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Review Article

Erythropoietin in COVID-19-Induced Neuroinflammation; EPO Plus Losartan Might be Promising

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ABSTRACT

Introduction: Neuroinflammation is the inflammatory reaction in the central nervous system (CNS) provoked by diverse insults. This phenomenon results in a cascade of release of inflammatory mediators and intracellular messengers such as reactive oxygen species. The elicited responses are the cause of many neurological and neurodegenerative disorders. Erythropoietin (EPO) has been considered effective in attenuating this inflammatory process in the CNS, yet its administration in COVID-19 needs meticulously designed studies.

Discussion: Neuroinflammation in COVID-19 due to probable contribution of renin-angiotensin system dysregulation resulting in surplus of Ang II and owing to the synergistic interaction between this octapeptide and EPO needs special consideration. Both of these compounds increase intracellular Ca^{2+} which may induce release of cytokine and inflammatory mediators leading to aggravation of neuroinflammation. In addition, Ang II elevates HIF even in normoxia which by itself increases EPO. It is implicated that EPO and HIF may likely increase in patients with COVID-19 which makes administration of EPO to these patients hazardous. Furthermore, papain-like protease of SARS-CoV2 as a deubiquitinase may also increase HIF.

Conclusion: It is hypothesized that administration of EPO to patients with COVID-19-induced neuroinflammation may not be safe and in case EPO is needed for any reason in this disease adding of losartan may block AT1R-mediated post-receptor harmful effects of Ang II in synergism with EPO. Inhibition of papain-like protease might additionally decrease HIF in this disease. More in vitro, in vivo and clinical studies are needed to validate these hypotheses.

Abbreviations: ALS: amyotropic lateral sclerosis; Ang II: angiotensin II; ARB: angiotensin receptor blocker; AT1R: angiotensin II type 1 receptor; AT2R: angiotensin II type 2 receptor; $[Ca^{2+}_i]$: intracellular calcium concentration; CNS: central nervous system, DAMP: danger/damage-associated molecular patterns; EPO: erythropoietin receptor; EPOR: erythropoietin receptor; HIF: Hypoxia-inducible factor; MAPK: mitogen-activated protein kinases; MMP: matrix metalloproteinase; MS: multiple sclerosis; NLR: NOD-like receptors; PAMP: pathogen associated molecular pattern; PRR: pattern-recognition receptors; RAGE: receptor for advanced glycation end products; ROS: reactive oxygen species; RNS: reactive nitrogen species; TBI: Traumatic brain injury; TIMP: tissue inhibitor of metalloproteinase; TLR: Toll-like receptors; TRPC: transient receptor potential canonical;

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Introduction

Neuroinflammatory cascade mediated by cytokines, chemokines, and other inflammatory mediators including intracellular messengers like reactive oxygen species in the CNS (1) eventuates into devastatingly debilitating outcomes in a time- and severity-dependent fashion. As a repairing phenomenon in a short mild form, neuroinflammation plays a significant role in neurodevelopment, neuroprotection and neuroplasticity. However, prolongation of this process may result in lifelong disabilities (2, 3). Hypoglycemia (4), ischemic brain diseases(5, 6), intracerebral hemorrhage (7, 8), traumatic brain injury (TBI) (9, 10), Alzheimer's disease (11-13), Parkinson's disease (14, 15) and other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) (16), and multiple sclerosis (MS) (17, 18) are accompanied by this pathology which might also be responsible for disorders such as epilepsy (19), depression (20, 21), obsessive-compulsive disorders (22) and schizophrenia (23). EPO, as an immunomodulator, has been shown to have attenuating effect on neuroinflammation irrespective to its origin (24-27). Although EPO's effect on the increase in blood pressure, platelets and probability of thrombophilia have been debated to be hazardous in patients, high doses (up to 400 units/kg) of this glycoprotein has been considered safe and effective in ameliorating neuroinflammatory responses such as seen in ischemic brain injuries in a few studies (27-33). Moreover, daily low dose of EPO (4000 units/day for a maximum of 2 weeks) was also reported to be effective in a patient with huge subdural hematoma who was at risk of brain death (34).

Pathophysiology of Neuroinflammation

Neuroinflammation triggered by a variety of stressors such as oxidative, traumatic or ischemic insults which result in activation of astrocytes as well as microglial cells initiate a cascade of inflammatory responses in the nervous system (35). Astrocytes while maintaining the homeostasis of neural tissue, simultaneously modulate neurotransmitter secretion and synaptic transmission. Astrocytic cells are morphologically and functionally of two lineage: radial glial-like and reactive astrocytes (36, 37). Clones of radial glial-like astrocytes exhibit characteristics of mitogenically active multipotent stem cells which generate neural cells and other astrocytes.(38, 39) Defending against pathogens or stressors is the responsibility of reactive astrocytes along with microglial and neural cells (40-42). In this process pattern-recognition receptors (PRRs) including Toll-like receptors (TLR), NOD-like receptors (NLRs), receptor for advanced glycation end products (RAGE), and scavenger, complement and mannose receptors play a crucial part (43-49).

Pathogen-associated molecular patterns (PAMPs) or host-derived danger/damage-associated molecular patterns (DAMPs) (heat shock proteins, ATP, S100B and HMGB) are recognized through intracellular PRRs (41, 50). Mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF-κB) signaling pathways activated by PAMPs and DAMPs induce expression of cascade of inflammatory proteins including ICAM-1, VCAM-1, E-selection, and iNOS.(51-54) The role of NF-κB pathway as an inducing factor in neuroinflammation in Parkinson's Disease, Alzheimer's Disease and other neurodegenerative diseases as well as in traumatic and ischemic brain injuries has been described (55-61).

In a neuroinflammatory response, cytokines (IL-1β, TNF-α, and IL-6), α-chemokines (MCP-1, MIP-1, and RANTES), and other inflammatory mediators such as cyclooxygenase-2 and matrix metalloproteinase 9 (MMP-9) are released following activation of astrocytes and microglia (62-64). MMPs are able to proteolyze the remains of extracellular matrix proteins following destruction of the brain tissue, open new routes to accommodate newly formed vessels in the injured area, regulate vascular endothelial growth factor (VEGF) release and modulate pro-inflammatory cytokines such as TNF-α (65-67). MMPs should be regulated by tissue inhibitor of metalloproteinase (TIMP), otherwise tissue destruction spreads from the inflamed core to the circumferential normal tissue, as well (68).

In neuroinflammation, blood brain barrier (BBB) is disrupted which allows the inflammatory mediators and cells to enter the brain parenchyma. Besides, as water channels, called aquaporins (AQPs) with constitutional pro-inflammatory characteristics, are dysregulated in inflammatory responses, water content of the brain parenchyma increases. This results in astrocytes swelling and migration, dysfunction of BBB, and cytokine release. (69, 70)

Amazingly, high metabolic rate and oxygen demand on one hand and the presence of vascular injury and shortage of oxygen delivery to the inflamed tissue in any type of brain injuries on the other hand, eventuates into tissue relative or absolute hypoxia in early phases (6-12 hours post-injury period) of the insult which induces hypoxia inducible factor-1α (HIF-1α). This factor promotes pro-apoptotic genes (BNIP3, NIX and NOXA) and upregulates caspase 3 [71]. Furthermore, free radicals (ROS, RNS) generated in the mitochondria in hypoxic milieu of the injured brain stabilize HIF-1α (72, 73). In normoxia, insulin-like growth factor-1 (IGF-1), thyroid hormone (T_3), cytokines (IL-β, IL-6, TGF-β, TNF-α), NF-ƙB, free radicals (ROS, RNS), thrombin, PAMPs and DAMPs upregulate HIF-1α, as well (74-80). Initially, HIF-1α release is associated with pro-apoptotic effects but after 48 hours it induces pro-survival proteomes like EPO, VEGF, glucose transporter-1, aldolase A, lactic dehydrogenase A and phosphofructokinase protein(81, 82). It is implied that in the acute phase of neuroinflammatory states accompanied by pro-apoptotic effects an urgent intervention may be of great benefit.

EPO and Neuroinflammation

Anti-inflammatory/anti-apoptotic properties of EPO have long attracted the attention of experts (83-85). In adults, this glycoprotein exerts some trophic protective effects in the brain(86, 87). Secreted or systemically administered EPO can cross the BBB slowly through extracellular pathways or transported to the brain by binding to its receptor, EPO-R (fig.1), presenting on the luminal surface of cerebral capillary endothelium (88, 89). In neuroinflammation the disrupted BBB lets this glycoprotein reach the brain parenchyma easily (89). EPO, along with EPO-R, can also be produced de novo especially in astrocytes and in the case of EPO-R, in a wide range of cells in the CNS including endothelial and neural progenitor cells (90, 91).

Proliferative effect of EPO on neural progenitor cell (NPC) in culture media has been investigated in animal studies which showed its capacity to promote differentiation of NPCs to mature neurons and oligodendrocyte in the hippocampus [92, 93]. In animal studies it was shown that

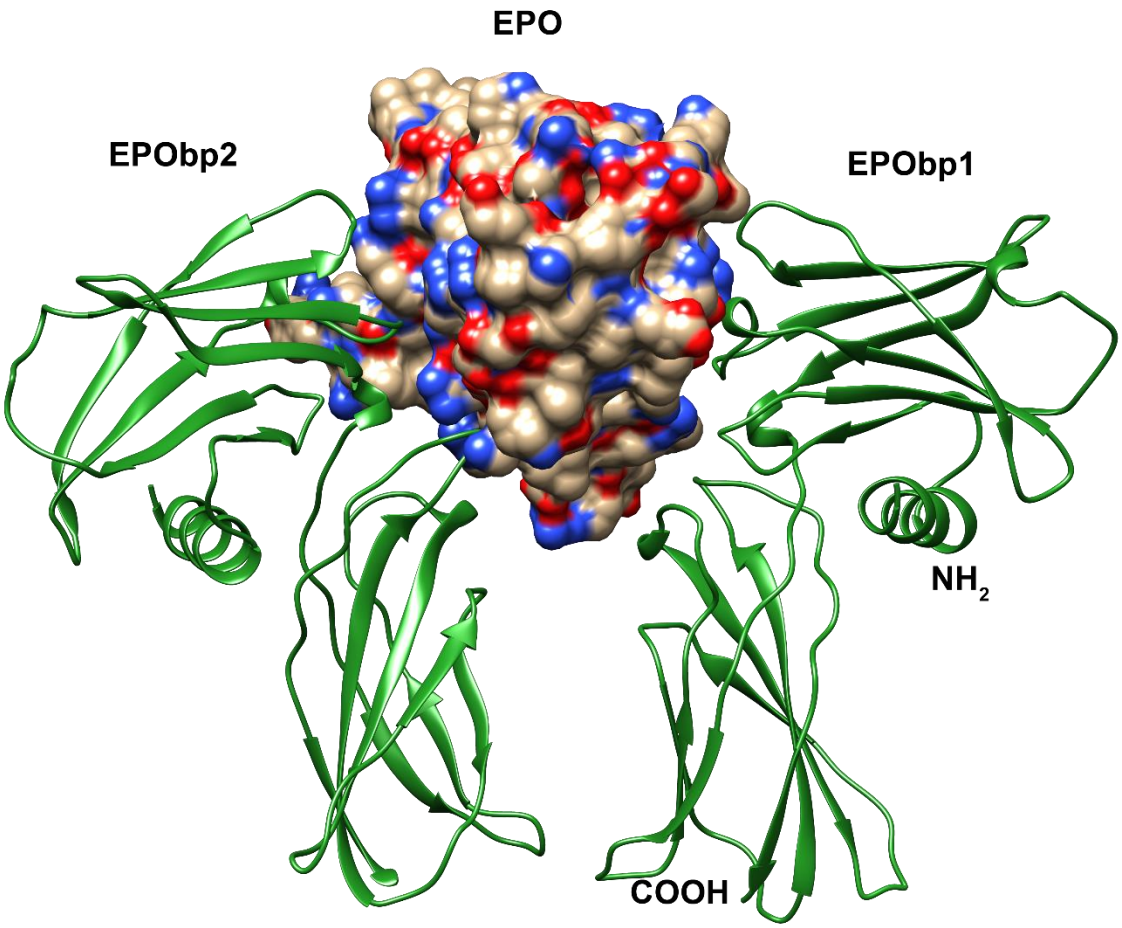

Figure 1. Cartoon overview presentation of the crystallographic structure of EPO-R in complex with surface presentation of the EPO (PDB identifier 1EER). EPO-R is shown in green color, while EPO is in color defined for each atom.

administration of EPO in the first 24 hours of brain ischemia results in induction of angiogenesis and neurogenesis, reduced neural loss and prevention of BBB disruption (94, 95). Moreover, EPO could induce expression of EPO-R, downregulate HIF-1α expression in ischemic region, decline the level of IL-β, increase sensorimotor and cognitive responses and decrease traumatic axonal injury specially in hypoxic context. (96, 97). Furthermore, upregulation of mitochondrial respiratory complex III and IV as well as regulation of neural energetics and stabilization of mitochondrial membrane potential by EPO prevents mitochondrial damage, inhibits oxygen free radicals, and cytochrome C release (98, 99). Activation of PI3K/Akt pathway by EPO was found to be effective against neural cell apoptosis (100). Janus kinase-2 (JAK-2) signaling pathway downstream to EPO-R activation in a positive cross talk with NF-kB promotes transcription of neuro-protective genes [(101)]. In addition, EPO-mediated activation of the signal transducers and activators of transcription 5 (STAT5) protein, downstream to JAK-2 signaling, leads to upregulation of B-cell lymphoma extra-large (Bcl-xL) and X-liked inhibitor of apoptosis protein (XIAP) with anti-apoptotic properties [(102)]. Elevation of Bcl/Bax ratio and prevention of release of caspase-3 and -9 by EPO lead to microglia survival without affecting their pro-inflammatory characteristics (103-105). In a

cell culture study, EPO was shown to have protective effect on microglia and astrocytes against oxidative stress injury (106). On the other hand, Inhibition of (AQP-4)-induced astrocyte swelling and downregulation of MMP-9 via increasing the expression of TIMP-1 by EPO aids in reducing neuroinflammation (107, 108).

EPO-R and EPO found on the plasma membrane of human $CD4^+$ and $CD8^+$ T cells suppress alloreactive human T-cell immunity through inhibition of downstream T-cell and IL-2 receptor signaling pathways (109).

EPO and Neuroinflammation in COVID-19

Generally, EPO administration in sepsis and infections is controversial due to its suppressive effect against the function of macrophages, documented in Salmonella infection.(110, 111) However, EPO in an animal study could improve survival in sepsis due to restoration of the aorta responsiveness to norepinephrine (NE), upregulation of eNOS and decline in iNOS (112). According to the outcome of several clinical trials that have shown similar cell protective effect and an improvement in the status of the COVID-19 patients after administration of erythropoietin, a randomized clinical trial is currently underway (113, 114). Although EPO exerts neuroprotective effects, its administration in COVID19-induced neuroinflammation as a special, yet imprecisely identified subject, needs meticulous consideration.

1.Renin-Angiotensin System (RAS) and COVID-19

A novel hypothesis, supported by a large body of literature, could attribute the pathophysiology of cytokine storm in COVID19 to the virus-induced downregulation of angiotensin converting enzyme 2 (ACE2). ACE2, while as a member of RAS family metabolizes Ang II to angiotensin [1-7], is the receptor of SARS-CoV2 on the host cell. Downregulation of ACE2 subsequent to SARS-CoV2 entry to cells leads to acute accumulation of Ang II. This sudden surplus of Ang II (whether locally produced or spilled over from the cells into the local or general circulation) results in supra-activation of type 1 angiotensin II receptor (AT1R) with all the pro-inflammatory, prothrombotic and pro-apoptotic effects eventuating into cytokine storm and tissue pathological changes (115, 116). A recent animal study showed that infusion of Ang II to swine resulted in pathological changes in the lungs similar to that of ARDS in COVID-19 (117). ACE2 deficiency was also shown to increase brain swelling and cell death in an animal model of brain ischemia (118).

It has been reported that Ang II blood level in patients with COVID-19, especially in moderate to severe form, is higher than that seen in milder cases or non-infected healthy people. The severity of the disease has also been correlated to the circulating level of Ang II (119, 120). Accordingly, administration of Ang II or applying any measure which may increase the level or effect of Ang II in patients with COVID-19 is not recommended (121).

2.RAS and Brain involvement in COVID-19

It merits mentioning that local RAS has been discovered in the brain and even in extensions of neural tissue like retina(122). Ang II contributes to some physiological functions in the brain such as the control of synaptic transmission and neuronal excitability, cognition and memory processing, regulation of autonomic responses and hormone secretion (123-125). Moreover, an angiotensinergic sympatho-

excitatory pathway in the brain connects the circumventricular area (lacking competent BBB) including subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT) to rostral ventrolateral medulla (RVLM) via paraventricular nucleus (PVN) in the hypothalamus or directly to the intermediolateral cell column in the spinal cord. Nevertheless, Ang II content in the brain should be regulated delicately as its excess may have devastating effects like oxidative stress and endothelial dysfunction (126, 127). ACE2, beyond its wide expression in the neurons, astrocytes, cerebral vascular smooth muscle cells and endothelium, has been reported in mice to predominate in circumventricular area, hypothalamus and brain stem (128-130). As this receptor of SARS-CoV2 downregulates with entry of the virus to the host cells, Ang II content increases especially in these areas if the virus reaches the brain. In addition, excess of circulating Ang II in COVID-19 may reach the brain especially at sites where BBB is incompetent or disrupted which results in AT1R over-stimulation. This effect increases ROS through activation of NADPH oxidase which leads to an increase in intracellular calcium concentration ($Ca^{2+}{}_i$) followed by inhibition of voltage-gated potassium channels resulting in inhibition of GABAergic interneurons and depolarization of glutaminergic with an excitotoxic effect (131-133). AT1R is located on both glutaminergic neurons in RVLM and GABAergic interneurons in caudal ventrolateral medulla (CVLM) (134). Furthermore, massive release of glutamate in excitotoxicity damages the function of ACE2 via shedding of its ectodomain by a member of "A Disintegrin And Metalloprotease (ADAM)" family called ADAM17 (135). Additionally, this results in further cell injury due to an increase in Ang II due to lack of available ACE2 and in exaggerated AT1R activation.

Activation of AT1R located in circumventricular area and cerebrovascular pericytes and endothelial cells by circulating or locally produced Ang II compromises neurovascular coupling and diminishes cerebral blood flow (low dose Ang II of 0.1 pmol/min leads to 23% reduction in CBF) [136, 137]. Intriguingly, it has been reported that Ang II-mediated activation of AT1R of microglial cells in the retina may result in neurovascular uncoupling and inflammation in this special type of neural tissue [138, 139]. This effect of Ang II on blood perfusion and inflammatory response in the neural tissue may explain the neuroimaging findings observed in most cases of COVID-19 (140).

EPO and Ang II

A cell culture study showed that recombinant human EPO exhibits synergistic effects with Ang II and NE on mobilization of intracellular Ca^{2+} in vascular smooth muscle cells lasting up to 60 minutes. This effect of EPO results in enhanced vasoconstriction and hypertension in the presence of Ang II (33, 141). Almost two decades ago, EPO was shown to affect Ca homeostasis in neural cells (142). Furthermore, EPO dose-dependently induces expression of TRPC channel protein up to 70% which facilitates Ca^{2+} influx. Moreover, Ang II exhibits similar TRPC-mediated Ca^{2+} current which soars up in synergism with EPO (143). Although cytosolic Ca^{2+} mediates several homeostatic pathways such as gene regulation, neural excitability, neurosecretion and synaptic plasticity, its intracellular concentration is finely regulated because any increase in its content, if sustained enough, may induce apoptosis-mediated loss of

neurons and other cells (144, 145). Besides, Ca^{2+} signaling has been linked to neuroinflammation as TNF-α was reported to enhance release of Ca^{2+} from its intracellular deposits. In addition, glutamate, ATP, cytokines and other inflammatory mediators increase the content of this ion in glial cells (146, 147). However, the interaction among EPO, Ang II and intracellular Ca^{2+} content needs further investigation due to its complexity.

Neuroinflammation generally is accompanied by excitotoxicity due to ineffective reuptake of glutamate in the synaptic cleft by excitatory amino acid transporter (EAAT) (148, 149). As mentioned earlier Ang II via AT1R contribute to this phenomenon by inhibiting glutamate transporter function in astrocytes (131, 150, 151). Intriguingly, a cell culture study elucidated that EPO in the absence of excitotoxic condition could increase calcium influx in cell culture of cortical neurons. However, EPO in excitotoxic conditions tends to repress elevation of $[Ca^{2+}_i]$, yet insignificantly. Besides, EPO could not repress the increase in $[Ca^{2+}_i]$ resulting from stimulation of metabotropic glutamate receptor (152). Bearing in mind that Ang II surplus is likely the cause of inflammatory responses in COVID-19 (115) and, on the other hand, Ang II dose dependently increases Ca^{2+} transient content in neural and glial cells (153, 154), it is legitimately expected that solitary EPO administration in COVID-19, in face of elevation of Ang II, may raise $[Ca^{2+}_i]$ in the absence of excitotoxic condition or at least may not be able to repress effectively the rise of $[Ca^{2+}_i]$ in excitotoxicity, both with probable hazardous outcome.

Ang II acts as a direct EPO secretagogue (155). Activation of both AT1R and AT2R by Ang II upregulates EPO (155, 156). Furthermore, activation of AT1R induces hypoxia-inducible factor α-1 (HIFα1) gene even in normoxia (157). This effect opposes the degradation of hydroxylated HIF through ubiquitination by von Hippel-Lindau protein (VHL) in normoxia (fig. 2) (158). Stimulation of AT2R has also been shown in a cell culture study to increase HIF1-α through a post-transcriptional regulatory pathway (159). In addition, another cell culture study demonstrated that intermittent hypoxia could activate HIF by NADPH oxidase which is by itself induced by Ang II in the CNS (160, 161). HIF1-α beyond its

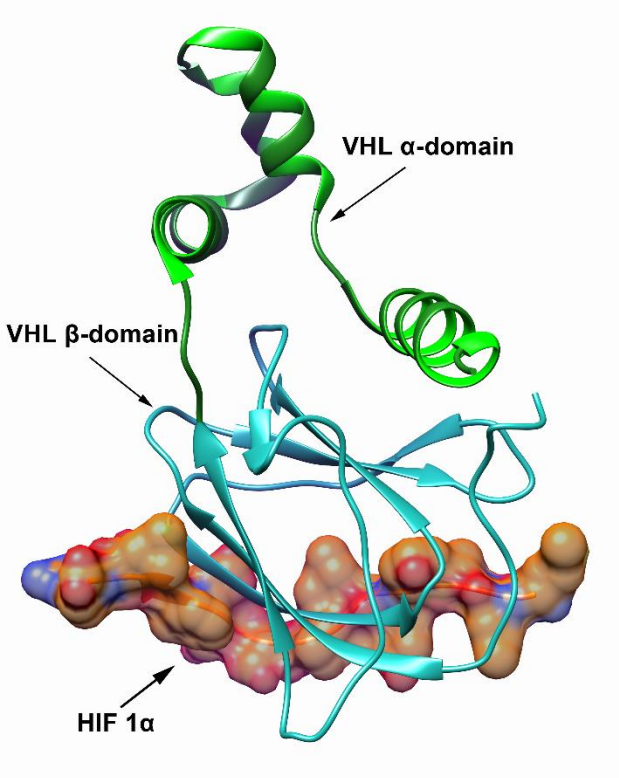

Figure 2. VHL with HIF-1α (Pdb identifier: 1lm8). VHL-α domain is depicted in green, VHL-β in blue, HIF (surface view) in defined color of each atom.

pro-inflammatory effects upregulates EPO expression (162). Thus, it is hypothetically expected that in conditions associated with higher content of Ang II (circulating, local or intracellular), like that happens in COVID-

19, local or circulating EPO production may rise.

Consequently, as to the positive feedback interactions between EPO and Ang II, EPO should be administered in patients with COVID-19 cautiously(141, 163).

Two Novel Hypotheses

EPO production may increase in COVID-19 due to the probable rise of HIF in the presence of PLpro

As mentioned before, in the presence of sufficient pressure of oxygen in the tissues, hydroxylated HIF1-α is degraded after being ubiquitinated by von Hippel-Lindau protein (VHL) (fig. 2), which is a recognition substrate component of an E3 ubiquitin ligase (158, 164). Considering deubiquitinating property of papain-like protease (PLpro) of coronaviruses (165-168), it is wise to investigate whether PLpro in cytosol of infected cells with SARS-CoV2 prevents ubiquitination-mediated degradation of HIF1-α in normoxia which may lead to a rise in local EPO, as well. If this hypothesis can be validated through in vitro and in vivo studies, discovering potential inhibitors of PLpro, as being currently attempted vigorously, might provide the means to suppress the pro-inflammatory effect of HIF in COVID-19.

EPO alone might be hazardous in COVID-19-Induced Neuroinflammation; losartan may reverse the harmful pathway

In an animal study synergistic neuroprotective effect of EPO and olmesartan (an AT1R blocker) in stroke was reported (169). In addition, neuroprotective and anti-inflammatory effects of losartan in retinal ischemia-reperfusion injury and diabetic retinopathy have been explained in animal studies (170, 171). Accordingly, it seems that due to the complex cellular interactions of Ang II and EPO, administration of a combination of EPO and an angiotensin receptor blocker (ARB) is more rational than solitary administration of EPO in attenuating COVID-19-induced neuroinflammation. Wisely, while EPO exerts anti-apoptotic and anti-inflammatory effects, ARBs block post-receptor untoward pathways of the surplus of Ang II in COVID-19. Considering the following data, it is legitimate to add losartan (instead of olmesartan) to EPO in treating neuroinflammation in COVID-19:

1.losartan apart from being an ARB was demonstrated in an in silico study to have the ability to change the conformational shape of PLpro of SARS-CoV2; other ARBs did not show such favorable results (fig. 3) [(115)]. In this context, losartan can be considered a potential inhibitor of PLpro.

2.losartan according to a bio-informatic study could decline the affinity of SARS-CoV2 to ACE2; other ARBs did not show sufficient docking energy (115),

3.losartan has low water solubility and like olmesartan which is lipid soluble may penetrate into the brain tissue effectively (172, 173).

4.losartan compared to olmesartan has modest antihypertensive property so that the patients with COVID-19 may experience less probability of hypotension with losartan (174).

5.Considering retina as a neural tissue, losartan was demonstrated to attenuate retinal neurovascular decoupling in patients with diabetic retinopathies(170).

Subclinical and randomized clinical trials are needed to prove these hypotheses.

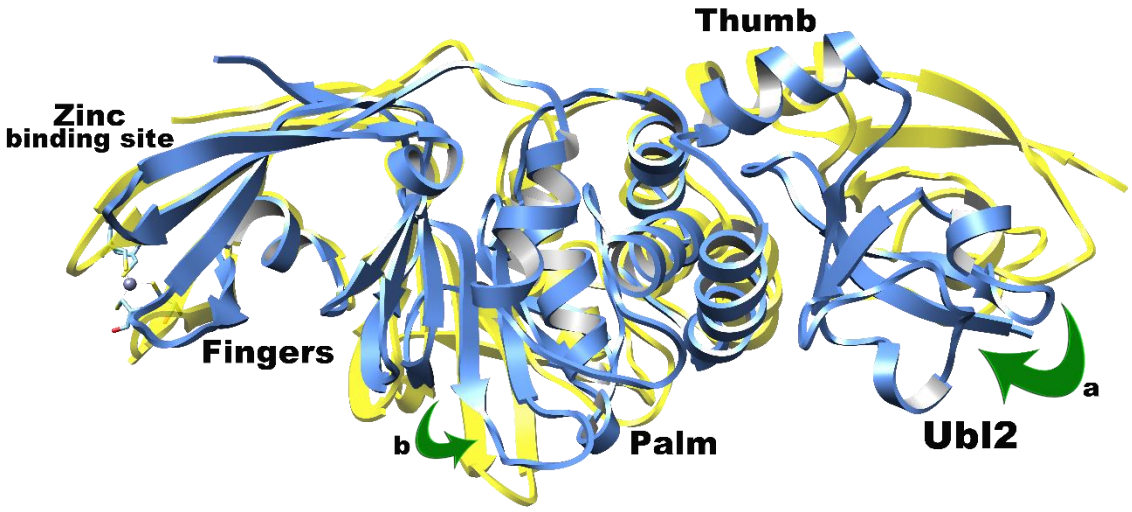

Figure 3. Superimposition of the structures of papain-like protease (PLpro) obtained in 100ns molecular dynamic (MD) simulation before (yellow) and after (blue) being affected by losartan. MD simulations of PLpro with and without losartan was performed by Gromacs 2018 package with gromos43a1 force field and the structural changes of PLpro were investigated: a. structural changes in UBL 2 b. structural changes in the cleavage site of the protein between finger and palm area.

Conclusion

According to a large number of studies, EPO's effect in subsiding neuroinflammation may reduce mortality and morbidity in many neurological disorders. Based on the hypothesis attributing COVID-19 pathophysiology to the excess of Ang II due to downregulation of ACE2, in which solitary administration of EPO might be harmful, combination of EPO and losartan might be promising in ameliorating neuroinflammatory reactions in COVID-19-induced brain disease.

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