The nervous system of adult animals is generally considered to be extremely radioresistant, particularly with respect to its morphological features. However, a variety of physiological responses have been reported after exposure to relatively low doses of radiation. The low-dose range is generally considered to be 0.25 Gy or less, a level at which no clinical symptoms appear. In this review, we will discuss the stimulatory effects of low-dose irradiation on physiological processes; assess introduce current knowledge regarding the safety of doses less than 100 mGy; and to evaluate the challenges and rewards of low-dose irradiation experiments using physiological analyses.

Key Words: low dose irradiation, behavior analysis, stimulatory effect, physiological technique, radiation safety

1. Reports on the stimulatory effect of low-dose irradiation

The experimental study of low-dose radiation began shortly after the discovery of X-rays by Dr. Wilhelm Röntgen in the late 19th century. Until recently, however, progress in this field was limited by two phenomena: (1) the kinds of effects resulting from exposure to high doses could not be obtained at low doses, and (2) the experiments were not reproducible. Even so, a few researchers forged ahead. According to Dr. Alison Casarett’s classic 1968 textbook Radiation Biology, low-dose radiation clearly has a stimulatory effect that should not be viewed as harmful.1) For example, the text cites evidence that potted plants exposed to low doses from 0.15 to 0.25 Gy exhibit excellent growth in terms of height and foliage. However, increasing the dose even a little has the opposite effect: leaves wilt and the plants grow poorly.

The definition of low-dose radiation is not fixed. Thirty to forty years ago, radiation experiments were often performed at doses of hundreds of Gy, and even a harmful dose of 2 Gy was called “low.” In recent years, however, the low-dose range has come to be considered 0.25 Gy or less, i.e., the level at which no clinical symptoms appear following exposure to radiation in the clinic.2)

To begin our discussion, we will introduce some experiments performed in our laboratory. When raised individually for a long period of time, male mice normally become aggressive: if a male mouse raised in a different environment is placed in the same cage, the long-term resident will start a fight to violently oust the intruder. We pre-exposed the full body of a resident mice to a low dose (0.05 Gy), and then monitored their aggressiveness. Almost no fights occurred for 5 to 7 days after irradiation,
and this effect continued for 2 weeks.\textsuperscript{3,4} Strikingly, when the dose was increased to 0.5 Gy, this suppres-
sive effect on aggression disappeared. This finding is im-
portant because it shows that the brain, which is generally
considered radioresistant with respect to its morphological
features, can respond functionally to low-dose radiation.\textsuperscript{5} Another point is that, despite
the fundamental principle that \textit{the effects of radiation increase as the dose increases}, we observed a differ-
ent phenomenon in the nervous system: an effect was
observed in the low-dose region, but when the dose
was increased, that effect disappeared. Follow-up ex-
periments on this phenomenon have been performed
by our group and by other researchers, and the repro-
cducibility of the main result has been confirmed.

Next, we will discuss an electroencephalography
(EEG) study that provides further confirmation that
the brain can respond to low-dose radiation.\textsuperscript{6,7} In
this study, we waited until a mouse entered deep
sleep. After confirming the sleep state by EEG, we
exposed the mouse to full-body irradiation (0.04 Gy)
in a sound-proof box equipped with a X-ray irra-
diation device. We found that the brain entered an
awakened state immediately after exposure. More-
ever, we found that surgically severing the olfac-
tory nerves blocked the response, implying that the
mouse sensed the X-rays \textit{via} the olfactory nerves.
The olfactory system has two main components.
In the main olfactory system, olfactory cells that
express odorant receptors sense odorous substances,
and this information projects widely from the main
olfactory bulb to the cerebral limbic system, e.g., the
piriform cortex In functional terms, this system plays
a critical role in searching for food. On the other
hand, the accessory olfactory system (also called the
vomeronasal system) begins with the vomeronasal
organ, where its receptors are expressed. Information
passes from sensory cells in this tissue through the
accessory olfactory bulb, is transmitted to the amygd-
ala, and ultimately arrives at the hypothalamus. The

amygdala is the center of emotional behaviors such
as aggression; thus this system may be involved in
the phenomenon described above in which attack
behavior was altered by low-dose irradiation. In
addition, the accessory olfactory system is also in-
volved in reproductive behaviors, and thus plays an
important role in the propagation of the species. For
instance, we observed that male mounting behavior
is significantly reduced by low-dose irradiation in a
limited dose range.\textsuperscript{8} The function of the accessory
olfactory system may be inhibited following low-
dose irradiation,\textsuperscript{9,11} as when the animal undergoes
olfactory bulbectomy, resulting in induction of a
behavioral change.

More interestingly, we found that, although mice
do not appear to notice the radiation, upon repeated
exposure they \textit{adapt} to the X-ray stimulation and
gradually stop responding. The elegance of this ex-
perimental method is that we can ascertain the respon-
siveness of the mouse’s nervous system to radiation.
When we continued our experiments by gradually
lowering the dose from 0.04 Gy, we confirmed that the
arousal response occurred even at a dose equivalent to
a clinical chest X-ray (unsubmitted data).

The third study also demonstrates how sensitive the
nervous system is to low-dose irradiation.\textsuperscript{12} In these
experiments, the mice are raised as a group. When
the mice are removed from the cage at 1 min intervals
and their rectal temperatures are measured, the last
mouse removed from the cage has a higher body tem-
perature. This observation is reminiscent of another
phenomenon we have observed: at a conference, as
researchers wait for their turn to present their work,
the last presenter often has the highest level of anxi-
ety. This is known in pharmacology as the \textit{predict-
able anxiety model}. We pre-exposed only the heads
of our mice to low doses, and then measured body
temperature 7 days after irradiation. In the control
group, the difference in the average body temperature
between the first three mice removed from the cage
and the last three mice was 2.3°C. In mice exposed to 0.15 Gy, however, we found the difference was only 1°C, obviously much smaller. In mice treated with the antianxiety drug diazepam, the difference was 1.1°C, implying that the drug relieved the anxiety. In other words, low-dose radiation seems to relieve stress. These changes in body temperature were statistically significant. This effect was not observed, however, when the dose was increased to 0.5 Gy.

Next, we will discuss a phenomenon called radioresistance. When mice are pre-exposed to full-body low-dose radiation (0.1–0.15 Gy), and then irradiated with a dose that would ordinarily be lethal to 50% of them (i.e., sub-lethal dose of 7.5–8 Gy), the pre-treated mice do not die. To investigate the mechanism, we forced mice to breathe a low concentration of ozone, and then irradiated the mice with a full-body sub-lethal dose 24 h later. Ozone is a chemical species with strong oxidization potential, and it is considered to produce active oxygen similar to radiation exposure. Nearly 50% of the mice in the control group died, but in the group treated with ozone, almost all survived. This treatment was effective even in mice that were exposed to a sub-lethal dose 30 days after inhaling the ozone. The data indicate that the effect of ozone persists in the body for at least 30 days, and our findings match those reported by other researchers, i.e., pre-exposure to low-dose radiation persists for at least 30 days. In light of the reports discussed in this section, it appears that limited exposure in the low-dose range has both stimulatory and protective effects.

2. Is exposure to 100 mGy or less of radiation really safe?

Now, based on the data we have compiled, we will consider whether exposure to a radiation dose of 100 mGy or less is really safe. The most recent recommendation by the International Commission on Radiation Protection (ICRP) states that, in the context of radiation exposure, we should pay special attention to the development of cataracts and cardiovascular disease (i.e., diseases affecting the heart and brain). This policy originates from the results of multiple studies showing that development of these diseases is more sensitive to radiation than previously thought. “Chernobyl heart,” the pediatric cardiac disease observed after the Chernobyl nuclear accident, illustrates the relationship between radiation exposure and specific illnesses. Previous studies showed that exposure to radiation causes deformities, but in almost all cases these were physical deformities such as short limbs or missing ears; by contrast, very few detailed reports have assessed the effects of radiation on the cardiovascular system. Hence, we analyzed the effects of exposure on the cardiovascular system during organogenesis.

The aortic arch in mammals is thought to have evolved from one of the blood vessels around the gills in fish. The pharyngeal arteries are vessels in which arteries 1 through 6 are paired. In mice, pharyngeal artery 4 is present on both the left and right sides at day 11.5 of embryonic development, but 24 h later, the left side remains as the aortic arch, whereas the right side disappears. Similarly, pharyngeal artery 6 on the left side forms the arterial duct.

Initially, our laboratory used immunosuppressants to study the process of aortic arch formation. We found that, normally, the aorta originates in the heart, arches to the left, and extends as a dorsal artery from the thoracic cavity into the abdominal cavity. By contrast, fetuses from dams treated with the immunosuppressant FK506 (tacrolimus) often formed an aortic arch that arches toward the right side. This drug interrupts the action of an intracellular protein called calcineurin, inhibiting release of phosphate from Nuclear factor of activated T-cells (NFAT), which acts downstream in the signal transduction pathway. Immunosuppression occurs because the message instructing the cell to increase...
immune function does not reach the DNA. When we increased the phosphate concentration in amniotic fluid to determine the involvement of phosphate, we observed a small change, but rightward aortic arch formation still occurred in several animals. However, when sodium or potassium was added to the amniotic fluid, right aortic arch formation did not occur at all. To investigate whether we could induce this phosphate effect more strongly, we replaced normal phosphorus with a radioactive isotope. Interestingly, rightward aortic arch formation occurred at a higher rate when 40 MBq of $^{33}$P was injected into the amniotic fluid.

Because rightward aortic arch formation occurred in both the internally exposed group and the group treated with FK506, we performed mass spectrometry on samples from fetuses of both groups, with the goal of determining whether the underlying mechanisms were the same. We found that the level of a protein called Na$^+/H^+$ exchange regulatory cofactor 1, which is involved in proton transport, was conspicuously reduced in both groups. To determine whether protons are involved in left–right axis determination in the early stages of development, we injected lansoprazole, a drug that inhibits proton pump function, into the amniotic fluid. When embryos were treated with lansoprazole alone, rightward aortic arch formation occurred at a high rate. In addition, we confirmed that, at a dose of 40 MBq, a decrease in proton pump function occurred that was roughly the same as that in the group treated with lansoprazole.

An important point in studying fetuses is this: At what stage of development should we evaluate the impact of internal exposure? In our laboratory, we performed evaluations on day 13.5 of embryonic development; if we were to wait until near term or after birth, we might overlook embryo death or be unable to confirm stillbirths that have liquified. Moreover, the rightward aortic arch that we have identified is a type of deformation that permits a nearly normal life after birth, and is never counted as an abnormality by observation alone. In other words, it is a type of abnormality that would most likely not be classified as an effect of internal exposure to radiation.

A study investigating the effects of exposure to low-dose radiation on the development of the heart using external exposure methods has been published. Pregnant C57Bl/6J mice received on embryonic day 11 (E11) a single total body dose of ionizing radiation that ranged from 0.02 Gy to 1.0 Gy. The results showed that this resulted in persistent changes in the expression of proteins belonging to mitochondrial respiratory complexes, redox and heat shock responses, and the cytoskeleton. An effect was observed even at a low dose of 0.1 Gy. The levels of total and active forms of the kinase MAP4K4, which is essential for embryonic development of the mouse heart, were persistently decreased after a radiation dose of 1.0 Gy. In the internal exposure data we reported above, the dose delivered to amniotic fluid was as low as 5 mGy, and the fetal radiation dose from the $^{33}$P source was considered to be less than 5 mGy. In particular, the decrease in the expression Na$^+/H^+$ exchange regulatory cofactor 1 caused by low-dose internal exposure resulted in a malformation that altered the aortic travel path. These studies provide important insights into the molecular mechanisms of cardiac dysfunction induced by very low doses of ionizing radiation during the prenatal period.

Next, to confirm the absence of abnormalities at a dose of 4 MBq or less, we performed a more detailed analysis of embryonic samples using a system that combines two-dimensional electrophoresis and mass spectrometry. Using this approach, we identified four species of proteins that were significantly up-regulated in low-dose-irradiated embryos relative to controls. The changes in the levels of these proteins suggested that the signaling function of the nervous
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system was inhibited by radiation exposure.\(^{19}\) In addition, to determine whether the data on nervous system abnormalities obtained from these tissue samples exhibit a kind of change associated with microcephaly reported in data from Hiroshima atomic bomb victims, we performed Western blotting to monitor the level of PQBP1 (polyglutamine-binding protein 1). PQBP1 expression was suppressed considerably in the 3.7 MBq group, and microcephaly-like changes occurred even at low dose rates and in embryos that underwent low-dose internal exposure. In this experiment, we found that the total dose 3 days after administration was about 0.06 Gy, and that the transfer rate to the placenta was 1% or less. This means that damage to the central nervous system occurred at an exposure level considerably lower than those used in previous studies of external exposure.

Here, we will introduce a view expressed by other researchers: Even low-dose exposure is dangerous. A very important point to consider when conducting this research is that the effects of low-dose radiation can appear or disappear depending on the irradiation conditions. For example, a review written by Dr. T. Sado pointed out that the stimulatory effects of low-dose radiation do not appear in mice reared in specific pathogen–free (SPF) conditions.\(^{20-22}\) Moreover, many researchers have reported that the effects of low-dose radiation differ depending not only on differences in strain, but also on whether the mice are raised alone or in a group. In other words, environment and stress at the time of exposure are related to the development of low-dose effects.

Next, we will describe a unique experiment performed by Dr. T. Nomura. First, he irradiated dams with X-rays at the organogenesis stage, and then repeatedly applied a coal tar component called TPA to the skin of the offspring twice a week for 18 weeks.\(^{23}\) He reported that fetuses that were not exposed to radiation did not develop skin cancer when treated with TPA, whereas the fetuses from dams that received low-dose exposure of 0.3 Gy did; moreover, the incidence of cancer increased as the dose increased. This elegant experimental system proved that the “memory” of radiation exposure is firmly preserved in the body of the fetus, and that, when a dangerous substance such as a chemical or food additive is encountered, the effect of the exposure to radiation materializes in the form of cancer. In other words, the post-exposure environment also influences the manifestations of low-dose effects.

Now, we will discuss the effects of long-term exposure. Several reports from outside of Japan suggest that the lifespan of some animals can be extended by long-term, low–dose rate irradiation. By contrast, it has been reported that the lifespan of mice is actually shortened in Japan.\(^{24}\)

While the effects of high doses of radiation on the brain have been studied and are reasonably well understood, the effects and mechanisms of the brain’s responses to low doses of radiation remain unclear. Low doses can also induce a wide array of cognitive impairments and deficits, even without inducing any significant morphological alterations.\(^{25}\) Recently, in experiments with two adjacent rats; one whose liver was directly exposed to radiation and the second to scatter radiation from the first rat to its body and brain,\(^{26}\) revealed that exposure to radiation doses as low as 0.115 cGy caused changes in gene expression and reduced spine density, dendritic complexity, and dendritic length in the prefrontal cortex tissues of females, but not males. This study showed that low dose scatter irradiation influences the brain and behavior in a sex-specific way.

As an example of cancer caused by low-dose exposure, recent reports show that the risk of cancer increases following CT examination (5–50 mGy). In the UK, a study of approximately 180,000 persons who underwent CT scans in early childhood revealed that two or three CT scans in early childhood revealed that two or three CT examinations tripled the relative risk of brain tumors, and five to ten CT examinations
tripled the risk of leukemia.\textsuperscript{27} Meanwhile, an Australian study of 680,000 minors revealed that the overall incidence of cancer in subjects who underwent a CT exam increased by 24\% relative to controls, and that the effect became even larger as the number of exams increased.\textsuperscript{28} Because large numbers of CT exams are performed in Japan, this procedure requires careful consideration.

Moreover, a recent large-scale epidemiological survey of more than 300,000 workers in the nuclear power industry reported an increase, albeit slight, in the risk of leukemia following low-dose exposure. We are exposed to a dose of approximately 2 to 3 mSv annually from the natural environment, and this study examined workers in the nuclear industry who were often exposed to doses from 1.1 to 50 mSv.\textsuperscript{29} This study demonstrates that the risk of leukemia increases as the dose of radiation increases, even in the low-dose range.

Likewise, based on the effects of the Chernobyl nuclear accident, exposures of 100 mSv or less may pose a danger to health.\textsuperscript{30} For example, among 345 patients with pediatric thyroid cancer in Ukraine (14 or younger at the time of surgery), exposures of 100 mGy or less accounted for more than half of the cases. The typical nuclide for internal exposure after a nuclear accident is caesium, which exhibits strange behavior once it enters the body. For example, if one ingests a single dose as large as 1000 Bq, the caesium is slowly eliminated and ultimately disappears. However, if the same dose is ingested over time in multiple smaller doses, the opposite is true: daily ingestion of caesium causes 100–200 times the daily ingested dose to accumulate in the body. Caesium is a potent potassium channel blocker, and \(^{137}\text{Ba}\), the decay product of \(^{137}\text{Cs}\), is also a potent potassium channel blocker that can cause arrhythmia. An examination of the level of \(^{137}\text{Cs}\) accumulation and frequency of ECG abnormalities in children in the Chernobyl disaster area of Belarus revealed that arrhythmia due to blockage of repolarization in cardiac muscle was present in 80\% of children with \(\geq 80\) Bq/kg \(^{137}\text{Cs}\) in their bodies.\textsuperscript{31} This is why we must limit internal exposure as much as possible, even in areas contaminated by the Fukushima Dai-ichi Nuclear Power Plant Accident.

\section*{3. Conclusion}

Let us summarize what we have covered.

\begin{itemize}
  \item[(1)] Is there a stimulatory effect in the low-dose range?
  Yes, the stimulation effect clearly exists. More specifically, in our research we have clearly observed a stimulatory effect on the nervous system, which was previously considered to be relatively insensitive to radiation.
  \item[(2)] Is exposure at 100 mSv or less really safe?
  No, the effects on embryonic development clearly manifest as morphological abnormalities. Moreover, epidemiological surveys by other researchers showed that the risk of cancer also increases.
  \item[(3)] What are the challenges in low-dose research?
  The effects of radiation appear or disappear depending on subtle changes in conditions and experimental settings, and it is difficult to identify a statistically significant index.
  \item[(4)] Why is this research rewarding?
  We believe that this field represents a straightforward way to explore new radiotherapy methods and the evolution of life, as detailed below. Additionally, we seek to accumulate data on low-dose exposure and contribute to the formulation of safety standards for international organizations such as the ICRP.
\end{itemize}

We wish to close by introducing an unusual experiment that we conducted pertaining to radiation and the evolution of life.\textsuperscript{32} In this experiment, we used earthworms native to the Tohoku region that spontaneously break into several segments when they reach a certain size. Each segment then continues growing by extending in the anterior/pos-
terior direction. These particular earthworms have an asexual reproduction cycle, and regrow to their original size in about 2 weeks. However, when the earthworms were grown over many generations on an agar culture medium prepared with an aqueous solution that emits $\beta$ radiation from radioactive $^{32}$P, histology revealed that testes and ovaries eventually differentiated with the body. Furthermore, when we looked inside the culture medium, we found eggs, indicating that the sex organs were functional. Given that life may have evolved in an environment in which the radiation levels were several times stronger than they are now, it is interesting to speculate that cells retain memories of the distant past. In other words, radiation may be a necessary ingredient for our continued existence.

Declaration of Conflicting Interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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和文要旨

低線量放射線研究の面白さと難しさ

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成体動物の神経系は、一般的に放射線抵抗性であると考えられている。しかし、比較的低線量の放射線に照射された後に、さまざまな生理学的反応が起こることも知られている。ここでの低線量域とは0.25 Gy以下の臨床症状が現れないレベルを指す。本稿では、生理学的プロセスに対する低線量照射の影響について解説した。また、100 mGy未満の安全性に関する最近の報告例も含めた。最後に生理学的分析を使用した低線量照射実験のこれからの課題について提案した。

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