Chapter 1

Mitigating Effects of Radon Inhalation on Neuropathic Pain in Mice and its Possible Application in Veterinary Care

Takahiro Kataoka, Norie Kanzaki, Kaori Sasaoka and Kiyonori Yamaoka*

Graduate School of Health Sciences, Okayama University, Japan

*Corresponding Author: Kiyonori Yamaoka, Graduate School of Health Sciences, Okayama University, 5-1 Shikata-cho 2-chome, Kita-ku, Okayama-shi, Okayama 700-8558, Japan, Tel: +81-86-235-6852; Email: yamaoka@md.okayama-u.ac.jp

First Published May 06, 2016

Copyright: © 2016 Kiyonori Yamaoka et al.

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source.

Abstract

Radon therapy using radon gas is performed in several countries. The main indications of this therapy are for pain-related diseases. Although several clinical studies have been reported, the mechanism underlying radon’s beneficial effects is still unknown. We have demonstrated that low-dose X- or γ-irradiation activates antioxidant functions and inhibits several kinds of oxidative damage in mice. We have also proved that radon inhalation has similar effects to X- or γ-irradiation in mice. Therefore, we attempted to examine whether radon inhalation has mitigating effects on neuropathic pain. Results show that radon inhalation has preventive and curative effects on chronic constriction injury (CCI)-induced neuropathic pain in mice and that these are due to the activation of antioxidant functions. Moreover, we compared the mitigating effects of radon and pregabalin on CCI-induced neuropathic pain in mice. The results showed that the alleviating effects of radon inhalation at a concentration of 1000 Bq/m³ for 24 hours were of the same level as those achieved by treatment with pregabalin at 1.4 mg/kg body weight. The combined effects of radon and pregabalin (3mg/kg body weight) were almost equivalent to treatment with pregabalin at 4.1mg/kg body weight. These findings suggested that this combined action results in an additive effect and that activation of antioxidant functions by radon inhalation contributes to mitigating effects. Although radon exposure systems for veterinary care were developed, there are no reports on the application of radon therapy to veterinary neuropathic pain. Radon therapy can be useful in...
the veterinary field. Further investigation of prospective veterinary application will be necessary.

**What is Radon?**

Radon is an element with atomic number 86. Although there are several radon isotopes, in this article, “radon” refers to radon-222 (atomic mass number 222). Radon is an inert, radioactive gas (α-ray emitter) present in the natural environment. The concentration of radon in the natural environment in Japan is about 15 Bq/m³. The concentration of radon differs depending on the area, the climate, and the weather. Radon has a physical half-life of 3.8 days, which is relatively short. Upon entry via lungs or skin, radon enters the bloodstream and spreads throughout the body. Therefore, tissues receive a large amount of energy when radon emits α-rays.

**Radon Therapy**

Radon therapy using radon gas is performed in several countries and is classified into two types of treatment methods: 1) hot springs containing radon and 2) mines where the concentration of radon in the air is high. It has been reported that not only radon but also thermal effects are thought to be important. For example, the conditions of radon therapy in the hot spring in Misasa Medical Center, Okayama University Hospital, are high radon concentration (about 2000 Bq/m³) and high room temperature (about 42°C), with patients being exposed to radon for about 10 times over several weeks. A report suggested that, although both radon and thermal treatment are effective, the effects of radon are much larger than those of thermal treatment [1].

**Stimulating Effects of Low-Dose X- or γ-Irradiation**

It is well known that exposure to radiation causes development of cancer. On the other hand, it has been reported that low-dose irradiation involves several types of stimulating effects, namely, activation of antioxidant and immune functions. For instance, low-dose X- or γ-irradiation increased the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in mouse spleen [2] and the activities of glutathione reductase (GR) and γ-glutamylcysteine synthetase (γ-GCS) and the levels of glutathione (GSH) and thioredoxin in mouse liver [3] and brain [4]. These biological responses could have beneficial effects against oxidative stress because their role is to detoxify reactive oxygen species (ROS). In fact, there are several reports showing that low-dose irradiation inhibits oxidative stress. In one of such, a single dose of 0.5 Gy X-irradiation was shown to inhibit ferric nitrilotriacetate (Fe³⁺NTA)-induced hepatopathy in rats [5]. The increase of antioxidant activity, such as that of SOD, induced by low-dose irradiation could play an important role in the inhibition of oxidative stress as levels of lipid peroxidation, which are indicators of oxidative stress, were reduced.
after low-dose irradiation. On the contrary, lipid peroxidation was increased after Fe\(^{3+}\)-NTA administration. Another report indicated that elevation of liver GSH levels by low-dose γ-irradiation inhibited carbon tetrachloride (CCl\(_4\))-induced hepatopathy in mice [6]. In both reports, animals were exposed to radiation before Fe\(^{3+}\)-NTA or CCl\(_4\) administration, as it is necessary to activate antioxidant functions in the liver before ROS or free radicals are produced. Interestingly, post low-dose irradiation was also shown to be effective against Fe\(^{3+}\)-NTA- or CCl\(_4\)-induced hepatopathy in mice [7,8]. These findings indicate that low-dose irradiation has preventive and curative effects against oxidative damage in mouse liver.

We have reported that low-dose X-irradiation inhibits cold-induced brain edema in mice [9]. Brain edema is induced by ROS, making it a good model to evaluate the activation of antioxidant functions by low-dose irradiation. The results showed that cold-induced injury increased the water content in brain, causing brain edema. However, low-dose X-irradiation prevented the edema via activation of antioxidant functions. These findings suggested that low-dose irradiation inhibits oxidative stress not only in the liver but also in the brain.

---

**Stimulating Effects of Radon Inhalation**

Recently, we reported that inhalation of radon shows effects similar to those of low-dose X- or γ-irradiation. Radon inhalation increased the SOD activity in brain, heart, lung, thymus, liver, pancreas, kidney, and small intestine of mice [10]. This activation of SOD contributed to the inhibition of global cerebral ischemia in gerbils [11] and dextran-induced colitis [12] and carrageenan-induced inflammatory paw edema [13] in mice.

**Animal Experience of Neuropathic Pain**

To determine whether radon inhalation has effects on neuropathic pain, we designed two kinds of studies: 1) pre- and 2) post-treatment with radon in chronic constriction injury (CCI)-induced neuropathic pain, using mice as model [14]. In these studies, mice inhaled radon at a concentration of 1000 or 2000 Bq/m\(^3\), which are similar to the radon concentrations used in clinical treatment in Misasa Medical Center. In the case of pre-treatment, mice inhaled radon at a concentration of 1000 or 2000 Bq/m\(^3\) for 24 hours and then received CCI surgery. The von Frey test was performed before radon inhalation (pre-test) and after CCI surgery. In case of post-treatment, mice received CCI surgery and then inhaled radon at a concentration of
1000 or 2000 Bq/m³ for 24 hours. The results showed that both pre-treatments of radon inhalation, 1000 and 2000 Bq/m³, relieved the CCI-induced neuropathic pain, the effects of 2000 Bq/m³ being larger than those of 1000 Bq/m³. Additionally, the effect tended to last for about a week. Post-treatment of radon also relieved the neuropathic pain, but the effects tended to last only about 5 days. To clarify the mechanism of the relief, antioxidant parameters, such as SOD and total GSH (t-GSH), were examined. Although CCI surgery significantly reduced SOD activity in plasma, radon inhalation at a concentration of 2000 Bq/m³ significantly increased that activity. The levels of tumor necrosis factor-alpha (TNF-α) and nitric oxide (NO) were significantly increased after CCI surgery, suggesting inflammation. However, radon inhalation decreased those levels. These findings indicate that radon inhalation leads to the activation of antioxidant functions and inhibits oxidative stress, eventually preventing and treating CCI-induced neuropathic pain.

We further examined the mitigating effects of radon inhalation on CCI-induced neuropathic pain in mice [15]. A combination of radon and pregabalin treatment reduces the adverse effects of pregabalin and the risk of lung cancer caused by radon inhalation. Therefore, in this study, we compared the effects of radon and pregabalin. The results showed that the mitigating effects of radon inhalation at a concentration of 1000 Bq/m³ were of the same level as those of the treatment with pregabalin at 1.4mg/kg body weight. The combined effects of radon and pregabalin (3mg/kg body weight) were almost equivalent to those of treatment with pregabalin at 4.1mg/kg body weight. These findings suggested that combination of pregabalin administration and radon inhalation has an additive effect. To clarify the mechanism of the combined effects, antioxidant molecules were assayed. The results showed that the activity of antioxidant enzymes, such as SOD and catalase, increased more due to radon inhalation than to pregabalin administration.

**Clinical Studies**

Patients with physical pain can achieve lasting pain relief by radon therapy in clinical practice. Radon is applied in both medical and rehabilitation therapies. There are a number of studies on the findings of radon therapy in humans in Europe [16-20]. In radon therapies by bath and by inhalation, it was shown that the therapy has a significantly positive effect on pain relief compared to the treatments under the same conditions but without radon. All these reports have demonstrated that radon bath, effectively and sequentially, reduced pain in patients with rheumatic disease. Moreover, these results contribute to the elucidation of the mechanism of treatment by radon. Falkenbach et al. and Yamato et al. have summarized the results of radon therapy [21,22].
We have reported that radon inhalation enhanced antioxidant and immune functions and changed vasoactive and pain-associated substances [23]. Briefly, patients with osteoarthritis were treated by radon therapy (2080 Bq/m³, temperature of 42°C, and humidity of 90%) for 40 min every 2 days in Misasa Medical Center, Okayama University Hospital. The initial abnormal values of those substances or parameters in patients with osteoarthritis became similar to the values encountered in the normal subjects (persons who live in the Misasa area) approximately 6 weeks after the first treatment. Therefore, radon inhalation plays a role in alleviating pain.

Veterinary Care for Neuropathic Pain

It is well known that neuropathic pain is commonly caused by intervertebral disc (IVD) disease, such as intervertebral disc degeneration and intervertebral disc herniation in dogs [24]. Chondrodystrophic dog species such as Miniature Dachshund, Pekingese, Shi Tzu, Poodle, and Beagle are predisposed to this disease. Clinical signs range from back pain to neuroglial deficits. Dogs with severe pain or with neurologic deficits that are not responding to medical therapy are candidates for surgical treatment. If the symptoms are not severe enough to perform surgery, some veterinary hospitals use acupuncture together with other pain relievers for the mitigation of symptoms [25].

Development of Radon Exposure System for Veterinary Care and Basic Studies on the Positive Effects of Radon Inhalation on Pet’s Health

To assess the application of radon inhalation in veterinary care, a radon exposure system was developed. Using this system, we examined whether radon inhalation was effective in healthy dogs and in cats with chronic renal failure [26]. The results suggested that radon therapy may increase blood circulation and energy consumption and is useful for treatment of chronic renal failure.

Future Issues for Veterinary Care

Radon therapy is mainly indicated for pain-related diseases. However, there are no reports on neuropathic pain in veterinary care. Since the radon inhalation method used for small animals has been established in previous studies, it can be applied for the study of its effectiveness in the veterinary field. Further investigation of the prospective veterinary application will be required.

Conclusion

Radon inhalation activates antioxidant functions in mice. This activation plays an important role in the mitigation of CCI-induced neuropathic pain. Moreover, combination of radon and pregabalin enhances the alleviation
effects against CCI-induced neuropathic pain. The radon therapy has the potential to be applied in veterinary care.

References


