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Alpha-lipoic acid may protect patients with diabetes against COVID-19 infection

A B S T R A C T

COVID-19 pandemic is spreading rapidly worldwide, and drug selection can affect the morbidity and mortality of the disease positively or negatively. Alpha-lipoic acid (ALA) is a potent antioxidant and reduces oxidative stress and inhibits activation of nuclear factor-kappa B (NF-kB). ALA reduces ADAM17 activity and ACE2 upregulation. ALA is known to have antiviral effects against some viruses. ALA may show antiviral effect by reducing NF-kB activation and alleviating redox reactions. ALA increases the intracellular glutathione strengthens the human host defense. ALA activates ATP dependent K^+ channels (Na^+, K^+-ATPase). Increased K^+ in the cell raises the intracellular pH. As the intracellular pH increases, the entry of the virus into the cell decreases. ALA can increase human host defense against SARS-CoV-2 by increasing intracellular pH. ALA treatment increases antioxidant levels and reduces oxidative stress. Thus, ALA may strengthen the human host defense against SARS-CoV-2 and can play a vital role in the treatment of patients with critically ill COVID-19. It can prevent cell damage by decreasing lactate production in patients with COVID-19. Using ALA with insulin in patients with diabetes can show a synergistic effect against SARS-CoV-2. We think ALA treatment will be beneficial against COVID-19 in patients with diabetes.

Dear Sir,

The new coronavirus disease 2019 (COVID-19) pandemic is spreading rapidly worldwide, and drug selection can affect the morbidity and mortality of the disease positively or negatively. Alpha-lipoic acid (ALA) is used in most patients with diabetes to treat peripheral neuropathy. We think ALA will have a protective effect against COVID-19 in patients with diabetes by various mechanisms. We will mention the protective effects of ALA against COVID-19 infection in patients with diabetes.

SARS-CoV-2 enters the cell by attaching to angiotensin-converting enzyme 2 (ACE2) like SARS-CoV. ACE2 shows its proteolytic activity at acidic pH values [1,2]. The most important feature that affects the entry of the virus into the cell is that the intracellular pH is low. The second important factor affecting the entry of the virus into the cell is the ACE2 level [1,2]. When ACE2 upregulation, the viral load may increase because of increased ACE2 levels [2]. ADAM17 is a metalloprotease and causes ACE2 shedding. ADAM17 causes ACE2 upregulation by shedding ACE2 [3]. Alleviating ADAM17 activity may reduce COVID-19 infection (Fig. 1).

ALA is used in the treatment of diabetic polyneuropathy. It increases insulin sensitivity and lowers blood glucose. ALA is a potent antioxidant and reduces oxidative stress and inhibits activation of nuclear factor-kappa B (NF-kB) (Fig. 1) [4]. ALA is known to have antiviral effects against some viruses. ALA may show antiviral effect by reducing NF-kB activation and alleviating redox reactions [5]. ALA increases the intracellular glutathione level, strengthens the human host defense against the coronavirus 229E strain, and inhibits HIV-1 replication [6]. Also, it has been reported that ALA inhibits the growth of the vaccinia virus in vitro environment with similar mechanisms, and thus it can be effective against poxviruses [5]. ALA has positive effects such as chelation of metal ions such as mercury, cadmium, and lead, redistribution of redox-active divalent metal ions such as copper, and zinc, restoration of endogenous and exogenous antioxidants such as vitamins C and E [7]. Increasing these antioxidants levels by ALA may provide an initial defensive mechanism against COVID-19 (Fig. 1) [6]. Zhong et al. administered 1200 mg ALA therapy to 17 patients with critically ill COVID-19. They reported that after 30 days of follow-up, the mortality rate was 2-fold lower in the ALA group than in the placebo group [8]. Besides, ALA reduces the ADAM17 activation and its effect by inhibits NADPH oxidase activity [9,10]. ALA can reduce the viral load by preventing ACE2 upregulation (Fig. 1). Since insulin therapy reduces ADAM17 activation [11], the combination of insulin and ALA may be an excellent option in patients with diabetes.

Hydroxychloroquine alkalizes intracellular pH by inhibiting K^+/H^+ antiporter [12,13]. Hydroxychloroquine causes K^+ to accumulate in the intracellular area and H^+ ion to stay in mitochondria. Hydroxychloroquine prevents the virus from entering the cell by increasing intracellular pH and altering the ACE2 structure [13]. ALA activates ATP-sensitive K^+ channels (Na^+, K^+-ATPase) (NKA). The channels pump 2 K^+ into the cell and 3Na^+ outside the cell [14,15]. ALA activates the pump, increasing intracellular pH (Fig. 1). ALA can increase human host defense against SARS-CoV-2 by increasing intracellular pH.

Serum and tissue lactate levels increase in patients with critically ill COVID-19. Since oxygenation of tissues is insufficient in patients with COVID-19, a hypoxic environment occurs [2,16]. In hypoxic conditions, anaerobic glycolysis pathways and lactate dehydrogenase enzyme become active and lactate production increases [17]. Increased lactate levels in the environment render the hypoxic conditions of the environment worse. Monocarboxylate transporters carry the increased lactate together with the H+ ion into the cell [18]. This event activates the Na^+/H^+ exchanger (NHE) to buffer intracellular pH. NHE is pumping H^+ ion out of the cell, Na^+ moves into the cell [16,18]. Ca^{2+} flows into the intracellular area simultaneously. Increased Na^+ in the cell causes swelling and edema of the cell (Fig. 1). Increased Ca^{2+} in the cell stimulates apoptosis, causing cell death [16,18]. Normally, intracellular pH is maintained in a narrow interval. Lactate increase activates NKA [19]; however, in the presence of excessively and consistently high lactate, NKA may not raise intracellular pH. Lowering the lactate level may reduce cell damage in COVID-19 [16]. ALA directly

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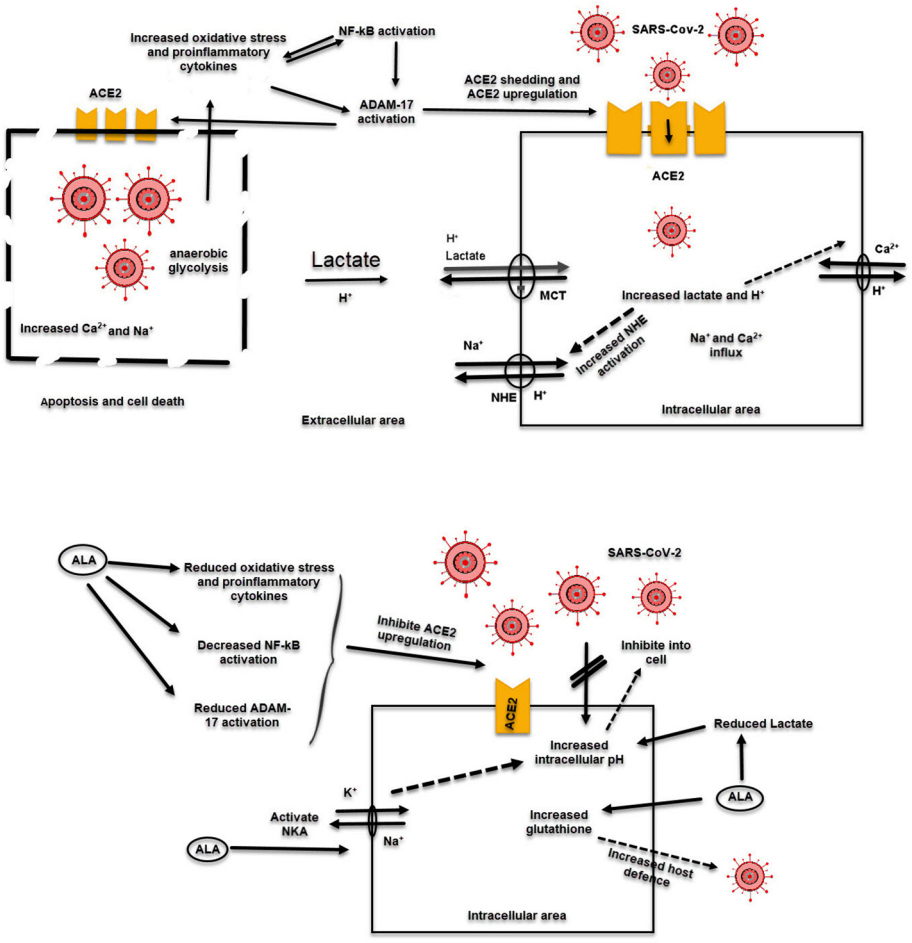

Fig. 1. The mechanism of SARS-CoV-2 entry into the cell and causing damage to the cell, and protective mechanisms of ALA against SARS-CoV-2 infection. *Abbreviations:* ALA, Alpha-lipoic acid; ACE2, angiotensin-converting enzyme 2; NKA, Na^+, K^+-ATPase; NHE, Na^+/H^+ exchanger; MCT, monocarboxylate transporters; NF-kB, nuclear factor-kappa B.

activates pyruvate dehydrogenase, lowering serum lactate levels [20]. ALA can prevent NHE activation by lowering the lactate level. It can show a cytoprotective effect in patients with critically ill COVID-19 by preventing the accumulation of Na^+ and Ca^{2+} in the cell (Fig. 1).

In conclusion, ALA treatment increases intracellular pH and antioxidant levels and reduces oxidative stress. Thus, ALA may strengthen the human host defense against SARS-CoV-2 and can play a vital role in the treatment of patients with critically ill COVID-19. It can prevent tissue and cell damage by decreasing lactate production in patients with COVID-19. Using ALA with insulin in patients with diabetes can show a synergistic effect against SARS-CoV-2. We think ALA treatment will be beneficial against COVID-19 in patients with diabetes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110185.

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