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Molecular hydrogen modulates gene expression via histone modification and induces the mitochondrial unfolded protein response

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Abstract

Molecular hydrogen (H_2) is a biologically active gas that is used medically to ameliorate various systemic pathological conditions. H_2 also regulates gene expression involved in intracellular signaling and metabolic pathways. However, it is unclear whether H_2 affects gene expression directly or through indirect effects as a consequence of health improvement. Therefore, we attempted to identify genes that exhibit similar changes in expression in response to H_2 by employing DNA microarrays and gene set enrichment analysis to analyze RNA from liver and lung of rats and mice with or without dietary stress. We found that H_2 activated the expression of sets of genes regulated by histone H3K27 methylation status. H_2 also modified the expression of many genes regulated by a wide variety of signaling pathways. RT-qPCR showed that H_2 up-regulated expression of Kcnc3, a H3K27-regulated gene, in organs such as liver, lung, kidney and brain. Furthermore, using immunohistochemistry and immunoblot analysis, we observed changes in H3K27 methylation status in the liver of mice and rats administered H_2. Moreover, we showed that H_2 simultaneously induced the H3K27 demethylase, Jmjd3, and mitochondrial unfolded protein response (mtUPR)-related genes. Recently, alteration of mitochondrial function was shown to cause induction of H3K27 demethylase or chromatin restructuring, followed by mtUPR activation through the alteration of H3K27 or H3K9 methylation states. Taken together, our study suggests that H_2 can induce beneficial effects through mtUPR activation via epigenetic histone modification and by modification of gene expression.

Keywords: DNA microarray; Gene set enrichment analysis; Histone H3K27; Hydrogen; Mitochondrial unfolded protein response.

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