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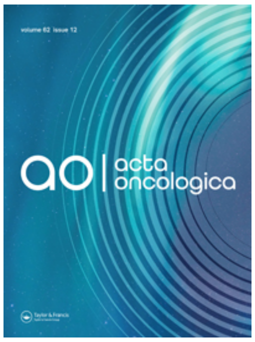

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K. J. Johanson

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FROM THE DEPARTMENT OF RADIATION BIOLOGY, THE GUSTAF WERNER INSTITUTE, UNIVERSITY OF UPPSALA, SWEDEN.

RETENTION OF ^{125}I GIVEN AS ^{125}I-5-IODO-2'-DEOXYURIDINE TO MICE AFTER 180 MeV PROTON OR ^{60}Co GAMMA IRRADIATION

by

K. J. JOHANSON

Iodine-labelled thymidine analogues, for example ^{125}I-5-iodo-2'-deoxyuridine (^{125}IUdR), are specific precursors for DNA and their only labelled catabolic products of significance appear as I^- (HUGHES et coll. 1964). To prevent accumulation of ^{125}I in the thyroid after the injection of ^{125}IUdR into mice, NaI may be introduced into the drinking water from the day before injection; most of the $^{125}I^-$ is then excreted in the urine (PRUSOFF et coll. 1960). This technique has been used in combination with whole body counting to investigate the effect of irradiation on ^{131}I retention in whole mice and in cotton rats after the administration of ^{131}IUdR (GITLIN et coll. 1962, O'FARRELL & DUNAWAY 1969). GITLIN et coll. reported a 50 to 60 per cent depressed retention of ^{131}I given as ^{131}IUdR even after 25 or 50 R 250 kV roentgen irradiation. The ^{125}I retention after ^{125}IUdR injection probably reflected quantitatively the ^{125}IUdR incorporation into DNA. JOHANSON & LARSSON (1972) stated that the ^{125}IUdR incorporation into DNA of the intestine and spleen of mice was much depressed after proton and

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gamma irradiation. The aim of the present investigation was to compare by whole body measurements the effects of 180 MeV proton and ^{60}Co gamma radiation on the incorporation and retention of ^{125}I given as ^{125}IUdR. It was also hoped to elucidate the possible use of such labelled DNA precursors that can be used for whole body scintigraphic investigations of cellular kinetics.

Materials and Methods

Animals. Female NMRI mice weighing 20 to 25 g were given water and food ad libitum; 0.1 % NaI was added to the drinking water from 24 hours before injection of ^{125}IUdR.

Irradiation. The mice were irradiated in plastic tubes. Gamma irradiation was administered 40 cm from a freely radiating ^{60}Co gamma source under conditions previously described (JOHANSON & LARSSON). The dose rate was 46 rad per minute as measured by Fricke dosimetry (SPINKS & WOODS 1964). Proton irradiation was given with the 180 MeV proton beam from the Uppsala synchrocyclotron as previously described (JOHANSON & LARSSON). The control mice were sham-irradiated under conditions similar to the gamma irradiation.

Administration of ^{125}IUdR. Two hours after irradiation the mice were given 0.08 μCi ^{125}IUdR (Radiochemical Centre, Amersham) per gram body weight intraperitoneally in isotonic saline at a specific activity of 100 μCi/μmol and then placed three in a cage (floor area 450 cm^2). The litter was changed near the middle of the period between injection and killing to decrease external contamination.

Radiometry and organ preparation. The ^{125}I activity of the whole mice was determined twenty hours after injection of ^{125}IUdR with a 3″ (7.6 cm) NaI(Tl) crystal with an 1.5″ (3.8 cm) well and 0.1 μCi ^{125}I in 'mice geometry' as a standard. The mice were killed by cervical dislocation within an hour of whole body counting and the small intestine and spleen prepared for ^{125}I activity determination. The retention of ^{125}I was calculated as a percentage of the dose injected and further expressed as a percentage of that of the control.

Results

The effect of irradiation of the ^{125}I retention is presented in Figs 1, 2 and 3. At low doses (40 rad, for spleen also 80 rad) the ^{60}Co gamma radiation seems to affect the ^{125}I retention with higher efficiency than the 180 MeV protons; this effect was observed in the organs examined (Figs 2, 3) as well as in the whole

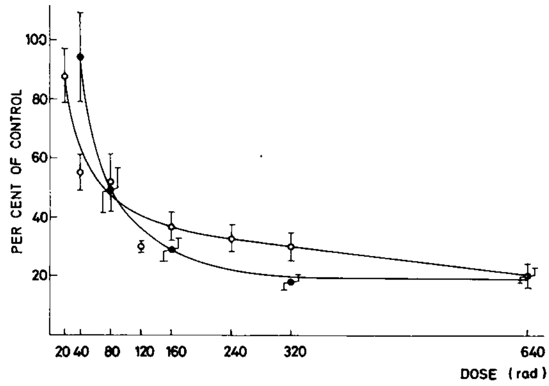

Fig. 1. Retained ^{125}I activity in irradiated mice, 20 hours after injection of ^{125}IUdR. ○ ^{60}Co gamma. ● Proton. Each point represents the average of 6 mice ± SE.

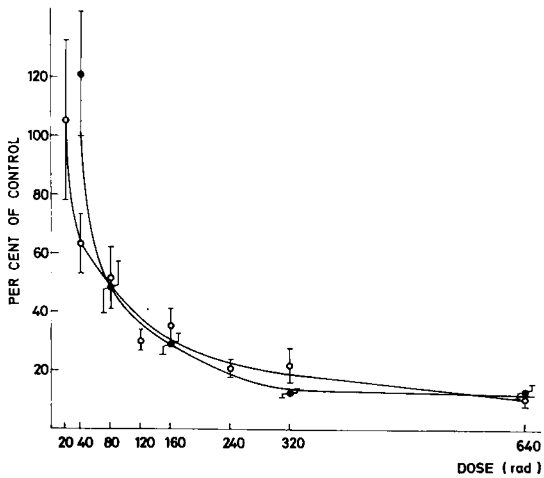

Fig. 2. Retained ^{125}I activity in the small intestine of irradiated mice, 20 hours after injection of ^{125}IUdR. ○ ^{60}Co gamma. ● Proton. Each point represents the average of 6 mice ± SE.

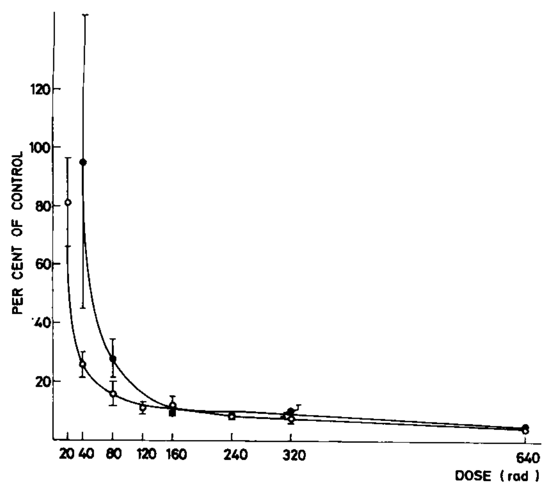

Fig. 3. Retained ^{125}I activity in the spleen of irradiated mice, 20 hours after injection of ^{125}IUdR. ○ ^{60}Co gamma. ● Proton. Each point represents the average of 6 mice ± SE.

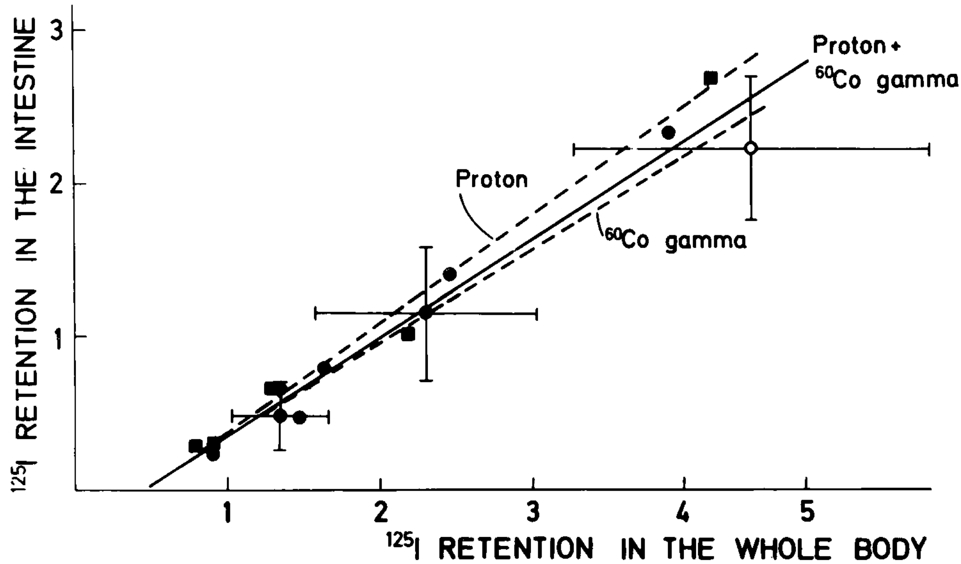

Fig. 4. Regression of ^{125}I activity retained in the small intestine as a function of the ^{125}I activity remaining in the whole body, 20 hours after injection of ^{125}IUdR. ○ Control. ■ Proton. ● ^{60}Co gamma.

body (Fig. 1). In the dose interval of 80 to 640 rad, ^{60}Co gamma and proton irradiation had similar effects on the ^{125}I retention in the small intestine, the small differences being within the experimental error. The same effects occurred in the spleen at doses between 160 and 640 rad; at 160 and 320 rad, however, the protons appeared to be more effective in affecting the ^{125}I retention in the whole body. The most marked decrease of ^{125}I retention occurred in the spleen after irradiation with 160 rad or more.

The ^{125}I retention in the whole body is compared to that in the small intestine and the spleen in Figs 4 and 5. The ^{125}I retention in the small intestine and spleen should be a better measure of the ^{125}IUdR incorporation into DNA than the ^{125}I retention in the whole body. Extrapolation in Fig. 4 gives about 0.4 per cent of the injected dose retained in the whole body when no ^{125}I remained in the small intestine.

Discussion

The ^{125}I retention proved to be 4.5 per cent in the unirradiated mice at 20 hours after the ^{125}IUdR injection. About 0.4 per cent of this amount was probably due to contamination of the skin as indicated in Fig. 4 as well as in the work

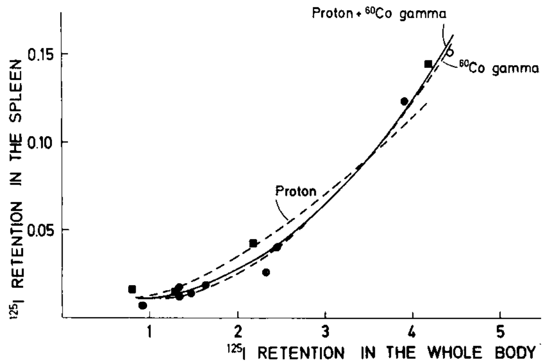

Fig. 5. Regression of ^{125}I activity retained in the spleen as a function of the ^{125}I activity remaining in the whole body, 20 hours after injection of ^{125}IUdR. ○ Control. ■ Proton. ● ^{60}Co gamma.

of HUGHES et coll. (1964). The remaining 4.1 per cent were probably mostly incorporated into DNA of proliferating tissues. In 6-week-old mice, 8.3 per cent of the injected ^{131}I, given as ^{131}IUdR, were retained at 20 hours after injection (HUGHES et coll.). Since these authors used younger mice than those of the present work a higher ^{131}I retention would be expected. The corresponding retention in cotton rats was 3 per cent at 2 days after injection (O'FARRELL & DUNAWAY).

Incorporation of ^{125}IUdR into DNA in proliferating tissues after irradiation has previously been investigated by the extraction and determination of the specific activity (JOHANSON & LARSSON). This method indicated that ^{125}IUdR incorporation into DNA of the small intestine was depressed to 22 per cent of the control 2 hours after proton irradiation at 200 rad and to 9 per cent after 400 rad. No significant differences were evident in the results obtained by autoradiographic and biochemical methods at the above doses at 24 hours after irradiation. Interpolation in Fig. 2 gives a ^{125}I retention in the small intestine of 23 per cent of the control after proton irradiation at 200 rad and about 13 per cent at 400 rad. It would appear that similar results may be obtained by evaluating the effects on the small intestine of irradiation with these three independent methods. A similar comparison of the results of the spleen experiments reveals more diverse results, probably due to the fact that a marked decrease in the DNA content of the spleen occurs after irradiation (cf. JOHANSON & LARSSON). This decrease reflects a similar decrease in the cell content.

The two types of radiation seem similarly to affect the ^{125}I retention in the dose range 80 to 640 rad (160 to 640 rad for the spleen). The RBE for 180 MeV protons of 1.2 ± 0.3 from previous work on the incorporation of ^{125}IUdR into intestinal DNA at two hours after irradiation (JOHANSON & LARSSON) appears to be in conformity with the present investigation.

The large differences at doses of 40 rad (and 80 rad for the spleen) are surprising. Figs 1, 2 and 3 indicate however, large standard deviations so that the individual variation was considerable. The possible effect of stress due to differences in the irradiation techniques cannot be excluded.

The findings have a bearing upon the problem on how to find suitable labelled precursors for diagnostic investigations of cellular proliferation in man. Only limited possibilities exist of labelling natural precursors of DNA with gamma or positron emitting nuclides. Although formate labelled with ^{11}C (positron emitter 0.97 MeV, half-life 20.5 min) can now be produced and labelling of thymidine with ^{11}C is under investigation (STENSTRÖM 1971), the low ^{11}C activities available and the short half-life become limiting factors. Labelled base analogues have to be used for external detection. Iododeoxyuridine seems to be the most useful; ^{131}IUdR and ^{125}IUdR, which are commercially available, and, for example, ^{123}IUdR or ^{132}IUdR may all be possible alternatives. ^{123}I has a half-life of 13.0 hours disintegrated by electron capture resulting in even gamma rays (0.159 MeV). ^{132}I is a beta emitter with a half-life of 2.3 hours; gamma rays of various energies are also emitted. The short half-life of ^{123}I will result in radiation exposure levels that cannot exceed a small percentage of those from ^{131}I in procedures completed during one day (MYERS 1963). ^{123}I can be produced by cyclotron from ^{123}Te or ^{123}Xe to give acceptable activities and rather pure ^{123}I (HUPF et coll. 1968, LEBOWITZ et coll. 1971). ^{132}I generators are commercially available. ^{123}IUdR or ^{132}IUdR may be a valuable tool in medical diagnosis for examining cellular proliferation in man. Thymidine is incorporated preferentially over IUdR by a factor 2 to 3 (FOX & PRUSOFF 1965, DETHLEFSEN 1970); on the other hand the reutilization of IUdR is less than that of thymidine.

SUMMARY

The effect of 180 MeV proton and ^{60}Co gamma radiation on ^{125}I retention 20 hours after ^{125}IUdR injection was investigated in the whole mouse, the small intestine and the spleen. The RBE for 180 MeV protons of 1.2 ± 0.3 from previous work seemed to be confirmed. Labelled precursors for diagnostic examinations of cellular proliferation in man are discussed.

ZUSAMMENFASSUNG

Die Wirkung von 180 MeV Protonen — und ^{60}Co Gamma-Strahlung auf die ^{125}I Retention 20 Stunden nach ^{125}IUdR Injektion wurde an der ganzen Maus, am Dünndarm und an der Milz untersucht. Der RBE-Wert für 180 MeV Protonen von $1{,}2 \pm 0{,}3$ von früheren Untersuchungen scheint bestätigt zu sein. Gezeichnete Vorstufen für diagnostische Untersuchungen der Zellproliferation beim Menschen werden diskutiert.

RÉSUMÉ

L'effet des protons de 180 MeV et de la radiation gamma du ^{60}Co sur la rétention de ^{125}I 20 heures après injection de ^{125}IUdR a été étudié sur la souris entière, l'intestin grêle et la rate. L'EBR pour les protons de 180 MeV évalué à $1{,}2 \pm 0{,}3$ dans un travail précédent paraît confirmée. L'auteur examine l'intérêt des précurseurs marqués pour les examens diagnostiques de la prolifération cellulaire chez l'homme.

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