Chapter

4-Hydroxynonenal Is Linked to Sleep and Cognitive Disturbances in Children: Once upon the Time of COVID-19

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Abstract

The better prognosis of COVID-19 in children conferred a higher survival rate, but a higher prevalence of post-COVID sequalae, including insomnia and defective cognition. COVID-19 triggered oxidative stress, with hyperlipidemia correlated with susceptibility to severe COVID-19. Consequently, lipids peroxidation could be a likely candidate for disease progression and sequalae. Hence, this overview explored one of the commonly studied lipid peroxides, 4-hydroxynonenal (4-HNE), in terms of gamma-amino butyric acid (GABA) and glutamate. Higher glutamate and lower glutamine, a GABA substrate, triggered severe COVID-19. Increased glutamate and inflammatory cytokines induced GABA endocytosis, reducing the anti-inflammatory and antioxidant effects of GABA. Defective glutathione antioxidant was detected in Down syndrome, the latter was associated with severe COVID-19. Increased 4-HNE, due to consumption of electronic devices and flavors containing 1-bromopropane, was increased in inflammatory neurologic disorders. A higher hippocampal 4-HNE triggered excitotoxicity and cognitive deficits. Hippocampal inflammation and loss were also evident in COVID-19. 4-HNE might play role in disturbing sleep and cognition in children during COVID-19, a hypothesis that could be verified in future research by redeeming 4-HNE in the sputum and urine of children. Currently, supplying children with optimum dietary antioxidants, while rationalizing the use of flavors is to be encouraged.

Keywords: COVID-19, insomnia, 4-Hydroxynonenal, cognition, GABA, lipid peroxidation

1. Introduction

Until early January 2023, over 660 million cases were diagnosed with coronavirus disease (COVID-19), most cases residing in Europe with much less cases in Africa, and the United States being the most affected country [1]. When first recognized in late 2019 and early 2020, COVID-19 was thought of as an 'adult and older' disease, exempting the younger population. Later, this revelation was falsified by positive infected cases found among neonates and children. Despite lower death rates at

younger ages, COVID-19 survivors are mainly those in the pediatric age group. The milder disease was related to lower immune responses in children [2].

Knowing that COVID-19 has affected 6.3% of children aged 5–14 years old from December 30, 2019 till September 13, 2022 [3] would give us clues about the magnitude of post-COVID in children, even if definite evidence is still missing [4]. Reports outlining the possibility of asymptomatic disease occurring in children [5] suggest that the global prevalence of COVID in children may be much higher than the registered cases. In contrast, other studies highlighted that children were especially afflicted by hyperinflammatory multisystem syndrome [6–8]. The issue arose when some studies detected that recurrent infection is likely to occur in school children, compared to pre-school age, and that some of the affected children tested negative for viral antigen and antibodies and they did not shed the virus [9–11], which can lead us to infinite unexplored areas of research targeting whether the virus remains dormant or not, for how long and where, in the neurological system and/or elsewhere. Are there late-onset sequalae that could affect the future quality of life of young generations or even be transmitted to their offspring after decades? The anonymous fate of viral infection in children who survived but did not shed the virus should draw the attention of investigators toward the outcomes of COVID-19 on various aspects, including cognition as one crucial vector in childhood determining the ability to learn, develop new skills, and have a future fruitful life.

During the post-COVID period, survivors suffered neuropsychiatric symptoms, including anxiety and mood disturbances [12]. Such neuropsychiatric sequalae were attributed to the viral invasion of the brain [13] and neural control over the immune system [14]. In their retrospective cohort study, Taquet, Geddes, et al. [15] noticed a higher liability for insomnia during 6 months post-COVID, one plausible explanation was the impact of inflammatory cytokines over neuroendocrine sleep mediators [16].

Although a direct link between insomnia and liability for a more severe COVID-19 was not conclusive, yet inferences could be made based on previous studies showing that persons who had less than 7 hours of daily sleeping were three times more vulnerable to getting a flu attack [17]. An association between disturbed sleep or even prolonged sleep and a state of low-grade systemic inflammation was suggested [18, 19], the latter impaired the immune defenses against the respiratory pathogens [16, 20, 21], added to a higher risk of developing pneumonia [22]. The deleterious effects of disturbed sleep over immunity were also emphasized in Module 2 of The National Institute for Occupational Safety and Health (NIOSH) [23] declaring more than 50% decline in the production of antibodies following influenza vaccination in presence of sleep shifting, compared to regular sleep.

As the susceptibility to COVID-19 is higher with cardiovascular diseases, diabetes mellitus (DM), and obesity, and as dyslipidemia is common among these vulnerable groups [24–26], a causal relationship might exist between lipid metabolism and COVID-19 morbidity. Apart from the structural, non-structural, and accessory proteins identified for severe acute respiratory syndrome virus (SARS-CoV-2), lipid-based structures remain to be identified, especially when knowing their pivotal role in viral fusion, entry, and replication and that the host lipid profile is altered following COVID-19 [27, 28]. The involvement of lipids in promoting the creation of severe acute respiratory syndrome (SARS-CoV-2) progeny is becoming increasingly an interesting entity that awaits further exploration. Interestingly, insomnia has been reported to alter lipid metabolism and trigger lipid peroxidation [29]. Both insomnia and lipid peroxidation were associated with cognitive decline [30, 31]. In this context, this overview will focus on the relationship between COVID-19, insomnia, and

4-hydroxynonenal (4-HNE), as the most studied among lipid peroxides, on one side, and cognitive defects, on the other side.

2. COVID-19 in children: insomnia and cognitive defects

The American Academy of Sleep Medicine [32] has quoted from the Centers of Disease Control (CDC) that sleep disturbances among middle- and high-school students were highly prevalent. This prevalence was also noticed in survivors of COVID-19 who experienced long-term insomnia [33] with younger age being more vulnerable [34]. During COVID-19, higher liability to insomnia was also reported in students, compared to workers, and in undergraduates, compared to postgraduates [35, 36].

Novel stressors were superimposed with the emergence of COVID-19, including locking down at home, studying in an isolated environment with no social interactions, lacking friends, missing both physical activities and teamwork-based learning, having one or more of beloved family members affected, added to dealing with stressed parents [37]. Learning at home has posed a greater stressful challenge to parents whose anxiety was transferred to their children [38]. All these stressors contributed to higher anxiety in children, and subsequent sleep issues [39], including, inability to fall asleep, insufficient duration of sleep, excessive sleep duration, nightmares, and unstable sleep timings. In turn, disturbed sleep, by triggering mood swings, caused a further reduction in social interactions [40], and impaired psychological and physical well-being [41]. Interestingly, being home alone, using electronic devices during studying, playing, or chatting, were associated with poor sleep quality in children with autism spectrum disorder (ASD) [42].

Attention, as one of the cognitive domains, tended to decline with insomnia. Focused attention, detected by responding to a specific stimulus while overlooking other stimuli, was reduced with insomnia [43]. Vigilance (sustained attention) or the ability to keep alertness over time [44] was negatively affected by insomnia with reduced accuracy and prolonged time needed to perform vigilance-related tasks [45]. Similarly, shifting attention or the ability to adapt and modify the focus of attention, requiring a higher level of cognition [46], was defective in cases with insomnia [47]. However, some other studies did not prove these correlations, especially for the simplest form of attention, focused attention [48, 49].

Another cognitive domain, memory, was negatively impacted by insomnia [50, 51], whether working memory or that of the implicit (procedural) or explicit (declarative) categories. These three memory categories correspond to the inability of keeping information for a short period [46], learning new skills, and recalling a new learned material after a delay, respectively [52]. In a meta-analysis, there was a mild correlation between insomnia and working memory, yet the authors declared that results could be biased by the heterogenicity between studied groups in different studies. Other studies denied such an insomnia-memory relationship [48, 53].

Whatever is the magnitude of controversy regarding the correlation between insomnia and cognitive defects, most studies agreed about the correlation between stress and both cognition [54, 55] and sleep, especially, at a young age [56].

What links cognition to sleep at the neuronal level? In terms of memory, the role of glutamate, the main excitatory neurotransmitter in the brain, in the encoding and consolidation of memory through binding to its ionotropic receptors, N-methyl-D-aspartate (NMDA), and its metabotropic receptors (mGLuRs), respectively, has been established [57, 58]. Li et al. [59] in a meta-analysis of the African population

concluded that the higher glutamate, and the lower its byproduct, glutamine, the more severe would be COVID-19 and related cognitive defects.

In astrocytes, glutamate is converted by glutamine synthetase to glutamine, the substrate of both gamma-aminobutyric acid (GABA) and glutamate [60]. GABA, the main inhibitory neurotransmitter in the mammalian brain, is also modulated, through NMDA activation when glutamate is released, then presynaptic auto-receptors $GABA_B$ stimulation, mediating GABA endocytosis [61]. In the brain, more than 50% of synapses are GABAergic [62], signifying the pleiotropic effects of GABA.

3. Gamma-aminobutyric acid linking sleep and cognition

GABA is an amino acid present in plants, bacteria, fungi, animals, and humans [63–65]. GABA in vertebrates is synthesized and metabolized (as shown in **Figure 1**) [66, 67].

GABA acts on two types of receptors, the fast ionotropic or ligand-gated ion channel, $GABA_A$, and the slow metabotropic or G protein-coupled receptor, $GABA_B$. The binding of GABA to $GABA_A$ results in chloride influx and a fast hyperpolarization of postsynaptic neurons. While $GABA_B$ receptors are present in presynaptic and postsynaptic [68]. Postsynaptic $GABA_B$ stimulation produces a slow, but long-term hyperpolarization. Presynaptic $GABA_B$ activation reduces the release of many neurotransmitters, including GABA itself, yielding either an excitatory or inhibitory brain signaling, depending on whether the suppressed neurotransmitter was

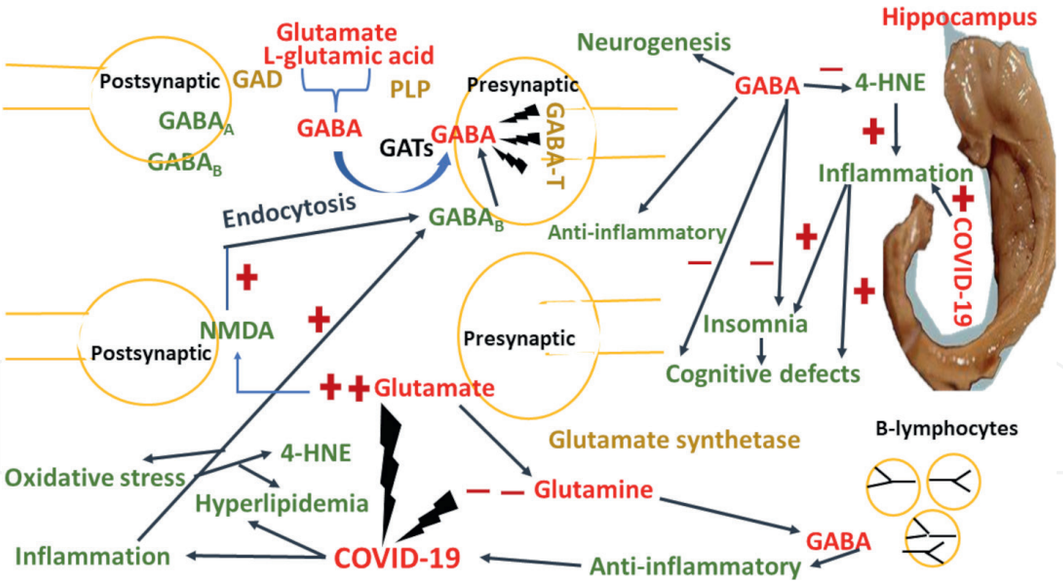

Figure 1.
GABA, glutamate, 4-HNE in COVID-19-related insomnia and cognitive defects. GABA in vertebrates is derived from L-glutamic acid or its salts, glutamate, by a decarboxylation reaction, catalyzed by GAD, and using PLP as a cofactor. After its release, GABA is uptaken by GATs 1, 2, and 3 as well as BGT-1 and metabolized by GABA-transaminases (GABA-T). Upon glutamate release, it simulates NMDA, with subsequent presynaptic $GABA_B$ activation, mediating GABA endocytosis. Increased glutamate, along with reduced glutamine, aggravates COVID severity. GABA is secreted from B-lymphocytes to exert anti-inflammatory effects. GABA promotes antioxidants, reducing lipid peroxides, including 4-HNE. COVID-19 triggers inflammation and oxidative stress. Both COVID-19 and increased hippocampal 4-HNE cause inflammation and neurodegeneration, precipitating insomnia and cognitive decline, which could be antagonized by GABA anti-inflammatory and neurogenesis effects. GABA: Gamma-aminobutyric acid; GAD: Glutamic acid decarboxylase; PLP: Pyridoxal 5′-phosphate; GATs: GABA transporters; BGT: Betaine GABA transporter; GABA-T: GABA-transaminases; Fe^{3+}: Ferric; GSH: Glutathione; NMDA: N-methyl-D-aspartate; 4-HNE: 4-Hydroxynonenal; COVID-19: Coronavirus disease.

inhibitory or excitatory. This means that if auto-receptors' presynaptic $GABA_B$ is stimulated, GABA release is dampened leading to a depolarizing postsynaptic current, or disinhibition. If a heteroreceptor $GABA_B$ was activated, glutamate release could be suppressed, which would favor an inhibitory status [69].

From functional perspective, GABA is implicated in sleep regulation and memory enhancement [70]. GABA deficiency can lead to insomnia, anxiety, and impaired stress responses [71–73]. The established role of GABA in sleep and sedation led to the wide use of benzodiazepines (BZs) as hypnotics and anxiolytics, acting by enhancing the binding of GABA to its receptors, $GABA_A$ [74, 75]. Unfortunately, BZs are associated with a high risk of tolerance and dependence [76] which mitigated their long-term use.

Despite the crucial role of GABA in the processes of sleep and cognition, it is not the only one, as inflammatory factors seem to contribute as well. In COVID-19, during the cytokine storm, excessive amounts of pro-inflammatory cytokines are produced, of which the tumor necrosis factor-alpha (TNF-α) induced the endocytosis of $GABA_A$, possibly rationalizing the associated sleep disturbances.

In the cognition domain, fast-spike GABAergic interneurons play a crucial role in the generation of electroencephalographic gamma rhythms [77], as well as hippocampal theta rhythm, corresponding to exploratory behavior [78]. Inhibitory postsynaptic potentials (IPSPs), generated by GABA, assist memory acquisition in rodents and humans [79, 80], and the progression to memory consolidation requires $GABA_B$ activation [81]. This GABA-cognitive function was experimentally verified when the passive avoidance learning of mice and rats was inhibited after the blockade of $GABA_B$ using baclofen [82, 83].

Furthermore, by promoting neurogenesis, GABA enriches long-term memory and learning processing [84]. This was emphasized in stressful conditions when mice with depressive-like symptoms exhibited defective neurogenesis and reduced microglia [85], along with reduced survival in neural stem progenitor cell culture [86]. In ASD, decreased glutamic acid decarboxylase (GAD), $GABA_A$, and $GABA_B$ were observed in postmortem specimens [87], with $GABA_A$ reduction possibly underlying the co-existing delayed linguistic abilities [88], along with behavioral deficits; the latter being also demonstrated in transgenic animal models [89].

Although multiple sclerosis (MS) is mainly a disease of young adults, it is the most common neurologic disorder due to immunologic dysfunction in children and adolescents [90]. In MS, where 65% of patients have disturbed memory and attention, low plasma GABA was detected [91]. Recent reports revealed aggravated or de novo symptoms of MS associated with COVID-19 [92]. Hence, GABA might be a likely candidate for COVID-related cognitive derangement.

4. Inflammation, oxidative stress, and GABA: key targets in COVID

A growing body of evidence supports the secretion of GABA and its precursors, glutamine, and glutamate, from murine and human B-lymphocytes, [93]. While $GABA_A$ reduces T-cell response to antigens [94] and dampens inflammation, it endorses regulatory T-cells [95]. In turn, T-cells enhance the expression of GABA receptor subunits [96]. Additionally, GABA transporter-1 (GAT-1), found only on antigen-primed T-cells, arrested the proliferation of CD4+ and CD8+ T-cells [97]. Such GABA immunomodulatory effect could prevent the tissue damage elicited by inflammatory responses in cases of autoimmune diseases, as inferred from rodent models of

DM and MS [98–100]. In patients with DM, the secretion of TNF-α and interleukin (IL)-6 (IL-6) from T-cells was successfully inhibited using GABA [101, 102].

Such systemic anti-inflammatory potentiality of GABA was detected also in macrophages and dendritic cells of rodents and humans, expressing the respective fast $GABA_A$ and slow $GABA_B$ receptors [103]. GATs dampen the functions and release of pro-inflammatory cytokines as demonstrated in a mouse model of autoimmune encephalomyelitis (EAE) [97]. Thus, it was not surprising to find that the most common subtype of $GABA_A$ in the brain, (α1β2γ2), was also expressed in immune cells [104]. Conversely, immuno-stimulation and cytokines release promoted the neuronal sequestration of extracellular GABA [67]. In the brain, neuroinflammation, vascular insufficiency, and the pro-inflammatory cytokines, such as TNF-α, interferon-gamma (IFN-γ), IL-6 and IL-1β enhanced GAT expression, favoring GABA degradation [105–108].

In the context of lung diseases, GABA, along with enhanced $GABA_A$ and $GABA_B$ activities could limit acute lung injury in rodent models and ameliorate clinical outcomes in humans on ventilation [109, 110]. As an inhibitor of platelet aggregation, GABA, by inhibiting the formation of the thromboxane A2 [111], might have an additional clinical privilege in patients whose pulmonary thrombosis is attributed to the severe COVID-19 [112, 113]. These assumed benefits of early treatment with GABA in COVID-19 were verified in mice infected with mouse hepatitis virus (MHV-1) [114], another coronavirus whose symptoms mimic those of COVID-19 [115].

The COVID-associated anxiety and stress could have resulted in lowered immunity [116], which could be reversed using GABA as was emphasized in human volunteers when oral GABA administration resulted in electroencephalographic evidence of relaxed alertness and anti-stress effects (higher alpha-to-lower beta) [117], while increasing salivary IgA [118], as a non-invasive index of enhanced upper respiratory immunity against bacteria and viruses [119].

Interestingly, extracellular glutamine, the GABA precursor, was implicated in viral replication of both DNA and RNA viruses to which SARS-CoV-2 belongs, by incorporation into the Kreb's cycle after conversion by glutaminase (GLS) to alpha-ketoglutarate (α-KG), so that the lack of glutamine hampered rhinoviruses replication [120]. Presumably, if GABA synthesis is inhibited, glutamine would be redirected to promote viral replication and, in case of viral infection, defective GABA synthesis would be anticipated secondary to the incorporation of glutamine in the viral replication cycle.

Knowing that COVID-19 can precipitate oxidative stress [121, 122] while GABAergic neurons are especially susceptible to the neuro-damaging effects of the reactive oxygen species (ROS), generated during oxidative stress [123], makes both GABA and oxidative stress likely candidates for aggravating the sequalae of COVID-19.

Hypercholesterolemia might perpetuate viral infections as was the case in mice infected with lymphocyte choriomeningitis virus (LCMV) [124]. Some viral infections and related treatments can induce long-term changes in lipid metabolism as well. After 12 years of SARS-CoV, survivors had higher cell membrane phospholipids, namely, phosphatidylinositol and lysophosphatidylinositol, attributed to corticosteroid administration during the infection [125]. In the post-infection period of SARS-CoV, lysocardiolipin acetyltransferase (LCLAT), phosphoinositide phosphatase (PIP), and diacylglycerol (DG) kinase, enzymes involved in lipid metabolism, were upregulated [126].

Coronaviruses consume the intracellular membranes of host cells to build their own replication nests called "double-membrane vesicles (DMVs)," where it preserves

its own viral proteins and robbed host factors, to ensure a suitable lipid bedding for a successful viral replication [127].

Of interest to our discussion is the increased total cholesterol (TC) in patients with COVID-19, favoring viral invasion, with a positive correlation to the severity of symptoms [93]. The lipid changes might be attributed to hypoxia and were also shared with patients having a chronic obstructive pulmonary disease (COPD) [128]. On the other hand, normal lipid metabolism seems preemptive in the context of pulmonary and neuronal disorders as sphingolipids were implicated in protection from a lung injury, added to their anti-inflammatory, anti-coagulant, along with their neuroprotective effects [129, 130]. Hyperlipidemia and oxidative stress during COVID make lipids peroxidation likely candidates for post-COVID syndrome.

5. Lipid peroxidation

Oxidative stress is conceived as an imbalance between oxidants and antioxidants, in favor of oxidation. In physiology, such oxidative stress is minimal and well-equilibrated in a process known as "the redox potential." It is noteworthy to mention that an imbalance in the antioxidant direction is deleterious and causes "reductive stress" [131].

Conversely, when the antioxidant mechanisms are overwhelmed, oxidative stress occurs. The consecutive reversible oxidative stress and irreversible oxidative damage are to be blamed for many pathologic conditions [132, 133]. With defective antioxidant mechanisms such as in the case of vitamin E (alpha-tocopherol) or vitamin C deficiency, excess reactive oxygen and nitrogen species are produced. The issue is that a propagation chain reaction perpetuates lipid peroxidation [131] as shown in (**Figure 2**). The interruption of chain reaction occurs when two free radicals are conjugated or when antioxidants break the chain.

Lipid peroxidation was formerly known for oils and fats in our diet. It involves oxidative damage to cellular structures, including cell membranes in plants and animals, causing cellular death. This destructive process includes the generation of lipid radicals, the uptake of oxygen, the re-organization of double bonds in unsaturated lipids, and the production of breakdown products such as alcohols, ketones, alkanes, aldehydes, and ethers. Lipid peroxidation results in an easily breakable cell membrane with plenty of polyunsaturated fatty acids (PUFAs) and transition metals. Lipid peroxidation reduces membrane fluidity and makes it more permissible and easily invaded. Apart from the loss of cell membrane integrity, protein synthesis is disrupted, as well as macrophage function, along with derangement of chemotactic signals and altered enzyme activity [134]. All membranes of cellular structures are damaged, including those of mitochondria, microsomes, peroxisomes, and cell membranes [135]. Lipid peroxidation toxicity affects the liver, kidneys, and to our interest, neurological structures, where it takes part in neurodegenerative, inflammatory, and infectious diseases [136].

Considering the brain as a susceptible organ to oxidative stress, the intracellular antioxidant, free glutathione (GSH) plays a crucial role by eliminating peroxides [137] in a reaction catalyzed by glutathione peroxidase (GSH-Px), oxidizing GSH to GSH disulfide (GSSG) [138]. Thus, the GSH/GSSG can be used as a determinant of the redox status of cells [139]. Defective GSH was previously correlated to Down syndrome in children [140]. Recently, Down syndrome was correlated to severe COVID-19 [141].

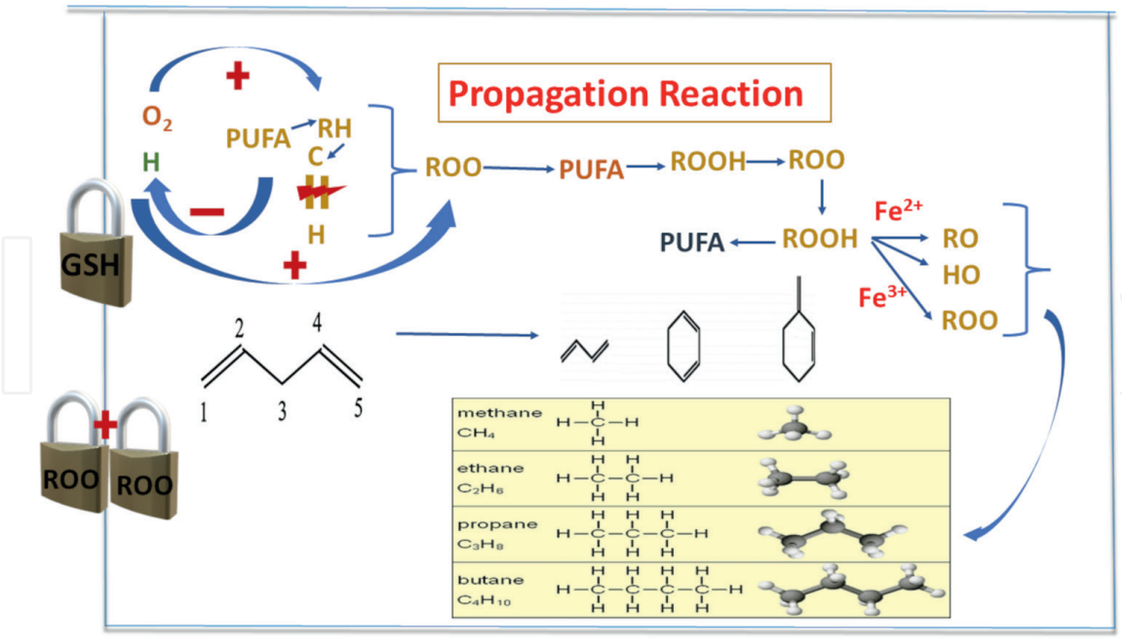

Figure 2.
Propagation reaction of lipid peroxidation. Lipid peroxidation is initiated with hydrogen subtraction and oxygen addition. Hydrogen subtraction is promoted in PUFAs by the presence of a double bond of the RH group, leaving the carbon with an unpaired electron. When combined with oxygen, ROO is produced, generating ROOH, capable of repeating the hydrogen subtraction from another PUFA, perpetuating the chain reaction. When lipid peroxides interact with Fe^{+2}, RO radicals are produced, when the interaction involves Fe^{+3}, ROO radicals are generated. These reactions will end up with cytotoxic aldehydes and hydrocarbon gases as ethane. The interruption of chain reaction occurs when two free radicals are conjugated or when antioxidants, such as GSH, break the chain. PUFA: Polyunsaturated fatty acids; RH: methylene; ROO: Peroxyl; ROOH: Hydroperoxide; $Fe^{2+:}$ Ferrous; RO: Alcoxyl; $Fe^{3+:}$ Ferric; GSH: Glutathione.

Most of brain GSH is derived from the reducing action of GSH reductase (GR) over GSSG to get back GSH. Another less amount of GSH can be synthesized *de novo* from glutamate, cysteine, and glycine [142].

In contrast to the antioxidant GSH, one of the lipid peroxides, 4-hydroxynonenal (4-HNE), an α, β-unsaturated aldehyde, is a potent neurotoxin, derived from the oxidation of ω-6 PUFA of cell membranes [143], such as arachidonic acid, linoleic and linolenic acid.

6. 4-Hydroxynonenal

4-Hydroxynonenal (4-HNE) is described as a short-chain reactive carbonyl compound [144], having amphiphilic properties yet with lipophilic tendency [143]. Its high electrophilicity makes it reactive to the amino acid residues, namely, cysteine (Cys), histidine (His), and lysine (Lys), in a decrescendo order. 4-HNE can adduct to the cysteine residue of the "flippase" enzyme (amino phospholipid-translocase), an enzyme that maintains lipid bilayer asymmetry by an ATP-dependent process [145]. Forming Michael adducts with nucleophilic sites, 4-HNE can interact with cellular DNA, lipids, and proteins [146]. The destiny of 4-HNE protein adducts is either proteolysis or covalent cross-linking. Additionally, 4-HNE can inactivate GR, reducing the antioxidant ability of GSH [147]. In turn, physiological concentrations of GSH can revert 4-HNE protein adducts to their unadducted condition [148].

The metabolism of 4-HNE occurs by oxidative and reductive processes, employing enzymatic and non-enzymatic pathways [144], in addition to conjugation to GSH catalyzed by the glutathione-S transferases (GST), which contributes to a major part in the detoxification process [149]. Although all these detoxifying processes are present in the mitochondria [150], yet it seems that the mitochondria play little role in 4-HNE degradation in intact tissue.

In the lungs, GST is more active than the liver, then comes the brain in the third place, however, the respiratory capacity to metabolize 4-HNE is limited by slow oxidative-reductive pathways, unlike the liver [151, 152]. 4-HNE can be detected in human breath and sputum [153] and its metabolites can be recovered in urine [154]. A slow metabolism of 4-HNE was previously reported when dealing with rat hearts and kidneys, along with other tissues [155].

To our knowledge, HNE concentration at or below 1 μM might be physiological, with in vitro toxicity at 10 μM–1 mM [156]. The physiological roles of HNE include, but are not limited to [see **Table 1**] [157–164]. Dianzani [156] mentioned that, in pathologic conditions, the high concentrations of 4-HNE suppress mitochondrial oxidation, lysosomal enzyme activity, adenyl cyclase, sodium pump, protein synthesis, and cell proliferation. Also, while physiological 4-HNE concentrations can affect proteins, favoring proteolysis of the deformed proteins [165], only extra-physiologic concentrations of 4-HNE can increase membrane fluidity [166].

In inflammatory disorders such as osteoarthritis, 20 μM HNE suppressed the high nuclear factor-kappa beta (NF-κB) induced by TNF-α overexpression in human

Targets of HNE	**Role**
Neutrophils chemotactic factor [157]	Increased inflammatory response to invading pathogens
AC [158]	Catalyze the breakdown of ATP to yield cAMP
PLC [159]	Hydrolysis of inositol phospholipids in cell membranes, yielding the intracellular second messengers: IP_3 and DAG
Caspases [160]	Protease enzymes that mediate programmed cell death, leading, for example, to tumor suppression and axonal degeneration
Hsp 70 [161]	Increased antigens delivery to APCs Suppression of inflammation
Aldose reductase [162]	Cytosolic NADPH-dependent oxidoreductase that catalyzes the reduction of monosaccharides, for example, the reduction of glucose to sorbitol, the first step in glucose metabolism
Hem oxygenases [163]	The degradation of heme to CO, biliverdin and heme iron, mediating anti-inflammatory, anti-apoptotic, and potential anti-viral functions
γ-GCS [164]	Catalyzes the production of γ-glutamylcysteine from both glutamate and cysteine, and other glutamylpeptides and can be used as predictor of defective GSH redox

AC: Adenyl cyclase; ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; PLC: Phospholipase C; IP_3: Inositol 1,4, 5-triphosphate; DAG: diacyl glycerol; Hsp 70: Heat shock proteins 70; APCs: Antigen-presenting cells; NADPH: Nicotinamide adenine dinucleotide phosphate hydrogen; CO: Carbon monoxide; γ-GCS: γ-glutamyl cys synthetase; GSH: Glutathione.
At physiologic concentration, HNE seems to exert immunostimulatory activity by enhancing neutrophils' chemotactic factor, increasing the production of multiple intracellular second messengers, such as cAMP, IP_3, DAG, mediate tumor suppression, and might promote axonal degeneration and aging, along with immune-stimulatory, anti-inflammatory, anti-apoptotic, and possibly anti-viral functions. HNE catalyzes glucose metabolism and interestingly, can increase antioxidant activity.

Table 1.
Physiological targets stimulated by hydroxynonenal (HNE).

osteoblasts [167]. While most studies focused on the link between 4-HNE and hepatic insult, few of them found that 4-HNE was also implicated in multiple respiratory and neurological disorders, such as bronchial asthma, COPD [168], Alzheimer's disease (AD), and Parkinson's disease (PD) [169]. The ability of 4-HNE to diffuse from one organ to another [170] might indicate the accumulation of HNE in the lungs, for instance, can affect the brain, and vice versa. Fortunately, GSH was able to suppress 4-HNE protein adducts in the liver, lungs, and brain [152].

In COPD, HNE adducts were increased in bronchial, bronchiolar, alveolar, and endothelial cells as well as macrophages and neutrophils. In alveolar epithelium, HNE adducts were inversely correlated to forced expiratory volume in 1 sec and positively linked to the pro-fibrotic cytokine, transforming growth factor-beta (TGF-β) [171]. In rat alveolar epithelial cells, HNE induced glutamylcysteinyl glycine (GCS), the rate-limiting enzyme in GSH synthesis [172], and enhanced the expression of antioxidants by recruiting nuclear factor erythroid 2-related factor-2 (Nrf2) [173, 174].

In vitro exposure to mild stress assisted the accelerated GSH-mediated removal of HNE and enhanced resistance to oxidative stress [175], which might not apply to chronic stress when antioxidants are consumed.

Measuring HNE in umbilical cord plasma, it was increased in full-term newborns exposed to acidosis and in full—as well as pre-term neonates experiencing asphyxia when compared to healthy controls [176]. A suggested role in autoimmunity was reported in children with systemic lupus erythematosus (SLE) when plasma HNE was increased, especially during the active disease stage [177].

The brain is a vulnerable organ that can be affected by oxidative stress owing to its relatively lower antioxidant capacity against a higher oxygen consumption rate, added to the abundance of PUFAs in neuronal cell membranes [178]. Upon 12-day exposure of rats to oral 1- bromopropane (1-BP), a cleaning agent for electronic and optical instruments and an intermediate in the synthesis of pharmaceuticals and flavors, the animals demonstrated behavioral evidence of impaired cognition with underlying oxidative stress as shown by the reduced level of GSH versus increased GSSG, owing to the inhibitory effect of 1-BP over GR, with subsequently increased 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) [179]. The increased 4-HNE was also replicated in patients with AD showing mild cognitive dysfunction [180]. It is to be noted that while human exposure to 1-BP is by inhalation, yet, in experimental animals, the inhalation route might not yield similar neurological effects as the oral route.

4-HNE can form adducts with glutamate transporter, excitatory amino acid transporter 2 (EAAT2) [181], dopamine transporter, sodium pump [182], dopamine 1 (D1)-like transporter [183], and immunoglobulins [184]. In cultured rat cerebrocortical neurons, HNE uncoupled cholinergic and glutamatergic receptors from the GTP-binding proteins [185]. In patients with ischemia–reperfusion and stroke, plasma HNE was elevated [186]. Immunohistochemical assay of the brain lesions in patients with the progressive demyelinating disease, multiple sclerosis, and the dominant autosomal disorder, Huntington's disease (HD), detected increased HNE [187, 188], along with elevation of the inflammatory marker C-reactive protein in serum of patients with advanced HD. In rat hippocampal cell culture, 10 μM HNE hampered sodium pump activity, resulting in increased intracellular free Ca^{2+} and predisposition to excitotoxicity [189]. The hippocampus is well known for its relevance to both cognition [190, 191] and insomnia-related cognitive issues at all ages, including children [192, 193], and inflammation and loss were recently reported in COVID-19 [194].

7. Hydroxynonenal- and GABA-targeted therapies

Based on the presumptive involvement of HNE in COVID-related insomnia and subsequent cognitive dysfunction, HNE-targeted therapy might offer an exit doorway that might rescue the young generation. For instance, carnosine, a dipeptide (β-alanyl-L-histidine) abundant in mammalian skeletal muscle, can inhibit the cross-linking of HNE protein adducts [195], and its analogs showed a similar neuroprotective effect as emphasized in rats [196].

Nutritional support seems crucial to sustaining the growth and development of childhood processes, including those related to their emotional, cognitive, and behavioral aspects. Above all, supplying dietary antioxidants, including vitamin E, vitamin C, and glutathione, could be helpful. The consumption of wheat germ oil, sunflower oil and seeds, hazelnuts, and peanut butter, as sources of vitamin E, and red and green pepper, orange, kiwi, and broccoli, providing vitamin C, with recommended daily dietary allowances at 4–13 years old of 7–11 and 25–45 mg, respectively [197].

Despite the controversies regarding the extent of systemic GABA to cross the BBB [198–200] as quoted by Tian et al. [114], supplying dietary GABA could add some benefit as an adjuvant to COVID treatment, especially since GABA has antioxidant properties [201, 202], GABA can be obtained from tomatoes, rice, soybean, and fermented food [70]. It is worthwhile that this policy can be adopted in the context of cognitive affection in children whose anxiety and insomnia could be the major contributing factors to the post-COVID syndrome.

8. Conclusion

Lipid peroxidation, along with inflammatory crisis, plays a crucial role, not only in the prognosis of COVID-19 but also in neurological sequalae, namely, sleep and cognitive issues, by affecting both GABA and glutamate neurotransmission.

4-HNE might have some role in both COVID-19 and its neurological sequalae, triggering hippocampal inflammation and neurodegeneration, by disturbing glutamate/ GABA neurotransmission.

Perhaps a nutritional supply of antioxidants and abstaining from the consumption of flavors could support our children to maintain optimal sleep and develop cognitive skills. The rationale use of electronic devices is also recommended. A more vigorous investigation is still needed to verify the hypothesis of 4-HNE involvement and to explore the feasibility of GABA—and HNE-targeted therapy in children who survived COVID-19 with residual issues regarding sleep and cognition.

Acknowledgements

No acknowledgments. Funding: The author declares that no funding resources were provided.

Conflict of interest

The author declares no conflict of interest.

Notes

- COVID-19 triggers insomnia and cognitive defects.
- Higher glutamate, with subsequent low GABA, was associated with severe COVID-19.
- Electronic Devices and flavors could lead to increased 4-HNE.
- Increased 4-HNE caused hippocampal inflammation, an area implicated in sleep and cognition.
- Supplying pediatric nutrition with antioxidants and abstaining from flavors consumption and overuse of electronic devices might prove preemptive in COVID-19, and related sleep and cognitive issues.

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