consume H_2; however, when H_2 is consumed from H_2-water, a very limited amount of H_2 can be consumed, because H_2 is dissolved in water at a saturated level of only 0.8 mmol/l under atmospheric pressure. After H_2-water is consumed, most H_2 in blood becomes undetectable within 30 min (14), probably *via* expiration from the lungs; thus, it has been an open question why H_2-water is effective despite its small amount and short exposure. In this study, it was found that H_2 can be accumulated and reserved in the liver with glycogen, which at least partly explains this question.

Moreover, it has been reported that H_2 acts as an anti-inflammatory and antiallergic regulator by inducing inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6 and some phosphorylating signal factors (9,10,14,32). On the other hand, the concept that obesity is a proinflammatory disease has been accepted (33); thus, consumption of H_2-water may suppress obesity by acting as an anti-inflammatory.

Alternatively, we found that consumption of H_2-water enhanced the expression of FGF21. Since it has not been shown that H_2 directly regulates transcription, H_2 is indirectly involved in FGF21 expression. Since FGF21 is a metabolic hormone that improves insulin sensitivity and glucose clearance, reduces plasma triglyceride concentrations and suppresses weight gain when fed a high-fat diet (26–29), all the findings shown in this study were elucidated by the enhanced expression of FGF21.

Indeed, we revealed that drinking H_2-water stimulates energy metabolism as measured by O_2 consumption and CO_2 production. The enhancement of energy metabolism may fully elucidate why consumption of H_2-water suppresses the gain of fat and body weights and improves metabolic parameters; however, it remains unknown whether the induction of FGF21 fully elucidates the enhancement of energy metabolism. Moreover, the relationships among the reduction of oxidative stress, induction of FGF21 expression and stimulation of energy metabolism are still unclear. It should be analyzed whether these relationships are direct or indirect. It might be valuable to examine the relationship of obesity with oxidative stress. Although the primary target of H_2 essentially remains unknown, these findings provide a clue to understand the mechanism of chronic treatment with H_2-water.

Finally, we would like to emphasize that the novel benefit of H_2 in therapeutic and preventive applications for metabolic syndrome could be achieved by the most convenient way, H_2-water.

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DISCLOSURE

The authors declared no conflict of interest.

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