Induction of endogenous antioxidant system by low dose radiation and its applicable possibility for treatment of active oxygen species related diseases

Kiyonori YAMAOKA

Summary

We clarified that adequate oxygen stress induced by low dose radiation activates not only chemical biological protective function, such as induction of the synthesis of SOD, GPX and HSP70, but also the biomembrane function, such as enhanced membrane fluidity and ATPase activity. It is possible that activation of these mechanisms alleviates in vivo oxidation injuries resulting in alleviation of pathologic condition, such as symptoms of hepatopathy and diabetes mellitus. Namely, adequate activation of the functions of the living body by low dose radiation can contribute to suppressing aging and to preventing or reducing active oxygen species related diseases which are thought to involve peroxidation and have been regarded as the diseases for which radon spring water is an effective treatment. Clarification in detail of the mechanisms of these phenomena is required to understand the effects of low dose radiation on the functions of the living body, including adaptive response.

Key words: antioxidant system, low dose radiation, radon inhalation, active oxygen species related diseases, adaptive response

Introduction

Excessive active oxygen produced in vivo by various causes, such as excessive stress, is toxic. Accumulation of oxidation injuries due to excessive active oxygen causes cell and tissue injuries, inducing various pathologic conditions such as aging and carcinogenesis. While, there are chemical defense mechanisms in the body that eliminate active oxygen or repair damaged molecules, defending against resultant injury\(^1\). It is interesting reports that appropriate oxidation stress activate the chemical biological defense mechanisms. In this study, to elucidate these phenomena and its mechanism by low dose radiation, we examined on the effects of low dose radiation on chemical biological defense mechanisms, structure and function of biomembranes, and vital oxidative injury.

Radon (Rn) is a radioactive gaseous element that emits \(\alpha\)-particle. If Rn is inhaled, the lung will be subjected to the action of free radicals created by the radiation and may suffer inflammation. Although Rn inhalation has been thought to be hazardous in general, Rn springs have been reported to have therapeutic effects on senile brain disorders and hypertension\(^2\). Another known effect of Rn spring is to promote the effects of such tissue perfusion agents as adrenaline in plasma, that is to say the level of plasma adrenaline is increased by Rn inhalation\(^3\). So far there are no epidemiologic data on the hazardous effects of Rn\(^4\). In this study, we also examined as will be seen later to clarify the mechanisms of therapeutic effects (e.g. clinical indications for Misasa Hot Spring, a Rn spring, include hypertension, diabetes mellitus and pain) of low dose Rn.

These representative results and discussion are
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1. Activation of chemical biological defense mechanisms by low dose radiation

1) Effects of low dose X-ray irradiation on SOD activity, LPO level and membrane fluidity and in organs of rats

Rats were irradiated with low dose X-ray over their entire bodies. The following results were obtained. Unlike high dose X-ray irradiation, the superoxide dismutase (SOD) activity was elevated, suggesting that X-ray irradiation at doses of 25 - 50 cGy activate the host defensive function (Fig.1)⁵,⁶. These changes were particularly marked in the organs related to immune functions of the animals which received low dose X-ray. Moreover, low dose X-ray irradiation reduced lipid peroxide (LPO; thiobarbituric acid (TBARS)) levels and made the state of the SH-group on membrane-bound proteins closer to that of juvenile animals, although the sensitivity to radioactivity varied depending on the age of the animals and among different organs and tissues. It was also found that these changes continued for longer periods after 25 cGy X-ray irradiation. Namely, the SOD activities in the spleen showed a persistent radiation-induced increase for at least 12 weeks, livers for 8 weeks, brains and thymuses for 4 weeks, and bone marrows for about 1 week. The TBARS levels in the brain and thymus showed persistent decreases due to irradiation for at least 12 weeks, and those in bone marrows for 8 hours (Fig.2)⁷.

In the same manner, we examined the effects of vitamin E (vit.E) and low dose X-ray irradiation on LPO (TBARS) level in human embryonic cells under various doses of irradiation. As a result, in comparison with controls, the TBARS levels in cells decreased by 10 % under addition of vit.E and non-irradiation. The TBARS levels in cells, like some organs and tissues of rats, decreased by 20 - 60 % at least for 1 - 24 hours after irradiation at doses of 10 - 100 cGy under non addition of vit.E, but conversely increased under addition of vit.E⁸.

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Fig.1 Dose- and Aging-dependent Changes in SOD Activity, LPO (TBARS) Level and Membrane Fluidity (W/S ratio) in Brain Cortex of Wistar Rats at 4 Hours after X-ray Irradiation⁹. ■ shows the data from sham-irradiated 7-weeks-old control, and each value indicates the mean ± SEM. Significance: *P < 0.05 and **P < 0.01 vs sham-irradiated 65- or 91-week-old control by t test. The number of rats per experimental point (N) = 10 - 15.

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Table 1

<table>
<thead>
<tr>
<th>Dose of X-ray [cGy]</th>
<th>Mean ± SEM</th>
<th>65 weeks old</th>
<th>91 weeks old</th>
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<tbody>
<tr>
<td>0</td>
<td>1.0 ± 0.1</td>
<td>**</td>
<td>*</td>
</tr>
<tr>
<td>25</td>
<td>2.0 ± 0.2</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>50</td>
<td>2.5 ± 0.3</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>100</td>
<td>3.0 ± 0.4</td>
<td>**</td>
<td>**</td>
</tr>
</tbody>
</table>

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Fig. 2.1 Time-dependent Changes in SOD Activity in Organs of F344/N Sprague-Dawley (Fischer) Rats after 25 cGy X-ray Irradiation. Each value indicates the mean ± SEM. *P < 0.05 vs sham-irradiated control by t test. N = 10 - 15.

2) Induction of two species of SOD and GSH synthesis-related proteins in some organs by low dose irradiation

Four hours after 25 cGy X-ray irradiation, the Cu/Zn-SOD activity in the spleen of mature rats showed a significant quantitative increase; this was accompanied by a marked increase in the mRNA for this enzyme as compared to the control (sham-irradiated) group. Irradiation had no effect on the Mn-

SOD activity. Moreover, the expression of the mRNA for Mn-SOD was similar to that of the unirradiated control group (Fig. 3). On the other hand, the activity of both Cu/Zn-SOD and Mn-SOD in the liver of fetal rats showed a significant quantitative increase, the expression of the mRNA for the two species of SOD increased at 4 hours after 100 cGy X-ray irradiation as compared to the control group. These findings suggested that the increase in SODmRNA level is due to novel transcription of SODmRNA by low dose irradiation.
Fig.3  Time-dependent Changes in the Concentrations of the mRNA for Two Species of SOD in Spleen of Mature Wistar Rat after 25 cGy X-ray Irradiation\(^6\).

In the same manner, we found that 50 cGy \(\gamma\)-ray irradiation induced the mRNAs for glutathione (GSH) synthesis-related proteins in mouse liver\(^1\) and brain\(^1\), and \(\gamma\)-glutamylcysteine synthetase (\(\gamma\)-GCS) in mouse liver\(^2\). Furthermore, it was also found that 25 cGy \(\gamma\)-ray irradiation elevated GSH in Raw 264.7 cells\(^1\) and this cells acquired the radioreistance\(^1\).

3) Change of GPX synthesis along with that of SOD synthesis in mice spleens after low dose X-ray irradiation

Since SOD is an enzyme that mediates the dismutation of \(O_2\) to \(H_2O_2\), the question as to whether the resultant \(H_2O_2\) is further detoxicated into \(H_2O\) and \(O_2\) or not must still be evaluated. Hence, we studied the effect of low dose X-ray irradiation on the synthesis of glutathione peroxidase (GPX), which is an antioxidant that catalyzes this reaction. The results suggest that \(H_2O_2\) produced by increased SOD activity can be detoxicated into \(H_2O\) and \(O_2\) due to simultaneous enhancement of the GPX activity by X-ray irradiation at 20 cGy, in contrast to irradiation at 400 cGy.

The results also show the enhancement in enzyme activities by induction of their synthesis shortly after irradiation at 20 cGy (Fig.4, Fig.5). Moreover, as this phenomenon was observed in BALB/c mice (which are more radiation-sensitive compared to other mouse strains) and radiation-resistant C57BL/6NJcl mice, it was considered to be a common phenomenon in the mouse or rat spleen\(^1\).

In the same manner, to test whether low dose X-ray irradiation induces mRNA for heat shock protein 70 (HSP70) or heme oxygenase (HOX), reverse transcriptase polymerase chain reaction (RT-PCR) method was performed in adrenal and stomach of Wistar rat\(^7\). Half an hour after 50 cGy irradiation, HSP70mRNA in stomach was induced. HOXmRNA in adrenal and stomach was markedly induced by radiation in dose dependent manner.
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4) Activation of the other biological defense mechanisms by low dose radiation

To elucidate the stimulative effect of whole body low dose X-ray irradiation on the immune system, in vivo, we studied its effects on some immune functions of mouse splenocytes. Results show that concanavalin A (Con A) and phytohemagglutinin (PHA) responses of splenocytes were significantly increased by irradiation of 2.5 cGy and 5 cGy, whereas lipopolysaccharide (LPS) response was significantly depressed by irradiation of 5 cGy. By irradiation of 2.5 cGy, Con A response was significantly increased.

Fig.4  Dose- and Time-dependent Changes in the Activities of both GPX and SOD in BALB/c Mice Spleens after X-ray Irradiation. The ratios of measured values at various intervals after irradiation as compared with the value at the same intervals after sham irradiation are shown. Each value indicates the mean ± SEM. *P < 0.05 by t test, irradiated group values vs sham-irradiated group value at same intervals. N = 8 - 12.

Fig.5-1  Dose- and Time-dependent Changes of the mRNAs for GPX in Spleens of BALB/c Mice after X-ray Irradiation. ‘Oh’ means ‘immediately’.

Fig.5-2  Dose- and Time-dependent Changes of the mRNAs for GPX in Spleens of both BALB/c and C57BL/6NJcl Mice after X-ray Irradiation. The ratios of measured values at various intervals after irradiation as compared with the value at the same intervals after sham irradiation are shown. The data, significance and numbers of mice are as described in Fig.4.
accelerated at each concentration of Con A, but the optimum concentration of Con A shifted to a higher value of 4 \( \mu \text{g/ml} \) from 2 \( \mu \text{g/ml} \) in the control group. When blood plasma obtained from 2.5 cGy irradiated mice was added into the medium at 0.05 - 1 %, the Con A response of splenocytes in another un-irradiated mouse was significantly accelerated over that where the plasms added came from the sham-irradiated control mice. Furthermore, 2.5 cGy irradiation also enhanced the biological activity of intracellular interleukin-1 (IL-1) of LPS-stimulated splenocytes\(^\text{18}\). Moreover, it was also found that 20 cGy X-ray irradiation stimulates production of prostanoids related to the inflammatory response in mice\(^\text{19}\).

2. Changes of structure and function of biomembranes by low dose radiation

1) Influence of low dose X-ray irradiation on structure and transport function of cell membranes of rat cerebral cortex

The concentration of cysteine (Cys) significantly increased at doses of 25 - 100 cGy and the concentration of cystine (Cys-Cys) significantly decreased at a dose of 25 cGy. It showed no dose dependent changes in tyrosine (Tyr), phenylalanine (Phe) and glycine (Gly). Similarly phospholipid and cholesterol levels were unchanged. \( \text{Na}^+\text{,K}^+\text{-ATPase} \) activities significantly decreased at a dose of 100 cGy or higher but significantly increased at doses of 25 and 50 cGy (Fig.6). These findings suggested that unlike high dose irradiation which promotes membrane damage, low dose irradiation stimulates the SH group of membrane proteins and enhances the ability to control the membrane transport mechanism as reflected by an increase in \( \text{Na}^+\text{,K}^+\text{-ATPase} \) activity\(^\text{20}\).

2) Effects of low dose X-ray irradiation on purine metabolism in mouse splenocytes

This study examines the influence of low dose X-ray irradiation on purine nucleotide metabolites such as adenosine, inosine, hypoxanthine, xanthine and uric acid, and hence generation of ATP-mediated energy in mouse splenocytes. It was found that, unlike high dose irradiation which promotes membrane damage, low dose irradiation enhances the ability to regulate the energy metabolisms as reflected by the increase in \( \text{Na}^+\text{,K}^+\text{-ATPase} \) activity and the adequate activation of the above salvage pathway. Namely, the levels of adenosine, inosine and uric acid significantly increased, while the levels of xanthine and hypoxanthine decreased significantly. Moreover, the cysteine level and SOD activity significantly increased at a dose of 20 cGy\(^\text{20}\).

![Fig.6](image1.png)

**Fig.6** Dose-dependent Changes in \( \text{Na}^+\text{,K}^+\text{-ATPase} \) Activity in Brain Cortex of Wistar Rats at 4 Hours after X-ray Irradiation\(^\text{18}\). Each value indicates the mean ± SEM. *\( P < 0.05 \) vs sham-irradiated control group by t test. The dotted line indicates the control values, i.e., the concentration in the cortex of rats not exposed to irradiation. \( N = 10 - 15 \).

![Fig.7](image2.png)

**Fig.7** Dose-dependent Effects of \( \gamma \)-ray Irradiation on Elevation of Blood Glucose Induced by Alloxan in Rats\(^\text{20}\). Rats were sacrificed at 48 hours after i.v. injection of alloxan (40 mg/kg body weight). *\( P < 0.05 \) and **\( P < 0.01 \) vs sham irradiated no-alloxan group. ## \( P < 0.01 \) vs sham irradiated alloxan group. \( N = 8 \).
A : sham-irradiated no-alloxan control groups.  

B : sham-irradiated alloxan (i. v., 40mg/kg) groups.  

C : 50 cGy-irradiated alloxan (i. v., 40mg/kg) groups.  

Photo. 1 Cell Injury by Alloxan and Effects of Low Dose γ-ray Irradiation Evaluated by Staining of Pancreas.

3. Remission of vital oxidative injury by low dose radiation  
1) Protection against alloxan diabetes before alloxan administration and delay of the onset of type 1 diabetes in nonobese diabatic mice by low dose γ-ray irradiation

We evaluated the protective effects of a single low dose whole body 60Co γ-ray irradiation against alloxan-induced hyperglycemia in rats. In rats that did not receive alloxan, the SOD activity in the pancreas significantly increased after irradiation at a dose of 50 or 100 cGy. In rats that received alloxan, pancreatic LPO (TBARS) level and blood glucose were increased. However, the increase in pancreatic TBARS level was prevented by irradiation at a dose of 50 or 100 cGy and the increase in blood glucose was also prevented by irradiation at a dose of 50 cGy (Fig.7). After alloxan administration, degranulation was observed in β cells, but this was prevented by low dose irradiation at a dose of 50 cGy (Photo.1).

In the same manner, we examined the effect of low dose γ-ray irradiation on the progression of type 1 diabetes (IDDM) using nonobese diabatic (NOD) mice. Elevated level of urine glucose was first detected at 15 weeks of age in control NOD mice, whereas it was delayed as long as 7 weeks in 50 cGy γ-ray irradiated mice. Greatest effect was observed in mice irradiated at 13 weeks of age, e.g. 2 weeks prior to the onset of disease. Detection of apoptotic cells by TUNEL staining revealed much less incidence of apoptosis in pancreas from γ-ray irradiated mice compared with that of control mice. Both increase in glucose and decrease in insulin level in the blood at 24 weeks of age were effectively suppressed by irradiation at 13 weeks of age. One week after the irradiation the specific activity of SOD in pancreas was found to be increased twice as much. The results indicate that low dose irradiation delays the onset of IDDM in NOD mice by suppressing apoptotic cell death in pancreas, probably through enhancing antioxidant defense.
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2) Inhibitory effects of prior low dose X-irradiation on Fe³⁺-NTA-induced hepatopathy in rats

Blood activities of hepatocellular enzymes such as lactate dehydrogenase (LDH), glutamic pyruvic transaminase (GPT) and glutamic oxalacetic transaminase (GOT) peaked at 12 hours after a single intraabdominal injection of ferric nitrilotriacetate (Fe³⁺-NTA) in rats. Enzymes such as alkaline phosphatase (ALP) and leucin amino peptidase (LAP) originating in the capillary bile ducts or bile secretory liver cells were also released into the blood between 6 - 24 hours after intraabdominal injection of Fe³⁺-NTA in rats. Furthermore, hyperoxidation of lipids occurred in rat hepatic cell membranes, reaching a peak at 6 hours after intraabdominal injection of Fe³⁺-NTA. It was found that a single prior 50 cGy wholebody X-ray irradiation significantly increased SOD activities and suppressed above-mentioned symptoms of transient hepatopathy in rats²⁶.

Fig.8 Time Dependent Changes in GOT and GPT Activities in C57BL/6 Mice Serum treated with Fe³⁺-NTA after 50 cGy γ-ray Irradiation². Each value indicate the mean ± SEM. *P < 0.05, **P < 0.01 and ***P < 0.001 by t test, each sham-irradiated or irradiated group value vs the control group value (3 hours after Fe³⁺-NTA administration). #P < 0.05, ##P < 0.01 and ###P < 0.001 by t test, each group value at various intervals after irradiation vs the values at the same intervals after sham-irradiation. N = 4 - 6.

3) Inhibitory effects of post low dose γ-ray irradiation on Fe³⁺-NTA-induced mice liver damage

The post 50 cGy γ-ray irradiation accelerated the rate of recovery from Fe³⁺-NTA-induced mice liver damage. Based on the changes in GOT activities, GPT activities (Fig.8) and LPO levels (malondialdehyde (MDA) concentrations), it was shown that hepatopathy was improved by low dose irradiation at 3 hours after Fe³⁺-NTA administration. This may be because of the enhancement of antioxidant agents such as total glutathione (GSH + GSSG), GPX, glutathione reductase (GR) (Fig.9) and γ-GCS by low dose irradiation. These findings suggest that low dose irradiation relieved functional disorders at least in the livers of mice with active oxygen species related diseases²⁵.

In the same manner, 50 cGy γ-ray irradiation elevated the chemical biological defense mechanisms, such as GSH level, in mouse liver and reduced CCl₄-induced liver damage²⁶,²⁷.

4) Inhibitory effects of low dose γ-ray irradiation on MPTP-induced brain damage

The elevation of endogenous thiol-related antioxidants and free radical scavenging enzymes in the brain of C57BL/6 female mice after low dose γ-ray irradiation and its inhibitory effect on 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP)-induced brain damage were investigated. The brain level of the reduced form of GSH increased soon after irradiation with 50 cGy of γ-rays, reached a maximum at 3 hours post-treatment, and remained elevated until 12 hours. Thioredoxin (TRX) was also transiently increased after irradiation. The activities of free radical scavenging enzymes, including Cu/Zn-SOD, catase (Cat) and GPX, were significantly induced after irradiation as well. Cerebral LPO level (MDA
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**Sham-irradiation**

- Irradiation

**Normal**

- 1.5

\[ \text{c} \text{erg} \text{-cell} \]

- \( \text{E} \text{-cell} \)

\[ \text{E} \text{-cell} \]

- \( \text{E} \text{-cell} \)

- \( \text{E} \text{-cell} \)

- \( \text{E} \text{-cell} \)

**Sham-irradiation**

- Normal

**Fe-NTA**

**Administration**

**Time after irradiation** [hr]

**Fe-NTA**

**Administration**

**Time after irradiation** [hr]

Fig. 9 Time Dependent Changes in LPO (MDA) Level, Total GSH Content, GPX Activity and GR Activity in Mice Livers Treated with Fe\(^{3+}\)-NTA after 50 cGy \( \gamma \)-ray Irradiation\(^{25} \). The data, numbers of mice and significance are as described in Fig.8.

**Fig. 10** Effects of \( \gamma \)-rays on MPTP-induced Elevation of LPO (MDA) in the Whole Brain. Mice were pre-irradiated with 50 cGy of \( \gamma \)-rays 1 hour before MPTP treatment\(^{26} \). Mice were killed 4 hours after MPTP administration (30 mg/kg body weight). \(* * * \ p < 0.001 \) vs control group. \( \dagger \ p < 0.001 \) vs MPTP alone-treated group. \( \text{N} = 5 \).

**Control**

**Saline**

**\( \gamma \)-Ray**

**MPTP**

Moreover, it was found that 500 cGy \( \gamma \)-ray irradiation to the chest regions inhibited the blood pressure of spontaneous hypertensive rats\(^{29} \).
4. Effects of Misasa radon spring inhalation on physiology and disorders

To clarify the mechanisms of therapeutic effects of Rn, we administered sprayed Rn (7-18 kBq/l) to rabbits by inhalation and examined the changes in LPO (TBARS) level, SOD activity and membrane fluidity in various organs, biogenic amine neurotransmitters in brain, adrenal secretion of catecholamines and blood components such as vasoactive substances.

1) Changes in LPO level, SOD activity and membrane fluidity in various organs

The LPO (TBARS) level of the brain was significantly decreased immediately after Rn inhalation for 90 minutes in both the low concentration group (7-10 kBq/l) and the high concentration group (14-18 kBq/l) as compared with that in the control group.
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Fig. 12 Changes in the Levels of 5-HT, 5-HIAA, NA, DA, HVA, 3-MT and DOPAC in Rabbit Brains\(^{30}\). Each indicate the mean ± SEM. The number of rabbit per experimental point is 5 at 0 kBq/l, 4 at 7 kBq/l, 6 at 13 kBq/l and 5 at 18 kBq/l. *p < 0.05 vs control.

Table 1 Effect of Rn Inhalation on Turn-over Ratios of Biogenic Amines in Rabbit Brains\(^{31}\)

<table>
<thead>
<tr>
<th>Rn [kBq/l]</th>
<th>control</th>
<th>7</th>
<th>13</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>[DOPAC+3-MT+HVA]/[DA]</td>
<td>1.42 ± 0.11</td>
<td>1.10 ± 0.03*</td>
<td>1.36 ± 0.06</td>
<td>1.54 ± 0.13</td>
</tr>
<tr>
<td>[HVA]/[DOPAC]</td>
<td>21.5 ± 3.08</td>
<td>13.3 ± 2.2</td>
<td>40.7 ± 19.8</td>
<td>16.0 ± 2.5</td>
</tr>
<tr>
<td>[HVA]/[3-MT]</td>
<td>4.14 ± 1.22</td>
<td>8.84 ± 2.51*</td>
<td>6.73 ± 1.20</td>
<td>6.72 ± 2.11</td>
</tr>
<tr>
<td>[NA]/[DA]</td>
<td>0.297 ± 0.047</td>
<td>0.183 ± 0.141</td>
<td>0.126 ± 0.026**</td>
<td>0.128 ± 0.020**</td>
</tr>
<tr>
<td>[5-HIAA]/[5-HT]</td>
<td>0.443 ± 0.085</td>
<td>0.867 ± 0.284</td>
<td>0.429 ± 0.088</td>
<td>0.499 ± 0.036</td>
</tr>
</tbody>
</table>

Each value indicates the mean ± SEM. The number of rabbit per experiment was 5 at control, 2 at 7 kBq/l, 6 at 13 kBq/l and 3 at 18 kBq/l. *P < 0.05 and **P < 0.01 vs control.

It further decreased in the low concentration group but slightly recovered in the high concentration group 2 hours after inhalation. The TBARS level of the lung showed no change immediately after inhalation but decreased significantly in both groups 2 hours after inhalation. With regard to SOD activity in the brain and lung, only that in the brain showed significant increase in the high concentration group immediately after inhalation; no other change was observed. Membrane fluidity, especially the fluidity of membrane protein, was significantly increased in the brains of both groups immediately after inhalation. In the lung, the membrane fluidity was significantly increased 2 hours after inhalation in both groups (Fig. 11). These findings suggest that the inhalation of Rn at Rn springs contributes to the prevention of brain disorders related to peroxidation reactions by promoting these physiologic changes\(^{30}\).

2) Changes in biogenic amine neurotransmitters in brain

Immediately after Rn inhalation, noradrenaline
Table 2 Changes of Catecholamines and Tissue Perfusion Rate by Rn Inhalation

<table>
<thead>
<tr>
<th>Rn [kBq/l]</th>
<th>control</th>
<th>14-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma catecholamines [pg/mg protein]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adrenaline</td>
<td>4.2 ± 1.7</td>
<td>22.9 ± 12.1 **</td>
</tr>
<tr>
<td>noradrenaline</td>
<td>10.9 ± 5.6</td>
<td>18.8 ± 8.2 *</td>
</tr>
<tr>
<td>adrenal catecholamines [ng/mg protein]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adrenaline</td>
<td>825 ± 544</td>
<td>249 ± 129 **</td>
</tr>
<tr>
<td>noradrenaline</td>
<td>134 ± 67</td>
<td>23.6 ± 14.9 **</td>
</tr>
<tr>
<td>tissue perfusion rate [ml/100g/min]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no medication</td>
<td>15.8 ± 1.8</td>
<td>21.4 ± 2.4 **</td>
</tr>
<tr>
<td>phentolamine</td>
<td>18.4 ± 1.7</td>
<td>22.6 ± 2.2 **</td>
</tr>
<tr>
<td>propranolol</td>
<td>17.4 ± 2.7</td>
<td>19.3 ± 2.9</td>
</tr>
<tr>
<td>atenolol</td>
<td>16.6 ± 2.6</td>
<td>18.4 ± 3.0</td>
</tr>
</tbody>
</table>

Each value indicates the mean ± SEM. The number of rabbits per experiment was 8-14 at control and 8-15 at 14-18 kBq/l. *p < 0.05 and **p < 0.01 vs control.

Table 3 Dynamic Changes in Vasoactive, Diabetes-associated and Pain-associated Substances of Rabbit Blood by Rn Inhalation

<table>
<thead>
<tr>
<th>radon [kBq/l]</th>
<th>control</th>
<th>7-10</th>
<th>14-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>histamine [µg/dl]</td>
<td>67 ± 12</td>
<td>146 ± 31 **</td>
<td>152 ± 62 **</td>
</tr>
<tr>
<td>atrial natriuretic polypeptide [pg/ml]</td>
<td>1660 ± 240</td>
<td>2170 ± 170 *</td>
<td>3330 ± 520 **</td>
</tr>
<tr>
<td>vasopression [pg/ml]</td>
<td>13.2 ± 3.6</td>
<td>3.2 ± 0.6 **</td>
<td>5.4 ± 0.8 **</td>
</tr>
<tr>
<td>angiotensin II [pg/ml]</td>
<td>34 ± 1</td>
<td>33 ± 1</td>
<td>32 ± 1</td>
</tr>
<tr>
<td>prostaglandin E2 [pg/ml]</td>
<td>26 ± 4</td>
<td>33 ± 10</td>
<td>18 ± 5</td>
</tr>
<tr>
<td>insulin [UI/ml]</td>
<td>4.3 ± 0.4</td>
<td>4.3 ± 0.6</td>
<td>8.5 ± 1.8 **</td>
</tr>
<tr>
<td>glucose-6-phosphate dehydrogenase [IU/37°C]</td>
<td>1.9 ± 0.2</td>
<td>2.8 ± 0.2 **</td>
<td>2.6 ± 0.3 **</td>
</tr>
<tr>
<td>pancreatic glucagon [10^4×pg/ml]</td>
<td>1.6 ± 0.1</td>
<td>1.9 ± 0.1 *</td>
<td>2.4 ± 0.3 **</td>
</tr>
<tr>
<td>blood glucose [mg/dl]</td>
<td>218 ± 21</td>
<td>195 ± 22</td>
<td>191 ± 19</td>
</tr>
<tr>
<td>3-endorphin [ng/wet g]</td>
<td>16.2 ± 2.5</td>
<td>19.0 ± 1.9</td>
<td>22.4 ± 3.5 *</td>
</tr>
<tr>
<td>M-enkephalin [ng/wet g]</td>
<td>6.1 ± 1.0</td>
<td>6.5 ± 1.1</td>
<td>11.8 ± 1.9 **</td>
</tr>
</tbody>
</table>

Each value indicates the mean ± SEM. The number of rabbits per experiment was ten at control, eight at 7-10 kBq/l and nine at 14-18 kBq/l. *p < 0.05 and **p < 0.01 vs control.

(NA), serotonin (5HT) and 5-hydroxyindoleacetic acid (5HIAA) levels in rabbit brain decreased significantly by inhalation of Rn spring of 13 kBq/l or over. Changes in tyrosine, dopamine (DA) and homovanillic acid (HVA) levels did not depend on the concentrations of Rn inhaled (Fig.12). The turnover ratios for these amines were evaluated (Table 1). The results suggested possible decrease in the activities of aromatic-L-amino acid decarboxylase, which are key enzymes of the metabolism of biogenic amines30).

3) Changes in adrenal secretion of catecholamines in relation to increase of tissue perfusion rate

In the Rn inhalation group, plasma adrenaline and NA levels were significantly higher, while adrenaline and NA levels were significantly lower than those in the control group. In the no medication and phentolamine subgroups, tissue perfusion rates in the Rn group were significantly higher than those in the control group. It is suggested that catecholamines are secreted from the adrenal glands by inhalation of Rn water and that the β1-action of catecholamines contributes to the increase in tissue perfusion (Table 2).

4) Changes in blood components indicated for hypertension, diabetes and pain

Significant dose-dependent increases were observed in histamine and α-ANP and significant
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decrease in vasopression in both high and low concentration groups compared with the control group. Angiotensin II and PGE₂ showed no significant changes. Insulin significantly increased in the high concentration group, and G6PDH activity and glucagon significantly increased in both high and low concentration groups. The blood glucose level decreased slightly. β-endorphin and M-enkephalin dose-dependently increased with significant differences between the high concentration group and control group (Table 3). Namely, vasodilation, alleviation of diabetic symptoms and morphine-like analgesic effects were observed, suggesting that these changes constitute part of the mechanisms of the Rn spring therapy include hypertension, diabetes mellitus and pain.

Conclusions

These findings suggest that an appropriate amount of active oxygen is produced in the body after low dose irradiation or Rn inhalation, and this contributes to the alleviation of the symptoms of active oxygen species related diseases such as diabetes after certain processes such as activation of the biological defense mechanism, or promoting these physiologic changes such as tissue perfusion, in contrast to the toxic effects of high dose irradiation. In future, clarification in detail of the mechanisms of these phenomena is required to understand the effects of low dose radiation on the functions of the living body, including adaptive response.

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References


低線量放射線による抗酸化系の誘導と活性酸素病治療への応用の可能性

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要約
ストレスなどの原因により生体内に生じた過剰な活性酸素は毒性を有し、これが細胞や組織障害につながり、老化や発癌など種々の病的状態を生み出している。これに対し、生体には活性酸素を消去したり、損傷を起こした分子を修復したりして結果的に生ずる障害を防御する機構がある。この抗酸化系防御機構は適度な酸化ストレス、即ち少量の活性酸素を生体内に発生させる環境下では、逆に活性化する可能性があり、注目されている。

本研究は、少量活性酸素を生体内に生じさせる低線量放射線による抗酸化系防御機構の活性化の有無、生体膜の構造変化と機能活性に及ぼす作用、活性酸素病などの遠因となる生体内酸化傷害に及ぼす作用。さらにはラドン（主にγ線放出）療法の適応症の機構について、今までに実施した我々の研究例を中心に総括し、評価するものである。

即ち、マウス、ラットへのX線、γ線照射実験やラビットへのラドン吸入実験により得られた成果例は次の通りである。低線量のX線、γ線照射やラドン吸入により、高線量放射の場合は逆に、過剰な発癌や臓器に放射線感受性に違いはあるものの活性酸化脂質量が減少し、膜流動性やATPase活性が若齢値に近づくように変化した。SOD、Cat、GPXなどの酵素活性が誘導合成に伴い亢進した。また、低線量放射線照射によりⅠ型糖尿病症状、鉄あるいは四塩化炭素の誘導による肝障害、MPTPの誘導による脳障害などが緩和された。さらに、ラドン吸入により組織循環の促進や疼痛の緩和などが明らかになった。これらの観察より、低線量放射線は抗酸化系防御機構を活性化するとともに生体膜機能の若返りを導くことが示唆できた。また、低線量放射線は糖尿病Ⅰ型症状や肝、脳障害を緩和することから、活性酸素病の治療応用への可能性も示唆できた。さらに、ラドン療法の適応症の代表例である疼痛緩和などについても機構解明の一端がなされた。

キーワード：抗酸化系、低線量放射線、ラドン、活性酸素病、適応応答

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