ORIGINAL ARTICLE

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Evaluation of radioiodinated 5-iodo-3-(2(*S*)-azetidinylmethoxy)pyridine as a ligand for SPECT investigations of brain nicotinic acetylcholine receptors

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5-Iodo-3-(2(*S*)-azetidinylmethoxy)pyridine (5IA), an A-85380 analog iodinated at the 5-position of the pyridine ring, was evaluated as a radiopharmaceutical for investigating brain nicotinic acethylcholine receptors (nAChRs) by single photon emission computed tomography (SPECT). [$^{123/125}$I]5IA was synthesized by the iododestannylation reaction under no-carrier-added conditions and purified by high-performance liquid chromatography (HPLC) with high radiochemical yield (50%), high radiochemical purity (> 98%), and high specific radioactivity (> 55 GBq/μmol). The binding affinity of 5IA for brain nAChRs was measured in terms of displacement of [^{3}H]cytisine and [^{125}I]5IA from binding sites in rat cortical membranes. The binding data revealed that the affinity of 5IA was the same as that of A-85380 and more than seven fold higher than that of (−)-nicotine, and that 5IA bound selectively to the $\alpha4\beta2$ nAChR subtype. Biodistribution studies in rats indicated that the brain uptake of [^{125}I]5IA was rapid and profound. Regional cerebral distribution studies in rats demonstrated that the accumulation of [^{125}I]5IA was consistent with the density of high affinity nAChRs with highest uptake observed in the nAChR-rich thalamus, moderate uptake in the cortex and lowest uptake in the cerebellum. Administration of the nAChR agonists (−)-cytisine and (−)-nicotine reduced the uptake of [^{125}I]5IA in all regions studied with most pronounced reduction in the thalamus, and resulted in similar levels of radioactivity throughout the brain. [^{125}I]5IA binding sites were shown to be saturable with unlabeled 5IA. Behavioral studies in mice demonstrated that 5IA did not show signs of behavioral toxicity. Furthermore, SPECT studies with [^{123}I]5IA in the common marmoset demonstrated appropriate brain uptake and regional localization for a high-affinity nAChR imaging radiopharmaceutical. These results suggested that [^{123}I]5IA is a promising radiopharmaceutical for SPECT studies of central nAChRs in human subjects.

Key words: 5-iodo-3-(2(*S*)-azetidinylmethoxy)pyridine, radioiodination, nicotinic acethylcholine receptor, brain, single photon emission computed tomography