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HUMBLE BEGINNINGS WITH BIG GOALS: SMALL MOLECULE SOLUBLE EPOXIDE HYDROLASE INHIBITORS FOR TREATING CNS DISORDERS

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Abstract

Soluble epoxide hydrolase (sEH) degrades epoxides of fatty acids including epoxyeicosatrienoic acid isomers (EETs), which are produced as metabolites of the cytochrome P450 branch of the arachidonic acid pathway. EETs exert a variety of largely beneficial effects in the context of inflammation and vascular regulation. sEH inhibition is shown to be therapeutic in several cardiovascular and renal disorders, as well as in peripheral analgesia, via the increased availability of anti-inflammatory EETs. The success of sEH inhibitors in peripheral systems suggests their potential in targeting inflammation in the central nervous system (CNS) disorders. Here, we describe the current roles of sEH in the pathology and treatment of CNS disorders such as stroke, traumatic brain injury, Parkinson's disease, epilepsy, cognitive impairment, dementia and depression. In view of the robust anti-inflammatory effects of stem cells, we also outlined the potency of stem cell treatment and sEH inhibitors as a combination therapy for these CNS disorders. This review highlights the gaps in current knowledge about the pathologic and therapeutic roles of sEH in CNS disorders, which should guide future basic science research towards translational and clinical applications of sEH inhibitors for treatment of neurological diseases.

Keywords

pharmacology; stroke; TBI; inflammation; preclinical studies; clinical trials; druggability

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Introduction

Three inflammatory pathways that produce eicosanoids derived from arachidonic acid (ARA) have been implicated in a variety of inflammation-plagued disorders such as stroke, hypertension, and renal disease. The first pathway entails cyclooxygenase (COX) enzymes that are responsible for the conversion of ARA to prostaglandins and thromboxane (a potent vasoconstrictor). Both aspirin, prescribed for at-risk stroke patients, and non-steroidal anti-inflammatory drugs are COX inhibitors (1). The second pathway consists of lipoxygenase (LOX) enzymes that are required to produce pro-inflammatory leukotrienes from ARA, and LOX inhibitors have been used therapeutically in seasonal allergies and asthma (2), (3). The third pathway is mediated by cytochrome P450 enzymes (CYP) and results in two types of products: hydroxyeicosatrienoic acids (HETEs) and epoxyeicosatrienoic acid isomers (EETs). EETs are produced by the metabolic activity of CYP enzymes which among other metabolites produce epoxides from double bonds (4). These compounds have been shown to exert potent, protective vasodilatory and anti-inflammatory effects on the cardiovascular and renal systems (5). Moreover, EETs also suppress hyperthermia, pathological fibrosis, the generation of reactive oxygen species, apoptosis, pain, and platelet aggregation (6), (7), (8), (9), (10), (11) Although the beneficial effects of EETs on the cardiovascular and renal systems have taken precedence over their roles in other systems, they assume an important role in central nervous system (CNS) signaling as well (12). While many of the effects of EETs on the CNS parallel their effects on peripheral systems, recent research reveals that EETs have distinct functions in the brain, which may have anti-inflammatory effects. Some of these functions relevant to regulation of inflammation include the modulation of angiogenesis, regulation of cerebral blood flow (CBF), and mediation of neuroendocrine signaling (12).

Soluble epoxide hydrolase (sEH), first assayed (13), (14) and characterized (15), (16) almost 40 years ago, is responsible for the degradation and conversion of EETs into dihydroxyeicosatrienoic acids (DHETs), which have diminished and different biological effects compared to EETs (5), (17). Furthermore, sEH inhibitors (sEHIs) harbor therapeutic potential by increasing the availability of EETs and other epoxy fatty acids (EpFAs) (18), (19). In the last two decades, sEHIs have enjoyed a rapid ascent into clinical research (Table 1) since their groundbreaking capacity to produce anti-hypertensive effects was discovered (20), (21). The aforementioned anti-hypertensive effects were then attributed to the ability of sEHIs to inhibit the actions of hormone angiotensin-II (22). This finding not only bolstered previous research on the potential treatment of hypertension with sEHIs, but also elucidated the relationship between sEHIs and the renal system. With the advent of more potent and bioavailable inhibitors, sEHIs entered clinical studies to evaluate their safety and efficacy for health problems such as hypertension and type 2 diabetes mellitus. In a phase IIa clinical trial, the sEHI AR9281 demonstrated decent tolerability, rapid absorption, no severe side effects, and a 90% inhibition rate of sEH activity in the blood (23). Additionally, combining sEHIs with the vasoconstrictor urotensin II resulted in a larger increase in blood vessel flux in healthy patients and patients with heart failure, suggesting sEHIs' potential to treat heart failure (24). GSK2256294, another sEHI, was evaluated in both healthy males and obese smokers a phase I clinical trial, and was found to have no serious adverse effects, with

contact dermatitis and headache the most common side effects (25). The same sEHI was also studied in elderly males and females with similar results (25). Fortified by the extensive research on hypertension and sEH, the putative neuroprotection of sEHIs emerged into the field of ischemic stroke. sEH is abundantly expressed in the cerebral cortex, striatum, hypothalamus, and brain stem, predominantly in neuronal cell bodies (6), (26) but also in astrocytes and oligodendrocytes (10). Coinciding with the benefits of sEHIs in hypertension and related cardiovascular disease, sEH activity may be present within the endothelium as well (27). Indeed, the inhibition of sEH attenuated inflammation and was associated with a smaller infarct size after middle cerebral artery occlusion (MCAO) in mice (6). Interestingly, sEH immunoreactivity was confirmed in both non-vascularized and vascularized areas of the brain, suggesting that the beneficial actions of sEHIs may similarly comprise of vascular as well as non-vascular pathways. Due to the robust ability of sEHIs to suppress the inflammatory response, sEHIs have become increasingly relevant in the possible treatment of CNS disorders (Figure 1). Other mechanisms by which sEHIs may have beneficial effects in the treatment of CNS disorders have also been unveiled, and they will be discussed in detail below.

In the present review, we seek to describe the current knowledge surrounding the potential role of sEHIs in treatment for CNS disorders such as stroke, traumatic brain injury (TBI), Parkinson's disease (PD), and other debilitating neurological conditions. Inflammation is a major mediator of cell death in the diseases mentioned above, and we will explore the anti-inflammatory mechanisms of sEHIs that serve as the basis for combating these disorders. In addition, we hope to synthesize research conducted on the intersection of sEH inhibition and stem cell treatment. The treatment of CNS diseases with stem cells has reached clinical trials, but to date most of the reported findings relate to safety with limited efficacy and may benefit from combination therapy, such as with sEHIs. While the anti-inflammatory effect of sEHIs observed in other body systems is a promising therapeutic tool for use in CNS disorders, unique properties of the brain and complex pathological processes of each neurological disorder may hinder their swift integration into clinical practice. In this review, we will provide an outline of possible and current challenges sEHIs may face on their way into the clinic. We also hope to highlight the gaps in current scientific and translational knowledge to provide guidance for future clinical studies geared towards advancing stem cell therapy and pharmacological sEHI treatment for neurological disorders.

Distribution of sEH

sEH is present in inflammatory cells and throughout multiple organs in mammals, including the liver and kidney (28), (29). It can be found in the endothelium and smooth muscle of vascular tissues, suggesting the enzyme's potential connection to hypertension (28). Within the cell, sEH is mainly located in the cytosol and peroxisomes, but this cytosolic/peroxisomal distribution changes with tissue type and physiological state (28). Interestingly, sEH is also highly prevalent in the cerebral cortex and striatum of the brain and typically resides in neuronal cell bodies, astrocytes, oligodendrocytes, and the smooth muscle of cerebral blood vessels (6, 30). As stated above, sEH is also found within the endothelium (27). These localization patterns, particularly sEH's propensity for endothelial cells and smooth muscle cells of cerebrovasculature, implicate the enzyme's possible involvement in

regulating CBF, brain activity, and neurological disease pathology (30). In fact, administering sEHIs decreases sEH activity and mitigates brain damage in stroke and TBI animal models (6, 31). This implies a neuroprotective effect upon sEH inhibition and advocates the development of potent sEHIs with favorable pharmacokinetic attributes as potential drug treatments for neurological diseases.

The unique distribution of sEH in the human body also reveals sexually dimorphic expression. sEH activity is higher in post-puberty male mice than in females (32), suggesting differential regulation by hormones such as testosterone (33) and estradiol (34). Detailed research must be conducted in the future to fully elucidate sex differences in sEH activity and distribution. This concept, along with the distinct impacts that specific neurological disorders have on the sexes, must be acknowledged when developing and evaluating the effects of potential sEHIs.

Absorption, Distribution, Metabolism, and Excretion (ADME) of sEHIs

Maintaining simplicity of formulation and enhancing ADME properties of sEH inhibitors is crucial to bolstering their efficacy (Figure 2) (35). Ideal sEHIs maximize bioavailability and delay elimination from the bloodstream as exhibited by longer half-lives, higher maximum drug concentrations in the blood (C_{max}), and larger area under the curve (AUC) values than earlier sEHIs such as 12-(3-adamantan-1-yl-ureido)-dodecanoic acid (AUDA) (36). Additionally, lower melting points are beneficial for boosting absorption in the body (37) and higher solubility in water improves oral administration and bioavailability (28), (38). Furthermore, decreasing crystalline stability and increasing oil solubility enables sEHIs to experience easier subcutaneous administration and dissolution in organic solvents used to transfer drugs (28).

Initial sEHIs included dicyclohexylurea (DCU), a potent but highly lipophilic and high melting compound. DCU is a byproduct of some industrial and laboratory synthesis procedures. However, DCU's pharmacological utility is restricted as excessive lipophilicity in a compound generates pharmacokinetic and formulation issues and hinders its specificity (28), (39). Adding polar functional groups to early sEHIs like DCU generated a new line of potent, more water soluble sEHIs including AUDA and its butyl ester (AUDA-BE) (36). Preclinical pharmacokinetics revealed that AUDA-BE, when injected intraperitoneally in mice, travels systemically to the brain, crosses the blood brain barrier (BBB), and inhibits sEH in the brain (6). sEH activity is inhibited by over 20% for 24 hours, confirming AUDA-BE's potency and bioavailability (6). AUDA-BE appears to exhibit superior bioavailability, but both AUDA and AUDA-BE are capable of crossing the BBB and inhibiting sEH (39). Intriguingly, AUDA-BE and AUDA's other butyl and ester forms can be transmitted intraperitoneally, subcutaneously, or orally via food, while AUDA can be dosed orally via drinking water (28). Adamantane was used in many early sEHIs like AUDA because it could be detected at very low concentrations by liquid chromatography-mass spectrometry (LC-MS) and because it was rapidly metabolized. AUDA compounds encounter swift metabolism via beta oxidation, hydroxylation of the adamantane, and subsequent excretion (28). They also have high melting points, low water solubility, and were designed as mimics

of EETs (28). Thus, they are also peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists.

Following AUDA came other sEHIs that were designed with strategic functional group placement, including 1-adamantan-1-yl-3-(5-(2-(2-ethoxyethoxy)ethoxy)pentyl)urea (AEPU) (35).Like many modern sEHIs, AEPU has a polar functional group located approximately 8 Å away from its central carbonyl group (28), allowing higher solubility in water and a lower melting temperature, thereby making AEPU's formulation more accessible. The inhibitor readily traverses membranes and possesses good bioavailability and effectiveness in vivo (28), (35). However, it was designed for transient activity and quick metabolic breakdown (28). Other new inhibitors, including *t*-AUCB (*trans*-4-(4-(3-adamantan-1-yl-ureido)-cyclohexyloxy)-benzoic acid) and TPAU (1-trifluoromethoxyphenyl-3-(1-acetylpiperidin-4-yl) urea) have succeeded earlier sEHIs with increased water solubility and abated metabolism due to their confined conformational structures (35), (36). One compound of interest is 1-trifluoromethoxyphenyl-3-(1-propionylpiperidine-4-yl) urea (TPPU), a potent, relatively easily-formulated sEHI with sufficient solubility in water. It is currently the most widely used sEHI in research. TPPU maintains its robust bioavailability in the brain after intraperitoneal injection (40) and oral administration (41), demonstrates vast systemic distribution to tissues, effectively crosses the BBB, experiences excellent absorption in the intestines, significantly inhibits sEH, possesses high metabolic stability, and is effectively administered via drinking water but must be formulated in a water miscible organic co-solvent (41), (42). Indeed, many sEHIs successfully pass the BBB and each new generation of inhibitors advances the previous generation with improved physical characteristics like increased water solubility. TPPU exhibits much greater stability, bioavailability, half-life duration, and efficacy in clearing inflammation than *t*-AUCB, appealing properties attributed to the substituted phenyl group attached to TPPU in contrast to the adamantyl group attached to *t*-AUCB (43). However, *t*-AUCB derivatives are broadly active on the sEH of many mammalian species while TPPU-like compounds are most active on primate and rodent sEHs. These results further emphasize the importance of sEHI structure and functional groups, and how these affect inhibitor efficacy and pharmacokinetic properties. It will be imperative to refine sEH structures with this in mind to develop optimized drugs for treating diseases.

While sEHIs like AUDA and TPPU can cross the BBB, their structure has not been specifically optimized for BBB penetration. Lipid solubility is key to crossing the BBB (44), but excessive lipophilicity hinders sEHI formulation, creates pharmacokinetic issues (28) and can allow the sEHI to be taken from the bloodstream by other tissues before it reaches the brain (44). Thus, a compromise must be made to improve BBB penetration while maintaining the inhibitor in the bloodstream (44). As low molecular weight and lipid solubility facilitate easier crossing of the BBB, it is possible that increasing hydrogen bonding capabilities or molecular weight by adding additional functional groups in some sEHIs may also prevent complete optimization of BBB crossing (28), (44). Thus, an ideal balance is necessary to maintain sEHI potency while simultaneously maximizing availability in the brain.

Most central pharmacophores in sEHIs are a urea, carbamate, or amide moiety (28). Modifying the secondary pharmacophore by including hydroxyl, carbonyl, sulfonyl, ether, ester, carbamate, and other functional groups enhances the inhibitor's physical attributes, such as by decreasing melting temperature and increasing binding to polar residues in the sEH catalytic tunnel (28). Adding polar groups to inhibitors in the proper position may increase the likelihood of hydrogen bonding with catalytic sites on sEH and improve target selectivity and pharmacokinetic and physical aspects (28). For instance, water solubility increases without compromising inhibitor efficacy when polar functional groups are present on a linear alkyl chain at a certain distance from the urea moiety (38). Thus, structural modifications of inhibitors can increase solubility in water or oil-based solvents or lower melting points in order to increase bioavailability (38), (45), (46). Augmenting bioavailability following oral administration and minimizing clearance from the bloodstream are current objectives driving the latest structural alterations to sEHIs (39). Of note, there has been a breakthrough within the past 15 years in promising compounds possessing extensive half-lives and exceptional oral bioavailability (28), (39). Pharmaceutical companies can potentially use these compounds as templates for developing highly effective sEHIs to treat a wide variety of diseases, including neurological maladies like TBI and ischemic stroke (39). In addition to developing sEHIs with slow metabolism and sufficient oral bioavailability, dual COX/sEH inhibitors are of current interest. A COX-2/sEH inhibitor administered to rats shows a synergistic effect in treating lipopolysaccharide induced pain (47). In fact, the compound shows an enhanced effect compared to co-administration of both celecoxib (a COX-2 inhibitor) and *t*-AUCB (47). Furthermore, COX-2/sEH inhibition also suppresses tumor growth by inhibiting angiogenesis, suggesting that creating future sEHIs that also contain the ability to inhibit COX may be desirable in the treatment of certain diseases (48).

There have been significant challenges faced in obtaining Food and Drug Administration approval for sEHIs evaluated in completed clinical trials (Table 2) (49), (50). Despite the lack of serious adverse effects caused by sEHI administration, some compounds, most notably GSK2256294, are on hold due to the rigorous standards that must be met for drug development pursuit. However, sEHIs are still undergoing evaluation for use in other disorders such as subarachnoid hemorrhage (51) and diabetes mellitus, (52). In addition, novel sEHIs may be discovered based on previously developed pharmacophore models, which have identified several new compounds from the Specs database capable of inhibiting sEH in extremely low concentrations (53). This technique may be the forefront of drug discovery concerning sEH inhibition in the coming years. Furthermore, company Eicosis is investigating the use of EC2506, a sEHI, as a treatment for diabetic peripheral neuropathy in a phase Ia clinical trial beginning in 2019 (Grant #R44ES025598). New sEHIs may be discovered naturally as well. Urea-based sEHIs have recently been isolated from the African plant Pentadiplandra brazzeana and shown to act as analgesics in a rat model (54). While some promising sEHIs are facing resistance in the receipt of FDA approval, other innovative sEHIs are working towards translation to CNS disorders and optimization to the human species, and this atmosphere is dynamic and evolving.

Inflammation and sEH

Inflammation is a biological response to an injury that attempts to minimize functional and structural damage relating to the insult. The response is characterized by the dilation of arterioles and capillaries, increased permeability of microvasculature, and the invasion of leukocytes into injured tissue (55). While inflammation initially serves as a mechanism to resolve injuries, it becomes a problem (and turns into a chronic condition) if it is not halted after a certain period of time (55). Inflammation is a hallmark of many conditions, many of which involve the CNS. When affecting the CNS, inflammation (referred to as neuroinflammation) involves the recruitment of leukocytes and lymphocytes to the CNS and the activation of glial cells (including microglia, the phagocytes of the brain) (39). In some pathogenic processes, such as in stroke and TBI, inflammation can also cause increased permeability of the BBB, allowing harmful blood products to enter the brain parenchyma (56). Neuroinflammation is a major cause of secondary injury cascades, and it is primarily regulated by microglia and peripheral leukocytes (31). Once activated, microglia produce pro-inflammatory cytokines that result in cytotoxic effects if not regulated. This property of microglia makes them a prime contributor to neuroinflammation (31). Due to its widespread and detrimental effects, treatment strategies have been designed to prevent or reverse neuroinflammation (31)

sEHIs may serve as therapeutic options when treating several disorders, some of which are neurodegenerative, due to their ability to prevent EET and other EpFA metabolism by sEH (57). EETs are made from ARA in the CYP reaction (31, 58). The ARA network produces many inflammatory mediators that are implicated in numerous diseases, making the pathway another target of therapeutic intervention (59). EETs have many roles in the body, but they are quickly broken down and inactivated by sEH, preventing them from utilizing their anti-inflammatory features (8). If sEH is inhibited, EET levels can increase and exert anti-inflammatory actions. The EET increase is limited by a variety of other degradation pathways making it difficult to increase EpFA to undesirable levels. Indeed, metal cations are shown to decrease in the serum during systemic inflammation, and they are known natural endogenous inhibitors of sEH (60). This implies that sEH activity is increased during inflammation. In fact, the increase is so dramatic that sEH message, protein, and catalytic activity can be used as a marker of tissue inflammation (61). Another way to decrease the concentration of sEH is through genetic deletion, which has been shown to reduce neuronal death, apoptosis, brain edema, and BBB permeability following TBI (31).

The exact method utilized by EETs to reduce inflammation is unknown, but it has been shown that in certain brain conditions, sEH increases in microglia while EETs and other EpFAs decrease. Microglia have a distinct role in neuroinflammation; they produce proinflammatory cytokines that cause neuronal damage and BBB disruption (31). If sEH is inhibited in microglia, EpFAs will resultingly increase and contribute to microglia deactivation and enhanced neuronal survival (31). EETs and other EpFAs have also been able to inhibit the expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, intercellular adhesion molecule 1 (ICAM-1) and the nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (55). VCAM-1, E-selectin, and ICAM-1 are all cell adhesion molecules, so without them leukocytes and other immune

system cells are unable to attach to injured tissue, and NF-κB helps regulate the immune response by upregulating enzymes that contribute to inflammation (55). Leukocytes, one of the trademarks of inflammation, are reduced in the presence of EpFAs but the exact mechanism by which it occurs has not been fully elucidated (39).

In neurological diseases such as ischemic stroke, epilepsy, Alzheimer's disease (AD), PD, and TBI, rudimentary research has begun showing the positive effects of increased EET and other EpFA concentrations following sEH inhibition. In ischemic stroke, EpFAs are protective against cell death in a way independent of effects on CBF and may be able to decrease the infarct size (55), (57), (61), complementing the vascular mechanism of EpFAs. Epilepsy patients may be treated pre or post seizure with the anti-inflammatory properties of EpFAs, as anti-convulsants are unable to prevent seizures (55), (62). Regarding AD and PD, EpFAs may be able to improve mitochondrial functioning and reduce neuroinflammation from oxidative stress (55). In TBI, EpFAs have the potential to decrease brain edema due to their ability to decrease neuroinflammation (31). sEHIs' ability to mount multi-pronged therapeutic processes appeals to complex injuries, such as stroke and TBI characterized by multiple cell death pathways, which likely cannot be arrested by a drug designed to target a singular degenerative process (39).

The ability of sEHIs to resolve inflammatory responses is promising, but more research is needed before they can be utilized clinically (36). sEH is present in most tissues, so the systemic use of inhibitors may have unintended effects outside of regulating inflammation (57). Additionally, EETs and other EpFAs have been postulated to afford several functions in the brain, such as inhibiting inflammation, and releasing peptide hormones, but the exact pathway that EETs use in the brain remains poorly understood (57). The specific mechanism of sEHIs is also unknown, though the inflammation-associated P38-MAPK is a potential target (31). Much of the current literature involving sEH and sEHIs is focused on cardiovascular and renal conditions. The inflammatory responses in these conditions differ from neurodegenerative diseases due to the presence of the blood brain barrier and a variety of CNS specific cells. Before sEHIs can be translated to a clinical setting for treating CNS disorders, additional studies are warranted to reveal how these molecules directly affect the brain and if unintended side effects are produced.

Stroke and sEH

Stroke, characterized by a loss of blood flow to the brain, remains a leading cause of disability and death globally, with approximately 800,000 stroke victims suffering each year in the United States alone (63). The extent of ischemic damage depends on the severity of CBF reduction, which determines the extent of oxygen and glucose deprivation from the cells. This hypoxic environment results in extensive apoptosis and necrosis (64). Subsequent activation of the tissue's immune response initiates the upregulation of pro-inflammatory cytokines (65), and a compromised BBB allows for the rapid influx of neutrophils, macrophages, leukocytes, B cells, and T cells to the stroke-damaged brain, further exacerbating neurodegeneration and aggravating the injury (66).

Despite the prevalence of stroke, treatment options are severely limited. Thrombolytic therapy using tissue plasminogen activator (tPA) remains the only treatment currently approved by the Food and Drug Administration, yet only 3–5% of stroke patients qualify for this therapy due to strict requirements and a narrow administrative window (67). Attempts for therapeutic options for ischemic stroke have largely failed in lab-to-clinic translation, possibly owing to a narrow targeting approach to therapy. Focusing on a single molecular pathway among the complex ischemic cascade seems a misguided treatment strategy. An alternative therapeutic approach focusing on an agent that targets multiple mechanisms across the ischemic process may prove more effective (39). By reducing endoplasmic reticulum stress and its sequelae, sEH harnesses this approach, and thus has emerged as a potential target for stroke treatment.

The use of sEH in stroke therapy is based on early genetic studies deciphering the connection between EPHX2 polymorphisms and susceptibility to cerebral ischemia. The Glu470Gly variant, corresponding with increased sEH activity, positively correlates with the incidence of cerebral ischemia among African-Americans (68). In parallel, within a Chinese population an independent association exists between variation of Arg287Gln, which results in decreased sEH activity, and a reduced risk of stroke (69). These findings indicate the protective influence of EPHX2 gene polymorphisms on the risk of ischemic injury, suggesting the significant role of sEH on the incidence and development of ischemic stroke to provide the basis for targeting sEH in stroke treatment.

The broad therapeutic potential of sEHIs may arise from the multi-faceted role of EETs on cardiovascular and cerebrovascular function. An upregulation of EET signaling following transient ischemia may serve as a preconditioning stimulus to protect the brain against future damage (70). These findings, along with the complex protective effects of EETs, suggest that this signaling pathway is activated by ischemic trauma to provide neuroprotection. To this end, both chemical sEH inhibition and gene deletion have been largely successful at providing neuroprotection and reducing the infarct size following ischemic stroke. Even a single low-dose administration of the *t*-AUCB at the time of MCAO reduces infarct volume, improves behavioral outcome as approved by the Stroke Therapy Academic Industry Roundtable (STAIR) criteria for rats, and dose-dependently decreases neuronal cell death (71). Moreover, a twofold elevation of the cumulative EETs-to-DHETs ratio in the brain cortex is recognized with even such low dose administration (71). *In vitro*, targeting multiple elements of neuroprotection with 14,15-EET, a substrate for sEH, and AUDA suppresses astrogliosis, enhances angiogenesis, decreases neural apoptosis, and reduces glial scar formation, confirming the broad protective effects of sEH inhibition (72). sEHIs applied to cultured astrocytes following oxygen-glucose deprivation also increase levels of EET and vascular endothelial growth factor (VEGF), indicating the significant role of astrocytes as possibly mediating sEHI-induced neuroprotection (73). Furthermore, greater ischemic damage is correlated with increased levels of sEH mRNA and less EET production in the mouse endothelium after exposure to oxygen-glucose deprivation (74). Despite these documented efficacy data, the precise mechanisms of sEHIs as multi-target protection against ischemic injury remain unclear. Further studies are needed in the field to examine the broad effects of sEHIs on stroke models *in vivo* and to elucidate the factors contributing to this ischemic protection.

Because EETs are well known vasodilators (75), a potential mechanism of ischemic protection by sEHIs may be through the preservation of CBF. In contrast, the reduction of infarct volume byAUDA-BE in ischemic mice reveals no change in regional CBF rates (6). While AUDA-treated rats display significantly smaller infarct size, AUDA produces no significant effect on vascular structure and acts independently of blood pressure changes (76). Interestingly, administration of *t*-AUCB at time of MCAO promotes a nonsignificant trend post-stroke towards enhanced CBF in the reduced infarct region, but does not significantly alter CBF (71). Compounding this observation, sEH knockout (SEHKO) mice, with targeted EPHX2 gene deletion, show significantly higher rates of CBF, suggesting sEHIs may operate via vascular mechanisms (77). Conversely, overexpression of sEH results in an impairment of the vasodilatory effects of sEHIs and a larger infarct size in mice (27). The explanation for this difference between chemical sEHI and EPHX2 gene deletion remains unknown, although the degree of inhibition appears as a contributing factor, in that chemical sEH inhibition may not be sufficient to enhance CBF compared to chronic loss of activity from gene deletion. This gap in knowledge warrants future investigation into the various degrees of inducing sEH inhibition, specifically focusing on CBF changes both regionally and collaterally. Clarifying the underlying vascular mechanisms of sEHIs is crucial to understanding the profile of sEH and their capacity as therapeutic targets.

Equally relevant to the regenerative capacity of sEHI pertains to the drug's protective capabilities in models that closely approximate the co-morbid elements of stroke, such as hypertension. Following MCAO, the resulting infarct volume is larger in spontaneously hypertensive stroke-prone rats (SHSPR) than in Wistar Kyoto (WKY) rats (78), making these models relevant targets for sEH inhibition therapy. AUDA still reduces infarct volume in SHSPRs following MCAO, but this protection operates independently of vascular mechanisms (76). Chronic sEHI treatment provides vascular protection through reduced blood pressure and increases microvessel density in SHSPR but not WKY rats, and generates neural protection in both species (79).The varying neuroprotection of sEHIs on both SHRSP and WKY rats suggests its broad therapeutic potential, applicable to a wide profile of models representative of the human population.

While current studies suggest the neuroprotective potential of sEHIs in treating ischemic stroke, there are still significant gaps in knowledge that must be examined for hopes of bringing this prospective therapy to the clinic. As discussed previously, the cellular and biological mechanisms underlying sEHI neuroprotection in stroke remain unclear and warrant investigation. Future studies should clarify the differential effects between acute chemical sEHI and EPHX2 gene deletion on ischemic mechanisms such as CBF regulation and inflammation. Moreover, chronic sEHI investigations are significantly lacking which are needed to further shed light on the effects of various degrees of inhibition in stroke models. Additionally, future studies should investigate the optimal timeline for sEH inhibition, as the progress of ischemic injury involves complex time-dependent processes such as the inflammatory response. Despite the significant role of inflammation in exacerbating ischemic damage, studies investigating the anti-inflammatory mechanisms of sEHI protection are severely limited. Of note, the administration of an sEHI (TPPU) following focal ischemia at reperfusion and 24 hours later reduces infarct size by 50% and suppressed inflammation, as measured by a decrease of IL-1β by 3.5 fold and tumor necrosis factor-

alpha by 2.2 fold (80). A decrease in infarct volume is achieved when sEHI is administered before and during MCAO, as well as during reperfusion, likely by targeting the peak of the inflammatory response exacerbating stroke damage. The effects of sEHI administration during post-ischemic reperfusion must be further examined on various models varying in ages and sex to confirm neuroprotective effects across a wider patient pool.

Evaluating various models in exploring the neuroprotective benefits of sEHI remains critical to establish clinical significance. Sex differences pertaining to the distribution of sEH in the body have implications in the field of stroke. Interestingly, SEHKO female mice do not exhibit reduced infarct volume consistent with gene deletion in male models, possibly due to decreased sEH expression (81). These findings suggest sexually dimorphic expression of sEH might explain in part the underlying differences in CBF and ischemic damage experienced between males and females. Along this line of investigation, sEH gene deletion, but not the *t*-AUCB, reduces infarct size in reproductively senescent female mice, yet neither method decreases infarct size in young mice (82). This indicates that sEHI protection against cerebral ischemia may be altered by age and gender. Since in mice, sEH levels are profoundly influenced by both, the lack of data evaluating female and/or aged models in sEH inhibition for ischemic stroke should direct future research to investigate the effects of this inhibition in various models emulating a representative stroke population. Recognizing the therapeutic potential of sEHIs involves a multi-target approach to ischemic stroke suggests that the complexity of this therapy will require further research to clarify the factors of sEH-mediated neuroprotection.

Traumatic Brain Injury and sEH

Operating under similar mechanisms as in stroke, sEH as a therapeutic target for traumatic brain injury (TBI) is much less documented. TBI affects unique groups of people in disproportionate rates, such as military personnel and incarcerated individuals. About 12% of military personnel (83) and 60.25% of incarcerated persons (84) have a history of TBI. TBI, characterized by a blow or penetration to the head, induces primary damage to the brain tissue, followed by cerebral inflammation representing a major secondary cell death pathway(85). EET and other EpFA levels in the brain increase following TBI (86) (31). Exogenous administration of14,15-EET and AUDA promotes angiogenesis, reduces neuroinflammation, suppresses astrogliosis, and improves behavioral outcome in ischemic stroke models (72). Moreover, administration ofTPPU significantly reduces inflammation, as evaluated by a decrease of pro-inflammatory cytokine TNF-α by 2.2 fold and of IL-1β by 3.5 fold (80). This capacity of sEHIs to attenuate inflammation and promote neuroprotection suggests the therapeutic promise of sEHIs in treating TBI in addition to stroke. Targeting sEH in TBI models reveals that SEHKO mice outperform wild-type mice on the beam walk, indicating improved motor coordination both pre- and post-TBI (88). Interestingly, SEHKO mice exhibit minor learning deficits in the Morris water maze independent of TBI (88). Sham-operated SEHKO mice also express an unexpected injured phenotype in the water maze assessing working memory, resembling similar deficits as brain-injured mice (88). A valid consideration for these unexpected findings is the role of the EPHX2 gene in both epoxide hydrolase and lipid phosphatase activity (89), possibly explaining the impaired behavioral phenotypes associated with SEHKO mice. Further studies investigating SEHKO

mice and selective sEH inhibition are needed to confirm the role of sEH in memory consolidation and motor coordination following TBI. Examining discrete brain regions (e.g., hippocampus) to evaluate memory deficits commonly associated with TBI would enhance our knowledge of the broader potential of sEHIs. Moreover, gene deletion of sEH significantly ameliorates TBI-induced brain tissue damage and neurological deficits, as shown by reduced neuronal cell death, brain edema, BBB permeability, apoptosis, matrix metalloproteinase 9 activity, and neutrophil infiltration (31). SEHKO mice also exhibit an increase in anti-inflammatory M2 microglia/macrophages and a decrease pro-inflammatory M1 microglia/macrophages in the injured cortex, as well reduced levels of cytokines IL-1β, IL-6, MIP-2, and MCP-1, suggesting the anti-inflammatory effect of sEH deletion in TBI (31). Pharmacological inhibition by AUDA also attenuates neuroinflammation, brain edema, and apoptosis following TBI (31). Both sEH gene deletion and pharmacological inhibition by sEHIs indicate functional benefits of targeting sEH in TBI.

While these limited studies suggest the neuroprotective and anti-inflammatory potential of sEH inhibition, significant gaps in knowledge must be addressed to validate its therapeutic promise for TBI. Although gene deletion of EPHX2 shows significant promise in attenuating TBI-induced functional and neurological deficits, discrepant results are observed between SEHKO individuals and chemical sEHIs. In stroke models, *t*-AUCB administration at time of MCAO does not significantly alter CBF (71), while SEHKO mice show markedly higher CBF rates (77). Moreover, gene deletion of sEH, but not *t*-AUCB, reduces infarct size in female mice following stroke (82). The challenges observed in sEH stroke models are of interest in TBI due to the overlap of injury mechanism. This warrants the need for investigating the effects of chemical sEHI administration and sEH gene deletion on neurodegeneration and inflammation in TBI models, to better understand the optimal extent of inhibition. The appropriate dosage of sEHIs also represents an area of future direction because of the profile of patient suffering from TBI. The incidence of TBI is especially prevalent in athletes (90) and military combat settings, with more than 300,000 US service members since 2000 sustaining a TBI (91). These TBI victims represent a younger and healthier patient pool compared to those suffering from stroke, given the pertinent association to co-morbidity factors such as aging and obesity. Therefore, the appropriate sEHI therapeutic threshold dosages may be lower for TBI patients than stroke, but still achieve a better prognosis. In the same vein, while stroke and TBI are highly unpredictable diseases, the occurrence of TBI in soldiers and athletes is likely higher than at-risk stroke patients, suggesting a unique opportunity for prophylactic sEHIs for TBI. Additionally, penetrating brain injury (PBI), comprising all TBIs which are not caused by a blunt mechanism, represents an area of future direction for sEHI therapy. Treatment for such open head wounds have shifted from aggressive removal of deep fragments to antibiotic prophylactic treatment to improve neurological outcomes (92). This represents an underexplored opportunity for delivery of sEHIs to prevent subsequent damage by anti-inflammatory and neuroprotective mechanisms. Although inhibition of sEH is gaining ground in the field of TBI therapy, further research is needed to ascertain the therapeutic potential of these inhibitors.

Parkinson's Disease and sEH

PD is one of the most prevalent neurodegenerative diseases, second only to AD (93). Within the next 20 years, the number of patients with PD is predicted to double (94). PD is responsible for the progressive deterioration of normal movement and balance capabilities along with other nonmotor symptoms (94). Over the course of PD, dopaminergic neurons of the substantia nigra die prematurely and Lewy bodies (abnormal protein aggregates of α-synuclein) accumulate in the brain (95). Both motor deficits characteristic of PD including speech impediments, dyskinesia, and nonmotor impairments such as psychosis are unable to be sufficiently treated with current medical or surgical approaches (95). Current medical options attempt to treat PD by increasing dopamine (DA) concentrations or through the stimulation of DA receptors. These approaches are likely not satisfactory due to their limited targeting of the basal ganglia and DA as opposed to a wider range of the neurotransmitters involved in PD (95). Other nonpharmacological treatment options such as physiotherapy are being examined; however, these preliminary findings have yet to yield accepted treatment options in humans (96). Though certain treatments may alleviate symptoms of PD, there is currently no cure and the trigger for the brain death characteristic of the disease is not well understood, restricting treatment to the later phases of the disease (97).

sEH levels are elevated in the regions of the brain that correlate with dopaminergic death in both humans and animal models of PD (93). The expression of sEH is also indicative of striatal α-synuclein phosphorylation (93). Because PD may not display symptoms until up to 80% of striatal DA has already been lost, a means for earlier diagnosis would be highly progressive in broadening the search for treatment options (98). Peripheral detection of elevated levels of sEH in the gut may be possible prior to dopaminergic death, potentially providing an early indicator of PD (97), (98).

The detrimental effects of sEH are well documented (93), (99). In a mouse model of PD, both a deficiency in sEH and the administration of sEH substrate, 14,15-EET, reduces tyrosine hydroxylase-positive cell death (99). The deletion of the sEH gene also protects against neurotoxicity in a PD mouse model (93). Although the inhibition of this gene does not provide a current treatment approach for PD patients, it does allow future medical therapies to target this enzyme as method for slowing the progression of PD.

Furthermore, the inhibition of sEH may also provide a treatment for PD (93). The clinical utility of sEH inhibition is recognized in various heart and lung diseases in asthma patients and smokers, as well as in the brain, discussed here (100), (101). sEH inhibition likely reduces both oxidative stress and neuroinflammation through the elevation of endogenous EETs and other EpFAs (99), (102). An inhibitor of sEH and COX-2, PTUPB provides significant neuroprotective activity in a model of PD using *Drosophila melanogaster* (102). TPPU, another inhibitor of sEH, significantly alleviates the reduction of DA, 3,4-dihydroxyphenylacetic acid and homovanillic acid post-MPTP-induced neurotoxicity in a mouse model (41), (93). Because the degeneration of dopaminergic neurons is one of the main characteristics of PD, sEH could ameliorate the progression of the disease (95). In tandem, its potential to slow PD progression suggests that TPPU would likely be more effective if its administration began earlier in the course of the disease, prior to the onset of

symptoms. Future trials examining the efficacy of such sEH inhibition treatments beginning at various stages of PD would guide the translational application of this drug to the clinic. The practical benefits of TPPU indicate that the repeated oral delivery of TPPU significantly reduces neurotoxicity in the striatum of mice (93). Indeed, orally administered TPPU demonstrates the ability to suppress apoptosis in PARK2 neurons, further demonstrating the negative effects of sEH and the benefits of its inhibition (93). As noted above, EETs have previously been used in cases of cerebral stroke, cardiac failure, and hypertension to ameliorate inflammation, caspase activation, and apoptosis, among other damaging processes (103). Inhibition of sEH has the potential to increase the half-life of endogenous EETs. EETs may aid in neuroprotection in models of PD through mechanisms similar to their cytoprotective properties in models of other disorders such as stroke, TBI, and epilepsy (discussed later) (103). Inhibition of sEH in PD has yet to be clinically verified. *In vivo* animal models lend support to both the significant detrimental implications of elevated sEH levels and the ameliorating effect of reducing the expression levels of the enzyme. It is critical to further study the use of elevated sEH levels in the brain as a biomarker of early PD detection and its treatment with sEH inhibition prior to onset of symptomatic loss of striatal DA and neuronal death. Moreover, the use of sEH inhibitors such as TPPU and EETs should be evaluated at different stages of PD in animal models and clinical trials to determine whether they are viable as treatment options for patients with preexisting and progressive stages of PD.

Other Neurological Disorders and sEH

Epilepsy

In addition to stroke, PD, and TBI, sEH has been implicated in epilepsy within the last five years. Epilepsy is defined as recurrent seizures characterized by extensive, synchronized excitatory signaling by neurons (104). Neuroinflammation, paramount to the disease process in other CNS disorders, has been linked to epileptic pathogenesis (105), (106). Due to its role in inflammation, sEH has become an attractive target for therapeutic intervention in epilepsy. AUDA treatment in rats subjected to induced temporal lobe status epilepticus and the inflammatory response decreases expression of inflammatory cytokines IL-1β and IL-6 in the hippocampus (107). The ratio of EETs to DHETs is also increased in the AUDA treated group, suggesting that the inhibition of sEH slowed the degradation of EETs. Notably, treatment with AUDA successfully increases seizure induction threshold, and decreases seizure susceptibility (107). This observation suggests that inhibition of sEH produces therapeutic, anti-inflammatory effects in the brain as well as in peripheral systems.

Although inflammation is key to epilepsy pathology, other findings suggest that sEHIs may confer protection via other mechanisms. Mice administered sEHIs and exogenous EETs are resistant to gamma-aminobutyric acid (GABA) antagonist seizure induction (108). It is hypothesized that CYP is involved with GABA signaling, which is a key epileptic pathway (108). However, these mice remain susceptible to seizures induced by other means, as evidenced by the failure of sEHI 1-(1-methanesulfonyl-piperidin-4-yl)-3-(4-trifluoromethoxy-phenyl)-urea (TUPS) to halt seizures produced by powerful convulsant tetramethylenedisulfotetramine (TETS) when administered after the seizure onset, but is

effective when initiated prior to the seizure (62). In addition, TUPS is effective at reducing TETS-induced cell death and neuroinflammation when administered in combination with GABA-A receptor agonist diazepam (62). These results suggest that EETs offer therapeutic ability by modulating excitatory signaling in addition to attenuating inflammation. EETs' effects on neuronal excitability are supported by an additional finding that EET isomer 11,12 EET hyperpolarizes CA1 pyramidal neurons in the hippocampus by inducing increased G-protein-activated K^+ conductance (109).

The applications of sEHIs in epilepsy hold promise, but clinical translation is lacking. In a study of 20 patients with temporal lobe epilepsy, sEH enzyme levels are increased compared to the control group (110). Furthermore, seizure duration and frequency correlate with sEH level (110). This suggests that there is a niche for sEHI intervention in humans, but more studies must be conducted to better elucidate the role of sEH in epilepsy.

Cognitive Impairment and Dementia

Pathologic manifestations of cognitive decline and dementia implicate sEH's important role in these debilitating neurodegenerative diseases. An estimated 13.9% of people over the age of 71 suffer from the cognitive decline, making it a major public health concern (111). Causes of dementia include AD, vascular pathology, accumulation of Lewy bodies, and others. Based on the documented pathological effects of EETs on vasculature, sEH has been identified as a potential therapeutic target for vascular cognitive decline. sEH has also been recently identified to have detrimental consequences in AD, and the relevant research will be discussed below.

Accumulation of beta amyloid protein aggregates (Aβ) is a hallmark of AD and a strong initiator of cytotoxicity. Recently, a pathological link between Aβ and the formation of epoxides from CYP P450 is detected in cerebral microsomes prepared from brain tissues of Sprague-Dawley rats that show a 30% decrease in 14,15 EET production when cultured with Aβ. These findings suggest that EpFA production is impaired in AD (112). While limited data support the relationship between sEH and AD, this study serves as a platform for future investigation.

The role of sEH in vascular cognitive impairment (VCI) is notable in individuals diagnosed with VCI that showed increased DHET levels in brain tissues post-mortem, suggesting upregulated activity of sEH (113). Moreover, increased sEH immunoreactivity in the cerebrovascular endothelium is observed adjacent to hyperintense white matter lesions (WMH), which are characteristic of VCI. The R287Q sEH polymorphism is also associated with increased WMH volume (113). Interestingly, there is an association between WMH and psychiatric diseases that involve cognitive impairment (114). This implies that there is an intimate relationship between cell signaling, cerebrovasculature, and behavior, and that sEH may represent a common denominator when investigating possible treatment options for these disorders. These results suggest that sEH may represent a viable target for the treatment of cognitive impairment in humans, though more *in vivo* and *in vitro* research must be conducted to establish a causative relationship.

Depression

Depression is the most common psychiatric disorder, and can cause crippling symptoms such as fatigue, suicidality, lack of appetite, and anhedonia. To date, treatment options for depression are relatively limited to selective-serotonin reuptake inhibitors (SSRIs), selective-norepinephrine reuptake inhibitors (SNRIs), and counseling (115). Even with the availability of SSRIs and SNRIs, many still do not respond to pharmacological intervention. Inflammation, like in other diseases affecting the brain, could have a feasible and damaging role in depression as well, as suggested by Zunszain, Hepgul, and Pariante (116). This paves the way for the notion that EETs may have advantageous effects on depressive symptoms due to their anti-inflammatory properties.

Seasonal major depression is accompanied by increased sEH derived oxylipins in patients during the winter, suggesting increased sEH activity (117). Although the clinical significance of this study is limited by the small sample size (n = 15), these results offer venues for more studies investigating the use of sEH derived oxylipins as potential biomarkers for depression. Furthermore, TPPU administration is associated with ameliorated depressive symptoms in social defeat stress models in mice (41). SEHKO mice and TPPU-treated mice also display greater resilience to social defeat stress, which corresponds to upregulated brain-derived neurotrophic factor signaling via the TrkB receptor (41), (118). This provides further evidence for sEH inhibition's integral role in depression pathology and its potential use as an antidepressant. More studies must be executed to uncover the exact mechanisms by which sEH is involved in depression.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage has a similar mechanism of injury as the disorders mentioned above, with acute inflammation serving as a major bad actor in poor outcomes (119). Therefore, sequestration of the inflammatory response in subarachnoid hemorrhage may be beneficial, and this may be mediated by an increased level of EETs. In SEHKO mice, less edema is observed in white matter tracts after subarachnoid hemorrhage-induction compared to wild-type mice (120). SEHKO mice are also found to express less VCAM-1 after subarachnoid hemorrhage, which is a marker of damaged endothelium (120). This may be the reason for the reduction in edema in these mice. 14,15-EET is also shown to be protective against delayed cerebral ischemia in mice subjected to subarachnoid hemorrhage (121). As described above, there is one clinical trial that has been launched, aiming to evaluate the effects of GSK2256294 (51). Although the use of sEHIs as treatment for subarachnoid hemorrhage is still in its rudimentary phase of clinical evaluation, preclinical data are supportive.

Obesity and sEH

Obesity is an increasingly common public health problem, particularly in westernized countries with poor diets consisting of simple carbohydrates and trans-fats (122). The estimated prevalence of obesity in the United States is 36.5% of adults (123). Obesity is a major risk factor for a variety of severe health conditions such as diabetes mellitus and cancer due to an increased chronic inflammatory state (124). While there are many factors

influencing weight, such as diet, genetics, and physical activity, the brain-gut axis plays an especially important role in endocrine signaling and microbiome interaction (122). sEH inhibition represents a promising treatment for cardiovascular diseases, discussed in detail above. There is accumulating evidence that sEH may contribute to obesity-related disorders as type II diabetes mellitus, hypertension, and cardiomyopathy (125).

In rats, there is an observed post-prandial decrease in sEH, marked by oxylipin (126). This decrease in sEH activity is additive with increased dietary potassium, which is shown to decrease risk of stroke (126), (127). However, rats treated with antibiotics to eradicate gut flora do not show the attenuation of sEH activity seen in non-treated rats (126). This information suggests that sufficient dietary potassium may induce inhibition of sEH modulated by the gut microbiome, and altogether may be protective against cerebrovascular accident. In rats fed a high-fat diet for 10 weeks, CYP-derived EET production is significantly decreased compared to rats with a normal diet (128). Mice treated with sEHIs for 5 weeks demonstrate a 32% decrease in caloric intake after being fed a high-fat high-fructose diet prior to the sEHI administration, leading to weight loss (129). The same mice also show decreased leptin levels after sEHI treatment (129). Furthermore, colonic inflammation associated with obesity is correlated with increased levels of sEH in mice, and its genetic deletion is associated with decreased inflammation (130). Therefore, diet, a major contributing factor to obesity, is shown to influence the production of EETs and activity of sEH. As discussed thoroughly above, increased availability of EETs/sEH inhibition may be protective in stroke. The established interaction between the gut microbiome (131) and brain, due to the findings that sEH activity may be partially dependent on gut bacteria modulation, may be of interest in future research concerning sEH in obesity and obesity-related disorders. In summary, sEH inhibition may promote a healthy gut, which not only has beneficial effects on the gastrointestinal tract and obesity, but also on the brain.

sEHI Therapeutic Effects in Other non-CNS Organs

sEHIs exhibit therapeutic effects in other non-CNS organs, such as the liver, heart, and kidney (132) (133) (134). Particularly, sEHIs mitigate tissue fibrosis in several organs such as the liver, as TPPU reduces collagen deposition, inflammation, and endoplasmic reticulum stress in the livers of mice given carbon tetrachloride (132). TPPU also attenuates heart remodeling associated with cardiac fibrosis by improving heart function, decreasing collagen deposition, reducing cardiac fibroblasts, and preventing cardiomyocyte hypertrophy (133). Additionally, sEHIs reduce myocardial infarct sizes after heart ischemia and preclude cardiac hypertrophy and arrhythmia via EET-related pathways in animal models (135), (136). Similarly, inhibiting sEH decreases inflammation, cell death, and oxidative stress, and precludes renal fibrosis in mouse kidneys (134). Moreover, sEHIs protect against hypertension-related damage to vascular and glomerular structures in the kidney and reduce collagen type IV expression (137), (138). In fact, administering AUDA prevents hypertension and type 2 diabetes-associated renal damage by decreasing urinary albumin and MCP-1 excretion and the infiltration of monocytes/macrophages in the kidney (139). Thus, sEHIs are capable of protecting the heart and kidney from cardiovascular diseases such as hypertension (20). Furthermore, sEHIs' anti-inflammatory properties and ability to mitigate systemic inflammation (140) may also prevent additional inflammation-induced

damage to these organs resulting from the actions of pro-inflammatory molecules and pathways following tissue insult (133), (141).

Stem Cells and sEH

The anti-inflammatory properties of sEHIs in CNS disorders can be enhanced by similar anti-inflammatory and regenerative characteristics of stem cell therapy. Although the mechanisms of stem cell therapeutic techniques remain not well understood, even short-lived stem cell engraftment may serve as key regenerative process towards direct replacement for damaged or dead cells (142) (143), (144). A concern of sEHI use is that it may reduce endogenous stem cell proliferation (145), and this may be amended through the engraftment of exogenous stem cells to maintain neurogenesis. Additionally, transplanted stem cells can provide indirect aid by secreting a variety of therapeutic molecules to stimulate the repair of dying brain cells (146), (147), (144) with anti-inflammatory factors among these secreted factors as highly potent for affording regeneration (148), (149), (150). Similarly, sEHIs exhibit anti-inflammatory properties (10), (151), making them prime candidates for combination therapy with stem cells. In tandem, stem cells can advance sEHI applications by compensating for the deteriorating endogenous cells through reduction of inflammation-plagued CNS disorders.

sEH overexpression in CNS disorders characterized by protein aggregate-mediated inflammation may benefit from a combination of sEH inhibition and stem cell therapy. In PD patients, sEH levels are elevated and centralized around inflamed areas associated with α-synuclein aggregation (97), a pathological hallmark of the disease. While α-synuclein aggregation in PD is primarily observed in the brainstem and cortex, such aberrant protein accumulation can also be detected peripherally. Thus, sEH, a mediator in the accumulation of α-synuclein, may be detected outside the CNS as well. If altered sEH levels can be assayed peripherally, then early diagnosis and intervention are possible to prevent extensive dopaminergic neuron loss in PD, whose symptoms are not recognized until 80% of the dopaminergic neurons are depleted. Interestingly, sEH inhibition reduces neurotoxicity in cell and animal models (93), and the treatment may be enhanced by the addition of stem cells (97). While sEH activity in plasma is very low, the activity and protein can be monitored in peripheral blood cells. Because endogenous stem cells from PD patients show increased concentrations of sEH, cell replacement with exogenous stem cells containing lower levels of sEH represents a viable method for promoting brain regeneration (97). Interestingly, similar to PD, a pathological link between inflammation and protein aggregation accompanies other CNS disorders; notably mutant huntingtin in HD (152), platelet-leukocyte aggregations in stroke (153), increased α-synuclein in TBI (154), increased amyloid and tau in dementia (155), depositions prion protein upregulation in clinical depression (156), and spectrin aggregate formations in epilepsy (157). Cognizant of these overlapping pathologies, combination therapy of stem cells and sEHI stands as potentially efficacious strategy to treat CNS disorders plagued by neuroinflammation and proteinopathy.

sEH inhibition may harbor an anti-inflammatory environment in CNS disorders due to the intrinsic properties of EETs (6), (10), (11), and this therapeutic pathway may be enhanced

by stem cell adjunctive therapy (Figure 3). Indeed, sEHIs have been studied in the context of stroke (6), (71), (158), epilepsy (108), PD (102), and TBI (31), which are well-documented disorders with neuroinflammation as a major secondary cause of cell death. In similar fashion, stem cell therapy in these disorders dampens inflammation (159), (160), (161), (162), (163), (164), (165). sEHIs suppress inflammation by reducing proinflammatory lipid mediators (140), but an equally potent anti-inflammatory mechanism is the activation of the EET-induced PPAR-γ pathway (151), which inhibits the NF-κB pathway and reduces VCAM-1 expression (8), (151), (158). Conversely, PPAR-α and PPAR-γ agonists are potent inducers of the sEH enzyme (166). In parallel, the anti-inflammatory properties of stem cells (160), (161), (167), acting likely via reduction of ICAM-1 is also seen in stem cell transplants in experimental stroke (168). Altogether, the postulated mechanism mediating inflammation in CNS disorders reveals equally common cellular and molecular targets to probe stem cells and sEHI interactions. Furthermore, the recognition of sEH-mediated inflammation and the poor stem cell survival following transplantation due to inflammation (169) offers novel insights for the use of sEHIs to enhance stem cell therapeutic effects.

sEHIs and stem cells share many signaling pathways, which may explain their similarities in the resulting functional outcomes. The Wnt and PI3K/AKT signaling pathways are involved in both sEH and stem cells (145), (170), (171), (172). Interestingly, both the PI3K/AKT and AKT/GSK3β pathways are regulated by EETs for promoting angiogenesis (173) and endothelial progenitor cell (EPC) function (174), respectively. In addition, the EET-mediated activation of the PI3K/AKT pathway provides protection after cerebral ischemia/reperfusion injury (173). With this in mind, the idea that sEHIs enhance stem cell therapeutic effects via PI3K/AKT or AKT/GSK3β pathway should be further explored to fully understand the benefits of sEHI on stem cell survival towards optimizing an sEH-based stem cell combination therapy.

sEHIs and stem cells both enhance the vasculature via the PPAR-γ pathway, an established regulator of angiogenesis. EETs are endogenous activators of PPAR-γ (8), (10), (151), which can modulate EPC function (7), (174). Moreover, sEHIs increase the expression of VEGF and hypoxia-inducible factor-1α (HIF-1α) via PPAR-γ (7), which are secreted by stem cells (160) and are neuroprotective for CNS disorders (175). Furthermore, MSCs can synthesize EETs (167), and in turn EETs are able to enhance stem cell migration following transplantation (176). Equally convincing evidence also show that, sEH and EETs can inhibit hematopoietic progenitor cell proliferation and MSC-derived adipocyte stem cell differentiation (145), (167), (177), suggesting that a much more careful assessment is necessary when contemplating sEH inhibition and stem cell combination therapy. Along this cautionary note, both the NF-κB and Wnt signaling pathways are involved in cancer stem cells (172), (178), (179). Supporting this, sEH expression is found to be increased in many different neoplastic tissues (10). Translational research efforts evaluating sEHIs' role in reducing the potential tumorigenic risk of stem cell therapy while maximizing their therapeutic effects (160), (179) will guide not just the efficacy, but also the safety of sEHI and stem cell combined therapy.

Synergistic Effects of sEHIs Combined with Other Compounds

While benefits of sEHIs are typically associated with EETs, which are anti-inflammatory and promote vasodilation (20), other EpFAs are also active and exert detrimental or beneficial effects (55). For instance, sEH metabolizes linoleic epoxides to linoleic diols, which demonstrate toxicity, modulate thermogenesis and brown adipose tissue, and cause vascular permeability and sepsis (180), (55). Epoxyeicosatrienoic acids (EEQs) from eicosapentaenoic acid (EPA) are implicated in anti-inflammation and various organs such as the lungs and uterus (181). Epoxydocosapentaenoic acids (EDPs) from docosahexaenoic acid (DHA) are often more active than EETs, highly present in the retina and brain (180), and possess potent anti-angiogenic (182) and vasodilatory (180) properties. In particular, 17,18-EEQ and 19,20-EDP decrease autophagy and ER stress in obese mice (183) and inhibit sEH metabolism more than other omega-3 regioisomers (180). Interestingly, EEQs and EDPs may exhibit a greater increase in vasodilation and decrease in pain and inflammation than EETs (184). Of note, omega-3 rich diets promote anti-inflammation and raise plasma and tissue concentrations of EEQ and EDPs in mammals, as these compounds are derived from omega-3 fatty acids (185). Moreover, sEHIs are more efficient in most assays if the animal's diet is high in omega-3 fatty acids and lacks omega-6 fatty acids (183), (185). sEHIs exhibit beneficial synergistic effects such as increased anti-inflammation when applied with other compounds. Combining sEHIs with a diet rich in omega-3 polyunsaturated fatty acids (PUFAs) mitigates hypertension induced by angiotensin-II, increases EPA and DHA epoxides in the kidney, decreases inflammation, and inhibits COX and LOX metabolic pathways compared with a diet rich in PUFAs and no administration of sEHIs (186). Moreover, using sEHIs in tandem with nonsteroidal anti-inflammatory drugs (NSAIDs) exerts synergistic effects such as increased antinociception and reduced COX enzyme expression which leads to decreased pain and inflammation, while avoiding detrimental thrombotic cardiovascular side effects associated with NSAIDs (187). Indeed, co-administration of aspirin and *t*-AUCB enables a lower dose of aspirin to be used, achieving the same anti-inflammatory benefits as a higher dose while minimizing the risk of blood clotting and gastrointestinal side effects (188). Administering the COX-2 inhibitor (coxib) celcecoxib together with *t*-AUCB reduces inflammation, increases eicosanoids like EETs that provide cardiovascular protection, and inhibits tumor angiogenesis to preclude tumors from growing and metastasizing in animal cancer models (48). Similarly, *t*-AUCB boosts 5-lipoxygenase (5-LOX) activation protein (FLAP) inhibitor MK886-mediated anti-inflammation and lipoxygenase inhibition, apparent by the reduction in the pro-inflammatory 5-LOX metabolites such as leukotriene and 5-HETE in a murine model (188). Furthermore, adding omeprazole, a CYP 450 inducer, together with TPPU has a combined effect which increases pain reduction, P450 activity, and EET levels (189). Combining PPAR-γ agonists and sEHIs reduces glomerular injury in the kidneys of hypertensive obese rats significantly more than the PPAR-γ agonist or sEHI alone (138). Of note, administering both sEHIs and phosphodiesterase inhibitors has a stronger effect on decreasing pain and elevating the plasma ratio of epoxy/dihydroxy fatty acids (190). With these favorable synergistic effects, it is possible that combining sEHIs and stem cells may augment the latter's anti-inflammatory characteristics and may exhibit other beneficial effects.

Administration of both sEHIs and exogenous EETs have beneficial effects on the brain and other body systems, as described above. Inhibition of sEH seems to be a more important objective than administering EETs themselves. EEQs and EDPs may have more anti-inflammatory properties than EETs, the availability of which would be increased by sEH inhibition and not by EET administration (184). The unique distribution of sEH in the brain also presents a therapeutic challenge. This supports the inhibition of sEH as a target, so that effects take place where the enzyme works, rather than the transplant of EETs. EETs are also susceptible to stomach acid degradation, beta oxidation, and hydroxylation (191). However, AUDA shows significantly more activity in the dilation of mesenteric vessels than other sEHIs, and this has been attributed to its ability to mimic epoxides (EETs and EpFAs) (192). Therefore, there is evidence that an ideal therapeutic regimen may entail the use of both EETs and sEHIs.

Conclusion

sEH is an enzyme that has been linked to many pathological conditions within the last 20 years, ranging from cardiovascular disease to neurological disease. Its association with CNS disorders has been more recently established, and inhibition of sEH shows robust therapeutic potential. Some of the applications of sEHIs include the attenuation of inflammation, regulation of blood flow, and protection of neurons from excitotoxicity. However, many more mechanisms could be uncovered and further investigation of sEH's involvement in CNS disorders is warranted. In addition to discovering other methods by which sEHIs may be beneficial to the progression of neurological diseases, the pharmacological properties of such drugs must be optimized. The envisioned safe and effective sEHI will likely possess druggable properties that include sufficient water solubility, a half-life justifying once a day dosing, and the capacity to cross the BBB. Although some sEHIs are known to cross the BBB, there has not been a systematic process to optimize CNS exposure of sEHIs. Formulating and manufacturing compounds that are tailored toward these properties will be crucial to the success of sEHIs for treating CNS disorders.

The neuroprotection of sEH inhibition in neurological disorders has been documented in stroke, as evidenced by reduced infarct size accompanied by dampened inflammatory response likely by decreasing pro-inflammatory cytokine secretion. sEHIs may also improve outcomes by modulating CBF, although equally compelling evidence suggest non-CBF mechanisms. Future studies must address deficits in current knowledge on stroke relating to vascular involvement, clinical differences between pharmacological inhibition of sEH and gene deletion, and sex differences that may result in differed treatment. While sEH inhibition is thought to operate under similar mechanisms in TBI treatment, many more investigations must be pursued to identify the exact targets of sEH-derived pathology in TBI.

The sEH represents a highly unique and innovative target for potential treatment in PD. Studies have shown that sEH levels in both the brain and gut may be a possible PD pathology indicator well before symptoms arise, highlighting its importance in the early stages of the disease. sEH inhibition has also been associated with decreased loss of dopaminergic neurons in the striatum, illustrating its therapeutic power. Moreover, the use of sEH as a PD biomarker and sEHIs as a therapeutic agent will likely translate to clinical

applications, which can be employed as a basis for other sEH-based investigations in other CNS disorders.

Extending the role of sEH in other neurological diseases remains in its infancy. In epilepsy, sEHIs have been shown to reduce inflammation and attenuate GABA-antagonist-induced excitotoxicity. Additionally, a decline in EETs correlates with Aβ aggregates, suggesting potent vascular effects of sEHIs in combating cognitive decline due to VCI and AD. Finally, sEHIs may reduce depression-related inflammation, indicating the participation of sEH in psychiatric disorders. Future directions include ascertaining the therapeutic properties and mechanisms of sEH inhibition on the array of these brain disorders.

Currently, stem cell therapies for CNS disorders such as PD, HD, stroke, TBI, and epilepsy are in clinical trials. Optimizing the delivery of exogenous stem cells and the ability to stimulate endogenous stem cells, and overcoming risk factors including tumorigenesis, are avenues to test the adjunctive therapeutic potential of sEHIs. CNS disorders are often characterized by chronic inflammation and neuronal death. sEHIs can reduce neuroinflammation by upregulating EETs and other EpFAs and promoting angiogenesis, thus alleviating some symptoms of CNS disorders, but also enhancing stem cell grafts' functional effects. In combination, sEH inhibition can reduce inflammation while the transplantation of exogenous stem cells can provide a neuroprotective effect. Elucidating the exact mechanisms by which sEH inhibition and stem cell therapy interact represents gaps in our knowledge that when resolved can allow a safe and effective combination therapy of sEHI and stem cells.

In conclusion, sEHIs offer many attractive therapeutic features that may aid in treating a variety of CNS disorders. This review outlined the most studied concepts, as well as highlighted the novelty of sEHI use in specific CNS disorders. It is possible that a majority of sEHI action comes from preserving eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) epoxides more than ARA (EETs) and blocking formation of linoleate diol (leukotoxin). Future basic science directions may uncover innovative mechanisms by which sEHIs can exert therapeutic effects, thereby guiding translational efforts towards realizing their full clinical potential for treating brain maladies.

Abbreviations

ARA	arachidonic acid
COX	cyclooxygenase
LOX	lipoxygenase
CYP	cytochrome P450
CBF	cerebral blood flow
EET	epoxyeicosatrienoic acid
DHET	dihydroxyeicosatrienoic acid

EpFA	epoxy fatty acid
CNS	central nervous system
sEH	soluble epoxide hydrolase
sEHI	soluble epoxide hydrolase inhibitor
TBI	traumatic brain injury
PD	Parkinson’s disease
MCAO	middle cerebral artery occlusion

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Highlights

- The neurobiology of sEH is underexplored despite preclinical and clinical studies demonstrating therapeutic effects of sEH inhibitors in peripheral diseases
- Compelling evidence shows sEH may play important roles in the pathology and treatment of neurological disorders.
- A robust inflammatory response closely accompanies the onset and progression of the pathology and symptoms of many brain diseases.
- Targeting sEH may alter the inflammatory response signaling pathways, thereby advancing a novel approach for CNS regenerative medicine
- Induced pluripotent stem cells and animal models are test beds for interrogating basic science mechanisms and clinical applications of sEH in CNS disorders.

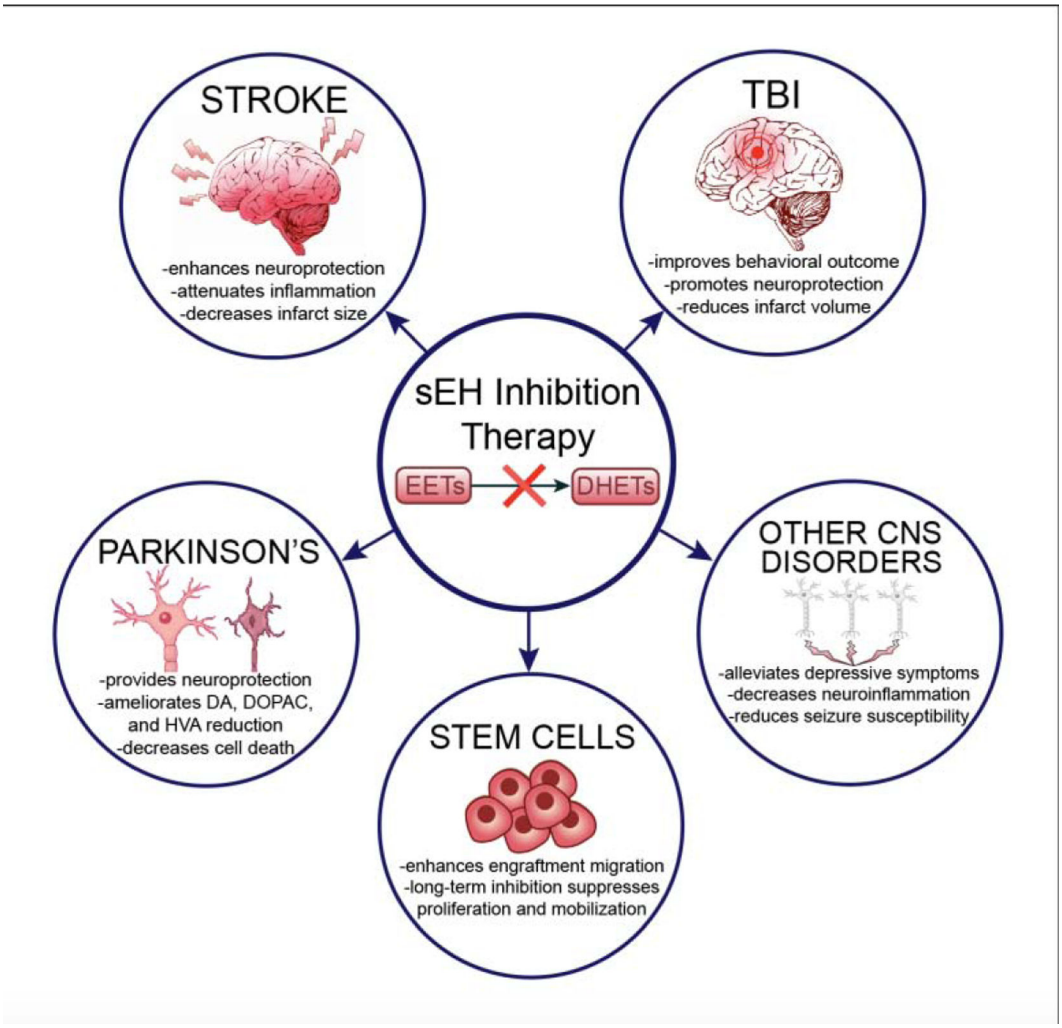

Figure 1.

The effects of sEH inhibition on major CNS disorders. sEH inhibition prevents the typical breakdown of EETs and other EpFAs into DHETS or other corresponding 1,2-diols, facilitating the regenerative process of certain disorders. This treatment may be coupled with stem cell therapy in order to improve treatment outcomes.

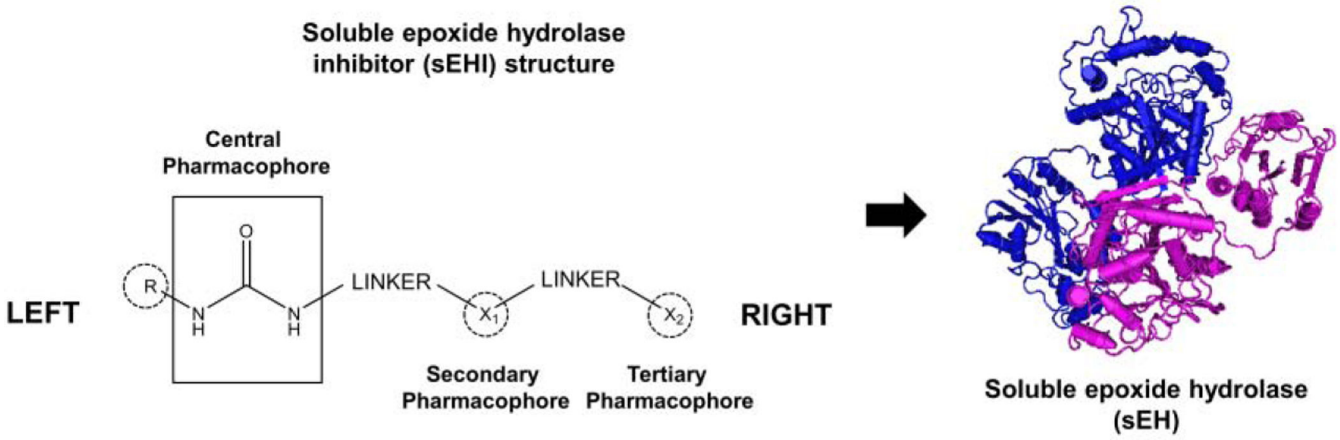

Figure 2.

Soluble epoxide hydrolase inhibitor (sEHI) structures. The chemical structures of several sEHIs. These compounds inhibit sEH, whose three-dimensional structure is depicted on the right (PDB ID: 1CQZ; MMDB ID: 11526).

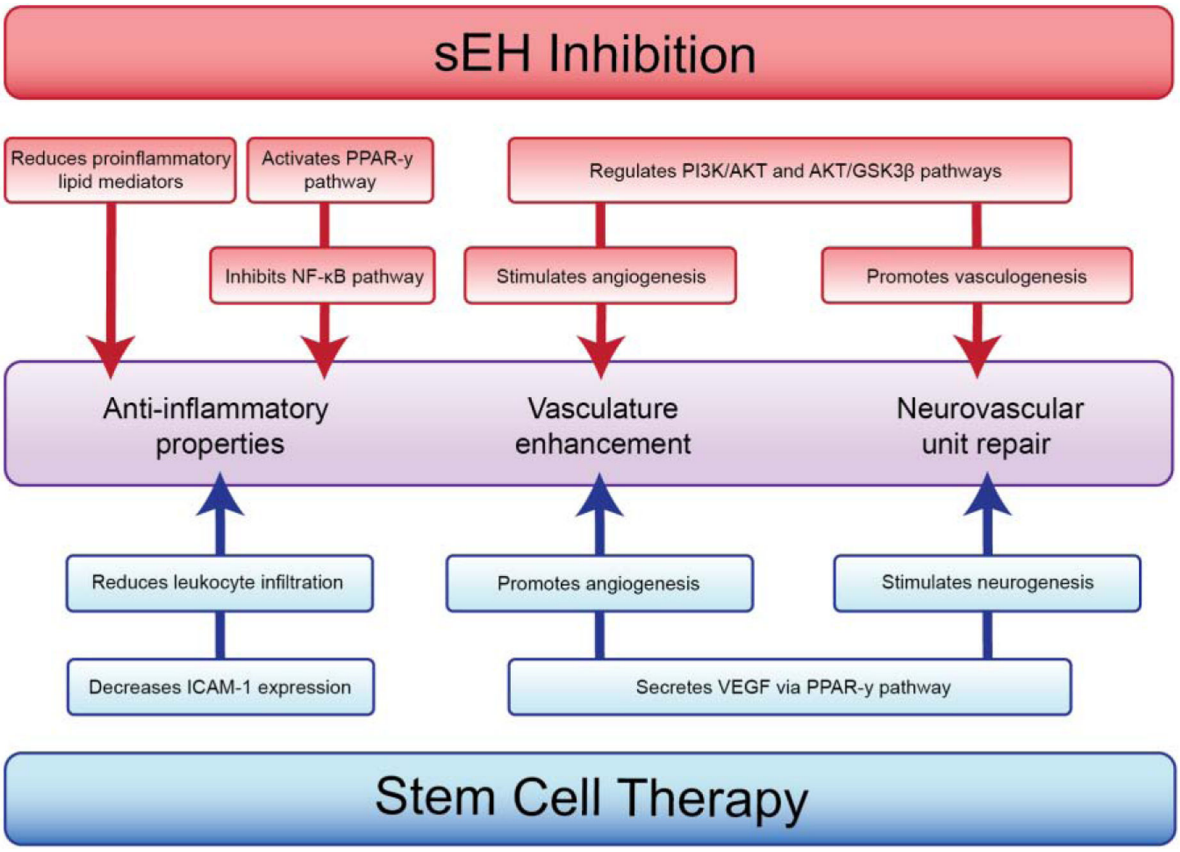

Figure 3.

The potential mechanisms by which sEH inhibition and stem cell therapy may be synergistic. Beneficial properties of each treatment may be enhanced when used in combination, improving outcomes of CNS diseases.

Table 1.

A summary of breakthroughs in the discovery and use of sEH. sEH reduction through gene deletion or the use of inhibitors demonstrates novel therapeutic applications in CNS disorders. sEH inhibition results in an increase in EETs which aids in the treatment of such neurological disorders.

Major Studies Contributing to the Emergence of sEH into CNS Disorders	
Study	**Discovery**
Gill et al., 1972	Incubation of the juvenoid 1-(4'-ethylphenoxy)-6,7-epoxy-3,7-dimethyl-2-octene with rat liver microsomes forms diol metabolites and is the first description of sEH in mammals
Hammock et al., 1976	Various experiments reveal sEH's biochemical characteristics such as an isoelectric point of 4.9, a molecular weight of 150,000, and increased activity in kidney and liver soluble fractions relative to microsomal fractions
Mumby & Hammock, 1979	In mouse livers, epoxide hydrase-mediated hydration rates change depending on the quantity of alkyl substitutions on the epoxide, exhibiting sEH substrate specificity for the first time
Gill & Hammock, 1979	sEHs hydrate both cis- and trans- epoxymethyl stearates in mouse livers, especially in the cytosolic fraction; the first description of epoxy fatty acids as substrates
Gill & Hammock, 1980	First comprehensive description of sEH, revealing that epoxide hydrase activity is present in various organs like the spleen, lung, colon, etc., but is highest in the liver and kidney; is higher in male mice compared to female mice, increases as mice age, does not require a cofactor, and is inhibited by inorganic ions.
Ota & Hammock, 1980	sEH (cytosolic) activity, unlike microsomal enzymes, was overlooked by other researchers because assays with high pH were utilized, which minimizes sEH activity; sEH activity is lowest in rats compared to mice and guinea pigs, but rats are frequently used for epoxide hydrolase distribution investigations; and studies with styrene oxide led to the misconception that epoxide hydrolase activity requires membrane binding
Hasegawa & Hammock, 1982	A spectrophotometric assay using substrate trans-stilbene oxide describes the measurement of mammalian cytosolic epoxide hydrolase activity
Grant, Storms, & Hammock, 1993	Structural analysis of the isolated sEH coding sequence reveals the first characterization and transient expression of the cloned cDNA in cell culture
Grant et al., 1994	Chromosomal location of murine sEH gene is determined at band D of chromosome 14, homologous to human chromosomes 8, 13, and 14
Pinot et al., 1995	sEH activity in mice is higher in males than in females. sEH is under regulation by peroxisome proliferators and hormones such as testosterone. sEH activity is also greater in the liver than the kidneys
Draper & Hammock, 1999	sEH activity present in rat inflammatory cells is indistinguishable from rat liver cytosolic sEH
Draper & Hammock, 1999	Zinc and other metals can act as inhibitors of sEH, suggesting a mechanism of enzyme down-regulation during inflammation
Yu et al., 2000	EETs are involved in renal vasculature activity, thus the use of an sEH inhibitor to decrease EET hydrolysis is a novel therapy for regulating blood pressure
Alkayed et al., 2002	Upregulation of EETs post ischemic stroke is an innate mechanism to protect the brain against future damage
Morisseau et al., 2002	Lipophilicity controls the water solubility of sEH inhibitors, which limits their potency as regulators of blood pressure and inflammation
Dorrance et al., 2005	AUDA, an inhibitor of sEH, reduces infarct size post ischemic stroke without affecting vascular structure
Liu et al., 2005	Inhibition of sEH through AUDA enhances laminar flow PPAR-y activity, which upregulates the anti-inflammatory effect demonstrating PPAR-y influences EETs
Schmelzer et al., 2005	sEH inhibitors reduce inflammation by reducing levels of proinflammatory cytokines and nitric oxide metabolites
Zhang et al., 2007	sEHI AUDA-BE reduces infarct size (post ischemic stroke) and is neuroprotective by non-vascular mechanisms
Zhang et al., 2008	sEH knockout mice, with EPHX2 gene deletion, demonstrate that sEH gene deletion protects against ischemic stroke via a vascular mechanism that reduces EET hydration
Illif et al., 2009	EETs aid in neurogenic vasodilation and are produced by perivascular nerves
Zhang et al., 2009	sEH in part explains sex-linked differences in blood flow and brain damage post ischemic stroke
Sarkar, Narayanan & Harder, 2011	Epoxygenase activity is impaired in Alzheimer's disease

Major Studies Contributing to the Emergence of sEH into CNS Disorders	
Study	**Discovery**
Vanella et. al., 2011	sEH inhibition, using siRNAs, decreases mesenchymal stem cell-derived adipocyte stem cell differentiation
Fromel et. al., 2012	Long-term sEH inhibition is detrimental to hematopoietic progenitor cell proliferation, mobilization, and vascular repair
Shaik et al., 2013	sEHI *t*-AUCB reduces infarct volume, neuronal cell death, and behavioral deficits if administered during MCAO
Strauss et al., 2013	sEH-KO mice display improved behavioral outcomes in comparison to wild-type mice post TBI
Inceoglu et al., 2013	Mice treated with sEHIs are resistant to GABA-antagonist induced seizures
Hung et. al., 2015	sEH inhibitor AUDA attenuates inflammation and decreases seizure susceptibility in a rat model of temporal lobe epilepsy
Li et. al., 2015	EETs enhance hematopoietic stem and progenitor cell engraftment migration in mammals
Qin et. al., 2015	Tyrosine hydroxylase-positive cell death can be reduced by sEH deficiency or administration of 14,15-EET in a PD mouse model
Liu et al., 2016	sEHIs 14,15-EET and AUDA cause suppressed astrogliosis, enhanced angiogenesis, decreased neural apoptosis, and reduced glial scar formation *in vitro*
Ren et. al., 2016	sEH inhibitor TPPU mitigates depressive symptoms in mice
Zhang et al., 2017	sEH inhibition post OGD increases EET and VEGF levels, indicating that astrocytes may help control sEHI-induced neuroprotection
Hung et al., 2017	sEH-KO mice and AUDA-treated mice display improved behavior, decreased brain edema, less brain tissue damage and apoptosis, and less BBB permeability post TBI
Lakkappa et. al., 2018	sEH inhibitor PTUPB provides neuroprotection in a Drosophila model of PD
Ren et. al., 2018	sEH inhibitor TPPU ameliorates reduction of DA, DOPAC, and HVA in a MPTP-induced mouse model of neurotoxicity

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Table 2.

A summary of completed and ongoing clinical trials involving sEHIs. sEHI treatment displays promise in a variety of disorders.

Clinical Trials Involving sEHIs			
Trial, Year Complete	**Drug**	**Disease**	**Results**
(23), 2009	AR9281	Hypertension/Impaired Glucose Intolerance	No officially published results
(24), 2010	AUDA	Heart Failure	AUDA reversed urotensin-ll induced vasoconstriction in heart failure patients
(49), 2014	GSK2256294	COPD	Reduction of high-density lipoprotein was observed after dose escalation in healthy males and male moderately obese smokers
(50), 2014	GSK2256294	Safety	No serious adverse events occurred with 10 mg oral dose in healthy adult and elderly males and females
(51)	GSK2256294	Subarachnoid Hemorrhage	Recruiting
(52)	GSK2256294	Diabetes Mellitus and Metabolic Disorders	Recruiting