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Short Research Article

Synthesis of lipophilic ammonium cations as tumour imaging agents for PET†

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Introduction

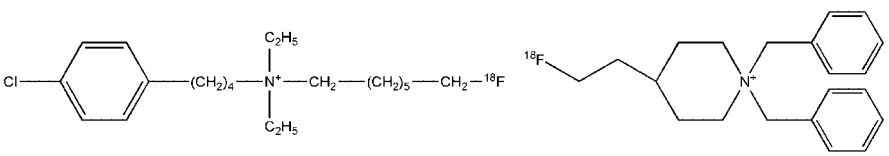
A mitochondrial damage related with a change in a membrane potential has an effect of a genetic mutation for carcinogenesis. The membrane potential difference between carcinoma cells and normal cells is known to be about 60 mV. Lipophilic cations are allowed to penetrate a membrane due to a negative potential of inner membrane lipid bilayer and they can be accumulated in carcinoma cells.[1,2] [^{18}F]Fluoroclofilium **1**, currently used for the treatment of arrhythmia as a cardiac imaging agent, has been prepared and a canine PET image has been achieved.

Recently, we have turned our attention to its dual properties which are lipophilic and cationic to develop novel tumour imaging agents using voltage differences.

Results and discussion

The F-18 labelled lipophilic ammonium cations, *N*-4-(4-chlorophenyl)butyl-*N*,*N*-diethyl-7-[^{18}F]fluoroheptylammonium([^{18}F]fluoroclofilium, 53%), its derivatives and [^{18}F]-*N*,*N*-dibenzyl-4-(2-fluoroethyl)piperidinium([^{18}F]BFP, 43%) have been synthesized (Scheme 1). The F-18 activity was produced by ^{18}O (p, n) ^{18}F reaction. All of the radioactive solution was dried together with Kryptofix 2.2.2 and K_2CO_3 in acetonitrile in a nitrogen stream at 90°C and [^{18}F]fluoride was introduced to the precursors in CH_3CN. The reaction mixture was pre-filtered with a small aluminum oxide Sep-Pak cartridge® and the resulting eluent was purified on HPLC (Column: RP-18, 300 × 3.9 mm; 4 μm; flow 1 ml/min; λ: 277 nm). The radiochemical purity of the [^{18}F]fluoroclofilium was more than 95%. [^{18}F]BFP was produced for 5 min at 93°C in a closed reaction vessel. [^{18}F]BFP was passed through a weak cation exchange Sep-Pak® cartridge. The radiochemical purity of [^{18}F]BFP was over 96% after purification.

Balb/c female mice were sacrificed for the biodistribution study of [^{18}F]fluoroclofilium and [^{18}F]BFP



1 **2**

Scheme 1

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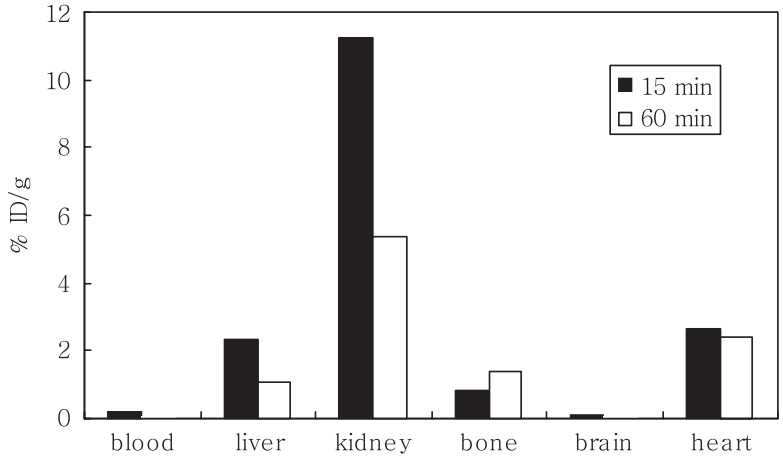

Figure 1 The biodistribution of [^{18}F]fluoroclofilium.

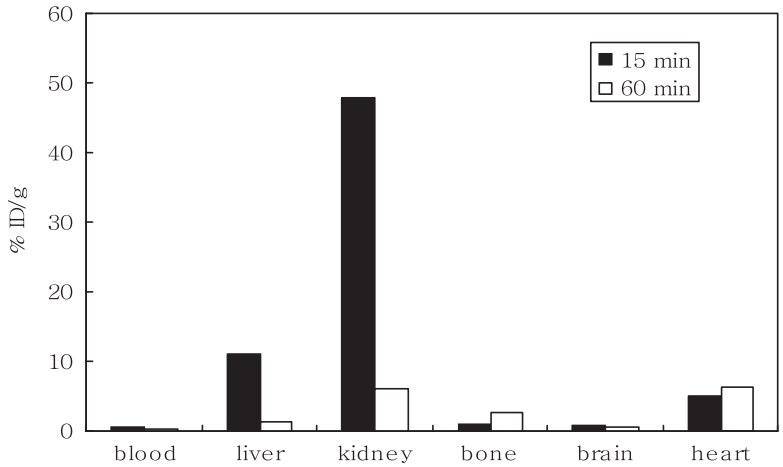

Figure 2 The biodistribution of [^{18}F]BFP.

after an IV injection. The data are given in Figures 1 and 2, respectively.

Since both [^{18}F]fluoroclofilium and [^{18}F]BFP are ionic compounds, highest uptake occurred in both kidneys. Both compounds showed an enhanced accumulation in bone at 60 min post injection(p.i.), which might be a result of the free fluoride from the [^{18}F]fluoroclofilium and [^{18}F]BFP. Both compounds showed similar excretion trends to the kidney and the liver although the absolute uptake value was lower than that of the kidney. The radioactivity of the blood was relatively lower than the other organs. The uptake ratios of the blood to the heart were 12 at 15 min p.i. and 48 at 60 min p.i. for [^{18}F]fluoroclofilium, 8 at 15 min p.i. and 21 at 60 min p.i. for [^{18}F]BFP. These results suggest that liphophilic ammonium cations have a potential for use as a myocardial PET imaging agent.[3] The biological evaluations using normal mice and tumor transplanted mice are ongoing.

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