"THE PRODUCTION OF RADIONUCLIDES FOR MEDICAL APPLICATION WITH THE 280 CM AVF CYCLOTRON IN GRONINGEN"

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Abstract

The medical application of some short lived carrier free radionuclides (^{11}C, ^{13}N, ^{55}Co, ^{197}Hg) produced with the external beam of the KVI cyclotron are outlined. Some approaches to labelling with these nuclides are discussed. The development of a multi-wire proportional counter for the imaging of low energy gamma rays is described. Images of positron emitters with a dual head Anger camera are shown.

I. Introduction

The main advantages of cyclotron produced neutron deficient nuclides lie in their short half lives and their carrier-free nature. These properties require a special chemistry in order to label complex molecules for in vivo diagnostic application. Due to the carrier-free state these radiopharmaceuticals will not disturb any biological equilibrium.

The energy range available with the KVI cyclotron makes a flexible choice of production method for each radionuclide possible. The nuclides in regular production in Groningen are ^{11}C, ^{13}N, ^{52}Fe, ^{55}Co, $^{81}Rb/^{81m}Kr$, ^{123}I and ^{197}Hg.

The gamma rays from the decay of the nuclides may be well suited for an Anger camera (^{123}I) but in cases of pure positron emitters the high gamma ray energy from the annihilation radiation requires special detection techniques as applied in positron cameras. In the case of low gamma ray energies or X-rays a multi-wire proportional counter has unique imaging qualities. The main activity of the group is to develop new radiopharmaceuticals and to evaluate their value for in vivo diagnostic applications. In order not to be limited by the radiation characteristics of the nuclides a camera for low energy gamma rays is under construction and a dual head Anger camera for the detection of positron annihilation radiation is assembled.

2. Radiopharmaceuticals

It can be expected that the production of radionuclides will lead to new applications in nuclear medicine. The design and synthesis of radiopharmaceuticals which allow the measurement of metabolic functions in a non-invasive way, however, would give a new impetus to nuclear medicine. The most evident way to measure metabolic functions is to label metabolites. Since most compounds circulating in the body are of organic nature, the label generally has to be carbon, nitrogen or oxygen. The labelling of competitive metabolites can also give information about metabolic functions, because the body does not differentiate between the competitive compound and the real metabolite. Even labelled anti-metabolites will give information about the metabolic functioning of the body, because they can block biosynthesis by competitive action. Carbon monoxide, for instance, will label the red blood cells and inhibit the uptake of oxygen.

Another class of organic compounds which are important are those which concentrate in tumour tissue, for instance bleomycin.

For reasons mentioned above and because of their half lives, ^{11}C, ^{13}N and ^{15}O are the most suitable nuclides of the carbon, nitrogen and oxygen isotopes. The radiation characteristics of these nuclides provide the possibility of external detection when applied in vivo.

3. Carbon-11

Carbon-11 ($t_{½}$ = 20.3 min) is produced via the ^{14}N (p,α) ^{11}C reaction. The pressurized nitrogen flow target[2] yields 1.5 mCi/μA min of $^{11}CO_2$. The energy of the incoming protons is 20 MeV. The $^{11}CO_2$ is used for lung function investigations as well as for the syntheses of ^{11}C-labelled radiopharmaceuticals.

3.1. ^{11}C-DOPA

Using $^{11}CO_2$ as precursor, β-(3,4 dihydroxyphenyl)-D,L-α-alanine-1-^{11}C(^{11}C-DOPA) is synthesized[3] Animal studies showed a specific distribution in the brain[4] which suggests that this positron-emitting compound is a potential agent for external detection of in vivo decarboxylase activity.

3.2. ^{11}C-steroids

All hormone sensitive tumours are thought to bind their respective hormones by a mechanism involving receptor molecules in the target tissue. In many cases the introduction of an ethynyl group in the 17-α position increases the hormonal activity of the compound. If the ratio between the binding of hormone responsive tumour tissue and the surrounding tissue is high enough, gamma ray emitting steroid hormones are useful for the in vivo detection of these tumours by scintigraphy. It is essential to administer these labelled hormones in a carrier-free form in order not to disturb the hormonal equilibrium. Carbon-11 labelled acetylene, obtained by irradiation of calcium carbide followed by hydrolysis, is a good percursor for the production of 17α-^{11}C-ethynylestradiol.[5] This labelled compound, in carrier-free state, has great potential for selecting hormone sensitive tumour tissue. However, the production of large amounts of carrier-free ^{11}C-acetylene has failed thus far. Investigations are in progress to increase the specific activity of the ^{11}C-acetylene produced.

For a number of steroid hormones the introduction of a 17α-methyl group is a good alternative. A carbon-11 labelled nucleophilic methyl donating reagent had to be developed for the fast introduction of the label. For addition to the 17-keton function of steroids ^{11}C-methyllithium could be the agent of choice. This compound also has a great potential for the one step incorporation of ^{11}C-methyl groups into a variety of other organic and bio-organic molecules. Following known procedures, $^{11}CH_3I$ was obtained from $^{11}CO_2$.[6] The ^{11}C-methyliodide is converted into ^{11}C-methyllithium by the exchange reaction $^{11}CH_3I$ + n-BuLi ⇌ $^{11}CH_3Li$ + n-BuI. Under the conditions used the conversion of $^{11}CH_3I$ into $^{11}CH_3Li$ is virtually quantitative. This new carbon-11 labelled synthetic tool is

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now used for the synthesis of ^{11}C-17α-methyl testosterone, a potentially useful compound for the detection of prostate tumours.

4. Nitrogen-13

Nitrogen-13 ($t_{½}$ = 10 min) is produced via the $^{16}O(p,\alpha)^{13}N$ reaction. Water is bombarded with a 20 MeV proton beam[8] yielding 15 mCi/μA/20 min of ^{13}N. After the irradiation the labelled mixture of nitrate and nitrite is reduced to carrier-free ammonia by devardas alloy and collected by steam distillation. The ammonia, if not used for liver function studies,[9] is oxydized to ^{13}NN gas for lung function ventilation or perfusion studies.

For ventilation studies ammonium chloride is added prior to oxydation by hypobromite.[10] The nitrogen-13 gas is evolved instantaneous and transferred into a spirometer. In the case of perfusion studies the carrier-free $^{13}NH_3$ is converted by the same oxydant into nitrogen-13 gas which stays in solution. Following the suggestion of Krizek[11] the excess of hypobromite is destroyed by ascorbic acid. After pH adjustment, an injectable solution of $^{13}N_2$ gas in saline with an activity of more than 10 mCi/ml can easily be obtained.

The advantage of nitrogen-13 gas above the commonly used xenon-133 gas is the very low solubility of nitrogen in water and fatty tissue.

In fig. 1 a lung ventilation and perfusion study on a dog are shown. The images were taken with the dual head Anger camera described later on. The amount of nitrogen-13 between the detectors is in the order of 100 μCi.

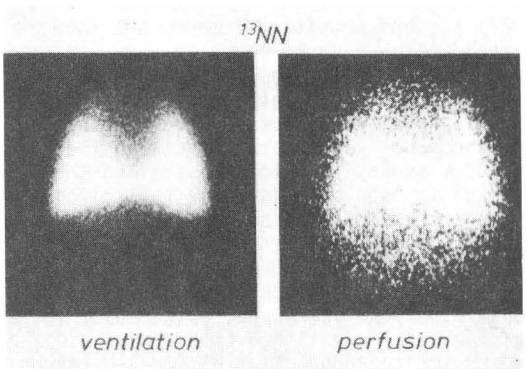

Fig. 1. Lung ventilation and perfusion study on a dog (mongrel, 20 kg) with nitrogen-13 gas.

5. Cobalt-55

Bleomycin labelled with ^{57}Co is one of the tumour localizing agents. Its in vivo stability and tumour affinity have been reported.[12,13] The low tumour affinity and the good target/non-target ratio of ^{57}Co-bleomycin implies that the bulk of the activity leaves the body (via the kidneys) in the first 48h post injection. For environmental reason one has to hospitalize the patient in order to collect all urine. This problem can be avoided by using ^{55}Co ($t_{½}$ = 18.2h). The ^{55}Co is produced[14] via the ^{56}Fe (p,2n) ^{55}Co reaction. With an incoming beam of 40 MeV protons and a target thickness of 19 MeV this reaction yields 4 mCi/μAh of ^{55}Co. The contaminants in the final product are ^{56}Co (< 1%) and ^{57}Co (< 0.01%).

The imaging of ^{55}Co-bleomycin can be done with the recently developed positron imaging devices[15]. In fig. 2 an image of a rat with two induced tumours in the kidney area is shown. The image was taken with a dual head Anger camera described later on. Both tumours are well localized on the background of the kidneys.

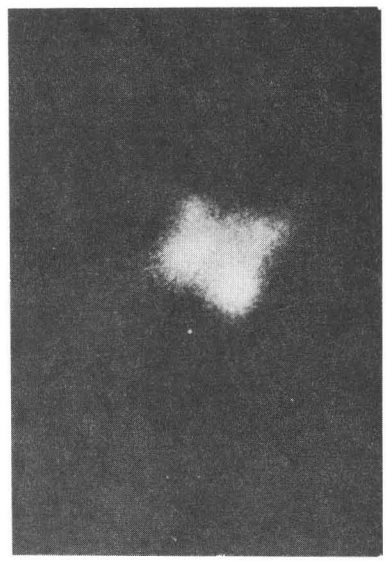

Fig. 2. Image of a rat with two induced tumours in the kidney area. The image was taken 24h post injection of 100 μCi ^{55}Co-bleomycin.

6. Mercury-197

Steroids labelled with radioactive mercury offer another possibility for the external detection of tumours. In order to have a very high specific activity the mercury is produced via the ^{197}Au (d,2n) ^{197,197m}Hg reaction. The energy of the incoming deuteron beam is 22 MeV and the target thickness is 14 MeV. On the basis of the excitation function[17] the yield is 0.6 mCi/μAh and 1.5 mCi/μAh for ^{197}Hg and ^{197m}Hg respectively. From the Q-values it is evident that some carrier in the form of ^{196}Hg and ^{198}Hg will always be present in the produced mercury.

7. Detector development

The gamma ray energies optimal for a conventional gamma camera are in the region of 100-200 keV. A great number of radionuclides of interest for nuclear medicine do not have gamma rays in this energy range. On the low energy side are ^{125}I, ^{133}Xe, ^{197}Hg, the rare earth nuclides, etc. The annihilation radiation of the positron emitting radionuclides is far out of the energy range mentioned above.

7.1. A multi wire proportional camera

In order to have a camera with a high spatial resolution for low energy gamma rays, a multi wire proportional camera is under construction.[1] The counter consists of three wire planes--one anode plane and two cathode planes, orthogonal to each other. Delay lines[18] are used for the read out of the wire planes. The delay lines are made of printed circuit boards (18 cm x 3 cm x 0.25 cm) covered with

0018-9499/79/0400-2272$00.75

copper strips (35 μm thick, 18 mm wide and 0.2 mm apart) connected at both ends to ground potential. A PTFE layer of 25 μm is positioned between the body and the helix wound around it. Compensation strips are placed beneath the delay line in order to compensate for phase errors.[18] The quality factor (= total delay of the line/rise time) of the delay lines is about 30, the total delay is 1.1 μs. Tests showed the intrinsic resolution to be 0.1 mm FWHM. When converters are used, a multi wire camera can also be used with high energy gamma rays.[15]

7.2. Positron camera

In order to have an imaging device for positron emitting radiopharmaceuticals, a positron camera is assembled from an uncollimated Anger camera and a positron sensitive attachment.[16] Modular electronics establish coincidence between annihilation radiation photo-events to within 35 ns (FWHM). In fig. 3 a block diagram of the positron imaging device is presented. Midplane spatial resolution is 16 mm FWHM and the centered point-source sensitivity is 140 Hz/μCi. Due to the geometry of the camera the sensitivity is not uniform. The summed singles countrate has to be limited to 300 kHz, due to the rather dated electronics of the camera and the attachment. The maximum coincident countrate is 3800 Hz. In this way a positron imaging device is assembled at modest cost while the gamma camera is still available for conventional scintigraphy. The system is connected via CAMAC with a computer system which permits a deferred selection of focal plane position.

The digitized position signals are stored on magnetic tape. By replaying the stored data any desired focal plane position can be reconstructed.

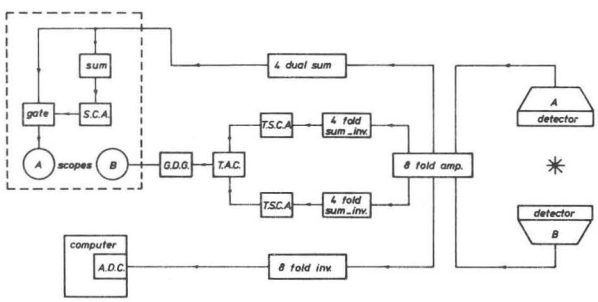

Fig. 3. Block diagram of the positron imaging system. The connection to the computer system is done via CAMAC.

Acknowledgement

The cooperation of the staff of the Kernfysisch Versneller Instituut (Professor R.H. Siemssen) and the considerable help of the operating team of the cyclotron is gratefully acknowledged.

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