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Radiosynthesis and in vivo evaluation of fluorinated huprine derivates as PET radiotracers of acetylcholinesterase

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ABSTRACT

Introduction: Developing positron emission tomography (PET) radiotracers for non-invasive study of the cholinergic system is crucial to the understanding of neurodegenerative diseases. Although several acetylcholinesterase (AChE) PET tracers radiolabeled with carbon-11 exist, no fluorinated radiotracer is currently used in clinical imaging studies. The purpose of the present study is to describe the first fluorinated PET radiotracer for this brain enzyme.
Methods: Three structural analogs of huprine, a specific AChE inhibitor presenting high affinity towards AChE in vitro, were synthesized and labeled with fluorine-18 via a mesylate/fluoro-nucleophilic aliphatic substitution: ([^{18} F]-FHUa, [^{18} F]-FHUb and [^{18} F]-FHUc). Initial biological evaluation included in vitro autoradiography in rat with competition with an AChE inhibitor at different concentrations, and microPET-scan on anesthetized rats. In vivo PET studies in anesthetized cat focused on [^{18} F]-FHUa.
Results and Conclusions: Although radiosynthesis of these huprine analogs was straightforward, they showed poor brain penetration potential, partially reversed after pharmacological inhibition of P-glycoprotein. These results indicated that current huprine analogs are not suitable for PET mapping of brain AChE receptors, but require physicochemical modulation in order to increase brain penetration.