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Editorial

Electrolyzed hydrogen water and photobiomodulation therapy have several features in common

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Electrolyzed hydrogen water (EHW) also known as "electrolyzed reduced water" or "alkaline ionized water" has been investigated for over 70 years, but is still generally regarded as an alternative and complementary medicine product[1]. More recently, inhaled hydrogen gas has also been investigated for the treatment of various medical conditions. Interestingly, it turns out that there are some similarities between the mechanisms of action of EHW or hydrogen gas and those of photobiomodulation therapy (PBMT), which will be summarized here. The diseases and conditions treated by EHW and PBMT also show significant overlap. The final similarity is that both modalities have suffered a long struggle to be accepted by the mainstream medical community, which has still not been completely achieved.

The interest in EHW as a medical treatment started in Japan as long ago as 1931[2]. In 1966, the Japan ministry of health and welfare officially approved the drinking of EHW, and licensed the electrolysis device used to produce it for home use, which was followed by the South Korean federal drug administration in 1978. At the present time hundreds of thousands of devices are sold each year, mainly in the far east, but also increasingly in western countries. They employ normal tap water and can be programmed to produce EHW from the cathode, or alternatively electrolyzed oxidized water can be produced from the anode to be used as a disinfectant.

EHW is defined by three measurable physical parameters: (i) the pH value varies between pH 7.7 and 9.0 but the buffering capacity is negligible; (ii) the redox potential varies between minus 400 and minus 800 mV; (iii) the H_2 concentration varies between 0.5 and 1.5 mg/L (8 mM)[3]. These parameters are interconnected because the redox potential becomes more negative with increasing pH as well as with increasing H_2 concentration[4]. Some (but not all) preparations of EHW have been shown to contain low concentrations of platinum nanoparticles derived from the platinum cathode material, and these have been proposed to play a role in the biological activity[5]. When the current is switched off the hydrogen gas starts to be slowly released from the solution, so the water should be drunk within 1–2 hours of preparation. The

only side effect of drinking EHW is increased urination as would also be produced by drinking equivalent volumes of tap or mineral water. The administered dose of EHW has varied between 500 mL and 2 L daily. The taste of EHW has been described as "deeply refreshing and smooth, with a slightly sweeter and more satisfying taste than plain water".

For many years the precise mechanism of action of EHW was unknown, and several speculative hypotheses ran wild in the scientific literature. The same comment has often been made about the mechanisms of action of PBMT in the early days, and various speculative mechanisms can still be encountered. Recently a careful analysis considered each of the proposed mechanisms for EHW and eliminated them one by one, until the only one that remained was "molecular hydrogen is the exclusive agent responsible for the therapeutic effects"[4]. The other mechanisms that were discarded were: (i) high pH; (ii) active atomic hydrogen; (iii) metal hydrides; (iv) increased bioavailability of minerals; (v) abundant free electrons; (vi) altered water structure (hexagonal or microclusters); (vii) reduced surface tension; (viii) "energetically enhanced"; (ix) "imbued with frequencies". One reason why molecular hydrogen was accepted as a therapeutic agent, was a landmark paper published in 2007 in *Nature Medicine* entitled "Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals"[6]. Until this paper came out hydrogen gas had been considered to be a biologically inert molecule incapable of reacting with anything important in cellular systems. Ohsawa and colleagues[6] showed that H_2 could quench the reactive oxygen species (ROS), hydroxyl radicals and peroxynitrite, but did not quench superoxide, nitric oxide or hydrogen peroxide. They also showed that cultured cortical neurons could be protected from oxygen-glucose deprivation injury and oxidative stress using H_2 saturated medium, and that inhalation of H_2 gas protected rats from an ischemic stroke induced by occlusion of the middle cerebral artery. Exactly, the same positive results have been demonstrated in PBMT experiments using NIR light in cells and animal models of stroke. Some clinical trials have been conducted using inhaled hydrogen gas for treating acute cerebral ischemia, acute cardiac infarction and post-cardiac arrest syndrome[7].

Other groups have used the injection of H_2 saturated saline into rats and mice to protect against cardiac, renal or intestinal ischemia-reperfusion injury, ischemia-induced lung damage, carrageenan induced paw edema, and endotoxin-induced lung dysfunction[8]. Again all of these experimental models have been advantageously treated with PBMT.

Hydrogen is a lipophilic gas that has a high affinity to lipid bilayers inside cells, and because it is the lightest known molecule (Mol Wt = 2), it can diffuse rapidly throughout the cell, including into the nucleus. Although many commentators refer to hydrogen as a direct chemical quencher of ROS (i.e., an antioxidant), some recent studies have suggested that there is more to the story, than H_2 just acting in a similar manner to antioxidant vitamins (A, C, E). This is just as well because accumulating evidence suggests that the use of anti-oxidant vitamin supplements can in some cases cause more harm than good[9]. There are increasing lines of evidence that the mechanism of action of molecular hydrogen is based on changes occurring within the mitochondria, in a very similar manner to those occurring with PBMT. Molecular hydrogen was shown to increase electron transport in the respiratory chain, raise mitochondrial membrane potential, and stimulate the production of adenosine triphosphate[8]. It can also inhibit the opening of the mitochondrial permeability transition pore, reduce pro-apoptotic factors (Bax and activated caspases), inhibit p53 signaling, and up-regulate the anti-apoptotic factors (Bcl2 and Bcl-XL) thus resulting in less apoptosis in age-related degenerative disorders. All these effects have been shown to occur with the use of red/NIR light in cell culture and animal experiments.

It should be noted that the normal intestinal microbiota in the human gut produce up to one liter of H_2 gas per day, while the volume of H_2 gas consumed in EHW is only about 50 mL per day. Despite the fact that H_2 is presumably not well absorbed from the colon, this has not prevented investigators from proposing ways to increase H_2 production in the gut, e.g., by consuming lactulose[10].

Hydrogen has been shown to have anti-inflammatory effects in a similar manner to PBMT. It can switch the macrophage phenotype from the pro-inflammatory M1 to the anti-inflammatory M2, thus reducing pro-inflammatory cytokines, interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and increasing anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor-β. All of these cellular effects have also been shown to occur with PBMT.

Other similarities between hydrogen and PBMT include the activation of mesenchymal stem cells, enhancement of tissue regeneration, upregulation of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and inhibition of pro-oxidant enzymes (NADPH oxidase and myeloperoxidase)[10]. In cell culture experiments H_2 was shown to increase cell proliferation, cellular adhesion and collagen production, in a similar manner to PBMT.

One open label pilot clinical trial recruited 20 patients with rheumatoid arthritis (RA) who drank 530 mL of EHW each day for 4 weeks[11]. After a 4-week wash-out period, the patients then drank the EHW daily for a third 4-week period. During the first 4-week period the clinical RA score decreased from 3.83 to 3.02 ($p < 0.01$), while during the wash out period there was another non-significant decrease in the RA score, followed by a third significant decrease from 2.83 to 2.26 ($p < 0.01$) during the second treatment period. Measurements of urinary 8-hydroxydeoxyguanine paralleled the clinical improvements. Four patients became completely symptom free at the end of the study.

Considering the similarities between EHW and PBMT, it is not surprising that there has been at least one attempt to combine these two modalities. Hong et al conducted a pilot trial on 18 patients with moderate Parkinson's disease (PD) who received PBMT using a 940 nm LED device at 6 mW/cm^2 applied to the back of the neck and head for five days a week for 2 weeks plus EHW to be consumed daily at the clinical site and at home (in sealed cans)[12]. The clinical PD scores started to improve at the end of the first week and continued to improve over the whole 3 weeks. One week after the end of treatment the scores worsened slightly but were still better than the baseline. Clearly more studies are required to determine whether the combined benefits of EHW and PBMT are additive or "synergistic" as claimed.

It will be interesting to if there is increased acceptance of EHW and inhaled H_2 as treatments in western countries in the coming years, and whether it parallels the wider acceptance of PBMT.

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Conflict of interest

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