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SARS-CoV-2 journey to the brain with a focus on potential role of docosahexaenoic acid bioactive lipid mediators

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ABSTRACT

Coronavirus Disease 2019 or COVID-19 have infected till day 82,579,768 confirmed cases including 1,818,849 deaths, reported by World Health Organization WHO. COVID-19, originated by Severe Acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), contributes to respiratory distress in addition to neurological symptoms in some patients. In the current review, we focused on the neurological complications associated with COVID-19. We discussed different pathways followed by RNA-virus, especially Flaviviridae family in the brain and passage through the Blood-Brain-Barrier BBB. Then, we explored SARS-CoV-2 mechanisms responsible of neuroinvasion and BBB disruption as well as the immunopathogenesis of SARS-CoV-2 in the central nervous system CNS. Since SARS-CoV-2 is an enveloped virus, enclosed in a lipid bilayer and that lipids are essential cell components playing numerous biological roles in viral infection and replication, we investigated the lipid metabolism remodeling upon coronavirus replication. We also highlighted the anti-inflammatory and neuroprotective potential of an omega-3 polyunsaturated fatty acid, docosahexaenoic acid DHA, as well as several bioactive lipid mediators. Altogether, our data allow better understanding of SARS-CoV-2 neuroinvasion and could assist in drug targeting to decline the burden of short-term and long-term neurological manifestations of SARS-CoV-2.

Contents

1. Introduction

Coronaviruses (CoVs) are positive-single-stranded ribonucleic

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acid (RNA) viruses, 26–32 kilobases, with a diameter of around 60–140 nm, belonging to Coronaviridae family [1]. Four CoVs genera are defined. These genera consist of α-coronaviruses, β-coronaviruses, γ-coronaviruses, and δ-coronaviruses [2]. Seven CoVs are identified to cause human disease. Among them, HCoV229E, NL63, OC43, and HKU1 are recognized as non-severe acute respiratory syndrome (SARS)-like CoVs, causing moderate diseases. SARS-CoV-1, MERS, and SARS-CoV-2 are extremely infective and can lead to death [3]. SARS-CoV-2 causing Coronavirus Disease 2019 (COVID-19) became a pandemic, since December 2019, infecting millions of people until day [4]. In December 2020, a new CoVs variant was identified in UK and called VUI-202012/01 (Variant Under Investigation). VUI-202012/01 is characterized by a set of 17 mutations [5]. Among these mutations, N501Y mutation in the spike protein S used by the virus to bind to the human Angiotensin-Converting Enzyme ACE2 receptor. Variations in spike protein might lead to more virulent and rapid viral infections among population.

COVID-19 follows three stages [6]. The Stage I (mild) initial infection happens at the time of inoculation and consists of an incubation period linked to mild symptoms including fever, dry cough, etc. The virus replicates in the host, predominantly in the respiratory system. In the stage II (moderate)-pulmonary without or with hypoxia, the virus multiplies and the inflammation in the lung are most common with some markers of systemic inflammation. A viral pneumonia, cough, fever, and sometimes hypoxia are observed in patients. Most patients need to be hospitalized at this stage. Following, the stage III (severe)—systemic hyperinflammation is the most severe stage of the disease in a minority of COVID-19 patients. At this stage, the patients have extrapulmonary systemic hyperinflammation syndrome and markers of systemic inflammation are elevated. Some inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7, C-reactive protein are considerably high in patients with severe disease [6].

Even though the virus principally is recognized as an acute respiratory infection, current data recommends that 36% of infected people have neurological symptoms [7].

To better understand the relationship between SARS-CoV-2 and neurological complications in patient, we studied different pathways followed by RNA viruses to counteract the Blood Brain Barrier BBB. Then, we focused on potential mechanisms adapted by SARS-CoV-2 for neuroinvasion as well as BBB disruption. Also, we discussed the immunopathogenesis of SARS-CoV-2 in CNS which is crucial for potential anti-viral drug targeting. Since lipid remodeling in viral infected host cells was observed in several viral infection, we investigated the lipid metabolism remodeling upon CoVs replication with a focus on anti-inflammatory and neuroprotective effect of docosahexaenoic acid DHA as well as bioactive lipid mediators against SARS-CoV-2 infection. Finally, we discussed the probable effect of SARS-CoV-2 on DHA passage across BBB by altering some proteins transporter expression.

2. Structure of SARS-CoV-2

To better understand the binding of SARS-CoV-2 to the cell host, we explored the virus ‘structure in this section (see Fig. 1). In fact, SARS- CoV-2 gene fragments express structural and non-structural protein. S, N, E and M genes code for structural proteins whereas non-structural proteins including proteases, NSP13 helicase, NSP12 polymerase are encoded by open reading frames (Orfs) [8]. CoVs crown-like shape is due to S proteins, a transmembrane glycoprotein, crucial for binding to ACE2 host receptor [9]. ACE2 is made of 805 amino acids with two catalytic domains and encoding gene located on X chromosome, Xp22.2 [10]. ACE2 is expressed in several organs including brain, heart, lung, kidney and liver [11]. Each S

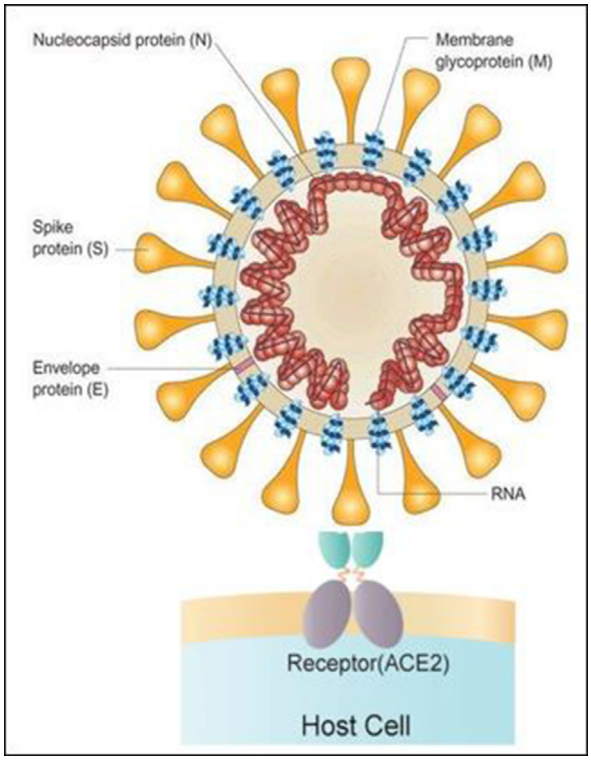

Fig. 1. SARS-CoV-2 structure showing structural proteins Spike S, Membrane glycoprotein M, Envelope E, Nucleocapsid N as well as binding to ACE2 receptors in host cell through Spike S protein.

glycoprotein includes two subunits named S1 and S2. S1 is responsible for host cell binding while S2 enables the membrane combination involving the virus and host cells [8,12]. The activation of S protein in the viral envelope is induced by the transmembrane serine protease 2 (TMPRSS2), a membrane-bound enzyme found near the ACE2 receptor. In human tissue, TMPRSS2 is mainly expressed in the small intestine, heart, lung, liver. In the brain, TMPRSS2 is highly expressed in the fetal brain whereas its expression level in the adult brain is low [13]. Direct proteolytic cleavage of viral S protein by TMPRSS2 on the surface of host cells induces the fusion of the plasma and viral membranes. Thus, leading to the release of the viral single stranded-RNA into the host ‘cytoplasm.

Another structural protein in SARS-CoV-2 is Nucleocapsid N protein detected at initial phases of the viral infection playing an important role in binding to viral RNA to form a nucleus and virus proliferation [14]. Moreover, the structural CoVs envelope protein or E protein forms small hydrophobic proteins or viroporins essential for viral assembly, viral release and contributing in pathogenic mechanisms [15]. In addition, CoVs membrane protein M is the main glycoprotein in viral particle and participate in the proliferation of the virus through decreasing cyclooxygenase COX-2 levels [16,17]. Concerning non-structural proteins, SARS-CoV-2 codes for a single papain-like protease PLpro with a significant function in viral replication and inhibition of the immune systems in host cells [18]. Another key proteins in viral replication are NSP13 helicase and NSP12 Polymerase having respectively nucleoside-triphosphatase NTPase, RNA helicase activity and RNA synthesis through intervention in the initiation and elongation phase [19,20]. All mentioned proteins are fundamental in several stages of viral infection, from viral entry to viral replication and development of viral vesicles.

3. Effect of RNA viruses, flaviviridae, on Blood-Brain-Barrier integrity

Several blood-borne acute viruses have revealed neuroinvasive properties in humans. Viruses can penetrate the CNS *via* two different routes: hematogenous dissemination route or neuronal retrograde dissemination [21]. In hematogenous dissemination, the virus expands in the body *via* the bloodstream and reaches the brain by crossing the BBB, while neuronal retrograde viral dissemination happens when a virus infects peripheral neurons then access the CNS through cells transport machinery [21].

To cross the endothelial monolayer of BBB, the virus can follow four different pathways [22]. In the diffusion mechanism or passive-aggressive mechanism, viruses can diffuse through endothelial monolayer with alteration of the endothelium integrity. Another pathway is the infection or energetic path where the monolayer endothelial is infected and viruses are found on the other side. Moreover, transcytosis or commuting way through endocytosis/exocytosis mechanism in the privation of productive infection and Trojan horse pathway was proposed in the literature [22].

These cerebral viral infections, known as viral encephalitis, are due to DNA viruses, retroviruses or RNA viruses [23]. Viral encephalitis can be associated with BBB disruption allowing the virus entrance as well as inflammatory cells into brain parenchyma [24]. Some acute viral infections including murine adenovirus type 1 (MAV-1), human immunodeficiency virus type 1 (HIV-1), West Nile virus (WNV), and lymphocytic choriomeningitis mouse virus (LCMV) infections were identified to produce disruption of BBB or endothelial junctions [24]. Although, these viruses were stated to induce an increase in BBB permeability, the mechanism of BBB damage is yet to be explored.

Since SARS-Cov-2 is a RNA virus belonging to Flaviviridae family, to better understand the way Flaviviridae viruses affect BBB, we explored in this section the effect of some viruses (Zika Virus ZIKV, West Nile virus WNV) on BBB. ZIKV, a single stranded RNA virus of the Flaviviridae family, was tested on *in vitro* model of human brain-derived endothelial cells hCMEC/D3 and showed that ZIKV can infect hCMEC/D3 cells without BBB disruption and without effect on tight junction protein expression. While no BBB disruption was detected during ZIKV infection, ZIKV particles were found on BBB basal side and infected underlying cells, thus proving that ZIKV can cross BBB by transcytosis [25]. These findings confirm same results showed by Papa et al., 2017 who confirmed that although BBB endothelial integrity was maintained, infectious virus particles were able to pass through the endothelial monolayer by endocytosis/exocytosis-dependent replication pathway or by transcytosis [26].

Although some researchers confirmed the hypothesis that ZIKV was not able to damage BBB [24,25], others showed a selective disruption of BBB by ZIKV using *in vitro* and *in vivo* studies on three different strains of ZIKV (ZIKV-H; ZIKV-PR; ZIKV-U) [27]. *In vitro*, primary human brain microvascular endothelial cells BMECs were infected by ZIKV and tight junctions 'analysis showed that some were upregulated such as ZO-1 and other junctions were down-regulated (Occludin and Claudin-5). While *in vitro*, BBB permeability was not affected even at high viral load, *in vivo* studies showed a significant disruption of BBB integrity in C57 BL/J mice infected with ZIKV-H.

Another Flaviviridae, West Nile virus WNV was considered for better understanding of RNA viruses neuroinvasion and BBB disruption with controversial results between several studies [28–30]. WNV-infected endothelial cells HUVECs resulted in loss of tight junctions claudin-1 and JAM-1 proteins but not occludin or ZO-1 [28]. Subsequently, lysosomal proteins degradation dependent on the GTPase dynamin and microtubule-based transport were observed. These results proposed that WNV used several pathways to cross BBB. Among these, endocytosis and degradation of *trans*-membrane proteins of the tight junction, degradation of basal membranes through production of matrix metalloproteases, stimulation of cells (immune, endothelial) to secrete pro-inflammatory cytokines that disrupt tight junctions. In addition, *in vitro*, WNV (NY99) strain was able to cross the endothelial barrier formed of primary infected HBMEC without disrupting its integrity [28]. During WNV replication, adhesion molecules VCAM1 and E-selectin were upregulated proposing that endothelial cells 'infection could help the migration of leukocytes, which can be linked to the viral penetration into the brain *via* 'Trojan Horse Mechanism' known also as cell-associated virus transport [22]. Type I interferon IFNAR signaling in astrocytes was reported also to be critical for BBB integrity maintenance [30,31]. *In vitro*, Daniels et al., 2014 showed that adding type I IFN to murine endothelial BMEC infected with WNV maintained BBB integrity without changes in tight junctions and decreased the viral passage through the endothelial layer. To confirm their result that IFNAR signaling in astrocytes improves *in vitro* BBB integrity in response to WNV, *in vivo* experiments were conducted on Ifnarfl/fl Gfap-Cre mice. In WNV-infected mice, an increase of BBB permeability, a viral neuroinvasion and an increase in mortality rate were observed with selective depletion of IFNAR in astrocytes.

A full understanding of pathways followed by Flaviviridae virus to disrupt BBB would be helpful in identifying special molecular targets and allow the progress in drugs against flavivirus neurological symptoms. Also, these mechanisms can help in predicting the way the novel Flaviviridae SARS-CoV-2 counteracts with BBB.

4. Pathways exploited by SARS- COV 2 for neuroinvasion and BBB disruption

COVID-19 may generate severe neurologic symptoms including headache, nausea, vomiting and disorders such as strokes, Guillain-Barre syndrome, and encephalopathies [32,33]. Several reports have attempted to characterize and reveal the relationship between SARS-CoV-2 and neurological complications.

The scarcity of clinical data make it difficult to understand why some people have neurological symptoms and others do not. This maybe due to the viral load associated with severe cases although the correlation between SARS-CoV-2 detection, viral load and neuroinfectivity is not fully understood. Further researches are required to explain the infectivity of SARS-CoV-2 in the brain.

Researchers reported that SARS-CoV-2 neuroinvasion happens following three main phases [34]. The viral invasion into the CNS is the first phase. This phase is followed by the neural infection phase where SARS-CoV-2 infects, reproduces and kills neural cells through ACE-2 *via* Spike1 protein subunit while the S2 subunit of ACE-2 allows viral cell membrane fusion [12,35]. The last phase is the immune-mediated CNS response to fight the virus [36].

Related to the first phase of SARS-CoV-2 neuroinvasion, viral invasion into the CNS happens through neuronal retrograde dissemination or retrograde axonal transport where the virus can invade from the nerve "ending" such as the peripheral nerves, and by the mechanism of active transport within the neurons [37]. This active transport occurs precisely *via* the motor proteins kinesin and dynein, and *via* microtubules, travel in a retrograde approach and reach the CNS [38]. These neurons could be motor, sensory and most often olfactory neurons. Particularly, after an intranasal infection, viruses can infect the olfactory receptor neurons, pass through the neuroepithelium of the olfactory mucosa to arrive to the olfactory bulb, reach the mitral cells and the olfactory nerve then spread to the hippocampus and different brain structures. The

suggestion that SARS-CoV-2 can enter the CNS *via* this olfactory route was recently considered [21].

Another pathway far SARS-CoV-2 neuroinvasion is the vascular or hematogenous route where the virus remains free for a period of time before it infects the endothelial cells of BBB. This period as well as the quantity of the virus are not determined until day.

To better understand SARS-CoV-2 passage through BBB, researchers studied S1 subunit passage through BBB considering that if the viral binding protein passes through BBB, it is expected that these proteins allow also the virus to cross the BBB. To investigate whether S1 protein can cross BBB, Rhea et al., 2020 intravenously injected radio-iodinated S1 (I–S1) in male mice and showed that I–S1 crossed BBB through adsorptive transcytosis [39]. 10 min after intravenous injection, the brain was collected and divided into eleven regions including olfactory bulb, striatum, hypothalamus, hippocampus, thalamus, cerebellum, midbrain, medulla, frontal cortex, parietal cortex, occipital cortex. The analysis showed that I–S1 reached all brain areas without differences among it [39]. Researchers also reported that I–S1 intranasal administration reached the brain with ten times lower level that the intravenous injection. Murine ACE2 was participating specially in I–S1 brain and lung uptake but not other organs (kidney, liver, spleen). Moreover, recent studies proposed that SARS-CoV-2 might bind to various receptors other than ACE2 [40]. The authors compared SARS-CoV-2 Spike proteins to those of SARS-CoV and showed that SARS-CoV-2 S proteins and SARS-CoV are extremely identical, with a sequence identity of 77%. The difference between both viruses is that SARS-CoV-2 S protein is somewhat more positively charged than SARS-CoV S protein, first one containing four more positively charged residues and five less negatively charged residues. Due to these positive charges, SARS-COV-2 maybe linked to negatively charged regions of other molecules. Analysis of the S protein binding to the host ACE2 receptor exhibited a 30% higher binding energy for SARS-CoV-2 than for the SARS-CoV S protein.

Another significant indication that SARS-CoV-2 can enter the CNS would be the recognition of the virus in cerebrospinal fluid (CSF). To address this issue, Alexopoulos et al., 2020 investigated the pathophysiologic mechanism of encephalopathy in COVID-19 patients, ICU hospitalized in University Hospital in Athens, and focused on CSF analysis and BBB disruption as well as COVID-19 antibody production in CSF. They detected CSF anti–SARS-CoV-2 antibodies using ELISA assay. 50% of patients have high CSF antibody and disrupted BBB [33]. Interestingly, CSF was normal and SARS-CoV-2 negative. These observations exclude the direct brain invasion by SARS-CoV-2 and confirm the findings of Al Saeigh et al., 2020 who studied the status of SARS-CoV-2 in CSF of two COVID-19 patients showing neurological problems [41]. Controversially, SARS-CoV-2 RNA was detected in CSF but not in nasopharyngeal swab of a 24 years old man with meningitis/encephalitis associated with SARS-CoV-2 [42].

5. Immunopathogenesis of SARS-CoV-2 in CNS

In normal healthy conditions, BBB controls the passage of immune cell into CNS and allows only the passage of specific immune cells responsible of maintaining the immune surveillance in CNS. These innate and adaptive immune cells include lymphocytes and macrophages [43]. During viral infections, the microvascular endothelial cells in BBB are activated allowing the entrance of infected immune cells into CNS through Trojan Horse mechanism [44].

The immunopathogenesis of SARS-CoV-2 is not well-defined till day although experimental analysis specified that COVID-19 patients had improved inflammatory response to the virus with high levels of cytokines and chemokines, involving TNF-α, IFN-γ, interleukin-1 receptor antagonist IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10 [45,46]. High amounts of cytokines and chemokines were linked to CNS dysfunctions. An increase of TNF-α was associated with cognitive problems with four-fold increase [47] while IFN-γ induced synaptic degeneration in Alzheimer Disease [48].

This response, known as a cytokine storm 'CS' is generated by the stimulation of numerous white blood cells (B cells, T cells, NK cells, macrophages, dendritic cells, neutrophils, monocytes) and tissue cells (epithelial and endothelial cells) [49]. In the brain, CS can be considered as a crucial factor to cause BBB disruption [34,50]. Monocytes and lymphocytes penetrate into the vessel walls and cause neuroinflammation, neurodegeneration and demyelination [50].

Consequently, SARS-CoV-2 infection can raise the risk of neurodegenerative diseases such as Alzheimer's disease AD, Parkinson's disease PD as well as many neurological diseases including stroke, seizure and encephalopathy *via* diverse immune paths including CS, autoimmune system activation. In fact, studies reported that AD and SARS-CoV-2 were linked together taking into consideration the role of Apolipoprotein E ApoE, cholesterol transport protein apolipoprotein [51]. Researchers showed that adding cholesterol to cells from blood serum using ApoE improves the entry of pseudotyped SARS-CoV-2 and the infectivity of the virion in elderly [48]. ApoE e4e4 (homozygous) genotype linked with a 14-fold raise in risk of AD compared to e3e3 genotype [52]. ApoE e4e4 alleles increases risks of severe COVID-19 infection [53]. Moreover, SARS-CoV-2 contributed to the development of PD through CS release in the CSF thus perturbating the neurotransmitters 'production and aggravating the neurodegeneration process [54]. In addition, neuroimaging studies showed that SARS-CoV-2 patients had ischemic and hemorrhagic strokes with a prevalence of 0.2–1% of patients [55,56]. This can be due to CS with high levels of pro-inflammatory cytokines IL1β, IL-6, and TNF-α, known to increase the risk of ischemic and hemorrhagic strokes [57]. Also, seizure and encephalopathy were observed in SARS-CoV-2 patients as a result of auto-immune-mediated injury due to the abnormal emission of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α [58].

Understanding the probable immunologic pathways in CNS of COVID-19 patients is essential to prevent the advance of neurological problems, especially in AD, PD, stroke, seizure and encephalopathy patients.

6. Lipid metabolism remodeling upon coronavirus replication

As previously mentioned, SARS-CoV-2 is an enveloped virus surrounded by a bilayer of lipids (phospholipids, cholesterol) and proteins (E, M, S, N protein). Phospholipids are amphipathic biomolecules including saturated and unsaturated fatty acids playing crucial biological functions. In case of infection, viruses enter the host cell, replicate within the cell and exit. The membrane phospholipids are vital in the viral life cycle as these lipids are involved in the combination of the host cell and viral membrane, viral replication, endocytosis and exocytosis [59,60]. In light of the importance of lipids in viral life cycle, a vital question is whether targeting lipid metabolism can be used to fight SARS-CoV-2.

Several studied reported an increase in lipid metabolism in cells after viral infection where the virus used host cells' lipid metabolism to propagate [61,62]. It has been revealed that phospholipids membranes are crucial for replication of positive-strand RNA viruses [61]. The vital function of Phosphatidylethanolamines PE in replication of Tomato bushy stunt virus TBSV was highlighted by Xu et al., 2015 who found that TBSV can supplement the sites of viral replication in yeast and plant cells with PE [63]. To characterize the

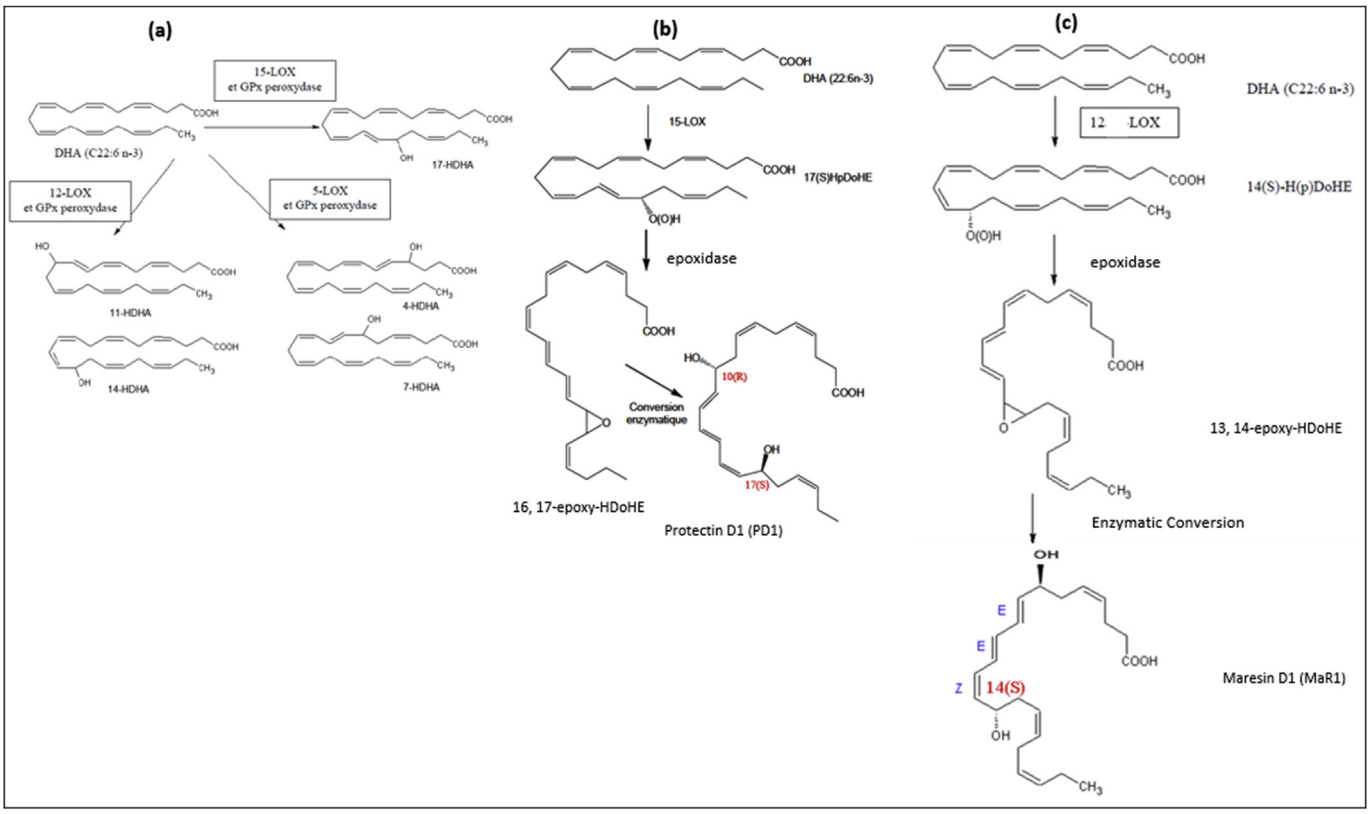

Fig. 2. Schematic representation of mono and di-hydroxylated-DHA derivatives mechanism: (a)Production of 11-hydroxy-DHA and 14-hydroxy-DHA from 12-LOX activity, 4-hydroxy-DHA and 7-hydroxy-DHA from 5-LOX activity, (b) Production of Protectin D1 PD1 through DHA lipoxygenation by 15-LOX to initially form 17 (S)-HpDoHE and that enzymatic epoxidation of 17 (S) -HpDoHE allows the formation of an epoxy intermediate which results in the synthesis of 10 (R), 17 (S) -dihydroxy-docosa4Z, 7Z, 11E, 13E, 15Z, 19Z-hexaenoic acid or protectin D1 (PD1), (c) Production of Maresin1 through DHA lipoxygenation by 12-LOX followed by epoxidase to produce an epoxy intermediate 13,14-epoxy HDoHE which results in Maresin1 formation.

changes in host lipidome, Yan B et al., 2019 executed ultra-high performance liquid chromatography–electrospray ionization–quadrupole–time of flight-mass spectrometry UPLC-ESI-Q-TOF-MS-based lipidomics upon Enterovirus A71 EV-A71 and coxsackievirus A16 CV-A16 infections. They showed that 47 lipids in 11 lipid classes were considerably disturbed after EV-A71 and CV-A16 infection. Arachidonic acid AA, docosahexaenoic acid DHA, docosapentaenoic acid DPA, and eicosapentaenoic acid EPA, were constantly upregulated with EV-A71 and CV-A16 infection. When testing the antiviral activity of AA, DHA and EPA, researchers found that supplying cell cultures exogenously with these unsaturated fatty acids significantly inhibited EV-A71 and CV-A16 replication [64]. These results suggest that adding excessive exogenous polyunsaturated fatty acids including AA, DHA, EPA might disrupt the specific lipid pathways modulated during the viral replication. Similarly, inhibitory effects of exogenous PUFA, Linolenic Acid LA and AA, were observed in human coronavirus 229E HCoV-229E replication [64]. Lipidomic analysis revealed that infected cells with HCoV-229E coronavirus have higher level of glycerophospholipids and fatty acids and that LA and AA metabolic axis were perturbated.

All these data highlight the importance of lipid metabolism regulation that could be a druggable target of coronavirus infections.

7. Anti-inflammatory and neuroprotective potential of docosahexaenoic acid as well as bioactive lipid mediators

Docosahexaenoic acid DHA was recognized to disable enveloped viruses and reduce proliferation of microorganisms [65]. Also, it showed an anti-inflammatory potential and neuroprotective effect against ZIKV infection since SH-SY5Y cells pre-treated with DHA and infected with ZIKV, had lower viral load at different times of infection [66]. In addition to DHA, some bioactive lipid mediators derivative from AA, EPA and DHA (lipoxins, resolvins, protectins and maresins) were recognized to reduce inflammation, increase phagocytosis of macrophages and decline microbial load.

Considering this, it is recommended that these PUFA as well as their metabolites might assist as endogenous anti-viral products and that human can be vulnerable to SARS-CoV-2 in case of PUFA/metabolites'lack [67].

To better understand the production of DHA bioactive lipid mediators, we discussed in this section different mechanism involved (Fig. 2, Fig. 3). In fact, DHA can be oxygenated by various lipoxygenases LOX [68]. Mono, Di and Tri-hydroxy-metabolites of DHA are known. The main mono-hydroxy metabolites of DHA are 11-hydroxy-DHA and 14-hydroxy-DHA from 12-LOX activity, 4-hydroxy-DHA and 7-hydroxy-DHA from 5-LOX activity and 17-hydroxy-DHA from 15-LOX activity. These enzymatic reactions require the presence of glutathione peroxidases GPx peroxidase [69,70]. Mono-hydroxy derivatives of DHA have the ability to inhibit platelet aggregation due to exogenous AA, adenosine-5′-diphosphate (ADP) or induced by collagen [71]. Recent work showed that DHA undergoes lipoxygenation by 15-LOX to initially form 17 (S) -HpDoHE and that enzymatic epoxidation of 17 (S) -HpDoHE allows the formation of an epoxy intermediate which results in the synthesis of 10 (R), 17 (S) -dihydroxy-docosa4Z, 7Z, 11E, 13E, 15Z, 19Z-hexaenoic acid or protectin D1 (PD1). Protectin

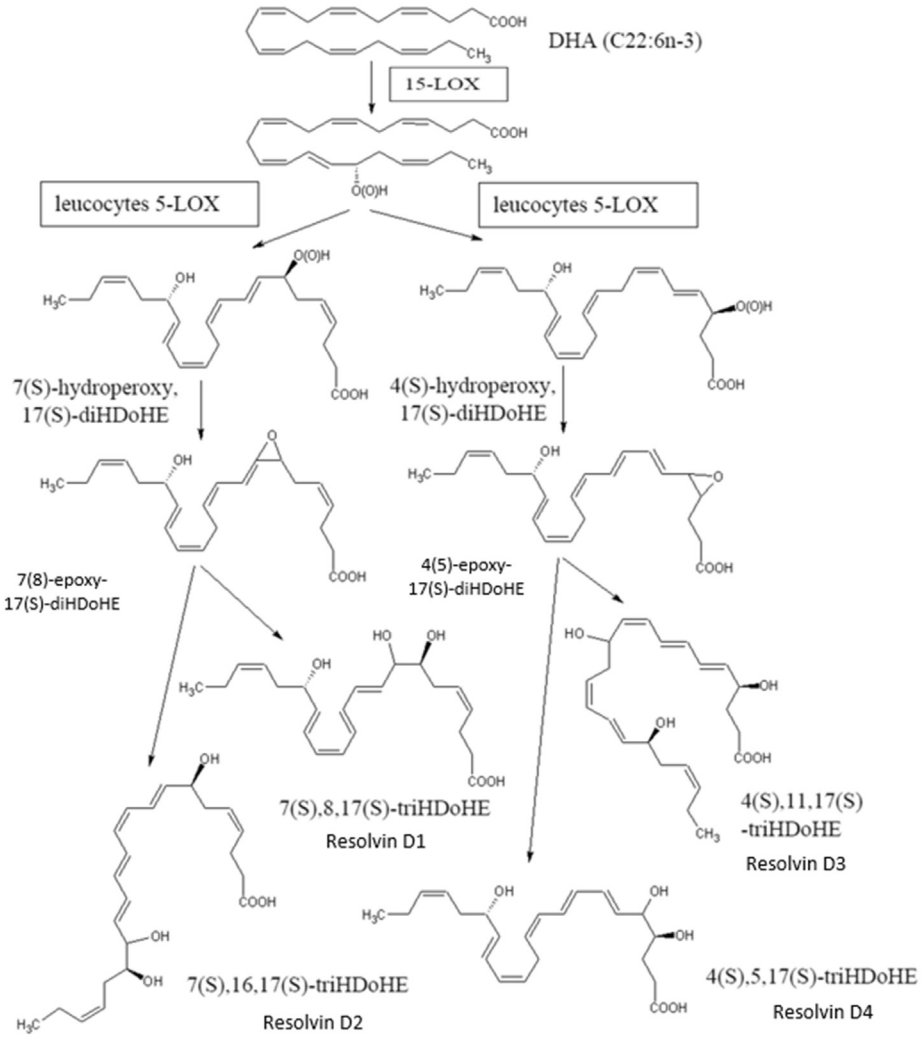

Fig. 3. Schematic representation of Resolvins (RvD1, RvD2, RvD3, RvD4) through DHA lipoxygenation from 15-lipoxygenase followed by epoxidation.

D1 (PD1) was demonstrated firstly in cells activated mononuclear cells and, in the brain, where it is named NPD1. NPD1 was called "protectin" due to its protective and anti-inflammatory effects in tissues [72–74]. PD1/NPD1 notably prevented neuronal apoptosis responsible for neurodegeneration in Alzheimer's disease [75,76]. It decreased allergic inflammation of the respiratory tract and associated asthma [77]. In strokes, NPD1 increased in the brain, decreased brain damage and inhibited leukocyte infiltration as well as pro-inflammatory genes expression [78]. Moreover, researchers characterized an isomer of PD1, called PDX with conjugated triene geometry E/Z/E for PDX and E/E/Z for PD1. PDX inhibited platelet aggregation *via* inhibition of COX-1 cyclooxygenase and the action thromboxane A2 (TxA2). This property is due to the particular geometry of the conjugated triene (trans, cis, trans) formed by double lipoxygenation [79]. Also, researchers showed that PDX is an inhibitor of COX-1 as well as COX-2 activated during ignition and that PDX decreased the release of species oxygen reactants produced by human neutrophils *in vitro*. PDX could be considered an anti-inflammatory and anti-aggregating agent. In addition to anti-inflammatory and anti-aggregating effects, PDX decreased virus replication Influenza in mice. Its production is inversely correlated with the pathogenicity of H5N1 virus [80]. Another di-hydroxy-DHA lipid mediators are Maresins with anti-inflammatory properties and "pro-resolvin" type protection [74]. 1-Maresin MaR1, a powerful mediator stimulating phagocytosis of macrophages, was first identified. Another isomer of MaR1 is formed by a double mechanism of lipoxygenation and is less potent *in vitro* and *in vivo* [81].

In addition to mono and di-hydroxylated DHA derivatives, trihydroxylated DHA lipid mediators named Resolvins or "resolution-phase interaction products" (Rv) have been proposed by Serhan et al. (2000). Resolvins were formed from n-3 PUFAs through a process triggered during inflammation and promoted by aspirin but also in the absence of aspirin. The compounds derived from EPA and DHA are called, respectively, resolvins E and resolvins D. These compounds were discovered in inflammatory exudates during the phase of resolution of the inflammatory response [82]. They act by preventing entry of neutrophils to sites of inflammation and reducing the volume of exudates. Researchers reported that RvD1, RvD2, RvD3 and RvD4 activate macrophage autophagy, reduce inflammatory cytokines and inhibit PMN infiltration (Fig. 3) [83–86].

Recently, Recchiuti A et al., showed that DHA-derived RvD1 and RvD2 reduced SARS-CoV-2 induced inflammatory responses in cystic fibrosis macrophage MΦ actions including reduction of inflammatory chemokines and cytokines [87].

We previously discussed the immunopathogenesis of SARS-CoV-2 in CNS and showed that many inflammatory responses in COVID-19 patients are accompanied with high levels of cytokines

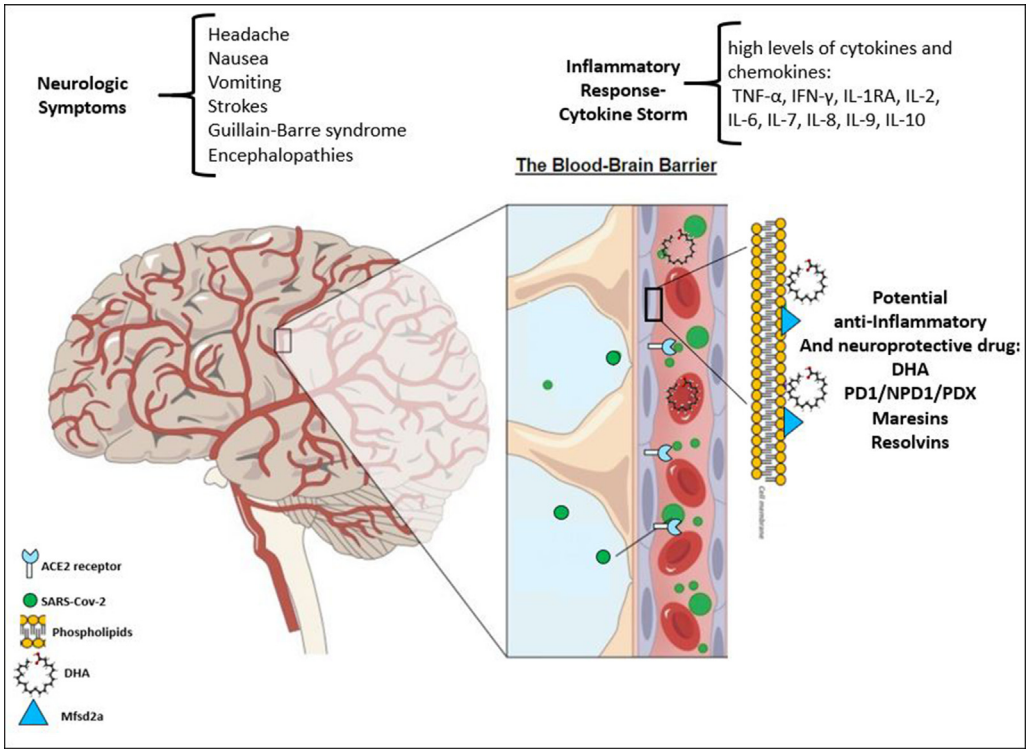

Fig. 4. SARS-Cov-2 journey to the brain: From neurological symptoms to potential anti-inflammatory and neuroprotective drug.

and chemokines, involving TNF-α, IFN-γ, interleukin-1 receptor antagonist (IL-1RA), IL-2, IL-6, IL-7, IL-8, IL-9, IL-10 [45,46]. Thus, DHA and lipid bioactive species such as resolvins, protectins and maresins could be potential candidates to be developed as new therapeutics to fight SARS-CoV-2.

8. Effect of SARS-CoV-2 on DHA passage across BBB

DHA, crucial for brain growth and neural development, is highly enriched in brain phospholipids including phosphatidylcholines PC, phosphatidylethanolamines PE and phosphatidylserines PS. A reduction in DHA level in the brain was found in patients with neurodegenerative diseases such as Alzheimer and Parkinson. DHA is synthesized de novo from its precursor alpha-linolenic acid 18:3 n-3 but this conversion rate in human is low. Thus, DHA should be imported to the brain and pass through BBB. We previously studied the passage of DHA across BBB and showed that different lyso/phospholipids are privileged carrier of DHA to the brain [88–90]. Recently, a transport protein expressed in human brain microvascular endothelial cells hBMECs named Mfsd2a, was reported as the main carrier mediating the brain uptake of DHA in form of lysoPC-DHA [91]. When hBMEC were infected by ZIKV, ZIKV was able to decrease Mfsd2A at the protein level *both in vitro* and *in vivo* [92]. Also, ZIKV infection impaired the lipid homeostasis by blocking lysoPC-DHA uptake and altering the major mechanism by which DHA enters the brain. Administration of exogenous DHA to infected mice by ZIKV SZ01 increase Mfsd2A level in brain and suppressed ZIKV RNA in the brain at day 5 and day 7 after DHA administration [92]. An important question is whether SARS-CoV-2 is able to down-regulate the expression of Mfsd2A in BBB endothelial cells. If so, the transport of DHA to the brain will be affected thus allowing less penetration of DHA to the brain which can be problematic for patients suffering from neurodegenerative disease. Hence, studying the effect of SARS-CoV-2 on Mfsd2a is crucial to know whether the DHA metabolism in the brain is affected or not.

9. Conclusion

In COVID-19 patients, neurological complications were observed during infection including headache, nausea, vomiting in addition to several neurological disorders. Considering effects of SARS-CoV-2 infection in CNS, a risk of permanent sequelae in the CNS might occur due to BBB disruption. Recent evidence revealed that BMEC of BBB can be infected by SARS-CoV-2 due to the expression of ACE2, receptor of SARS-CoV-2. This infection can lead to an inflammatory response known as Cytokine Storm where high levels of cytokines and chemokines were ex-pressed. In addition, a lipid remodeling was linked to SARS-CoV-2 infection hence proposing the potential of lipid metabolism regulation as a druggable target for CoVs infections [67]. In fact, DHA as well as its bioactive lipid mediators such as protectins (PD1/NPD1/PDX), maresins and resolvins are known with anti-inflammatory and neuroprotective effect. These biomolecules are potential candidates as new therapeutics to fight SARS-CoV-2 at stage II and stage III of the disease (Fig. 4). Several clinical trials are on their way in COVID-19 patients and in older people to estimate whether omega-3 PUFA diet enhancement could defend patients against COVID-19. Further studies of the biosynthesis, lipid metabolism and target molecules would allow a better understanding of the physiological importance of omega-3 PUFA and bioactive lipid mediators in maintaining tissue homeostasis, and also as potential therapeutic targets for inflammation in case of viral infection. Also, a deep comprehension of SARS-CoV-2 neuroinvasion pathway allow drug targeting to decline the burden of neurological manifestations of SARS-CoV-2.

Author contributions

M.H has designed, written and planned the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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