Published in final edited form as:

Radiat Res. 2016 December ; 186(6): 624–637. doi:10.1667/RR14569.1.

Modeling Heavy-Ion Impairment of Hippocampal Neurogenesis after Acute and Fractionated Irradiation

Eliedonna Cacao and

Department of Health Physics and Diagnostic Sciences, University of Nevada, Las Vegas, Nevada

Francis A. Cucinotta¹

Department of Health Physics and Diagnostic Sciences, University of Nevada, Las Vegas, Nevada

Abstract

Radiation-induced impairment of neurogenesis in the hippocampal dentate gyrus is a concern due to its reported association with cognitive detriments after radiotherapy for brain cancers and the possible risks to astronauts chronically exposed to space radiation. Here, we have extended our recent work in a mouse model of impaired neurogenesis after exposure to low-linear energy transfer (LET) radiation to heavy ion irradiation. To our knowledge, this is the first report of a predictive mathematical model of radiation-induced changes to neurogenesis for a variety of radiation types after acute or fractionated irradiation. We used a system of nonlinear ordinary differential equations (ODEs) to represent age, time after exposure and dose-dependent changes to several cell populations participating in neurogenesis, as reported in mouse experiments. We considered four compartments to model hippocampal neurogenesis and, consequently, the effects of radiation in altering neurogenesis: 1. neural stem cells (NSCs); 2. neuronal progenitor cells or neuroblasts (NB); 3. immature neurons (ImN); and 4. glioblasts (GB), with additional consideration of microglial activation. The model describes the negative feedback regulation on early and late neuronal proliferation after irradiation, and the dynamics of the age dependence of neurogenesis. We compared our model to experimental data for X rays, and protons, carbon and iron particles, including data for fractionated iron-particle irradiation. Heavy-ion irradiation is predicted to lead to poor recovery or no recovery from impaired neurogenesis at doses as low as 0.5 Gy in mice. This is only partially ameliorated by dose fractionation, which suggests important implications for Hardon therapy near the Bragg peak, and possibly for space radiation exposures as well. Predictions of the threshold doses where neurogenesis recovery fails for given radiation types are described, and the role of subthreshold transient impairments are briefly discussed.

INTRODUCTION

Detriments in cognition and memory are likely to occur after radiation therapy for brain cancer (1–5) and are also a concern for astronauts exposed to cosmic rays during long-duration space travel (6). In cancer therapy a range of neurocognitive detriments have been

¹Address for correspondence: University of Nevada, Las Vegas, Department of Diagnostic Sciences and Health Physics, Box 453037, Las Vegas, NV 89195-3037; francis.cucinotta@unlv.edu.

reported, including progressive deficits in short- and long-term memory loss, spatial relations, visual motor processing, quantitative skills and impaired learning (1–5). The hippocampus is pivotal in maintaining normal cognitive function, and neurogenesis is believed to play a key role in hippocampal regulation (7). Recently, the use of proton and carbon beams near the Bragg peak in so-called Hadron therapy has increased (8–10), leading to concerns of possible neurological effects. A large portion of space radiation is comprised of high-linear energy transfer (LET) particles, including heavy ions, stopping protons and neutrons. High-LET radiation may lead to lower dose thresholds for cognitive effects and possible qualitative differences compared to X rays (6). The pathogenesis of neurological impairments is not well understood, however, changes to rates of proliferation and apoptosis of neuronal precursor cells in the dentate gyrus of the hippocampus have been suggested in published studies of rodent models (11–16), and behavioral changes reported in these animals suggest that altered neurogenesis is manifested directly in cognitive detriments (11–13).

Neurogenesis continues throughout life in the subgranular zone (SGZ) of the hippocampus and subventricular zone (SVZ) lining the lateral ventricular of all mammalian species (6). In the SGZ, newly born neurons migrate into the dentate granule cell layer and mature, ultimately connecting with the CA3 region of the hippocampus (6, 17–20). There are various precursor cell populations in the hippocampus and new neurons, astrocytes and oligodendrocytes are observed to be generated in adult animals (17–23). Published studies show that at least two types of neural stem cells (NSCs) occur: radial and horizontal astrocytes or glia-like stem cells (17–19). However, cell fate of NSCs in the adult hippocampus has not yet been established. “Older” stem cells may retain or deviate from the properties of self-renewal or cell fate decisions of embryonic neuroepithelial cells or fetal radial glia (20). Lineage tracing to study NSC properties has resulted in different conclusions, which may in part be due to different labeling approaches of cell populations used in different experiments (19). Seri *et al.* (17) proposed that radial astrocyte (NSC) undergo asymmetric division to generate neuroblasts (NB). Both Steiner *et al.* (18) and Encinas *et al.* (21) considered that NSCs give rise to both neurons and astrocytes. Others have developed some unified hypothesis suggesting that NSCs in the adult hippocampus undergo maintenance via self-renewal and generate new neurons, astrocytes and other glial cells (19, 20).

Previously published studies in mice and rats have shown that neurogenesis is altered after low-LET irradiation, e.g., X rays, electrons and medium- or high-energy protons for doses as low as 1 Gy and perhaps at lower doses (11–16). However, radiation damage to the complex hierarchy of cells in the hippocampus likely varies with different types of radiation. An important question arises as to whether high-LET radiation impairs neurogenesis in quantitatively or qualitatively distinct manners compared to X rays, including the dose dependencies of such impairments. Additional questions address how to estimate threshold doses below which full recovery is possible, and how to extrapolate such findings to different radiation types and from rodent models to humans. Experiments with carbon and iron particles suggest that cognitive impairments may occur at lower doses and persist much longer without recovery of neuroblasts and immature neurons compared to X rays (24–31). The main purpose of this study is to explore these questions by extending a predictive

mathematical model of radiation-induced changes to neurogenesis, which was previously applied to X-ray experiments (32), to consider high-LET irradiation. This model uses a system of nonlinear ordinary differential equations (ODEs) to represent age, time after irradiation and dose-dependent changes to the major cell populations reported in mouse experiments (32). In the remainder of this article, the Methods section introduces the model equations describing neurogenesis without and with radiation exposure. This is followed by extensive comparisons to experimental data and discussion of several predictions of the model. We will show that heavy ions lead to distinct neurogenesis impairments, compared to X rays, due to the nonlinear nature of the system and the distinct rate constants that occur related to the more efficient damage induction per unit dose for heavy-ion irradiation.

METHODS

Adult Hippocampal Neurogenesis and Neuronal Cell Population

As described in our previously reported model, we represent hippocampal neurogenesis by considering four major compartments (Fig. 1A), each of which represents a neuronal cell population (32): 1. neural stem cells (n_1); 2. neuroblasts (n_2); 3. immature neurons [ImNs (n_3)] and 4. Glioblasts [GBs (n_4)].

Glioblast differentiation is not considered in our model at this time. Based on several assumptions (32), the dynamics of the neuronal cell population can be described by the ordinary differential Eqs. (1)–(4):

$$\frac{dn_1(t)}{dt} = (p_1 - d_1)n_1(t); \quad (1)$$

$$\frac{dn_2(t)}{dt} = 2x_a d_1 n_1(t) - (d_2 + a_2)n_2(t); \quad (2)$$

$$\frac{dn_3(t)}{dt} = d_2 n_2(t) - a_3 n_3(t); \quad (3)$$

$$\frac{dn_4(t)}{dt} = x_b d_1 n_1(t) - a_4 n_3(t), \quad (4)$$

where d_1 and d_2 are rates of differentiation from NSCs to NBs and GBs, and NBs to ImNs, respectively; a_2 , a_3 and a_4 are apoptosis rates of NBs, ImNs and GBs, respectively; x_a and x_b are the fractions of NSCs that differentiate into NBs and GBs, respectively, such that $x_a + x_b = 1$; p_1 is the rate of NSC proliferation or self-renewal. A factor of 2 in the first term of Eq. (2) accounts for the symmetric division of NBs (17).

Feedback processes on proliferation dynamics are conveyed using rate constants that are dependent on cell concentrations, following the approach of Smirnova *et al.* used for radiation responses of other tissues (33–35). We represent NSC proliferation as follows:

$$p_1 = \frac{\Psi}{1 + (\theta_1 n_1 + \theta_2 n_2 + \theta_3 n_3)}, \quad (5A)$$

where Ψ is the maximum proliferation rate and multipliers θ_1 , θ_2 and θ_3 represent the dissimilar contributions of NSCs, NBs and ImNs in the feedback on NSC proliferation. Due to a lack of experimental data, we assume that self-renewal of NSCs is highly dependent on NB and ImN cell populations and that possible contributions of other neuronal cell populations are not significant. Furthermore, negative feedback on proliferation is dominated by radiation-induced changes in NBs and ImNs (32). This assumption simplifies Eq. (5A) and becomes:

$$p_1 = \frac{\Psi}{1 + \theta_2 n_2 + \theta_3 n_3}. \quad (5B)$$

Neuronal Cell Population after Irradiation

The schematic diagrams in Fig. 1B and C show the effect of radiation exposure on neuronal cell populations. Based on the extent of radiation-induced damage, we have categorized cells as undamaged (n_j), weakly damaged (n_{jW}) and heavily damaged (n_{jH}), where $j = 1-4$, which represents the four previously described compartments. Furthermore, a cell population is added to describe the number of apoptotic cells due to irradiation ($n_{IR-apop}$). Radiation-damage-rate constants are described by k_j , which is divided into two components to illustrate weakly (k_{jW}) and heavily (k_{jH}) damaged cells. We considered two radiation-damage models:

Model A. The fate of weakly damaged cells is to undergo either repair or apoptosis (misrepaired cells). This model was previously considered for low-LET irradiation (32).

Model B. Weakly damaged cells go through repair, misrepair (leading to apoptosis) or conversion to heavily damaged cells. Heavily damaged cells are assumed to lead directly to apoptosis at the rate of k_j .

The processes of repair or misrepair by weakly damaged cells are represented by rate constants α_{jR} and α_{jM} , respectively. We assume that the sum of repair and misrepair rates, $\alpha_j = \alpha_{jR} + \alpha_{jM}$, is a fraction of radiation-damage rate, as defined by $\alpha_j = \omega k_j$. Therefore, neuronal cell population after irradiation can be represented by the coupled ordinary differential Eqs. (6)–(10):

$$\frac{dn_1(t)}{dt} = (p_1 - d_1 - k)n_1(t) + \alpha_{1R}n_{1W}(t); \quad (6)$$

$$\frac{dn_2(t)}{dt} = 2x_a d_1 n_1(t) - (d_2 + a_2 + k_2) n_2(t) + \alpha_{2R} n_{2W}(t); \quad (7)$$

$$\frac{dn_3(t)}{dt} = d_2 n_2(t) - (a_3 + k_3) n_3(t) + \alpha_{3R} n_{3W}(t); \quad (8)$$

$$\frac{dn_4(t)}{dt} = x_b d_1 n_1(t) - (a_4 + k_4) n_4(t) + \alpha_{4R} n_{4W}(t); \quad (9)$$

$$\frac{dn_{IR-apop}(t)}{dt} = \sum_j \left[\alpha_{jM} n_{jW}(t) + k_j n_{jH}(t) \right] - v_{IR-apop} n_{IR-apop}(t) \text{ where } j = 1-4. \quad (10)$$

For the two radiation-damage models, the weakly and heavily damaged cell populations are described by the following for each $j = 1-4$ representing neuronal cell population [Eqs. (11) and (12)].

Radiation-damage model A:

$$\frac{dn_{jW}(t)}{dt} = k_{jW} n_j(t) - \alpha_j n_{jW}(t); \quad (11A)$$

$$\frac{dn_{jH}(t)}{dt} = k_{jH} n_j(t) - k_j n_{jH}(t). \quad (12A)$$

Radiation-damage model B:

$$\frac{dn_{jW}(t)}{dt} = k_{jW} n_j(t) - (\alpha_j + k_j) n_{jW}(t); \quad (11B)$$

$$\frac{dn_{jH}(t)}{dt} = k_{jH} n_j(t) + k_j n_{jW}(t) - k_j n_{jH}(t). \quad (12B)$$

Published radiation-response studies of neurogenesis suggest that neural stem cells are resistant to high- and low-LET radiation for doses up to approximately 10 Gy (29, 30), and that gliogenesis was found to be more radioresistant than production of new neurons (12–

14). Similar to our previous model, this work focuses on heavy-ion damage to neuroblasts (n_2) and immature neurons (n_3), and we assume that $k_2, k_3 \gg k_2, k_4$, for doses up to 10 Gy based on recently published experimental findings (29).

Considering the feedback of radiation damages on proliferation, Eq. (5B) is modified to Eq. (13) to describe NSC proliferation. Dissimilar contributions of weakly and heavily damaged cells due to differences in their specific death rates are expressed by dimensionless multipliers Φ and Γ , respectively, as shown in Eqs. (14A) and (14B). The negative feedback caused by activated microglia on NSC proliferation is manifested by $\theta_{mg}\mu$, where μ describes the increase in newly born activated microglia relative to a nonirradiated condition and θ_{mg} accounts for the contribution of this feedback on proliferation.

$$p_{1,IR} = \frac{\Psi}{1 + \theta_2(n_2 + \Phi n_{2W} + \Gamma n_{2H}) + \theta_3(n_3 + \Phi n_{3W} + \Gamma n_{3H}) + \theta_{mg}\mu}; \quad (13)$$

$$\frac{\Gamma_A}{\Phi_A} = \frac{k_j}{\alpha_j}; \quad (14A)$$

$$\frac{\Gamma_B}{\Phi_B} = \frac{k_j}{(\alpha_j + k_j)}. \quad (14B)$$

We used parametric equations to describe the time- and dose-dependent effects of newly born activated microglia on proliferation and of neurogenic cell fate of hippocampal neurogenesis (32). The increase in newly born activated microglia (μ) is experimentally determined through dual-labeling with BrDu and CD68, markers of proliferating cells and activated microglia, respectively. We describe the fold change in neurogenic fate of newly born neurons () as the ratio of fraction of NSCs that differentiate into neurons in irradiated ($x_{a,IR}$) over nonirradiated (x_a) conditions. Fraction of NSCs that differentiate into neurons (x_a) is experimentally characterized by BrDu and NeuN dual-labeled cells, with the latter as a marker of mature neurons. Parametric equations to describe μ and are as follows [Eqs. (15) and 16]):

$$\frac{d\mu(\tau)}{dt} = \begin{cases} 0 & \text{for } t < t_d \\ \left[A_0 \left(\frac{\text{dose}}{\text{dose} + A_1} \right) + B\tau + C\tau^2 \right] e^{-\lambda\tau} & \text{for } t \geq t_d \end{cases}; \quad (15)$$

$$\frac{d\Delta(\tau)}{dt} = \begin{cases} 1 & \text{for } t < t_d \\ \left[A_0 \left(\frac{\text{dose}}{\text{dose} + A_1} \right) + B_0\mu + B_1\mu\tau + C\tau^2 \right] e^{-\lambda\tau} & \text{for } t \geq t_d \end{cases}, \quad (16)$$

where τ is a time delay to exemplify the late onset of newly born activated microglia and change in neurogenic fate. This time delay is defined as $\tau = t - t_d$, where $t_d = 30$ days.

Acute and Fractionated Radiation Exposure

A simplified version of radiation-damage models A and B can be derived by assuming that rates corresponding to proliferation, differentiation and damage repair are negligible compared to the rates for damage induction during the acute irradiation period (a few minutes or less). Equations (6)–(12) can then be readily integrated, with the following solutions at the end of acute radiation exposure of duration, t_{IR} [Eqs. (17)–(19)]:

$$n_j(t_{IR}) = n_j(0)e^{(-k_j t_{IR})} = n_j(0)e^{\left(-\frac{D}{D_{0j}}\right)}. \quad (17)$$

Radiation-damage model A:

$$n_{jW}(t_{IR}) = n_j(0) \left[\frac{D_{0j}}{D_{0jW}} \right] \left[1 - e^{\left(-\frac{D}{D_{0j}}\right)} \right]; \quad (18A)$$

$$n_{jH}(t_{IR}) = n_j(0) \left[\frac{D_{0j}}{D_{0jH}} \right] \left[1 - e^{\left(-\frac{D}{D_{0j}}\right)} \right]. \quad (19A)$$

Radiation damage model B:

$$n_{jW}(t_{IR}) = n_j(0) \left[\frac{D}{D_{0jW}} \right] e^{\left(-\frac{D}{D_{0j}}\right)}; \quad (18B)$$

$$n_{jH}(t_{IR}) = n_j(0) \left[\frac{D}{D_{0jH}} + \frac{1}{2} \left(\frac{D}{D_{0jW}} \right)^2 + \frac{1}{2} \left(\frac{D}{D_{0jW}} \right) \left(\frac{D}{D_{0jH}} \right) \right] e^{\left(-\frac{D}{D_{0j}}\right)}. \quad (19B)$$

The terms $k_j t_{IR}$, $k_{jW} t_{IR}$ and $k_{jH} t_{IR}$ for acute irradiation are conveniently re-expressed as D/D_{0j} , D/D_{0jW} and D/D_{0jH} , respectively, where D is the absorbed dose in Gy, D_{0j} , D_{0jW} and D_{0jH} are the characteristic doses, where 37% of the cells are undamaged, weakly damaged and heavily damaged, respectively. For both radiation-damage models, the D_{0j} terms obey [Eq. (20)]:

$$\frac{1}{D_{0j}} = \frac{1}{D_{0jW}} + \frac{1}{D_{0jH}}. \quad (20)$$

Equations (17)–(19) then become the initial conditions to solve Eqs. (6)–(12), with the k_j terms no longer contributing for postirradiation times.

For chronic irradiation, Eqs. (6)–(12) can be directly integrated. However, for fractionated irradiation (as is used in radiotherapy), equations are solved in two steps for each radiation fraction: first with the dose-dependent k terms on, followed by a second period with the k terms off.

Data Analysis and Mathematical Modeling

All data analysis and modeling were performed using MATLAB® 2015a (MathWorks® Inc., Natick, MA). Solver function ode45 was used to solve the system of coupled ordinary differential equations describing the dynamics of nonirradiated and irradiated neurogenesis.

RESULTS

Age Dependence and Dynamics of Neuronal Cell Population (in Nonirradiated Mice)

Parameters for hippocampal neurogenesis of C57BL mouse were numerically estimated based on our assumptions and the available experimental data of the neuronal cell populations being considered in the model. Nestin transgenic mice were used as reporter for the NSC population, while immunohistochemical markers Ki67 and Dcx were used for the NB and ImN cell populations, respectively, and double labeling with BrDu was used (21, 29, 30, 36, 37). In this work, we assumed that NSC proliferation is highly dependent on radiosensitive NBs and ImNs such that θ_1 is set to zero, implying the resistant NSC cell population has insignificant effect on the proliferation dynamics compared to NBs and ImNs. Moreover, we set the maximum proliferation rate (Ψ) to be much higher than the NSC to NB or GB differentiation rate (d_1), to achieve a stable equilibrium state and avoid the state of complete extinction. Using the estimated parameters and initial values for each neuronal cell population [refer to ref. (32)], the dynamics of age-dependent mouse hippocampal neurogenesis were developed (see Fig. 2), where comparison of mouse and human life stages based in part on the age-scaling described in (38, 39) is also shown. The number of NSCs decline rapidly at early ages while reaching a steady state at older ages.

Impaired Hippocampal Neurogenesis after Irradiation

Table 1 shows the parameters for mouse hippocampal neurogenesis after exposure to different radiation types. These parameters are numerically estimated based on the experimental observations reported by Sweet *et al.* for protons (16), Rola *et al.* for carbon particles (25) and Rola *et al.* and Rivera *et al.* for iron particles (24, 25, 27, 29, 30), and compared to parameters used for X-ray exposure (32). We observed that NB radiosensitivity varied only modestly for different radiation types, while ImNs appeared to be more sensitive to high-LET radiation. On the other hand, ImNs were more radioresistant than NBs independent of radiation type. To our knowledge, there are no published investigations that generate a more precise estimate for some parameters, such as characteristic doses of weakly (D_{0jW}) and heavily (D_{0jH}) damaged cells and fraction of repairable weakly damaged cells ($\xi = \alpha_j R / \alpha_j$). We assume that for different radiation types (proton, carbon and iron), the fraction of weakly (D_{0j}/D_{0jW}) and heavily (D_{0j}/D_{0jH}) damaged cells are the same at 0.01 and 0.99

for NBs, respectively, and 0.06 and 0.94 for ImNs, respectively. Our previous model for X-ray exposure estimated the fraction of weakly and heavily damaged cells to be 0.04 and 0.96 for NBs, respectively, and 0.20 and 0.80 for ImNs, respectively. Furthermore, we assume that the fraction of repairable weakly damaged cells is the same for NBs and ImNs, and that it is much higher after exposure to X rays, protons and carbon ($\xi = 0.99$), than for iron ($\xi = 0.01$). All other parameters are kept the same as in our previous model (32). These estimated parameters are constrained to depict experimental observations of neurogenesis response to different radiation types. We consider the modeling of radiation-induced impairment of neurogenesis on 60- and 75-day-old mice, where initial values for neuronal cell population interpolated from Fig. 2A are as follows: $n_{1,60d} = 20098$; $n_{2,60d} = 9,829$; $n_{3,60d} = 89,319$; $n_{4,60d} = 46,539$; $n_{1,75d} = 16,326$; $n_{2,75d} = 7,819$; $n_{3,75d} = 70,896$; and $n_{4,75d} = 41,852$.

We compared the radiation-damage models A and B, and both gave very similar modeling results (data not shown). This might be due to the very low fraction of weakly damaged cells, which are estimated to be 0.01 for NBs and 0.06 for ImNs, or the lack of published experimental data to estimate parameter values. Therefore, the additional modeling results shown in this article are based on radiation damage model A. Radiation-induced cell loss was next assessed at various postirradiation times for different radiation types. Figure 3 shows the dose-dependent response of hippocampal neurogenesis to acute exposure of proton, carbon and iron particles at a specified postirradiation time, compared to their respective experimental data. Additional modeling results of the dose-dependent response of neurogenesis at different postirradiation times are shown in Supplementary Fig. S1 (<http://dx.doi.org/10.1667/RR14569.1.S1>). Results show that acute exposure to X-ray or proton radiation displays an exponential decay of NBs and ImNs until 270 days postirradiation. However, acute exposure to iron particles exhibited a reverse sigmoidal curve starting at 180 days postirradiation, where rapid decay of both NBs and ImNs occurs at 0.25–0.50 Gy. An identical behavior was observed for acute exposure to carbon radiation where reverse sigmoidal curve began at 270 days postirradiation and rapid decay of NBs and ImNs occurred at 2.5–3.0 Gy.

Inflammatory Response and Neurogenic Fate at Late Postirradiation Times

Radiation-induced injury has been shown to cause activation of microglial cells and recruitment of peripheral monocytes accompanied by local production of pro-inflammatory cytokines, such as IL-6 (14). Overexpression of IL-6 promotes astroglialogenesis and oligodendroglialogenesis, which might divert NSCs into gliogenesis at the expense of neurogenesis (13, 14). We have described the negative feedback regulation on proliferation at late postirradiation exposure times by an increase in newly born activated microglia and by a possible alteration of neurogenic fate or shift of NSC proliferation from neurogenesis to gliogenesis. Parametric Eqs. (15) and (16) describe the fractional increase in newly born activated microglia (μ) and fold decrease in neurogenic fate (λ), respectively. Estimated parameters are presented in Table 2 after first considering experimental data for activated microglia for X rays (12, 15) and iron particles (27). For protons and carbon particles, experimental data was not available and we considered the data for the kinetics of impaired neurogenesis to infer parameter values. Also, Rola *et al.* (25) had noted similar CCR2 immunoreactivity, a marker of neuroinflammation, after carbon and iron-particle irradiations

of male C57BL/6 mice. We thus assumed the same values for parameters for X-ray and proton irradiation, while other parameters are adjusted to depict existing experimental data and the qualitative behavior of cell kinetics for carbon and iron irradiations. Figure 4A shows the dose-dependent response of μ and λ at 60 days after receiving acute iron radiation exposure, compared to experimental data (27), while Fig. 4B shows a comparison of μ and λ at 60 days after receiving acute exposure to different radiation types (X ray, proton, carbon and iron).

Predictions of the dynamics of hippocampal neurogenesis until 300 days (10 months) after acute exposure (1–10 Gy doses) to different radiation types are presented in Fig. 5. The age dependence of NSC number is described (Fig. 2) and plays an important role in the time courses predicted in Fig. 5. Acute exposures among all radiation types considered (X ray, proton, carbon and iron) show similar behavior where severe transient radiation damages occur on the first few days postirradiation (<7 days) followed by a recovery until 30–90 days postirradiation, at which point activated microglial cells modulate responses. Restoration to normal condition is more evident for NBs than ImNs, and the negative feedback regulation by the inflammatory response on proliferation begins to manifest at 30 days postirradiation in NBs and at 60–90 days postirradiation in ImNs. At 300 days postirradiation, the dynamics after acute irradiation show that recovery of impaired neurogenesis can occur at <7 Gy X-ray or proton, <4 Gy carbon and <0.4 Gy iron irradiations. The carbon data is for entrance energy particles of moderate LET, and we would expect a much lower dose threshold for carbon particles near the Bragg peak of much higher LET. Based on the predictions of Fig. 5, we considered threshold doses (Fig. 6) where neurogenesis recovery fails by 270 day. Threshold doses were found to be highly dependent on the rate of ImN damage (D_{03}) and predicted to be highly dependent on radiation type with threshold doses below 1 Gy for high-LET particles.

Neurogenesis Response to Fractionated versus Acute Radiation Exposures

Figure 7 shows comparisons of the neurogenesis response to acute and fractionated exposure by different radiation types. The effect on ImNs by fractionated (5×0.20 Gy/day) and acute (1 Gy) irradiation, (the latter assumed to be applied on the final day of the fractionation schedule), is shown in Fig. 7A. Results are similar for radiation damage at day 1 postirradiation, with acute exposure resulting in slightly more damage than fractionated exposure at 90 days postirradiation. However, experimental data of iron-radiation exposure (29) indicated that the difference in ImN damage between acute and fractionated exposure is not significant at both 1 and 90 days postirradiation. Our model results for neurogenesis dynamics after acute (1 Gy) and fractionated (5×0.20 Gy/day) radiation exposure show no significant difference in ImN damage recovery (<1.5-fold recovery from fractionated than from acute exposure) until 270 days after proton or carbon irradiation. However, these results can be contrasted to those for the higher LET iron irradiation, where there is a convincing difference of threefold ImN damage recovery from fractionated exposure than from acute exposure. In Fig. 7B–D, we further evaluated the effects of higher dose of different radiation exposures (5 Gy acute exposure vs. 5 fractionated exposures of 1 Gy/day) on NBs and ImNs at various postirradiation exposure times. Significant differences in NB damage between acute and fractionated exposures is evident for X rays, protons, carbon and

iron. However, better recovery of NB damage from fractionated exposure at 270 days postirradiation was observed for X-ray (0.99), proton (0.99) and carbon (0.99) radiation, with little to almost no recovery observed for iron (0.22) radiation. On the other hand, significant differences in ImN damage between acute and fractionated radiation exposure is only visible at 270 days postirradiation, at which point almost complete recovery of ImN damage from fractionated exposure is attained for X rays (0.93), protons (0.92) and carbon (0.86) particles, while there is little recovery for iron particles (0.38). In addition, fold increase in ImN damage recovery from fractionated over acute exposure at 270 days postirradiation to X rays, protons, carbon and iron was 1.6, 1.6, 4.7 and 7.6, respectively. Modeling dynamics of neurogenesis after acute (5 Gy) and fractionated (5×1 Gy/day) exposure of each radiation type is shown in Supplementary Fig. S2 (<http://dx.doi.org/10.1667/RR14569.1.S1>).

DISCUSSION

We used a mathematical model to consider the radiation type dependence of radiation impairment of adult neurogenesis in the dentate gyrus of hippocampus. It has been previously shown that impaired neurogenesis is associated with cognitive detriments after radiation exposure (15, 28). However, there is still debate as to the functional role of neurogenesis in the SGZ, while an important role for learning and memory, including pattern separation, is expected (7, 42–44). Furthermore, at low to moderate doses of heavy ion radiation, other detrimental central nervous system (CNS) effects have been detailed [reviewed in ref. (6)], including impairment of executive function (45, 46) and changes to dendritic morphology (47, 48). Therefore, it is not clear if impairment of neurogenesis in the hippocampus is causative of all or a portion of cognitive detriments observed, or whether other mechanisms, including widespread and persistent oxidative stress (49, 50), and other brain regions such as the prefrontal cortex, are the dominant modes for the cognitive detriments found in animal experiments. Because it is likely that multiple mechanisms are in play, alternative approaches to experimental design should be considered to further elucidate causative mechanisms for cognitive detriments due to radiation exposure (51). Nevertheless, impairment of neurogenesis is known to be a critical factor in cognitive detriments and disease, and understanding the role of dose, radiation type and dose rate is an important area of investigation.

There has been significant progress in experimental research for detailing the many aspects of radiation impairment of neurogenesis (11–16), by, e.g., high-LET radiation (24–31, 52, 53). However, studies have been limited in the number of doses, postirradiation time points, age at irradiation, and radiation types considered. Thus, mathematical modeling can serve as a useful tool to interpret experimental results and extrapolate to other conditions. We used a standard approach to modeling of cell kinetics, using a system of ordinary differential equations to describe key cell populations, including NSCs, NBs, GBs and ImNs. Neurogenesis is more active at a younger age, while a decrease in neurogenesis occurs with increasing age in mice less than 200 days old, and the mice used in radiation experiments are typically up to 90 days old. Age-related neurogenesis dynamics were previously considered in the model (32), and played an important role in late time point comparisons at 1–3 months postirradiation, and among studies in mice of different ages. A description of the age

dependence of the various cell compartments was made and was augmented by an age-dependent radiosensitivity parameter for NBs for comparisons of radiation experiments at different mouse ages (32).

The effects of radiation type enter the model through cell damage parameters for NBs, ImNs and GBs, with kinetic rates of repair of weakly damaged cells and for apoptotic conversion of weakly and heavily damaged cells. Because of the spatial patterns of energy deposition at the microscopic scale, heavy ions cause more severe types of DNA damage compared to X rays (54, 55), including damages to neuron cells (56). We considered two kinetic models of radiation damage and repair. Model A corresponds to one-hit models of damage of both weakly and heavily damaged cells. Model B is a two-hit model of damage with repair/misrepair allowing for a transition from weakly to heavily damaged cells and thus capable of describing shouldered survival curves. However, we found that available experimental data was not able to distinguish between damage models. For dose fractionation or chronic exposures, the two models could lead to distinct results, and this area should be further investigated. The D_0 values for NBs and ImNs, and conversion rates to apoptotic cells, were well constrained by the experiments considered, however, parameters related to the repair/misrepair rates for weakly damaged cells are not well determined, and we would need dose fractionation or variable dose-rate experiments to improve estimates of their values and to better analyze model assumption such as the choice between Model A and B or related models.

In our approach, the negative feedback on NSC proliferation is assumed to be dependent on the concentration of normal and radiation-damaged NSCs, NBs and ImNs. Contributions of undamaged and weakly damaged cells on the feedback mechanism are assumed to be equal, while that of heavily damaged cells is computed to be slightly higher (32). In this approach radiation type is manifested in the damage probabilities for various weakly and heavily damaged cell populations, which therefore modulate the negative feedback on NSC proliferation with distinct dose dependences as a function of radiation type. Several of the parameters were not found to play a significant role and could be assumed that radiation-damaged NBs and ImNs have the same contribution, such that $\Phi_2 = \Phi_3 = \Phi$ and $\Gamma_2 = \Gamma_3 = \Gamma$, or that Φ and Γ could be set to unity with no significant difference in comparisons of model to experiments. However, the weak dependence found for several parameters in describing experiments could also reflect the limited experimental data available to confine estimates. The radiation type dependence of the negative feedback was predicted to be enhanced due to the more efficient damage to ImNs by heavy ions compared to X rays.

The dose thresholds' failure to recover from impairment of adult neurogenesis after acute irradiation were found to be highly correlated with loss of ImNs and resulting effects on NSC proliferation, and was highly dependent on radiation type (Fig. 6). In future work we will extend these predictions to dose fractionation and chronic irradiation schemes. Also it would be extremely useful to obtain data at intermediate LET values between the published results for carbon and iron beams (24–31), such as lower energy carbon or silicon particles. However, an important issue remains with respect to how to extrapolate these results from mice to humans. An interesting analogy is depression of the bone marrow system where the threshold doses for impaired hematopoiesis is about twofold lower for humans compared to

mice (57, 58) with a corresponding decreased lethal dose for humans. Because of the higher order functions and complexities of the human brain compared to mice, we expect that threshold doses could be lower for humans relative to mice.

The role of neuroinflammation, specifically in newly born or activated microglial cells, has a dependence on dose, radiation type and time after exposure based on several published studies. The study of Monje *et al.* (13, 14) using X-ray doses of 2 and 10 Gy suggested an important role for microglia activation in reduced NSC proliferation, and that a possible shift of stem cell proliferation from NB to GB occurred, especially at the 10 Gy dose. However, in other studies with X rays or low-LET proton radiation, a reduced role for activated microglia and no concurrent shift leading to an increase in gliosis were reported (16, 59, 60). Sweet *et al.* (16) have suggested that differences may occur due to the time and frequency of BrDu labeling, including the possibility that pools of NSCs may be dividing at different times. In contrast to these results, studies with iron particles demonstrated a significant microglia response for doses as low as 0.5 Gy (25, 27). In this report we developed a parametric model based on reported experiments for microglia activation. Activated microglia lead to a delayed response, playing an important role in the impairment of neurogenesis at later times (>30 days) and ultimate failure to recover from such impairments. However, there is limited experimental information on microglia activation available beyond three months postirradiation, which will be needed to improve model predictions.

Threshold doses for neurogenesis impairment could also be affected in radiation cancer patients undergoing concurrent chemotherapy, and due to the role of stress on neurogenesis (61). In space travel, other factors could play a role, including microgravity and altered circadian rhythm (6, 62), exercise (60, 63), as well as stress. Also of likely importance are the health effects of transient impairments at doses below that of the threshold dose for permanent impairment. Subthreshold impairments could be of clinical significance, as suggested in mouse experiments, where cognitive impairments have been observed for doses as low as 0.1 Gy for high-LET radiation (45–48, 50). However, as previously mentioned, there are multiple damage mechanisms occurring, and it is not clear if impaired neurogenesis is the dominant process for such detriments. For particle irradiation at low doses, stochastic effects may play a role in subthreshold impairments due to clustered damages occurring to small groups of NBs and ImNs, and possible effects on the “wiring” connections between the dentate gyrus and CA3 or other region of the hippocampus, and the ultimate function of new neurons. A large proportion of immature neurons are lost to apoptosis in nonirradiated animals, however, it is unclear if redundancy ultimately protects against the loss of additional or specific ImNs, possibly diminishing the stochastic effects of energy deposition by high-LET particle irradiation.

In summary, we have developed a biophysical model of the dose and radiation type dependence of impaired neurogenesis that agrees well with X-ray, proton and heavy-ion experiments. The model was used to make predictions of the time course for neurogenesis after radiation exposure and, as described in our previously published study, the age dependence of these responses (32). An important observation is that the ultimate outcome of impaired neurogenesis could take as long as nine months to be fully elucidated, while

experiments to date have typically been performed for no longer than six months postirradiation. Our predictions for dose thresholds for impaired neurogenesis in mice after acute irradiation can be extended to fractionated and chronic irradiation schemes, however, several parameters related to rates of repair/misrepair of damaged cells will need to be better constrained by additional experiments to understand the robustness of such predictions. Other studies will be needed to determine analogous thresholds in humans. In addition, we suggest that subthreshold transient impairments are likely to have important adverse health consequences for both patients and space travelers exposed to heavy ion irradiation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the National Cancer Institute (NCI grant no. 1RO1CA208526-01) and the University of Nevada, Las Vegas, NV.

References

1. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Onc.* 2011; 12:703–8.
2. Dias GP, Hollywood R, Bevilacqua MCN, da Luz ACD, Hindges R, Nardi AE, et al. Consequences of cancer treatments on adult hippocampal neurogenesis: implications for cognitive function and depression symptoms. *Neuro-Onc.* 2014; 0:1–17.
3. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. *Front Oncol.* 2012; 2:73. [PubMed: 22833841]
4. Monje ML, Palmer T. Radiation injury and neurogenesis. *Curr Opin Neurol.* 2003; 16:129–34. [PubMed: 12644738]
5. Monje ML, Vogel H, Masek M, Ligon KL, Fischer PG, Palmer TD. Impaired human hippocampal neurogenesis after treatment for central nervous system malignancies. *Annals Neurology.* 2007; 62:515–20.
6. Cucinotta FA, Alp M, Sulzman FM, Wang M. Space radiation risks to the central nervous system. *Life Sci Space Res.* 2014; 2:54–69.
7. Deng W, Aimone JB, Gage FH. New neurons and new memories: how dose adult hippocampal neurogenesis affect learning and memory? *Nat Rev Neurosci.* 2010; 338:72–5.
8. Allen A, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K, et al. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. *Radiotherapy Oncol.* 2012; 103:8–11.
9. Kamada T, Tsujii H, Blakely EA, Debus J, De Neve W, Durante M, et al. Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. *Lancet Oncol.* 2015; 16(2):e93–100. [PubMed: 25638685]
10. Shulz-Ertner D, Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol.* 2007; 25:953–64.
11. Parent JM, Lowenstein DH, Fike JR. X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. *Neurosci.* 2000; 99:33–41.
12. Mizumatsu S, Monje ML, Morhardt DR, Rola R, Palmer TD, Fike JR. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res.* 2003; 63:4021–7. [PubMed: 12874001]
13. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. *Nat Med.* 2002; 8:955–62. [PubMed: 12161748]

14. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science*. 2003; 302:1760–5. [PubMed: 14615545]
15. Rola R, Raber J, Rizk A, Otsuka S, VandenBerg SR, Morhardt DR, et al. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp Neurol*. 2004; 188:316–30. [PubMed: 15246832]
16. Sweet TB, Panda N, Hein AM, Das SL, Hurley SD, Olschowka JA, et al. Central nervous system effects of whole-body proton irradiation. *Radiat Res*. 2014; 182:18–34. [PubMed: 24937778]
17. Seri B, Garcia-Verdugo JM, Collado-Morente L, McEwen BS, Alvarez-Buylla A. Cell types, lineage and architecture of the germinal zone in the adult dentate gyrus. *J Comp Neurol*. 2004; 478:359–78. [PubMed: 15384070]
18. Steiner B, Kronenberg G, Jessberger S, Brandt MD, Reuter K, Kempermann G. Differential regulation of gliogenesis in the context of adult hippocampal neurogenesis in mice. *Glia*. 2004; 46:41–52. [PubMed: 14999812]
19. Bonaguidi MA, Song J, Ming G, Song H. A unifying hypothesis on mammalian neural stem cell properties in the adult hippocampus. *Curr Opin Neurobiol*. 2012; 22:754–61. [PubMed: 22503352]
20. Alvarez-Buylla A, Garcia-Verdugo J, Tramontin AD. A unified hypothesis on the lineage of neural stem cells. *Nat Rev Neurosci*. 2001; 2:287–93. [PubMed: 11283751]
21. Encinas JM, Michurina TV, Peunova N, Park JH, Tordo J, Peterson DA, et al. Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. *Cell Stem Cell*. 2011; 8:566–79. [PubMed: 21549330]
22. Kempermann G, Song H, Gage FH. Neurogenesis in the adult hippocampus. *Cold Spring Harb Perspect Biol*. 2015; 7:a018812. [PubMed: 26330519]
23. Doetsch F. The glial identity of neural stem cells. *Nature Neurosci*. 2003; 6:1127–34. [PubMed: 14583753]
24. Rola R, Otsuka S, Obenaus A, Nelson GA, Limoli CL, VandenBerg SR, et al. Indicators of hippocampal neurogenesis are altered by 56Fe-particle irradiation in a dose-dependent manner. *Radiat Res*. 2004; 162:442–6. [PubMed: 15447038]
25. Rola R, Sarkissian V, Obenaus A, Nelson GA, Otsuka S, Limoli CL, et al. High-LET radiation induces inflammation and persistent changes in markers of hippocampal neurogenesis. *Radiat Res*. 2005; 164:556–60. [PubMed: 16187787]
26. Casadesus G, Shukitt-Hale B, Stellwagen HM, Smith MA, Rabin BM, Joseph JA. Hippocampal neurogenesis and PSA-NCAM expression following exposure to 56Fe particles mimics that seen during aging in rats. *Exp Geront*. 2005; 40:249–54.
27. Rola R, Fishman K, Baure J, Rosi S, Lamborn KR, Obenaus A, et al. Hippocampal neurogenesis and neuroinflammation after cranial irradiation with 56Fe particles. *Radiat Res*. 2008; 169:626–32. [PubMed: 18494546]
28. Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mizumatsu S, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res*. 2004; 162:39–47. [PubMed: 15222778]
29. Rivera PD, Shih HY, LeBlanc JA, Cole MG, Amaral WZ, Mukherjee S, et al. Acute and fractionated exposure to high-LET 56Fe HZE-particle radiation both result in similar long-term deficits in adult hippocampal neurogenesis. *Radiat Res*. 2013; 180:658–67. [PubMed: 24320054]
30. DeCarolis NA, Rivera PD, Ahn F, Amaral WZ, LeBlanc JA, Malhortra JA, et al. 56Fe particle exposure results in a long-lasting increase in a cellular index of genomic instability and transiently suppresses adult hippocampal neurogenesis in vivo. *Life Sci Space Res*. 2014; 2:70–9.
31. Manda K, Ueno M, Anzai K. Space radiation-induced inhibition of neurogenesis in the hippocampal dentate gyrus and memory impairment in mice: ameliorative potential of the melatonin metabolite. *AFMK J Pineal Res*. 2008; 430–8. [PubMed: 18631288]
32. Cacao E, Cucinotta FA. Modeling impaired hippocampal neurogenesis following radiation exposure. *Radiat Res*. 2016; 185:319–31. [PubMed: 26943452]
33. Smirnova, OA. Environmental radiation effects on mammals: a dynamical modeling approach. New York: Springer; 2011.
34. Smirnova OA, Hu S, Cucinotta FA. Analysis of the lymphocytopoiesis dynamics in nonirradiated and irradiated humans: a modeling approach. *Radiat Res*. 2014; 181:240–50. [PubMed: 24673256]

35. Smirnova OA, Hu S, Cucinotta FA. Dynamics of acutely irradiated skin epidermal epithelium in swine: modeling studies. *Health Phys.* 2014; 107:47–59. [PubMed: 24849903]
36. Ben Abdallah NM, Slomianka L, Vyssotski AL, Lipp HP. Early age-related changes in adult hippocampal neurogenesis in C57 mice. *Neurobiol Aging.* 2010; 31:151–61. [PubMed: 18455269]
37. Andres-Mach M, Rola R, Fike JR. Radiation effects on neuronal precursor cells in the dentate gyrus. *Cell Tissue Res.* 2008; 331:251–62. [PubMed: 17786480]
38. Lazic SE. Modeling hippocampal neurogenesis across the lifespan in seven species. *Neurobiol Aging.* 2012; 33:1664–71. [PubMed: 21621300]
39. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, Huttner HB, et al. Dynamics of hippocampal neurogenesis in adult humans. *Cell.* 2013; 153:1219–27. [PubMed: 23746839]
40. Seib D, Martin-Villalba A. Neurogenesis in the normal ageing hippocampus: A mini-review. *Gerontology.* 2015; 61:327–35. [PubMed: 25471300]
41. Ziebell F, Martin-Villalba A, Marciniak-Czochra A. Mathematical modelling of adult hippocampal neurogenesis: effects of altered stem cell dynamics on cell counts and bromodeoxyuridine-labelled cells. *J R Soc Interface.* 2014; 11.
42. Taupin P, Gauge FH. Adult neurogenesis and neural stem cells of the central nervous system in mammals. *J Neurosci Res.* 2002; 69:745–9. [PubMed: 12205667]
43. Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. *Curr Opin Neurobiol.* 2004; 14:186–91. [PubMed: 15082323]
44. Shors TJ, Townsend Da, Zhao M, Kozorovitskiy Y, Gould E. Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus.* 2002; 12:578–85. [PubMed: 12440573]
45. Lonart G, Parris B, Johnson AM, Miles S, Sanford LD, Singletary SJ, et al. Executive function in rats is impaired by low (20 cGy) doses of 1 GeV 56Fe particles. *Radiat Res.* 2012; 178:289–94. [PubMed: 22880624]
46. Britten RA, Davis LK, Jewell JS, Miller VD, Hadley MM, Sanford LD, et al. Exposure to mission relevant doses of 1 GeV/nucleon 56Fe particles leads to impairment of attentional set-shifting performance in socially mature rats. *Radiat Res.* 2014; 182:292–8. [PubMed: 25029107]
47. Parihar VK, Pasha J, Tran KK, Craver BM, Acharya MM, Limoli CL. Persistent changes in neuronal structure and synaptic plasticity caused by proton irradiation. *Brain Struct Funct.* 2015; 220:1161–71. [PubMed: 24446074]
48. Parihar VK, Allen B, Tran KK, Macaraeg T, Chu E, Kwok S, et al. What happens to your brain on the way to Mars? *Science Adv.* 2015; 1.
49. Limoli CL, Giedzinski E, Baure J, Rola R, Fike JR. Redox changes induced in hippocampal precursor cells by heavy ion irradiation. *Radiat Environ Biophys.* 2007; 46:167–72. [PubMed: 17103219]
50. Haley GE, Yeiser L, Olsen RH, Davis MJ, Johnson LA, Raber J. Early effects of whole-body 56Fe irradiation on hippocampal function in C57BL/6J mice. *Radiat Res.* 2013; 179:590–6. [PubMed: 23510274]
51. Lazic EL. Using causal models to distinguish between neurogenesis-dependent and -independent effects on behavior. *J R Soc Interface.* 2012; 9:907–17. [PubMed: 21957118]
52. Yang M, Kim H, Kim J, Kim S, Kim J, Bae C, et al. Fast neutron irradiation deteriorates hippocampus-related memory in adult mice. *J Vet Sci.* 2012; 13:1–6. [PubMed: 22437529]
53. Encinas JM, Vazquez ME, Switzer RC, Chamberlin DW, Nick H, Levine HG, et al. Quiescent adult neural stem cells are exceptionally sensitive to cosmic radiation. *Exp Neurol.* 2008; 210:274–9. [PubMed: 18076878]
54. Cucinotta FA, Nikjoo H, Goodhead DT. Model of the radial distribution of energy imparted in nanometer volumes from HZE particles. *Radiat Res.* 2000; 153:459–68. [PubMed: 10761008]
55. Cucinotta FA, Durante M. Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings. *Lancet Oncol.* 2006; 7:431–5. [PubMed: 16648048]
56. Alp M, Parihar VK, Limoli CL, Cucinotta FA. A computational modeling approach to quantify energy deposition in irradiated neurons, dendrites and spines. *PLoS Comp Biol.* 2015; 11:e1004428.

57. Gordon MY. A Comparison of the radiosensitivity and O.E.R. of human and mouse marrow progenitor cells cultured in agar in diffusion chambers. *Int J Radiat Biol Relat Stud Phys Chem Med.* 1975; 28:285–90. [PubMed: 1081516]
58. Dowd, SB., Tilson, ER. *Practical radiation protection and applied radiobiology.* 2. Philadelphia: Saunders; 1999. p. 118-20.
59. Liao AC, Craver BM, Tseng BP, Tran KK, Parihar VK, Acharya MM, et al. Mitochondrial-targeted human catalase affords neuroprotection from proton irradiation. *Radiat Res.* 2013; 180:1–6. [PubMed: 23672429]
60. Naylor AS, Bull C, Nilsson MKL, Bjork-Eriksson T, Eriksson PS, et al. Voluntary running rescues adult hippocampal neurogenesis after irradiation of the young mouse. *Proc Natl Acad Sci U S A.* 2008; 105:14632–7. [PubMed: 18765809]
61. Eglend M, Zunszain PA, Pariante CM. Molecular mechanisms in the regulation of adult neurogenesis during stress. *Nat Rev Neurosci.* 2015; 16:189–200. [PubMed: 25790864]
62. Information needed to make radiation protection recommendations for space missions beyond low-earth orbit. NCRP Report No. 153. Bethesda: National Council on Radiation Protection and Measurements; 2006.
63. Wu MD, Hein AM, Moravan MJ, Shaftel SS, Olschowka JA, O'Banion MK. Adult murine hippocampal neurogenesis is inhibited by sustained IL-1 β and not rescued by voluntary running. *Brain Behav Immun.* 2012; 26:292–300. [PubMed: 21983279]

FIG. 1.

Hippocampal neurogenesis model. Panel A: Schematic diagram of neurogenesis model showing cell population, n_j , where $j = 1-4$, represents neural stem cells [NSCs (n_1)], neuroblasts [NBs (n_2)], immature neurons [ImNs (n_3)] and glioblasts [GBs (n_4)]. Panels B and C: Neurogenesis model after irradiation. Apoptotic cell population due to exposure is indicated by $n_{IR-apop}$. Radiation damages are described by rate constants k_j , where $k_j = k_{jW} + k_{jH}$. Damage repair and misrepair rates are represented by α_{jR} and α_{jM} , respectively, where $\alpha_j = \alpha_{jR} + \alpha_{jM}$. Panel B: The fate of weakly damaged cells (n_{jW}) is to undergo either repair or apoptosis (misrepaired). Panel C: A fraction of weakly damaged cells is converted to heavily damaged cells (n_{jH}).

FIG. 2.

Age-dependent neuronal cell population of mouse hippocampal neurogenesis. Modeling dynamics of neuronal cell population includes NSCs, NBs and ImNs, described as surviving fraction with corresponding experimental (exp.) data (panel A) (21, 37) or cell population with comparison of mouse and human life stages (panel B) (38).

FIG. 3.

Panels A–C: Dose-dependent response of hippocampal neurogenesis to acute exposure of proton, carbon or iron radiation, respectively. Neurogenesis is evaluated using proliferation marker Ki67 (left side) and ImN marker Dcx (right side) at a specified postirradiation time, in comparison to experimental data [protons (H) (16), carbon (C) (25) and iron (Fe) (24, 25)].

FIG. 4.

Newly born activated microglia and change in neurogenic fate at 60 days postirradiation. Panel A: Fractional increase in newly born activated microglia (left side) and fold decrease in neurogenic fate of newly born cells (right side) after acute exposure of iron radiation [model vs. experimental results (27)]. Panel B: Different particle radiation (X ray/proton vs. carbon vs. iron) effects on fractional increase in newly born activated microglia (left side) and fold decrease in neurogenic fate of newly born cells (right side).

FIG. 5.

Panels A–D: Modeling dynamics of hippocampal neurogenesis, represented by fraction of Ki67 (left side) and Dcx (right side), after acute exposure to different doses of X-ray, proton, carbon and iron radiation, respectively.

FIG. 6.

Threshold doses for immature neurons exposed to different radiation types. Threshold dose, defined as the minimum dose of radiation where recovery does not occur by 270 days postirradiation, is plotted against the characteristic dose for damage of immature neurons (D_{03}).

FIG. 7.

Acute and fractionated exposure to different radiation types. Panel A: Neurogenesis is evaluated using immature neuron marker Dcx after acute (1 Gy) or fractionated (5×0.20 Gy/day) exposure to proton, carbon or iron radiation at 1 (left) and 90 days postirradiation. [experimental results for iron irradiation are from ref. (29)]. Panels B–D: Effects of higher dose of acute (5 Gy) or fractionated (5×1 Gy/day) radiation exposure on proliferation marker Ki67 (left side) and Dcx (right side) at 60, 90 and 270 days postirradiation, respectively.

TABLE 1
Parameters for Mouse Hippocampal Neurogenesis after Exposure to Different Radiation Types

	X ray (12, 32)	Proton (16)	Carbon (25)	Iron (24, 25, 27)		
Energy (MeV/u)	150 kVp (20 mA)	1,000	290	1,000	600	300
LET (keV/μm)	-	0.4	13	148	175	239
Age of mice (days)	60	70–84 (used: 75)	75	75	60	60–84 (used: 75)
Parameters (unit)						
D_{02} (Gy)	0.75	0.80	0.80			0.50
D_{02W} (Gy)	18.75	80	80			50
D_{02H} (Gy)	0.78	0.81	0.81			0.51
D_{03} (Gy)	7.5	3.5	2.5			1.3
D_{03W} (Gy)	37.5	60	43			22.8
D_{03H} (Gy)	9.4	3.7	2.7			1.37
$\xi = \alpha_{JR}/\alpha_j$	0.99	0.99	0.99/0.01			0.01

Note. For identical baseline parameters not shown (ω , VIR - $apop$, Φ , θ_{mg}), refer to ref. (32).

TABLE 2

Parameters for Newly Born Activated Microglia and Neurogenic Fate of Different Radiation Types

	Parameters (unit)	Proton	Carbon	Iron
Increase in newly born activated microglia (μ)	A₀	0.05	0.08	0.09
	A₁ (Gy)	9	6	3
	B (day ⁻¹)	-7.5×10^{-6}	-7.5×10^{-6}	-7.5×10^{-6}
	C (day⁻²)	-1×10^{-5}	-1.25×10^{-5}	-1.5×10^{-5}
	λ (day ⁻¹)	0.03	0.03	0.055
Decrease in neurogenic fate ()	A ₀	-0.06	-0.06	-0.06
	A₁ (Gy)	9	6	3
	B ₀	-9.6×10^{-3}	-9.6×10^{-3}	-9.6×10^{-3}
	B ₁ (day ⁻¹)	1×10^{-5}	1×10^{-5}	1×10^{-5}
	C (day⁻²)	1×10^{-6}	1.25×10^{-6}	1.5×10^{-6}
	λ (day ⁻¹)	0.04	0.04	0.04

Note. Values shown in bold text vary for different radiation types.