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LETTER TO THE EDITOR

Comment on "Smooth or Risky Revisit of an Old Malaria Drug for COVID-19?"

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Dear Sir,

We read with great interest the article by Pahan P and Pahan K "Smooth or Risky Revisit of an Old Malaria Drug for COVID-19?" (Pahan and Pahan 2020). The authors reported that hydroxychloroquine (HQ) treatment in novel coronavirus 2019 (COVID-19) infection can lead to hypertension (HT) and neurodegenerative diseases (ND). We fully agree with these views of the authors. Also, we think the risk of HT and ND increases during COVID-19 infection. We would like to mention the mechanisms of increased risk of ND in COVID-19 infection due to the Na^+/H^+ exchanger (NHE) activation and HQ use.

HQ is an antimalarial but is also considered a disease-modifying rheumatic drug (DMARD). HQ is widely used in the treatment of systemic lupus erythematosus and rheumatoid arthritis. It shows an antiviral effect against some viruses (Wang et al. 2015). HQ interacts with many ion channels. HQ shows its major effect by blocking the K^+/H^+ exchanger (Cumhur Cure et al. 2020). When this exchanger is blocked, pumping H^+ ion from mitochondria to cytosol stops, and cytosolic K^+ level increases. Since the H^+ ion decreases in the cytosol, the cytoplasmic pH becomes alkaline. Angiotensin-converting enzyme 2 (ACE2) shows activity at acidic pH, and the COVID-19 binds easily to ACE2 at acidic pH (Cumhur Cure et al. 2020). The basic treatment mechanism of HQ in COVID-19 infection is to increase the intracellular pH and prevent the virus from binding to ACE2. Besides, HQ prevents the virus from binding to ACE2 by changing its structure (Pahan and Pahan 2020). However, HQ can inhibit ACE2 from degrading angiotensin II by changing its structure.

Due to the invasion of ACE2 by the virus, from angiotensin II to angiotensin 1–7 conversion stops. Therefore, the angiotensin II level increases in the body (Vaduganathan et al. 2020). Angiotensin II level was found to be high in patients with COVID-19 infection (Vaduganathan et al. 2020). Angiotensin II is a toxic substance for the body and activates NHE (Jaballah et al. 2015). While NHE pumps 3 Na^+ ions into the cell, it pumps 2 H^+ ions out of the cell (Cure and Cumhur Cure 2020). When this pump is activated, the flow of Ca^{2+} into the cell starts simultaneously by Na^+/Ca^{2+} exchanger (Cure and Cumhur Cure 2020). Since the H^+ ion decreases in the cell, intracellular pH increases. An increase in H^+ ion in the extracellular field increases the reactive oxygen species, leading to endothelial dysfunction. Besides, increased NHE activation leads to an increase in blood glucose, blood pressure, and procoagulant factors (Cure and Cumhur Cure 2020). COVID-19 infection is more severe in patients with HT and diabetes mellitus. Because of the increase in renin-angiotensin system activation and angiotensin II levels in patients with HT and diabetes, NHE is already active.

In the brain, 6, 7, and 9 isoforms of NHE play a protective role against ND. Decreased NHE activation in the brain plays an important role in ND development (Milosavljevic et al. 2014). Endosomal pH is regulated by V-ATPase and NHE. While V-ATPase pumps the H^+ ion into the endosome, the NHE pumps the H^+ ion out (Prasad and Rao 2015). As the endosome pH increases, amyloid-β and tau protein production decrease (Milosavljevic et al. 2014; Prasad and Rao 2015). Theoretically, an increase of NHE activity can prevent

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ND development. Also, HQ can prevent ND by making alkaline intracellular pH. However, NHE activation or endosomal pH alkalizing drugs such as HQ cannot be used in ND treatment. Since when endosomal pH increases, vesicle trafficking alters, lysosomal functions, and autophagy decrease (Pahan and Pahan 2020; Prasad and Rao 2015).

In infected patients, there is an increase in angiotensin II level due to the virus's blocking of ACE2. When HQ is initiated to these patients, the ACE2 structure changes with HQ (Pahan and Pahan 2020); therefore, angiotensin II degradation decreases, and the patients' blood pressure may increase. Increased angiotensin II causes NHE activation and secondary to this activation, Ca^{2+} accumulation occurs in the neurons (Bezprozvanny 2009). Ca^{2+} accumulation has a neurotoxic effect [9]. HQ may cause Na^{+} channel blockade. Na accumulation occurs in the cell due to Na^{+}/K^{+}ATPase blockade (Roden and Anderson 2006). Na^{+} accumulation activates Na^{+}/Ca^{2+} exchanger, thus, Ca^{2+} accumulates in the neural cells (Roden and Anderson 2006). Disruption of neuronal Ca^{2+} conduction pathways can lead to ND (Bezprozvanny 2009). Both COVID-19 infection and HQ use can increase blood pressure and ND risk by increasing angiotensin II levels. Using HQ in COVID-19 infection can have negative consequences. Detailed studies are needed to determine whether HQ using harms COVID-19 infection.

Compliance with Ethical Standards

Conflict of Interest None.

References

Bezprozvanny I (2009) Calcium signaling and neurodegenerative diseases. Trends Mol Med 15:89–100

Cumhur Cure M, Kucuk A, Cure E (2020) Colchicine may not be effective in COVID-19 infection; it may even be harmful? 2020. Clin Rheumatol 39:2101–2102

Cure E, Cumhur Cure M (2020) COVID-19 may affect the endocrine pancreas by activating Na+/H+ exchanger 2 and increasing lactate levels. J Endocrinol Investig

Jaballah M, Mohamed IA, Alemrayat B, Al-Sulaiti F, Mlih M, Mraiche F (2015) Na+/H+ exchanger isoform 1 induced cardiomyocyte hypertrophy involves activation of p90 ribosomal s6 kinase. PLoS One 10:e0122230

Milosavljevic N, Monet M, Léna I, Brau F, Lacas-Gervais S, Feliciangeli S, Counillon L, Poët M (2014) The intracellular Na(+)/H(+) exchanger NHE7 effects a Na(+)-coupled, but not K(+)-coupled proton-loading mechanism in endocytosis. Cell Rep 7:689–696

Pahan P, Pahan K (2020) Smooth or risky revisit of an old malaria drug for COVID-19? J NeuroImmune Pharmacol 15:174–180

Prasad H, Rao R (2015) The Na+/H+ exchanger NHE6 modulates endosomal pH to control processing of amyloid precursor protein in a cell culture model of Alzheimer disease. J Biol Chem 290: 5311–5327

Roden DM, Anderson ME (2006) Proarrhythmia. Handb Exp Pharmacol 171:73–97

Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD (2020) Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 382:1653–1659

Wang LF, Lin YS, Huang NC, Yu CY, Tsai WL, Chen JJ, Kubota T, Matsuoka M, Chen SR, Yang CS, Lu RW, Lin YL, Chang TH (2015) Hydroxychloroquine-inhibited dengue virus is associated with host defense machinery. J Interf Cytokine Res 35:143–156