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The role of Soluble Epoxide Hydrolase and its Inhibitors in Depression

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Abstract

Evidence suggests that around 30% of patients with depression do not respond to antidepressant treatment, with most of them having sub-chronic levels of inflammation. Soluble epoxide hydrolases (sEH) are enzymes present in all living organisms, which metabolize cytochrome P (CYP)-derived epoxy fatty acids to their corresponding diols. Accumulating evidence suggests that sEH plays a key role in the anti-inflammatory properties exerted by the metabolism of omega-3 polyunsaturated fatty acids (ω-3 PUFAs). Crucial evidence demonstrates that protein expression of sEH in the brain of mice experiencing depressive-like behaviour, as well as in patients with major depressive disorder is higher than in controls. Of note, treatment with sEH inhibitors exert anti-inflammatory, neurogenic and antidepressant-like effects in pre-clinical models of depression. In this review, the author discusses the role of sEH in the metabolism of ω-3 PUFAs in the context of depression, and the clinical value of sEH inhibitors as alternative therapeutic strategies for patients suffering from this condition.

INTRODUCTION

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are important regulator of normal physiology (Jump, 2002; Laye et al., 2018). They play a fundamental role in maintaining both the structure and the function of neurons and glial cells in the brain (Laye et al., 2018). Omega-3 PUFAs cannot be produced endogenously and they require exogenous supplementation. The predominant plant-derived dietary ω-3 PUFA, alpha-linoleic acid, is a precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are metabolised by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) enzymes into a range of lipid mediators, which exhibit potent immune regulatory activities (Gabbs et al., 2015). COX and LOX enzymes convert ω-3 PUFAs into prostanoids, mono- and polyhydroxy fatty acids and leukotrienes, while CYP450 monooxygenases convert ω-3 PUFAs into epoxy and hydroxy fatty acids (Astarita et al., 2015). Epoxy fatty acids are then metabolized via epoxide hydrolases, primarily soluble epoxide hydrolase (sEH), to the corresponding fatty acyl diols (Gabbs et al., 2015) (Figure 1). In the review, the author would like to discuss the role of sEH in the CYP-mediated metabolism of ω-3 PUFAs, which might be involved in the pathogenesis of depression, and discuss the clinical significance of using sEH inhibitors for patients suffering from this condition.

sEH IN THE CYP METABOLISM OF ω-3 PUFAs

CYP450 are a superfamily of enzymes which can metabolise both endogenous and exogenous compounds (Gabbs et al., 2015). In the case of ω-3 PUFAs, CYP isoforms metabolize both EPA and DHA into bioactive lipid mediators. In particular, the CYP system produces anti-inflammatory epoxy and hydroxy fatty acids (Gabbs et al., 2015). Epoxy fatty acids include epoxyeicosatetraenoic acids (EpETEs) from EPA, and epoxydocosapentaenoic acids (EpDPAs) from DHA. Hydroxy fatty acids include hydroxyeicosapentaenoic acids (18-,

19-, 20-HEPEs) from EPA, and hydroxydocosahexaenoic acids (20-, 21-, 22-HDHAs) from DHA. Epoxy fatty acids (EpETEs and EpDPAs) are then metabolised into their respective diols, dihydroxyeicosatetraenoic acids (DiHETEs) and dihydroxydocosapentaenoic acids (DiHDPAs), by the sEH enzyme (Figure 1). Human sEH is a 62 kDa enzyme composed of two domains: the N-terminal domain hydrolyses lipid phosphates, while the C-terminal domain converts epoxides to their corresponding diols (Newman et al., 2005). The human sEH protein is encoded in the EPHX2 gene, which is widely expressed in several tissues, including brain, liver, lungs, kidney, heart, vascular endothelium and smooth muscle (Gill and Hammock, 1980). In the brain, the sEH protein is produced in neurons, astrocytes and microglia (Sura et al., 2008). Increasing evidence suggests that EpETEs and EpDPAs have strong anti-inflammatory properties (Wagner et al., 2014; Wagner et al., 2017), which are implicated in the pathogenesis of several neuropsychiatric disorders, including depression (Hashimoto, 2015, 2016, 2018).

INFLAMMATION IN DEPRESSION

There is a significant amount of evidence demonstrating the involvement of inflammation in the pathophysiology of depression (Dantzer et al., 2008; Gold, 2015; Miller and Raison, 2016). Meta-analyses of studies conducted in untreated depressed patients have reported an increase in the levels of inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), when compared with controls (Dowlati et al., 2010; Strawbridge et al., 2015; Young et al., 2014). These findings are of fundamental importance as cytokines can directly contribute to the development of the depressive symptoms (Raison and Miller, 2013). Indeed, increased levels of cytokines circulating in the periphery can penetrate the more permeable areas of the blood-brain barrier (BBB) to affect brain signalling relevant for the depressive symptoms (Borsini et al., 2015; Miller and Raison, 2016). In particular, cytokines have

been shown to alter neurogenesis, a mechanism potentially disrupted in depression, and required for antidepressant efficacy (Boldrini et al., 2014; Boldrini et al., 2009; Santarelli et al., 2003). Indeed, using the aforementioned human hippocampal progenitor cells, we have previously demonstrated the ability of IL1β, IL6 and interferon-alpha (IFN-α) to cause reduction in neurogenesis and increased apoptosis, via activation of the downstream inflammatory signaling pathways transcription factor signal transducer and activator of transcription 1 (STAT1) and nuclear factor-kappa B (NF-kB) (Borsini et al., 2017; Borsini et al., 2018; Borsini et al., 2020), both of which are often observed to be dysregulated in patients with depression (Cattaneo et al., 2020; Miklowitz et al., 2016). Accordingly, evidence from post-mortem studies have revealed an increase in gene expression of the proinflammatory cytokine TNF-α in the prefrontal cortex (PFC) and hippocampi of individuals with a history of depression (Dean et al., 2010). Similarly, studies conducted in animal models of depression have also reported lipopolysaccharide (LPS)-induced depressive-like behaviours, as well as hippocampal neurogenic alterations (Zhang et al., 2016)**.** Overall, these investigations demonstrate that inflammation is an underlying mechanism and a contributing factor for the development of depression, and that treatment with anti-inflammatory drugs could effectively improve depressive symptoms.

sEH IN DEPRESSION

Several meta-analyses demonstrated that ω-3 PUFAs could reduce depressive symptoms beyond placebo (Hsu et al., 2018; Liao et al., 2019; Mello et al., 2014; Sarris et al., 2016; Sublette et al., 2011). The most recent network meta-analysis has compared the efficacy of different dosages of ω-3 PUFAs across 910 MDD patients in 10 trials with 3 adjuvant therapy strategies (high-dose (>=2g/d) n-3 PUFAs, low-dose (<2g/d) n-3 PUFAs and placebo). Results showed that both the high and the low-dose of ω-3 PUFAs were superior to placebo,

and that the efficacy of high-dose ω-3 PUFAs was superior to that of low-dose. In line with these findings, clinical studies within our and other laboratories, again using similar concentrations of ω-3 PUFAs, have showed that diets rich in EPA and DHA provide beneficial anti-inflammatory and anti-depressant effects (Chang et al., 2019; Colombo et al., 1989; Luo et al., 2020; Rapaport et al., 2016; Su et al., 2014; Yu et al., 2020; Zhou et al., 2019). Moreover, we have also previously demonstrated that *in vitro* treatment of human hippocampal progenitors with EPA and DHA can prevent reduction in neurogenesis caused by IL1β, much like treatment with antidepressants, sertraline and venlafaxine, does (Borsini et al., 2017). Importantly, EPA-rich ω-3 PUFAs could be recommended for the treatment of depression, with a recommended dosage of 1-2 g of net EPA daily, from either pure EPA or an EPA and DHA (>2:1) formula (Guu et al., 2019).

Given the fundamental role of inflammation in depression, it is likely that sEH, which regulates ω-3 PUFAs metabolism, might contribute to the pathophysiology of depression. A previous study conducted by Ren et al. found a higher increase in the expression of the sEH protein in the brain (PFC, striatum, and hippocampus) of mice showing depressive-like behaviours, as well as in the brain (parietal cortex) of patients with major depressive disorder (Ren et al., 2016), pointing towards a possible role for increased sEH levels in depression. In particular, the sEH enzyme allows the conversion of the anti-inflammatory ω-3 PUFAs CYP-derived epoxy EpETEs and EpDPAs into their *less active* diols, DiHETEs and DiHDPAs (Ishihara et al., 2019). DiHETEs and DiHDPAs are also known to exert less strong anti-inflammatory properties when compared with their precursors EpETEs and EpDPAs (Ishihara et al., 2019). This therefore suggests that, reducing EpETEs and EpDPAs bioavailability, by activating the sEH enzyme, can decrease the biological action of these epoxy fatty acids (EpETEs and EpDPAs) eventually leading to depressive symptoms. Taken together, this

evidence suggests a key function for sEH in the pathophysiology of depression, and for its inhibitors as a potential alternative therapeutic strategy for patients suffering from this condition (Ren et al., 2016; Swardfager et al., 2018).

An observational study using patients with seasonal depression showed plasma changes in CYP- and sEH-derived epoxy acids during winter depression (Hennebelle et al., 2017). In particular, CYP-derived 14, 15-EpETE decreased while sEH-derived 16, 17-DiHDPA and 19, 20-DiHDPA increased during winter, when compared with summer. These findings suggest that increase in sEH-dependent metabolism underlie a more inflammatory states in patients with seasonal depression, due to the less bioavailability of the anti-inflammatory ω-3 PUFAs-derived epoxy fatty acids (EpETEs and EpDPAs). Similarly, another study in patients with type 2 diabetes and major depression found respectively, a negative and a positive correlation between serum levels of 10, 11-EpDPE and 17, 18-DiHETE, and depressive symptoms (Anita et al., 2021), again confirming the relevance of these epoxy acids in the context of depression.

Interestingly, in line with the above findings, we identified the same CYP-derived epoxy metabolites to be increased in plasma samples of depressed patients exposed to nutritional intervention with either EPA or DHA (Borsini et al., 2021). In particular, in patients receiving EPA, there was a 42% increase in 8, 9-EpETE, whereas in patients receiving DHA we found a 46% increase in 10, 11-EpDPA and a 47% increase in 13, 14-EpDPA. To our knowledge this is the first study to measure this sub-group of epoxy metabolites in a clinical sample of patients with major depression who were exposed to treatment with either EPA or DHA. Moreover, in exploratory correlation analyses, we found that higher levels of the aforementioned metabolites were associated with lower levels of depressive symptoms (Borsini et al., 2021). Therefore, given the crucial role of sEH in the pathophysiology of

depression and ω-3 PUFAs metabolism, treatment with EPA alone, or EPA and DHA, in combination with a sEH inhibitor would be a novel therapeutic approach for patients suffering from this condition.

THE ROLE OF sEH INHIBITORS IN DEPRESSION

Several pre-clinical studies have shown that treatment with the sEH inhibitor 1-[1-propionylpiperidin4-yl]-3-[4-(trifluoromethoxy) phenyl] urea (TPPU) exerts antidepressant effects, as it reduces depressive-like behavior and inflammation, and increases synaptogenesis (Ren et al., 2016; Wu et al., 2017; Wu et al., 2019). In particular, in healthy mice, treatment with TPPU decreased depressive-like behaviors (Wu et al., 2017), whereas in LPS-treated mice, it conferred resilience to social defeat stress, via decreasing serum level of TNF-α (Ren et al., 2016). As such, TPPU is likely to be more effective than treatment with selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, which do not show therapeutic effects in the same LPS-induced model of depression (Zhang et al., 2014). Moreover, in LPS-treated mice, sEH knockout increased PFC and hippocampal expression of the synaptogenesis markers brain-derived neurotrophic factor-tropomyosin receptor kinase B (BDNF-TrkB), glutamate receptor subunit (GluA1) and postsynaptic density protein (PSD-95) (Ren et al., 2016). Similarly, treatment with TPPU attenuated corticosterone-induced cell injury throughout BDNF-TrkB expression and nerve growth factor (NGF)-induced neuronal outgrowth in PC12 cells (Wu et al., 2019). This evidence suggests that decreased inflammation and increased synaptogenesis are necessary for the antidepressant effects of TPPU. Indeed, TPPU is a small molecular weight compound, which in mice can crossed the blood brain barrier with a ~3.5 times higher concentration in the brain than in plasma, and ultimately exert most of its properties centrally (Ulu et al., 2016).

In line with the above findings, we showed for the first time that co-treatment of human hippocampal neurons with the CYP-derived epoxy 17, 18-EpETE and 19, 20-EpDPA, and TPPU, significantly enhances the neurogenic and anti-apoptotic effect of 17, 18-EpETE and 19, 20-EpDPA against treatment with IL1β, IL6 or IFN-α alone (Borsini et al., 2021). As previously discussed, sEH enzyme allows the conversion of EpETEs and EpDPAs into their less active diols DiHETEs and DiHDPAs (Ishihara et al., 2019). Since we showed that both 17, 18-EpETE and 19, 20-EpDPA have themselves neurogenic and anti-apoptotic properties, our findings confirm that maximising their bioavailability, by inhibiting sEH enzyme activation, enhances these biological actions. Of particular interest is the fact that, in our study, treatment with 17, 18-EpETE or 19, 20-EpDPA and TPPU, but not with 17, 18-EpETE or 19, 20-EpDPA alone, fully prevented the increase in the production of downstream cytokines, induced by IL1β, IL6 and IFN-α, as well as the decrease in the gene expression of aquaporin4 (AQP4), induced by IFN-α. In particular, the effect on AQP4 was much stronger for 19, 20-EpDPA than for 17, 18-EpETE (Borsini et al., 2021). This is in line with our other findings showing the ability for 19, 20-EpDPA, but not for 17, 18-EpETE, both with TPPU, to prevent IFN-α-induced increase in apoptosis, while both equally prevented reduction in neurogenesis (Borsini et al., 2021). Of note, in post-mortem and ex vivo studies of depression AQP4 expression was usually decreased in the hippocampus (Lu et al., 2019; Medina et al., 2016; Rajkowska et al., 2013). Indeed, AQP4 is expressed in hippocampal neural progenitors and in astrocytes (Mader and Brimberg, 2019), and it is particularly important for the suppression of apoptosis (Borsini et al., 2018). In fact, in our study, AQP4 can be considered a mechanistic target for the anti-apoptotic effect of 19, 20-EpDPA in the context of IFN-α, but only when in presence of TPPU (Borsini et al., 2021). Taken together our study confirms previous evidence for TPPU to regulate both inflammatory and neurogenic-related pathways, though which it putatively exerts its antidepressant-like properties.

While sEH inhibitors like TPPU have been previously used both in *in vitro* and *in vivo* models of inflammation (Ren et al., 2016; Wu et al., 2017; Wu et al., 2019), new drugs, GSK2256294A and EC5026, able to selectively inhibit the sEH enzyme, have been recently tested and validated for its safety and tolerability respectively, in a clinical cohort of obese smokers with pulmonary inflammation and in patients with neuropathic pain (Hammock et al., 2021; Lazaar et al., 2016). Due to its low molecular weight, GSK2256294A has also been used in patients developing neuroinflammation after subarachnoid haemorrhage (ClinicalTrials.gov identifier NCT03318783), therefore making GSK2256294A a valid option for drug repurposing also in the context of other inflammation-associated brain disorders, including depression, where at least a sub-group of patients often presents chronic levels of peripheral and central inflammation (Cattaneo et al., 2020; Chamberlain et al., 2019; Enache et al., 2019).

CONCLUSION

In this review, the author discussed the role of sEH in the metabolism of ω-3 PUFAs in the context of depression, and the clinical value of sEH inhibitors as alternative therapeutic strategies for patients suffering from this condition. Crucial findings demonstrate that protein level of sEH are significantly elevated in the brain of depressed patients and of mice with a depressive-like phenotype (Ren et al., 2016). These data suggest that increased levels of sEH can enhance metabolism of the anti-inflammatory ω-3 PUFA epoxides EpETEs and EpDPAs, eventually leading to depressive symptoms. Accordingly, findings from our study (Borsini et al., 2021) and from other investigations (Anita et al., 2021; Hennebelle et al., 2017) show a decrease in the level of the same epoxides (EpETEs and EpDPAs) in patients with depression. However, treatment with the sEH inhibitor TPPU can prevent depressive-like behaviour in mice (Ren et al., 2016; Wu et al., 2017), and hamper increased inflammation and reduced neurogenesis in cellular models of depression (Borsini et al., 2021).

In conclusion, considering the role of sEH in the metabolism of epoxides, treatment of ω-3 PUFA in combination with a sEH inhibitor represents an alternative and valid therapeutic approach for patients with neuropsychiatric conditions. This approach may well address the currently unmet treatment needs for clinical depression.

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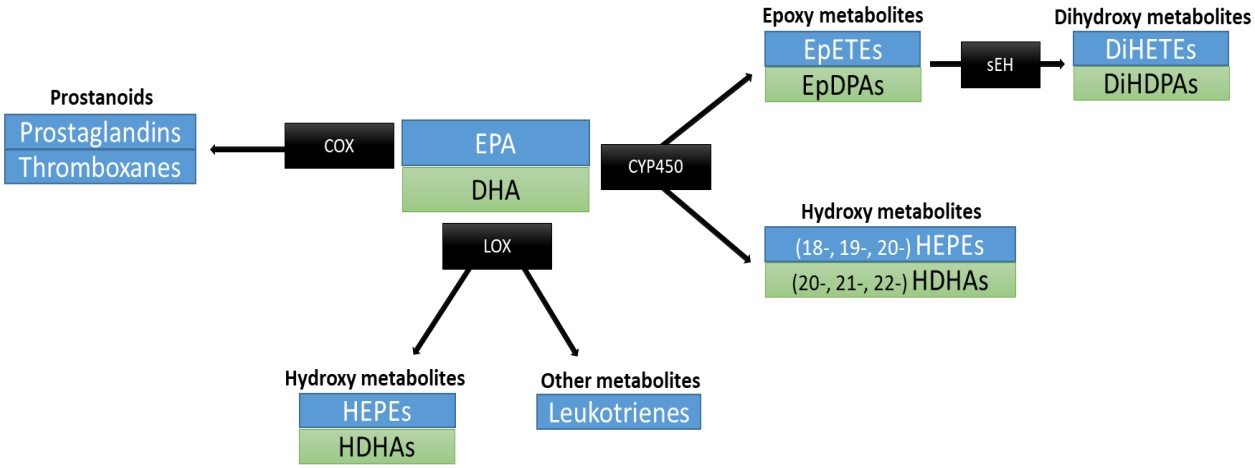

Figure 1. Enzymatic synthesis pathways of ω-3 PUFAs. ω-3 PUFAs are metabolised by COX, LOX and CYP450 enzymes. COX and LOX enzymes convert ω-3 PUFAs into prostanoids, hydroxy fatty acids and leukotrienes, while CYP450 monooxygenases convert ω-3 PUFAs into epoxy and hydroxy fatty acids. Epoxy fatty acids are then metabolized via the sEH enzyme to the corresponding dihydroxy metabolites.

Legend: eicosapentaenoic acid (EPA); docosahexaenoic acid (DHA); soluble epoxide hydrolase (sEH); cyclooxygenase (COX); lipoxygenase (LOX); cytochrome P450 (CYP450); hydroxyeicosapentaenoic acids (HEPEs); hydroxydocosahexaenoic acids (HDHAs); epoxyeicosatetraenoic acids (EpETEs); epoxydocosapentaenoic acids (EpDPAs); dihydroxyeicosatetraenoic acids (DiHETEs); dihydroxydocosapentaenoic acids (DiHDPAs).