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SPECIAL ARTICLE

Are hemoglobin-derived peptides involved in the neuropsychiatric symptoms caused by SARS-CoV-2 infection?

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Follow-up of patients affected by COVID-19 has unveiled remarkable findings. Among the several sequelae caused by SARS-CoV-2 viral infection, it is particularly noteworthy that patients are prone to developing depression, anxiety, cognitive disorders, and dementia as part of the post-COVID-19 syndrome. The multisystem aspects of this disease suggest that multiple mechanisms may converge towards post-infection clinical manifestations. The literature provides mechanistic hypotheses related to changes in classical neurotransmission evoked by SARS-CoV-2 infection; nonetheless, the interaction of peripherally originated classical and non-canonic peptidergic systems may play a putative role in this neuropathology. A wealth of robust findings shows that hemoglobin-derived peptides are able to control cognition, memory, anxiety, and depression through different mechanisms. Early erythrocytic death is found during COVID-19, which would cause excess production of hemoglobin-derived peptides. Following from this premise, the present review sheds light on a possible involvement of hemoglobin-derived molecules in the COVID-19 pathophysiology by fostering neuroscientific evidence that supports the contribution of this non-canonic peptidergic pathway. This rationale may broaden knowledge beyond the currently available data, motivating further studies in the field and paving ways for novel laboratory tests and clinical approaches.

Keywords: COVID-19; SARS-CoV-2; hemoglobin; neurotransmitters; hemorphins; hemopressins; neurology; psychiatry

Introduction

COVID-19 quickly spread from China to the rest of the world, reaching pandemic status, causing a shift in routines to prevent contamination and leaving those who survive infection by SARS-CoV-2 with a wide range of sequelae. The incidence and prevalence of affective disorders have increased strikingly as the pandemic progresses, which might first be attributed to social isolation.[1] Intriguingly, however, humans infected by SARS-CoV-2 are showing remarkable clinical findings: anxiety, depression, cognitive disorders, and dementia have been found in post-acute COVID-19 patients.[2] The post-acute COVID-19 syndrome consists of symptoms that persist beyond 4 weeks from their onset, with long-term complications.[3] When compared to samples from 2017, depression is seven-fold higher in COVID-19 survivors, whereas the pooled prevalence of anxiety was 47%, which jointly highlights a high impact of SARS-CoV-2 infection on people's mental health.[2] The retrospective study by Taquet et al.[4] provides data supporting a close causal correlation between COVID-19 and neuropsychiatric disorders. The incidence of clinical manifestations as measured within 90 days post-infection was about 18%, while dementia was detected in 1.6% of COVID-19 patients older than 65 years.[4]

Rogers et al.[5] compared psychiatric and neuropsychiatric manifestations in COVID-19 versus previous coronaviruses outbreaks: severe acute respiratory syndrome (SARS), starting in 2002, and Middle East respiratory syndrome (MERS), starting in 2012. Although some patients are able to recover without experiencing mental illness, the impacts of SARS, MERS, and COVID-19 followed similar courses.[5] Encephalopathy, stroke,

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confusion, dizziness, insomnia, and cognitive impairments are the most common neurological findings in SARS-CoV-2 infected patients.[6] The cognitive impairments associated with human COVID-19 emerged from executive functioning, memory encoding, and memory recall tasks.[7] Attention declines rapidly (over minutes) in people who have had COVID-19 at all severity levels, with greater and faster vigilance decline in tasks and mild episodic deficits, when compared to age-matched controls.[8] This body of evidence points towards an undoubted necessity for elucidating the neurobiological changes that might underpin these neuropsychiatric consequences.[9] The multisystemic nature of COVID-19 supports the hypothesis that multiple mechanisms may converge to the aforesaid post-infection clinical findings.[10,11] Therefore, the search for the mechanistic basis implicated in this neuropathology should move the spotlight in different directions.

Multiorgan compromise in COVID-19 may suggest that peripherally originated molecules are part of the multiple mechanisms producing post-infection clinical manifestations. Indeed, early erythrocyte death has been observed in COVID-19,[12-14] which would cause excess production of hemoglobin-derived peptides (HDPs). A wealth of robust evidence shows that HDPs are able to control cognition, memory, anxiety- and depression-like behaviors through different mechanisms,[15] and may be unbalanced in disease states.[15-17] In this sense, the present review is dedicated to fostering neuroscientific evidence that supports working hypotheses on the involvement of HDPs in post-COVID-19 neuropathology.

Mechanisms involved in COVID-19 neuropathology

Early reports at the beginning of the COVID-19 pandemic described loss of smell in infected humans; this exteroceptive disorder already suggested alterations in the central nervous system.[18] As outcomes from neuropsychiatric studies were added to the literature, the possibility that SARS-CoV-2 would exhibit neurotropism became accepted fact, supported by signs, symptoms, and diagnoses.[2] Computational analyses suggest interactions of SARS-CoV-2 proteins with human molecules governing synaptic vesicle trafficking, endocytosis, axonal transport, neurotransmission, growth factors, and mitochondrial and blood-brain barrier elements.[19] Since COVID-19 results from a viral infection, it is also plausible to hypothesize that neuroinflammation will play an essential role. Current literature reporting on COVID-19 highlights that inflammatory and immune aspects affect neural tissue, presenting as encephalitis and Guillain-Barré syndrome, among other manifestations.[20] Other reports showed an association of SARS-CoV-2 infection with diseases of the cerebral microvasculature, encephalopathy, agitation, and confusion, which might be related to cytokine-mediated changes in frontal perfusion and function.[21,22]

It is now well established that SARS-CoV-2 neuroinvasion through the trigeminal and vagus nerves[9] and blood-brain barrier disruption[23-25] are the mechanisms of viral entry into neural tissue, causing direct effects beyond those caused by peripheral infection.[26] Activity of the viral spike protein (S) seems to be deeply implicated in blood-brain barrier disruption and leakage.[27] Therefore, changes in brain perfusion, neuronal lifespan, and microglial metabolism may be involved. Peripheral molecules overproduced during COVID-19 penetrate the brain as a result of increased permeability in astrocytic-neurovascular contact, likely influenced by nitric oxide, oxidative stress, cytokines (interleukins), and others.[28] This combination may activate central metabolic pathways capable of boosting the neurotransmission mediated by excitatory amino acids and N-methyl-D-aspartate (NMDA) receptors; such massive overactivation of pathways routes may lead to undesired excitotoxicity-mediated neuronal death.[29] Nevertheless, modifications in levels and function of other neurotransmitters would be expected, as manifested by depletions in dopamine, serotonin and norepinephrine. This downregulated neurotransmission would aid the concomitantly overactivated excitatory glutamatergic pathways, resulting in the neuropsychiatric symptoms of COVID-19.[23] Postmortem analyses performed in single-nucleus transcriptomes sampled from the frontal cortex and choroid plexus revealed that SARS-CoV-2 neuroinvasion modifies the expression of genes mediating excitatory neurotransmission, such as *VAMP2*, *SNAP25*, and *ATP6V0C*.[30,31]

Besides altering the aforementioned classical neurotransmitters, other molecules, such as neuropeptides, enzymes, and receptors, may play further roles in COVID-19 neurobiology. Despite the current lack of consistent clinical evidence on the neuroprotective effect exerted by components of the renin-angiotensin system (RAS), treatment with angiotensin converting enzyme (ACE) inhibitors, or angiotensin receptor antagonists on COVID-19-related neural damage,[32,33] it has been clearly established that ACE2 is the apparatus employed for host-cell infection by different SARS-CoV-2 variants. Interaction of the viral S protein with ACE2, a broadly expressed transmembrane dipeptidyl carboxypeptidase, is one of the mechanisms orchestrating viral infection in different tissues.[34,35] In this regard, it is plausible that some hormone peptide cascades at different tissues would be implicated in the puzzling multisystemic pathophysiology of COVID-19.

Peptides other than those belonging to the RAS are capable of acting on many targets that include interactions with angiotensinergic components. For example, HDPs released as a result of hemoglobin hydrolysis, which occurs naturally at the end of the erythrocyte life span, are able to modulate RAS. Some HDPs are capable of inhibiting ACE activity and of activating angiotensin IV (Ang IV) receptor (AT4),[36-38] a centrally expressed transmembrane protein that is characterized as an insulin-regulated aminopeptidase (IRAP)[39] and has been shown to contribute to cognitive function (memory and learning).[40,41] To date, about two dozen HDPs have been identified, opening wide avenues for investigation.[37] The neuronal metabolic pathways potentially modulated by these abundant peptides and by their interaction with the RAS during COVID-19 warrant future research.

Hemoglobin-derived peptides as an alternative pathway underlying neuropsychiatric manifestations in COVID-19

Erythrocytes, or red blood cells, are the blood components in charge of transporting gases throughout the tissues perfused by the bloodstream. These anucleate cells contain a complex of proteins with relative affinity for O_2 and for CO_2 – bicarbonate, through hemoglobin and band-3/anion exchanger 1, respectively. The purpose of this membrane-anchored protein complex is to define erythrocyte function and the erythrocyte life cycle.[42] During COVID-19, the morphophysiology of erythrocytes is dramatically affected, disturbing their biophysical properties to such an extent that cell deformation persists during the post-COVID-19 recovery phase, increasing the odds of impacting the cerebral microcirculation.[43] SARS-CoV-2 infection is able to affect erythrocyte dynamics as well as hemoglobin[13] and band-3 structure and function,[44] provoking untimely erythrocyte death through oxidative and inflammatory mechanisms.[13,45-47] The extracellular hemoglobin resulting from erythrocyte death also plays a pathophysiological role by enhancing oxidative reactions that hasten cell death.[48]

COVID-19-related early erythrocyte death may induce excess release of peptides – the aforementioned HDPs – through the action of several catalytic enzymes upon hemoglobin. These HDPs are divided in two classes, according to the hemoglobin subunits used as substrate by proteolytic enzymes: hemorphins, which result from hydrolysis of beta-globin, and hemopressins, which are produced by enzymatic proteolysis of the alpha-globin chain (Table 1). Both hemorphins and hemopressins are able to act on different targets, including the central nervous system.[13,49] Starting from the premise that HDP are pieces in the homeostatic puzzle, it is admissible that decreases in the functional population of erythrocytes and increases in HDP levels would modify the balance of tissues in which HDP targets are expressed.

To date, there are no data on HDP involvement in COVID-19. The few studies assessing the antimicrobial potential of HDPs are from assays using bacteria[51] and this does not exclude a correlation between HDPs and infections caused by other SARS-CoVs, influenza, Ebola virus, and malaria, which are known to cause hemolysis.[52-54] Existing research has focused mostly on HDP formation, usually dedicated to assessing the involvement of non-viral enzymes (aminopeptidase, cathepsins, dipeptidyl-peptidase, ACE, and others)[49] and HDP-molecular interactions regulating physiological effects. Nevertheless, the protease enzymes which form HDPs may coincide with those underlying viral infection and replication processes, such as 3CLpro.[55] This possibility and the impact of these potential protein interactions on HDP levels are matters for further studies.

Mounting evidence shows that HDPs exert effects on opioid receptors,[56] endothelial-mediated vasomotion control,[16] calmodulin-dependent cell actions, and additional modulation of the kinetics of several enzymes,[57,58] including some involved in the regulation of neuronal function. For example, HDPs are capable of inhibiting enzymes regulating enkephalin degradation[59]; ACE activity, thus reducing angiotensin II production and bradykinin degradation[49]; and catalytic actions of AT4/IRAP upon oxytocin.[60] The expression of these molecular targets in astrocytes and neurons supports the idea of a positive correlation between changes in HDP levels and the neuropsychiatric clinical manifestations of COVID-19. The plausibility of this hypothesis is further strengthened by evidence that HDPs regulate the release of neurotransmitters such as serotonin, norepinephrine, dopamine, and glutamate,[38,61] whose unbalance underlies COVID-19 clinical manifestations.[4,6,20,23,24,28]

HDPs modulate the dynamics of neurohormones, such as adrenocorticotropin and oxytocin, which are capable of defining behaviors.[37,49] Recently, we have reported the effects of two HDPs, LVV-hemorphin 7 (LVV-H7) and LVV-hemorphin 6 (LVV-H6), on the organization of

Table 1 Bioactive peptides derived from α- and β-globin chains

Hemoglobin chain	Nomenclature	Sequence
Hbα	Neokiotorphin	Thr-Ser-Lys-Tyr-Arg
Hbα	Kyotorphin	Tyr-Arg
Hbα	Hemopressin	Pro-Val-Asn-Phe-Leu-Ser-His
Hbα	RVD-Hpα	Val-Asp-Pro-Val-Asn-Phe-Lys-Phe-Leu-Ser-His
Hbα	VD-Hpα	Arg-Val-Asp-Pro-Val-Asn-Phe-Lys-Phe-Leu-Ser-His
Hbβ	Hemorphin-4	Tyr-Pro-Trp-Thr
Hbβ	Hemorphin-5	Tyr-Pro-Trp-Thr-Gln
Hbβ	Hemorphin-6	Tyr-Pro-Trp-Thr-Gln-Arg
Hbβ	Hemorphin-7	Tyr-Pro-Trp-Thr-Gln-Arg-Phe
Hbβ	VV-hemorphin-4	Val-Val-Tyr-Pro-Trp-Thr
Hbβ	VV-hemorphin-5	Val-Val-Tyr-Pro-Trp-Thr-Gln
Hbβ	VV-hemorphin-6	Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg
Hbβ	VV-hemorphin-7	Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe
Hbβ	LVV-hemorphin-4	Leu-Val-Val-Tyr-Pro-Trp-Thr
Hbβ	LVV-hemorphin-5	Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln
Hbβ	LVV-hemorphin-6	Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg
Hbβ	LVV-hemorphin-7	Leu-Val-Val-Tyr-Pro-Trp-Thr-Gln-Arg-Phe
Hbβ	VD-Hpβ	Val-Asp-Pro-Glu-Asn-Phe-Arg-Leu-Leu-Cys-Asn-Met

Adapted from da Cruz.[50]

behavioral responses to aversion, locomotion/exploration, and depressive-like behaviors in rodent experimental models. Through different mechanisms, LVV-H6 and LVV-H7 reduced anxiety-like responses in the elevated plus maze paradigm and depression-like behavior as assessed by immobility time during forced swim tests.[62,63] The effects of LVV-H7, in particular, were dependent on oxytocin receptors, since agonistic actions upon the AT4 receptor are postulated as a path to reducing oxytocin degradation exerted by this IRAP catalytic domain in physiological conditions.[15,39,64] Consequently, the antagonism of oxytocin receptors blocked the central effects of peripherally injected LVV-H7 in naive rats. Our previous study also reported mRNA expression of beta-globin fragments (encoding HDP) in brain areas such as the frontal cortex, amygdala, hippocampus, and hypothalamus, known for organizing different behaviors.[63] In light of our recent report, the assessment of modifications in central and peripheral HDP levels is a field that should be better explored in patients displaying neurological and psychiatric manifestations of COVID-19.

While AT4 activation either by HDP or by Ang IV helps maintain homeostasis and is implicated in improvement of performance in cognitive tasks,[40,41,64-66] previous studies show that HDP levels are modified in the neocortex of patients with Alzheimer's disease.[67] It raises the need for considering changes in concentration, composition, and duration of exposure to HDP as variables to be tested in further experimental designs assessing COVID-19 consequences. This increase in brain HDP levels is robust evidence of their involvement in a dementing disease, allowing us to propose that Alzheimer's disease may share pathophysiological mechanisms with the cognitive impairments and dementia observed following COVID-19. A recent report argues that AT4 is a target for the pleiotropic actions of molecules mediating brain inflammation in rodent models of Alzheimer's disease, besides showing that oxidative stress is another pathogenic element.[65]

As stated above, AT4/IRAP has a catalytic domain that is responsible for degrading molecules such as oxytocin, which participate in the control of emotions, memory, and learning, as well as an allosteric domain with high binding affinity for the agonists Ang IV or LVV-H7.[60,68] These agonistic effects result in the activation of intracellular pathways triggered from the allosteric domain, the main molecular mechanisms through which AT4/IRAP contributes to homeostasis.[66,69,70] There is evidence that AT4 activation produces calcium influx, long-term potentials mediated by glutamate receptors,[71] and central dopaminergic and cholinergic release in neurons.[40] AT4 is functionally expressed in oligodendrocytes, astrocytes, and neurons; therefore, the activity of this receptor would be triggered by HDPs already at the terminals composing the neurovascular junction and, subsequently, within descending central pathways which control behavior.[39,41,64,70,72-74] These possible functions suggest that AT4 overactivation by HDPs could be a pathway driving the neurochemical changes seen in COVID-19.

The extent of multiorgan manifestations in the post-acute COVID-19 syndrome shows a coexistence of neuropsychiatric and hematologic sequelae,[3] which raises the possibility that hemoglobin and HDP are playing roles in both acute and long-lasting clinical signs. It is worth hypothesizing that the need for dialysis in chronic renal disease and in COVID-19 patients with compromised renal function may change hematopoiesis and erythropoietin (EPO) balance and increase levels of circulating HDP, since this therapeutic approach is likely to produce hemolysis and low hemoglobin-related anemia.[75] A stimulus for increasing the secretion of endogenous EPO or the use of exogenous EPO as a therapy may improve COVID-19-related symptoms, since this cytokine hormone is responsible for stimulating hematopoiesis.[76] These hypothetical primary benefits would result from reductions in tissue hypoxia, boosting the immune system to fight SARS-CoV, 2 and perhaps the neuroprotective effects of EPO.[77] Nevertheless, the hypoxia likely found in severe COVID-19 seems paradoxically related to low EPO levels, thus supporting the therapeutic choice of using EPO while considering possible long-term side effects.[78] Viruez-Soto et al.[79] assessed whether the high levels of EPO which occur naturally in populations living at high altitude would interfere with clinical status in COVID-19. Higher mortality rates were found in permanent residents of high altitudes with low EPO and hemoglobin levels.[79] Although the literature shows promising data on the neuroprotective effects of EPO and EPO-derived peptides,[80,81] further research is needed to unravel the potential interrelation among hypoxia, EPO, and HDP in COVID-19 patients displaying neuropsychiatric symptoms. Whether hypoxia and the activity of proteases related to SARS-CoV-2 infection would modify EPO secretion, HDP formation, and activity remains to be investigated.

Reductions in EPO levels caused by COVID-19 may result in HDP changes. This raises the possibility that the cognitive functions well known to be controlled by AT4 agonism by HDP[38,41,60,65,68,70] are impaired as a secondary consequence of reductions in EPO-evoked hematopoiesis and neuroprotection. However, the vast majority of HDPs are poorly studied in health and disease. The literature still lacks reports on a correlation among EPO, HDPs, and COVID-19 neuropathology. In regard to the wide range of mechanistic possibilities involving HDPs, the neural consequences arising from SARS-CoV-2 infection and the interrelation among hematological alterations, HDP, and long-term neuropsychiatric manifestations of COVID-19 warrants better understanding. Pathways triggered by erythrocyte death and resulting HDP release should be considered in further research, since COVID-19 neuropathology is undeniably associated with exacerbated influences of peripheral molecules on the central nervous system. Figure 1 illustrates the neurobiological mechanisms potentially involved in COVID-19 clinical manifestations.

Conclusions

How long the COVID-19 pandemic will continue to plague humanity is still unknown. Uncontrolled contagion and newly arising SARS-CoV-2 variants may cause terrible

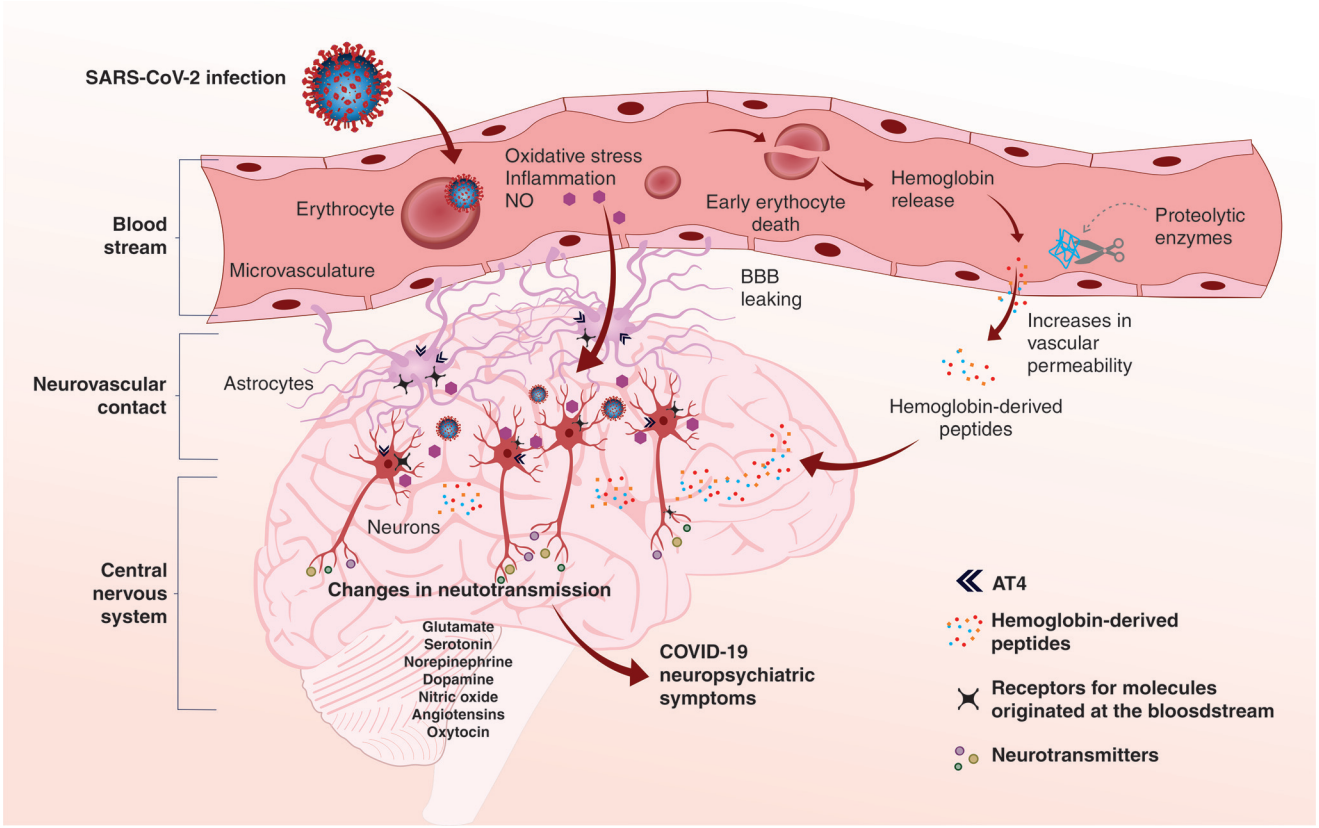

Figure 1 Representative figure illustrating the mechanisms postulated throughout the text, from early erythrocyte death induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to the neuropsychiatric manifestations of coronavirus disease 2019 (COVID-19). AT4 = angiotensin IV receptor; NO = nitric oxide.

consequences, including neuropsychiatric manifestations. Study of the systemic molecular pathways inducing neurobiological responses to COVID-19 is key. Pathways triggered by early erythrocyte death and the routes potentially influenced by HDP warrant further research, as novel approaches may emerge from deeper knowledge on these molecular mechanisms. For example, the development of drugs interfering with AT4 activity and with pathways potentially activated by HDP represent promising pharmacological treatments, either to prevent complications or to treat neuropsychiatric manifestations in COVID-19 patients. These approaches may empower the scrambling to prevent long-term damages, ultimately improving quality of life and diminishing healthcare expenditures.

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The authors dedicate this article in honor of the more than 600,000 Brazilians who have lost their lives to date as a result of denialism and negligence during the COVID-19 pandemic,[82] and in protest against the dramatic situation that Brazil is experiencing as a consequence of deep cuts to its science budget.[83]

Disclosure

The authors report no conflicts of interest.

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