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Histamine protects bone marrow against cellular damage induced by ionising radiation

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Abstract

Purpose: Based on our previous data on the histamine radioprotective effect on small intestine, in the present work we aimed to determine whether histamine is able to protect bone marrow cells against ionising radiation damage.

Materials and methods: 56 mice and 40 rats were divided into four groups. Histamine and histamine-irradiated groups received a daily subcutaneous histamine injection (0.1 mg/kg) starting 24 h before irradiation. Irradiated groups received a single dose on whole-body using Cesium-137 source and were sacrificed three days after irradiation. We evaluated the number of medullar components, bone marrow trophism, oedema, vascular damage, and other histological characteristics and also proliferation markers by immunohistochemistry.

Results: Histamine treatment substantially reduced the grade of aplasia, the oedema and vascular damage induced by ionising radiation on bone marrow of mice and rats. Additionally, histamine preserved medullar components increasing the number of megakaryocytes (14.0 ± 1.0 vs. 7.3 ± 1.0 in mice; and 9.9 ± 1.3 vs. 4.1 ± 1.0 in rats, $P < 0.01$) and also myeloid (253.4 ± 37.6 vs. 7.8 ± 1.5 in mice; and 52.0 ± 3.7 vs. 31.8 ± 3.1 in rats, $P < 0.01$), lymphoid (97.4 ± 6.5 vs. 19.8 ± 1.6 in mice; and 23.4 ± 0.9 vs. 11.7 ± 2.5 in rats, $P < 0.01$) and erythroid cells (165.0 ± 9.1 vs. 8.8 ± 2.8 in mice; and 27.3 ± 2.3 vs. 15.6 ± 3.5 in rats, $P < 0.01$) per mm^2. This effect was associated with an increased proliferation rate of bone marrow cells.

Conclusions: Histamine reduces ionising radiation toxicity on bone marrow cells being a suitable candidate for use as radioprotector, especially for patients undergoing radiotherapy who are at the risk of bone marrow or small intestine damage.

Keywords: *histamine, ionising radiation, radioprotection, proliferation, bone marrow*

Introduction

After surgery, radiotherapy is arguably one of the most widely used treatments for cancer, especially for localised disease that has not spread. However, ionising radiation is toxic not only to tumour cells but also to healthy tissues causing serious adverse effects to patients (Betzen and Overgaard 1997; Steel 1997; Grdina et al. 2002; Barcellos-Hoff et al. 2005; Hall and Giaccia 2006a).

The ratio of tumour response to normal-tissue damage is called the therapeutic index and can be manipulated by dose fractionation or by the use of drugs that preferentially either increase the tumour response (radiosensitisers) or reduce the biological effects of radiation on normal tissues (radioprotectors) (Betzen and Overgaard 1997; Grdina et al. 2002; Hall and Giaccia 2006a, 2006b). Despite many years of research there are surprisingly few radiation protectors in use today whose clinical use is limited due to their toxicity; thus, the development of effective and non-toxic agents is yet a challenge for oncologists and radiobiologists (Grdina et al. 2002; Hall and Giaccia 2006b; Dziegielewski et al. 2008). In clinical radiotherapy, the tolerance of normal tissues for radiation depends on the ability of clonogenic cells to maintain a sufficient number of mature cells suitably structure to preserve organ function. Casarett has suggested a classification of mammalian cell radiosensitivity based on histological observation of

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early cell death and has divided cells into four categories. Group I of Casarett's classification, the most sensitive group, consists of vegetative undifferentiated intermitotic cells and includes the stem cells of the self-renewing systems such as intestinal crypt cells and bone marrow stem cells (Betzen and Overgaard 1997; Hall and Giaccia 2006a).

We have previously reported that histamine treatment can selectively modulate cellular damage produced by ionising radiation increasing radiosensitivity of breast cancer cells while notably preserve intestinal crypts reducing toxicity on small intestine (Medina et al. 2006, 2007).

Histamine (2-(imidazol-4-yl)ethylamine) is a biogenic amine with a broad spectrum of activities in numerous physiological and pathological situations and is synthesised by the enzyme L-histidine decarboxylase (HDC). Histamine plays a key role in immunity and haematopoiesis and is involved in bone marrow cell physiology, enhancing differentiation and proliferation (Endo et al. 1995; Pós et al. 2004; Schneider and Dy 2004; Horvath et al. 2006). Histamine exerts its actions through the activation of four histamine receptors, three of which are expressed in bone marrow cells (H1, H2 and H4 histamine receptors) (Liu et al. 2001; Horvath et al. 2006).

The bone marrow pluripotent stem cells such as erythroblast are particularly radiosensitive and after whole body irradiation an important grade of aplasia is observed increasing the possibility of haemorrhage and/or infection occurrence that could be lethal. The survival of stem cells determines the subsequent repopulation of bone marrow after irradiation (Betzen and Overgaard 1997; Hall and Giaccia 2006a.)

Therefore, the aim of the present work was to determine whether histamine could be able to preserve the histological characteristics of bone marrow in whole body irradiated-mice and rats. In addition, we investigated whether histamine effect could be associated with bone marrow cell proliferation by immunohistochemical studies of proliferation markers.

Materials and methods

Treatment and irradiation

Fifty six 10-week-old male nude mice (NIH nu/nu) and forty 10-week-old male Sprague-Dawley rats were employed. To evaluate the protective capability of histamine, nude mice were used as a suitable model to further study its effect in these mice bearing xenografted human tumours. Animals were purchased from the Division of Animal Production Laboratory, School of Veterinary Sciences, University of La Plata, Buenos Aires, and were randomly separated into four groups ($n = 14$ or 10 each). Animals were maintained in our animal health care facility at 22–24°C and 50–60% humidity on a 12 h light/dark cycle with food and water available *ad libitum*.

Histamine and histamine-irradiated groups received a daily subcutaneous histamine injection (0.1 mg/kg) starting 24 h before irradiation and continued until the end of the experimental period, and untreated groups received saline. Histamine-irradiated group and untreated-irradiated group were irradiated using Cesium-137 source (IBL 437C type H) of 189 TBq (dose rate: 7 Gy/min) with a single dose of 10 Gy (mice) or 5 Gy (rat) on whole-body. The rationale for choosing these doses is that they are close to the doses that would be lethal to the 50% of population after 30 days of exposure ($^{30}LD_{50}$) for nude mice (10.9 Gy) and Sprague-Dawley rat (5.8 Gy) (data not shown). Then the animals were killed three days after irradiation by cervical dislocation. Four animals of each group received an intraperitoneal injection of 5-bromo-2′-deoxyuridine (BrdU) (100 mg/kg in saline; Sigma Chemical Co., St Louis, MO, USA) 1 h before sacrifice. Animal procedures were in accordance with recommendations of the Guide for the Care and Use of Laboratory Animals of the National Research Council, USA, 1996.

Histopathological studies

Bone marrows were fixed with Bouin's solution and were embedded in paraffin and cut into serial sections of 3 μm thick. Tissue morphology was examined on tissue sections after haematoxylin-eosin staining.

Parameters analysed in the bone marrow were:

a) Trophism (Duhamel et al. 1976; Nieto and Rozman 1980):
   Normal: Normal appearance of bone marrow.
   Grade I Aplasia: Consist of an alteration of the relationship between adipose tissue and active marrow tissue where the latter is replaced by adipose tissue in a different proportion according to age.
   Grade II Aplasia: Hipocellular change with a clear alteration in the relationship of adipose tissue/functional bone marrow tissue.
   Grade III Aplasia: Adipose marrow, only lipid vacuoles and stromal cells are observed.
b) Type of medullar elements and number of megakaryocytes, erythroid, lymphoid and myeloid cells per squared millimeter (mm^2) of bone marrow.
c) Stromal characteristics.

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Immunohistochemical staining

After deparaffinisation, specimens were placed in citrate buffer (10 mM, pH 6.0) and heated in a microwave oven twice for 2 min for antigen retrieval. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide in methanol. After blocking, tissues were incubated with primary mouse anti proliferating cell nuclear antigen (PCNA) (1:100, DakoCytomation, Glostrup, Denmark), mouse anti BrdU (1:150, Sigma Chemical Co., St Louis, MO, USA), rabbit anti-histamine (1:100, Sigma Chemical Co.), or rabbit anti HDC (1:100, Euro-Diagnostica AB, Sweden) antibodies overnight in a humidified chamber at 4°C. Immunoreactivity was detected by using horseradish peroxidase-conjugated anti-mouse or anti-rabbit antibodies, as appropriate, and visualised by diamino-benzidine staining (Sigma Chemical Co.). To evaluate subcellular localisation of these proteins, nuclei were stained with haematoxylin. Light microscopy was performed on an Axiolab Karl Zeiss microscope (Göttingen, Germany). All photographs were taken using a Canon PowerShot G5 camera (Tokyo, Japan). The immunostaining assessment was performed blind to the data by consensus agreement of two observers (VM and MC). To control the signal specificity, serial sections were made from five selected positive cases which were subjected to the same staining procedure, with phosphate buffered saline to replace the first antibody. This control staining did not give rise to a signal.

Statistical analysis

Data shown are mean ± standard error of the mean (SEM). Statistical evaluations were made by analysis of variance (ANOVA) that was followed by Tukey's Multiple Comparison Test. P values <0.05 were considered significant. All statistical analyses were performed with GraphPad Prism Version 5.00 software (San Diego, CA, USA).

Results

Effect of histamine on histological characteristics of irradiated bone marrow

Results indicate that histamine treatment remarkably reduced the grade of medullar aplasia, oedema, and vascular damage produced by ionising radiation on mouse bone marrow. In addition, histamine notably preserved medullar components, increasing significantly the number of megakaryocytes (14.0 ± 1.0 vs. 7.3 ± 1.0, $P < 0.001$) and also myeloid (253.4 ± 37.6 vs. 7.8 ± 1.5, $P < 0.001$), lymphoid (97.4 ± 6.5 vs. 19.8 ± 1.6, $P < 0.001$) and erythroid cells (165.0 ± 9.1 vs. 8.8 ± 2.8, $P < 0.001$) per mm^2 in irradiated mice (Table I, Figure 1). Accordingly, histamine elicited a moderate conservation of the medullar progenies preserving several myeloid precursor foci and few erythropoietic groups and diminished the haemorrhagic replacement of hematopoietic tissue compared to untreated and irradiated rat group. In addition, histamine augmented the number of lymphoid and erythroid cells in non-irradiated rat bone marrow (Table II, Figure 2).

Effect of histamine on cell proliferation of irradiated bone marrow

In order to determine whether histamine radioprotective effect was associated with an increase in bone marrow cell proliferation, we evaluated in bone marrow cells the expression of PCNA, a well known indicator of active proliferation (Kelman 1997) and the BrdU incorporation, a thymidine analog. Bone marrow cells from untreated mice exhibited high PCNA expression and BrdU incorporation especially

Table I. Histopathological characteristics of mouse bone marrow.

Group	Trophism	Myeloid cells per mm^{2a}	Lymphoid cells per mm^{2a}	Megakaryocytes per mm^{2a}	Erythroid cells per mm^{2a}	Stromal characteristics
Untreated[b]	Normal	379.4 ± 7.8	97.4 ± 19.4	20.3 ± 2.3	144.2 ± 1.3	Without alterations
Histamine[c]	Normal	350.8 ± 13.0	93.5 ± 5.1	17.7 ± 1.6	152.0 ± 11.7	Without alterations
Untreated-10 Gy[d]	Grade III Aplasia	7.8 ± 1.5^{f}	19.8 ± 1.6^{f}	7.3 ± 1.0^{f}	8.8 ± 2.8^{f}	Congestive vessels, massive hemorrhage
Histamine-10 Gy[e]	Grade I Aplasia	$253.4 \pm 37.6^{g,h}$	97.4 ± 6.5^{h}	$14.0 \pm 1.0^{g,h}$	165.0 ± 9.1^{h}	Minor congestion, slight oedema

[a]Mean value of the experimental group calculated from the average number of cells per squared millimeter (mm^2) of bone marrow. Errors indicate the standard error of the mean for $n = 3$ independent experiments.
[b]Representative of bone marrows from at least eight saline-treated animals.
[c]Representative of bone marrows from at least eight 0.1 mg/kg.day histamine-treated animals.
[d]Representative of bone marrows from at least eight saline-treated and irradiated animals.
[e]Representative of bone marrows from at least eight histamine-treated and irradiated animals.
[g]$P < 0.01$, [f]$P < 0.001$ vs. untreated group, [h]$P < 0.001$ vs. untreated-10 Gy group (ANOVA and Tukey's Multiple Comparison Test).

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in undifferentiated, immature myeloid cells; and no significant difference was observed after histamine treatment in non-irradiated mice. Complete loss of PCNA expression and a clear decrease in BrdU-positive cells was observed after irradiation, indicating the absence of proliferation. Conversely, histamine treatment notably increased the level of expression of PCNA and the BrdU incorporation in irradiated-mice (Figure 3A). Similar results were observed in rats in which PCNA expression and BrdU immunoreactivity were demonstrated in immature bone marrow cells that were not modified by histamine treatment. In irradiated rats, PCNA and BrdU detection was notably reduced and histamine administration enhanced the immunoreactivity of both proliferation markers (Figure 3B).

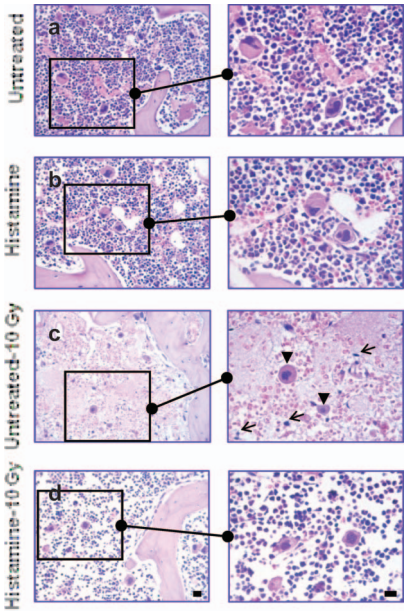

Figure 1. Effect of histamine and ionising radiation on mouse bone marrow histopathology. (a) Microphotography of bone marrow from untreated mice showing presence of medullar populations in an accurate proportion. (b) Bone marrow from histamine-treated mice displaying the same characteristics as untreated group. (c) Bone marrow from untreated and 10 Gy irradiated mice exhibiting total deprivation of all progenies that were replaced by vascular congestion and interstitial haemorrhage. Only a few megakaryocytes (◀) and isolated lymphoid cells (←) are observed. (d) Bone marrow from 10 Gy irradiated and histamine-treated mice showing marked conservation of the medullar progenies, slight interstitial oedema and scarce vascular congestion. Haematoxylin-eosin staining. Pictures were taken at 400× and 800× magnification. Scale bar = 20 μm.

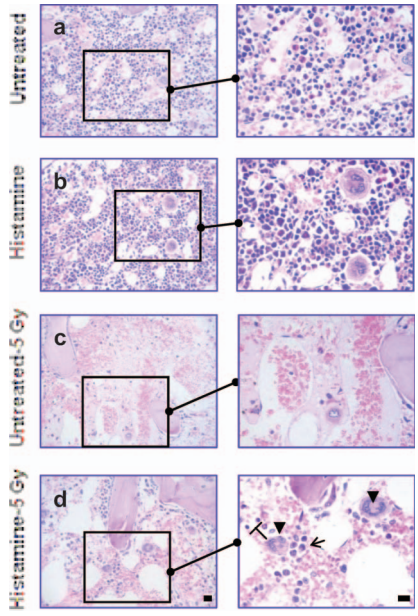

Figure 2. Effect of histamine and ionising radiation on rat bone marrow histopathology. (a) Normal appearance of rat bone marrow with normal number of all medullar progenies. (b) Normal appearance of histamine treated rat bone marrow with conservation of all progenies and a slight increase in the number of megakaryocytes. (c) Grade III bone marrow aplasia in an irradiated rat, absence of almost all the medullar elements. (d) Grade II bone marrow aplasia in an irradiated and histamine treated rat, in spite of the cellular impoverishment, the presence of several immature myeloid cells (←), almost normal number of megakaryocytes (◀) and few erythroid precursors foci (⊢) are observed. Haematoxylin-eosin staining. Pictures were taken at 400× and 800× magnification. Scale bar = 20 μm.

Table II. Histopathological characteristics of rat bone marrow. See key for groups in Table I footnotes.

Group	Trophism	Myeloid cells per mm^{2a}	Lymphoid cells per mm^{2a}	Megakaryocytes per mm^{2a}	Erythroid cells per mm^{2a}	Stromal characteristics
Untreated[b]	Normal	322.2 ± 18.2	93.5 ± 10.3	10.4 ± 0.8	198.8 ± 6.5	Without alterations
Histamine[c]	Normal	318.4 ± 11.6	126.0 ± 9.1[g]	15.6 ± 1.0	279.4 ± 6.5[g]	Without alterations
Untreated-5 Gy[d]	Grade III Aplasia	31.8 ± 3.1[f]	11.7 ± 2.5[f]	4.1 ± 1.0[f]	15.6 ± 3.5[f]	Congestive vessels, massive hemorrhage
Histamine-5 Gy[e]	Grade II Aplasia	52.0 ± 3.7[f,h]	23.4 ± 0.9[f,h]	9.9 ± 1.3[h]	27.3 ± 2.3[f,h]	Moderate congestion, slight edema

[a]Mean value of the experimental group calculated from the average number of cells per squared millimeter (mm^2) of bone marrow. Errors indicate the standard error of the mean for $n = 3$ independent experiments.
[g]$P < 0.01$, [f]$P < 0.001$ vs. untreated group, [h]$P < 0.01$ vs. untreated-5 Gy group (ANOVA and Tukey's Multiple Comparison Test).

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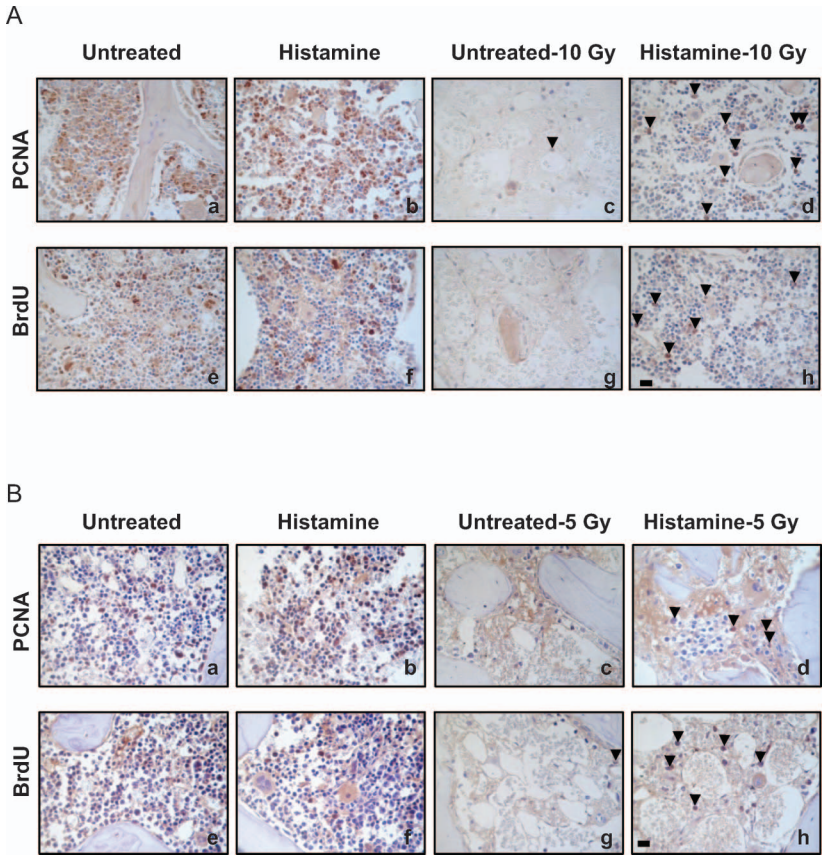

Figure 3. Effect of histamine and ionising radiation on bone marrow cell proliferation. (A) Representative bone marrow sections from untreated (a,e), histamine-treated (b,f), untreated and 10 Gy irradiated (c,g) and 10 Gy irradiated and histamine-treated mice (d,h). (B) Representative bone marrow sections from untreated (a,e), histamine-treated (b,f), untreated and 5 Gy irradiated (c,g) and 5 Gy irradiated and histamine-treated rats (d,h). a,b,c,d illustrate PCNA immunoreactivity; e,f,g,h show BrdU immunoreactivity. Pictures were taken at 630× magnification. Scale bar = 20 μm. Arrows (◀) indicate specifically stained cells in irradiated bone marrow.

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Effect of histamine on histidine decarboxylase and intracellular histamine immunoreactivity of irradiated bone marrow cells

We further determined the effect of histamine and ionising radiation on HDC and intracellular histamine immunoreactivity. Results show that blast cells and myeloid lineage precursors expressed HDC, histamine synthesising enzyme, and present intracellular histamine in mouse bone marrow. In addition, histamine treatment increases the expression of HDC in irradiated bone marrow cells especially in megakaryocytes and immature bone marrow precursors (Figure 4A). Low expression of HDC and histamine content is observed in untreated and treated non-irradiated rat bone marrows. In irradiated rats, a comparatively higher expression of HDC and intracellular histamine was observed in histamine treated animals (Figure 4B).

Discussion

Radiation therapy is a well recognised treatment modality for cancer. Although effective, adverse effects due to radiotherapy are unavoidable, even with localised delivery techniques (Betzen and Overgaard 1997; Steel 1997; Grdina et al. 2002; Barcellos-Hoff et al. 2005; Hall and Giaccia 2006a). Cell death after irradiation occurs mostly at cells attempt to divide. Therefore, the acute effects of irradiation result from the death of a large number of cells in tissues with a rapid rate of turnover. These include effects in the epidermal layer or skin, gastrointestinal epithelium, and hematopoietic system, in which the response is determined by a hierarchical cell lineage, composed of stem cells and their differentiating offspring (Betzen and Overgaard 1997; Hall and Giaccia 2006a.) During radiotherapy for intra-abdominal and pelvic cancers, radiation, seriously affect radiosensitive tissues such as small intestine and bone marrow (Emami et al. 1991; Hall and Giaccia 2006a). In the past 50 years a variety of chemical agents were investigated for their radioprotective capability; however, no appropriate drug has yet been introduced for routine clinical use in the treatment of cancer due to their systemic toxicity (Mozdarani 2003; Hall and Giaccia 2006b; Dziegielewski et al. 2008).

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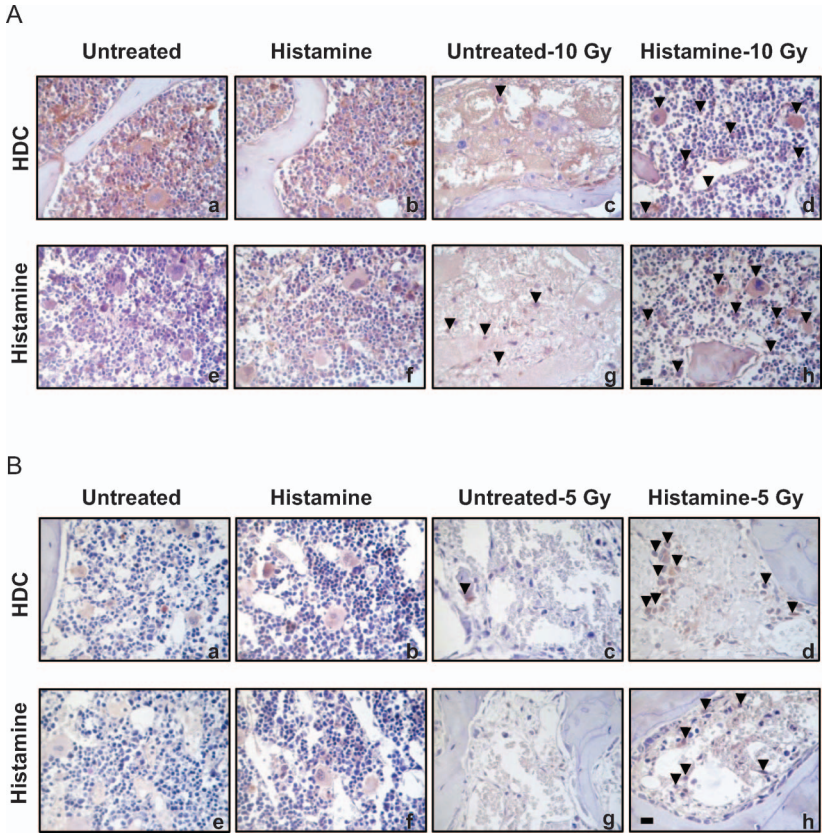

Figure 4. Effect of histamine and ionising radiation on HDC and intracellular histamine immunoreactivity. (A) Representative bone marrow sections from untreated (a,e), histamine-treated (b,f), untreated and 10 Gy irradiated (c,g) and 10 Gy irradiated and histamine-treated mice (d,h). (B) Representative bone marrow sections from untreated (a,e), histamine-treated (b,f), untreated and 5 Gy irradiated (c,g) and 5 Gy irradiated and histamine-treated rats (d,h). a,b,c,d show HDC immunoreactivity; e,f,g,h display histamine immunoreactivity. Pictures were taken at 630× magnification. Scale bar = 20 μm. Arrows (◀) indicate specifically stained cells in irradiated bone marrow.

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In the present study, we evaluated the capability of histamine to prevent ionising radiation-induced toxicity on mouse and rat bone marrow. Results demonstrated that histamine significantly reduced the grade of aplasia exerted by ionising radiation on bone marrow in mouse and rat species. Histamine administration ameliorated the oedema and vascular damage produced by ionising radiation while it elicited a significant conservation of the medullar progenies. Histamine radioprotective effect was demonstrated in two different rodent species suggesting that histamine could exert a radioprotective action in other mammals. In addition, we have previously described that histamine also protects small intestine against ionising radiation toxicity reducing mucosal atrophy, oedema, vascular damage and preserving villi, and crypts (Medina et al. 2007). Moreover, it was reported that a faster bone marrow repopulation was observed in wild type in comparison with HDC −/− knockout mice (completely depleted of endogenous histamine) and that intracellular HDC and histamine content in regenerating bone marrow populations in HDC+/+ mice increased after total-body irradiation (Horvath et al. 2006). In agreement, we have demonstrated that histamine treatment enhanced HDC expression in irradiated bone marrow cells. Additionally, it was described that histamine H1 and H2 receptor expression increased while histamine H4 receptor expression was down-regulated during restoration (Horvath et al. 2006) supporting the regulatory role of histamine in bone marrow regeneration. Moreover, preliminary results showed that histamine radioprotective effect is preferentially prevented by treatment with Famotidine, an H2 receptor antagonist (data not shown). In this line, we also demonstrated that histamine prevents morphological and functional radiation-induced damage on submandibular glands (submitted manuscript).

The present results indicate that the radioprotection exerted by histamine on bone marrow cells is mediated at least in part by an increase in the rate of proliferation as evidenced by the enhanced PCNA protein expression and BrdU incorporation. In agreement with this, we have recently reported that histamine prevents radiation-induced toxicity in small intestine by increasing proliferation of

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damaged intestinal mucosa and also suppressing apoptosis (Medina et al. 2007). In this line, other authors supported the role of histamine as stimulator of hematopoietic precursor cell proliferation (Endo et al. 1995; Pós et al. 2004; Schneider and Dy 2004).

We hypothesised that the different bone marrow tolerance observed in the two rodent species could be related to the diverse histamine tissue content, being higher in mice. Coincidently, the radioprotective effect of histamine was also higher in mouse than in rat bone marrow. These results suggest that histamine can also be acting as a free-radical scavenger. In this line, it was previously described that the H2 receptor antagonist cimetidine is a very powerful hydroxyl radical scavenger and that the methylated imidazole with a sulphur and amino group containing side chain is the part of the molecule responsible for this activity (Ching et al. 1993). Furthermore, it was reported that imidazole is a radioprotective agent (Prasad 1995) and also other biogenic amines as polyamines, have antioxidant properties (Weiss and Landauer 2000).

Our findings suggest that histamine might increase the therapeutic index of radiation offering a good protection against radiation damage. Histamine dihydrochloride (developed as a subcutaneous formulation) is being safely used in clinical trials as an adjuvant for the potential treatment of different cancers, exhibiting no unexpected or irreversible side-effects (Mitchell 2003; Agarwala et al. 2004; Galmarini 2004; Romero et al. 2009). Additionally, no local or systemic side-effects were observed upon histamine administration in mice or rats. These features make histamine a suitable candidate for use as chemical radioprotector, especially for patients undergoing radiotherapy who are at risk of bone marrow or small intestine damage. In addition, histamine as a radioprotector could be used not only by radiotherapy patients but also by radiation workers, or personnel at risk of nuclear accidents or threats.

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Declaration of interest: The authors have no conflicts of interest. They alone are responsible for the content and writing of the paper.

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