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Omega-3 fatty acids in the psychological and physiological resilience against COVID-19

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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

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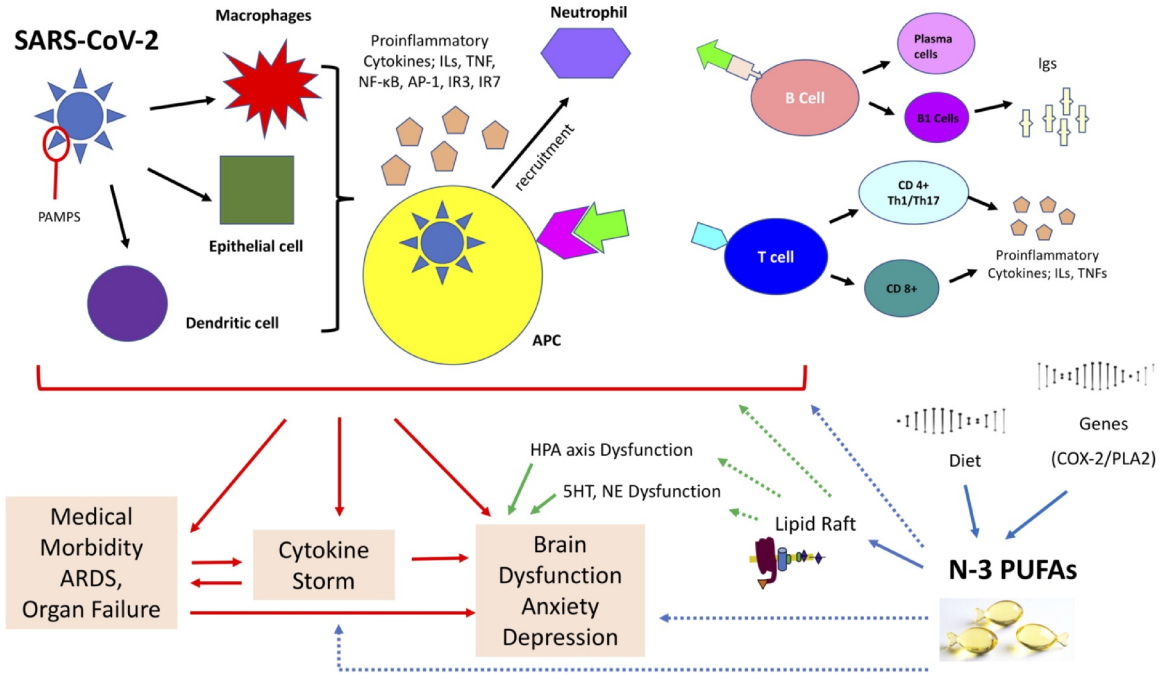

Fig. 1. After SARS-CoV-2 enters the human body, macrophages, epithelial cells and dendritic cells will recognize the PAMPS and act as APC, and activate signaling pathways and NF-κB, AP-1, IRF 3 and IRF7. NF-κB, AP-1 will increase genetic expression of proinflammatory cytokines including ILs and TNF. 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 (PLA_2 and COX_2 genes in chromosome 1) and environmental factors (diet, inflammation, or cytokines). N-3 PUFAs have been shown to modulate the migration, increase the phagocytotic 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.

Abbreviations: APC, antigen presenting cells; AP-1, activator protein 1; ARDS, acute respiratory distress syndrome; COX_2, cyclooxygenase 2; DIC, disseminated intravascular coagulation; HPA, hypothalamus-pituitary-adrenal (HPA) axis; Ig, Immunoglobulin; ILs, interleukins; IRF, interferon response factor; NF-κB, nuclear factors κB; NK cells, natural killer cells; N-3 PUFAs, omega-3 polyunsaturated fatty acids; PAMPS, pathogen associated molecular patterns; PLA_2, phospholipase A2; ROS, reactive oxidative species; TNF, tumour necrosis factor.

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 having a milder form of COVID-19 [15]. However, if the SARS-Cov-2 do reach alveoli, it will have more replications, active the specific adaptive immune response. This may result in interleukin (IL) − 6 cytokine storm and disseminated intravascular coagulation (DIC), both are common causes of death in COVID-19 infection [15]. On the other hand, IL-6 has been associated with mood disorders [16], and has been investigated as a potential treatment for mood disorders [5].

The innate immune system recognizes the pathogen-associated molecular patterns (PAMPs) produced during SARS-CoV-2 infection, and will activate signaling pathways and transcription factors including nuclear factor κB (NF-κB), activator protein 1 (AP-1), interferon response factor 3 (IRF3), and IRF7. NF-κB and AP-1 will then induce genetic expression of proinflammatory cytokines including tumor necrosis factor (TNF) and IL-1 and chemokines including CCL2 and CXCL8. However, the mechanism where interferon (IFN)-α and IFN-β are used to suppress viral replication at early stages appeared to be bypassed during SARS-Cov-2 infection, which may result in uncontrolled viral replication [17]. Thus, strengthening innate immunity is a crucial step to block the progression of COVID-19. Furthermore, the proinflammatory cytokines will recruit other innate immune cells including macrophages, neutrophils, and natural killer (NK) cells, and lead to the activation of adaptive immunity, where T helper (Th)1/Th17 cells may cause immunopathologic lung injury that leads to pneumonia [18]; while B cells may produce specific antibodies that may help neutralize SARS-CoV-2 [18]. In addition, impaired lymphocyte function has been suggested to contribute to the development of mood disorders [19], which has increased global incidence during the Pandemic [13].

4. 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 phagocytotic 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

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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

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