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Review

Hydrogen therapy may be a novel, safe and effective treatment for infertility patients with varicocele

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Hydrogen gas recently was discovered as a novel therapeutic medical agent in many biomedical fields. It has potent antioxidant, anti-inflammatory and anti-apoptotic protective effects on cells and organs. Increasing evidence showed that reactive oxygen species (ROS) play an important role in spermatogenesis dysfunction in patients with varicocele. Varicocelectomy and antioxidant treatment can improve the quality of sperm by reducing the production of ROS. Our hypothesis is that hydrogen therapy may be a novel, safe and effective treatment for male infertility with varicocele.

Key words: Hydrogen, therapy, infertility, varicocele.

INTRODUCTION

Hydrogen constitutes approximately 75% of the universe's elemental mass (Buchholz et al., 2008). Hydrogen, mainly used in fossil fuel processing, is seldom consider as a therapeutic gas (Shen et al., 2010). However, Oshawa et al. (2007) found that hydrogen gas has antioxidant and ant apoptotic properties that protect the brain against ischemia–reperfusion injury and stroke by selectively neutralizing hydroxyl radicals and peroxynitrite. Other research also indicated that hydrogen gas can also be effective for myocardial and liver ischemia–reperfusion injury, small intestinal transplantation injury and DM (Buchholz et al., 2008; Sun et al., 2009; Hayashida et al., 2008; Fukuda et al., 2007; Kajiyama et al., 2008).

Growing evidence supports that oxidative stress, which is mainly caused by reactive oxygen species (ROS), plays an important role in spermatogenesis dysfunction of patients with varicocele (Shiraishi and Naito, 2005; Smith et al., 1996; Alkan et al.,1997; Barbieri et al., 1999;Hendin et al., 1999; Ko ¨ksal et al., 2000; Köksal et al., 2002; Romeo et al., 2003). Varicocelectomy and antioxidant can markedly decrease the production of ROS and improve the quality of sperm (Cervellione et al., 2006; Shiraishi and Naito, 2006; Chen et al., 2008; Cam et al., 2004). However, there is no study exploring the effect of hydrogen therapy for infertility with varicocele, in which ROS play a very important role.

HYDROGEN IS AN IMPORTANT PHYSIOLOGICAL REGULATORY FACTOR WITH ANTIOXIDANT PROTECTIVE EFFECTS

So far, human completely failed to relieve the pathological cascade of oxidative damage after reperfusion injury, which lead to cellular necrosis and apoptosis, however, a recent study provided evidence that inhaled hydrogen gas (H_2) had antioxidant and ant apoptotic properties that protect the brain against ischemia–reperfusion injury and stroke by selectively reducing hydroxyl radical and peroxynitrite, which are much more reactive than other ROS (Oshawa et al.,2007).Ischemia/reperfusion (I/R) injury during small intestinal transplantation frequently causes complications, such as dysmotility, inflammation and organ failure.

Inhalation of hydrogen significantly improved intestinal

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transplant injury and prevented remote organ inflammation via its antioxidant effects. The result indicated that administration of perioperative hydrogen gas may be a potent and clinically applicable therapeutic strategy for intestinal I/R injury by reducing the production of ROS (Buchholz et al., 2008).

Hayashida et al. (2008) reported that hydrogen-rich saline was an effective alternative pharmacological strategy in myocardial ischemia reperfusion management by significantly reducing infant size and improving post-ischemic functional recovery of rat hearts, the results revealed that hydrogen-rich saline may induce protective effects through the anti-oxidative stress and apoptotic pathways. Inhalation of H_2 gas during ischemia and reperfusion significantly reduced infarct size without altering hemodynamic parameters, thereby preventing deleterious left ventricular (LV) remodeling; the anti-oxidant properties of H_2 were confirmed by the study. Fukuda et al. (2007) reported that inhalation of hydrogen gas is applicable for hepatic injury caused by ischemia/reperfusion in mice by suppressing hepatic cell death and reducing levels of serum alanine aminotransferase and hepatic malondialdehyde, the results suggested that hydrogen gas was a value method to reduce oxidative stress.

Mitochondrial dysfunction was associated with oxidative stress which majorly caused of dopaminergic cell loss in the substantial Nitra in Parkinson's disease. Hydrogen can prevent both the development and progression of the nigrostrital degeneration and the dopaminergic cell loss, the results showed hydrogen water is likely able to retard the development and progression of Parkinson's disease by reducing the production of ROS (Fu et al., 2009).

Chronic physical restraint stress enhanced levels of oxidative stress in the brain of mice, which impaired learning and memory, continuous consumption of hydrogen water reduces oxidative stress in the brain, and prevented the decline in the proliferation of neural progenitors, and the stress-induced decline in learning and memory caused by chronic physical restraint, the results showed that hydrogen water is applicable as preventive treatment for chronic physical restraint stress by reducing oxidative stress (Nagata et al., 2009).

Oxidative stress was associated with diabetes; hydrogen-rich water intake was associated with a trend of decreased oxidative stress in diabetes patients. The results showed that a sufficient supply of this water may prevent or delay development and progression of T2DM and insulin resistance by providing protection against oxidative stress (Kajiyama et al., 2008).

ROS IS INVOLVED IN THE SPERM DYSFUNCTION OF VARICOCELE

Varicocele is characterized by abnormal tortuosity and dilation of the veins of the pampiniform plexus within the spermatic cord. The prevalence of varicocele in the gener al population is 15-20%, but it is notably greater (25 to 40%) in infertile couples with male factor infertility (Agarwal et al., 2009; French et al., 2008).

Varicocele is characterized by the stasis of the internal spermatic vein, leading to elevated scrotal temperature, testicular hypoxia and retrograde blood flow of adrenal and renal metabolites. However, the exact etiology of this condition remains poorly understood (Shiraishi and Naito, 2005).

A growing number of studies indicated that oxidative stress, which is mainly caused by reactive oxygen species (ROS), plays an important role in sperm dysfunction of patients with varicocele (Shiraishi and Naito, 2005; Smith et al., 1996; Alkan et al., 1997; Barbieri et al., 1999; Hendin et al., 1999; Koksal et al., 2000, 2002; Romeo et al., 2003). In non oligospermic men with varicocele, spermatozoa, ROS was significantly elevated and the concentration of seminal plasma antioxidant was lower in men with varicocele irrespective of fertility status, and it was concluded that seminal oxidative stress was strongly associated with varicocele and sperm dysfunction (Ozdamar et al., 2004).

Oxygen and oxygen-derived oxidant, responsible for the testicular dysfunction, commonly known as reactive oxygen species (ROS), such as hydrogen peroxide, the superoxide anion, the hydroxyl radical which is generated in biological systems from superoxide anion and hydrogen peroxide by the Haber–Weiss reaction or from hydrogen peroxide by the Fenton reaction and is the strongest of the oxidant species and reacts indiscriminately with nucleic acids, lipids and proteins (Mazzilli et al., 1994; Halliwell and Gutteridge, 1990; Bektaşoğlu et al., 2006; Ohsawa et al., 2007). Human spermatozoa are especially sensitive to lipid peroxidation induced by those ROS because of their high content of polyunsaturated fatty acids (Mazzilli et al., 1994). A specific and stable end-product of lipid peroxidation, the aldehyde 4-hydroxy-2-nonenal (4-HNE), can diffuse within, or even escape from, the cell and attack targets far from the site of the original free radical event. 4-HNE is a potent alkylation agent that reacts with DNA and proteins, generating various forms of adducts that are capable of inducing specific cellular stress responses such as cell signaling and apoptosis (Shiraishi and Naito, 2005).8-hydroxy-2′-deoxyguanosine (8-OHdG) is a product of oxidative DNA damage and also a sensitive marker of oxidative DNA damage caused by ROS (Toyokuni et al., 1997; Kaneko et al., 1996; Leinonen et al., 1997; Shen et al., 1999). A recent study indicated that the expression of 8-OHdG was significantly higher in the varicocele than in the normal group, the results showed that oxidative DNA damage caused by oxidative stress was related to impaired spermatogenesis in patients with varicocele(Ishikawa et al., 2007).

Nitric oxide (NO) was increased in the spermatic veins

of men affected by varicocele. Moreover, in sub-fertile men with varicocele active metabolites of NO such as peroxynitrite was also increased in sub-fertile men with varicocele, which suggested that a possible role for NO in sperm dysfunction, similar results also were indicated in adolescents with grade II and III varicocele (Romeo et al., 2003). NO with the superoxide anion yielding peroxynitrite and peroxynitrous acid are strong oxidant molecules that can cause molecular damage to a variety of tissues. The peroxynitrous acid reacts with the cysteine residues of proteins or glutathione, forming S-nitrosothiols, which causes deregulation of cellular signal transduction processes; it also has harmful effects on cellular energetic through the inhibition of complex I in mitochondrial respiration (Romeo et al., 2003). Peroxynitrite also modifies the tyrosine residues, producing nitro tyrosine. Moreover, in blood vessels nitro tyrosine has been recognized to cause selective vascular endothelial dysfunction through the promotion of DNA damage and apoptosis (Mihm et al., 2000). In adolescents with a varicocele, there is an increase in nitro tyrosine concentration within the spermatic vein that can cause protein nitration and cytotoxicity via its reaction with various molecular targets. This could have repercussions on both sperm and testis function (Romeo et al., 2003).

A recent study suggested that elevation of scrotal temperature is one of the major factors to impair spermatogenesis and steroid genesis in testis with varicocele. Oxidative stress is shown to be closely associated with this heat stress, following the apoptosis of germ cells (Shiraishi et al., 2010). Varicocelectomy and antioxidant can markedly decrease the production of ROS and improve the quality of sperm. Cervellione et al. (2006) evaluated the long-term effect of varicocelectomy as measured by plasma oxidative stress parameters, peroxidative plasma levels were significantly reduced 1 year after surgery, the results showed that the varicocelectomy with construction of venous shunt can reduce the oxidative stress in patients with a significant degree of varicocele (Romeo et al., 2003). Increased amounts of 4-HNE–modified proteins in varicocele testes suggest that varicocele disturbs the balance between reactive oxygen species formation and antioxidant, resulting in oxidative stress (OS) in the testis. The levels of 4-HNE–modified proteins reduced in responders and spermatogenesis was improved after varicocelectomy, the results showed that OS in varicocele testes produces adverse effects on spermatogenesis and seminal reactive oxygen species and antioxidant levels are restored after varicocelectomy (Shiraishi and Naito, 2006). 8-OHdG is a sensitive marker of oxidative DNA damage caused by ROS in human sperm, A significant decrease in sperm DNA 8-OhdG was noted in all patients after varicocelectomy, the result showed that oxidative stress had a pivotal role in sperm dysfunction in patients with varicocele and semen quality was improved and oxidative stress was attenuated by varicocelectomy (Chen et al., 2008). A study indicated that ROS production and apoptosis in the testicles were induced with experimental varicocele; vitamin E had a protective role (Cam et al., 2004).

HYPOTHESIS

Our hypothesis is that hydrogen therapy may be novel, safe and effective treatment for infertility patients with varicocele.

The rationale behind this hypothesis is that molecular hydrogen can selectively reduce hydroxyl radical and peroxynitrite in vitro and in vivo, hydroxyl radical and peroxynitrite are much more reactive than other ROS. H_2 possesses a number of advantages as a potential antioxidant. (1) Thanks to its favorable distribution characteristics, H_2 can easily penetrate biomembranes and diffuse into the cytosol, mitochondria and nucleus (Ohsawa et al., 2007). (2) It effectively neutralizes hydroxyl radical in living cells and it is able to successfully target organelles (Ohsawa et al., 2007). (3) Its rapid gaseous diffusion might make it highly effectively protect nuclear DNA and mitochondria by reducing cytotoxic radicals (Ohsawa et al., 2007). (4) Due to its selectivity as an antioxidant, H_2 is mild enough not to disturb metabolic oxidation reduction reactions or to disrupt ROS involved in cell signaling, it has no serious unwanted side effects (Ohsawa et al., 2007).

It is safe for H_2 to be applied in Hydreliox used for the prevention of decompression sickness and nitrogen narcosis during very deep technical diving (Abraini et al., 1994). It is also safe for hydrogen water to be used in a human experiment (Kajiyama et al., 2008).

Hydrogen gas may be a hydrogen therapy novel, safe and an effective treatment for infertility patients with varicocele.

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