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LETTER TO THE EDITOR

Possible application of H_2S-producing compounds in therapy of coronavirus (COVID-19) infection and pneumonia

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In recent years, the gasotransmitter hydrogen sulfide (H_2S) has been recognized as a biological mediator of immense importance both in eukaryotes and prokaryotes (Kimura 2014; Xiao et al. 2018). H_2S is produced in the cells mostly through the reverse transsulfuration pathway (TSP). Transsulfuration is a vital metabolic process common in prokaryotes and eukaryotes that have been studied in detail in mammals including human and several other organisms. It has been demonstrated by different groups that defects in the H_2S synthesizing enzyme system are involved in a plethora of diseases in humans including cancer and a number of neurodegenerative diseases (Wallace and Wang 2015; Bhattacharyya et al. 2016). Although at high concentration H_2S is a poison, at low concentrations, it elicits cytoprotection during oxidative stress by decreasing reactive oxygen species (ROS) production in a wide range of physiologic and pathologic conditions (Kaya-Yasar et al. 2017; Faller et al. 2018). It is interesting that cysteine is sulfur-rich and likely involved as a modulator of ROS due to S–S bonds. To this end, sulfide-rich water in baths is routinely used in sanatoriums to treat multiple diseases.

In recent decades, we studied the effects of endogenous and exogenous hydrogen sulfide at the cellular and organism levels (Yurinskaya et al. 2020; Shilova et al. 2020; Zatsepina et al. in press). In our investigation, we explored slow- and fast-releasing H_2S donors as well as deletions of the genes responsible for H_2S production and demonstrated a strong anti-inflammatory effect of this gas which ameliorates various manifestations of inflammation including ROS, NO, TNF-α, and interleukin-6.

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Along these lines, there are studies demonstrating antiviral and anti-inflammatory activity of H_2S in several rodent models (Bazhanov et al. 2018; Bazhanov et al. 2017).

In an animal model, hydrogen sulfide donors are usually introduced by inhalation to efficiently alleviate lung injury and pneumonia induced by bacteria or viruses (Zhang et al. 2019; Sakaguchi et al. 2014; Kakinohana et al. 2019). It was also shown in rodent models that pre- and posttreatment with hydrogen sulfide prevents ventilator-induced lung injury by limiting inflammation and oxidation (Faller et al. 2017). Since hydrogen sulfide is a toxic gas, its use "as is" for inhalation is problematic. Water-soluble sulfide salts such as Na_2S and NaHS generate free H_2S in aqueous solutions. Thus, diluted solutions of inorganic sulfides could be used for inhalation with a nebulizer, but an important drawback of these compounds is their regulatory status. There are no clinical data nor any documented evidence of sulfide inhalation, and it is important to note that pharmaceutical grade sulfides are not available. For these reasons, we focused on sodium thiosulfate ($Na_2S_2O_3$) that is an FDA-approved drug used in the treatment of cyanide poisoning, certain extravasation injuries, and for calciphylaxis associated with chronic kidney disease. USP grade sodium thiosulfate (STS) is available as a drug substance and also as a sterile solution for injections.

The molecule of $Na_2S_2O_3$ contains divalent sulfur (S^{-2}) and could be a slow donor of hydrogen sulfide in aqueous solutions and biological systems. This compound is also a potent reducing agent and scavenger of ROS reducing Fe+3 to Fe+2. Sodium thiosulfate is a harmless substance which has been approved by the FDA and used for decades for the treatment of cyanide poisoning (Bebarta et al. 2017). Importantly, sodium thiosulfate was widely used in model organisms to mitigate lung injury (Zhang et al. 2019). Thiosulfate can produce H_2S through a nonenzymatic or by an enzymatic pathway (Snijder et al. 2015; Leskova et al. 2017) and, hence, may be successfully applied in humans not only by inhalation but orally and intravenously as well (Farese et al. 2011). In

humans, the short-term therapeutic use of STS has been carried out for the treatment of calciphylaxis (Singh et al. 2011).

Similarly, in humans, there are reports where sodium thiosulfate was successfully used to ameliorate the progression of lung injury and pneumonia in adults and children (Egorychev et al. 1987; Gorbacheva et al. 2009a, b; Barkov 2006). The literature recommended inhalation treatment of patients with pneumonia with 2 ml of 5% solution of sodium thiosulfate via nebulizer 2 times daily. The treatment course for pneumonia was 10–15 inhalations. The doses of intravenous injections are given in Farese et al. 2011; Singh et al. 2011.

Objectives

Based on the above data and considerations, we suggest the application of a harmless H_2S donor (sodium thiosulfate) to treat patients at any stage of the COVID-19 virus infection.

The administration of Na thiosulfate should be done using a nebulizer for aerosol inhalation according to the doses and regimen successfully applied previously in several clinics against pneumonia induced by bacteria and viruses. This could be done along with intravenous injections of Na thiosulfate as systemic inflammation demands a systemic route of administration. In the first stage of infection, the H_2S produced should exercise its antiviral potential to prevent coronavirus amplification. At the later stages when pneumonia is developed, Na thiosulfate inhalation will ameliorate lung injury. Clinicians would likely select initially patients that are febrile and with mild respiratory complaints and mild hypoxia.

Additionally, pre- and posttreatment (inhalation) with sodium thiosulfate will prevent ventilator-induced lung injury.

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