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Short Communication

Can hydrogen retard the progression of osteoarthritis?

Ding Li and WanChun Wang*

Department of Orthopaedics, the Second Xiangya Hospital of Central South University, Middle Ren-Min Road No. 139, Changsha, Hunan 410011, China.

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There is a direct relationship between reactive oxygen species (ROS) and the progression of osteoarthritis (OA). Hydrogen is considered as a selective antioxidant, which can neutralize the superfluous ROS. This investigation aimed to describe whether hydrogen can be used as a new treatment to retard the progression of OA based on recent studies. The peer-reviewed literature published prior to July, 2011 in the PubMed database was searched using pre-defined search criteria. Articles, published in English, were selected for their relevance to ROS, hydrogen or OA. The pathogenesis of OA is multifactor. Studies have revealed that ROS can contribute to the onset and progression of OA by inducing indispensable chondrocyte death and matrix degradation. Meanwhile, hydrogen is considered to be a selective antioxidant and can be used as a kind of therapeutic medical gas which has recently been explored in animal model and in clinic. We propose a hypothesis that hydrogen may be a new treatment to retard the progression of OA, although further researches need to be carried out *in vivo* or clinical studies.

Key words: Osteoarthritis, chondrocytes, cartilage, hydrogen, reactive oxygen species.

INTRODUCTION

The degenerative joint disease osteoarthritis (OA) is the most commonly diagnosed form of chronic musculoskeletal disease worldwide. The risk of OA increases significantly with age and most often occurs in the elderly population. The incidence of OA has been estimated to increase 2 to 10-fold from 30 to 65 years of age, and to continue increasing thereafter (Sakalauskiene and Jauniskiene, 2010). The transformation of the articular cartilage plays a key role in the whole development of OA (Martel-Pelletier and Pelletier, 2010). The avascular matrix is the most important component of the articular cartilage which is synthesized by the chondrocytes. Although, the mechanism of OA is not very clear yet, the occurrence of OA is generally considered as a degeneration progression of the chondrocytes and matrix. This degeneration progression seems to be significantly related to the oxidative stress, and the reactive oxygen species (ROS) play an important role in this progression.

*Corresponding author. E-mail: liding2209@gmail.com. Tel: +86 15874291410.

Meanwhile, lots of studies have indicated that hydrogen could be used as a kind of antioxidant to treat certain diseases. All of these were based on the same mechanism, the antioxidant effect of hydrogen, which is able to neutralize the free radicals that resulted from oxidative damages, such as ROS and reactive nitrogen species (Ohsawa et al., 2007).

METHODOLOGY

The PubMed database until July 1, 2011 was searched using the search terms: Osteoarthritis, chondrocytes, cartilage, hydrogen and reactive oxygen species. Articles published in English were selected for review based on their relevance to the topic “hydrogen could be used as a kind of antioxidant to retard the progression of osteoarthritis, which can neutralize the detrimental ROS”.

RESULTS

OA and ROS

ROS were considered as an important factor which cause

different kinds of diseases and target lots of medicine aim (Juma'a et al., 2009; Kumar et al., 2011). Also, it had been reported that ROS were intimately involved in the whole pathology of OA (Henrotin et al., 2003). ROS are free radical byproducts formed by the normal cellular metabolism of oxygen, including hydroxyl radical, superoxide anion and hypochlorite ion, as well as O_{2}- -derived non-radical species, such as hydrogen peroxide (Halliwell and Cross, 1994). They have unpaired electron and are ready to accept another electron or transfer their unpaired electron to another molecule. As a result, ROS react to adjacent molecules, such as DNA, protein and lipids, thus causing damages (Halliwell, 1991).

As a kind of quiescent cell, the chondrocyte lack self-renewal, which accelerates the occurrence of OA. Cell senescence is described as the loss of the ability of mitotic cells to further divide the so called replicative senescence. Like other kind of cells, chondrocyte senescence is associated with the shortening of telomeres, called telomere dysfunction. It was demonstrated that in human chondrocytes, ROS induced genomic instability, including telomere instability resulting in replicative senescence and dysfunction, and the treatment with an antioxidative agent resulted in the tendency to elongate telomere length and replicative lifespan in cultured chondrocytes (Yudoh et al., 2005). Oxidative damage caused by ROS can also contribute to chondrocyte apoptosis. Caspase-3, tyrosine kinase and NO were identified as inducers of chondrocyte apoptosis (Blanco et al., 1995; Hashimoto et al., 1998). However, recent studies have suggested that NO cannot independently induce chondrocyte apoptosis and requires some sort of co-factor (Clements et al., 2004). Intriguingly, it was found that when the intracellular antioxidant level was very low, chondrocytes were remarkably resistant to apoptosis. Further investigation revealed that NO was only able to cause cell death in the presence of ROS (Del Carlo and Loeser, 2002). It was also reported that ROS could damage the mitochondria, resulting in diminishment of DNA integrity and repair capacity and ultimately leading to chondrocyte death (Grishko et al., 2009).

ROS affect the cartilage matrix too. They inhibit the formation of the matrix and induce the extracellular matrix degradation. ROS could decrease the collagen and protein synthesis through suppressing the mitochondrial oxidative phosphorylation and adenosine triphosphate (ATP) formation (Johnson et al., 2000). It was suggested that insulin-like growth factor-1 (IGF-1) might be the promoter of the matrix formation, but there were evidences indicating that ROS contributed to the chondrocyte IGF-1 resistance and reduced the proteoglycan synthesis by causing an imbalance in the activity between the phosphatidylinositol 3-kinase-Akt pathway and the MEK-ERK MAPK signaling pathway (Yin et al., 2009). The decomposition was more than the synthesis, which speedups the progression of matrix degradation.

H_2 and ROS

As discussed previously, ROS play a crucial role in the progression of OA. When the ROS production exceeds the antioxidant capacities of the chondrocytes, the occurrence of OA might be triggered. Meanwhile, hydrogen is considered to be a selective antioxidant and can be used as a kind of therapeutic medical gas which has recently been explored in animal model and in clinic. In 2001, at the first time, it was proved that the hyperbaric hydrogen gas was beneficial in the treatment of chronic liver inflammation caused by the hepatic schistosomiasis. Its therapeutic property was ascribed to scavenging of hydroxyl radical (Gharib et al., 2001). Hydrogen not only reacted with hydroxyl radical, but also selectively reduced the peroxynitrite which was a strong oxidant, but it did not affect the physiological ROS (Ohsawa et al., 2007). It was noticed that inhaling 2% hydrogen gas could reduce the cell apoptosis in the neonatal hypoxia-ischemia rat model (Cai et al., 2008). A number of studies had also proven that hydrogen was able to treat many other diseases, where hydrogen acted as a ROS-scavenger to protect cell from oxidative damage (Fu et al., 2009; Mao et al., 2009; Nakao et al., 2010). In addition, another possible mechanism for hydrogen to protect cells was that it could increase the level of natural antioxidant enzymes. Hydrogen-rich water could increase the extracellular superoxide dismutase (SOD) level and would also be expected to contribute to an improvement in the insulin resistance (Kajiyama et al., 2008). It was reported that a treatment with 2% hydrogen gas could increase the SOD and catalase activities in serum and lung of septic mice with moderate or severe cecal ligation and puncture (Xie et al., 2010).

DISCUSSION

Based on earlier observations, we propose an hypothesis that hydrogen may be a new treatment to retard the progression of OA by injecting hydrogen-saturated saline into the cavitas articularis or inhaling hydrogen gas, which can decrease the damage of cartilage caused by the oxidative stress. Hydrogen is abundant in resource, easy to produce and cheap in price. It has several potential advantages as a safe and potent therapeutic medical gas to treat OA compared with current pharmaceutical drugs. First, the molecular weight is so light that hydrogen is highly diffusible and can diffuse across the membrane rapidly into the cell and penetrate into important subcellular compartments, such as mitochondria and nuclei. The mitochondria are the primary site of the generation of ROS. Hydrogen can protect DNA from damage when it reaches nuclei (Huang et al., 2010). Secondly, hydrogen is a selectively antioxidant which selectively scavenges the detrimental ROS, such as hydroxyl radicals and peroxynitrite without affecting the

physiological levels of the nitric oxide (Ohsawa et al., 2007). In a *vitro* research, hydrogen would not eliminate physiological superoxide anion and hydrogen peroxide, both of which play physiological roles to kill some types of bacteria along with neutrophils and macrophages (Ohsawa et al., 2007). Indeed, hydrogen does not influence physiological parameters, such as temperature, blood pressure, pH or pO_2 (Hong et al., 2010). Thirdly, the product of hydrogen reacting with hydroxyl radicals is water, which is harmless to body and need no further decomposition when compared with vitamin C and E (Niki, 1987). Finally, hydrogen is considered to be very safe to human body. Even under hyperbaric conditions, no evident negative influence on human body has been observed in inhaling overdosing hydrogen (Abraini et al., 1994), and the excrescent hydrogen will be expired via lung.

Hydrogen had been explored as a treatment against many disorders for years, but there are still many questions needed to be answered, such as why hydrogen is a selective antioxidant, whether hydrogen will affect some signaling pathways that we have not discovered and how much hydrogen is enough to release oxidative stress. We think that hydrogen has the potential to treat OA, lessen pain and retard the progression of OA. Most of the prior studies were conducted *in vitro* or in animal models. However, further research needs to be carried out in *in vivo* or clinical studies.

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