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In vivo quantification of 5-HT$_{1A}$–[^{18}F]MPPF interactions in rats using the YAP-(S)PET scanner and a β-microprobe

Philippe Millet,[a,*] Marcelle Moulin,[a,b] Antonietta Bartoli,[c] Alberto Del Guerra,[c] Nathalie Ginovart,[a,d] Laurent Lemoucheux,[e] Stephano Buono,[e] Daniel Fagret,[b] Yves Charnay,[f] and Vicente Ibáñez[a]

[a] *Psychiatric Neuroimaging Unit, Division of Neuropsychiatry, Department of Psychiatry, University Hospital of Geneva, Switzerland*
[b] *INSERM, E340 Unit, France*
[c] *Department of Physics, University of Pisa, Pisa, Italy*
[d] *Department of Psychiatry, University of Geneva, Switzerland*
[e] *Advanced Accelerator Application, Saint Genis Pouilly, France*
[f] *Morphology Unit, Division of Neuropsychiatry, Department of Psychiatry, University Hospital of Geneva, Switzerland*

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We performed full modeling analysis of 5-HT$_{1A}$–[^{18}F]MPPF interactions using the β-microprobe (βP) and a YAP-(S)PET scanner. Sixteen Wistar rats were used for βP (n=5) and YAP-(S)PET (n=5) acquisitions and metabolite studies (n=6). Time–concentration curves were obtained in the hippocampus, raphe dorsalis, frontal cortex and cerebellum, using three injections of [^{18}F]MPPF at different specific activities. B'_{max} values were estimated from a two (2T-5k)- and three (3T-7k)-tissue-compartment model with βP and YAP-(S)PET time–concentration curves. The simplified reference tissue model (SRTM) was used to estimate binding potential (BP_{SRTM}) values from data obtained with the first injection and the cerebellum as the reference region. Overall, the 3T-7k model provided a better fit than the 2T-5k model, as evaluated from AIC criteria in all experiments. The rank order of receptor density (B'_{max}) values was as follows: hippocampus > raphe ≈ frontal cortex > cerebellum. Non-negligible specific binding was observed in the cerebellum (B'_{max} (βP) = 1.5 ± 0.9 pmol/ml). Significant correlations (p<0.001) between B'_{max} and BP_{SRTM} values were evident with both βP (r=0.895) and YAP-(S)PET (r=0.695). The YAP-(S)PET system underestimated the [^{18}F]MPPF binding levels in brain due to limited resolution (i.e. partial volume), but led to similar conclusions.

Keywords: β-Microprobe; YAP-(S)PET; [^{18}F]MPPF; 5-HT$_{1A}$; Compartmental model

Introduction

Serotonin (5-HT) is involved in a number of physiological functions and etiology of mental disorders, including depression, stress-related diseases, anorexia nervosa, and schizophrenia (Pucadyil et al., 2005). The neurotransmitter exerts its actions via a heterogeneous family comprising at least 15 distinct receptor subtypes that are widely distributed throughout the CNS and peripheral tissues (Bockaert et al., 2006). Among these, the metabotropic 5-HT$_{1A}$ receptors play a key role in serotonergic neurotransmission, since in the dorsal raphe nucleus, 5-HT and 5-HT$_{1A}$ agonists exert a negative feedback influence on firing activity (Pucadyil et al., 2005). Furthermore, different adaptative changes of pre- and post-synaptic 5-HT$_{1A}$ receptors may contribute to anxiolytic/antidepressant therapy (Hensler, 2003).

The Positron Emission Tomography (PET) technique has facilitated considerable progress in research on 5-HT$_{1A}$ receptors *in vivo*. Two main radioligands have been employed to date. The first is the well-known [^{11}C]WAY-100635, an antagonist with high affinity for 5-HT$_{1A}$ receptors (Pike et al., 1996). Quantitative studies show that the radioligand is suitable to assess 5-HT$_{1A}$ receptor binding (Farde et al., 1998). However, the pharmacological properties of this ligand are not appropriate for measuring changes in endogenous serotonin (Jagoda et al., 2006). Le Bars et al. (1998) showed that [^{18}F]MPPF, a radioligand with similar affinity for 5-HT, is a better indicator of 5-HT neurotransmission in the brain.

Several groups have performed *in vivo* characterization of [^{18}F]MPPF, both in animals (Ginovart et al., 2000; Plenevaux et al., 2000b) and humans (Passchier et al., 2001). Studies to date clearly demonstrate that [^{18}F]MPPF binds specifically to 5-HT$_{1A}$ receptors. However, the effects of variations in the synaptic concentrations of endogenous ligand ([5-HT]) on [^{18}F]MPPF binding remain a subject of controversy.

* Corresponding author. University Hospital of Geneva, Unité de Neurophysiologie Clinique et Neuro-imagerie 2, chemin du Petit-Bel-Air CH-1225 Chêne-Bourg, Geneva, Switzerland. Fax: +41 22 305 53 75.
E-mail address: Philippe.Millet@sim.hcuge.ch (P. Millet).
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