RADIOBIOLOGICAL SIGNIFICANCE OF ^{125}I MICRODOSIMETRY

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Abstract

Significant difference in the microscopic dose distribution due to ^{125}I and ^{131}I in the thyroid gland is reported. Its radiobiological significance is studied using varying doses of these two radionuclides in one month old rats. The total body weight increase, thyroidal retentivity of radioiodine, 24 hour uptake and the thyroid weight at the end of the treatment are measured in both the treated and control groups. Thyroid weight is taken as an index of thyroid cell population and any reduction in its increase with age compared to that in controls(which is taken as 100% cell survival)is considered as due to the impairement of proliferative capacity of the thyroid cells. Average gland doses due to ^{125}I and ^{131}I for 50% cell survival are 40500 and 18500 rad respectively. The 24 hour uptake is significantly reduced in 71 uCi ^{131}I treated rats whereas in all other treated ones there is no change compared to controls. Body weight increase is impaired in both the treatments, more so with ^{125}I. These differences are explained in terms of differences in dose distributions across a thyroid follicle due to ^{125}I and ^{131}I.

Introduction

For the same activity administered the mean dose to the thyroid gland is 2-3 times less with ^{125}I compared to ^{131}I. Microscopic dose distribution across a thyroid follicle, which is a basic unit of the thyroid gland, shows that with ^{125}I the dose at the colloid-cell interphase is 2-6 times and 4-10 times that over the nuclus and that at the basal membrane respectively depending upon the colloid content in the gland whereas with ^{131}I it is practically uniform[1-3].

The radiobiological significance of this difference in microscopic dose distribution was studied in the adult rat thyroid by different workers[4-6]. However, the normal adult rat thyroid has a closed, well differentiated cell system with little proliferation and upon irradiation(with about 500 rads of X-rays) shows little change as judged by weight, cell counts or DNA and RNA content[5]. So to see the effects of irradiation on thyroid cell population, particularly on its proliferative capacity, it is necessary to promote the cell multiplication artificially, say by administration of methyl thiouracil.

Instead, young rats of one month age were chosen for the present investigation. At this age their thyroid cells are rapidly proliferating[7] and the thyroid weight increases by a factor of 2-3 within a span of 2 months. So a study of the radiation effects is possible without the administration of a drug.

Materials and Methods

One month old Holtzman strain male rats were used for the study. They were fed with standard dry pellet Hindustan Liver rat food and tap water ad libitum. 5 rats were taken for each dosage. One of the following doses in a volume of 0.2 ml was injected intraperitoneally to each group:100, 50, 25,12.5 and 2.5 uCi of $Na^{125}I$; 71, 24.2 and 4.8 uCi of $Na^{131}I$. Two groups of 5 rats each served as respective controls for the two radionuclides. The total body weight and thyroid retention of radioiodine(by in vivo counting with an end window

G.M. Counter over the thyroid) were measured periodically.

When the rats attain 3 months age they were injected intraperitoneally a tracer dose of ^{125}I for measuring the thyroid uptake at the end of the treatment. 24 hours after administration of the tracer the rats were sacrificed. The two lobes of the thyroid from each rat were taken out and weighed correct to 0.2 mg. The thyroidal activity was obtained using a Nuclear Chicago Autogamma well counter and was expressed as the percentage of the injected activity per unit thyroid weight.

Results and Discussion

Variation of Thyroid Weight and Radioiodine Uptake with Age:

Fig.1 shows the variation of thyroid weight and 24 hour radioiodine uptake as a function of age. The mean thyroid weight of 30 d old rats is 6.8 ± 2.3 mg for a mean body weight of 45.2 ± 7.3 g while that of 100 d old ones is 24.2 ± 2.6mg for a mean body weight of 210 ± 18.1 g corresponding to an increase in the thyroid weight by a factor of 3.5. However, the variation in thyroid weight expressed as a fraction of body weight is only from 0.154 ± 0.006 at 30 d to 0.115 ± 0.006 at 100 d. The 24 hour thyroid radioiodine uptake expressed as a percentage of the injected dose per unit thyroid weight in mg varies from 0.059 ± 0.0049 to 0.016 ± 0.0049 with the age of the rat. Higher uptake per unit thyroid weight in the one month old rats indicates the hyperactivity of their thyroids.

Biological Half-life of Radioiodine in Thyroid:

The in vivo thyroid activity is monitored periodically for all the animals and Fig.2 gives the retention pattern in arbitrary units as a function of time. In case of ^{125}I, the retention could be expressed as a single exponential with a half-life of 10-13 d, irrespective of the dose administered. So only the data corresponding to 100 uCi group is presented in Fig.2. The pattern of retention of ^{131}I was more complex, consisting of at least two components. The size and half-life of the two components depended on the dose administered. The half-life of the fast component increased and that of the slow component decreased with the decrease of dose.

Estimation of Average Gland Dose:

The average gland dose, D, is estimated for each treated rat from the knowledge of its 24 hour uptake, U, the thyroid weight, m, in g and the effective half-life, T, in h using the well known equation

$$D = 1.44\, AUT \sum_i \Delta_i \phi_i / m \quad \text{rad}$$

where A is the activity administered in uCi, Σ_i the summation sign, Δ_i, the equilibrium absorbed dose constant in g-rad/uCi-h, and ϕ_i, the absorbed fraction in the thyroid gland for i th component. The value of $\Sigma \Delta_i \phi_i$ is calculated to be 0.0506 for ^{125}I using the values of Δ_i and ϕ_i listed in MIRD pamphlets[9-11] and includes both penetrating and non-penetrating components. For ^{131}I the contribution due to photons is neglected. Considering the thyroid as a sphere the absorbed fraction for ^{131}I beta radiation is obtained using Berger's tabulation of ϕ for different sphere sizes. The value of ϕ is about 0.8 for the rat thyroid[10].

The mean gland dose corresponding to 100 uCi ^{125}I treated group is 34322 ± 9560 rad. The value for 71 uCi ^{131}I treated group is 21820 ± 4034 rad.

Body Weight vs. Days after Administration of Activity

Figs. 3 and 4 give the ratio, Y, of the body weight on the day of observation to that on the day of the administration of activity, plotted against the time, X, elapsed from the day of administration of activity for the ^{125}I and ^{131}I treated groups respectively. The data in each case is statistically analysed and the respective regression equations, correlation coefficients, r, and the standard errors, S_{XY}, are given in the same figures.

The data shows that there is a reduction in the body weight ratio of the treated groups in comparison to the control groups and the reduction is more pronounced in the case of ^{125}I. The reduction in the body weight indicates that there is probably a disturbance in the release of the right amount and right type of iodinated compounds which affect body growth and that the disturbance is pronounced with ^{125}I.

24 hour Radioiodine Uptake at the end of Treatment:

The 24 hour uptake was obtained for all the treated and control groups by administration of a tracer dose of ^{125}I, just one day prior to sacrifice. The results are given in Table 1. The uptake value for all the treated groups (except that of 71 uCi ^{131}I) is the same as that of the corresponding control group(C). The lower uptake of 71 uCi ^{131}I group may be due to a damage of the iodine trapping mechanism and/or due to a decrease in the number of follicular cells per unit thyroid weight.

Table 1: Radioiodine Uptake at the end of ^{125}I and ^{131}I treatments

^{125}I treatment		^{131}I treatment	
Mean Gland Dose(rad)	24 hour uptake	Mean Gland Dose(rad)	24 hour uptake
34322(100uCi)	0.028 ± 0.0059	21800(71uCi)	0.020 ± 0.0094
24867(50uCi)	0.033 ± 0.0092	15793(24.2uCi)	0.044 ± 0.0099
12604(25uCi)	0.030 ± 0.0078	2500(4.8uCi)	0.044 ± 0.0047
6182(12.5uCi)	0.025 ± 0.0073	C	0.037 ± 0.0047
1299(2.5uCi)	0.032 ± 0.011		
C	0.029 ± 0.0065		

Percentage Cell Survival vs. Average Radiation Dose to the Thyroid:

In Fig.5 the percentage cell survival is plotted against the average gland dose for both ^{125}I and ^{131}I treated groups. The thyroid weight at the end of the treatment normalised to the then body weight is taken as an index of cell survival. The percentage cell survical is calculated by the following equation:

$$\% \text{ cell survival} = (m/M)_j \times 100/(m/M)_o$$

where $(m/M)_j = \sum_{i=1}^{n_j} (m_{ij}/M_{ij})/\ n_j$ and $(m/M)_o = \sum_{i=1}^{n_o} (m_{io}/M_{io})/n_o$.

Here m_{ij} and M_{ij} are the thyroid and body weights of the ith rat in jth treated group consisting of n_j number of rats. m_{io} and M_{io} are the thyroid and body weights of ith rat in the control group consisting of n_o rats.

The values of D_{50}(the gland dose for 50% cell survival) for ^{131}I and ^{125}I respectively are 18500 and 40500 rad. Their ratio, 0.46, suggeststhat RBE for ^{125}I compared to ^{131}I is less than one which is contrary to expectation. This may be explained in terms of the differences in microscopic dose distribution across a thyroid follicle due to ^{125}I and ^{131}I.

Using Berger's scaled absorbed dose distributions[12], the dose distribution across a thyroid follicle was computed assuming colloid mass as 50% of the gland mass. In each follicle it is considered to be in the form of a sphere of 25 um radius sorrounded by follicular cells of length 9 um with their nuclei 3 um away from the apical membrane. In Fig.6, the ratio of dose rate at any point R_s, to that at the center of the colloid, R_o, is plotted against the distance s. The values of R_s/R_o at the colloid cell interphase, over the nucleus and at the basal membrane are 0.49, around 0.25 and 0.14 respectively. The average gland dose corresponds to that at colloid-cell interphase as the colloid content is assumed as 50% of the total gland mass with all the thyroid iodine concentrated in it[2].

So in case of ^{125}I treatment, the nuclei of the follicular cells at 50% cell survival level received only about 20000 rad as against the gland dose of 40500 rad. For ^{131}I, however, dose distribution across the follicle is more or less uniform and so the gland dose (18500 rad for 50% cell survival)itself is the dose to the nucleus. Thus, if the dose to the nucleus is considered the 50% survival dose is same with both the nuclides.

The same microdosimetric considerations explain the differences found in 24 hour uptake at the end of ^{131}I and ^{125}I treatments and their respective controls. The percentage cell survival at which the significant reduction in 24 hour uptake was observed with ^{131}I is 44.3%. The corresponding gland doses with ^{131}I and ^{125}I are 21800 and 46500 rad respectively. The dose at the basal membrane(which is considered as the site for trapping of iodine) of the follicular cell of 9 um length is about one fourth that at the colloid-cell interphase, that is, about 12000 rad in case of ^{125}I. So the absence of reduction in 24 hour uptake in ^{125}I treated groups is due to the inhomogeneity in dose distribution resulting in only about 12000 rad at the site of trapping compared to the gland dose of 46500 rad. Since in case of ^{131}I treated group the gland dose(21800 rad) itself is the dose to the basal membrane also the reduction in 24 hour uptake observed can be expected.

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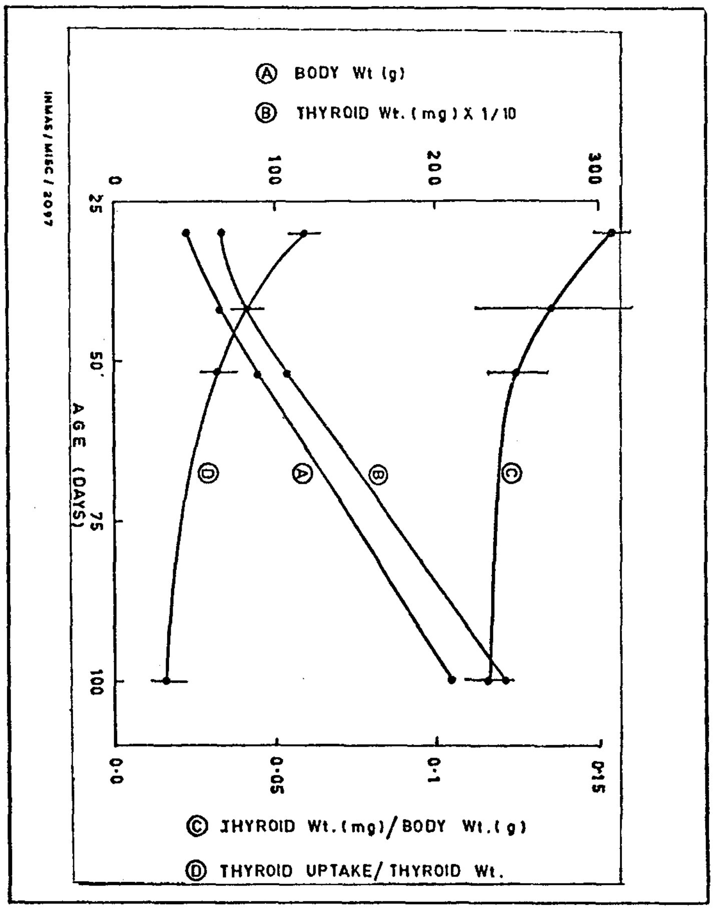

FIG. 1. Variation of body weight (A), thyroid weight (B), thyroid weight expressed as a fraction of the body (C), and 24 hour thyroid radioiodine uptake per unit thyroid weight (D) with age of rats.

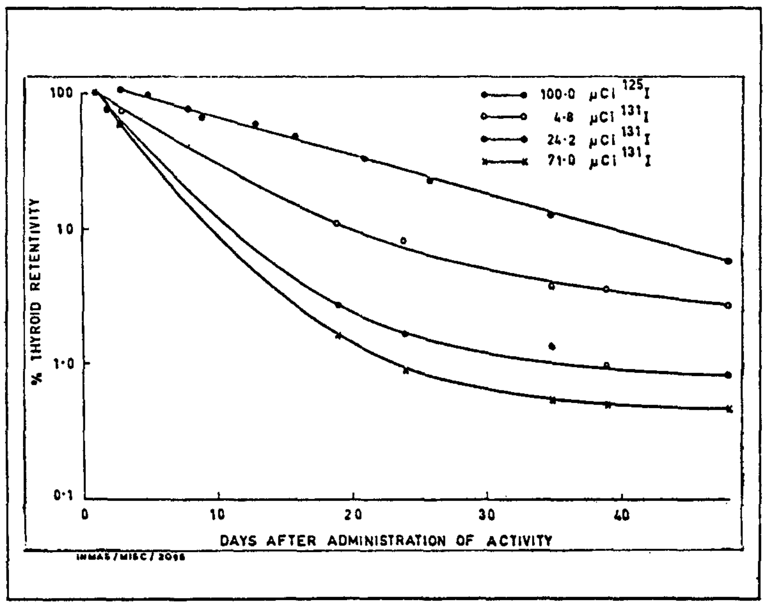

FIG. 2. Thyroid retentivity of radioiodine as a function of time in days after the administration of the activity.

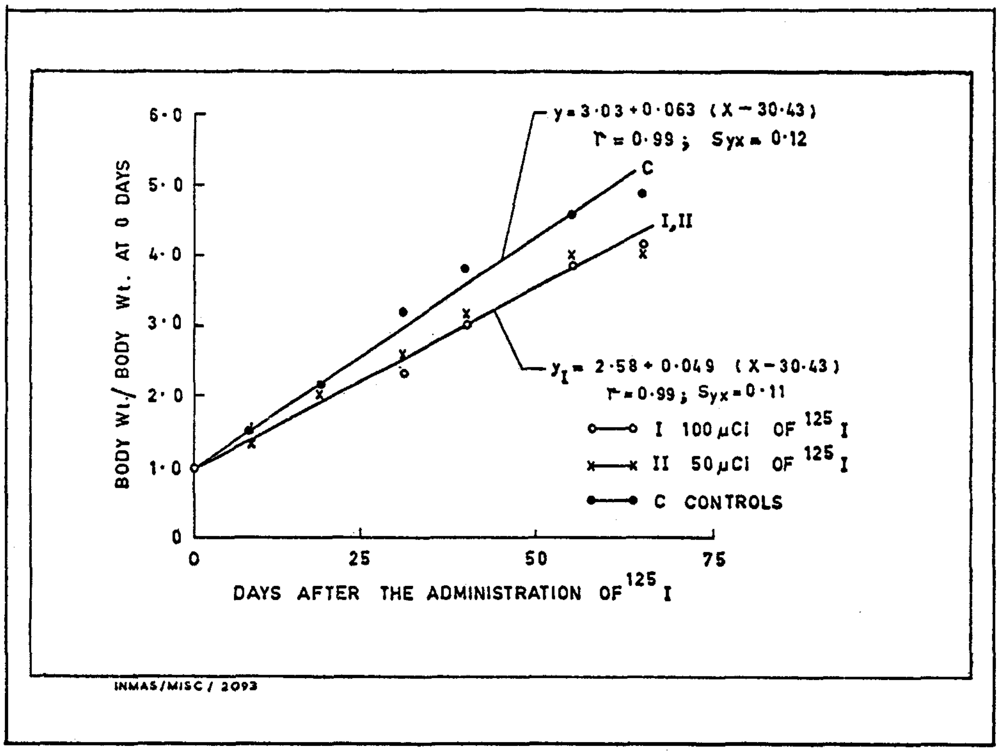

FIG. 3. Variation of the body weight ratio of ^{125}I treated groups and the respective controls as a function of time after the administration of the activity.

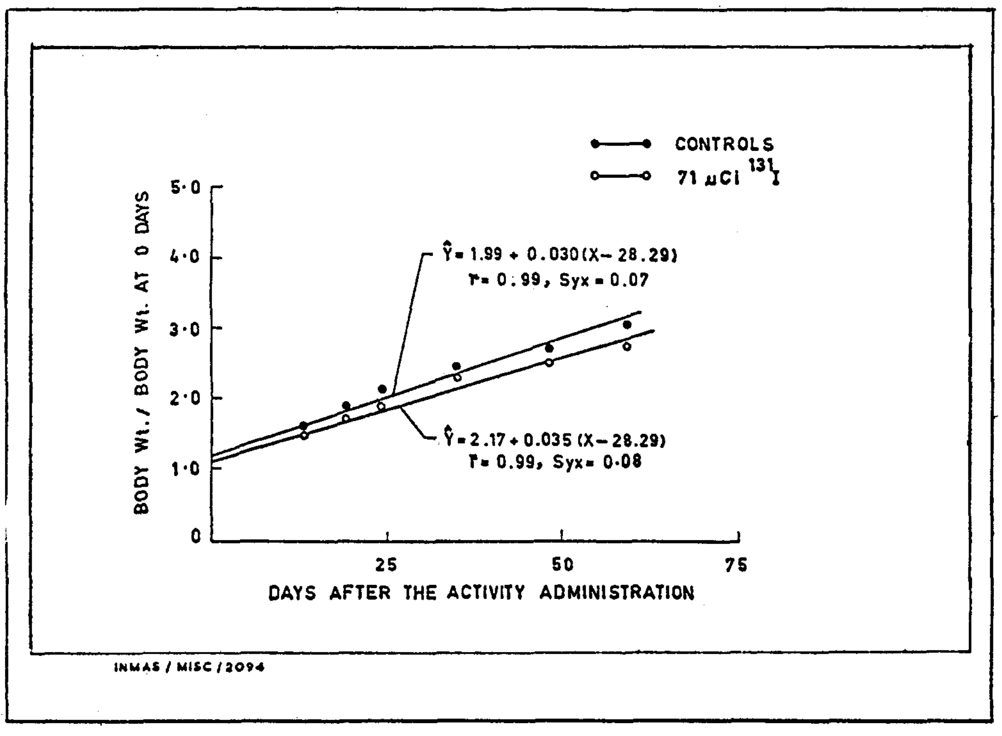

FIG. 4. Variation of the body weight ratio of ^{131}I treated groups and the respective controls as a function of time after the administration of the activity.

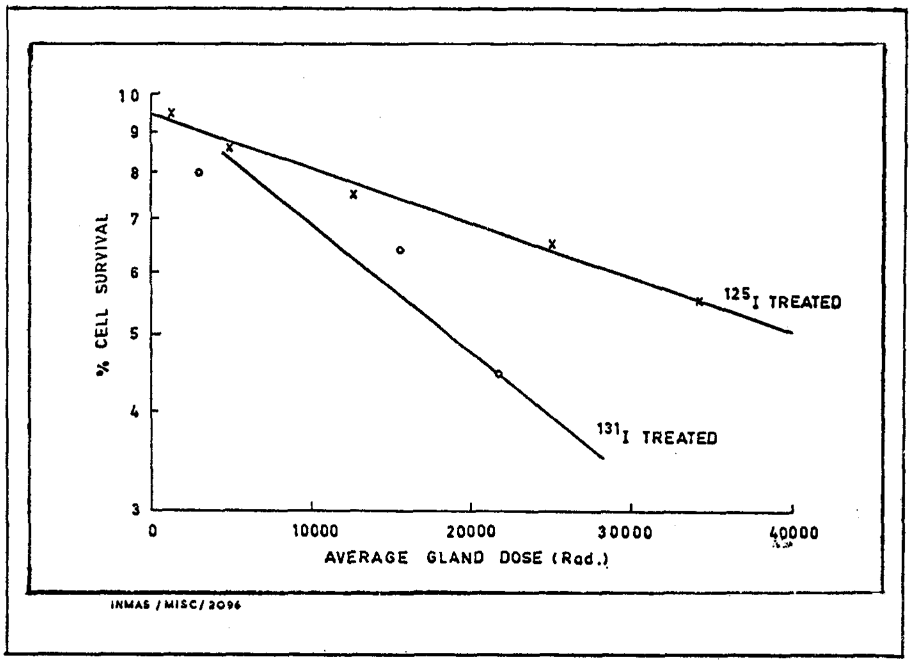

FIG. 5. Cell survival curves for ^{125}I and ^{131}I treated groups.

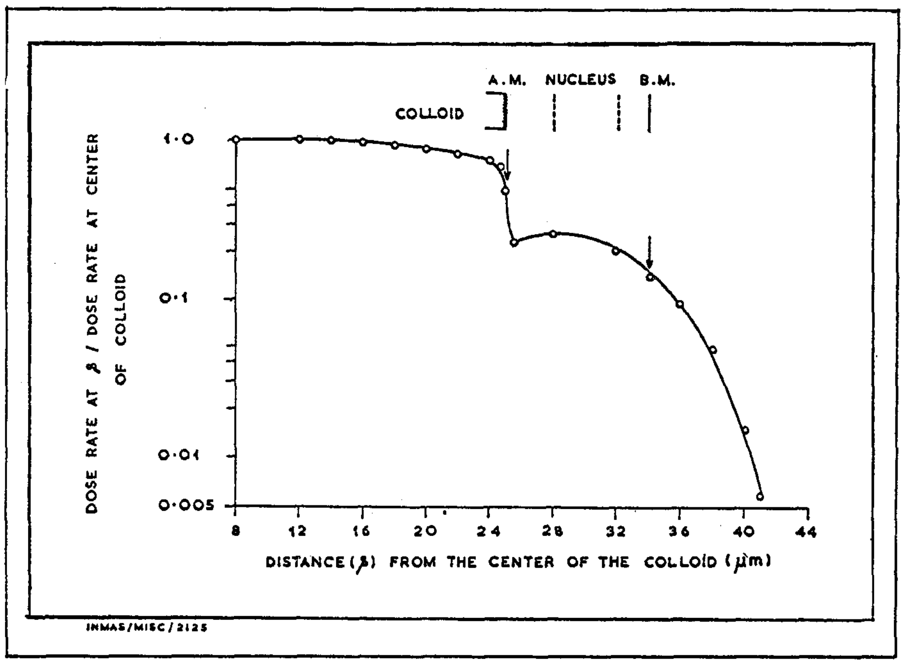

FIG. 6. Dose rate ratio, R_ρ/R_o, for ^{125}I as a function of distance from the center of the colloid. At distances below 8 μm the ratio is 1.0. The two arrows point to the positions of Apical Membrane (A.M.) and Basal Membrane (B.M.) of the follicular cell. Position of the nucleus is also shown.