Synthetic techniques of radiopharmaceuticals production labeled with C-11 for PET in cardiology

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Abstract. Positron emission tomography (PET) and PET-Computerised Tomography (CT) are unique, non-invasive diagnostic techniques, in which the local, temporal and quantitative distributions of radioactive labelled substances are measured to investigate physiological processes. It is well known that PET centre of Bakulev Scientific Centre for Cardiovascular Surgery is the oldest one in Moscow. During more than fifteen years a large number of patients have received PET scans. Due to main stream of Scientific Centre, emphasis is placed on examining the heart functioning. For the diagnosis innervation of the heart muscle a number of radiopharmaceuticals are used, including PET radiopharmaceuticals such as $^{11}\text{C}\text{-CGP 12177}$, $^{11}\text{C}\text{-meta-hydroxyephedrine}$ as well as its synthetic analogues labelled with other PET radionuclides ($^{18}\text{F}$, $^{68}\text{Ga}$). $^{11}\text{C}\text{-meta-hydroxyephedrine}$ is one of the most perspective radiopharmaceutical for an investigation of cardiac receptors function due to required materials availability for a radio synthesis in Russia. The main advantage of proposed $^{11}\text{C}\text{-meta-hydroxyephedrine}$ synthesis technique is the use of a catalyst which allows one decrease reaction time from 5 minutes to 30 seconds. Obtained results allow one decrease reaction time of methylation and increase radiochemical and technological yields.

1. Introduction
Cardiac neurotransmission imaging with PET allows in vivo assessment of presynaptic reuptake and neurotransmitter storage as well as of regional distribution and activity of postsynaptic receptors. Thus, the biochemical processes that occur during neurotransmission can be investigated in vivo at a micro molar level using radiolabeled neurotransmitters and receptor ligands. PET of cardiac neurotransmission characterizes myocardial neuronal function in primary cardioneuropathies, in which the heart has no significant structural abnormality, and in secondary cardioneuropathies caused by the metabolic and functional changes that take place in different diseases of the heart. One of the many radiopharmaceuticals that have been designed and tested to assess cardiac neurotransmission is $^{11}\text{C}\text{-meta-hydroxyephedrine}$. $^{11}\text{C}\text{-meta-hydroxyephedrine}$ is a false neurotransmitter that has the same neuronal uptake mechanism as norepinephrine, but is not degraded by monoamine oxidase and catechol methyltransferase, the enzymes responsible for the metabolism of norepinephrine in the heart. The storage and release properties seem to differ from those of the physiologic neurotransmitters. $^{11}\text{C}\text{-meta-hydroxyephedrine}$ can be synthesized with chemical purity greater than 95% and specific activity from 33.300 to 74.000 GBq/mmol [1].
There is a new activity at Bakulev Scientific Center for Cardiovascular Surgery on synthetic techniques of radio pharmaceutical production labeled with $^{11}$C for PET in cardiology in connection with the benefits of receptor radio pharmacology and clinical cardiology mentioned above. The staff of the PET center has accumulated a big experience in the production of PET radiopharmaceuticals. $^{11}$C-meta-hydroxyephedrine is one of the most perspective radiopharmaceutical for an investigation of cardiac receptors function due to required materials availability for a radio synthesis in Russia. Pharmaceuticals based on fluorine and gallium cannot be used for adequate analysis of biochemical processes because of it is not full analog of natural metabolites. In turn, a production of the other receptor radiopharmaceuticals labeled with $^{11}$C is difficult because of stringent legislation in the area of precursors. Furthermore, there are no commercially available precursors for the other concerned radiopharmaceuticals in Russia. Additionally, $^{11}$C-meta-hydroxyephedrine production is rather inexpensive.

2. Materials, methods and experiment
There is a facility for PET radionuclide production at Bakulev Scientific Center, namely, $^{11}$C. It is a low-energy $^1$H$^-$ radial-sector cyclotron with internal ion source CTI RDS-111 (see figure 1), providing proton beams of up to 40 $\mu$A, with an energy of approximately 10.6 MeV after losses in the vacuum and target entrance windows [2]. The self-shielded cyclotron was commissioned in 2000. Its RF system as well as ion source (see figure 2) were upgraded in 2014 in order to increase the reliability of radionuclides production [3]. Now it can produce up to 10 GBq of radionuclide $^{11}$C after 1.2 cm$^3$ gas target irradiation filled by N$_2$ with 2% of $^{16}$O$_2$ during 5 minutes. This activity is enough for production up to 3 GBq of radiopharmaceutical. Unfortunately, manufacturing these cyclotrons was ended in September 2016.

![Figure 1. Cyclotron complex view (a) and its target (b).](image)

Radiochemistry laboratory takes part in a project of a unit development for radiochemical synthesis. So, the prototype of Positomi-PRO [4] synthesis unit was used for methylation.

Technique of $^{11}$C-meta-hydroxyephedrine synthesis is based on using the so called "wet" production method of $^{11}$C-methyliodide by means of $^{11}$CO$_2$ reaction with LiAlH$_4$ in diethyl ether solution (0.1 M). After that the reaction product is dissolved by 59% water solution of HI. Produced $^{11}$CH$_3$I is distilled from the reaction mixture and trapped in a 0.01 M metaraminol solution under presence of acetonitrile/dimethyl sulfoxide mixture in proportion 3:1.
The reaction of metaraminol $^{11}$C-methylation was carried out during 5 minutes under the following conditions: reactor temperature – $100^\circ$C and pressure (250 – 300) kPa. The reaction yield and composition were evaluated by radio-thin layer chromatography (TLC) on silica gel plate in a mixture of acetone/benzol in proportion 3:1. Typical chromatogram, obtained with HPLC Akvilon unit, is shown in figure 3.

The reaction of metaraminol $^{11}$C-methylation was carried out in two cases. In the first case the reaction of metaraminol $^{11}$C-methylation was carried out in free base form as it was done in [5]. In the second one the reaction was performed in free base form with an addition of equimolar amount of tetrabutylammonium hydroxide (TBA) [6]. Radiochemical yields for two mentioned cases are shown in figure 4.
Figure 3. The analysis of compounds labelled with $^{11}$C in the reaction mixture by means of radio-TLC.

Figure 4. The radiochemical yield of $^{11}$C-methylation vs reaction time.

3. Conclusion

It was obtained that the reaction catalysis of metaraminol $^{11}$C-methylation by means of TBA resulted in radiochemical yield increase up to 75% while it was 60% under usual technique of $^{11}$C-meta-hydroxyephedrine synthesis. It was shown that TBA implementation allows one to use metaraminol hydrochloride instead of free base metaraminol form. Developed $^{11}$C-meta-hydroxyephedrine synthesis technique may help one to use PET in receptor radio pharmacology and domestic cardiology.

Acknowledgments

This work was supported by Competitiveness Program of National Research Nuclear University MEPhI.

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