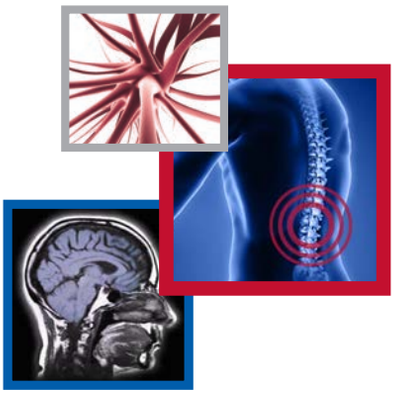
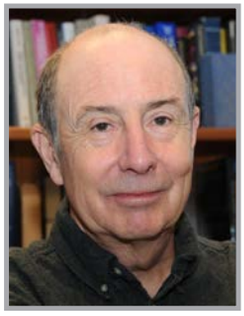
EDITORIAL

The soluble epoxide hydrolase as a pharmaceutical target for pain management





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A newly characterized drug target, the soluble epoxide hydrolase (sEH), offers hope for developing new agents for the control of both inflammatory and neuropathic pain. Although over 70% of the pharmaceuticals used worldwide are based on targets in the arachidonate cascade (including, among others, aspirin, cyclooxygenase [COX-2 inhibitors [COXIBs], NSAIDs, and blockers of the lipoxygenase 5 pathway), the cytochrome P450 branch of the cascade has been little studied and is currently the target of no pharmaceutical agents **(Figure 1)**. Several P450 enzymes are involved in the production of both pro- and anti-inflammatory derivatives of arachidonic acid and of particular relevance to this editorial are the epoxides of arachidonic acid, also known as epoxyeicosatrienoic acids (EETs). EETs and other fatty acid epoxides are increasingly recognized as anti-inflammatory mediators acting directly to reduce NF-κB nuclear translocation but also to reduce a variety of inflammatory enzymes such as COX-2 which are induced in inflammation. It has proven difficult to modulate the P450s selectively *in vivo* with pharmaceuticals. However, the anti-inflammatory EETs and other fatty acid epoxides are rapidly metabolized by a single enzyme known as the sEH **(Figure 1)**. The resulting diols are far more polar and quickly move out of tissues into circulation. In most cases they are less biologically active than the epoxides, but in some cases the diols are actually proinflammatory. Thus inhibitors of the sEH will stabilize the anti-inflammatory EETs, and they have been evaluated in rodent models for a variety of inflammation-driven processes including cardiac hypertrophy, atherosclerosis, renal inflammation and fibrosis in addition to other indications [1]. There are a variety of small molecule transition state mimics available capable of inhibiting the human sEH in the low nano- to pico-molar concentration. Some of these inhibitors have good topical and oral availability and good pharmacokinetics including the sEH inhibitor shown in **Figure 2**. These compounds show good target engagement *in vivo* as demonstrated by their ability to stabilize and thus increase blood levels of epoxidized fatty acids while decreasing the concentrations of the corresponding diols [2].

The sEH inhibitors have been shown to reduce inflammation with greater potency than NSAIDs in a number of

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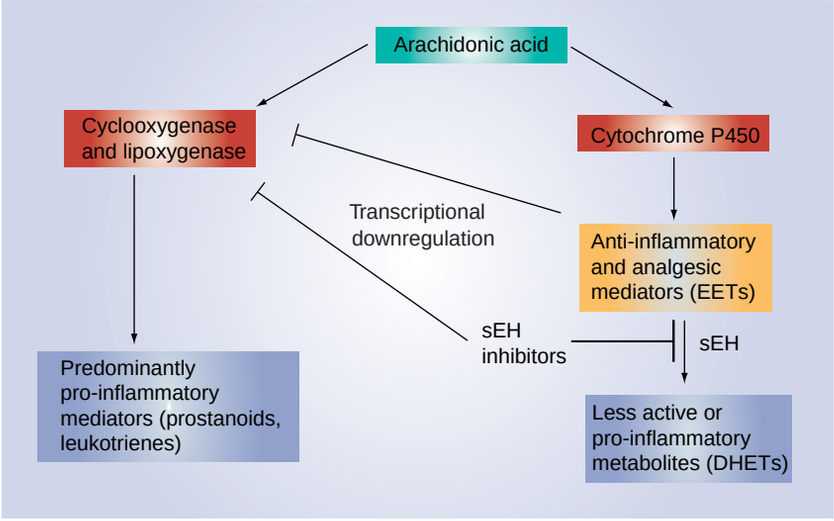

Figure 1. Simplified arachidonate cascade. The metabolites of arachidonic acid and several other fatty acids are potent chemical mediators controlling many aspects of physiology including inflammation and pain. The cascade is the target of over 70% of pharmaceuticals. The sEH inhibitors which stabilize anti-inflammatory and analgesic epoxyeicosanoids or EETs recently were shown to reduce neuropathic as well as inflammatory pain.
DHET: Dihydroxyeicosatetraenoic acid; EET: Epoxyeicosatrienoic acid; sEH: Soluble epoxide hydrolase.

models and actually to synergize with aspirin, NSAIDs, COXIBs and 5-lipoxygenase-activating protein inhibitors (which block the lipoxygenase 5 pathway to leukotrienes and other predominantly inflammatory metabolites) [3]. The sEH inhibitors synergize with the natural EETs as well as their ω-3 homologs. Given their effectiveness in reducing inflammation in some rodent models, it was not surprising that the sEH inhibitors should also reduce inflammatory pain [4,5]. Using both thermal and mechanical models of hyperalgesia and allodynia in pain states initiated by lipopolysaccharide, TNFα, and carrageenan, sEH inhibitors were shown to return the pain sensation to normal in a dose-dependent fashion. One surprise was that the compounds had little if any effect in a state devoid of pain [6]. In fact the ability of the sEH inhibitors, unlike morphine, to reduce pain perception was dependent upon a facilitated pain state. A second surprise was that sEH inhibitors could eliminate pain caused by the injection of the prostaglandin PGE_2 [7]. Of course, PGE_2-induced pain cannot be treated with either NSAIDs or steroids. As with inflammation, the sEH inhibitors synergize in reducing inflammatory pain with NSAIDs and COXIBs, and they reduce some of the vascular side effects associated with the use of these drugs [8].

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The major surprise occurred when the sEH inhibitors were used in neuropathic pain models. These models include nerve damage as well as Type 1 diabetes. These neuropathic pain models are often thought to mimic a variety of chronic pain conditions. Again the sEH inhibitors and EETs reduced pain in a dose-dependent fashion [9]. This is shown for one sEH inhibitor in **Figure 2**. Although NSAIDs such as diclofenac are widely used for neuropathic pain, their behavior in controlled studies is erratic. In our models celecoxib had no beneficial effect on diabetes-induced neuropathic pain, and diclofenac slightly reduced pain as shown in **Figure 2**. However, the sEH inhibitors synergized with these cyclooxygenase inhibitors to reduce pain perception in this and other models. This observation raises the possibility that sEH inhibitors can be used effectively in combination with NSAIDs and COXIBs not only to treat inflammatory pain but possibly also neuropathic and other chronic pain conditions while reducing the side effects associated with the long-term use of these cyclooxygenase inhibitors. For example, sEH inhibitors in mice reverse the imbalance in prostacyclin:thromboxane ratios and the increase in platelet instability associated with long-term use of rofecoxib [8]. In fact compounds that inhibit both sEH and COX-2 are very effective analgesic agents [10].

The sEH inhibitors are more effective than morphine in relieving some pain conditions. Unlike many opiates there is no reduction in pain perception in the absence of a facilitated pain state, there is no detectable change in behavior or sedation and there is limited hypoalgesia from the sEH inhibitors. In diabetic neuropathic pain the sEH inhibitors have proven more potent and long lasting than the commonly used gabapentin (Neurontin®) for pain relief. The detailed mechanism of action of the sEH inhibitors and epoxy fatty acids in the reduction of neuropathic pain is not understood, although there seems to be an interaction with the opioid system [11,12]. However, in the case of inflammatory pain cAMP appears necessary for the analgesic activity of EETs. This is shown by the dramatic synergism of sEH inhibitors with phosphodiesterase (PDE) inhibitors such as rolipram [7]. The PDE inhibitors have been explored for pain relief but their use is limited by a variety of side effects including

nausea and sedation. Thus a formulation of PDE inhibitors and sEH inhibitors could offer a fruitful drug combination.

The sEH inhibitors clearly act both centrally and peripherally. Topical treatment or injection into the paw of a rat with sEH inhibitors causes a marked reduction in hyperalgesia in the treated but not the contralateral paw, showing that some of the efficacy is local. Efficacy can also be obtained by systemic injection or oral administration. However, intrathecal administration is more than 100-times more potent than oral or subcutaneous administration indicating that there is also a clear central effect. Pharmacological studies clearly implicate the GABA system. The efficacy of sEH inhibitors can be reduced dramatically by blocking the biosynthesis of neurosteroids or the use of antagonists of the GABA-gated chloride channel such as picrotoxin.

In the field of pain management and particularly for treatment of neuropathic pain, new agents are needed by physicians. Most of the pharmaceuticals in the pain management field exploit a limited number of targets known to result in analgesia. Pharmaceuticals acting on novel targets are needed to provide physicians with therapeutic alternatives, particularly in the area of neuropathic pain, which remains a poorly served medical need. In the absence of human studies the use of sEH inhibitors or possibly the use of the natural eicosanoids or their mimics is a potential rather than a reality for pain management. However, the high potency and efficacy of sEH inhibitors in multiple pain models raises the hope that sEH inhibitors as well as natural epoxidized fatty acids and mimics can be developed as effective pain management tools [13].

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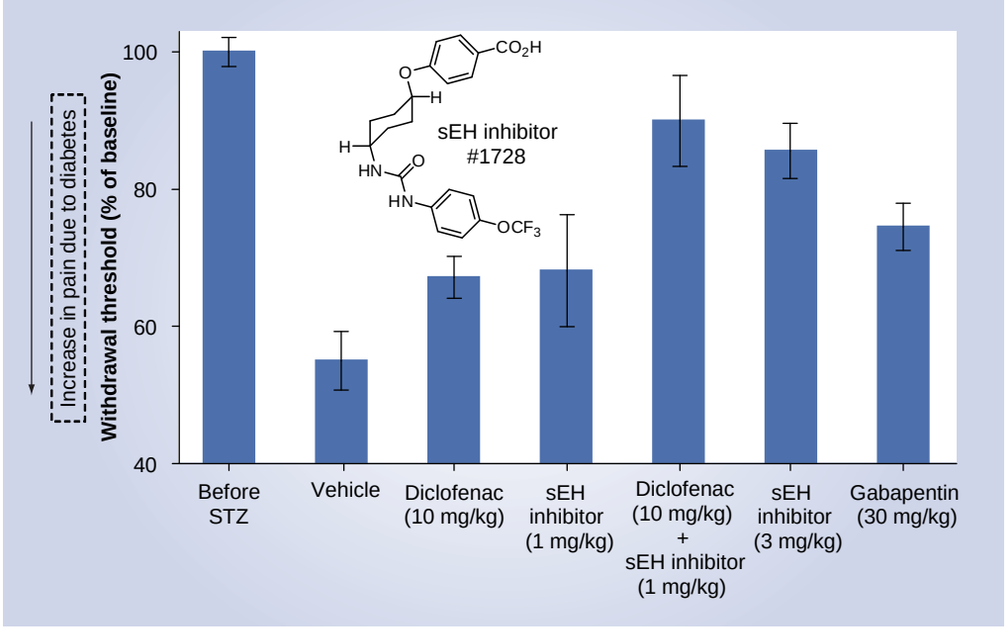

Figure 2. Soluble epoxide hydrolase inhibitors reduce diabetes-induced neuropathic pain alone and in combination with a COX inhibitor. In the STZ-induced Type 1 diabetes model, the withdrawal threshold of rats from a mechanical stimulus is reduced by about 50% indicating pain. Drugs that are prescribed for this type of pain such as gabapentin (Neurontin®, last column on the right) normalize the reduced threshold towards levels of pain observed before diabetes is induced (first column on the left). Even though a high dose of the mixed COX-1/2 inhibitor diclofenac is minimally effective, its efficacy is synergistically increased by a low dose of sEH inhibitor. At a higher dose, however, the sEH inhibitor alone is more efficacious than a tenfold higher dose of gabapentin. Diabetes was induced by a single intravenous dose of STZ (55 mg/kg) and animals were tested 7 days later. Pain was measured by the von Frey mechanical allodynia assay using an electronic anesthesiometer (IITC, Woodland Hills, CA, USA). Each group consisted of six animals, error bars represent standard error of mean.
sEH: Soluble epoxide hydrolase; STZ: Streptozocin.

Financial & competing interests disclosure

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