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Quinazoline Analogue as a Pet Tracer for Imaging PDE10A: Radiosynthesis and Biological Evaluation

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Abstract : The family of phosphodiesterases (PDEs) plays a critical role in control of the level, localization, and duration of intracellular 3’-5’-cyclic adenosine monophosphate (cAMP) and 3’-5’-cyclic guanosine monophosphate (cGMP) signals by specifically hydrolyzing these cyclic nucleotides. As the involvement of cyclic nucleotide second messengers in cell signaling and homeostasis is established, the regulation of these pathways in the brain by various PDE isoforms is an area of considerable interest, as they are involved in nearly all brain functions and in the etiology of neuropsychiatric diseases. The PDE10A isoform, isolated from different species and characterized regarding structure and function, has received much attention in recent years, particularly in the context of schizophrenia and Huntington’s disease, which are both related to a role of PDE10A in the regulation of striatal dopaminergic neurotransmission. Quinazoline analogue 1-(4-methoxyphenyl)-6,7-dimethoxyquinazoline, was evaluated as specific PET marker for phosphodiesterase (PDE) 10A. Here, we report the radiosynthesis of [11C]2 and the in vitro and in vivo evaluation of [11C]2 as a potential positron emission tomography (PET) radiotracer for imaging PDE10A in the central nervous system (CNS). The radiosynthesis of [11C]2 was achieved by O-methylation of the corresponding des-methyl precursor with [11C]methyl iodide. [11C]2 was obtained with ~50% radiochemical yield. PET imaging studies in rat brain displayed initial specific uptake with very rapid clearance of [11C]2 from brain. Though [11C]2 is not an ideal radioligand for clinical imaging of PDE10A in the CNS. Modified analogue of quinazoline having a higher potency for inhibiting PDE10A and improved pharmacokinetic properties will be necessary for imaging this enzyme with PET.

Keywords : PDE10A, PET, radiotracer, quinazoline
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