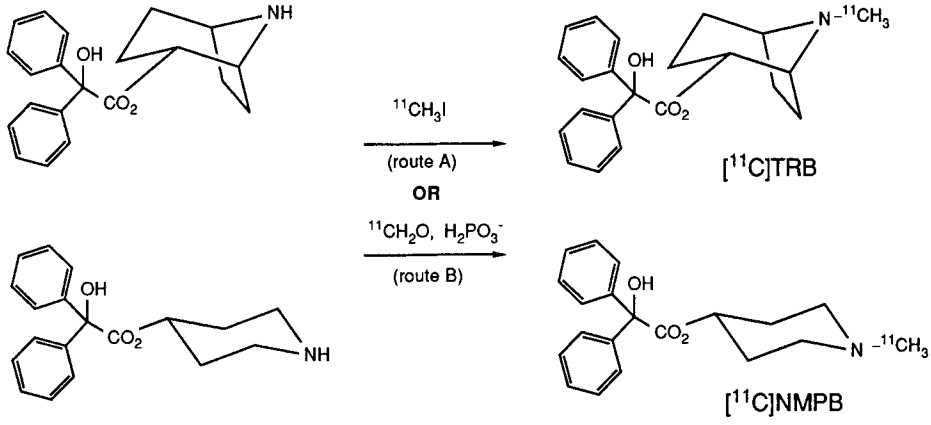
RADIOSYNTHESIS AND COMPARISONS IN THE BIODISTRIBUTION OF CARBON-11 LABELED MUSCARINIC ANTAGONISTS: (+)2α-TROPANYL BENZILATE AND N-METHYL-4-PIPERIDYL BENZILATE. G.K. Mulholland, C.A. Otto, D.M. Jewett, M.R. Kilbourn, P.S. Sherman, R.A. Koeppe, K.A. Frey, D.E. Kuhl. Division of Nuclear Medicine, University of Michigan, Ann Arbor, MI 48109

Two potent centrally active antimuscarinic drugs, (+)2α-tropanyl benzilate TRB (1) and N-methyl-4-piperidyl benzilate NMPB (2) were selected for carbon-11 labeling after initial in vitro and ex vivo screenings suggested their potential as muscarinic receptor imaging agents (3). Reaction of the desmethyl derivatives of TRB and NMPB with [^{11}C]formaldehyde/neutral aqueous phosphite, 95° (4) or [^{11}C]methyl iodide, followed by preparative normal phase HPLC, afforded [^{11}C]TRB and [^{11}C]NMPB in moderate (with [^{11}C]CH_2O) to excellent (with [^{11}C]CH_3I) yields based on [^{11}C]CO_2 (30-45 min synthesis). Radiochemical purities were above 99% (TLC and RPHPLC).



The biodistributions of [^{11}C]TRB and [^{11}C]NMPB (sp. activity 75-400 Ci/mmol at time of injection) in rats were examined at 2, 20, 30, 60 and 90 min post-injection. Brain uptake curves for the two compounds were similar. Peak levels (4% ID/brain for TRB, 3.7% for NMPB) were observed at 20 min. Retention of radioactivity in brain was greater with [^{11}C]TRB than with [^{11}C]NMPB. Percent ID/brain values at 90 min were 3% and 1.7% respectively. Regional brain distributions of the two agents were nearly identical and compared favorably with known muscarinic receptor densities in rat brain (5). Striatum to cerebellum ratios and cortex to cerebellum ratios increased with time to values of ~ 11 and ~ 8 respectively, at 90 min. Levels of radioactivity in pons-medulla were approximately twice that in cerebellum for both compounds. More than 85% of control uptake of both [^{11}C]TRB and [^{11}C]NMPB into cortex at 30 min was blocked by quinuclidinyl benzilate (1 mg/kg, pretreatment 90 min prior to injection of C-11 agent). Thus it appears that brain uptake of these compounds is largely receptor mediated. Significant apparent receptor mediated heart uptake of [^{11}C]TRB was observed at 30 min. In contrast, heart uptake of [^{11}C]NMPB was low. Analysis of [^{11}C]TRB tissue radioactivity at 30 min by TLC (SiO_2, 10:10:1:1 CH_2Cl_2:Et_2O:EtOH:Et_3N) showed that >97% of activity in brain (83% recovery) had the same R_f as authentic TRB. About 90% of heart activity (89% recovery) appeared to be unmetabolized [^{11}C]TRB as was 40% of the radioactivity in whole blood (94% recovery).

Sequential PET studies of [^{11}C]TRB in a baboon show encouraging regional uptake of brain activity which was abolished by predosing the animal with scopolamine (0.2 mg/kg). In view of the ease of synthesis and favorable biodistribution

properties of these radioligands. Further studies of [^{11}C]TRB and [^{11}C]NMPB are planned.

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1. Atkinson, E.R., McRitchie, D.D., Shoer, L.F., Harris, L.S., Archer, S., Aceto, M.D., Pearl, J., Luduena, F.P., J. Med. Chem., 20, 1612, 1977.

2. Sokolovsky, M., Egozi, Y., Kloog, Y. Monogr Neural Sci 7 30, 1980.

3. Otto, C.A., Mulholland, G.K., Perry, S.E., Combs, R., Sherman, P.S., Fisher, S.K. In Vitro and Ex Vivo Evaluation of N-Methyl Benzilates as Potential PET Agents for Muscarinic Receptors. Submitted to Seventh Intl. Symposium on Radiopharmaceutical Chemistry, Groningen, The Netherlands, 1988.

4. Mulholland, G.K., Toorongian, S.A., Jewett, D.M. J Nucl Med 28, 635p, 1987.

5. Birdsall, N., Hulme, E., Burgen, A. Proc. R. Soc. London B207, 1, 1980.