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DESIGN, SYNTHESIS AND EVALUATION OF REDOX RADIOPHARMACEUTICALS: A POTENTIAL NEW APPROACH FOR THE DEVELOPMENT OF BRAIN IMAGING AGENTS

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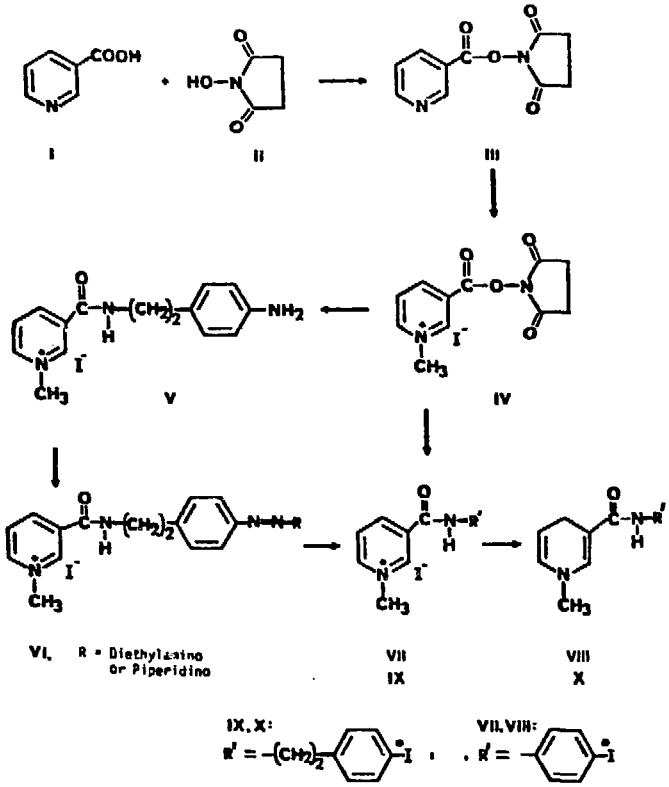
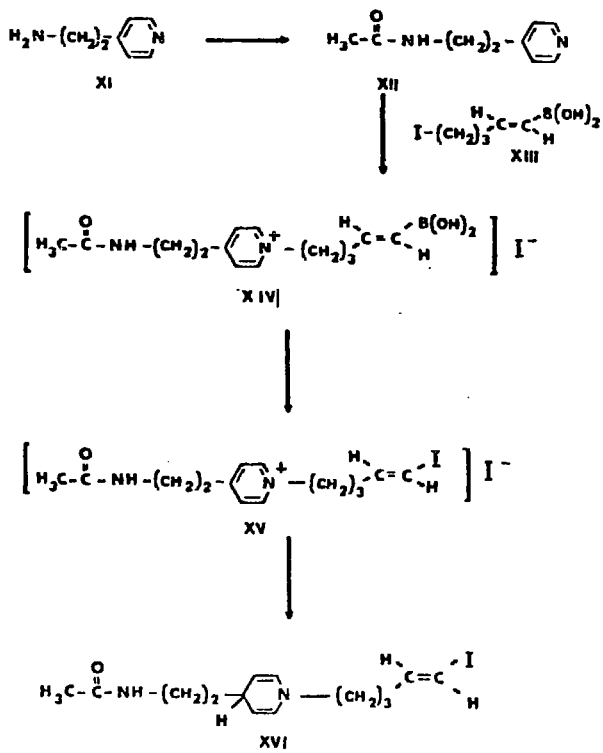
^{123}I-labeled lipophilic radiopharmaceuticals which cross the intact blood-brain barrier and mimic regional blood flow (1) can potentially be used for scanning brain lesions by either planar or single photon computerized tomographic (SPECT) techniques (2). The strategies that have been pursued to develop brain imaging agents include the screening of a variety of radioiodinated amphetamines (3) resulting in the development of p-[^{123}I]iodo-N-isopropylamphetamine (IMP) for SPECT studies in humans (4), and "pH shift" agents (5) resulting in the development of N,N,N'-trimethyl-N'-[2-hydroxy-3-methyl-[^{123}I]iodobenzyl]-1,3-propanediamine (HIPDM) which also shows excellent properties in human studies (6). Other promising recent advances in this area include the development of p-[^{123}I]iodophentermine (7), radioiodinated piperazine analogues (8), and ^{201}Tl complex of diethyldithiocarbamic acid (9) as potential brain imaging agents.

The goals of this paper are to describe the fabrication (Scheme I) and complete evaluation of a dihydropyridine ⇄ pyridinium salt type redox system (10) for the delivery of radioiodinated agents to the brain. The work in part has been described recently (11). For preliminary evaluation, the pivotal intermediate, N-succinimidyl (1-methylpyridinium iodide)-3-carboxylate (IV) was prepared by condensation of nicotinic acid (I) and N-hydroxysuccinimide (II) in the presence of dicyclohexylcarbodimide, followed by quaternization of III with methyl iodide. Coupling of IV with 4-[^{125}I]iodoaniline, prepared by ^{125}I-I_2 treatment of 4-aminophenylmercuric acetate, gave 1-methyl-3-[N-(4-iodophenyl)carbamoyl]-pyridinium iodide (VII) which after sodium dithionite reduction gave 1-methyl-3-[N-(4-iodophenyl)carbamoyl]-1,4-dihydropyridine (VIII). Compound IV was also coupled with (4-aminophenyl)ethylamine to give V which was diazotized and sequentially transformed into triazines VI, 1-methyl-3-[N-[β-(4-[^{125}I]iodo-phenyl)ethyl]carbamoyl]pyridinium iodide (IX) and 1-methyl-3-[N-[β-(4-[^{125}I]-iodophenyl)ethyl]carbamoyl]-1,4-dihydropyridine (X) (Scheme I). Compounds, 1-(E-1-[^{125}I]iodo-1-penten-5-yl)-4(2-N-acetylaminoethyl)pyridinium iodide (XV) and 1-(E-1-[^{125}I]iodo-1-penten-5yl)-4-(2-N-acetylaminoethyl)-1,4-dihydropyridine (XVI), were also prepared via the synthesis and Na[^{125}I]-chloramine-T iodination of XIV as shown in Scheme II in order to determine the relative redox properties and brain specificities of new structurally modified dihydropyridine ⇄ pyridinium agents.

Tissue distribution studies of ^{125}I-labeled 4-iodoaniline and the redox agents were performed in rats. [^{125}I]Iodoaniline initially showed moderate (0.58% dose/gm) brain uptake with subsequent release of the radioactivity from the brain. [^{125}I]Iodoaniline, however, when coupled to a dihydropyridine carrier (VIII) showed significantly higher (>1% dose/gm) uptake and retention in the brain (Fig. 1). The [^{125}I]iodophenylethyl analogue X showed uptake (>1% dose/gm) and retention in the brain very similar to VIII. Apparently the lipophilic agents, VIII and X, cross the blood-brain barrier and are oxidized (quaternized) within the brain. The blood-brain barrier then prevents their release resulting in high uptake and retention in the brain and high brain:blood ratios (Fig. 2). The nonlipophilic quaternary compounds VII and IX do not cross the blood-brain barrier and, therefore, do not show brain uptake. Compound XVI showed initial moderate (0.49% dose/gm) brain uptake and quick washout from the brain. The differences in the properties of XVI as compared to VIII and X could apparently be due to the different structural features and inability of XVI to undergo facile oxidation in the brain.



Scheme I



Scheme II

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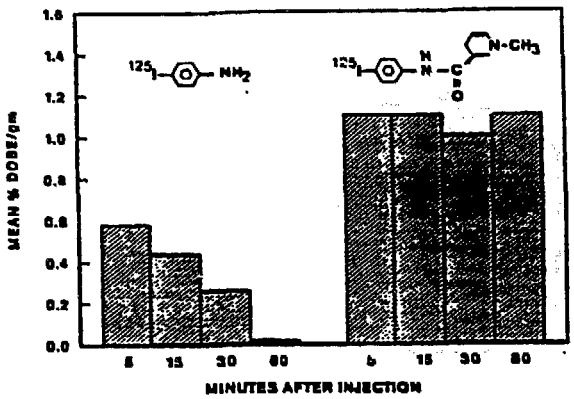

Fig. 1. Dihydropyridine coupled 4-[^{125}I]-iodoaniline agent (VIII) shows significantly higher uptake and retention in the brain as compared to the parent 4-[^{125}I]-iodoaniline independently. Agent X shows properties similar to VIII.

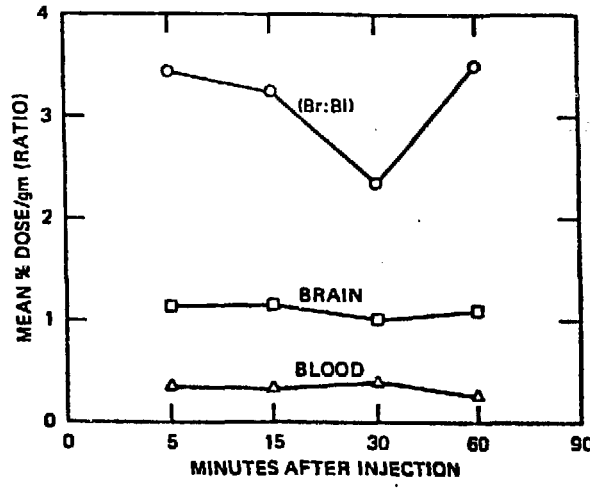

Fig. 2. High uptake and retention in the brain and low blood levels of VIII result in high brain: blood ratios. Agents VIII and X show similar properties.

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1. Oldendorf, W. H., Proc. Soc. Exp. Biol. Med., 19, 1182 (1974).
2. Budinger, T. F., J. Nucl. Med., 21, 279 (1980).
3. Winchell, H. S., Baldwin, R. M., Lin, T. H., J. Nucl. Med., 21, 940 (1982).
4. Kuhl, D. E., Barrio, J. R., Huang, S. C., Selin, C., Ackerman, R. F., Lear, J. L., Wu, J. L., Lin, T. H., Phelps, M. E., J. Nucl. Med., 23, 196 (1982).
5. Kung, H. F., Blau, M., J. Nucl. Med., 21, 147 (1980a).
6. Polak, J. F., Holman, B. L., Moretti, J. L., Eisner, R. C., Lister-James, J., English, R. J., J. Nucl. Med., 25, 495 (1984).
7. Elmaleh, D. R., Kuzuka, H., Boudreaux, G., Hanson, R. N., Proceedings of the 5th International Radiopharmaceutical Chemistry Symposium, Tokyo, Japan, July 1984. J. Lab. Cmpds. and Radiopharm. XXI, p. 88, 1078 (1984).
8. Hanson, R. N., El-Shounbagy, T., Hasson, M., Proceedings of the 5th International Radiopharmaceutical Chemistry Symposium, Tokyo, Japan, July 1984. J. Lab. Cmpds. and Radiopharm. XXI, p. 92 (1984).
9. Vyth, A., Fennema, P. J., van der Schoot, J. B., Pharm. Weekblad Sci. Ed., 5, 213 (1983).
10. Bodor, N. J., Simpkins, W., Science, 221, 65 (1983).
11. Tedjamulia, M. L., Srivastava, P. C., Knapp, F. F. Jr., J. Med. Chem., 28, 1574 (1985).