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Nuclear Medicine and Biology 39 (2012) 447–460

NUCLEAR MEDICINE — AND — BIOLOGY

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Synthesis of oncological [^{11}C]radiopharmaceuticals for clinical PET

Filippo Lodi[a,*], Claudio Malizia[a], Paolo Castellucci[c], Gianfranco Cicoria[b], Stefano Fanti[c], Stefano Boschi[a]

[a]*PET Radiopharmacy, Nuclear Medicine Unit, Azienda Ospedaliero Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy*
[b]*Medical Physics, Azienda Ospedaliero Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy*
[c]*PET Center, Nuclear Medicine Unit, Azienda Ospedaliero Universitaria di Bologna, Policlinico S. Orsola-Malpighi, Bologna, Italy*

Received 22 June 2011; received in revised form 14 October 2011; accepted 22 October 2011

Abstract

Positron emission tomography (PET) is a nuclear medicine modality which provides quantitative images of biological processes in vivo at the molecular level. Several PET radiopharmaceuticals labeled with short-lived isotopes such as ^{18}F and ^{11}C were developed in order to trace specific cellular and molecular pathways with the aim of enhancing clinical applications. Among these [^{11}C]radiopharmaceuticals are *N*-[^{11}C]methyl-choline ([^{11}C]choline), L-(*S*-methyl-[^{11}C])methionine ([^{11}C]methionine) and 1-[^{11}C]acetate ([^{11}C]acetate), which have gained an important role in oncology where the application of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is suboptimal. Nevertheless, the production of these radiopharmaceuticals did not reach the same level of standardization as for [^{18}F]FDG synthesis. This review describes the most recent developments in the synthesis of the above-mentioned [^{11}C]radiopharmaceuticals aiming to increase the availability and hence the use of [^{11}C]choline, [^{11}C]methionine and [^{11}C]acetate in clinical practice.

Keywords: Clinical PET; Oncology; [^{11}C]radiopharmaceuticals; Radiosynthesis; [^{11}C]choline; [^{11}C]methionine; [^{11}C]acetate

1. Introduction

Positron emission tomography (PET) is a powerful nuclear medicine modality which provides imaging of biological processes in vivo [1]. This technique is based on administration and detection of the biodistribution of radiopharmaceuticals labeled with positron-emitting radionuclides, allowing better quality imaging than conventional single-photon-emitting tomography, with higher sensitivity and good spatial resolution; also PET allows an accurate quantification of regional radiopharmaceutical concentration [2].

Several PET radiopharmaceuticals labeled with short-lived isotopes such as ^{18}F ($t_{1/2}$=109.8 min) and ^{11}C ($t_{1/2}$=20.4 min) were developed in order to visualize specific cellular and molecular pathways and then applied in oncology, neurology and cardiology [3–7]. In particular, ^{11}C is an attractive PET radionuclide because carbon is a ubiquitous element in biomolecules thus, [^{11}C]-labeling does not change the chemical structure and the biochemical properties in vivo. Moreover, the possibility to choose from different labeling positions in the same molecule provides the possibility to refine the radiopharmaceutical in terms of metabolic stability and nonspecific background ratio [8]. The short life of ^{11}C also enables comparative PET studies with the same [^{11}C]radiopharmaceutical (multitracer studies) in a short time frame with more favorable patient dosimetry [9]. On the other hand, the production of these radiopharmaceuticals must be performed in PET facilities with on-site cyclotrons and should be as fast as possible to reduce the loss of activity due to decay.

In the last few years, [^{11}C]radiopharmaceuticals have gained increased importance in clinical PET, with relevant applications mainly in clinical oncology, in case of limitation of the gold standard PET radiopharmaceutical 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG), a glucose analogue used for staging, restaging and assessing the therapy response of a variety of tumors [10]. Among [^{11}C]radiopharmaceuticals, *N*-[^{11}C]methyl-choline ([^{11}C]choline), L-(*S*-methyl-[^{11}C]) methionine ([^{11}C]methionine) and 1-[^{11}C]acetate ([^{11}C] acetate) (Fig. 1) are widely used in clinical PET with

* Corresponding author.
E-mail address: filippo.lodi@aosp.bo.it (F. Lodi).

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doi:10.1016/j.nucmedbio.2011.10.016

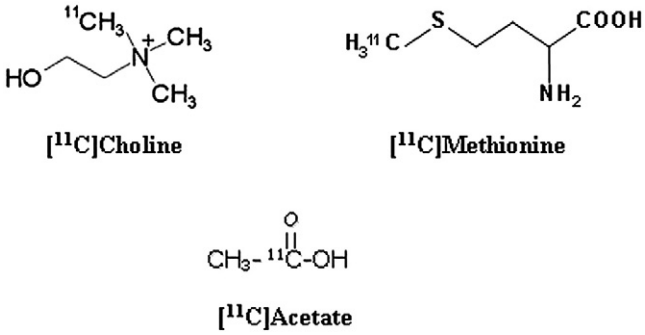

Fig. 1. Oncological [^{11}C]radiopharmaceuticals in clinical PET.

important applications in oncology [11]. Fast and efficient labeling reactions and purification methods are needed to have high radiochemical yield, resulting in high radiopharmaceutical activities available for clinical use. Several labeling methods have been described in the literature to meet the increasing demand of these radiopharmaceuticals for clinical routine. Each of them presents some advantages and disadvantages as well as differences in radiochemical yield, overall synthesis time, purification procedures, radiochemical and chemical purity of the final product and suitability for process automation.

The aim of this paper is to review some of the most recent publications about the synthesis of the widely used oncological [^{11}C]radiopharmaceuticals: [^{11}C]choline, [^{11}C]methionine and [^{11}C]acetate.

2. Production of [^{11}C]radiopharmaceuticals

The first step of [^{11}C]radiopharmaceuticals synthesis is the radionuclide production. ^{11}C is produced by cyclotron as [^{11}C]CO_2 or [^{11}C]CH_4 by ^{14}N(p,α)^{11}C nuclear reaction. [^{11}C]CO_2 is produced using a mixture of nitrogen with trace amount to 2% of oxygen, while [^{11}C]CH_4 is produced using a mixture of nitrogen with 5%–10% of hydrogen as gas target. Another way to produce [^{11}C]CH_4 is the reduction of [^{11}C]CO_2 with hydrogen on a nickel catalyst at high temperature [12]. [^{11}C]CO_2 can be recovered from cyclotron and purified by means of cryogenic trapping with liquid nitrogen or by trapping on molecular sieves [13]. [^{11}C]CH_4 can be recovered and purified with a Porapak N trap [12].

The use of in-target produced [^{11}C]CH_4 improves the specific activity (SA) [14,15] but requires a long time to reach maximum yield, and in general, total obtained activity is lower compared to [^{11}C]CO_2 target [15]. [^{11}C]CO_2 and [^{11}C]CH_4 are usually employed for the preparation of more reactive [^{11}C]-labeling agents which are directly involved in [^{11}C]radiopharmaceuticals synthesis.

The most commonly used are [^{11}C]methylating agents such as [^{11}C]methyl iodide ([^{11}C]CH_3I) and [^{11}C]methyl triflate ([^{11}C]CH_3OTf), which are employed in alkylation reactions ([^{11}C]methylations) [16].

[^{11}C]CH_3I can be prepared by using two different methodologies: the "wet chemistry," which is based on [^{11}C]CO_2 reduction by $LiAlH_4$ and followed by iodination with hydroiodic acid (HI) [13,17,18], and the "gas phase chemistry," which synthesizes [^{11}C]CH_3I from radical iodination of [^{11}C]CH_4 by molecular iodine (I_2) [12,19] (Fig. 2).

These methods present some pros and cons in terms of [^{11}C]CH_3I radiochemical yield, SA, synthesis reagents and cleaning procedures after the production.

Compared to "gas phase chemistry," the "wet chemistry" method generally provides [^{11}C]CH_3I in higher yields (almost twofold higher) and in shorter synthesis time: these features are advisable in [^{11}C]-labeling and in clinical practice because of the short half-life of this radionuclide and for the high activities needed to study several patients in shorter time. However, the use of reagents like HI and $LiAlH_4$ makes difficult the managing of the synthesis preparation and cleaning procedures. Moreover, $LiAlH_4$ represents a carrier of cold CO_2 which may decrease the SA of [^{11}C]CH_3I. Average SA values reached with this method are 1–5 Ci/μmol decay corrected (DC) at the end of synthesis (EOS). Low $LiALH_4$ amount with freshly distilled solvent, low target volume and high-purity gas with traps for cold CO_2 in the line from gas target to cyclotron are recommended to increase [^{11}C]CH_3I SA [13].

On the contrary, an advantage of the "gas phase chemistry" resides in the ease of use in cleaning procedures because of HI elimination and in the possibility to run more syntheses of [^{11}C]CH_3I without adding or changing reagents. Furthermore, elimination of $LiAlH_4$ contributes to the higher SA of [^{11}C]CH_3I (even more than 15 Ci/μmol DC at EOS [12]), a clear advantage of this method when higher SA radiopharmaceuticals are needed (i. e. high-affinity receptorial molecules). Although high SA is always a good prerequisite, oncological [^{11}C]radiopharmaceuticals such as [^{11}C]choline and [^{11}C]methionine are generally transported into the cell and are not receptorial affinity molecules, making SA a less critical factor.

Because of its higher chemical reactivity, [^{11}C]CH_3OTf enables fast and low-temperature labeling reactions with smaller amount of desmethyl precursors. [^{11}C]CH_3OTf is synthesized by passing [^{11}C]CH_3I, through a silver triflate (AgOTf) column at high temperature (200°C) [20–22] (Fig. 3).

[^{11}C]methylation reaction can be performed by "bubbling" technique or on solid-phase support. In the first

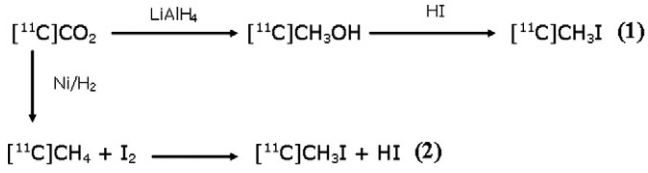

Fig. 2. Production of [^{11}C]CH_3I: (1) $LiAl_4$/HI method ("wet chemistry"), (2) iodination of [^{11}C]CH_4 ("gas phase chemistry").