Psychiatry Research 252 (2017) 94–101

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Altered soluble epoxide hydrolase-derived oxylipins in patients with seasonal major depression: An exploratory study

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ARTICLE INFO

Keywords:
Oxylipins
Fatty acids
Seasonal major depression
Depression
Soluble epoxide hydrolase
Omega-3
Omega-6
Cytochrome p450
Lipidomics

ABSTRACT

Many cytochrome p450-derived lipids promote resolution of inflammation, in contrast to their soluble epoxide hydrolase(sEH)-derived oxylipin breakdown products. Here we compare plasma oxylipins and precursor fatty acids between seasons in participants with major depressive disorder with seasonal pattern (MDD-s). Euthymic participants with a history of MDD-s recruited in summer-fall were followed-up in winter. At both visits, a structured clinical interview (DSM-5 criteria) and the Beck Depression Inventory II (BDI-II) were administered. Unesterified and total oxylipin pools were assayed by liquid chromatography tandem mass-spectrometry (LC-MS/MS). Precursor fatty acids were measured by gas chromatography. In nine unmedicated participants euthymic at baseline who met depression criteria in winter, BDI-II scores increased from 4.9 ± 4.4 to 19.9 ± 7.7. Four sEH-derived oxylipins increased in winter compared to summer-fall with moderate to large effect sizes. An auto-oxidation product (unesterified epoxyketooctadecadienoic acid) and lipoxygenase-derived 13-hydroxyoctadecadienoic acid also increased in winter. The cytochrome p450-derived 20-COOH-leukotriene B4 (unesterified) and total 14(15)-epoxyeicosatetraenoic acid, and the sEH-derived 14,15-dihydroxyeicostrienoic acid (unesterified), decreased in winter. We conclude that winter depression was associated with changes in cytochrome p450- and sEH-derived oxylipins, suggesting that seasonal shifts in omega-6 and omega-3 fatty acid metabolism mediated by sEH may underlie inflammatory states in symptomatic MDD-s.

1. Introduction

Unlike most other fields of medicine, the clinical management of major depressive disorder (MDD) remains without clinically useful biomarkers with which to predict and monitor the course of the disease. The field also lacks a unified pathophysiological model with which to integrate the observed biological phenomena. For instance, highly reproducible evidence supports elevated concentrations of inflammatory cytokines (Dowlati et al., 2010) and lower levels of omega-3 fatty acids (Lin et al., 2010) in peripheral blood of depressed patients compared to controls. Further evidence suggests that inflammatory markers such as cytokines may decline with treatment and/or symptomatic improvement (Hannestad et al., 2011); however, those markers lack clinical utility, in part due to poor sensitivity and specificity for the disease state, or a lack of quantitative assays that can be appropriately standardized between laboratories (Noble et al., 2008). The forgoing findings, however, do suggest the potential importance of inflammatory and lipid pathways in the pathophysiology of MDD, and in principle, the potential utility of these biomarkers to monitor MDD.

Of all the MDD subtypes, MDD with seasonal pattern (MDD-s; formerly referred to as Seasonal Affective Disorder) is perhaps the best

Abbreviations[1]*:* AA, arachidonic acid; α-LNA, α-linolenic acid; BDI-II, Beck Depression Inventory II; BHT, butylated hydroxytoluene; COX, cycolooxygenase; CYP, cytochrome p450; DHA, docosahexaenoic acid; DSM-V, Diagnostic and Statistical Manual of Mental Disorders version V; EDTA, ethylenediaminetetraacetic acid; EPA, eicosapentaenoic acid; LC-MS/MS, liquid chromatography mass spectrometry; LOQ, imit of quantification; LOX, lipoxygenase; MDD, major depressive disorder; MDD-s, major depressive disorder with seasonal pattern; PUFA, polyunsaturated fatty acids; she, soluble epoxide hydrolase; TPP, triphinylphosphine; UPLC-MS/MS, ultra performance liquid chromatography

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http://dx.doi.org/10.1016/j.psychres.2017.02.056
Received 24 October 2016; Received in revised form 10 February 2017; Accepted 24 February 2017
Available online 27 February 2017

validated and most predictable, with an onset of depressive episodes that typically occurs in winter (Rosenthal et al., 1984). Based on clinical diagnostic criteria, the prevalence of MDD-s has been estimated at 0.4% in the USA (Blazer et al., 1998) and 1.7–4.0% in Canada where it accounts for 18% of recurrent MDD cases (Levitt et al., 2000). Moreover, MDD-s is an excellent model of atypical depression because it is characterized mostly by hypersomnia, carbohydrate craving, increased appetite and weight gain (Garvey et al., 1988; Rosenthal et al., 1984). MDD-s is thought to be caused by a shift in circadian rhythm associated with a longer nocturnal melatonin secretion, and a dysregulation of monoamine neurotransmitter (serotonin, dopamine, and norepinephrine) systems (Lam and Levitan, 2000; Sohn and Lam, 2005). MDD-s can be treated with antidepressants such as selective serotonin reuptake inhibitors, cognitive behavioral therapy or light therapy (Westrin and Lam, 2007), but many who suffer from MDD-s do not seek treatment, facilitating observation of both unmedicated depressed and euthymic states within the same individuals within a short period of time. The effectiveness of treatment is limited, leading to a high rate of recurrence (Forneris et al., 2015; Gartlehner et al., 2015; Kaminski-Hartenthaler et al., 2015; Nussbaumer et al., 2015) and a necessity for a more comprehensive understanding of the pathophysiology.

The oxidation of polyunsaturated fatty acids (PUFA) produces bioactive lipid mediators known as oxylipins, which are involved in regulating pro-inflammatory and resolution pathways in blood and various tissues (Gabbs et al., 2015; Serhan et al., 2008). Oxylipins can be formed non-enzymatically due to auto-oxidation or enzymatically by cyclooxygenase (COX), lipoxygenase (LOX), cytochrome p450 (CYP) or soluble epoxide hydrolase (sEH) enzymes (Arnold et al., 2010b; Fer et al., 2008; Gabbs et al., 2015; Moghaddam et al., 1996; Morisseau et al., 2010; Nieves and Moreno, 2006; Reinaud et al., 1989; Yamamoto et al., 1988). CYP enzymes catalyze the epoxidation of PUFA into their epoxide metabolites that are converted to their corresponding diols by sEH (Imig and Hammock, 2009; Morisseau et al., 2010; Zeldin et al., 1993) (Fig. 1).

Changes in oxylipin metabolism may be related to depression. In mice, direct inhibition of sEH was reported to reduce immobility in the forced swim test and the tail suspension test, demonstrating antidepressant-like effects, and the likely involvement of fatty acid epoxides or diols in depression-like behavior (Ren et al., 2016). Those findings are consistent with evidence of increased levels of the sEH protein in postmortem brain samples from patients with MDD or bipolar disorder compared to healthy controls (Ren et al., 2016); however, it remains to be determined whether peripheral blood concentrations of these lipid mediators are altered in depressed states in living people. A recent meta-analysis reported increased lipid peroxidation in major depression that was normalized following antidepressant treatment (Mazereeuw et al., 2015), but the basis for these changes remains unclear.

In view of preclinical and post-mortem evidence implicating sEH in depressive disorders, we hypothesized that fatty acid diols produced through sEH activity would be higher in the plasma of MDD-s patients during the winter compared to summer. Therefore, in patients with a history of MDD-s recruited in the summer and followed into winter depression, we quantified plasma oxylipins and their precursor fatty acids in both states. We screened for 84 oxidized fatty acid metabolites in plasma (Supplementary Table 1) derived from different polyunsaturated fatty acids (Fig. 1). To our knowledge, no data are currently available on plasma concentrations of these metabolites in any subtype of major depression, and we explored both total oxylipins, representing unesterifed and esterified fractions, and free (unesterified) oxylipins. Unesterifed oxylipins are considered to constitute the bioactive pool, whereas total oxylipins include the esterified pool, the primary transport and storage form that could be released via lipase enzymes (Shearer and Newman, 2008).

2. Methods

2.1. Participants

Ethical approval for this study was obtained from the local Research Ethics Board. All participants provided informed written consent prior to beginning the study. Participants aged between 18–65 years were recruited. All participants had a history of MDD-s based on at least two episodes of depression that presented a seasonal pattern over the past 3 years. Subjects who used an antidepressant, hypnotic or antipsychotic, or had abnormal liver, kidney or lung function, anemia, hypothyroidism, neurological or neurodegenerative conditions, cancer, inflammatory disease, other acute medical conditions or infection were excluded.

Each participant underwent 2 study visits, a baseline visit during the summer or early fall and a follow-up during the winter. At each visit, depressive status was assessed using a Structured Clinical Interview for DSM-5 criteria (American Psychiatric Association, 2013). Participants also completed a Beck Depression Inventory-II (BDI-II) (Beck et al., 1961). A blood sample was collected in K_2-EDTA tubes and centrifuged for 10 min at 1000*g* at 4 °C. Plasma was isolated and stored at −80 °C until analysis. Only participants who were euthymic in the summer and depressed in the winter were included in the final analysis.

2.2. Oxylipin extraction by solid phase extraction

Free (unesterified) and total (unesterified and esterified) oxylipins were extracted by solid phase extraction (SPE), as previously described (Schuchardt et al., 2013; Yang et al., 2009).

To analyze free oxylipins, 10 µL surrogate standard solution, 10 µL of antioxidant solution and 1 mL of SPE buffer containing 5% methanol and 0.1% acetic acid in ultrapure water were added to 200 µL of plasma. The surrogate standard solution contained 500 nM of d11-11(12)-EpETrE, d11-14,15-DiHETrE, d4-6-keto-PGF1a, d4-9-HODE, d4-LTB4, d4-PGE2, d4-TXB2, d6-20-HETE and d8-5-HETE in methanol (i.e. 5 pmol of each deuterated oxylipin per sample). The antioxidant solution contained 0.2 mg/mL of butylated hydroxytoluene (BHT) and triphenylphosphine (TPP) and 1 mg/mL ethylenediaminetetraacetic acid (EDTA) in methanol/water (50/50, v/v). The antioxidant solution was filtered through a Millipore filter prior to use, to remove solid particles.

For total oxylipins, 50–100 µL of plasma were mixed with 10 µL surrogate standard solution (500 nM), 10 µL of antioxidant solution and 100 µL of extraction buffer (0.1% acetic acid and 0.1% BHT in methanol) and kept in −80 °C overnight (Arnold et al., 2010b). Samples were then hydrolyzed in 200 µL of 0.25 M sodium carbonate solution at 60 °C for 30 min under constant shaking. The samples were allowed to cool, and 25 µL acetic acid and 1575 µL ultrapure water were added. The pH was confirmed to be between 4 and 6 by spiking a litmus paper with a few µL from one of the samples.

Oxylipins were extracted by SPE with 60 mg Waters Oasis HLB 3 cc cartridges (Waters, Milford, MA, USA). The columns were first rinsed with one volume of ethyl acetate and two volumes of methanol and conditioned with two volumes of SPE buffer. Plasma samples prepared as described above were poured onto the column, which was topped to volume with SPE buffer. The column was washed twice with SPE buffer and dried under vacuum suction (~20 psi) for 20 min. Oxylipins adsorbed to the SPE column were eluted with 0.5 mL methanol and 1.5 mL ethyl acetate into a 2 mL centrifuge tube containing 6 µL of 30% glycerol in methanol. The collected fraction was dried in a speed-

[1] 84 oxylipins measured and their abbreviations are listed in Supplementary Table 1.