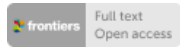


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Hydrogen Inhalation Protects against Ototoxicity Induced by Intravenous Cisplatin in the Guinea Pig

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Abstract

Introduction: Permanent hearing loss and tinnitus as side-effects from treatment with the anticancer drug cisplatin is a clinical problem. Ototoxicity may be reduced by co-administration of an otoprotective agent, but the results in humans have so far been modest. **Aim:** The present preclinical *in vivo* study aimed to explore the protective efficacy of hydrogen (H₂) inhalation on ototoxicity induced by intravenous cisplatin. **Materials and Methods:** Albino guinea pigs were divided into four groups. The Cispt ($n = 11$) and Cispt+H₂ ($n = 11$) groups were given intravenous cisplatin (8 mg/kg b.w., injection rate 0.2 ml/min). Immediately after, the Cispt+H₂ group also received gaseous H₂ (2% in air, 60 min). The H₂ group ($n = 5$) received only H₂ and the Control group ($n = 7$) received neither cisplatin nor H₂. Ototoxicity was assessed by measuring frequency specific ABR thresholds before and 96 h after treatment, loss of inner (IHCs) and outer (OHCs) hair cells, and by performing densitometry-based immunohistochemistry analysis of cochlear synaptophysin, organic transporter 2 (OCT2), and copper transporter 1 (CTR1) at 12 and 7 mm from the round window. By utilizing metabolomics analysis of perilymph the change of metabolites in the perilymph was assessed. **Results:** Cisplatin induced electrophysiological threshold shifts, hair cell loss, and reduced synaptophysin immunoreactivity in the synapse area around the IHCs and OHCs. H₂ inhalation mitigated all these effects. Cisplatin also reduced the OCT2 intensity in the inner and outer pillar cells and in the stria vascularis as well as the CTR1 intensity in the synapse area around the IHCs, the Deiters' cells, and the stria vascularis. H₂ prevented the majority of these effects. **Conclusion:** H₂ inhalation can reduce cisplatin-induced ototoxicity on functional, cellular, and subcellular levels. It is proposed that synaptopathy may serve as a marker for cisplatin ototoxicity. The effect of H₂ on the antineoplastic activity of cisplatin needs to be further explored.

Keywords: ABR; copper transporter 1; *in vivo*; inner hair cells; organic cation transporter 2; outer hair cells; perilymph metabolomics; synaptophysin.

Figures

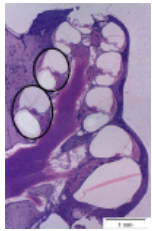


Figure 1 Micrograph showing a mid-modiolar cross-section...

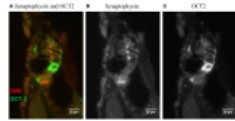


Figure 2 (A) A fluorescent image (40...

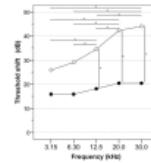


Figure 3 Guinea pigs were subjected to...

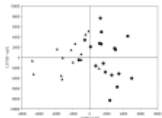


Figure 4 OPLS-DA scores plot (R2X 0.219,...

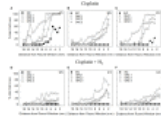


Figure 5 Representative cochleograms from animals in...

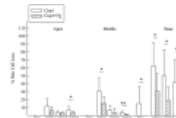


Figure 6 The percentage of lost IHCs...

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