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Development and Evaluation of 18F-radiolabeled Acetaminophen (Paracetamol) for Tumour Imaging Based on COX-2 Overexpression

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Background of the Study:
Overexpression of COX-2 receptors is observed in a variety of tumour. Therefore, development of suitable 18F-labeled PET radiotracers of selective COX-2 inhibitors is an attractive option to target selective and specific inhibitors of COX-2. The binding free energy [ΔG(-KCal/mole)] of Acetaminophen and F-18 labelled derivative of Acetaminophen have been calculated using AUTODOCK 4.2 and crosschecked using www.swissdock.ch against the PDB code 3LN1 and has been found to be comparable in both cases. This encouraging result provides the necessary impetus towards development of F-18 labelled derivative of Acetaminophen based on its property of selective COX-2 inhibition in designing PET radiopharmaceutical for tumour imaging.
Herein, we report the fully automated radiosynthesis of the novel F-18 Fluoroethylated paracetamol by direct radio-fluoroethylation of paracetamol and subsequent purification with SEP-PAK® cartridge purification. The evaluation of the PET radiotracer has been carried out by PET/CT imaging, bio-distribution in mice tumour model and histopathological studies.
Methodology:
The fully automated radiosynthesis of 18F-Fluoroethylated paracetamol using general purpose synthesis module which, in principle, is similar to GE TRACERlab FXFDG , has been carried out in three steps: (i) Radiosynthesis of the fluoroethylating agent, [18F]Fluoroethyl tosylate (ii) Coupling of [18F]Fluoroethyl tosylate with paracetamol in DMSO solvent and (iii) purification by SPE using Sep Pak® Plus ALOX N cartridges. Pharmacokinetic studies was evaluated by PET/CT imaging study in healthy rabbit at two different time points. Biodistribution study was carried out in nude mice bearing tumour (MDA-MB-231). COX-2 overexpression in tumours was confirmed by histopathological studies.
Results:
The non-decay corrected radiochemical yield is around (25±3) % (n = 3) within 60±2 mins (total synthesis time). The radiochemical purity is > 95 % as confirmed by radio-TLC and radio-HPLC coupled with UV (λ=276 nm). Biodistribution study demonstrated significant tumor accumulation and retention over a period of two hours post injection. COX-2 overexpression in tumour was confirmed by histopathological studies using mouse anti-COX2 antibody. One-hour post injection PET/CT imaging study in healthy rabbit showed very fast clearance from liver and blood, however, with high accumulation of the tracer in highly proliferating regions like bone marrow and sub-mandibular jaws. The thick leg joints showed significant uptake which can be attributed to age related inflammation in aged rabbit and the well-known fact that COX-2 is overexpressed in inflammation. Both the kidneys as well as urinary bladder showed very high tracer accumulation indicating clearance via renal route.
The PET/CT image of two-hours post injection showed complete blood clearance with elimination via renal route, however with bone marrow accumulation. No bone uptake other than the thick joints was observed throughout the period of PET/CT study confirming in vivo stability of the tracer. Thick joint uptake can be attributed to age-related inflammation of the aged rabbit and the well-known fact that COX-2 is overexpressed in inflammation.
Conclusion:
F-18 labelled Paracetamol has successfully been designed, developed and evaluated as a PET tracer for tumour imaging agent based on COX-2 overexpression in a variety of tumours.

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