Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Omega-3 fatty acids in the psychological and physiological resilience against COVID-19

Jane Pei-Chen Changa,b,c, Carmine M. Pariante†, Kuan-Pin Su†,b,c,d,⁎

a Mind-Body Interface Laboratory (MBI-Lab) and Department of Psychiatry, China Medical University Hospital, Taichung, Taiwan
b College of Medicine, China Medical University, Taichung, Taiwan
c Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, United Kingdom
d An-Nan Hospital, China Medical University, Tainan, Taiwan

ARTICLE INFO

Keywords:
Omega-3
Covid-19
Immunomodulation

ABSTRACT

As the infected cases of COVID-19 reach more than 20 million with more than 778,000 deaths globally, an increase in psychiatric disorders including anxiety and depression has been reported. Scientists globally have been searching for novel therapies and vaccines to fight against COVID-19. Improving innate immunity has been suggested to block progression of COVID-19 at early stages, while omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been shown to have immunomodulation effects. Moreover, n-3 PUFAs have also been shown to improve mood disorders, thus, future research is warranted to test if n-3 PUFAs may have the potential to improve our immunity to counteract both physical and mental impact of COVID-19.

1. Introduction

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are essential fatty acids for our brain and immune system, and can only be obtained from diet. There have been several studies showing that deficiency of n-3 PUFAs have been associated with several psychiatric disorders including major depressive disorder (MDD) [1], perinatal depression [2], attention deficit hyperactivity disorder (ADHD) [3], and dementia [4]. On the other hand, interventional studies with n-3 PUFAs supplementation have been show potential to improve the clinical outcome of MDD [5], perinatal depression [6], ADHD [7], anxiety disorder [8] and mild cognitive impairment [9]; and even prevent interferon-induced depression [10]. Moreover, a recent practice guideline on n-3 PUFAs on MDD has also been published by the International Society for Nutritional Psychiatry Research (ISNPR) [11]. The guideline suggested a clinical interview is recommended to validate the clinical diagnoses prior to the prescription of n-3 PUFAs, the ratio of EPA/DHA in the formula should be greater than 2, and the dosage should be 1–2 g of net EPA. The guideline further emphasized that quality of the supplementation will affect the therapeutic activity and that potential adverse effects such as gastrointestinal and dermatological conditions should be closely monitored along with metabolic profiles. Thus, in the current Pandemic, n-3 PUFAs may perhaps serve as a potential nutraceutical to prevent COVID-19 associated neuropsychiatric sequelae such as depression and anxiety or the relapse of MDE in those with pre-pandemic MDD.

2. COVID-19 and psychiatric disorders

COVID-19, up until now, has infected more than 20 million people and took 778,219 lives globally (18th of August 2020) (https://www.worldometers.info/coronavirus/). Individuals of older age, smoking habits, chronic medical conditions, and immunocompromised status are more susceptible for contracting COVID-19 and resulting in fatal complications [12]. Moreover, those who survived the Pandemic, regardless COVID-19 infection, may have an increase in anxiety and mood disorders [13]. This brief review aims to discuss the potential role and application of n-3 PUFAs in fighting against COVID-19 both mentally and physically via immunomodulation [14] (Fig. 1).

3. COVID-19, immune reactions, mood disorders

The first two weeks after infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2, the virus causing COVID-19) are crucial. Whether the patient will develop serious complications such as acute respiratory distress syndrome (ARDS) or other organ failure depends on the individual’s innate immunity and the exposure to the viral...
load [15]. If the virus is successfully blocked at the upper airway and does not reach the lungs, then the individual has a greater chance of presenting the virus to lymphocytes such as IgM to neutralize the virus. On the other hand, the levels of N-3 PUFAs are thought to be influenced by genetic factors (PLA2 genes). Thus, strengthening innate immunity is crucial to block the progression of COVID-19. Furthermore, the proinflammatory cytokines will recruit more innate immune cells to the site, such as neutrophils. Moreover, after APC will then activate T cell to switch to either CD4+ (combat bacteria) Th1 or Th17 cells or CD8+ (combat virus) and produce more proinflammatory cytokines, which may lead to pathologic changes in the lung tissues, for example pneumonia; result in fatal IL-6 cytokine storm and DIC leading to ARDS and organ failure. Moreover, after B cells detect antigen, they will produce antibodies such as IgM to neutralize the virus. On the other hand, the levels of N-3 PUFAs are thought to be influenced by genetic factors (PLA2, COX2 genes in chromosome 1) and environmental factors (diet, inflammation, or cytokines). N-3 PUFAs have been shown to modulate the migration, increase the phagocytic capacity, decrease the cytokine production and ROS of innate immune cells including macrophages and neutrophil, promote activation of NK cells, modulate the T cell activation by altering activation of APCs (such as macrophages or dendritic cells) and prevent differentiation of CD4+ cells to Th1 cells. N-3 PUFAs are also able to increase innate-like B cells, B1 cells and production of Igs. N-3 PUFAs are also able to treat mood disorders via reduction of proinflammatory cytokines, alteration of HPA axis and alteration of neurotransmission via their effects on lipid rafts.

Abbreviations: APC, antigen presenting cells; AP-1, activator protein 1; ARDS, acute respiratory distress syndrome; COX2, cyclooxygenase 2; DIC, disseminated intravascular coagulation; HPA, hypothalamus-pituitary-adrenal (HPA) axis; Ig, Immunoglobulin; ILs, interleukins; IRF, interferon response factor; NF-κB, nuclear factor κB; ROS, reactive oxidative species; TNF, tumour necrosis factor.

Fig. 1. After SARS-CoV-2 enters the human body, macrophages, epithelial cells and dendritic cells will recognize the PAMPs and act as APC, and activate signaling pathways and NF-κB, AP-1, IRF3 and IRF7. NF-κB, AP-1 will increase genetic expression of proinflammatory cytokines including ILs and TNF. The proinflammatory cytokines will recruit more innate immune cells to the site, such as neutrophils. Moreover, after APC will then activate T cell to switch to either CD4+ (combat bacteria) Th1 or Th17 cells or CD8+ (combat virus) and produce more proinflammatory cytokines, which may lead to pathologic changes in the lung tissues, for example pneumonia; result in fatal IL-6 cytokine storm and DIC leading to ARDS and organ failure. Moreover, after B cells detect antigen, they will produce antibodies such as IgM to neutralize the virus. On the other hand, the levels of N-3 PUFAs are thought to be influenced by genetic factors (PLA2, COX2 genes in chromosome 1) and environmental factors (diet, inflammation, or cytokines). N-3 PUFAs have been shown to modulate the migration, increase the phagocytic capacity, decreases the cytokine production and ROS of innate immune cells including macrophages and neutrophil, promote activation of NK cells, modulate the T cell activation by altering activation of APCs (such as macrophages or dendritic cells) and prevent differentiation of CD4+ cells to Th1 cells. N-3 PUFAs are also able to increase innate-like B cells, B1 cells and production of Igs. N-3 PUFAs are also able to treat mood disorders via reduction of proinflammatory cytokines, alteration of HPA axis and alteration of neurotransmission via their effects on lipid rafts.

Fig. 1. N-3 PUFAs, immune reaction, mood disorders

N-3 PUFAs and its metabolites, pro-resolvin mediators (SPMs) including prostaglandins, leukotrienes, thromboxanes, maresins, protectins and resolvins (Fig. 1), have been shown to have immunomodulatory functions [20]. N-3 PUFAs help to modulate the migration, increase the phagocytic capacity, decreases the cytokine production and the reactive oxidative species (ROS) of innate immune cells including macrophages and neutrophils [14]. Moreover, n-3 PUFAs and its metabolites also promote activation of NK cells and modulate the T cell activation by altering activation of antigen-presenting cells (APCs, such as macrophages or dendritic cells) and prevent the differentiation of CD4+ cells to Th1 cells [14]. In addition, n-3 PUFAs also increase innate-like B cells, B1 cells, and immunoglobulin (Ig)M production by B cells, by increasing the number of APCs [14], which may altogether strengthen the innate immunity. Moreover, n-3 PUFAs, especially EPA, have shown effect in treating mood disorders via reduction of pro-inflammatory cytokines, alteration of hypothalamus-pituitary-adrenal (HPA axis), and modulation of neurotransmission via lipid rafts [21]. (Fig. 1).
5. Potential role of N-3 PUFAs in COVID-19

In sum, by strengthening baseline immunity may help prevent fatal outcomes and psychiatric sequelae in those individuals infected with COVID-19 or prevent the relapse of pre-pandemic psychiatric disorders. Thus, a healthy and balanced diet may be what we need to improve our immunity, and future research are warranted to test if n-3 PUFAs may be the potential nutraceutical to help maintain both our mental and physical wellbeing during this Pandemic.

Disclosure statement

Drs Chang and Su declared no conflict of interests. Dr. Pariante received research funding from Janssen Pharmaceutical NV/Janssen Pharmaceutical Companies of Johnson & Johnson for research on depression and inflammation.

Author statement

Jane Pei-Chen Chang: Writing-Original draft preparation; Investigation; Carmine Pariante: Writing-Reviewing and Editing; Investigation; Kuan-Pin Su: Conceptualization; Writing-Reviewing and Editing; Investigation; Supervision

Acknowledgements and Funding/Support

Drs Chang and Su are supported by the following grants: MOST 106–2314-B-039-027-MY3, 108–2320-B-039–048, 108–2813-C–039–133-B and 108–2314-B-039–016 from the Ministry of Science and Technology, Taiwan; NHRI-EX108–10528NI from the National Health Research Institutes, Taiwan; MYRG2018–00242-ICMS from University of Macau, China; CMRC–CMA-3 from Higher Education Sprout Project by the Ministry of Education (MOE), Taiwan; CMU108-SR-106 from the China Medical University, Taichung, Taiwan; and CMU104-S-16–01, CMU103-BG–4–1, CRS-108–048, DMR-108–216, DMR-109–102, DMR-HHC-109–11, DMR-HHC-109–12 from the China Medical University Hospital, Taichung, Taiwan. Dr. Pariante is supported by the grants “Immunopsychiatry: a consortium to test the opportunity for immunotherapeutics in psychiatry” (MR/L014815/1) and ‘Persistent Fatigue Induced by Interferon-alpha: A New Immunological Model for Chronic Fatigue Syndrome’ (MR/J002739/1), from the Medical Research Council (UK), and by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London.

Reference

[1] P.Y. Lin, S.Y. Huang, K.P. Su, A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression, Biol. Psychiatry 68 (2010) 140–147.
[2] M.P. Freeman, Omega-3 fatty acids and perinatal depression: a review of the literature and recommendations for the future research, Prostaglandins Leukot. Essent. Fatty Acids 75 (2006) 291–297.
[3] J.P. Chang, K.P. Su, V. Mondelli, C.M. Pariante, Omega-3 polyunsaturated fatty acids in youths with attention deficit hyperactivity disorder: a systematic review and meta-analysis of clinical trials and biological studies, Neuropsychopharmacology 43 (2018) 534–545.
[4] P.Y. Lin, C.C. Chiu, S.Y. Huang, K.P. Su, A meta-analytic review of polyunsaturated fatty acid composition in dementia, J. Clin. Psychiatry 73 (2012) 1245–1254.
[5] D. P.Y. Lin, D. Michoulon, M.P. Freeman, et al., Are omega-3 fatty acids anti-depressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression, Mol. Psychiatry, 17 (2012) 1161–1163.
[6] K.P. Su, S.Y. Huang, T.H. Chiu, et al., Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial, J. Clin. Psychiatry 69 (2008) 644–651.
[7] J.P. Chang, K.P. Su, V. Mondelli, et al., High-dose eicosapentaenoic acid (EPA) improves attention and vigilance in children and adolescents with attention deficit hyperactivity disorder (ADHD) and low endogenous EPA levels, Transl. Psychiatry 9 (2019) 303.
[8] K.P. Su, P.T. Tseng, P.Y. Lin, et al., Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms: a systematic review and meta-analysis, JAMA Netw. Open 1 (2019) e182327.
[9] C.C. Chiu, K.P. Su, T.C. Cheng, et al., The effect of omega-3 fatty acids monotherapy in Alzheimer’s disease and mild cognitive impairment: a preliminary randomized double-blind placebo-controlled study, Prog Neuropsychopharmacol Biol Psychiatry 32 (6) (2008) 1538–1544.
[10] K.P. Su, H.C. Lai, H.T. Yang, et al., Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized controlled trial, Biol. Psychiatry 76 (2014) 559–566.
[11] T.W. Gou, D. Michoulon, J. Sarris, et al., International Society for Nutritional Psychiatry Research Practice Guidelines for omega-3 fatty acids in the treatment of major depressive disorder, Psychother. Psychosom 88 (2019) 263–273.
[12] G. Lippit, C. Mattiuzzi, F. Sanchis-Gomar, B.M. Henry, Clinical and demographic characteristics of patients dying from COVID-19 in Italy versus China, J. Med. Virol. (2020) Epub ahead of print.
[13] S.W. Kim, K.P. Su, Using psychoneuroimmunity against COVID-19, Brain Behav. Immun 87 (2020) 4–5.
[14] S. Gutierrez, S.L. Svala, M.E. Johansson, Effects of Omega-3 Fatty Acids on Immune Cells, Int. J. Mol. Sci 20 (2019) 5028.
[15] P.M. Mattirciadi, R.W. Dal Negro, R. Nisini, The first, holistic immunological model of COVID-19: implications for prevention, diagnosis, and public health measures, Pediatr. Allergy Immunol. (2020) Epub ahead of print.
[16] G.E. Hodes, C. Menard, S.J. Russo, Integrating Interleukin-6 into depression diagnosis and treatment, Neurobiol. Stress 4 (2016) 15–22.
[17] M. Rokni, V. Ghaemi, Z. Tavakoli, Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: comparison with SARS and MERS, Rev. Med. Virol 30 (2020) e2107.
[18] E. Prompetchara, C. Ketloy, T. Palaaga, Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic, Asian Pac. J. Allergy Immunol. 38 (2020) 1–9.
[19] A.H. Miller, Depression and immunity: a role for T cells? Brain Behav. Immun 24 (2010) 1–8.
[20] K.P. Su, Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a ‘mind-body interface’? Neurosignals 17 (2009) 144–152.
[21] J.P. Chang, K.P. Su, The lipid raft hypothesis: the relation among omega-3 fatty acids, depression, and cardiovascular diseases, Taiwan J. Psychiatry 24 (2010) 168–180.