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Radiosynthesis of 1-{4-[4-(2-[18F] Fluoroethoxy)-phenyl] Piperazine-1-yl} ethenone and its evaluation in animal models bearing C57BL6 melanoma xenograft
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Abstract
Background and objective:
Sigma receptors were initially described to be a subtype of opioid receptor, but later due to its unique characteristics it has been postulated as a distinguished receptor system. It is divided into Sigma 1 and Sigma 2 subtypes. Sigma receptors are well known for their over-expression in high density, in different types of tumors as in those of breast, melanoma, non-small-cell lung carcinoma, prostate, glioma and tumor of neural origin. Literature study shows that piperidine or piperazine moiety is an important pharmacophore showing binding affinity with the sigma receptors overexpressed on specific tumors. The present effort is directed towards radiosynthesis of [18F]fluoroethylated analogue of 1-Acetyl-4(4-Hydroxyphenyl) piperazine and evaluation of its potential as a tumor marker.
Materials and Method:
18F-fluoride production and radiosynthesis were performed using GE PETtrace cyclotron and GE TRACERlab module (Configured for 2-[18F]FDG production) respectively. [18F] radiofluorination was carried out using dry [18F] tetrabutylammonium fluoride. The radiosynthesis was carried out by a one-pot, two-step process. In the first step, [18F]fluoroethyl tosylate was synthesized by fluorination of ethylene ditosylate. In the second step, [18F]fluoroethyl tosylate was tagged with piperazine analogue to form [18F]fluoroethylated-piperazine analogue. The reaction mixture was purified using neutral alumina and Light C18 cartridges. The final product was eluted from the column with 10% ethanol. In-vitro cell uptake study was done by using melanoma cell line (B16F10). Bio-distribution in tumor xenograft model was carried out in C57BL6 mice with melanoma. Towards this B16F10 cell line (5x105 cells per mice) were injected in C57BL/6 mice. After 15 days the size of tumor was found to be 0.75-1 cm3. The size was considered to be sufficient for carrying out the studies. [18F] activity of 200 μCi per mice was injected through tail vein. Mice were sacrificed at 30, 60, and 120, min post injection for biodistribution studies. The same mice which was used for bio-distribution after 120 min pi was used for imaging using PET-CT camera at 60 min pi.
Result and Discussion:
The reaction conditions were optimized in order to obtain maximum yield of the radiolabeled product. The purity of the product was evaluated using Radio-TLC and radio-HPLC analysis and found to be more than 99%. A bed volume of 4 g neutral alumina and two Light C18 cartridges were found to be sufficient for efficient purification. A non-decay corrected radiochemical yield of 30% (n=4) was obtained with the reaction time of 60 min. In-vitro cell binding study shows good uptake in B16F10 cell line. Biodistribution study shows the compound to have good in-vivo stability and a significant tumor uptake till two hours. Tumor/blood ratio was found to increases with time. Hepatic and renal clearance pattern was observed at 120min pi.
Conclusions:
[18F]fluoroethylated piperazine analogue was successfully synthesized and purified, with a radiochemical purity of 99%. The radiotracer showed sufficient in-vivo stability. Biodistribution studies shows significant tumor uptake. Further uptake studies with different tumor xenograft models are underway.

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