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Potential radiotracers based on the 4' -O-methylhonokiol structure for PET visualization of neuroinflammation

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Introduction Neuro-inflammatory processes are known to underlie the mechanism of neuronal damage and play a key role in the neurodegenerative disease progression. The cyclooxygenase 2 (COX-2) enzyme is one of the most studied neuroinflammatory biomarkers and an attractive target for PET imaging. Neolignan 4'-O-methylhonokiol (MH) isolated from Magnolia officinalis, has high anti-inflammatory activity and selectively inhibits the expression of COX-2 with IC50=0.062 μM, as was recently shown by Kim H.S. et.al., 2015. Here we report the synthesis of novel labeled MH derivatives ([11C]MPbP and [18F]FEtPbP) and their preliminary evaluation on the lipopolysaccharide (LPS)-induced neuroinflammation rat model.

Pic 1

Methods The MH derivatives [11C]MPbP (4'-[11C]methoxy-5-propyl-1,1'-biphenyl-2-ol) and [18F]FEtPbP (4'-(2-[18F]fluoroethoxy)-2-hydroxy-5-propyl-1,1'-biphenyl) were obtained by 11C-methylation and 18F-fluoroethylation of the precursor with Boc-protecting group using synthons [11C]CH3I and [18F]FCH2CH2Br, respectively. After HCl hydrolysis of intermediates the crude reaction mixtures were purified by semi-preparative HPLC. Neuroinflammation in rats was induced by an intraperitoneal injection of LPS from E.coli (2 mg/kg) before 24 h the administration of [11C]MPbP, [18F]FEtPbP, celecoxib or placebo into the tail vein (0.1-0.2 mCi/0.5 ml of phosphate buffer pH 7.4, containing ethanol (5-7%, v/v)). Celecoxib, a well-known non-steroid anti-inflammatory drug and a selective inhibitor of COX 2 was used as a reference. Ex vivo radioligand biodistribution was performed by direct radiometry of organs and tissues samples. The uptake of radioactivity was determined by the dose administered per gram of tissue (% ID/g).

Results and discussion [11C]MPbP and [18F]FEtPbP were obtained in decay-corrected isolated radiochemical yields 20 and 35 % based on the activity of the corresponding alkylating agent. The biodistribution data showed that the observed uptake in the brain of neuroinflammatory rats was 4 times higher than it was in intact animals. In addition, it was shown that [11C]MPbP or [18F]FEtPbP increased uptake occurred in the parts of rat brain where COX-2 expression was observed (pons&medulla). A decrease in the radiotracer uptake by 2-3 times in these regions with the celecoxib pretreatment may serve as evidence of this hypothesis.

Conclusion Synthesis of [11C]MPbP and [18F]FEtPbP, labeled MH analogs has been developed. On the rat neuroinflammation model, it has been shown that these radiotracers have the potential for PET imaging of neuroinflammation.

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