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Possible role of Epoxyeicosatrienoic acid in prevention of oxidative stress mediated neuroinflammation in Parkinson disorders

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ABSTRACT

Parkinson's disease (PD) is a multifactorial neurodegenerative disease involving oxidative stress, neuroinflammation and apoptosis. Epoxyeicosatrienoic acids (EETs) are arachidonic acid metabolites and they play a role in cytoprotection by modulating various cell signaling pathways. This cytoprotective role of EETs are well established in cerebral stroke, cardiac failure, and hypertension, and it is due to their ability to attenuate oxidative stress, endoplasmic reticulum stress, inflammation, caspase activation and apoptosis. The actions of EETs in brain closely parallel the effects which is observed in the peripheral tissues. Since many of these effects could potentially contribute to neuroprotection, EETs are, therefore, one of the potential therapeutic candidates in PD. Therefore, by increasing the half life of endogenous EETs *in vivo* via inhibition of sEH, its metabolizing enzyme can, therefore, constitutes an important therapeutic strategy in PD.

Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder with a characteristic symptoms such as bradykinesia, rigidity, resting tremor and posture instability [1–4]. It is a multifactorial disease involving age, genetic and environment factors. Aging is associated with mitochondrial dysfunction, increased free radical production and oxidative stress, which may lead to genomic instability and DNA mutations, with reduced survival [5–7]. For the past 15 years, genetic characterization of PD has shown sequence or copy number variants in at least six genes [(synuclein alpha (SNCA), leucine-rich repeat kinase 2 (LRRK2), E3 ubiquitin-protein ligase parkin (PARK2), PTEN induced putative kinase 1 (PINK1), PARK7 – protein deglycase DJ-1, ATPase Type 13A2 (ATP13A2)] which have been identified to cause monogenic forms of PD [7,8]. Environmental factors such as head trauma and exposure to pesticides (rotenone, paraquat, dieldrin, etc.), solvents (trichloroethylene, carbon tetrachloride, n-hexane etc.), and metals (lead, iron, manganese etc.) are reported to cause destruction of dopaminergic neurons through oxidative and inflammatory reactions [9]. The morphologic hallmark of PD is the presence of alpha-synuclein (α-syn)-rich Lewy bodies within the dopaminergic neurons, which are mainly formed due to mutations in α-syn gene, leading to protein aggregation. Lewy body formation is observed both in familial and sporadic forms of PD [10–14]. Molecular level analysis of PD confirm that oxidative stress, mitochondrial

Abbreviations: sEH, soluble epoxide hydrolase; mEH, microsomal epoxide hydroxylases; EETs, Epoxyeicosatrienoic acids; PD, Parkinson's disease; SNCA, synuclein alpha; LRRK2, leucine-rich repeat kinase 2; PARK2, E3 ubiquitin-protein ligase parkin; PINK1, PTEN induced putative kinase 1; DJ-1, PARK7 – protein deglycase; ATP13A2, ATPase Type 13A2; COX, cyclooxygenase; LOX, lipoxygenase; CYP 450, cytochrome P450; PLA2, phospholipase A2; DiHETEs, dihydroxyeicosatrienoic acids; ROS, reactive oxygen species; AUDA, (12-(3-adamantan-1-yl-ureido)-dodecanoic acid; GC–MS, gas chromatography–mass spectrometry; LC–MS, liquid chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; MCA, middle cerebral artery; PPAR, peroxisome proliferator-activated receptor; TRPV4, transient receptor potential cation channel; mitoKATP, mitochondrial ATP-sensitive K+ channels; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3kinase; EDHF, endothelium-derived hyperpolarizing factor; SN, substantia nigra; ATO, arsenic trioxide; IL, interleukins; TNF, tumor necrosis factor; NF-κB, nuclear factor κB; IKK, IκB kinase; STAT3, signal transducer and activator of transcription 3; V-CAM, vascular cell adhesion molecule; I-CAM, intercellular adhesion molecule; TRPV1, transient receptor potential vanilloid type 1; CNS, central nervous system.

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dysfunction and neuroinflammation are the major contributing factors [15].

Plasma membrane arachidonic acid (AA) released by phospholipids by phospholipase A2 (PLA2) is metabolized to prostaglandins and thromboxane by cyclooxygenase (COX), to leukotrienes by lipoxygenase (LOX), and to Epoxyeicosatrienoic acid (EETs) by cytochrome P450 (CYP450) oxidases (Fig. 1) [16,17]. Four EETs regioisomers, 5,6-, 8,9-, 11,12-, and 14,15-EET are produced by CYP450 epoxygenases pathway. These regioisomers are quickly metabolized to inactive or less active metabolites by soluble or to a lesser degree the microsomal epoxide hydroxylases (sEH or mEH) and their estimated *in vivo* half-life is of few seconds to minutes [18] (Figs. 1 and 2). EETs are present in heart, lungs, kidneys, gastro-intestinal tract and in brain [19,20]. Sura et al., reported the preferential expression sEH in neuronal cell bodies, oligodendrocytes, astrocytes, meningeal blood vessels, and in choroid plexus of human brain [20]. EET's are reported to exhibit anti-inflammatory and antioxidant properties which protect against mitochondrial dysfunction and apoptosis and play an important role in regulation of cerebral blood flow [21]. A diverse class of agents such as amides, ureas, thioamides, thioureas, carbamates, acyl hydrazones, chalcone oxides, etc., has been reported to possess sEH inhibitory potential [22]. Some of the sEH inhibitors have been extensively studied for their cytoprotective benefits in hypertension, ischemic heart disease, heart failure, renocardiac failure, diabetic neuropathy, cancer and obesity [23–31]. Although EETs are widely distributed in the brain, little research has been carried out to exploit their cytoprotective benefits in the treatment/prevention of PD [25,32].

The hypothesis proposed

The cytoprotective properties of EETs have been well established in various peripheral disorders and they may play a similar role in the brain cells. The cytoprotective effect of EETs, however, is limited by their metabolism via soluble epoxide hydrolase [23,25,33–38]. Therefore, we hypothesize that increasing the half life of endogenous EET's through inhibition of its major metabolizing enzyme, soluble epoxide hydrolase [39], is, therefore a novel approach to prevent/treat the PD [21,40–44].

Justification of proposed hypothesis

The pathogenesis of PD is associated with oxidative stress, mitochondrial dysfunction, protein aggregation, misfolding, inflammation, excitotoxicity, and apoptosis [45]. Oxidative stress results due to overproduction of reactive species or a failure of cell buffering mechanisms that normally limit their accumulation. This oxidative stress results in damage to proteins, lipids, and nucleic acids has been found in the substantia nigra (SN) of PD patients [46]. The ROS production occurs due to a variety of factors including dopamine metabolism, exposure to environmental toxins, mitochondrial dysfunction, probably all of which can result in inhibition of mitochondrial Complex I activity in the SN of PD patients [45–47]. PD patients display impairment of endogenous protective mechanism such as lowered antioxidants such as glutathione, superoxide dismutase, etc. EETs have been reported to promote endogenous mechanisms to buffer free radicals, thereby reducing the oxidative damage to sub-cellular organelles [21,48]. A study by Liu et al. demonstrated that EETs attenuate oxidative stress, mitochondrial dysfunction, caspase activation, and apoptosis in carcinoma cells treated with arsenic trioxide (ATO) [49]. The results showed that pretreatment with 11,12-EET increased the expression of the antioxidant enzymes superoxide dismutase and catalase and inhibited ATO-induced apoptosis and activation p38 mitogen-activated protein kinase, c-Jun NH2-terminal kinase, caspase-3, and caspase-9, which could have potential neuroprotective and therapeutic implications for PD [49]. However the specific signaling mechanisms by which EETs exert their direct protective effects in astrocytes and neurons still remain unclear.

Neuroinflammation secondary to oxidative stress is one of the primary mechanisms involved in PD. Elevated pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α have been reported in the SN of PD patients [50]. The accumulation of alpha-synuclein

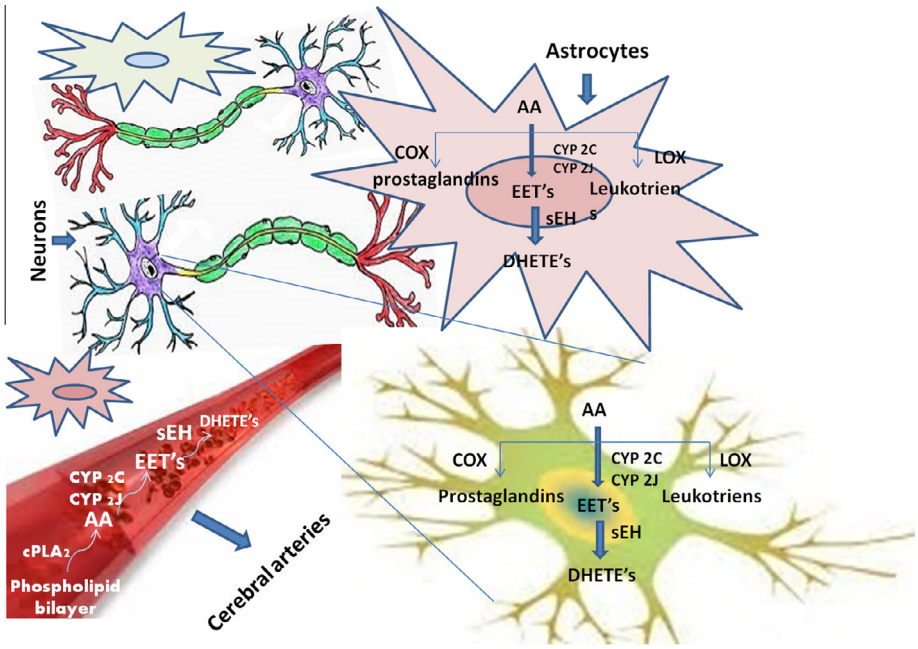

Fig. 1. Arachidonic acid pathway in astrocytes, dopaminergic neurons, and cerebral blood vessels. AA – archidonic acid, COX-2 – cyloclooxygenase-2, LOX – lipoxygenase, EET's – Epoxyeicosatrienoic acids, sEH – soluble epoxide hydrolase, CYP2C – cytochrome p450 2C, CYP2J – cytochrome p450 2J, DHETs – dihydroxyeicosatrienoic acids, cPLA – phospholipase A.