CONF-8410351--1

"Potential New Approaches for the Development of Brain Imaging Agents for Single-Photon Applications"

For, Proceedings of the Workshop on Amphetamines and pH-Shift Agents for Brain Imaging, Basic Research and Clinical Results, Rheinisch-Westfalische Gesellschaft for Nuclearmedizin, Bonn, Federal Republic of Germany, October 1984, Walter de Gruyton, Co., publishers.

CONF-8410351--1

DE86 002247

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Research supported by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-840R21400 with Martin Marietta Energy Systems, Inc.

INTRODUCTION

Iodine-123-labeled lipophilic radiopharmaceuticals which cross the intact blood-brain barrier and mimic regional blood flow (Oldendorf, 1974) can potentially be used for scanning brain lesions by either planar or single photon computerized tomographic (SPECT) techniques (Budinger, 1980). After intravenous administration the delivery of such lipophilic substances to the brain is flow limited and the initial levels of cerebral radioactivity are thus proportional to regional perfusion. After equilibrium is reached, many agents are cleared or "washed out" from the brain tissue at a rate directly proportional to regional blood flow and many others show reversible permeability to the blood-brain barrier (freely enter and exit). Such agents are not optimal for brain imaging due to their rapid clearance. A variety of strategies have, therefore, been pursued to design agents which, will show rapid first-pass extraction, followed by rapid blood clearance with resulting good brain:blood ratios and exhibit prolonged cerebral retention with minimal redistribution. In this manner imaging technologies which take long acquisition periods, such as SPECT, can be used to qualitatively and potentially quantitatively determine the regional distribution of the tracer, which reflects blood perfusion.

One strategy that has been pursued is the screening of a variety of structurally-modified radioiodinated amphetamines (Winchell et al, 1980 and 1982) which show high cerebral extraction. These studies have resulted in the

development of p-[^{123}I]iodo-N-isopropylamphetamine (IMP) (Kuhl et al, 1982; Lee et al, 1982) which is being used for SPECT studies in humans, and exhibits high cerebral extraction and slow wash-out. The amphetamines apparently bind strongly to high-affinity non-specific sites. Another strategy involves the "pH shift" agents, using radiolabeled amines that are "trapped" in the brain by the slightly lower cerebral pH in comparison to plasma (Lasser et al, 1983; Kung and Blau, 1980a and 1980b; Kung et al, 1980). The extension of this concept has resulted 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 (Polak et al, 1984; Holman et al, 1984).

Iodine-123 has excellent radionuclidic and chemical properties for use in diagnostic radiopharmaceuticals. The emission of the abundant (84%) 159 keV gamma photon allows the use of routinely available Anger-type cameras which are available in all nuclear medicine clinics. It is interesting to note that although the importance of iodine-123 has been discussed for two decades, only recently has the potential usefulness of this radionuclide really been demonstrated. The current interest and further development of tissue-specific iodine-123-labeled radiopharmaceuticals have been catalyzed to a great extent by the successful use of [^{123}I]IMP. The dramatic increase in the number of papers presented at the American Society of Nuclear Medicine Meetings (Figure 1) can be attributed to recent developments with IMP and related agents and the evaluation of chemical strategies for incorporation of this radionuclide into different tissue-specific agents. An additional index of the growth in this area is the increase in papers presented at these meetings using SPECT (Figure 2). It would appear that we are now on a threshold for the rapid increase in the development and use of

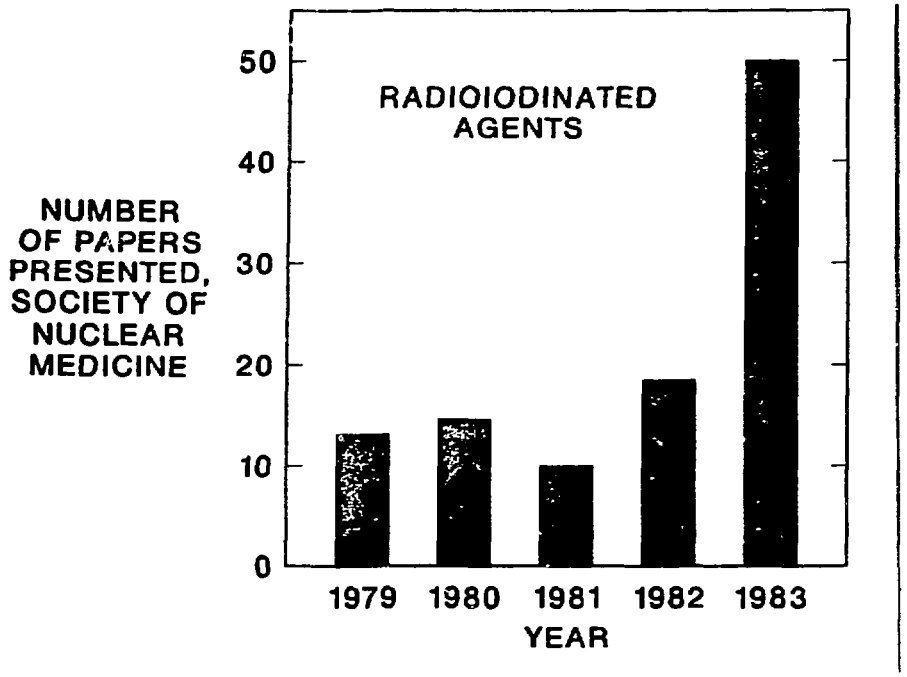


Fig. 1. Number of papers discussing radioiodinated agents at the U.S. Society of Nuclear Medicine Meetings from 1979-1983.

iodine-123-labeled agents. Not only are agents like [^{123}I]-IMP and iodine-123-labeled fatty acids being more widely used, but the commercial availability of iodine-123 in the United States and Europe is rapidly increasing.

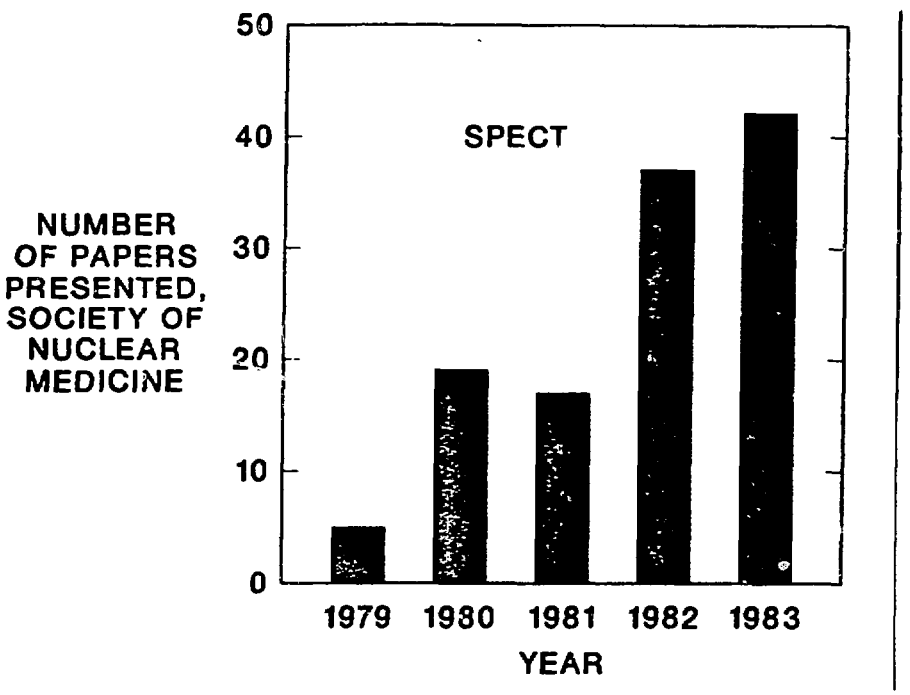


Fig. 2. Number of papers on single-photon computerized tomography (SPECT) presented at the U.S. Society of Nuclear Medicine Meetings from 1979 through 1983.

The goals of this paper are to describe new strategies being pursued at several institutions for the brain-specific delivery of radionuclides that can be used to evaluate regional cerebral perfusion by single photon imaging techniques. A comprehensive review of the literature is beyond the scope of these proceedings and our goal is to, therefore, present a description of several examples of interesting new strategies that have recently been reported. In addition, we also describe a new approach being pursued at our institution for the brain-specific delivery of radioiodinated iodophenylalkyl-substituted dihydronicotinamide systems which show good brain uptake and retention in preliminary studies in rats. Following transport into the brain these agents appear to undergo facile intracerebral oxidation to the quaternized analogues which do not cross the intact blood-brain barrier and are effectively trapped in the brain.

New Methyl-Substituted Amphetamine Analogues

Investigators continue their search for molecules that can be modified and readily radiolabeled and evaluated as potential cerebral imaging agents. As described earlier, the excellent properties of iodine-123 give this radionuclide great promise for incorporation into brain-specific agents that can be used like IMP or HIPDM. In addition, the wide variety of radiolabeling methods which are useful for the incorporation of iodine-123 into these molecules further stimulates this area of research. From a structural perspective, the iodine atom is about the size of a methyl group and can thus be introduced into tissue-specific molecules in many cases without drastically altering the size and shape or polarity of the molecule. This is in direct contrast to the presence of bulky chelating groups required to bind radionuclides which have more complex oxidation states, such as technetium-99m. An example of important differences in chemical strategies and difficulties in

incorporating the highly desirable technetium-99m radionuclide into these types of agents is illustrated by the tremendous effort, as of yet unsuccessful, in preparing a technetium-99m analogue of HIPDM (Kung et al, 1983 and 1984a and 1984b). Although the success of these efforts is highly desirable and will undoubtedly be achieved, the pursuit of iodine-123-labeled agents continues.

The interesting properties and success with [^{123}I]IMP in clinical studies have prompted the evaluation of other structural analogues having the basic amphetamine structure in an effort to optimize structural features that may lead to higher cerebral retention and less redistribution and wash-out. An evaluation of the effects of α-dimethyl-branching on the cerebral extraction and retention properties of a structurally modified amphetamine anlaogue, phentermine (Figure 3), has recently been reported (Elmaleh et al, 1984). Phentermine (α,α-dimethylphenethylamine) is a potent sympathomimetric drug which is used as an anorexic (Shelton et al, 1946). The CNS effects of this agent suggested that p-iodinated analogues may retain these neurological properties and also show high cerebral uptake. In addition, the presence of geminal dimethyl-branching at the α-position would inhibit subsequent metabolism by interfering with transformation via the monoamine oxidase system (MAO) and other catabolic events. The p-[^{125}I]iodophentermine exhibited the expected high cerebral extraction and retention in rats (1.7% dose/gm at 5 and 30 min) further confirmed by gamma camera imaging with the [^{123}I]-labeled analogue in dogs. This agent therefore shows good promise for further evaluation and a careful comparison with IMP and HIPDM to study the relative cerebral and lung uptake and retention properties should be pursued.

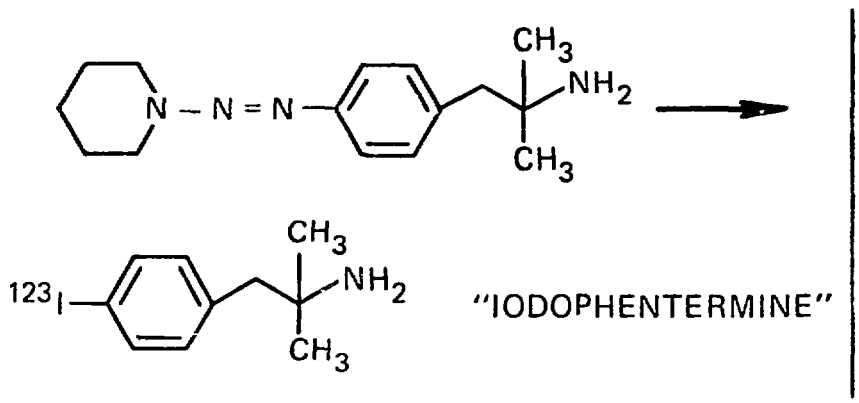
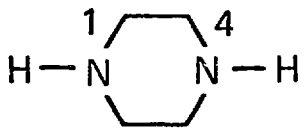


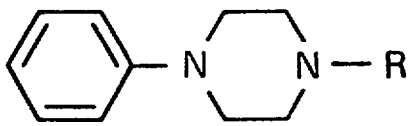
Fig. 3

New Radioiodinated Nitrogen Heterocycles

An interesting class of radioiodinated nitrogen-containing heterocyclic agents which have recently been studied (Hanson et al, 1984) are the N,N-di-substituted piperazines (Figure 4). The parent compound, piperazine, was used as early as the beginning of the twentieth century for the treatment of gout since it readily dissolved uric acid. A variety of aryl-substituted piperazines act on the central nervous system including "anti-aggressive" effects (Haech and Hiller, 1982), "anti-hypertensive" activity (Hampton and Pollard, 1937; Fregnan and Porta, 1981), and "neuroleptic" activity (Janseen et al, 1961; Janseen, 1965). The effects in the latter class are most pertinent to the current discussion of the potential use of radioiodinated arylpiperazines, since "Fluanison" is a methoxyphenylpiperazine-substituted butyrophenone that shows potent CNS activity. Another example is "Prazosin" (1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-piperazine) an agent that also shows "antihypertensive" activity (Cohen, 1970).



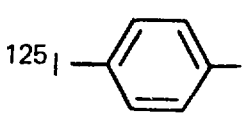
PIPERAZINE



1-SUBSTITUTED
4-PHENYLPIPERAZINES

Figure 4

The presence of two nitrogen atoms in the piperazine ring system allowed the preparation of a wide variety of nonsymmetrical N,N'-disubstituted piperazine derivatives. The N-aryl piperazine moiety represents a convenient group for the introduction and stabilization of radioiodide. Several N-(p-iodophenyl)-N'-substituted piperazine derivatives were prepared and the [^{125}I]-labeled analogues evaluated in rats (Figure 5). These interesting agents show good



RATS, 4 MINUTES

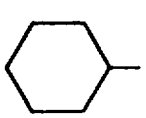
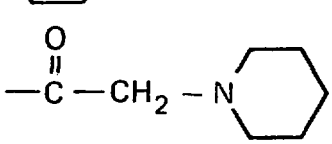
R	% DOSE/gm BRAIN	BRAIN/BLOOD
$H_3C-(CH_2)_3-$	2.1%	34
	0.8%	35
	1.3%	31

Figure 5

brain uptake and very high brain:blood ratios, although the relative distribution and retention properties of these analogues in other organs were not reported (Hanson et al, 1984). From the data reported, however, it would appear that a combination of optimal brain uptake and high brain:blood ratios are exhibited by the N'-alkyl-substituted anlaogue. The alicyclic analogue shows considerably less absolute brain uptake and the presence of more complex heterocyclic-carbonyl substituted N'-substituent does not seem to interfere with high cerebral extraction. Distribution data have only been reported, however, for 4 min after injection and these studies will undoubtedly be extended over a longer period of time to evaluate the important parameters of retention.

Thiocarbamic Acid Complexes of Cationic Radionuclides

There is also interest in important applications of complexes formed with cationic radionuclides since many metallic elements that have useful radionuclides can form complexes with organic agents that can determine the tissue distribution properties and thus target these agents for specific clinical applications. Complexes of both single photon and positron-emitting radionuclides can be prepared. Although the present discussion is focussed on single-photon radionuclides, it should be noted that efforts at several institutions are directed at developing lipid-soluble complexes with positron emitters such as gallium-68 (Green et al, 1985; Krohn et al, 1984) and cryptate-type complexes of rubidium-82 (Krohn et al, 1984). These agents hold promise to evaluate both regional cerebral blood flow and myocardial perfusion. The development of these types of agents using positron-emitting radionuclides obtained from generator systems ($^{82}Sr/^{82}Rb$, $^{68}Ge/^{68}Ga$, etc.) is very important since their availability would allow use with positron-emission tomographic devices at institutions that do not have a cyclotron.

Complexes with the single photon emitters would presumably have wider availability. An interesting and important observation has recently been reported involving the pronounced brain uptake of thallium-201 complexed with diethyldithiocarbamic acid (DDC). Thallium-201 is the only widely available agent for the routine evaluation of regional coronary perfusion and for the differentiation of ischemia from infarction by comparison of stress and redistribution at rest. The whole body distribution of thallium-201 in man is well established and although [^{201}Tl]-chloride shows high myocardial, lung, kidney and thyroid uptake, ^{201}Tl does not cross the intact blood-brain barrier under normal conditions. The [^{201}Tl]DDC complex (Figure 6) is easily formed by reaction of [^{201}Tl]chloride with sodium diethyldithiocarbamate and forms a highly lipid-soluble complex that is easily extracted by organic solvents and can be analyzed by routine chromatographic methods. The mondentate [^{201}Tl]DDC complex also is highly soluble in physiological saline and can be administered

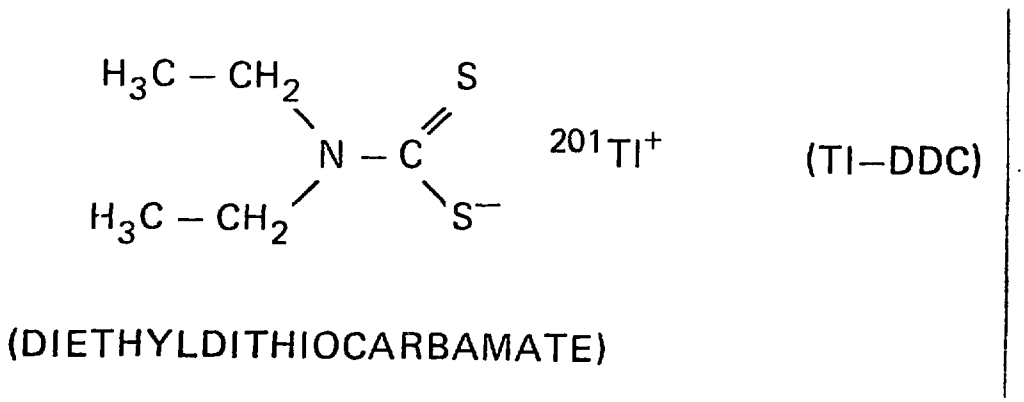


Figure 6

immediately following preparation. This agent readily crosses the intact blood-brain barrier in rats (Vyth et al, 1984) and rabbits (van Royen et al, 1984) and shows high cerebral uptake and rapid blood clearance resulting in high brain:blood ratios. Although the use of DDC as a detoxification agent for thallicosis had been reported a number of years ago (Sunderman, 1967), this

application has only recently been pursued. The possibility of cerebral concentration of [^{201}Tl]DDC was prompted by the reported increased neurological symptoms during NaDDC treatment of thallium intoxication (Rauws et al, 1969). Because of the ready availability of thallium-201 in nuclear medicine facilities, [^{201}Tl]DDC could represent a useful and widely available cerebral perfusion agent. A description of clinical studies with [^{201}Tl]DDC is included in another section of these proceedings (van Royen et al, 1984).

The formation of high lipid-soluble complexes between metallic cations and DDC and related anions has been well known for a number of years (Sandell and Onishi, 1979; Hulanicki, 1967). In fact, NaDDC extraction followed by further chemical separation and spectrophotometric analysis is a standard procedure for the analysis of trace elements in sea water (Sturgeon et al, 1980; Kremling and Peterson, 1974; Kinrade and Van Loon, 1974). The pH requirements, solubility and spectral properties of DDC complexes of many different metallic cations is well documented (Sandell and Hulanicki, 1967; Hulanicki, 1967). Since there are a variety of cationic metallic radionuclides that have attractive properties for diagnostic applications, it would appear at first glance that the use of DDC complexes of other radionuclides such as indium-111, gallium-67, copper-64 or copper-67, etc., would be possible. It appears, however, the thallium-201 is essentially a unique example of a highly aqueous soluble DDC complex since thallous ion is monovalent and thus forms a monodentate complex. We have prepared the tridentate [^{111}In]DDC_3 and [^{67}Ga]DDC_3, and bidentate [^{64}Cu]DDC_2 complexes, and as expected, they are very lipophilic and exhibit very low solubility in saline. Thus, unfortunately they cannot be used in the

same elegant manner as [^{201}Tl]DDC to measure brain blood flow. However, there are a large number of structurally-modified thiolate ligands similar to DDC which may show higher aqueous solubility (Sandell and Onishi, 1967) and these should be explored to determine their potential usefulness in forming aqueous soluble complexes with other useful radionuclides.

We have recently evaluated the tissue distribution of [^{64}Cu]DDC in rats. As described earlier, copper(II) readily forms a highly lipid soluble Cu-DDC complex. Copper-64 is a very attractive isotope for potential use in diagnostic nuclear medicine since it is one of the few neutron-deficient radioisotopes which can be inexpensively produced in a nuclear reactor via neutron irradiation of the enriched ^{63}Cu by the ^{63}Cu(n,γ)^{64}Cu reaction. It is normally processed to give $^{64}CuCl_2$ (Brown and Callahan, 1972). While the monodentate Tl-DDC forms a complex which is lipophilic yet highly soluble in physiological saline, the high K_D value for $Cu(DDC)_2$ results in very low aqueous solubility. The [^{64}Cu]DDC was therefore complexed with 6% delipidated BSA and administered to rats (Table 1). Although the plasma levels remained

Table 1. Brain and Blood Levels of Radioactivity after Intravenous Administration of $^{64}CuCl_2$ and [^{64}Cu]Copperdiethyldithiocarbamate ([^{64}Cu]DDC_2) to Female Fischer Rats

Agent, Time	Percent dose/gm	
	Brain	Blood
^{64}Cu-DDC		
5 min	0.40-0.60	1.93-2.21
60 min	0.28-0.31	0.86-0.94
$^{64}CuCl_2$		
5 min	0.10-0.11	1.62-2.26
60 min	0.05-0.05	0.73-0.82

high, probably as a result from high affinity to ceruloplasmin, the [^{64}Cu]DDC complex showed considerably higher (4 to 6 fold) brain uptake than control studies with [^{64}Cu]-Cl_2. We have also prepared similar [^{111}In]$(DDC)_3$ and [^{67}Ga]$(DDC)_3$ comlexes but these tridentate agents are difficult to formulate and show low brain uptake, presumably at least partly due to their very high lipid solubility. Nonetheless, the evaluation of structurally-modified dithiocarbamate complexes should be pursued since other neutral, yet more aqueous soluble agents, may show useful biodistribution properties and promise for radiopharmaceutical applications. As an example, the bis-ethanol dithiocarbamate complex of Cu(II) has been reported to show aqueous solubility (Geiger and Muller, 1943; Serfass and Levine, 1947).

Radioiodinated Iodophenyl-alkyl-Substituted Dihydronicotinamide Systems

A new approach for brain specific sustained release of therapeutic drugs has recently been described by Bodor et al (Bodor and Simpkins, 1983; Bodor and Farag, 1983a and b) which involves the chemical transformation (Figure 7) of the quaternary form of a drug [Q^+], which normally does not penetrate the blood-brain barrier, to a reduced lipid soluble form [HQ]. After intravenous administration the lipid soluble [HQ] is readily distributed throughout the body and easily crosses the intact blood-brain barrier (Figure 1). The NAD$\rightleftarrows$ NADH oxidation, however, regenerates the original impermeable form [Q^+] from [HQ] within the brain. This results in a unique "trapping" of the parent drug in the brain (intracellular pool). This approach has been successfully used for the cerebral delivery of dopamine to rats (Bodor and Farag, 1983a and 1983b). We have further extended these studies to evaluate the potential utility of this unique approach

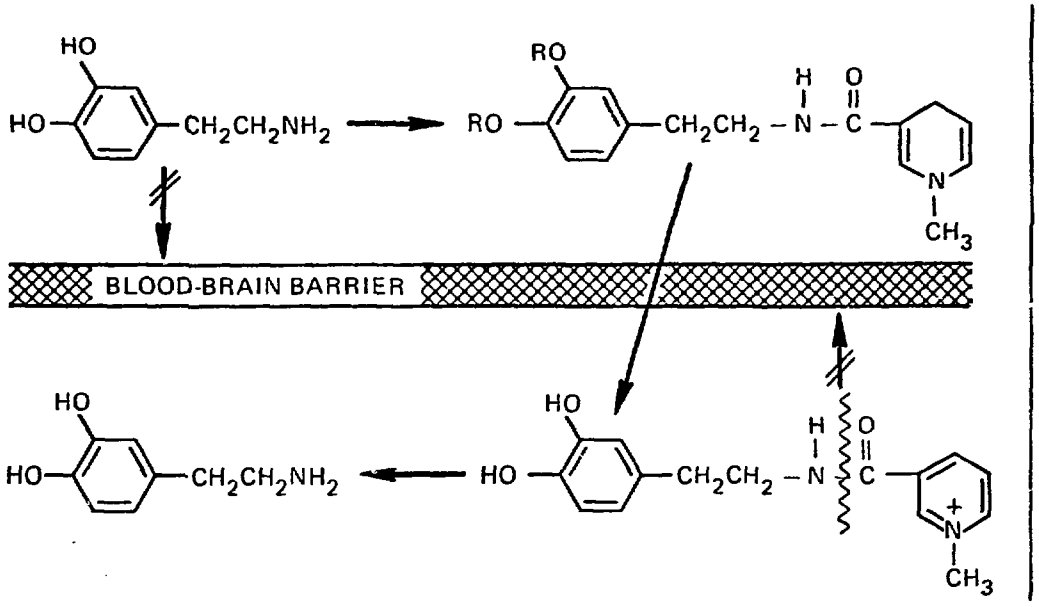
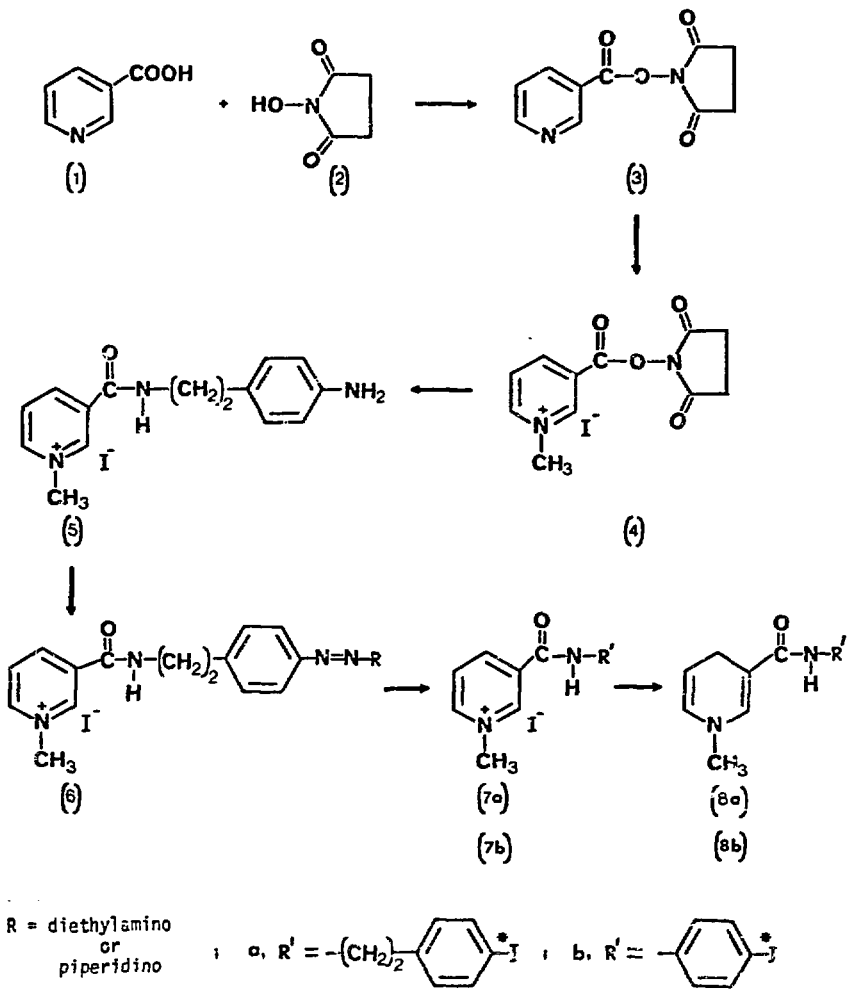


Figure 7

for the cerebral delivery of radiopharmaceuticals as a means to potentially measure regional cerebral perfusion as described below (Srivastava et al, 1984; Tedjamulia et al, 1985). It was anticipated that the hydrophilic [Q^+] would be "trapped" in the brain and rapidly cleared from the blood and other body tissues. This would result in high brain uptake and acceptable brain:blood ratios required for optimal brain imaging. As a part of our interest in the development of new brain imaging agents, the goals of the present study were to develop a chemical approach to prepare model [^{125}I]-labeled phenylalkylamines linked to a dihydropyridine carrier and to evaluate the biodistribution properties of these agents in rats.

A radioiodinated moiety such as p-iodophenethylamine coupled with dihydropyridine in the lipid soluble form (9, Scheme I) should be transported across the blood-brain barrier and oxidized to the quaternary form (8) within the brain and thus remain "trapped." At this stage the CO-NH bond could also be potentially cleaved by the NAD$\rightleftarrows$NADH system to regenerate the radioiodinated

phenylethylamine. For preliminary tissue distribution studies in rats the model radioiodinated compound, 1-methyl-3-[N-[β-(4-iodophenyl)ethyl]carbamoyl]-1,4-dihydropyridine (9), was prepared as shown in Scheme I. Condensation of nicotinic acid (1) with N-hydroxysuccinimide (2) in dimethylformamide (DMF) in the presence of dicyclohexylcarbodimide (DCC) gave the activated ester, N-succinimidyl pyridine-3-carboxylate (3) as a useful intermediates for the formation of "CONH" bond when coupled with amines (Srivastava et al, 1974). Quaternization of (3) with methyl iodide and coupling with p-aminophenyl-ethylamine gave 1-methyl-3-[N-[β-(p-aminophenyl)ethyl]carbamoyl] pyridinium iodide (5). Diazo coupling of (5) with piperidine or diethylamine at 0°C using hydrofluoric acid (HF, 48%) and sodium nitrite gave the alicyclic or diethyl triazene substrates (6) without an intramolecular cyclization with the carboxamide group (Ivanovics et al, 1974). Triazene decomposition with sodium iodide (Na[^{125}I]) and anhydrous HF in acetone at 0°C readily furnished 1-methyl-3[N-[β-(4-[^{125}I]iodophenyl)ethyl]carbamoyl]pyridinium iodide [^{125}I](7a), the [Q+] form of the product. Sodium dithionite reduction of [^{125}I](7a) then provided the desired compound [^{125}I](8a). In order to evaluate the relative in vivo susceptibility to oxidation and subsequent brain uptake of model dihydropyridine carriers, an 4-[^{125}I]iodoaniline coupled model agent, 1-methyl-3-N-(4-[^{125}I]iodophenyl)carbamoyl-1,4-dihydropyridine [^{125}I](8b), was also prepared as shown in Scheme I. Nucleophilic attack by the amino group of p-iodoaniline on the activated ester (4) gave 1-methyl-N-3-(p-iodophenyl)-carbamoylpyridinium iodide (7b). Because of synthetic considerations, in this



Scheme I

case, the p-radioiodide was fabricated prior to coupling the amine with the activated ester (4). Iodine-125-labeled p-iodoaniline was prepared by $[^{125}I]I_2$ treatment of commercially available 4-aminophenylmercuric acetate following a general method developed in our laboratory for the synthesis of radioiodinated compounds from the corresponding mercuric acetate precursors (Srivastava et al, 1985).

The tissue distribution of radioiodinated compounds $[^{125}I]$8a and $[^{125}I]$8b was evaluated in rats. The quaternary compound (7a) showed very low brain uptake whereas the lipophilic, dihydro compound (8a) exhibited significantly

higher brain uptake, as expected from the studies reported by Bodor et al (Bodor and Simpkins, 1983; Bodor and Farag, 1983a; 1983b). Our studies with model radioiodinated agents further confirm that structurally-modified, reduced compounds (e.g. 8) more easily cross the blood-brain barrier as compared to the parent, quaternary drugs e.g. (7).

Oxidation of the oxygen sensitive dihydro products (8a) and (8b) was inhibited, prior to injection, by addition of vitamin E as a stabilizer. Vitamin E was also added to [^{125}I](7) prior to administration as a control and to evaluate any effect of vitamin E on the tissue distribution of [^{125}I](8). As expected, the quaternary compound (7) showed low brain uptake and high activity in the blood pool (Figure 8), whereas the lypophilic, dihydro compound (8) showed significant brain uptake (Figure 9) and exhibited good brain:blood ratios. Iodine-125-labeled 4-iodoaniline, itself, has been reported to exhibit brain uptake (0.47%/gm, 5 min) and rapid clearance (0.03%/gm, 60 min) in rats. In our studies, 4-[^{125}I]iodoaniline showed similar distribution properties (uptake and clearance) in rats. Superior distribution properties of [^{125}I]9b as compared to 4-[^{125}I]iodoaniline clearly demonstrate that coupling of such radioiodinated amines with dihydropyridine carrier may be an effective way to achieve high uptake and retention in the brain.

These preliminary studies have demonstrated that dihydropyridine-linked lipophilic agents [^{125}I](8a) and [^{125}I](8b) cross the blood brain barrier and are quaternized within the brain preventing their release. The quaternary forms [^{125}I](7a) and [^{125}I](7b), however, cannot cross the blood-brain barrier and thus show low brain uptake. We have also shown that the facile oxidation of

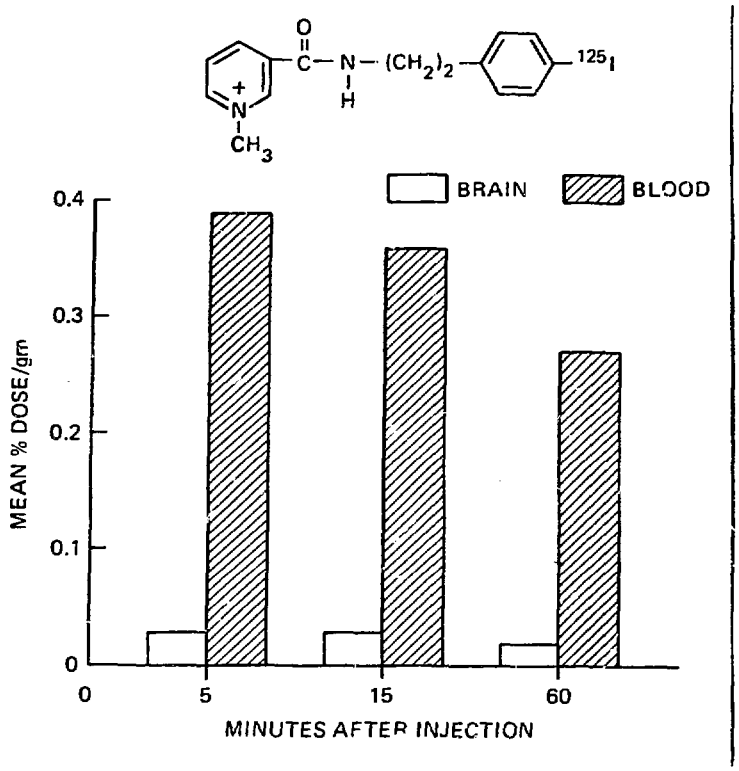


Figure 8. Comparison of the relative brain and blood levels (mean % dose/gm) after administration of [^{125}I](7a) to Sprague-Dawley rats.

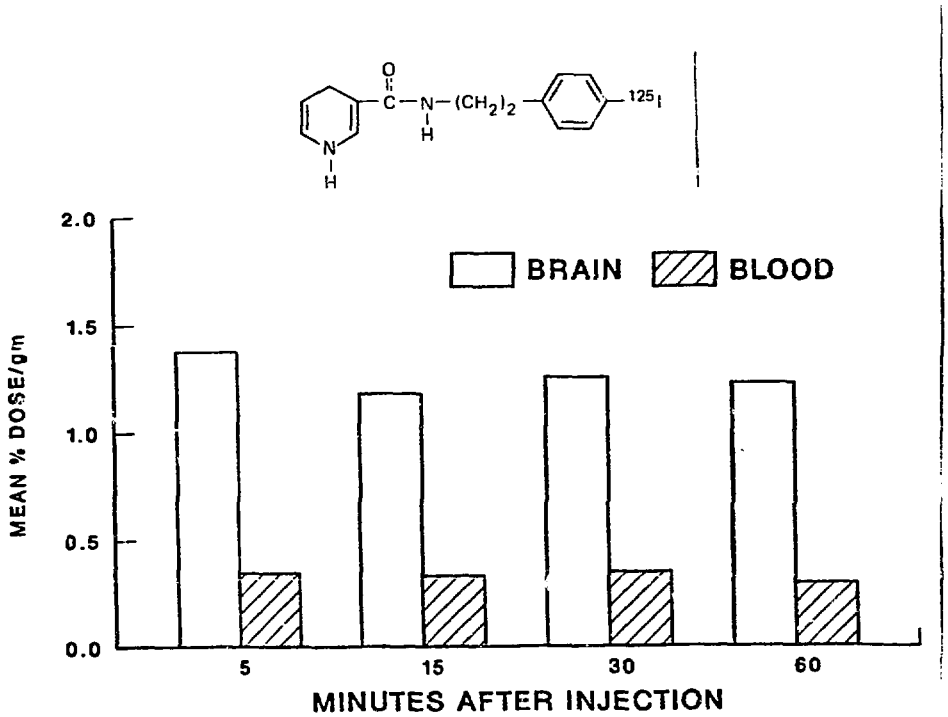


Figure 9. Comparison of the relative brain and blood levels (mean % dose/gm) after administration of [^{125}I](8a) to Sprague-Dawley rats.

dihydropyridine compounds to the corresponding quaternary compounds on storage or prior to *in vivo* administration can be inhibited by adding vitamine E as a stabilizer. These studies have shown that brain-specific delivery of radiopharmaceuticals using the Boder approach is possible. In addition, these data also suggest that a more detailed evaluation of the brain specific sustained release of radiopharmaceuticals for potential application in evaluation of regional cerebral blood perfusion should be pursued.

SUMMARY

A variety of new strategies for the development of cerebral perfusion agents radiolabeled with single-photon emitters are being pursued. There is still considerable interest in the use of iodine-123 and the commercial availability of this radionuclide is increasing. In addition to the iodine-123-labeled agents, the recent success with the interesting [^{201}Tl]DDC complex may well be a prelude to the development and evaluation of other useful neutral and tissue-specific complexes of cationic radionuclides. It is important for radiopharmaceutical scientists and clinical investigators to continue to closely interact and work together to effectively communicate the specific requirements of agents for applications for the measurement of regional cerebral perfusion.

ACKNOWLEDGEMENTS

This research was sponsored by the Office of Health and Environmental Research, U.S. Department of Energy under contract DE-AC05-840R21400 with Martin Marietta Energy Systems, Inc. The authors thank H. Biersack, M.D., his colleagues and the Rheinisch-Westfalische Gesellschaft fur Nuclearmedizin for the opportunity to particpate in this symposium held in Bonn on October 12-13, 1984. The authors thank L. S. Ailey for typing the manuscript.

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