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RADIOPROTECTION BY DMSO AGAINST THE BIOLOGICAL EFFECTS OF INCORPORATED RADIONUCLIDES IN VIVO

Comparison with other radioprotectors and evidence for indirect action of Auger electrons

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Dimethyl sulfoxide (DMSO) was studied for its capacity to protect against the biological effects of chronic irradiation by incorporated radionuclides. Spermatogenesis in mice was used as experimental model and spermatogonial cell survival was the biological endpoint. DMSO was injected intratesticularly 4 h prior to a similar injection of the radiochemical and the spermhead survival determined. Iodine-125 was localized in either the cytoplasm ($H^{125}IPDM$) or in the DNA ($^{125}IUdR$) of the testicular cells. Protection was observed against the high-LET type effects of DNA-bound ^{125}I as well as the low-LET effects of cytoplasmically localized ^{125}I with dose modification factors (DMF) of 3.1 ± 1.0 and 4.4 ± 1.0 respectively. No protection ($DMF = 1.1 \pm 0.1$) was observed against the effects of high-LET 5.3 MeV alpha particles of ^{210}Po. The present findings provide supporting evidence that the mechanism responsible for the extreme biological damage caused by DNA-bound Auger emitters is largely radical mediated and therefore indirect in nature.

Several radionuclides used in medical diagnosis decay via electron capture (EC) and/or internal conversion (IC). These radionuclides emit numerous low-energy Auger electrons resulting in highly localized energy deposition in the immediate vicinity of the decay site (1, 2) . It has been shown that their radiotoxicity depends strongly on the subcellular distribution of the radionuclide (3–7). When the Auger emitter ^{125}I is localized in the cytoplasm of the cells via $H^{125}IPDM$ (N,N,N′-trimethyl-N′-(2-hydroxyl-3-methyl-5-iodobenzyl)-1,3-propanediamine), its radiotoxicity is akin to that of low-LET radiations such as external x-rays (6) . In contrast, when the same radionuclide is incorporated into the DNA of the testicular cells via $^{125}IUdR$ (^{125}Iododeoxyuridine), its biological effects are as lethal as 5.3 MeV alpha particles emitted by ^{210}Po (8, 9).

The mechanism of action of ionizing radiation in causing biological damage is of two types: direct and indirect. The direct effect is the result of energy deposition in critical structures, the integrity of which are essential for cell viability. The indirect effect is a consequence of interactions between the variety of free radicals ($OH^{\cdot}$, $H^{\cdot}$, etc.) produced in the radiolysis of water and critical biological molecules (10) . Direct effects are primarily responsible for the damage caused by high-LET radiations such as alpha particles, whereas indirect effects play a predominant role in the case of low-LET radiations (e.g. β, x-rays) (10).

The mechanism by which DNA-bound Auger emitters impart high-LET type effects in biological systems has been of considerable interest. The capacity of different chemicals to mitigate the biological effects of these radionuclides has provided insights into their mechanism of radiation action. Our earlier studies in the mouse testis

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model with cysteamine (6, 11), AET (S-(2-aminoethyl) isothiouronium bromide hydrobromide) (12), and soybean oil (13) resulted in protection against the effects of both cytoplasmically localized and DNA-bound ^{125}I. These chemicals also protected the spermatogonia against alpha particle damage, although to a lesser extent (7, 11). Vitamins A and C, well-known antioxidants, also protected the mouse spermatogonia from DNA incorporated ^{125}IUdR and cytoplasmically localized H^{125}IPDM (13, 14), but provided no protection against the effects of high-LET alpha particles (13, 14). These results led us to suggest that indirect action of radical species is the primary mechanism of radiation damage caused by DNA-bound Auger emitters.

Dimethyl sulfoxide (DMSO) is a well-known radioprotector whose protective action is due to free radical scavenging (15). With survival of human kidney cells as the endpoint, Vos and Kaalen (16) showed protection by DMSO against the effects of external irradiation and found a linear dependence of the dose modification factor (DMF) on the concentration. DMSO also gave very good protection (DMF = 5.7) for golden hamster embryo cells exposed to gamma rays (17). Mouse bone marrow cells irradiated in vitro in the presence of DMSO, and implanted into lethally irradiated mice, were protected against acute external irradiation (15). DMSO, when applied topically, provided complete protection against the formation of cataracts following acute x-ray irradiation (18). As a radical scavenger, the ability of DMSO to protect against the direct action of high-LET alpha particles is expected to be minimal (6, 13, 14, 19).

Although extensive literature is available on the protective capacity of DMSO against acute external irradiation very little is known about its ability to protect against effects of internal radionuclides. Unlike traditional external beam experiments, internal radionuclides irradiate tissue chronically over a period of time that depends on the physical half-life of the radionuclide and the biological half-time of the radiochemical. In the present work, the capacity of DMSO to protect against the effects of the radionuclides ^{125}I and ^{210}Po, incorporated in mouse testes, was investigated using the spermhead survival assay (6, 13, 14, 19). The Auger emitter ^{125}I was used in two chemical forms: ^{125}IUdR which binds to the DNA in the cell nucleus, and H^{125}IPDM which localizes in the cytoplasm of the testicular cells. The radioprotection provided by DMSO against the low-LET effects of H^{125}IPDM, high-LET type effects of ^{125}IUdR and high-LET effects of ^{210}Po-citrate, yields information regarding the mechanism of action of DNA-bound Auger emitters.

Material and Methods

Experimental model

There are a series of cell stages including stem cells, spermatogonia, spermatocytes, spermatids, and spermatozoa in the spermatogenic cycle of mouse testes. The spermatogonial cells (types A_1-A_4, In, B) are the most sensitive to ionizing radiation with an LD_{50} of about 0.4 Gy (20). The precursors (A_{is} and A_{al}) and postgonial cells are substantially more radioresistant than the spermatogonial cells (20). This differential radiosensitivity allows determination of the biological effects of radiation on spermatogonial cells at very low doses. Following an initial radiation insult, the spermatogonial cell survival can be assayed by monitoring the testicular spermhead count 29–36 days after irradiation, the time required for the spermatogonial cells to mature into sonication resistant spermatids of stages 12–16 (20, 21). It may be noted that human spermatogonial cells are approximately 3 times as sensitive to ionizing radiation as those of mice (22, 23). Therefore, this model is relevant to man.

Radiochemicals

The radionuclide ^{125}I as sodium iodide was obtained from ICN Radiochemicals, (Irvine, CA). Stable HIPDM was kindly provided by Prof. Hank F. Kung (University of Pennsylvania, Philadelphia, PA). The H^{125}IPDM was prepared using the exchange reaction of Lui et al. (24). The ^{125}IUdR was synthesized in-house according to our previously published procedures (25). The radionuclide ^{210}Po, embedded in a silver matrix, was obtained commercially (NRD Inc., Grand Island, NY) and separated using the procedures described elsewhere (26). The radiochemical ^{210}Po-citrate was prepared using the procedures given in our earlier publication (8).

Experimental procedures

The experimental procedures for examining the radioprotective capacity of various chemicals, using the spermhead survival assay, were reported in detail in our previous publications (6, 12–14, 19). In the present work, male Swiss Webster mice (Taconic Farms, Germantown, NY), 8–9 weeks of age, in groups of 4, were anesthetized under ether and 3 μl of an aqueous DMSO solution (0.5 μg in normal saline) was injected intratesticularly (i.t.) into the right testis of each mouse using a microsyringe. This amount of DMSO, when injected intratesticularly, was non-toxic as determined by the spermhead survival assay (see below). After 4 h, 3 μl of a solution containing the radiochemical was injected similarly into the right testis. The advantages of this mode of administration over intraperitoneal or intravenous modes are the following: a) a fixed amount of radioprotector is always delivered in the organ, b) only small amounts of radioactivity are required, and c) the effects of the Auger electrons emitted by ^{125}I can be readily delineated without the complications of cross-dose to the testis from activity in the body.

The optimal day after irradiation (minimum spermhead count) to perform the spermhead survival assay has al-

ready been established for each radiochemical in the absence of the radioprotectors (6, 8). These studies were repeated in the presence of DMSO to ensure that the optimal assay day was not affected. Briefly, several mice preinjected with DMSO were administered a fixed amount of the radiochemical, and sacrificed in groups of three at different times postinjection. The injected testes were removed, homogenized in 1 ml of deionized water for 15 s, and sonicated for 30 s. The sonication-resistant spermheads (spermatids of stages 12–16) (20) were counted under a light microscope. The minimum spermhead count was obtained on the 29th and 36th day for the radioiodinated chemicals and ^{210}Po-citrate respectively. These optimal days were the same as those obtained in the absence of DMSO (6,8).

Dose–response relationships in the presence of DMSO were obtained by injecting different amounts of the radiochemical into the testes of mice (groups of four). On the optimal day, all animals were sacrificed and the testes removed and processed for spermhead counting as described above. Mice intratesticularly injected with saline, or saline containing 0.5 μg DMSO, served as controls. Additional animals were injected with the radiochemical alone to serve as contemporaneous controls.

Biological clearance from the testis

The biological clearance of the radiochemicals (H^{125}IPDM, ^{125}IUdR, ^{210}Po-citrate) from the testis following their i.t. injection has already been established in the absence of any radioprotectors (6, 8, 13). To verify that the presence of DMSO had no effect on the clearance of the radiochemicals, clearance studies were repeated. Mice, in groups of three, were preinjected with 0.5 μg of DMSO and followed 4 h later with an injection of the radiochemical. The mice were sacrificed at different times postinjection and the testicular activity assayed using either a NaI well counter (^{125}I) or liquid scintillation counter (^{210}Po). The clearance data, thus obtained, are required to calculate the mean absorbed dose to the organ.

Subcellular distribution

The biological effects of Auger emitters depend highly on the subcellular distribution of the radiochemical. The subcellular distribution for the radiochemicals employed in these studies were previously determined in the absence of radioprotectors (6, 8). To confirm that the presence of DMSO had no effect on the testicular and subcellular distribution of the radiochemicals, animals were injected i.t. with DMSO followed 4 h later by an injection of the radiochemical. The animals were sacrificed 24 hours after injection, the testes were removed, and the subcellular distribution was determined, using the experimental protocol described elsewhere (27). The presence of DMSO had no effect on the testicular and subcellular distribution of the radiochemicals (H^{125}IPDM, ^{125}IUdR, ^{210}Po-citrate).

Results

Biological clearance of the radiochemicals

Fig. 1 shows the biological clearance of the radiochemicals from the testis in the absence (6, 8, 13) and presence of DMSO. The clearance pattern for all three radiochemicals was unaffected by the presence of DMSO. Accordingly, the mean absorbed dose to the testis per unit activity administered was also unaffected by DMSO. Hence, the mean absorbed doses per unit activity administered, taken from our earlier publications, are 0.83 Gy/MBq (13), 2.82 Gy/MBq (6), and 2980 Gy/MBq (7) for ^{125}IUdR, H^{125}IPDM, and ^{210}Po-citrate, respectively.

Dose response relationships

The fraction of surviving spermheads as a function of the mean absorbed dose to the testis in the absence and presence of DMSO are given in Figs. 2–4. A least squares fit to the data to a two-component exponential function yields:

$$S(^{125}\text{IUdR}, (8)) = 0.46\ e^{-D/0.0041} + 0.54\ e^{-D/0.22}$$

$$S(\text{DMSO} + ^{125}\text{IUdR}) = 0.46\ e^{-D/0.0070} + 0.54\ e^{-D/0.69}$$

$$S(\text{H}^{125}\text{IPDM}, (6)) = 0.21\ e^{-D/0.018} + 0.79\ e^{-D/0.89}$$

$$S(\text{DMSO} + \text{H}^{125}\text{IPDM}) = 0.22\ e^{D/0.11} + 0.78\ e^{-D/4.0}$$

$$S(^{210}\text{Po-citrate}, (8)) = 0.30\ e^{-D/0.0020} + 0.70\ e^{-D/0.156}$$

$$S(\text{DMSO} + ^{210}\text{Po-citrate}) = 0.30\ e^{-D/0.0095} + 0.70\ e^{-D/0.17}$$

where S is the survival fraction and D the dose in Gy. Using the above equations, the 37% survival doses (D_{37})

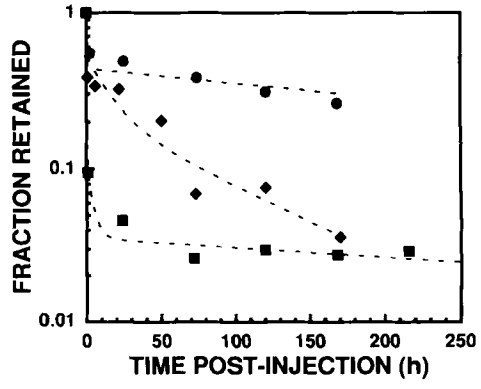

Fig. 1. Biological clearance of radiochemicals from the testis following intratesticular injection in the absence (- - - (6, 8, 13)) and presence of DMSO: H^{125}IPDM (◆), ^{125}IUdR (■), ^{210}Po-citrate (●). Note that the presence of DMSO had no effect on the biological clearance of the radiochemicals.

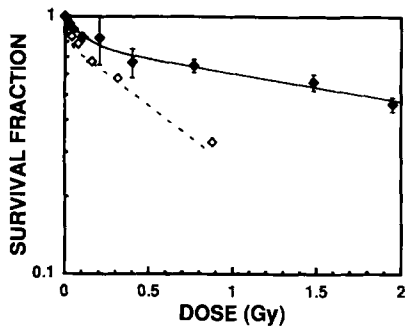

Fig. 2. Dependence of spermhead survival fraction on absorbed dose to the testis following intratesticular injection of H^{125}IPDM. The dashed line represents the historical dose-response range in the absence of DMSO (6) with contemporaneous controls (◇). (◆) represent the dose-response in the presence of DMSO. Error bars represent the standard deviation of the mean of two independent experiments.

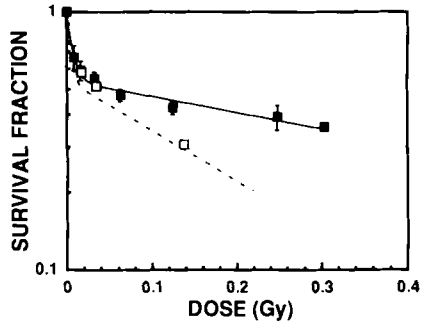

Fig. 3. Spermhead survival as a function of absorbed dose to the testis following intratesticular injection of ^{125}IUdR: 1) Historical dose—response in the absence of DMSO (- - - (13)), 2) present dose response in the absence of DMSO (□), and 3) dose-response in the presence of DMSO (■). Two independent experiments were performed. The error bars are the standard deviation of the mean.

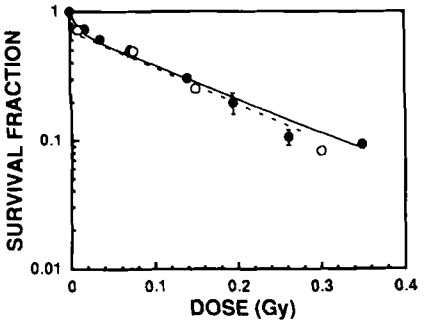

Fig. 4. Spermhead survival versus absorbed dose to the testis from ^{210}Po-citrate in the absence (historical controls: - - - dashed line (8), contemporaneous controls (○)) and presence (●) of DMSO. Two independent experiments were performed. The error bars denote the standard deviation of the mean.

in the presence of DMSO are calculated to be 0.27 ± 0.050 Gy, 3.0 ± 0.62 Gy, and 0.11 ± 0.013 Gy for ^{125}IUdR, H^{125}IPDM, and ^{210}Po-citrate respectively. The corresponding D_{37} values in the absence of DMSO, presented in our earlier publications, are 0.085 ± 0.021 Gy (8) 0.68 ± 0.060 Gy (6), and 0.10 ± 0.01 Gy (8), respectively. The contemporaneous controls indicated in Figs. 2–4 were obtained to confirm the data in the absence of DMSO.

Discussion

The dose modification factor (DMF), defined as the ratio of the absorbed doses required in the presence and absence of the radioprotector to cause the same biological effect, is usually taken as a measure of radioprotection. Using the D_{37} values given above, the DMF values for DMSO can be readily calculated as 3.1, 4.4, and 1.1 for ^{125}IUdR, H^{125}IPDM, and ^{210}Po-citrate, respectively. When these DMF values for DMSO are compared with those obtained previously for a variety of radioprotectors using the same experimental model and biological endpoint, the protection provided by DMSO against the effects of the iodinated radiochemicals is similar to that observed when MEA (6, 11), AET (12), or soybean oil (13) were used as radioprotectors (Table). In contrast, DMSO provided essentially no protection against the effects of 5.3 MeV alpha particles of ^{210}Po, whereas substantial protection was provided by MEA, AET and soybean oil. These findings for DMSO are similar to those obtained when the antioxidants vitamins A (13) and C (14) were used as protectors (Table). These results suggest that the mechanism by which DMSO protects against radiation damage is different from that of MEA or AET.

The biological effects of Auger emitters and the mechanisms by which they impart damage have been of considerable interest and been much debated. Three mechanisms have been proposed to explain the extreme biological toxicity of DNA-bound Auger emitters: a) chemical transmutation of the parent atom (e.g. ^{125}I to ^{125}Te) (28), b) charge-induced molecular fragmentation by the highly ionized residual daughter atom (29, 30), and c) localized energy deposition by the low energy Auger electrons (29–31). The transmutation hypothesis can be ruled out by the in vitro observations of Kassis et al. (32) for ^{77}BrUdR, ^{123}IUdR, and ^{125}IUdR. They found that the number of ^{77}Br, ^{123}I and ^{125}I disintegrations required to achieve the same biological effect were in the ratio 3:2:1. If transmutation was primarily responsible for the biological damage, then the number of disintegrations (transmutations) should have been the same for each Auger emitter. Further evidence against the transmutation hypothesis comes from our in vivo results which show that DNA-bound ^{131}IUdR (transmutes to stable ^{131}Xe) (25) is as lethal as cytoplasmically localized ^{131}I (no transmutations in the DNA). The charge induced molecular fragmentation hypothesis has

Table

Dose modification factors for different radioprotectors

Radioprotector	Dose modification factors			
	^{125}IUdR	H^{125}IPDM	H^{131}IPDM	^{210}Po-citrate
MEA (6, 11)	3.6 ± 1.1	3.8 ± 0.6	3.8 ± 0.9	2.6 ± 0.6
AET (12)	4.0 ± 1.2	3.4 ± 0.4	-	2.4 ± 0.5
Soybean Oil (13)	3.6 ± 0.9	3.4 ± 0.9	-	2.2 ± 0.11
Soybean Oil + Vitamin A (13)	4.8 ± 1.3	5.1 ± 0.6	-	2.1 ± 0.15
Vitamin C (14, 19)	2.3 ± 0.6	-	2.2 ± 0.3	0.9 ± 0.2
DMSO	3.1 ± 1.0	4.4 ± 1.0	-	1.1 ± 0.2

also been refuted experimentally (31), leaving energy deposition as the primary mechanism for the high-LET type damage imparted by Auger emitters. Given that the biological damage is primarily radiation-induced, then what is the mode of radiation action: direct (deposition of energy in the primary radiosensitive targets) or indirect (radical mediated)? Our experiments with radioprotectors concerning mitigation of the effects of incorporated radionuclides provide guidance. If direct action is the primary mechanism, then, as in the case of high-LET alpha particles, one would not expect DMSO to offer substantial protection against the biological effects of DNA-bound ^{125}I. However, the present results show that DMSO offers substantial and equal protection against the high-LET type effects of ^{125}IUdR and the low-LET effects of cytoplasmically localized H^{125}IPDM (Table), whereas essentially no protection was offered against the high-LET effects of alpha particles emitted by ^{210}Po (Table). These findings are very similar to our earlier observations using the well known antioxidants vitamins A and C (Table) and the same radiochemicals (13, 14, 19). This experimental evidence is further substantiated by the theoretical calculations of Wright et al. (33) and Pomplun et al. (34) which demonstrated that when Auger emitters are localized on the DNA, the preponderance of interactions were of an indirect nature.

Recently, Hofer & Bao (35) implied that indirect effects do not play a major role in the biological action of Auger electrons. They showed that when CHO cells, containing ^{125}IUdR, were frozen for decay accumulation, both 'high-' and 'low-LET' type effects were imparted depending on the length of time that the cells were allowed to progress through their cell cycle prior to freezing at −196°C in culture medium containing DMSO. When MEA was added before freezing, protection was afforded against the 'low-LET' type effects while no protection was provided against the 'high-LET' type effects of ^{125}I. Based on these findings, obtained under frozen in vitro conditions, the authors suggested that the mechanism by which Auger electrons impart high-LET type biological damage does not appear to be indirect in nature. This implication contradicts our earlier conclusions based on in vivo data obtained by using the same radioprotector MEA (6) as well as more recent data with AET and other radioprotectors (Table), and the present data with DMSO. Hofer & Bao (35) suggested that this apparent contradiction may arise because of the very small quantities of MEA used in the mouse testes experiments and hinted that the observed radioprotection in vivo was unexpected and may be attributed to cellular or molecular factors other than radical scavenging. While radical scavenging is not the only mechanism by which MEA protects (other mechanisms include hydrogen atom donation, etc.), our MEA data show a clear difference in radioprotection when the mouse testes are irradiated internally with high-LET alpha particles versus Auger electrons. Nor were the very small concentrations of MEA required in the mouse testis compared with cultured cells surprising, since the spermatogonial cells in the mouse testis are an order of magnitude more sensitive than cultured cells. Therefore, the number of free radicals produced in our experiments will be fewer since free-radical production is proportional to the total dose delivered. In addition, the testes are irradiated chronically over several days and so the rate of free radical production is very low and presumably lower concentrations of radioprotector are required. This is in contrast to the high concentrations of MEA required to protect against acute irradiation conditions where all radicals are produced in a short period of time. It is of interest to note that the experiments by Hofer & Bao (35) are similar in nature to acute irradiation in so far that the decays were accumulated while the cells were frozen at −196°C in the presence of DMSO.

Regardless of the reasons for the differences between the in vivo and in vitro data, the present experiments with DMSO, a well-known radical scavenger, render additional support for the indirect nature of the biological damage caused by Auger electrons.

To conclude, the protection of spermatogonial cells by DMSO against the effects of the prolific Auger emitter ^{125}I is substantial regardless of its subcellular distribution. Essentially no protection was provided against the effects of

high-LET alpha particles. These results, obtained using DMSO as a radioprotector, together with our earlier findings for vitamins A and C, provide ample evidence that the mechanism by which DNA-bound Auger emitters impart their damage is primarily radical mediated and hence indirect in nature.

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REFERENCES

1. Sastry KSR. Biological effects of the Auger emitter ^{125}I: A review. Report No. 1 of AAPM Nuclear Medicine Task Group No. 6. Med. Phys. 1992; 19: 1361–70.
2. Howell RW. Radiation spectra for Auger-electron emitting radionuclides: Report No. 2 of AAPM Nuclear Medicine Task Group No. 6. Med Phys 1992; 19: 1371–83.
3. Hofer KG, Harris CR, Smith JM. Radiotoxicity of intracellular Ga-67, I-125, H-3. Nuclear versus cytoplasmic radiation effects in murine L1210 leukaemia. Int J Radiat Biol 1975; 28: 225–41.
4. Kassis AI, Howell RW, Sastry KSR, Adelstein SJ. Positional effects of Auger decays in mammalian cells in culture. In Baverstock KF, Charlton DE, eds. DNA damage by Auger emitters. London: Taylor & Francis, 1988: 1–14.
5. Rao DV, Sastry KSR, Grimmond HE, et al. Cytotoxicity of some indium radiopharmaceuticals in mouse testes. J Nucl Med 1988; 29: 375–84.
6. Rao DV, Narra VR, Howell RW, Sastry KSR. Biological consequence of nuclear versus cytoplasmic decays of I-125: Cysteamine as a radioprotector against Auger cascades in vivo. Radiat Res 1990; 124: 188–93.
7. Rao DV, Narra VR, Howell RW, Lanka VK, Sastry KSR. Induction of spermhead abnormalities by incorporated radionuclides: Dependence on subcellular distribution, type of radiation, dose rate, and presence of radioprotectors. Radiat Res 1991; 125: 89–97.
8. Rao DV, Narra VR, Howell RW, Govelitz GF, Sastry KSR. In-vivo radiotoxicity of DNA-incorporated I-125 compared with that of densely ionising alpha-particles. Lancet 1989; 2: 650–3.
9. Howell RW, Rao DV, Hou D-Y, Narra VR, Sastry KSR. The question of relative biological effectiveness and quality factor for Auger emitters incorporated into proliferating mammalian cells. Radiat Res 1991; 128: 282–92.
10. Dertinger H, Jung H. Molecular radiation biology. Heidelberg: Springer Verlag, 1970.
11. Narra VR, Harapanhalli RS, Howell RW, Sastry KSR, Rao DV. Chemical protection against radionuclides in vivo: Implications to the mechanism of the Auger effect. In: Howell RW, Narra VR, Sastry KSR, Rao DV, eds. Biophysical Aspects of Auger Processes. Woodbury, NY: American Institute of Physics, 1992: 319–35.
12. Narra VR, Harapanhalli RS, Goddu SM, Howell RW, Rao DV. Radioprotection against biological effects of internal radionuclides in vivo by S-(2-aminoethyl)isothiouronium bromide hydrobromide (AET). J. Nucl. Med. 1995; 36: 259–66.
13. Harapanhalli RS, Narra VR, Yaghmai V, et al. Vitamins as radioprotectors in vivo. II. Protection by vitamin A and soybean oil against radiation damage caused by internal radionuclides. Radiat Res 1994; 139: 115–22.
14. Narra VR, Harapanhalli RS, Howell RW, Sastry KSR, Rao DV. Vitamins as radioprotectors in vivo. I. Protection by vitamin C against internal radionuclides in mouse testes: Implications to the mechanism of the Auger effect. Radiat Res 1994; 137: 394–9.
15. Ashwood-Smith MJ. Radioprotective and cryoprotective properties of DMSO. In: Jacob SW, Rosenbaum EE, Wood DC, eds. Dimethyl sulfoxide. New York: Marcel Dekker, 1971: 147–87.
16. Vos O, Kaalen MCAC. Protection of tissue-culture cells against ionizing radiation II. The activity of hypoxia, dimethyl sulphoxide, dimethyl sulphone, glycerol and cysteamine at room temperature and at −196°C. Int J Radiat Biol 1963; 5: 609–21.
17. Watanabe M, Suzuki M, Suzuki K, Hayakawa Y, Miyazaki T. Radioprotective effects of dimethyl sulfoxide in golden hamster embryo cells exposed to γ-rays at 77°K : II. Protection from lethal, chromosomal and DNA damage. Radiat Res 1990; 124: 73–8.
18. Hagemann RF, Evans TC, Riley EF. Modification of radiation effect on the eye by topical application of dimethyl sulfoxide. Radiat Res 1970; 44: 368–78.
19. Narra VR, Howell RW, Sastry KSR, Rao DV. Vitamin C as a radioprotector against ^{131}I in vivo. J Nucl Med 1993; 34: 637–40.
20. Meistrich ML, Hunter NR, Suzuki N, Trostle PK, Withers HR. Gradual regeneration of mouse testicular stem cells after exposure to ionizing radiation. Radiat Res 1978; 74: 349–62.
21. Oakberg EF. Spermatogonial stem-cell renewal in the mouse. Anat Rec 1971; 169: 515–32.
22. Clifton DK, Bremner WJ. The effect of testicular X-irradiation on spermatogenesis in man. J Andrology 1983; 4: 387–92.
23. Meistrich ML, Samuels RC. Reduction in sperm levels after testicular irradiation of the mouse: A comparison with man. Radiat Res 1985; 102: 138–47.
24. Lui B, Chang J, Sun JS, et al. Radioactive iodine exchange reaction of HIPDM: Kinetics and mechanism. J Nucl Med 1987; 28: 360–5.
25. Narra VR, Howell RW, Harapanhalli RS, Sastry KSR, Rao DV. Radiotoxicity of some I-123, I-125, and I-131 labeled compounds in mouse testes: Implications for radiopharmaceutical design. J Nucl Med 1992; 33: 2196–201.
26. Azure MT, Howell RW. Isolation of polonium-210 from silver. Appl Radiat Isotop 1994; 45: 637–8.
27. Rao DV, Sastry KSR, Govelitz GF, Grimmond HE, Hill HZ. In vivo effects of iron-55 and iron-59 on mouse testis: Biophysical dosimetry of Auger electrons. J Nucl Med 1985; 26: 1456–65.
28. Apelgot S, Coppey J, Gaudemer A, et al. Similar lethal effect in mammalian cells for two radioisotopes of copper with different decay schemes, Cu-64 and Cu-67. Int J Radiat Biol 1989; 55: 365–84.
29. Ertl HH, Feinendegen LE, Heiniger HJ. Iodine-125, a tracer in cell biology: Physical properties and biological aspects. Phys Med Biol 1970; 15: 447–56.
30. Burki HJ, Roots R, Feinendegen LE, Bond VP. Inactivation

of mammalian cells after disintegrations of H-3 or I-125 in cell DNA at −196°C. Int J Radiat Biol 1973; 24: 363–75.

31. Hofer KG, Keough G, Smith JM. Biological toxicity of Auger emitters: Molecular fragmentation versus electron irradiation. Curr Topics Radiat Res Q 1977; 12: 335–54.
32. Kassis AI, Makrigiorgos GM, Adelstein SJ. Implications of radiobiological and dosimetric studies of DNA-incorporated I-123: The use of the Auger effect as a biological probe at the nanometre level. Radiat Prot Dosim 1990; 31: 333–8.
33. Wright HA, Hamm RN, Turner JE, Howell RW, Rao DV, Sastry KSR. Calculations of physical and chemical reactions with DNA in aqueous solution from Auger cascades. Radiat Prot Dosim 1990; 31: 59–62.
34. Pomplun E, Roch M, Terrisol M. Simulation of strand break induction by DNA incorporated ^{125}I. In: Howell RW, Narra VR, Sastry KSR, Rao DV, eds. Biophysical Aspects of Auger Processes. Woodbury, NY: American Institute of Physics, 1992: 137–52.
35. Hofer KG, Bao S-P. Low-LET and high-LET radiation action of ^{125}I decays in DNA: Effect of cysteamine on micronucleus formation and cell killing. Radiat Res 1995; 141: 183–92.