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Hydrogen: An Endogenous Regulator of Liver Homeostasis

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Basic and clinical studies have shown that hydrogen (H_2), the lightest gas in the air, has significant biological effects of anti-oxidation, anti-inflammation, and anti-apoptosis. The mammalian cells have no abilities to produce H_2 due to lack of the expression of hydrogenase. The endogenous H_2 in human body is mainly produced by anaerobic bacteria, such as *Firmicutes* and *Bacteroides*, in gut and other organs through the reversible oxidation reaction of $2\ H^+ + 2\ e^- \rightleftharpoons H_2$. Supplement of exogenous H_2 can improve many kinds of liver injuries, modulate glucose and lipids metabolism in animal models or in human beings. Moreover, hepatic glycogen has strong ability to accumulate H_2, thus, among the organs examined, liver has the highest concentration of H_2 after supplement of exogenous H_2 by various strategies *in vivo*. The inadequate production of endogenous H_2 play essential roles in brain, heart, and liver disorders, while enhanced endogenous H_2 production may improve hepatitis, hepatic ischemia and reperfusion injury, liver regeneration, and hepatic steatosis. Therefore, the endogenous H_2 may play essential roles in maintaining liver homeostasis.

Keywords: gut microbiota, oxidative stress, inflammation, apoptosis, glucose homeostasis, lipids homeostasis

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INTRODUCTION

Hydrogen (H_2) is the lightest and diffusible gas molecule. H_2 is produced as an endproduct of carbohydrate fermentation, and is reoxidized primarily by sulfate-reduction, methanogenesis, and acetogenesis (Wolf et al., 2016). However, due to lack of the functional hydrogenase genes, mammalian cells fail to produce H_2 themselves; the endogenous H_2 in mammalian is mainly produced by hydrogenases-containing bacterial species present in human gastrointestinal tract, the respiratory system, mouth and pharynx, vagina, and skin (Zhang et al., 2018b; Tan et al., 2019). Over 200 pathogens and pathobionts, and 70% of microbial species in gastrointestinal tract listed in the Human Microbiome Project encode genes for hydrogenases (Wolf et al., 2016; Benoit et al., 2020). Early in 1975, *Malcolm Dole et al.* firstly reported that exposed hairless albino mice with squamous cell carcinoma to a mixture of 97.5 percent H_2 and 2.5 percent oxygen (O_2) at a total pressure of 8 atmospheres for periods up to 2 weeks would cause a marked regression of the skin tumors possibly by neutralizing toxic free radicals (Dole et al., 1975). In 2007, the milestone publication in *Nature Medicine* by *Ikuroh Ohsawa et al.* had confirmed that H_2 acted as a therapeutic antioxidant by selectively reducing the cytotoxic hydroxyl radicals in PC12 cells, however, H_2 did not react with other reactive oxygen species (ROS), which possess physiological

roles (Ohsawa et al., 2007). Thus, inhalation of H_2 gas markedly suppressed focal ischemia and reperfusion (I/R)-induced brain injury in rats by buffering the effects of oxidative stress. From then on, researchers have extensively investigated the functions and mechanisms of H_2, studies indicated that supplement of exogenous H_2 has the potential abilities to protect against acute or chronic damage of tissues or organs, including brain, heart, blood vessel, lung, stomach, intestine, pancreas, liver, gallbladder, kidney, testis, ovary, breast, eye, ear, bones, skin, *et al.* (Guo et al., 2013; Sun et al., 2013; Zhang et al., 2016a; Zhang et al., 2016b; Ge et al., 2017; Zhang et al., 2017; Frajese et al., 2018; Zhang et al., 2018b; Chen et al., 2019; Tan et al., 2019; Tao et al., 2019). H_2 dissolved in medium protected PC12 cells against cell death in a dose-dependent manner, as that $H_2 > 25$ μM had significant anti-oxidative effect (Ohsawa et al., 2007). The concentrations of H_2 is about 168 μM in small intestine and 43 μM in the stomach of mice, with similar levels predicted in humans (Benoit et al., 2020), this indicates that the concentration of endogenous H_2 in human body is significantly higher than that needed for anti-oxidative effect.

THE EXOGENOUS HYDROGEN IN LIVER DISEASES

Liver has strong ability to increase and accumulate H_2 after supplement (Kamimura et al., 2011; Sun et al., 2011; Sobue et al., 2015; Iketani et al., 2017; Yamamoto et al., 2019). Among the organs examined *in vivo*, liver has the highest mean maximum concentration (Cmax, 29.0 ± 2.6 μmol/L) in rats by continuous inhalation of 3% H_2 (Yamamoto et al., 2019). The concentration of H_2 in liver peaked approximately 5 min following intraperitoneal injection of 8 ml/kg H_2 rich saline in mice, and returned to the normal levels 40 min later (Sun et al., 2011). Oral intake of H_2 rich water rapidly but transiently increased H_2 concentrations in liver and atrial blood, while H_2 concentrations in arterial blood and kidney were one-tenth of those in rat liver and atrial blood (Sobue et al., 2015). Mechanistically, hepatic glycogen accumulated H_2 after oral administration of H_2 rich water *in vivo*, and the *in vitro* experiment also confirmed that glycogen solution maintained H_2, explaining why consumption of even a small amount of H_2 over a short span time efficiently improved various liver diseases in animal models (Kamimura et al., 2011; Ohta, 2014).

The imbalance of redox homeostasis plays an important role in liver homeostasis (Chen et al., 2020). Supplements of exogenous H_2 by the strategies of drinking H_2 rich water, intraperitoneal injection of H_2 rich saline, H_2 saturated lactate Ringer's solution infused *via* portal vein, and breathing H_2 gas *et al.*, safeguarded various acute or chronic liver injuries in animal models, for example, hepatic I/R injuries, including hepatic portal vein occluding, partial hepatectomy, and cold I/R in liver transplantation *et al.* (Fukuda et al., 2007; Xiang et al., 2012; Matsuno et al., 2014; Tan et al., 2014; Zhang et al., 2015a; Shimada et al., 2016; Lu et al., 2017; Bai et al., 2018; Ishikawa et al., 2018; Li et al., 2018a; Li et al., 2018b; Zhang et al., 2018a; Ge et al., 2019; Uto et al., 2019; Zhang et al., 2019), bile duct ligation (BDL)- (Liu et al., 2010; Liu et al., 2016), sepsis- (Sun et al., 2011; Iketani et al., 2017; Yan et al., 2019), drugs- (Sun et al., 2011; Koyama et al., 2014; Zhang et al., 2015b; Gao et al., 2016), and carbon dioxide (CO_2) pneumoperitoneum- (Chen et al., 2018) induced liver injuries, *et al.* by suppressing excessive oxidative stress, inflammation and cell death *et al.* (**Supplementary Table 1**). In addition, H_2 alleviated chronic intermittent hypoxia (IH)-induced liver injury *via* reducing oxidative stress levels (Yang et al., 2018), and improved chronic IH-induced renal injury through reducing renal iron transporting related proteins expression to alleviate iron overload (Guan et al., 2019). It is known that liver is an essential organ that orchestrates systemic iron balance by producing and secreting hepcidin, which acts as the iron hormone, induces degradation of the iron exporter ferroportin to control iron entry into the bloodstream from dietary sources, iron recycling macrophages, and body stores (Wang and Babitt, 2019). However, it is not known whether H_2 can modulate liver iron sensing and body iron homeostasis.

The liver is a central hub for lipids metabolism, with uptake, esterification, oxidation and secretion of fatty acids (FAs) all occurring in hepatocytes (Chen, 2015; Gluchowski et al., 2017). Hepatic FAs originate from three sources, plasma non-esterified free FAs (lipolysis in adipocytes and unabsorbed portions of lipoproteins after lipoprotein lipase hydrolysis in peripheral tissues), *de novo* biosynthesis from acetyl CoA derived from different sources, and lipoproteins such as chylomicron remnants (leftover of triacylglycerol (TAGs) from the dietary source) (Chen, 2015). FAs in hepatocytes are esterified with glycerol 3-phosphate to generate TAG or with cholesterol to produce cholesterol esters, which are either stored in hepatic lipid droplets or secreted into the circulation in the forms of very low-density lipoprotein (VLDL) particles (Rui, 2014; Chen, 2015). FAs are also incorporated into phospholipids, which are an essential component of cell membranes, and the surface layer of lipid droplets, VLDL, and bile particles (Rui, 2014). During fasted state, FAs are transported into mitochondria for β-oxidation to generate acetyl CoA, which in mitochondria can be used for the production of ketone bodies (Chen, 2015). H_2 has the abilities to modulate lipids profiles and functions *in vivo*. H_2 rich saline decreased plasma total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol levels, and reduced the levels of apolipoprotein (apo) B100 in LDL and apo E in VLDL, improved hyperlipidemia-injured high-density lipoprotein (HDL) functions, including the capacity of enhancing cellular cholesterol efflux and protecting against LDL oxidation, in high-fat diet (HFD)-fed Syrian golden hamsters (Zong et al., 2012). In a before-after self-controlled study, patients with potential metabolic syndrome consuming H_2 rich water for 10 weeks resulted in decreased serum TC and LDL-cholesterol levels, and apo B100 and apo E levels, improved dyslipidemia-injured HDL functions, including the ability to inhibit LDL oxidation, the ability to suppress TNF-α-induced monocyte adhesion to endothelial cells (ECs) and TNF-α-induced ECs apoptosis, and the ability to stimulate cholesterol efflux from macrophage foam cells (Song et al., 2013). These were further confirmed in patients

with hypercholesterolemia in a double-blinded, randomized, and placebo-controlled trial (Song et al., 2015). They found that H_2 treatment increased plasma HDL3-mediated cholesterol efflux *via* ATP-binding cassette transporter A1 from macrophages *ex vivo*; enhanced HDL antiatherosclerotic functions as that of suppressing LDL oxidation, oxidized-LDL-induced THP-1 monocytes adhesion to ECs, ox-LDL-induced ICAM-1, VCAM-1, and IL-6 expression in ECs, and oxidized-LDL-induced ECs apoptosis; decreased plasma levels of TC and LDL cholesterol, apo B100; and decreased plasma levels of malondialdehyde (MDA), interleukin-6 (IL-6) and TNF-α, increased the activity of superoxide dismutase (SOD) in plasma, and increased the activity of paraoxonase-1 (PON-1), an antioxidant enzyme associated with HDL, in both plasma and HDL3 fractions (Song et al., 2015). Using cigarette smoke exposure mice model, *Qin Shucun et al.* found that H_2 saturated saline minimized the impaired plasma lipid profiles and HDL functionalities, moreover, improved the impaired process of reverse cholesterol transport (RCT), in which it promoted the efflux of excess cholesterol from peripheral tissues and returned it to the liver for utilization, direct secretion into bile and feces disposal (Zong et al., 2015). Therefore, H_2 is an essential regulator of lipids profiles, HDL functions and RCT *et al.*

Hepatic glucose production accounts for ~90% of endogenous glucose production, and it is crucial for systemic glucose homeostasis, and the net hepatic glucose production is the summation of glucose fluxes from gluconeogenesis, glycogenolysis, glycogen synthesis, glycolysis, and other pathways (Petersen et al., 2017). H_2 has been shown to maintain the glucose homeostasis, improve fatty liver diseases in animal models and in human beings. Drinking H_2 rich water reduced obesity, decreased levels of plasma glucose, insulin, and triglyceride, and improved hepatic oxidative stress in *db/db* mice, and alleviated fatty liver in *db/db* mice and HFD-fed wild-type mice (Kamimura et al., 2011; Jackson et al., 2018). Mechanistically, H_2 increased O_2 consumption and CO_2 production without influencing movement activities, and enhanced the expression of hepatic fibroblast growth factor 21 (FGF21), which functioned to improve carbohydrate and lipid homeostasis (Kamimura et al., 2011; BonDurant and Potthoff, 2018). H_2 rich saline alleviated streptozotocin (STZ) and HFD-induced nonalcoholic fatty liver disease (NAFLD) in rats, decreased fasting blood glucose and insulin levels, improved insulin sensitivity and glucose tolerance, lowered hepatic TNF-α, IL-1β, 8-hydroxy-2′-deoxyguanosine (8-OHdG), 3 −nitrotyrosine levels, and Caspase-3 activity, increased hepatic expression of PPARα, which induced the expression of medium-chain acyl-CoA dehydrogenase and acyl-CoA oxidase 1, the rate-limiting enzymes in mitochondrial and peroxisomal fatty acids β-oxidation, respectively, and PPARγ, which contributed to hepatic steatosis (Zhai et al., 2017; Wang et al., 2020). Intraperitoneal injection of H_2 gas had the therapeutic effect on methionine-choline-deficient (MCD) diet-induced NAFLD in mice *via* inhibiting hepatic MDA levels and JNK phosphorylation (Zhou et al., 2020). *Daisuke Kawai et al.* revealed that H_2 rich water improved MCD diet-induced nonalcoholic steatohepatitis (NASH) in mice by decreasing plasma ALT levels, hepatic TNF-α and IL-6, oxidative stress and apoptosis related markers, free fatty acid (FFA) uptake-related gene fatty acid translocase (FAT) (Kawai et al., 2012). H_2 rich water also reduced tumor numbers and maximum tumor size in STZ-induced NASH-related hepatocarcinogenic mice model (Kawai et al., 2012). However, they found that H_2 decreased hepatic PPARα and its targeted gene FFA β-oxidation-related gene acyl-CoA oxidase expression in MCD diet-induced NASH mice model (Kawai et al., 2012). Therefore, the regulated effects of H_2 on PPARα might be dependent on the animal models examined, it is possible that H_2 regulates hepatic lipid metabolism *via* maintaining the balance of hepatic *de novo* lipogenesis/FFAs uptake and β-oxidation. H_2 also had the protective effects on chronic-plus-binge ethanol (EtOH) feeding-induced liver injury, possibly by inducing acyl ghrelin to suppress the expression of pro-inflammatory cytokines TNF-α and IL-6 and induce the expression of IL-10 and IL-22, thus activating antioxidant enzymes against oxidative stress (Lin et al., 2017). In human beings, drinking H_2 rich water improved lipids and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance (Kajiyama et al., 2008), reduced liver fat accumulation in overweight patients suffering from mild-to-moderate NAFLD (Korovljev et al., 2019), improved liver function and reduced viral load in patients with chronic hepatitis B (Xia et al., 2013), attenuated biological reaction to radiation-induced oxidative stress without compromising anti-tumor effects in patients with liver tumors (Kang et al., 2011), and alleviated liver injury of colorectal cancer patients treated with mFOLFOX6 chemotherapy (Yang et al., 2017). Therefore, exogenous H_2 has the abilities to regulate hepatic glucose and lipids metabolism, attenuate virus and chemotherapy related liver injuries, and improve I/R or drugs-induced hepatic inflammation and oxidative stresses.

THE ENDOGENOUS HYDROGEN IN LIVER HOMEOSTASIS

H_2 has antioxidant activity and, in the healthy colon, physiological concentrations of H_2 might protect the mucosa against oxidative insults, whereas an impaired H_2 economy might facilitate inflammation or carcinogenesis (Carbonero et al., 2012). Moreover, the decreased endogenous H_2 levels might also play essential roles in Parkinson's disease, cerebral and myocardial I/R injuries, and chronic heart failure pathogenesis, while supplement of exogenous H_2 may act as a possible therapy for these brain and heart diseases (Fu et al., 2009; Fujita et al., 2009; Shinbo et al., 2013; Yoritaka et al., 2013; Zhai et al., 2013; Hasegawa et al., 2015; Ostojic, 2018; Shibata et al., 2018; Suzuki et al., 2018). In liver, the endogenous H_2 produced by intestinal flora had the ability to improve Concanavalin A (Con A)-induced hepatitis by decreasing serum TNF-α and IFN-γ, while inhibition of intestinal flora by antibiotics aggravated Con A-induced hepatitis (Kajiya et al., 2009). Feeding diet with 20% high amylose cornstarch enhanced

H_2 generation in intestine, and subsequently alleviated hepatic I/R injury in rats (Tanabe et al., 2012). Lactulose accelerated liver regeneration after hepatectomy in rats by inducing endogenous H_2 production, which may increase hepatic SOD expression and activity, decrease hepatic MDA, IL-6 and TNF-α levels (Yu et al., 2015). Supplement of exogenous H_2 by H_2 rich saline had a similar protective effect as lactulose, in contrast, the antibiotics inhibited the regeneration-promoting effect of lactulose by reducing H_2 production (Yu et al., 2015). L-arabinose, a naturally occurring plant pentose, elicited gut-derived endogenous H_2 production and alleviated HFD-induced metabolic syndrome, including reduced body weight gain especially fat weight, alleviated liver steatosis, improved glucose homeostasis, reduced systemic dyslipidemia and inflammation in mice (Zhao et al., 2019). Mechanistically, L-arabinose modulated gene-expressions involved in lipid metabolism and mitochondrial function in key metabolic tissues (Zhao et al., 2019). Therefore, endogenous H_2 is an essential regulator of liver homeostass, such as improving hepatitis, hepatic I/R injury, liver regeneration, hepatic steatosis as well as glucose and lipids homeostasis.

DISCUSSION

The total H_2 levels in mammals are dependent on the balance between H_2-producing fermentative bacteria, such as colonic *Firmicutes* and *Bacteroidetes et al.*, and H_2 consumers, H_2 acts as a substrate for acetic acid producing bacteria, methanogenic bacteria, and sulfate reducing bacteria to utilize and support their energy metabolism (Nakamura et al., 2010; Carbonero et al., 2012; Wolf et al., 2016). The H_2 cycling is central to microbial composition and metabolic homeostasis in the human gastrointestinal tract (Wolf et al., 2016). The gastrointestinal tract-products such as host and/or microbial metabolites (including H_2) and pathogen-associated molecular patterns translocate to the liver *via* the portal vein or by free diffusion and influence liver functions (Tripathi et al., 2018). In contrast, liver transports bile salts, antimicrobial molecules as well as other liver metabolites to the intestinal lumen through the biliary tract and systemic circulation, some of which maintain microecology balance by controlling unrestricted bacterial overgrowth (Tripathi et al., 2018). Therefore, H_2 might be as a novel bridge between gut and liver, and play an important role in gut-liver axis (**Figure 1**).

Colonic gases, including H_2, CO_2, methane (CH_4), nitrogen and O_2 as well as other trace gases including volatile amines, NH_3, mercaptans, and sulfur-containing gases, such as hydrogen sulphide (H_2S), which is synthesized by cystathionine γ-lyase (CSE), cystathioine β-synthase (CBS), and 3-mercaptopyruvate sulfurtransferase (3-MST) in concert with cysteine aminotransferase (CAT) in mammalian cells, and is also a by-product of H_2 metabolism by sulphate-reducing bacteria, are among the most tangible features of digestion, clinically, changes in volume or composition of colonic gases have linked with bowel disorders, including lactose and glucose intolerance, small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome (IBS), inflammatory bowel diseases, constipation, colorectal cancer *et al.*, and measurement of H_2 and CH_4 by breath can indicate lactose and glucose intolerance, SIBO and IBS (Nakamura et al., 2010; Carbonero et al., 2012; Mani et al., 2014). It should be noticed that both probiotics and harmful bacteria (such as carcinogenic strains of *Helicobacter pylori*) can produce H_2 (Olson and Maier, 2002; Benoit et al., 2020), therefore, during H_2 breath test, the relative ratio and balance of these two kinds of bacteria in human body should be taken into consideration for evaluating the long term benefits or harms of H_2 breath in health.

Similar to the protective effects of endogenous H_2 on hepatic I/R injury, H_2S can also act as an endogenous gas molecule that protects against hepatic I/R injury (Hine et al., 2015). Through knockdown or knockout (KO) of H_2S-generating enzymes in cells or in animals, endogenous H_2S has been shown to have essential roles in affecting glucose and lipids metabolism, insulin sensitivity, hepatic oxidative

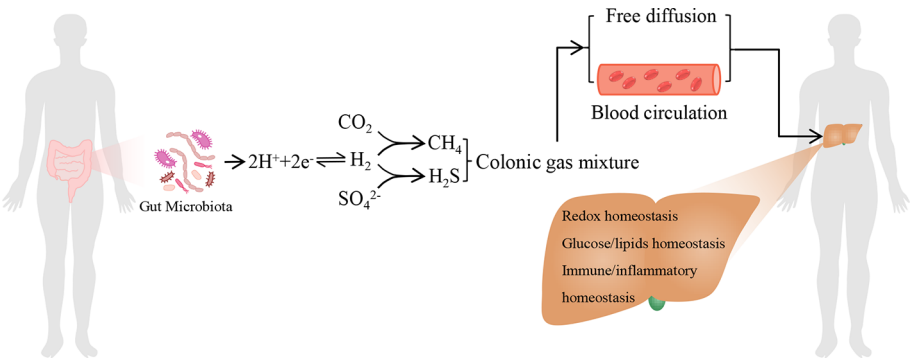

FIGURE 1 | The model of endogenous H_2 in modulating liver homeostasis. The endogenous H_2 is primarily produced by hydrogenase-expressing fermentative bacteria in the gastrointestinal tract. Moreover, H_2S and CH_4 are by-products of H_2 metabolism derived from sulphate-reducing bacteria and methanogenic bacteria, respectively. It should be noticed that hepatocyte can also produce H_2S and CH_4. The colonic gas mixture, including H_2, H_2S, CH_4, and other bioactive gas molecules produced by gut microbiota, can arrive at the liver by free diffusion or by blood circulation. These gas molecules may influence hepatic redox homeostasis, glucose and lipids homeostasis, immune and inflammatory homeostasis, respectively, together by another one or more. Therefore, H_2 may act as a novel bridge between gut and liver, and play a central role among the colonic gas mixture in modulating liver homeostasis.

stress, hepatic mitochondrial bioenergetics (modulating mitochondrial structure and function, respiratory chain, and cellular bioenergetics), hepatic fibrosis and autophagy *et al.* (Mani et al., 2014; Sun et al., 2015; Ci et al., 2017; Wang et al., 2017; Wenzhong et al., 2017; Untereiner and Wu, 2018; Wu et al., 2019). However, genetically manipulating the H_2S-producing enzymes in mammalian cells could not exclude the biological effects of endogenous H_2S produced by sulphate-reducing bacteria in animals. In addition, CH_4 is another by-product of H_2 metabolism derived from methanogenic bacteria, and *Mihály Boros* group found that CH_4 can also be produced by rat liver mitochondria, it has hepatic protective effects by exogenous supplement (Ghyczy et al., 2008; Ye et al., 2015; He et al., 2016; Strifler et al., 2016; Yao et al., 2017; Feng et al., 2019; Li et al., 2019a; Li et al., 2019b), however, the hepatic functions of endogenous CH_4 produced by methanogenic bacteria or by hepatocytes are not clear. As that H_2, H_2S, and CH_4 are endogenous gas molecules, they may exist as colonic gas mixture and transport into liver by blood circulation or free diffusion, H_2S and CH_4 can also be produced in liver. Therefore, the functional crosstalk among H_2, H_2S and CH_4 in liver, and the influences of these gas mixture on hepatic homeostasis are interesting topics for further investigation. It seems that H_2 might have a central role among these gases in regulating liver homeostasis (**Figure 1**). The temporal and spatial metabolism of microbial H_2 in human body is relevant to health status, modulating endogenous H_2 metabolism either by diminished utilization or enhanced production, and the strategies such as developing personalize dietary supplementation and precision medicine based on an individual's H_2-producing or consuming microbiome, might provide a novel means of regulating liver homeostasis.

AUTHOR CONTRIBUTIONS

Concept and idea: YZ and HY. Preparation of figure and table: YZ, JX. YZ wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00877/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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