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RADIOISOTOPES FOR DIAGNOSTICS – RECENT DEVELOPMENTS

Sažetak: U radu su prikazane i razmatrane mogućnosti proizvodnje i primene pojedinih radioaktivnih izotopa u nuklearnomedicinskoj dijagnostici i dat je "presek" sadašnjeg stanja i trendova u savremenoj radiofarmakologiji. Najznačajniji za primenu u SPECT vizualizacionom modalitetu su ^{97}Ru, ^{111}In, ^{123}I i ^{201}Tl. Za primenu u pozitronskoj emisionoj tomografiji (PET) osnovni su "organski" emiteri. Posebno mesto imaju ^{11}C i ^{18}F osim ^{13}N i ^{15}O. U novije vreme pažnja se posvećuje izotopima kao što su ^{64}Cu i ^{124}I mada se oni još uvek nalaze u fazama kliničkih ispitivanja. Uvid u savremenu literaturu nesumnjivo ukazuje da brojni autori ističu naglašene mogućnosti kliničke primene ovih radiofarmaka. Deo rada je posvećen razvoju novijih generatorskih sistema za proizvodnju kratkoživućih pozitronskih emitera kao što su ^{68}Ga (nastao od ^{68}Ge) i ^{63}Cu (nastao od ^{63}Zn). Uporedo s analizom fizičkohemijskih svojstava pomenutih radioaktivnih izotopa u radu su pomenute i mogućnosti njihove primene u medicinskoj praksi.

Ključne reči: gama emiteri, pozitronski emiteri, radiofarmaci, nuklarna medicina

Abstract: The production of some radioisotopes (rather than ^{99m}Tc) for the use in the emission tomography is discussed. In SPET the most important are: ^{97}Ru, ^{111}In, ^{123}I and ^{201}Tl. In PET the main are the «organic» radioisotopes - positron emitters, particularly ^{11}C and ^{18}F (besides ^{13}N and ^{15}O). Some others, like ^{64}Cu and ^{124}I, are emerging. Emphasis is also given on the development of the generator systems for the production of short-lived positron emitters ^{68}Ga (from the parent ^{68}Ge) and ^{62}Cu (from the parent ^{62}Zn). Several examples of the application of these radioisotopes in the diagnostic nuclear medicine are included.

Key words: Gamma emitters, positron emitters, nuclear medicine, diagnostics, radiopharmaceuticals

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Introduction

Technetium-99m continues to be the most widely used radioisotope in diagnostics and it seems to be no rival in a foresseable future. It fulfils all criteria necessary for a a broad use: reliable production at low price, easy and regular availability and known chemistry. The chromatographic ^{99}Mo/^{99m}Tc generators based on the parent ^{99}Mo obtained from uranium fission became the common and very reliable source of large activities of ^{99m}Tc of high quality meeting all criteria prescribed by Pharmacopoeia (1). Uranium fission ensures large activities of so-called (n,f)^{99}Mo needed for the regular generator production (2). Excellent physical and chemical properties of ^{99m}Tc made this radioisotope applicable in a large variety of indications in the diagnostic imaging. It could be even said that the earlier approach of tailoring the radioisotopes to the medical needs is changed. In many cases medical indications are tailored so that one can use ^{99m}Tc. A plethora of data regarding the production and the use of ^{99m}Tc and ^{99m}Tc-radiopharmaceuticals can be found in the literature (3-6).

However, it is known that the goals of nuclear medicine in imaging can not be fulfiled by using exclusively ^{99m}Tc.This paper brings a brief review on the production of some possible contenders for the use in diagnostic imaging (7-11). Some of these radioisotopes are already applied in the form of various radiopharmaceuticals. Several examples, together with the diagnostic indications, are also included.

Developments in the production of radioisotopes

Although there are many candidates covering a wide spectrum of nuclear, physical and chemical properties, the vast majority of all SPET (Single Photon Emission Tomography) and PET (Positron Emission Tomography) studies is performed with a relatively small number of radioisotopes. Their production is mainly carried out in cyclotrons. Some useful radioisotopes (besides ^{99m}Tc) are obtained also in nuclear reactors.

The single-photon emitters of intermediate half-lives produced in cyclotrons or nuclear reactors for planar and SPET (Single Photon Emmision Tomography) imaging are listed in Table I. The main physical characteristics and nuclear reactions for their routine production are also shown. They are all (except ^{203}Pb) already commercially available. Technetium-99m is also included as it is used in about 80% of all nuclear medicine imaging studies.

The reactions for the production of ^{123}I are listed in Table I. It is an excellent example how the production meets the ever changing demands on the improvement of the yield and quality of medically important radioisotopes. Now it proceeds mainly on the gaseous target of highly enriched ^{124}Xe in a medium energy cyclotron. This method was developed in the last decade and, in the contrast to the others, previously used, reactions shown in Table I, it delivers ^{123}I in high yield and far the best radionuclidic purity. The metallic radioisotopes ^{67}Ga, ^{111}In and ^{201}Tl are also produced in medium energy cyclotrons. The targetry and the chemical separation problems have been well studied. Thallium-201 is most often obtained by using ^{201}Tl(p,3n)^{201}Pb ® ^{201}Tl reaction. Besides ^{99}Mo and ^{99m}Tc, very important radioisotope is ^{131}I which is obtained in large activities in nuclear reactors by using ^{130}Te(n,g)^{131}Te(b$^-$)®^{131}I nuclear reaction or by uranium fission. It is not quite suitable for imaging but it is widely used due to known chemistry and easy availability at low price. The targetry, irradiation and chemical processing are well established. Tin-117m is primarily an electron emitter and therefore suitable for therapy but can be, at low diagnostic doses, used also in imaging.

Table I. Radioisotopes ă-emitters for planar and SPET (Single Photon Emission Tomography) imaging produced in cyclotrons and nuclear reactors

Radio isotope ($T_{1/2}$)	Nuclear reaction	Energy of projectiles, (MeV)	Mode of decay	Principal Eγ, MeV (Abundance, %)
^{67}Ga (3.26 d)	^{68}Zn(p,2n)	26	EC (100)	0.093 (37); 0.185 (20)
^{97}Ru (2.89 d)	^{103}Rh(p,α3n)	60	EC(100)	0.216 (86); 0.325 (10)
^{99}Mo (66 h)	^{235}U(n,f) ^{98}Mo(n,γ)	-	β^- (100)	0.181 (6); 0.740 (12)
^{99m}Tc (6 h)	^{99}Mo/^{99m}T generator	-	EC (100)	0.141 (87)
^{111}In (2.8 d)	^{112}Cd(p,2n)	25	EC (100)	0.173 (91); 0.247 (94)
^{117m}Sn (14 d)	(n, n´γ)*	-	IT	0.159 (86)
^{123}I (13.2 h)	^{123}Te(p,n) ^{124}Te(p,2n) ^{127}I(p,5n)^{123}Xe** ^{124}Xe(p,x)^{123}Xe**	14.5 26 65 29	EC (100)	0.159 (83)
^{131}I (8 d)	^{130}Te(n,γ)^{131}Te*** ^{235}U(n,f)	-	β^-	0.364 (81)
^{201}Tl (3.06 d)	^{201}Tl(p,3n)^{201}Pb****	28	EC(100)	0.166 (11)
^{203}Pb (2.17 d)	^{203}Tl(p,n) ^{205}Tl(p,3n)	16 60	EC(100)	0.279 (81)

* Fast neutrons; **^{123}Xe ($T_{1/2}$ = 2.08 h) decays to ^{123}I by EC (87%) and b^+ emission (13%);***

^{131}Te ($T_{1/2}$ = 24.8 min) decays (b^-) to ^{131}I; **** ^{201}Pb ($T_{1/2}$ = 9.4 h) decays to ^{201}Tl by EC(100%)

Positron emitters are a large group of radioisotopes used in PET (Positron Emission Tomography) studies. The most important are, together with nuclear reactions for their routine production, shown in Table II.

Table II. Radioisotopes positron emitters for PET (Positron Emission Tomography) imaging

Radioisotope ($T_{(1/2)}$)	Nuclear reaction	Energy of projectiles, MeV	Mode of decay	Principal Eγ, MeV (Abundance, %)
^{11}C (20 min)	$^{14}N(p,\alpha)$	13	β^+ (99.8) EC (0.2)	0.511 (199.6)
^{13}N (10 min)	$^{16}O(p,\alpha)$	16	β^+ (100)	0.511 (200)
^{15}O (2 min)	$^{14}N(d,n)$ $^{15}N(p,n)$	8 10	β^+ (97) EC (0.1)	0.511 (199.8)
^{18}F (110 min)	$^{18}O(p,n)$ $^{20}Ne(d,\alpha)$	16 14	β^+ (97) EC (3)	0.511 (194)
^{64}Cu (12.7 h)	$^{64}Ni(p,n)$	12	β^+ (17.4) β^- (39) EC (43.6)	0.511(34.79) 1.346 (0.4)
^{73}Se (7.1 h)	$^{75}As(p,3n)$ $^{75}As(d,4n)$	40 45	β^+ (65) EC(35)	0.511 (130) 0.361 (97)
^{75}Br (1.6 h)	$^{76}Se(p,2n)$ $^{76}Se(d,3n)$	30 35	β^+ (75.5) EC(24.5)	0.511 (151) 0.287 (92)
^{76}Br (16.1 h)	$^{76}Se(p,n)$ $^{77}Se(p,2n)$	16 25	β^+ (57) EC(43)	0.511 (114) 0.559 (74) 0.657 (16) 1.854 (15)
^{94m}Tc (54 min)	$^{94}Mo(p,n)$	13	β^+	0.511 (132) 0.870 (91) 1.522 (5.3)
^{124}I (4.2 d)	$^{124}Te(p,n)$ $^{124}Te(d,2n)$	26	β^+ EC	0.511 (46) 0.603 (61) 0.722 (10)

Several generator systems for the production of positron emitting daughter radioisotopes were also investigated. Table III presents the generator systems which are already in use for the production of ^{62}Cu (from parent ^{62}Zn), ^{68}Ga (from parent ^{68}Ge) and ^{82}Rb (from parent ^{82}Sr). The parents are obtained in cyclotrons. However, only ^{62}Zn can be routinely produced in medium energy cyclotrons. For ^{68}Ge and ^{82}Sr spallation reactions are needed.

Examples of radiopharmaceuticals and diagnostic indications for their application

Radiophamaceuticals labeled with g-emitting radioisotopes (rather than ^{99m}Tc) for SPET for the selected diagnostic indications are shown in Table IV.

Table III. Generator systems for the production of short-lived daughter radioisotopes for PET (Positron Emission Tomography) imaging

Parent ($T_{1/2}$)	Nuclear reaction (Energy of projectiles, MeV)	Daughter ($T_{1/2}$)	Mode of decay	Principal Eγ, MeV (Abundance, %)
^{62}Zn (9.2 h)	^{63}Cu(p,2n)^{62}Zn (26)	^{62}Cu (9.7 min)	β^+ (98) EC (2)	0.511(196)
^{68}Ge (271 d)	RbBr(p,spall)^{68}Ge (800, 500)	^{68}Ga (68 min)	β^+ (90) EC (10)	0.511(180) 1.077 (3)
^{82}Sr (25 d)	Mo(p,spall)^{82}Sr (800)	^{82}Rb (1.3 min)	β^+ (96) EC (40)	0.511(192) 0.776 (13.4)

Table IV. Radiopharmaceuticals labeled with radioisotopes ă- emitters and some indications for their applications in SPET (Single Photon Emission Tomography) imaging

Radioisotope	Chemical form	Application
^{67}Ga	Citrate	Abscesses; inflammatory processes; various tumors
^{111}In	DTPA IgG MoAb WBC	Distribution of cerebrospinal fluid Infection and inflammation imaging Tumor-specific agent Acute inflammation, abscesses, infection
^{123}I	Iodide Iodo-Tyr^3-octreotide MIBG Fatty acids MoAb IMT	Thyroid imaging Somatostatin-receptor bearing tumors Neural crest tumors; symphatic nerve function Measurement of myocardium metabolism Infection and inflammation; cancer detection Brain metabolism; brain tumors
^{201}Tl	Chloride	Coronary artery disease; functional assesment of the myocardium

DTPA-diethylenetriamine pentaacetic acid; IgG-immunoglobuline G; Tyr-tyrosine; MoAb-monoclonal antibodies; WBC-white blood cells; MIBG-m-iodobenzylguanidine; IMT-L-3-iodo-a-methyltyrosine

In PET imaging over 1000 compounds have been labeled to study specific biochemical processes and physiological functions. However, to date most of the studies are performed by using short-lived «organic» positron emitters, eg. ^{11}C ($T_{1/2}$ = 20 min), ^{13}N ($T_{1/2}$ = 10 min), ^{15}O ($T_{1/2}$ = 2.0 min) and ^{18}F ($T_{1/2}$ = 110 min). The examples are given in Table V.

Table V. Radiopharmaceuticals labeled with short-lived «organic» positron emitters and some indications for their applications in PET (Positron Emission Tomography) imaging

Radioisotope	Chemical form	Application
^{11}C	DG Fatty acids and amino acids Carbon monoxide Receptors Methyl glucose	Investigation of various metabolites; brain tumors Blood volume Assesment of receptor and transmitter pharmacology Glucose metabolism
^{13}N	Ammonia Amino acids	Tissue perfusion and metabolic function; blood flow Metabolism
^{15}O	Water, carbon dioxide, carbon monoxide	Oxygen metabolism; blood flow; blood volume
^{18}F	FDG	Oncology; glucose metabolism in central nervous system and cardio vascular system; several indications in neurology (ischemia, stroke, dementia, etc)

DG-2-^{11}C-deoxyglucose; FDG-2-fluoro-^{18}F-deoxy-D-glucose

Conclusion

Technetium-99m remains the work-horse in diagnostic imaging. In the past decades millions of people around the world have benefited from ^{99}Mo/^{99m}Tc generators for the production of ^{99m}Tc which is used either directly or in the form of various radiopharmaceuticals. However, there is a number of radioisotopes which could expand the possibilities for the new or to improve already existing diagnostic procedures. For SPET the most promising, present and future broad-based radioisotopes seem to be ^{97}Ru, ^{111}In, ^{123}I and ^{201}Tl. For PET the main are the «organic» positron emitters, particularly ^{11}C and ^{18}F. It is estimated that ^{18}F is used in about 80% of PET studies (similarly as ^{99m}Tc in SPET). Emphasis is also on the generator system for production of ^{68}Ga. The radioisotopes which are emerging and their applications are already established are also ^{64}Cu and ^{124}I as well as ^{62}Cu obtained via ^{62}Zn/^{62}Cu generator system. A large number of radiopharmaceuticals for diagnostic imaging were investigated. Rapid (particularly in the case of short lived radioisotopes), efficient and automated procedures for the production of radioisotopes and precursors, labeling and quality control are needed. In general, the development of tracers for SPET and PET is a challenging multidisciplinary research field in synthetic chemistry and biochemistry.

Acknowledgement: This work was financially supported by the Ministry of Science and Environmental Protection of the Republic of Serbia, Project No.142004B.

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