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Radiotoxicity of Gadolinium-148 and Radium-223 in Mouse Testes: Relative Biological Effectiveness of Alpha-Particle Emitters *In Vivo*

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Abstract

The biological effects of radionuclides that emit α particles are of considerable interest in view of their potential for therapy and their presence in the environment. The present work is a continuation of our ongoing effort to study the radiotoxicity of α-particle emitters *in vivo* using the survival of murine testicular sperm heads as the biological end point. Specifically, the relative biological effectiveness (RBE) of very low-energy α particles (3.2 MeV) emitted by ^{148}Gd is investigated and determined to be 7.4 ± 2.4 when compared to the effects of acute external 120 kVp X rays. This datum, in conjunction with our earlier results for ^{210}Po and ^{212}Pb in equilibrium with its daughters, is used to revise and extend the range of validity of our previous RBE–energy relationship for α particles emitted by tissue-incorporated radionuclides. The new empirical relationship is given by $RBE_\alpha = 9.14 - 0.510\ E_\alpha$, where $3 < E_\alpha < 9$ MeV. The validity of this empirical relationship is tested by determining the RBE of the prolific α-particle emitter ^{223}Ra (in equilibrium with its daughters) experimentally in the same biological model and comparing the value obtained experimentally with the predicted value. The resulting RBE values are 5.4 ± 0.9 and 5.6, respectively. This close agreement strongly supports the adequacy of the empirical RBE-E_α relationship to predict the biological effects of α-particle emitters *in Vivo*.

INTRODUCTION

Alpha-particle emitters are being explored for use in radioimmunotherapy, and they are present in the environment (i.e. ^{222}Rn). Therefore, there is an increasing need to understand the biological effects caused by internal α-particle emitters. Alpha particles emitted by radionuclides generally have energies that range from about 3 to 9 MeV with corresponding linear energy transfers (LETs) ranging from about 125 to 60 keV/μm. Barendsen (1) has reviewed the relationship between the relative biological effectiveness (RBE) and LET for different types of lethal damage in cultured mammalian cells. For *in vitro* studies, the RBE is strongly dependent on LET with a maximum at about 120 keV/μm. Similarly, Miller *et al.* (2) have investigated oncogenic transformation as a function of LET in cultured C3H 10T1/2 cells and found that the RBE for stochastic effects (RBE_M) is also maximum at about 120 keV/μm. Although there is a relative abundance of such data obtained *in vitro*, there are few studies investigating the relationship between RBE and LET *in vivo*. Given that the biological effects of ionizing radiation are highly dependent on LET (3, 4), and that there are numerous radionuclides of importance to nuclear medicine and radiation protection that emit high-LET α particles, it is essential that the effects of α-particle emitters be investigated *in vivo* as a function of the emitted α-particle energy (E_α) and LET. In our earlier study (5), empirical RBE–LET and RBE–E_α relationships were established *in vivo*

over a limited range of α-particle energies (5.3–8.8 MeV) using spermatogenesis in mouse testes as the experimental model. In the present study, we extend the RBE–E_α relationship to as low as 3.2 MeV using the radionuclide ^{148}Gd, thereby covering most of the α-particle energies emitted by incorporated radionuclides. This relationship is tested by determining the RBE experimentally for ^{223}Ra in equilibrium with its daughters, a decay series which emits a spectrum of α particles with energies ranging from 5.3 to 7.5 MeV, and comparing the resulting experimental RBE with the calculated RBE based on the empirical RBE–E_α relationship.

MATERIALS AND METHODS

Biological Model

Spermatogenesis in the mouse testis is used as the experimental model with testicular sperm head survival serving as the biological end point. This same model was used in our earlier reports on the biological effects of α-particle emitters (5) and other radionuclides (6–11). The process of spermatogenesis in mouse and man is very similar, except for the time scale: about 5 weeks for mouse and 10 weeks for man (12, 13). This complex process (14) begins with the stem cell (A_{is}) differentiating to form a pair of cells which further divide to give type A_1 spermatogonial cells. The type A_1 cells in turn divide repeatedly through several spermatogonial cell stages designated as A_2, A_3, A_4, In and B. For mice, it takes about 7 days for the cells to pass through the spermatogonial cell stages. The type B spermatogonia divide to become spermatocytes which mature over a 14-day period to spermatids. Finally, the spermatids pass through 16 stages during a 14-day process before they become functional sperm. The spermatids are resistant to sonication for about 7 days (stages 12–16).

Oakberg (15) and others (14, 16) have documented the highly differential radiosensitivity of these numerous cell populations in mammalian testes. The spermatogonial cells (types A_1–A_4, In, B) are the most sensitive to X rays (LD_{50} ~ 0.40 Gy in mice), while the remaining cell populations are substantially less sensitive, with LD_{50} values ranging from 2 to 600 Gy (17). Therefore, when the testes are irradiated with low doses which principally affect only the highly radiosensitive spermatogonial cells, a reduced testicular sperm head population is manifested when assayed 29–36 days postirradiation, the time required for the spermatogonia to become sonication-resistant spermatids of stages 12–16 (7–12, 18, 19). Thus we have historically referred to this assay as the sperm head survival assay because the sperm head count is used as an indirect measurement of survival of spermatogonial cells.

Radionuclides and Radiochemistry

Gadolinium-148, a pure α-particle emitter [3.2 MeV, continuously-slowing-down approximation (csda) range in water 20 μm (20)] with a physical half-life (t_p) of 75 years, was obtained precalibrated (within 5%) from the Medical Radioisotope Program at Los Alamos National Laboratory as Gd(III) in 0.5 *M* HCl. The radiochemical ^{148}Gd-citrate was prepared by mixing the stock solution with 1 *M* sodium citrate (pH 4.7) in accordance with our earlier procedures for ^{210}Po-citrate (11). The ^{148}Gd activity was assayed using a Beckman Model 5500 automatic liquid scintillation counter and Fluorosol® (National Diagnostics, Manville, NJ) cocktail.

The radionuclide ^{223}Ra (t_p = 11.4 days) was produced according to the procedures described by Fisher *et al*. (21). In brief, a ^{226}Ra target was irradiated with neutrons to produce ^{227}Ra according to the reaction ^{226}Ra (n/γ) ^{227}Ra. As shown in Fig. 1, ^{227}Ra (t_p = 42 min) undergoes β-particle decay to ^{227}Ac (t_p = 21.77 years), which decays, in turn, to ^{227}Th (t_p = 18.7 days). After neutron irradiation of the target, the ^{227}Ac was separated chemically from the target irradiation product mixture and then purified to remove silica solids, actinide

contaminants (uranium and plutonium) and iron. The ^{227}Ac, in equilibrium with its decay products (see Fig. 1), was transferred to an anion exchange column and eluted with 0.35 *M* nitric acid. The ^{227}Th remained alone on the column while the eluate containing the ^{227}Ac and ^{223}Ra was recycled back into the original container for later use. Ten days later, the anion exchange column was eluted again with 0.35 *M* nitric acid to obtain pure ^{223}Ra. The resulting solution was boiled down three times with HCl to form ^{223}RaCl, the final product.

The radiochemical ^{223}Ra-citrate was prepared using the same procedures described above for ^{148}Gd-citrate. Radium-223 decays to stable ^{207}Pb via a series of short-lived radioactive daughters (Fig. 1), many of which also emit α particles with csda ranges in water from 35–70 μm (20). The daughter radionuclides were in equilibrium with the parent ^{223}Ra at the time of radiolabeling. The activity of ^{223}Ra and daughters was determined by counting their characteristic γ rays using a Canberra (Meriden, CT) Model GCW2525 HpGe well detector housed in a Model 747 shield, and a Series 100 multichannel analyzer. Gamma-ray yields were taken from Browne and Firestone (22). The efficiency of the detector as a function of photon energy was determined using standards traceable to the National Institute of Standards and Technology.

General Procedures

Male Swiss Webster mice (Taconic Farms, Germantown, NY), 9–10 weeks of age and weighing about 30 g, were maintained in the University animal care facility and provided food and water *ad libitum*. As in our earlier work (7, 9, 10), the radiochemicals were injected intratesticularly along the long axis of the right testis (standard 3 μl volume) of mice anesthetized with ether. The needle was slowly withdrawn from the organ during the injection to facilitate a reasonably uniform distribution of activity in the organ. Our earlier studies on the macroscopic distribution of radioactivity in the testis show that citrate radiochemicals [^{114m}In-citrate (8), ^{111}In-citrate (8), ^{210}Po-citrate (11), ^{55}Fe-citrate (23)], and all other radiochemicals that we have studied such as $^{212}PbCl_4^{2-}$ (5), distribute fairly uniformly throughout the testis. These data, in conjunction with the consistency of our database of D_{37} values (~0.67 Gy) for low-LET radiation effects including those caused by external X rays (8) and intratesticularly injected radiochemicals that emit β particles (8, 24), γ rays (16) and very short-range Auger electrons (cytoplasmically localized Auger emitter) (8, 9, 24, 25), provide evidence that this “line injection” results in a sufficiently uniform distribution of radioactivity throughout the organ to allow intercomparison of the biological effects of different types of emitters based on the mean absorbed dose (16, 24).

There are several advantages to employing the intratesticular mode of administration over intravenous and intraperitoneal: (1) The testis is very small (0.1 g) so that photon radiations emanating from the organ deposit very little of their energy and therefore usually contribute minimally (<10%) to the total absorbed dose to the organ. (2) Only very small amounts of radioactivity (a few becquerels for α-particle emitters) are required to deliver cytotoxic doses to the testis. Hence the testicular absorbed dose from penetrating radiations emitted by radioactivity that has cleared from the testis and entered the body is negligible. (3) The dose to other organs in the body is negligible for the intratesticular mode, thereby eliminating complications due to organ toxicity. In summary, the intratesticular mode of administration allows clear delineation of the biological effects of the particulate radiations emitted by the radionuclide(s) without interference from penetrating low-LET photon radiations (γ rays and X rays) (11, 16).

Clearance of the Radionuclides from the Testis

The clearance of the radionuclides from the testis was determined by administering a fixed amount of radioactivity into the right testis of 30 animals. At various times after injection,

animals were sacrificed in groups of three by an overdose of anesthetic. For ^{223}Ra-citrate, the testes were immediately removed and placed in 1-ml airtight tubes, and the testicular activity of parent and daughters was immediately assayed using the HpGe well detector. The 154.2 keV and 269.4 keV, 271.1 keV and 401.7 keV, 427.0 keV, 350.1 keV and 897.2 keV γ-ray peaks were used to quantify the activity of ^{223}Ra, ^{219}Rn, ^{211}Pb, ^{211}Bi and ^{207}Tl, respectively. The γ-ray yields of ^{211}Po and ^{215}Po were too low to monitor. For each time, the fraction of injected radioactivity retained in the testis compared to the control (activity injected into resected testes) was calculated, thereby yielding the biological retention of the activity in the organ.

Sperm Head Survival Assay

The optimal day on which to assay the sperm head survival fraction was determined by injecting the right testis of 30 additional animals with 420 Bq ^{148}Gd-citrate (delivers 7.4 cGy) or 508 Bq ^{223}Ra-citrate (delivers 5.6 cGy). The animals were sacrificed in groups of three by an overdose of ether and the right testis of each animal was resected. The testicular sperm head count was obtained by placing each testis in 1 ml deionized water, homogenizing, sonicating and counting the sonication-resistant sperm heads in a hemocytometer (7–9). The surviving fraction *S* is the ratio of sperm head counts in the test group to the number of counts in the controls (injected with 1 *M* sodium citrate, pH 4.7). The optimal day is the day after injection at which the sperm head count is a minimum.

The sperm head survival fraction was then determined as a function of the testicular absorbed dose. Animals (10 groups of 3) were injected intratesticularly with various concentrations of the radiochemical to deliver a range of absorbed doses to the testis. On the optimal day after injection, all of the animals were sacrificed and the sperm head survival fraction was determined for each group as described above (8, 9).

RESULTS AND DISCUSSION

Biokinetics and Optimal Assay Day after Administration of ^{148}Gd

The biological clearance of ^{148}Gd from the testis after intratesticular administration is shown in Fig. 2. A least-squares fit of the data to a two-component exponential expression gives

$$f(^{148}\mathrm{Gd}) = 0.917\, e^{-0.693t/0.359} + 0.083\, e^{-0.693t/221}, \quad (1)$$

where *f* is the fraction of initially injected radioactivity remaining in the testis and *t* is the time after injection in hours. The effective clearance is also essentially given by Eq. (1) because of the 75-year physical half-life of ^{148}Gd. In keeping with our earlier protocols (5, 8), the sperm head survival was monitored as a function of time after injection of a fixed amount of ^{148}Gd-citrate (420 Bq) to determine the day on which the minimum sperm head count is obtained (i.e. optimal day for sperm head survival assay). The optimal day was the 36th day after injection, which was consistent with our earlier observations for long-lived (t_p = 138 days) ^{210}Po-citrate(11).

Testicular Dosimetry and Dose–Response Relationship for ^{148}Gd

The testicular absorbed dose from the radionuclides was calculated as described previously (5, 7–10). Briefly, the mean testicular absorbed dose *D* is given by (26)

$$D=\frac{\tilde{A}}{m}\sum_{i}\Delta_i\varphi_i, \quad (2)$$

where the cumulated activity $\tilde{A}$ is the time integral of the activity in the organ $\int A(t)dt$, Δ is the mean energy emitted per nuclear transition, φ is the absorbed fraction, m is the average mass of the testis (0.1 g), and i denotes the ith radiation component emitted by the radionuclide. In keeping with our dosimetry procedures for an optimal assay day of 36 days after injection, the cumulated activity was integrated over 13 days (8, 11). The 13-day integration period corresponds to the time during which the spermatogonial cells were irradiated, and the surviving spermatogonial cells eventually become sonication-resistant spermatids 36 days after injection (8, 11). Substitution of the effective half-lives into Eq. (1), and integration over 13 days, gave $\tilde{A}$ = 17.0 Bq-h per Bq of ^{148}Gd injected. The radionuclide ^{148}Gd emits a single 3.2 MeV α particle per decay (22); hence $\Delta = 5.12 \times 10^{-13}$ Gy-kg/Bq-s. With a testicular mass of 0.1 g and φ = 1, the mean testicular absorbed dose per unit cumulated activity is 1.82×10^{-5} Gy/Bq-h.

The sperm head survival fraction S/S_o is shown in Fig. 3 as a function of the average testicular absorbed dose from ^{148}Gd. This two-component exponential dose–response relationship is consistent with our earlier results for internal and external radiation sources (7–10) and with results reported by others (27, 28). A least-squares fit of the data to Eq. (3),

$$S/S_o=(1-a)e^{-D/D_1}+ae^{-D/D_2}, \quad (3)$$

gives $a = 0.58 \pm 0.065$, $D_1 = 8.28 \times 10^{-3} \pm 3.0 \times 10^{-3}$ Gy, and $D_2 = 0.20 \pm 0.043$ Gy. Hence the dose required to achieve 37% survival (D_{37}) is 0.090 ± 0.029 Gy.

Relative Biological Effectiveness as a Function of Alpha-Particle Energy

The RBE is defined, for a specific radiation (A), as

$$\mathrm{RBE(A)}=\frac{\text{Dose of reference radiation required to produce a specific level of response}}{\text{Dose of radiation A required to produce an equal response}},$$

with all physical and biological variables, except radiation quality, being held as constant as possible (29). Therefore, particular attention must be paid to the selection of the reference radiation (5, 10, 16, 30). In our earlier work using the same experimental model, the effects of a variety of sources of low-LET radiation were examined including external X rays (8) and intratesticularly administered β-particle and γ-ray emitters (8, 16, 24). A D_{37} of 0.67 ± 0.03 Gy was obtained for external irradiation with acute 60 or 120 kVp X rays (8). Similarly, when the testes were irradiated chronically with 477 keV γ rays from intratesticularly administered ^{7}Be-chloride or medium-energy β particles from H^{131}IPDM (24), D_{37} values of 0.65 ± 0.10 and 0.61 ± 0.06 Gy were obtained, respectively. These and other supporting data are discussed in ref. (16) and show that low-LET radiations (photons, electrons), whether delivered acutely or chronically, externally or internally, yield about the same D_{37} values. Therefore, any low-LET radiation, delivered acutely or chronically, can be used as the reference radiation for the purpose of calculating RBE values in the sperm head survival assay. In keeping with our past studies (5, 11), the D_{37} for acute 120 kVp X rays has been used to calculate RBE values for the α-particle emitters used in the present work.

With external X rays serving as the reference radiation, the RBE of the 3.2 MeV α particles emitted by ^{148}Gd is 7.4 ± 2.4 at D_{37}. In other earlier studies, an RBE of 6.7 ± 1.4 was obtained for ^{210}Po-citrate (5.3 MeV) (11), and ^{212}Pb in equilibrium with its daughters ^{212}Bi (6.0 MeV) and ^{212}Po (8.8 MeV) yielded RBE values of 6.0 and 4.6, respectively (5). These earlier data were used to construct a relationship between the RBE and the energy of the α particles (5). The data presented in this work for the 3.2 MeV α particles of ^{148}Gd allow us to revise our earlier RBE–E_α relationship to cover essentially the entire range of α-particle energies emitted by radionuclides in general. Figure 4 illustrates the revised RBE–E_α relationship. A least-squares fit of the data to a linear function yields Eq. (4),

$$\mathrm{RBE}_\alpha = 9.14 - 0.510\,\mathrm{E}_\alpha, \tag{4}$$

where RBE_α is the RBE of an α particle emitted with initial energy E_α in MeV. This empirical expression, which is valid over the range $3 < E_\alpha < 9$ MeV, is useful for predicting biological response after internal administration of α-particle emitters. It should be noted that when the microscopic distribution of the α-particle emitter is highly nonuniform (31), the RBE value can be different from that predicted by this relationship.

Test of the RBE–E_α Relationship Using ^{223}Ra

The radionuclide ^{223}Ra has a complex decay series (Fig. 1). There are about five α particles emitted in the series with energies ranging from 5.3 to 7.5 MeV, as well as a host of low-LET radiations. Therefore, ^{223}Ra in equilibrium with its daughters is a good radionuclide to test the adequacy of the empirical RBE–E_α relationship given by Eq. (4).

The biological clearance pattern of ^{223}Ra-citrate after intratesticular administration is shown in Fig. 2. The data were fitted by the least-squares method to the following three-component exponential expression:

$$f(^{223}\mathrm{Ra}) = 0.928\,e^{-0.693t/0.0110} + 0.0645\,e^{-0.693t/4.54} + 0.00704\,e^{-0.693t/25.1}, \tag{5}$$

where t is hours after injection. The ^{223}Ra and its daughters were found to be in equilibrium in the testis in our experiment. The optimal day for the sperm head survival assay was determined experimentally to be the 29th day post-injection for ^{223}Ra. This optimal day is consistent with our earlier data for radiochemicals with relatively fast effective clearance patterns (5, 7, 32). Using Eq. (5), and the physical half-life of ^{223}Ra (11.43 days), the cumulated activity was calculated by substituting the effective half-times of the three exponential components (0.011, 4.7 and 23.0 h) into Eq. (5) and integrating over 7 days (5, 7, 32). The cumulated activity thus obtained was 0.67 Bq-h per Bq of injected activity. The major radiations emitted by ^{223}Ra and its daughters are shown in Table I with their energies (33), yields (33) and branching ratios (22) shown accordingly. The mean absorbed dose to the testis per unit cumulated activity is calculated for each radiation (34), with the total being 4.33×10^{-8} Gy/Bq-s. The experimental dose–response relationship for ^{223}Ra in equilibrium with its daughters is shown in Fig. 5. A least-squares fit of the data to Eq. (3) gave $a = 0.77 \pm 0.032$, $D_1 = 0.0012$ Gy, $D_2 = 0.169 \pm 0.025$ Gy. From this equation, a D_{31} value of 0.124 ± 0.020 Gy can be calculated. Hence the corresponding RBE for ^{223}Ra in equilibrium with its daughters is 5.4 ± 0.9.

Is the experimental RBE of 5.4 for ^{223}Ra in equilibrium with its daughters expected based on our empirical RBE-E_α relationship? It has been shown that when a radionuclide emits a mixed radiation field, the overall RBE can be calculated using $R = \sum q_i\,\mathrm{RBE}_i$, where q_i is the fraction of absorbed dose from the ith radiation and RBE_t is the relative biological

effectiveness of the *i*th radiation (5). Table I gives the fraction of the total mean absorbed dose (q_i) that arises from each α particle emitted in the series, and the corresponding RBE_i calculated using Eq. (4). The numerous photons, conversion electrons and Auger electrons emitted by ^{223}Ra and its daughters (33) are all assigned an RBE of 1. It may be noted that the low-LET radiations constitute a negligible fraction of the total absorbed dose to the testis (Table I). The last column of Table I gives the product $q_i\ RBE_i$ and the resulting sum $\sum q_i\ RBE_i=5.6$, which is the expected overall RBE for ^{223}Ra in equilibrium with its daughters. This RBE value of 5.6 is in excellent agreement with our experimental RBE value of 5.4, thereby verifying the adequacy of the RBE–E_α relationship given by Eq. (4).

CONCLUSIONS

Although there is considerable experimental data on the biological effects of α particles *in vitro* (35–42), there is a dearth of *in vivo* data that systematically explore the dependence of RBE on the energy of α particles emitted by incorporated radionuclides. In this work, an empirical RBE–E_α relationship was obtained using spermatogenesis in mouse testes as the experimental model and survival as the biological end point. The range of α-particle energies covered by this relationship is from 3 to 9 MeV, covering the majority of α-particle energies emitted by radionuclides in general. The validity of the empirical relationship was verified using ^{223}Ra (in equilibrium with its daughters), which emits a spectrum of α-particle energies. There was an excellent agreement between the predicted RBE value based on the empirical relationship (Eq. 4) and the value determined experimentally. Therefore, this relationship should be useful for prediction of deterministic effects of internal α-particle emitters.

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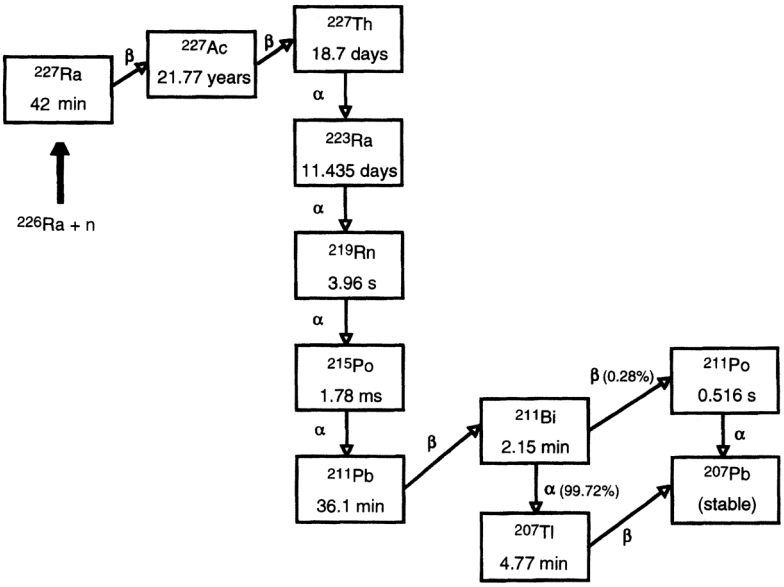

FIG. 1.

Production of ^{223}Ra and its decay scheme. The radionuclide ^{223}Ra is obtained by chemical separation from the products of the ^{226}Ra (n,γ) ^{227}Ra reaction and the ^{227}Ra daughters ^{227}Ac and ^{227}Th.

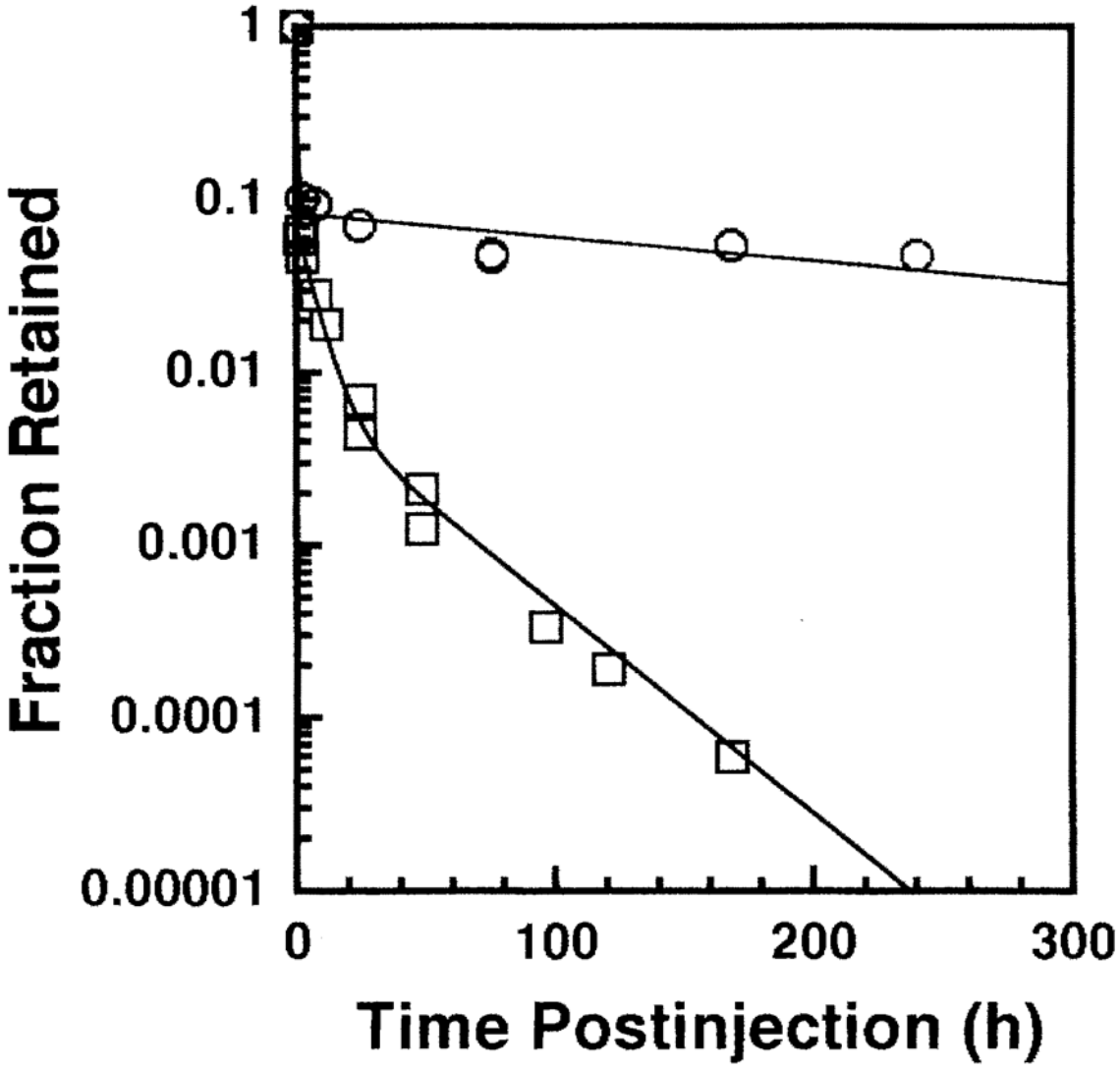

FIG. 2.
Biological elimination of ^{148}Gd-citrate (○) and ^{223}Ra-citrate (□) after intratesticular administration in mice. The data points represent the average of two independent experiments.

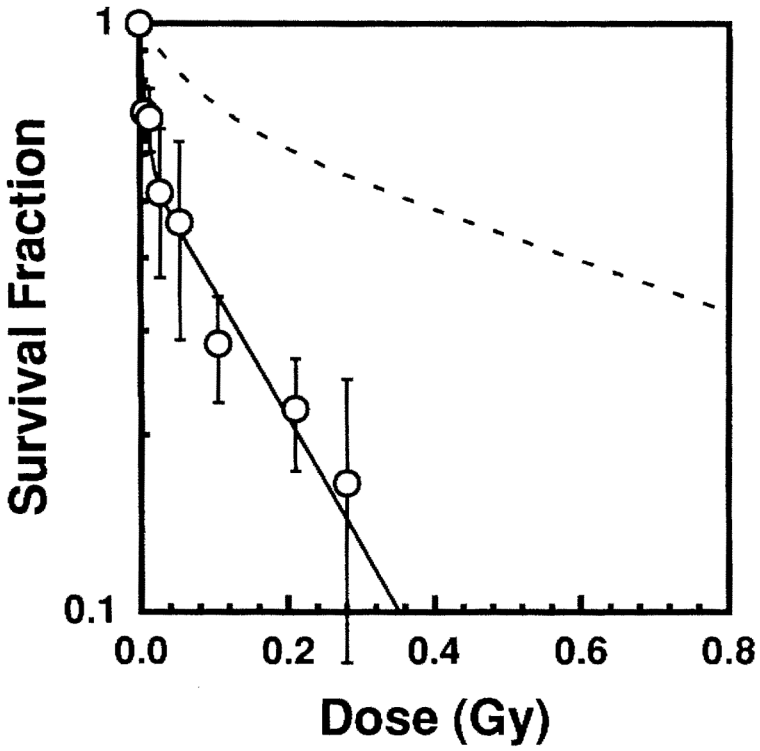

FIG. 3.

Sperm head survival fraction as a function of absorbed dose to mouse testis from intratesticularly administered ^{148}Gd-citrate (○). The data points are the average of two independent experiments. Error bars represent the standard deviation of the mean. The dashed line represents the dose–response curve for acute external 120 kVp X rays (8).

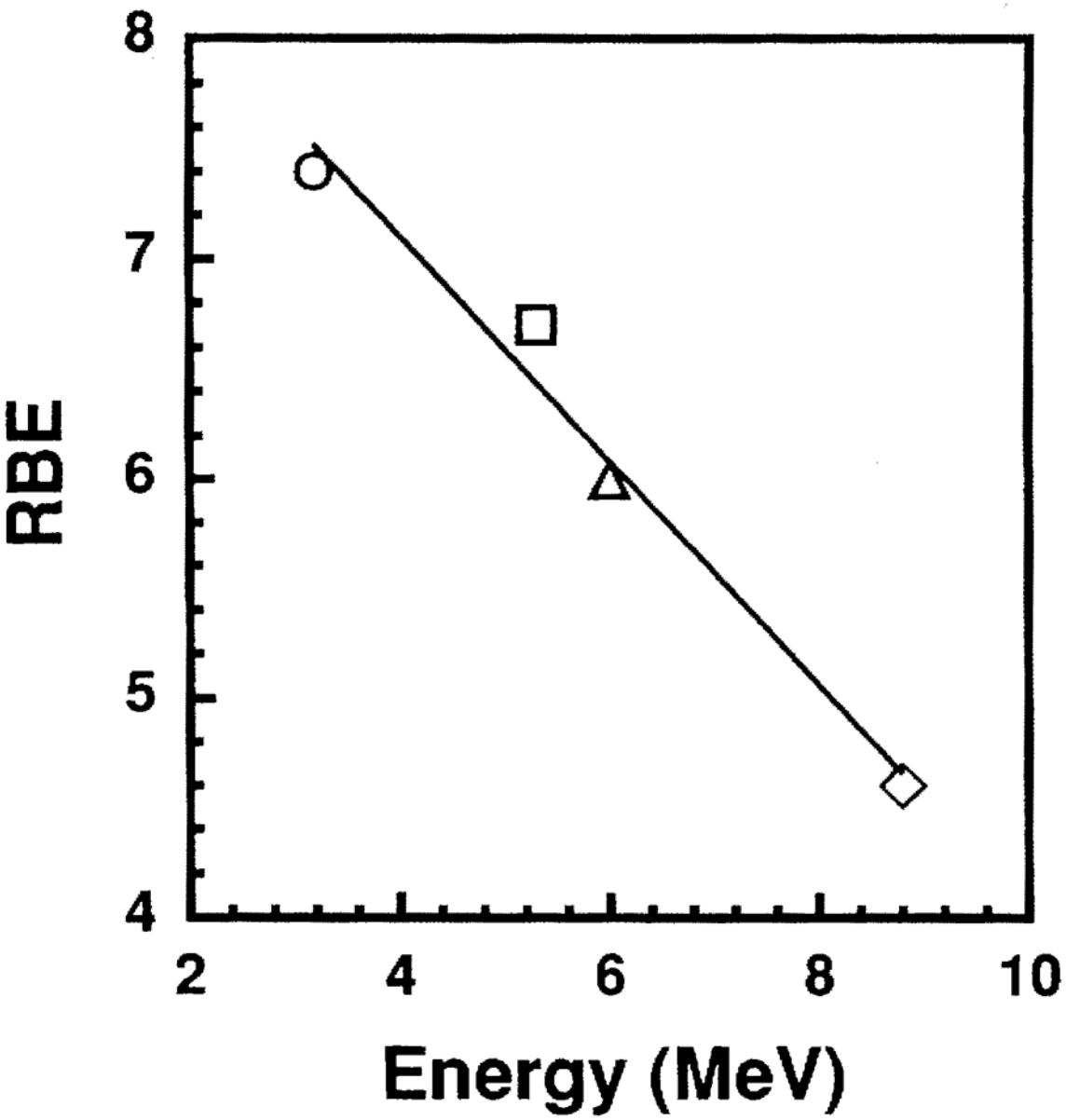

FIG. 4.

Relative biological effectiveness at 37% survival as a function of α-particle energy emitted by internal emitters. (○) 3.2 MeV from ^{148}Gd, (□) 5.3 MeV from ^{210}Po (11), (△) 6.0 MeV from ^{212}Bi (5), (◇) 8.8 MeVfrom^{212}Po(5).

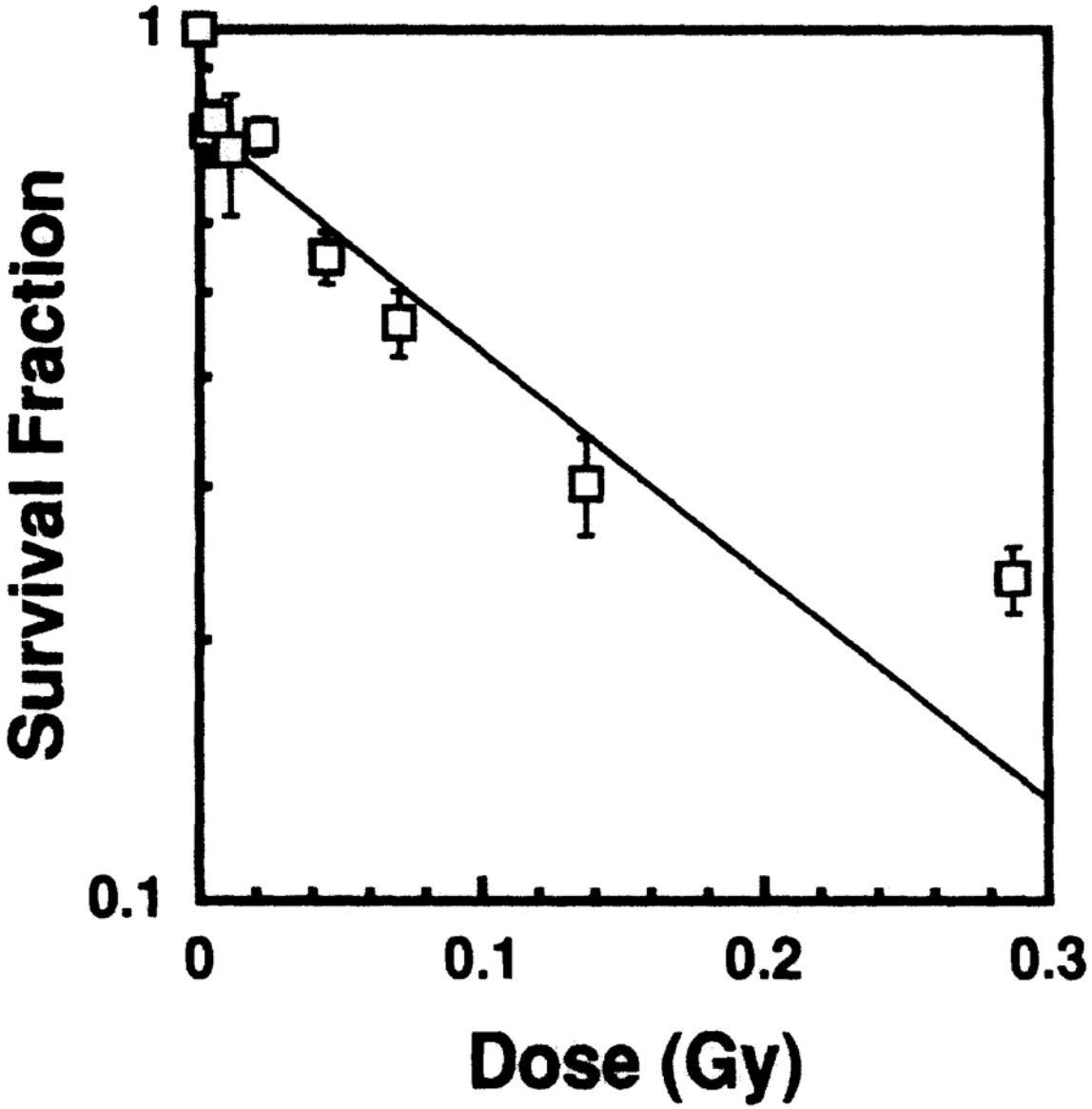

FIG. 5.
Sperm head survival fraction as a function of absorbed dose to mouse testis from intratesticularly administered ^{223}Ra-citrate. Two experiments were performed, the data points representing the mean. The error bars are the standard deviation of the mean.

TABLE I

Testicular Dosimetry Calculations and Dose-Weighted RBE

Radionuclide	Particle type, energy (MeV)[a]	Branching ratio[b]	n_i[a] (yield/decay)	s_i[c](Gy/Bq-s)	q_i[d]	RBE_i[e]	$q_i \times RBE_i$
^{223}Ra	α, 5.288	1	0.0015	1.26×10^{-11}	0.000292	6.45	0.00188
^{223}Ra	α, 5.340	1	0.0013	1.11×10^{-11}	0.000256	6.42	0.00164
^{223}Ra	α, 5.366	1	0.0013	1.11×10^{-11}	0.000257	6.41	0.00164
^{223}Ra	α, 5.433	1	0.0226	1.97×10^{-10}	0.00454	6.37	0.0289
^{223}Ra	α, 5.502	1	0.0099	8.77×10^{-11}	0.00203	6.34	0.0128
^{223}Ra	α, 5.540	1	0.0911	8.09×10^{-10}	0.0187	6.32	0.118
^{223}Ra	α, 5.607	1	0.2407	2.16×10^{-9}	0.0499	6.28	0.314
^{223}Ra	α, 5.716	1	0.5223	4.78×10^{-9}	0.110	6.23	0.688
^{223}Ra	α, 5.747	1	0.0945	8.70×10^{-10}	0.0201	6.21	0.125
^{223}Ra	α, 5.858	1	0.0032	2.98×10^{-11}	0.000689	6.16	0.00424
^{223}Ra	α, 5.872	1	0.0085	7.95×10^{-11}	0.00184	6.15	0.0113
^{219}Rn	α, 6.425	1	0.0744	7.66×10^{-10}	0.0177	5.87	0.104
^{219}Rn	α, 6.531	1	0.0012	1.25×10^{-11}	0.000288	5.81	0.00167
^{219}Rn	α, 6.553	1	0.1210	1.27×10^{-9}	0.0293	5.80	0.170
^{219}Rn	α, 6.819	1	0.8025	8.77×10^{-9}	0.203	5.67	1.15
^{215}Po	α, 7.386	1	0.9994	1.18×10^{-8}	0.273	5.38	1.47
^{211}Bi	α, 6.279	0.9972	0.1596	1.60×10^{-9}	0.0370	5.94	0.220
^{211}Bi	α, 6.623	0.9972	0.8377	8.86×10^{-9}	0.205	5.77	1.18
^{211}Po	α, 6.569	0.0028	0.0054	1.58×10^{-13}	0.0000037	5.79	0.0000212
^{211}Po	α, 6.891	0.0028	0.0055	1.69×10^{-13}	0.0000039	5.63	0.0000219
^{211}Po	α, 7.450	0.0028	0.9892	3.31×10^{-11}	0.000764	5.34	0.00408
All[f]	Photons			5.37×10^{-12}	0.000124	1.00	0.000124
All[g]	Conversion e^-			1.08×10^{-9}	0.0249	1.00	0.0249
All[h]	Auger e^-			1.38×10^{-11}	0.000319	1.00[i]	0.000319
Totals				4.33×10^{-8}	1.00		5.63[j]

[a] Energies and yields taken from Eckerman *et al*. (33).

[b] Branching ratios taken from Browne and Firestone (22).

[c] Mean absorbed dose per unit cumulated activity (*S* value) calculated using computer code of Howell *et al.* (34).

[d] q_i = fraction of total absorbed dose delivered by the *i*th radiation.

[e] RBE for α particles calculated using Eq. (4).

[f] Photon contribution from ^{223}Ra in equilibrium with its daughters.

[g] Conversion electron contribution from ^{223}Ra in equilibrium with its daughters.

[h] Auger electron contribution from ^{223}Ra in equilibrium with its daughters.

[i] Assumes radionuclides are localized outside the cell nucleus (citrate radiochemicals localize in cytoplasm).

[j] Weighted RBE for ^{223}Ra in equilibrium with its daughters calculated using $R = \Sigma\, q_i\, RBE_t$ (5).