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REVIEW

Inhibition of the Soluble Epoxide Hydrolase as an Analgesic Strategy: A Review of Preclinical Evidence

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Yuxin Wang
Karen M Wagner
Christophe Morisseau
Bruce D Hammock

Department of Entomology and Nematology, UC Davis Comprehensive Cancer Center, University of California Davis, Davis, CA 95616, USA

Abstract: Chronic pain is a complicated condition which causes substantial physical, emotional, and financial impacts on individuals and society. However, due to high cost, lack of efficacy and safety problems, current treatments are insufficient. There is a clear unmet medical need for safe, nonaddictive and effective therapies in the management of pain. Epoxy-fatty acids (EpFAs), which are natural signaling molecules, play key roles in mediation of both inflammatory and neuropathic pain sensation. However, their molecular mechanisms of action remain largely unknown. Soluble epoxide hydrolase (sEH) rapidly converts EpFAs into less bioactive fatty acid diols in vivo; therefore, inhibition of sEH is an emerging therapeutic target to enhance the beneficial effect of natural EpFAs. In this review, we will discuss sEH inhibition as an analgesic strategy for pain management and the underlying molecular mechanisms.

Keywords: epoxy fatty acids, chronic pain, molecular mechanisms

Introduction

Pain is a critical signal and a survival mechanism, but enhanced and persistent pain is an unpleasant sensation and emotional experience which has a profound impact on individuals and society.[1,2] There are approximately 100 million Americans suffering from chronic pain, with an associated $560–635 billion yearly cost in direct medical expenses and lost productivity.[3] In 2016, approximately 20% of US adults had chronic pain (approximately 50 million), and 8% of US adults (approximately 20 million) had high-impact chronic pain according to the Centers of Disease Control and Prevention (CDC).[4] Opioids are major pharmaceutical treatments available to control pain; however, they have serious side effects, leading to increasing risks for abuse and overdose-related deaths.[5] We need additional analgesic agents that can be integrated into multimodal pain control strategies.[6] Therefore, pain management research has become one of the top priorities in the US and developing new therapeutic approaches for pain management that are both effective and safe is practically important for our society.

The natural purpose of pain is to protect body from damage or potentially damaging situation.[7] However, chronic pain is not always related to tissue damage and does not always serve a protective function.[8] Based on the biological and physiological processes involved, pain is classified as either nociceptive, neuropathic, or inflammatory.[9] Nociceptive pain can be triggered by exposure to extreme

Correspondence: Bruce D Hammock
Email bdhammock@ucdavis.edu

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heat, cold or noxious pressure.[10] Neuropathic pain, which is caused by a lesion or disease of the somatosensory nervous system may occur spontaneously in the absence of stimuli or be evoked by sensory stimuli inducing hyperalgesia and allodynia.[11] Inflammation is characterized by redness, heat, swelling, pain or hypersensitivity, and loss of function usually occurs subsequent to injury and involves the release of cytokines and immune cell infiltration.[12] Since different forms of pain involve a variety of distinct biological processes, a better understanding of the molecular mechanisms underlying the pain is key for the development of more effective and safe therapies in the near future.

Eicosanoids are the metabolites of arachidonic acid (ARA) and related unsaturated fatty acids produced by three oxidative pathways, cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450). They are important lipid signaling molecules involved notably in the regulation of inflammation and pain.[13–15] While the COX and LOX pathways are well studied, the CYP450 is less understood and is at the center of this review. In this pathway, polyunsaturated fatty acids (PUFAs) including linoleic acid (LA), α-linolenic acid (ALA), dihomo-γ-linolenic acid (DGLA), arachidonic acid (ARA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and others are metabolized by CYP monooxygenases, especially CYP2C and CYP2J isoforms, to form a mixture of monohydroxy-fatty acids (hydroxyeicosatetraenoic acids (HETEs) from ARA) and epoxy-fatty acids (EpFAs; such as epoxy-eicosatrienoic acids (EETs) from ARA) with diverse biological actions, especially in inflammatory related diseases (Figure 1).[13,16–18] In this review, we will discuss the roles of CYP450 and their metabolites in the pathology of chronic pain and the underlying mechanisms of action of these metabolites.

Soluble Epoxide Hydrolase and Pain

The Effect of Epoxy-fatty Acids in Pain Model

The EpFAs, especially EETs, which function primarily as both autocrine and paracrine signaling molecules, have well described beneficial effects on multiple cardiovascular diseases, the renal system, angiogenesis, inflammation, and cancer.[19–21] Using an animal model of inflammatory pain, the total oxylipin concentrations were measured both in the spinal cord and brain of rats after base hydrolysis of the lipid esters. EpFAs, especially from ARA and DHA, but neither the parent fatty acid nor the corresponding

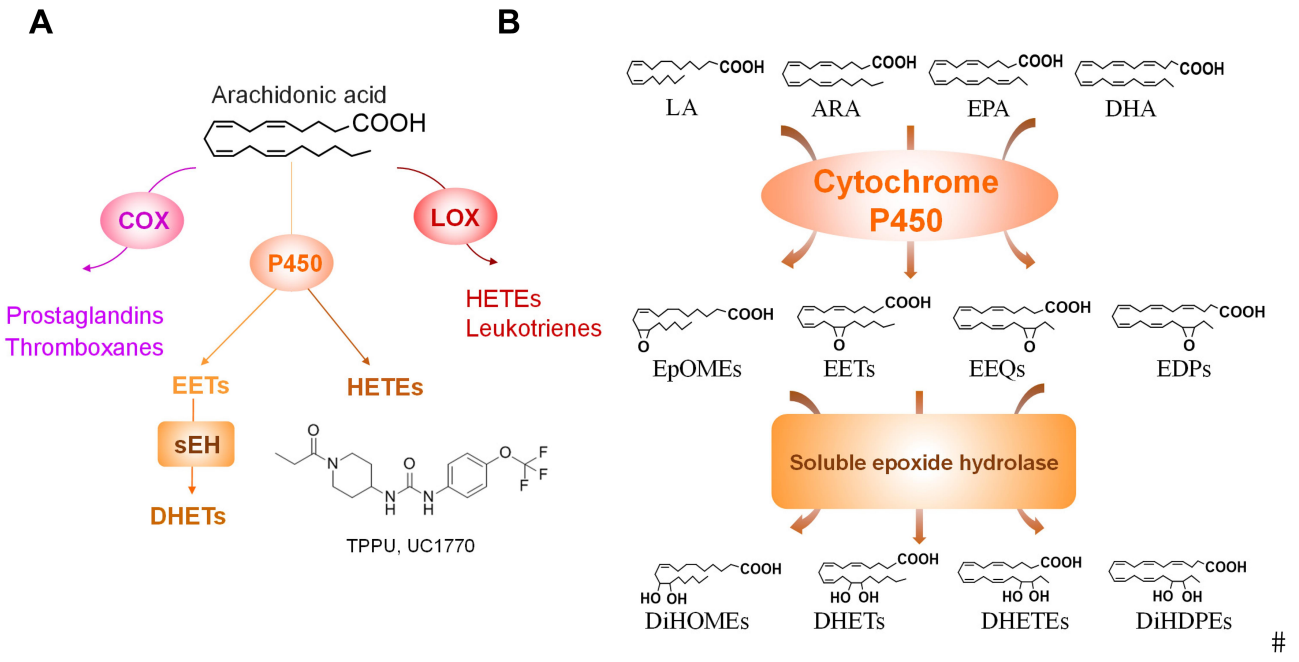

Figure 1 (**A**) Metabolism of ARA by COX, LOX, and CYP enzymes leads to formation of oxylipin metabolites. The structure of the sEHI TPPU is shown. (**B**) The CYP/sEH pathway that produces epoxy-fatty acids and corresponding diols. For simplicity, only one regioisomer of the epoxides and diols are shown here.

Abbreviations: ARA, arachidonic acid; COX, cyclooxygenase; LOX, lipoxygenase; CYP, cytochromes P450; EETs, epoxyeicosatrienoic acid; HETEs, hydroxyeicosatetraenoic acids; DHETs, dihydroxy-eicosatrienoic acids; LA, linoleic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; EpOMEs, epoxy-octadecenoic acid; EEQs, epoxy-eicosatetraenoic acid; EDPs, epoxy-docosapentaenoic acid; DiHOMEs, dihydroxy-octadecenoic acid; DiHETEs, dihydroxyicosa-tetraenoic acid; DiHDPEs, dihydroxy-docosapentaenoic acid.

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diols, selectively modulate nociceptive pathophysiology, and spinal administration of epoxy-docosapentaenoic acids (EpDPE) reduces both mechanical and thermal pains associated with inflammation, supporting an important function of EpFAs in modulating nociceptive signaling.[22] Additional studies showed that EpFAs are effective in both inflammatory and neuropathic pain models, suggesting them as potential novel therapeutics for pain management.[23–25] However, in vivo, the EpFAs are rapidly metabolized by soluble epoxide hydrolase (sEH) to generate the corresponding and less-bioactive, even pro-inflammatory, dihydroxy-eicosatrienoic acids (DHETs) (Figure 1B).[26–29] Therefore, sEH inhibitors (sEHIs) were developed to increase in vivo EpFAs levels, and thus reduce blood pressure, improve insulin sensitivity, and decrease inflammation.[28,30–33] The sEH is considered an emerging therapeutic target for enhancing the beneficial function of EpFAs in numerous diseases, including cardiovascular diseases, inflammatory bowel diseases, hypertension, and metabolic disorders, which have inflammation as a common underlying cause.[28,30–33]

The Effect of sEHIs in Pain Model

In an inflammatory pain model induced with intraplantar injection of 10 μg lipopolysaccharides (LPS) in one hind paw of rats, using an sEHI 1-trifluoromethoxyphenyl-3-(1-acetylpiperidin-4-yl)-urea (TPAU) through intraplantar injection significantly blocked inflammatory pain in a dose-dependent manner.[24] Moreover, an sEH metabolite 12,13-dihydroxy-9*Z*-octadecenoic acid (12,13-DiHOME) was increased in peripheral nervous tissue during acute zymosan- and complete Freund's adjuvant (CFA)-induced inflammatory pain.[34] In this CFA-induced inflammatory pain model, oral administration of 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl (TPPU) reduces 12.13-DiHOME concentrations and reduces zymosan- and CFA-induced thermal hyperalgesia in vivo.[34] These results showed the analgesia effect of sEHIs in inflammatory pain. In addition, compared to the traditional nonsteroidal anti-inflammatory drug celecoxib, sEHIs are superior and have better efficacy in both diabetic neuropathy and inflammatory pain models.[35]

Wagner et al. demonstrated that compared with gabapentin, subcutaneously injection of the sEHI trans-4-[4-(3-trifluoromethoxyphenyl-1-ureido)-cyclohexyloxy]-benzoic acid (*t*-TUCB) elicited a similar degree of withdrawal threshold improvement without the same degree of spontaneous locomotion decline in mice with neuropathic pain.[36] In diabetic Akita mice (Ins2Akita or Ins2C96Y), which progress naturally and are more similar to the human disease state than chemical ablation of beta islet cells. The results showed *t*-TUCB is an analgesic in diabetic neuropathy, and this effect is related to sexual dimorphism since the female mice are less susceptible to the diabetic phenotype.[37] These results indicate the sEHI has analgesic effects with limited side effects in diabetic neuropathy pain.

Synergistic Effect of sEHI with Other Pharmaceutical Inhibitors in Pain

Besides potent effects from sEHI itself, recent research showed combinations of sEHI and other enzyme inhibitors might achieve greater analgesic efficacy therapeutically. For example, the combination treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) and the sEHI 12-(3-adamantan-1-yl-ureido)dodecanoic acid *n*-butyl ester (AUDA-nBE) produced significantly beneficial effects for alleviating LPS-induced inflammatory pain in mice.[38] The NSAIDs and sEHI combination therapy also reduced COX-2 protein expression and shifted oxylipin metabolomic profiles,[38] suggesting that this therapy has efficacy in decreasing inflammation but also decreased side effects of NSAIDs in cardiovascular and gastrointestinal tract complications.[38–40] A COX-2/sEH dual inhibitor, 4-(5-phenyl-3-{3-[3-(4-trifluoromethylphenyl)-ureido]-propyl}-pyrazol-1-yl)-benzenesulfonamide (PTUPB) exhibited antiallodynic activity that was more effective than the same dose of either a COX-2 inhibitor (celecoxib) or a sEH inhibitor *t*-AUCB alone, as well as co-administration of both inhibitors in a nociceptive behavioral assay.[41] In addition, fatty acid amide hydrolase (FAAH) is another enzyme catalyzing the hydrolysis of bioactive lipid mediators—fatty acid ethanolamides (FAEs). Previous results demonstrated combinations of a sEHI, TPPU, and FAAH inhibitor, URB937, showed high antihyperalgesia activity in two pain models: carrageenan-induced hyperalgesia in mice and streptozocin-induced allodynia in rats, revealing a possible functional crosstalk between FAEs and EpFAs in regulating pain responses.[42] Moreover, phosphodiesterase-4 (PDE-4)-targeted therapies have shown promise for treating patients with a variety of autoimmune diseases.[43] Co-inhibition of sEH and PDE-4, greatly increases the level of EpFAs and is thus more efficient at reducing acute pain perception.[44] A novel PDE-4/sEH dual inhibitor *N*-(4-methoxy-2-(trifluoromethyl)benzyl)-1-propionylpiperidine-4-carboxamide (MPPA) at 3 mg/kg (oral administration) reduced

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LPS-induced inflammatory pain. MPPA also does not alter self-motivated exploration of rats with inflammatory pain or the withdrawal latency in control rats, suggesting that MPPA has good efficacy together with limited off-target effects.[45]

The Underlying Mechanisms of sEHI/EpFAs in Pain Management

Cyclic Adenosine Monophosphate (cAMP) Signaling Pathway in Pain

Cyclic adenosine 3′,5′-monophosphate (cAMP) was the first identified second messenger and plays a fundamental role in many cellular responses to hormones and neurotransmitters.[46–48] The intracellular levels of cAMP are regulated by the balance between two enzymes: adenylyl cyclase (AC), which catalyzes cAMP formation from ATP,[49] and cyclic nucleotide phosphodiesterase (PDE) that degrades intracellular cyclic nucleotides.[50] PDE inhibitors have been shown as therapeutic approach to neuroprotection, repair, and cardiovascular system.[51,52] Rolipram, a selective PDE-4 inhibitor and theophylline, a nonspecific PDE inhibitor exerted dose-dependent analgesic and anti-inflammatory effect against acetic acid-induced writhing in mice and carrageenan-induced paw edema in rats.[53]

Rolipram induced artificially elevated cAMP in healthy mice, while co-administration with the sEHI 1-trifluoromethoxyphenyl-3-(1-acetylpiperidin-4-yl) urea (TPAU) largely blunted pain-related behavior, which indicate the analgesic effect of sEH inhibitor and PDE-4 inhibitor.[44] These results indicate the analgesic effect of sEHIs is dependent on cAMP. In another study, EETs or sEHI lead to antihyperalgesia and was correlated to upregulation of, steroidogenic acute regulatory protein (StARD1), a carrier protein which assists neuro-steroid production.[54] In summary, these results further give mechanistic evidence showing the analgesic effect of sEHIs through cAMP signaling pathway (Figure 2).

PPARs Signaling in Pain

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to a nuclear hormone receptor superfamily, which contains three isoforms: PPARα, PPARβ/δ and PPARγ.[55,56] The three PPARs share a high homology but differ in tissue distribution and ligand specificity.[57] PPARs primary function as important fatty acid sensors which not only regulate lipid, carbohydrates, and amino acid metabolism, but also play key roles in various pathophysiology processes.[55] Extensive research showed PPARs may also involve in the control of the

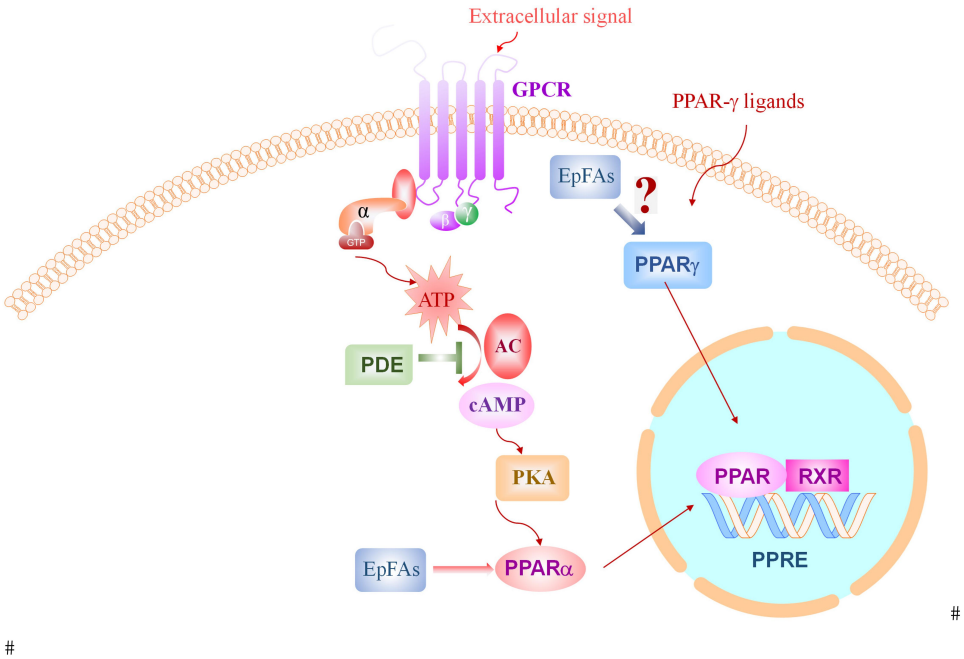

Figure 2 The effect of sEH inhibition and EpFAs on cAMP-PPAR signaling pathways.
Abbreviations: GPCR, G-protein-coupled receptors; PPAR, peroxisome proliferator-activated receptor gamma; EpFAs, epoxy fatty acids; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PDE, phosphodiesterase; RXR, retinoid X receptor; PPRE, peroxisome proliferator hormone response elements.

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nociceptive response and neuropathic pain.[58,59] There is evidence showing cAMP is the major stimulator of PPAR activity and cAMP signaling pathway modulates PPAR function, possibly by transactivation,[60,61] suggesting the link between cAMP and PPAR signaling pathways. Interestingly PPAR agonists are potent inducers of the sEH message and protein.

A relevant study on PPARs and pain investigated the activation of PPAR in the rat spinal cord following subcutaneous injection of CFA into a hind paw.[62] The results showed only the PPARα isoform was activated using electrophoretic mobility-shift assay (EMSA) method. LoVerme et al. showed in mice that PPARα agonists suppress pain behaviors induced by tissue injury, nerve damage, or inflammation.[63] In addition, PPARα$^{-/-}$ female mice are hypersensitive to the cold, mechanical allodynia, and heat hyperalgesia,[64] suggesting genetic ablation of PPARα is involved in neuropathic and visceral nociception.[64] Leukotriene B_4, a potent agent that initiates, coordinates, and amplifies the inflammatory response, is an activating ligand for the transcription factor PPARα.[65] These results suggest the critical role of PPARα in the control of nociception and inflammation. Thus, further studies of combined effects on sEHI and PPARα agonist in pain preclinical models are needed and development of this novel class of compounds could represent a useful new pharmacological approach for the pain relief.

PPARγ is another subtype of PPAR, which is present in several tissues and cell types.[66] Intrathecally administered PPARγ agonists dose-dependently decreased mechanical and cold hypersensitivity in the rats,[58] demonstrating the important role of PPARγ in the neuropathic pain. Further studies demonstrated that activation of PPARγ has beneficial effects of modification of astrocyte metabolism and mitochondrial function which are important in inflammation.[67,68] In addition, the PPARγ agonist, rosiglitazone, attenuated CFA-induced inflammatory pain through induction of heme oxygenase (HO)-1, leading to the differentiation of pro-inflammatory M1 macrophages to anti-inflammatory M2 phenotype.[69] In an angiotensin-II (AngII) induced cardiac hypertrophy model, sEH is upregulated by AngII. Rosiglitazone is a potent sEH inducer and the protective role of PPARγ activation in AngII-induced cardiac hypertrophy is partially through downregulating sEH.[70,71] Thus, the beneficial actions of rosiglitazone should be enhanced and some of its side effects reduced by co-administration with sEHI since the combined administration of both pharmacological agents rosiglitazone and the sEH inhibitor *t*-AUCB led to synergistic improvement of vascular function and reduced fibrotic kidney damage.[72]

EETs, together with the sEHI 12-(3-adamantan-1-yl-ureido) dodecanoic acid (AUDA), increased PPARγ transcription activity in endothelial cells and 3T3-L1 preadipocytes and PPARγ antagonist GW9662 abolished the EET/AUDA-mediated anti-inflammatory effect, indicating PPARγ is an effector of EETs.[73] Further study demonstrated that dual PPARγ/sEH inhibitor RB394 showed the ability to blunt diabetic complications such as hypertension, insulin resistance, hyperlipidemia, and kidney injury in metabolic syndrome modeled in obese spontaneously hypertensive (SHROB) rats and obese diabetic Zucker fatty/spontaneously hypertensive heart failure F1 hybrid (ZSF1) rats.[74] Another study showed the dual inhibitor RB394 or combination of sEHI and PPARγ agonist significantly prevented renal fibrosis development by preventing renal inflammation and oxidative stress.[75] Interestingly the sEHI will of course counter the sEHI induction and other possible deleterious side effects of high dose PPARγ agonists.[76] Kim et al. demonstrated that sEHI *t*-TUCB could promote anti-inflammatory effects in ureteral obstruction in mice, the mechanism is mainly through increased levels of EETs and inhibition the PPARγ reduction.[77] Altogether, these results indicate that PPARγ is an important effector in the anti-inflammatory effect of sEHI, while more evidence is still needed for the mechanism study of sEHI in the pain management through PPAR signaling pathways (Figure 2).

The Transient Receptor Potential (TRP) Superfamily in Pain

The superfamily of TRP channels play critical roles in the responses to the major classes of external stimuli, including light, sound, chemicals, temperature, and touch.[78] Mutations in several TRP genes have been implicated in pain pathological states.[79] Most TRPs are nonselective cation channels, only a few are highly Ca^{2+} selective, or permeable for highly hydrated Mg^{2+} ions.[79]

Transient receptor potential ankyrin 1 (TRPA1) is the most well-studied pain regulator among TRP superfamily, which is one of the Ca^{2+}-permeable cation ion channels involved in the transduction of potentially harmful stimuli and in amplification of nociceptive transmission in their central terminals.[80–83] Studies revealed TRPA1 is a potential target in pain relief. A TRPA1 selective antagonist significantly reduced mechanical hyperalgesia evaluated

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by the von Frey assay and completely inhibited the noxious cold hyperalgesia in CFA induced persistent inflammation in mice.[80] Furthermore, TRPA1 also plays key roles in the inflammatory pain, neuropathic pain and migraine.[84] Both genetic deletion of *Trpa1* and pharmacological inhibition of TRPA1 abrogated pain-like behaviors in mice.[85]

In addition to TRPA1, transient receptor potential cation channel subfamily V member 1 (TRPV1) is another Ca^{2+} permeant nonselective member of TRP family which has been implicated in a variety of cellular and physiological processes, including noxious physical and chemical stimuli detection, making it one of the promising targets for pain-relieving drugs.[86,87] $TRPV1^{-/-}$ mice showed no vanilloid-evoked pain behavior in the detection of painful heat and showed little thermal hypersensitivity in the inflammation, and $TRPV1^{-/-}$ mice showed an attenuated fever in response to LPS.[88,89] These results conclude TRPV1 is essential in the inflammatory thermal hyperalgesia, nociception, and pain sensation. Finally, several TRPV1 agonists such as JNJ-39,439,335, NEO6860, and ABT-102 have been in clinical trials targeting pain relief.[90–92] Altogether, these results suggest examination of TRPV1 as a mechanistic target for pain treatment.

sEH was shown to regulate pain via TRP channels. The sEH enzyme has been reported as co-localized with TRPV1 in the primary trigeminal ganglion neurons (TGNs).[93] Pretreatment with 10 μM EETs antagonist 14.15-epoxyeicosa-5(*Z*)-enoic acid (14,15-EEZE) attenuated the calcitonin gene-related peptide (CGRP) release, which is a marker of neurogenic inflammation.[93] The CGRP release is induced by TRPV1 agonist capsaicin or K^+, but sEHI AUDA did not have this effect,[93] suggesting that there are inadequate levels of EETs released to be stabilized by AUDA. These data suggest EETs may act as intracellular regulators of neuropeptide release, which may have important clinical implications for treatment of neurogenic inflammation. Further investigation into the therapeutic potential of sEHI through TRP channels is needed.

Endoplasmic Reticulum (ER) Stress Signaling Pathway in Pain

The endoplasmic reticulum (ER) is an organelle in which newly synthesized secretory and transmembrane proteins are assembled and folded into their correct tertiary structures.[94] However, protein misfolding caused by various stimuli and gene mutations, leads to the disruption of ER function and activation of ER stress signaling pathway. Eukaryotic cells have developed an evolutionarily conserved adaptive mechanism called unfolded protein response (UPR), whose purpose is to clear unfolded proteins, promote proper folding by increased chaperones and reduced protein synthesis, and restore ER homeostasis.[95] The UPR influences cellular metabolism through diverse mechanisms, including calcium and lipid transfer, which are key involvement in the pathogenesis of diseases, including pain, neurodegeneration, and cardiovascular disease.[96–98] When unfolded proteins accumulate in the ER, the N-terminus in the lumen of the ER chaperone Grp78 releases transmembrane ER proteins involved in inducing the UPR to prevent their aggregation. However, when misfolded proteins accumulate, Grp78 releases, allowing aggregation of these transmembrane signaling proteins, launching and activating the UPR.[99] The UPR is distinguished by the action of three signaling proteins named IRE1α (inositol-requiring protein-1α), PERK (protein kinase RNA (PKR)-like ER kinase), and ATF6 (activating transcription factor 6).[95]

The ER stress signaling pathway has been demonstrated as playing key roles in the pathogenesis of pain. The IRE1α–unspliced X-box-binding protein 1 (XBP1) axis operates as a crucial mediator of eicosanoid metabolism and prostaglandin synthesis in myeloid immune cells by promoting the expression of both COX-2 and microsomal prostaglandin E synthase-1 (mPGES-1), and genetic ablation or pharmacological inhibition of this pathway diminishes pain-related behaviors in mice.[100] Other research showed that an IRE1α small interfering RNA (siRNA) improved the neurological morphology and reduced diabetic peripheral neuropathy (DPN) in rats.[101] It also rescued ER stress-related apoptosis in the sciatic nerve,[101] indicating IRE1α–XBP1 signaling may be helpful for the improvement of pain management. In addition, Lupachyk et al. examined the role of ER stress signaling in the development of peripheral neuropathy in streptozotocin (STZ)-induced diabetic rodents and found two structurally dissimilar chemical chaperones (trimethylamine oxide [TMAO] and 4-phenylbutyric acid [4-PBA]), which can counteract ER stress by promoting normal protein folding, significantly suppressed ER stress marker proteins whose upregulation was induced by STZ,[102,103] reduced thermal and mechanical responses, and enhanced sensitivity to touch with diabetes.[103] They also observed the neuropathic effects of CCAAT-enhancer-binding proteins (C/EBP) homologous protein (CHOP), one of the

components of the ER stress-mediated apoptosis pathway in the DPN.[104] The results showed genetic ablation of CHOP showed attenuation of motor and sensory nerve conduction velocity deficits, thermal hypoalgesia, and intraepidermal nerve fiber loss, while diabetes-induced mechanical hypoalgesia and tactile allodynia remained at similar levels in both $CHOP^{-/-}$ and wild-type mice,[102] suggesting different aspects of ER stress and the UPR were targeted in diabetic neuropathy.

Numerous studies showed sEH is a physiological modulator of ER stress signaling involved in many disorders.[105–107] Thus, the sEH enzyme is a nonchannel, non-neurotransmitter therapeutic and well characterized target for pain.[108] Both pain and ER stress markers are elevated in peripheral nervous system of type I diabetic rats. Further results showed TPPU, a widely used potent sEH inhibitor, blocks pain-related behavior and suppresses markers of the ER stress signaling pathway (p-PERK, p-IRE1α, and cleaved-ATF6).[108,109] In addition, TPPU reversed the tunicamycin (Tm) induced ER stress response and pain-related behaviors both alone and synergistically together with chemical chaperon 4-PBA.[108] This observation suggests a beneficial drug interaction among chemical chaperones and sEHI. Another sEHI *t*-TUCB, attenuated neuropathic pain without the same degree of spontaneous locomotion that is observed with gabapentin.[36] Altogether, these results indicate dosing with sEHI represents an analgesic strategy for pain relief through the ER stress signaling pathway (Figure 3).

Interaction and Complementarities of the Three Mechanistic Pathways

There is evidence showing an interaction among cAMP-PPAR, TRP channels and ER stress signaling pathways. These include ER stress regulated uncoupling protein 1 (UCP1) expression via PPARγ suppression in beige adipocytes,[110] and UCP1 increased by both PPARγ stimulation and cAMP activation through their ability to stimulate the expression of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α).[111] In Zn-induced lipolysis, Zn exposure evoked ER stress and dysregulation of Ca^{2+} homeostasis, and then activated cAMP/protein kinase A (PKA) pathway resulting in hepatic lipolysis,[112] highlighting the importance of the ER stress–cAMP/PKA axis in Zn-induced lipolysis.

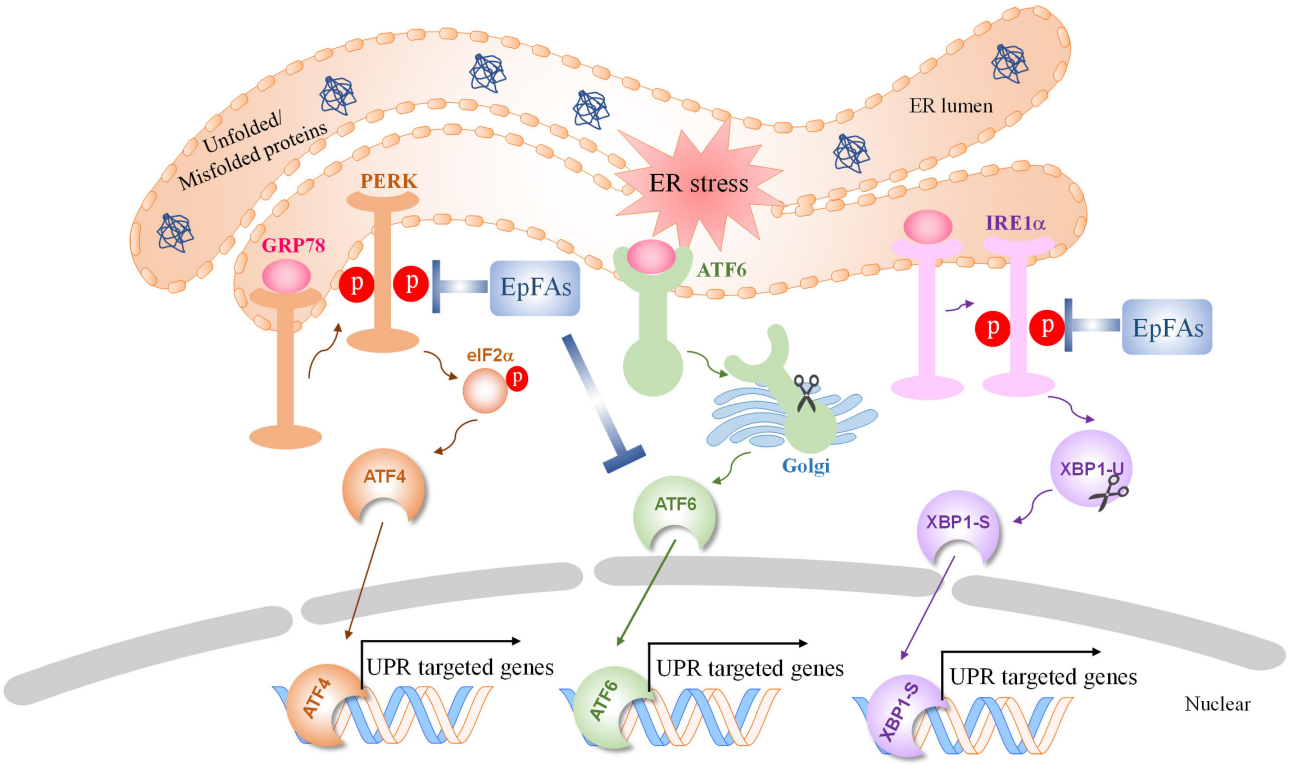

Figure 3 The effect of sEH inhibition and EpFAs on Endoplasmic Reticulum (ER) stress signaling pathways.
Abbreviations: ER, endoplasmic reticulum; PERK, protein kinase R (PKR)-like endoplasmic reticulum kinase; GRP78, glucose-regulated protein; eIF2α, eukaryotic initiation factor 2α; ATF4, activating transcription factor 4; ATF6, activating transcription factor 6; IRE1α, inositol-requiring enzyme 1α; XBP1-U, un-spliced X-box-binding protein 1; XBP1-S, spliced X-box-binding protein 1; EpFAs, epoxide fatty acids; UPR, unfolded protein response.

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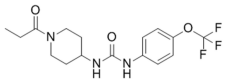
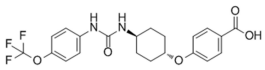
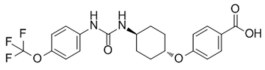
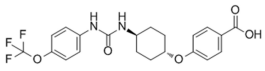
However, there is no research about the interaction of these signaling pathways in pain research, illustrating additional studies are needed to explore the link between these signaling pathways in the pain biology and the putative role of EpFAs.

Preclinical Research and Clinical Trials of sEHIs

Currently, several preclinical studies are evaluating the effects of sEHIs in the pain management in animals. TPPU, an potent sEHI, has multimodal analgesics effects in a rat chronic pain model without changing the motor control and functioning in control animals.[113] There are also several reports evaluating the sEHIs in the pain management in veterinary medicine. In a chronic laminitic horses, sEH activity in the digital laminae is significantly higher (P= 0.01) than in healthy horses,[114] and treatment with the sEHI *t*-TUCB for 10 days significantly reduced the forelimb lifts and the pain scores compared with baseline (P= 0.04).[114] A follow-up study showed that no adverse effects were detected on clinical and laboratory examinations during and after *t*-TUCB administration. No new episodes of laminitis have been noted up to the 120 days following treatment.[115] Consistent with these studies, in another randomized controlled trial which used LPS-induced inflammatory joint pain in adult mares, treatment of 1 mg/kg *t*-TUCB lowered the pain, lameness and tactile allodynia, further demonstrating the analgesia effect of *t*-TUCB.[116] Additionally, administration of *t*-TUCB orally for five days significantly reduced pain at a dose of 5 mg/kg in aged dogs with natural arthritis.[117] Together, sEHI have already shown efficacy for inflammatory and neuropathic pain in rodents, with no apparent adverse or addictive effects, as well as relieving natural-onset pathological pain in horses and dogs (Table 1). Since horses and dogs are sensitive to side effects of NSAIDs and COXIBs, the well-established synergism of sEH inhibitors with these drugs and their reduction of side effects offers an attractive drug combination in veterinary medicine.

In human, 1-(1-acetypiperidin-4-yl)-3-adamantanylurea (APAU), a potent and selective sEHI, has been in clinical development targeting hypertension and type 2 diabetes, and was well tolerated, no dose-related adverse events were observed during either study in healthy subjects.[118] The sEHI GSK2256294 (chemical name: 1R,3S)-*N*-[[4-cyano-2-(trifluoromethyl)phenyl]methyl]-3-[[4-methyl-6-(methylamino)-1,3,5-triazin-2-yl]amino]-cyclohexanecarboxamide was well-tolerated and demonstrated sustained inhibition of sEH activity on COPD human patients.[119] Recently a new class of oral non-narcotic analgesics based on inhibition of the sEH, EC5026 (chemical name: (S)-1-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-{1-(2-methylbutanoyl] piperidin-

Table 1 Preclinical Studies of Soluble Epoxide Hydrolase Inhibitors in Pain Model

No.	Seh Inhibitor	Species	Routes	Dose	Model	Reference
1	TPPU 	Rat	Oral gavage	3 mg/kg	Streptozocin induced neuropathic pain model	Wagner et al. 2020[113]
2	*t*-TUCB 	Horse	Intravenously	0.1 mg/kg	Chronic laminitis	Guedes et al. 2017[114]
3	*t*-TUCB 	Mares	Intravenously	1 mg/kg	LPS-indued inflammatory radiocarpal synovitis	Guedes et al .2018[116]
4	*t*-TUCB 	Dogs	Orally	5 mg/kg	Canine osteoarthritis	McReynolds et al. 2019[117]

4-yl}urea), has finished the Phase 1a clinical trial, showing no adverse effect on healthy volunteers.[120] EC5026 is developed to treat neuropathic pain and should enter a Phase 2 clinical trial soon.

Conclusion

Currently, a large population in the US suffer with chronic pain, due to lack of efficacy, high expense, and safety problems, making chronic pain a serious health problem. It is important to identify novel therapeutic targets for chronic pain, to develop effective and safe methods for chronic pain treatment. Substantial studies have shown the EpFAs play essential roles in the pathology of inflammation and chronic pain, and our review further discusses the underlying molecular mechanisms of EpFAs/sEHI actions as an analgesic strategy for pain management. Recently several clinical trials of sEH inhibitors aiming at different diseases including chronic pain, hypertension, and COPD, emphasizing the importance of sEH as a promising therapeutic target. While more mechanisms need to be explored, inhibition of sEH to stabilize the beneficial effect of EpFAs is a potent and safe approach for pain management.

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Disclosure

Karen M Wagner reports personal fees from EicOsis LLC, outside the submitted work. Christophe Morisseau reports grants from NIEHS, outside the submitted work. The University of California holds patents on the use of sEH inhibitors to treat inflammation, inflammatory pain, and neuropathic pain. Bruce D Hammock is a cofounder and Karen M Wagner is an employee of EicOsis L.L.C., a startup company advancing sEH inhibitors into the clinic. The authors report no other potential conflicts of interest in this work.

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