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Original Research Article

Potential protective role of hydrogen against cisplatin-induced side effects during chemotherapy: A mini-review of a novel hypothesis for antagonism of hydrogen

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Abstract

Purpose: *To review the potential protective role of hydrogen against cisplatin-induced side effects during chemotherapy.*
Methods: *We searched PubMed and SCOPUS using the following keywords and combinations in titles, keywords, abstracts and full texts: cisplatin; side effects; chemotherapy; tumor; toxicity; hydrogen; reactive oxidative species; and ischemic reperfusion.*
Results: *The pathogenesis of cisplatin-induced side effects is suggested based on the increased level of reactive oxidative species (ROS). Cisplatin induces ROS-dependent platelet apoptosis via the extracellular signal-regulated kinase (ERK) signaling pathway, which might have contributed to cisplatin-induced hematotoxicity, and in particular, thrombocytopenia. Molecular hydrogen has been shown to have therapeutic effects against damage to various organs (especially kidney, brain and liver) caused by ischemic reperfusion (IR) through selective elimination of the most cytotoxic ROS hydrogen radicals without affecting other types of ROS involved in signal transduction in vitro and in vivo.*
Conclusion: *Hydrogen may not only alleviate hematotoxicity in patients with hemorrhagic tendencies during cisplatin-based chemotherapy, but also has a potential protective effect against other side effects induced by cisplatin.*

Keywords: *Reactive oxygen species, Hydrogen radicals, Cisplatin, Hepatotoxicity, Chemotherapy, Side effects, Antagonism*

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INTRODUCTION

Cis-diamminedichloroplatinum II (cisplatin) is one of the most effective platinum-based agents, and has broad spectrum anti-neoplastic effects on various tumors. Unfortunately, cisplatin-based chemotherapy is usually accompanied by several side effects, including nephrotoxicity, peripheral neuropathy, and hematologic toxicity [1], in which reactive oxidative species (ROS) play key roles [2].

Cisplatin induces the generation of various ROS, including hydroxyl radicals, hydrogen peroxide, and superoxide anions, in cells [3,4]. Hydroxyl radicals are the most cytotoxic oxidants that indiscriminately interact with lipids, proteins, and nucleic acids, thus leading to lipid peroxidation, inactivation of proteins, and DNA fragments [3,4]. Cisplatin induces ROS-mediated platelet apoptosis via the extracellular signal-regulated kinase (ERK) signaling pathway, which might

contribute to cisplatin-induced hematotoxicity, and in particular, thrombocytopenia. Moreover, two anti-oxidants (N-acetylcysteine [NAC] and dithiothreitol [DTT]) effectively abolish ROS production, ERK activation, and platelet apoptosis elicited by cisplatin [2]. Although many anti-oxidants, such as NAC, vitamin E, vitamin C, allopurinol, erdosteine, edaravone, and melatonin, exhibit protective effects in animal models involving cisplatin treatment, high-dose anti-oxidants often cause other side effects and interfere with the anti-tumor effects of cisplatin in clinical applications [5-7]. Specifically, hydrogen peroxide and superoxide anion play key roles in cell proliferation, differentiation, and apoptosis as signaling molecules [3]. Therefore, more effective and safe agents are needed.

Molecular hydrogen has been shown to have therapeutic effects against damage to various organs, especially the kidneys, brain, and liver induced caused by ischemic reperfusion (I/R) through selective elimination of the most cytotoxic ROS hydrogen radicals without affecting other types of ROS involved in signal transduction *in vitro* and *in vivo* [8-23]. Specifically, Ohsawa and colleagues [10,13,16,22] reported that molecular hydrogen selectively eliminates ROS levels, especially hydroxyl radicals, and exhibits protective effects in PC12 cultured cells, cell-free systems, and acute rat models of cerebral artery occlusion induced by focal ischemia and reperfusion. Furthermore, it has been reported that hydrogen inhibits ROS and oxidative stress-induced damage involving the hippocampus and learning tasks in chronic physically-restrained mouse models [16]. In addition, inhalation of hydrogen gas also inhibits liver injury caused by I/R through selectively abolishing hydrogical radicals in a mouse model [15]. Moreover, the protective effects of hydrogen-rich water against nephrotoxicity induced by cisplatin has been demonstrated in rat models based on dynamic contrast-enhanced CT (DCF-CT) analysis [10]. These data indicate that the beneficial effects of molecular hydrogen can be used to attenuate the injuries of various organs caused by elevated ROS and oxidative stress.

This work is based on the hypothesize that hydrogen may not only alleviate hematotoxicity in patients with hemorrhagic tendencies during cisplatin-based chemotherapy, but also has potentially protective effects against other adverse side effects induced by cisplatin (Figure 1).

METHODS

The online database, PubMed and SCOPUS, were searched using the following keywords and combinations in titles, keywords, abstracts and full texts: cisplatin; side effects; chemotherapy; tumor; toxicity; hydrogen; reactive oxidative species; and ischemic reperfusion.

RESULTS AND DISCUSSION

Compared with other known treatments, transfusion of hydrogen may have more advantages in preventing cisplatin-induced adverse side effects in patients receiving cisplatin-based chemotherapy. We reviewed related articles, and summarized three main pieces of evidence in support of our hypothesis.

1) Hydrogen selectively eliminates the most cytotoxic ROS hydrogen radicals to generate innocuous water, but does not affect the other types of physiologically beneficial ROS involved in signal transduction and biological activities without compromising the anti-tumor effects of cisplatin [3]. Thus, hydrogen may not only alleviate hematotoxicity in patients with hemorrhagic tendencies during cisplatin-based chemotherapy, but also has potentially protective effects against other side effects incurred by cisplatin.

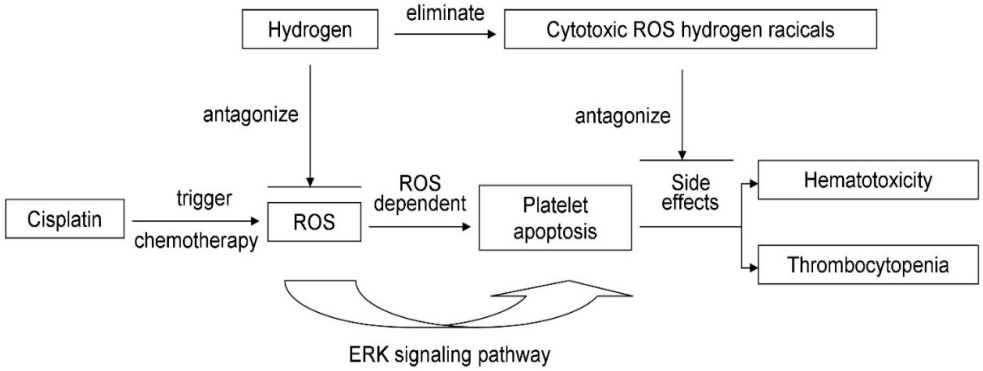

Figure 1: Hypothesis illustrating hydrogen antagonizing cisplatin-induced side effects in chemotherapy. ROS: reactive oxidative species; ERK: extracellular signal-regulated kinase

2) As a mild but effective anti-oxidant, hydrogen is much smaller in weight than most known anti-oxidants, and is electronically neutral. Moreover, hydrogen can diffuse rapidly into tissues and cells, penetrate biomembranes, and diffuse into nuclei, the cytosol, and mitochondria, which are the main sources of ROS production, and selectively abolish hydroxyl radicals in living cells [8-23].

3) A hydrogen concentration of 1 or 2 % shows an efficient protective effect on organ injuries in animal models, and hydrogen does not explore or burn at a concentration < 4.7 %.

4) Production of ROS is suggested in platelets during storage [24]. In fact, increasing periods without agitation induce platelet apoptotic cascades, including depolarization of MMP, down-regulation of Bcl-2, up-regulation of Bax and Bak, activation of caspases, and PS exposure, which are closely correlated with elevation of intracellular ROS levels during storage [25,26]. Furthermore, thrombin elicits platelet apoptosis through the production of ROS [27,28]. Hydrogen may protect platelet apoptosis and improve the quality of platelets in hydrogen during storage. Therefore, hydrogen may have the potential to be used as a new class of anti-apoptotic agents for platelet storage.

CONCLUSION

In conclusion, our review of the literature and existing data indicate that hydrogen not only inhibits cisplatin-induced hematotoxicity (especially bleeding), but also improves long-lasting improvement in function of kidneys and other organs by attenuating oxidative stress, preventing platelet apoptosis, and providing protection against injured organs.

DECLARATIONS

Acknowledgement

None provided.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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