Creese et al. for screening new neuroleptics, butyrophenones, or thioxanthines. Measurement of the effect of drugs of these classes on serum prolactin levels in the rat also serves to identify dopamine receptor blockers and is much simpler (10). Of greater importance is the fact that there are many drugs of these classes already in clinical use. New drugs of the same type usually differ only quantitatively in potency, sedative effects, and extrapyramidal side effects but do not increase the proportion of patients who will respond, the extent of improvement, or the rapidity of response. Vast numbers of schizophrencias are chronically impaired despite neuroleptic treatment. The real need is to develop entirely different chemical approaches to the prophylaxis and treatment of schizophrenia.

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References and Notes
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We agree with Meltzer that determining the “mean” effective clinical dose of an antischizophrenic drug is a difficult process, since dosage requirements vary tremendously from patient to patient. Using the clinical doses for chlorpromazine, clozapine, and (+)-butaclamol suggested by Meltzer, we have recalculated the correlation between affinity for dopamine receptors and clinical potency (Fig. 1) and found the same high correlation coefficient (r = 0.87) observed previously with different doses for these three drugs (I). Employing the I_{50} value (concentration that inhibits receptor binding by 50 percent) rather than the apparent K_{i} (inhibition constant, indicating 50 percent receptor occupation), as recommended by Meltzer, does not influence correlations between the drugs’ affinities for the receptor and clinical efficacy, since the K_{i} is obtained from the I_{50} value by multiplying I_{50} for each drug by the constant factor 0.5 in these experiments.

Because of the imprecision in establishing clinical doses, we examined the relationship of neuroleptic affinity for the dopamine receptor and pharmacological activity in several animal behaviors that depend on dopamine receptor blockade (J). We observed close correlations with blockade of [3H]haloperidol binding and neuroleptic inhibition of apomorphine-induced stereotyped behavior in rats (r = 0.94), prevention of apomorphine-induced vomiting in dogs (r = 0.93), and inhibition of amphetamine-induced stereotyped behavior in rats (r = 0.92).

Meltzer suggests that screening effects of neuroleptic drugs on serum prolactin levels may be simpler and more meaningful than measuring their affinity for the dopamine receptor. Such prolactin studies require several groups of animals and multiple doses, thus consuming many rats and much drug. Moreover, drugs can influence blood prolactin levels by many mechanisms other than blockade of dopamine receptors. By contrast, a few micrograms of a drug and a few milligrams of brain tissue suffice for dopamine receptor assays; up to 100 drugs can be screened in a morning, providing precise molar affinities of each drug for the dopamine receptor.

However, binding studies of the dopamine receptor (I, 2) were not undertaken only to develop a cheap method for screening new drugs. Earlier evidence that antischizophrenic neuroleptic phenothiazines and butyrophenones block dopamine receptors derived largely from studies with intact animals, in which drug effects on other systems may only indirectly alter dopamine activity. Studies of an adenylate cyclase that is stimulated selectively by dopamine (3) provided a biochemical means of screening neuroleptic drugs in vitro. Although phenothiazine potencies based on the dopamine-sensitive adenylate cyclase correlate with in vivo pharmacological data, the correlation is quite poor for butyrophenones; some workers even suggested that butyrophenones do not act by dopamine receptor blockade (4). Direct labeling of the dopamine receptor with [3H]haloperidol has provided impressive predictions of the clinical and pharmacological activities of both butyrophenones and phenothiazines, affording a novel unequivocal demonstration that pharmacological actions of these drugs are mediated at synaptic receptors for dopamine. Dopamine is an important neurotransmitter in the brain, whose activity has been implicated in numerous diseases including Parkinson’s disease and schizophrenia. We feel that biochemical characterization of the dopamine receptor will find its greatest contribution in elucidating molecular mechanisms that regulate synaptic transmission in normal and diseased states.

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