Quantifying Local Cerebral Blood Flow by N-Isopropyl-p-[^{123}I]Iodoamphetamine (IMP) Tomography

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A model was validated wherein local cerebral blood flow (LCBF) in humans was quantified by single-photon emission computed tomography (SPECT) with intravenously injected N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) combined with a modification of the classic method of arterial input sampling. After intravenous injection of IMP in rat, autoradiograms of the brain showed activity distributions in the pattern of LCBF. IMP was nearly completely removed on first pass through monkey brain after intracarotid injection (CBF = 33 ml/100 g/min) and washed out with a half-time of approximately 1 hr. When the modified method of arterial input and tissue-sample counting applied to dog brain, there was good correspondence between LCBF based on IMP and on that by microsphere injection over a wide flow range. In applying the method to human subjects using SPECT, whole-brain CBF measured 47.2 ± 5.4 ml/100 g/min (mean ± s.d., N = 5), stable gray-white distinction persisted for over 1 hr, and the half-time for brain washout was approximately 1 hr. Perfusion deficits in patients were clearly demonstrated and quantified, comparing well with results now available from positron ECT.

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Single-photon emission computed tomography (SPECT) (*1,2,23*) has been applied to physiological measurements of local cerebral glucose utilization using [^{18}F]fluorodeoxyglucose (*3–5*), local cerebral blood volume using Tc-99m red cells (*6,7*), and local cerebral blood flow (LCBF) using inhalation (*8*) or intracarotid injection (*9*) of inert gases. The relatively inert indicator [^{123}I]iodoantipyrine (*10*) was also used with SPECT to demonstrate cerebral infarcts (*11*), but quantification failed because of rapid redistribution. Because of the desirable biologic and chemical behavior of positron-emitting isotopes of carbon, oxygen, nitrogen, and fluorine, there is emphasis now on positron-emission computed tomography (PECT) in brain research (*12*), but the present expense of this cyclotron-based approach encourages further exploitation of the SPECT method, which is potentially capable of more widespread use.

Winchell et al. (*13,14*) proposed that the initial distribution of N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) might be useful for imaging relative regional brain perfusion in humans because first-pass extraction efficiency in rat brain was high, washout was slow, brain-blood ratios were high, and the physical properties of I-123 ($T_{1/2}$ = 13 hr, 159-keV photon) were favorable for scanning. Localization in the brain was considered to be primarily in high-capacity, relatively nonspecific, binding sites for amines. Kuhl et al. (*15,16*) then demonstrated LCBF mapping in humans by SPECT of IMP.

We report here the validation of a method for quantitative mapping of LCBF in human brain by SPECT, using intravenously injected IMP combined with a modification of the well-known method of arterial input sampling. These results suggest that SPECT of IMP, or of other similar compounds, has promise for diagnostic study of cerebrovascular disorders as an alternative to PECT in clinical research.

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METHODS

Carrier-free Na^{123}I was purified before use to remove the excess sodium bicarbonate base. Thin-layer chro-

matography was done on precoated silica-gel strips (EM SG60 F-254). Five milligrams of IMP (RS-isomer) and 200–300 mCi of NaI(I-123) were mixed and sealed in a pyrex tube (0.8 × 12 cm), which was then heated at 150 °C for 30 min. After cooling, the reaction mixture was extracted with 2 ml ethyl ether and washed with 1 ml of 0.15 *N* NaOH containing 0.1 *N* $NaHSO_3$ and 0.1 *N* KI to remove unreacted radioiodide. The product was further purified by extracting with 2 × 2 ml of 0.3 *N* HCl, then made basic with 0.3 *N* NaOH and extracted with 2 ml ethyl ether. After washing with 2 × 2 ml sterile water, the ether extract was purged to dryness with nitrogen. The IMP (I-123) was then taken up in 0.3 *N* HCl and the pH adjusted to 4–7 with 0.3 *N* NaOH and normal saline to obtain an isotonic solution. This was finally sterilized by passage through a 0.22-μm Millipore filter.

The radiochemical yield was 70–80% and radiochemical purity was greater than 98%, as determined by thin-layer chromatography on silica gel using two different solvent systems: (a) MeOH/$CHCl_3$/glacial AcOH, 15/85/1 (R_f = 0.40, R_f for free iodide = 0.0); and (b) EtOAc/EtOH, 1/1 (R_f = 0.1, R_f for free iodide = 0.8). In occasional samples, levels of free iodide were as high as 4%. Rigorous quality control—such as radiochemical purity, specific activity, sterility, and pyrogenicity tests—were performed on all batches. Less than 4% of injected activity was I-124. For dog experiments, IMP was labeled with I-125 rather than I-123.

For autoradiography, awake male Sprague-Dawley rats were given a 45-sec continuous infusion of IMP (5 mCi/kg body weight, 8.4 mCi/mg IMP) and killed at 45 sec, 5 min, 12 min, and 1 hr. The brains of the rats were rapidly removed, frozen in dry ice, and cut into 20-micron sections. These were placed on film* for 13 hr, producing images due primarily to the 127-keV internal conversion electrons from I-123 (*17*).

Brain extraction and washout were measured in two adult rhesus monkeys anesthetized with intramuscular ketamine hydrochloride and intravenous sodium pentobarbital. Earlier, the right external carotid arteries had been ligated at their origins. One monkey was ventilated with room air, the other with a 10% carbon dioxide/oxygen mixture to increase CBF, and mean CBF was measured by ^{15}O-water method (*18*). To determine the single-pass extraction of IMP (*19,20*) and subsequent washout of brain activity, a bolus injection (0.3 ml) of IMP was made into the right common carotid artery, and the time course of activity through the brain was measured by a collimated scintillation detector placed against the head.

For body distribution measurements in man, five normal adult males were given intravenous injections of 1–5 mCi of IMP (~8.4 mCi/mg IMP) and, during the subsequent 48 hr, urine and blood samples were taken and images were made of the head, chest, and abdomen with a scintillation camera (medium energy collimator).

To determine the partitioning of IMP between red cells and plasma in vitro, IMP was incubated with human whole blood (hematocrit 0.44) for 5 min at 37 °C. Red-cell and plasma fractions were then separated and counted in a well counter. To determine the exchangeability of IMP between red cells and plasma, the radioactive red-cell fraction was reconstituted with normal plasma to the original hematocrit. After 5 min at 37 °C, the red-cell and plasma fractions were again separated and counted in a well counter. To determine possible metabolism of IMP within the red cell, IMP was incubated with whole blood as above, the red-cell fraction was separated, and its activity was then extracted with ether after alkalinization and analyzed using reversed-phase high-pressure liquid chromatography†; column, ultrasphere ODS (5μ, 4.6 × 250 mm); precolumn, ultrasphere ODS (5 μ, 4.6 × 20 mm); mobile phase, linear gradient from 100% of the mixture 55% 100 m*M* potassium phosphate buffer/45% MeOH to 100% MeOH; flow rate, 1.0 ml/min.

To determine the fraction N of arterial whole-blood activity that was unmetabolized IMP in dog and human subjects, whole-blood samples were taken at different times after intravenous injection of IMP, extracted four times with either ether or octanol, and the solvent and blood phases were then counted in a well counter and compared. Activity extracted in the solvent phase was then analyzed by high-pressure liquid chromatography as above.

Values of LCBF based on IMP and microsphere deposition were determined by a modification [Eq. (2), below] of the arterial input sampling method (*21,22*) in four mongrel dogs in whom excursions of LCBF were induced by inflatable intracranial balloons. Each dog was anesthetized with intravenous sodium pentobarbital and ventilated with room air. One drop of Tween-80 was mixed into 10% dextran by vortex mixer, and in this medium carbonized polystyrene microspheres, measuring 15 ± 5 μ and labeled with either Nb-95 or Sr-85, were suspended by ultrasonification between injection. During the initial control state, niobium-95 microspheres were injected as a bolus through a cannula placed in the left atrium of the heart, while arterial blood was withdrawn for 5 min, at a constant 4.3 ml/min, through a femoral catheter by a Harvard pump. The brain was then compressed for 5 min by inflating a small balloon that had been inserted into the subdural space. Then IMP(I-125) (50 μCi, 1 mg IMP) was injected into a peripheral vein simultaneously with the injection of strontium-85 microspheres into the left atrium of the heart, and a second arterial blood sample from the femoral artery was withdrawn at constant rate for a period of 5 min. Following this, the dog was killed. A similar procedure was applied to a fifth dog, except that

instead of cerebral compression, penicillin solution was injected into the cerebral cortex, and final IMP and microsphere injections were made 30 min later when persistent focal EEG spike activity had indicated active seizures (*29*). In all dogs, the excised brain was divided into approximately 25 samples, each containing approximately equal amounts of gray and white matter, and activities of the three radionuclides in whole blood and brain tissue were measured in a well scintillation counter. Values of LCBF for the control state (microspheres) and for the altered state (microspheres and IMP) were calculated for each brain sample using Eq. (2) (see below).

SPECT of human subjects was performed using the Mark IV scanner (*11*) a four-sided arrangement of 32 independent collimated NaI(Tl) scintillation detectors that rotated continuously about the brain at 50 sec/rev. The system count rate was 15,400 cps/μCi/ml in scans of a reference cylinder (18 cm diam) filled with Tc-99m solution. The full width at half maximum (FWHM) spatial resolution was approximately 1.7 cm within the image plane and 1.7 cm in the axial direction. Before scanning the brain, scans were made of a reference cylinder filled with I-123 solution, which provided calibration and correction values to compensate for attenuation and differences in detector sensitivity. These values were used to convert the final cross-sectional data into accurate maps of activity concentration (details in Ref. 11). Before the study, each subject was given three drops of potassium iodide solution by mouth in order to block thyroid uptake of any free I-123 or I-124 ion. The head of the subject was positioned in the Mark IV scanner. Five millicuries of IMP (~0.6 mg) were injected into an arm vein; at the same time the scanner was started and a 5-min period of blood withdrawal was begun, by a Harvard pump at 0.9 ml/min, from a small catheter placed in the radial artery. Scanning progressed continuously for one hour. In some subjects the brain was scanned repeatedly at one level, while in others a series of different levels were scanned. For measurement of LCBF at 5 min, a brain image was reconstructed from data collected in the first ten scanner revolutions (i.e., to 8.3 min) and was corrected to represent the 5-min activity values (multiplied by the ratio of counts in the sixth revolution to mean counts in the first ten revolutions). Zonal averages of brain activity, C_b, were determined and LCBF was calculated by Eq. (2) (below). For mean CBF, activity was averaged over the entire brain image.

For quantification of LCBF, the following relationships will hold under the assumptions that LCBF does not change and that the tracer is delivered continuously to the brain, is freely diffusible, is completely removed on single pass through brain, back-diffuses slowly from brain to blood, and can be distinguished in arterial blood from its polar metabolites that do not enter brain tissue:

$$\dot{C}_b = FC_a - kC_b$$

$$F = \frac{C_b(T)}{C_a * e^{-kt}} = \frac{C_b(T),}{e^{-kT}\int_0^T C_a(t)e^{kt}\,dt}, \qquad (1)$$

where F is the cerebral blood flow in ml/100 g/min, C_a is the arterial whole-blood concentration of true tracer (μCi/ml), C_b is the brain activity concentration (μCi/100 g), $\dot{C}_b$ is the rate of change of C_b, k is the rate constant (per min) for back diffusion, t is time, T is time of measurement, and * denotes the operation of convolution. Brain tissue is considered to include its contained blood, which constitutes only a few per cent of its total volume (*30*).

Using data from two human subjects, we obtained values of F and k in Eq. (1) by nonlinear regression analysis. C_b was determined by scan and C_a by octanol extraction of arterial whole-blood activity measured throughout a one-hour period. The half-time for back diffusion ($T_{1/2} = 0.693/k$) was then calculated.

If measurements are made sufficiently early (e.g., at 5 min) so that back diffusion is small, the model becomes the familiar method, based on organ deposition and arterial input sampling, for the measurement of regional blood flow with labeled microspheres (*21,22*), but adjusted to correct for metabolite activity in arterial blood:

$$F = RC_b/(NA), \qquad (2)$$

where R is the constant withdrawal rate of arterial blood in ml/min, A is the total activity (5 min) in the withdrawn arterial whole blood in μCi, and N is the fraction of A that is true tracer activity.

When Eq. (2) was used for dog's brain, C_b was determined by tissue counting in a well counter; in human subjects C_b was determined by scan. With IMP, the value of N was measured using octanol extraction of the arterial blood reference sample; with labeled microspheres, N = 1.

RESULTS

Body distribution and kinetics. After intravenous injection of IMP, autoradiography of the rat brain (Fig. 1) demonstrated persistent distribution of local brain activity in a pattern closely resembling the distribution of LCBF found with C-14 iodoantipyrine autoradiography (*17*). Unlike such autoradiography, however, choroid plexus activity was prominently increased, especially in the earliest sections. There was good contrast between gray and white matter at 5 min, but this deteriorated by 1 hr.

After intracarotid injection of IMP, the activity time course in monkey brain was measured (Fig. 2) and analyzed (*19,20*). At CBF = 33 ml/100 g/min and arterial blood pH = 7.35, the extraction fraction was 92% and

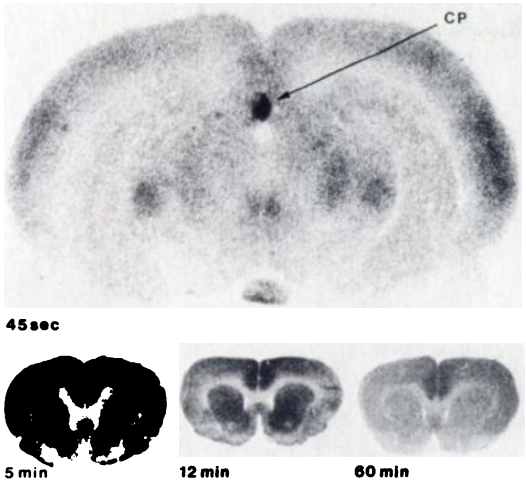

FIG. 1. Brain autoradiograms of rats, killed at four different times after bolus i.v. injection of IMP in the conscious animal, show persistent activity patterns resembling distribution of local cerebral blood flow. Note high uptake corresponding to high flow rate in choroid plexus (CP) in roof of third ventricle, a feature not seen in C-14 iodoantipyrine autoradiography.

washout was biexponential: half-times were 1.8 min for 8% of the trapped activity and 63 min for the remainder. At CBF = 66 ml/100 g/min and arterial blood pH = 7.10, extraction fraction fell to 74%, with washout half-time 4.2 min for 16% of the trapped activity and 44 min for the remainder.

Figure 3 illustrates the distribution of activity in brain, lung, and liver of human subjects during the first 48 hr after intravenous injection of IMP. There was rapid uptake in brain and lungs and a slower uptake in liver. No concentration was ever seen in the eyes. With potassium iodide premedication, the thyroid gland was not visualized; without premedication it was faintly seen. Brain activity persisted at about the 1-hr level. In lung, there was an early washout of ~16% of activity with a half-time of 13 min; the remainder had a very slow multiexponential washout. Liver activity peaked at 3 hr, then washed out more slowly over several days.

At 3 hr after injection, the administered dose was distributed among the brain (5%), lung (33%), liver (33%), and remainder of the body (29%). Urinary excretion of tracer averaged 23% during the first 24 hr and 17% during the second. Assuming the average subsequent half-time for washout from all sites to be 66 hr, the total radiation exposure delivered to a 70-kg human following an intravenous dose of 5 mCi of IMP containing 4% I-124 was calculated to be: brain 0.7 rad, lung 4.9 rad, liver 4.1 rad, and whole body 0.45 rad. Approximately half of the radiation exposure was due to the undesirable contaminant I-124.

In vitro studies using human whole blood (hematocrit 0.44) showed that IMP was freely exchangeable between red cells and plasma. When incubated at 37 °C, IMP quickly penetrated into red cells, establishing approxi-

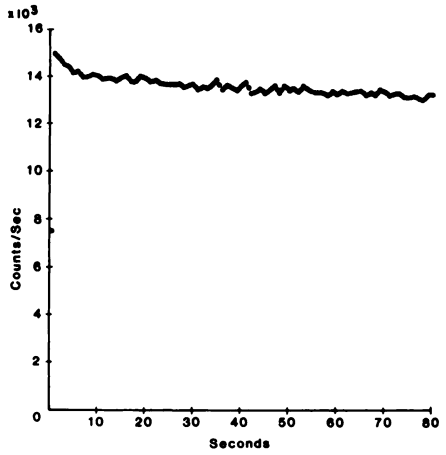

FIG. 2. Time course of brain activity in monkey after bolus injection of IMP into carotid artery, when CBF = 33 ml/100 g/min and arterial blood pH = 7.35. Single-pass extraction was 92%. Half-time for washout was 1.8 min for 8% of trapped activity and 63 min for remainder.

mately a 1.8/1 differential concentration with plasma. When the radioactive red cells were reconstituted with normal plasma, IMP moved quickly into plasma, reestablishing the original differential distribution. No apparent metabolism of IMP occurred within the red cells. Under our experimental conditions, analysis of

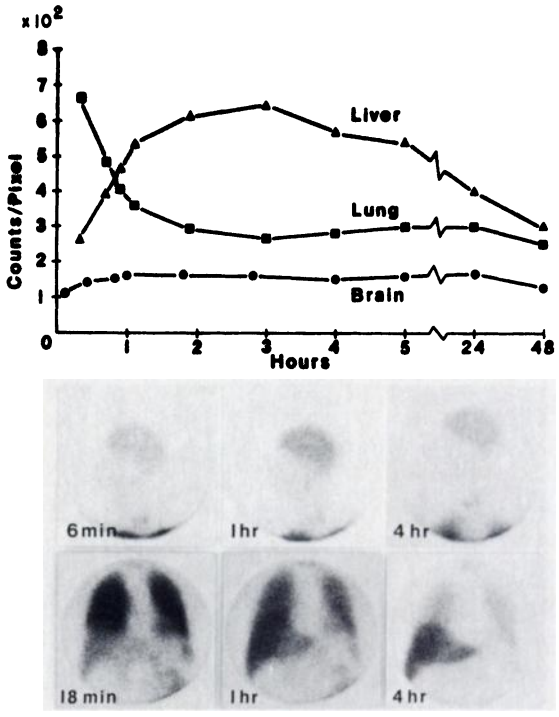

FIG. 3. Organ distribution of activity in human after intravenous injection of IMP. Uptake is immediate in brain and lungs, but progressive to three hours in liver. There is rapid washout of much of lung activity, but brain activity remains constant during first 24 hr. All data are corrected for physical decay. Scintiphotos of head and trunk are shown for different times. Note faint image of thyroid iodide uptake (no KI was given to this subject) and no evidence of eye uptake.

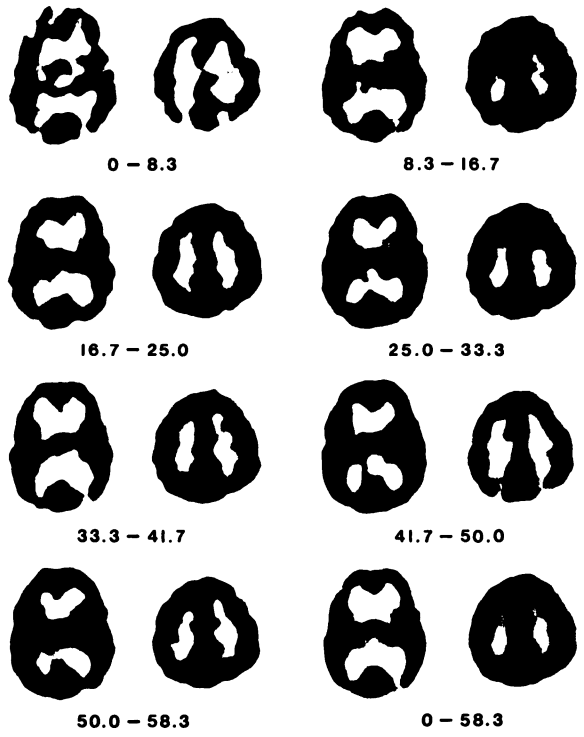

FIG. 4. Continuous sequences of Mark IV scans made at fixed levels, parallel to cantho-meatal plane, during first hour after intravenous injection of IMP in two normal human subjects. In each set, left scan was made through third ventricle and right scan at a higher level, through the centrum semiovale. Time intervals are listed in minutes after injection. Each scan duration was 500 sec (10 revolutions), accumulating ~1 million counts. Relatively poorer quality of first pictures is caused by rapid activity increase during scan and fewer total counts detected. Increased activity in region of third ventricle and trigone is considered due to rapid blood flow in choroid plexus.

ether-extracted red-cell activity by high-pressure liquid chromatography showed only IMP.

After intravenous injection of IMP in human subjects, thin-layer chromatography (silica gel, MeOH/$CHCl_3$/AcOH, 15:85:1) of collected urine identified not only unmodified IMP, but also metabolites, namely, p-iodoamphetamine, p-iodophenylacetone, p-iodobenzoic acid, p-iodohippuric acid, free iodide, and unidentified compounds. A significant part of arterial whole-blood activity was associated with unidentified polar metabolites of IMP. Fractions extracted from arterial whole blood by either ether/alkali or by octanol were equal in activity, and analysis by high-pressure liquid chromatography showed that the extracted activity represented only IMP. Octanol extraction was subsequently used to quantify the value of N, the fractional part of arterial whole-blood activity representing unmetabolized IMP. In normal human subjects, we found that the value of N for the initial 5-min integrated arterial whole-blood sample was 0.75 ± 0.06 (mean ± s.d., N = 5); in all subsequent samples through the first hour, N was approximately 0.50. Similar values were found for dog's blood.

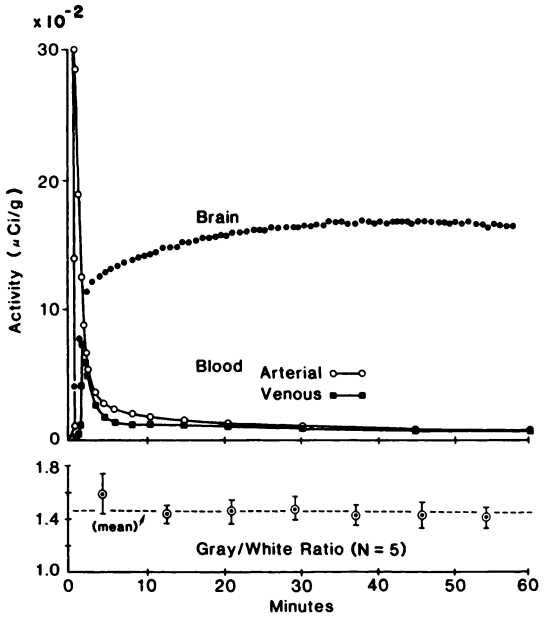

FIG. 5. Top: Time course of brain and blood activity during first hour after intravenous injection of IMP in normal human subject. Brain activity was measured from continuous sequence of ECT scans. Bottom: ECT-determined ratio of gray- to white-matter LCBF was relatively stable over one hour in five human subjects.

Serial brain scanning (Fig. 4) and blood sampling gave the first-hour relationships shown in Fig. 5. By 5 min, brain activity had risen rapidly to ~75% of its eventual maximum value; arterial blood activity had already peaked and fallen to a low, but still significant, level. Brain and arterial activity varied little throughout the next hour, when 5% of the administered dose was maintained in the brain, and the ratio of brain activity to either arterial or venous blood activity was about 22/1. The cortex/white matter activity ratio was relatively stable at 1.5; the mean value throughout the first hour was only 8% lower than the 5-min value.

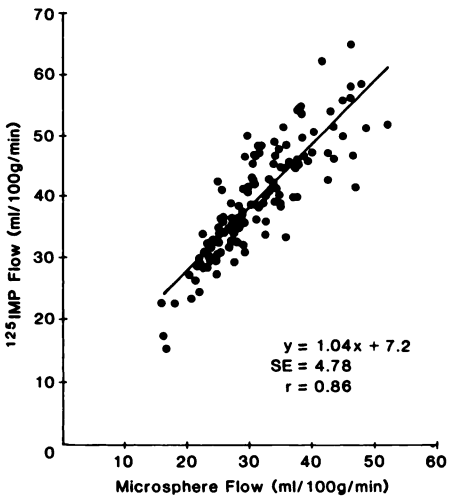

FIG. 6. Correspondence in four dogs between LCBF determinations based on IMP and on labeled microspheres, using method of the brain deposition and arterial input sampling [Eq. (2)].

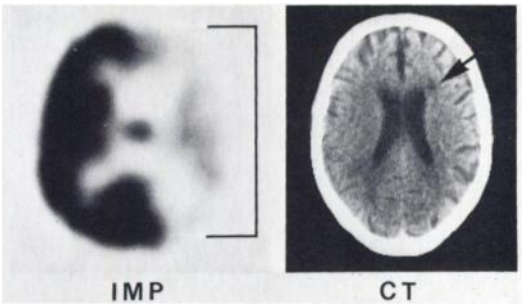

FIG. 7. IMP tomography in stroke. These brain scans of a 57-yr-old hypertensive man were made 3 mo after he experienced sudden onset of left hemiparesis. Permanent reduction (21%) in CBF of entire right hemisphere (bracket) is clearly demonstrated by IMP tomography. The only abnormalities seen in CT scan were bilateral diffuse atrophy and a small lacunar infarct (arrow).

Brain to blood back diffusion was estimated in two human subjects. We determined the full time course through 1 hr for brain activity (full cross section), measured by serial scans of a single brain level, and for arterial whole-blood IMP activity (N-corrected). Upon applying Eq. (1), the half-time for back diffusion from brain to blood was determined to be 73.7 min in one subject (Fig. 5) and 43.8 min in the other. These values were in agreement with the washout data found in monkey brain after intracarotid injection of IMP.

Quantification of CBF. In the dog's brain, the method of brain deposition and arterial input sampling [Eq. (2)] gave good correspondence between LCBF determinations based on IMP and those based on microsphere deposition in tissue samples (Fig. 6). The values plotted in the figure represent compression-induced flow alterations of minus 25% to plus 100% from the control state, in which mean LCBF was 26.1 ml/100 mg/min (mean, N = 4) as determined by the microsphere method. In the single dog studied during persistent penicillin-induced seizure activity, there was good correspondence between IMP- and microsphere-based flows at rates as high as 160 ml/100 mg/min.

In five normal human male subjects (age 44.6 ± 16.9 yr, mean ± s.d.), the method of Eq. (2) was again applied, but with Mark IV scanning rather than brain-sample counting. The average for overall CBF was 47.2 ± 5.4 ml/100 g/min (mean ± s.d., N = 5).

Clinical results. IMP scans performed on patients with cerebral disorders gave results consistent with the expectation that local activity in brain tissue would reflect LCBF. In stroke, local deficits in IMP uptake were out of proportion to structural alterations detected by TCT (Fig. 7). The quality of images from SPECT of IMP approximated those from PECT with FDG(F-18) (Fig. 8). Local brain activity was not increased in zones of abnormally permeable blood-brain barrier or in tumors, even when tumor hypervascularity had been identified by arteriography.

DISCUSSION

From these studies we conclude that after intravenous injection in humans, IMP is nearly completely removed on first pass through the brain, where it is bound in proportion to LCBF. This distribution is maintained for over 1 hr despite slow washout, because as activity is slowly lost, it is also slowly replenished by new IMP delivered from a pulmonary reservoir. Metabolism of IMP (*13*,*14*) begins promptly, as noted by rapid appearance of nonextractable blood activity, rising hepatic activity, and subsequent appearance of metabolic by-products in urine. Oldendorf (*24*) has found that introduction of polar groups will reduce brain uptake of amines to a level barely measurable. Therefore, with octanol extraction of whole-blood samples, one can separate activity due to unmetabolized IMP from that of its polar metabolites, which will not be taken up by the brain and which apparently did not accumulate in regions of abnormally permeable blood-brain barrier.

These circumstances justify applying a modification of the method of tissue deposition and arterial input sampling described for measurement of regional organ flow using microspheres (*21*,*22*). If these are injected into the left atrium of the heart, they flow with the arterial blood and are distributed in proportion to the local blood flow within the brain. By constant-rate sampling

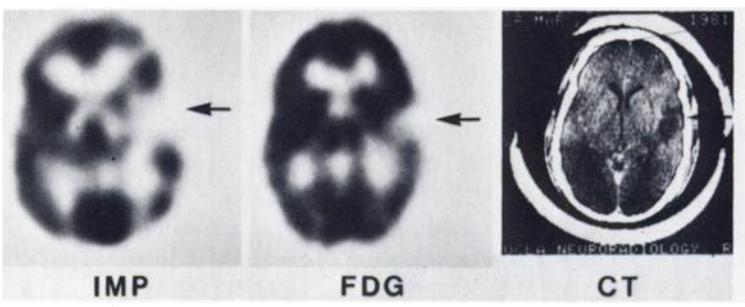

FIG. 8. IMP tomography in a seizure disorder. This 18-yr-old man was studied because of onset of temporal-lobe seizures. IMP tomography showed focally decreased LCBF in cortex of right temporal lobe (arrow), FDG(F-18) tomography (Ortec ECAT II) showed corresponding decreased glucose utilization (arrow), and TCT scan showed a nonenhancing region of decreased density in right temporal lobe (arrow) with minimal mass effect (Grade 2 astrocytoma). IMP scan: 5 mCi, 16.6 min duration, 2.2 million counts; FDG scan: 7 mCi, 15.5 min duration, 1.7 million counts. Note similarity of appearance and information in IMP and FDG scans.

from the arterial circulation during the passage of the microspheres, the tracer activity withdrawn by syringe is in the same proportion to the withdrawal rate as local brain activity is to local brain blood flow. In applying Eq. (2), we make the assumptions (a) that at 5 min after injection, IMP behaves like microspheres, with nearly complete extraction from the blood on a single pass through the brain; (b) that correction can be made for the presence of nontracer activity in reference arterial blood; (c) that nontracer activity contributes little to brain activity; and (d) that brain activity can be quantified by SPECT.

When Eq. (2) was applied with tissue-sample counting in dog's brain, there was good correspondence between LCBF values determined by IMP and by microspheres, even at flow rates as high as 160 ml/100 g/min. Proper correction for nonextractable metabolite activity in arterial blood disproved our earlier observation (*15,16*) that flow rates of this magnitude were significantly underestimated by the IMP method. When Eq. (2) was applied with SPECT to normal human subjects, we found a mean CBF of 47.2 ± 5.4 ml/100 g/min (mean ± s.d., N = 5), which agrees well with values of approximately 50 ml/100 g/min determined in normal humans by the Kety-Schmidt method (*25*), the intracarotid Xe-133 injection method (*26*), the intracarotid ^{15}O-water method (*18*), and by positron-emission computed tomography of inhaled $C^{15}O_2$ (*27*). This similarity lends support to the validity of the IMP method.

In order to minimize error due to brain washout and the time required for continuous artrial blood sampling, CBF was quantified at 5 min after injection, when brain activity was ~75% of its eventual maximum. For comprehensive survey of the brain, imaging could be repeated for at least another hour, since the activity pattern changed little. These later images could also be quantified in CBF units if their activity distributions were corrected to represent 5-min reference values. This was accomplished by dividing measurements of later zonal activities by the fractional increase above reference expected at that time. The fractional increase in activity per unit time was calculated as the ratio of total counts in scans of the same brain level made at 1 hr and at 5 min divided by the time interval of 55 min, under the assumptions that CBF was in steady state, relative brain distributions were unchanged, and brain activity had increased approximately linearly during this interval.

The validity of the IMP-ECT method in human studies is supported by our results for mean whole-brain CBF, which correspond closely with those reported from the Kety-Schmidt method. The particular advantage of the ECT method, however, is in revealing blood flow patterns in smaller structures, and here accuracy is adversely affected by the finite spatial resolution of the scanner (*28*). This causes underestimation of LCBF in gray matter and overestimation in white, which is reflected in our cortex to white-matter flow ratios of approximately 1.5 (Fig. 5), even though the true ratio is greater. In structures larger than about several centimeters in diameter, LCBF would be quantified more accurately in Mark IV scans.

Initial brain uptake of IMP probably depends on its lipophilicity and subsequent trapping on its affinity for high-capacity, relatively nonspecific binding sites in brain and capillary endothelium (*13*). In single-pass studies in monkey brain, an increase in CBF from 33 to 66 ml/100 g/min (accompanied by a decrease in arterial blood pH from 7.35 to 7.10) decreased the IMP extraction fraction from a value of 92% to 74%. We noted no corresponding decrease in net trapping at higher LCBF in the dog's brain. The question remains unanswered whether a pH dependence and/or a diffusion limitation is operating, and further studies are needed to define the performance of this IMP method under conditions of high CBF and low pH. We do have evidence (unpublished results) that the partition coefficient (n-octanol/HEPES buffer, pH 6.0–8.9) varies with pH.

In the normal brain, we have shown that alterations in LCBF cause proportional alterations in local IMP deposition, but it is not known how the trapping and release mechanisms for IMP in diseased brain are affected by other conditions of local metabolism, pH, or permeability. As previously reported, we found no IMP trapping in gliomas, even when carotid arteriography showed them to be hypervascular (*31*). We considered the possibility that polar metabolite activity might concentrate with time in regions of abnormally permeable blood-brain barrier, but found no evidence of this in scans made 1 hr after injection. At present, it appears that any discrepancy between LCBF and IMP trapping due to local disease is most likely to be in the direction of reducing local IMP deposition, i.e., producing an exaggerated defect in the scan pattern. In some circumstances, this potential limitation in quantification of LCBF might be of value, paradoxically, in enhancing diagnostic localization of the disease process.

FOOTNOTES

* Kodak SB-54 film.
† Beckman Model 334.

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