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# Oral administration of mannitol may be an effective treatment for ischemia–reperfusion injury

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## SUMMARY

Inhalation of hydrogen gas has been proved to be an effective treatment for ischemia–reperfusion injury. There has been considerable evidence of hydrogen's protective effect to diseases related to oxidative injury, such as the ischemia–reperfusion injury of the brain, liver and heart. Our previous studies demonstrated that intraperitoneal injection of hydrogen-rich saline protected hypoxic-ischemic brain injury, myocardial and intestine ischemia–reperfusion injury in rats. Bacteria in the large intestine can produce endogenous hydrogen, and our preliminary experiments revealed that oral administration of mannitol in humans and animals can significantly increase the level of endogenous hydrogen. Therefore, we speculated that oral administration of mannitol may be effective against ischemia–reperfusion injury, which is a convenient, effective and unique treatment for ischemia–reperfusion injury.

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## Introduction

Ischemia–reperfusion injuries produce various types of reactive oxygen species (ROS). Of all these ROS,  $H_2O_2$  and NO are very important to health as they are signaling molecules and their toxic effects could be negligible at a low concentration. But OH and ONOO<sup>-</sup> are very toxic, often leading to cell oxidative damage [1]. In 2007 and 2008, inhalation of 2% hydrogen was proved to be effective to prevention of cerebral ischemia–reperfusion injury [2–4]. Other ways of hydrogen administration, such as drinking of hydrogen-rich water, intraperitoneal and intravenous injection of hydrogen saline, have also been proved against be effective to myocardial, retinal, intestinal, hepatic and cerebral ischemia–reperfusion injury [5–11].

However, these ways of hydrogen administration are all somehow inconvenient for regular application. Fortunately, in humans and animals, there is a certain account of endogenous hydrogen generated by some anaerobic bacteria in the large intestine. It is reported that the mobilization of them was effective in prevention of some diseases [12–14]. Our recent studies showed that oral administration of mannitol significantly increased endogenous hydrogen level (data not shown). So, we raise the hypothesis that oral administration of appropriate dosage of mannitol may be preventive against ischemia–reperfusion injury by increasing hydrogen content in vivo.

## Exogenous hydrogen and ischemia–reperfusion injury

When ischemia induced injury occurs, the treatment principle is to restore blood flow as soon as possible. However, with the resumption of blood supply in the ischemic region, more serious injury may be induced, which is called “ischemia–reperfusion injury”. The mechanism of ischemia–reperfusion injury is not clear, but it is generally accepted that the increase in ROS, inflammatory response, calcium overload and increased cell apoptosis are involved. The increase of ROS, the most important start-up and effect factors, causes oxidative damage to biological macromolecules, leading to cell apoptosis and necrosis [15]. Therefore, ischemia–reperfusion injury is a typical oxidative damage, and ROS scavenger treatment is under intensive research. In 2007, Ohsawa reported that inhalation of hydrogen could significantly prevent cerebral ischemia–reperfusion injury by selectively eliminating ROS [2]. Subsequently, other researchers proved that both inhalation of hydrogen and drinking of hydrogen-rich water had therapeutic effect on ischemia–reperfusion injury in the brain, liver and heart [3,4,6,9]. Moreover, hydrogen-rich saline injection has also been proved to be effective against neonatal hypoxic-ischemic brain injury and small intestine ischemia–reperfusion injury [5,9–11].

## The existence of endogenous hydrogen and its role in the treatment of diseases

However, inhalation of hydrogen, drinking of hydrogen water and intraperitoneal injection of hydrogen saline are somehow

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inconvenient. For inhalation of hydrogen, there exists the risk of explosion in the process, the operation is complicated and special equipment is essential for the production of 2% hydrogen, making it difficult to be widely used in clinical application. For injection and drinking of hydrogen-rich water, it is difficult to guarantee the content of hydrogen. Therefore, searching for more convenient and practical methods of hydrogen administration is necessary. It is noteworthy that endogenous hydrogen exists in humans and animals from anaerobic metabolism of bacteria in the large intestine [16]. Therefore, it is strikingly attractive to increase endogenous hydrogen for the purpose of treatment and prevention of diseases. Studies have shown that the hydrogen level in normal terminal breath is about 5–10 ppm, but in patients with lactose intolerance and bacterial disorders, it may archive to more than 90 ppm [17]. The level of hydrogen has been measured in different organs of normal mice and it is found that in the large intestine, spleen, liver and gastric mucosa the level of hydrogen is very high. For example, in the liver it reaches to 42  $\mu$ M, and in the large intestine and spleen it is even higher [18]. A research on PC12 cells has shown that as long as the hydrogen level in the medium maintains 25  $\mu$ M, it shows a clear anti-oxidation effect [2]. These results suggested endogenous hydrogen in vivo reaches even more than the level required for anti-oxidation. In other words, endogenous hydrogen may have important biological effects. Drugs inhibiting the absorption of glucose in diabetics such as acarbose have a side effect of flatulence, but they often show a heart protective effect. Recent studies showed that the main component of these gases is hydrogen, whose increase may contribute to the heart protective effect [12]. Oral administration of curcumin could also promote the production of endogenous hydrogen, which may be one of the mechanisms for curcumin treatment of some diseases [13]. Moreover, it is reported that oral administration of a special designed bacteria producing hydrogen gas can prevent Con A-induced hepatitis, whereas the protective effect disappeared after antibiotic treatment, indicating that improving hydrogen produced by intestinal bacteria can be a treatment of diseases [14].

## Hypothesis

Mannitol, whose intravenous injection is an effective treatment of cerebral edema, is also a widely used food additive. Mannitol by oral administration is difficult to be directly absorbed by body, so a large amount of it may cause diarrhea due to increased intestinal permeability. The phenomenon that oral administration of mannitol can increase hydrogen has been observed in many clinical cases [19–22]. Because of the risk of explosion during electrocauterization due to hydrogen produced by mannitol, its use was criticized and restricted in many centers [22–24]. It's reported that the main mechanism of the hydrogen production is the fermentation of mannitol by hydrogen producing intestinal bacteria [25]. Levitt reported that the formation of  $H_2$  is dependent upon the delivery of ingested fermentable material to the colonic bacteria [26]. Based on these results, we speculated that oral administration of mannitol may increase hydrogen gas in vivo and prevent oxidative stress disease. With this assumption we conducted preliminary human trials and found that 2 h after human oral administration of a small amount of mannitol (20%, 0.5–1 ml/kg body weight), the hydrogen in breath could be increased to 150–200 ppm, and was retained at such a high level for more than 3 h (data not shown). It is noteworthy that after consumption of 500 ml of hydrogen-rich water, the hydrogen in respiratory gas only reached to 100 ppm and lasted for no more than 1 h. These results indicated that oral administration of a small amount of mannitol could be a method to produce endogenous hydrogen. Therefore, we speculate that oral administration of a small amount of mannitol may have a protective effect

on cerebral ischemia–reperfusion by inducing endogenous hydrogen. What fascinates us is that oral administration of mannitol is far more convenient, comfortable, cheaper and simpler than other ways to administer hydrogen. In addition, mannitol is contained in many food and drugs, such as seaweed and cordyceps sinensis. These food and drugs often have a preventive role in many diseases. If oral administration of a small amount of mannitol is proved to be effective for some diseases by inducing endogenous hydrogen, it will not only provide a new research direction to pharmacological effects of mannitol, but also may reveal the mechanism of the therapeutic effects of some food and drugs. Moreover, it may indicate that not just mannitol, many drugs that promote the growth of intestinal bacteria may have a similar role. In addition to brain ischemia–reperfusion injury, many illnesses, which hydrogen has proved to be effective in, may be prevented with this convenient and practical treatment.

## Conflicts of Interest

None declared.

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