Low-dose radiation, diabetes & its complications

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Dose-Response Annual Meeting
Amherst, April 21-22, 2015
• LDR/LDR-induced hormesis and adaptive response

• LDR preventive effects on various injuries

• Diabetes/Diabetic complications

• Possible mechanisms

• Current debates for the risks & benefits
UNSCEAR 1986 report: (United Nations Scientific Committee on the Effects of Atomic Radiation)

- Low LET radiation
  - < 20 rad (200 mGy)
- High LET radiation
  - < 5 rad (50 mGy)
- Low dose rate
  - < 0.05 mGy/min
Injury endpoints
- DNA damage
- Cell death
- Mortality

Function endpoints
- DNA repair activity
- Immune response
- Cell proliferation
- Cell metabolism

Before

(cGy)
**Hormesis: Life longevity**


Long-term effects of acute and chronic irradiation in mice. I. Survival and tumor incidence following chronic irradiation of 0.11 r per day.

LORENZ E, HOLLCROFT JW, MILLER E, CONGDON CC, SCHWEISTHAL R.
Hormesis: DNA repair and antioxidant activities


Hormesis: DNA repair and antioxidant activities

Relative to control, DNA repair activity varies with increasing dose of radiation. The graph shows two different radiation doses: large dose radiation (Gy) and low dose radiation (Gy).

Liu SZ et al. 1990
Hormesis: DNA repair and antioxidant activities


Injury endpoints
- DNA damage
- Cell death
- Mortality

Function endpoints
- DNA repair activity
- Immune response
- Cell proliferation
- Cell metabolism

Hormesis
(U-shape curve)
(suppression & stimulation)
**Adaptive response**

Adaptive response of human lymphocytes to low concentrations of radioactive thymidine.

Olivieri G, Bodycote J, Wolff S.


Chromatid aberration, cytogenetic adaptive response
Adaptive response

Incidence of chromosome aberrations, %

Cai L and Liu 1990
Low-dose radiation

- Protective proteins ↑
- DNA repair ↑
- Antioxidants ↑

High dose of radiation

- Gene mutation
- DNA damage
- Chromosome damage
- Cell death

Adaptive response
Adaptive response


- **Cai L**. Research of the adaptive response induced by low-dose radiation: where have we been and where should we go? *Hum Exp Toxicol.* 1999 Jul;18(7):419-25.

Low-dose radiation

Adaptive response

High dose of radiation

- Protective proteins ↑
- DNA repair ↑
- Antioxidants ↑

- Gene mutation
- DNA damage
- Chromosome damage
- Cell death
Adaptive response
(Cross adaptive response)

Low-dose radiation

High dose of chemicals

- Protective proteins $\uparrow$
- DNA repair $\uparrow$
- Antioxidants $\uparrow$

- Gene mutation
- DNA damage
- Chromosome damage
- Cell death
Research of the adaptive response induced by low-dose radiation: where have we been and where should we go?

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Can we use the hormesis and/or adaptive response induced by LDR to clinic setting?

Inducing AR are called adapting dose or AR dose. So far, AR has been characterized both in vitro with human, rabbit and calf lymphocytes, normal or tumor cell lines, and in vivo with mouse bone marrow cells, splenocytes and germ cells.2-3 AR could be expressed in multiple biological endpoints including unscheduled DNA synthesis, micronuclei, chromosome aberrations, gene muta-

How does the AR dose relate to human environmental (ecological) exposure?

Humans live with a background radiation which may play an essential role in human health.
• LDR/LDR-induced hormesis and adaptive response

• LDR preventive effects on various injuries

• Diabetes/Diabetic complications

• Possible mechanisms

• Current debates for the risks & benefits
Inhibitory Effects of Prior Low-dose X-ray Irradiation on Carbon
Tetrachloride-induced Hepatopathy in Acatalasemic Mice

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Da-Ho YU¹, and Shinji SUGIURA¹
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THE EFFECTS OF ENVIRONMENTAL LOW-DOSE IRRADIATION ON
TOLERANCE TO CHEMOTHERAPEUTIC AGENTS

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(Submitted 12 July 2010; Returned for Revision 30 August 2010; Accepted 22 September 2010)

Abstract—The nuclear disaster at Chernobyl, Ukraine, in April of 1986 continues to impact the environment on many different levels. Studies of epidemiological, environmental, and genetic impacts have been prolific since the accident, revealing interesting results concerning the effects of radiation. The long-tailed field mouse, Apodemus flavicolli s, was collected from distinct localities near the Chernobyl site and evaluated based on in vivo responses to the current clinically employed chemotherapeutic agents bleomycin (BLM) and vinblastine (VBL), as well as the immune modulator lipopolysaccharide (LPS). Maximum tolerable doses of three different cancer drugs were administered to the rodents from three different lifestyles: native mice living and reproducing in a radioactive environment,
Inhibitory Effects of Prior Low-dose X-irradiation on Ischemia-reperfusion Injury in Mouse Paw

Takahiro KATAOKA, Yuko MIZUGUCHI, Masaaki YOSHIMOTO, Takehito TAGUCHI and Kiyonori YAMAOKA*

Edema/Ischemia-reperfusion injury/Low-dose irradiation/Reactive oxygen species/Antioxidation function.

We have reported that low-dose, unlike high-dose, irradiation enhanced antioxidation function and reduced oxidative damage. On the other hand, ischemia-reperfusion injury is induced by reactive oxygen species. In this study, we examined the inhibitory effects of prior low-dose X-irradiation on ischemia-reperfusion injury in mouse paw. BALB/c mice were irradiated by sham or 0.5 Gy of X-ray. At 4 hrs after irradiation, the left hind leg was bound 10 times with a rubber ring for 0.5, 1, or 2 hrs and the paw thickness was measured. Results show that the paw swelling thickness by ischemia for 0.5 hr was lower than that for 2 hrs. At 1 hr after reperfusion from ischemia for 1 hr, superoxide dismutase activity in serum was increased in those mice which received 0.5 Gy irradiation and in the case of the ischemia for 0.5 or 1 hr, the paw swelling thicknesses were inhibited by 0.5 Gy irradiation. In addition, interstitial edema in those mice which received 0.5 Gy irradiation was less than that in the mice which underwent by sham irradiation. These findings suggest that the ischemia-reperfusion injury is inhibited by the enhancement of antioxidation function by 0.5 Gy irradiation.
Inhibitory Effects of Prior Low-dose X-irradiation on Cold-induced Brain Injury in Mouse

Masaaki Yoshimoto,¹ Takahiro Kataoka,¹ Teruaki Toyota,¹ Takehito Taguchi,¹ and Kiyonori Yamaoka¹,²

Abstract—We examined the inhibitory effects of low-dose X-irradiation on mouse brain tissue with cold-induced injury by comparing tissue samples from three groups of mice: control, sham-irradiated cold-exposed, and X-ray-irradiated (0.5 Gy) cold-exposed mice. The water content in brain increased significantly in the sham-irradiated group following the cold-induced injury relative to the control group. However, water content in brain tissue from the X-ray-irradiated group was significantly lower than that from the sham-irradiated group. Levels of antioxidants, such as superoxide dismutase and glutathione, in brain tissue from the X-ray-irradiated group were higher than those from the sham-irradiated group. Moreover, the cold injury-induced cell death, particularly apoptosis, while low-dose irradiation inhibited cell death, especially among glial cells, but not numeral cells. These findings suggest that prior low-dose X-irradiation activated antioxidant function and inhibited cold-induced brain injury.

KEY WORDS: cold injury; brain edema; 0.5 Gy irradiation; antioxidative function.
BELLE Article:

Low-dose radiation and its clinical implications: diabetes

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Induction of hormesis and adaptive response by low-dose radiation (LDR) has been extensively indicated. Adaptive response induced by LDR was not only resistant to damage caused by a subsequently high-dose radiation, but also cross-resistant to other non-radiation challenges, such as chemicals. Mechanisms by which LDR induces the preventive effect on radiation- or chemical-induced tissue damage include induced or up-regulated expression of protective proteins, such as heat shock proteins and antioxidants. Since oxidative damage to tissues is a low-intensity or power laser (LIL or LPL) radiation on skin wound healing, which has stimulated clinical use of LIL to cure skin ulcer in diabetic patients. Mechanisms by which LDR prevents diabetes, though are unclear now, may include the induction of pancreatic antioxidants to prevent β cell from oxidative damage and immunomodulation to preserve pancreatic function. For LIL therapeutic effect on diabetic wound healing, mechanisms may include its antioxidant action, immunomodulation, cell proliferation stimulation as well as improvement of sys-
• LDR/LDR-induced hormesis and adaptive response
• LDR preventive effects on various injuries
• Diabetes/Diabetic complications
• Possible mechanisms
• Current debates for the risks & benefits
Total Prevalence

Prediabetes

New cases in 2010

25.8 million (8.7% population)

79 million

1.9 million

National Diabetes Fact Sheet, 2011
Diabetes is a metabolic disorder that is characterized by high blood glucose and either insufficient or ineffective insulin.
Hyperglycemia, hyperlipidemia, hypertension & inflammation

Oxidative stress

Diabetes Oxidative stress Cardiovascular diseases
Oxidative stress

Hyperglycemia, hyperlipidemia, hypertension & inflammation

Diabetes → LDR → Oxidative stress → Cardiovascular diseases
Protection against alloxan diabetes by low-dose 60Co gamma irradiation before alloxan administration.

Takehara Y, Yamaoka K, Hiraki Y, Yoshioka T, Utsumi K.

LDR:

- Increases pancreatic SOD,
- Decreases alloxan-induced pancreatic oxidative damage
- No hyperglycemia
Prevention of Type I Diabetes by Low-Dose Gamma Irradiation in NOD Mice

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Pretreatment with nonlethal, low-dose irradiation has been shown to have a protective effect against oxidative injury in animal tissues. Since oxidative injury of tissues is known to be a major cause of many human diseases, we examined the effect of low-dose irradiation on the progression of type I diabetes in mice. Nonobese diabetic (NOD) mice were treated with γ irradiation and the progression of the disease was monitored. An elevated level of glucose in urine was first detected at 15 weeks of age in the control NOD mice, whereas the detection was delayed as long as 7 weeks when the mice received a single dose of 0.5 Gy total-body irradiation between 12 and 14 weeks of age. The greatest effect was observed in insects (1), increased resistance to oxygen toxicity (2), improvement of social behavior in mice (3), and enhancement of immune function (4). In an attempt to assess the biological implications of low-dose irradiation, levels of antioxidant enzymes have been studied. Manno et al. first reported an enhancement of SOD activity in rat liver by low-dose irradiation (5). Increased activities of SOD (6–10), glutathione peroxidase (GPx) (7, 10), and catalase (10) induced by low-dose irradiation have also been confirmed. These results have suggested the existence of significant biological effects of low-dose irradiation. Although how much such an enhancement of antioxidant enzyme activities contributes to the biological effects of radiation is not known, antioxidant defense is likely to be enhanced in the irradiated tissues.
LDR prevention of the development of diabetes in NOD mice.

Pane A represents the time point at which the first mouse from the groups with single LDR (0.5 Gy) at 12, 13 or 14 wks of age and without LDR (control group) spontaneously developed diabetes (hyperglycemia).

Results indicate that the first mouse developed diabetes is at 22 wks of age in the group of mice with LDR at 13 wks of age, which is 7 weeks later than that (15 wks of age) in control group.

Panel B represents the incidence of diabetic mice in different groups.

Results indicate that 10 % of mice with LDR at 13 wks of age developed diabetes at 24 wks of age, which is much lower than those in control and other LDR-treated groups.

Takahashi et al. (2000).
Amelioration of Type II Diabetes in db/db Mice by Continuous Low-Dose-Rate $\gamma$ Irradiation

Mie Tsuruga, a Keiko Taki, a Genichiro Ishii, b Yurie Sasaki, a Chiharu Furukawa, a Takashi Sugihara, c Takaharu Nomura, d Atsushi Ochiai b and Junji Maga e a,1

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Although the mechanism underlying radiation hormesis is unclear, one of the candidate molecular targets is the radiation-induced biological response to oxidative stress. ERK1/2 kinase regulating growth factor-induced intracellular signaling is activated by low-dose radiation, which
LDR → Diabetes
Diabetic

LDR

?  

Diabetic Complications

Does LDR also prevent diabetic complications?
Diabetic Complications

LDR

Heart
Kidney
Skin
Neuronal system
Attenuation of diabetes-induced renal dysfunction by multiple exposures to low-dose radiation is associated with the suppression of systemic and renal inflammation

Chi Zhang,¹,³ Yi Tan,²,³ Weiyong Guo,⁴ Cai Li,³,⁵ Shunzi Ji,¹ Xiaokun Li,¹,³,⁶ and Lu Cai²,³,⁷

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Zhang C, Tan Y, Guo W, Li C, Ji S, Li X, Cai L. Attenuation of diabetes-induced renal dysfunction by multiple exposures to low-dose radiation is associated with the suppression of systemic and renal inflammation. Am J Physiol Endocrinol Metab 297: E1366–E1377, 2009. First published September 29, 2009; doi:10.1152/ajpendo.00478.2009.—Renal protection against diabetes-induced pathogenic injuries by multiple exposures to low-dose radiation (LDR) was investigated to develop a novel approach to the prevention of renal disease for diabetic subjects. C57BL/6J mice were given multiple low-dose streptozotocin (STZ; 60 × 6 mg/kg) to produce a type 1 diabetes. Two weeks after diabetes onset, some of...
LDR’s prevention of renal inflammation and damage

25 mGy X-rays every two days for 2, 4, 8, 12, and 16 weeks

Harvest & examine cardiac inflammation and oxidative damage
Suppressive Effects of Continuous Low-Dose-Rate $\gamma$ Irradiation on Diabetic Nephropathy in Type II Diabetes Mellitus Model Mice

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INTRODUCTION

The prevalence of type II diabetes is increasing worldwide. Diabetic complications involving retina, glomeruli, peripheral nerves, cardiovascular tissues, wound healing and pregnancy are serious lethal symptoms in adult diabetic patients. Nephropathy, characterized by impaired microvessels and excessive deposition of extracellular matrix (ECM) in the glomerular mesangium and tubulointerstitium, is a common cause of end-stage renal failure. The development of diabetic nephropathy is seen in up to roughly 30% of all type II
Multiple Low-Dose Radiation Prevents Type 2 Diabetes-Induced Renal Damage through Attenuation of Dyslipidemia and Insulin Resistance and Subsequent Renal Inflammation and Oxidative Stress

Minglong Shao¹,²,³, Xuemian Lu³, Weitao Cong²,⁴, Xiao Xing¹,⁵, Yi Tan²,⁶, Yunqian Li⁷, Xiaokun Li²,⁴, Litai Jin²,⁴, Xiaojie Wang⁴, Juancong Dong¹, Shunzi Jin¹*, Chi Zhang²,³*, Lu Cai²,⁶

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A

B

Nrf-2
β-actin

4 weeks 8 weeks

Nrf-2 mRNA/β-actin (fold of control)

Con Con/50mGy DM DM/25mGy DM/50mGy DM/75mGy

4 weeks 8 weeks

Nrf-2 protein/β-actin (fold of control)

Con Con/50mGy DM DM/25mGy DM/50mGy DM/75mGy

4 weeks 8 weeks
LDR’s prevention of cardiac inflammation and damage

25 m Gy X-rays every two days for 2, 4, 8, 12, and 16 weeks

Diabetic

Harvest & examine cardiac inflammation and oxidative damage
Attenuation of Diabetes-Induced Cardiac Inflammation and Pathological Remodeling by Low-Dose Radiation

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INTRODUCTION

Diabetes mellitus, commonly known as diabetes, is a group of disorders characterized by a defect in the transfer of glucose from the bloodstream of a person into his or her cells. Cardiac disease is a major cause of the mortality of diabetic patients. The mechanisms responsible for the development of the diabetes-induced cardiac damage are related to multiple factors, including hyperglycemia, hyperlipidemia and inflammation (1–3).

Inflammatory mediators, including adipokines, chemokines, adhesive molecules and cytokines, play important roles in the development of cardiac pathogenesis in diabetes (3–7). For instance, TNFα was reported to cause...
Attenuation of Diabetes-Induced Cardiac Inflammation and Pathological Responses in Low-Dose Radiation

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ON

known as diabetes, is a d by a defect in the odstream of a person ase is a major cause of eents. The mechanisms of the diabetes-induced multiple factors, including ad inflammation (1–3). iding adipokines, checytokines, play impor-ardiac pathogenesis in Experimental patho-
Inflammatory mediators, including adipokines, chemokines, adhesive molecules, and cytokines, play important roles in the development of cardiac pathogenesis in diabetes (3, 7). For instance, TNF-α was upregulated in hyperglycemic mice treated with whole-body low-dose radiation exposure (25 mGy X rays) once every 2 days for 2, 4, 8, 12, and 16 weeks. Diabetes caused significant increases in cardiac inflammation, shown by higher levels of TNF-α.
The diagram shows the relative expression levels of 3-NT and 4-HNE under different conditions: Control, LDR, Diabetes, and Diabetes/LDR. The graphs indicate significant differences in expression levels, with specific annotations for each condition and comparison groups.
Repetitive exposures to low-dose X-rays attenuate testicular apoptotic cell death in streptozotocin-induced diabetes rats

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\textbf{ARTICLE INFO}

\textbf{ABSTRACT}

LDR’s prevention of diabetes-induced testicular apoptosis

Mitochondrial potential and increased expressions of Bax mRNA and protein. All these changes were significantly attenuated in certain extends by repetitive exposures to LDR. To investigate the mechanisms by which LDR attenuates diabetes-induced testicular apoptotic cell death, serum sex hormone (testosterone, luteinizing hormone and follicle stimulating hormone) levels, and both serum and testic-
Serum/testicular
STZ-induced diabetes:

- No treatment
- LDR
- NAC X 4 wks

Age-matched controls

(A) Apoptotic cells, %

(B) MDA, nmol/mg protein
Low Dose Radiation Overcomes Diabetes-induced Suppression of Hippocampal Neuronal Cell Proliferation in Rats

We investigated the effect of low dose radiation on diabetes induced suppression of neurogenesis in the hippocampal dentate gyrus of rat. After 0.01 Gy, 0.1 Gy, 1 Gy and 10 Gy radiation was delivered, the dentate gyrus of hippocampus of streptozotocin (STZ)-induced diabetic rats were evaluated using immunohistochemistry for 5-bromo-2-deoxyuridine (BrdU), caspase-3, and terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) staining. The number of BrdU positive cells in the non-diabetic rats, diabetic rats without radiation, diabetic rats with 0.01 Gy radiation, diabetic rats with 0.1 Gy radiation, diabetic rats with 1 Gy radiation and diabetic rats with 10 Gy radiation were 55.4 ± 38.5/mm², 33.3 ± 6.4/mm², 67.7 ± 10.5/mm², 66.6 ± 10.0/mm², 23.5 ± 6.3/mm² and 14.3 ± 7.2/mm², respectively. The number of caspase-3 positive cells was 132.6 ± 37.4/mm², 378.6 ± 99.1/mm², 15.0 ± 2.8/mm², 57.1 ± 16.9/mm², 191.8 ± 44.8/mm² and 450.4 ± 58.3/mm², respectively. The number of TUNEL-positive cells was 24.5 ± 2.0/mm², 21.7 ± 4.0/mm², 20.4 ± 2.0/mm², 18.96 ± 2.1/mm², 58.3 ± 7.9/mm², and 106.0 ± 9.8/mm², respectively. These results suggest low doses of radiation paradoxically improved diabetes induced neuronal cell suppression in the hippocampal dentate gyrus of rat.

Key Words: Radiation, Hippocampus, Diabetes Mellitus

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Low-Dose Radiation Exposure and Protection Against Atherosclerosis in ApoE<sup>−/−</sup> Mice: The Influence of P53 Heterozygosity


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INTRODUCTION

Analyses of mortality in the Japanese atomic bomb survivors have raised concern about the effect of radiation on noncancer disease death rates, due to a statistically significant increase of these with radiation dose (1, 2). Similarly, increases for heart disease were statistically significant for doses above about 0.5 Sv (3) but it is unclear from the human data whether radiation exposure at doses below 0.5 Gy are associated with an increased risk of
Does LDR also have certain therapeutic effects on diabetes-complications?
LDR’s therapeutic effect on diabetic wound healing

Diabetic mice with skin wound/LDR

Non-diabetic mice with skin wound

Diabetic mice with skin wound

Compare

Rats

Diabetic

60 days

75 m Gy X-rays for 5 days, 2 day break & 5 days ...

day 5                  10                  15
Guo W et al. Radiation Res 2010
Low-dose radiation (LDR) induces hematopoietic hormesis: LDR-induced mobilization of hematopoietic progenitor cells into peripheral blood circulation.

Li W, Wang G, Cui J, Xue L, Cai L.
Summary

- LDR prevents type 1 diabetes, and type 2 diabetes.
- LDR can prevent diabetes-induced renal and cardiac renal inflammation and damage.
- LDR can prevent diabetes-induced testicular damage.
- LDR can prevent diabetes-induced neuronal damage, and atherosclerosis.
- More importantly, LDR provides a therapeutic effect on diabetic wound healing.
LDR/LDR-induced hormesis and adaptive response

LDR preventive effects on various injuries

Diabetes/Diabetic complications

Possible mechanisms

Current debates for the risks & benefits
Whole Body Exposure to Low-dose Gamma Radiation Promotes Kidney Antioxidant Status in Balb/c Mice

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Antioxidant status/Kidney/Low-dose γ-irradiation/Radiation hormesis.

We examined the effect of whole body low-dose γ-irradiation on the status of the antioxidant defense system in the rodent kidneys at different time intervals. Young male Balb/c mice were exposed to whole body radiation from a $^{60}$Co source at doses of 10, 25 and 50 cGy (48.78 cGy/min). Antioxidant status and lipid peroxidation were estimated in the kidneys at 4, 12 and 24 h after irradiation. Lipid peroxidation increased between 33% and 49% and reduced glutathione between 12% and 47% at 12 h at different radiation doses. Reduced glutathione level remained significantly ($p < 0.05$) elevated even at 24 h after irradiation to 25 cGy. Superoxide dismutase activity also increased by 37% at 12 h on exposure of animals to all the doses up to 50 cGy. Catalase activity increased significantly at 12 h on exposure to 10 cGy and 50 cGy. Interestingly, glutathione peroxidase activity increased by 31% at 4 h and subsequently returned to control levels at 24 h after exposure to 50 cGy. Glutathione reductase activity increased by 10–12% at 12 h after exposure to 25 cGy and 50 cGy. The results suggest that the whole body exposure of animals to
Research Article

Low-Dose Radiation Activates Akt and Nrf2 in the Kidney of Diabetic Mice: A Potential Mechanism to Prevent Diabetic Nephropathy

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Low-dose radiation exposure induces a HIF-1-mediated adaptive and protective metabolic response

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Because of insufficient understanding of the molecular effects of low levels of radiation exposure, there is a great uncertainty regarding its health risks. We report here that treatment of normal human cells with low-dose radiation induces a metabolic shift from oxidative phosphorylation to aerobic glycolysis resulting in increased radiation resistance. This metabolic change is highlighted by upregulation of genes encoding glucose transporters and enzymes of glycolysis and the oxidative pentose phosphate pathway, concomitant with downregulation of mitochondrial genes, with corresponding changes in metabolic flux through these pathways. Mechanistically, the metabolic reprogramming depends on HIF1α, which is induced specifically by low-dose irradiation linking the metabolic pathway with cellular radiation dose response. Increased glucose flux and radiation resistance from low-dose irradiation are also observed systemically in mice. This highly sensitive metabolic response to low-dose radiation has important implications in understanding and assessing the health risks of radiation exposure.

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The advance of diagnostic imaging and interventional radiology has attracted growing interest in the biological effects of low-dose (≤0.1 Gy) ionizing radiation (IR).¹ Because of a lack of means for the direct assessment of such low-dose IR exposure, however, there are great uncertainties about its health risk.¹ Currently, a linear no-threshold (LNT) dose model is used to predict low-dose biological effects, and the use of other models, which predict a threshold dose, is currently under study. Biological tissues consist of ~75% water by weight. A major fraction of IR exposure induces hydrolysis resulting in different types of reactive oxygen species (ROS).⁹ IR induces the production of ROS proportional to its dose. High-dose IR induces an excess amount of ROS that can overwhelm the cellular antioxidant capacity causing oxidative stress and damages.⁹ When mildly increased, ROS, however, can
Possibilities for LDR’s prevention of diabetes and diabetic complications

LDR

- Immuno-modulation
- Antioxidant capacity
- HSC stimulation & target cell proliferation
- Systemic & wound regional microcirculation
- ROS/RNS → Diabetes → ROS/RNS → Diabetic complications
- Autoimmune reaction
- STZ or ALX
Possible mechanisms

- LDR stimulate the target tissue antioxidant capacity (Nrf2 & its downstream antioxidants)
- LDR stimulate glucose metabolisms
- LDR stimulate stem cells to injured tissue to recover the damage tissue
- LDR may stimulate the enzymes that were introduced by Dr. David Lefer, to generate H₂S
- *Hormesis*, and adaptive response
• LDR/LDR-induced hormesis and adaptive response

• LDR preventive effects on various injuries

• Diabetes/Diabetic complications

• Possible mechanisms

• Current debates for the risks & benefits
Is it potentially applied in clinics? How to balance?

- LDR benefits
- LDR risks
Original Study

Lung Cancer Hormesis in High Impact States Where Nuclear Testing Occurred

Steven Lehrer, Kenneth E. Rosenzweig

Abstract
Hormesis is a favorable biological response to low toxin exposure. In the case of radiation, large doses are typically considered harmful, but recent research suggests that low-level exposure can have beneficial effects. If verified, this could challenge the prevailing Linear No Threshold (LNT) model of radiation carcinogenicity.

Conclusion
Our analysis adds to the body of evidence suggesting that the LNT model of radiation carcinogenicity in lung cancer might not be correct. Low-level radiation exposure might protect against lung cancer rather than cause it.
Letter to the Editor: Low-dose whole body irradiation: a potential therapeutic modality?

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To the Editor: The recent article published by Zhang et al. (11) in this Journal is indeed very interesting and has great clinical relevance with far-reaching consequences. This appears to be the first detailed report that suggests that multiple exposures to...
But since the turn of the current century, researchers have been reexamining radiation hormesis, applying LDR treatment in various disease settings in laboratory animals.

Various studies in mice have found that exposure to low-dose radiation protects against the effects of subsequent exposure to mid-lethal doses of X-rays, minimizing DNA damage and mortality.

A similar effect has been observed when the radiation is received in utero. Exposure of pregnant mice to “Chernobyl radiation” (doses and types of radiation encountered by the bulk of humans living near the site of the 1986 nuclear accident), did not harm the newborn mice. And the researchers found that later doses of radiation did less harm to the mice’s DNA health and levels of white blood cells than were seen in untreated mice.

Within the last few years, LDR has shown promise in combating the complications of diabetes. Studies have found that diabetic rats show faster wound healing when dosed with low levels of radiation. And other rodent experiments have found that radiation at very low doses can prevent kidney damage, one of the most common long-term complications of diabetes.