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DESIGN AND EVALUATION OF RADIOTRACERS FOR DETERMINATION OF REGIONAL CEREBRAL BLOOD FLOW WITH PET

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ABSTRACT

The tracer kinetics of 4-Fluoro(^{18}F)-, 4-Bromo(^{82}Br)- and 4-Iodo(^{125}I)-antipyrine and ^{15}O-water were compared in a cat or baboon animal model. First-pass cerebral extraction and clearance with alterations in $PaCO_2$ were measured for whole brain. The Renkin/Crone model was used to evaluate brain capillary permeability-surface area product for 4-^{18}FAP in cats. Positron-emission-tomographic measurements required development of an instrument and technique for control of the arterial concentration of the radiotracer as a ramp function, so that tracer concentration changes due to radioactive decay or altered physiological processes could be accurately described with PET. Pharmacokinetic and tissue-distribution studies in cats were used to determine dosimetry for 4-^{18}FAP. 4-Bromoantipyrine labeled with ^{78}Br (t =6.5 m) is suggested as a tracer for determination of rCBF with PET.

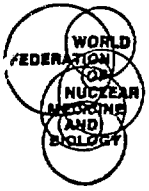
KEYWORDS

Tracer kinetics; cerebral blood flow; position emission tomography; radiotracer design.

INTRODUCTION

Recent research in neuroscience and nuclear medicine with radionuclides of short halflife and position emission tomography (PET) has focused on the measurement of local cerebral glucose uptake and metabolism (Reivich, Kuhl, Wolf and co-workers, 1979; Sokoloff and colleagues, 1977), and of the regional cerebral metabolic rate of oxygen (Depresseux, Raichle and co-workers, 1981; Lenzi and others, 1981). Cerebral blood flow can be evaluated by conventional techniques with ^{133}Xe, and the new PET technology using ^{77}Kr, $^{13}NH_3$, $^{15}OH_2$ and other tracers. None of the freely diffusible radiotracers are completely satisfactory for all CBF determinations. 4-Iodoantipyrine-^{14}C (IAP) is the standard for evaluation of rCBF by the autoradiographic diffusible tracer technique (Sakurada and co-workers, 1978). Unfortunately, the rapid in vivo deiodination of IAP limits the integrity of a IAP tracer to the first 30-90 s after injection. Antipyrine does not have an adequate partition coefficient through the blood brain barrier. Other missing links include: an adequate model to couple CBF and local cerebral metabolic processes; and documentation that PET can be used to quantitatively determine rCBF in normal and physiopathological states.

NUCLEAR MEDICINE AND BIOLOGY



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RESULTS AND DISCUSSION

^{18}F-4-Fluoroantipyrine (4-^{18}FAP) and ^{82}Br-4-bromoantipyrine (4-^{82}BrAP) were synthesized. ^{125}I-4-iodoantipyrine (4-^{125}IAP) was purchased from NEN. The BNL 60" cyclotron was used to prepare > 100 mCi batches of $^{15}OH_2$ by the $^{14}N(d,n)^{15}O$ nuclear reaction (Vera Ruiz, Wolf, 1978). The irradiated target gas (10 atm N_2 + 4.5% H_2) containing the $^{15}OH_2$ was purged by pressure drop from the Al target into a multi-injection vial containing 5 ml of water for injection. The $^{15}OH_2$ was transported $\sim$ 1 km from the cyclotron and injected into the animal positioned in the PETT III within 3 m after the end of the bombardment. The baboon experiments required > 50 mCi of $^{15}OH_2$.

Animal experiments were performed on 15 cats induced with ketamine and maintained with 0.75% enflurane and pancuronium. They underwent tracheotomy or intubation, arterial, and venous cutdowns. Following these procedures, the cats were placed in a sterotaxic apparatus with the head rigidly fixed center of the focal plane of a limited angle planar positron camera (LAPC). The cats were mechanically ventilated. An infant car seat, modified by construction of a low density head holder, was used to restrain a baboon in the PETT III. The baboon was administered ketamine, and then anesthesized with halothane/oxygen.

Arterial blood preasure, temperature and arterial blood gases were monitored. Alterations of the $PaCO_2$ were carried out by hyperventilation and the addition of inspired CO_2. The 4-^{18}FAP was injected as an intravenous bolus. Distribution of 4-^{18}FAP was determined in 2-4 cats sacrificed at 30, 60, and 120 m intervals following injection of the tracer by organ dissection and assay of the tissue. These data have the characteristics of a freely diffusible tracer. The distribution data was used to calculate the absorbed radiation dose which was 36 mRad/mCi whole body and 504 mRad/mCi to the critical organ which was the kidney. Thin layer chromatography (tlc) of blood collected at 24 m following a 14 m ramp injection of 4-^{18}FAP demonstrated the integrity of the tracer. One metabolite ($\sim$8%) was noted in the tlc of urine; whereas 2 metabolites of 12-17% each were found in the bile. The partition coefficients for ^{131}I-4-iodoantipyrine and ^{18}F-4-fluoroantipyrine were determined in n-octanol/pH=7.0 phosphate buffer were 11.4 and 5.2, respectively. The brain to blood partition coefficients for 4-^{18}FAP and 4-^{82}BrAP in cats were determined simultaneously in 3 cats.

^{18}F-4-Fluoroantipyrine (4-^{18}FAP) was prepared by fluorination of antipyrine 1 with ^{18}F-F_2 purged through 15 mg of 1 in 5 ml of acetic acid at room temperature (Shiue and Wolf, 1980). The $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction on Ne containing carrier F_2 was used to produce ^{18}F-F_2 (Lambrecht and Wolf, 1973; Casella and others, 1980). Fluorination of 2 gave ^{18}F-4,4-difluoro-3-hydroxy-2,3-dimethyl-1-phenylpyrazolidin-5-one (2), 4-fluoroantipyrine (3), and 4,4-difluoro-3-methyl-1-phenyl2-pyrazolin-5-one (4). The product distribution depended on the ratio of 1 and F_2. The product was purified by retention of reactant impurities on a silica gel column (1 x 12 cm) by elution of 4-^{18}FAP with ethyl acetate. The eluent was cut 1/1 with Pet ether and the 4-^{18}FAP collected in the eluent from a second silica gel column. Currently, production results in radiochemical yields of 18% (based on recovered ^{18}F) in a synthesis time of 90 m in > 98% radiochemical purity at a specific activity of 1 mCi/mg/20 mCi ^{18}F-F_2. PETT III experiments required 2.5 mCi of 4-^{18}FAP. 4-^{82}BrAP was prepared by an exchange reaction (Shiue, 1981).

Cerebral extraction and clearance was measured by a single pass extraction fraction technique (Duncan and collaborators, 1981) for whole brain at different levels was estimated with the Renkin/Crone model. The relationship $\ln(1-E)=-PS/F_w$, where F_w represent CBF converted to the flow rate of water was used to determine a value of PS = (110 ± 14) in cats (Fig. 1). Perhaps fortuitously the PS of 4-^{18}FAP was comparable to that of ^{15}O-H_2O obtained in the rhesus monkey using a slightly

different experimental method (Raichle and collaborators, 1976). The first pass cerebral extraction technique indicated that 4-^{18}FAP was more effectively (10-15%) extracted at high flow than $^{15}OH_2$ in sequential determinations the same cat serving as its own control.

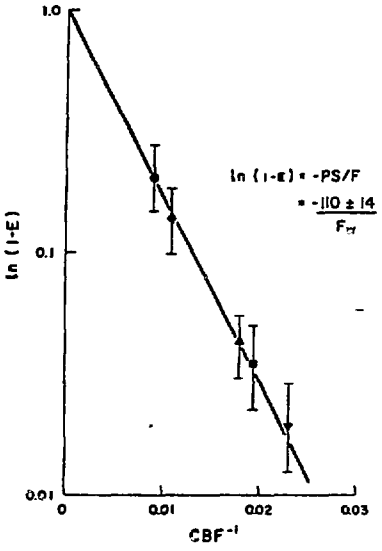

Figure 1

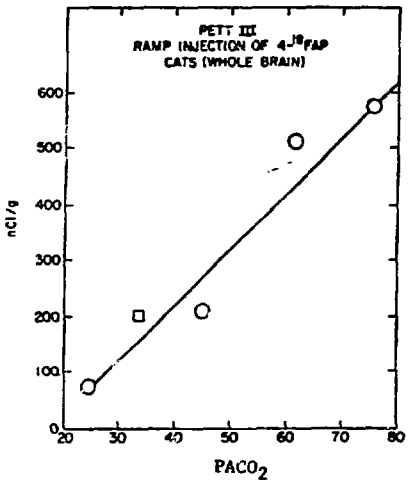

Figure 2

The ramp injection technique and PETT III was used to evaluate whole brain radioactivity of 4-^{18}FAP under altered and controlled physiological conditions ($PACO_2$) throughout a 1 h experiment (Fig. 2).

The dual-label radiotracer technique with 4-^{125}IAP and 4-^{18}FAP, or 4-^{18}FAP and 4-^{82}BrAP was used to obtain relative distributions of the radiotracers in the cat brain at 60 s. Comparative detailed dissection data are depicted in Table I. 4-^{82}BrAP displayed a rapid clearance from blood with < 4% ^{82}Br remaining in the blood 10 m following an intravenous bolus injection. Only one radioactive fraction was found in the tlc of the blood. The 60 s relative distributions of 4-BrAP and 4-IAP are comparable within the gross structure of the cat brain (Table I).

Either 4-^{75}BrAP, 4-^{78}BrAP or 4-^{18}FAP hold promise as tracers for rCBF in combination with PET. The advantages of ^{18}F and ^{75}Br are that the halflife permits synthesis and distribution to centers not having a cyclotron. The disadvantage of 4-^{18}FAP is the time required for synthesis. We propose that ^{78}Br ($t_{\frac{1}{2}}$=6.5 m, β^+) is the radiolabel of choice for rCBF investigations at institutions having both PET and cyclotron facilities. Efforts are underway to develop the ^{78}Se(p,n)^{78}Br cyclotron production and radiochemistry. Studies are in progress to evaluate rCBF with PETT VI using 4-^{18}FAP, and 4-^{75}BrAP in combination with multi-labeled microspheres and/or 4-FAP-^{14}C in normal and pathological states using the baboon. The tracers having the characteristic of a freely diffusible tracer should permit our direct comparison of the microsphere (or autoradiographic) technique with PET.

TABLE I. Relative distribution of 4-^{125}IAP, 4-^{82}BrAP and 4-^{18}FAP in structures of the cat brain at 60 seconds post intravenous injection of either tracer with 4-^{125}IAP in cats. Data reported relative to cerebellum = 1.00 as calculated on percent per gram basis.

	4-^{125}IAP	4-^{82}BrAP	4-^{18}FAP
Cerebellum	1.00	1.00	1.00
Cerebellum hemisphere	1.23	1.22	-
Corpus collosium	0.59	0.66	0.34
Cortex	3.05	3.30	0.86
Thalmus	1.14	1.16	0.36

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