Hydrogen Gas and its Role in Cell Signaling

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Abstract

Hydrogen gas (H_2) was once thought to be inert in biological systems but it has now become apparent that exposure of a wide range of organisms, including animals and plants, to H_2 or hydrogen-rich water (HRW) has beneficial effects. It is involved in plant development, and alleviation of stress and illness, such as reperfusion injury. Here, an overview of how H_2 interacts with organisms is given.

Introduction

Molecular gaseous hydrogen (H_2) was believed to be inert and non-functional in biological systems, including in mammals [1]. However, there now is a body of literature that suggests that exposure to H_2 has biological effects in a wide range of organisms [1,2]. In 1975 Dole et al. [3], using mice, suggested that H_2 could be used for a cancer therapy, whilst H_2 has been shown to relieve stress challenges in plants [2], and to be a protectant against radiation exposure [4]. However, the exact nature of the interaction of H_2 with biological systems is not well understood, and there is debate as to whether it has effects through cell signaling pathways.

Exposure of Organisms to Molecular Hydrogen

Although hydrogen gas is not abundant in the atmosphere cells can still be exposed to it. Organisms can produce H_2, for example through the use of hydrogenases [5]. In plants H_2 generation was increased addition of auxin [6] and by abscisic acid, ethylene, jasmonate, salt and drought, suggesting that it is important in stress signaling [7]. It appears that H_2 is not endogenous in humans but exposure is likely caused through the action of colonic bacteria [4].

Exposure of organisms is more likely through exogenous means. Treatments with hydrogen gas, hydrogen-rich water (HRW) or hydrogen rich saline solutions (HRS) are now being advocated for a range of conditions and to alleviate stress responses [1]. Therefore the interactions of H_2 with cells will be important to understand.

Is Hydrogen Gas Acting on Cell Signaling Mechanisms?

The role of gases in cell signaling is not new, with abundant evidence that hydrogen sulfide and nitric oxide (NO) have biological effects [8]. If H_2 is acting as a signal it should: be made where and when it is needed, be able to move around, be recognized as being present, and be removed when it is no longer needed. As previously mentioned cells can be exposed to H_2 and since H_2 is small and inert it will be able to move through both soluble (eg cytoplasm) and hydrophobic (membranes) phases of the cell. It is harder, however, to envisage how it may be recognized as a signaling factor, by a receptor for example, since unlike many reactive signals, such as NO, it will not readily react with other cellular components, which could also lead to its removal. Therefore, its role in cell signaling is not easy to see.

One of the actions of H_2 has been reported to be through the modulation of antioxidant levels in cells. It is known that H_2 reacts with hydroxyl radicals and peroxynitrite, the latter known to have cell signaling roles. However H_2 does not appear to react with other reactive signaling molecules such as superoxide, NO or H_2O_2, and therefore seems to not directly affect their signaling actions [1], although the closure of stomatal aperture by H_2 was shown to involve both reactive oxygen species and NO [9]. Effects on antioxidant levels have been reported [10,11] and these would affect signaling by H_2O_2 and NO. Wu et al. [10] also showed that H_2 modulated levels of gene expression in plants, suggesting that signaling effects were evident, as reviewed by others [1].

A mechanism that has been reported is the modulation by H_2 of the heme oxygenase (HO) system. HRW treatment of mice up-regulated HO-1 expression [11]. In cucumber HRW also increased the expression of HO-1 with concomitant increases in protein levels [12]. Root growth effects of HRW were sensitive to the HO-1 inhibitor zinc protoporphyrin IX (ZnPP) with the blocking effects being reversed by the presence of carbon monoxide (CO). Addition of the antioxidant ascorbic acid (AsA) failed to have an effect, suggesting that the HO system was key here.

Effects on other cell signaling mechanisms have also been reported. In mice HRW reduced levels of the intercellular signals TNF-α, IL-6, and IL-1β: this would lead to altered inflammatory responses. Intracellularly, the levels of endoplasmic reticulum stress proteins (p-elF2α, ATF4, XBP1s and CHOP) were reduced [11]. In a similar way, in plants it was found that H_2 influenced genes encoding hormone receptors, whilst endogenous H_2 production itself was induced by plant hormones [7].

Therefore it can be seen that H_2 has multiple ways to affect cellular function. Taking a generic approach, some of the influences of H_2 on cell activities are summarized in Figure 1.

Figure 1 here

Use of Hydrogen Gas to Modulate Cellular Activity

It is evident that in most cases treatments with H_2 gas or HRW have beneficial effects regardless of whether H_2 is acting as a cell signaling component, although Liu et al [13] reported that treatment of rice with HRW inhibited elongation of roots and shoots and decreased fitness parameters. On the other hand, it has been suggested to improve resistance of plants to a number of stresses including drought, salinity, cold and heavy metals [14]. Studies on cadmium toxicity in plants show that HRW reduces oxidative damage and lipid peroxidation, and hence bestows tolerance [2]. Others report that plant growth may benefit from HRW treatments [12]. H_2 was involved in root formation [6] in a study where H_2 increased NO levels, implicating nitrate reductase-dependent NO generation. In a similar study, adventitious root development in cucumber under drought stress was promoted by treatment with HRW and it was suggested that another gas, CO, was involved [15]. Postharvest effects have also been reported [14,16], with some of the benefits being assigned to changes in antioxidant levels. This would certainly be a cleaner treatment than some of the alternatives, such as the use of hydrogen sulfide [17].

In animals, including humans, H_2 has been mooted to be of benefit [1]. It has been suggested to be a cancer therapy [3] and to protect against radiation damage [4]. It has also been shown to have beneficial effects in ischaemia-reperfusion injury and stroke, where reactive oxygen species and oxidative stress are known to be important [18]. Another target of HRW is inflammatory bowel disease [11] where it was protective against colon shortening and colonic wall thickening. One of the challenges of modern medicine is neurological disease; HRW may also help here. Symptoms are relieved by drinking HRW and it has been suggested that it may help patients with Parkinson’s disease [19].

Conclusion

From being considered simply an inert gas there is now a body of evidence that suggests that the effects of hydrogen gas on a range of organisms is worthy of further investigation. It appears to impinge on cell signaling activities, even if it is unclear how it may do so. However, there is indicative evidence that treatments with H_2 gas or HRW may be beneficial for both animals and plants, with increased health and crop yields.

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Figure 1: A summary of roles of molecular hydrogen (H_2) in cells.