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Review

Production of iodine-124 and its applications in nuclear medicine

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HIGHLIGHTS

- Improve the discussion and disseminate the knowledge of recent advances in nuclear medicine.
- Stimulate the offer of alternative ways using the recent developed positron emitters.
- Contribute to democratize the use of radiopharmaceuticals in developing countries.
- Promote social benefit, starting a new era in diagnostic imaging in developing countries.

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ABSTRACT

Until recently, iodine-124 was not considered to be an attractive isotope for medical applications owing to its complex radioactive decay scheme, which includes several high-energy gamma rays. However, its unique chemical properties, and convenient half-life of 4.2 days indicated it would be only a matter of time for its frequent application to become a reality. The development of new medical imaging techniques, especially improvements in the technology of positron emission tomography (PET), such as the development of new detectors and signal processing electronics, has opened up new prospects for its application. With the increasing use of PET in medical oncology, pharmacokinetics, and drug metabolism, ^{124}I-labeled radiopharmaceuticals are now becoming one of the most useful tools for PET imaging, and owing to the convenient half-life of I-124, they can be used in PET scanners far away from the radionuclide production site. Thus far, the limited availability of this radionuclide has been an impediment to its wider application in clinical use. For example, sodium [^{124}I]-iodide is potentially useful for diagnosis and dosimetry in thyroid disease and [^{124}I]-M-iodobenzylguanidine ([^{124}I]-MIBG) has enormous potential for use in cardiovascular imaging, diagnosis, and dosimetry of malignant diseases such as neuroblastoma, paraganglioma, pheochromocytoma, and carcinoids. However, despite that potential, both are still not widely used. This is a typical scenario of a rising new star among the new PET tracers.

Contents

Abbreviations: CT, computed tomography; mAbs, monoclonal antibodies; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography

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1. Introduction

In recent years, positron emission tomography (PET) has become a powerful non-invasive technique for molecular imaging. It provides functional physiological and biochemical information as well as information on in vivo pharmacological processes, especially quantitative distributions of radiopharmaceutical. Moreover, PET is well-known to be a powerful technique for accurate in-vivo quantification of the temporal distribution of radiolabeled antibodies over several days.

In short, PET can be described as a technology that uses the detection of coincidence events to form an image of functional processes. Short-lived positron-emitting isotopes are incorporated into an organic substance, which can be used as a marker of metabolic activity. Images of the radioactivity distribution throughout the body can show rapidly growing tissues such as tumors, metastasis, or even infections. PET images can be viewed in conjunction with computed tomography (CT) scans to determine an anatomic correlate. Most of the modern scanners combine the PET system with a conventional CT-scanner or even with magnetic resonance imaging (MRI) to optimize the image reconstruction involved with positron imaging. The resulting combination of functional and anatomic imaging information is a useful tool for non-invasive diagnosis and patient management (Freudenberg et al., 2008).

Some of the radionuclides for PET, such as ^{11}C, ^{13}N, and ^{15}O, are isotopes of natural elements that constitute most biochemical substances and drugs. In such cases, the radiopharmaceuticals developed are ideal probes for molecular imaging because they are biochemically indistinguishable from their natural counterparts. However, for practical application, the half-lives ($t_{1/2}$) of these three radionuclides are too short (^{11}C: $t_{1/2}=20$ min; ^{13}N: $t_{1/2}=10$ min, and ^{15}O: $t_{1/2}=2$ min), which may limit both the chemical synthesis processes as well as the length of PET studies.

Halogens (F_2, Cl_2, Br_2, and I_2) are unique in nature. The radiolabeling of biochemicals with halogen radioisotopes such as bromine or iodine alters the biological behavior of the molecule. Fortunately, halogen atoms in drug molecules are quite common, and sometimes the halogen containing drug molecules might have a greater affinity for a receptor or an enzyme than non-halogenated molecules (Park et al., 2001). Organic molecules containing an aromatic ring can be easily labeled with radionuclides. Several recent reviews have discussed the development of many new halogenated PET radiopharmaceuticals with potential clinical applications (Wadsak and Mitterhauser, 2010; Glaser et al., 2003).

Radionuclides of iodine are widely used in nuclear medicine for the labeling of monoclonal antibodies, receptors, and other radiopharmaceuticals, especially in diagnostic and therapeutic applications where quantitative imaging over a period of several days is necessary. Unfortunately, the nuclides that are most commonly used, i.e., ^{123}I, ^{125}I, and ^{131}I, all have specific limitations. Iodine-123 has a relatively short half-life, considering the fact that the activity of the radiopharmaceutical has to be followed over several days. For iodine-125, the photon energy is too low for optimal imaging, especially for quantitative imaging, and its half-life is undesirably long. For iodine-131, the most widely used of the three isotopes, the photon energy is too high for optimal imaging. Furthermore, single-photon emission computed tomography (SPECT) imaging does not permit a rigorous attenuation correction, although a satisfactory empirical correction may sometimes be achieved.

The ^{124}I radioisotope has a high potential for use in nuclear medicine, and as a positron-emitter, it offers a superior quality of detection in comparison with other positron emitters. Its applications range from simple imaging of the thyroid and parathyroid to functional studies of neurotransmitter receptors, through monoclonal antibodies for the study of cancer. It has furthermore been used to label molecules such as m-iodobenzylguanidine, fatty acids, and fibrinogen, allowing the study of diseases of different organs such as brain and heart. Several areas of molecular imaging can incorporate these advantages of this radioisotope. Considering its relatively long half-life of 4.2 days, however, it is most beneficial for immuno-PET, as it allows quantitative imaging over a period of several days (Pentlow et al., 1996). Moreover, the labeling chemistry for ^{124}I is well established, and a wide variety of compounds (Koehler et al., 2010; Chacko and Divgi, 2011) have been labeled for molecular imaging purposes with PET.

In the specific case of ^{124}I, some of its characteristics can be considered as disadvantages. This radioisotope has a relatively low ratio of disintegration resulting in positrons (about 23%), a relatively complex decay scheme which includes high-energy gamma emissions (highest about 1.7 MeV). Despite these facts, the amount of recent studies, results and publications prove that ^{124}I is still considered as a suitable radioisotope for PET applications (Pentlow et al., 1996; Herzog et al., 2002).

This review is focused on the general production methods for ^{124}I, and also presents several details and advances on targeting, chemistry, and clinical applications.

2. Iodine-124 production

There are several reactions which can be used to produce ^{124}I, depending on the cyclotron, particles, and the energies available to carry out the irradiations. A list of the potential reactions is presented in Table 1. ^{124}I has mainly been produced by using enriched tellurium-124 via the ^{124}Te(d,2n)^{124}I reaction (Lambrecht et al., 1988; Clem and Lambrecht, 1991; Firouzbakht et al., 1993; Weinreich and Knust, 1996; Bastian et al., 2001). In recent years, the ^{124}Te(p,n)^{124}I reaction has been increasingly used (Scholten et al., 1995; Sheh et al., 2000; Hohn et al., 2001; Qaim et al., 2003; Glaser et al., 2004). These routes have also been evaluated in two coordinated research projects (CRPs) of the IAEA (Gul et al., 2001; Capote et al., 2007).

Aslam et al. (2010) recently evaluated the major proton- and deuteron-induced reactions on Te isotopes for the production of ^{124}I. Their results showed that the proton-induced reaction on

Table 1
Selected published data on ^{124}I production.

Nuclear reaction	Target material	Energy range (MeV)	Impurities	Yield	Specific activity	Reference
^{124}Te(p,n)^{124}I	TeO_2 99.8% Te 5% Al_2O_3	11.6→0	^{123}I	6.88 MBq/μAh	–	Nagatsu et al. (2011)
^{124}Te(p,n)^{124}I	TeO_2 99.8% Te	12.6	^{123}I	13.0 MBq/μAh	–	Schmitz (2011)
^{124}Te(p,n)^{124}I	$Al_2{}^{124}Te_3$ 99.5% Te	11→2.5	^{125}I and ^{126}I < 0.001%	8.47 MBq/μAh (229 μCi/μAh)	–	Nye et al. (2007)
^{124}Te(p,n)^{124}I	TeO_2 99.5% Te 6% Al_2O_3	11→2.5	^{125}I < 0.02% ^{126}I < 0.001%	6.4 MBq/μAh (173 μCi/μAh)	–	Nye et al. (2006)
^{124}Te(p,n)^{124}I	TeO_2 99.86% Te 5% Al_2O_3	14→7.0	^{125}I-0.03% ^{126}I-0.007%	21.1 MBq/μAh	–	Sajjad et al. (2006)
^{124}Te(p,n)^{124}I	TeO_2 99.8% Te	12.5→5.0	^{125}I-0.053%	9.0 ± 1.0 MBq/μAh	27.6 GBq/μmol	Glaser et al. (2004)
^{124}Te(p,n)^{124}I	TeO_2 99.8% Te 5% Al_2O_3	13.5→9.0	^{123}I < 1 ^{125}I < 0.01% ^{126}I < 0.0001% at time of application	5.8 MBq/μAh	–	Qaim et al. (2003)
^{124}Te(d,2n)^{124}I	TeO_2 89.6%	16→6.0	Impurities ≤ 5% at 40 h EOB	–	12 Ci/μmol	Weinreich and Knust (1996)
^{124}Te(d,2n)^{124}I	TeO_2 96 % Te	13.5→9.0	N/C	–	450 GBq/μmol	Knust et al. (2000)
^{124}Te(d,2n)^{124}I	Te 99.8%	14→10	^{125}I-1.7%	17.5 MBq/μAh	–	Bastian et al. (2001)
^{124}Te(p,n)^{124}I	Te 96.21%	12→6.8	N/C	0.09 mCi/μAh	–	Kondo et al. (1977)
^{nat}Sb(α,xn)^{124}I	^{nat}Sb	22→13	^{125}I, ^{126}I-27%	0.45 at 5 d EOB	–	Watson et al. (1973), Ismail (1989, 1990), Hassan et al. (2006), Uddin et al. (2011), and Aslam et al. (2011)
^{121}Sb(α,n)^{124}I	^{121}Sb 99.45%	22→13	^{123}I < 4% ^{125}I, ^{126}I < 0.2%, at 5 d EOB	2.1 MBq/μAh	–	Hassan et al. (2006)
^{123}Sb(α,3n)^{124}I	^{123}Sb 98.28%	42→32	^{125}I 1.8% ^{126}I 0.6% ^{123}I < 5% 60 h EOB	–	–	Uddin et al. (2011)
^{123}Sb(^{3}He,2n)^{124}I	^{123}Sb	45→32	^{125}I 1.19% ^{123}I 14%	15.5 MBq/μAh	–	Aslam et al. (2011)
^{nat}Sb(^{3}He,xn)^{124}I	^{nat}Sb	35→13	^{125}I 1.3% ^{126}I 1.2%, values at 5 d EOB	0.42 MBq/μAh	–	Tarkanyi et al. (2009) and Hassan et al. (2006)

enriched ^{124}Te targets is the method of choice for small cyclotrons with energies below 16 MeV because ^{125}I is extremely low. Furthermore, the reaction is superior to ^{124}Te(d,2n)^{124}I owing to lower impurity levels. It should be mentioned that Scholten et al. (1995) have suggested this before. Hohn et al. (2001) has measured the excitation functions of the ^{125}Te(p,xn)^{123,124,125}I reactions from threshold up to 100 MeV and found the optimum energy to range from 21 to 15 MeV for the production of ^{124}I via ^{125}Te(p,2n). This reaction could be used advantageously at medium-sized machines. Although, initially, the impurity of ^{125}I is higher it is similar to the impurity level for the ^{124}Te(d,2n) reaction after four days cooling time.

As alternatives to ^{124}I production, a relatively large number of experiments have been performed over the years on cross section determination of ^{3}He- and alpha-particle-induced reactions on natural or enriched antimony (Watson et al., 1973; Sharma et al., 1988). However, the discrepancies in the data are large; Tarkanyi et al. (2009) performed a careful investigation of the data available on these reactions and suggested that the origin of the contradictions could result from most of the data having been measured more than 15 years ago. They furthermore suggested that special attention should be paid to the thickness of the used targets, the beam energy degraders used, and the beam current measurements since these are the main sources of systematical errors and cumulative energy shifts. Similarly, Gul (2009) analyzed the data for ^{3}He-induced reactions and found considerable disagreements between the theory and some of the experimental data. Aslam et al. (2011) and Uddin et al. (2011) recently re-investigated the antimony route and concluded that the ^{123}Sb(α,3n)^{124}I process can produce sufficient amounts of ^{124}I with relatively low levels of ^{125}I and ^{126}I impurities, while the yield is comparable to that of the ^{124}Te(p,n)^{124}I. The (α,3n) reaction would, however, require an intermediate energy cyclotron with an α-particle beam.

The (p,n) reaction on ^{124}Te leads to a good target yield with a high radionuclidic purity of ^{124}I produced. Apart from that, it can be produced at small-sized cyclotrons that produce traditional PET isotopes such as ^{18}F and ^{11}C. For this reason the use of the ^{124}Te (p,n) reaction has increased in recent years. Except for the incident beam energy, the production methods for ^{123}I and ^{124}I that use enriched tellurium are based on virtually the same technical system.

The practical implementation of ^{124}I production systems in dedicated PET cyclotrons demands specific configurations, depending on the selected production methodology. The research needed to support the selected production methodology extends far beyond the knowledge and evaluation of excitation functions of the nuclear reactions involved. The study of physical and chemical parameters, during and after irradiation, of the target plays a key role (Beyer and Pimentel-Gonzales, 2000). In fact, the economic viability of the chosen method depends, among other factors, largely on the ability to extract the ^{124}I produced and especially on the capability of recovering the target material. Indeed, the price becomes prohibitive to those methodologies that do not involve any re-use and is decisive for the economic feasibility of the proposed chemical separation techniques of the ^{124}I produced. This point was emphasized by Kondo et al. (1977), Acerbi et al. (1975) and Zielinski et al. (1977); where, for instance, 60% to 90% of the tellurium target is recovered.

2.1. Thermal considerations

Most of the research on the thermal stability of the irradiated sample has focused on the development of targets that enable efficient cooling and a lower heat density during irradiation. One of the more important factors that determine the thermal stability of the irradiated target is its composition. Van den Bosch et al. (1977), studied tellurium dioxide as a possible target material and concluded that this particular chemical form has advantageous properties over metallic Te, which was used before by Acerbi et al. (1975), Kondo et al. (1977) and Lambrecht et al. (1989). The main advantages of tellurium dioxide are the higher melting point (733 °C) and the good solidification properties, whereas elemental tellurium tends to blow up upon heating and favors the volatilization of iodine in the presence of oxygen. Indeed, many other studies have used TeO_2 as the target material (Glaser et al., 2004; Beyer et al., 1981; Michael et al., 1981; Oberdorfer et al., 1981; Zaidi et al., 1983; Comor et al., 2004).

To improve heat exchange, it is common to add around 5% by mass of Al_2O_3 to TeO_2. This increases the uniformity of the target material, giving a glassy solid structure and an enhanced adherence of the target layer with the target plate (Sheh et al., 2000; Qaim et al., 2003; Sajjad et al., 2006; Nye et al., 2006, 2005). Nye et al. (2007) and Nye and Nickles (2007) studied Al_2Te_3, which has a higher melting point (895 °C) and forms a glassy surface upon heating. McCarthy investigated the use of Cu_2Te as the target material (McCarthy et al., 1999), while electroplated targets with enriched Te were used in ^{123}I and ^{124}I production by Lambrecht et al. (1988, 1989) and Van den Winkel (2004). More recently, several improvements for obtaining thick electrodeposited tellurium on nickel-coated copper substrates for ^{124}I production were proposed (Sadeghi et al., 2008; Al-Yanbawi and Al Jammaz, 2007).

Another factor of consideration proposed by Van den Bosch et al. (1977), is the selection of the target support, where some criteria should be met. First of all, the target support should present the best compromise between thermal conductivity and chemical resistance. In addition, there should be good adhesion between TeO_2 and the target support material, while only low- and short-lived-induced radioactivity should develop in the target support during irradiation with residual proton energy. As a result, the typical target plate is either made of platinum, as mentioned by Sheh et al. (2000), Qaim et al. (2003), Glaser et al. (2004), Comor et al. (2004), Nye et al. (2006) and Alekseev et al. (2005), or tantalum (Nye et al., 2005; Alekseev et al., 2005). Other examples of materials that have been employed as target supports are nickel electroplated in copper (Lambrecht et al., 1988, 1989; Sadeghi et al., 2008) and an alloy of 90% platinum and 10% iridium (Weinreich and Knust, 1996; Knust et al., 2000; Smith et al., 2011).

In addition to target composition and target support, some efforts have been made to increase the thermal performance of the irradiated targets. The first targets were cooled directly by water at the back side. Van den Bosch and others increased the cooling with a thin water layer in front of the target (Van den Bosch et al., 1977; Michael et al., 1981); whereas Kondo et al. (1977) developed a target assembly with encapsulated solid or powdered targets. Beyer et al. (1981) and Gelbart et al. (1997) used water cooling at the back side of the target and pressurized air in front because they reasoned that such a system would decrease the loss of target material during irradiation. Some authors replaced the pressurized air with helium (Qaim et al., 2003; Glaser et al., 2004; Comor et al., 2004; Brown et al., 1999).

Another solution to improve heat transfer from the target surface, which was reported by several groups, is to increase its irradiation area and effective thickness by orienting the target at an inclined angle with respect to the direction of the incident beam (Sheh et al., 2000; Nye et al., 2006, 2007; Beyer and Pimentel-Gonzales 2000). Recently, using a capsulated target, Nagatsu and Fukada developed a robotic, fully automated system for the large scale production of iodide-124 (Nagatsu et al., 2011).

2.2. Target processing: dry distillation of ^{124}I

The method currently used for isolating ^{124}I produced from oxide target material is based on the liberation of iodine by heat. Termed dry distillation, it consists of submitting the heated target material in a quartz tube under a gas flow, which removes traces of TeO_2 and traps the radioiodine while retaining the target material on the target plate. This method was first proposed for ^{131}I production by the research groups of Shikata and Amano (1973) and also at the Eindhoven cyclotron by Van den Bosch et al. (1977). More recently, it was applied by the Jülich group for the isolation of ^{123}I (Michael et al., 1981; Knust et al., 1990). Later on, it was adapted for the ^{124}I production by Weinreich and Knust (1996), Qaim et al. (2003), Glaser et al. (2004), Nagatsu et al. (2011), Nye et al. (2005, 2006), Sajjad et al. (2006), Knust et al. (2000), Beyer and Pimentel-Gonzales (2000), Smith et al. (2011), Guenther et al. (1998) and Barnhart et al. (2003). Although in the above mentioned literature dry distillation is focused on TeO_2 as a target material, it should be mentioned that Nye and colleagues obtained excellent results in the dry distillation of ^{124}I with Al_2Te_3 as a target material (Nye et al., 2007).

Furthermore, judging from the literature mentioned, there is a wide variation in the setup parameters (Table 2). The considerations made by Knust et al. (2000), however, emphasize that to obtain a nearly quantitative removal of ^{124}I from irradiated $^{124}TeO_2$ targets, the gas volume between the furnace and the trap should

Table 2
Dry distillation setup parameters.

Target material	Distillation temperature	Flow and transport gas	Distillation time (min)	Trapping method	Distillation efficiency (%)	Reference
TeO_2	755 °C induction furnace	O_2	2		> 90	Michael et al. (1981)
TeO_2	770 °c electrical furnace	24 ml/min O_2	20	NaOH solution	> 95	Zweit et al. (1991)
TeO_2	740 °C electrical furnace	20 ml/min Air	6	Stainless steel	80–95	Knust and Weinreich (1997)
TeO_2 5% Al_2O_3	740 °C electrical furnace	40 ml/min Air	6	Stainless steel loop	80	Knust et al. (2000)
TeO_2 6.7% Al_2O_3	670 °C electrical furnace	5 cm^3/min O_2	7	Pyrex-capillary	> 95	Sheh et al. (2000)
TeO_2 5% Al_2O_3	750 °C electrical furnace	12–14 ml/min air	20	NaOH solution	90	Qaim et al. (2003)
TeO_2	> 733 °C electrical furnace	45 ml/min O_2	20	NaOH solution	91	Glaser et al. (2004)
TeO_2 6% Al_2O_3	740 °C electrical furnace	Air		Quartz	85–90	Nye et al. (2005)
TeO_2 6% Al_2O_3	750 °C electrical furnace	15 ml/min Air	15	Quartz capillary/Pt wire inside	95	Nye et al. (2006)
TeO_2	700 °C electrical furnace	20 ml/min Air	5	NaOH solution		Sajjad et al. (2006)
Al_2Te_3	910 °C	20 ml/min N_2	15	Quartz capillary/Pt wire inside		Nye et al. (2007)
TeO_2 5% Al_2O_3	710 °C	10 ml/min O_2	15 (total time 2.5 h)	Ethanol solution	92 ± 4	Nagatsu et al. (2011)
TeO_2	740 °C electrical furnace	40 ml/min Air	6	Stainless steel loop	80–95	Smith et al. (2011)

be minimized, and the iodine activity should be taken up in a small solvent volume. Some authors have warmed the region between the furnace and the trap to prevent premature precipitation of the distilled iodine (Qaim et al., 2003; Glaser et al., 2004; Nye et al., 2006). Another consideration brought up by Qaim et al. (2003) is the importance of annealing TeO_2/Al_2O_3 at 450 °C and the stepwise raising of the temperature during target preparation to convert small amounts of TeO_3 to TeO_2. According to the authors, this procedure has to be performed to avoid higher loss of Te during distillation. An intermediate trap using Al_2O_3 wool as a filter was used by Glaser et al. (2004) and Ylimaki et al. (2004) to retain volatile tellurium oxide.

3. Iodine radiolabeling

The best approach for preparing a radiopharmaceutical is to replace one of the original atoms of a molecule of biological interest with one of its radioactive isotopes. Carbon, oxygen, and nitrogen atoms can be replaced with their positron-emitting isotopes (i.e. ^{11}C, ^{15}O, or ^{13}N), which do not modify the biological properties of the molecule. For halogenated compounds, radiohalogenation with the positron emitters ^{18}F or ^{76}Br can also be considered. When isotopic labeling is not possible, analogous labeling with a radiohalogen offers an interesting alternative. However, adding a halogen such as an iodine atom to a molecule may modify the physicochemical properties and the in vitro and in vivo pharmacological characteristics of the pharmaceuticals. To minimize such effects, radioactive iodine should be introduced in a position as far as possible from the pharmacophore.

The chemistry of iodine is very similar to that of bromine. The binding strength of the C–I bond is 45 kcal/mol and that of C–Br is 59 kcal/mol. This carbon–halogen bond energy is an important factor for the in vivo stability of the radiolabeled compound. As the chemical reactivity of iodine is lower than that of fluorine and bromine, iodinated radiotracers can be prepared more easily than their fluoro and bromo analogues. As a result, some diseases can be more properly diagnosed with iodinated compounds. Some of these diseases are discussed below.

3.1. Hypoxia

Hypoxia is the result of an improper balance between the supply and consumption of oxygen and is a characteristic property of solid tumors. Hypoxia has been correlated with local recurrence and metastasis in a range of human tumor types. Also, hypoxia has also been shown to reduce the sensitivity of several commonly used chemotherapeutic agents. This way, identification of hypoxic tumor tissue is of high clinical relevance. More details about hypoxia, as well as the adverse effect of low oxygen tension on radiation therapy, are well described in the literature, specially Serganova et al. (2006).

As already mentioned, PET is well known to be a powerful noninvasive nuclear medicine technique, that also offers the potential to measure and quantify physiological process in vivo (Wuest and Wuest, 2013). However, one important point that should be considered is that the ability to image tumor hypoxia with nuclear medicine techniques, and the optimum time for imaging, depend on the pharmacokinetics of the radiotracers and the half-life of the radionuclide. The influence factors include the delivery of the radiotracer to the tumor by blood flow, the kinetics of radiotracer uptake in hypoxic cells relative to that in well-oxygenated cells, the clearance of the free radiotracer from the bloodstream, and the washout of the “trapped” radiotracer from the hypoxic cells.

The first clinical studies to image hypoxia using PET were based on halogenated tracers of 2-nitroimidazoles, such as [^{18}F]FMISO, and were performed by Rasey et al. (1996), Koh et al. (1992) and Lee and Scott (2007). Clinical application of this tracer is, however, limited by its unfavorable biokinetics. The relatively high lipophilicity is responsible for slow specific accumulation in hypoxic tissue as well as slow clearance from normoxic tissue, resulting in low target-to-background contrast (Vallabhajosula, 2007).

The development of a new class of 2-nitroimidazole compounds have been radiolabeled and studied as a potential hypoxia imaging agents, such as [^{18}F]FAZA, fluorazomycin arabinoside (Souvatzoglou et al., 2007). Some hypoxia markers of this class were also labeled with longer-lived radionuclides such as ^{123}I, ^{131}I and ^{124}I and proved its value for detection of hypoxia in vitro (Mannan et al., 1991) and in vivo (Kumar et al., 2005; Lee et al., 2000). The 2-nitroimidazole derivative [^{124}I]IAZA was studied by Reischl et al. (2007) to investigate its potential as a PET hypoxia tracer in comparison with its ^{18}F analog [^{18}F]FAZA and the more established hypoxia tracer [^{18}F]FMISO. The study was performed in a mouse model of human cancer, using small animal PET. [^{18}F]FAZA showed superior biokinetics compared to [^{18}F]FMISO and [^{124}I]IAZA. However, the hypothesis that longer uptake times would result in significantly improved tumor background ratios could not be confirmed in this study. Also, deiodination and subsequent uptake of radiolabel into thyroid tissue is a disadvantage, but can be greatly reduced by adequate thyroid blocking.

Zanzonico et al. (2004) evaluated another hypoxia imaging agent, iodine-124 labeled iodine azomycin galactoside [^{124}I]IAZG, and compared with [^{18}F]FMISO in the same tumor-bearing animals using micro PET imaging. The authors showed that the optimum time for imaging is 24–48 h post-injection for [^{124}I]IAZG, and 3–4 h post-injection for [^{18}F]FMISO and that tumor-to-whole body activity contrast is higher for [^{124}I]IAZG than for [^{18}F]FMISO images, at the respective optimum imaging times. Also, a considerable deionization of [^{124}I]IAZG in vivo, of free iodine, by the thyroid was confirmed.

Regarding the positron emitter itself, two points should be considered: first, the long half-life and low positron abundance (22%) of ^{124}I may require higher administered activities to achieve adequate count statistics and may result in higher patient doses. However, depending on the patient's condition, this should not be a major concern.

Second point is related to the positron energy distribution. The positrons emitted by ^{124}I with higher energy may degrade spatial resolution, and the abundant (80%) high energy gamma rays (603 and 723 keV) may introduce random coincidence artifacts. However, some quantitative PET studies (Pentlow et al., 1991, 1996; Herzog et al., 2008; Bading et al., 2008) have reported that the spatial resolution of ^{124}I images is only slightly degraded relative to ^{18}F images.

In short, the authors pointed out some disadvantages of using [^{124}I]IAZG for imaging hypoxia but nothing to prevent its potential clinical use.

3.2. Tumor proliferation

The ability to image cell proliferation is an approach that has significant impact for both the diagnosis and therapeutic intervention in a great variety of tumors. Most of the recent published work has focused on DNA analogs, which are incorporated into the replicated DNA strand where attention is directed towards the developments of agents with longer half-lives and a greater resistance to degradation (Guenther et al., 1998; Blasberg et al., 2000; Bading and Shieds, 2008).

A noninvasive measurement of tumor cell proliferation could be used in the evaluation of tumor growth and to estimate its

malignancy grade. Also could be used to identify the most rapidly proliferating regions of the tumor, which would provide spatial information for radiation treatment planning and stereotactic biopsies.

^{124}I-iododeoxyuridine [^{124}I]IUdR and ^{124}I-uracil [^{124}I]FIAU are nucleoside analogs that are under investigation as possible imaging agents, as shown by several authors (Guenther et al., 1998; Blasberg et al., 2000; Roelcke et al., 2002). The main limitation of this approach is the rapid in vivo dehalogenation of the radiotracers.

Various studies seeking the reduction of radiohalogen background, including late-phase imaging (24 h) to allow washouts of the radiohalogen (Tjuvajev et al., 1993), biomodulation to block dehalogenation (Borbath et al., 2002) and molecular modification of the radiotracers to reduce dehalogenation (Toyohara and Fujibayashi, 2003), have achieved limited success (Blasberg et al., 1996).

Toyohara et al. (2003) developed a radioiodinated nucleoside analogs for imaging tissue proliferation with low energy gamma emitting ^{125}I. This study has determined biological data that may provide useful information for the determination of suitable approaches for developing radioiodinated nucleoside analogs. The authors suggested that the 4-thio-2-deoxy derivative, 5-[^{125}I]iodo-4-thio-2-deoxyuridine ([^{125}I]ITdU), is a more sensitive and specific tracer for imaging tissue proliferation than the 4-oxo-2-arabino-fluorinated 5-[^{125}I]iodo-(2-fluoro-2-Darabinofuranosyl) uracil ([^{125}I]FIAU). It was pre-clinically confirmed that ITdU, in which the 4′-oxo of 5-iodo-2′ deoxyuridine had been replaced by 4′- sulfur, is resistant to metabolic decomposition by thimithymidine phosphorylase and is therefore an agent that directly reflects DNA synthesis (Toyohara et al., 2002). If ITdU is radiolabeled with ^{124}I in the same way, this compound might be a suitable proliferation-imaging agent for PET with a metabolically stable and sufficiently long half-life for extended observation of DNA synthesis.

More recently, Stahlschmidt et al. (2008) have synthesized a new nucleoside analog [^{124}I]drFIB for imaging cell proliferation. The radiolabeled procedure was optimized to produce radiochemical yields up to 85% with a 1 h reaction at 140 °C. With this procedure, a routine ^{124}I production of 30 MBq/run, relatively high specific activities, approaching 100 MBq/mmol, can be expected.

3.3. Reporter gene expression

The reporter gene concept for molecular imaging is becoming a standard in various molecular biology protocols. The most commonly used PET imaging reporter systems are the HSV1-tk gene (herpes simplex virus type-1 thymidine kinase) (Serganova et al., 2007; Blasberg and Tjuvajev, 1999; Tjuvajev et al., 1996; Haberkorn et al., 1997) and the D_2R receptor gene (MacLaren et al., 1999) systems. The HSV1-tk gene has been also used as a suicide gene for cancer gene therapy (Serganova et al., 2007; Wang et al., 2006; Alauddin et al., 2001). The location and magnitude of HSV1-tk gene expression can be monitored repeatedly by PET, using ^{18}F-FHBG, ^{18}F-FHPG and ^{124}I-FIAU (Tjuvajev et al., 1996, 2002; Kim et al., 2010; Jacobs et al., 2001; Iyer et al., 2001) and ^{124}I-FIRU (Kim et al., 2010). However, conventional reporter genes such as the HSV1-tk and D_2R receptor gene systems have some limitations (Chung, 2002; Simoes et al., 2005; Groot-Wassink et al., 2002). They require the synthesis of complicated positron-emitting compounds, and the high cost of PET equipment (as compared with the widely distributed simple gamma camera systems) may restrict their clinical use. Also, substrates used in the HSV1-tk system can be toxic to cells, and those used in the D2 receptor system can give rise to physiological problems related to cell signal transduction.

The group of Shin et al. (2002) has proposed an alternative imaging reporter gene. It is the sodium/iodide symporter (NIS). This is a transmembrane protein which actively transports iodide ions into thyroid cells (Chung, 2002). NIS has a central role in the radioiodine diagnosis and treatment of thyroid diseases (Dai et al., 1996), and it has some favorably features when compared with those of HSV1-tk and D_2R (Shin et al., 2002, 2004). Some of these features are briefly described below.

After cloning the NIS gene (Smanik et al., 1996), some investigators reported the successful accumulation of radioiodine in several carcinoma cell lines and tumors transfected with the NIS gene (Min et al., 2002; Cho et al., 2002; Petrich et al., 2002; Spitzweg et al., 2001). An imaging system based on the NIS gene can produce images with simple cheap radionuclides such as ^{123}I, ^{131}I or ^{99m}Tc-pertechnetate. Both simple gamma camera systems and PET systems can acquire images using a suitable radionuclide, such as ^{99m}Tc and ^{124}I, respectively (Ahn, 2012).

According to Chung (2002), NIS has many advantages as an imaging reporter gene. Some of them are: the wide availability of its substrates, that is, radioiodine and ^{99m}Tc, and the well-understood metabolism and clearance of these substrates in the body. In addition, the NIS gene has another advantage; it is not likely to interact with the underlying cell biochemistry. Regarding the iodide compound, it does not metabolize in most tissues, and although sodium influx may be a concern, still no adverse effects were observed.

3.4. Apoptosis

Apoptosis is a form of programmed cell death, which is gene regulated. It is an active, energy-dependent mechanism for the elimination of cells that have been injured, infected, or immunological recognized as being harmful or superfluous. Apoptosis can be observed in a wide variety of malignant tumors, particularly in hypoxic zones adjoining areas of necrosis, and it is the endpoint of most forms of anticancer therapy.

During apoptosis mechanism, phosphatidylserine, a phospholipid normally sequestered on the inner leaflet of the cell membrane, is abruptly translocated to the external leaflet (Fadok et al., 1992). Phosphatidylserine exposure during apoptosis can be exploited as a PET imaging target, using ^{124}I labeled Annexin V as proposed by Glaser et al., as well as others authors (Blankenberg et al., 1999; Dekker et al., 2005a, 2005b; Glaser et al., 2003).

Dekker et al. (2005a, 2005b), studied a functional comparison of annexin V analogues labeled indirectly and directly with iodine 124. In this study, they used a similar approach (Zalutsky and Narula, 1987; Collingridge et al., 2003), but at this time they prepared [^{124}I]4IB-ovoalbumin and [^{124}I]4IB-annexin V using the active ester [^{124}I]N-hydroxysuccinimidyl-4-iodobenzoate. These tracers were tested in vitro and in vivo model of programmed cell death and compared with previous results obtained by Keen et al. (2005). They concluded that directly labeled protein was a superior tracer for mouse model of programmed cell death. Mainly because more steps were required to produce the indirectly labeled tracer, the overall radiochemical yield was lower. In addition they found lower hepatic accumulation of [^{124}I]4IB-annexin V in animals with apoptosis-positive livers, when compared with animals receiving [^{124}I] annexin V.

3.5. Antibodies diagnosis and immuno PET application

Monoclonal antibodies (mAbs) have been approved for diagnostic and therapeutic use in a broad range of medical indications, especially in oncology. The introduction of immuno-PET, i.e., the combination of PET with mAbs, is an attractive novel option for improving diagnostics and tumor characterization because it

combines the high sensitivity and resolution of a PET camera with the specificity of mAbs (Verel et al., 2005; van Dongen et al., 2007).

^{124}I satisfies special criteria to be appropriate for immuno-PET, and matches to the biodistribution dynamics of intact antibodies (Verel et al., 2003), due to its half-life. Additionally, the vast experience of radiolabeling proteins with others iodine radionuclides, i.e., ^{131}I, ^{125}I, and ^{123}I, promotes a significant level of confidence, since existing chemistry and protocols are directly applicable to ^{124}I (Nayak and Brechbiel, 2009).

The chemistry associated with radioiodination of monoclonal antibodies and other proteins have been studied extensively (Murray et al., 1991; Wilbur et al., 1989; Wilbur, 1992; Bolton and Hunter, 1973; Verel et al., 2004; Glaser et al., 2002; Collingridge et al., 2002). These studies have been carried out to determine which oxidant might be used with radioiodide to obtain efficient labeling without damaging the biologic proprieties of proteins. So far, the best results was obtained by Wilbur et al. (1989), using the PIB (N-succinimidyl 4-iodobenzoate) as oxidant, showing increased stability in vivo and, as a consequence, the uptake in the thyroid was reduced when compared to the same antibody radio-iodinated using Chloramine-T methods.

As an example in human application, Divgi et al. (2007) demonstrated that iodine 124 labelled antibody chimeric G250, [^{124}I]-cG250, can identify accurately clear-cell renal carcinoma, the most common and aggressive renal tumor. Chimeric G250 was radiolabelled according to the IodoGen method. More specific details on this method can be found in Salacinski et al. (1981).

Brouwers et al. (2002) have compared ^{131}I-G250, ^{124}I-cG250, and ^{18}F-FDG for detection of metastatic renal-cell carcinomas. They observed that ^{131}I-cG250 was able to detect 30% of metastatic lesions. With ^{18}F-FDG this result was 69%. However, the results were far better when ^{124}I-cG250 was used, with 94% sensitivity of tumor detection (Divgi et al., 2007; Brouwers et al., 2002). When the comparison is made between ^{124}I-cG250 and ^{131}I-cG250, both the resolution, contrast, and the possibility of quantification were better with ^{124}I-cG250 (Divgi et al., 2007).

3.6. ^{124}I-labelled radiopharmaceuticals

Table 3 lists the ^{124}I-labelled radiopharmaceuticals that have been applied in PET. The molecules have been arranged according to their target area in nuclear medicine.

4. Conclusions

The present review has summarized the recent advances in ^{124}I radionuclide production and medical use. The main subjects discussed have involved targetry, target processing and PET technology application.

Regarding the ^{124}I production yield, considering the target material and the bombarding particles, some recent results, including the current authors (to be published), have shown that ^{3}He and α particles induced reactions on antimony isotopes are inferior to proton and deuteron induced reactions on tellurium.

When the concern is the proper cyclotron for ^{124}I production, the ^{124}Te(p,n) reaction is ideally suited at small cyclotrons with energies below 16 MeV. Also, when the comparison is made with ^{124}Te(d,2n) reaction, the choice for (p,n) reaction has shown to be superior due to lower impurity levels' production. In the energy range $E_p = 12 - 8$ MeV the yield is 16 MBq/μAh, with very small ^{123}I impurity and extremely low ^{125}I content. This production route gives the purest ^{124}I. Today, it is the worldwide-preferred production method for large-scale production, in several “baby” cyclotrons.

Table 3
PET application of ^{124}I-labelled radio-pharmaceuticals.

PET imaging application	Ligands	^{124}I-labelled radio-pharmaceuticals	Reference
Tumor	Proteins and peptides	[^{124}I] I-SHPP N-succinimidyl 3-(4-hydroxy-5-[^{124}I]iodophenyl) propionate	Glaser et al. (2002)
	Insulin	[^{124}I]A14-iodoinsulin	Glaser et al. (2001) and Iozzo et al. (2002)
	Meta-iodobenzylguanidine	[^{124}I]MIBG Meta[^{124}I]-iodobenzylguanidine	Lee et al. (2010), Lopci et al. (2011) and Kvaternik et al. (2011)
Renal cell cancer	Antibodies	[^{124}I]-cG250 Carbonic anhydrase IX (Chimeric G250)	Divgi et al. (2007), Salacinski et al. (1981), Brouwers et al. (2002), and Pryma et al. (2011)
Colorectal		[^{124}I]-CDR huA33 Humanized A33 Monoclonal antibody	Lee et al. (2001)
		[^{124}I]-Anti-CEA minibodies carcinoembryonic antigen	Sundaresan et al. (2003)
Hypoxia agents		[^{124}I]IAZA 1-α-D(5-deoxy-5[^{124}I]iodo-arabinofuranosyl)-2-nitroimidazole	Reischl et al. (2007)
		[^{124}I]IAZG Iodoazomycin galactoside	Zanzonico et al. (2004)
Tumor proliferation		[^{124}I]IUdr 5-[^{124}I]iodo-2′-deoxyuridine	Guenther et al. (1998), Blasberg et al. (2000), and Roelcke et al. (2002)
		[^{124}I]-FIAU 2′Fluoro-2′-deoxy-1β-D-arabinofuranosyl-5-[^{124}]ioduracil	Tjuvajev et al. (1996, 2002) and Jacobs et al. (2001)
		[^{124}I]drFIB 1-(2-deoxy-β-D-ribofuranosyl)-2-4-difluro-5-[^{124}I]iodobenzene	Stahlschmidt et al. (2008)
Ischemic heart	Meta-iodobenzylguanidine	[^{124}I]MIBG Meta[^{124}I]-iodobenzylguanidine	Lopci et al. (2011), Kvaternik et al. (2011)
Apoptosis	Annexin V	[^{124}I]iodo annexin V 36-kDa protein	Dekker et al. (2005, 2005) and Glaser et al. (2003)

The positron-emitting radioiodine ^{124}I, with its 4.2 day half-life, is particularly attractive for the in vivo detection and quantification of relatively slow biological and physiological processes. Moreover, the chemistry of iodine is well known and there are already established procedures for the labeling of numerous compounds with ^{125}I and ^{123}I, thus conveniently allowing the application of this specialized know-how to the corresponding procedures for ^{124}I.

Considering the balance between advantages and disadvantages, for the specific case of ^{124}I, it was mentioned that its relatively low ratio of disintegration resulting in positrons and a relatively complex decay scheme are considered as disadvantages. However, from several mentioned recent results, ^{124}I is still considered as a proper radioisotope for PET applications. It is specially suitable for in-vivo studies of the prolonged time course of uptake of higher molecular weight compounds such as the monoclonal antibodies (mAbs) in solid tumors. Also, when the focus is the production feasibility and economic aspects, ^{124}I is viable. Here, the point to be detached is the cost of target material and the capability of recovering it. The cost becomes prohibitive when the recovering and re-use of target material are not considered.

In the discussion about labeling of proteins and peptides with ^{124}I, it can be observed that still there is some debate about the radioiodination method. Currently, there is a large use of direct radioiodination. In this method, [^{124}I]I^-, in the presence of an oxidant, is incubated with the protein. From reported data, the advantages are its simplicity and the mild condition for the labeling. This method is suitable for extracellular matrix proteins that do not have rapid internalization. On the other hand, some authors have indicated that indirect radioiodination is more suitable for others applications. This method does not lead to a situation where some proteins lose part of their biologic activity, and is less associated to problems due to dehalogenation. Therefore, neither of the methods should be considered as a general recommendation. It is well known that different purposes for the imaging study have different conditions and may require specific imaging probes.

It has also discussed the great potential for wide spread application of ^{124}I as a PET radionuclide for many molecular imaging purposes. There is a strong expectation that, in the near future, the general availability of ^{124}I, as well as its diverse application, may increase significantly.

Finally, it is well known that technological developments can highly impact in several areas, especially health care. This is particularly true for a high-technology discipline such as nuclear medicine. Innovations in the generation of new radionuclides by advances in isotope production methods, labeling chemistry, and molecular biology techniques, together with the introduction of new imaging technology have been paving the way to important clinical studies using radiolabeled antibodies, peptides, or other molecules. This also have been benefitting the diagnosis and treatment of various tumors in a large extent.

Authors' contributions

All authors had the same contribution.

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