Knowledge Discovery of Suppressive Effect of Disease and Increased Anti-oxidative Function by Low-dose Radiation Using Self-organizing Map

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We previously reported that low-dose radiation induces the anti-oxidative function in many organ systems of mice. This results in the suppression of several kinds of oxidative stress-induced damage. However, to date, a proven cure has not been established. This study was conducted with the objective of revealing the health effects of low-dose radiation obtained from our previous reports and searching for a new treatment based on low-dose radiation, such as radon therapy. We extracted the characteristics of the effects of low dose radiation suppressing diseases and enhancing the anti-oxidative function using fuzzy answer by self-organizing map (SOM) based on mutual knowledge. The relationship between the suppressive effect and increased anti-oxidative function was shown in our result, and the concentration dependence of the effect against pain was shown on the output map. Although the effect against other organs depending on concentration was unpredictable, our results indicate that low-dose radiation may also be suitable for treatment of liver disease and brain disease. The results presented could encourage development and application of treatment using low-dose radiation, such as radon therapy.

Key Words: self-organizing map, low-dose radiation, radon therapy, anti-oxidative function

1. Introduction

Data analysis using an artificial neural network (ANN) has the potential to uncover hidden patterns and relationships within data. A self-organizing map (SOM) is an unsupervised ANN that models the ability of a neuron to handle information in the primary visual area of the brain. SOM captures the characteristics of the data by learning, and it can summarize multidimensional data in a map.1, 2) SOM is known as a versatile tool for complex analyses in the medical field because it facilitates efficient visualization of multidimensional numerical data and provides the characteristics of complex data using fuzzy answer. For example, it has been reported that SOM is valuable for determining gene expression patterns3–6) and for diagnostic assistance.7–9) Therefore, SOM has the possibility of various interpretations.

In a previous study, we analyzed the oxidative damage in mouse liver subjected to low-dose radiation, such as radon inhalation, X-ray irradiation, and alcohol administration.10) Our results showed that
low oxidative stress via low-dose radiation under specific conditions increases anti-oxidative function owing to the defense system in the living body. Much evidence pointing to the benefit of low-dose radiation exists.\textsuperscript{11–26} For example, we found that radon inhalation activates the anti-oxidative function and alleviates pain in mice.\textsuperscript{14, 19, 21, 24} In fact, radon therapy is performed for mainly pain-related diseases by using radon inhalation in Japan and Europe.\textsuperscript{27, 28} However, although we found that low-dose radiation suppresses various diseases throughout the body in animal studies, it is unknown whether all these diseases are possible indication of radon therapy for pain. If the most effective specific conditions of low-dose radiation for therapy is found, low-dose radiation could be potentially used as medicine for the relief of various diseases. Enhancement of the anti-oxidative function by low-dose radiation operates like antioxidants such as Vitamin C and E.\textsuperscript{25} Moreover, low-dose radiation can be combined with antioxidant and medicine.\textsuperscript{15} Low-dose radiation treatment could be strategically applied to patients suffering from the side effects of medicine.

Although numerous studies have been conducted on the effect of a specific treatment against a specific disease, very few have reported comprehensive evaluation of the suppressive effect and anti-oxidative function induced by low-dose radiation. This study reveals the health effect of low-dose radiation from our previous reports to search for a new treatment using low-dose radiation, such as radon therapy. In this study, we extracted the characteristics of the suppressive effect and the increased anti-oxidative function induced by low-dose radiation using ANN.

2. Methods

2.1 Datasets

Dataset 1 was selectively extracted from our reports over the past five years. They show the suppressive effects on the oxidative stress-related diseases induced by low-dose radiation\textsuperscript{11–26} (Table 1). SOD (superoxide dismutase) activity, total GSH (glutathione) contents, and Cat (catalase) activity were measured in almost all these reports. Dataset 1 had 168 records in 16 reports and 29\% missing value.

Other reports showing the oxidative stress-related disease suppressive effect of antioxidants were collected from Google Scholar by a coauthor without prior knowledge. The coauthor searched through approximately thirty reports using the keywords “(animal disease model in Dataset 1), mouse, SOD, GSH, Cat” without knowing the purpose of this study. Dataset 2 was coordinated with Dataset 1 and selectively extracted from these reports\textsuperscript{29–45} (Table 2). Dataset 2 had 122 records in 17 reports and 6\% missing values.

These datasets had four dimensions, SOD activity, total GSH contents, Cat activity, and the suppressive effect including missing values. We used the average of the indexes of disease condition as the suppressive effect. These datasets were normalized in (SOD, GSH, Cat, suppression)=\((0, 0, 0, 0)\) as control and (SOD, GSH, Cat, suppression)=\((1, 1, 1, 1)\) as injury. Thus, these showed the rate of the suppressive effect and increased anti-oxidative function in these reports. These were additionally normalized using the following formula: \(x_i=\frac{(x_i'-A)}{S}\). Here, \(x_i'\) are the values of SOD, GSH, Cat, and suppression of data \(i\). A is the average of SOD, GSH, Cat, or suppression. \(S\) is the standard deviation of SOD, GSH, Cat, or suppression. The outliers were brought within the range \(-3\leq x_i \leq 3\). Missing values were typically reinforced by SOM.\textsuperscript{46} The average was approximately zero, standard deviation was approximately one, and the data range was \(-3\) through \(3\) (Table 3). These values fluctuate a little with changes in normalization and reinforcement of the missing value.
A SOM has an input layer and an output layer with associated weights. It constructs an output map from multidimensional input data by learning. Briefly, a SOM finds the best matching unit (BMU) closest to the input data by searching for the minimum value of the distance between the input data and the associated weight in the output map. The characteristics of the input data were reflected in the neighborhood of the BMU by SOM repeatedly updating the output map (Fig. 1A). SOM places data with similar patterns into similar locations. Data analysis using SOM has the advantage that we could visually and intuitively acquire it from the output map. We calculated data using SOM PAK (SOM Programming Team of the Helsinki University of Technology Laboratory of Computer and Information Science, Espoo, Finland). Here, the number of learning, the neighborhood radius, and the learning rate were 100000 times, 30 units, and 0.5, respectively. The map size was 50×50 units for Dataset 1 or 2 and 70×70 units for Dataset 1 and Dataset 2 depending on the number of records. We experimentally defined these parameters because a decisive approach for the definition of these has not yet been realized.

Lewis released common knowledge ahead of developing semantic meaning.47 However, there is controversy over semantic meaning.48–50 Schiffer presented the following formula for mutual knowledge:51

\[ K_{Sp}, K_{Ap}, K_{SK_{Ap}}, K_{AK_{Ap}}, K_{SK_{AK_{Ap}}}, K_{SK_{SK_{Ap}}}, K_{SK_{SK_{AK_{Ap}}}}, \ldots \]
| organ | injury | treatment | description | reference |
|-------|--------|-----------|-------------|-----------|
| brain | ischemia | shikonin | the chief active component isolated from the roots of the Lithospermum erythrorhizon | [35] |
| liver | diabetes | banana leaf extract (BLE) | an aqueous leaf extract of L. speciosissumama (Banana) | [36] |
|       | diabetes | BLE | *a* | [36] |
|       | diabetes | silydione | isolated component from the Rhodiniae Radix | [37] |
| CC4-induced hepatitis | silymarin | silybutam | *silybutam | [28] |
| CC4-induced hepatitis | silymarin | TRI | *s* | [30] |
| CC4-induced hepatitis | silymarin | TR2 | eburic acid | [31] |
| CC4-induced hepatitis | silymarin | 5',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (DMC) | main compound isolated from the buds of C. operculatus | [31] |
| CC4-induced hepatitis | silymarin | MGEE | ethanolic extract of Macaranga gigantea besseilaceae | [34] |
| CC4-induced hepatitis | terminalia arjuna (TA) | medicinal plant widely used in the preparation of ayurvedic formulations | [39] |
| alcohol-induced hepatitis | testosteron | a sex hormone, the major estrogen in humans | [38] |
| alcohol-induced hepatitis | testosteron | estradiol | a 70% ethanol extract of L. christinae | [40] |
| alcohol-induced hepatitis | testosteron | estradiol | isolated component from L. christinae herbs | [40] |
| alcohol-induced hepatitis | betulinic acid (BA) | a pentacyclic triterpene that exists widely in food, medicinal herbs, and plants, especially birch bark | [42] |
| alcohol-induced hepatitis | saponin powder of japonicus protect (PJ) | isolated from the root of panax grandiflorum and panax notoginseng | [32] |
| carnegieman-induced paw edema | indometacin (Indo) | component for an analgesic agent | [43] |
| carnegieman-induced paw edema | ST1 | an active and major ingredient submerged from antrosox camphorata | [43] |
| kidney | diabetes | salidrose | *s* | [37] |
| CC4-induced hepatitis | TA | *s* | [39] |
| CC4-induced hepatitis | Vitamin E | *s* | [39] |
| paw | carnegieman-induced paw edema | indo | isolated component from many herb plants | [44] |
| serum | CC4-induced hepatitis | scopoletin | one of main compounds in polygonum cuspidatum | [33] |
| alcohol-induced hepatitis | saponin powder of PJ | *s* | [32] |
| alcohol-induced hepatitis | resveratrol | a major phytoalexim produced by plants in response to various stresses and promotes disease resistance | [41] |

*Note: *a = specific reference required.
where \( K_{sp} \) means “Speaker (S) knows proposition (p).” Although there is an iterated notion problem in this theory, SOM computationally learns a lot of information. It is reasonable to suppose that the output map constructs a knowledgebase because the output map of SOM summarizes the characteristics of the input data. In this study, we defined that \( K_{SOM1p1} \) means “An output map (SOM1) knows the characteristics of input data (p1).” for the accuracy improvement (Fig. 1B). Therefore, SOM was applied based on mutual knowledge theory for comprehensive evaluation of datasets with different characteristics, called MK-SOM. We first calculated multiple output maps as multiple knowledge sets using Dataset 1 and Dataset 2. Then, MK-SOM made mutual knowledge by learning these output maps.

In this report, we visualized 2 types, U-matrix visualization and component map, of output map. U-matrix stands for the gap between neighboring units to visualize clusters in high dimensional data. Larger values mean that nodes are far apart, whereas smaller values mean that nodes are close. If output map is drawn using gray-scale, light color depicts closely spaced nodes and darker color depicts more widely
separated nodes. Thus, groups of light colors can be considered as clusters. On the other hand, component map represents the characteristics of each component. We showed them using their gray-scale image. Moreover, the location of control group (control), disease group (injury), and necessary groups were shown on each output maps, we did not indicate all information of the input data.

2.3 Ward’s method

Ward’s method is commonly used in hierarchical cluster analysis.52) In Ward’s method, the square sum between the centroid and each data point in the cluster is minimized. It is known to be a more sensitive hierarchical cluster analysis method than other cluster analyses because data are uniformly classified. We showed the borders and clusters (A, B, C, and D group) on the SOM’s output maps based on the result of clustering by Ward’s method to confirm the data layout on the output map.

2.4 Procedure

First, Datasets 1 and 2 were separately analyzed using Ward’s method and basal SOM for evaluation of suppressive effect and anti-oxidative function by radiation or antioxidant. Next, Datasets 1 and 2 were analyzed together using Ward’s method and MK-SOM for comprehensive evaluation of suppressive effect and the anti-oxidative function induced by radiation and antioxidants. In the analysis of Datasets 1 and 2 together, we used MK-SOM because basal SOM has low accuracy (Table 4). In particular, the suppressive effect of pain and liver disease was investigated because there were enough of these types of data in the datasets. Moreover, we assessed the correlation between the extent of suppression of pain and liver disease through the increased anti-oxidative function.

3. Results

3.1 Evaluation of suppressive effect by low-dose radiation or antioxidant using basal SOM

Dataset 1 and Dataset 2 were analyzed using Ward’s method and basal SOM. The result obtained showed the characteristics extraction and clustering of suppressive effect by radiation or antioxidant.

The dendrograms resulted in two main clusters. Moreover, each dataset was classified into four clusters according to the characteristics of the data (Fig. 2A, 2B). It is worth noting that all of the data for irradiation belonged to the classification of suppressive effect cluster.

Fig. 2C and 2D reflect the characteristics of Dataset 1 and Dataset 2, respectively. Although groups A, B, C, and D showed in order of worsening according to the above clustering, groups A, B, C, and D were adjacent, except for group D in Fig. 2D. This result shows that SOM offers substantial advantage over Ward’s method. SOM uncovered hidden patterns and relationships within the data with fuzzy answers. Thus, we expected that the data of groups A, B, and C would show the suppressive effect. However, as indicated by the arrows in Fig. 2C, groups A and D were separated because the randomized initial map was not fit and the learning was insufficient in a part of the edge of the output map. This problem requires more investigation of SOM as a data analysis tool in further research. However, the fuzzy output maps

|           | Dataset 1 | Dataset 2 | average |
|-----------|-----------|-----------|---------|
| basal SOM | 0.017     | 0.003     | N/A     |
| Comprehensive evaluation using basal SOM | 0.363 | 0.219 | 0.291 |
| Comprehensive evaluation using MK-SOM | 0.096 | 0.036 | 0.066 |
show the suppressive effect. Fig. 2C presents the suppressive effect from right to left and Fig. 2D presents it from upper left to lower right.

Thus, we found that the change of SOD activity, total GSH content, and Cat activity by low-dose radiation and antioxidant was complicated.

3·2 Evaluation of anti-oxidative function by low-dose radiation or antioxidant using basal SOM

Component maps were drawn based on the change of SOD activity, total GSH content, and Cat activity in Fig. 2C and 2D (Fig. 3). When the dataset was normalized with zero as control and one as injury, the color of the component maps got brighter as the value of the indexes increased. Despite the fact that the anti-oxidative function is related to disease suppression, the anti-oxidative function had no correlation between control and injury. However, as illustrated in Fig. 3, the increased anti-oxidative function might be vertical to the suppressive effect.

Thus, we stated that SOM reflected the characteristics of Dataset 1 or Dataset 2, especially the suppressive effect and increased anti-oxidative function, in Sections 3·1 and 3·2. Furthermore, we comprehensively evaluated the effect of low-dose radiation and antioxidant. Dataset 1 and Dataset 2 were combined, and their characteristics presented on the same output map (Fig. 4).

The dendrogram was similar to that in Fig. 2A. However, some data moved from group B to group
Virtually all the remaining data were irradiation data. Although groups A and B and groups C and D showed the same main cluster according to the above clustering, groups A, B, and C were adjacent (Fig. 4B). The fuzzy output map shows the suppressive effect from upper right to lower left. In this output map, we found that the relationship of the groups was different from that in Fig. 2C and 2D, because group B was mapped beyond group A. MK-SOM showed well the characteristics of the data by only irradiation in group B. In addition, group C as well as groups A and B show the suppressive effect. Therefore, only cream containing ultralow volume radionuclides 0.1 mSv/h administration for 2 h had no suppressive effect on the output map (Fig. 4C).

Pain alleviation effect by low-dose radiation using MK-SOM

Fig. 4 shows that low-dose radiation and antioxidant suppress pain. The concentration dependence of the pain alleviation effect is shown on the output map (Fig. 4C, 4D). We found that the pain alleviation effect by 1000 Bq/m³ radon inhalation for 24 h is similar to that by antioxidants. Inhalation of 2000 Bq/m³ of radon for 24 h or a combination of 1000 Bq/m³ radon inhalation for 24 h and pregabalin 3 mg/kg body weight administration also had full effect on the pain.

Suppressive effect except for pain by low-dose radiation using MK-SOM

Disease suppressive effect according to the concentration of radon was not apparent, except for pain. Fig. 4E showed the location of data against liver disease suppressive effect by radiation. The liver disease suppressive effect depended exclusively on the concentration of antioxidant (Fig. 4F). However, 2000 Bq/m³ radon inhalation for 24 h, the combination of 2000 Bq/m³ radon inhalation for 24 h and 300 mg/kg body weight administration of Vitamin C or E, or more than 2000 Bq/m³ radon inhalation for 24 h had an effect on liver injury.
We noticed that the location of data against brain disease was not similar with others. It was shown in Fig. 4B. Because these input data meant the suppressive effect but anti-oxidative function could not make a reasonable prediction. However, the area contained a part of the data of pain and liver disease which our result would expect as the new indication of radon therapy. Moreover, the area shaded the gap between the neighboring units in U-matrix visualization on SOM. Although this result could not unclear by the clustering of Word’s method, the shade on the output map showed the hidden pattern by fuzzy answer.
Comprehensive evaluation of anti-oxidative function by low-dose radiation and antioxidant using MK-SOM

A component map was drawn showing the change of SOD activity, total GSH content, and Cat activity in Fig. 4B (Fig. 5). As with Fig. 3, the change of anti-oxidative function was vertical to the suppressive effect. We assessed the correlation of how pain and liver disease was suppressed through the increased anti-oxidative function. According to the component maps, all anti-oxidative functions, such as SOD activity, total GSH content, and Cat activity, progressively increased with stability in group A. Moreover, it is important to note that the specific characteristic was extracted from the circled area in group B. We stated above that MK-SOM showed the characteristic of the data for only irradiation in group B. This result clarifies that low-dose radiation increases the anti-oxidative function and operates like antioxidant.

4. Discussion

Statistics is a common tool for data analysis, and recently, new data analysis methods based on statistics, such as ANN, have also been presented. SOM, which is a kind of ANN, is widely used in various fields. One reason SOM is valuable in a wide variety of fields is its visualization in low-dimensional representation. SOM always gives a noteworthy solution. The other reason is flexibility. We analyzed complex information by updating the output map through constant learning. By learning, the updated units returned relevant knowledge about the input data. It could be argued that the output map is based on knowledge of the input data. The knowledge of the output map is more comprehensive than the input data because SOM has many units that reflect the characteristics of the input data. However, the accuracy of SOM is significantly affected by the quality of the input data.

The datasets used in this study were collected from reports about the different kinds of injuries in the different kinds of organs. It is impossible to standardize the condition of these injuries. Therefore, we conducted normalization of animal disease model for comprehensive evaluation of the unorganized datasets. In addition, SOM was applied based on mutual knowledge theory (Fig. 6B). The mutual knowledge of Datasets 1 and 2 was obtained by assimilation of SOM 1 for Dataset 1 and SOM 2 for Dataset 2. It is logical to think that SOM was utilized to uncover hidden patterns and relationships within the data with a fuzzy answer. It appears that researchers developed their own knowledge in consultation with other researchers. The goal of ANN is to emulate the...
cognitive function of the human brain; however, we believe that the developing of our cognitive function requires significant involvement with others. The accuracy of MK-SOM in this study was warranted by quantization error, as shown Fig. 6. Finally, we established an analysis method for evaluation of the effect of low-dose radiation. SOM lacks absolute parameters, such as initialization, learning rate, and map shape. However, because such parameters were not relevant in this paper, they were not discussed. Moreover, we could not prepare a training data and validation data because the number of data is small. The important part of this study is only how accurately it presents the effects of radiation from the input data.

Our results present very valuable findings. The output map showed evidence suggesting that low-dose radiation suppresses depression, cerebral infarction, type-1 diabetes, hyperuricemia, hepatopathy, neuropathic pain, inflammatory pain, and so on in animal study. Moreover, the output map also reflected evidence showing the anti-oxidative function and the suppressive effect of oxidative stress-related disease by antioxidants. The comprehensive evaluation allowed knowledge discovery of suppressive effect and increased anti-oxidative function by low-dose radiation. For example, pain was suppressed according to the dose of irradiation (Fig. 4C). However, other injuries were not suppressed according to the dose of irradiation. For liver injury, low-dose radiation might be predisposed to suppress injury because much of the data were mapped in the suppressive effect area on the output map. Inhaled radon is transported to tissue through the blood circulation and dissolved from blood into tissue based on a tissue/blood partition coefficient. Adipose tissue can retain more radon (more than 10 times) than the other tissues, because the partition coefficient is much higher. It is known that liver has more blood flow and can easily store excess fat. This result against liver disease might also indicate the potential for radon therapy. Moreover, we obtained results showing how pain and liver disease is suppressed through increased anti-oxidative function from this study. All the anti-oxidative functions, such as SOD activity, total GSH content, and Cat activity,
progressively increased with stability in the more suppressing area (Fig. 5). We clarified the effect of radon inhalation as being dose-dependent and dose rate-dependent. SOD activities react differently in each organ. The results suggest that radon therapy may also be suitable for treatment of brain disease. Our results also indicate the potential for radon therapy as the data against brain disease on the output map showed the specific characteristic (Fig. 2C, 4B). The component map of Cat activity showed extreme increases. Treatment by low-dose radiation of brain disease should be effective by searching for the activated point of all of the anti-oxidative functions, such as SOD activity, total GSH content, and Cat activity. In the liver diseases and brain diseases, we have reported the evidence of the suppressive effects of depression, ischemic injury, cold-induced brain injury, acute alcohol-induced hepatopathy, and carbon tetrachloride-induced oxidative damage. We would find other indications of radon therapy in the future. Therefore, examination of the suppressive effect of radon inhalation against liver disease and brain disease is indispensable in future work based on the result of this study and the evidence presented here.

The aim of this study is knowledge discovery of suppressive effect and increased anti-oxidative function by low-dose radiation. Our results add to the limited scientific evidence and suggest some new indications for radon therapy by fuzzy comprehensive evaluation using MK-SOM. Specifically, it is highly possible that radon inhalation suppresses pain, liver disease and brain disease by maintaining increased SOD activity, total GSH content, and Cat activity. The data presented in this study provide an essential basis for future studies aimed at the assessment of radon therapy. ANN such as SOM has attracted a great deal of interest in medical field in the last decade. For example, big data analysis is a very challenging problem today. We analyzed only small data in this study, but this analysis method has a great possibility in the evaluation of the health effects by radiation as big data analysis. From now on, we will challenge a more sensitive subject.

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自己組織化マップを用いた低線量放射線による疾患抑制効果と抗酸化機能亢進に関する特徴抽出

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我々はこれまで、低線量放射線はマウス諸臓器中で抗酸化機能を亢進し、酸化ストレス関連疾患を抑制することを報告してきた。しかしながら、これらの結果は対象疾患も低線量放射線による処置の条件も様々で、有効性が立証された治療法は確立されていない。そこで、本研究では、これらの結果から低線量放射線の健康効果を明らかにすることを目的とし、ラドン療法のような低線量放射線を活用した治療法の新規適応症を探索した。データの解析には自己組織化マップ（SOM）を用い、不安定な抗酸化機能の変化を自己組織化マップの曖昧な表現で視覚的に直感的に捉えることにより、出力された疾患抑制効果と抗酸化機能亢進の関連性を検討した。その結果、ラドン療法の適応症である疲労への効果には明らかな線量依存性があることがわかり、肝疾患や脳疾患においても、線量依存性はないもののその効果を期待できると予測できた。本研究は、ラドン療法のような低線量放射線を活用した治療法の応用に貢献できると考える。