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# Metabolic/inflammatory/vascular comorbidity in psychiatric disorders; soluble epoxide hydrolase (sEH) as a possible new target

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## Abstract

The common and severe psychiatric disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are associated with inflammation, oxidative stress and changes in lipid metabolism. Those pathways are implicated in the premature development of vascular and metabolic comorbidities, which account for considerable morbidity and mortality, including increased dementia risk. During endoplasmic reticulum stress, the soluble epoxide hydrolase (sEH) enzyme converts anti-inflammatory fatty acid epoxides generated by cytochrome p450 enzymes into their corresponding and generally less anti-inflammatory, or even pro-inflammatory, diols, slowing the resolution of inflammation. The sEH enzyme and its oxylipin products are elevated post-mortem in MDD, BD and schizophrenia. Preliminary clinical data suggest that oxylipins increase with symptoms in seasonal MDD and anorexia nervosa, requiring confirmation in larger studies and other cohorts. In rats, a soluble sEH inhibitor mitigated the development of depressive-like behaviors. We discuss sEH inhibitors under development for cardiovascular

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diseases, post-ischemic brain injury, neuropathic pain and diabetes, suggesting new possibilities to address the mood and cognitive symptoms of psychiatric disorders, and their most common comorbidities.

**Keywords**

omega-3 fatty acids; soluble epoxide hydrolase; lipidomics; depression; drug development; ER stress; NLRP3; inflammasome; metabolism; mitochondrial dysfunction; dementia; neuroprogression; neurodegeneration; obesity; diabetes; heart disease; stroke

## 1. Inflammation and anti-inflammatory agents in depression

The phenomenon of increased inflammation in MDD has been well-established, with most evidence stemming from the measurement of cytokine messengers in peripheral blood, notably interleukin-6 (IL-6), tumor necrosis factor (TNF) and others (Dowlati et al., 2009; Kohler et al., 2017). In MDD, treatment with antidepressants, specifically the selective serotonin reuptake inhibitors, may reduce TNF and IL-6 (Hannestad et al., 2011) suggesting that some cytokines may be transient state markers (Goldsmith et al., 2016). These inflammatory signals appear to be relevant to mood states across the spectra of common and severe psychiatric disorders, including MDD, BD and schizophrenia (Goldsmith et al., 2016), due in part to production of psychoactive tryptophan metabolites that result from cytokine signaling (Schwarcz et al., 2012).

Despite this evidence, support for anti-inflammatory agents as antidepressants has been mixed, showing generally minimal clinical benefit. The strongest evidence seems to support the use of celecoxib, a selective cyclooxygenase 2 inhibitor, when used as an adjunct to monoaminergic antidepressants (Kohler et al., 2014). Specifically, in those with inflammatory comorbidity, treatment with anti-cytokine therapies has been shown to benefit mood symptoms (Kappelmann et al., 2016), and a study in treatment resistant depression suggested that the anti-TNF antibody infliximab may have mood benefits only in patients who have evidence of elevated peripheral inflammatory activity (i.e. C-reactive protein [CRP]) (Raison et al., 2013).

Although inflammation may be involved in psychiatric disorders, the evidence overwhelmingly indicates high heterogeneity in this relationship (Kohler et al., 2007), likely indicating that particular subsets of patients may benefit from anti-inflammatory treatments. Such treatments will require more accurate and specific quantitative biomarkers that can be reproduced reliably between laboratories to inform their use. The extensive variability in the measurement of cytokine levels within and between laboratories (Noble et al., 2008), and substantial heterogeneity between studies comparing cytokines between patients to controls (Kohler et al., 2007), or comparing patients to themselves pre- vs. post-treatment (Hannestad et al., 2011), suggests suboptimal utility as diagnostic or prognostic biomarkers. Considerably less work has examined the possibility of lipid metabolic biomarkers, although prostaglandins measured quantitatively have shown promise (Calabrese et al., 1986; Nishino et al,1989.; Ohishi et al., 1989). There exists a clear need to identify specific markers of inflammation in depressive disorders, the sources of heterogeneity in related inflammatory

pathways, and the underlying causes. There is always the worry that blood or urinary biomarkers whether cytokine or lipid may not reflect levels in the central nervous system.

## 2. Inflammatory, vascular and metabolic comorbidities of depression

There has been much speculation about the causes of increased inflammation in depression, including effects of stress, poor nutrition, physical inactivity, obesity, smoking, gut permeability, disturbances in commensal gut microbiota, mitochondrial dysfunction, autoimmity, and sleep disturbances (Anderson 2017; Berk et al.,2013; Robertson et al., 2017). In a meta-analysis, Howren et al. showed that CRP elevations in MDD were mediated by obesity (Howren et al., 2017), which is highly prevalent in MDD and a risk factor for the development of diabetes and cardiovascular diseases that contribute prominently to the excess morbidity and mortality associated with psychiatric disorders (de Melo et al., 2017).

The increased risk for the development of cardiovascular disease associated with MDD and BD has been recognized recently in a consensus statement from the American Heart Association (Goldstein et al., 2015). Emerging evidence suggests that this risk begins in early life presentations, manifest as elevated cardiovascular and metabolic risk factors such as higher BMI, cardiac pulse pressure, and IL-6 (Hatch et al., 2017), and increased cognitive vulnerability to those risk factors. In one study, elevated triglycerides and diastolic blood pressure were associated with poorer executive function in adolescents with BD, a diathesis which was not identified in unaffected adolescents (Naiberg et al., 2016). In young male adults with depression, subclinical atherosclerosis, as indicated by intima-media thickening of the carotid arteries, was found (Elovainio et al., 2005), and in mid- and later-life, depressive disorders carry an increased risk of heart disease and stroke (Pan et al., 2011; Van der Kooy et al., 2007).

While causality is difficult to discern, elevations in inflammatory markers may increase over time with exposure to a mood disorder, mediated largely by changes in lifestyle factors including lack of physical activity (Figure 1). In a study of healthy elderly, depressive symptoms contributed to increased IL-6 and CRP over time, but the reverse effect was not observed (Stewart et al., 2009). Similarly, in a study of outpatients with coronary artery disease, depressive symptoms predicted increased IL-6 and CRP over 5 years, but baseline IL-6 and CRP did not predict subsequent depressive symptoms. Moreover, the prospective association could be explained by physical inactivity, BMI and smoking (Duivis et al., 2011). Therefore, the epidemiology does not unilaterally support a causal relationship for inflammation leading to depression; however, inflammation is now well-known to be involved in the development of obesity, atherosclerosis and type 2 diabetes (Libby et al., 2009; Winer et al., 2014), which are commonly comorbid with depression. In BD, adipose accumulation is accelerated during episodes (Fiedorowicz et al., 2015) and increased adiposity is seen in MDD across the lifespan, from adolescence (Coryell et al., 2016) to older adults with heart disease (Swardfager et al., 2010). Therefore, these comorbidities are likely contributors to findings of increased inflammation in MDD and BD. Logically, anti-inflammatory agents might then be targeted to mitigate the effects of depressive disorders on cardiac and metabolic health. The question remains as to which specific inflammatory pathways might be useful both for diagnosis and therapy.

Identifying particular inflammatory pathways elevated in psychiatric disorders that support cardiovascular disease progression has been challenging. Inflammation promotes atherosclerosis via a number of mechanisms, some involving TNF or P-selectin activation of vascular endothelial cells, white blood cell infiltration, and promotion of vascular smooth muscle cell proliferation by inflammatory signaling or platelet derived factors (Libby, 2002). Widely used cardiovascular preventative antiplatelet therapy with low-dose aspirin may prevent the onset of depression, particularly in older men with elevated homocysteine (Almeida et al., 2012), and some evidence suggests that adjunctive aspirin may speed the onset of antidepressant action (Mendlewicz et al., 2006). Accordingly, certain platelet derived lipid species, have been associated with depressive symptoms in coronary artery disease patients (Mazereeuw et al., 2015), and with poorer cognitive performance in depressed CAD patients (Mazereeuw et al., 2014). These preliminary results suggest that some platelet-mediated inflammatory lipid pathways may be related to depressive symptoms (Mazereeuw et al., 2013), but further lipidomic studies will be needed to confirm which species may be most relevant.

Considerable attention has been paid to the omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are often found to be lower in MDD (summarized in (Otoki et al., 2017)), and which can have anti-inflammatory, antidepressant and cardioprotective properties (Kromhout et al., 2012; Mocking et al., 2016). However, the clinical benefits of omega-3 PUFA treatment have been modest and highly variable (Mocking et al., 2016), which might necessitate precision medicine approaches, such as biomarkers to support their use, such as measures of oxidative stress (Mazereeuw et al., 2017) or structural lipids impacted by changes in omega-3 fatty acid metabolism (Otoki et al., 2017). An alternative approach would be to consider novel treatments that specifically target dysregulation within the pathways that contribute to reductions in omega-3 PUFAs, and perhaps more importantly, to changes in their bioactive metabolites.

## 3. Inflammatory, anti-inflammatory and pro-resolving lipid species

As shown in Figure 2, PUFAs such as arachidonic acid (AA), EPA and DHA are metabolized by cyclooxygenases (COX) (Smith et al., 2000; Wada et al., 2007), lipoxygenases (LOX) (Funk, 2001; Yamamoto et al., 1988) or cytochrome P450 enzymes (Fer et al., 2008; Morisseau et al., 2010; Spector and Kim, 2015) to produce a plethora of ‘oxylipin’ lipid mediators that regulate inflammation and resolution pathways in tissues. Fatty acid epoxides, derived from AA, EPA and DHA through the cytochrome p450 pathway are potent anti–inflammatory mediators (Capozzi et al., 2016; Morin et al., 2008; Morin et al., 2010; Morisseau et al., 2010; Node et al., 2001), likely acting via G protein-coupled receptors (GPCRs) present in the target tissues (Ding et al., 2014; Liu et al., 2016). These GPCRs and the enzymes within the biosynthetic cascades of the PUFAs that activate them, offer a new and vast arena for the development of novel pharmacotherapies.

Fatty acid epoxides are hydrolyzed by soluble epoxide hydrolase (sEH) and converted to their respective diols (Morisseau et al, 2010.; Zeldin et al., 1993; Zeldin et al., 1995). These diols have been reported as being mostly inactive or less active compared to the epoxide

metabolites in regulating cardiovascular function (Lee et al, 1999.; Node et al., 1999) and inflammation (Capozzi et al., 2016; Morin et al., 2008; Node et al., 1999). For this reason, interest has grown in sEH inhibitors as therapeutic agents for several inflammation-related pathologies (Shen and Hammock, 2012), such as myocardial infarction (Kompa et al., 2013; Xu et al., 2013), atherosclerosis (Li et al., 2016; Shen et al., 2015; Ulu et al., 2008; Zhang et al., 2009), inflammatory pain (Inceoglu et al., 2015; Rose et al., 2010; Wagner et al., 2011; Wagner et al., 2013), neuropathic pain (Wagner et al., 2014; Wagner et al., 2017) and metabolic syndrome (Iyer et al., 2012; Luria et al., 2011).

Inhibitors of sEH have yet to pass regulatory approval and attach themselves to a clinical indication, but *in vitro* and *in vivo* studies have generated promising results. Some of the leading candidates have already entered/passed early-phase clinical trials (see Table 1). These leading molecular entities include a urea (Table 1: Chemical AR928; also UC1153) or an amide group (Table 1: GSK2256294), which bind directly to the active sites of sEH as transition state mimics. sEH inhibitors of other structures have been identified and described previously, including those having a carbamate structure (Morisseau et al., 1999; Lee et al., 2014).

Due to the anti-inflammatory effects of CYP450 derived lipid epoxides and the less beneficial effects of the sEH derived diols, activation of sEH in depressive disorders suggests a plausible new link. Since cytokines tend to vary between patients (Hannestad et al., 2011), the question before the field is whether oxylipins, in particular fatty acid epoxides and their respective diols, might inform a more specific and targetable inflammatory status in depressive states, and therefore may be more useful in predicting response to current therapies, or in identifying potential new treatments targetting oxylipin diols derived from sEH.

A recent meta-analysis of omega-3 PUFA data demonstrated that EPA-rich omega-3 PUFA may be recommended for the adjunctive treatment of depression (Sarris et al., 2016). In a variety of bioassays, and particularly in inflammation driven models, epoxides of EPA and DHA have proven to have anti-inflammatory activities (Kodani et al., 2015). Given the crucial role of sEH, and to a lesser extent the microsomal epoxide hydorolase (Marowsky et al., 2017), in the metabolism of the anti-inflammatory omega-3 epoxides, it is likely that omega-3 PUFA (particularly EPA), in combination with a sEH inhibitor, would be a novel therapeutic approach for depression (Hashimoto, 2016).

## 4. Soluble epoxide hydrolase in psychiatric disorders

As discussed, the search for the source of chronic, low-grade inflammation in psychiatric disorders, and for inflammatory mediators of the relationships between psychiatric disorders and adverse cardiovascular and metabolic outcomes, has been met with mixed results. Emerging evidence suggests that sEH activity is elevated in several psychiatric disorders. The ratios of sEH-derived products to their respective substrates (i.e. diol:epoxide ratio) were significantly elevated in anorexia nervosa, an eating disorder characterized by an aversion to fat consumption (Shih et al., 2016). In one small preliminary study of participants with MDD with seasonal pattern (also known as seasonal affective disorder),

increased plasma concentrations of fatty acid diols produced by the sEH pathway were reported within-subjects during depressive episodes (Hennebelle et al., 2017). These two studies provide the first evidence *in vivo* of increased sEH activity in psychiatric disorders, encouraging replication in additional cohorts.

Studies on post-mortem brain also reported increased sEH protein expression in parietal cortex of patients suffering from major depressive disorder, bipolar disorder and schizophrenia (Ren et al., 2016). Consistent with that evidence, pharmacological targeting of sEH was found to reduce inflammation and resolve behavioral impairments in animal models of depression, pain, and schizophrenia (Ma et al., 2013; Ren et al., 2016). Inflammation-induced and social defeat stress models of depression are both characterized by an increase expression of sEH in mouse prefrontal cortex and hippocampus. In these models, a single administration or a chronic intake of a potent sEH inhibitor prevents depression-like behavior such as increased immobility in the tail suspension and forced swim tests, or reduced sucrose preference (Ren et al., 2016). The sEH knock-out mice confer resilience to social defeat stress, identifying a role of sEH in stress resilience (Ren et al., 2016). A single administration of sEH inhibitor has also been reported to reduce hyperlocomotion and restore prepulse inhibition in a phencyclidine (PCP)-induced model of schizophrenia (Ma et al., 2013). Those findings suggest that sEH inhibitors offer potential as therapeutic drugs, which may alleviate stress-responsive symptoms across psychiatric disorders.

Inhibiting sEH activity has also shown promise for other neurological disorders such as epilepsy and seizure. Mouse seizure models are characterized by an increased sEH expression in hippocampus accompanied by an increased in inflammatory markers such as IL-1β and IL-6 (Hung et al., 2015). Administration of sEH inhibitors prevented neuroinflammation and reduced the number and duration of seizures in mouse models (Hung et al., 2015; Inceoglu et al., 2013; Vito et al., 2014). Decreasing neuronal excitability may reduce excitotoxicity that results from excessive calcium influx due to overstimulation of NMDA receptors, which has been proposed as a mediator of inflammation-induced depressive symptoms and neurodegeneration in mood disorders (O'Connor et al., 2009; Schwarcz et al., 2012; Swardfager et al., 2009).

The potential benefits of sEH inhibition in psychiatry might also be mediated partially by direct effects on neurotransmission. Inhibition of sEH has been reported to enhance prefrontal cortex neuronal synaptic neurotransmission, increase field excitatory postsynaptic potentials, the input-output curve, and long-term potentiation in extracellular recordings, by increasing expression of glutamate receptors, including NMDA, AMPA and mGluRs (Wu et al., 2015). sEH inhibition also promotes axonal growth in cultured sensory and cortical neurons (Abdu et al., 2011). The sEH inhibitors therefore offer promise to probe neuronal, vascular and inflammatory processes relevant to the symptoms, progression and complications of psychiatric disorders.

## 5. Potential benefits of sEH inhibition in protection against depression comorbidities

### 5.1 Cardiovascular & Cerebrovascular

The peripheral and cerebral vasculature may be vulnerable in psychiatric disorders, including both the large and small blood vessels (Naiberg et al., 2017). The sEH enzyme was identified as a susceptibility factor for heart failure because it increased hydrolysis of cardioprotective epoxyeicosanoid levels (Monti et al., 2008). By genetic knock-out or chemical inhibition of sEH, protection can be afforded in various models of brain and vascular injury, pain, lung and kidney disease, and the development of hypertension and diabetes (Imig and Hammock, 2009; Ingraham et al., 2011). Other inflammatory comorbidities such as asthma are also common in depression (Boudreau et al., 2014; Lavoie et al., 2006), and lipoxin activity in asthma has been related to sEH (Ono et al., 2014). The many potential protective mechanisms related to sEH inhibition remain under investigation, but they have been related to vascular endothelial function, neuroprotection, angiogenesis, anti-platelet actions, reduced oxidative stress, attenuated inflammatory responses to ischemia, and resolution of inflammation (Iliff and Alkayed, 2009). Protective mechanisms of sEH inhibitors may also involve attenuating hyperlipidemia, macrophage and monocyte infiltration into atherosclerotic lesions, and monocyte adhesion to endothelial cells activated by inflammation (notably TNF) and platelets (Li et al., 2016).

Potentially relevant to observations of accelerated thickening of the large vessels in depressive disorders, polymorphisms in sEH genes have been associated with the risk of ischemic stroke in humans (Fava et al., 2010; Gschwendtner et al., 2008). sEH is overexpressed in human atherosclerotic plaque, and it promoted carotid-artery injury induced neointima formation in a rat model by enhancing vascular smooth muscle cell proliferation and migration in response to platelet derived growth factor signaling (Wang et al., 2015). In addition to risk of stroke, sEH may be involved in protection from the resulting ischemic damage. Pharmacological inhibition or genetic knock-out of sEH affords robust protection against ischemic brain injury and increase neuronal survival (Koerner et al., 2007; Yuan et al., 2016; Zhang et al., 2007; Zhang et al., 2008). Pharmacological inhibition of sEH can attenuate astrocyte infiltration, glial scar formation, microglial activation, neuronal apoptosis, infarct volume, blood flow deficiency and behavioral deficits following experimental cerebral ischemia (Dorrance et al., 2005; Qu et al., 2015; Simpkins et al., 2009; Stulc, 1989; Taguchi et al., 2016).

Histopathological evidence from the Oregon Brain Aging Study suggests that elevated sEH may also be involved in vulnerability to disease of the cerebral small vessels, since sEH products were elevated in brain tissue from people with vascular cognitive impairment and vascular endothelial sEH protein levels were elevated in the small vessels of affected tissues (Nelson et al., 2014). It is possible that sEH expression could exacerbate dysfunction of the small vessels, leading to psychiatric symptoms and cognitive deficits due to cardiovascular risk factor-induced perturbations in vascular homeostasis even prior to observable structural brain abnormalities (Vanella et al., 2015).

There is considerable evidence to support the notion that disruption of the neural circuitry of reward is involved in the pathophysiology of mood disorders (Russo and Nestler, 2013). Changes in communication between the nodal structures within reward systems and multiple other networks have been documented in functional MRI studies. The grey matter in the nodal structures depends on its ability to couple increased demand for oxygen and glucose on activation with vasodilatory signals that augment local blood volume. The potential for sEH to attenuate vasodilation when overexpressed (Chadderdon et al., 2016), and hence impair neurovascular coupling, is notable, particularly since sEH is present in the brain and cerebral vasculature affecting the concentrations of vasoactive arachidonic acid metabolites (Nelson et al., 2014). Emerging evidence suggests that microstructural changes in the white matter connecting nodal grey matter structures may also underlie disruption of neural networks (Versace et al., 2013), which would also be consistent with changes in arterioles and the small vessels that penetrate and supply blood to the white matter. The biological bases for neural circuit disruption in mood disorders are likely to be multifactorial. The sEH hypothesis would be consistent with observations of the impact of inflammation on reward systems (Swardfager et al., 2016).

### 5.2 Neurocognition and Neuroprogression in Depressive Disorders

Deficits in neurocognition detected commonly in MDD and BD are underappreciated but common and important contributors to the burden of mood disorders (Millan et al., 2012). The severity of deficits can increase with the number and severity of successive mood episodes, suggesting a neuroprogressive phenomenon (Berk et al., 2011). The most common cognitive deficits in MDD and BD, including a propensity for poorer executive function, attention, and psychomotor processing speed, resemble those seen in older people due to cerebrovascular disease, which often manifests as hyperintensities in the white matter visible on structural MRI (Hachinski et al., 2006).

Throughout the lifespan, there appears to be a trifecta of cardiovascular dysregulation, depression and cognitive vulnerability. Substantiating the vulnerability of the cerebral vasculature in mood disorders, white matter hyperintensities, particularly in the frontal regions, are more common in BD than unaffected individuals (Aylward et al., 1994; Beyer et al., 2009). Some studies have reported associations between white matter hyperintensities and psychiatric disorders, including BD, MDD and conduct disorder/attention deficit disorder in early life, including in children 12 years of age (Lyoo et al., 2002). Moreover, recent evidence suggests that the small vessels may be particularly vulnerable to vascular risk factors and that these changes may be related to executive function in adolescents with bipolar disorder, as indicated by photography of the retinal blood vessels (Naiberg et al., 2016). Together the cognitive and imaging findings might suggest that the common and severe mood disorders are associated with increased vascular risk factors and a vulnerability of the cerebral vasculature thereto.

There appears to be an interaction between depression and metabolic dysfunction in predicting brain vulnerability, as indicated by increased risks of dementia (Katon et al., 2015), and vascular cognitive impairment (particularly impairments in executive function) (Swardfager and MacIntosh, 2017), in those with both depression and diabetes later in life.

In adult BD studies, elevated BMI or insulin resistance appears to moderate the course of the disease and response to treatment (Calkin et al., 2009; Calkin et al., 2015). Diabetes is known to increase the risk of depression (Rotella and Mannucci, 2013a), and vice versa (Rotella and Mannucci, 2013b), although the consequences of metabolic dysfunction on the course and severity of MDD are not as well documented as those in BD. Conversely, the impact of depression on diabetes outcomes appears to be indirect, mediated by health behaviors and specific symptom domains (Carter and Swardfager, 2016). For instance, anhedonia can be particularly difficult to treat pharmacologically, and it appears to have a detrimental impact on glycemic control and mortality in type 2 diabetes that is mediated by decreased physical activity (Nefs et al., 2016). Anhedonia has been related to inflammation (Swardfager et al. 2016) and to small vessel disease (Lavretsky et al., 2008). Neuroprotective benefits of sEH inhibition, particularly given the vasoactive properties of sEH substrates, their protective effects against vascular risk factors, and their metabolic benefits, suggest that they may impact the course of neurocognitive decline.

### 5.3 Obesity & insulin resistance

Since inflammation in psychiatric disorders may arise in part due to increased rates of obesity (Howren et al., 2009), it may be relevant that sEH inhibitors have been shown to modulate inflammation in adipose tissue in obese mice (Lopez-Vicario et al., 2015); specifically, inhibition of sEH favoured the polarization of macrophages towards an anti-inflammatory M2 phenotype, which is known to protect against the development of insulin resistance and type 2 diabetes (Wang et al., 2014). As reviewed previously (Luther and Brown, 2016), sEH increases in animal models of obesity and diabetes, whereas the epoxylipid sEH substrates promote islet cell function and peripheral tissue insulin sensitivity. Clinically, genetic polymorphisms the she gene EPHX2, and circulating epoxy lipid concentrations, correlate with insulin sensitivity (Luther and Brown, 2016). Moreover, obesity and diabetes are risk factors for cardiovascular disease, and sEH inhibition can improve coronary endothelial function, prevent cardiac remodeling and reduce diastolic dysfunction in obese insulin-resistant mice (Roche et al., 2015). Thus, sEH may have beneficial roles both in maintaining glucose homeostasis, and in protecting the vasculature from the consequences of obesity and diabetes (Kodani and Hammock, 2015; Zuloaga et al., 2014).

Since physical inactivity is a prominent risk factor in depression, it is especially notable that evidence from non-human primates suggests that sEH may be involved in the mechanism by which physical inactivity contributes to deficits in insulin resistance and glucose-stimulated small vessel vasodilation (Chadderdon et al., 2015). Specifically, the ratio of sEH-derived diols to fatty acid epoxide substrates was increased after forced physical inactivity, and this correlated with microvascular insulin resistance and the inability to dilate and augment blood volume. Exercise can have anti-depressant effects, but those effects have been small and inconsistent (Rethorst et al., 2009), suggesting the need to identify molecules that could augment its benefits. Strategies that might be of benefit include augmenting cytochrome p450-derived sEH substrates, or sEH inhibitors, which may be able to augment neurovascular responses in those with sEH activation or increasing the omega-3 to omega-6 ratio in the diet.

## 6. Perspectives and Synthesis

Adopting a Mediterranean diet has been shown to be beneficial in the prevention of cardiovascular disease and dementia. Recently, a small randomized controlled trial of a modified Mediterranean diet demonstrated antidepressant effects (Jacka et al., 2017). This finding is of interest because the diet has been shown to encourage the formation of endogenous lipid electrophiles (e.g. 10-nitrooctadec-9-enoic acid) that inhibit sEH (Charles et al., 2014). In mice, inhibition of sEH by endogenous nitrolipids seems to be responsible for some of the beneficial effects of the Mediterranean diet (e.g. antihypertensive effects) (Charles et al., 2011). Notably, clinical evidence also suggests that the Mediterranean diet can modify markers of inflammation and endoplasmic reticulum (ER) stress (Yubero-Serrano et al., 2012).

Increasingly, it appears that sEH inhibitors, and mimics of epoxylipids, are effective in situations where the ER stress response is activated. For example, ER stress increases in neuropathic pain and the epoxyeicosatrienoic acids that reduce ER stress markers tend to be effective against neuropathic pain. Moreover, agents apart from epoxylipids that reduce neuropathic pain also tend to reduce ER stress (Inceoglu et al., 2015). As the intracellular hub for protein synthesis, the ER is responsible for supporting cellular homeostasis with protein and lipid synthesis. The ER stress response, a cascade of kinase and phosphatase activation, can signal apoptosis when the ER becomes overwhelmed with excessive demand for protein folding or elimination of misfolded proteins.

Evidence in support of heightened ER stress in MDD is now accumulating. For instance, peripheral expression of *BiP, EDEM1, CHOP*, and *XBP1*, the major indicators of the ER stress response, were elevated 1.34-fold to 1.68-fold in community dwelling individuals with MDD (Nevell et al., 2014). Increased ER stress proteins GRP78, GRP94, and calreticulin, have been found in the temporal cortex in MDD post-mortem, and GRP78 appears to be affected by antidepressants (Bown et al., 2000). In animal studies, rats that developed learned helplessness in the inescapable shock paradigm had upregulated *GRP78, GRP94, ATF6*, and *XBP-1* compared to rats who were not subjected to shock, or those that did not develop learned helplessness (Timberlake and Dwivedi, 2015). Collectively, these and other studies have suggested a role for ER stress in the development of depressive disorders due to deficiencies in resilience to chronic stress.

ER stress is activated by reactive oxygen species, which can arise from mitochondrial dysfunction or hyperglycemia, leading some authors to propose that central insulin and peroxisome proliferator-activated receptor-γ (PPAR-γ) systems may be targeted in depression (Gold et al., 2013). It was also noted that a state of innate immune activity, termed “parainflammation”, tends to accompany the ER stress response, which might account for some of the chronic low-grade inflammatory activity seen in MDD and BD (Gold et al., 2013). The inflammatory findings would be consistent with ER stress stimulating inflammasome activity via NLRP3 (Bronner et al., 2015), an important sensor of metabolic dysfunction increasingly thought to link oxidative stress and inflammation in depressive and neurodegenerative disorders, and in type 2 diabetes, obesity and cardiovascular diseases that are commonly comorbid with depressive disorders (Singhal et

al., 2014). Since reactive oxygen species are a major factor in activating the ER stress response, one could consider an axis of effects as mitochondrial dysfunction increase ROS, which in turn feed back to cause more mitochondrial dysfunction and also drive the ER stress response from a homeostatic mechanism towards autophagy, apoptosis and inflammation. The demonstrated impact of the epoxylipids and of the sEH inhibitors on processes underlying each of these conditions, suggests a plausible new mechanism by which these harmful cascades may be interrupted. Autophagy, apoptosis and inflammation are implicated in not only psychiatric disorders, but also in neurodegeneration, for which psychiatric disorders are a risk factor.

## 7. Conclusions

Collectively, the data suggest a need for further work to validate preliminary findings of increased epoxide hydrolase activity in psychiatric disorders. Oxylipins are detectable in peripheral blood and LC-MS/MS oxylipin assays are now available, offering quantitative measures of cytochrome p450 and sEH products that can be standardized between laboratories for clinical studies. Due to the emerging picture of concomitant neural, vascular and metabolic insult in depressive disorders, and their cumulative impact on cognitive and functional decline, protection of the brain and vasculature afforded by dietary and pharmacological sEH inhibition in animal studies to date suggests a unique opportunity to explore new anti-inflammatory therapeutics in psychiatry that address both the symptoms of the disorders and their long-term sequelae.

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## Highlights

- Soluble epoxide hydrolase (sEH) metabolizes anti-inflammatory lipids
- sEH activation may be a link between mood disorders and inflammation
- sEH inhibitors are under development for vascular, nerve and metabolic disorders
- sEH-dervied oxylipins are elevated in the brain and blood in mood disorders
- inhibiting sEH mitigated the development of depressive-like behaviors in rats
- inhibiting sEH may protect against inflammatory comorbidities in psychiatry

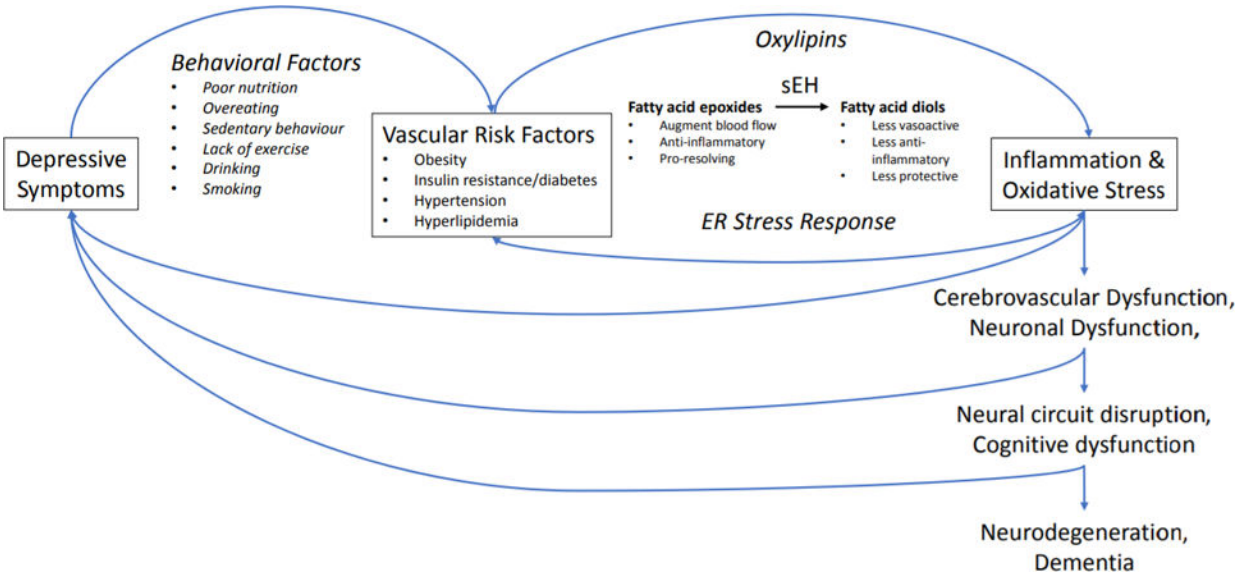



**Figure 1. Hypothetical relationships between depressive disorders, vascular risk factors and cognitive vulnerability mediated by inflammatory activity and oxidative stress**

Anti-inflammatory lipid mediators (e.g. fatty acid epoxides) are metabolized by soluble epoxide hydrolase (sEH) into less beneficial (less bioactive) and sometimes even pro-inflammatory or cytotoxic oxylipin diol species. Increased sEH activity in the brain and vasculature in depressive disorders may confer vulnerability to vascular risk factors that affect neurovascular coupling/cerebral blood flow/brain metabolism and contribute to cognitive and mood symptoms, and predispose cerebrovascular disease that contribute to neuroprogression and cognitive decline.

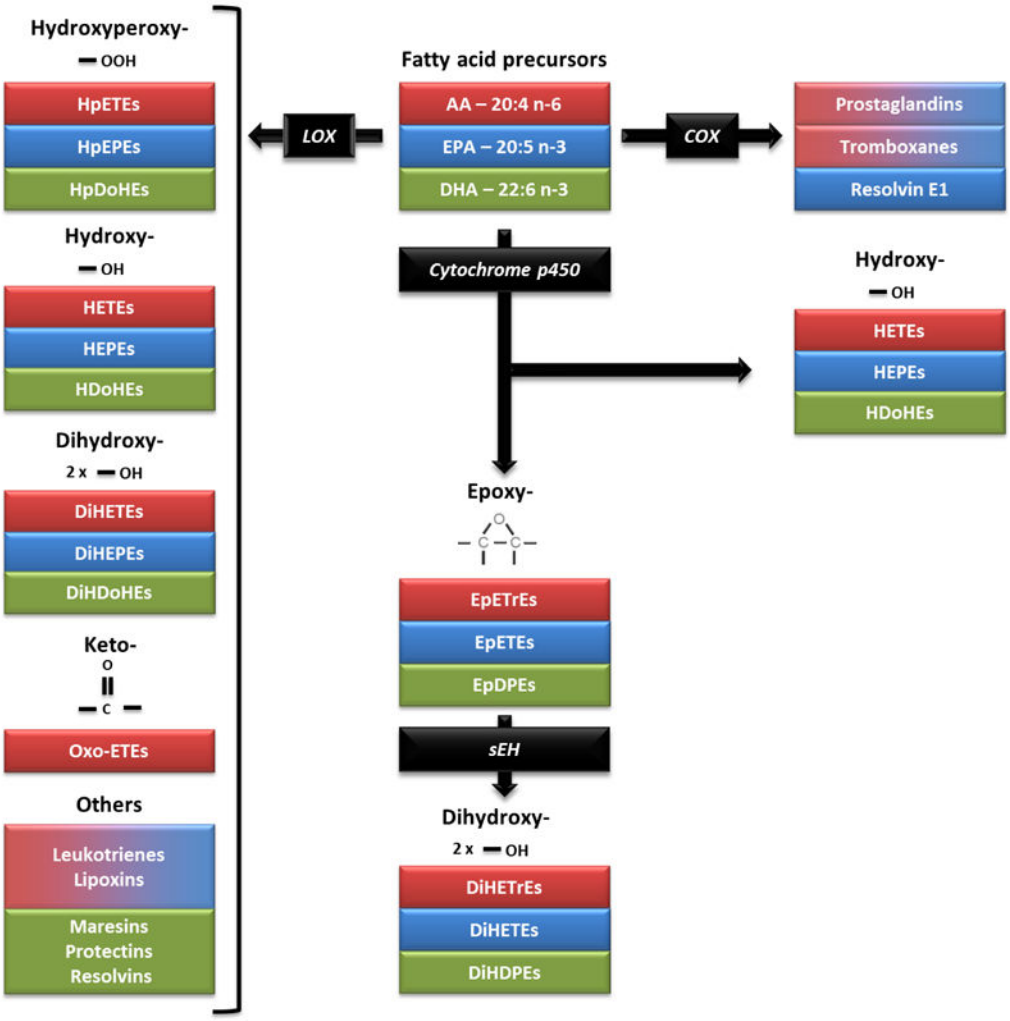



**Figure 2. Enzymatic synthesis of oxylipins from arachidonic acid (AA; 20:4 n-6), eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3)**

Polyunsaturated fatty acids, including AA, EPA and DHA, are precursors to oxidized fatty acid metabolites, commonly known as oxylipins. In this figure, fatty acid precursors and their respective metabolites share the same color code. Prostaglandins, thromboxanes and resolvins are produced from AA and EPA though the cyclooxygenase pathway (COX) pathway. The lipoxygenase (LOX) pathway produces hydroperoxy-metabolites, such as hydroperoxyeicosatetraenoic acids (HpETEs), hydroperoxyeicosapentaenoic acids (HpEPEs) and hydroperoxydocosahexaenoic acids (HpDoHEs), that are rapidly converted into hydroxy-metabolites, including hydroxyeicosatetraenoic acids (HETEs), hydroxyeicosapentaenoic acids (HEPEs) or hydroxydocosahexaenoic acids (HDoHEs). Hydroxy-metabolites from the LOX pathway can then be converted into dihydroxy metabolites, such as dihydroxyeicosatetraenoic acids (DiHETEs), dihydroxyeicosapentaenoic acids (DiHEPEs) or dihydroxydocosahexaenoic acids (DiHDoHEs), and into keto-metabolites, such as oxo-eicosatetraenoic acids (oxo-ETEs). Leukotrienes and lipoxins from AA and EPA, as well as maresins, protectins and resolvins from DHA are also synthesized through the LOX pathway. Cytochrome p450 enzymes are

oxidative enzymes that generate hydroxy-metabolites on activated or terminal carbons or epoxides at olefinic bonds. Epoxides generated by Cytochromie p450s include epoxyeicosatrienoic acids (EpETrEs), epoxyeicosatetraenoic acids (EpETEs) and epoxydocosapentaenoic acids (EpDPEs). These largely anti-inflammatory epoxy-metabolites can be converted largely by soluble epoxide hydrolase (sEH) into their respective diols, dihydroxyeicosatrienoic acids (DiHETrEs), dihydroxyeicostetraenoic acids (DiHETEs) and dihydroxydocosapentaenoic acids (DiHDPES).

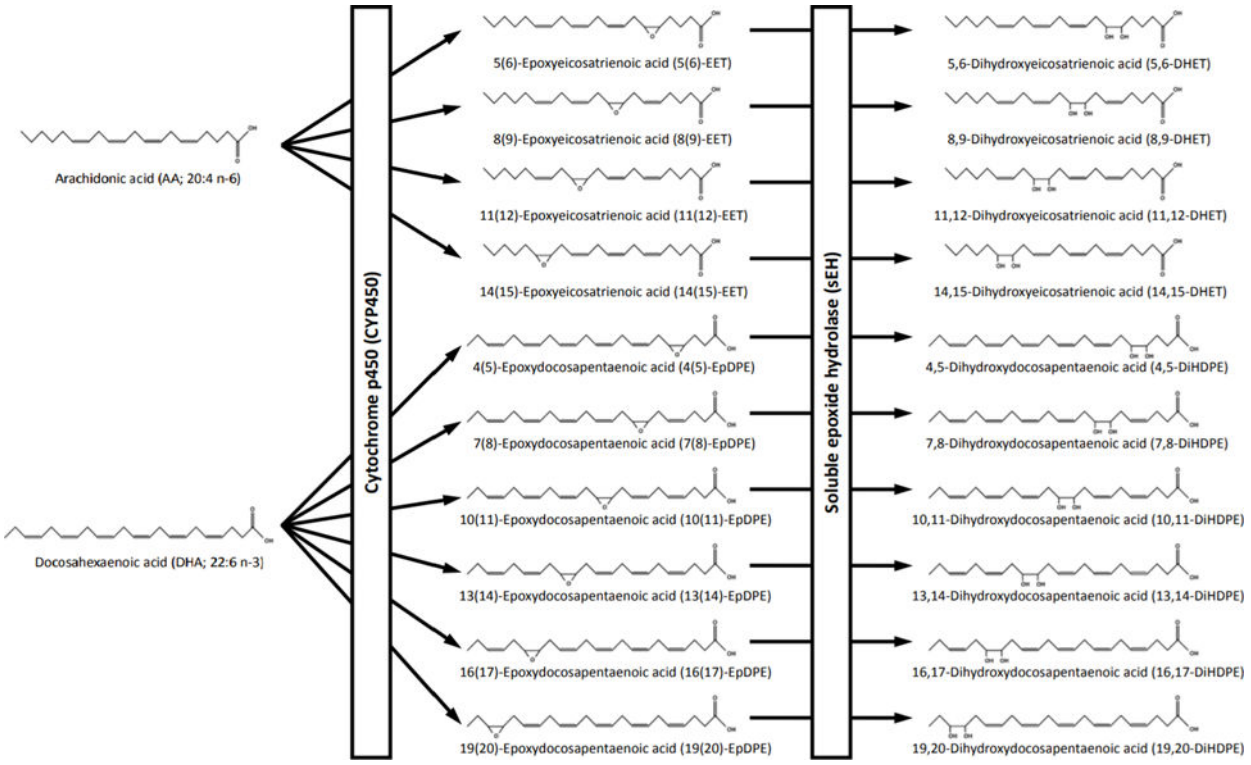
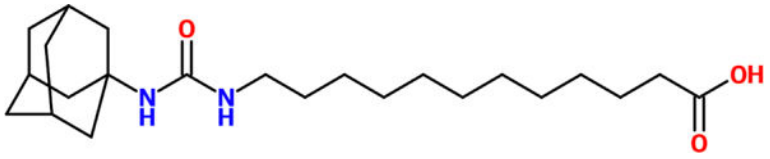
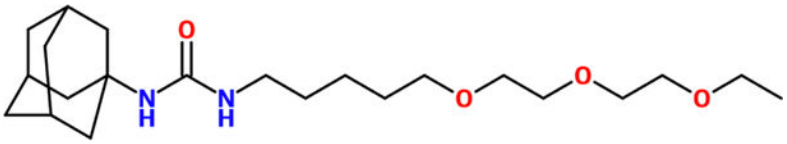
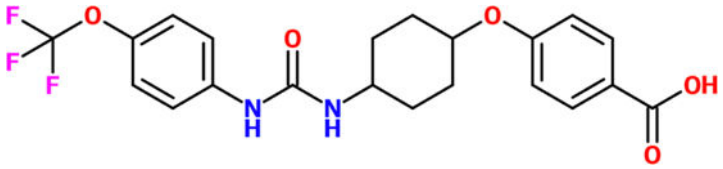


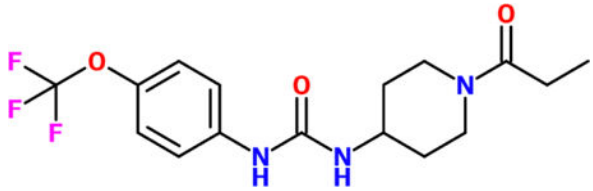
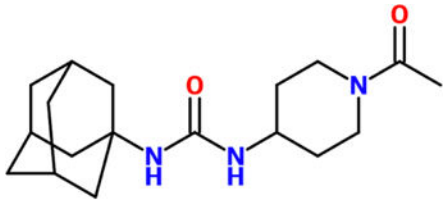
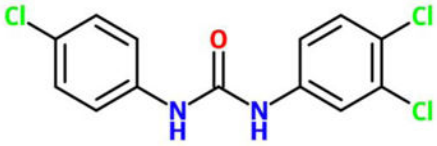

**Figure 3.**

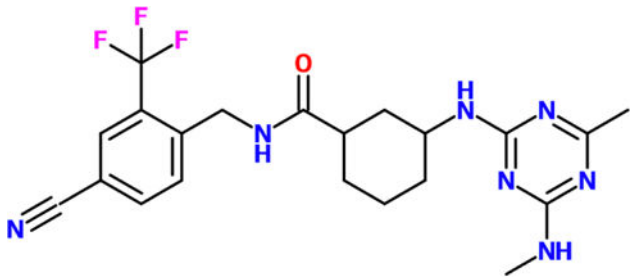
Biotransformation of arachidonic acid and docosahexaenoic acid into epoxides by cytochrome p450s, and subsequent biotransformation to corresponding diols by sEH.

## Table 1

Structures of sEH inhibitors commonly in research, and three compounds[α] used in clinical trials.

| Compound* | Structure | $IC_{50}$ for human sEH# | Comments |
|---|---|---|---|
| AUDA, UC700 |  | 3nM <11nM> | Early sEH inhibitor with high lipophilicity and high melting point designed to mimic the 14, 15-EET structure. It is also a PPAR alpha agonist and it would be expected, from its structure, to be biologically active as an EET mimic. All lipophilic high melting sEH inhibitors are only available biologically in true solution in an organic co-solvent. |
| AEPU, UC950 |  | 1nM <5nM> | A water miscible sEH inhibitor with low melting point, and activity on the sEH from many species. Rapidly penetrates cell membranes, protein binding is low, and it was designed for rapid metabolism |
| *t*-TUCB, UC1728 |  | 900pM <1nM> | A lipophilic sEH inhibitor with broad potency across many species. Improved pharmacokinetics compared with AUDA due to removal of the metabolically labile adamantane group. Commonly used in equine and companion animal studies. Lipophilic and high melting point. |

| Compound* | Structure | $IC_{50}$ for human sEH# | Comments |
|---|---|---|---|
| TPPU, UC1770 |  | 600pM <10nM> | Widely used and commercially available sEH inhibitor of moderate water solubility. A lipophilic and high melting point compound, which must be administered in an organic co-solvent. High target occupancy. Currently the most commonly used model sEH inhibitor. Most piperidines have low potency outside of primate and rodent species. |
| AR9281[α], APAU, UC1154 |  | 15nM <6nM> | No off-target effects seen in Phase I and II clinical trials in hypertensive – pre-diabetic patients run by Arête Therapeutics. More water soluble than most piperidine sEH inhibitors. Very short half-life in most species. It shows poor target occupancy. Like UC950, it is an excellent tool if a short half-life water soluble compound is needed. |
| TCC[α] |  | 13 nM <21nM> {353nM} | Triclocarban is an old topical antimicrobial commonly used in cosmetics and hard soaps. It is lipophilic and has a short half life due to N-glycosylation. It was successful in a double blind 30 person clinical trial as a topical with diclofenac with diabetic neuropathy. Note the very poor activity on murine enzyme. The study was run by a |

| Compound* | Structure | $IC_{50}$ for human sEH# | Comments |
|---|---|---|---|
| | | | collaboration between Sphaera and Synthia Dermatec. |
| GSK2256294[α] |  | 400pM [27pM] | A lipophilic high melting compound run in three Phase I trials, and with some efficacy data on cigarette induced pulmonary disease. Good pharmacokinetics and no adverse effects noted. It is available for experimental use. The pM potency was reported by GSK using a different substrate. |

*Several synonyms are used in the literature for the compounds.

#$IC_{50}$ can be highly reproducible but the value depends upon the substrate structure and its concentration as well as other incubation conditions. Unless otherwise noted by <>, {} or [] these values were determined with the spectral substrate CMNPC and the pure human recombinant sEH. Many sEH inhibitors are so powerful that they violate Michaelis-Menton assumptions. Most are transition state mimics showing slow – tight binding kinetics so that the target occupancy driven by kinetic $k_{off}$ appears the best predictor of *in vivo* efficacy. $IC_{50}$ on the rat is noted by <>, and $IC_{50}$ on the mouse is noted by {}.