[^{18}F]Fluoroethylflumazenil: A Novel Tracer for PET Imaging of Human Benzodiazepine Receptors

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Introduction: 5-(2´-[^{18}F]fluoroethyl)flumazenil ([^{18}F]FEF) is a ^{18}F-labeled PET tracer for central benzodiazepine receptors. Compared to the established [^{11}C]flumazenil, it has the advantage of the longer half-life of the fluorine-18 label. After optimization of its synthesis and determination of its in vitro receptor affinities we performed first PET studies in humans.

Subjects and Methods: PET studies in seven healthy human volunteers were performed on a Siemens ECAT EXACT whole-body scanner after injection of 100-280 MBq [^{18}F]FEF. In two subjects, a second PET scan was conducted after pre-treatment with unlabeled flumazenil (1 mg or 2.5 mg I.V., respectively, 3 min before tracer injection). A third subject was studied both with [^{18}F]FEF and with [^{11}C]flumazenil. Brain radioactivity was measured for 60-90 min p.i. and analyzed with a ROI-oriented approach and on a voxelwise basis with spectral analysis. Plasma radioactivity was determined from arterial blood samples and metabolites were determined by HPLC.

Results: In human brain, maximum radioactivity accumulation was observed 4±2 min p.i. with a fast clearance kinetics resulting in 50% and 20% of maximal activities at about 10 and 30 min, respectively. [^{18}F]FEF uptake followed the known central benzodiazepine receptor distribution in the human brain (occipital cortex > temporal cortex > cerebellum > pons). Pre-treatment with unlabeled flumazenil resulted in reduced tracer uptake in all brain areas except for receptor-free reference regions like the pons. Parametric images of distribution volume and binding potential generated on a voxelwise basis revealed 2- to 3-fold lower in vivo receptor binding of [^{18}F]FEF compared to [^{11}C]flumazenil, while relative uptake of [^{18}F]FEF was higher in the cerebellum, which is most likely due to its relatively higher affinity for benzodiazepine receptors containing the α6 subunit. Metabolism of [^{18}F]FEF was very rapid. Polar metabolites represent about 50-60% of total plasma radioactivity at 5 min. and 80-90% at 20 min. p.i.

Conclusion: Although [^{11}C]flumazenil has some advantages over [^{18}F]FEF (higher affinity, slower metabolism, slower kinetics), our results indicate that [^{18}F]FEF is a suitable PET ligand for quantitative assessment of central benzodiazepine receptors, which can be used independently of an on-site cyclotron.

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[^{18}F]FEF-Summenbild und Verteilungsvolumen nach Spektralanalyse