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Hydrogen Medicine Therapy: An Effective and Promising Novel Treatment for Multiple Organ Dysfunction Syndrome (MODS) Induced by Influenza and Other Viral Infections Diseases?

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Abstract

Hydrogen, a non-cytotoxic molecule, is one of nature's most simple elements [1,2]. Recent studies revealed that intraperitoneal injection of hydrogen-rich saline has surprising anti-inflammation, anti-oxidant, anti-apoptosis effects and protected organism against polymicrobial sepsis injury, acute peritonitis injury both by reducing oxidative stress and via decreasing mass proinflammatory responses. It is also well known that the majority of viral -induced tissue damage and discomfort are mainly caused by an inflammatory cytokine storm and oxidative stress rather than by virus itself [3-5]. Studies have shown that suppressing the cytokine storm and reducing oxidative stress can significantly alleviate the symptoms of influenza and other severe viral infections diseases [3-7]. However, none of the studies have been focused on the solution as an anti-virus infection therapy yet. Therefore, we hypothesize that hydrogen-rich solution therapy may be a safe, reliable, and effective treatment for Multiple Organ Dysfunction Syndrome (MODS) induced by influenza and other viral infectious diseases.

Keywords: Hydrogen Medicine; Anti-Oxidant; Anti-Inflammation; Inflammatory Cytokine Storm; Molecular Hydrogen; Multiple Organ Dysfunction Syndrome (MODS)

Introduction

Hydrogen is one of nature's most simple elements. As a gas (H_2), it is a colorless, tasteless, odorless, highly flammable diatomic molecule which has been used for fossil fuel processing and ammonia production. In the past decade, molecular hydrogen was considered a surprising agent, which can significantly reduce oxidative stress by selectively reducing hydroxyl radical (•OH) and Peroxynitrite (ONOO-) [1,8-10]. It has recently been revealed that hydrogen can both down-regulate expression of oxidative-related genes and pro-inflammatory cytokine genes directly and indirectly [2-5,11,12]. Oxidative stress and systemic inflammatory response syndrome have been confirmed to play critical roles in tissue and organ damages after polymicrobial sepsis injury, acute peritonitis injury, and peritonitis, which can develop into lethal sepsis with inappropriate treatment [13,14]. In spite of some available antibiotic therapies for the some stages of sepsis, Multiple Organ Dysfunction Syndrome (MODS) induced by sepsis is still the leading cause of death in the Intensive Care Unit (ICU) [15,16]. Recent studies reveal potential protective effects of hydrogen against sepsis and acute peritonitis by decreasing proinflammatory responses, oxidative stress, and apoptosis, which indicate hydrogen medicine as a new no-toxic therapy for bacterial infections [13,14]. Other researchers have also demonstrated that chronic hepatitis B, acute pancreatitis, and sepsis can also be alleviated by treatment of hydrogen medicine [10,14,17]. However, none of the research ever investigated the therapeutic effect of hydrogen gas for MODS induced by influenza and other viral infectious diseases in which inflammation and oxidative stress also play pivotal roles.

Influenza and other severe viral infections

Viruses that cause influenza, Ebola, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS) are emerging as infectious pathogens in this century that are extremely difficult to control effectively, triggering MODS [18-21]. The trends, spread, scope, and development speed of these emerging infectious diseases cannot

be estimated, as their routes of transmission and patterns of spread are extensive and different. Diseases induced by these viruses also differ from each other. To be specific, influenza virus can cause flu, whereby the patient has a stuffy nose, cough, sore throat, runny nose, headache, muscle pain and discomfort symptoms [22]. SARS induces diffuse alveolar damage, acute lung injury, leading to Acute Respiratory Distress Syndrome (ARDS), hypoxemia, and high mortality rate [20,23-25]. Like SARS, MERS, a new type of corona virus, can cause symptoms even with many complications including renal failure [18,19].

The body will be in a state of stress that is caused by the excitement of the sympathetic system after invasion of these pathogens [26,27]. Therefore, oxidative stress increases the release of catecholamine [28]. As auto-oxidation of catecholamine occurs, a large number of free radicals can be produced, accelerating formation of oxidative stress [1]. Meanwhile, oxidative stress activates the complement system, producing a variety of chemotactic substances, such as C3 fragments, leukotrienes etc, which attract and activate neutrophils ultimately [29]. Thus, inflammatory infiltrates develops in many corresponding organs. Furthermore, all these pathogens also stimulate the immune system continuously to launch an inflammatory response flaring out of control [30]. Proinflammatory cytokines are secreted throughout the body; these cytokines also initiate activation of inflammation cells like neutrophils, eosinophils, basophils, lymphocytes, and monocytes to produce more proinflammatory cytokines [5,30]. Those cytokines and inflammation cells are reciprocal causation, developing into a cytokine storm(systemic inflammatory response syndrome)[30,31]. The term cytokine storm is used to accommodate the observation that multiple excessive inflammatory causes can induce excessive release of inflammation factors like interleukin-1, interleukin-6, interleukin-12, tumor necrosis factor-α, interferon-α, interferon-β, interferon-γ, Monocyte Chemoattractant Protein-1 and interleukin-8 thereby leading to a disease that appears similar to sepsis [30,31]. Importantly, excessive inflammation reactions can also induce acute oxidative stress [2]. Together, both cytokine storm and oxidative stress promote each other and induce MODS, result in high mortality rate [15].

Until now, numerous studies have indicated cytokine storm and oxidative stress are highly associated with the pathological process when getting infected with these viruses [32-34]. Although cytokine storm and oxidative stress probably try to eliminate theses pathogens, they seem to generate multi-organ damage resulting in lethal clinical symptoms such as extensive pulmonary oedema, alveolar and other tissue haemorrhage, and acute respiratory distress syndrome, etc [6,7,33]. Moreover, when inflammation and oxidative stress damage tissue and organs, healing occurs with fibrosis, aggravating persistent multiple organ dysfunction [30]. Therefore, timely elimination of these mass of cytokines and oxidative stress would presumably protect normal organs from the damaging effects of pathogen infection.

At present, there are some therapies which include vaccines and drugs such as Oseltamivir, Amantadine, Curcumin and Ribavirin, as well as S1P1R for influenza and other viral infections diseases [35-39]. However, due to the highly variable nature of these pathogens, no ideal therapy comprehensively conforms to the criteria of effective, selective, non-toxic, and tolerance-inducing anti-influenza and other viral therapy. Furthermore, studies have showen that oseltamivir can alleviate clinical diseases symptoms and reduce morbidity and mortality [40,41]. However, there are still controversies over the prevention, treatment, and tolerance effects of oseltamivir on influenza virus [22]. Importantly, recent research showed that epistatic interactions between neuraminidase mutations promote the number of oseltamivir-resistant influenza virus populations [42]. Moreover, the clinical application revealed oseltamivir had many adverse effects such as nausea, vomiting, and an increased risk of headaches as well as renal and psychiatric syndromes [22]. Therefore, more attention should be paid to the trade-off between benefits and drawbacks when deciding to choose oseltamivir for a therapy.

Although anti-influenza and other viral therapies have been widely studied in the past decades, no therapy can achieve the desired standards. Medical researchers have been striving hard to identify effective, novel, non-toxic, and convenient compounds to protect patients against influenza and other viral infections.

Hypothesis

Our hypothesis is that hydrogen-rich solution therapy may be a safe, reliable, effective, and specific treatment for MODS induced by influenza and other viral infectious diseases. Given the theory that molecular hydrogen can both significantly down regulate expressions of inflammation-related genes and selectively reduce hydroxyl radical and Peroxynitrite, we have reasons to consider that cytokine storm and oxidative stress can be suppressed when getting infected with avian influenza and other severe viruses [1,11,12,43-45]. Our theory is unique because it not only puts forward a new kind of non-toxic anti-viral therapy but also makes hydrogen-based medicine able to heal disease in to the whole body.

Proinflammatory cytokines including interleukin-1β , interleukin-6, Interferon-γ, intercellular cell adhesion molecule-1, inducible nitric oxide synthase, monocyte chemotactic protein 1, chemokine ligand 2 and tumor necrosis factor -α as well as Proliferating Cell Nuclear Antigen are the main contributors for cytokine storm[30,46-48]. Numerous studies have consistently shown that the contributors were significantly down regulated after applying hydrogen medicine therapy [10,14,26,27,41]. Besides, with the deepening biological mechanism of hydrogen research being developed, scientists gradually found that hydrogen therapy can significantly suppress many pathological signal transduction channels such as NF-κβ, MAPK, Lyn-P, and MEK-1 as well as ERK1/2 pathways and ultimately achieve the goal of recovery from many diseases [44,45,49-53]. In addition, it is worth noting that as H2 is moderate enough, it can selectively react with only hydroxyl radicals (•OH) and peroxynitrite(ONOO-), the main contributors of oxidative stress in vitro and in vivo without disturbing metabolic redox reactions

[1]. Last but not least, as H2 is an endogenous substance, the goal of better tissue compatibility than other anti-viral drugs can be achieved [54-56].

Since persistent tissue damage, MODS and high mortality rate are highly associated with oxidative stress and cytokine storm induced by influenza and other severe viral infections hydrogen can significantly reduce oxidative stress and restrain excessive production of cytokines [9,57-60]. We hypothesize that hydrogen can be potentially effective for MODS induced by influenza and other viral infectious diseases. That is to say, hydrogen may be a promising novel anti-influenza and other severe viral infections protectant. We believe work on hydrogen-based medicine for anti-viral therapy in vitro and in vivo should commence as soon as possible. In view of the outbreak, transmission, and widespread nature of these viruses, and the global issues caused by new variation pandemics threats, hydrogen medicine may give us more hope for greater survival and fewer human morbidity and mortality (Figure 1).

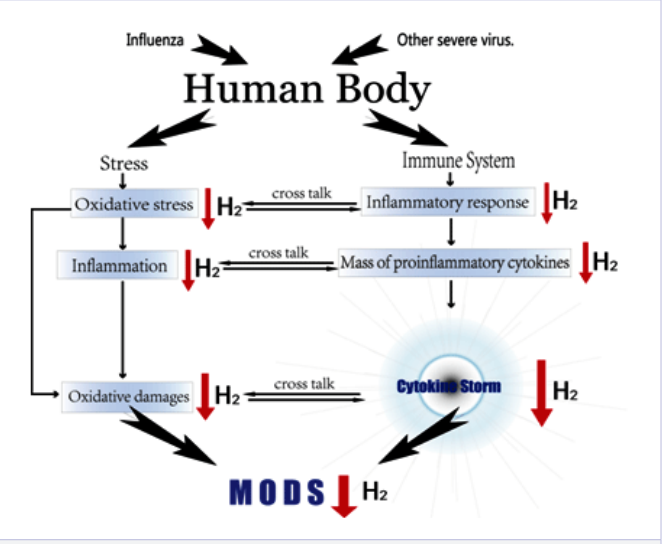

Figure 1: H2 as a potential therapy for MODS induced by influenza and other viral infectious diseases.

Proposed delivery way of hydrogen

It's interesting to note that H2 therapy can be administered through inhalation, oral intake of hydrogen-rich water, injection of hydrogen-rich saline, direct diffusion of hydrogen: bath, eye drops and immersion, as well as increase hydrogen in intestine [11,61-69]. Although each delivery way has its own characteristic and advantages, injection of hydrogen-rich saline allows enough amount of hydrogen to have its own anti-oxidant, anti-inflammation, anti-apoptosis effect at the shortest time [11,70]. Moreover, it is emergency to cure patients with influenza and other severe viral infectious diseases. Therefore, it would be most suitable to choose injection hydrogen-rich saline method as the primary hydrogen therapy for influenza and other severe viral infectious diseases.

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