FLUORINE-18 PRODUCTION AT A 590 MeV SYNCHROCYCLOTRON: RADIOPHARMACEUTICAL SYNTHESIS AND BIODISTRIBUTION.

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SUMMARY

Production of useful Fluorine-18 quantities from the $^{18}O(p,n)^{18}F$ nuclear reaction is reported using a 590 MeV proton beam. The cross-section for this reaction is relatively low at these energies, and thus the fluorine yield is also low. In order to maximize the production yield, a target was constructed designed especially for the beam characteristics of the cyclotron. Despite the relative low cross-section at this high energy, fluorine saturation activities of about 9 Ci may be obtained. The chemical reactivity of the ^{18}F-solution recovered was investigated, and positron emission tomography (PET) was used to image the metabolic distribution of fluorine-18 in a rabbit skull.

INTRODUCTION

Positron Emission Tomography (PET) is a non-invasive technique to measure *in vivo* the uptake and metabolism of different molecules by organs in the human body [1]. Such molecules include both labelled drugs or pharmaceuticals and biological substrates such as glucose and fatty-acids which participate in human metabolism. The measurements obtained in this way directly reflect the functional and metabolic state of the organ, which may have important therapeutic consequences. The development of PET, together with an effective choice of physiological radiopharmaceuticals, has made possible the study of dynamic biochemical processes [2].

0022-1139/88/$3.50

One of the principal drawbacks to the clinical application of PET is the short half-lives of the most important physiological positron emitters: carbon-11 (^{11}C, 20 min), nitrogen-13 (^{13}N, 10 min), oxygen-15 (^{15}O, 2 min) and fluorine-18 (^{18}F, 110 min). The production of these radionuclides requires a cyclotron or a reactor, and due to their short half-lives, physiological positron emitters (with the exception of ^{18}F) must be produced in close proximity to the PET camera. Unfortunately, the University Hospital of Geneva does not possess such a cyclotron. The only commercial organization in Switzerland which is capable of providing positron emitting isotopes is situated at Villigen (Paul Scherrer Institute) [3], requiring a journey time of about four hours for the delivery of radiopharmaceuticals. It is, therefore, clear that even substances labelled with ^{18}F cannot easily be delivered to Geneva.

We have obtained beam time at the Synchrocyclotron of the European Organization For Nuclear Research (CERN) which is situated 30 min by car from the Geneva Hospital. A project has been established to provide sufficient amounts of ^{18}F for the synthesis of clinically-interesting radiopharmaceutical compounds.

We report here the development and construction of a water-target especially designed for the production of ^{18}F from a high energy proton beam (590 MeV), and we describe an animal experiment performed with a PET camera, using the fluorine-18.

THEORETICAL CONSIDERATIONS

Given the nature of the available beam at CERN (protons), only three nuclear reactions are potentially useful for the production of fluorine-18:

^{20}Ne (p, 2pn) ^{18}F	[4]
^{27}Al (p, 2α2n) ^{18}Ne --> ^{18}F	[5]
^{18}O (p, n) ^{18}F	[6]

For technical reasons the last reaction ^{18}O (p, n) ^{18}F was chosen as the must suitable.

The theoretical production of ^{18}F from such a nuclear reaction is given by the product of the cross section of the nucleus considered (σ), the number of irradiated atoms in the target (n) and the proton beam flux (ϕ), expressed by the equation:

$$A = \sigma \cdot n \cdot \phi \qquad (1)$$

where **A** is the ^{18}F saturation activity (Bequerel, Bq). The value of σ is characteristic of the nucleus and a function of the particle energy, and ϕ is a characteristic parameter of the cyclotron available.

An ideal procedure for the production of ^{18}F from the nuclear reaction $^{18}O(p, n)^{18}F$ can be summarized by the following parameters:

target material	$H_2{}^{18}O$ (with ^{18}O enrichment > 98%)
target length	max 10 mm (corresponding to 3 x 10^{22} atom ^{18}O / cm^2)
beam energy	protons of 10-15 MeV
beam current	25 μA (corresponding to 1.56 x 10^{14} protons/sec)
cross section	close to 140 mb (1 mb = 10^{-27} cm^2)

Substituting into equation (1) gives:

A = 6.5 x 10^{11} Bq (17 Ci) at saturation

In this experiment, ^{18}F-production is limited by the target length; the low energy of the protons gives them a short range in water, and thus limits the number of nuclei irradiated. An additional problem is the heat dissipation in such a small volume of water corresponding to an energy loss of 4.6 MeV/g/cm^2 resulting in 115 W/g/cm^2 in the above conditions.

For our experiment, the characteristics of the CERN synchrocyclotron are far from ideal for this type of nuclear reaction. The high energy of the proton beam (590 MeV), while resulting in a relatively low cross section, offers the possibility of considerably increasing the target length. The corresponding parameters can be summarized as follows:

target material	$H_2{}^{18}O$ (with ^{18}O enrichment > 98%)
target length	300 mm (corresponding to 9 x 10^{23} atom ^{18}O / cm^2)
beam energy	protons of 590 MeV
beam current	2.5 μA (corresponding to 1.56 x 10^{13} protons/sec)
cross section	close to 6.6 mb

Again, using equation (1):

$A = 9.3 \times 10^{10}$ Bq (2.5 Ci) at saturation

The cross section for ^{18}O has not been published for such high energy incident protons. A value close to 6.6 mb at 590 MeV has been measured at CERN [7]. In the literature, Ruth and Wolf [8] report that the maximum value of the cross-section for ^{18}O appears as a small peak between 3 and 15 MeV. The small amount of energy lost by the beam (2.6 MeV/g/cm^2) in traversing the 300 mm long target does not, therefore, result in any significant increase in the cross-section value; the exit beam energy is still far in excess of the optimum value of around 6 MeV.

Another non-optimal factor is the relatively low beam current of the machine (2.5 μA), which is typically ten times less than that commonly used for ^{18}F production. Nevertheless, the combination of a low proton flux and a high energy gives us the interesting possibility of irradiating a very large water target, without the problem of heat dissipation. Thus, even with a cross section 20 times less and an intensity around 10 times less than that commonly used, a proton beam of 590 MeV seems acceptable for the production of ^{18}F in useful quantities.

EXPERIMENTAL APPROACH

Based on the above theoretical considerations, a target system has been developed, as illustrated in figure 1. The main problem is to keep the volume of water in the target system as low as possible in order to minimize the cost of expensive ^{18}O-enriched water. A closed circulating flow was chosen, with an anionic-exchange resin (BIO-RAD AG1X8, 100-200 Mesh) in the system. The diameter of the stainless steel target container was 20mm, with a length of 300 mm along the axis of the beam, and both ends were closed by a 0.5 mm thick window. Stainless steel tubing of 0.5 mm internal diameter was used for all the connections

and a high-pressure pump (GILSON Model 303) was required to circulate the water through the target and the anionic-exchange column. The total volume of enriched water was 110 ml, operating at a flow rate of 10 ml/min, and the maximum pressure measured inside the system was close to 50 bars, which is acceptable. During the irradiation, the fluorine-18 created by the $^{18}O(p, n)^{18}F$ reaction was exchanged on the hydroxide form of the resin and at the end of the bombardment the two pneumatic actuator switching valves (RHEODYNE 7000P) were rotated in order to elute the ^{18}F from the column with dilute potassium carbonate or tetrabutylammonium hydroxyl solution. The entire volume of enriched water was kept within the target system, and only a few µl were lost during each elution of the column.

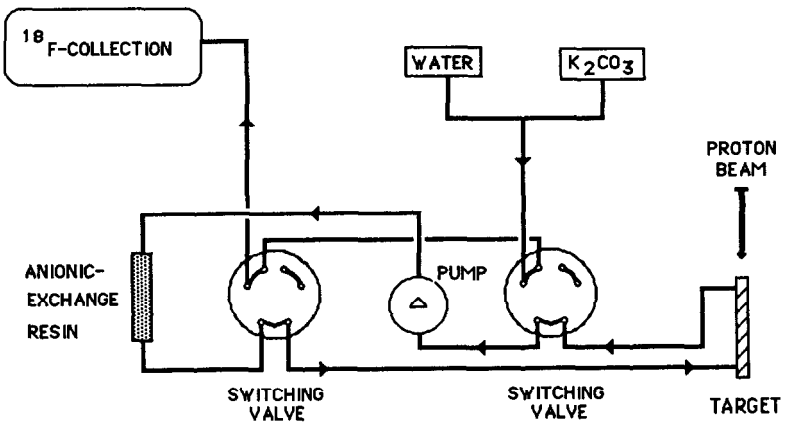

Fig. 1. Schematic of the closed system water target and the ^{18}F separation system.

RESULTS AND DISCUSSION

Fluorine-18 preparation

Typically, the target is irradiated for one hour, and then the circulating flow is maintained for a further hour in order to complete the adsorption of ^{18}F from the water. The short-lived radioisotopes (^{15}O and ^{11}C) decay sufficiently in a couple of hours, and an activity close to 500 mCi of ^{18}F could generally be expected in a few ml of eluted solution. It was possible to recover more than 90% of the ^{18}F exchanged on the resin, corresponding to an overall experimental yield close to 60% based on a theoretical calculation of the ^{18}F produced at the end of bombardment. At the present time, the experiment has not yet been performed on the 98% enriched water, but on a 1.6% ^{18}O-enriched water. Consequently only a few millicuries of ^{18}F have been produced.

In the experiments for ^{18}F-production described in [9,10], two main problems occured: firstly, the frailty of the very thin target windows (about 25 μm), and secondly, the heat dissipation in the water target, both of which are a consequence of the low energy of the beam (about 10-15 MeV). However such problems do not arise in our experiment due to the relatively high proton energy (590 MeV). Stainless steel target windows of 0.5 mm thickness can be used without significant loss of beam energy, and due to the large volume of enriched water irradiated (110 ml) no problem with heat dissipation occured.

Quality control

Decay studies of the remaining radioactive solution, performed on a Ge-(Li) γ-ray spectrometer indicate, in addition to the ^{18}F-production, a significant proportion of ^{11}C and a trace of ^{7}Be (half-life, 53 days) as illustrated in the figure 2. The presence of ^{7}Be in the solution was identified from its 473 KeV characteristic emission.

Carbon-11 was probably created from the $^{18}O(p, 3p5n)^{11}C$ nuclear reaction and appeared in the aqueous solution as carbonic acid. The anionic form was verified by its capability to be exchanged onto the same column that was used for the extraction of the fluoride. The concentration of carbon-11 in the eluted solution is not a problem because of

its shorter half-live and the ease with which it may be evaporated by simple heating [11]. Metallic contaminants such as beryllium-7 are to be expected, due to the high energy of the proton beam and the possibility of the nuclear spallation reaction from carbon and oxygen atoms. A more critical point is a possible contamination from the anionic exchange resin where the fluorine-18 is adsorbed during bombardment prior to being eluted.

Indeed, the nucleophilic fluorination efficiency is greatly disturbed by the presence of trace contaminants in the ^{18}F-solution. Thus, the chemical reactivity of the ^{18}F-

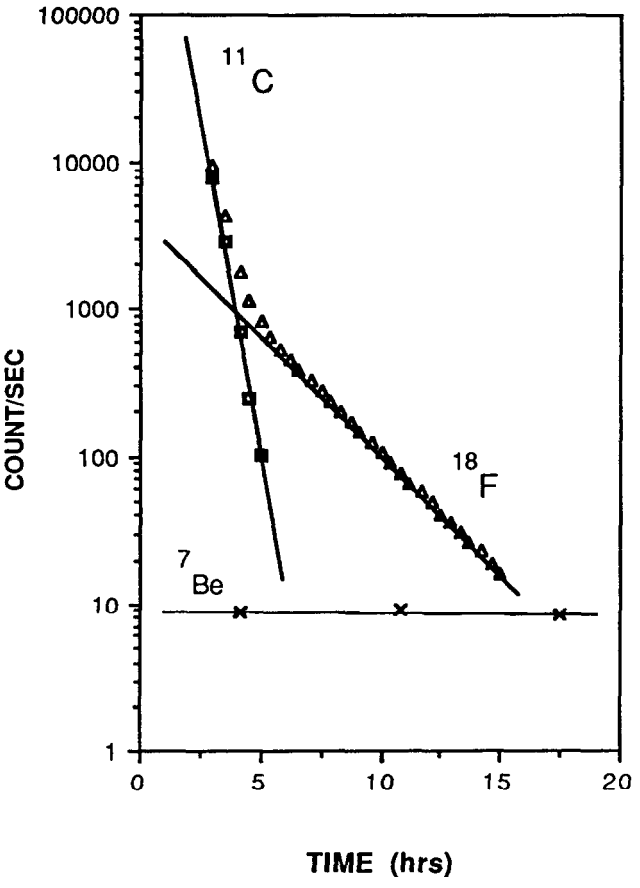

Fig. 2. Decay curve for a sample solution recovered from the anionic exchange column. The ^{11}C decay was calculated by subtraction of the extrapolated ^{18}F activity.

solution recovered was investigated by the potential for radiochemical labelling of the 1.3.4.6-tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-*β*-D-mannopyranose (Aldrich Chem. Co.). This experiment was performed at the MRC Cyclotron Unit (Hammersmith Hospital, London) in order to use their available radiochemical labelling facilities. Two different batches of fluorine-18 solution were prepared: one obtained directly from the cyclotron production, and the other recovered from an anionic resin previously loaded with the same fluorine-18 solution. Both batches were investigated separately for labelling efficiency, using the first steps in the 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose method of Hamacher et al. [12].

An aqueous solution of no-carrier-added ^{18}F (10 mCi) was mixed with a solution of 4.6 mg (0.03 mmol) potassium carbonate and 26 mg (0.06 mmol) kryptofix 222 (MERCK) in acetonitrile/water (86/14); the solution was evaporated to dryness, and then the residual water was removed completely by adding acetonitrile (three times) and azeotropic distillation under argon. A solution of 20 mg (0.04 mmol) 1.3.4.6-tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-*β*-D-mannopyranose in 2 ml dry acetonitrile was transferred to the ^{18}F-kryptofix 222 complex and mixed under reflux at 80° C for 10 min. The labelling efficiency of each synthesis was then estimated by silica gel thin layer radiochromatography. The labelled compound migrated from the origin, and was easily differentiated from the free fluorine-18 remaining at the origin. The two batches of ^{18}F-solution showed no significant difference, with a ratio of labelled-^{18}F to unlabelled-^{18}F close to 35 %.

An animal experiment

A rabbit of 1 Kg was anaesthetized by neuroleptic-analgesia prior to receiving an intravenous injection of about 2.5 mCi (9.25×10^7 Bq) of Na^{18}F solution. Forty-five minutes later, the animal was installed between the two detectors of the positron camera and a number of scans were performed. The PET camera currently used in the Division of Nuclear Medicine of the University Hospital of Geneva, is based on the High Density Avalanche Chamber (HIDAC) detector, and has been described elsewhere [13]. During data

acquisition, the camera rotates step by step through 180° around the rabbit. The image reconstruction is based on backprojection with frequency-space filtering [14]. Data may be displayed as transverse, sagittal or frontal sections, and in addition a three-dimensional shaded surface display can be produced. Such a three-dimensional surface of the skull of the rabbit is shown in Fig. 3 from oblique-anterior-right.

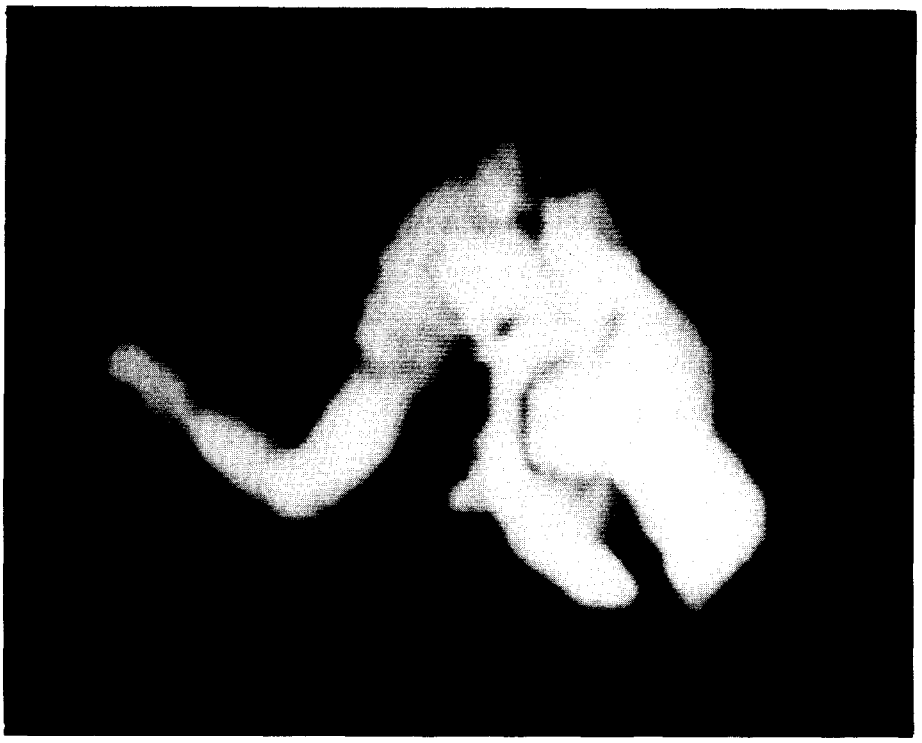

Fig. 3. Shaded-graphics display of the skull of a rabbit imaged 45 min after injection of a solution of $Na^{18}F$.

The cervical spine is seen attached to the posterior part of the skull, and details of the upper and lower jaw are easily recognized. It has been demonstrated that fluorine incorporation in bone mineral occurs inside the lattice of the apatite crystal [15], depending more on the newly-deposited bone mineral than on the anionic exchange process on already-existing crystals [16]. Thus, the skull image obtained by the

radiopharmaceutical bone fixation corresponds to the metabolic incorporation of ^{18}F into the bone rather than to a morphological view of the skull.

In conclusion, the production of ^{18}F from a water target using relatively high energy protons (590 MeV) appears to be possible, giving the potential for the high yield production of a good, chemically-reactive form, suitable for the synthesis of some clinically-interesting radiopharmaceutical compounds.

ACKNOWLEDGEMENTS

The authors are particularly grateful to the staff of the SC-synchrocyclotron from CERN and to Drs. V.W. Pike, F. Brady and J.C. Clark from the MRC Cyclotron Unit, Hammersmith Hospital for the permission to use their radiochemical facilities, and for helpful advice. This work was supported by the Fonds National Suisse under grant numbers 3.948-0.87 and 3.853-0.85.

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