Third Annual SNM Lectureship

Images of the Brain: Past as Prologue

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The invention of the Anger scintillation camera and the development of ^{99m}Tc tracers brought about a tenfold increase in nuclear brain scanning between 1963 and 1973, an increase that plateaued with the introduction of x-ray computed tomography. A second growth curve began in 1976 at which time there were four PET centers in the United States, a number that grew to 60 worldwide over the next decade. PET, SPECT, MRI, and MRS are leading us into a new era of in vivo brain chemistry, based on regional bioenergetics and neurotransmission. The immediate impact is in epilepsy, stroke, brain tumors and the dementias, with psychiatric diseases becoming a major focus of research. Receptivity has become a biochemical as well as a psychological approach to mental functions. The finding of elevated D_2 dopamine receptors in schizophrenia in living patients may be the forerunner of a new biochemical approach to psychiatry.

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A continuum of advances has made possible in vivo measurements of brain chemistry which are analogous to the in vitro measurements made by Berson and Yalow of the extremely small concentrations of peptide hormones in blood. It is hard to believe that in 30 years time we progressed from primitive images of the brain carried out with radioiodinated albumin and the rectilinear scanner invented by Benedict Cassen in 1951 to modern positron tomographic images showing several neuroreceptors within the brain of a living human being. We can now image dopamine receptors concentrated in the caudate nucleus and putamen, opiate receptors extending beyond the caudate nucleus and putamen to include the frontal cortex, thalamus, hippocampus and temporo-parietal regions, and serotonin receptors even more widely distributed. The absence of dopamine and opiate receptors in the visual cortex suggests that these two systems may not be involved in the process of cognition but in the control of emotions or movement.

How PET began

The evolution of positron emission tomography (PET) began in the early 1960s with the work of James Robertson and Lucas Yamamoto at Brookhaven National Laboratory, David Kuhl at the University of Pennsylvania, and the group at Washington University in St. Louis under the direction of Michel Ter-Pogossian.

We are entering a new era of human biochemistry (Fig. 1) involving three major spheres of research activity—positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), and magnetic resonance spectroscopy (MRS). All of these techniques can help solve some of the extremely important problems confronting us today, including mental and degenerative diseases of the brain, crime, violence, and substance abuse.

Progress in nuclear medicine can be viewed today as concentric circles (Fig. 2). Cyclotron-produced radioactive tracers such as carbon-11 (^{11}C), fluorine-18 (^{18}F), nitrogen-13 (^{13}N), and oxygen-15 (^{15}O) make up a central core, from which advances diffuse in ever-widening circles, based on the use of tracer compounds labeled with ^{99m}Tc and iodine-123 (^{123}I). Positron emission tomography provides better chemistry and better quantification than we have ever had. For the first time, we can express our results in absolute units of meters, kilograms and seconds, the MKS system, rather than relative concentrations, the only thing possible until now.

Invented in the early 1930s by Ernest Lawrence, the

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A NEW ERA IN HUMAN BIOCHEMISTRY

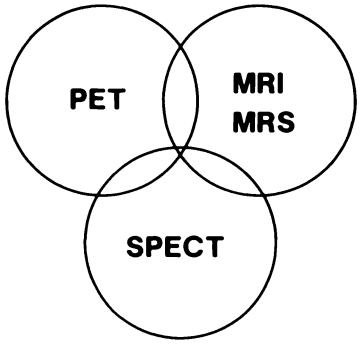

FIGURE 1
PET, SPECT, MRI, and MRS are major areas of medical imaging

cyclotron provided a source of new radioactive tracers never dreamed of by George Hevesy when he invented the tracer principle. Paradoxically, the invention of the nuclear reactor by Enrico Fermi in 1941 to a certain degree delayed the application of cyclotron-produced positron-emitting tracers in the field of nuclear medicine. Reactor-produced tracers such as carbon-14 (^{14}C) and iodine-131 (^{131}I) were less expensive, had longer half-lives and were more readily available.

Inventors such as Hal Anger directed their attention toward tracers that emitted gamma rays rather than positrons. The subsequent development of ^{99m}Tc at Brookhaven National Laboratory in 1960 and introduced into nuclear medicine by Paul Harper at the University of Chicago provided the increased number of photons needed to produce meaningful images with the Anger camera. At present, however, brain scanning with the Anger camera has essentially disappeared as a result of the introduction of computerized tomography and magnetic resonance imaging.

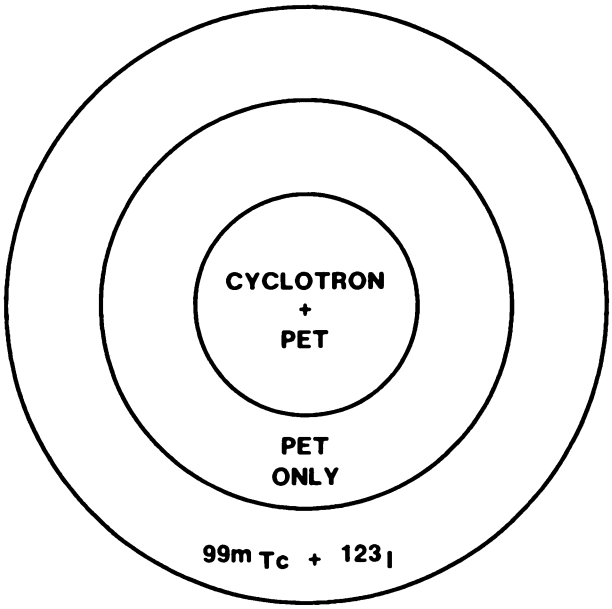

FIGURE 2
Progress in nuclear medicine based on the cyclotron and PET are being extended to compounds labeled with ^{99m}Tc and ^{123}I

In 1976 there were four medical cyclotron centers in the United States. There are now 60 medical cyclotrons throughout the world, which documents the growth of positron emission tomography over the past ten years. Advances in cyclotron technology include increasing use of automation, simplification, more reliable operation, focusing on ^{11}C, ^{18}F, ^{15}O, and ^{13}N, and decreasing size and cost.

Chemistry of the brain

In his classic book *Principles of Psychology* published in 1890, the famous philosopher and psychologist William James made this statement "Chemical action must of course accompany mental activity but little is known of its exact nature." Two years later he wrote "Between a mental event and a brain event there will be an immediate relation, the expression of which, if we had it, would be the elementary psychophysic law." Chemistry permits us to relate the structure of the brain to the functioning of the mind. The processes of cognition, emotion, movement, pain perception, and other mental functions are based on physical and chemical processes within the structure of the brain. For the first time, using the techniques of nuclear medicine, we can carry out in vivo measurements of brain chemistry with a sensitivity and specificity equal to that of radioimmunoassays of peptide hormones in body fluids. Increased neuronal activity is reflected in increases in regional blood flow, glucose utilization, oxygen metabolism, neurotransmitter secretion, and neuroreceptor activity.

Bioenergetics

A major event along the road to measurements of in vivo brain chemistry was the work of Sokoloff and his colleagues who in 1977 developed the ^{14}C deoxyglucose method of measuring local cerebral glucose utilization (*1*). Measurable increases in glucose metabolism could correlate with regional neuronal activity produced by sight, sound, or somatosensory stimulation.

Extending the work of Sokoloff, Ido, Wolf, et al. at Brookhaven National Laboratory and the University of Pennsylvania were able to carry out the first studies of [^{18}F]deoxyglucose in the living human brain (*2–4*). Sensory stimulation can induce increased glucose metabolism in regions such as the visual cortex during the process of seeing and the auditory cortex during listening, in the frontal cortex in the process of thinking, and in the motor cortex during movement (*5–7*). During development of the brain in childhood, glucose metabolism is significantly greater than in the adult brain (*8*).

Neurotransmission

Santiago Ramon y Cajal was awarded the Nobel Prize in 1906, based on his discovery that the nervous system is not one huge continuous network but a system

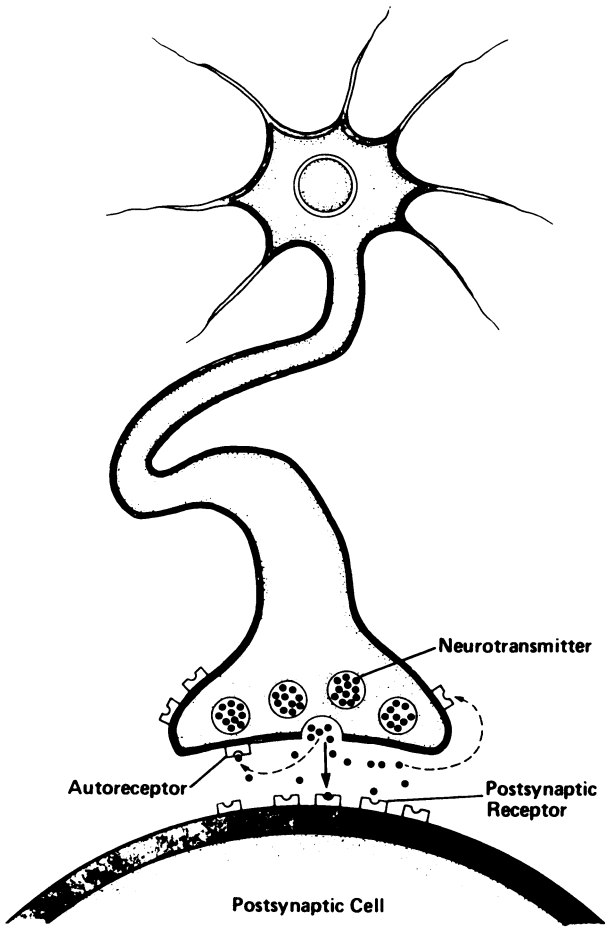

FIGURE 3
Neurotransmitters and neuroreceptors are involved in transfer of information among neurons

of billions of discontinuous neurons. Each neuron in the brain has an average of ~10,000 connections with other neurons as axons connect with dendrites (Fig. 3). Communication between neurons occurs by the process of chemical neurotransmission, one of the most important principles in modern neurobiology. Information is carried along axons by the process of electrical depolarization. At the nerve terminal vesicles containing neurotransmitters such as dopamine, serotonin, opiates, norepinephrine, or acetylcholine are released from these vesicles into the synapse (and possibly into surrounding regions) in proportion to the number of impulses coming down the presynaptic axon. These "chemical messengers" cross the synapse and react with receptors located on the postsynaptic neurons. The transfer of information then, from one nerve cell to another, depends largely on the chemical combination of the neurotransmitter and the neuroreceptor.

We can think of information about the outside world reaching our nervous system as sensations encoded in the depolarization process traveling down the presynaptic neurons. How we react to the presynaptic information is determined by the quantities and types of receptors distributed throughout the post-synaptic neurons. Chemical transmission helps transform sensations into perceptions. Expressions describing how people react differently to the same sensory input include Johnson's comment to Boswell in 1763: "I have often amused myself thinking how different a place London is to different people," or as Wordsworth said: "Every natural form I linked to some feeling, all that I beheld respired with inner meaning."

Chemical neurotransmission forms the basis of much modern pharmacology. The most widely used prescription drug in the United States today is cimetidine which blocks histamine receptors. Another example is propranolol that blocks beta adrenergic receptors. Another is haloperidol which blocks dopamine receptors and is widely used in the treatment of schizophrenia.

Opiate receptors

In 1973, Pert and Snyder (*9*) at Johns Hopkins, Terenius (*10*) at Uppsala University, and Simon and his colleagues (*11*) at New York University demonstrated the existence of opiate receptors in the brain of experimental animals. The same year Kuhar, Pert, and Snyder showed by autoradiography in experimental animals and in the human brain at autopsy that opiate receptors were in those locations where you expect them to be in light of the known distribution of neuronal pain pathways (*12*). This finding provided strong evidence that the receptors played a role in the process of transmission of the sensation of pain. In order to extend the autoradiographic studies from animals to human beings by positron emission tomography, the first step is to label a ligand with a high affinity for the receptor with a positron-emitting radioactive tracer. The opiate carfentanil was selected for the study of opiate receptors because of its extremely high affinity which accounts for its potency being ~8,000 times greater than that of morphine (*13*). The distribution of mu-type opiate receptors in the human brain is seen in Fig. 4. The binding of the [^{11}C]carfentanil by the receptors can be blocked by the prior administration of naloxone, a nonradioactive drug used to treat patients suffering from an overdose of narcotics (*14*). The initial distribution of the tracer reflects blood flow as the tracer binds to both the opiate receptors and the nonspecific binding sites. As time goes by, the tracer dissociates from the low affinity nonspecific binding sites but remains bound to the opiate receptors. After 30 min essentially all the tracer has left the nonspecific binding sites. With a smaller dose of naloxone, the blockade of the receptors is incomplete.

High concentrations of opiate receptors in the human brain are found in the limbic system, including the amygdaloid nuclei, regions believed to be involved in aggression, rage, and other emotional reactions. It is possible to relate quantitatively the dose of naloxone to the degree of blocking of [^{11}C]carfentanil binding to the receptors (*15*).

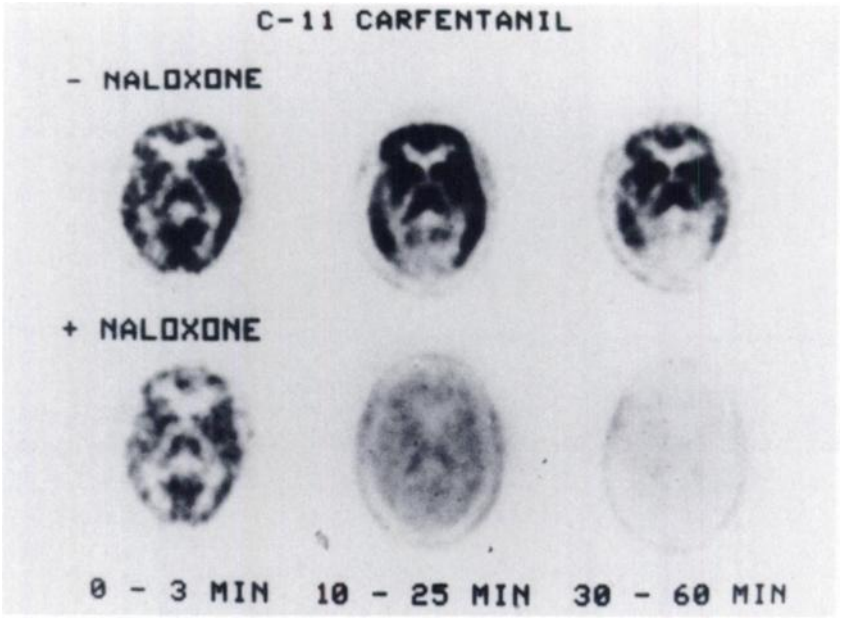

FIGURE 4
Progressive binding of [^{11}C]carfentanil to opiate receptors is shown in upper row of images. Initial distribution (0–3 min) reflects blood flow as tracer binds to both receptors and nonspecific binding sites. Later (30–60 min) activity is seen in areas of brain rich in opiate receptors. Binding of [^{11}C]carfentanil is blocked by prior administration of naloxone (lower row)

Thus we can now measure the effects of drugs on neuroreceptor binding sites. Recently Louis Lasagna, a pioneering clinical pharmacologist, said: "Often we don't know how to tailor specific drugs to specific patients very well. We could do that better and make a quantum jump in efficacy without even coming up with any new drugs."

Imagine what it would be like to treat patients for hypertension with all the potent drugs available today without measuring the blood pressure. Yet psychiatrists and other physicians prescribe neurotropic drugs that affect mental function and have only the patients' subjective response to go by. We can now measure the effects of some of these drugs on specific receptors in individual patients. The dose of neurotropic drugs, such as methodone, required to achieve a specific pharmacological effect is very broad. Some patients do well on 10 mg of methodone a day, while others require 80 mg a day to remain symptom-free. Since less than one percent of the administered methodone reaches the receptors, it is likely that the broad variability of dose among individuals is related to other metabolic factors, such as liver metabolism. If we can monitor the effects of such drugs in a specific patient, it may be possible to tailor-make treatment on an individual basis. This is one of our goals in the use of a simple dual-probe detector for the study of global brain chemistry by means of positron-emitting tracers (*16*).

Studies in experimental animals and now in human beings indicate that stimulating drugs, so-called "agonist" drugs that stimulate the receptors, bring about pharmacological effects with only a small percentage occupancy of the receptors. In the case of "antagonist" drugs that block the receptors, to get a pharmacologic effect ~90 or more percent of the receptors have to be blocked.

A well-established principle in neurobiology is that some neurons and neurotransmitter systems are stimulatory while others are inhibitory. The UCLA group and others have shown that one of the characteristics of partial or focal epilepsy is hypometabolism of glucose at the site of origin of the seizures (*17,18*). Preliminary experiments in our laboratory suggest that there is increased binding of [^{11}C]carfentanil in these hypometabolic sites which suggests that perhaps there is decreased endogenous enkephalin occupying the opiate receptors in the hypometabolic region (*19*).

Among our goals is to try to find out what factors stimulate endogenous secretion of neurotransmitters, such as enkephalin. Sexual arousal may be one such factor. Sexual arousal resulted in a decrease in [^{11}C] carfentanil binding in the thalamus attributable to an increased secretion of an endogenous enkephalin, the endogenous opioid substance (*20*).

Dopamine receptors

In 1978 Kuhar and his associates used tritiated spiperone to portray the distribution of dopamine receptors in experimental animals by autoradiography (*21*). His studies were based on the development of this agent by Leysen and Laduron of Jannsen Pharmaceutica, an example of the synergistic role of the neuropharmaceutical industry, neurosciences and PET (*22,23*). To extend this approach to human beings, the compound [^{11}C]N-methylspiperone was synthesized and made possible quantitative imaging of the distribution of D_2 dopamine receptors in the living human brain (*24,25*).

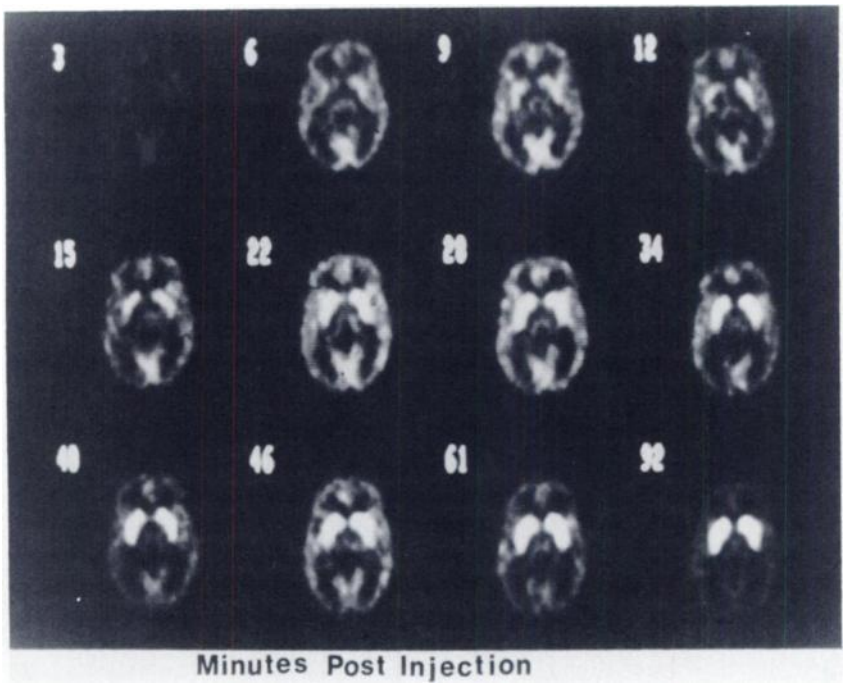

FIGURE 5
Serial images at times indicated in minutes after i.v. injection of ^{11}C-N-methyl spiperone (Reprinted with permission from *Clinical Chemistry*)

In a typical study after the injection of [^{11}C]N-methylspiperone ([^{11}C]NMSP) (Fig. 5), the tracer is initially distributed in proportion to brain blood flow but then progressively accumulates in the D_2 dopamine receptor binding sites. Since our focus is on in vivo quantification, the goal is not to "see" the caudate nucleus, or the putamen, (we can "see" these organs quite well with CT or magnetic resonance imaging). We want to measure the concentration and quantity of the receptors, and their state of occupancy by endogenous neurotransmitters or exogenous drugs. A simple initial approach to quantification is to compare [^{11}C]NMSP, the binding in the caudate nucleus, a receptor rich area, to that in the cerebellum which does not contain dopamine receptors (*26*). The fact that the rise in caudate/cerebellar activity was a linear function of time suggested that perhaps the relatively simple model could be used to quantify receptor density. We next observed that dopamine-receptor blocking drugs, such as haloperidol, decreased the slope of the line showing the rise of the caudate/cerebellum ratio as a function of time. Our results and those of the Brookhaven group (*27*) indicate a high percentage (~80–90%) of receptor occupancy in patients being treated with neuroleptic drugs, such as haloperidol.

We also observed a striking decline with age in the caudate/cerebellar ratio after 43 min and in the slope of the line relating the caudate/cerebellar activity ratio to time. In normal males between the ages of 19 and 70 yr, there was a 46% decrease. The fall in females was less, being 25% over the same age span (*26*).

Focus on quantification

A four-compartment model is useful in quantifying receptor densities with tracers, such as the irreversibly-bound tracer ^{11}C N-methylspiperone. Measurement of regional activity, such as that in the caudate nucleus includes the amount of the tracer that is bound to the receptor, the amount of free tracer in contact with the receptors, and a third component that represents nonspecific binding (*28,29*). The time-course of activity in a region, such as the caudate nucleus, can be represented by two multi-exponential curves, one describing the unblocked state and the second the blocked state, for example, after the administration of nonradioactive haloperidol prior to the second dose of [^{11}C]NMSP. The first curve includes the binding of the free ligand to the receptor; in the blocked state receptor-binding does not occur, so that the curve includes only free and nonspecifically bound [^{11}C]NMSP. Using these kinetic curves, we have all the data needed to calculate the rates of transfer of the tracer from one compartment to another, but this is not a practical approach for two reasons. The first problem is statistical errors resulting from the limited number of photons. The second is propagation of errors that result in great inaccuracies. In practice, there are several ways to measure nonspecific binding. One is to use a neutral zone, such as the cerebellum, to reflect nonspecific binding. A second approach is to compare the blocked and unblocked state in the same region, using a drug such as naloxone, to block the receptors. A third method is to use an active and inactive isomer, for example, levetimide is an inactive

isomer of dexetimide which is bound by muscarinic cholinergic receptors. The levetimide tracer reflects nonspecific binding (*30*).

We can also use a three-compartment model if we assume that the free and nonspecifically bound ligand are in instantaneous equilibrium.

In choosing a specific ligand to quantify receptors under specific circumstances, it is important to differentiate the factors that influence the rate of binding of the tracer to the receptor. Under certain conditions one may be measuring simply the delivery of the ligand to the receptors. Under other circumstances, the rate of accumulation of the tracer in a region such as the caudate nucleus will be sensitive to the number of receptors in the region. If the number of receptors is great and therefore the rate of binding of the free ligand is very fast, the rate-limiting step will be the delivery of the tracer to the site, rather than receptor number. Under such circumstances, one trick is to lower the number of receptors by the administration of a standardized blocking dose of a drug such as haloperidol. Then the rate of accumulation of the subsequently-administered tracer ligand will reflect the binding of the ligand by the receptor.

A single equation can describe the increase with time in concentration in a particular region, such as the caudate. Following the method of Patlak (*31,32*), as well as that of Gjedde (*33,34*), if one graphs the caudate/plasma activity against normalized, integrated arterial plasma concentration (Fig. 6), after ~20 min a steady state is reached, and the relationship is a straight line, the slope of which is $\frac{k_3 \cdot k_1}{k_2 + k_3}$ where the rate constants represent those shown in Fig. 7. If we measure the rate of binding to the receptor, k_3, in both the blocked and unblocked states, we can calculate receptor density, using the following equation:

$$\beta_{max} = \frac{\eta}{(k_{off} \cdot MW)} \frac{[\text{Serum haloperidol}]}{\frac{1}{k_3 \text{ blocked}} - \frac{1}{k_3 \text{ unblocked}}}$$

The above equation is used to calculate dopamine receptor density. β_{max} = receptor concentration; η = the partition coefficient of haloperidol between brain and blood; k_{off} the dissociation rate constant; k_3 the rate of accumulation in the blocked and unblocked state.

One of our most striking findings until now is that in schizophrenic patients (including patients never previously treated with drugs) the concentration of D_2 dopamine receptors in the caudate nucleus is higher than in age and sex matched controls. Although the number of patients is relatively small, if our results can be confirmed, they indicate that an increase in D_2 dopamine receptors in the caudate nucleus may be involved in the pathogenesis of schizophrenia. A "dopamine-receptor" hypothesis has been suggested by others in the past, based on the fact that schizophrenic patients respond to treatment with dopamine receptor blocking agents, the fact that chronic amphetamine administration at times produces a syndrome similar to schizophrenia, and the finding in autopsy studies by Crow et al. in London, and Lee and Seeman in Toronto which indicate that certain schizophrenia patients have increased dopamine receptors in the caudate and putamen (*35–37*).

Thus we can now estimate dopamine levels using

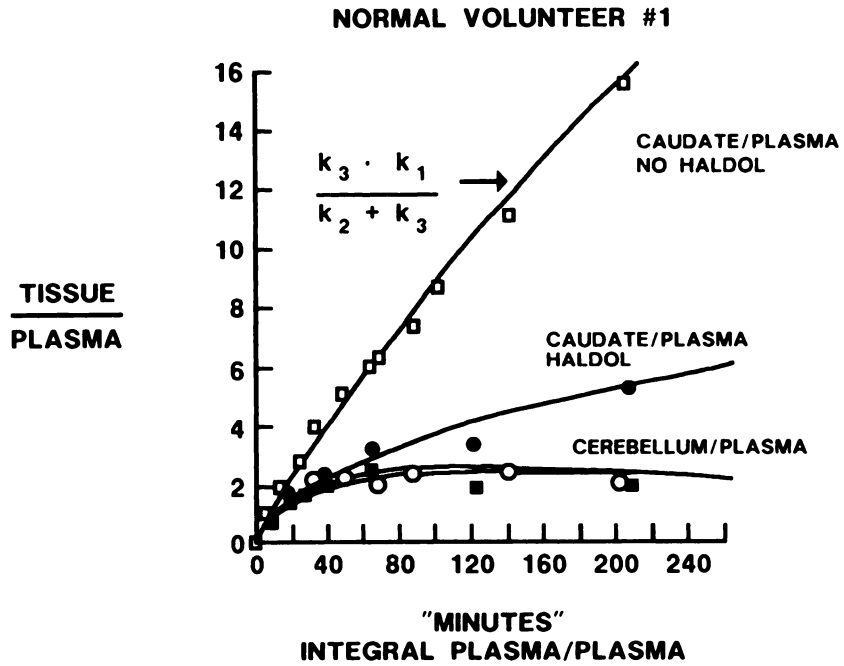

FIGURE 6
Accumulation of ^{11}C-N-methyl spiperone in caudate nucleus and cerebellum as function of integrated plasma activity of tracer, before and after a dose of haldol that blocks accumulation of tracer by D2-dopamine receptors

IDEAL TRACER CHARACTERISTICS

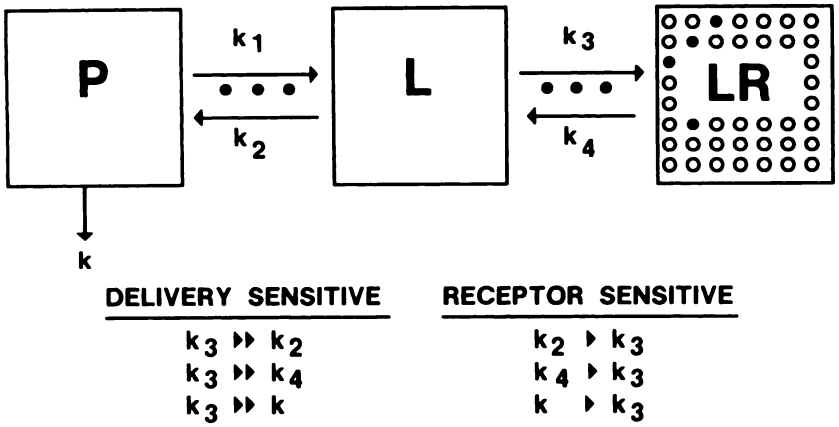

FIGURE 7
Three compartment model describing accumulation of radiolabeled ligands from plasma (P) through free ligand (L) and binding to receptor (LR). Depending on binding characteristics of tracer used and relative number of ligand and receptor molecules, rate of accumulation will be a function of rate of delivery of tracer to receptor sites or receptor number

tracers such as L-dopa, or dopamine receptor concentrations, using tracers such as ^{11}C-N-methylspiperone or [^{11}C]raclopride and [^{18}F]deoxyglucose to look at glucose metabolism to reflect neuronal activity.

Brodie, Wolf et al. at NYU and Brookhaven have found that glucose metabolism in the caudate nucleus of schizophrenic patients in the untreated state, is less than that in normal persons (*38*). When such patients are treated with neuroleptic drugs, there is increased glucose metabolism in the caudate, where the levels had previously been low. Alavi and colleagues have reported similar results, but have emphasized that in schizophrenia cortical glucose metabolism is reduced to an even greater degree than that in the caudate nuclei (*39*).

In the *City of God*, Augustine said: "Some medical men called anatomists have disected the bodies of the dead to learn the nature of disease. Yet those relations which form the concord or as the Greeks called it, the harmony of the whole body, no one has been able to discover, because no one has been audacious enough to seek for them."

What the Greeks call harmony may be reflected in regional secretion of neurotransmitter substances and the status of their receptors. Certain neurotransmitters and their receptors such as those involving dopamine, enkephalin, and serotonin may not be limited to point-to-point neurotransmission, but may modulate neuronal activity over regions of the brain. Other neurotransmitters, such as acetylcholine or norepinephrine, are probably involved chiefly in neurotransmission across specific synapses. For example, at the neuromuscular junction, acetylcholine and acetylcholine receptors seem to be closely linked.

Clinical PET

A widely debated topic is the clinical role of PET. Hippocrates said: "It is disgraceful in every art and more especially in medicine, after much trouble, much display, and much talk to do no good after all."

PET studies of brain chemistry can not only teach us about how the structure of the brain is related to the function of the mind, but also have practical applications. Among the most useful are studies of patients with brain tumors. Carbon-11 methionine is being used routinely at Johns Hopkins and in Sweden to delineate brain tumors and differentiate them from the effects of therapy, including radiation (*40*). Epilepsy is a second area of clinical usefulness of PET studies. Areas of hypometabolism delineated with [^{18}F]deoxyglucose help determine the areas of the brain from which seizures originate (*41*). If the patients cannot be successfully treated with drugs, they become candidates for surgery.

The future

One of the most important discoveries in the history of science was the discovery by Hornykiewicz and his Viennese colleagues that dopamine is deficient in the corpus striatum of patients with Parkinson's disease (*42*). This discovery that dopamine levels in the caudate were reduced to ~15% of normal led to the development of L-dopa therapy of Parkinson's disease. A simple amino acid, such as L-dopa, given to a patient with what was believed to be a degenerative disease could result in tremendous improvement in mental and motor functions. The dramatic effect of L-dopa can be even more strikingly demonstrated in those unfortunate persons with MPTP toxicity to the point that they are totally immobilized. When treated with L-dopa, they can function almost normally (*43*). Despite the unbelievable complexity of function of the billions of neurons in our brains, in a disease such as Parkinson's disease, a simple chemical can make all the difference. The example is one of the reasons for the excitement in the study of diseases such as Alzheimer's disease, depression, anxiety and other important diseases of the mind and brain.

The technology of nuclear medicine makes possible

measurement of in vivo chemistry in an absolute, as well as a relative sense, extending to living human beings what Yalow and Berson accomplished in in vitro studies of body fluids. Discoveries concerning the chemical basis of mental functions are as revolutionary today as those in atomic physics at the turn of the century or genetics in the 1950s. The history of the living world can be summarized as the elaboration of ever more perfect eyes within a cosmos in which there is always something more to be seen.

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