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OF OXYGEN -15 AND CARBON -11 GENERATED IN RATS

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MASTER

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Abstract

The distribution of induced ^{15}O and ^{11}C activity in live and dead rats was determined following local irradiation with a 32 MeV proton beam. Results indicate that rapid biological redistribution of some of the induced activity occurs within a minute following irradiation. Sufficient activity remains, bound in the intracellular water, to define the proton beam in tissue. Thus, mapping of the induced ^{15}O activity proves to be a valid means of beam localization.

Introduction

An attractive characteristic of heavy charged particle therapy is the ability to confine the major fraction of the dose to a designated volume in tissue.⁽¹⁾ This ability is due to the well defined range of the particles, and the distinctive energy distribution along the beam path. The dose distribution of the heavy charged particle beam, referred to as a Bragg ionization curve, permits overlying tissue to receive a dose reduced by a factor of 2 to 5 compared to conventional techniques.^(1,2) By comparison, x-ray therapy beams attenuate exponentially with depth in tissue, resulting in maximum dose near the skin. Thus heavy charged particle therapy is effective in achieving desirable dose distribution. A predictable dose distribution is obtained for charged particles in a homogeneous medium, and in tissues where the density distribution is known. In tissue of different densities the beam will have a variable penetration. Bone, with a density range from 1.08 g for trabecular bone to 2.2 for dense bone,⁽³⁾ will terminate the beam at a shallower depth than will muscle. Fat or gas containing tissue, where the density range is approximately 0 to .9 will result in deeper beam penetration than in muscle, which has unit density. Without exact knowledge of the various tissue densities through which the beam penetrates the range of the beam is uncertain. Hence successful use of Bragg peak therapy requires an in vivo beam localization technique, or precise knowledge of tissue density distribution.

In vivo beam localization is made possible thru the detection of interactions between the charged particles and the tissue. One of the most practical interactions is the in vivo activation of positron emitting nuclides such as ^{11}C , ^{13}N , and especially ^{15}O . Induced positron activity, principally ^{11}C , has been used to localize a therapeutic alpha particle beam in phantoms and patients.⁽⁴⁾ The

depth distribution of positron emitters generated in vitro by a negative pion beam has been measured.⁽⁵⁾ The dose required to localize a therapeutic proton beam has been calculated to be approximately 20 rads, using on-line detection of induced ^{15}O .⁽⁶⁾ Preliminary experiments using proton activation in plastic indicate a reduced dose requirement, and confirm a spatial resolution of about 1 cm.⁽⁷⁾

Ninety per cent of the oxygen in the body is found in water. Body water is partitioned into two arbitrary compartments - intracellular (IC), and extracellular (EC) including vascular fluids. Intracellular water makes up 57% of the total body water in man, extracellular water 43%. A continuous exchange of fluid between these compartments takes place. It is expected that such a flow will cause a redistribution of beam induced radioactivity, and thus affect the spatial resolution of in-vivo beam localization.

This study evaluates the effect of biological transport of induced positron emitting nuclides on field definition by comparing induced ^{15}O radioactivity distribution in live and dead animals following localized proton irradiation.

Experimental Procedures

Animals

Six Dahl (albino) male rats - 3 dead and 3 live - weighing approximately 320 grams were used in this study. The rats were anesthetized with an intraperitoneal injection of Dibutal - 35 mg per Kg of body weight. The rats were mounted on a phenolic board 6 mm thick and positioned so that the right rear leg was over a 2.5 diameter hole.

Irradiation

The board was positioned so that the hole was located on the axis of a 32 MeV proton beam (approximate range in tissue 1 cm) from the BNL 60 inch Synchrocyclotron. The dose was measured with a helium filled ion chamber at

atmospheric pressure, with a 2 cm gap. The beam was collimated to 1 cm diameter upstream of the ion chamber. Each exposure was terminated after ~ 15 secs, when 300 n coulombs was collected from the ion chamber.

Determination of Induced Positron Activity

Following irradiation the rats were removed from the accelerator vault and taken to an adjacent room where the positron annihilation gamma radiation from the induced radioactivity of the exposed area was determined at regular intervals. This was done through the use of a positron detector consisting of two sodium iodide scintillators in coincidence (see figure 2).

The scintillation crystals were 2.5 cm in diameter, 2.5 and 5 cm long, and located approximately 12 cm above and below the irradiated field. Discriminators on each scintillation counter triggered an output pulse for each positron gamma ray detected. Prompt coincidences, signalling a positron, were recorded as well as delayed coincidences (which equal in rate the accidental coincidence events).

Experiment 1. Time distribution

A 1 cm in diameter area on the right rear leg of a live and dead rat was irradiated. Following exposure the induced radioactivity of the irradiated area was measured at known times over a period of 30 minutes and recorded.

Individual data points were corrected for accidental coincidence counts and the absolute value of the initial decay rate for ^{11}C ($T_{1/2} = 20.4$ min) and ^{15}O ($T_{1/2} = 2.07$ min) was determined by a least squares fit.

Experiment 2. Spatial Distribution

The right rear leg of 2 dead and 2 live rats was irradiated. After exposure

the distribution of induced activity was determined by measuring the count rate at ~ 2 mm intervals, as the irradiated area was moved across the detector axis. Activity over the thorax was also recorded at selected intervals.

The coincidence count at each position was corrected for radioactive decay by the formula:

$$\dot{N}(0) = \dot{N}(t) [e^{-t/\tau_o} + K e^{-t/\tau_c}]^{-1}$$

where: $\tau_o = 2.99$ = mean life time for ^{15}O

$\tau_c = 29.47$ = mean life time for ^{11}C

$K = 0.201$ initial ^{11}C activity/initial ^{15}O activity

were determined from analysis of experiment 1.

The values were then normalized by the average activity value at the peak (position zero), and the statistical error determined by the following equation:

$$\dot{N}(0,x) = \frac{1}{\sqrt{\frac{1}{\text{counts}(t,x)} + \frac{1}{\text{counts}(t,0)}}} \cdot \frac{\dot{N}(0,x)}{\dot{N}(0,0)}$$

The final data were graphed on semi-log paper and the widths of the distributions determined by graphical analysis.

Experiment 3. Source distribution

The radioactivity across a 1 cm diameter ^{22}Na test source was determined at 2 mm intervals. The resulting distribution was compared with those of the rats in experiment #2.

Results

Experiment #1

Mathematical analysis using a least squares fit determined that the decay curves (Fig 3) were comprised of two components, ^{15}O and ^{11}C . The parameters resulting from the fitting program were the same for the live and dead rat, except for a scale factor - the initial activity. The ratio of initial activities, live: dead, was $0.63 \pm .03$.

Experiment #2

The spatial distribution of the radioactivity across the irradiated fields in the case of the live and dead rats (Fig 4) were compared by determining the standard deviations, and the widths at one half, and one tenth of the maximum amplitude. A small difference between the live and dead rat was noted for each width measurement. Yet in spite of the small differences the spatial distribution of the radioactivity of the irradiated field for the live rat was almost exactly the same as for the dead rat. In order to verify the results the distribution curves for the live and dead rats were compared to that of the 1 cm ^{22}Na source and except for a small difference the radioactivity distribution curves were essentially the same. The following table shows the average full width at .5 and .1 maximum, and the standard deviation, for the live and dead rats. and for the ^{22}Na test source. The curves are gaussian, amplitude = $e^{-\frac{x^2}{2\sigma^2}}$.

	LIVE	DEAD	SOURCE	
FW.1M	2.60	2.77	2.68	cm
FW.5M	1.46	1.56	1.55	
2 σ	1.22	1.32	1.37	

Activity observations over the thorax yielded no counts in the dead rat, and in the case of the live animal approximately 2% of the maximum count rate of the irradiated leg.

Discussion

In considering Fig 3 the observation that the decay curves for the live rat and the dead rat are rather accurately superimposable indicates that the loss of radioactivity from the irradiated field during the observation period is that due to physical decay, and not due to biological transport. However the

37% difference in magnitude of the initial induced activity suggests that some biological redistribution had occurred. This was documented by finding a detectable amount of activity over the thorax.

Since this loss of radioactivity was not reflected in the decay curve it must be assumed that redistribution was essentially completed during the first minute following irradiation. (Determination of the radioactivity was not started until 1.5 minutes following irradiation, this time required to remove the animal from the vault and position it in the detector.)

The rapid biologic transport of the ^{15}O activated water from the irradiated field could represent clearing of these molecules from the extracellular and vascular compartments. The maximum inter-capillary distance is of the order of $100\mu\text{m}$, thus activated molecules are no more than approximately 50 microns from a blood capillary (Fig 6). Diffusion over this small distance could be complete within a minute following irradiation. The circulation time of blood from the leg to the heart is less than 10 seconds. The exchange of material between capillary and extracellular space is about 95% complete within one circulation time. Consequently, clearance of activated water from the EC compartment could be expected to be completed prior to the beginning of counting.

In order to confirm this explanation subsequent experiments must be performed that will begin scintillation counting on line immediately following irradiation.

The persistence of 63% of the radioactivity within the irradiated field demonstrates the presence of a compartment from which diffusion or transport time is long in comparison to the 30 minute observation period. Recent experiments performed by Ling and Walton⁽⁸⁾ suggest that water is bound by cytoplasmic proteins. The retained radioactivity apparently represents this bound intracellular water.

Conclusion

Despite the rapid biological redistribution of some induced ^{15}O during the first minute after irradiation, there is sufficient remaining activity to define the beam outline in tissue. Thus, on line detection of ^{15}O positron activity appears to be a practical means of in vivo beam localization.

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Figure 1 - Rat mounted for irradiation. Cyclotron beam pipe is at right edge of photograph.

Figure 2 - Rat mounted in positron detector. Scintillation counters are visible above and below styrofoam board.

Figure 3 - Decay curves for live and dead rats. The solid lines are from a least squares fit using oxygen -15 and carbon -11 components.

Figure 4 - Spatial distribution of activity in irradiated legs of live and dead rats. The top curve (live) represents a scan duration from 2.17 to 7.8 minutes after irradiation, the middle curve (live) from 2.5 to 6.5 minutes, the bottom curve (live) 6.5 to 10.2 minutes after irradiation.

Figure 5 - Spatial distribution of ^{22}Na source 1 cm diameter, ~ 5 mm thick.

FIG. 6 Schematic cross section of 3 mammalian muscle fiber bundles.