

*Positron-Emission Tomography
in Schizophrenia Research*

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The Use of Positron-Emission Tomography in Identifying and Quantitating Receptors Involved in Schizophrenia

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Schizophrenia is a devastating mental disorder that is the focus of a great deal of research. Some symptoms of the disease, such as auditory hallucinations and delusions, can be ameliorated with drug treatment, whereas other symptoms, such as social withdrawal and cognitive decline, remain uncontrolled. It is possible that these latter symptoms that are often termed "negative symptoms" are the result of anatomical and neurochemical abnormalities, whereas those symptoms of the disease such as auditory hallucinations that are termed "positive symptoms" may be a result of only neurochemical disorders (Crow 1986; Trimble 1987; Weinberger 1988a).

The drugs used to treat schizophrenia are designated neuroleptics. The term *neuroleptic* was chosen to emphasize the similarity of pharmacological profiles of drugs with entirely different chemical structures (Carlsson 1978). Especially prominent features of the effects of neuroleptics include the following: a state of affective indifference; a decrease in locomotor activity; a decrease in excitation, agitation, and aggressiveness; and an antipsychotic action in patients with acute as well as chronic psychoses.

AFFINITY VERSUS EFFICACY

Since the first use of neuroleptics for the treatment of schizophrenia in 1952 (Delay et al. 1952), there has been growing evidence that the antipsychotic drugs exert their influence at least in part by reducing dopaminergic neuronal activity mediated by the D₂ receptor (Seeman

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1981, 1987). The dopamine hypothesis is widely accepted in explaining the neuropharmacological abnormalities that occur in schizophrenia. The central tenet of the hypothesis is that people who have the disease have an apparent hyperactivity of the dopaminergic mechanisms in critical brain regions. There are several lines of evidence to support this hypothesis, and these have been outlined by Seeman (1987). They are

1. The clinical side effects of the neuroleptics
2. The psychotomimetic effects of dopamine-mimetic drugs
3. Neuroleptic acceleration of catecholamine turnover
4. Antipsychotic potency correlates with D₂ blockade in responders
5. Elevated density of D₂ receptors in schizophrenia.

By far the most convincing of these observations is the correlation of clinical antipsychotic potency of these drugs with the affinity of the drug for the D₂ receptor. The correlation between the clinically efficient dose and the binding affinity of the neuroleptic drugs for D₂ receptors is given in Figure 5-1 (data from Closse 1984; Peroutka and

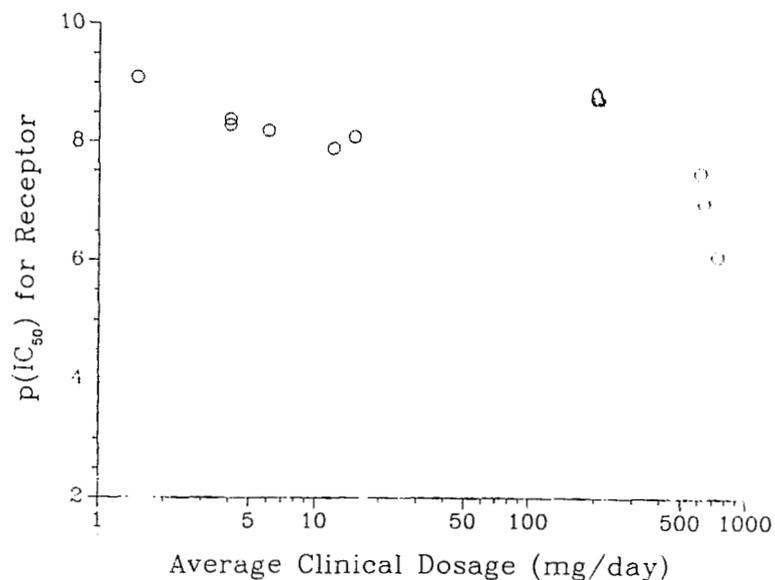


Figure 5-1. Plot of the affinity of common neuroleptic drugs for the D₂ receptor with the typical clinical dosage. Clinical dosages taken from Peroutka and Snyder 1980. Values for the p(IC₅₀)'s taken from Closse et al. 1984.

Snyder 1980). This correlation can be compared with the correlation with other receptor subtypes. The plot of the affinity for the D₁ receptor is given in Figure 5-2. There is no correlation with this site. The similar plot for serotonin receptors is given in Figure 5-3. The plot of the affinity for the muscarinic receptor in Figure 5-4 shows a slight inverse correlation with the clinical dose. Figure 5-5 shows the plot for the sigma receptor that demonstrates no correlation between clinical dose and receptor affinity (Closse 1984; Peroutka 1980). The sigma receptor was initially thought to represent a subtype of the opiate receptors. However, the inability to block the behavioral effects of sigma drugs with naloxone and the opposite stereospecificity of opiate and sigma drugs gave evidence that the sigma receptor is different from the opiate receptor. The moderate potency of sigma drugs on phencyclidine (PCP) receptors then led to the belief that the PCP receptor mediated the action of sigma drugs (Snyder and Largent 1989). Sigma receptors are now classified as a separate receptor type. The high affinity of haloperidol to sigma receptors has generated interest with respect to their role in psychoses.

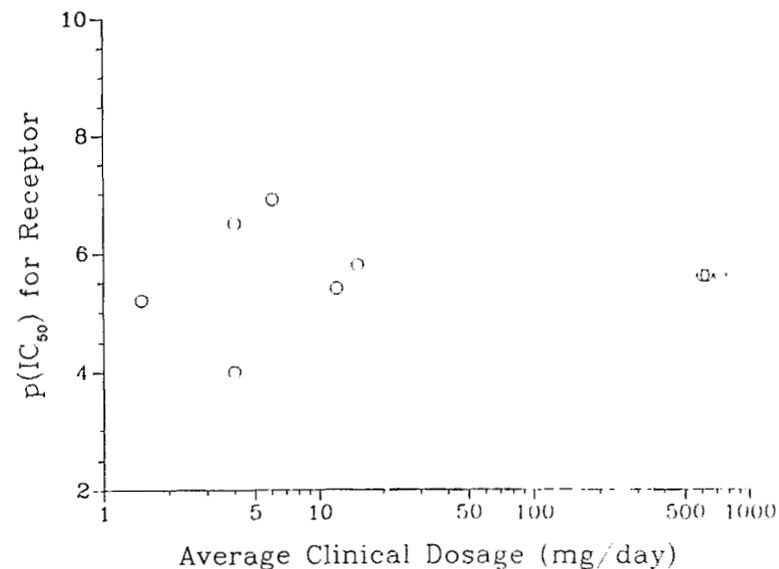


Figure 5-2. Plot of the affinity of the common neuroleptic drugs for the D₁ receptor with the typical clinical dosage. Clinical dosages taken from Peroutka and Snyder 1980. Values for the p(IC₅₀)'s taken from Closse et al. 1984.

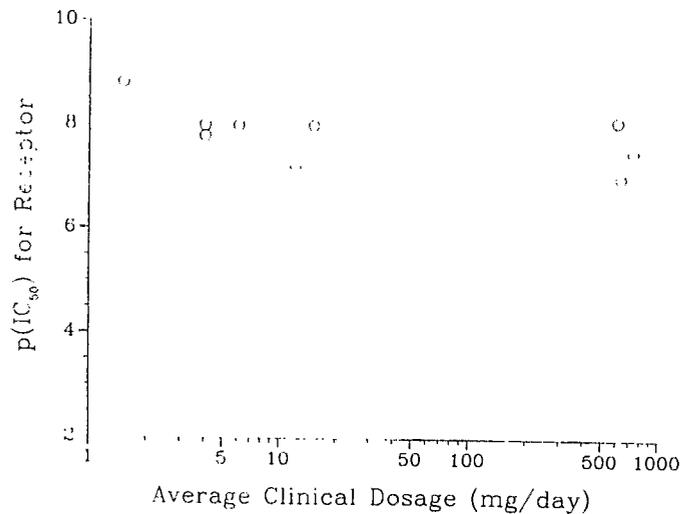


Figure 5-3. Plot of the affinity of the common neuroleptic drugs for the serotonin receptors with the typical clinical dosage. Clinical dosages taken from Peroutka and Snyder 1980. Values for the $p(IC_{50})$'s taken from Closse et al. 1984.

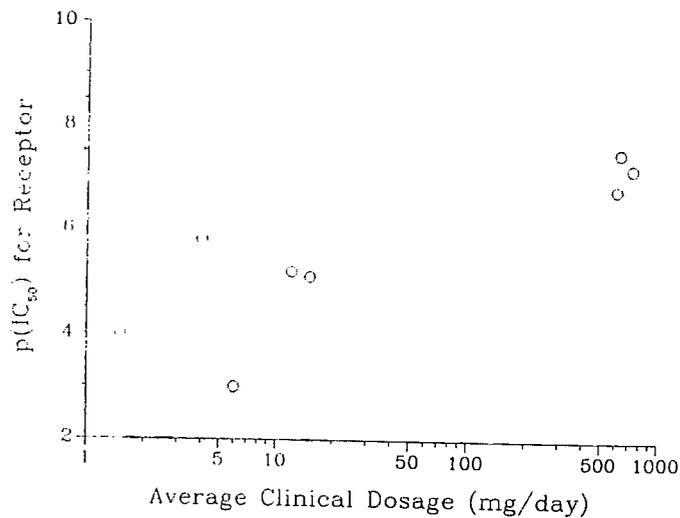


Figure 5-4. Plot of the affinity of the common neuroleptic drugs for the muscarinic receptors with the typical clinical dosage. Clinical dosages taken from Peroutka and Snyder 1980. Values for the $p(IC_{50})$'s taken from Closse et al. 1984.

POSTMORTEM STUDIES

Postmortem studies of schizophrenic patients have shown that the D₂ receptor level was elevated in some subjects in this group (Seeman 1984). There was a bimodal distribution of receptor densities, one mode of which was significantly higher than the normal control group. The question that immediately arose was whether this elevation was due to the disease or resulted from the chronic use of neuroleptic drugs. It has been shown in animals that prolonged blockade of D₂ receptors elevates the number of receptors by approximately 30% (Seeman 1987). A study of postmortem brains of schizophrenic patients on haloperidol therapy in comparison with those who had been off drugs for 3 months and normal control subjects demonstrated a significant increase in D₂ receptor number only in those patients who were on neuroleptics at the time of death (Kornhuber et al. 1989b). Positron-emission tomography (PET) has the ability to ascertain the answer to this question directly because it is, in principle, possible to obtain information that may be used to determine the number of receptors available for binding.

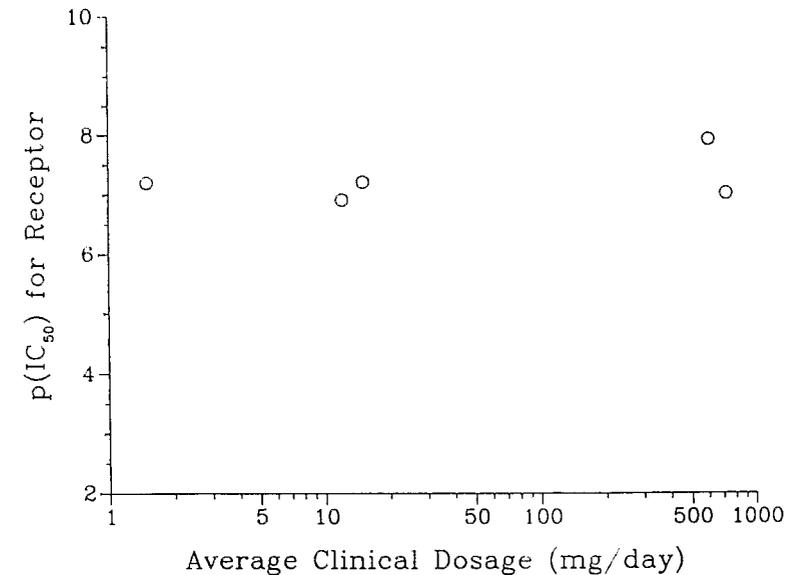


Figure 5-5. Plot of the affinity of the common neuroleptic drugs for the sigma receptors with the typical clinical dosage. Clinical dosages taken from Peroutka and Snyder 1980. Values for the $p(IC_{50})$'s taken from Closse et al. 1984.

PET STUDIES

PET is the only technique available at present that can accurately quantitate the receptor density in the living human brain, and several studies have been carried out in an attempt to accomplish this feat. There is a considerable amount of controversy at present as to the best technique to use to measure this receptor density, but there seems to be general agreement within the field that PET can be used to quantify receptor density in the living human brain once the intricacies of the experiment are understood. The controversy in general revolves around the choice of radiolabeled ligand used to measure receptor density. Some groups promote the use of low-affinity ligands that give dynamic information about the receptor availability, and other groups promote the use of very high-affinity ligands that are not displaced by endogenous ligands. These two techniques should in theory give the same results, but in fact they do not (Andreasen 1988). The explanation of these discrepancies must await further experimentation.

Another observation that requires further investigation is that in most patients, the symptoms of schizophrenia are decreased only after several weeks of treatment with neuroleptics. This corresponds to a fall in the homovanillic acid (HVA) concentration after the initial increase observed when neuroleptic therapy is begun. PET may be able to shed light on this phenomenon as one is able to correlate plasma drug levels with the receptor availability. Some work has been carried out that shows a good correlation between the receptor occupancy and the plasma level of the drug (Cambon et al. 1987; Smith et al. 1988; Wolkin et al. 1989).

The definitive test of the dopamine hypothesis of schizophrenia must also await a better understanding of the involvement of other receptor systems in the disease. It is not clear at this point in time whether the dopamine system is the only neurotransmitter system involved in the disease or whether there are several systems involved. This latter possibility seems more likely in view of the feedback loops known to exist between the dopamine system and other receptor systems (Vinick and Heym 1987). Compounds acting at sigma sites, for example, can alter dopaminergic function in the absence of direct interactions with the dopamine receptors. Some of the most effective "atypical" neuroleptics act at the sigma sites, as do some of the typical neuroleptics such as haloperidol, which binds to both D₂ and sigma sites with nearly equal affinity.

It has been suggested that antipsychotic activity and extrapyramidal side effects (EPS) may reside in different pathways in the brain (Carlsson 1978). The antipsychotic effect may reside in the limbic

structures and the extrapyramidal effects in the striatum. This hypothesis could be tested with PET if the relevant labeled drugs were available.

There is a renewed interest in the atypical neuroleptic clozapine in part because of the minimal ability of this drug and other atypical drugs to produce EPS. One hypothesis for the mode of action suggests that the relative affinity of this drug for the serotonin receptor system in contrast to the affinity for the dopamine receptor system may have a significant role in the ability of this drug to relieve some of the symptoms of psychosis while producing minimal EPS (Matsubara and Meltzer 1989).

The role of other receptor systems in producing EPS is also unclear (Creese 1985). There is some indirect evidence that there is a correlation between the amount of time a neuroleptic is bound to a receptor and the EPS. The longer the drug is bound the greater the EPS.

METHODS FOR THE MEASUREMENT OF RECEPTOR DENSITY WITH PET

Receptor imaging is possible with PET because of the high sensitivity of PET when compared with other imaging modalities. Most of the receptors of interest in schizophrenia exist in nanomolar concentration in the living brain. As a result, it requires a technique that can measure these levels accurately. The PET measurement of the concentration of the radiolabeled drug does not give the information needed to directly make an assessment of the receptor number or affinity. To make these assessments requires the use of a model of the system (Frost 1988). Simpler methods may be used to estimate some of the parameters once these estimates have been shown to be valid by doing a complete kinetic analysis of the system. The application and interpretation of the PET data are subjects of some controversy and the resolution should give insight into the physiological processes involved.

There are two basic methods to determine the distribution of ligands in specific areas of the brain. The first of these is the direct visualization of the ligand bound to the receptor that requires that the ligand of interest be tagged with the radiolabel. The second indirect method is to use a radiolabeled ligand specific for a particular receptor and then try to block the uptake of the receptor with the compound of interest. The first method is certainly preferable if the radiolabeled compound can be synthesized, since this method also allows the regional distribution to be determined and gives evidence of the effects of transport and nonspecific binding.

Direct Visualization

The most straightforward method for determining the *in vivo* distribution and binding characteristics of a new ligand is to label the ligand with a positron emitting label. This has been done with a number of compounds (Fowler and Wolf 1982; Kilbourn 1990). The bio-distribution can be determined directly from the PET image and can be compared directly with the expected distribution based on animal data and the known affinity of the compound with receptor subtypes. The effects of the lipophilicity of the drug as well as any transport system can be evaluated with the application of the appropriate model to the PET data. The receptor that has been studied most thoroughly is the D₂ receptor.

Blocking Experiments

If the radiolabeled ligand of interest can be synthesized, blocking experiments can be done to determine the type of receptor to which it is bound. Often some information as to the receptor type can be inferred from the literature concerning the *in vitro* data and from the regional distribution of the radiolabeled compound, but the best method is to block the drug with a receptor-specific ligand whose distribution is known and see how much the uptake in the region of interest is decreased. The difference between the receptor affinity *in vitro* and the distribution *in vivo* is often quite striking. The role of transport and metabolism is considerable and cannot be ignored when determining the clinical efficacy of a particular drug.

If the radioligand binds to several types of receptors, as is the case with many of the neuroleptics, it is necessary to block one type of receptor while observing the uptake in another. This type of experiment can also often shed light on the amount of nonspecific binding of the radioligand.

Methods of Evaluation

There are many methods being used by PET groups to try and gain useful quantitative information about the receptor system under study. These are those that are irreversibly bound over the usual course of the PET experiment and those that are reversibly bound over the course of the experiment. The most familiar example of the first type (irreversibly bound) is *N*-methylspiroperidol labeled with either fluorine-18 (¹⁸F-NMS; Arnett et al. 1986) or carbon-11 (¹¹C-NMS; Wagner et al. 1983). This ligand does not reach equilibrium during the course of the experiment. This can be easily determined by plotting the bound-free ratio as a function of time for the com-

pound. The bound-free ratio is determined by dividing the concentration of radioligand in a region of interest by the concentration of radioligand in a region with little or no specific binding of the ligand. If the compound is at equilibrium with the tissue, then this ratio should be a constant. In the case of ¹⁸F-NMS, the ratio is still increasing even after 4 hours. Since NMS does not reach equilibrium, the mathematical models that make this assumption cannot be used to determine the parameters of the binding.

There are several methods that have been successfully used to analyze the data from ¹⁸F-NMS experiments. The simplest of these is the "ratio index" method, which involves plotting the ratio of an area of specific binding to an area of nonspecific binding over time. In the case of ¹⁸F-NMS, this means plotting the striatum value over the cerebellum value versus time. It has been shown that this can be related to the receptor density if the assumption is made that the affinity (K_d) values are constant. This technique has been used to determine the extent of receptor occupancy during treatment with neuroleptics (Smith et al. 1988; Wolkin et al. 1989). This method has the distinct advantage of being very simple to use and not requiring arterial blood sampling.

The next in the order of complexity are the Patlak-Gjedde graphical methods, which use the plasma activity value derived from the arterial blood curve and the incorporation of radioactivity in the striatum (Patlak and Blasberg 1985; Patlak et al. 1983; Wong et al. 1986a, 1986b). The derivation of this model is quite involved and requires several assumptions to be made. This technique has been used by several groups for the analysis of labeled NMS data, and the method has been extended to other compounds that are not receptor binding in nature. In a variation of this method, the plasma curve can be replaced with the cerebellar curve with similar results. A rearrangement of the basic equations used to derive the Patlak-Gjedde methods leads to the incorporation quotient as first described by Patlak (1981). The advantage of this method is that it is the ratio of two large numbers (the activity in the region of interest and the plasma integral to that point in time) that tends to minimize the statistical noise in the image as well as variations in the plasma curve.

The most complex method of modeling that can be used for this type of irreversibly bound agent is the three-compartment four-parameter kinetic model or the four-compartment six-parameter kinetic model (Logan et al. 1987; Wong et al. 1986c). Both of these models require an arterial input function as well as a metabolite analysis of the activity in the blood to be accurate. The debate here is whether one is justified in using six parameters when four parameters

fit the data just as well. It can be argued that the use of the six parameters most closely resembles what is occurring in the body, but considering the complexity of the actual physiological processes and the simplifications that have already been made in using the six-parameter model, it may not be significantly worse to use the simpler four-parameter model. This is a direct result of the fact that the data themselves have uncertainties of 5–10% associated with them. The uncertainty in the data arises from the scanning and reconstruction procedure, the blood counting, and the plasma analysis. It is not possible at this time to achieve lower noise levels in PET.

In the case of the reversibly bound compound, things can in principle be simpler. It must be demonstrated that the system is truly at equilibrium (Sedvall et al. 1986). Equilibrium is defined as that point when the rates of the forward and reverse chemical reactions (or association reactions) are equal. In some instances, compounds that appear to be at equilibrium are in reality not. An example is [^{14}C]cocaine in humans. If the bound-free ratio (striatum divided by cerebellum in this case) is plotted versus time, the curve goes through a maximum and then decreases. This suggests that the system was momentarily at equilibrium with respect to influx and efflux, but that the efflux of the compound from the tissue could not keep up with the declining levels of tracer in the bloodstream. Thus, the equilibrium methods of analysis could be used in this case only at the time point where the curve went through a maximum. The Patlak-Gjedde methods using the slope of the line of tissue/plasma versus plasma integral/plasma also cannot be used, since the plot of the function is never linear. The incorporation quotient has been used in this case, since the terms that are dependent on time cancel out of the equations (Fowler et al. 1989a, 1989b).

In general, the method of analysis is fairly specific for a particular radioligand, and a method of analysis must be found that is valid for that particular radioligand. The graphical methods are easy to use and seem to be valid for most irreversibly bound ligands. The full kinetic analysis requires a significant amount of computer time and someone who understands how to manipulate the parameters to obtain the best solution to the equations (Zeeberg et al. 1988a, 1988b).

DOPAMINE RECEPTORS

D₂ Receptors

The concept that some forms of schizophrenia are inextricably entwined with the D₂ receptor is well accepted. The extremely high correlation between the potency of the neuroleptic drugs and their

affinity for the D₂ receptor has been clearly demonstrated. There are many complexities even in our present understanding of the dopamine system that can cause difficulties in the interpretation of the data. The current model of the dopamine receptor system is given in Figure 5-6. The feedback loops of the synthesis-modulating autoreceptor (SMAR) and the release-modulating autoreceptor (RMAR) as well as the catabolic pathways may quickly respond to the presence of dopamine in the synaptic cleft. The speed of this response will affect the level of the dopamine during an experiment and could alter the measured value of the receptor concentration depending on the binding characteristics of the ligand used to measure receptor occupancy.

The flow of dopamine into the synapse is regulated at several points, and the drugs used to maintain the dopamine level in the synaptic cleft may cause an effect by acting at any of these points. The classic neuroleptics such as haloperidol, chlorpromazine, and fluphenazine block the D₂ receptor in the postsynaptic membrane. This causes the

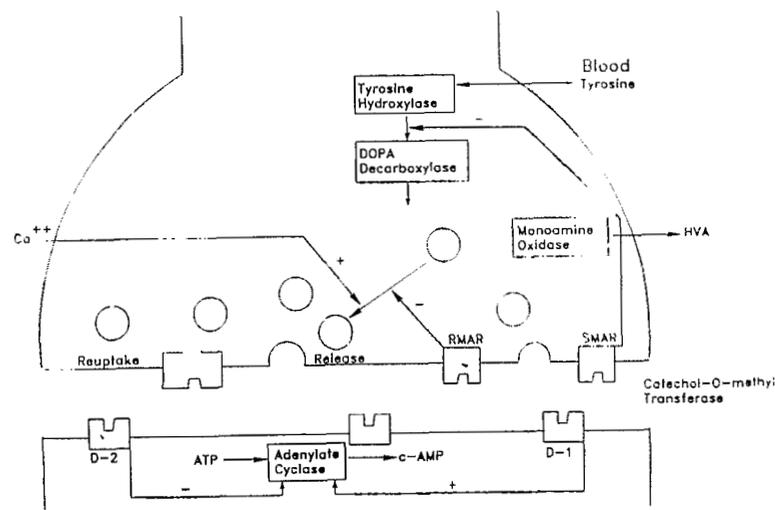


Figure 5-6. Schematic diagram of the dopamine receptor synaptic cleft with the associated feedback loops. HVA = homovanillic acid. RMAR = receptor-modulated autoreceptor. SMAR = synthesis-modulated autoreceptor. A positive symbol (+) indicates that this agent stimulates the next step toward the release of the neurotransmitter, whereas a negative symbol (-) indicates an inhibition of the following step. Rectangular boxes represent enzyme systems in the neuron.

amount of dopamine in the synaptic cleft to increase and blocks the transmission of the signal along the neuron. Drugs such as cocaine or nomifensine that block the reuptake of the dopamine into the presynaptic neuron also increase the levels of dopamine in the synaptic cleft. The difference is that the neuroleptics cause a diminution of the signal being passed through the synapse, whereas cocaine, nomifensine, and similar drugs allow the signal to be passed and increase sensitivity.

PET has been used to assess whether there are changes in the number of D₂ receptors in schizophrenic patients. Previous postmortem studies had demonstrated that some schizophrenic patients had increases in the number of D₂ receptors. The results were confounded by the fact that they were not done in the living human brain and that most of the brains studied were from patients who had a history of previous neuroleptic treatment. The PET studies were able to measure the D₂ receptor density in the brain of living schizophrenic patients who had never received neuroleptic treatment (Farde et al. 1986, 1987a; Wong 1986a). The two studies came to opposite conclusions so that no definitive answer is yet available. It is not clear at this point if the difference lies in the patients chosen or in the technique used to measure the receptor density. A report has recently been written about the various possibilities (Andreasen et al. 1988), but no definite conclusion had been reached at the time of this writing. It seems most likely that the answer lies in the affinity of the two ligands used to determine receptor density. It has been clearly shown in vitro that the affinity of the ligand used toward the D₂ receptor will have an effect on the apparent receptor density as determined with PET (Seeman et al. 1989). If the ligand has a high affinity for the receptor as NMS does, then the receptor concentration as measured by PET will be nearly constant as the concentration of endogenous dopamine is changed. If, on the other hand, the affinity of the ligand is close to that of dopamine, the apparent receptor density will change as dopamine concentration in the synapse is changed, since dopamine will compete effectively with the labeled drug for the available sites.

In interpreting these results, it should be kept in mind that there may be a group of schizophrenic patients with elevated D₂ receptor levels and a group with no D₂ receptor density increase. The work of Seeman et al. (1984) in postmortem brains of schizophrenic patients in which a bimodal distribution of D₂ receptors was observed supports this notion. This distinction may also be of relevance to the responder versus nonresponder categories of schizophrenic patients, i.e., those who respond favorably to neuroleptic treatment as opposed to those who do not respond well to this therapy (Wolkin et al. 1989).

Schizophrenia may represent a heterogeneous disease with sub-categories corresponding to different pathological processes that produce similar behavior patterns (DeLisi et al. 1985b).

D₁ Receptors

D₁ receptors have not until recently been considered as relevant in the etiopathogenesis of schizophrenia. A recent study has shown (Hess et al. 1987) that in postmortem brains the D₁ receptor density was significantly decreased in schizophrenic patients as compared with a control group. This investigation also showed an increase in the D₁ receptor affinity (K_d) in the brains of schizophrenic patients. In addition, the schizophrenic individual showed an increase in the D₂ receptor density (56%). It is at odds with another study that showed no such increase in postmortem brains of schizophrenic patients (Pimoule et al. 1985).

Evidence suggests that there may be a synergistic effect between the D₁ and D₂ receptor systems, and certain dopamine-mediated behaviors are antagonized by combinations of D₁ and D₂ antagonists more effectively than by either one of them alone (Beaulieu 1987; Carlson et al. 1987). The ratio of activity of the D₂ to the D₁ receptor may be important in understanding psychopathology in schizophrenic patients (Clark and White 1987). Preliminary PET studies have been done to map the D₁ receptor distribution in the human brain (Farde et al. 1987a, 1987b). PET studies are underway to characterize the ability of different neuroleptics to block the D₁ versus the D₂ receptors in the human brain and the relationship between their D₁/D₂ blocking ability and their effectiveness (Lundberg et al. 1989).

SIGMA RECEPTORS

The sigma receptor was first identified by the binding of *N*-allylnormetazocine (NANM) in the brain of rats (Martin et al. 1976). It was clearly different from the PCP receptor that was in large part responsible for its discovery and that is associated with the *N*-methyl-*D*-aspartate (NMDA) receptors. A classification system to distinguish the principal differences between the sigma site and the PCP site has been proposed (Quirion et al. 1987). Some of the typical neuroleptic drugs such as haloperidol show strong binding to the sigma sites. In fact, haloperidol has an affinity for sigma receptors at least as strong as its affinity for the D₂ receptor. It has been shown that sigma-selective drugs injected into the brains of rats cause movement disorders that are similar in nature to the side effects caused by the common neuroleptics (Walker et al. 1988). The distribution of sigma sites in

postmortem human brain has been determined using ^3H -labeled haloperidol (Table 5-1; Weissman et al. 1988).

Role of Sigma Receptors

There has been growing interest in the role of sigma receptors in the course of mental disorders since the identification of these receptors as a class of receptors separate from the opiate receptors. There have been several studies relating the affinity of these receptors with the psychiatric disorder of schizophrenia (Largent et al. 1988; Snyder and Largent 1989). It is known that many of the more effective neuroleptics also bind to the sigma receptor. It has been suggested that screening of new drugs for the treatment of these disorders may be done by determining the affinity of a new drug for the sigma receptor (Manallack et al. 1988).

It is hoped that new drugs that act through different mechanisms from the classic neuroleptics may offer a chance for effective therapy that does not have the commonly associated side effects. One mechanism of action that has been receiving considerable attention is through the sigma receptors. Models using rodent behavior as a test have been made on several drugs, and some promising drugs have been discovered. It may be possible to label these drugs with a positron-emitting compound and thereby determine the distribution and relative receptor occupancy of a new drug. The experience with ^{18}F -labeled haloperidol has shown that receptor affinity is not the only

Table 5-1. Distribution of sigma receptors in the human brain

Brain region	Receptor density (fmole/mg protein)
Cerebellar cortex	130 \pm 8
Orbitofrontal cortex	111 \pm 18
Nucleus accumbens	110 \pm 23
Occipital pole cortex	106 \pm 15
Frontal pole cortex	101 \pm 5
Superior temporal gyrus	97 \pm 4
Somatosensory cortex	86 \pm 16
Caudate nucleus	84 \pm 17
Hippocampus formation	73 \pm 22
Substantia nigra	71 \pm 8
Thalamus	58 \pm 14
Cervical spinal cord	56 \pm 7
Pontine nuclei	45 \pm 9

Note. Receptor densities are means \pm SD.

Source. Data from Weissman et al. 1988.

factor that needs to be considered when trying to find new drugs that may offer therapeutic benefit.

Examples of Sigma Drugs

Rimcazole shows some efficacy in the treatment of schizophrenia and is essentially inactive at the D_2 , S_2 , and other receptor sites (Snyder and Largent 1989). This drug is bound with good efficiency to the sigma sites in the brain and may be giving the therapeutic effect through this pathway (Beart et al. 1989).

The distribution of ^{18}F -haloperidol in the human brain shows how the sigma receptors may be bound by this drug (D. J. Schlyer, C. Y. Shiue, J. S. Fowler, et al., 1990, unpublished observations). There can be little doubt that some of either the primary effects of haloperidol or the extrapyramidal side effects of the drug are caused in part by the binding to the sigma receptors. To date it has not been possible to specifically block the sigma receptors with another drug in humans to determine the difference in uptake.

In the area of psychopharmacological research, it has been shown that psychoactive drugs that bind with high affinity to the sigma receptor tend to be more effective in alleviating the "negative symptoms" of schizophrenia such as depression and anxiety in those patients in whom the drugs are effective, whereas psychoactive drugs that have a high affinity for the D_2 sites are more effective in alleviating the "positive symptoms" of schizophrenia.

PET can play a role in the evaluation of these hypotheses by allowing measurement of the in vivo affinity of these psychoactive drugs to the sigma receptor and by determining, in vivo, the possible disruption in the sigma receptors of subgroups of schizophrenic patients. The actual availability of these drugs can be quite different from that predicted on the basis of the in vitro receptor affinity. It is the availability in living humans that is the critical factor in the effectiveness of these drugs.

OTHER RECEPTOR TYPES

Other receptor systems such as the serotonin, gamma-aminobutyric acid (GABA), and the excitatory amino acid NMDA have also been implicated in the etiopathogenesis of schizophrenia (Hanada et al. 1987; Kerwin et al. 1988). One strategy to test the involvement of a given neurotransmitter in schizophrenia has been to correlate the therapeutic efficacy of a neuroleptic with the affinity for a particular type of receptor site. This task is a difficult one in the sense that the known correlation between drug efficacy and D_2 receptors may overshadow other weaker interactions. One such study was carried

out with 22 neuroleptics and serotonin, α -adrenergic, and histamine receptors (Peroutka and Snyder 1980). The clinical doses of the neuroleptics used correlated extremely well with the affinity for the D₂ receptor but not at all with the other receptor systems. It may well be that the binding at these other systems has a powerful effect on the extrapyramidal symptoms demonstrated in patients on neuroleptic therapy.

This strategy has also been utilized to characterize the unique therapeutic profile of clozapine, an antipsychotic agent effective for the alleviation of "negative symptoms." In the case of clozapine, its therapeutic efficacy has been related by some to its ability to block serotonin receptors and by others to its ratio of D₁/D₂ receptor blockade (Meltzer et al. 1989). Preliminary work with PET to monitor the distribution and blocking of clozapine in the brain has been achieved with [¹¹C]clozapine (Lundberg et al. 1989). This study showed a widespread distribution in the cortex and subcortical structures. No blocking experiments were done to determine the nature of the binding.

Serotonin

Another strategy has been to measure the concentration of the different receptor types in the brain of diagnosed schizophrenic patients. Postmortem studies have demonstrated decreased serotonin receptors in brains of schizophrenic patients (Bennett et al. 1979). It is known that most of the neuroleptic drugs have some serotonergic component in their binding characteristics (Mumford et al. 1978). Indirect evidence is also provided by studies investigating regions with a high density of serotonergic receptors such as the frontal cortex. These studies appear to show that many patients with schizophrenia manifest clinical symptoms suggestive of prefrontal cortex dysfunction (Weinberger 1988b). There have been several PET studies to determine the metabolic rate in the prefrontal cortex of schizophrenic patients (Buchsbaum et al. 1984; DeLisi et al. 1985a; Farkas et al. 1984; Widen et al. 1981; Wolkin et al. 1985). The reports are conflicting and no clear picture has emerged, but several studies suggest a hypofrontality (Buchsbaum et al. 1984; Wolkin et al. 1985).

NMDA Receptors and Others

Glutamate can be neurotoxic, an effect mediated in part by the NMDA receptor complex. The role of this complex in schizophrenia is currently under investigation with PET using ¹¹C-labeled MK-801 as a PET tracer for the NMDA receptor (Wong et al. 1989). This is an application of PET to confirm in vivo the results obtained in

postmortem brains using ³H-labeled MK-801 (Kornhuber et al. 1989a).

The role of the other receptor systems in the etiopathogenesis of schizophrenia and their role in the clinical efficacy and the extrapyramidal side effects of the neuroleptics is now beginning to be explored with PET. The correlation between drug response and receptor availability is an area where PET can play an active role in the future.

IN VIVO DISTRIBUTION OF NEUROLEPTICS

There have been several studies done with PET where the in vivo distribution of D₂ receptors using labeled neuroleptics or analogue drugs have been carried out. The first of these with a highly selective agent was with ¹¹C-NMS (Wagner et al. 1983). The distribution observed was that expected of a D₂ antagonist. A similar study was carried out with ¹⁸F-NMS that showed an identical distribution as would be expected (Arnett et al. 1986). The distribution of ¹⁸F-NMS is shown in Figure 5-7. The high uptake in the basal ganglia and low

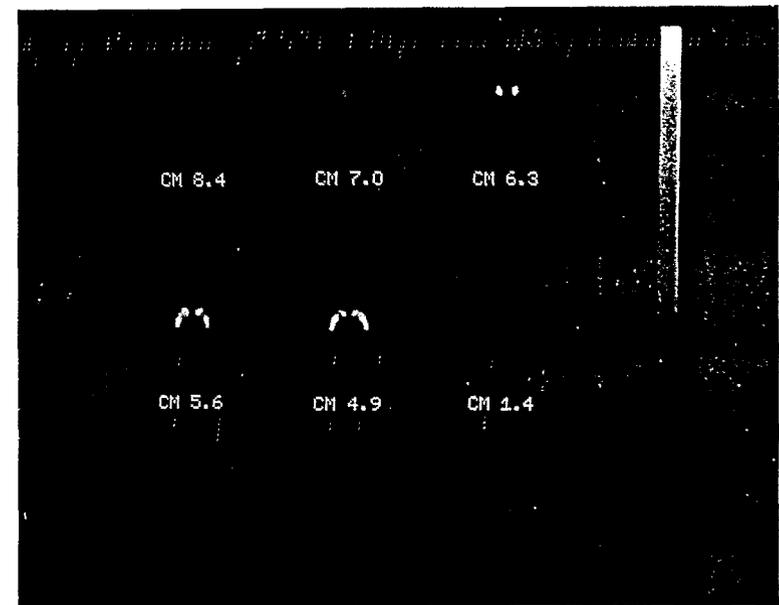


Figure 5-7. Distribution of ¹⁸F-labeled *N*-methylspiroperidol in the human brain (Arnett et al. 1986).

uptake in the rest of the brain is exactly the distribution of D₂ sites in the brain. The correlation between the receptor density as measured in vitro and the uptake in the various regions of the brain is shown in Figure 5-8. The linear relationship demonstrates that the NMS is binding nearly exclusively to D₂ receptors at 3 hours postinjection.

The fact that haloperidol blocks the uptake of ¹⁸F-NMS in the striatum suggests that this drug must be binding to the D₂ receptor. When ¹⁸F-haloperidol was prepared and injected into human subjects, it was clear that the distribution did not reflect the distribution of D₂ receptors in the same way that ¹⁸F-NMS did. A comparison of the distribution of ¹⁸F-haloperidol to that of ¹⁸F-NMS is shown in Figure 5-9. The distribution of the haloperidol is widespread and probably reflects uptake at a number of receptor subtypes, especially the sigma receptor, as well as nonspecific binding. There is not a linear correlation between the measured in vitro receptor densities and the uptake in the various regions of the brain.

The distribution of ¹¹C-labeled raclopride has also been determined in humans (Farde et al. 1985, 1987b). The distribution is very

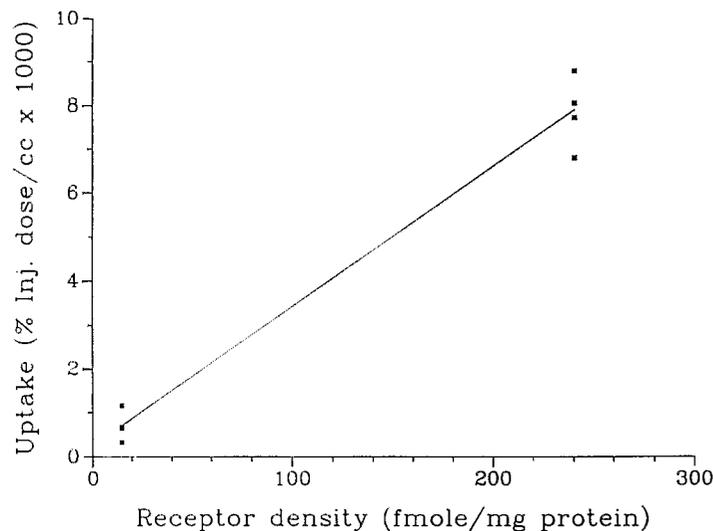


Figure 5-8. Correlation between the in vitro D₂ receptor density of different regions of the brain with the observed uptake of *N*-methylspiroperidol in that region. Uptake is taken from Arnett et al. 1986 and receptor density is taken from Luabeya et al. 1984.

similar to that for ¹⁸F-NMS at longer times. The drug washes out of the striatum much more quickly than the ¹⁸F-NMS due to the lower affinity of raclopride for the D₂ receptor. This lower affinity has some advantages and disadvantages when used to measure the binding potential of the D₂ receptor. The lower affinity means that ¹¹C-raclopride will be in competition with the dopamine present in the synapse. Thus, the measured level of receptors can be influenced by differences in the levels of endogenous dopamine. This effect will cause problems when trying to measure absolute receptor densities unless it can be demonstrated that the dopamine levels in the inter-synaptic cleft are so small that they do not compete effectively. This competition may be an advantage if a study wishes to observe effects on the levels of dopamine when other drugs are given.

The distribution and binding have also been studied with PET for

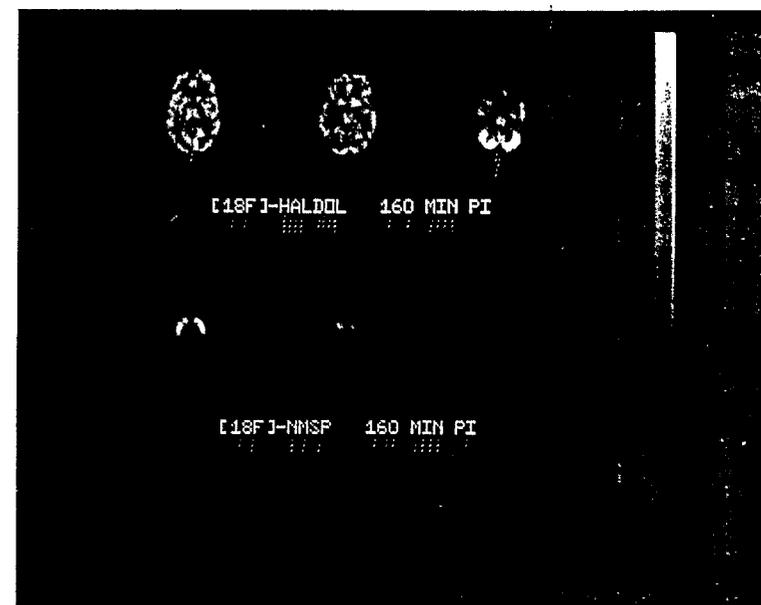


Figure 5-9. Comparison of the distribution of ¹⁸F-labeled *N*-methylspiroperidol (¹⁸F-NMSP) with the distribution of ¹⁸F-labeled haloperidol in the human brain. Distribution of the haloperidol does not follow the D₂ receptor distribution (D.J. Schlyer, C.Y. Shiue, J.S. Fowler, et al., 1990, unpublished observations).

chlorpromazine and clozapine (Comar et al. 1979; Lundberg et al. 1989). In the case of chlorpromazine, its metabolism makes interpretation of the PET data difficult, since the metabolites also cross the blood-brain barrier and are incorporated into the tissue.

DRUG DESIGN AND EXTRAPYRAMIDAL SIDE EFFECTS

One of the most serious problems associated with neuroleptic therapy is that nearly all these drugs cause some EPS. The causes of these effects are not known with certainty, but they are likely related to the binding potential of the neuroleptic drugs with the neurotransmitter receptor systems. It has been shown that the sedative effects of the neuroleptics correlate well with the α -adrenergic binding potential and that the motor dysfunctions are associated with binding at the cholinergic receptors.

One way PET can make a great contribution to the field of neuropharmacology is to determine the distribution of the drugs and correlate this distribution with the binding potential at a series of different sites in vivo. This distribution can be quite different from the in vitro affinity of the drug for the receptors, since the distribution of these lipophilic drugs is often not directly related to the regional receptor density and affinity of the drug for the receptor. Once the correlation between the EPS and the receptor occupancy has been determined, new drugs can be designed to maximize the therapeutic effect while minimizing the EPS.

CONCLUSIONS: FUTURE OF PET IN MENTAL DISORDERS

The real contributions that PET can make to the field of psychiatry are in understanding the physiological basis for the disease and in the design and evaluation of new therapeutic agents. In addition, the correlation of drug dosage with receptor occupancy can provide objective information on the therapeutic dosage levels. The observed binding profile of the drug when compared with the clinical effect can yield understanding of the basis of action. New drugs can be developed by altering their design until they give desired binding profiles as determined by the PET experiment. These factors alone make PET very powerful in both the understanding of the disease and the methods of treatment.

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