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RESEARCH ARTICLE

EVOLUTION, ADAPTIVE STRESSORS AND MOLECULAR HYDROGEN

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Abstract

Molecular hydrogen (H₂) has demonstrated therapeutic properties across numerous models. To date, the mechanism underlying the beneficial responses to H₂ exposure remains elusive. The initial hypothesis that molecular hydrogen acts as a direct, selective antioxidant in vivo does not reconcile models where H₂ has shown to increase oxidative stress, nor does it explain numerous other physiological changes that have been observed throughout the literature. Some researchers have proposed that H₂ acts as a hormetic stressor. This hypothesis does not reconcile H₂ being non-toxic in nature, even at high doses. Hormetic stressors have contributed to evolutionary adaptations, with the absence of these stressors causing cellular dysfunction. H₂ has played an intimate role in the evolution of our planet's atmosphere, the evolution of mitochondria and of life on the planet. Endogenously produced H₂ volumes vary dramatically between individuals and are expected to have varied through human evolution. Our cells have evolved to tolerate erratic and intermittent exposure to H₂. Intermittent exogenous H₂ exposure yields results similar to various hormetic stressors. Continued research elucidating how H₂ acts as an adaptive stressor, both through endogenous levels and exogenous supplementation, are highly warranted.

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Introduction:-

Article:

The seminal article published in Nature Medicine in 2007 demonstrated potential therapeutic benefits of molecular hydrogen (H₂), attributing the results to direct scavenging of the hydroxyl radical (Ohsawa et al., 2007). This attribution of mechanism of action does not resolve results demonstrating increases in oxidative stress (Hirayama et al., 2019) or fully elucidate the significant observations in gene expression alteration (Nishiwaki et al., 2018). As published results have broadened in therapeutic outcomes, researchers have been unable to determine the underlying mechanisms, as it has long been believed that H₂ is a physiologically inert, non-functional gas within our body (Ohta, 2014). As research has progressed and empirical evidence has amassed, totalling an estimated 1500 unique publications demonstrating its beneficial effects, with close to 100 of them having been conducted in humans, the mechanisms by which H₂ exerts its beneficial effects in the body continue to elude the research community (Kawamura et al., 2020). Some researchers have hypothesized that when ingested H₂ acts as a hormetic stressor (Murakami et al., 2017; Hirayama et al., 2019; LeBaron et al., 2019), but this hypothesis has not yet been reconciled with what is known regarding the safety profile of H₂, due to it being non-toxic in nature (LeBaron et al., 2019b).

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Hormesis is typically defined as any intervention or process which exposes an organism to toxicity, producing a biphasic response. Typically, exposure to low levels of a hormetic stressor yields a beneficial response, whereas exposure to high levels produces a deleterious response. Conversely, exposure to H₂ has typically demonstrated a more beneficial response at higher doses. It is commonly accepted that correctly dosed hormetic stressors lead to positive adaptations of the organism (Mattson, 2008). It has also been suggested that adaptive responses to hormetic stressors have played a fundamental role in evolution (Mattson, 2009). In fact, the most commonly accepted forms of hormesis to the human body, such as exercise (Radak et al., 2005), cold exposure (Le Bourg, 2007), heat exposure (Rattan, 2005), fasting (Horne et al., 2015), caloric restriction (Masoro, 2007), radiation (Vaiserman, 2008) and even ethanol (Parsons, 2001), all have been present throughout and can be explained by evolution, with the likelihood that humans were exposed to variable levels of these stressors, often at high levels and in an erratic manner, throughout the evolution of our species.

The role of H₂ exposure as a beneficial form of hormesis can be reconciled when considering a different perspective on how and why hormetic stressors positively impact cellular signalling (Calabrese, 2013). Since hormetic stressors play both an adaptive role in our current physiology, and have played a fundamental role in driving evolutionary change, logic follows that we have evolved to anticipate and require adequate levels of stressors for our cellular communication to operate harmoniously. This is corroborated by the known deleterious effects of the lack of exercise-induced hormesis, defined as a sedentary lifestyle (Buford et al., 2010).

It is known that H₂ has played an integral role in our evolution, with the “hydrogen hypothesis” being put forth to explain the eukaryote origins of our mitochondria (Martin and Müller, 1998), which suggests that the first eukaryote emerged from a symbiotic association between a hydrogen-dependent archaeobacterium (the host) and eubacterium (the symbiont) that was able to respire, but generated H₂ as a waste product of anaerobic heterotrophic metabolism. It is now commonly accepted that mitochondria and hydrogenosomes, which expel H₂ as a waste product, share a common evolutionary origin (Martin and Mentel, 2010). Moreover, it has been reported that the oldest water ever discovered on our planet had measurable and significant levels of dissolved H₂ gas (Lollar et al., 2014). Further, it is recognized that H₂ has played a pivotal role in our planet and atmosphere, with H₂ escape leading to oxygenation (Zahnle et al., 2018). It has also been known since the 1950s how critical H₂ in the Earth’s atmosphere was for promoting early life (Urey, 1952).

The human body produces up to 12L of hydrogen gas per day via bacterial breakdown of carbohydrates in the small intestine (Ohno et al., 2012). It has recently been proposed that exercise-driven gut-microbial production of H₂ gas is a possible factor of metabolic health (Ostojic, 2020) while inadequate endogenous H₂ production may play a role in development of Parkinson’s disease (Ostojic, 2018); moreover, it has been suggested that endogenously produced H₂ may serve in regulation of liver homeostasis (Zhang et al., 2020). In turn, exogenous supplementation with hydrogen-rich water has been demonstrated to produce significant improvements in metabolic health (LeBaron et al., 2020), protective effects against non-alcoholic fatty liver disease (Korovljiev et al., 2019) and improvements in symptoms of Parkinson’s disease (Yoritaka et al., 2013) in human pilot research. Furthermore, it is possible that endogenous production of H₂ varies widely across individuals, depending on factors such as diet, and has varied widely throughout our species evolution and history. Due to the intermittent and erratic access to carbohydrates prior to the Neolithic revolution, it is likely that endogenous hydrogen production throughout most of our evolution was also intermittent, with high doses followed by periods of deprivation and absence. This could shed an evolutionary explanation on why consumption of hydrogen water, and intermittent hydrogen inhalation, were shown to be effective in a rodent model of Parkinson’s Disease, but continuous H₂ gas inhalation and additional endogenous production via lactulose were not (Ito et al., 2012).

If humans have evolved and adapted to anticipate intermittent exposure to hydrogen gas, leading to spikes and drops in cellular concentrations, optimal cellular communication may depend on this erratic change. As specific, intermittent, and constantly changing dietary protocols would likely come with low compliance, exogenous H₂ supplementation may be the answer to address these potential evolutionary adaptations. Determining the extent of the importance of H₂, both endogenous and exogenous, on our physiology, particularly regarding stress adaptation, warrants well constructed exploratory research.

Competing Interests:

The author is employed by, and has financial interest in, commercial entities involved in the development and distribution of molecular hydrogen products intended for therapeutic benefits.

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