Comparison of 4 Radiolabeled Antagonists for Serotonin 5-HT$_7$ Receptor Neuroimaging: Toward the First PET Radiotracer

Laetitia Lemoine[1,2], Julien Andries[3], Didier Le Bars[1,3,4], Thierry Billard[1,3], and Luc Zimmer[1,2,4]

[1]*CERMEP-Imagerie du Vivant, Lyon, France;* [2]*University of Lyon 1, CNRS UMR5292, INSERM U1028, Lyon Neuroscience Research Center, Lyon, France;* [3]*University of Lyon 1, CNRS UMR5246, Institute of Chemistry and Biochemistry, Villeurbanne, France; and* [4]*Hospices Civils de Lyon, Lyon, France*

Brain serotonin 7 (5-hydroxytryptamine 7, or 5-HT$_7$) is the most recently identified serotonin receptor. It is involved in mood disorders and is studied as a target for antidepressants. Because no radioligand has yet been successfully used to study this receptor by PET neuroimaging, the objective of the present study was to develop a 5-HT$_7$ ^{18}F-labeled radiotracer. **Methods:** Four structural analogs of SB269970, a specific 5-HT$_7$ receptor antagonist, were synthesized. The nitro precursors of these analogs were radiolabeled by ^{18}F nucleophilic substitution. Analog antagonist effects were investigated by cellular functional assay. The cerebral distribution of radiolabeled molecules was studied by in vitro autoradiography in rats, and respective selectivity was determined by competition with the 5-HT$_7$ receptor antagonist SB269970 at different concentrations. Ex vivo small-animal PET studies in rats and in vivo PET studies in cats focused on the 1-(2-{(2R)-1-[(fluorophenyl)sulfonyl] pyrrolidin-2-yl}ethyl)-4-methylpiperidine (FP3) series. **Results:** Four analogs were synthesized from the SB269970 pharmacophore and divided into an FP3 (^{18}F-4FP3 and ^{18}F-2FP3) and an 1-(2-{(2R)-1-[(fluorophenyl)sulfonyl]pyrrolidin-2-yl}ethyl)-4-(2-methoxyphenyl) piperazine (FPMP) (^{18}F-2FPMP and ^{18}F-4FPMP) series. The chemical and radiochemical purities of the 4 radiolabeled molecules were greater than 98%. All presented suitable affinity for 5-HT$_7$ (apparent dissociation constant [K_D] between 1.6 and 14 nM), although the FPMP series showed moderate agonist activity for 5-HT$_{1A}$ receptors. Lipophilicity values were predictive of good radiotracer blood–brain barrier penetration (logD from 1.4 to 3.9). In vitro competition with a 5-HT$_7$ antagonist, SB269970, revealed that only radioligands from the FP3 series were displaced by the 5-HT$_7$–specific antagonist: subsequent in vivo study, therefore, focused on this series. Ex vivo ^{18}F-4FP3 and ^{18}F-2FP3 autoradiography was in accordance with the 5-HT$_7$ brain distribution, with few brain radioactive metabolites. PET scans in cats showed that pretreatment with a 5-HT$_7$ antagonist significantly reduced ^{18}F-2FP3 but not ^{18}F-4FP3 binding. **Conclusion:** The 4 PET radiotracers had suitable characteristics for 5-HT$_7$ receptor probing in vitro, although the FP3 series seemed to be more specific for in vivo imaging of 5-HT$_7$ receptors. In particular, on the basis of the in vivo results, ^{18}F-2FP3 appears to be the first PET radiotracer to enable in vivo imaging of 5-HT$_7$ receptors in animal models, possibly leading to neuroimaging studies in humans.

Key Words: PET; tracer development; 5-HT$_7$ receptors; rat; cat

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Serotonin (5-hydroxytryptamine, or 5-HT) is a central neurotransmitter involved in many physiologic functions and in neurologic and psychiatric disorders. Pharmacologic studies identified numerous serotoninergic receptor families and subtypes, classified by structural, functional, and pharmacologic criteria into 7 distinct receptor classes (5-HT$_{1–7}$) (*1*).

The 5-HT$_7$ subtype is the most recently cloned serotonin receptor (*2*). 5-HT$_7$ receptors are coupled to G proteins (*3*) and are found in rodents, pigs, primates, and humans, with relatively high concentrations in the hippocampus, thalamus, and hypothalamus and lower levels in the cortex and amygdala (*4–6*). The 5-HT$_7$ receptor exhibits a high degree of interspecies homology (~95%) but low sequence homology with other 5-HT receptors (<40%) (*3,6*). Three 5-HT$_7$ receptor isoforms, which differ only in their carboxyl terminal tails and have the same pharmacologic profile, are expressed in rats and humans (*7*).

The recent availability of selective 5-HT$_7$ receptor antagonists (*7–9*) and of 5-HT$_7$ receptor knockout mice (*10*) has considerably advanced understanding of the physiologic function of this receptor (*11*). 5-HT$_7$ has been identified as important in circadian rhythms and sleep (*12*). It also binds several antidepressants (e.g., mianserin and maprotiline) and antipsychotics (e.g., clozapine and risperidone) with high affinity and may be a therapeutic target for schizophrenia and mood disorders. Selective 5-HT$_7$ antagonists were indeed recommended in schizophrenia and depression (*13–15*). Several reports, based on receptor distribution and preliminary pharmacologic analyses, suggested 5-HT$_7$ receptors as a new serotoninergic target for memory enhancement, epilepsy, and pain (*16–19*).

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For correspondance or reprints contact: Luc Zimmer, CERMEP-Imagerie du Vivant, 59 Boulevard Pinel, F-69003 Lyon, France.
E-mail: zimmer@cermep.fr
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