ARTICLES
INTERVENTION AND PREVENTION

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Molecular Hydrogen Improves Obesity and Diabetes by Inducing Hepatic FGF21 and Stimulating Energy Metabolism in *db/db* Mice

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Recent extensive studies have revealed that molecular hydrogen (H_2) has great potential for improving oxidative stress-related diseases by inhaling H_2 gas, injecting saline with dissolved H_2, or drinking water with dissolved H_2 (H_2-water); however, little is known about the dynamic movement of H_2 in a body. First, we show that hepatic glycogen accumulates H_2 after oral administration of H_2-water, explaining why consumption of even a small amount of H_2 over a short span time efficiently improves various disease models. This finding was supported by an *in vitro* experiment in which glycogen solution maintained H_2. Next, we examined the benefit of *ad libitum* drinking H_2-water to type 2 diabetes using *db/db* obesity model mice lacking the functional leptin receptor. Drinking H_2-water reduced hepatic oxidative stress, and significantly alleviated fatty liver in *db/db* mice as well as high fat-diet-induced fatty liver in wild-type mice. Long-term drinking H_2-water significantly controlled fat and body weights, despite no increase in consumption of diet and water. Moreover, drinking H_2-water decreased levels of plasma glucose, insulin, and triglyceride, the effect of which on hyperglycemia was similar to diet restriction. To examine how drinking H_2-water improves obesity and metabolic parameters at the molecular level, we examined gene-expression profiles, and found enhanced expression of a hepatic hormone, fibroblast growth factor 21 (FGF21), which functions to enhance fatty acid and glucose expenditure. Indeed, H_2 stimulated energy metabolism as measured by oxygen consumption. The present results suggest the potential benefit of H_2 in improving obesity, diabetes, and metabolic syndrome.

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INTRODUCTION

Oxidative stress is involved in many lifestyle-related diseases, including diabetes, atherosclerosis, heart failure, Alzheimer's disease, and Parkinson diseases (1–6). Recent studies have revealed that molecular hydrogen (H_2) acts as a novel antioxidant and prevents or ameliorates diseases associated with oxidative stress in animal experiments (7–18) and clinical tests (19–22).

the liver and leads to hyperglycemia and hyperlipidemia (23). *Db/db* mice lack a functional leptin receptor, and have been extensively studied as a model for type 2 diabetes (24,25).

In this study, we showed that H_2 can be accumulated in the liver with glycogen after oral administration. Next, chronic consumption of H_2-water reduced oxidative stress in the liver of *db/db* mice, and improved obesity and diabetes. As a mechanis-