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Use of cyclotrons in medicine

S.M. Qaim*

Institut für Nuklearchemie, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

Abstract

Cyclotrons are versatile ion-accelerating machines which find many applications in medicine. In this short review their use in hadron therapy is briefly discussed. Proton therapy is gaining significance because of its capability to treat deep-lying tumours. A strong area of application of cyclotrons involves the production of short-lived neutron deficient radiotracers for use in emission tomography, especially positron emission tomography. This fast and quantitative in vivo diagnostic technique is being increasingly used in neurology, cardiology and oncology. Besides routine patient care, considerable interdisciplinary work on development of new positron emitters is under way. A short account of those efforts is given. The use of cyclotrons in the production of radionuclides for internal radiotherapy is also briefly described.

Keywords: Cyclotron; Radionuclide; Emission tomography; Hadron and internal radiotherapy

1. Introduction

Cyclotrons are versatile devices, producing accelerated ion beams which find application in many areas. In the field of medicine their use is both in diagnosis and therapy. In vivo diagnostic studies are performed using suitable radionuclides, i.e. pure gamma emitters or positron emitters. Whereas the former are produced using both nuclear reactors and cyclotrons, the latter, being neutron deficient, can be produced only at a cyclotron via charged-particle-induced reactions. Therapy, especially hadron therapy, on the other hand, is generally carried out either directly by accelerated ions themselves or by neutrons generated as secondary products. Another approach to therapy, termed internal radiotherapy, involves the use of radionuclides of suitable decay characteristics. The introduction of the radionuclide to the place of malignant tissue is done either mechanically in the form of a seed or stent (brachytherapy), or it may follow a biochemical pathway (endoradiotherapy). The therapeutic radionuclides are generally produced using a nuclear reactor. However, some of them are produced at cyclotrons as well. In this short review a very brief account of the therapeutic use of accelerated ions and fast neutrons generated by them is given. The major emphasis is on the production of radionuclides at cyclotrons for utilization in nuclear medicine, both for diagnosis and therapy.

2. Radiation therapy

2.1. Standard radiation therapy

Standard radiation therapy implies almost exclusively teletherapy and involves the use of low-energy electrons, X-rays, γ-rays, high-energy electrons or high-energy photons. Occasionally slow neutron capture therapy is also used. This may involve the introduction of a boron-containing chemical in some specific part of the body, followed by irradiation with slow neutrons. The captured neutron interacts with boron according to the reaction $^{10}B(n,\alpha)^{7}Li$. The α- and ^{7}Li-particles emitted in this reaction are absorbed in the tissue and generate a lot of heat, thereby inducing the therapeutic effect. Due to

*Tel.: +49-2461-613282; fax: +49-2461-612535.
E-mail address: s.m.qaim@fz-juelich.de (S.M. Qaim).

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the very high chemical toxicity of boron, however, the technique needs very stringent control. Another more recent approach is the use of Gd. The thermal neutron capture cross sections for ^{155}Gd and ^{157}Gd are extremely high (61 000 and 25 4000 barns, respectively) and the γ-rays emitted from the excited nuclei show very promising therapeutic effect. Slow neutron capture therapy is generally performed at a nuclear reactor. Due to considerable effort involved in the establishment of a medical facility around a reactor, this type of therapy has hitherto found only limited use.

2.2. Hadron therapy: application of cyclotron

An important and modern modality of therapy involves the use of hadrons, i.e. neutrons and charged particles, both produced at cyclotrons. Extensive reviews exist on this topic in the literature.

Two important considerations in radiation therapy are linear energy transfer (LET) and relative biological efficiency (RBE). Use of hadrons in comparison to conventional therapy can have the advantage of a better physical selectivity, i.e. an improved dose profile and a higher biological efficiency, corresponding to greater killing in the tumour (see for instance, Kraft et al., 1997). However, the various types of hadrons differ in their properties. Typical LET values for different radiations are given in Table 1 (Jones, 2001). For ion beams the values refer to high-energy particles. For a given physical dose, high LET radiation is more effective at cell killing than low LET radiation. We discuss below briefly only the neutron and proton therapies since they are more commonly used.

Fast neutrons are densely ionizing radiation and have high LET values. Their biological effect arises from their scattering from hydrogen as well as through the emission of charged particles in their interactions with the carbon, nitrogen and oxygen in the body.

Fast neutrons are generated at the cyclotrons generally via one of the two interactions: (a) deuteron break-up at a Be target and (b) protons on Be. The spectrum in the former case is harder and forward-peaked; in the latter case it is softer and more isotropic. Very commonly about 50 MeV deuterons and 65 MeV protons are utilized for neutron production, and the beam currents used are between a few μA and 50 μA. Fast neutron therapy appears to be especially effective against very resistant tumours. A large number of laboratories perform neutron therapy both routinely and at a research level; a comprehensive list has been given by Jones (2001).

Table 1
Typical LET values[a]

Radiation	LET (keV/μm)
Cobalt-60 γ-rays	2
250 kV X-rays	3
Protons	3
α-particles	5
π-mesons	10
Carbon ions	15
Neon ions	50
Fast neutrons	75
Argon ions	150
Boron neutron capture	150

[a] Taken from Jones (2001).

In contrast to neutrons, the protons have relatively low LET values. However, they deposit most of the energy towards the end of their absorption path. Therefore proton beams exhibit a unique dose distribution which consists of a relatively flat entrance dose region (plateau) followed by a sharp dose peak (the Bragg peak). This occurs towards the end of the proton path in the tissue, i.e. when the proton has lost most of its energy. The loss of the remaining energy is then associated with a very rapid loss of intensity, causing thereby dense ionization which leads to a strong dose. For comparison, the depth dose curves for 66 MeV p(Be) neutrons and 200 MeV protons are given in Fig. 1 (Jones, 2001), together with those for conventional radiotherapy beams. The major advantage of proton therapy is the capability to treat deep-lying tumours, close to critical structures. This is possible mainly due to the high selectivity of the Bragg peak. By tailoring the proton beam energy, it is possible to obtain the therapy effect at varying depths in the malignant tissue. Furthermore, the Bragg peak can be spread out to cover the whole target volume. This is done by active electromagnetic or mechanical techniques (see for instance, Jones, 2001).

The energies involved in proton therapy range between about 60 and 250 MeV. In general a very well collimated or sharp pencil beam is required. It has to be of much higher quality than in the production of neutrons (see above) or radioactive tracers (see below). The beam intensities needed are, however, low. A typical beam incident on an organ target may lie in the range of 5–10 nA. The incident beam on the collimator/homogenizer, however, may reach values up to 1 μA. Proton therapy has been gaining considerable attention in recent years and now about 30 centres exist worldwide (cf. Jones, 2001; Sisterson, 2001) where this therapy is used for patient care as well as for further therapeutical research. A special design cyclotron for therapeutical use has also been developed (cf. Prieels et al., 2001).

3. Radionuclide production

Radionuclides produced at cyclotrons are generally very suitable for diagnostic studies via emission

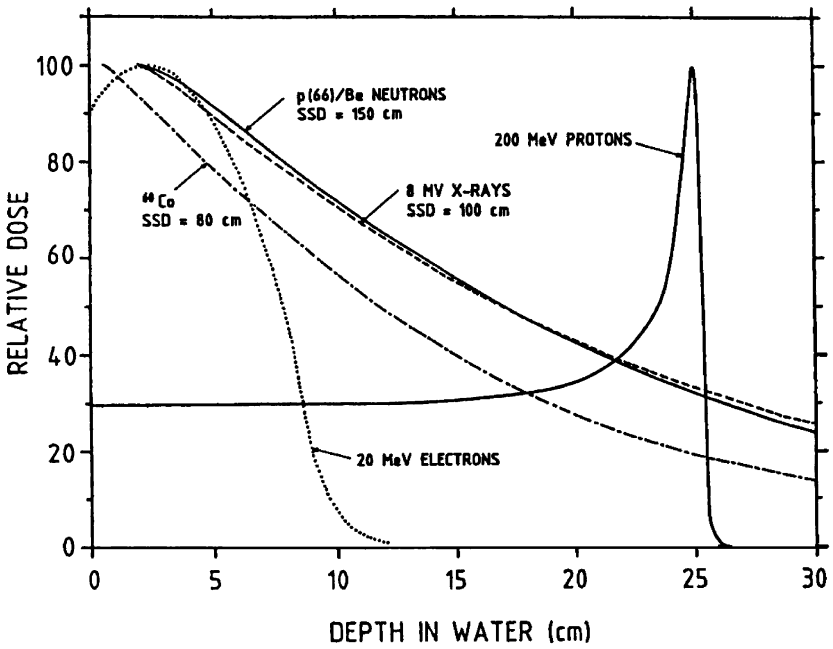

Fig. 1. Depth dose curves for a 66 MeV p/Be neutron therapy beam and a 200 MeV proton therapy beam compared with conventional radiotherapy beams (after Jones, 2001).

tomography, viz. single photon emission computed tomography (SPECT) and positron emission tomography (PET). Since they are mostly neutron deficient, they cause relatively low radiation dose to the patient. Some of the cyclotron produced radionuclides also find application in internal radiotherapy.

3.1. Cyclotrons for radionuclide production

Over the last two decades several types of cyclotrons have been developed to meet the specific demands of radionuclide production; a summary is given in Table 2 (cf. Wolf and Barclay Jones, 1983; Qaim, 2001). The smallest cyclotron accelerates only deuterons up to about 3.7 MeV, i.e. below the break-up threshold of the deuteron (to avoid neutron background). It is used exclusively in a hospital environment to produce ^{15}O via the ^{14}N (d,n) process. The next stage cyclotron is a single-particle negative ion machine for proton acceleration up to an energy of 11 or 12 MeV. It is capable of producing the four major β^+ emitters, viz. ^{11}C, ^{13}N, ^{15}O and ^{18}F, although the absence of the deuteron beam is somewhat disadvantageous regarding the production of ^{15}O, and the rather low proton energy gives a low yield of ^{13}N. The next higher-energy cyclotron is generally a two-particle machine with $E_p \leqslant 20$ MeV and $E_d \leqslant 10$ MeV. It is ideally suited for production of the commonly used PET radionuclides. Production of a few SPECT radionuclides like ^{67}Ga, ^{111}In and ^{123}I in small amounts is also possible. The even higher energy machines have capabilities of producing many more radionuclides, in particular when besides p and d, also ^{3}He and α-particle beams are available. On the other hand, when energies above 100 MeV are involved, only the proton beam is of interest.

3.2. Tracers for SPECT studies

For SPECT studies radionuclides with a single or major gamma-ray in the energy range of 70–250 keV are required. The most commonly used SPECT radioisotope ^{99m}Tc ($T_{\frac{1}{2}} = 6.0$ h, $E_\gamma = 141$ keV, $I_\gamma = 87\%$) is produced using a nuclear reactor. Its widespread use is mainly based on its convenient availability as a $^{99}Mo/^{99m}Tc$ generator. Many of the cyclotron produced gamma-ray emitting radionuclides like ^{67}Ga, ^{111}In, ^{123}I and ^{201}Tl are also finding increasing applications. All of those radionuclides are produced via (p,xn) reactions using a medium-sized cyclotron of $E_p = 30$ MeV, as mentioned above, although small quantities can also be produced via (p,n) reactions at small cyclotrons. In recent years very high-intensity medium-sized cyclotrons have been developed with the specific aim of producing radioisotopes. Extracted beams of about 1 mA are available; they fall on solid targets at low angles and allow production of all the above mentioned SPECT-radionuclides in large quantities (cf. Qaim, 2003).

Table 2
Cyclotrons used for radionuclide production[a]

Classification	Characteristics	Energy (MeV)	Major radionuclides produced
Level I	Single particle (d)	<4	^{15}O
Level II	Single particle (p)	$\leqslant 12$	^{11}C, ^{13}N, ^{15}O, ^{18}F
Level III	Single or two particle (p, d)	$\leqslant 20$	^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{86}Y, ^{124}I (^{123}I, ^{67}Ga, ^{111}In)
Level IV	Single or multiple particle (p, d, ^3He, ^4He)	$\leqslant 40$	^{38}K, ^{73}Se, $^{75-77}Br$, ^{123}I, ^{81}Rb (^{81}Kr), ^{67}Ga, ^{111}In, ^{201}Tl, ^{22}Na, ^{57}Co, ^{44}Ti, ^{68}Ge, ^{72}As, ^{140}Nd
Level V	Single or multiple particle (p, d, ^3He, ^4He)	$\leqslant 100$	^{28}Mg, ^{72}Se, ^{82}Sr , ^{117m}Sn, ^{123}I
Level VI	Single particle (p)	$\geqslant 100$	^{67}Cu, ^{68}Ge, ^{82}Sr, etc.

[a] Taken from Qaim (2001).

The metallic radioisotopes ^{67}Ga ($T_{\frac{1}{2}}=3.3$d, $E_\gamma=185$ keV, $I_\gamma=20\%$) and ^{111}In ($T_{\frac{1}{2}}=2.8$ d, $E_\gamma=173$ keV, $I_\gamma=91\%$) form strong metal complexes and are of considerable interest in diagnostic nuclear medicine, especially for tumour localisation. Similarly ^{201}Tl ($T_{\frac{1}{2}}=3.06$ d, X-rays and $E_\gamma=166$ keV, $I_\gamma=10.2\%$) is widely used in myocardial perfusion studies. The radioisotope ^{123}I ($T_{\frac{1}{2}}=13.2$ h, $E_\gamma=159$ keV, $I_\gamma=83\%$) is still more interesting. It is a very useful analogue label for organic molecules and its nuclear properties are almost ideal for SPECT studies. The most commonly used method for ^{123}I-production consists of the $^{124}Xe(p,x)$-process. It involves highly enriched ^{124}Xe. The natural abundance of ^{124}Xe is only 0.1%; consequently the highly enriched ^{124}Xe is very expensive. This places heavy technological demands on the process, both with regard to gas handling and radioiodine separation. The ^{123}I produced, however, is of the highest possible purity.

As mentioned above, the reactor produced ^{99m}Tc-radiopharmaceuticals are widely used. However, they are almost exclusively limited to flow tracers. The cyclotron produced ^{123}I, on the other hand, behaves as an ''organic'' isotope and lends itself to the design of metabolic radiopharmaceuticals applying the analogue approach. The great demand for radioiodinated tracers for in vivo applications has stimulated search for easy no-carrier-added radioiodination procedures. Several ^{123}I-radiopharmaceuticals are now commonly used for functional diagnostics via SPECT (cf. Stöcklin et al., 1995).

The above discussion shows that cyclotrons are very useful machines for producing SPECT-radioisotopes in the medium and heavy mass regions. Thus they contribute appreciably to diagnostic nuclear medicine via the emission tomographic method SPECT.

3.3. Commonly used tracers for PET studies

The development of PET has made it possible to quantitatively measure regional. activities of a molecule (labelled with a positron emitter) with high sensitivity and a spatial resolution of a few millimetres. With the help of biomathematical models, turnover rates of metabolic substrates can be determined.

The commonly used short-lived organic positron emitters, viz. ^{11}C, ^{13}N, ^{15}O and ^{18}F are listed in Table 3 (cf. Qaim, 2003). The production methods and the effective energy ranges are also given. In general, low-energy nuclear reactions like (p,n), (p,α), (d,n), (d,α), etc. are used and a small-sized cyclotron is adequate for production purposes. As mentioned above, these positron emitters can be produced only using ion beams. The excitation functions of all the production reactions show strong resonances. The data for the $^{18}O(p,n)^{18}F$ reaction, commonly used for production of ^{18}F, are shown in Fig. 2 (cf. Hess et al., 2001). The thick target yields given in Table 3 were calculated from the known excitation functions. The target materials (and some additives) used in routine production are also given. The chemical form of the radionuclide produced depends upon the target filling.

The tagging of a short-lived positron emitting radionuclide to an organic compound requires new concepts. Thus a new type of fast organic radiochemistry has emerged (cf. Stöcklin and Pike, 1993; Stöcklin et al., 1995). It involves the production and separation of the radionuclide, the labelling of an organic compound with the radionuclide, as well as the purification and quality control of the product on a very fast scale. An extreme example is ^{15}O with its 2 min half-life. It is extensively used in simple chemical forms like $[^{15}O]\,O_2$ for studying oxygen metabolism in the brain or $[^{15}O]\,H_2O$ for measuring blood flow. Oxygen-15 labelled *n*-butanol, because of its optimum lipophilicity, is also of interest for measuring cerebral blood flow by PET. In the case of ^{11}C, with a half-life of 20.4 min, no carrier-added syntheses of a large number of compounds have been carried out. The major problem while working with ^{11}C is the specific activity of the labelled compound. Due to ubiquitous carbon in nature, extreme care needs to be exercised while preparing the radioactive product. In comparison, ^{18}F with a half-life of 110 min allows more

Table 3
Common methods of production of short-lived organic positron emitters[a]

Nuclide	$T_{\frac{1}{2}}$ (min)	Mode of decay	Production route	Energy range (MeV)	Thick target yield (MBq/μA h)	Target	In-target product
^{11}C	20.4	β^+ (99.8) EC (0.2)	$^{14}N(p,\alpha)$	13→3	3820	$N_2(O_2)$	^{11}CO, $^{11}CO_2$
^{13}N	10.0	β^+ (100)	$^{16}O(p,\alpha)$	16→7	1665	$H_2{}^{16}O$	$^{13}NO_2^-$, $^{13}NO_3^-$
^{15}O	2.0	β^+ (99.9) EC (0.1)	$^{14}N(d,n)$	8→0	2368	$N_2(O_2)$	^{15}OO,
			$^{15}N(p,n)$	10→0	2220	$N_2(O_2)$	^{15}OO
^{18}F	109.6	β^+ (97) EC (3)	$^{18}O(p,n)$	16→3	3893	$H_2{}^{18}O$ $^{18}O_2/(F_2)$	$^{18}F^-_{aq}$, $[^{18}F]F_2$
			$^{20}Ne(d,\alpha)$	14→0	1110	$Ne(F_2)$	$[^{18}F]F_2$

[a] Taken from Qaim (2003).

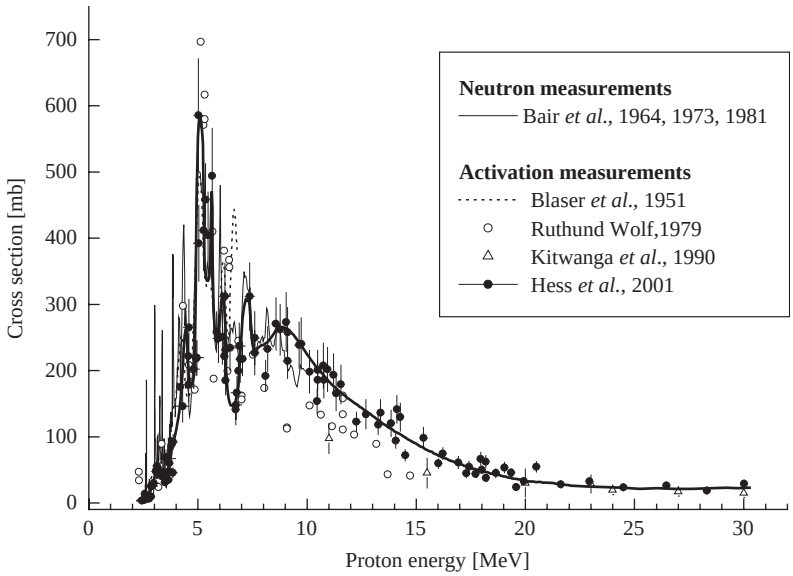

Fig. 2. Excitation function of the $^{18}O(p,n)^{18}F$ reaction. Results of both neutron and activation measurements are shown. The rather bold curve is an eye-guide to the activation data (after Hess et al., 2001).

elaborate syntheses and applications. Furthermore, due to its very low positron end-point energy the resolution of PET scans is high. In fact ^{18}F has become the standard PET nuclide and 2-[^{18}F] FDG is now the most commonly used PET tracer.

Besides the four organic positron emitters given in Table 3, two other short-lived positron emitters, viz. ^{68}Ga ($T_{\frac{1}{2}}=68$ min) and ^{82}Rb ($T_{\frac{1}{2}}=1.3$ min), are produced via generator systems. The former is widely used for PET attenuation correction and labelling of some compounds, and the latter in myocardial blood flow studies at centres without cyclotrons. Their respective long-lived parents ^{68}Ge ($T_{\frac{1}{2}}=271$ d) and ^{82}Sr ($T_{\frac{1}{2}}=25$ d) are produced either via (p,xn) reactions at energies up to 70 MeV or via spallation at 500–800 MeV.

PET has undergone tremendous development during the last decade. It is now widely used in neurology, cardiology and oncology. This is attributed to concerted developments in many directions, e.g. (a) high-intensity cyclotrons dedicated to radionuclide production, (b) high-current targetry and efficient radiochemical separations, (c) fast methods of labelling organic compounds

Table 4
Major PET radiodiagnostics[a]

Radiopharmaceutical	Application	
	Neurology	
$[^{15}O]O_2$	Oxygen consumption	
$[^{15}O]H_2O$	Blood flow	Dementia,
$[^{15}O]$butanol	Blood flow	Ischaemia,
2-$[^{18}F]$FDG	Glucose metabolism	Stroke
L-6-$[^{18}F]$FDOPA	Presynaptic dopaminergic function	Parkinsonism
L-[S-methyl-^{11}C]methionine	Amino acid metabolism and –transport	Brain tumours
$[^{11}C]$raclopride	D_2-receptor density or –occupany	Schizophrenia, Therapy control
$[^{18}F]$N-methyl-spiperone	D_2-receptor density or –occupany	Schizophrenia, Therapy control
$[^{11}C]$flumazenil	Benzodiazepine receptor mapping	Epilepsy
	Cardiology	
$[^{13}N]NH_3$	Blood flow	
2-$[^{18}F]$FDG	Glucose metabolism	Ischaemia,
$[^{11}C]$acetate	Oxidative metabolism (oxygen consumption)	Viability
$[^{11}C]$ or $[^{18}F]$ fatty acids	β-oxidation	
	Oncology	
2-$[^{18}F]$FDG	Glucose metabolism	
$[^{11}C]$methionine	Amino acid metabolism	
5-$[^{18}F]$fluoruracil (FU)	Therapy control	
5-$[^{18}F]$fluorodeoxyuridine (FUDR)	Cell proliferation	

[a] After Stöcklin et al. (1995).

with radionuclides, (d) fast separation and purification methods (GC, HPLC, etc.), (e) advances in radiopharmacology, (f) tracer evaluation and (g) construction of high-resolution PET scanners. PET is used today both in patient care and medical research. Some of the positron emitting radiopharmaceuticals commonly used in diagnostic nuclear medicine are given in Table 4 (cf. Stöcklin et al., 1995). Automated syntheses apparatuses are now commercially available. Further radiopharmaceutical development work is continuing.

3.4. Development of new positron emitters

With the increasing significance of PET in diagnostic nuclear medicine, considerable demand has arisen for more versatile positron emitters. On one hand longer-lived β^+ emitters (with half-lives between several hours and a few days) are needed to be able to study slow metabolic processes and, on the other, β^+ emitting analogues of SPECT and therapeutic radionuclides are desired for quantification purposes. We discuss below some of the research and development work needed to bring a potentially interesting radionuclide to the stage of practical application.

In general, the demand is on interdisciplinary work related to nuclear data measurement, high-current targetry, chemical processing, automation of the procedure and quality control of the product. Furthermore, PET phantom measurements are needed to demonstrate the suitability of the desired nuclide for imaging purposes. The demands on nuclear data may become rather heavy since the longer-lived positron emitters are often associated with isomeric states. Due to low transition energies of those states and due to difficulties in theoretical calculations of isomeric cross sections (cf. Strohmaier et al., 1997), extensive and challenging experimental work is necessary to be able to define the expected level of radioactive isomeric impurity. Similarly, considerable innovative efforts have to be devoted to other developmental aspects. We discuss some of those aspects in relation to the study of two types of new β^+ emitters mentioned above.

3.4.1. Longer-lived β^+ emitters

These could be used for labelling organic compounds (e.g. in case of halogens) or for preparation of metal complexes (e.g. in case of copper). Some of the important or potentially important β^+ emitting radionuclides applied to study slow pharmacokinetics have been recently reviewed (cf. Qaim, 2002, 2003). Out of all of these β^+ emitters, five radionuclides, namely ^{64}Cu ($T_{\frac{1}{2}}=12.7$ h), ^{73}Se ($T_{\frac{1}{2}}=7.1$ h), ^{76}Br ($T_{\frac{1}{2}}=16.0$ h), ^{120g}I

($T_{\frac{1}{2}} = 1.3$ h) and ^{124}I ($T_{\frac{1}{2}} = 4.18$ d) are of considerable current interest, though as yet some of them have not been applied in investigations on humans.

We consider in some detail the development of the β^+ emitting radionuclide ^{124}I ($T_{\frac{1}{2}} = 4.18$ d) which has been attracting considerable attention in recent years. The radionuclide has been under discussion for about 25 years, initially as a very disturbing impurity in SPECT investigations with ^{123}I but, over the last decade, as a useful marker of organic compounds for studying slow metabolic and therapeutic processes using PET. For its production, originally the ^{124}Te(d,2n)^{124}I reaction was employed (cf. Lambrecht et al., 1988) but after careful studies by Scholten et al. (1995) on the ^{124}Te(p,n)^{124}I reaction, that method is becoming the method of choice for the production of ^{124}I (cf. Sheh et al., 2000; Qaim et al., 2003a) since it leads to the purest form of ^{124}I. Furthermore, the production can be carried out at a low-energy cyclotron. The high-purity product also allowed an accurate determination of the β^+ emission intensity (through a comparison of the intensities of X-rays and annihilation radiation) as 22.0%, a value lower than the literature data based on impure sources. Recently the ^{125}Te(p,2n)^{124}I reaction has also been investigated (cf. Hohn et al., 2001). The optimum energy range is $E_p = 21 \rightarrow 15$ MeV. Thus a medium-sized cyclotron is needed. The expected ^{124}I yield is considerably higher than via the other two low-energy reactions. However, the level of ^{125}I impurity is about 1%. The final choice of the production route will depend upon the level of tolerable impurity present in ^{124}I.

The targetry and radiochemical separation related to ^{124}I production are based on established technology for dry distillation of radioiodine from a $^{124}TeO_2$ target. The final product in solution exists >98% as iodide and is very suitable for subsequent labelling work.

The suitability of ^{124}I for PET measurements was tested using a 3D Hoffmann brain phantom (cf. Herzog et al., 2002). A typical result is shown in Fig. 3 and is compared with that for ^{18}F (the accepted standard for PET). In the case of ^{124}I, there is some blurring and the image resolution is reduced. However, the result demonstrates that ^{124}I, in spite of its higher positron energy ($E_{\beta^+} = 2.13$ MeV) and associated γ-rays of energies 603 and 1691 keV, is not much inferior to ^{18}F, as far as the resolution is concerned.

The radionuclide ^{124}I is both a diagnostic and a therapeutic radioisotope. Some applications were recently enumerated (cf. Hohn et al., 2001). Concerning diagnostic studies, the uptake kinetics of iodo-radiopharmaceuticals can be conveniently followed using this radioisotope and PET. A further application entails quantification of biodistribution of ^{123}I-radiopharmaceuticals used in SPECT, for example IMT and β-CIT. Regarding therapeutic use, ^{124}I was found to be very suitable for labelling biomolecules for tumour research. Recently, the dosimetry in radiotherapy of benign thyroid tumours was studied using this radioisotope. It was found that the quantitative ^{124}I-PET can lend itself advantageously to regional dosimetry. Because of the combination of PET and endoradiotherapy, allowing precise dosimetry, this radionuclide is superior to the commonly used reactor radionuclide ^{131}I.

3.4.2. *Positron emitting analogues*

A β^+ emitting analogue could be applied for quantification of a SPECT radiopharmaceutical. Similarly, in endoradiotherapy with β^- emitting particles, therapy planning and dosimetric calculations could be done advantageously using a β^+ emitting analogue. Some of the β^+ emitters that have been developed and used to date under the analogue approach include ^{66}Ga (for ^{67}Ga), ^{94m}Tc (for ^{99m}Tc), ^{110m}In (for ^{111}In), ^{120g}I (for ^{123}I), ^{83}Sr (for ^{89}Sr), ^{86}Y (for ^{90}Y) and ^{124}I (for ^{131}I). The first four deal with quantification of SPECT radionuclides and the latter three with dosimetric considerations in the use of therapeutic radionuclides. Their production methods have been recently developed.

The application of ^{66}Ga, ^{110m}In and ^{120g}I as analogue tracers for SPECT radiopharmaceuticals is still in development. The use of ^{94m}Tc ($T_{\frac{1}{2}} = 52$ min, $E_{\beta^+} =$ 2.47 MeV, $I_{\beta^+} = 70\%$), on the other hand, is now far more advanced. Several methods for its production have been attempted (for a review see, Qaim, 2000). However, the ^{94}Mo(p,n)-reaction was found to be the best from the viewpoint of both yield and purity. To date it has been used for quantification of several reactor produced ^{99m}Tc-radiopharmaceuticals, especially myocardial perfusion agents, like teboroxime (CardioTec) and methoxyl isobutyl isonitrile (MIBI). Very recently ^{94m}Tc has been applied in studies related to changes in dopamine transporter concentrations, e.g. with TRODAT-1. Further applications are in development and the demand for this radioisotope is expected to increase.

The use of β^+ emitting analogues of therapeutic radioisotopes is a relatively new approach and has been very successful in dose distribution studies of pure β^- emitting therapeutic radionuclides like ^{89}Sr and ^{90}Y. In particular the radionuclide ^{86}Y ($T_{\frac{1}{2}} = 14.7$ h, $E_{\beta^+} =$ 1.96 MeV; $I_{\beta^+} = 33\%$) has become the most suitable β^+ emitter for quantification of radiation dosimetry of ^{90}Y-labelled radiotherapeuticals. It is produced via the ^{86}Sr(p,n)^{86}Y reaction at a small-sized cyclotron (cf. Rösch et al., 1993). As an example, the uptake kinetics of ^{86}Y-citrate in normal spine, liver and five different metastases are given in Fig. 4 (cf. Herzog et al., 1993). The activity concentration found in the metastases is higher than in normal bone (spine). By obtaining this type of activity accumulation data via PET, it is possible to do proper dosimetric calculations while using ^{90}Y-therapeuticals.

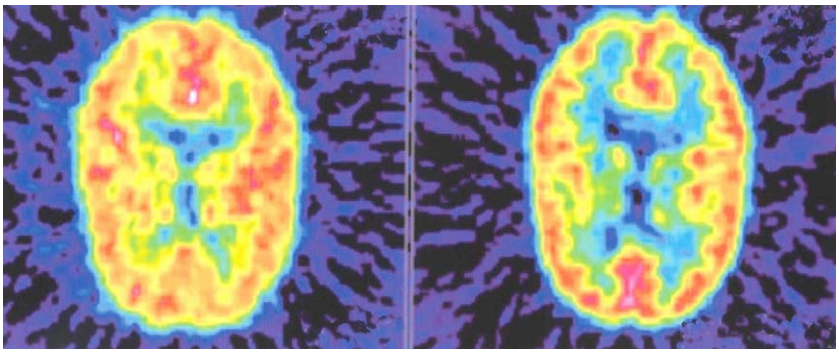

Fig. 3. PET images of a 3D Hoffmann brain phantom—a model that imitates the structures of the brain. The longer-lived ^{124}I (left side) yields an image similar to that obtained with the ^{18}F standard radionuclide (right side), though with reduced image resolution and image contrast. The results still demonstrate the suitability of ^{124}I for PET studies (after Herzog et al., 2002).

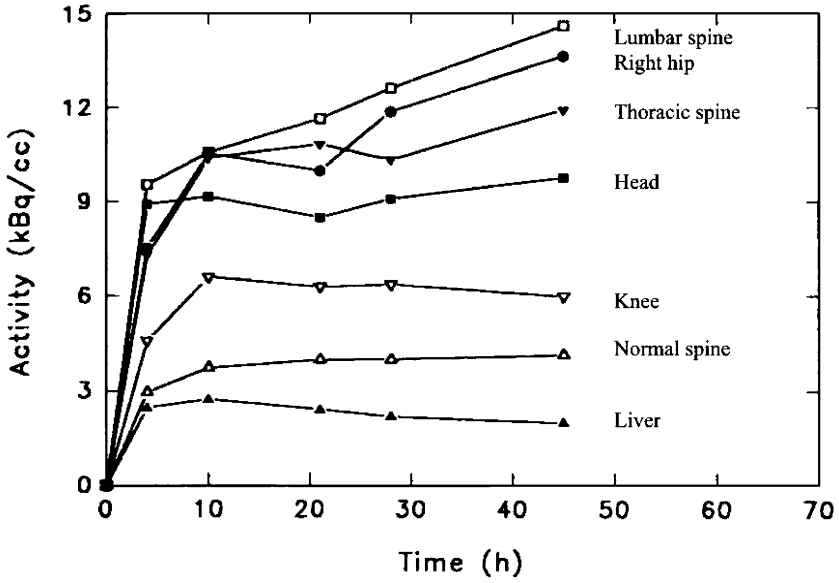

Fig. 4. Uptake kinetics of ^{86}Y-citrate in normal bone (spine), liver and five metastases (in knee, head, thoracic spine, right hip and lumbar spine) of a female patient, measured via PET (after Herzog et al., 1993).

3.5. Therapeutic radionuclides

In recent years the use of low energy but highly ionizing radiation has been gaining considerable significance in internal radiotherapy. Besides widely used brachytherapy, efforts related to endoradiotherapy have been intensified. The low-energy Auger electrons have a range of about 10 μm and can have a therapy effect only if they reach the cell nucleus. The alpha-particles have a range of about 100 μm and can already have a therapy effect if they reach the cell membrane. The β^- particles have ranges of about 1 mm and more, depending upon their energies. They can lead to therapy effects even if they reach the cell environment. The X-rays of energies 20–30 keV have ranges between 1 and 2 mm. Evidently, for achieving the internal radiotherapy effect via the biochemical pathway (i.e. endoradiotherapy), great skills in radiopharmaceutical production and application are demanded (cf. Stöcklin et al., 1995).

Therapy-related radionuclides are generally produced in nuclear reactors. Many of the newly developed radionuclides are, however, produced at cyclotrons (cf. Qaim, 2003). Of particular interest are the radionuclides ^{67}Cu ($T_{\frac{1}{2}}$ = 2.60 d, E_{β^-} = 0.6 MeV), ^{103}Pd ($T_{\frac{1}{2}}$ = 17.0 d, Auger electrons and X-rays), ^{186}Re ($T_{\frac{1}{2}}$ = 3.8 d, E_{β^-} = 1.1 MeV), ^{211}At ($T_{\frac{1}{2}}$ = 7.2 h), E_{α} = 5.9 MeV) and ^{225}Ac ($T_{\frac{1}{2}}$ = 10.0 d, E_{α} = 5.8 MeV). For ^{67}Cu production, the ^{68}Zn(p,2p) reaction is most suitable. It demands a medium-sized cyclotron of $E_p > 50$ MeV. The radionuclide is used for labelling monoclonal antibodies

(mab) for tumour therapy. The significance of ^{103}Pd has tremendously increased in recent years. In the USA about 20 small-sized but high-intensity cyclotrons were built over the last decade to produce ^{103}Pd via the ^{103}Rh(p,n) reaction. It is almost a pure X-ray and Auger electron emitter and is being increasingly used in treatment of prostate cancer via brachytherapy. The radionuclide ^{186}Re is a heavier homologue of technetium. It forms very stable coordination compounds and has therefore great endotherapeutic potential. Its production at a cyclotron via the ^{186}W(p,n)^{186}Re reaction is in development. The last two radionuclides mentioned above, i.e. ^{211}At and ^{225}Ac are α-emitters. ^{211}At has been in use in endoradiotherapy for about 30 years but, in recent years, with enhanced progress in tumour targeting, the interest in this radionuclide has further increased. It is produced via the ^{209}Bi(α,2n)^{211}At reaction at $E_\alpha = 28.0$ MeV. The radionuclide ^{225}Ac is very promising both in itself and as generator of ^{213}Bi. It is generally obtained from the burnt up nuclear fuel via an elaborate chemical processing. An interesting new production route is the ^{226}Ra(p,2n)^{225}Ac reaction using a highly radioactive target at a medium-sized cyclotron.

The above examples demonstrate that cyclotrons are also capable of delivering special radionuclides for therapeutic use. Furthermore, a recent new concept, suggesting the use of the (n,p) reaction with fast neutrons produced at cyclotrons (Qaim et al., 2003b), may prove to be very advantageous for the production of a few therapeutic radionuclides like ^{67}Cu, ^{89}Sr, etc.

4. Conclusion

A wide variety of cyclotrons and accelerators with energies ranging between 3 and 800 MeV find applications in medicine. They are used on the one hand for radiation therapy (delivering both ion-beams and neutrons) and, on the other, for producing radiotracers for applications in diagnosis via emission tomography as well as in internal radiotherapy. Of particular interest is PET which relies heavily on radiopharmaceuticals labelled with short-lived organic positron emitters. Those radioisotopes can be produced only at cyclotrons.

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