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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 peripheral and brain 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 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.

1. Inflammation and anti-inflammatory agents in depression

The phenomenon of increased inflammation in major depressive disorder (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., 2010; 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, bipolar disorder (BD) and schizophrenia (Goldsmith et al., 2016), likely due in part to production of psychoactive tryptophan metabolites (Schwarcz et al., 2012).

Despite that 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

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patients who have evidence of elevated peripheral inflammatory activity before treatment (i.e. elevated 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., 2017), likely echoing observations 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., 2017), 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., 1988). 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. In addition, 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 microbiota, mitochondrial dysfunction, autoimmunity, 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., 2009), 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 that 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 (Fig. 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 (Duijvis et al., 2011). Therefore, the epidemiology does not unilaterally support a causal relationship for inflammation leading to

depression; however, inflammation is 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., 2011). 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. Some biomarkers to direct therapies might include 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 Fig. 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 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;

Fig. 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, which contributes to neuroprogression and cognitive decline.

Fig. 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 through 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 Cytochrome p450s include epoxyeicosatrienoic acids (EpETEs), 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 (DiHETEs), dihydroxyeicosatetraenoic acids (DiHEPEs) and dihydroxydocosapentaenoic acids (DiHDPEs).

Fig. 3. Biotransformation of arachidonic acid and docosahexaenoic acid into epoxides by cytochrome p450s, and subsequent biotransformation to corresponding diols by sEH.

Zeldin et al., 1993; Zeldin et al., 1995) (Fig. 3). These diols have been reported to be 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., 2006; 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 recently entered/passed phase I clinical trials (see Table 1) with no serious adverse events (Lazaar et al., 2016). These leading molecular entities include a urea (Chemical AR9281; also UC1153) or an amide group (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 or even harmful effects of the sEH derived diols (Hu et al., 2017), 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 that target 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 and Hammock, 2015). Given the crucial role of sEH, and to a lesser extent the microsomal epoxide hydrolase (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”), altered plasma concentrations of oxylipins, including increased 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 reported increased sEH protein expression in parietal cortex of patients suffering from MDD, BD and schizophrenia (Ren et al., 2016). Consistent with that evidence,

Table 1
Structures of sEH inhibitors commonly in research, and three compounds^a used in clinical trials.

Compound ^a	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
<i>t</i> -TUCB, UC1728		900pM	
TPPU, UC1770		600pM < 10nM >	
AR9281 ^a , APAU, UC1154		15nM	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 ^a		13nM < 21nM > {353nm}	
GSK2256294 ^a		400pM [27pM]	

^aSeveral synonyms are used in the literature for the compounds. [#]IC₅₀ 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. IC₅₀ on the rat is noted by < > , and IC₅₀ on the mouse is noted by {}.

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-1 β 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 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 (Millan et al., 2012), 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 (Lyyo 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 BD, 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, there appears to be an impact of depression on diabetes outcomes, which is 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, diabetes & 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 epoxy lipid sEH substrates promote islet cell function and peripheral tissue insulin sensitivity. Clinically, genetic polymorphisms in the sEH 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). In diabetes, a DHA-derived diol was reported to mediate microvascular retinal toxicity (Hu et al., 2017). 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; Hu et al., 2017).

Since physical inactivity is prominent 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., 2016). 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 nitro lipids 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 epoxy lipids, 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 epoxy lipids 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 (Neve 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 reactive oxygen species, 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 epoxy lipids 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 psychiatric symptoms of the disorders, and their long-term somatic sequelae.

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References

- Abdu, E., Bruun, D.A., Yang, D., Yang, J., Inceoglu, B., Hammock, B.D., Alkayed, N.J., Lein, P.J., 2011. Epoxyeicosatrienoic acids enhance axonal growth in primary sensory and cortical neuronal cell cultures. *J. Neurochem.* 117, 632–642.
- Almeida, O.P., Flicker, L., Yeap, B.B., Alfonso, H., McCaul, K., Hankey, G.J., 2012. Aspirin decreases the risk of depression in older men with high plasma homocysteine. *Transl. Psychiatry* 2, e151.
- Anderson, G., 2017. Linking the biological underpinnings of depression: role of mitochondria interactions with melatonin, inflammation, sirtuins, tryptophan catabolites, DNA repair and oxidative and nitrosative stress, with consequences for classification and cognition. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 80, 255–266.
- Aylward, E.H., Roberts-Twillie, J.V., Barta, P.E., Kumar, A.J., Harris, G.J., Geer, M., Peyser, C.E., Pearson, G.D., 1994. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. *Am. J. Psychiatry* 151, 687–693.
- Berk, M., Kapczinski, F., Andreazza, A.C., Dean, O.M., Giorlando, F., Maes, M., Yucel, M., Gama, C.S., Dodd, S., Dean, B., Magalhaes, P.V., Amminger, P., McGorry, P., Malhi, G.S., 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci. Biobehav. Rev.* 35, 804–817.
- Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med.* 11, 200.
- Beyer, J.L., Young, R., Kuchibhatla, M., Krishnan, K.R., 2009. Hyperintense MRI lesions in bipolar disorder: A meta-analysis and review. *Int. Rev. Psychiatry* 21, 394–409.
- Boudreau, M., Bacon, S.L., Ouellet, K., Jacob, A., Lavoie, K.L., 2014. Mediator effect of depressive symptoms on the association between BMI and asthma control in adults. *Chest* 146, 348–354.
- Bown, C., Wang, J.F., MacQueen, G., Young, L.T., 2000. Increased temporal cortex ER stress proteins in depressed subjects who died by suicide. *Neuropsychopharmacology* 22, 327–332.
- Bronner, D.N., Abuita, B.H., Chen, X., Fitzgerald, K.A., Nunez, G., He, Y., Yin, X.M., O'Riordan, M.X., 2015. Endoplasmic reticulum stress activates the inflammasome via NLRP3- and caspase-2-driven mitochondrial damage. *Immunity* 43, 451–462.
- Calabrese, J.R., Skwerer, R.G., Barna, B., Gullledge, A.D., Valenzuela, R., Butkus, A., Subichin, S., Krupp, N.E., 1986. Depression, immunocompetence, and prostaglandins of the E series. *Psychiatry Res.* 17, 41–47.
- Calkin, C., van de Velde, C., Ruzickova, M., Slaney, C., Garnham, J., Hajek, T., O'Donovan, C., Alda, M., 2009. Can body mass index help predict outcome in patients with bipolar disorder? *Bipolar Disord.* 11, 650–656.
- Calkin, C.V., Ruzickova, M., Uher, R., Hajek, T., Slaney, C.M., Garnham, J.S., O'Donovan, M.C., Alda, M., 2015. Insulin resistance and outcome in bipolar disorder. *Br. J. Psychiatry* 206, 52–57.
- Capozzi, M.E., Hammer, S.S., McCollum, G.W., Penn, J.S., 2016. Epoxygenated fatty acids inhibit retinal vascular inflammation. *Sci. Rep.* 6, 39211.
- Carter, J., Swardfager, W., 2016. Mood and metabolism: anhedonia as a clinical target in Type 2 diabetes. *Psychoneuroendocrinology* 69, 123–132.
- Chadder, S.M., Belcik, J.T., Bader, L., Kievit, P., Grove, K.L., Lindner, J.R., 2016. Vasoconstrictor eicosanoids and impaired microvascular function in inactive and insulin-resistant primates. *Int. J. Obes.* 40, 1600–1603.
- Charles, R.L., Burgoyne, J.R., Mayr, M., Weldon, S.M., Hubner, N., Dong, H., Morisseau, C., Hammock, B.D., Landar, A., Eaton, P., 2011. Redox regulation of soluble epoxide hydrolase by 15-deoxy-delta-prostaglandin J2 controls coronary hypoxic vasodilation. *Circ. Res.* 108, 324–334.
- Charles, R.L., Rudyk, O., Pryszazhna, O., Kamynina, A., Yang, J., Morisseau, C., Hammock, B.D., Freeman, B.A., Eaton, P., 2014. Protection from hypertension in mice by the mediterranean diet is mediated by nitro fatty acid inhibition of soluble epoxide hydrolase. *Proc. Natl. Acad. Sci. U. S. A.* 111, 8167–8172.
- Coryell, W.H., Butcher, B.D., Burns, T.L., Dindo, L.N., Schlechte, J.A., Calarge, C.A., 2016. Fat distribution and major depressive disorder in late adolescence. *J. Clin. Psychiatry* 77, 84–89.
- de Melo, L.G.P., Nunes, S.O.V., Anderson, G., Vargas, H.O., Barbosa, D.S., Galecki, P., Carvalho, A.F., Maes, M., 2017. Shared metabolic and immune-inflammatory, oxidative and nitrosative stress pathways in the metabolic syndrome and mood disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 78, 34–50.
- Ding, Y., Fromel, T., Popp, R., Falck, J.R., Schunck, W.H., Fleming, I., 2014. Biological actions of 11,12-epoxyeicosatrienoic acid in endothelial cells are specific to the R/S-enantiomer and require the G(s) protein. *J. Pharmacol. Exp. Ther.* 350, 14–21.
- Dorrance, A.M., Rupp, N., Pollock, D.M., Newman, J.W., Hammock, B.D., Imig, J.D., 2005. An epoxide hydrolase inhibitor, 12-(3-adamantan-1-yl-ureido)dodecanoic acid (AUDA), reduces ischemic cerebral infarct size in stroke-prone spontaneously hypertensive rats. *J. Cardiovasc. Pharmacol.* 46, 842–848.
- Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lancot, K.L., 2010. A meta-analysis of cytokines in major depression. *Biol. Psychiatry* 67, 446–457.
- Duivis, H.E., de Jonge, P., Penninx, B.W., Na, B.Y., Cohen, B.E., Whooley, M.A., 2011. Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: prospective findings from the heart and soul study. *Am. J. Psychiatry* 168, 913–920.
- Elovainio, M., Keltikangas-Jarvinen, L., Kivimäki, M., Pulkki, L., Puttonen, S., Heponiemi, T., Juonala, M., Viikari, J.S., Raitakari, O.T., 2005. Depressive symptoms and carotid artery intima-media thickness in young adults: the cardiovascular risk in young finns study. *Psychosom. Med.* 67, 561–567.
- Fava, C., Montagnana, M., Danese, E., Almgren, P., Hedblad, B., Engstrom, G., Berglund, G., Minuz, P., Melander, O., 2010. Homozygosity for the EPHX2 K55R polymorphism increases the long-term risk of ischemic stroke in men: a study in Swedes. *Pharmacogenet. Genomics* 20, 94–103.
- Fer, M., Dreano, Y., Lucas, D., Corcos, L., Salaun, J.P., Berthou, F., Amet, Y., 2008. Metabolism of eicosapentaenoic and docosahexaenoic acids by recombinant human cytochromes P450. *Arch. Biochem. Biophys.* 471, 116–125.
- Fiedorowicz, J.G., Andersen, L.E., Persons, J.E., Calarge, C., 2015. Rapid adipose deposition with mood disorders. *Ann. Clin. Psychiatry* 27, 283–288.
- Funk, C.D., 2001. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 294, 1871–1875.
- Gold, P.W., Licinio, J., Pavlatou, M.G., 2013. Pathological para-inflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, IGF1 and PPAR-gamma systems. *Mol. Psychiatry* 18, 154–165.
- Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. *Mol. Psychiatry* 21, 1696–1709.
- Goldstein, B.I., Carnethon, M.R., Matthews, K.A., McIntyre, R.S., Miller, G.E., Raghuveer, G., Stoney, C.M., Wasiak, H., McCrindle, B.W., American Heart Association, A., Hypertension, Obesity in Youth Committee of the Council on Cardiovascular Disease in the Y, 2015. Major depressive disorder and bipolar disorder predispose youth to accelerated atherosclerosis and early cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 132, 965–986.
- Gschwendtner, A., Ripke, S., Freilinger, T., Lichtner, P., Muller-Mysok, B., Wichmann, H.E., Meitinger, T., Dichgans, M., 2008. Genetic variation in soluble epoxide hydrolase (EPHX2) is associated with an increased risk of ischemic stroke in white Europeans. *Stroke* 39, 1593–1596.
- Hachinski, V., Iadecola, C., Petersen, R.C., Breteler, M.M., Nyenhuis, D.L., Black, S.E., Powers, W.J., DeCarli, C., Merino, J.G., Kalaria, R.N., Vinters, H.V., Holtzman, D.M., Rosenberg, G.A., Dichgans, M., Marler, J.R., Leblanc, G.G., 2006. National institute of neurological disorders and stroke-Canadian stroke network cognitive impairment harmonization standards. *Stroke* 37, 2220–2241.
- Hannestad, J., DellaGioia, N., Bloch, M., 2011. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* 36, 2452–2459.
- Hashimoto, K., 2016. Soluble epoxide hydrolase: a new therapeutic target for depression. *Expert Opin. Ther. Targets* 20, 1149–1151.
- Hatch, J.K., Scola, G., Olowoyeye, O., Collins, J.E., Andreazza, A.C., Moody, A., Levitt, A.J., Strauss, B.H., Lancot, K.L., Goldstein, B.I., 2017. Inflammatory markers and brain-derived neurotrophic factor as potential bridges linking bipolar disorder and cardiovascular risk among adolescents. *J. Clin. Psychiatry* 78, e286–e293.
- Hennebelle, M., Otaki, Y., Yang, J., Hammock, B.D., Levitt, A.J., Taha, A.Y., Swardfager, W., 2017. Altered soluble epoxide hydrolase-derived oxylipins in patients with seasonal major depression: an exploratory study. *Psychiatry Res.* 252, 94–101.
- Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom. Med.* 71, 171–186.
- Hu, J., Dziumbla, S., Lin, J., Bibli, S.I., Zukunft, S., de Mos, J., Awwad, K., Frömel, T., Jungmann, A., Devraj, K., Cheng, Z., Wang, L., Fauser, S., Eberhart, C.G., Sodhi, A., Hammock, B.D., Liebner, S., Müller, O.J., Glaubitz, C., Hammes, H.P., Popp, R., Fleming, I., 2017. Inhibition of soluble epoxide hydrolase prevents diabetic retinopathy. *Nature* 552, 248–252.
- Hung, Y.W., Hung, S.W., Wu, Y.C., Wong, L.K., Lai, M.T., Shih, Y.H., Lee, T.S., Lin, Y.Y., 2015. Soluble epoxide hydrolase activity regulates inflammatory responses and seizure generation in two mouse models of temporal lobe epilepsy. *Brain Behav. Immun.* 43, 118–129.

- Iliff, J.J., Alkayed, N.J., 2009. Soluble epoxide hydrolase inhibition: targeting multiple mechanisms of ischemic brain injury with a single agent. *Future Neurol.* 4, 179–199.
- Imig, J.D., Hammock, B.D., 2009. Soluble epoxide hydrolase as a therapeutic target for cardiovascular diseases. *Nat. Rev. Drug Discov.* 8, 794–805.
- Inceoglu, B., Betteieb, A., Trindade da Silva, C.A., Lee, K.S., Haj, F.G., Hammock, B.D., 2015. Endoplasmic reticulum stress in the peripheral nervous system is a significant driver of neuropathic pain. *Proc. Natl. Acad. Sci. U. S. A.* 112, 9082–9087.
- Inceoglu, B., Jinks, S.L., Schmelzer, K.R., Waite, T., Kim, I.H., Hammock, B.D., 2006. Inhibition of soluble epoxide hydrolase reduces LPS-induced thermal hyperalgesia and mechanical allodynia in a rat model of inflammatory pain. *Life Sci.* 79, 2311–2319.
- Inceoglu, B., Zolkowska, D., Yoo, H.J., Wagner, K.M., Yang, J., Hackett, E., Hwang, S.H., Lee, K.S., Rogawski, M.A., Morisseau, C., Hammock, B.D., 2013. Epoxy fatty acids and inhibition of the soluble epoxide hydrolase selectively modulate GABA mediated neurotransmission to delay onset of seizures. *PLoS One* 8, e80922.
- Ingraham, R.H., Gless, R.D., Lo, H.Y., 2011. Soluble epoxide hydrolase inhibitors and their potential for treatment of multiple pathologic conditions. *Curr. Med. Chem.* 18, 587–603.
- Iyer, A., Kauter, K., Alam, M.A., Hwang, S.H., Morisseau, C., Hammock, B.D., Brown, L., 2012. Pharmacological inhibition of soluble epoxide hydrolase ameliorates diet-induced metabolic syndrome in rats. *Exp. Diabetes Res.* (2012), 758614.
- Jacka, F.N., O'Neil, A., Opie, R., Itsiopoulos, C., Cotton, S., Mohebbi, M., Castle, D., Dash, S., Mihalopoulos, C., Chatterton, M.L., Brazionis, L., Dean, O.M., Hodge, A.M., Berk, M., 2017. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). *BMC Med.* 15, 23.
- Kappellmann, N., Lewis, G., Dantzer, R., Jones, P.B., Khanderaker, G.M., 2016. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatry*.
- Katon, W., Pedersen, H.S., Ribe, A.R., Fenger-Gron, M., Davydow, D., Waldorff, F.B., Vestergaard, M., 2015. Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study. *JAMA Psychiatry* 72, 612–619.
- Kodani, S.D., Hammock, B.D., 2015. The 2014 Bernard B. Brodie award lecture-epoxide hydrolases: drug metabolism to therapeutics for chronic pain. *Drug Metab. Dispos.* 43, 788–802.
- Koerner, I.P., Jacks, R., DeBarber, A.E., Koop, D., Mao, P., Grant, D.F., Alkayed, N.J., 2007. Polymorphisms in the human soluble epoxide hydrolase gene EPHX2 linked to neuronal survival after ischemic injury. *J. Neurosci.* 27, 4642–4649.
- Kohler, C.A., Freitas, T.H., Maes, M., de Andrade, N.Q., Liu, C.S., Fernandes, B.S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C.L., Miller, B.J., Lancot, K.L., Carvalho, A.F., 2017. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr. Scand.* 135, 373–387.
- Kohler, O., Benros, M.E., Nordentoft, M., Farkouh, M.E., Iyengar, R.L., Mors, O., Krogh, J., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71, 1381–1391.
- Kompa, A.R., Wang, B.H., Xu, G., Zhang, Y., Ho, P.Y., Eisennagel, S., Thalji, R.K., Marino Jr., J.P., Kelly, D.J., Behm, D.J., Krum, H., 2013. Soluble epoxide hydrolase inhibition exerts beneficial anti-remodeling actions post-myocardial infarction. *Int. J. Cardiol.* 167, 210–219.
- Kromhout, D., Yasuda, S., Geleijnse, J.M., Shimokawa, H., 2012. Fish oil and omega-3 fatty acids in cardiovascular disease: do they really work? *Eur. Heart J.* 33, 436–443.
- Lavoie, K.L., Bacon, S.L., Barone, S., Cartier, A., Ditto, B., Labrecque, M., 2006. What is worse for asthma control and quality of life: depressive disorders, anxiety disorders, or both? *Chest* 130, 1039–1047.
- Lavretsky, H., Zheng, L., Weiner, M.W., Mungas, D., Reed, B., Kramer, J.H., Jagust, W., Chui, H., Mack, W.J., 2008. The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *Int. J. Geriatr. Psychiatry* 23, 1040–1050.
- Lazaar, A.L., Yang, L., Boardley, R.L., Goyal, N.S., Robertson, J., Baldwin, S.J., Newby, D.E., Wilkinson, I.B., Tal-Singer, R., Mayer, R.J., Cheriyan, J., 2016. Pharmacokinetics, pharmacodynamics and adverse event profile of GSK2256294, a novel soluble epoxide hydrolase inhibitor. *Br. J. Clin. Pharmacol.* 81, 971–979.
- Lee, H.C., Lu, T., Weintraub, N.L., VanRollins, M., Spector, A.A., Shibata, E.F., 1999. Effects of epoxyeicosatrienoic acids on the cardiac sodium channels in isolated rat ventricular myocytes. *J. Physiol.* 519 (1), 153–168.
- Lee, K.S.S., Liu, J.Y., Wagner, K., Pakhomova, S., Dong, H., Morissuea, C., Yang, J., Wang, P., Ulu, A., Mate, C., Nguyen, L., Hwang, S.H., Edin, M., Mara, A., Wulff, H., Newcomer, M., Zeldin, D., Hammock, B.D., 2014. Optimized inhibitors of soluble epoxide hydrolase improve in vitro target residence time and in vivo efficacy. *J. Med. Chem.* 57, 7016–7030.
- Li, D., Liu, Y., Zhang, X., Lv, H., Pang, W., Sun, X., Gan, L.M., Hammock, B.D., Ai, D., Zhu, Y., 2016. Inhibition of soluble epoxide hydrolase alleviated atherosclerosis by reducing monocyte infiltration in Ldlr(-/-) mice. *J. Mol. Cell Cardiol.* 98, 128–137.
- Libby, P., 2002. Inflammation in atherosclerosis. *Nature* 420, 868–874.
- Libby, P., Ridker, P.M., Hansson, G.K., 2009. Inflammation in atherosclerosis: from pathophysiology to practice. *J. Am. Coll. Cardiol.* 54, 2129–2138.
- Liu, X., Qian, Z.Y., Xie, F., Fan, W., Nelson, J.W., Xiao, X., Kaul, S., Barnes, A.P., Alkayed, N.J., 2016. Functional screening for G protein-coupled receptor targets of 14,15-epoxyeicosatrienoic acid. *Prostaglandins Other Lipid Mediat.* 132, 31–40.
- Lopez-Vicario, C., Alcaraz-Quiles, J., Garcia-Alonso, V., Rius, B., Hwang, S.H., Titos, E., Lopategi, A., Hammock, B.D., Arroyo, V., Claria, J., 2015. Inhibition of soluble epoxide hydrolase modulates inflammation and autophagy in obese adipose tissue and liver: role for omega-3 epoxides. *Proc. Natl. Acad. Sci. U. S. A.* 112, 536–541.
- Luria, A., Betteieb, A., Xi, Y., Shieh, G.J., Liu, H.C., Inoue, H., Tsai, H.J., Imig, J.D., Haj, F.G., Hammock, B.D., 2011. Soluble epoxide hydrolase deficiency alters pancreatic islet size and improves glucose homeostasis in a model of insulin resistance. *Proc. Natl. Acad. Sci. U. S. A.* 108, 9038–9043.
- Luther, J.M., Brown, N.J., 2016. Epoxyeicosatrienoic acids and glucose homeostasis in mice and men. *Prostaglandins Other Lipid Mediat.* 125, 2–7.
- Lyoo, I.K., Lee, H.K., Jung, J.H., Noam, G.G., Renshaw, P.F., 2002. White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Compr. Psychiatry* 43, 361–368.
- Ma, M., Ren, Q., Fujita, Y., Ishima, T., Zhang, J.C., Hashimoto, K., 2013. Effects of AS2586114, a soluble epoxide hydrolase inhibitor, on hyperlocomotion and prepulse inhibition deficits in mice after administration of phencyclidine. *Pharmacol. Biochem. Behav.* 110, 98–103.
- Marowsky, A., Meyer, I., Erismann-Ebner, K., Pellegrini, G., Mule, N., Arand, M., 2017. Beyond detoxification: a role for mouse mEH in the hepatic metabolism of endogenous lipids. *Arch. Toxicol.* 91, 3571–3585.
- Mazereeuw, G., Herrmann, N., Andreazza, A.C., Scolá, G., Ma, D.W., Oh, P.I., Lancot, K.L., 2017. Oxidative stress predicts depressive symptom changes with omega-3 fatty acid treatment in coronary artery disease patients. *Brain Behav. Immun.* 60, 136–141.
- Mazereeuw, G., Herrmann, N., Bennett, S.A., Swardfager, W., Xu, H., Valenzuela, N., Fai, S., Lancot, K.L., 2013. Platelet activating factors in depression and coronary artery disease: a potential biomarker related to inflammatory mechanisms and neurodegeneration. *Neurosci. Biobehav. Rev.* 37, 1611–1621.
- Mazereeuw, G., Herrmann, N., Xu, H., Blanchard, A.P., Figeys, D., Oh, P.I., Bennett, S.A., Lancot, K.L., 2015. Platelet activating factors are associated with depressive symptoms in coronary artery disease patients: a hypothesis-generating study. *Neuropsychiatr. Dis. Treat.* 11, 2309–2314.
- Mazereeuw, G., Herrmann, N., Xu, H., Figeys, D., Oh, P.I., Bennett, S.A., Lancot, K.L., 2014. Platelet-activating factors are associated with cognitive deficits in depressed coronary artery disease patients: a hypothesis-generating study. *J. Neuroinflammation* 11, 119.
- Mendlewicz, J., Kriwin, P., Oswald, P., Souery, D., Alboni, S., Brunello, N., 2006. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *Int. Clin. Psychopharmacol.* 21, 227–231.
- Millan, M.J., Agid, Y., Brune, M., Bullmore, E.T., Carter, C.S., Clayton, N.S., Connor, R., Davis, S., Deakin, B., DeRubeis, R.J., Dubois, B., Geyer, M.A., Goodwin, G.M., Greenwood, P., Jay, T.M., Joels, M., Mansuy, I.M., Meyer-Lindenberg, A., Murphy, D., Rolls, E., Saletu, B., Spedding, M., Sweeney, J., Whittington, M., Young, L.J., 2012. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat. Rev. Drug Discov.* 11, 141–168.
- Mocking, R.J., Harmsen, I., Assies, J., Koeter, M.W., Ruhe, H.G., Schene, A.H., 2016. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Transl. Psychiatry* 6, e756.
- Monti, J., Fischer, J., Paskas, S., Heinig, M., Schulz, H., Gosele, C., Heuser, A., Fischer, R., Schmidt, C., Schirdewan, A., Gross, V., Hummel, O., Maatz, H., Patone, G., Saar, K., Vingron, M., Weldon, S.M., Lindpaintner, K., Hammock, B.D., Rohde, K., Dietz, R., Cook, S.A., Schunck, W.H., Luft, F.C., Hubner, N., 2008. Soluble epoxide hydrolase is a susceptibility factor for heart failure in a rat model of human disease. *Nat. Genet.* 40, 529–537.
- Morin, C., Sirois, M., Echave, V., Albadine, R., Rousseau, E., 2010. 17,18-epoxyeicosatetraenoic acid targets PPARgamma and p38 mitogen-activated protein kinase to mediate its anti-inflammatory effects in the lung: role of soluble epoxide hydrolase. *Am. J. Respir. Cell Mol. Biol.* 43, 564–575.
- Morin, C., Sirois, M., Echave, V., Gomes, M.M., Rousseau, E., 2008. EET displays anti-inflammatory effects in TNF-alpha stimulated human bronchi: putative role of CPI-17. *Am. J. Respir. Cell Mol. Biol.* 38, 192–201.
- Morisseau, C., Inceoglu, B., Schmelzer, K., Tsai, H.J., Jinks, S.L., Hegedus, C.M., Hammock, B.D., 2010. Naturally occurring monoepoxides of eicosapentaenoic acid and docosahexaenoic acid are bioactive antihyperalgesic lipids. *J. Lipid Res.* 51, 3481–3490.
- Morisseau, C., Goodrow, M.H., Dowdy, D., Zheng, J., Greene, J.F., Sanborn, J.R., Hammock, B.D., 1999. Potent urea and carbamate inhibitors of soluble epoxide hydrolases. *Proc. Natl. Acad. Sci. U. S. A.* 96, 8849–8854.
- Naiberg, M.R., Hatch, J.K., Selkirk, B., Fiksenbaum, L., Yang, V., Black, S., Kertes, P.J., Goldstein, B.I., 2017. Retinal photography: A window into the cardiovascular-brain link in adolescent bipolar disorder. *J. Affect Disord.* 218, 227–237.
- Naiberg, M.R., Newton, D.F., Collins, J.E., Dickstein, D.P., Bowie, C.R., Goldstein, B.I., 2016. Elevated triglycerides are associated with decreased executive function among adolescents with bipolar disorder. *Acta Psychiatr. Scand.* 134, 241–248.
- Nefs, G., Pop, V.J., Denollet, J., Pouwer, F., 2016. Depressive symptoms and all-cause mortality in people with type 2 diabetes: a focus on potential mechanisms. *Br. J. Psychiatry* 209, 142–149.
- Nelson, J.W., Young, J.M., Borkar, R.N., Woltjer, R.L., Quinn, J.F., Silbert, L.C., Grafe, M.R., Alkayed, N.J., 2014. Role of soluble epoxide hydrolase in age-related vascular cognitive decline. *Prostaglandins Other Lipid Mediat.* (113–115), 30–37.
- Neveill, L., Zhang, K., Aiello, A.E., Koenen, K., Galea, S., Soliven, R., Zhang, C., Wildman, D.E., Uddin, M., 2014. Elevated systemic expression of ER stress related genes is associated with stress-related mental disorders in the Detroit neighborhood health study. *Psychoneuroendocrinology* 43, 62–70.
- Nishino, S., Ueno, R., Ohishi, K., Sakai, T., Hayaishi, O., 1989. Salivary prostaglandin concentrations: possible state indicators for major depression. *Am. J. Psychiatry* 146, 365–368.
- Noble, J.E., Wang, L., Cerasoli, E., Knight, A.E., Porter, R.A., Gray, E., Howe, C., Hannes, E., Corbisier, P., Wang, J., Wu, L., Altieri, I., Patriarca, M., Hoffman, A., Resch-Genger, U., Ebert, B., Voigt, J., Shigeri, Y., Vonsky, M.S., Konopelko, L.A., Gaigalas, A.K., Bailey, M.J., 2008. An international comparability study to determine the sources of uncertainty associated with a non-competitive sandwich fluorescent ELISA. *Clin. Chem. Lab. Med.* 46, 1033–1045.

- Node, K., Huo, Y., Ruan, X., Yang, B., Spiecker, M., Ley, K., Zeldin, D.C., Liao, J.K., 1999. Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science* 285, 1276–1279.
- Node, K., Ruan, X.L., Dai, J., Yang, S.X., Graham, L., Zeldin, D.C., Liao, J.K., 2001. Activation of Galpha s mediates induction of tissue-type plasminogen activator gene transcription by epoxyeicosatrienoic acids. *J. Biol. Chem.* 276, 15983–15989.
- O'Connor, J.C., Lawson, M.A., Andre, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K.W., Dantzer, R., 2009. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol. Psychiatry* 14, 511–522.
- Ohishi, K., Ueno, R., Nishino, S., Sakai, T., Hayaishi, O., 1988. Increased level of salivary prostaglandins in patients with major depression. *Biol. Psychiatry* 23, 326–334.
- Ono, E., Dutilleul, S., Kazani, S., Wechsler, M.E., Yang, J., Hammock, B.D., Douda, D.N., Tabet, Y., Khaddaj-Mallat, R., Sirois, M., Sirois, C., Rizcallah, E., Rousseau, E., Martin, R., Sutherland, E.R., Castro, M., Jarjour, N.N., Israel, E., Levy, B.D., National Heart, L., Blood Institute's Asthma Clinical Research, N., 2014. Lipoxin generation is related to soluble epoxide hydrolase activity in severe asthma. *Am. J. Respir. Crit. Care Med.* 190, 886–897.
- Otoki, Y., Hennebelle, M., Levitt, A.J., Nakagawa, K., Swardfager, W., Taha, A.Y., 2017. Plasma phosphatidylethanolamine and triacylglycerol fatty acid concentrations are altered in major depressive disorder patients with seasonal pattern. *Lipids* 52, 559–571.
- Pan, A., Sun, Q., Okereke, O.I., Rexrode, K.M., Hu, F.B., 2011. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA* 306, 1241–1249.
- Qu, Y.Y., Yuan, M.Y., Liu, Y., Xiao, X.J., Zhu, Y.L., 2015. The protective effect of epoxyeicosatrienoic acids on cerebral ischemia/reperfusion injury is associated with PI3K/Akt pathway and ATP-sensitive potassium channels. *Neurochem. Res.* 40, 1–14.
- Raisoin, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70, 31–41.
- Ren, Q., Ma, M., Ishima, T., Morisseau, C., Yang, J., Wagner, K.M., Zhang, J.C., Yang, C., Yao, W., Dong, C., Han, M., Hammock, B.D., Hashimoto, K., 2016. Gene deficiency and pharmacological inhibition of soluble epoxide hydrolase confers resilience to repeated social defeat stress. *Proc. Natl. Acad. Sci. U. S. A.* 113, E1944–1952.
- Rethorst, C.D., Wipfl, B.M., Landers, D.M., 2009. The antidepressive effects of exercise: a meta-analysis of randomized trials. *Sports Med.* 39, 491–511.
- Robertson, R.C., Seira Oriach, C., Murphy, K., Moloney, G.M., Cryan, J.F., Dinan, T.G., Paul Ross, R., Stanton, C., 2017. Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain Behav. Immun.* 59, 21–37.
- Roche, C., Besnier, M., Cassel, R., Harouki, N., Coquerel, D., Guerrot, D., Nicol, L., Loizon, E., Remy-Jouet, I., Morisseau, C., Mulder, P., Ouvrard-Pascaud, A., Madec, A.M., Richard, V., Bellien, J., 2015. Soluble epoxide hydrolase inhibition improves coronary endothelial function and prevents the development of cardiac alterations in obese insulin-resistant mice. *Am. J. Physiol. Heart Circ. Physiol.* 308, H1020–H1029.
- Rose, T.E., Morisseau, C., Liu, J.Y., Inceoglu, B., Jones, P.D., Sanborn, J.R., Hammock, B.D., 2010. 1-Aryl-3-(1-acylpiperidin-4-yl)urea inhibitors of human and murine soluble epoxide hydrolase: structure-activity relationships, pharmacokinetics, and reduction of inflammatory pain. *J. Med. Chem.* 53, 7067–7075.
- Rotella, F., Mannucci, E., 2013a. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. *J. Clin. Psychiatry* 74, 31–37.
- Rotella, F., Mannucci, E., 2013b. Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. *Diabetes Res. Clin. Pract.* 99, 98–104.
- Russo, S.J., Nestler, E.J., 2013. The brain reward circuitry in mood disorders. *Nat. Rev.* 14, 609–625.
- Sarris, J., Murphy, J., Mischoulon, D., Papakostas, G.I., Fava, M., Berk, M., Ng, C.H., 2016. Adjunctive nutraceuticals for depression: A systematic review and meta-analyses. *Am. J. Psychiatry* 173, 575–587.
- Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H.Q., 2012. Kynurenines in the mammalian brain: when physiology meets pathology. *Nat. Rev.* 13, 465–477.
- Shen, H.C., Hammock, B.D., 2012. Discovery of inhibitors of soluble epoxide hydrolase: a target with multiple potential therapeutic indications. *J. Med. Chem.* 55, 1789–1808.
- Shen, L., Peng, H., Peng, R., Fan, Q., Zhao, S., Xu, D., Morisseau, C., Chiamvimonvat, N., Hammock, B.D., 2015. Inhibition of soluble epoxide hydrolase in mice promotes reverse cholesterol transport and regression of atherosclerosis. *Atherosclerosis* 239, 557–565.
- Shih, P.B., Yang, J., Morisseau, C., German, J.B., Zeeland, A.A., Armando, A.M., Quehenberger, O., Bergen, A.W., Magistretti, P., Berrettini, W., Halmi, K.A., Schork, N., Hammock, B.D., Kaye, W., 2016. Dysregulation of soluble epoxide hydrolase and lipidomic profiles in anorexia nervosa. *Mol. Psychiatry* 21, 537–546.
- Simpkins, A.N., Rudic, R.D., Schreihof, D.A., Roy, S., Manhani, M., Tsai, H.J., Hammock, B.D., Imig, J.D., 2009. Soluble epoxide inhibition is protective against cerebral ischemia via vascular and neural protection. *Am. J. Pathol.* 174, 2086–2095.
- Singhal, G., Jaehne, E.J., Corrigan, F., Toben, C., Baune, B.T., 2014. Inflammation in neuroinflammation and changes in brain function: a focused review. *Front. Neurosci.* 8, 315.
- Smith, W.L., DeWitt, D.L., Garavito, R.M., 2000. Cyclooxygenases: structural, cellular, and molecular biology. *Annu. Rev. Biochem.* 69, 145–182.
- Spector, A.A., Kim, H.Y., 2015. Cytochrome P450 epoxygenase pathway of polyunsaturated fatty acid metabolism. *Biochim. Biophys. Acta* 1851, 356–365.
- Stewart, J.C., Rand, K.L., Muldoon, M.F., Kamarck, T.W., 2009. A prospective evaluation of the directionality of the depression-inflammation relationship. *Brain Behav. Immun.* 23, 936–944.
- Stulc, J., 1989. Extracellular transport pathways in the haemochorial placenta. *Placenta* 10, 113–119.
- Swardfager, W., Herrmann, N., Dowlati, Y., Oh, P.I., Kiss, A., Walker, S.E., Lancot, K.L., 2009. Indoleamine 2,3-dioxygenase activation and depressive symptoms in patients with coronary artery disease. *Psychoneuroendocrinology* 34, 1560–1566.
- Swardfager, W., Herrmann, N., Marzolini, S., Saleem, M., Farber, S.B., Kiss, A., Oh, P.I., Lancot, K.L., 2011. Major depressive disorder predicts completion, adherence, and outcomes in cardiac rehabilitation: a prospective cohort study of 195 patients with coronary artery disease. *J. Clin. Psychiatry* 72, 1181–1188.
- Swardfager, W., MacIntosh, B.J., 2017. Depression, Type 2 diabetes, and poststroke cognitive impairment. *Neurorehabil. Neural Repair* 31, 48–55.
- Swardfager, W., Rosenblat, J.D., Benlamri, M., McIntyre, R.S., 2016. Mapping inflammation onto mood: inflammatory mediators of anhedonia. *Neurosci. Biobehav. Rev.* 64, 148–166.
- Taguchi, N., Nakayama, S., Tanaka, M., 2016. Single administration of soluble epoxide hydrolase inhibitor suppresses neuroinflammation and improves neuronal damage after cardiac arrest in mice. *Neurosci. Res.* 111, 56–63.
- Timberlake 2nd, M.A., Dwivedi, Y., 2015. Altered expression of endoplasmic reticulum stress associated genes in Hippocampus of learned helpless rats: relevance to depression pathophysiology. *Front. Pharmacol.* 6, 319.
- Ulu, A., Davis, B.B., Tsai, H.J., Kim, I.H., Morisseau, C., Inceoglu, B., Fiehn, O., Hammock, B.D., Weiss, R.H., 2008. Soluble epoxide hydrolase inhibitors reduce the development of atherosclerosis in apolipoprotein e-knockout mouse model. *J. Cardiovasc. Pharmacol.* 52, 314–323.
- Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A., 2007. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int. J. Geriatr. Psychiatry* 22, 613–626.
- Vanella, L., Canestraro, M., Lee, C.R., Cao, J., Zeldin, D.C., Schwartzman, M.L., Abraham, N.G., 2015. Soluble epoxide hydrolase null mice exhibit female and male differences in regulation of vascular homeostasis. *Prostaglandins Other Lipid Mediat.* 120, 139–147.
- Versace, A., Andreazza, A.C., Young, L.T., Fournier, J.C., Almeida, J.R., Stiffler, R.S., Lockovich, J.C., Aslam, H.A., Pollock, M.H., Park, H., Nimgaonkar, V.L., Kupfer, D.J., Phillips, M.L., 2013. Elevated serum measures of lipid peroxidation and abnormal prefrontal white matter in euthymic bipolar adults: toward peripheral biomarkers of bipolar disorder. *Mol. Psychiatry* 29 (January). <http://dx.doi.org/10.1038/mp.2012.188>. [Epub ahead of print].
- Vito, S.T., Austin, A.T., Banks, C.N., Inceoglu, B., Bruun, D.A., Zolkowska, D., Tancredi, D.J., Rogawski, M.A., Hammock, B.D., Lein, P.J., 2014. Post-exposure administration of diazepam combined with soluble epoxide hydrolase inhibition stops seizures and modulates neuroinflammation in a murine model of acute TETS intoxication. *Toxicol. Appl. Pharmacol.* 281, 185–194.
- Wada, M., DeLong, C.J., Hong, Y.H., Rieke, C.J., Song, I., Sidhu, R.S., Yuan, C., Warnock, M., Schmaier, A.H., Yokoyama, C., Smyth, E.M., Wilson, S.J., FitzGerald, G.A., Garavito, R.M., Sui de, X., Regan, J.W., Smith, W.L., 2007. Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. *J. Biol. Chem.* 282, 22254–22266.
- Wagner, K., Gilda, J., Yang, J., Wan, D., Morisseau, C., Gomes, A.V., Hammock, B.D., 2017. Soluble epoxide hydrolase inhibition alleviates neuropathy in Akita (Ins2 Akita) mice. *Behav. Brain Res.* 326, 69–76.
- Wagner, K., Inceoglu, B., Dong, H., Yang, J., Hwang, S.H., Jones, P., Morisseau, C., Hammock, B.D., 2013. Comparative efficacy of 3 soluble epoxide hydrolase inhibitors in rat neuropathic and inflammatory pain models. *Eur. J. Pharmacol.* 700, 93–101.
- Wagner, K., Inceoglu, B., Gill, S.S., Hammock, B.D., 2011. Epoxygenized fatty acids and soluble epoxide hydrolase inhibition: novel mediators of pain reduction. *J. Agric. Food Chem.* 59, 2816–2824.
- Wagner, K., Yang, J., Inceoglu, B., Hammock, B.D., 2014. Soluble epoxide hydrolase inhibition is antinociceptive in a mouse model of diabetic neuropathy. *J. Pain* 15, 907–914.
- Wang, L., Opland, D., Tsai, S., Luk, C.T., Schroer, S.A., Allison, M.B., Elia, A.J., Furlonger, C., Suzuki, A., Paige, C.J., Mak, T.W., Winer, D.A., Myers Jr., M.G., Woo, M., 2014. Pten deletion in RIP-Cre neurons protects against type 2 diabetes by activating the anti-inflammatory reflex. *Nat. Med.* 20, 484–492.
- Wang, Q., Huo, L., He, J., Ding, W., Su, H., Tian, D., Welch, C., Hammock, B.D., Ai, D., Zhu, Y., 2015. Soluble epoxide hydrolase is involved in the development of atherosclerosis and arterial neointima formation by regulating smooth muscle cell migration. *Am. J. Physiol. Heart Circ. Physiol.* 309, H1894–1903.
- Winer, D.A., Winer, S., Chng, M.H., Shen, L., Engleman, E.G., 2014. B lymphocytes in obesity-related adipose tissue inflammation and insulin resistance. *Cell Mol. Life Sci.* 71, 1033–1043.
- Wu, H.F., Yen, H.J., Huang, C.C., Lee, Y.C., Wu, S.Z., Lee, T.S., Lin, H.C., 2015. Soluble epoxide hydrolase inhibitor enhances synaptic neurotransmission and plasticity in mouse prefrontal cortex. *J. Biomed. Sci.* 22, 94.
- Xu, D.Y., Davis, B.B., Wang, Z.H., Zhao, S.P., Wasti, B., Liu, Z.L., Li, N., Morisseau, C., Chiamvimonvat, N., Hammock, B.D., 2013. A potent soluble epoxide hydrolase inhibitor, t-AUCB, acts through PPARgamma to modulate the function of endothelial progenitor cells from patients with acute myocardial infarction. *Int. J. Cardiol.* 167, 1298–1304.
- Yamamoto, S., Ueda, N., Ehara, H., Maruyama, T., Yokoyama, C., Kaneko, S., Yoshimoto, T., Komatsu, N., Watanabe, K., Hattori, A., et al., 1988. Biochemical studies on mammalian lipoxigenases. *Ann. N. Y. Acad. Sci.* 524, 12–26.
- Yuan, L., Liu, J., Dong, R., Zhu, J., Tao, C., Zheng, R., Zhu, S., 2016. 14,15-epoxyeicosatrienoic acid promotes production of brain derived neurotrophic factor from astrocytes and exerts neuroprotective effects during ischaemic injury. *Neuropathol. Appl. Neurobiol.* (42), 607–620.
- Yubero-Serrano, E.M., Gonzalez-Guardia, L., Rangel-Zuniga, O., Delgado-Lista, J., Gutierrez-Mariscal, F.M., Perez-Martinez, P., Delgado-Casado, N., Cruz-Teno, C.,

- Tinahones, F.J., Villalba, J.M., Perez-Jimenez, F., Lopez-Miranda, J., 2012. Mediterranean diet supplemented with coenzyme Q10 modifies the expression of proinflammatory and endoplasmic reticulum stress-related genes in elderly men and women. *J. Gerontol. A: Biol. Sci. Med. Sci.* 67, 3–10.
- Zeldin, D.C., Kobayashi, J., Falck, J.R., Winder, B.S., Hammock, B.D., Snapper, J.R., Capdevila, J.H., 1993. Regio- and enantiofacial selectivity of epoxyeicosatrienoic acid hydration by cytosolic epoxide hydrolase. *J. Biol. Chem.* 268, 6402–6407.
- Zeldin, D.C., Wei, S., Falck, J.R., Hammock, B.D., Snapper, J.R., Capdevila, J.H., 1995. Metabolism of epoxyeicosatrienoic acids by cytosolic epoxide hydrolase: substrate structural determinants of asymmetric catalysis. *Arch. Biochem. Biophys.* 316, 443–451.
- Zhang, L.N., Vincelette, J., Cheng, Y., Mehra, U., Chen, D., Anandan, S.K., Gless, R., Webb, H.K., Wang, Y.X., 2009. Inhibition of soluble epoxide hydrolase attenuated atherosclerosis, abdominal aortic aneurysm formation, and dyslipidemia. *Arterioscler. Thromb. Vasc. Biol.* 29, 1265–1270.
- Zhang, W., Koerner, I.P., Noppens, R., Grafe, M., Tsai, H.J., Morisseau, C., Luria, A., Hammock, B.D., Falck, J.R., Alkayed, N.J., 2007. Soluble epoxide hydrolase: a novel therapeutic target in stroke. *J. Cereb. Blood Flow Metab.* 27, 1931–1940.
- Zhang, W., Otsuka, T., Sugo, N., Ardeschiri, A., Alhadid, Y.K., Iliff, J.J., DeBarber, A.E., Koop, D.R., Alkayed, N.J., 2008. Soluble epoxide hydrolase gene deletion is protective against experimental cerebral ischemia. *Stroke* 39, 2073–2078.
- Zuloaga, K.L., Krasnow, S.M., Zhu, X., Zhang, W., Jouihan, S.A., Shangraw, R.E., Alkayed, N.J., Marks, D.L., 2014. Mechanism of protection by soluble epoxide hydrolase inhibition in type 2 diabetic stroke. *PLoS One* 9, e97529.