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Synthesis and evaluation of vesamicol analog (–)-*o*-[^{11}C]methylvesamicol as a PET ligand for vesicular acetylcholine transporter

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(–)-*o*-Methylvesamicol ((–)-OMV) exhibited *in vitro* a high affinity for vesicular acetylcholine transporter (VAChT) (*K*i, 6.7 nM) and a relatively low affinity for sigma$_1$ receptor (*K*i, 33.7 nM). We prepared (–)-[^{11}C]OMV by a palladium-promoted cross-coupling reaction using [^{11}C]methyl iodide, in a radiochemical yield of 38 ± 6.9% (n = 3), a radiochemical purity of 98 ± 2.3% (n = 5), and a specific activity of 11 ± 7.0 TBq/mmol at 30 minutes after EOB (n = 5). Then, we evaluated *in vivo* whether (–)-[^{11}C]OMV has properties as a PET radioligand for mapping VAChT. In rats, the brain uptake of (–)-[^{11}C]OMV was 1.1%ID/g at 5 minutes postinjection, and was retained of a high level for 60 minutes. The brain uptake was significantly inhibited by the co-injection (500 nmol/kg) of cold (–)-OMV (58–66%), (–)-vesamicol (57–65%), and two sigma receptor ligands with modulate affinities for VAChTs: SA4503 (56–71%) and haloperidol (39–64%) in all of the brain regions, including the cerebellum with a low density of VAChTs, but not of sigma$_1$-selective ligand (+)-pentazocine. However, the pretreatment with a large excess amount of (±)-pentazocine (50 μmol/kg) reduced the uptake in a different manner in the brain regions: 25% reduction in the striatum with a high density of VAChTs, and a 50–55% reduction in the other regions with a lower density of VAChTs. *Ex vivo* autoradiography using (–)-[^{11}C]OMV showed a similar regional brain distribution of [^{3}H](–)-vesamicol. In the PET study of the monkey brain, the regional brain distribution pattern of (–)-[^{11}C]OMV was different from that of [^{11}C]SA4503. The uptake of (–)-[^{11}C]OMV was relatively higher in the striatum, was reversible, and an apparent equilibrium state was found at 20–40 minutes. In conclusion, (–)-[^{11}C]OMV exhibited appropriate brain kinetics during the time frame of ^{11}C-labeled tracers and bound mainly to VAChTs; however, the binding to sigma$_1$ receptors was not disregarded. Therefore, (–)-[^{11}C]OMV-PET together with help of [^{11}C]SA4503-PET may evaluate VAChTs.

Key words: (–)-*o*-[^{11}C]methylvesamicol, VAChT, PET, vesamicol