Original article

Synthesis and biological evaluation of potential 5-HT\textsubscript{7} receptor PET radiotracers

Julien Andries\textsuperscript{a}, Laetitia Lemoine\textsuperscript{b,c}, Didier Le Bars\textsuperscript{a,c,d}, Luc Zimmer\textsuperscript{b,c,d}, Thierry Billard\textsuperscript{a,c,*}

\textsuperscript{a} Université de Lyon, Université Lyon 1, CNRS, Institute of Chemistry and Biochemistry (ICBMS - UMR CNRS 5246), 43 Bd du 11 novembre 1918, 69622 Lyon, France
\textsuperscript{b} Université de Lyon, Université Lyon 1, CNRS UMR5292, INSERM U1028, Lyon Neuroscience Research Center, 59 Bd Pinel, 69003 Lyon, France
\textsuperscript{c} CERMEP-Imagerie du Vivant, 59 Bd Pinel, 69003 Lyon, France
\textsuperscript{d} Hospices Civils de Lyon, 59 Bd Pinel, 69003 Lyon, France

A B S T R A C T

Brain serotonin 7 receptor (5-HT\textsubscript{7}) is involved in several mood disorders and drug candidates targeting this subtype are currently in development. Positron emission tomography (PET) is a molecular imaging modality offering great promise for accelerating the process from preclinical discovery to clinical phases. As no PET radiopharmaceutical has yet been used successfully to study the 5-HT\textsubscript{7} receptor in vivo, our objective is to develop the first 5-HT\textsubscript{7} fluorine-18 labeled radiotracer.

Four structural analogs of SB269970, a specific 5-HT\textsubscript{7} receptor antagonist, divided in FP3 series and FPMP series were synthesized. Their antagonist effects were investigated by cellular functional assay. Nitro-precursors of these analogs were radiolabeled via a [18F]fluorine radiolabeling and in vitro autoradiographies were performed in rat brain.

Chemical and radiochemical purities of fluorine radiotracers were >99% with specific activities in 40–129 GBq/mole range. The four derivates presented antagonism potencies toward 5-HT\textsubscript{7} receptors (pKB) between 7.8 and 8.8. The four PET radiotracers had suitable characteristic for 5-HT\textsubscript{7} receptor probing in vivo even if the FP3 series seemed to be more specific for this receptor. These results encourage us to pursue in vivo studies.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a central neurotransmitter involved in physiological functions, as well as neurological and pathological disorders. Pharmacological studies allowed identification of numerous serotoninergic receptors families and subtypes which were classified by structural, functional and pharmacological criteria into seven distinct receptor classes (5-HT\textsubscript{1–7})\textsuperscript{[1]}

The 5-HT\textsubscript{7} subtype is the most recently cloned serotonin receptor \textsuperscript{[2]}, 5-HT\textsubscript{7} receptors (5-HT\textsubscript{7}R) are coupled to Gs proteins \textsuperscript{[3]} and are found in rodent, pig, non-human and human primate with relatively high concentrations in hippocampus, thalamus, and hypothalamus and, with lower levels, in cortex and amygdala \textsuperscript{[4]}

The recent availability of selective 5-HT\textsubscript{7} receptor antagonists \textsuperscript{[5]} and of 5-HT\textsubscript{7} receptor knockout mice \textsuperscript{[6]} has considerably advanced the understanding of the physiological function of this receptor \textsuperscript{[7]}

The 5-HT\textsubscript{7} receptor has been identified as important in circadian rhythms and sleep \textsuperscript{[8]}

As in the case of the 5-HT\textsubscript{6} subtype, 5-HT\textsubscript{7} receptors also bind several antidepressants (e.g., mianserin, maprotiline) and antipsychotics (clozapine, risperidone) with high affinity, indicating that this receptor may represent a therapeutic target for schizophrenia and mood disorders. In fact, selective 5-HT\textsubscript{7} antagonists were proposed as a potential treatment for schizophrenia or depression \textsuperscript{[9]}

Several reports, based on receptor distribution and preliminary pharmacologic analyses, suggest that 5-HT\textsubscript{7} receptors might represent another serotoninergic target for memory enhancement, epilepsy and pain \textsuperscript{[10]}

Therefore an ability to image serotonin 5-HT\textsubscript{7} receptors in human brain in vivo is needed to assess directly this receptor involvement in neuropsychiatric diseases and their possible therapies. With the development of positron emission tomography (PET) as a molecular imaging method, the opportunity has evolved to perform in vivo observations both in animal models and in humans \textsuperscript{[11]}

These studies can be performed at "tracer concentrations" implying the intravenous administration of a "radiotracer" at a very small amounts (3–10 μg) and far away from levels at which pharmacological effects might occur. This implies the availability of a PET radiotracer which specifically labels the 5-HT\textsubscript{7} receptor.

If several selective antagonists exist \textsuperscript{[5]}, few have been radiolabeled for use in radioligand binding and autoradiography studies