ESTABLISHMENT OF THREE STRUCTURALY RELATED 6-O-18F-FLUOROETHYLATED OPIOID RECEPTOR TRACERS OF DIFFERENT INTRINSIC ACTIVITIES: AUTOMATED PRODUCTION AND EVALUATION OF [^{18}F]FPEO, [^{18}F]FBPN AND [^{18}F]FDPN

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Objective: To assess of the impact of the intrinsic activity of opioid receptor (OP)-tracers, we have identified and established a triplet of the F-18 labeled orvinols diprenorphine (DPN), buprenorhine (BPN) and phenethylorvinol (PEO). These three tracers cover the full spectrum of agonist/antagonist properties and are available by an automated synthesis strategy that enables routine production.

Methods: 6-*O*-^{18}F-fluoroethylated orvinol derivatives of antagonist diprenorphine ([^{18}F]FDPN), partial agonist buprenorphine ([^{18}F]FBPN) and agonist phenethylorvinol ([^{18}F]FPEO) were prepared in an automated three-step, two pot synthesis based on a low-pressure SPE purification of the ^{18}F-alkylation agent [^{18}F]FETos, followed by ^{18}F-fluoroethylation of their respective 3-*O*-trityl protected 6-*O*-desmethyl-precursors. The cold compounds were characterised for affinity, selectivity and intrinsic activity on cloned cells expressing the human ORs. The regional brain distribution kinetics of the three ^{18}F-fluoroalkylated orvinols was investigated in vivo in rats with a small animal PET scanner.

Results: The compounds were synthesized and formulated in yields of 23 ± 4 %, a specific activity of 50-150 TBq/mmol, > 99 % radiochemical purity in a total of 100 minutes after end-of-bombardment (N > 60). In vivo investigations by PET imaging of all three compounds in rat brain revealed a rapid entry of tracers to the brain and a high retention in regions with a high target expression. Pre-treatment with Naloxone blocked the brain uptake for all three compounds, consistent with a specific binding of the tracer to the opioid receptors. The results from the biological evaluations revealed that the 6-*O*-^{18}F-fluoroethylated orvinol derivatives tolerated the alteration of the native structure by substituting the 6-*O*-methyl moiety by a 6-*O*-fluorethyl group with a conserved pattern of affinity, selectivity and intrinsic activity of the compounds of study.

Conclusions: The developed chemistry protocol for purification of [^{18}F]FETos production together with the successful implemented on an flexible automated synthesis module enables fluoroethylated orvinols. The triplet FDPN, FBPN and FPEO allows for the first time systematic investigations of the effect of intrinsic activity on ligand-exchange kinetics in opioid receptor imaging protocols.