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Management of Arthritis by Exposure to Low-Dose Ionizing Radiation

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THIS STUDY was designed to examine the effect of low-dose level of γ-radiation (0.25 and 0.50 Gy) on the inflammation process using the adjuvant-induced arthritis model (AIA) in rats in an attempt to explore the effect of radiation on inflammatory mediators, oxidative stress and certain hepatic trace elements. Animals were divided into 4 groups, control and other 3 groups were injected with AIA; of which 2 groups of rats were exposed to a single dose level of γ-rays radiation of 0.25 and 0.50 Gy on day 14 after induction of arthritis into the hind paw. Serum prostaglandins (PGE_2), tumour necrosis factor-α (TNF-α), malondialdehyde (MDA), blood glutathione (GSH) levels and some hepatic trace elements (Zn, Cu, Fe, and Se) were investigated one week after exposure to radiation. Data collected from arthritic non-irradiated rat's revealed increase in PGE_2, TNF-α and MDA levels, while noticeable decline in contents of GSH and reduction in the concentration levels of hepatic trace elements were observed. Irradiation of arthritic rats at radiation dose level of either 0.25 or 0.50 Gy exhibited a marked increase in blood GSH level and maintained restoration of hepatic trace elements within normal levels. Low-dose of radiation has attenuated the increase in TNF-α and PGE_2 level in serum and minimized the serum MDA level. Our results demonstrated that low-dose γ-radiation has a suppressing effect on the development of the pathology in AIA in rats which might be useful in clinical implications.

Keywords: Arthritis, rats, γ-radiation.

Inflammation can be described as a complicated process involving damage of the microvasculature, leakage of blood elements in the interstitial spaces, migration of leukocytes into the inflamed area and release of chemical mediators locally in response to infections by pathogens and injuries (Willoughby, 1989 and Melvyn *et al.,* 2012).

Phagocytic cells may also migrate into the inflamed area; the cellular lysosomal membranes may be ruptured with consequent release of lytic enzymes (Serhan *et al*., 2005). The main features of the inflammatory response are vasodilatation, increased vascular permeability and the release of chemical components. There may also be a change in biosynthesis, metabolic and catabolic profiles of many organs and activation of cells of the immune system as well as of complex enzymatic systems of blood plasma (Toumi *et al*., 2003). It was previously observed that exposure of rats before induction of adjuvant arthritis to radiation dose level of 0.50 Gy led to suppression of paw oedema volume in a manner similar to treatment with non steroidal anti inflammatory drugs (NSAIDs) (El-Ghazaly *et al.*, 1985&1986), and reduction of the release of histamine and PGE_2 for perfused guinea pig lung (Khayyal *et al.*, 1989). Moreover, several studies indicated the efficacy of low dose γ-radiation in management of arthritis in rats (Sasai *et al.*, 1999, Arenas *et al*., 2006 and Nakatsukasa *et al.*, 2008&2010).

This study was devoted to examine the effect of low-dose level of γ-radiation (0.25 and 0.50 Gy) on the inflammatory process using the adjuvant induced arthritis model in rats as an attempt to explore the effect of radiation on inflammatory mediators, oxidative stress biomarkers and some hepatic trace elements.

Materials and methods

Animals

Adult male Wistar rats (120-180 g), obtained from the NCRRT, Cairo, Egypt, were housed in wire mesh cages and kept under conventional at 25°C. Rats were allowed free access to water and standard rat's pellets.

Radiation facilities

Irradiation of animals was carried out at the NCRRT, Egypt, using the Gamma Cell-40 biological irradiator furnished with a ^{137}Caesium source. Rats were irradiated at a dose level of 0.25 & 0.50 Gy delivered at a dose rate of 0.79 rad/ sec.

Experimental model (The adjuvant-induced arthritis model)

According to the method of Pearson (1964), a sub-plantar injection of 0.1ml Freund's complete adjuvant (FCA) was inoculated into the right hind paw of rats. To assess the time course of the FCA-induced oedema, the paw volume

was measured before 0, 4, 8, 14, 18 and 21 days after FCA inoculation using the electrical device described by Kemper and Ameln (1959), where changes in the dielectric matter (air, in this instance) of a condenser induced by the rat paw causes capacital alterations which are measured in the form of arbitrary units.

Animal grouping

Rats were divided into 4 groups each of 8 animals. Group1, control non-arthritics, non-irradiated. Group 2, arthritic non-irradiated rats. Group 3, arthritic rats were exposed to a single low-dose radiation level of 0.25Gy, two weeks after induction of arthritis and were kept for one week before collection of samples. Group 4, arthritic rats such as group 3 but exposed to 0.50Gy. Animals were sacrificed after the third week. A blood sample was then withdrawn from the heart using a heparinised syringe to be used for the determination of GSH. One portion of blood was centrifuged for separation of serum, used for the determination of MDA, PGE_2 and TNF-α. The liver was then isolated and kept frozen for investigation of trace elements.

Biochemical assay

TNF-α (Biosource Europe S.A., Belgium) and PGE_2 (R&D Systems Inc., Minneapolis, USA) were estimated according to the manufacture instructions of specific ELISA kits. GSH was measured according to the method of Beutler *et al.* (1963), serum MDA was determined according to Yoshioka *et al.* (1979). Trace elements (Zn, Cu, Fe, and Se) were measured by using Atomic Absorption Unicam 939 Solar Spectrometer, England, after digestion of liver samples in pure nitric acid and H_2O_2 (4:1) by using Microwave Sample Preparation Labstation, MLS-1200 MEGA, Italy (Kingston and Jassie, 1988).

Statistical analysis

Data were expressed as mean± S.E. Statistical analysis was performed using instate software, version 2 (Graph Pad Software, Ine. San Diego, USA). One way analysis of Variance (ANOVA) followed by Tukey-Kramer multiple comparison tests. The level of $P< 0.05$ indicates significant difference.

Results

The normal blood GSH and serum MDA levels of the non arthritic non irradiated rats were 10.39mg/ml and 4.32mmol/ ml, respectively (Table 1).

Inoculation of FCA into rats hind paw caused an increase in the levels of GSH as well as MDA recording a percentage of 24 and 75%, respectively as compared to control value. Exposure of rats to a radiation dose level of 0.25Gy, two weeks after inoculation of adjuvant caused a further increase in blood GSH levels by 47% and 67% for serum MDA. However, an acute exposure at dose level of 0.50Gy, two weeks after inoculation of the FCA led to remarkable increase in blood GSH by 140% and dramatic decrease in the serum level of MDA recording 33% instead of 75% for the arthritic non irradiated rats.

TABLE 1. Effect of low-dose γ-radiation exposure at 0.25 and 0.50 Gy on blood GSH and serum MDA in arthritic rats.

Groups	**GSH** (mg/ ml)	**MDA** (nmol/ ml)
Non-arthritic-non-irrad. **% change**	10.39± 0.27 ---	4.32± 0.12 ---
Arthritic non-irradiated **%change**	12.92± 0.19* 24	7.56± 0.16* 75
Arthritic-irrad. 0.25Gy **% change**	15.22± 0.16*# 47	7.20± 0.25 67
Arthritic-irrad. 0.50Gy **% change**	24.92± 0.25*# 140	5.74± 0.28*# 33

Results are expressed as mean± S.E. of 8 observations.

ANOVA was carried out by Tukey-Kramer's test.

*Significant difference from respective non-irradiated, non-arthritic group at $P< 0.05$.

#Significant difference from non-irradiated arthritic at $P< 0.05$.

The serum TNF-α and PGE_2 levels of normal rats were 573 and 3694pg/ ml, respectively (Table 2). Inoculation of FCA caused a remarkable increase in both TNF-α and PGE_2 by 35 and 29%, respectively as compared to control value. Irradiation of animals, two weeks after adjuvant inoculation at dose levels of either 0.25 or 0.50Gy markedly decreased the concentration levels of serum TNF-α and PGE_2. Both low dose radiation levels significantly ameliorate the effect of FCA, as compared to the arthritic non- irradiated rats.

Table 3. displayed the concentration levels of hepatic essential trace elements. Inoculation of FCA into non-irradiated rats resulted in a remarkable decrease in the levels of these trace elements (Zn, Cu, Fe and Se), the percentage change of these declines were: 43.56, 29.18, 16.70 and 9.28% respectively. Exposure of animals to radiation dose level of 0.25 and 0.50Gy, after

induction of arthritis by two weeks, caused a significant improvement in the hepatic trace elements contents, the percentage were 27.30, 20.51, 1.60 and 6.84, respectively at dose level 0.25Gy, while at dose 0.50 Gy the percentage change were as follow: 23.8, 16.43, 0.91 and 6.14% respectively for Zn, Cu, Fe, and Se.

TABLE 2. Effect of exposure to a low-dose γ-radiation on serum tumour necrosis factor-α and prostaglandin-E_2 in arthritic.

Groups	**TNF-α** (pg/ ml)	**PGE_2** (pg/ ml)
Non-arthritic-non irradiated **% change**	573± 19 --	3694± 75 ---
Arthritic non –irradiaded **%change**	771± 15.4* 35	4749± 45 29
Arthritic- irrad. 0.25 Gy **% change**	594± 21# 4	3447± 49.34*# -7
Arthritic- irrad. 0.50 Gy **% change**	621± 24# 9	3942± 64*# 7

Legends are as in Table 1.

TABLE 3. Effect of low-dose γ-radiation exposure to dose levels of 0.25 and 0.50 on hepatic trace element contents.

Groups	**Zn** (μg/ g)	**Cu** (μg/ g)	**Fe** (μg/ g)	**Se** (ng/ g)
Non-arthritic non irrad. **% change**	50.43± 1.03 --	4.74± 0.15 --	187± 2.4 --	230± 1.3 --
Arthritic non –irrad. **%change**	28.46± 0.91* 43.56	3.36± 0.11* 29.18	156± 3.9* 16.70	208± 2* 9.28
Arthritic irrad. 0.25 Gy **% change**	36.67± 1.5*# 27.30	3.77± 0.11* 20.51	190± 4.5# 1.60	214± 6.7 6.84
Arthritic irrad. 0.50 Gy **% change**	38.43± 1.12*# 23.8	3.96± 0.23* 16.43	1.86± 4.8# 0.91	244± 4# 6.14

Legends are as in Table 1.

Discussion

In the present study, the effect of low dose level of γ-radiation (0.25 and 0.50Gy) on the inflammatory process using the adjuvant-induced arthritis model was investigated in rats in an attempt to explore the effect of radiation on inflammatory mediators, oxidative stress and certain hepatic trace elements. The present results revealed a reduction in serum TNF-α, and serum PGE_2 levels indicating that protection was offered by low-dose radiation on adjuvant-induced arthritis, these results are in accordance with those of Nakatsukasa *et al*. (2008) who, studied the effect of low-dose γ-radiation on collagen-induced

arthritis (CIA) mice, it was found that paw swelling, redness, and bone degradation were suppressed by irradiation, which also delayed the onset of pathological change and reduced the severity of the arthritis. Production of TNF-α, interferon-gamma, and interleukin-6 (IL-6), which play important roles in the onset of CIA, was suppressed by the irradiation. The authors suggested that, low-dose γ-radiation could attenuate CIA through suppression of pro-inflammatory cytokines and autoantibody production.

In AIA, macrophages play a major role in the inflammatory process, since after activation they are capable of synthesizing inflammatory cytokines such as TNF-α and IL-1β (Arend and Dayer, 1995 and Feldmann *et al.*, 1996). These cytokines induce the expression of inducible cyclooxygenase-2 (COX-2), resulting in the production of PGE_2. Thus, suppression of TNF-α and serum PGE_2 appears to be one of the mechanisms of irradiation-induced attenuation of AIA. It could be suggested that suppression of TNF-α, and PGE_2 production could play an important role in the observed suppressing effect of low-dose irradiation on AIA. Moreover, it was reported that, production of IL-6 was significantly suppressed by irradiation (Sasai *et al*., 1999). They suggested that low-dose irradiation suppresses the production of anti-bovine CII antibody in CIA in mice via mechanisms that include suppression of IL-6 production and down-regulation of plasma cells (Nakatsukasa *et al.,* 2008 and Shin *et al.,* 2010).

Suppression of adjuvant-induced arthritis observed in rats following whole body irradiation could be explained by the immunosuppressant effect of ionizing radiation. Radiation can affect the immune system at three main points of cell proliferation (Patt and Quastler, 1963). These are the formation of stem cells in the bone marrow, the early differentiation of cells in the thymus and the proliferation of immunocompetent cells. Moreover, irradiation of T-cells in vitro results in a decrease in production of IgM rheumatoid factor (Ceuppens *et al.,* 1982) which is implicated in rheumatoid arthritis. The phenomenon of immunosuppression by irradiation has been made used in medical practice for suppressing immune response in organ and tissue transplantation as well as in the treatment of patients with severe rheumatoid arthritis (Kotzin *et al.,* 1981 and Trentham *et al.,* 1981). Ionizing radiation has also been used experimentally in rats for the treatment of adjuvant arthritis (Leirisalo-Repo, 1990) and collagen arthritis (Nakatsukasa *et al.,* 2008 and Pernot *et al.,* 2012).

Regarding the oxidative markers, results revealed that, irradiation of animals; two weeks after adjuvant inoculation, at radiation dose level of either 0.25 or 0.50Gy caused a marked increase in blood GSH. Also exposure at dose level of 0.50Gy led to a dramatic decrease in the serum MDA level.

In general, the relation between low-dose radiation and anti-inflammatory effect is mediated mainly through anti-oxidative properties which are the principal mechanism of its action (Kojima *et al.,* 2004). Cells have enzymatic and non-enzymatic systems against reactive oxygen species (ROS). The antioxidant enzymes--superoxide dismutase (SOD): manganese SOD (MnSOD) and copper-zinc SOD (CuZnSOD), as well as GSH, are the most important intracellular antioxidants in the metabolism of ROS. Overproduction of ROS challenges antioxidant enzymes (Durovic *et al.,* 2008). Induction of these antioxidant systems in vitro and in vivo by low-dose radiation has been reported and has been attributed to suppression of lipid peroixodation in rats (Yamaoka *et al.,* 1991).

Avti *et al* (2005) showed that whole body exposure to 25 cGy and 50 cGy gamma radiation modulated the antioxidant defence system in the liver and lungs of mice. The induction of endogenous glutathione and antioxidant enzyme activities for SOD, catalase (CAT), glutathione peroxidase (GPX), and glutathione reductase (GR) may be beneficial in protecting the cells from ROS-induced oxidative stress. Similar results were obtained in brain by Kojima *et al* (1999) in mice after irradiation with 50cGy. They observed induction of cerebral endogenous anti-oxidative potency and might be effective in prevention and/or therapy of ROS related to neurodegenerative disorders such as Parkinson's and Alzheimer's disease. In contrast to high doses, low doses (0.25-0.5Gy) of radiation can increase the cellular GSH level in mice in vivo. The ability to induce cellular defence mechanisms in response to environmental changes is a fundamental characteristic of eukaryotic and parakaryotic cells. Kojima *et al.* (2004) suggested that low doses of gamma rays activate immune functions via induction of GSH which in turn enhance the appearance of natural killer (NK) in splenocytes lowering tumour growth.

There was a receptive attention for assessing the sudden unexpected finding of low dose-induced reduction of the enzyme thymidine kinase in

mouse bone marrow *in vivo* (Zamboglou *et al.*, 1981 and Feinendegen *et al.*, 1983&1984). This change appeared with a delay of hours as an apparent consequence of temporary intracellular signalling that also concomitantly increased the concentration of free glutathione, and both responded concomitantly to ROS (Feinendegen *et al.*, 1987). The results concerning the elevation in blood GSH following low dose irradiation was confirmed by the elevation in selenium concentration in liver as well. Selenium is a micronutrient essential for the immune system and can also modulate radiation-induced reaction (Mckenzie, 2000 and Rafferty *et al.*, 2002). Se has an essential role in maintaining the activities of the antioxidant enzymes GPX and thioredoxin reductase (Mustacich *et al.*, 2000). Also, exposure of animals to radiation dose level of 0.25 and 0.50Gy caused a significant increase in Zn, Cu and Fe concentration in liver. This could be attributed to the induction of endogenous antioxidant enzyme activities (Durovic *et al.*, 2008).

In conclusion, we have demonstrated that low-dose gamma-ray irradiation has a suppressing effect in the adjuvant-induced arthritis model in rats. Irradiation caused a delay in the onset of pathological changes including limbs swelling, suppression of pro-inflammatory cytokins and induction of antioxidants as well as endogenous metalloenzyme activities. Although this study suggests that low-dose irradiation would suppress onset of arthritis, the effects of low-dose irradiation on ongoing autoimmunity in animals and patients with arthritis are issue that remain to be addressed.

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استخدام الجرعات المنخفضة من الإشعاع الجامي المؤين في تعديل رد الفعل الالتهابي المفصلي في الجرذان

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قسم البحوث الدوائية الإشعاعية، المركز القومي لبحوث و تكنولوجيا الإشعاع ، ص. ب. ٢٩ مدينة نصر ، مصر و *قسم الأدوية و السموم ، كلية الصيدلة ، جامعة القاهرة ، مصر.

يختص هذا البحث بدراسة أمكانيه استخدام الجرعات المنخفضة من الإشعاع الجامي المؤين في تعديل رد الفعل الالتهابي المفصلي وذلك باستخدام نموذج التهاب المفاصل المزمن المحدث نتيجة حقن ماده فروينذز المسببة للارتشاح في النسيج الخلوي في خف الجرذان وقد تم دراسة هذه التجربة في ثلاثة مجموعات من الجرذان (بالإضافة إلي المجموعة الضابطة) وقد تم تعريض احدي المجموعات التي تم حقنها بماده فروينذز لمستوي إشعاعي ٠ر٢٥ جراي ومجموعه أخري من الجرذان تعرضت لمستوي إشعاعي ٠ر٥٠ جراي وذلك كجرعة أشعاعيه منفردة في اليوم الرابع عشر بعد حقن ماده فروينذز ثم ذبح الحيوانات بعد أسبوع وقد تم قياس كل من بروستاجلاندين وعامل الورم النخري- الفا ومالوندى الدهايد في المصل وجلوتاثيون في الدم وكذلك قياس المحتوي الكبدي لعناصر النحاس والزنك والحديد والسلينيوم وقد أظهرت نتائج هذه الدراسة فاعلية استخدام الجرعات المنخفضة من الإشعاع الجامى على تثبيط مستويات بروستاجلاندين ومعامل الورم النخرى-الفا في المصل فى نموذج الالتهاب المحدث فى المفاصل بمادة فروينذز وفيما يختص بدلالات التأكسد فقد وجد أن تعرض الجرذان للإشعاع الجامى عند جرعات ٠ر٢٥، ٠ر٥٠ جراى قد أدى الى زيادة ملحوظة فى جلوتاثيون بالدم بالإضافة إلى انخفاض مستوى مالوندى الدهايد فى المصل. أيضا أظهرت النتائج زيادة المحتوى الكبدي من العناصر الضئيلة (الزنك – الحديد – السلينيوم) وذلك بعد التعرض لجرعات منخفضة من الإشعاع المؤين، وهذا يرجع إلى تحفيز الإنزيمات المضادة للتأكسد بعد التعرض لتلك الجرعات المنخفضة من الإشعاع المؤين ويمكن استنتاج أن الإشعاع الجامى باستخدامه في جرعات منخفضة له تأثير مثبط لالتهاب المفاصل وهذه الدراسة تستلزم اهتماما تجريبيا اكلينكيا فيما بعد.