A Comparative Evaluation of Brain Metabolites following Whole Body and Cranial Irradiation: A Prospective 1H MRS Study

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Introduction: Radiation incidents have the potential to inflict serious biological and ecological damage. Moderate dose radiation exposure (1-10Gy) occurs due to radiation accident or during course of radiation therapy (1). Local irradiation of a specific tissue produces a localised lesion whereas total body irradiation produces a more generalised syndrome. In the last few years, it has become clear that the biological responses after single large dose of radiation to brain differ from those seen after fractionated brain irradiation. It means brain respond differently with the type of exposure of radiation given. We hypothesise that response of brain during whole body irradiation would be different from that of cranial (whole brain) irradiation. Moreover, information on early effects of whole body irradiation and cranial radiation on brain metabolism is still limiting. In the present study, we have made use of in vivo proton MRS to identify early or immediate effect of radiation during whole body irradiation and cranial irradiation on brain and to further look for differential response if any.

Aim of the study: To explore early metabolic alterations in brain in mice after exposure to either cranial or whole body irradiation using 1H MR spectroscopy.

Materials and Methods: A total of 30 strain 'A' male mice (8 to 10 weeks old) were taken and acclimatized for 48 hours in polypropylene cages under standard temperature, humidity conditions prior to group allocation and treatment. Out of three different groups (n = 10 in each group), two groups received a total dose of 8gy as whole body and whole brain respectively through Tele ^{60}Co irradiation facility (Bhabhatron II) with source operating at 2.496 Gy/min. Last group served as sham irradiated controls. The MRS experiments were carried out at day 1, 3, 5 and 10 post irradiation. All animal handling and experimental protocols were performed in strict accordance by institutional animal ethical committee. All MRS experiments were performed on anaesthetised animals (i.p., xylazine (10mg/kg BW) and ketamine (80mg/kg BW)) at 7T on a Bruker Biospec system. The MRS voxel was localised in the cortex-hippocampus region of mouse brain (1.5 x 3.5 x 3.0 mm^3; 15.75µl). After local field homogeneity optimisation (FASTMAP) and water suppression (VAPOR), MR spectra were acquired using PRESS (Point Resolved Spectroscopy) sequence with TR of 2500 msec and TE of 20 msec and 512 averages. Total acquisition time of 21.33 min. was used for acquisition of MR spectra. MRS raw data (FID) was processed using LC model for quantitation. The data for each metabolite was tested for homogeneity of variances and one way ANOVA was used to compare means.

Result and Discussion: Single voxel MR spectra were acquired from hippocampal region of mice brain. Spectral analysis was done using LC Model (Figure 2). The detectable metabolites were normalised with total creatinine. Normalised metabolite ratios revealed significant differences in myo-inositol (mI) and tauirne (tau) levels in case of whole body irradiation as compared to controls (Figure 3). Whereas, no significant differences were observed in cranial irradiation group compared to controls. In the study reported here, significant changes in level of mI and taurine metabolites were observed from day 3 onwards post irradiation in whole body irradiated mice and persisted till day 10 post irradiation. Myo-inositol, tau and other organic osmolytes present in brain together are proposed as a part of the volume regulation process (2-3). Changes observed in hippocampal area in whole body irradiated group could be a result of dysregulation of osmotic control in astrocytes or other glial cells due to radiation induced oxidative stress.

The results were startling as no changes were observed in case of cranial radiation, though it might have also elicited free radical induced oxidative stress as in case of whole body irradiation but in our study no changes in the brain physiology or brain metabolism were observed. The differential response during both the types of exposure could be explained because of involvement of systemic inflammatory response of central nervous system in case of whole body irradiation only. There are few reports which have shown radiation induced prominent induction of cytokine, local neuroimmune and inflammatory reactions during whole body radiation exposure (4). Furthermore, it could be the extent of damage during 8 Gy of whole body radiation exposure; as in mice 8 Gy is close to lethal dose. Secondly, it is well known that radiation generates free radical induced oxidative stress. During whole body irradiation, brain and body immune system as well as anti oxidant system is compromised that may result in persistency of oxidative stress in brain. In case of localised irradiation (as in case of cranial irradiation in our study), radiation induced cellular response is limited to brain; giving an opportunity to antioxidant system of body to cope up with oxidative stress in localised damaged tissue.

Conclusion: The study reflected alteration in brain metabolism only after whole body radiation exposure. The differential response might be because of large extent of damage and compromised anti oxidant system in case of whole body irradiation compared to cranial irradiation.

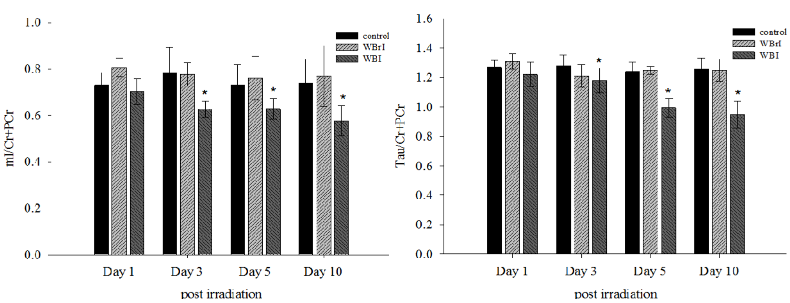

Figure 2: Temporal levels of mI/Cr+PCr and tau/Cr+PCr ratios in irradiated group compared to controls.

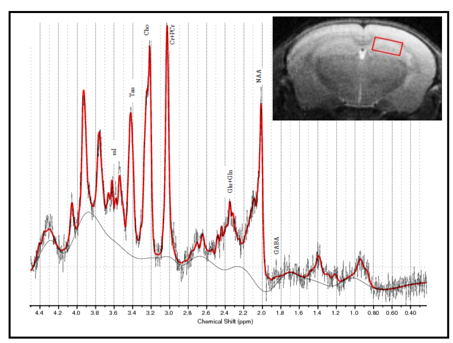

Figure 1: Representative LC Model processed ^{1}H MR spectrum from hippocampus region of mice brain

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