A Simple On-column Preparation of [^<18>F]Fluorocholine from [^<18>F]Fluoromethyl Triflate

II. 2. A Simple On-column Preparation of [^{18}F]Fluorocholine from [^{18}F]Fluoromethyl Triflate

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The successful application of [^{11}C]choline to tumor imaging by PET[1] has been promoting the development of ^{18}F-labeled choline analogues as a longer-lived imaging agent. The preparations of ^{18}F-labeled fluoromethyl, fluoroethyl and fluoropropyl derivatives from corresponding ^{18}F-fluoroalkylating agents have been reported to date[2-5]. Among them ^{18}F-fluoromethylated choline analogue ([^{18}F]fluorocholine, see Fig. 1) is expected to be the most promising agent for measuring the phosphorylation rate in cancer cells[3].

The method for the radiosynthesis of [^{18}F]fluorocholine is based on the conventional reaction in a glass vessel where [^{18}F]fluoromethyl bromide is first trapped by a reaction solvent and then it is heated to carry out [^{18}F]fluoromethylation on *N,N*-dimethylaminoethanol[2]. On the other hand, our approach to the automated synthesis of PET radiopharmaceuticals, especially from [^{11}C]methyl iodide and [^{11}C]methyl triflate, is based on a simple on-column method using a short column where the flowing labeling agent is efficiently trapped and the reaction takes place at the same time without heating. It was exemplified by the [^{11}C]choline synthesis using disposable solid-phase extraction (SPE) cartridges[6]. We have recently succeeded in applying this on-column method to the preparation of [^{18}F]fluorocholine.

[^{18}F]Fluoromethyl triflate, a novel labeling agent, was prepared from [^{18}F]fluoromethyl bromide by passing through a AgOTf column heated at 200°C (see Fig. 1 and 2). The latter labeling agent was prepared by the K.222-supported substitution of [^{18}F]fluoride with CH_2Br_2 and distilled from a reaction vessel with a He flow (100

mL/min)[7]. It was then passed through 4 Sep-Pak Plus silica cartridges (Waters) to separate it from the volatile starting material, CH_2Br_2, which inevitably contaminated the He for carrying [^{18}F]fluoromethyl bromide from a reaction vessel. [^{18}F]Fluoromethyl bromide was eluted roughly between 4 and 8 min after starting the distillation, while it took more than 10 min to elute CH_2Br_2 from the silica columns. The on-line conversion of [^{18}F]fluoromethyl bromide to [^{18}F]fluoromethyl triflate was almost quantitative. Overall decay-corrected radiochemical yields of [^{18}F]fluoromethyl triflate were 47±8% based on [^{18}F]fluoride.

The on-column preparation of [^{18}F]fluorocholine from [^{18}F]fluoromethyl triflate was carried out using the remotely operated system shown in Fig. 2. The flowing [^{18}F]fluoromethyl triflate was passed through two connected SPE columns, a Sep-Pak Plus C18 cartridge retaining *N,N*-dimethylaminoethanol (0.1-0.5 mL) and a Sep-Pak Plus Accell CM cartridge. They were then washed with ethanol (10 mL) and water (10 mL) to completely elute the precursor. [^{18}F]Fluorocholine was eluted from the Accell CM with saline (5 mL). [^{18}F]Fluoromethyl bromide was also passed through the Sep-Pak cartridges to compare the reactivity of the labeling agents.

[^{18}F]Fluorocholine was prepared from [^{18}F]fluoromethyl triflate in radiochemical yields of over 80% (decay-corrected) with 0.2 mL of the precursor loaded on the C18 cartridge, whereas it was obtained from [^{18}F]fluoromethyl bromide in less than 10%, although this low yield was observed to be twice improved by decreasing the He flow rate down to 30 mL/min. Thus, it is demonstrated that [^{18}F]fluoromethyl triflate has higher reactivity than [^{18}F]fluoromethyl bromide and provides a simple on-column preparation of [^{18}F]fluorocholine suitable for routine clinical use.

[^{18}F]Fluorocholine was prepared from [^{18}F]fluoride via [^{18}F]fluoromethyl triflate in overall decay-corrected yields of 40% within 30 min.

References

1) Hara T., Kosaka N., Shioura N., Kondo T., J. Nucl. Med. **38** (1997) 842.
2) DeGrado T. R., Coleman R. E., Wang S., Baldwin S. W., Orr M. D., Robertson C. N., Polascik T. J., Price D. T., Cancer Res. **61** (2000) 110.
3) DeGrado T. R., Baldwin S. W., Wang S., Orr M. D., Liao R. P., Friedman H. S., Reiman R., Price D. T., Coleman R. E., J. Nucl. Med. **42** (2001) 1805.
4) DeGrado T. R., Reiman R., Price D. T., Wang S., Coleman R. E., J. Nucl. Med. **43** (2002) 92.
5) Hara T., Kosaka N., Kishi H., J. Nucl. Med. **43** (2002) 187.
6) Pascali C., Bogni A., Iwata R., Cambie M., Bombardieri E., J. Label. Comp. Radiopharm. **43** (2000) 195.
7) Bergman J., Eskola O., Lehikoinen P., Solin O., Appl. Radiat. Isot. **54** (2001) 927.

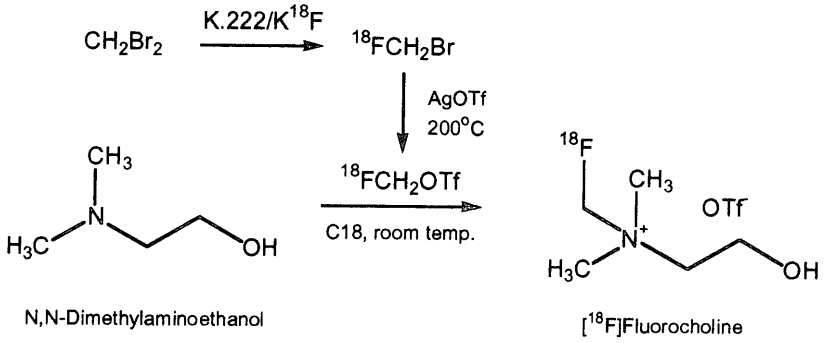

Fig. 1. A synthetic scheme of [^{18}F]fluorocholine from [^{18}F]fluoride.

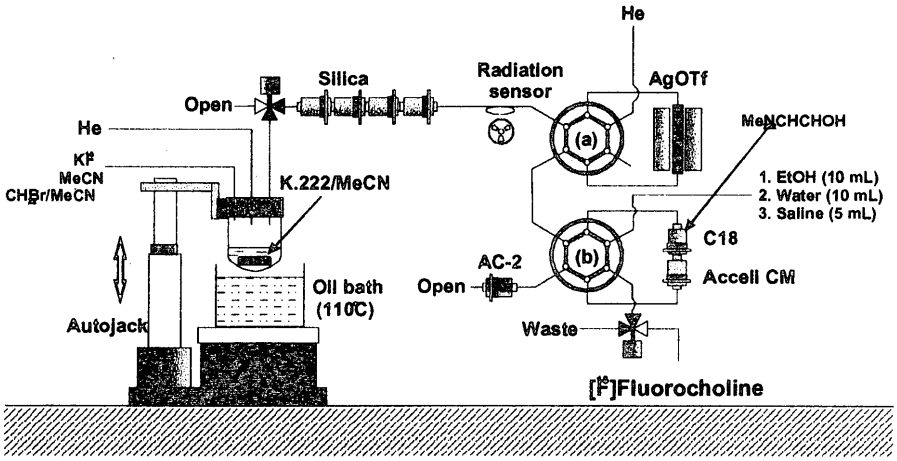

Fig. 2. A flowchart of the system for the preparation of [^{18}F]fluorocholine.