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Short Research Article

Radiosynthesis of *cis*-4-[^{124}I]iodo-L-proline as a prototype probe for imaging anterograde axoplasmic transport systems using positron emission tomography (PET)†

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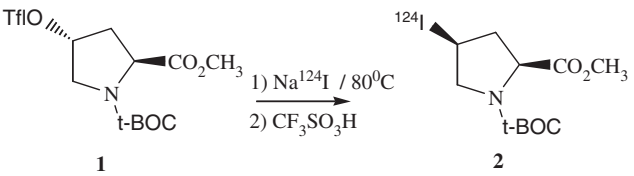
Introduction

Axonal transport of proteins has largely been imaged using the classical *ex vivo* autoradiography method using either anterograde tracers[1] or retrograde tracers. Typically, amino acids are labelled with tritium for use as anterograde or retrograde tracers. However, there are no reports of positron emission tomography (PET) anterograde or retrograde tracers because the short half-life of PET isotopes such C-11 and F-18 does not permit imaging of slow processes. Iodine-124 is a positron emitter with a half-life of 4.2 days, which may permit observation of slow processes *in vivo* using PET imaging. Iodine-124 has not found widespread application in PET imaging because of its lower positron abundance (23%) and a complex decay scheme which affects the resolution of PET images.[2] However, when delivered directly into brain tissue, iodine-124 yields a 'point source' imaging in custom-calibrated microPET cameras. We report the synthesis and evaluation of *cis*-4-[^{124}I]iodo-L-proline **2** as a prototype probe for the *in vivo* imaging of anterograde axoplasmic transport system in the rodent using microPET (Scheme 1).



1 **2**

Scheme 1

Results and discussion

cis-4-[^{124}I]iodo-L-proline **2** was prepared by treating a solution of *N-tert*-butoxycarbonyl-*trans*-4-(trifluoromethylsulfonyloxy)-L-proline methyl ester[3] **1** in dry THF with $Na^{124}I$ in 0.1 N sodium hydroxide and heating the solution at 80°C in a sealed tube for 2 h. After cooling to room temperature the reaction mixture was heated in 2 M trifluoromethanesulfonic acid at 125°C for 30 min. It was then evaporated to dryness and after neutralization with 3 N NaOH the mixture was loaded onto LiChrolut SCX, H+ form Seppak. After washing the Seppak with sterile water, *cis*-4-[^{124}I]iodo-L-proline was eluted with sterile 0.1 M trisodium phosphate at pH 7. Finally, the solution was filtered through a sterile 0.22 μm Millipore filter to give the injectable solution. The yield (17%) was low and the [^{124}I]iodo-L-proline had to be used immediately due its instability. The specific activity was determined to be 1.0–1.5 Ci/μmol. First, the whole body distribution of [^{124}I]iodo-L-proline was quantitatively studied in a mouse after the injection of 0.148 MBq (3 μCi) in the tail vein. PET data were obtained for 90 min using a list mode acquisition and were reconstructed using a filtered back projection protocol. The radioligand was distributed heterogeneously in the mouse body, with the highest uptake

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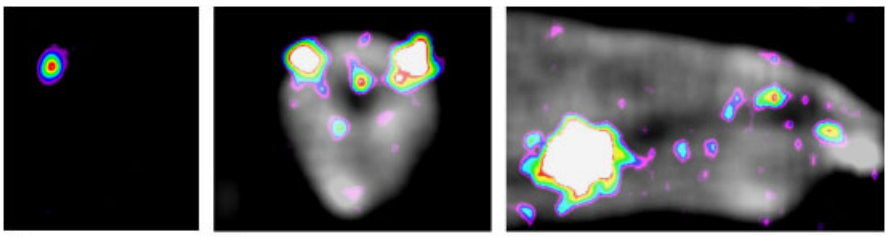

Figure 1 PET images obtained after an intra-ocular injection of *cis*-4-[^{124}I]iodo-L-proline. (a) shows a 15-min static acquisition (horizontal plane) obtained immediately after the unilateral injection of the radiopharmaceutical into the left eye. Note that tissue radioactivity does not suggest a spill of the injected ligand. (b) shows a static 15-min PET image superimposed on the transmission scan (coronal plane) obtained 8 h after a bilateral ocular injection of *cis*-4-[^{124}I]iodo-L-proline. (c) shows a sagittal slice of the same scan illustrated in (B); note the high uptake observed in the thyroid gland. Figure available in colour online at www.interscience.wiley.com

of the radioligand being in the kidneys, liver, gallbladder, pancreas, spleen and urinary bladder walls. In summary, the biodistribution of [^{124}I]iodo-L-proline resembles the distribution of 4-*cis*-[^{18}F]fluoroproline.[4] In the second part of the experiment, the distribution of *cis*-4-[^{124}I]iodo-L-proline was evaluated following the unilateral and bilateral injections of this radioligand (3 μL, ~0.6–0.8 μCi). Under deep anesthesia with isofluorane 3%, the *cis*-4-[^{124}I]iodo-L-proline was administered via intra-ocular injection (retrobulbar approach) using a Hamilton syringe with a 30G needle. Figure 1 summarizes the results.

In conclusion, our preliminary data suggest that it is possible to obtain PET images following injection of sub-μCi amounts of *cis*-4-[^{124}I]iodo-L-proline with 1.5 Ci/μmol specific activity. However, higher doses of radiotracer with higher specific activity may give better results.

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