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IMAGING RECEPTORS AND THEIR INTERACTIONS: IMPLICATIONS FOR PSYCHIATRY

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INTRODUCTION

In the past ten years various receptor ligands for dopaminergic systems have been labeled and their regional distribution and time course imaged using positron emission tomography (PET). These have included chlorpromazine, spiperone and several analogs, and more recently raclopride, haloperidol and RO15-1788. In addition, labeled compounds have been developed to probe the opiate, benzodiazepine and serotonin receptors among others. The interest in evaluating dopamine receptors in the human brain has clearly been related to the known anti-psychotic effect of dopamine antagonists. It received a large impetus with the improved resolution of PET cameras and the synthesis and application of ^{11}C and ^{18}F labeled N-methyl spiperone (NMS) and derivatives which resulted in dramatic images of the human striatum. In the present report, we shall summarize some of our recent findings on the dopamine (DA) system which bear on the psychiatric issues of 1) the objective determination and monitoring of adequate neuroleptic dose; 2) whether neuroleptic non-response is due to a failure of drug delivery; and 3) preliminary data on the cholinergic system and its putative interaction with the DA system. This latter approach will be discussed in terms of future research in psychiatry.

METHODS

All studies have used either normal human volunteers or schizophrenic patients who have given informed consent. With the exception of studies on the cholinergic receptor, all of the results reported below were obtained from subjects studied in a repeated measures design, with ^{18}F-N-methyl spiperone as the tracer for the dopaminergic system and the PETT VI camera. Details of the experimental procedures and technical information are described in the appropriate references.

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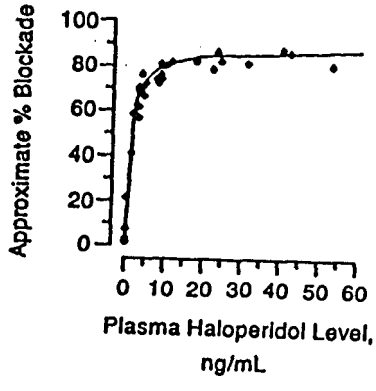
RESULTS AND DISCUSSION

Monitoring Neuroleptic Dose: In the first study (1), the availability of the DA receptor was assessed with 18-F-N-methyl spiperone in a washout paradigm in which pharmacodynamic equilibrium was first established, plasma neuroleptic concentrations were measured, and then binding of the labeled ligand was measured at three time points following cessation of neuroleptic administration. By 1 week after the last therapeutic dose, the concentration of free receptors in the schizophrenic group was indistinguishable from the normal controls. Nevertheless, some of the patients were clearly decompensating while others were not. This finding is consistent with the notion that the DA receptor might be the initial target of neuroleptics, but that their antipsychotic action is mediated by the biochemical interactions which follow the blockade. Although these results clearly indicate that the post synaptic DA receptors become available for the binding of NMS at a rate consistent with plasma clearance of haloperidol, they do not preclude the sequestration of haloperidol (or other neuroleptics) in the brain at sites other than the DA receptor. The persistence of non-specifically bound lipophilic drug in white matter (2) with a relatively long time required for clearance, is not necessarily relevant to either striatal blockade or pharmacologic activity. That blockade of the dopaminergic system causes responses in other functionally linked neurotransmitter systems which, in concert, are ultimately responsible for the behavioral response is an alternative interpretation of the data.

The relationship between plasma neuroleptic concentration and availability of striatal DA receptors was further examined in a series of 26 patients with a total of 35 separate PET measures performed in conjunction with plasma assay (3).



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As can be seen from the figure, there is a hyperbolic relationship of these measures with a virtually linear relationship of receptor blockade to haloperidol concentration at low plasma levels. At high plasma concentrations, however, a further increase in plasma levels has a minimal effect on the inhibition of NMS binding. The genu is at a plasma haloperidol value of about 10 ng/ml which is generally obtained at oral doses of 10 to 20 mg/day. While it is clear that the input function cannot be <u>total</u> haloperidol in the plasma, since over 90% is protein bound, it is equally clear that the relationship exists between this easily measured value and available DA receptors. Hence, our results show that adequacy of a dose to achieve a maximum therapeutic effect as assessed by striatal DA blockade can be routinely achieved at doses long considered to be clinically effective.

<u>Responders and Nonresponders</u>: A major problem for clinicians is posed by psychotic patients who fail to clinically respond to what might be expected to be adequate doses of antipsychotic agents. This result could be due to either a failure of drug delivery or to a failure of drug response. In a preliminary study (4), we addressed this problem by examining a small group (n-5) of neuroleptic responders and an equal group of non-responders. The latter group was treated for up to six weeks with doses of haloperidol of as much as 80 mg per day. Both groups showed <u>equal</u> blockade of striatal DA receptors, which means that failure to respond may not be ascribed to failure of drug delivery, but rather to lack of drug activity. This study also suggests that there must be heterogeneity in schizophrenic patients based on drug response. In other words, blockade of the DA receptor may be necessary, but certainly is not sufficient to assure response.

<u>Neurotransmitter Interactions</u>: From the considerations above, it is likely that neurotransmitter systems do not function in isolation. As a first step in measuring the pharmacologic functioning of a psychotropic drug, we have developed the labeled cholinergic (ACh) ligand, ^{11}C-benztropine, for the purpose of probing the cholinergic system in humans and the interactions of this and the dopaminergic systems. This ligand was chosen on the basis of its long half life, its ability to alleviate the

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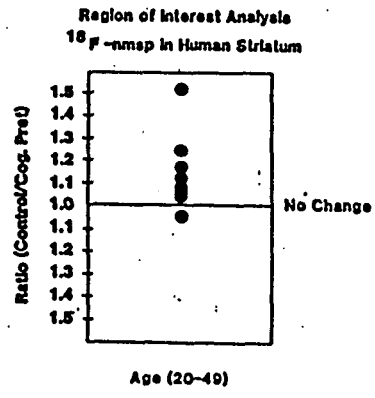
extrapyramidal consequences of DA blockade, and the large body of animal work which suggests a striatal locus for the interaction of these two neurotransmitter systems. ^{11}C-Benztropine labels the living human cortex in the punctate fashion seen with QNB (quinuclidinyl benzilate) and its distribution parallels that of the cholinergic system as mapped in post mortem studies (5). PET studies with cholinergic agonist and antagonists in non human primates have confirmed that benztropine is binding cholinergic receptors.

In addition to obvious studies of the relationship of age to ACh receptor density and expected changes in such illnesses as Alzheimer's disease, we have begun to look at the effect of cholinergic intervention on the DA system by giving unlabeled benztropine to normal subjects and examining the availability of DA receptor binding as measured by the uptake of ^{18}F-NMS. As expected from considerations such as the rapid relief of extrapyramidal symptoms afforded by parenteral benztropine, pretreatment of seven normal subjects with this agent diminished the uptake of ^{18}F-NMS in all but one subject ().



This observation suggests that it is feasible to examine the effects of psychotropic agents, not only at their initial site of action, but downstream as the initial drug-receptor interaction is propagated. It should be clear that evidence of a neurotransmitter interaction following a pharmacologic intervention is in itself evidence of a pharmacologic

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effect.

Finally, these effects may also be seen with outcome measures of neural activity such as glucose metabolism as the image analysis strategies for pattern recognition become more sophisticated. We hope that performing the in vivo PET measurements described in this paper will lead to the development of new drugs and to a better understanding of brain chemistry. An improved understanding of the dynamic neurochemical interactions which are involved in the psychotic disorders should lead to more rational and effective treatment.

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