Perspectives on a Time-Dependent Model of Neuroleptic Action

by David Pickar

Abstract

The best support for the hypothesized involvement of central nervous system dopamine systems in the pathophysiology of schizophrenia is the association between the affinity of neuroleptic drugs for the D₂ dopamine receptor and their potency as antipsychotics. Discrepancy between the time course of receptor binding and the development of antipsychotic effects, however, limits this model. Preclinical studies have now shown that activation of presynaptic nigrostriatal and mesolimbic dopamine neurons by acute neuroleptic administration is reversed during chronic administration. Clinically, neuroleptic-induced time-dependent reductions in plasma levels of the dopamine metabolite, homovanillic acid (HVA), have been linked to the antipsychotic response in schizophrenic patients. These data support the notion that slowly developing alterations in presynaptic dopamine activity play a role in the mechanism of action of neuroleptic drugs. Differences between plasma and cerebrospinal fluid (CSF) HVA responses to neuroleptic treatment, although not fully explained, may be related to prominent contributions of mesocortical metabolism to CSF levels of HVA. A time-dependent dopaminergic model of neuroleptic action with implications for the pharmacotherapy of schizophrenia is presented.

CNS Dopamine Systems

The three principal "long" dopamine systems that link the ventral tegmental area (VTA) and the substantia nigra (SN) of the midbrain to the basal ganglia and the forebrain and that bear the greatest relevance to psychiatric illness and neuropharmacology (Cooper et al. 1982) are schematically shown superimposed on a normal human magnetic resonance scan in figure 1.
The nigrostriatal dopamine system projects from the SN to the neostriatum, principally the putamen and caudate, and mediates extrapyramidal movement. Its degeneration is the pathophysiological basis for the motor dysfunction of Parkinson's disease; extrapyramidal side effects (EPS) of neuroleptics result from neuroleptic-induced alteration in nigrostriatal system activity. The
mesolimbic dopamine system comprises cell bodies in the VTA and SN with projection to the limbic system including innervations in the septum, olfactory tubercle, nucleus accumbens, and amygdala. The importance of the limbic system in emotional and behavioral homeostasis has been recognized since the 1950's; dysfunction of the mesolimbic dopamine system has been proposed as a primary pathophysiology of schizophrenia (Stevens 1973). The mesocortical dopamine system, the most recently delineated of the CNS dopamine systems, involves dopaminergic innervation of the neocortex by cells originating in the midbrain (Glowinski et al. 1984). Integrity of mesocortical neurons is required for normal prefrontal cortical cognition and behaviors in primates (Brozoski et al. 1979). A potentially important source of internal dopamine system regulation is the inhibitory effect of mesocortical neurons on subcortical dopamine systems (Pycock et al. 1980). Some unique characteristics of mesocortical dopamine neurons that may be relevant to the pharmacotherapy and pathophysiology of schizophrenia include their responsivity to environmental (Thierry et al. 1976) and pharmacological stress (Tam and Roth 1985), elevated basal firing rates, and diminished responsivity to both dopamine agonists and antagonists (Bannon and Roth 1983). Although most of our understanding of CNS dopamine systems derives from experiments in rodents, and to a lesser degree in primates, much is applicable to humans. Nevertheless, the human brain differs substantially even from nonhuman primates, principally in cortical development. It is expected that cortical dopamine systems play particularly important roles in human behavior and in neuropsychiatric disorders (Weinberger 1987).

Neuroleptics and Dopamine

The observation that neuroleptic drugs rapidly increase dopamine metabolites in rat brain led to the landmark interpretation by Carlsson and Lindqvist (1963) that neuroleptics reduce dopamine transmission by postsynaptic receptor blockade (Carlsson 1978). These findings have now been replicated innumerable times and are the cornerstone for the receptor blockade model of neuroleptic action. The development of radiolabeled dopamine receptor antagonists in the 1970's provided further direct support for the hypothesis that antipsychotic effects of neuroleptics result from receptor blockade. Classic studies by Creese et al. (1976) and Seeman et al. (1976) showed that the greater affinity of a given neuroleptic for the nonadenyl-cyclase-dependent D2 receptor, the more potent the neuroleptic is as an antipsychotic. Thus, chlorpromazine, which has less affinity for the D2 receptor than does fluphenazine, requires greater doses than fluphenazine to produce comparable antipsychotic effects. The high concentration of D2 receptors in striatal and limbic structures (but not in the frontal cortex) is consistent with the hypothesis that subcortical dopamine systems are the primary sites mediating the antipsychotic effects of neuroleptic drugs.

A limitation to the receptor blockade model of neuroleptic action is the discrepancy between the time course required for receptor occupancy and for the development of antipsychotic effects (Pickar 1986). As demonstrated by recent human positron emission tomography (PET) studies using the labeled D2 antagonist, 11C-raclopride, high D2 receptor occupancy occurs within hours of oral administration of even modest clinical doses of neuroleptics (Sedvall et al. 1986). In contrast, antipsychotic effects of neuroleptic drugs are slowly progressive, with therapeutic effects on positive and negative symptoms developing over weeks (Breier et al. 1987; Pickar et al. 1987a). Further, indirect markers of neuroleptic blockade—e.g., circulating receptor blocking potency determined by neuroleptic radioreceptor assay or neuroleptic-induced increase in prolactin—have proved to be poor predictors of clinical response (Meltzer et al. 1983). "Rapid neuroleptization," a technique of acute, high-dose neuroleptic administration designed to "saturate" receptor sites (Donlon and Tupin 1975), has proved unsuccessful in accelerating the antipsychotic response (Anderson et al. 1976; Neborsky et al. 1981).

To address time-dependent pharmacological effects of neuroleptic drugs, preclinical studies have focused on differences between acute and chronic neuroleptic administration on CNS dopamine function. Within hours of neuroleptic administration, striking increases in firing rates of dopamine neurons are seen (Bunney et al. 1973), an effect thought to result from feedback presynaptic activation secondary to receptor blockade (Bunney 1984). These electrophysiological changes parallel rapid increases in dopamine metabolite production (reflecting increased neurotransmitter turnover) (Bacopoulous et al. 1978; Roth 1983) and in tyrosine hydroxylase activity,
the rate-limiting step in catecholamine synthesis (Lerner et al. 1977). When neuroleptic administration is continued over weeks, however, the enhanced neuronal activity is reversed. Increasing numbers of dopamine neurons become electrophysiologically inactivated, presumably the result of "depolarization block" (Bunney and Grace 1978; Bunney 1984). Biochemically, the initial increase in dopamine turnover and in tyrosine hydroxylase activity is altered, and metabolites return to pretreatment levels (Lerner et al. 1977, Bacopoulous et al. 1978; Roth 1983).

In addition to producing differential short- and long-term effects on dopamine neuronal activity, neuroleptic drugs show specificity for individual dopamine systems (table 1). All known antipsychotic agents show time-dependent electrophysiological effects (activation followed by deactivation) on mesolimbic neurons. Typical neuroleptics (i.e., neuroleptics that produce extrapyramidal side effects) show characteristic time-dependent effects on nigrostriatal neurons; "atypical" neuroleptics (i.e., neuroleptics that tend to produce minimal or no EPS such as clozapine, sulpiride, and thioridazine) show minimal electrophysiological effects in this system (Chiodo and Bunney 1983; White and Wang 1982). Biochemical differences between typical and atypical neuroleptics in nigrostriatal dopamine neurons are, however, less clear.

An intriguing aspect of the pharmacology of neuroleptic drugs is that both typical and atypical neuroleptics are without time-dependent effects on mesocortical neurons, an effect thought to result from the absence of autoreceptors on mesocortical neurons (Bacopoulous and Roth 1981, Bannon et al. 1982). Neuroleptics produce acute but modest increases in mesocortical neuronal activity; these effects remain essentially unchanged during prolonged drug administration. Data from post-mortem studies suggest that this unique characteristic also occurs in humans (Bacopoulous et al. 1979b). In recent PET studies, the predominance of D₁ rather than D₂ receptors in the human frontal cortex has been confirmed (Sedvall et al. 1986, Farde et al. 1987), a finding that may have implications for pharmacotherapeutic approaches to schizophrenia (Hess et al. 1987).

### The Plasma HVA Strategy

The measurement of amine metabolites in body fluids has been the most widely applied approach for bridging preclinical concepts to the clinical setting. The measurement of HVA in CSF is particularly attractive since CSF HVA is

| Table 1. Response of dopamine systems in the central nervous system to neuroleptic administration |
|----------------------------------|----------------------------------|----------------------------------|
| Brain area                       | Acute neuroleptic administration | Chronic neuroleptic administration |
|                                 | Typical   | Atypical   | Typical   | Atypical   |
| Nigrostriatal                    |           |           |           |           |
| Firing rate¹                    | ++++      | 0         | Depolarization block | 0         |
| Turnover                        | ++++      | +         | Tolerance³ | +         |
| Mesolimbic                      |           |           |           |           |
| Firing rate                     | +++       | +++       | Depolarization block | Depolarization block |
| Turnover                        | +++       | +++       | Tolerance | Tolerance |
| Mesocortical                    |           |           |           |           |
| Firing rate                     | +         | +         | +         | +         |
| Turnover                        | +         | +         | +         | +         |

*Note*—"Typical" refers to neuroleptic drugs that cause extrapyramidal side effects. "Atypical" refers to neuroleptic drugs that tend to cause extrapyramidal side effects.

¹Single cell activity

²Dopamine release and metabolism

³Time-dependent reversal of initial increase
derived largely from the CNS. The invasiveness of the procedure, however, has limited its application. In contrast to determinations of CSF, plasma metabolite measurement is a strategy suited for longitudinal study. The basis for using plasma levels of HVA to reflect CNS dopamine activity is animal experimentation in which levels of HVA in plasma are found to change in parallel with HVA in key brain regions in response to pharmacological challenge including neuroleptic drugs (Bacopoulos et al. 1979a, 1980; Kendler et al. 1982; Sternberg et al. 1983b). Nevertheless, circulating levels of HVA are prominently influenced by peripheral (non-CNS) sources. Although the precise peripheral and CNS contributions to levels of plasma HVA are unknown, it has been estimated in rodents (Sternberg et al. 1983b) and in humans (Swann et al. 1980) that 40–60 percent of total free levels of plasma HVA is derived from the CNS under basal conditions. The single greatest source of non-CNS-derived HVA is the peripheral sympathetic nervous system (Kopin 1985) with other contributions from the adrenal medulla, carotid body, and kidney (van Loon 1983).

Neuroleptic-Induced Reduction in Plasma HVA

We have used levels of plasma HVA to examine neuroleptic-induced changes in dopaminergic system activity in DSM-III diagnosed (American Psychiatric Association 1980) schizophrenic patients under controlled research ward conditions (Pickar et al. 1984, 1986) with biochemical assays performed by high-pressure liquid chromatography with electrochemical detection (Chang et al. 1983; Scheinin et al. 1983). Neuroleptic administration is associated with time-dependent decreases in plasma HVA (Pickar et al. 1986). Following an initial drug-free placebo period of (mean ± SEM) 34 ± 6 days, fluphenazine is administered at doses established clinically during the first week of treatment and maintained throughout (mean ± SEM mg/day: 30 ± 5). As shown in figure 2a, modest increases in plasma HVA are observed during the first week of treatment. Significant reductions in levels of plasma HVA from drug-free baseline occur during the third week of drug administration and are sustained throughout the 5 weeks of study. The clinical significance of the neuroleptic-induced change in plasma HVA levels is suggested by the correlation between plasma HVA levels and corresponding nurses’ ratings of psychosis as shown in figure 2b. Neuroleptic-induced reduction in levels of plasma HVA occur in parallel with reduction in psychosis ratings, suggesting their mutual association with neuroleptic treatment. Complementary group data (not shown here) from 11 schizophrenic patients (Pickar et al. 1986) revealed that cessation of chronic neuroleptic treatment was associated with significant increases in mean weekly levels of plasma HVA after 5 drug-free weeks; positive correlation again was found between plasma HVA levels and psychosis ratings during the course of neuroleptic withdrawal. Analysis of individual patient data supports these findings: the greater the neuroleptic-induced reduction in symptoms, the greater the reduction in plasma HVA level; the more severe the exacerbation following drug discontinuation, the greater the rise in plasma HVA level. Thus, alterations in pre-
Figure 2b. Levels of plasma homovanillic acid and corresponding nurses’ psychosis ratings and their correlation (insert) during fluphenazine treatment

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Synaptic dopamine activity, reflected in these studies by change in levels of plasma HVA, occur slowly in response to change in neuroleptic treatment and parallel change in clinical state.

Results from several other published studies examining the effects of neuroleptic treatment on levels of plasma HVA show some consistencies with our findings. Bowers et al. (1983, 1984) and Bowers and Swigar (1987) studied psychotic patients in a general hospital setting and observed that rapid (favorable) neuroleptic responses were associated with elevated plasma levels of both HVA and the noradrenergic metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), and marked neuroleptic-induced reduction in plasma HVA. Patients who had poor short-term response to neuroleptic treatment showed minimal neuroleptic-induced alteration in plasma metabolite levels. Davis et al. (1985) reported that chronic haloperidol administration was without significant effect on plasma levels of HVA in schizophrenic patients. This lack of neuroleptic effect may be accounted for by the fact that the patients studied by Davis et al. showed minimal or no response to neuroleptic treatment (K. Davis, personal communication). These investigators did observe, however, significant positive correlations between plasma HVA levels and symptom severity before and during neuroleptic treatment—findings consistent with the significant correlations between absolute levels of plasma HVA (when drug-free and neuroleptic-treated) and symptomatology in our studies (Pickar et al. 1986). Harris et al. (1984) was unable to demonstrate neuroleptic-induced decrease in plasma HVA levels, although
treatment was heterogeneous in type and duration. Results from studies currently in progress in other research centers may help to assess the clinical utility of the longitudinal measurement of plasma HVA as a marker for neuroleptic response.

Some support for the specificity of neuroleptic-induced reduction in plasma levels of HVA has been gained from the experimental administration of verapamil to schizophrenic patients. We had hypothesized that verapamil, a slow channel calcium blocker widely used in cardiac therapeutics and reportedly useful in reducing hypomanic symptomatology (Dubovsky et al. 1982; Giannini et al. 1984), might exert antispsychotic effects by reducing or modulating calcium-dependent dopaminergic presynaptic transmission. Gould et al. (1983) postulated that the reportedly unique effects of the dephenylbutylpiperidine group of neuroleptics on negative symptoms (Lapierre and Lavallee 1975; Lapierre 1978) are related to their calcium-blocking properties. Clinically, verapamil significantly worsened paranoia ratings and exacerbated psychosis ratings in some patients. Biochemically, verapamil significantly increased plasma and CSF levels of HVA and significantly decreased plasma levels of MHPG (Pickar et al. 1987b). This dissociation of plasma HVA and MHPG is of particular interest since plasma MHPG is an excellent marker of the peripheral sympathetic nervous system and peripherally derived HVA is largely associated with noradrenergic metabolism (Kopin 1985). This effect is not unique to verapamil, however; we have found that exogenous steroid administration also dissociates plasma HVA and MHPG response in normal controls and in depressed patients (Wolkowitz et al. 1985, 1987b).

The Debrisoquin Technique

To examine further the plasma HVA model of neuroleptic-induced alteration in dopamine function, we have used the debrisoquin administration technique to enhance the CNS "signal" to circulating levels of plasma HVA (Swann et al. 1980; Maas et al. 1985; Pickar et al. 1987; Davidson et al. 1987a, 1987c). Debrisoquin, a selective monamine oxidase (MAO) inhibitor that does not cross the blood-brain barrier (Medina et al. 1969), decreases the peripheral formation of HVA; thus, the absolute plasma levels of HVA are decreased, but the relative brain HVA contribution is enhanced (Swann et al. 1980; Maas et al. 1985). In contrast to decreased plasma HVA levels, CSF HVA is unaltered (Maas et al. 1985; Pickar et al. 1987). Since the large majority of non-brain HVA is derived from metabolism of noradrenergic nerves and the overwhelming majority of plasma MHPG is peripherally derived (Kopin 1985), the comeasurement of plasma levels of MHPG provides "control" for remaining peripheral HVA production in debrisoquin-treated subjects.

In our preliminary studies, debrisoquin reduces plasma MHPG to a significantly greater degree than it reduces plasma HVA (Pickar 1987), supporting the notion that debrisoquin enhances the CNS-derived concentration of HVA in plasma. The results of ongoing studies using debrisoquin may help to clarify the significance of plasma HVA measurement for CNS dopaminergic activity.

The CSF HVA "Dilemma"

A persistent dilemma in the use of plasma HVA levels to reflect CNS dopamine activity is the different plasma and CSF HVA responses to neuroleptic administration. CSF levels of HVA are rapidly and markedly increased by short-term neuroleptic administration (Bowers 1973; Sedvall et al. 1974; Post and Goodwin 1975; Wode-Helgodt et al. 1977) with at least partial reversal ("tolerance") occurring during longer term treatment (Post and Goodwin 1975) in some, but not all patients (Bowers and Heninger 1981; Bowers 1984). In contrast, increases in plasma HVA levels in response to short-term neuroleptic treatment are a more variable finding. We observed increased levels of plasma HVA in some patients during the first week of fluphenazine treatment (Pickar et al. 1986). Davis et al. (1985) reported no increase in plasma HVA levels 6 hours after haloperidol administration. In later experiments, however, these investigators observed haloperidol-induced increases in plasma HVA levels when sampled 24 hours after the initiation of haloperidol treatment in both debrisoquin- and non-debrisoquin-treated patients (Davidson et al. 1987a, 1987c). Recently, Davila et al. (1987) reported that in schizophrenic patients treated with a peripheral decarboxylase inhibitor (to enhance the CNS HVA "signal") haloperidol increased plasma HVA within 4 hours of drug administration.

Although CSF HVA levels have, in general, been weak correlates of neuroleptic response, Bowers and Heninger (1981) reported that patients who showed CSF HVA tolerance patterns had fewer symptoms and EPS than patients with-
out tolerance at 5 weeks of treatment. Lack of tolerance was, however, associated with a high incidence of psychiatric hospitalizations among first-degree family members (Bowers 1984). The significance of CSF HVA tolerance patterns to neuroleptic response is raised by Sternberg et al. (1983a), who found that lithium treatment blocked the development of tolerance even in responsive patients; moreover, Bagdy et al. (1985) reported significant decreases in levels of CSF HVA within 2 weeks following the discontinuation of chronic (years) neuroleptic treatment. In a study addressing total body dopamine turnover, Karoum et al. (1987) found that haloperidol increased total dopamine and dopamine metabolite urinary excretion when examined as a ratio to total norepinephrine and its metabolite excretion; it is unknown whether this increase would be reversed by longer term treatment, as seen in plasma or, rather, remain elevated as in CSF.

In evaluating the contrasting plasma and CSF HVA neuroleptic response patterns, consideration should be given to several recent lines of evidence suggesting that the mesocortical dopamine system may be more influential in determining levels of CSF HVA than might be expected on the basis of its relatively low absolute dopamine content and the proximity of subcortical dopamine systems to the cerebral ventricles. Stanley et al. (1985) reported significant positive correlations between CSF HVA and frontal cortical, but not subcortical HVA, in post-mortem examination of psychiatric patients and controls. Similarly, Elsworth et al. (1987) reported that in post-mortem examination of rhesus monkeys, CSF HVA was significantly correlated with HVA content in the prefrontal cortex (mesocortical innervation) but not with HVA content in subcortical structures such as the putamen and caudate or in other cortical regions. A relationship between CSF HVA levels and the mesocortical dopamine system is also suggested by computed tomographic (CT) studies of schizophrenic patients in which CSF HVA is decreased in proportion to loss of brain tissue (Nyback et al. 1982; van Kammen et al. 1983, 1986; Houston et al. 1986; Losonczy et al. 1986). In our recent study of 22 schizophrenic patients (Doran et al. 1987), CSF HVA was inversely correlated with rankings of prefrontal cortical atrophy (r = - .54, p < .01) but neither with generalized cortical atrophy (r = -.18, NS nor with ventricular-brain ratio (r = .08, NS) (Doran et al. 1987).

Some special characteristics of mesocortical dopamine neurons may also be relevant to their influence on CSF HVA levels. Basal mesocortical neuronal activity (“turnover”), reflected by HVA production, is many times greater than turnover rates of subcortical dopamine systems; consistent with CSF findings, “tolerance” to neuroleptic stimulation of dopamine turnover is minimal or absent (Bannon and Roth 1983); and, finally, mesocortical neurons are particularly sensitive to stress (Glowinski et al. 1984), including, in all likelihood, lumbar puncture.

The concept that levels of CSF are a “net” reflection of mesocortical and subcortical HVA production provides an interesting, though complex, perspective for interpreting clinical data. The persistent elevation of CSF HVA induced by neuroleptic drugs, for example, and its relatively weak correlation with clinical response may be the result of a prominent mesocortical contribution during neuroleptic treatment. Similarly, low levels of CSF HVA in schizophrenic patients or inverse correlation between CSF HVA and symptomatology (Bowers 1978; Lindstrom et al. 1985, van Kammen et al. 1986; Pickar et al. 1988) may reflect diminished mesocortical activity coupled with enhanced subcortical activity, an “ideal” biological substrate for psychosis (Weinberger 1987).

### A Time-Dependent Model of Neuroleptic Action

Sequential pharmacological events of a hypothetical time-dependent dopaminergic model of neuroleptic action are presented in table 2. Neuroleptic occupancy and blockade of D2 receptors are the initiating events that result in acute decrease in dopamine neurotransmission in subcortical dopamine systems.

Feedback activation of presynaptic neurons characterized by increased activity of tyrosine hydroxylase, increased dopamine turnover, and increased electrophysiological activity occurs within hours of receptor blockade. Neuronal activation persisting from days to weeks gradually is replaced by reduction to (or below) baseline, with diminished tyrosine hydroxylase activity and dopamine turnover and the development of “depolarization block” in increasing numbers of neurons. Mesocortical neuronal activation produced by neuroleptic treatment further reduces and/or stabilizes presynaptic neuronal activity through mechanisms that may involve other neurotransmitter or neuromodulatory systems (see article by W. Freed, this issue).

This stepwise model might...
Table 2. Time-dependent model of neuroleptic action

<table>
<thead>
<tr>
<th>Sequential pharmacologic events</th>
<th>Time course</th>
<th>Associated effects</th>
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<tbody>
<tr>
<td>1. D₂ receptor binding</td>
<td>Hours</td>
<td>Binding affinity correlated with potency; Increased prolactin secretion; Acute extrapyramidal symptoms (e.g., dystonia)</td>
</tr>
<tr>
<td>2. Feedback activation of presynaptic neurons</td>
<td>Hours</td>
<td>Increased cerebrospinal fluid levels of homovanillic acid; Increased plasma levels of homovanillic acid; Nonspecific behavioral effects</td>
</tr>
<tr>
<td>Subcortical &gt; cortical</td>
<td>Days</td>
<td>Reversal of plasma homovanillic acid; Continued cerebrospinal fluid elevation; Emerging antipsychotic effects</td>
</tr>
<tr>
<td>3. Reversal of presynaptic activation in nigrostriatal &amp; mesolimbic neurons</td>
<td>Days</td>
<td>Extrapyramidal symptoms (e.g., Parkinsonism)</td>
</tr>
<tr>
<td>Persistent increase in mesocortical activity</td>
<td>Weeks</td>
<td>Reduced levels of homovanillic acid in plasma; Cerebrospinal fluid tolerance patterns; Clinical stability; Variable degree of residual positive &amp; negative symptoms</td>
</tr>
<tr>
<td>4. Stabilization of presynaptic activity at new setpoint</td>
<td>Weeks</td>
<td>Decreased extrapyramidal symptoms</td>
</tr>
<tr>
<td>Enhanced cortical inhibition of subcortical systems</td>
<td>Months</td>
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account for some clinical facets of neuroleptic treatment. For example, sustained antipsychotic response may be less a function of persistent, high-level receptor occupancy/blockade than of preserving presynaptic adaptation. Neuroleptic response would therefore require plasticity (Friedhoff 1986); as suggested by the preliminary data of Davila et al. (1987), dopamine systems with less capacity to alter function in response to receptor blockade would be expected to be associated with poorer neuroleptic response. The stability of presynaptic adaptation (e.g., its resistance to disruption by stress or by other neuronal system input) might define favorable long-term response. The data of Lieberman et al. (1987) and Davidson et al. (1987b) in which adverse response to methylphenidate infusion during neuroleptic treatment or to L-dopa administration when drug-free, respectively, predicted relapse after neuroleptic discontinuation are consistent with this notion.

Enhancement of neuroleptic response might be achieved by intervention at various points in the antipsychotic process. One strategy might be to amplify mesocortical dopamine inhibition of subcortical dopamine activity. We have reported that the triazolobenzodiazepine, alprazolam, significantly improved antipsychotic effects of fluphenazine in two schizophrenic patients (Wolkowitz et al. 1986); in a subsequent larger series, favorable response to alprazolam augmentation correlated with prominent atrophy of and with alprazolam-induced decrease in plasma levels of HVA (Wolkowitz et al., in press).

In preliminary laboratory experiments we observed in rats that acute alprazolam administration enhanced neuroleptic-induced HVA increases in the frontal cortex (R. Labarca, unpublished data). The possibility is raised that the clinical efficacy of alprazolam results from alprazolam-induced enhancement of frontal cortical dopamine turnover and resultant inhibition of subcortical dopamine function. Other neurotransmitter systems that either directly or indirectly influence dopamine function (e.g., cholecystokinin and endogenous opioids) might also be targets for pharmacological "manipulation" to enhance the antipsychotic response.

The identification of pathophysio-
logically distinct forms of schizophrenia on the basis of favorable and unfavorable neuroleptic response has been an influential theme of schizophrenia research over the past decade (Andreasen et al. 1982, Crow 1985) Different etiologies (e.g., postviral autoimmune response and genetic metabolic error), however, can still result in similar net CNS dopaminergic dysfunction and a clinical picture satisfying diagnostic criteria for schizophrenia. Further, dopaminergic pathophysiology that result in schizophrenia-like psychosis need not necessarily respond in the same way or to the same degree to neuroleptic treatment. Whereas the receptor blockade model of neuroleptic action leaves little latitude for heterogeneous defect, the time-dependent model of neuroleptic action can readily integrate a range of dopaminergic dysfunctions (Abnormal tyrosine hydroxylase activity or other genetically determined enzyme dysfunctions, for example, could diminish the critically important activation of presynaptic dopamine neurons, cortical degeneration might remove internal dopamine modulation. In both cases poor neuroleptic response would result. New technologies such as PET and molecular biological techniques may prove useful for schizophrenia research by identifying specific pathophysiological defects in CNS dopamine function. Once these defects are identified, the prospects improve for focused and effective treatment.

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