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Review Article

Soluble Epoxide Hydrolase (sEH): A Novel Therapeutic Target in Mitigating the Symptoms of Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is a progressive neurodegenerative disease characterized by the degeneration of dopaminergic neurons in the substantia nigra, which results in motor control problems. One of the main pathological aspects is the presence of alpha-synuclein aggregates, which are called Lewy bodies. Neuroinflammation is at the centre of PD progression and the contribution of activated microglia, lymphocyte invasion, and increased pro-inflammatory cytokines to neuronal damage. Epoxyeicosatrienoic Acids (EETs), the products of arachidonic acid metabolised through cytochrome P450 epoxygenase, have anti-inflammatory and neuroprotective effects. Specifically, NF-kB activation is inhibited, and BDNF-mediated neuronal survival and neurite outgrowth are enhanced by 11,12-EET. However, EETs are rapidly degraded into less active diols (DHETs) by soluble Epoxide Hydrolase (sEH). sEH inhibition prevents the breakdown of EET, thus elevating their levels and therapeutic potential. The sEH is an attractive approach to inhibiting neuroinflammation and safeguarding dopaminergic neurons in PD.

Keywords: Arachidonic acid, Cytochrome P450, Epoxyeicosatrienoic Acids, Parkinson's disease, Soluble Epoxide Hydrolase.

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INTRODUCTION

Parkinson's Disease (PD) is characterized by the gradual onset of motor and nonmotor symptoms and is considered to have a neurological basis.[1] PD is a progressive neurological disease that impairs various functions over time and reduces the quality of life.[2] James Parkinson first described the cardinal clinical features of Parkinson's disease (PD), in An Essay on the Shaking Palsy, which is now recognized as the second most common age-related neurodegenerative disorder after Alzheimer's disease.[3] PD causes several motor symptoms, including bradykinesia (slowness of movement), rigidity (stiffness of the limbs and trunk), postural imbalance (poor balance and coordination), and tremors (trembling in the hands and arms). Most patients with PD also have nonmotor symptoms, such as constipation, urine impairment, dysphagia, melancholy, psychosis, apathy, olfactory dysfunction, autonomic dysfunction, and sleep difficulties.[4-6] The average age of disease onset is 65 years, and the disease is more common in the older population. In developed countries, between 0% and 3% of the general population and approximately 1% of individuals have PD.[7,8] PD had 1.02 million new cases in 2017, according to the Global Burden of Disease study. Between 1990 and 2016, the number of people diagnosed as having PD increased by 21.7% from 6.1 million according to the Age-Standardized Prevalence Rate (ASR).[9] The incidence rate of PD varies across different regions. The Asian continent has a lower incidence of PD, whereas the European continent has a PD incidence rate ranging from 5 to 340 per 0.1 million people.[10] In India, the prevalence of PD is estimated to be 14 per 100,00 people in the average age range. In northern provinces, the prevalence was 247 per 100,00 people in those aged 60 years and above. The prevalence of PD is considerably lower in the southern region of India.[11] PD is caused by two major pathogenic mechanisms: the early selective depletion of dopamine neurons and the accumulation of toxic substances in the brain. Misfolded α-synuclein accumulates in several organs and tissues in patients with PD.[12,13] Lewy bodies and neurites are pathologically significant to PD because they actively contribute to the disease pathophysiology and serve as a prominent indicator of the condition.[14] Moreover, apoptosis, oxidative stress, mitochondrial dysfunction, endoplasmic reticular stress, α-synuclein proteostasis, and other dysregulated cellular pathways, processes, and mechanisms are present in PD.[15] Several variables, including aging, environmental factors,

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and anomalies in gene functions, activate these mechanisms.[16] Environmental factors include traumatic brain damage, metal poisoning, and exposure to pesticides (e.g., rotenone and paraquat), the herbicide dieldrin, and solvents (e.g., n-hexane, trichloroethylene, and carbon tetrachloride).[17] Studies have identified the association of the six genes α-synuclein, leucine-rich repeat kinase 2 (*LRRK2*), parkin (*PARK2*), PTEN-induced putative kinase 1 (*PINK1*), parkin (*PARK7*)-protein deglycase DJ-1, and ATPase Type 13A2 with PD.[18,19] Neuroinflammatory pathways, including astrogliosis, lymphocytic infiltration, and microglial activation, play a role in neuronal degeneration.[20]

Alpha-synuclein, the hallmark of PD, affects the Central Nervous System (CNS), peripheral nervous system, and gastrointestinal nervous system. Studies have indicated that the gut bacteria substantially control the brain-gut axis through immune, hormonal, and direct neuronal processes. Dysregulation of the brain-gut-microbiota axis, which has been related to the etiology of PD and gastrointestinal symptoms that often precede movement symptoms, is a hallmark of PD. The stimulation of enteric neurons and glial cells may cause alpha-synuclein misfolding. In addition, gut dysbiosis, bacterial proliferation in the small intestine, and increased intestinal permeability may overstimulate the innate immune system, resulting in systemic inflammation.[21] Endocrine signaling and microbial interaction are highly dependent on the brain-gut axis. Type II diabetes, high blood pressure, and arrhythmia are all linked to fat accumulation. Increasing evidence indicates that sEH may play a role in these conditions.[22] The enzyme CYP450 epoxygenase converts arachidonic acid, a naturally occurring polyunsaturated fatty acid, into essential Eicosapentaenoic Acid (EPA). EPA acts as a lipid messenger and exhibits various benefits in patients with obesity- and diabetes-related cardiovascular illnesses. EPA is converted into inert Dihydroxyeicosatrienoic acids (DHETs) through sEH metabolization. Pharmacological inhibition of soluble epoxide hydrolase (sEH), the enzyme responsible for the metabolism of epoxyeicosatrienoic acids (EETs), has emerged as a promising therapeutic strategy for enhancing insulin secretion, preserving endothelial function, lowering blood pressure, and mitigating obesity-associated metabolic and organ damage.[23] Loss of neurons in the substantia nigra may be related to inflammation in PD and is often associated with microglia activation.[24] Thus, anti-inflammatory therapy exerts a beneficial effect on patients with PD.[25] Soluble Epoxide Hydrolase (sEH) is a major player in the association of inflammation with PD. Epoxy fatty acids control neuroinflammation. The epoxy fatty acid 14,15 Epoxyeicosatrienoic Acid (EET) exerts anti-inflammatory effects. Hydrolysis of 14,15 EET by sEH produces the equivalent diol,14,15-DHET, which does not exhibit anti-inflammatory effects.[26] Therefore, blocking sEH can reduce neuroinflammation by increasing the 14,15 EET level in the brain and thus is a potential treatment strategy in PD.

Parkinson's disease and inflammation

Neuroinflammation and other pathogenic pathways in PD, including mitochondrial dysfunction and oxidative stress, interact intricately.[27] Neuroinflammatory responses in PD are characterized by the upregulation of several enzymes involved in excitatory processes, including Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, Inducible Nitric Oxide Synthase (iNOS), and myeloperoxidase, and the morphological stimulation of glia cells. Moreover, these responses are involved in the recruitment of T cells from the peripheral immune system.[28,29] The released cytokines and activated microglia trigger the inflammatory response.[30] Microglia, the primary immune cells of the CNS, account for 5%-15% of the brain's total volume and 20% of the glial cell population.[31] Astrocytes have numerous branches that extend through neurons and blood vessels, creating functional networks using gap junctions, also known as neurovascular units. High levels of neuromelanin in the substantia nigra pars compacta neurons are one of the elements that activate microglia-mediated neuroinflammation.[32] In addition, numerous genes affect the activation of microglia. For example, a Parkin deficit may indirectly boost microglia activation by increasing the susceptibility of neurons to inflammation-related stress and disrupting the balance between neurons and microglia.[33] Deficiency of the protein deglycase DJ-1 in astrocytes may cause neurodegeneration by reducing their responsiveness to neuroinflammation.[34] Microglia play a dual role in the brain by acting as neuroprotective cells that remove endogenous or exogenous chemicals. They also have high levels of glutathione peroxidase and reduced glutathione, which protect them from hazardous hydrogen peroxide levels. Notably, the brain and cerebrospinal fluid of patients with PD contain more proinflammatory chemicals, and their microglia and T cells are more engaged. Microglia are activated by the discharge of the byproducts of dopaminergic neuronal death, including oxidized proteins, lipids, and DNA.[35] Hyperactive microglia accelerate the degeneration of nigral dopaminergic neurons in the PD brain, thus regulating the production of several proinflammatory cytokines. Tumor necrosis factor-alpha, interleukin-1, interleukin-6, and interferon-gamma are all examples of cytokines.[24]

Astrocytes play an essential role in neuroinflammation-mediated cell death in PD.[36] Astrocytes are the brain's most common glial cells.[37] and play a pivotal role in ensuring the proper functioning of the nervous system. Astrocytes regulate blood flow, synapse signaling, and water transfer, as well as preserve the brain's structure and metabolism.[38,39] The glial-derived neurotrophic factor is produced by astrocytes and is essential for the development and survival of dopaminergic neurons.[39-41] Moreover, astrocytes affect the blood-brain barrier, which is compromised in people with PD.[39,42] Glial fibrillary acidic protein is more frequently expressed in reactive astrocytes, cell bodies, and extensions. Astrocytes become activated and amplify immune signals after

being exposed to various molecules, such as proinflammatory mediators produced by activated microglia. Furthermore, the accumulation of mutant α-synuclein in astrocytes in rodents resulted in microglial stimulation, astrogliosis, and DA neuron and motor neuron degradation (Figure 1).[24,43,44]

Chemistry of soluble epoxide hydrolase enzymes

The synthesis of xenobiotic chemicals begins with the catalysis of epoxides into diols by the ubiquitous enzyme soluble Epoxide Hydrolase (sEH), which is a member of the epoxide hydrolase family present in all living things.[25,26,45] Water is used by epoxide hydrolases to break down epoxide molecules into their constituent diols (Figure 2).[46] The enzyme sEH metabolises the endogenous chemical mediators that control blood pressure and inflammation.[47] Four immune variants of epoxide hydrolases have been identified, including microsomal epoxide hydrolase, microsomal cholesterol oxide hydrolase, cytosolic sEH, and leukotriene epoxide hydrolase.[48-50] Leukotriene epoxide hydrolase hydrates leukotriene A4, whereas cholesterol epoxide hydrolase hydrates the molecule attached to cholesterol's 5,6-epoxide. Epoxides in circular systems and monosubstituted and 1,1-disubstituted epoxides may be hydrated by microsomal epoxide hydrolase. Studies have purified and partially characterized sEH from many mammalian species.[51,52] Microsomal epoxide hydrolase and sEH proteins are produced through transcription and translation of EPHX1 and EPHX2 genes.[53]

Soluble epoxide hydrolase

sEH converts and eliminates EETs, a class of P450 eicosanoids, in the body.[54] sEH is present in the blood vessels' endothelium and the vascular wall's smooth muscle. The skin, mammary gland, testicles, liver, kidney, lungs, heart, brain, spleen, adrenals, gastrointestinal tract, urinary bladder, and arterial walls contain sEH.[55] Mammalian sEH is a bifunctional enzyme with a pkDa hydrolase domain at its C-terminal and a 25-kDa N-terminal phosphatase region. It comprises two monomers, each with 555 amino acids and a size of 62.5 kilodaltons. The sEH protein in mice and humans is a domain-swapped homodimer with two globular domains per component and a proline-rich linkage connecting them. (Ile-219-Asp-234 for human sEH and Thr-219-Asp-234 for murine sEH).[56] The C-terminal domain of sEH is structurally similar to single-domain epoxide hydrolase enzymes found in fungi, plants, and organisms, such as *Caenorhabditis elegans*, and bacterial haloalkane dehalogenase. The N-terminal domain of sEH is homologous to haloacid dehalogenase found in bacteria and mammals.[57] The EPHX2 protein, located on the 8p12-p21 region of chromosome 8, is responsible for sEH function. This protein participates in the synthesis of xenobiotic compounds and favors trans-substituted epoxides, such as trans-stilbene oxide.[58,59] Variations in the sEH gene have been identified, with glutamine at exon eight being replaced by arginine and arginine being inserted between codons 402 and 403 in exon 13. These variations substantially affect the activity of the protein, with the arginine-inserted variant being less active than the glutamine-287 variant.[60] Despite significant variations in the loop regions of proteins, the tertiary and quaternary structures of both murine and human sEH enzymes are similar, with a difference of approximately 4 Å in the distance between the two subunits (Table 1).[61,62]

The N-terminal region of the protein is absent from plant sEH.[63] The α/β-hydrolase fold, a characteristic and highly conserved protein structure composed of a core sheet of eight parallel β-strands joined by α-helices, is present in all these enzymes.[55] The N-terminal phosphatase domain degrades lipid phosphates, whereas epoxides are converted to diols by the C-terminal epoxide hydrolase area.[64] Epoxide hydrolases catalyze the opening of the oxirane ring on substrates containing soluble and microsomal epoxides. Activation of an epoxide occurs through hydrogen bonding with the general acids Y381 and Y465 and through the nucleophilic attack by D333, forming an intermediate alkylenzyme. Subsequently, the tetrahedral intermediate forms with the help of H523 and a water molecule and then collapses, releasing the product diol from the alkylenzyme intermediate.[65]

sEH belongs to the class of α/β hydrolases, including bacterial haloalkane dehalogenase.[66] The catalytic mechanism involves the formation of a covalent alkyl enzyme ester intermediate due to the nucleophilic attack by Asp333.[67] The alignment analysis identified a putative catalyst triad of amino acids within sEH. A mutagenesis study revealed that, similar to other α/β hydrolase enzymes, Asp333 and His523 play a role in the catalytic process of sEH.[68] The catalytic mechanism of epoxide hydrolase is dependent on the residue His523, which was found to be conserved in all epoxide hydrolases across species and whose deletion in mouse sEH resulted in only 0.1% of the activity of wild-type sEH. The amino acid Asp333 serves as the initiation site for a α-hydroxy acyl-enzyme that acts as an intermediary.[69] This intermediate is hydrolyzed following the addition of water to the carbonyl carbon of the ester link, producing the dihydro diol product.[70] The presence of His523 and Asp495 creates a proton-deficient environment, which activates water and catalyzes the hydrolysis of the α-hydroxy acyl-enzyme intermediary into the dihydro diol product.[71] sEHIs reduce inflammation, regulate blood flow, and protect neurons from excitotoxicity. A reduced infarct size and a diminished inflammatory response after stroke are the indicators of the neuroprotective benefits of sEH inhibition, which are likely caused by a reduction in the production of proinflammatory cytokines. Similarly, inhibiting sEH reduced oxidative stress, cell death, and inflammation as well as renal fibrosis in mice kidneys.[22,72] Decreased expression of collagen type IV and protection from hypertension-related kidney vascular and glomerular damage are the two benefits of sEH.[73,74] Moreover, sEH inhibition is associated with a decreased

loss of dopaminergic neurons in the striatum, demonstrating its therapeutic potential. sEH can be used as a PD biomarker and sEHI as a medicinal drug in clinical applications. These findings serve as the foundation for additional sEH-based studies in other CNS illnesses.[22]

Leukotriene epoxide hydrolase

A group of lipid mediators called leukotrienes plays a role in allergic reactions and inflammation. Leukotriene A4 hydrolase, which contains Zn^{2+}, is a multifunctional enzyme having hydrolase and aminopeptidase activity.[75] The breakdown of the unstable epoxide leukotriene A4 into the diol LTB4 by epoxide hydrolase is the last and rate-limiting step in the biochemical production of leukotriene B4.[76] Leukotriene B4 promotes neutrophil, monocyte, and eosinophil recruitment and activation. Moreover, leukotriene B4 promotes the synthesis of several proinflammatory cytokines and mediators, suggesting that it can intensify and prolong tissue inflammation.[77] In the human body, leukocytes primarily produce leukotriene from arachidonic acid by using 5-lipoxygenase.[78] COX-2 and 5-LOX contribute to dopaminergic neurotoxicity caused by LPS.[79] Furthermore, the 5-LOX inhibitor can reduce rotenone-induced cell damage, suggesting that 5-LOX is implicated in rotenone-induced damage in PC-12 cells.[32] Moreover, inhibiting the generation of proinflammatory leukotrienes reduces neurotoxicity by preventing microglial toxic action.[80]

Microsomal epoxide hydrolase

A smooth endoplasmic reticulum enzyme called microsomal epoxide hydrolase is widely expressed in numerous species and most tissues.[81] Cytochrome P450 (CYP450) oxidizes unsaturated hydrocarbons to produce epoxides and arene oxides, which are then converted to water by microsomal epoxide hydrolase. An alkylenzyme (ester) intermediate is formed when a carboxylate from the active site reacts with one of the oxirane carbons in the substrate; this ester is then hydrolyzed by water at its carbonyl carbon.[82] The first epoxide hydrolase to be discovered is the membrane-bound human microsomal epoxide hydrolase, which

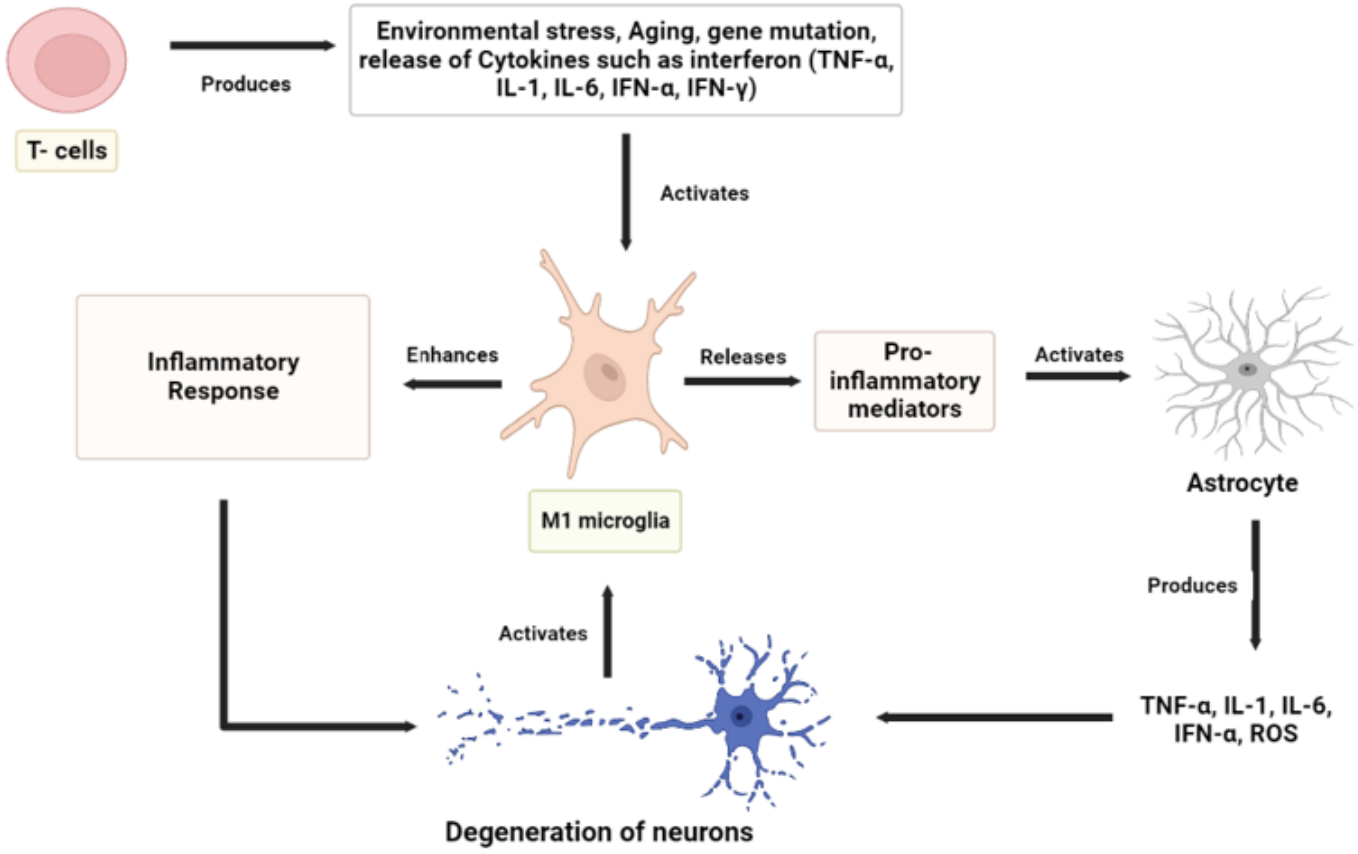


Figure 1: Pathophysiology of PD and neuroinflammation: Pathological variables include protein aggregation, gene mutations, environmental factors, and cytokines secreted by infiltrating T cells that cause activation of M1 microglia in PD. The activation of astrocytes by pro-inflammatory mediators from M1 microglia increases the production of nitric oxide and superoxide radicals, accelerating dopaminergic neuronal degeneration. Degenerative dopaminergic neurons can release mediators that further activate glia and increase the inflammatory response. As the illness progresses, decaying dopaminergic neurons emit α-synuclein, Adenosine Triphosphate (ATP), and metalloproteinase-3, which stimulate microglial activation, increase neuroinflammatory responses in the brain, and accelerate the neurodegenerative process.[24] Microglial activation enhances the production of reactive oxygen species and nitrogen species, the synthesis of cytokines, and the release of trophic substances necessary for the regular maintenance of neuronal survival.[35] ATP produced from injured neurons and nearby astrocytes regulates the migration of microglia to inflammatory and wounded regions. Microglia present in the brain bind to the P2Y receptor following its binding to ATP, releasing significant amounts of IL-1, TNF-α, and nitric oxide.[24]

Table 1: Various forms of soluble Epoxide Hydrolase.

Sl. No.	Compound	Function	References
1.	Mouse Gene	The mouse gene is found on chromosome 14 and codes for 554 amino acid residues with 19 exons. The transcript was initially cloned from a mouse liver, and a mouse splice variant's first two exons have been altered using a sequence from the gene's second intron. This particular splice variant, expressed in the granulosa cells of preovulatory follicles but lacks the residues necessary for phosphatase activity, is not transcribed.	57,143,144
2.	Human Gene	The human gene comprises 19 exons on chromosome 8 that code for 555 amino acid residues. The human promoter has numerous SP-1 sites, although no TATA box. The expression of the promoter minimally, one SP1 place must be present upstream of the transcription start site. The sEH gene is silenced in HEPG2 cells through the methylation of these SP-1 sites. When treated with Hcy, the human sEH promoter contains UPRE, which increases the expression of sEH in human HUVECs. Hcy dramatically increases the expression of sEH mRNA, partially due to the activity of ATF-6. Hcy-mediated demethylation of the binding site improves ATF-6 binding.	57,145,146

is essential for regulating chemically volatile and potentially dangerous epoxides. They are produced as the metabolic intermediates of various xenobiotics.[83] Epoxide Hydrolases in the microsome (EPHX1) and soluble form (EPHX2) regulate the redox state of various xenobiotic- and lipid-derived substrates. Thus, genetic variations in these pathways may reduce cellular damage caused by epoxides.[84] Studies have reported the association between mEH and neuroinflammatory disorders. Moreover, the prevalence of PD and the decreased effectiveness of the Y113H polymorphism are correlated.[85] In the MPTP model of PD, the genetic deletion of mEH inhibits the death of dopaminergic neurons.[86]

Cholesterol epoxide hydrolase

The hydration of cholesterol 5,6 α-oxide (α-oxide) as well as various other steroidal 5,6 β-oxides is catalyzed by the liver microsomal enzyme cholesterol oxide hydrolase. Cholesterol oxides formed in the presence of NADPH, FeS04, and ADP during *in vitro* lipid peroxidation may be removed by this enzyme.[87] Moreover, 7-dehydrocholesterol 5,6 β-oxide covalently modifies the active site of cholesterol oxide hydrolase in rat liver microsomes, rendering the enzyme inactive. 5,6 β-Iminocholestanol is a potent competing inhibitor of the enzyme that catalyzes the uptake of 3-[3 H]-7-dehydrocholesterol 5,6 β-oxide.[71]

Epoxy Fatty Acids (EpFAs), a crucial class of lipid signaling molecules that includes EETs, are hydrolyzed by sEH.[57] In inflammation and vascular control, EETs exert various positive effects. However, the breakdown and conversion of EETs into DHETs by sEH, which was first defined over 40 years ago,[22] exerts weaker and different biological effects than EETs. sEH acts on the epoxides of linoleic acid (leukotoxin and isoleukotoxin) and arachidonic acid, contributing to endogenous lipid metabolism and xenobiotic detoxification (cis Epoxyeicosatrienoic Acids). The inflammatory condition is believed to be linked to elevated linoleate and arachidonic acid diol titers, respectively.[88,89] Diols produced from leukotoxin or epoxy linoleate promote inflammation by activating endothelin-1 and iNOS, which hampers calcium homeostasis and membrane permeability. Urinary arachidonate diols, which are elevated in pregnancy-induced hypertension, modulate renal water retention.[90] Patients carrying the common K55R genetic variant in the sEH gene (Ephx2) exhibited 30% lower EET levels with enhanced sEH activity. The mortality rate was 28.6% in these patients after stroke compared with 5.3% in control participants. In other studies, sEH expression was markedly increased in epilepsy and PD animal models.[91]

Arachidonic acid and the Mechanism of Epoxyeicosatrienoic Acids(EETs)

Arachidonic acid, an omega-6 polyunsaturated fatty acid, is esterified in the cell membranes of various cells. During the metabolism of phospholipid membranes, phospholipase A2 is primarily responsible for arachidonic acid production.[92] Phospholipase A2 is an enzyme that transforms membrane phospholipids into arachidonic acid in response to various physiological cues. CYP450, which produces EETs; Lipoxygenase (LOX), which generates leukotrienes; and Cyclooxygenase (COX), which produces prostaglandins and thromboxane, are the three components involved in the metabolism of phospholipid membranes.[93,94]

Cyclooxygenase (COX)

Cyclooxygenase is an essential enzyme in the production of prostanoids. COX-1 and COX-2 are its two isoforms. COX-1 is present in the mesothelium, smooth muscle, platelets, and blood vessels, whereas COX-2 is primarily found in parenchymal cells in various tissues.[95] In response to brief lipopolysaccharide stimulation, COX-1 causes acute inflammation and instructs the cell to either enhance or reduce leukotriene production.[93,96] COX-1 prefers to link with and colocalize in the perinuclear membrane or ER with thromboxane synthase, prostaglandin F synthase, and two additional prostaglandin D synthase isozymes, all of which aid in the synthesis of thromboxane A2

and prostaglandin D2.[93] Inflammation, platelet aggregation, cardiovascular diseases, pain, and cancer have all been linked to COX, which includes prostaglandins.[97]

Lipoxygenase (LOX)

Arachidonic, linoleic, and linolenic acids are three Polyunsaturated Fatty Acids (PUFA) oxidised by the monomeric protein family LOX to produce hydroperoxides. LOXs are widely distributed in cyanobacteria, plants, and animals. Also, 5-LOX, which is present in all mammals and oxygenates the carbon-5 on arachidonic acid, and 9-LOX and 13-LOX, found in plants, catalyses are found in plants and catalyse the oxygenation of linoleic and linolenic acids, respectively.[97] 5-Hydroperoxy eicosatetraenoic acid (5-HPETE) is formed by 5-LOX and subsequently transformed into Leukotriene A4 (LTA4) by leukotriene synthase. LTA4 is controlled by two enzymes. LTA4 hydrolase activity converts a water molecule into a diol, which acts as a chemotactic and degranulating agent in polymorphonuclear cells, causing inflammation. Glutathione S-transferase is the second enzyme involved in the production of LTC4.[93,98] Asthma, pulmonary disease, and atherosclerosis are linked to LOX metabolites, such as leukotrienes and hydroxy eicosatetraenoic acids. Enzyme activity for hydroxylases and epoxygenases is part of the CYP450 pathway.[99]

CYP450

Heme functions as a cofactor in the superfamily of cytochrome-containing proteins. CYP450 can metabolize diverse xenobiotic compounds by oxidizing molecules with iron. CYP450 enzymes are involved in various processes, including O-dealkylation, S-oxidation, epoxidation, and hydroxylation. Various bodily tissues express cytochromes, and they are primarily present in hepatic and intestinal organs.[100] Cytochromes 2C and 2J are members of the CYP450 family that metabolize arachidonic acid to produce EETs, whereas cytochromes 4A and 4F catalyze the omega hydroxylation of arachidonic acid to produce 20-hydroxyeicosatetraenoic acid.[101] Depending on the double bond across which the epoxide is added, cytochrome epoxygenases generate one of the four stereoisomers of EET from arachidonic acid: 14,15- EETs, 11,12- EETs, 8,9- EETs, or 5,6- EETs. These EET isomers are promptly converted by sEH into inactive or less active DHET metabolites and lose their biological activity (Figure 3).[99]

Epoxyeicosatrienoic Acids (EETs) and its Metabolic Pathways

Endothelial malfunction and neural death can both be prevented by the anti-inflammatory and antioxidant activity of EETs. Moreover, EETs regulate cerebral blood flow, control neuronal plasticity, attenuate oxidative stress, block endoplasmic reticulum stress responses, reduce brain injury, and restore neurological function in conditions affecting the nervous system.[101,102] EETs are powerful anti-inflammatory molecules that are produced through a cytochrome P450 enzyme-mediated process. DHETs are created when sEH hydrolyzes EETs; however, they exhibit weak biological activity.[103] sEHI affects NF-kB, PPAR function, and key arachidonic acid metabolic enzymes, such as cyclooxygenase and lipoxygenase.[46] sEH inhibitors exert beneficial effects because of their powerful anti-inflammatory effects, such as triggering Brain-Derived Neurotrophic Factor (BDNF)-TrkB to cause endoplasmic reticulum stress and inflammation to cause mitochondrial malfunction. A promising therapeutic approach for treating inflammation and diseases, such as PD, involves inhibiting sEH activity.[104] BDNF-TrkB activation protects neurons from damage caused by inflammation by reducing endoplasmic reticulum stress, mitochondrial dysfunction, and other inflammatory outcomes. Metalloproteinase-2 and metalloproteinase-9 are inhibited by Epoxyeicosatrienoic Acids, which prevent mitochondrial dysfunction. The MEK-ERK-CREB communication cascade is activated when BDNF attaches to its target TrkB. Neurogenesis, synaptic plasticity, and neurite outgrowth may all be affected by the BDNF-TrkB signaling pathway. By reducing NF-κB, EETs mitigate endoplasmic reticulum stress and oxidative damage. In addition, EETs inhibit apoptosis by triggering B-cell lymphoma 2 (Bcl-2) and caspase-3 while preventing the activation of Bcl-2-Associated X protein (BAX).[105] EETs signaling affects certain neuronal and glial cell functions, substantially affecting CNS function and disorders. EET signaling affects certain neuronal and glial cell functions, thus affecting CNS function and disorders. IkB kinase (IKK) inhibition by EETs blocks the nuclear translocation of NF-κB, halting the growth of TNF-α and inhibiting its adhesion. Thus, various enzymes exhibit dysregulation, including the inflammatory mediators LOX-5, COX-2, and Nitric Oxide Synthase (iNOS).[54]

EET and NF-κB

To exert their anti-inflammatory effect, EETs block the activation of NF-κB, a major transcription factor implicated in the synthesis of inflammatory genes. RelA (p65), one of the five components of NF-κB, is present in the majority of cell types. NF-κB dimers are found in the cytoplasm because of their association with IκB, a protein that inhibits NF-κB. Phosphorylation of IκB is inhibited by the IKK, a suppressor of the NF-κB kinase complex. NF-κB then translocates into the nucleus, binding to its particular binding sites and initiating transcription. IκB is subsequently

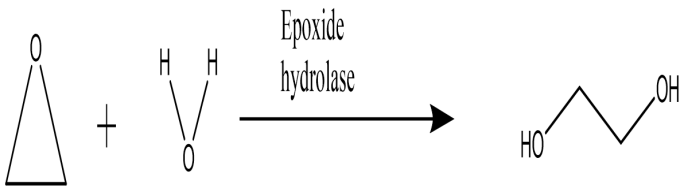


Figure 2: Epoxide hydrolase adds a water group to an epoxide to catalyse diol production.

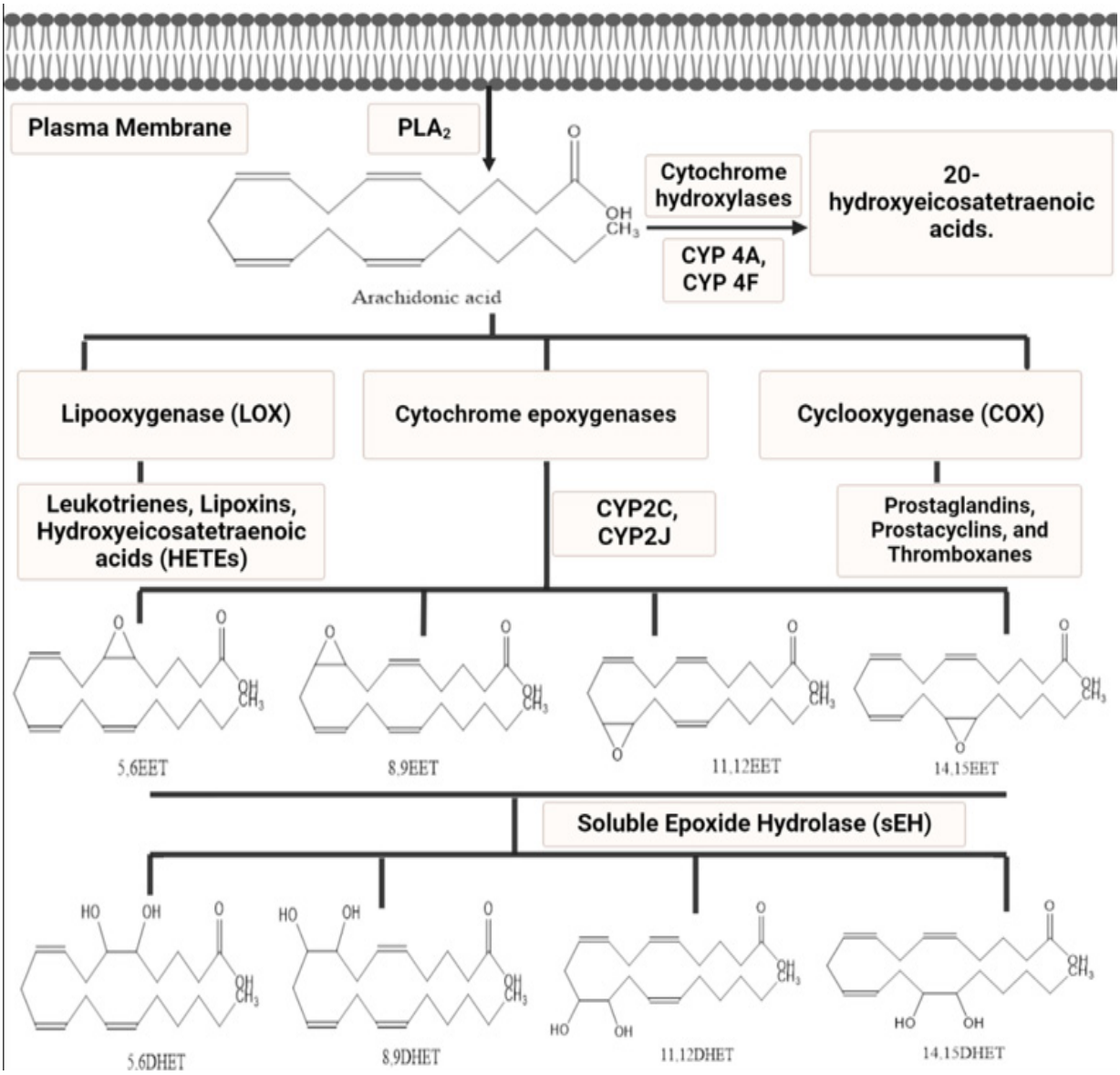


Figure 3: Arachidonic acid metabolic pathway: Calcium (Ca^{2+}) stimulated phospholipase A2 releases the arachidonic acid in the plasma membrane. There are four primary processes by which arachidonic acid is metabolised: Cyclooxygenase (COX), Lipooxygenase (LOX), Cytochrome P450 (CYP) epoxygenases, and cytochrome hydroxylases. Arachidonic acid is metabolised by COX to prostaglandins, prostacyclins, and thromboxanes and then by LOX to leukotrienes, lipoxins, and Hydroxyeicosatetraenoic Acids (HETEs). CYP P450 epoxygenases and CYP P450 hydroxylase convert free arachidonic acid to EETs or 20-HETE. The arachidonic acid is metabolised by the CYP450 (including the 2J and 2C families) to produce the EETs 5,6, 8, 9, 11, 12, and 14, respectively. The sEH then hydrolyses the EETs to produce DHETs with minimal biological activity.

ubiquitinated and degraded by the proteasome.[106] 11,12-EET inhibited the post-stimulation NF-κB reporter activity of HEK293 cells and human endothelial cells. 11,12-EET can prevent TNF-α-induced nuclear transfer of RelA, IκBα disintegration, and IKK activity, indicating that the EET-mediated control of NF-B precedes IKKα activity (Figure 4).[107,108]

EET and Peroxisome Proliferator-Activated Receptor Gamma (PPAR)

Peroxisome proliferator-activated receptor is a nuclear receptor and one of the three ligand-activated transcription factors. PPARs regulate various physiological responses, including inflammation, cell proliferation/differentiation, and fatty acid/glucose metabolism.[109] The key feature of this process is that intracellular EET directly activates the reaction instead of activating a second messenger channel through cell surface receptors. EETs, which originate from arachidonic acid or PLA2, produce intracellular phospholipids and initiate autocrine activities. The absorption of EETs from the extracellular fluid induces paracrine activities in neighboring cells. In the presence of FABP, EET is retained in the cytoplasm, where it engages with transcription factors, ion channels, and signal transduction components.[110,111] In conclusion, EETs can directly interact with biological proteins. By binding to Fatty Acid Binding Proteins (FABPs) and PPARγ, EET remains in the cytoplasm, where it directly interacts with transcription factors, ion channels, and elements of signal

transduction pathways. Alternatively, EETs are combined with phospholipids to activate signaling pathways, depending on phospholipids or their binding with ion channels (Figure 5).[111]

EET and G-protein-coupled receptor

Several of the effects of EETs may be mediated when they bind to a possible G-protein-coupled receptor. 11,12-EET significantly increased KCa channel activity in smooth muscle cells isolated from bovine coronary arteries by 0.5-10 times only in the presence of GTP.[106,110] 14,15-EET has been demonstrated to have a high affinity for a receptor expressed on guinea pig-derived mononuclear cells, which was supposed to be a G-protein-coupled receptor that increased cAMP formation.[106]

Soluble Epoxide Hydrolase Inhibitors (sEHIs)

Soluble epoxide hydrolase inhibitors are potential treatment options for various medical conditions because of their ability to increase EET levels while reducing DHET levels. sEHI can be used to treat multiple clinical indications, including pain, immunological disorders, ocular diseases, neurological diseases, hypertension, diabetes, stroke, and dyslipidemia.[112] Inhibition of sEH, which controls EET levels, exerts anti-inflammatory effects, reducing cytokine-mediated inflammation. To exert its anti-inflammatory effect, sEH must control EET levels by inhibiting NF-kB-mediated gene transcription. Neurons in the striatum and substantia nigra, two regions of the brain affected by PD, are preserved when the 1-Methyl-4-phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-mediated loss of cells containing tyrosine hydroxylase in the substantia nigra is inhibited by reducing sEH or by genetically deleting Ephx2.[56] Epoxide-containing Trans-3-phenyl glycidyl and chalcone oxide compounds were the first sEH inhibitors, and although they are potent and selective, they are unstable and only temporarily affect she.[113] However, most epoxide-containing substances are alternate enzyme substrates with low turnover rates that only temporarily block *in vitro* and are ineffective *in vivo*.[114] After

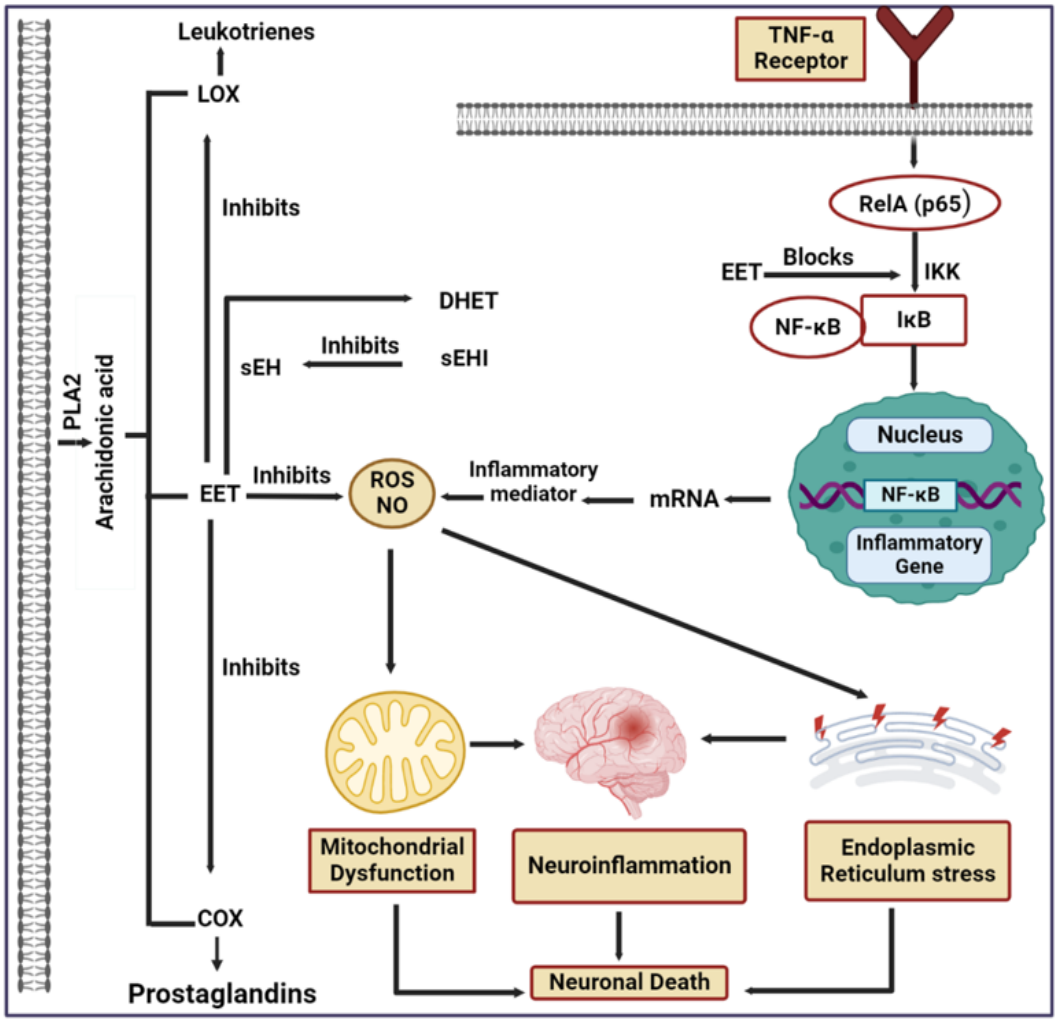


Figure 4: EET and Nuclear factor kappa-B: Decreased NF-κB activation is a crucial step in the anti-inflammatory effect of EETs. NF-κB activation appears to be decreased by EETs by blocking IκB kinase. EETs reduce and inhibit adherence to TNF-α, thus reducing inflammation by blocking the nuclear translocation of the Nuclear Factor (NFkB) and inhibiting IkB Kinase (IKK). This leads to the downregulation of several enzymes, such as iNOS, ROS, LOX-5, and COX-2, which are upregulated in inflammation.

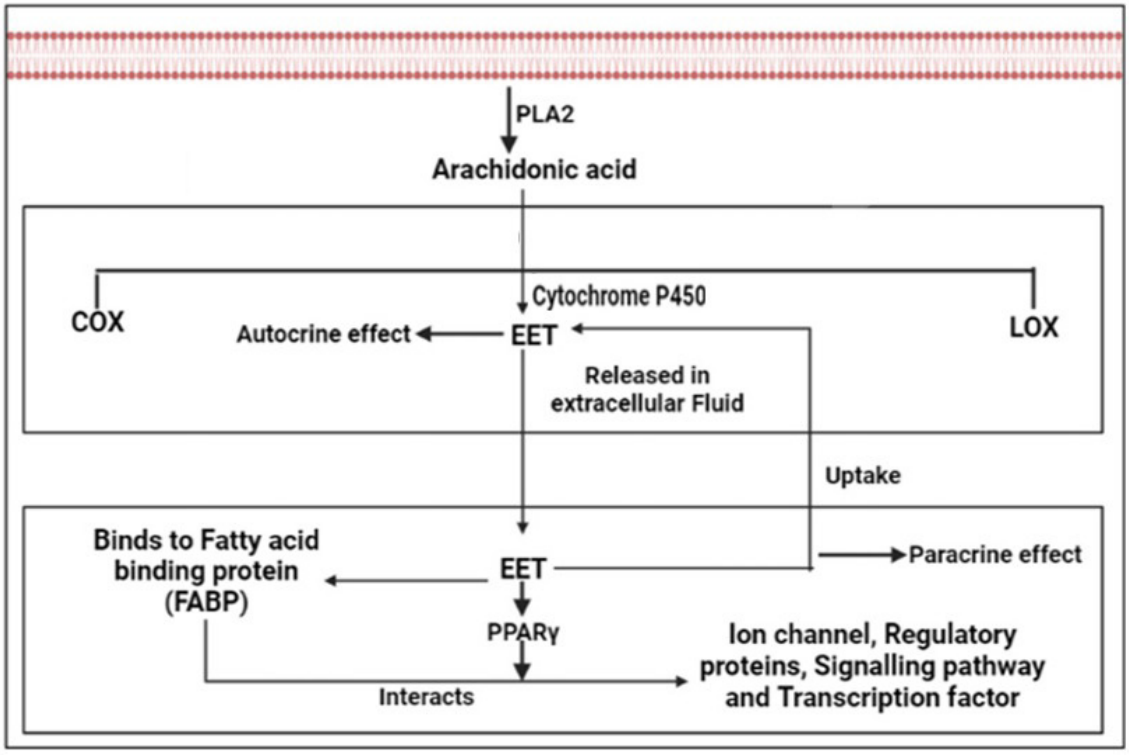


Figure 5: EET and PPARγ: Cytochrome P450 epoxygenase is involved in the production of EETs. Arachidonic acid from intracellular phospholipids is activated by cytosolic phospholipase A2 (cPLA2) and converted to EETs by cytochrome P450, which exhibits an autocrine action. When EETs are released into the extracellular fluid, they exhibit paracrine actions. This occurs when EET binds to FABP or EET directly interacts with intracellular effector mechanisms. EET is found in the cytosol and binds to FABP and PPARγ, where it directly interacts with transcription factors, ion channels, regulatory proteins, and components of signal transduction pathways.

testing more than 150 compounds, chalone oxides were identified as the highly effective regulators of epoxide hydrolases.[115]

4-Phenylchalcone oxide is a substrate for sEH. It generates a covalent intermediate that restricts its use *in vivo* because it is unstable in the glutathione-containing environment and is progressively broken down by sEH.[56] 1,3-Dicyclohexylurea (DCUs), one of the first urea derivatives, exhibited poor pharmacokinetic characteristics but excellent *in vivo* inhibitory effects against the sEH enzyme. sEH was dose-dependently inhibited by DCU but not by microsomal epoxide hydrolase. 1-Cyclohexyl-3-dodecyl-urea, another potent inhibitor based on urea, was similarly hampered due to its rapid metabolism in hepatic microsomes.[116-118] High expression of sEH is observed in various brain regions, including oligodendrocytes, astrocytes, meningeal blood vessels, and choroid plexus, suggesting its role in neuromodulation. sEH expression and function are crucial to define the PD etiology. Dopaminergic cell death, which is associated with TH-positive cell death, endoplasmic reticulum stress, and sEH expression in certain brain locations, is decreased by sEHIs in patients with PD and animal PD models.[50,56]

sEHI 12 (((tricyclo(3.3.1.13,7) dec-1 ylamino)carbonyl)amino)-dodecanoic acid [or AUDA]] induces an increase in the EET level. More neurons survive after being exposed to a dynamic environment in PD and other neurodegenerative diseases. Pretreatment with AUDA alleviated MPTP-induced dementia and protects TH-positive cells in the substania nigra; however, no effect was observed after treatment.[119,120] Two tyrosine residues (Tyr381 and Tyr465) are present in the active area of the hydrolase and donate hydrogen bonds to enable Asp333 to open the epoxide ring, as indicated by the X-ray crystalline structure of the human sEH and AUDA complex (Protein Data Bank (PDB) code: 1ZD3). For rapid DHET production, hydrolysis might be used after ester synthesis. The protein's hydrolase catalytic pocket is a snug fit for amide- and urea-based sEHI. Asp 333 interacts with the N-H of urea and amide as well as Tyr 381 and Tyr 465, and the carbonyl oxygen of urea and amide through hydrogen bonds. Urea and amide derivatives are being researched and developed as the long-term inhibitors of sHE.[112] 1-Trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU), one of the powerful sEHIs, considerably reduced the number of TH-positive cells and the levels of procaspase 9 protein and MPTP-induced striatal dopamine in rats. MPTP inhibits caspase 12 activation, HO-1 elevation, alpha-synuclein aggregation, and oxidative stress while preventing protein aggregation, apoptosis, and endoplasmic reticulum stress.[121] Treatment of EETs with 4-(5-phenyl-3-3-3-(4-trifluoromethylphenyl)-ureido-propyl-pyrazole-1-yl) Benzenesulfonamide (PTUPB), the dual inhibitor of sEH and COX-2, exerts antioxidant, anti-inflammatory, and anti-apoptotic

effects. Moreover, the concurrent suppression of COX-2 by PTUPB can reduce neuroinflammation-induced cell death.[122]

ROS are produced due to the inhibition of the mitochondrial complex induced by rotenone. The dysfunction of mitochondrial complex I caused by rotenone was markedly reversed by the sEHI N-(1-acetylpiperidin-4-yl)-N-(adamant-1-yl)urea (APAU). ROS are peroxidized in membrane lipids, reducing the permeability of the mitochondrial membrane when their concentration is too high. Pretreatment with sEHI and APAU significantly reduced ROS-induced lipid peroxidation and alterations in the mitochondrial membrane potential.[123] In conclusion, the findings reveal that sEH inhibition or deletion can prevent the degeneration of dopaminergic neurons (Table 2).[124]

Preliminary results have demonstrated the presence of sEHI in plants. Honokiol (5,3′-diallyl-2,4′-dihydroxy biphenyl), which is isolated from *Magnolia officinalis*, exhibited strong sEH activity suppression. Honokiol has various therapeutic effects, including restoring PPARγ expression, preventing dopaminergic neuron degeneration, reducing oxidative stress and astrocytic stimulation, and restoring typical motor behavioral performance.[125,126] 1, 3-Bis (4-methoxybenzyl) urea, a key ingredient of urea-based sEHIs, is abundant in the stems of the *Pentadiplandra brazzeana* shrub. In a rat model of nociceptive pain, 1, 3-bis (4-methoxybenzyl) urea considerably reduced inflammation-related discomfort. Among the sEH antagonists found in nature, these compounds rank high in terms of their efficacy.[127] In contrast to other naturally occurring compounds, including flavonoids, alkaloids, and phenolic compounds, the majority of the compounds from *Docynia indica* fruits displayed moderate to significant sEH inhibitory effects.[128] The sEH-inhibiting effects of selaginin derivatives were clinically evaluated. Selaginin derivatives have demonstrated potential in treating cardiovascular disease. All selaginella derivatives inhibited sEH and PHOME hydrolysis enzymatic activity in a dose-dependent manner.[129] Crude extracts of the aerial parts of *Glycosmis stenocarpa* were analyzed for their potential to act as sEH inhibitors. The results revealed that methanol extract, n-hexane, chloroform, and ethyl acetate

Table 2: Synthetic drugs having sEH inhibitory activity.

Sl. No.	Compound	Function	References
1.	4-Phenylchalcone oxide	Pharmacological inhibition of the proinflammatory microglial enzyme sEH impacts microglial activation and neuronal death following cardiac arrest. Microglia are activated during cardiac arrest and play a part in the loss of neurons. The sEH inhibitor 4-phenyl chalcone oxide significantly reduced neuronal death after cardiac arrest and improved memory.	147
2.	1,3-Dicyclohexylurea (DCUs)	It has been discovered that human serum contains DCU, a potent endogenous inhibitor of sEH. In mammals, soluble epoxide hydrolase prevents kidney, heart, and brain damage, cardiovascular disease, high blood pressure, and anti-inflammatory effects.	74
3.	1-cyclohexyl-3-dodecyl-urea (CDU)	Human aortic Vascular Smooth Muscle (HVSM) cell proliferation is reduced by the highly selective urea-based sEH inhibitor CDU, independent of any impact on sEH. CDU inhibits endothelial cells when activated with essential fibroblast growth factor or serum.	148
4.	12(((tricyclo(3.3.1.13,7)dec-1 ylamino) carbonyl)amino)-dodecanoic acid [AUDA]	The sEH inhibitor AUDA butyl ester decreased the infarct size in mice after occluding the middle cerebral artery. Studies suggest that sEH suppression leads to elevated EETs levels, which have therapeutic advantages for lipid and glucose metabolism, blood pressure, and inflammation. The sEH inhibition-induced increase in EETs may also inhibit the NF-kB pathway from being activated.	117
5.	1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU)	TPPU is a potent inhibitor of sEH with the capacity to enter the brain. It has good efficacy against various chronic inflammatory illnesses in preclinical animal models.	149
6.	N-(1-acetylpiperidin-4-yl)-N-(adamant-1-yl)urea (APAU)	ROT-induced changes in oxidative, pro-inflammatory, and apoptotic markers were lessened considerably by APAU.	123
7.	4-(5-phenyl-3-3-3-(4-trifluoromethylphenyl)-ureido-propyl-pyrazole-1-yl) benzenesulfonamide (PTUPB)	The dual sEH/COX-2 inhibitor PTUPB reduces inflammation and blood pressure by increasing EETs and decreasing COX-2 inflammatory prostanoids.	150

extract all exerted an inhibitory effect on sEH enzyme activity *in vitro*.[130] Flavonoids, one of the main components in *Epimedium koreanum Nakai*, were discovered to be responsible for the plant's antioxidative, anti-inflammatory, cardioprotective, and other therapeutic activities. Both sEH and tyrosinase are significantly inhibited by flavonoids.[131] Kurarinone, a rare natural chemical extracted from *Sophora flavescens*, mitigated behavioral impairment and dopaminergic neurotoxicity generated by MPTP, including the loss of neurotransmitters and TH-positive cells. Kurarinone reduced MPTP-induced neuroinflammation by inhibiting microglial activation along the NF-κB signaling pathway (Table 3).[56]

sEH as a target in PD

Finding new compounds that can simultaneously affect numerous downregulation mechanisms is crucial due to the complicated etiology of PD. The progression of PD is a major reason, and it is essential to discover preventive medicines that can be used for extended periods without causing harm.[132] However, no antiparkinsonian drug, either alone or in combination, can completely halt the progression of the disease. Thus, neuroprotective medications are required to prevent disease progression. Reactive stress, inflammation, mitochondrial malfunction, and apoptosis have all been linked to PD.[133,134] The metabolism of endogenous physiologically active EETs is significantly affected by sEH. EETs and other lipid epoxides were increased following the use of sEHIs. sEHIs reduce blood pressure and inflammation and increase insulin sensitivity.[74,135] CYP450 enzymes can convert olefins into a broad range of epoxy fatty acids. EETs and Epoxydocosapentaenoic acids (EDPs), both arachidonic acid and docosahexaenoic acid, can be synthesized. EETs have been linked to inflammation and the development of various disorders such as pain, obesity, depression, and PD, as evidenced by anti-inflammatory studies and the development of many animal models.[136,137]

EETs exert cytoprotective effects in various peripheral disorders and brain cells. However, the sEH metabolism of EETs hinders their ability to protect cells from damage. A novel approach to avoiding PD involves inhibiting sEH, the primary enzyme in the metabolism of endogenous EETs.[111,124,138] Because sEH promotes alpha-synuclein and phosphorylated-synuclein buildup in the striatum, it may be pivotal in the genesis of PD and dementia with Lewy bodies. Similarly, sEHI prevents apoptosis in dopaminergic neurons derived from PARK2 iPSCs. Neurodegenerative conditions related to α-synuclein protein, including PD and dementia with Lewy bodies, may be prevented or treated using sEHIs.[139] Dying dopaminergic neurons contribute to PD, which is connected to oxidative stress. In the oxidative metabolism of

Table 3: Herbal extract having sEH inhibitory activity.

Sl. No.	Herbal Extract	Function	References
1.	*Pentadiplandra brazzeana*	*P. brazzeana's* roots contain urea compounds that have potent sEH-inhibiting effects. The plant root contains the highest concentration of 1, 3-bis (4-methoxybenzyl) urea, and in an *in vivo* inflammatory pain model, it demonstrated local analgesic benefits.	127
2.	*Docynia indica*	For developing sEH inhibitors, 3-methoxy-4-hydroxy-benzoic acid and 2,6-dihydroxy 3,4 -dimethoxy chalcone may be used as potential compounds. These findings suggest that fruits from *D. indica* could be used as dietary supplements to treat cardiovascular conditions and other related illnesses.	128
3.	Honokiol isolated from *Magnolia officinalis*	With good IC_{50} values established using the fluorescent substrate and 14,15-epoxyeicosatrienoic acid, honokiol extracted from *Magnolia officinalis* demonstrated substantial suppression of sEH activity. These findings indicate that honokiol has an sEH inhibitory effect, as seen by the decreased microsomal epoxide hydrolase activity.	125
4.	*Selaginella tamariscina*	Selaginellin derivatives are a promising first line of drugs for developing sEH-targeting inhibitors.	151
5.	*Glycosmis stenocarpa*	Higher sEH inhibitory actions were detected in isomahanine and bisisomahanine, which have a chromene ring on pyranocarbazole. It demonstrates a potential natural source carbazole-type alkaloid inhibitor of sEH.	129
6.	*Epimedium koreanum* Nakai	Distinct flavonoid compounds from E. koreanum inhibited sEH and tyrosinase in different ways. The outcomes demonstrated that some substances had the potential to act as sEH and tyrosinase inhibiting agents.	131
7.	Sophora flavescens	In a mouse model of Parkinson's disease, kurarinone from *S. flavescens* was reported to lessen Parkinson-like behaviours. By targeting sEH, an enzyme that controls multiple chemicals linked to inflammation, blood pressure, and pain, its researchers found that it can reduce neuroinflammation in the brain.	56

both external and indigenous components, epoxides are formed as a possibly unstable intermediary that contributes to cellular harm caused by oxidative stress. Numerous xenobiotic and lipid-derived substrate oxidation states are regulated by microsomal epoxide Hydrolase 1 (EPHX1) and soluble Epoxide Hydrolase 2 (EPHX2) pathways, which exhibit substantial individual variation and may protect cells from epoxide-related harm.[84] Because of its specific toxicity toward dopaminergic neurons, MPTP, one of the most frequently used pharmacological inducers of PD in experimental animals, causes symptoms similar to those reported in PD. Recent studies have suggested the role of sEH in the pathogenesis of PD due to the correlation between increased sEH mRNA and PD in MPTP models.[124,139] In patients with dementia, sEH expression is negatively correlated with the expression of TH, a biomarker of dopaminergic neurons.[124] After receiving a dosage of MPTP, these dopaminergic neurons are protected from neurotoxicity when sEH is suppressed by medication or genetic deletion. Several sEH single-nucleotide polymorphisms exist, including K55R, R103C, C254Y, and R287Q. The catalytic efficiency of the R287Q variant is considerably lower for 14,15-EET.[140,141] Thus, individuals carrying the R287Q variation have an increased risk of PD.[141] In PD, the omega-3 PUFA docosahexaenoic acid exhibits beneficial effects. This PUFA is abundantly present in noggin and is essential for healthy brain growth and function. CYP450 converts docosahexaenoic acid into Docosahexaenoic Acid Epoxides (EDPs), and sEH further hydroxylates EDPs to produce equivalent diols, dihydroxydocosapentaenoic acids. In rats, docosahexaenoic acid supplementation reduced rotenone-induced motor impairment and TH loss. In addition, docosahexaenoic acid supplementation increased the striatal expression of Nrf2 and antioxidant gene mRNA. However, the sEH inhibitor TPPU completely reversed these effects of docosahexaenoic acid supplementation.[142]

CONCLUSION

One of the main risk factors for PD is neurodegeneration, which also causes other life-threatening consequences such as dysphagia, cognitive decline, sleep disorders, etc. The suppression of inflammatory cell recruitment, alteration of the arachidonic acid metabolite profile, and additional targeting of the PPARγ and NF-kB pathways are the mechanisms of inflammation inhibition, which result in the inhibition of COX-2, 5-LOX, and iNOS. The primary anti-inflammatory mediators are the EETs, the byproducts of the CYP450 enzyme-mediated route used to metabolise arachidonic acid. EETs have shown cytoprotective benefits in various circumstances by reducing oxidative stress, inflammation, and apoptosis. Furthermore, it has been demonstrated that EETs reduce apoptosis, caspase activation, and mitochondrial dysfunction brought on by ROS. The substantia nigra of PD patients has been found to have increased levels of pro-inflammatory cytokines such as COX-2, IL-1β, IL-6, and TNF-α. By inhibiting the degradation of EETs to DHETs, which have significantly less biological activity by sEHI, it may enhance the concentration of EETs, producing anti-inflammatory activity. Thus, taking sEHI, which inhibits the sEH enzyme, could be a viable therapeutic approach to alleviating PD symptoms. In conclusion, psychiatric and neurological diseases such as depression, schizophrenia, Lewy body dementia, and Parkinson's disease have been associated with genetic deletion of Ephx2 (the gene that encodes sEH) and elevation of sEH expression.

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ABBREVIATIONS

ATF-6: Activating Transcription Factor-6; **AUDA:** 12-(((Tricyclo[3.3.1.1$^{(3,7)}$]dec-1-ylamino)carbonyl)amino) dodecanoic Acid; **CDU:** 1-Cyclohexyl-3-dodecylurea; **COX:** Cyclooxygenase; **DCU:** 1,3-Dicyclohexylurea; **EETs:** Epoxyeicosatrienoic Acids; **Hcy:** Homocysteine; **HUVECs:** Human Umbilical Vein Endothelial Cells; **LOX:** Lipoxygenase; **NF-κB:** Nuclear Factor Kappa B; **PTUPB:** 4-(5-Phenyl-3-[3-(4-trifluoromethylphenyl)ureido]propyl-pyrazol-1-yl) benzenesulfonamide; **ROT:** Rotenone; **APAU:** N-(1-Acetylpiperidin-4-yl)-N-(adamant-1-yl)urea; **sEH:** Soluble Epoxide Hydrolase; **TPPU:** 1-(Trifluoromethoxyphenyl)-3-(1-propionylpiperidin-4-yl)urea; **UPRE:** Unfolded Protein Response Elements.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements / guidelines.

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