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REVIEW

Radioisotopes Used as Radiotracers for *in vitro* and *in vivo* Diagnostics

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Many of modern diagnostic methods cannot be achieved without radioisotopes. In this review, an overview of the most common radioisotopes (radionuclides) used as markers for *in vitro* and *in vivo* studies is provided. To determine the extremely low concentrations of some biological molecules (hormones, drugs, toxins, nucleic acid, *etc*.) in biological fluids for *in vitro* studies, β and/or γ emitters with different half-lives: H-3, C-14, P-32, P-33, I-125, Cr-51 were frequently used. The majority of all radionuclides (90 %) were utilized for *in vivo* diagnostics. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are imaging modalities widely used in diagnostic nuclear medicine. The most important diagnostic radionuclides are technetium-99m (for single photon emission computed tomography) and fluorine-18 (for positron emission tomography).

Keywords: Radionuclides, Radiotracers, Single photon emission computed tomography, Positron emission tomography, Technetium-99m.

INTRODUCTION

Radioisotopes (radionuclides) are playing an increasingly important part in human life. They are widely used in medicine, industry and scientific research and new applications for their use are constantly being developed. Based on radionuclides, nuclear medicine has been developed as an independent medical field [1-3]. Clinical uses of radionuclides fall into three general areas: 1) *in vitro* diagnostic studies, 2) *in vivo* diagnostic studies-medical imaging and 3) *in vivo* therapeutic procedures:

(1) *in vitro* diagnostics mean that samples of the patient (blood, body fluids, tissues) are analyzed for various materials (*e.g.*, tumour and viral markers, thyroid and sex hormone, drugs, vitamins, *etc.*) with radionuclide laboratory methods such as radioimmunoassay (RIA) and immunoradiometric assay (IRMA) [4].

(2) During *in vivo* examinations radionuclids/radiopharmaceutcals are delivered to the patient's body in various ways (usually intravenously, sometimes orally, with inhalation or with direct injection to the tissues) [5]. By the process of radioactive decay radionuclide is detected from outside by special types of cameras, while it shows different distribution patterns in the human body to provide very precise pictures about the area being imaged. Imaging modalities widely used in nuclear medicine include γ camera scintigraphy, single photon emission computed tomography (SPECT) and positron emission tomography (PET) [6,7].

(3) Although in nuclear medicine nearly 95 % of the radionuclides are used for diagnostic purposes, it is possible to use radionuclides for the treatment of some pathologic processes in patients. The radionuclides/radiopharmaceutical can be delivered to a targeted location in tissue and therapeutic radiation can take place locally with the preservation or with minimal impact on surrounding organs (isotope therapy) [8,9].

In this review article the most common radiotracers routinely used for diagnosis *in vitro* (H-3, C-14, P-32, P-33, I-125, Cr-51) and *in vivo* (Tc-99m, I-131, I-123, Ga-67, In-111, Tl-201, F-18, O-15, C-11, N-13) are described and discussed. The basic introduction of SPECT and PET are also incorporated in the text. For better understanding the topic, particularly for the readers who are not familiar with the issue, some fundamentals about radioactivity are included.

Basic terms about radioactivity: All elements can exist as two or more isotopes that differ in the number of neutrons in the nucleus. Some isotopes are stable indefinitely, while others are unstable-radioactive. The term radionuclide relates to a radioactive element, man-made or from natural sources, with a specific atomic weight. Radioactivity is the property of a nucleus in unstable atoms that causes them to spontaneously decompose in the form of subatomic particles or photons. Radioactive decay is the spontaneous transformation of one nuclide into another nuclide or different energy state; in the transformation process, radiation is emitted. Radioactive isotopes decay with a defined half-life (the time required for

the amount of a particular radionuclide to decrease to one half of its original value), primarily through release of helium nuclei (α-particles), electrons or positrons (β-particles) and γ-radiation [10]. The general properties of radiation are presented in Table-1.

The System International (SI) unit for radioactivity is becquerel (Bq), which is defined as one disintegration per second. For practical application, Bq is too small unit; therefore, the prefixes like kBq, MBq and GBq are common. Another unit of radioactivity is curie (Ci) - quantity of radioactive material which decays at the rate of 3.7×10^{10} disintegrations per second. Dose (radiation dose) is a general term used to express (quantify) how much radiation exposure something (a person or other material) has received. The exposure can subsequently be expressed in terms of the absorbed, equivalent and effective dose. The unit of measure for absorbed dose is the gray (Gy). The ability of some types of radiation to cause more significant levels of biological damage, taken into account with radiation weighting factor used to determine equivalent dose, is expressed in sieverts (Sv). Effective dose, also expressed in Sv, is based upon the estimates of the relative risk of stochastic effects from the irradiation of the different tissues [11,12].

Radiolabeling: The basic concepts of radioisotopes as radiotracers were laid down by a Hungarian scientist, György Hevesy (1885-1966) who was awarded the Nobel Price (1943) for the invention of tracer and radioisotope labeling methods with which very small amounts and concentrations of substance can be tracked. In general, labeling involves the application of known synthetic methods to target molecules in which at least one atom is present as an isotope other than its naturally most abundant one. Molecules that contain such an isotope are referred to being "labeled" because such isotopically distinct atoms serve to mark the molecule for later detection by various means. The special case of isotopic labeling is radioisotopic labeling- a technique where the substance is labeled by including radioactive isotopes (radionuclides) in its chemical composition. These radionuclides or radiotracers can be determined by detecting the radiation generated in the isotope-decay process. A solo radionuclide or a labeled compound with radionuclide used in nuclear medicine is called a radiopharmaceutical (terms commonly used in literature such as radiotracer, radiodiagnostic agent, or tracer, are terms all referred to as a radiopharmaceutical) [13].

Radiotracers for *in vitro* diagnostic studies: The concentrations of biological compounds in body fluids, even hormones and vitamins present in extremely small quantities, may be measured using radionuclides by techniques such as RIA, competitive protein binding analysis, receptor-ligand binding, enzyme assays, protein-protein and protein-DNA interactions. Although radiotracers for *in vitro* measurements have been replaced progressively by non-radioactive markers (such ELISA), many laboratories still use this techniques.

Radionuclides routinely used as *in vitro* tracers have half-lives ranging from several days to thousands of years. Such half-lives and the related specific activities of such radionuclides make them ideally suited to applications such as DNA synthesis studies, RIA, binding studies, drug screening and ADME work. In contrast, when the half-life of a radionuclide is very short, any compound labeled with it will be difficult to prepare, use and measure within the time of decay. This group of radioisotopes decay by emission of β particles and/or γ-rays. Applications using α-emitters are limited due to limited penetration ability. β-Emitters can be measured by liquid scintillation counting, autoradiography and thin end-window ionization counting. γ-Emitters are usually measured by solid scintillation methods [14].

Table-2 gives more detailed information regarding the most commonly used radioisotopes for *in vitro* measurements, along with handling precautions and potentially affected organs upon exposure. Radioisotopes of hydrogen, carbon, phosphorus, sulphur and iodine have been used extensively to trace the path of biochemical reactions. Peptides or proteins are mostly labeled with I-125, C-14 and H-3, in order to enhance the sensitivity of detection, to quantitative the binding of peptides to other molecules, or for RIA. Radiolabeling with P is predominantly applied to the incorporation of labeled phosphate into nucleic acids and phospholipids. Cr-51 is used for labeling red blood cells; by reinjecting chromium-tagged red cells into their original host, it might be possible to measure the longevity of erythrocytes in their native environment, *etc*.

Radiotracers for *in vivo* diagnostic studies: The nuclear characteristics of the radioisotopes, such as chemical properties, mode of decay and half-life, determine their potential application in medicine for *in vivo* diagnostic studies [5]. The two most desirable characteristics of radionuclides used for imaging are: no particle emission (particular radiation does not penetrate tissue completely) and low energy of γ radiation. High energy absorption may result in cellular damage and cannot be used to produce an image; oppositely, if energy of γ photon is too low (*e.g.*, < 50 keV), radiation will not be able to penetrate completely from within the body. Thus, the ideal characteristics of the radioisotopes for *in vivo* diagnostic are: pure γ-emitter, relatively short half-life (6 h to 3 days), γ energy: 100-250 keV, readily available and inexpensive [1].

Single photon emission computed tomography and its radionuclides: Single photon emission computed tomography (SPECT) is a technique in which single photons are detected by a γ camera which can view organs from many different angles.

TABLE-1
GENERAL PROPERTIES OF RADIATION

Property	Type of radiation			
	α	β^-	β^+	γ
Charge	2+	1-	1+	No charge
Mass (g)	6.64×10^{-24}	9.11×10^{-28}	9.11×10^{-28}	No mass
Relative penetrating power	1	100	100	10.000
Penetrating in tissue	0.001 mm	7 mm	7 mm	Total penetration
Nature of radiation	Helium nuclei	Electrons	Positrons	High-energy photons

TABLE-2
RADIOISOTOPES USED FOR *in vitro* MEASUREMENTS

Isotope	Half-life $T_{1/2}$	Decay mode E_{max} (MeV)	Max range in air	Shielding required	Critical organ	Special consideration	Use for labeling
H-3	12.3 years	β^- 0.0086	4.6 mm	none	Whole body	Not an external hazard (can not penetrate gloves or the dead layer of skin), but an internal hazard that may be absorbed through the skin or inhaled.	Proteins, peptides, nucleic acids, drugs and toxins, ADME* work
C-14	5730 years	β^- 0.158	22 cm	1 cm plexiglass	Whole body, especially body fat	Most ^{14}C-labeled compounds are rapidly metabolized and exhaled as $^{14}CO_2$ which could be inhaled.	Proteins, peptides, nucleic acids, drugs and toxins, ADME work
I-125	60 days	γ 0.0355	n/a	none; for quantities up to 1 mCi 0.78 mm lead shielding	Thyroid	About 30 % of free iodine taken into the body will concentrate in the thyroid.	Pproteins, usually at tyrosine residues, peptides, wide range of drugs, pesticides, herbicides, environmental pollutants and other molecules of biochemical interest, Foremost isotope for RIA
P-32	14.3 days	β^- 1.710	5.5 m	1 cm plexiglass	Bone (internal), skin, eyes (external)	^{32}P-labeled compounds are readily absorbed through the skin. Eye protection is recommended.	Nucleotides, phosphoproteins, DNA, RNA
P-33	24.4 days	β^- 0.248	45 cm	1 cm plexiglass	Bone	Large quantities (> 1 mCi) and volatile compounds must be handled in a fume hood.	Nucleotides, phosphoproteins, DNA, RNA
S-35	87.4 days	β^- 0.167	24 cm	1 cm plexiglass	Testes, whole body	Some compounds, such as ^{35}S-methionine, may vapourize upon opening of container.	Proteins that incorporate sulfur-containing amino acids (methionine), nucleic acids
Cr-51	27.7 days	EC 0.320	n/a	3 mm lead	Lower large intestine	Cr is slowly eliminated from the body. 5 % of the uptake is transferred to bone and retained with a biological half-life of 1000 days.	Red blood cells

*ADME = administration, distribution, metabolism, elimination

Single photon emission computed tomography images are produced from multiple 2D projections by rotating one or more γ cameras around the body. The advantages of SPECT over planar scintigraphy can be seen in the improvement of contrast between regions of different function, better spatial localization, improved detection of abnormal function and importantly, greatly improved quantification [15].

The most commonly used radionuclides for SPECT are: technetium-99m (^{99m}Tc), iodine-123, gallium-67, indium-111 and thallium-201. The radioisotope decays and emits γ rays, which can be detected by a γ camera to obtain 3D images [16].

Technetium-99m: The ideal radioisotope for SPECT imaging is technetium-99m, due to its favourable physical and radiation characteristics, its availability through commercially available generator systems and its low cost per dose [17,18]. A recent bulletin of the World Nuclear Association (WNA) on nuclear medicine stated: "Over 10,000 hospitals worldwide use radioisotopes in medicine and about 90 % of the procedures are for diagnosis. The most common radioisotope used in diagnosis is technetium-99m (in technical jargon: ^{99m}Tc), with some 30 million procedures per year, accounting for 80 % of all nuclear medicine procedures worldwide" [19]. The element technetium (from the Greek word technetos, meaning artificial) was discovered in 1937 by Carlo Perrier and Emilio Segrè [20]. There are currently more than 20 known isotopes of technetium, all being radioactive. Its metastable ^{99m}Tc isotope has become the mainstay of diagnostic nuclear medicine. The nuclear properties of ^{99m}Tc are ideal for diagnostic imaging: it has a 6.02 h half-life and γ-ray emission energy of 141 keV with 89 % abundance. The decay is long enough to allow a radiochemist to carry out the preparation, quality control, administration of labeled compound to the patient and all nuclear medicine practitioners to collect images with commercial γ cameras. At the same time, the absence of tissue-damaging radiation allows the injection of activities higher than 30 mCi with low time exposure for the body. Another reason for the wide clinical use of this nuclide was the development of the $^{99}Mo/^{99m}Tc$ generator, which is commonly present in every department of nuclear medicine. ^{99m}Tc is readily available as pertechnetate ($^{99m}TcO_4^-$) in a sterile, pyrogen-free and carrier-free state from ^{99}Mo-^{99m}Tc generators, is relatively low cost and is easy-to-label kit preparations for in-house use. Another advantage is the low radiation to patients, due primarily to its short half-life. The decay within hours also facilitates the handling of waste. The chemistry of technetium allows it to form a stable complex with a relatively wide range of chemical chelation agents [21]. An intensive search for new ^{99m}Tc-radiopharmaceuticals based on a rational approach (*e.g.* cationic complexes

for myocardial perfusion agents [22], neutral lipophilic compounds for brain perfusion tracers [23,24]) and a steadily growing knowledge of Tc-complexation chemistry has resulted in efficient tracer agents for measurement of kidney function (^{99m}Tc-mertiatide), myocardial perfusion (^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin) and brain perfusion (^{99m}Tc-exametazime, ^{99m}Tc-bicisate) [25-29].

Table-3 gives more detailed information regarding the most commonly used radioisotopes, primarily Tc-99m, its physical half-life, forms and diagnostic use for SPECT.

TABLE-3
RADIOISOTOPES USED IN MEDICAL DIAGNOSIS (SPECT)

Isotop Name (Symbol)	Physical half-life $T_{1/2}$	Mode of decay (%)	γ-Ray energy (MeV)	Form	Diagnostic use
Technetium-99m (^{99m}Tc)	6.0 h	IT (100)	0.140	Sodium pertechnetate	Thyroid scintigraphy; salivary gland scintigraphy; gastric mucosa imaging; Brain scintigraphy, lachrimal duct scintigraphy;
				Sodium pertechnetate labeled red blood cells (Tc-RBC)	*In vivo* labeling of RBC for regional blood pool imaging, first-pass cardiac radionuclide angiography, detection of occult gastrointestinal bleeding
				Tc-albumin colloid (Nanocolloid)	Bone marrow scintigraphy; inflammation scintigraphy and lymphoscintigraphy
				Tc-albumin macroaggregated (MAA)	Lung perfusion scintigraphy, radionuclide venography
				Tc-albumin microaggregated	Liver and spleen scintigraphy
				Tc-apcitide	Acute venous thrombosis imaging
				Tc-Iminodiacetic acid (IDA) derivatives (lidofenin, disofenin, mebrofenin)	Hepatobiliary scintigraphy (to evaluate hepatocyte function, biliary duct obstruction, control after surgical intervention)
				Tc-etidronate/medronate/ oxidronate	Skeletal scintigraphy, diagnosis primary and metastatic bone tumors, metabolic bone disease, localization of fractures, evaluation of bone pain
				Tc-Ethyl-cysteinate dimer (ECD)	Brain perfusion imaging, diagnosis of acute cerebral infarction when CT is negative, detection of an abnormal focus in patients with head trauma after accidents, differentation of focal abnormalities in cerebral blood flow typical in multi-infarct dementia and degenerative dementia
				Tc-hydroxy-methyl-propyleneamine oxime (HMPAO; Tc-exametazime)	Brain perfuzion imaging, diagnosis of acute cerebral infarction when CT is negative, diagnosis of cerebrovascular disease and differentation of focal abnormalities in multi-infarct dementia and degenerative dementia
				Tc-gluceptate	Renal and brain imaging
				Tc-labeled red blood cells	Determination of red cell volume; short-term red cellsurvival studies
				Tc-Metoxy-isobutyl-isonitrile (MIBI)	Detection of myocardial perfusion abnormalites, diagnosis and localization of myocardial infarction, assesment of global ventricular function, detection of breast tumors and hyperparathyroidism; tumor viability and proliferation
				Tc-Mercaptoacetyltriglycine (MAG3)	Renal imaging/renography (anatomical and functional, evaluate renal tubular function, control after kidney transplants, diagnose urinary obstruction
				Tc-pentetate (DTPA)	Renal studies, determination of glomerular filtration rate (GFR) ; inhalation scintigraphy to measure regional lung ventilation; cerebral scintigraphy based on leaks in the blood-brain barrier (BBB)
				Tc-pyrophosphate	Bone imaging; myocardial infarct imaging; blood pool imaging; detection gastrointestinal bleeding
				Tc-Dimercaptosuccinic acid (DMSA)	Renal scintigraphy, detection of medullary thyroid cancer
				Tc-fanolesomab/sulesomab	Imaging and diagnosis of infections and inflammation
				Tc-sulfur colloid	Liver and spleen imaging; bone marrow imaging; Detection of intrapulmonary and gastrointest. bleeding; Esophageal transit studies; Lung ventilat. imaging
				Tc-teboroxime; -tetrofosmin	Myocardial perfusion imaging (detection of reversible myocardial ischemia and myocardial infarction)

Iodine-123 (^{123}I)	13.2 h	EC (100)	0.159	Sodium iodide	Thyroid function studies; thyroid imaging
				Iobenguane (MIBG)	Adrenomedullary imaging and tumor detection, detection of pheochromocytoma
				Iodohippurate sodium	Determination of renal function, renal imaging; renal blood flow; urinary tract obstruction
				Iofetamine hydrochloride	Cerebral imaging
				Ioflupane	SPECT cerebral imaging
Iodine-131 (^{131}I)	8.0 days	β^- (100)	0.287	Sodium iodide	Thyroid function studies; thyroid imaging
			0.364	Iodinated fats and fatty acids	Pancreatic function; intestinal fat absorption
			0.637	Iodinated human serum albumin	Cerebral and periferal vascular flow; plasma volume determination; brain scan;placenta localization
				IHSA microaggregated	Pulmonary perfuzion imaging
				Iodohippurate sodium	Determination of renal function, renal imaging; renal blood flow; urinary tract obstruction
				Iodinated levothyroxine	Metabolic study of endogenous thyroxine
				Iobenguane (MIBG)	Adrenomedullary imaging and tumor detection
Calcium-47 (^{47}Ca)	4.5 d	β^- and γ	0.670 1.297	Calcium chloride	Calcium metabolism studies
Chromium-51 (^{51}Cr)	27.7d	EC (100)	0.320	Chromium disodium edetate	Determination of glomerular filtration rate
				Chromic chloride	Determination of serum protein loss into the gastrointestinal tract
				Sodium chromate labeled red blood cells	Determinarion of red cell volume or mass; red cell survival time; spleen imaging
Cobalt-57 (^{57}Co)	271 days	EC (100)	0.122	Radioactive vitamin B_{12}	In Schilling test for absence of intrinsic factor (pernicious anemia) or other defects of intestinal vitamin B_{12}
Cobalt-58 (^{58}Co)	71 days	EC; β^+ (14.9)	0.811		
Cobalt-60 (^{60}Co)	5.2 years	β^- (100)	1.173		
Galium-67 (^{67}Ga)	78.2 h	EC (100)	0.093	Galium citrate	Detection of malignant diseases such as Hodgkin's disease, lymphomas and bronchogenic carcinoma; localization of acute inflammatory diseases and infections
Indium-111 (^{111}In)	2.8 days	EC (100)	0.171	Indium oxine labeled red blood cells	Detection of gastrointestinal bleeding
				Indium oxine labeled leukocytes	Detection of abscesses, infections and inflammation
				Indium oxine labeled plateles	Detection of deep vein thrombosis; cardiac thrombosis
				Indium chloride	Tumor detection; Hematopoietic bone marrow imaging
				Indium pentetreotide	Primary and metastatic neuro-endocrine tumors detection (neuroblastomas, pituitary adenomas, medullary thyroid carcinomas
Iron-55 (^{55}Fe)	2.73years	β^- and γ		Labeled red blood cells	Red cell maturation studies
Iron-59 (^{59}Fe)	45 days	β^- (100)	1.099		
Iron-59 (^{59}Fe)	45 days	β^- (100)	1.099	Ferric chloride, -citrate; -sulfate	Ferrokinetics
Potassium-43 (^{43}K)	22.3 h	β^- and γ		Potassium chloride	Myocardial scan; determination of total exchengeable potassium
Selenium-75 (^{75}Se)	120 days	γ		Selenomethionine	Imaging of pancreas and parathyroid glands
Sodium-24 (^{24}Na)	14.66 h	β^- and γ		Sodium chloride	Determination of sodium space, total exchangeable sodium
Thallium-201 (^{201}Tl)	73 h	EC (100)	0.167	Thallous chloride Thallium-201	Myocardial perfusion imaging in order to delineate between ischemic and infarcted myocardium; detection of hyperparathyroidism and brain tumors, Tumor viability and proliferation
Xenon-133 (^{133}Xe)	5.24d	β^- and γ		^{133}Xe Gas	Lung ventilation studies; pulmonary perfusion imaging; assessment of cerebral blood flow

IT = Isomeric transition; EC = Electron capture

Positron emission tomography and its radionuclides: Positron emission tomography (PET) is a 3-D nuclear medicine imaging technique which is based on detection of the annihilation radiation emitted from a certain positron-emitting radionuclide. When the radionuclide decays, the positron will annihilate with an electron nearby, thus creating two 511 keV photons emitted opposite to each other (180°). This can be observed by PET detectors arranged in an array of full or partial ring around the patient body axis. Data are then reconstructed using a standard algorithm. By using this coincidence-detection method, the traditional collimator of the SPECT scanner can be removed, therefore, the spatial resolution and sensitivity can be highly improved [7,30,31].

The common radioisotopes used in PET are short-lived: carbon-11, nitrogen-13, oxygen-15, fluorine-18, as well as gallium-68 and rubidium-82, all β^+-emitters [32].

TABLE-4
RADIOISOTOPES USED IN MEDICAL DIAGNOSIS (PET); ALL PRODUCE γ-RAY ENERGY OF 0.511 MeV

Isotop Name (Symbol)	Physical half-life $T_{1/2}$	Mode of decay (%)	Form	Diagnostic Use
Fluorine-18 (^{18}F)	110 min	β^+ (97)	^{18}F-Fluorometilfluoride	Blood flow (CBF)
			^{18}F-Fluorodeoxyglucose	For the study of metabolism in the brain and heart and for the detection of epilepsy and various tumors. Glucose metabolism; Tumor viability and proliferation
			^{18}F-Fluorodopa	For the assessment of the presynaptic dopaminergic function in the brain
			^{18}F-fluoro-L-tyrosine	Protein synthesis and amino acid transport; Tumor viability and proliferation
			Sodium ^{18}Fluoride	Bone scintigraphy and for the synthesis of F-fluorodeoxyglucose and for other F-labeled PET radiopharmaceuticals
Oxygen-15 (^{15}O)	2 min	β^+ (100)	^{15}O-Carbon-dioxide; ^{15}O-Water;	Blood flow (CBF); For myocardial and cerebral perfusion studies.
			Molecular oxygen ($^{15}O_2$)	Oxygen extraction fraction (OEF) and metabolism
			^{11}Carbon-monoxide-labeled RBC	Blood volume
Nitrogen-13 (^{13}N)	10 min	β^+ (100)	^{13}N-ammonia	Blood flow (CBF); for measurement of myocardial and cerebral perfusion
Carbon-11 (^{11}C)	20.4 min	β^+ (100)	^{11}C-Butanol	Blood flow (CBF) measurement in brain and other organs
			^{11}C-methionine	Tumor viability and proliferation For the detection of different types of malignancies, reflecting the amino acid utilization (protein synthesis and amino acid transport)
			^{11}C-Raclopride	Detection of various neurologic and psychiatric disorders (Parkinson's disease and schizophrenia)
			^{11}C-Thymidine	Tumor viability and proliferation
			^{11}C-sodium acetate	For the measurement of oxygen consumption in the heart and brain
			^{11}C-Flumazenil	For the neuroreceptor characterization in humans
			^{11}C-Methylspiperone	To determine the dopamine-2-receptor density in patients with neurologic diseases

Fluorine-18 (often associated with the compound fluorodeoxyglucose, FDG) is the most employed tracer with the PET technique since it allows imaging in a large variety of malignant tumors and metabolism diseases. In cancer imaging the radioactive sugar can help in locating a tumor, because cancer cells take up or absorb sugar more avidly than other tissues in the body [33].

Radionuclides: C-11, N-13 and O-15 are the same atoms which naturally comprise the organic molecules used in the body. Labeling with these radionuclides, a compound is chemically and biologically identical to the original. In that way, it is possible to label both naturally occurring compounds such as neurotransmitters, sugars, *etc*. and synthesized compounds (such as drugs) and follow them through the body.

Other than those cyclotron-produced PET radionuclides mentioned above, generator-produced gallium-68 and rubidium-82 have also shown high potentials in PET imaging. The advantage of in-house generator produced radionuclide is that the generator itself serves as a top-of-the-bench source for short half-life radionuclides in the places that are located far from a cyclotron facility. Besides, it is quite simple to obtain radionuclides from the generator and less expensive compared to cyclotron-produced radionuclides.

In the past decade, copper-64 and zirconium-89, because of their long half-lives (12.7 h and 78.4 h, respectively), have been increasingly recognized for labeling nanoparticles or slowly localizing antibodies [34].

Commonly used PET imaging radionuclides are listed in Table-4.

Sometimes, prophylactic formulations, known as classical radioprotectors, may be used before procedure that includes the application of radiotracers to prevent risk of potential tissue damage [35].

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