Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-009-1274-y

ORIGINAL ARTICLE

[^{18}F]F15599, a novel 5-HT$_{1A}$ receptor agonist, as a radioligand for PET neuroimaging

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Received: 27 April 2009 / Accepted: 24 August 2009

Abstract
Purpose The serotonin-1A (5-HT$_{1A}$) receptor is implicated in the pathophysiology of major neuropsychiatric disorders. Thus, the functional imaging of 5-HT$_{1A}$ receptors by positron emission tomography (PET) may contribute to the understanding of its role in those pathologies and their therapeutics. These receptors exist in high- and low-affinity states and it is proposed that agonists bind preferentially to the high-affinity state of the receptor and therefore could provide a measure of the functional 5-HT$_{1A}$ receptors. Since all clinical PET 5-HT$_{1A}$ radiopharmaceuticals are antagonists, it is of great interest to develop a ^{18}F labelled agonist.
Methods F15599 (3-chloro-4-fluorophenyl-(4-fluoro-4{[(5-methyl-pyrimidin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl)-methanone) is a novel ligand with high affinity and selectivity for 5-HT$_{1A}$ receptors and is currently tested as an antidepressant. In pharmacological tests in rat, it exhibits preferential agonist activity at post-synaptic 5-HT$_{1A}$ receptors in cortical brain regions. Here, its nitro-precursor was synthesised and radiolabelled via a fluoronucleophilic substitution. Radiopharmacological evaluations included in vitro and ex vivo autoradiography in rat brain and PET scans on rats and cats. Results were compared with simultaneous studies using [^{18}F]MPPF, a validated 5-HT$_{1A}$ antagonist radiopharmaceutical.
Results The chemical and radiochemical purities of [^{18}F]F15599 were >98%. In vitro [^{18}F]F15599 binding was consistent with the known 5-HT$_{1A}$ receptors distribution (hippocampus, dorsal raphe nucleus, and notably cortical areas) and addition of Gpp(NH)p inhibited [^{18}F]F15599 binding, consistent with a specific binding to G protein-coupled receptors. In vitro binding of [^{18}F]F15599 was blocked by WAY100635 and 8-OH-DPAT, respectively, prototypical 5-HT$_{1A}$ antagonist and agonist. The ex vivo and in vivo studies demonstrated that the radiotracer readily entered the rat and the cat brain and generated few brain radioactive metabolites. Remarkably, in microPET studies, [^{18}F]F15599 notably displayed a pattern of brain labelling that did not correlate with in vitro observations. Thus, in cat, the highest binding was observed in dorsal raphe and cingulate cortex with little binding in other cortical regions and none in hippocampus. In vivo binding was abolished by WAY100635, indicating specific labelling of 5-HT$_{1A}$ receptors.
Conclusion [^{18}F]F15599 is a radiofluorinated agonist presenting interesting characteristics for probing in vitro and in vivo the high-affinity states of the 5-HT$_{1A}$ receptors. Its differential labelling of 5-HT$_{1A}$ receptors in vitro and in vivo may result from its reported preferential interaction with receptors coupled to specific G-protein subtypes.

Keywords Serotonin 1A receptor · PET · Agonist · Rat · Cat

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Published online: 30 September 2009