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Polyunsaturated fatty acids moderate the effect of poor sleep on depression risk

Francis E. Lotrich [a,*], Barry Sears [b], Robert K. McNamara [c]

[a] Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States
[b] Inflammation Research Foundation, Marblehead, MA, United States
[c] Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, OH, United States

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ABSTRACT

Although potentially modifiable risk factors for interferon-alpha (IFN-α)-associated depression (IFN-MDD) have been identified, it is not currently known how they interact to confer risk. In the present study we prospectively investigated interactions among poor sleep quality, high-stress, pre-existing depressive symptoms, and polyunsaturated fatty acid status. Non-depressed hepatitis C patients ($n=104$) were followed prospectively during IFN-α therapy. IFN-MDD occurs in 20–40% of patients and was diagnosed using the Structured Clinical Interview of DSM-IV (SCID-IV), with incidence examined using Cox regression. Baseline Pittsburgh Sleep Quality Inventory (PSQI), Perceived Stress Scale (PSS), Beck Depression Inventory (BDI), and a range of plasma long-chain fatty acid levels were measured (gas chromatography) – focusing on the ratio of arachidonic acid (AA) to docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (AA/EPA+DHA). The AA/EPA+DHA ratio ($B=0.40\pm0.16$; $p=0.006$), PSQI ($B=0.12\pm0.04$; $p=0.001$), PSS ($B=0.07\pm0.02$; $p<0.001$), and baseline BDI ($B=0.05\pm0.02$; $p<0.001$) each individually predicted IFN-MDD incidence. In step-wise Cox regression eliminating non-significant variables, two interactions remained significantly predictive: PSQI*AA/EPA+DHA ($p=0.008$) and PSS*AA/EPA+DHA ($p=0.01$). Receiver Operator Curves (ROC) were used to examine the specificity and sensitivity of IFN-MDD prediction. When sleep was normal (PSQI < 5), AA/EPA+DHA was strongly predictive of IFN-MDD (AUC=91 ± 6; $p=0.002$). For example, among those with AA/EPA+DHA less than the median (4.15), none with PSQI < 5 developed depression. Conversely, neither PSS nor PSQI was statistically associated with depression risk in those with an elevated AA/EPA+DHA ratio. These data demonstrate that the AA/EPA+DHA ratio moderates the effect of poor sleep on risk for developing IFN-MDD and may have broader implications for predicting and preventing MDD associated with inflammation.

1. Introduction

Emerging evidence suggests that the pathophysiology of major depressive disorder (MDD) is frequently associated with chronic low-grade inflammation [1]. This is supported in part by findings that some MDD patients exhibit elevated levels of prostaglandin E_2 [2] and pro-inflammatory cytokines such as interleukin-6 [3]. Moreover, many initially non-depressed subjects develop a depressive episode during chronic administration of the pro-inflammatory cytokine interferon-alpha (IFN-α) [4–6]. Because 25–40% of patients develop interferon-associated depression (IFN-MDD) within 2–4 months of treatment [7], prospective examination of patients treated with IFN-α represents a valuable opportunity to identify risk and resilience factors. To date several putative modifiable risk factors for IFN-MDD have been identified [8], and developing a better understanding of how these risk factors interact may inform novel preventative strategies for IFN-MDD specifically and inflammation-associated MDD more generally.

1.1. Sleep is a risk factor for MDD

Poor sleep quality is commonly associated with subsequent depression incidence [9–11], and also predicts IFN-MDD [12,13]. In

Abbreviations: (ALA), Alpha-linolenic acid; (AA), Arachidonic acid; (BDI), Beck Depression Inventory; (DGLA), Dihomo-gamma-linolenic acid; (DHA), Docosahexaenoic acid; (EPA), Eicosapentaenoic acid; (FAME), Fatty acid methyl ester; (GLA), Gamma-linolenic acid; (IFN-α), Interferon-alpha; (IFN-MDD), Interferon-alpha-associated depression; (LES), Life events scale; (LA), Linoleic acid; (LC*n*-3), Long chain omega-3; (MDD), Major depressive disorder; (MADRS), Montgomery–Asberg Depression Rating Scale; (PSS), Perceived Stress Scale; (PSQI), Pittsburgh Sleep Quality Inventory; (PUFA), Polyunsaturated fatty acid; (ROC), Receiver operator curve; (SSRI), Selective serotonin reuptake inhibitor; (SCID-IV), Structured Clinical Interview of DSM-IV

* Correspondence to: Department of Psychiatry, Western Psychiatric Institute and Clinic, 3811 O'hara Street, Pittsburgh, PA 15213. Tel.: +1 412 246 6267.
E-mail address: lotrichfe@upmc.edu (F.E. Lotrich).

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particular, a physiological predictor of IFN-MDD is lower early night delta power [14], which also predicts MDD recurrence [15–17]. Whether improving sleep quality – specifically improving delta power during sleep – can prevent depression remains to be determined.

1.2. Long chain fatty acid status is a risk factor for MDD

Deficits in the long-chain omega-3 (LC*n*-3) fatty acids eicosapentaenoic acid (EPA, 20:5*n*-3) and docosahexaenoic acid (DHA, 22:6*n*-3) are associated with MDD [18]. In particular, the ratio of the omega-6 arachidonic acid (AA, 20:*n*-6) to LC*n*-3 fatty acids (the AA/EPA+DHA ratio) is elevated in MDD patients [19–24]. Likewise, IFN-MDD is also associated with a high AA/EPA+DHA ratio [25]. In fact, LC*n*-3 supplements have recently been demonstrated to prevent IFN-MDD in some people [26]. One proposed mechanism is via decreased inflammation [27], though direct brain effects may be plausible [28]. Although LC*n*-3 fatty acid levels may also interact with poor sleep quality to moderate adverse effects cognition [29], how or whether they interact with sleep quality to effect depression risk is not known.

1.3. Pre-existing sub-syndromal depression symptoms are a risk factor for MDD

Third, a history of prior MDD episodes and/or current subsyndromal symptoms may predispose to IFN-MDD [30]. Prophylactic selective serotonin reuptake inhibitors (SSRIs) can halve the incidence of IFN-MDD [31–34]. Unfortunately, SSRIs do not eliminate the IFN-MDD incidence, and may have side effects such as retinopathy [33] and worsened irritable anger [35,36]. Although LC*n*-3 fatty acids have antidepressant properties [37] and may augment SSRI antidepressant effects [38,39] it is not known how or whether LC*n*-3 fatty acid biostatus and MDD history interact to modify IFN-MDD risk.

1.4. Stress is a risk factor for MDD

Fourth, psychosocial stressors are a significant predictor of depressive episodes [40]. Consistent with this, altered hypothalamic–pituitary–adrenal axis activity may predict IFN-MDD [41,42]. Interestingly, a fatty acid synthase polymorphism moderated the effect of perceived stress on depression [43] suggesting a plausible interaction between AA/EPA+DHA and stress.

The present study thus sought to prospectively investigate the interactions between the AA/EPA+DHA ratio and other risk factors such as psychosocial stress and sleep quality on depression vulnerability. Our primary hypothesis was that these risk factors would interact in a synergistic manner to increase risk for developing subsequent IFN-MDD. Based on prior evidence linking pro-inflammatory processes with poor sleep quality [44,45], stressful life events [46–48], and an elevated AA/EPA+DHA ratio [24,49–51], these findings may have relevance for predicting and preventing inflammation-associated MDD more broadly.

2. Materials and methods

2.1. Subjects

Non-depressed adult subjects (between ages 18 and 80) were examined for plasma fatty acid levels and completed a set of questionnaires prior to subsequent IFN-α therapy for HCV ($n=104$). Our primary interest is IFN-MDD incidence. These subjects partially overlapped with those in a prior study [25]. Exclusion criteria were active mood, anxiety, psychotic, or drug/alcohol use disorders within 6 months prior to starting IFN-α treatment – using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV); known neurologic disease; or taking corticosteroids, antidepressants, anticonvulsants, and/or antipsychotics (although they could be taking as-needed sleeping medications). All subjects started weekly injections of pegylated (PEG) IFN-α2 (PEG-IFN-α2a: 135 μg/week or PEG-IFN-α2b: 120 or 150 μg/week) augmented with oral ribavirin. This study was approved by the University of Pittsburgh Institutional Review Board.

2.2. Assessments

Prior to initiating IFN-α therapy, and monthly for four months after therapy was initiated, depression was assessed using the Beck Depression Inventory-II (BDI) and the Montgomery–Asberg Depression Rating Scale (MADRS) as previously described [25]. IFN-MDD was diagnosed using either an abbreviated SCID-IV interview focused on depression and/or in any subject started on an antidepressant by their physician – as previously described in more detail [25]. The Perceived Stress Scale (PSS) [52], the life events scale (LES) [53,54], and the Pittsburgh Sleep Quality Inventory (PSQI) [57] were administered at baseline. For the LES, we examined both total number of stressful life events in the past year, as well the total score after adjusting each event for impact (self-rated on a scale from −3 to +3).

2.3. Gas chromatography

Plasma from whole blood was obtained from all subjects between 10 A.M. and 4 P.M. prior to initiating treatment for hepatitis C (HCV), and stored at −80 °C until analysis. Folch reagent (2 mL Chloroform/Methanol 2:1) was added to 0.3 ml of plasma to extract the lipid layer, dried under nitrogen, and reconstituted with chloroform (100 uL). The lipid extract was then transferred to a reversed-phase packed SPE column (Alltech, Nicholasville, KY) and washed with chloroform (10 mL), to remove triglycerides, and then acetone (10 mL) to remove the cholesteryl esters. Phospholipids were then eluted with methanol (20 mL), and the combined methanol fractions evaporated. The sample was methylated using NaOH/MeOH (0.5 mL) and the derivatization was completed with BF_3/MeOH followed by heating for 15 min at 85 °C. To ensure total fatty acid methyl ester (FAME) extraction, NaCl (0.3 mL) was used before extraction with hexane. Sodium sulfate was added to the hexane layer to remove water, and the organic phase decanted and evaporated using nitrogen. Samples were then reconstituted with hexane (0.5 mL) and analyzed.

FAME's were analyzed using an HP 6890/5973 gas chromatograph/mass selective detector (Agilent Technologies, Santa Clara, CA). The column used to separate FAME's was an Agilent DB-FFAP 15×0.1 mm^2 with 0.1 um of film thickness. Helium was used as carrier gas at a flow rate of 17.6 ml/min and a constant pressure of 53.8 psi. The initial temperature was set at 160 °C and increased after injection of 1 ul of sample to 240 °C at a rate of 15 °C per minute. Once the temperature of 240 °C was reached, it was maintained for 6 min for a total run time of 14.33 min. The transfer line was maintained at 280 °C and the filament at 70 eV for EI. The data were evaluated using a TIC for compound identification and SCAN mode to measure relative percent of each fatty acid. Fatty acid identification was based on retention times of authenticated FAME standards (GLC 473B) and controls (GLC 462 and GLC 463) to ensure reproducibility (NuCheck Prep, Elysian, MN). Data are expressed as weight percent of total fatty acid pool (mg fatty acid/100 mg fatty acids). We assessed the omega-6 fatty acids linoleic acid (LA; C18:2*n*-6), gamma-linolenic acid (GLA; C18:3*n*-6), dihomo-gamma-linolenic acid (DGLA; C20:3*n*-6), and arachidonic acid (AA; C20:4*n*-6), and the omega-3 fatty acids alpha-linolenic