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Therapeutic Approach for Covid-19 Patients

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Abstract

The biochemical effects of hydroxychloroquine, ivermectin, azithromycin molecules, and the zinc cation on functional properties of human erythrocyte will be presented. Among a wide range of therapeutically applications attributed to hydroxycloroquine the anti-inflammatory role will be herein highlight as well as for the azithromycin. The intervention of the ivermectin molecules into cell abortion mechanism of the virus replication will be described. The action of hydroxychloroquine, ivermectin, azithromycin molecules, and of zinc cation to prevent the spread and the replication SARS2-CoV2 Virus, as a first therapeutic approach for Covid-19 symptomatic patients, will be the aim of the present opinion.

Keywords: Erythrocyte acethylcholinesterase receptor; Hydroxycloroquine; Azithromycin; Ivermectin; Zinc cation

Abbreviations: ARS: Acute Respiratory Syndrome; RBC: Red Blood Cells; NO: Nitric Oxide; HCQ: Hydroxychloroquin; PTK: Protein Tyrosine Kinase; PTP: Protein Tyrosine Phosphatase; AChE: Acetylcholinesterase; ACh: Acetylcholine; NORS: Nitrogen Reactive Species

Introduction

Biochemical Effects of Hydroxychloroquine, Ivermectin Azithromycin, and Zinc cation on Erythrocyte Properties, Inflammation and SARS2-CoV2 Virus Spread and Replication

Several scientific articles based on SARS-CoV2 Virus (Covid-19) infection evidenced human dead by acute respiratory syndrome (ARS), heart coronary and brain diseases [1-3]. In the ARS the nose and mouth seem to be until now the dominant entrance doors for Covid-19 and the targets to wear masks avoiding corona virus transmission. As explained before the corona virus enters into erythrocytes or red blood cells (RBC) present in the microcirculation vessels of the eyes and forward travel for all circulatory vascular network [4]. These reinforce the number of the infected RBC already present in blood circulation by passage through the infected respiratory tract and afterword will be possible to occurs virus allocation in all cellular tissues of human organs like brain, heart and gut among others [2,3,5].

It was evidenced that Covid-19 enters into RBC through the anion exchange erythrocyte membrane band3 protein (AIE band 3 protein) in its tetrameric molecular structure [6]. It is unknown if did the corona virus left the RBC by the transmembrane band3 protein but, if yes the problem may be partial solved by blockers molecules target to internal domains of band 3 protein on dimeric and tetrameric molecular arrangements [7].

Considering the RBC membrane AIE 3 protein it is need to recall the bidirectional mechanism passage of nitric oxide (NO) through its channel namely its influx from arterial blood in lungs where the oxygen partial pressure (PaO2) is high to the NO efflux from RBC to capillaries in tissue cells with low PaO2 respectively [8]. The hydroxychloroquine (HCQ) molecule binds to cytoplasmic N-terminal domain of transmembrane band 3 protein in human RBC [9]. This N terminal domain allocated also the protein tyrosine kinase (PTK), the protein tyrosine phosphatase (PTP), some glycolytic enzymes in dependence of the haemoglobin molecules oxygenation degree [10]. PTK and PTP are implicated in membrane band 3 protein phosphorylation and dephosphorylation [11].

Human erythrocyte membrane bound acetylcholinesterase (AChE) enzyme activity is dependent on band 3 protein phosphorylation`s degree and it is associate with a Gprotein namely Gαpi1/2 and Gb [12]. RBC membrane band 3 protein phosphorylation promotes increased AChE enzyme activity [12].

Our works shown that human erythrocyte membrane AChE adopt different conformational states according is in the active or less active enzyme states [12]. Acetylcholine (ACh) being the AChE natural substrate behave as conformational structural inductor of active and less active states because at high plasma concentration inhibits the esterase activity [13]. AChE inhibitors

contribute to the conformational less active form of the enzyme [12]. Erythrocyte membrane AChE has a receptor function in the RBC signal transduction mechanism of nitric oxide (NO) as we evidenced [14]. The active complex AChE-ACh associates with the Gαi1/2 promotes inhibition of the adenylyl cyclase (AC) activity with lowering the cyclic AMP level [15,16]. At variance the AChE-ACh Gαi1/2 activates the protein kinase C (PKC) that in turn activating PTK originate the band 3 protein phosphorylation [15,16]. All this intraglobular signals favour the approach and exchange of NO from of the S-nitrosohemoglobin to band 3 protein allowing the efflux of NO from erythrocyte [15,16].

Several experimental studies evidenced the RBC ability to scavenger and to deliver NO, is in dependence of internal signal transduction mechanisms associated to the AChE receptor-ligand molecular forms, the complex CD47 receptor plus fibrinogen binding, cAMP concentrations, band 3 protein phosphorylation degree and the following AC, PKC, PTP, PTK, phosphodiesterase-3 (PDE-3) and phosphoinositol 3 kinase (PI3K) enzyme activities degree [14-16]. The HCQ is one of the known antimalarial drugs which inhibits RBC AChE enzyme activity by an unknown mechanism [17]. However, as HCQ bind to the N terminal domain of membrane Band3 protein may occupy the allocated space for PTK lefting band3 protein dephosphorylation favouring a less active structural conformation of AChE [9,12]. This synergic influence generates by HCQ presence contributes to erythrocyte scavenger NO originating NO derivative molecules and nitrogen reactive species (NORS) inside the erythrocytes of Covid -19 patients. The corona virus permanence inside the RBC could allow its degradation by internal enzymes and a way for ending the virus dissemination.

The antibiotic ivermectin inhibit RBC membrane AChE and by similarity to the others AChE inhibitors action interfear on NO signal transduction mechanism by not changed the normal amount of NO efflux from RBC or diminished in it and consequently increase the internal erythrocyte NO derivative molecules and NORS [14,18].

The SARS2-CoV2 is internalized by RBC but some of them can continue present in blood circulation because its spike binds to the CD147 one of the external membrane protein present in RBC and white blood cells (WBC) [19]. Ivermectin and azithromycin have the ability to shield the SARS2-CoV2 spikes avoiding the recognition by CD147 of RBC and its propagation to all body tissues cells [19]. Ivermectin inhibits the erythrocytes aggregation and agglutination tendencies [19]. The SARS2-CoV2 attaching to the angiotensin converting enzyme 2 (ACE2) receptors present in some endothelial cell's membranes of lungs, adrenal glands and epithelial cells of gut enter into those cells where replicate [20]. The ivermectin binding to the cargo importin alpha/beta1 and block the passage of the positive-sense single stranded RNA virus or SARS-CoV-2 to the nucleus eliminating its replication [21]. The SARS2-CoV2/ ACE2 receptor complex favours the acute phase of inflammation and its spread generating the systemic inflammatory installation in infected humans. So, the proinflammatory factors namely the interleukin-10 (IL-10), the monocyte chemotactic protein 1 (MCP-1) and the interleukin-6 (IL-6) are those present on high serum levels of the Covid -19 patients committed with ARS [22]. The azythromycin is an antibiotic but acts also as anti-inflammatory agent interfering with lungs epithelial apoptosis derived from the presence of factors generating in the inflammatory process [23].

Besides like the other cytokines participation on the classic signalling IL-6 deserves special attention due to the trans signalling pathways in dependence or association with plasminogen activator inhibitor-1 (PAI-1) [24]. The cross -loop between IL-6 and PAI-1 induce endothelium dysfunction tied with coagulopathy [24]. The presence of the normal amount of zinc nutrition in the human been is necessary for a normal erythropoiesis, RBC membrane integrity, component of erythrocyte carbonic anhydrase and Cu/Zn superoxide dismutase. Deficiency of zinc in originate increase RBC membrane fragility and the control of its normal concentration is absolutely necessary to the erythrocyte viability. Zinc has antioxidant and anti-carcinogenic properties and is one inhibitor of RBC AChE enzyme activity [25]. The less active complex form of AChE-Zn maintains or reduce the normal efflux of NO from erythrocytes what is a positive contribution to reduce the oxidative state resulting from the systemic inflammation generate by the presence of the Covid-19 virus [25].

So, in some persistent Covid -19 infected patients where the above therapeutic drugs do not stop the infection anticoagulants, like heparin infusion, anti-inflammatory steroids compounds and colchicine could be adding as second wave of treatment, under physician surveilance [19,26].

Conclusion

The first tendency in the beginning of the Covid -19 pandemic situation was to compare the ARS mortality to the acute generalized body inflammation and organs failure highlight in fatal sepsis. This initial analogy continues to be object of deep research worldwide as we can see in PubMed and herein is described some venues for the virus to achieve into all cells of human body. This is doing by exposing the therapeutic way of action or mechanisms of hydroxicloroquine, azythromycin, ivermectin and zinc in order to avoid the dissemination and spread of SARS2-CoV2 to all cells of the human. Erythrocyte is a partner of the resolution of Covid -19 infection and inflammatory process as previous showed in other situations caused by less fatal pathophysiological situations [27-29].

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