in cerebral F2-IsoPs andprotected the medium spiny neurons from dendritic atrophy and dendritic spine loss	

the prophylactic effect of ibuprofen in PD pathology (Casper et al. 2000; Tsuji et al. 2009; Hsieh et al. 2011; Ramazani et al. 2019). In vitro studies have shown MPTP induced excitotoxicity in dopaminergic neurons could be prevented with ibuprofen (Hsieh et al. 2011). Data obtained from a meta-analysis carried on the regular ibuprofen users showed that these individuals have forty percent reduced risk of PD onset (Moore et al. 2010). Meta-analysis in patients also showed the therapeutic effect of ibuprofen and must be explored further in clinics (Gagne and Power 2010) .

Effect of ibuprofen on synapses

Activated microglial cells are responsible for the release of various pro-inflammatory cytokines, chemokines, reactive oxygen species (ROS), reactive nitrogen species (RNS) and excitatory amino acids at synapses and cell bodies during disease pathogenesis and contribute to the neurodegeneration (Mosley et al. 2006; Wilkinson and Landreth 2006; Uttara et al. 2009). The dopaminergic terminals are responsible for the unloading of dopamine in the striatum. It has been reported that MPTP induced parkinsonian model exhibit the COX dependent microglial activation (Członkowska et al. 2002). Microglial cells could also cause neuritic beading or synaptic stripping along dendrites which lead to synaptic disconnection and consequent loss of neurotrophic factors support and affect the neuronal communication (Vijitruth et al. 2006; Takeuchi et al. 2005; Schiefer et al. 1999; Volpe et al. 1998; Isacson et al. 1985). In LPS exposed microglia it has been observed that COX-2 inhibition reduces the level of NO suggesting that microglia mediate the secondary injury through various inflammatory factors and also suggested the positive modulatory effect of exogenous COX-2 inhibitor on activated microglial related neuronal toxicity (Minghetti et al. 1997). Due to high iron in dopaminergic neurons of substantia nigra these are highly susceptible for oxidative and inflammatory injury and COX-2 mediated enzymatic reactions contributes to dopaminergic neuronal death by oxidizing dopamine to a reactive quinine or through direct oxidation of DNA (Nikolic and van Breemen. 2001; Hastings 1995). The COX-2 also responsible for the prostaglandin synthesis which remain actively present in dendritic spines, responsible for the amplification of synaptic signaling (Kaufmann et al. 1996). Since ibuprofen is a proved COX-2 inhibitor it could prevent the discussed COX-2 mediated effects and might prevent the neuronal degeneration though detailed investigations are required. It has also been reported that anti-inflammatory agent like ibuprofen could prevent the microglia proliferation through modulation of cell cycle progression and apoptosis (Elsisi et al. 2005). Ibuprofen also offer the protection against terminal degeneration of dopaminergic neurons by inhibition of COX-2 activity (Sanchez-Pernaute et al. 2004). Though various studies are available indicating the neuroprotective role of ibuprofen in neuroprotection in context to functional factors in synapses however the detailed investigation is still lacking and need further investigations.

Effect of ibuprofen against NO production

PD pathology is very well correlated with increased level of iNOS as reported by us and others previously. Increased level of NO is reported to enhance the production of proinflammatory prostaglandins by increasing the COX activity without the involvement of cGMP (Salvemini et al. 1993). Since ibuprofen is able to inhibit the iNOS expression thus regulate the level of NO during pathological conditions and offer the neuroprotective effects (Aeberhard et al. 1995; Stratman et al. 1997; Asanuma and Miyazaki 2007). Such increased activity of iNOS and COX-2 involve the activation of nuclear factor-kB (NF-kB) which also reported to be involve during PD pathogenesis and contribute in production of inflammatory cytokines (Lee et al. 2009). Rock et al. 2004; Lawrence 2009). It has been reported that LPS exposed microglial cells exhibit the increased NF-kB activity which in turn activates the production of the inducible form of COX and facilitate the neuronal death (Choi et al. 2009). Both iNOS and neuronal NOS are expressed in the microglial cells and neurons and are responsible for the production of NO (Kraft and Harry 2011; Contestabile et al. 2012). Inflammatory stimuli or oxidative environment to microglial cells and neurons showed elevated levels of NF-kB which facilitate the production of inflammatory cytokines (IL-1b, IL-6, IFN-γ), COX-2, iNOS, TNF-α and apoptosis-promoting factors (p53, Bax) (Kim and Joh 2006). These activated inflammatory mediators further enhance the production of NO and worsen the diseased condition (Ajmone-Cat et al. 2010). In an in vitro NO- generating system the NO quenching activity of ibuprofen was estimated and it had been observed that it could prevent the dopaminergic neuronal death directly in dose dependent manner through scavenging of NO (Asanuma and Miyazaki 2007). The free radical scavenging capacity of ibuprofen has been reported in various models (Van Antwerpen and Nève 2004).

Effects of ibuprofen on peroxisome proliferator-activated receptor-γ

Peroxisome proliferator-activated receptors (PPAR) are also known as the nuclear hormone receptors present in the fat tissue, spleen and brain (Chaturvedi and Beal 2008). These are the ligand inducible transcription factors regulate essentially required genes of various metabolic processes and cell differentiation along with their anti-inflammatory effects during neurodegeneration (Desvergne and Wahli 1999; Straus and Glass 2001; Kapadia et al. 2008; Yonutas

and Sullivan 2013). PPAR are also related to the development of tissue differentiation, inflammation, mitochondrial function, wound healing, lipid metabolism and glucose metabolism regulation (Chaturvedi and Beal 2008). It has been reported that PPAR agonists exhibited the neuroprotective effects by inhibiting oxidative stress, inflammation and apoptosis (Bordet et al. 2006; Heneka and Landreth 2007). A study on various NSAIDs on various cell systems has demonstrated that the pharmacological effects of NSAIDs may be related to both their profile of inhibition of prostaglandin endoperoxide H synthase enzymes and the activation of PPAR α and / or γ isoforms (Jaradat et al. 2001). It has also been reported that like pioglitazone (PPAR γ agonist), ibuprofen is also capable to reduce the neurodegeneration related glial inflammation and gliosis thus offer protective effects against neuroinflammatory responses (Heneka et al. 2005). It has also been reported that ibuprofen has PPAR-γ agonistic property which offered neuroprotection during methamphitamine induced neurotoxicity (Tsuji et al. 2009). PPAR γ mediated inhibitory effect of ibuprofen has also been suggested on migration and proliferation of cardiac smooth muscle cells (Dannoura et al. 2014). The ibuprofen activated PPAR-γ regulates the transcriptional activity of transcription factors including signal transducer and activator of transcription (STAT), NF-κB, activating transcription factor-1 (ATF-1/4), reduces the iNOS and COX-2 levels and may contribute in neuroprotective activities (Chaturvedi and Beal. 2008). Ibuprofen activates PPAR-γ receptor through its receptor specific binding ability and could offer neuroprotective activity. Reports have suggested that ibuprofen significantly rescued the dopaminergic neurons from the toxic effects of glutamate, 6-OHDA and MPP^+ in mesencephalic cultures involving role of transcription factors and inflammatory responses (Casper et al. 2000; Tsuji et al. 2009; Hsieh et al. 2011; Chaturvedi and Beal 2008). In view of above evidences the studies are required to evaluate how ibuprofen interact with PPAR γ and establish the therapeutic dose regime of it in clinics.

Ibuprofen as an antidepressant and antioxidant

The possible mechanisms involved in PD pathogenesis are mitochondrial dysfunction, oxidative stress and neuroinflammation. Mitochondrial dysfunction is responsible for the excessive ROS generation that in turn causes oxidative stress and energy crisis and direct the vulnerable neurons towards apoptosis. The free radicals that are generated could cause lipid peroxidation in the cell. A study in rotenone exposed rats showed that ibuprofen exhibited the antioxidant properties in addition to COX inhibition (Zaminelli et al. 2014). Some other in vivo and in vitro studies conducted in various neurotoxin induced experimental models have shown similar results. Use of ibuprofen has shown potential neuroprotective effects in such studies by means of restoring the antioxidant potential (Hsieh et al. 2011; Zaminelli et al. 2014; Naeem et al. 2017; Mandal et al. 2018). Few medical reports have suggested that ibuprofen showed antidepressant effect however, further detailed investigations are required to utilize this in clinics with the said aspect.

Conclusion

It is apparent from the studies that PD pathogenesis is closely associated with the inflammatory processes mostly mediated through activated glial cells (Singh et al. 2016; Joshi and Singh 2018). Use of NSAIDs is recommended for Parkinson's pathology however the reported studies with meta-analysis implicate the diverse and controversial findings (Ren et al. 2018) suggesting further explorations. This review has focused on effects of ibuprofen on various disease related factors and mechanisms and suggested that use of ibuprofen may have entailment in diverse aspects of disease pathogenesis (Fig. 1). Since PD is multifactorial disease and involve various degenerative pathways along with neuroinflammation, the combination therapy may execute better therapeutic effects. In addition, the treatment regimen will also be for longer duration so optimal dose, timing, its beneficial/adverse effects must also be explored.

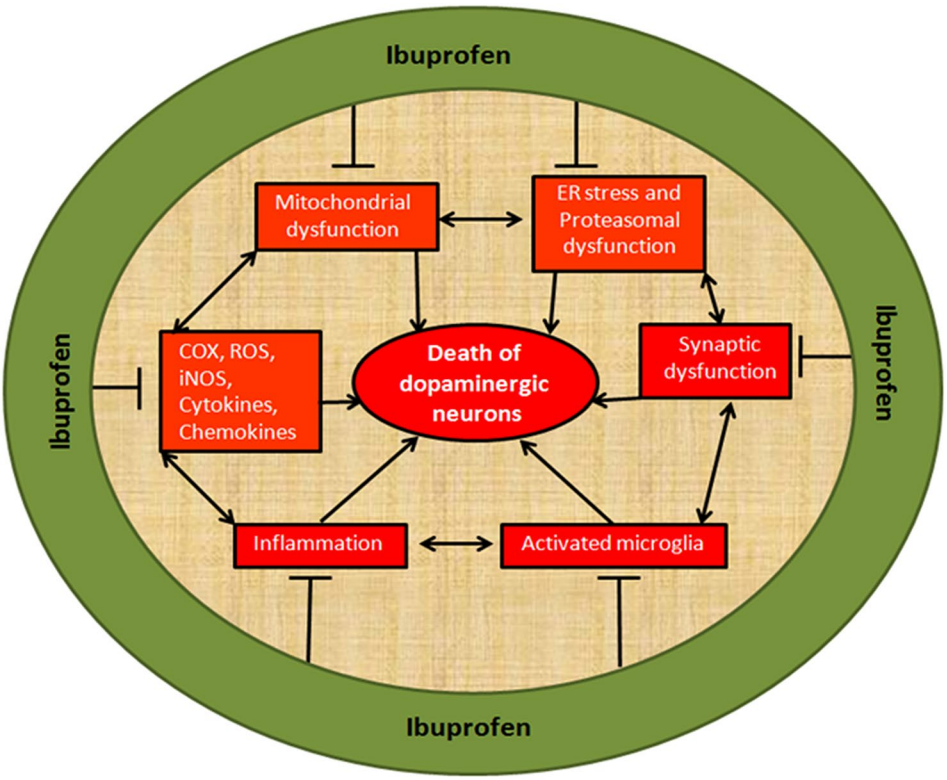

Fig. 1 Schematic representation for the mechanistic action of Ibuprofen during neurodegenerative conditions on the onset of Parkinson's disease

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