Simplified Detection System for Neuroreceptor Studies in the Human Brain

Alden N. Bice, Henry N. Wagner, Jr., J. James Frost, T. K. Natarajan, Myung C. Lee, Dean F. Wong, Robert F. Dannals, Hayden T. Ravert, Alan A. Wilson, and Jonathan M. Links

Divisions of Nuclear Medicine and Radiation Health Sciences, The Johns Hopkins Medical Institutions, Baltimore, Maryland

A simple, inexpensive dual-detector system has been developed for measurement of positron-emitting receptor-binding drugs in the human brain. This high efficiency coincidence counting system requires that only a few hundred microcuries of labeled drug be administered to the subject, thereby allowing for multiple studies without an excessive radiation dose. Measurement of the binding of [^{11}C]carfentanil, a high affinity synthetic opiate, to opiate receptors in the presence and in the absence of a competitive opiate antagonist indicates the potential utility of this system for estimating different degrees of receptor occupation in the human brain.

J Nucl Med 27:184–191, 1986

For many years, nuclear medicine has relied chiefly on the gamma camera to produce images of the distribution of suitable radiotracers within the body. More recently, a transaxial imaging process, positron emission tomography (PET) (*1,2*) has come into prominence. This imaging modality is based on the detection of annihilation radiation resulting from positron emission and provides a method for quantifying radiotracer concentrations within the body. Since positron emitting radioisotopes exist for several elements of biologic interest (e.g., ^{11}C, ^{13}N, ^{15}O, and ^{18}F, a hydrogen substitute) the potential number of clinical applications of PET is large. A recent application of positron tomography is the noninvasive measurement of dopamine, serotonin, and opiate receptors in the human brain (*3–6*).

Despite the many clinical possibilities of PET there are practical considerations which presently limit the use of PET devices to larger hospitals or clinics. One consideration is the cost of the PET device. Another is the level of administered activity necessary to produce a transaxial image with adequate resolution and signal-to-noise ratio. Typically, 5–20 mCi quantities of the short-lived (^{11}C-, ^{13}N-, ^{15}O-, or ^{18}F-labeled) radiotracers are administered in a PET study. A suitable accelerator (usually a cyclotron) must be located in close proximity to the PET device to produce sufficient quantities of the radiotracer when needed.

Received Dec. 27, 1984; revision accepted Oct. 28, 1985.

For reprints contact: Alden N. Bice, PhD, Div. of Nuclear Medicine, 615 North Wolfe St., Rm. 2001, Baltimore, MD 21205-2179.

In certain types of studies, a transaxial image of the distribution of a positron-emitting radionuclide is not needed to obtain valuable clinical data. For example, the information of interest may be the level of uptake of the positron emitting radiotracer in the entire brain or a large region of it. In such cases simpler devices, which require far lower levels of administered radioactivity, may be used. The monitoring of human opiate receptor occupancy or number under different pharmacologic perturbations is one area where such nonimaging studies may prove beneficial.

Recently, carbon-11 (^{11}C)carfentanil (*6,7*), a derivative of the opiate fentanyl, with a high affinity for opiate receptors, was used to visualize the opiate receptors in the baboon and human brain by PET scanning. The animal and human subjects were also scanned using [^{11}C]carfentanil following pretreatment with 1 mg/kg naloxone, an opiate antagonist. Following naloxone pretreatment the uptake of [^{11}C]carfentanil was markedly reduced compared with that observed in the unblocked control study. The percentage inhibition of binding by naloxone approached 90% (when corrected for recovery coefficient effects (*6*), for the caudate nucleus and medial thalamus at 30–60 min postinjection. The large reduction in the activity uptake in the brain after pretreatment by an opiate receptor competitor suggested that it might be possible to detect and eventually quantify the changes in receptor occupancy with a nonimaging device.

The present report describes our initial investigation

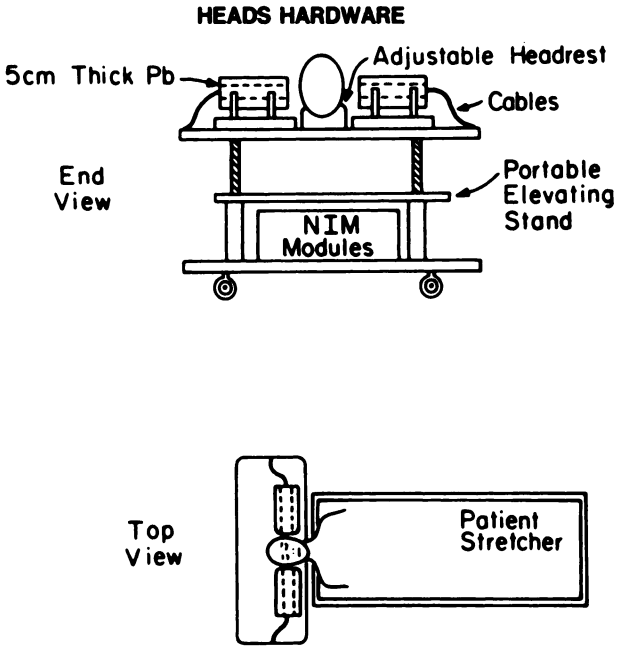

FIGURE 1
Arrangement of two collimated scintillation crystals used for detecting coincident 511 keV annihilation gamma-rays from human head. Detectors and electronics are mounted on portable elevating stand which can be adjusted to match patient stretchers

of a simple, inexpensive coincidence counting system developed for determining the relative uptake of positron-labeled receptor-binding drugs in the human brain.

MATERIALS AND METHODS

Detection System

A dual scintillation crystal system was constructed to detect positron annihilation events by coincident detection of 511 keV gamma-ray pairs. Figure 1 illustrates the arrangement of the detectors in our prototype high efficiency annihilation detection system (HEADS). Two 3 in. × 3 in. sodium iodide (NaI) scintillators were positioned in cylindrical lead collimators that were placed close to the subject's head. The collimator-to-collimator separation was 19.6 cm, with the scintillation crystals being recessed 2.5 cm from the collimator edge. Five-centimeter-thick lead shielding served to reduce the number of unwanted gammas originating in other body regions that otherwise would enter the crystal and possibly be recorded.

The use of coincidence detection of the two 511-keV annihilation gamma-rays limited the field-of-view (FOV) for positron activity to the volume between the two scintillation detectors. Therefore, subjects were positioned so that the volume of the brain to be studied was located between the two crystal faces. Positioning of subjects was facilitated by a movable headrest mounted between the opposing detectors. The headrest and detectors were mounted on the upper table of a portable elevating stand (Fig. 1) which could be adjusted in height to match most patient stretchers.

Figure 2 presents a schematic diagram of the HEADS electronics. Each NaI crystal and its optically coupled photomultiplier tube (PMT) feed a preamplifier (EG&G Ortec Model no. 276) and a linear amplifier (EG&G Ortec Model no. 590A). The analog amplifier signals are energy discriminated by timing single channel analyzers (SCA) included in the linear amplifier modules. Only events that correspond to the 511 keV photopeak are sent to the primary (true and random) coincidence unit (EG&G Ortec Module no. 418A). From one of the channels a second SCA output is delayed 9 μsec by an EG&G Ortec Module no. 416A gate and delay generator and sent to another (random)

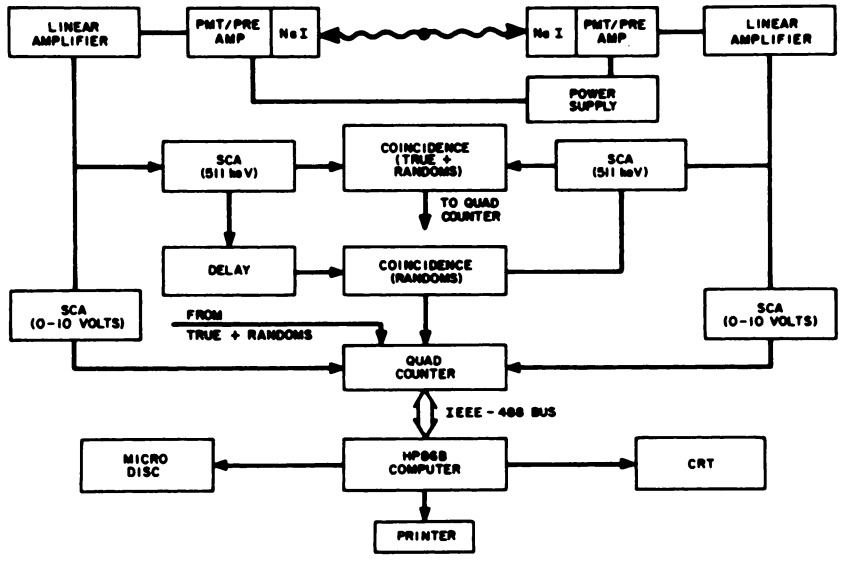

FIGURE 2
Schematic diagram of HEADS electronics for coincident detection of 511 keV annihilation gamma-rays

coincidence unit. This latter coincidence circuit records the number of random (uncorrelated) 511 keV gamma-ray coincidences that occur within a specific time window, of the same duration as the primary coincidence. These random events are subtracted from the total number of events recorded in the primary concidence unit to yield the true coincidence counts.

The number of random coincidence events depends quadratically on the activity in the field-of-view and on the width of the coincidence timing window. When the activity is low ($< \sim 50$ μCi in the case of the HEADS system) the random events are insignificant. It is possible to decrease the number of random coincidences at higher levels of activity by shortening the coincidence timing window. How narrow this window can be set is dictated by the crystal decay time, and the quality of the electronic components. We have used a coincidence resolving time of a few hundred nanoseconds.

In addition to determining the number of true and random coincidences, the total number of events (above 10 keV energy) processed by each channel per acquisition interval was recorded. This information was used to correct for system deadtime.

Logic pulses representing the four parameters (true and random coincidences, random coincidences, all events left channel, and all events right channel) were continually accumulated by an EG&G Ortec Model no. 874 quad-counter. A Hewlett-Packard 86B microcomputer automatically started, stopped, interrogated and reset the quad-counter. At regular time intervals the computer read, by way of an IEEE-488 bus line, the contents of the quad-counter buffer, stored the new parameter data, reset the quad-counter and resumed another acquisition interval. For these studies, the four parameters were recorded every 10 sec although computer controlled data acquisition allows for acquisition intervals of a few hundred milliseconds to hundreds of seconds.

During data acquisition time-activity curves were displayed on-line (with deadtime and random event corrections). Concurrently, raw data were output to a small line printer. At measurement completion all parameter data were automatically stored on a microfloppy disk.

Human Studies

All studies were performed with the subject's head centered in the two-detector system such that the midpoint between the most anterior border of the head of the caudate and the most posterior extent of the thalamus was located in the center of the field-of-view. The locations of the corpus striatum and thalamus were determined either from a computed tomographic (CT) image (if available from a previous PET study of the subject) or from a lateral x-ray using the stereotactic method of Fox et al. (*8*).

For both the CT and lateral x-ray procedure a thermoplastic mask was worn by the subject. In the latter method, lead string was affixed to the mask to obtain a reference coordinate system. After determination of the position of the thalamus and corpus striatum within the skull, reference points were marked on the subject's mask. These reference points were then used to center the subject's head in relation to the cross marks on the detector collimators. Once the subject was positioned, additional reference marks were added to the exterior of the mask to aid in the accurate repositioning of the subject in repeat studies. Velcro straps were then affixed to the mask to maintain the subject's position for the duration of the study.

Using the HEADS system, 11 normal volunteers were studied after the i.v. administration of [^{11}C]carfentanil. Time-activity curves of the ^{11}C activity were obtained for at least 60 min postinjection. The raw time-activity data were then corrected for system deadtime, random coincidences, and ^{11}C decay. If multiple studies were performed with the same subject, differences in injected activity between studies were corrected by scaling the time-activity curves.

A total of 21 studies were performed. Prior to each study [^{11}C]carfentanil was synthesized (*7*) and shared with a concurrently scheduled carfentanil PET study. The administered dose of [^{11}C]carfentanil ranged between 200 and 400 μCi. The injected carfentanil mass per study was between 0.1 and 0.6 μg.

Three types of patient studies were performed. Each subject performed a baseline study where only [^{11}C]carfentanil was injected intravenously. Five subjects were administered 1 mg/kg naloxone (i.v.) 5 min prior to a [^{11}C]carfentanil injection. Four subjects were administered intravenously naloxone (either 1, 0.1, or 0.01 mg/kg) 15 min after the [^{11}C]carfentanil.

Calibration

Prior to each study the energy windows of both detection channels were checked for proper centering about the 511 keV photopeak using a ^{68}Ge–^{68}Ga line source. Changes in system sensitivity were monitored prior to each study by placing a calibrated 2 μCi ^{68}Ge–^{68}Ga line source in front of one detection crystal and recording the number of true coincidence events in a 2 min interval. This procedure was then repeated with the line source placed in front of the second NaI crystal. Differences in system sensitivity between studies with the same subject were corrected by scaling the time-activity curves.

RESULTS

Sensitivity

Since a primary use of the HEADS system is to measure the degree of neuroreceptor blockade pro-

duced by varying doses of neurotropic drugs, a major goal is that the system be sensitive enough to perform serial studies with acceptable radiation dose. Measurement of a 16-cm-diam cylindrical phantom filled with ^{68}Ga in water yielded a minimum coincidence counting rate of 16,000 cps/ml/μCi of ^{68}Ga for 3″ × 3″ NaI detectors spaced 24.6 cm apart.

For comparison, the same 16-cm-diam phantom provided a count rate of about 12,000 cps/ml/μCi of ^{68}Ga in the EG&G Ortec Neuro ECAT PET scanner operated in the high resolution mode. The PET scanner requires, by virtue of the projection/reconstruction procedure (*9,10*), that much larger numbers of events be recorded in order to have acceptable statistical errors for the image.

The dual-detector system requires that only about 1,000 events be recorded per counting interval to maintain a statistical error of under 4%. This can be achieved in the [^{11}C]carfentanil HEADS studies by using about 300 μCi of activity. When [^{11}C]carfentanil was given alone, 200–400 μCi of (i.v.) injected activity yielded coincidence counting rates of 100–200 cps at early time points and 5–10 cps at 60 min postinjection.

Human Studies

The upper curve in Fig. 3A shows a typical corrected (see Methods) time-activity curve for a study in which [^{11}C]carfentanil was given alone. The lower curve in Fig. 3A is an example of the activity in the same subject when pretreated with 1 mg/kg (i.v.) of naloxone. Naloxone, a competitive antagonist for opiate receptors (*11*) rapidly occupies receptor sites thereby inhibiting the specific binding of carfentanil in the brain.

Both curves in Fig. 3A show a similar initial rise in activity, reflecting the arrival of the tracer in the field-of-view. When [^{11}C]carfentanil is administered alone, the activity in the field-of-view plateaus for a few minutes and then decreases linearly with time. The radioactivity in this study reflects total binding (i.e., specific or receptor plus nonspecific binding). The radioactivity in the postnaloxone (binding inhibition) study represents only nonspecific binding since virtually all receptors are occupied. At 3–4 min postinjection, the latter study already shows decreased activity compared to the prior study. In addition, the decrease in ^{11}C activity is more rapid in the binding inhibition study than when only [^{11}C]carfentanil was given. At 30–40 min postinjection the measured ratio of total to nonspecific uptake is ~2 for all subjects.

Figure 3B shows the difference between the curves representing the total and the nonspecific binding. This curve represents the kinetics of specific receptor binding in the field-of-view. The specific binding reaches a maximum between 15 and 20 min postinjection and then slowly decreases, demonstrating the dissociation and clearance of the receptor-bound drug.

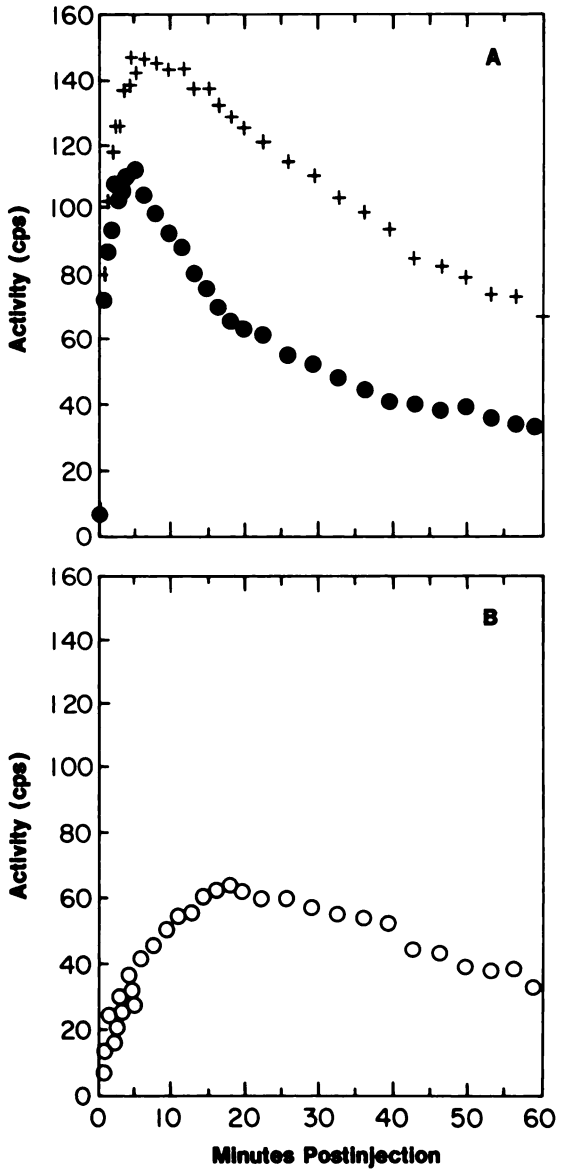

FIGURE 3
A: Time-activity curves obtained with HEADS system using [^{11}C]carfentanil. Subject was positioned such that corpus striatum and thalamus were centrally located between two 3 in. × 3 in. detectors. + Symbols correspond to (i.v.) administration of ~300 μCi of [^{11}C]carfentanil, potent opiate antagonist. Dark circles indicate uptake in head of second (i.v.) injection of ^{11}C-labeled carfentanil (~300 μCi) following pretreatment with 1 mg/kg of opiate receptor antagonist, naloxone. Statistical errors (±1 σ) are less than size of data points. B: Difference between two time-activity curves in Fig. 3A. This curve is representative of specific opiate receptor binding as function of time in total volume between detectors. Statistical error bars are smaller than size of data points

In four subjects i.v. injections of different doses of naloxone were administered 15 min after a carfentanil injection. Figure 4A shows three measured time-activity curves from the same subject. Curve 1 is a [^{11}C]carfentanil uptake curve as previously described. Curves 2

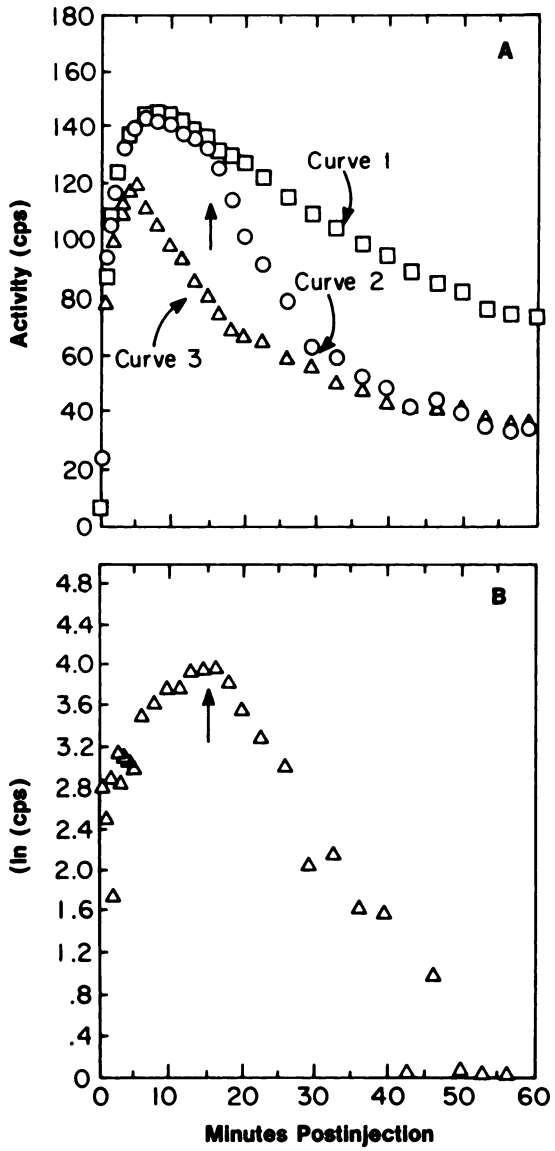

FIGURE 4

A: Three time-activity curves obtained with same subject using HEADS system. For each measurement subject was positioned such that corpus striatum and thalamus were centrally located in field-of-view. Curve 1 represents normal uptake of [^{11}C]carfentanil. Curve 3 represents uptake of [^{11}C]carfentanil following pretreatment with 1 mg/kg of naloxone, i.v. Curve 2 represents time course of carfentanil in brain when 0.1 mg/kg of naloxone is administered i.v. 15 min after carfentanil (indicated by vertical arrow). Curves are normalized for differences in injected activity, which ranged from 200–290 μCi. Statistical errors ($\pm 1\ \sigma$) are less than size of data points. There was no change measured in absolute sensitivity of HEADS system between studies. PI stands for postcarfentanil injection. B: Semi-logarithmic plot of difference between pre-blocked and displacement studies (Curves 2 and 3) in Fig. 4A. Ordinate represents natural logarithm of this difference of corrected coincidence cps and abscissa is time postcarfentanil injection. Curve is reflection of time course of specific binding of carfentanil to μ-type opiate receptors in presence of receptor competitor. Linear appearance of carfentanil clearance in semilogarithmic plot indicates first order kinetics. Vertical arrows indicate time of naloxone injection

and 3 represent a competitive displacement study and a binding inhibition study, respectively. For the displacement study shown, 0.1 mg/kg of naloxone was administered. Figure 4A indicates a sharp drop in activity after 15 min postinjection (see arrow, Fig. 4A) which continues until the level of the nonspecific binding is attained.

Taking the difference between the displacement and the binding inhibition curves will again show the time course of carfentanil specific binding, but now with the presence of an opiate receptor competitor 15 min after the carfentanil injection. Figure 4B shows this difference curve, but graphed such that the natural logarithm of the difference is plotted compared with time postcarfentanil injection. Figure 4B shows that beyond 15 min the specifically bound carfentanil decreased exponentially, with a half-time of clearance, determined by linear regression, of 6.3 min.

Figure 4B suggests that the clearance of specifically bound carfentanil is dependent upon the amount of naloxone available at the opiate receptor sites. Figures 5A–C, shows the effect of varying displacement doses of naloxone in three different subjects. Each pair of curves in Figs. 5A, B, and C represents two measurements on a subject; a [^{11}C]carfentanil uptake study and a [^{11}C]carfentanil displacement study as previously described. Figure 5A shows the displacement of [^{11}C]carfentanil by 1 mg/kg naloxone administered intravenously 15 min after the [^{11}C]carfentanil. Figure 5B shows a similar study when 0.1 mg/kg naloxone was intravenously injected 15 min after [^{11}C]carfentanil; Fig. 5C shows a similar study when 0.01 mg/kg naloxone was injected intravenously 15 min after the [^{11}C]carfentanil. Comparing the curves in Figs. 5A, B, and C it can be seen that the rate of clearance decreases with decreasing amount of naloxone injected. Using linear regression analysis the decrease in activity is found to be about 17% faster between 16 and 25 min in the 1.0 mg/kg naloxone displacement study than the 0.1 mg/kg naloxone displacement study although the slopes of the respective control studies are equal between 15 and 60 min. Compared to the 0.01 mg/kg naloxone displacement study, the 0.1 mg/kg displacement study shows a 43% faster divergence from the control curve over the 16–25-min time period.

A binding inhibition study (not shown) was also performed on the subject whose other studies are shown in Fig. 5C. The difference between the 0.01 mg/kg displacement study and the binding inhibition study in this subject again revealed that the specifically bound drug decreases exponentially after 15 min, but with a half-time of clearance of 13 min.

DISCUSSION

The monitoring of human opiate receptor occupancy under different pharmacologic perturbations is one

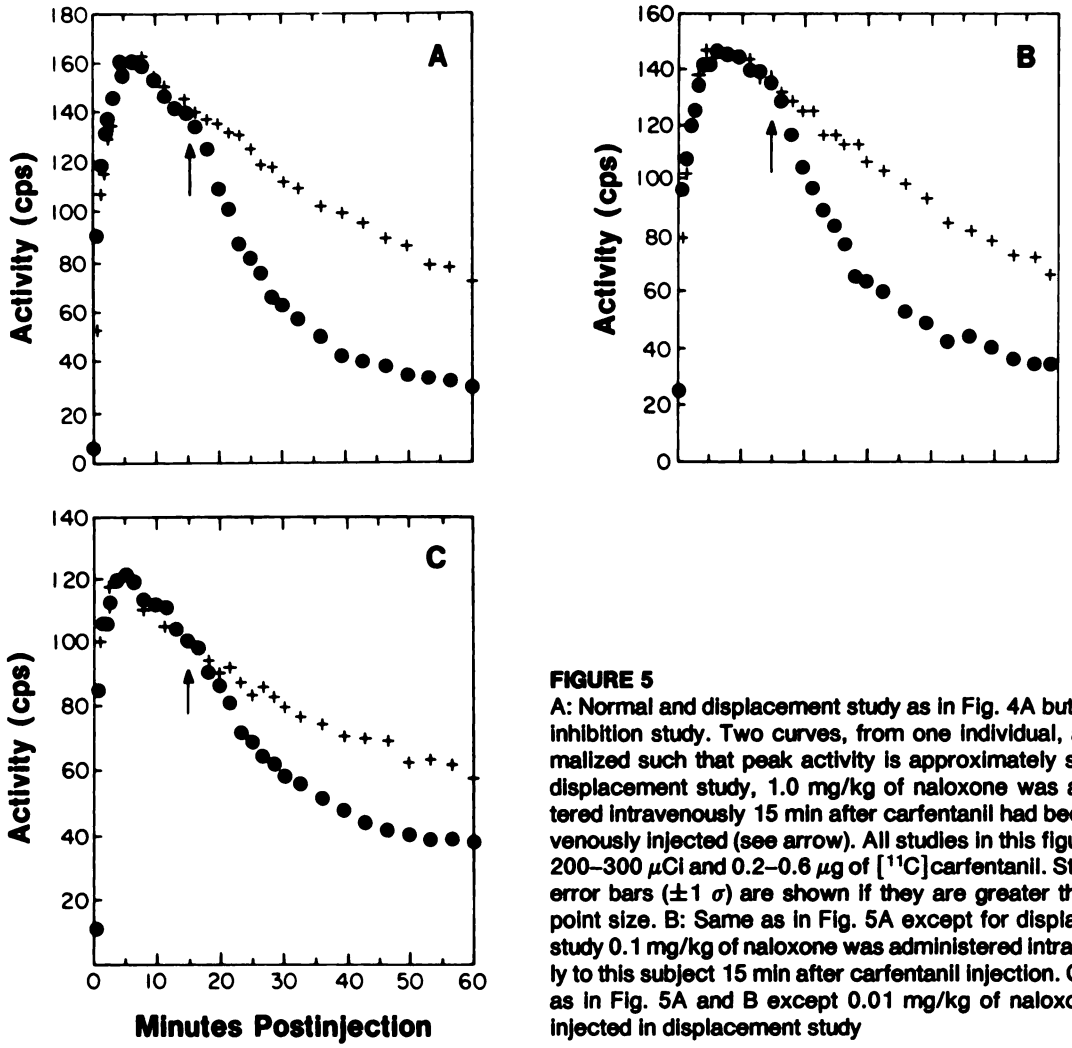

FIGURE 5
A: Normal and displacement study as in Fig. 4A but without inhibition study. Two curves, from one individual, are normalized such that peak activity is approximately same. In displacement study, 1.0 mg/kg of naloxone was administered intravenously 15 min after carfentanil had been intravenously injected (see arrow). All studies in this figure used 200–300 μCi and 0.2–0.6 μg of [^{11}C]carfentanil. Statistical error bars ($\pm 1\ \sigma$) are shown if they are greater than data point size. B: Same as in Fig. 5A except for displacement study 0.1 mg/kg of naloxone was administered intravenously to this subject 15 min after carfentanil injection. C: Same as in Fig. 5A and B except 0.01 mg/kg of naloxone was injected in displacement study

area where a nonimaging device may prove useful. To investigate this possibility we used [^{11}C]carfentanil, a positron-emitting, opiate-receptor-binding radiopharmaceutical and a dual-detector system, for measuring annihilation events in the brain.

Either a single scintillation detector or a pair of scintillation detectors can be used to record the annihilation events. A single detector used in this capacity suffers from several experimental biases that are difficult to correct. For instance, a single detector will "view" preferentially activity closest to its crystal face due to both attenuation effects and detector solid angle considerations. Furthermore, single detector measurements are sensitive to the location of the radioactive source (within the brain) because of the rapid variation of the detector's sensitivity with varying detector to source distances. A dual scintillation crystal system, operated in coincidence to simultaneously record the 511 keV gamma-ray pair, is less sensitive to these problems. This principle is widely used in positron imaging systems (*12–14*) and recently was utilized to sample the activity concentrations within the chambers of the heart (*15*).

The dual-detector system described in this paper was constructed with high sensitivity and low cost as major design goals. The cost of this prototype system was under $20,000. The detection efficiencies were sufficient to allow [^{11}C]carfentanil opiate receptor studies with the administration of only a few hundred microcuries. Although 3 in. × 3 in. NaI crystals are used in the HEADS system, our measurements indicate that it is possible to use NaI crystals of various sizes depending on the desired field-of-view. We have not investigated other scintillator materials but even increased sensitivity to annihilation radiation could be obtained using bismuth germanate crystals (*16*).

At an increase in cost, the use of faster electronics would improve the time-activity data further. Faster electronics would decrease the fraction of valid events lost due to system dead time. For the HEADS system, injected activities up to 400 μCi produced losses of up to 20% of valid coincidence events. Faster electronics

would also decrease the random coincidences and therefore improve the statistical error of the measurements.

The use of new PET two-dimensional block technology (*17*) could further enhance the sensitivity and give greater versatility to a two-detector system while keeping the cost low.

The high sensitivity of the HEADS system is an important feature because it allows for many studies of the same subject, something that is less easily justified on a routine basis with PET owing to the much higher radiation dose to the subject. It is possible to forego the imaging capability and use the PET device as a multiple-detector, nonimaging coincidence device. This cost-ineffective operation of the PET device would not yield the high sensitivity of a two-detector system, where the detection crystals are as close to the subject's head as possible. Most PET machines have coincident detector separations 2–3 times that of HEADS. The solid angle of detection varies as the square of the separation distance, so that the few detectors in the opposing PET detector banks that view the same region of a subject's head as our two-detector system would have less sensitivity.

The major limitation of the simplified coincidence system is the lack of imaging capability. This implies that a HEADS system will often be an adjunctive device to a PET scanner, especially when detailed spatial information about receptor-binding is required. As our results suggest, there are clinically useful neuroreceptor studies that do not require a detailed mapping of receptor binding. It is this category of measurements for which a HEADS system is optimally suited.

The observed difference between the [^{11}C]carfentanil time-activity curves (Fig. 3A) in the presence and absence of naloxone indicates that such a system can be used to determine different levels of opiate receptor blockage with different levels of administered drug. Figure 3B shows that specific receptor binding kinetic information is obtainable for carfentanil.

In vivo animal studies support the hypothesis (*18*) that ligand rebinding to opiate receptors occurs. The addition of a competitor ligand after carfentanil injection should hinder the receptor rebinding of carfentanil and hasten its clearance from the brain. Figure 4A shows the results of administering naloxone at the peak of specific receptor binding and demonstrates this effect. Figure 4B indicates a first order clearance rate for the [^{11}C]carfentanil from the brain. This finding is consistent with the kinetics expected from a rapid uptake of naloxone by the opiate receptors and hindered receptor rebinding of carfentanil (*18*). Similar reasoning indicates that the clearance of specifically bound carfentanil should be dependent on the amount of competitor ligand (naloxone) available at the opiate receptor sites. The data presented in Fig. 5 provide evidence of this and again confirm that the two-detector system is capable of measuring a quantity related to receptor binding. The observation of a slower (exponential) decrease in specifically bound carfentanil when 0.01 mg/kg of naloxone was administered than when 1.0 mg/kg naloxone was injected (i.v.) 15 min after the carfentanil demonstrates further the receptor compartment kinetics of carfentanil.

Although we have presented data demonstrating the sensitivity of our HEADS detection system to various levels in the human brain, of a positron-emitting opiate receptor-binding drug, the use of such a system is not confined to opiate receptor binding drugs. The regional activity compared with time of several positron-emitting neuroreceptor-binding drugs are being examined under different pharmacologic conditions, including the study of [^{11}C]-*N*-methylspiperone (*3–5*) binding to dopamine D-2 receptors in the basal ganglia both in the presence and absence of haloperidol and to serotonin receptors in the frontal cortex area of the brain. Results from our initial studies are encouraging.

The possibility of multiple studies on the same individual with this detection system implies that each subject could act as their own control in binding inhibition studies. For example, when investigating an opiate addict the subject could be given a control [^{11}C]carfentanil uptake study following the withdrawal of all opiate drugs. Additional measurements on such subjects, such as the binding inhibition of therapeutic doses of methadone or naltrexone, could then be related to the baseline values. Monitoring of the effects on receptor occupancy of morphine and related drugs in the treatment of patients with chronic pain would also be accomplished by similar methods. Periodic in vivo measurements could be performed without significant radiation risk to the subject.

The high sensitivity and simplicity of the two detector coincidence system opens up several potentially useful clinical neuroreceptor studies with positron-emitting tracers in human beings. The small amounts of activity needed in such studies facilitates delivery of positron-emitting drugs to sites, such as community hospitals, that are removed from a medical accelerator by several half-lives, 20 min in the case of ^{11}C and 110 min in the case of fluorine-18. With the current availability of suitable positron-emitting neuroreceptor-binding drugs the widespread application of simple devices might hasten our understanding of several neurologic diseases and disorders, as well as help in the clinical care of many patients.

ACKNOWLEDGMENTS

This work was supported in part by NIH grant number NS 15080. The authors thank Ms. Danni Dooley for the manuscript preparation.

REFERENCES

1. Phelps ME, Mazziotta JC: Positron emission tomography: Human brain function and biochemistry. *Science* 228:799-809, 1985
2. Phelps ME, Hoffman EJ, Mullani NA, et al: Application of annihilation coincidence detection to transaxial reconstruction tomography. *J Nucl Med* 16:210-233, 1975
3. Wagner HN Jr., Burns HD, Dannals RF, et al: Imaging dopamine receptors in the human brain by positron tomography. *Science* 221:1264-1266, 1983
4. Wagner HN Jr., Burns HD, Dannals RF, et al: Assessment of dopamine receptor densities in the human brain with carbon-11-labeled *N*-methylspiperone. *Ann Neurol* (Suppl) 15:579-584, 1984
5. Wong DF, Wagner HN Jr., Dannals RF, et al: Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. *Science* 226:1393-1396, 1984
6. Frost JJ, Wagner HN Jr., Dannals RF, et al: Imaging opiate receptors in the human brain by positron tomography. *J Comput Assist Tomogr* 9(2):231-235, 1985
7. Dannals RF, Ravert HT, Frost JJ, et al: Radiosynthesis of an opiate receptor binding radiotracer: [^{11}C]carfentanil. *Int J Appl Radiat Isot* 36(4):303-306, 1985
8. Fox PT, Perlmutter JS, Raichle ME: A stereotactic method of anatomical localization for positron emission tomography. *J Comput Assist Tomogr* 9(1):141-153, 1985
9. Budinger TF, Derenzo SE, Greenberg WL, et al: Quantitative potentials of dynamic emission computed tomography. *J Nucl Med* 19:309-315, 1978
10. Hoffman EJ, Van dee Stee M, Ricci AR, et al: Prospects for both precision and accuracy in positron emission tomography. *Ann Neurol* (Suppl) 15:525-534, 1984
11. Gilman AG, Goodman LS, Gilman A, eds: *The Pharmacological Basis of Therapeutics*, New York, MacMillan Publishing Co., 1980, pp 494-534
12. Brownell GL: Localization of intracranial lesions using coincidence counting radiation detection equipment. In *Medical Physics*, Vol. III, Chicago, Year Book Medical Publishers, Inc., 1960, pp 332-338
13. Phelps ME, Hoffman EJ, Mullani NA, et al: Application of annihilation coincidence detection to transaxial reconstruction tomography. *J Nucl Med* 16:210-224, 1975
14. Brownell GL, Correia JA, Zamenhof RG: Positron instrumentation. In *Recent Advances in Nuclear Medicine*, Vol. 5, New York, Grune and Stratton, 1978, pp 1-49
15. Hutchins GD, Votaw JR, Funk KM, et al: A one-dimensional multigated time-of-flight acquisition sysem. *IEEE Trans Nucl Sci* NS-32(1):835-838, 1985
16. Cho ZH, Farukhi MR: Bismuth germanate as a potential scintillation detector in positron cameras. *J Nucl Med* 18:840-844, 1977
17. Nutt R, Casey M, Carroll LR, et al: A new multi-crystal two-dimensional detector block for PET. *J Nucl Med* 26: P28, 1985 (abstr)
18. Frost JJ, Wagner HN Jr.: Kinetics of binding to opiate receptors in vivo predicted from in vitro parameters. *Brain Res* 305:1-11, 1984