The Dopamine Hypothesis: An Overview of Studies With Schizophrenic Patients

by John L. Haracz

Abstract

For the past decade, the dopamine hypothesis of schizophrenia has been the predominant biochemical theory of schizophrenia. Despite the extensive study of tissue samples obtained from schizophrenics, indirect pharmacological evidence still provides the major support for the hypothesis. Direct support is either unconvincing or has not been widely replicated. The dopamine hypothesis is limited in theoretical scope and in the range of schizophrenic patients to which it applies. No comprehensive biological scheme has yet been proposed to draw together the genetic, environmental, and clinical features of schizophrenia. Recent refinements of the dopamine hypothesis may aid in the delineation of biologically homogeneous subgroups. Positive symptoms (e.g., hallucinations, delusions) and negative symptomatology (e.g., affective flattening, social withdrawal) may result from different pathophysiological processes. Schizophrenia research might benefit from an increased attention to neurophysiological adaptations.

The dopamine (DA) hypothesis of schizophrenia was founded on indirect pharmacological evidence. Early observations suggested a dopaminergic hyperactivity in schizophrenia: the symptoms of acute paranoid schizophrenia resemble the psychosis induced in nonschizophrenics by amphetamine, an indirect DA agonist (Young and Scoville 1938; Connell 1958; Bell 1965; Angrist et al. 1974); DA agonists exacerbate schizophrenic symptoms (Yaryura-Tobias, Diamond, and Merlis 1970; Janowsky et al. 1973; Angrist and Gershon 1977); a therapeutic effect is produced by drugs that block central dopaminergic transmission (Carlsson and Lindqvist 1963; Randrup and Munkvad 1972; Matthysse 1973). More recently, additional pharmacological support for the DA hypothesis has been generated by clinical and preclinical studies of numerous neuroleptic compounds. The clinical antipsychotic potencies of the neuroleptics were closely correlated with various measures of their antidopaminergic potency, such as the in vitro inhibition of DA receptor binding (Creese, Burt, and Snyder 1976; Seeman et al. 1976; Peroutka and Snyder 1980), the reversal of animal behaviors induced by DA agonists (Creese, Burt, and Snyder 1976), the elevation of human plasma prolactin levels (Langer et al. 1977), and inhibition of the electrically stimulated release of DA from brain slices (Seeman and Lee 1975).

The pharmacological support of the DA hypothesis has motivated a search for confirmatory evidence with the use of schizophrenic subjects. Several extensive reviews of the preclinical pharmacological evidence have appeared elsewhere (Matthysse 1974; Snyder et al. 1974; Meltzer and Stahl 1976; Carlsson 1978; Hornykiewicz 1978). The present article will review the biological studies that constitute direct and indirect tests of the DA hypothesis with schizophrenic subjects. Experimental reports will be organized into three

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groups according to the aspect of dopaminergic activity under study: (1) presynaptic dopaminergic mechanisms, (2) DA receptor sensitivity, and (3) the clinical effects of drugs that alter dopaminergic activity.

**Presynaptic Dopaminergic Mechanisms**

**Post-mortem Brain DA and Homovanilllic Acid (HVA).** Several groups have tested the DA hypothesis by examining post-mortem brain levels of DA and its major metabolite, HVA, in schizophrenics and controls. DOPAC (3,4-dihydroxyphenylacetic acid), an intermediate in the formation of HVA, has also been measured. The literature contains some reports of altered DA and HVA levels in the brains of schizophrenics, but these results have not been widely replicated (table 1).

Farley and coworkers obtained post-mortem brain samples from 4 chronic paranoid schizophrenics and 12 controls with no history of neurologic or psychiatric illness (Farley, Price, and Hornykiewicz 1977; Farley, Shannak, and Hornykiewicz 1980). DA and HVA concentrations did not differ between schizophrenics and controls in the caudate, nucleus accumbens, putamen, and medial or lateral olfactory areas (table 1). Significantly elevated DA, but not HVA, was found in the ventral septum of the schizophrenics.

Crow et al. (1978, 1980) determined DA and HVA levels in the post-mortem brains of 19 general hospital controls and 19 chronic schizophrenics who were diagnosed according to Feighner’s criteria (Feighner et al. 1972). They reported no differences between the groups in the nucleus accumbens and putamen (table 1). In the caudate, the schizophrenics had significantly elevated DA and decreased HVA concentrations compared to controls. There were no differences in DOPAC concentrations in any of the areas. As will be discussed later, elevated numbers of DA receptors were also found in caudate samples from the same patients (Crow et al. 1978; Owen et al. 1978). In post-mortem specimens from 9 chronic schizophrenics and 10 general hospital controls, Crow et al. (1979) later found significantly elevated DA in the caudate and putamen of the schizophrenics (table 1). Regional HVA and DOPAC did not differ between the groups.

Bird et al. (1977) measured DA concentrations in post-mortem brain samples from more than 50 controls, obtained from a general hospital, and a similar number of psychotic patients. The psychotic group was subdivided into “schizophrenia” and “schizophrenia-like” categories according to Schneiderian first-rank phenomena and chronicity of illness (Mackay et al. 1980a). The overall group of psychotics had significantly elevated DA levels in the nucleus accumbens and anterior

### Table 1. DA and HVA levels in post-mortem brains of schizophrenics and controls

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<th>Caudate DA</th>
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Note: ↑, ↓ = significantly increased or decreased in schizophrenics compared to controls (p < .05); N = no significant difference between schizophrenics and controls (p > .05); — = levels not reported. An effort was made to identify unique subject groups.
perforated substance, but there were no abnormal findings in putamen, caudate, septal nuclei, and amygdala central nucleus (Bird et al. 1977; Bird, Spokes, and Iversen 1979a, 1979b, 1980). The “schizophrenia” subgroup was itself subdivided into groups of patients who were over or under 25 years of age. Only the under-25 group of schizophrenics had significantly increased DA in the caudate and nucleus accumbens compared to controls (Mackay et al. 1980a). All but three of the schizophrenics in this study received chronic neuroleptic treatment before death.

Bacopoulos et al. (1979) determined post-mortem HVA levels in the brains of 25 schizophrenics who had received neuroleptics for periods ranging from 6 months to 17 years before death. Compared to age-matched controls, the schizophrenics had significantly elevated HVA in the cingulate gyrus, temporal lobe, and orbital frontal cortex, but there were no differences in the nucleus accumbens or putamen (Bacopoulos et al. 1979; Bacopoulos, Bird, and Roth 1979). Levels in the caudate nucleus were not reported. HVA concentrations were within the control range in three schizophrenics who apparently had not been treated with neuroleptics. It was proposed that the elevated HVA in the cortical regions indicated a lack of tolerance to the neuroleptic effects in these areas, possibly suggesting a cortical site of antipsychotic action.

Winblad et al. (1979) recently measured post-mortem concentrations of DA and HVA in the brains of 28 nonpsychiatric controls and 12 schizophrenics, 6 of whom had been “lobotomized” 25 to 30 years before death. All the schizophrenic patients had been on neuroleptics and were diagnosed according to Bleulerian criteria. There were no significant differences between controls and schizophrenics in the DA concentrations of caudate, putamen, hypothalamus, thalamus, mesencephalon,pons, hippocampus, frontal lobe, and the cingulate gyrus (table 1). HVA levels did not significantly differ between the groups in the caudate and putamen.

Finally, the concentrations of DA and its metabolites were determined by Kleinman and coworkers in post-mortem brain specimens from 17 normals and 32 psychiatric patients (Kleinman et al. 1980; Wyatt et al. 1981). Psychiatric diagnoses fell into the following groups using Research Diagnostic Criteria (Spitzer, Endicott, and Robins 1975): chronic undifferentiated schizophrenia (n = 11), chronic paranoid schizophrenia (n = 11), and other psychotic disorders (n = 10). No significant differences for DA, DOPAC, or HVA were found in either the nucleus accumbens or the hypothalamus of any of the patient groups relative to controls.

Since the majority of the schizophrenics in the above studies received neuroleptics shortly before death, drug effects must be considered in the interpretation of the positive findings. Drug-free schizophrenics and controls were reported to have similar DA and HVA concentrations in several brain regions (Bacopoulos et al. 1979; Kleinman et al. 1980). Preliminary studies indicated that schizophrenics and non schizophrenics did not differ in the post-mortem fluorescence histochemistry of catecholamine neurons in cortical and subcortical regions (Olson, Nystrom, and Seiger 1973a, 1973b; Olson 1974). These findings do not support the presence of elevated DA turnover in the brains of schizophrenics.

Cerebrospinal Fluid (CSF) HVA. CSF HVA measurements have been used to estimate the activity of central dopaminergic neurons (Bowers 1972; Sourkes 1973). The nigrostriatal DA system appears to be the major source of CSF HVA (Sourkes 1973). The mesolimbic and mesocortical DA tracts, which are more likely to be the etiologically important tracts in schizophrenia, probably make a relatively small contribution to CSF HVA (Meltzer and Stahl 1976). Until the central sources of HVA are better understood, it will be difficult to judge the meaning of CSF HVA findings in schizophrenia.

Bowers (1973) measured HVA and 5-hydroxyindoleacetic acid (5-HIAA), a serotonin metabolite, in CSF from 18 patients who were being treated for “acute psychotic reactions” included in the “schizophrenia spectrum.” Neuroleptic treatment was withheld for 2 weeks before CSF sampling, and probenecid was administered to allow accumulation of the CSF metabolites. Two control groups consisted of unipolar depressive patients and healthy volunteer in-mates. CSF levels of HVA, 5-HIAA, and the 5-HIAA/HVA ratio did not differ between schizophrenics and controls. When the schizophrenics were divided according to the presence or absence of Schneider’s (1959) first-rank symptoms, the 5-HIAA/HVA ratio of the Schneider-positive group was significantly increased in comparison with the Schneider-negative patients, depressed patients,
and inmates. The higher HVA concentration of the Schneider-negative group was just short of significance compared to the Schneider-positive group ($p < 0.1$). The Schneider-negative patients had significantly higher HVA levels than the inmate controls. CSF probenecid concentrations were not measured in any of the subjects, so a differential probenecid effect cannot be excluded as a cause of these findings.

Normal baseline HVA levels were found in the CSF of schizophrenics in studies that did not make use of probenecid (Chase, Schnur, and Gordon 1970; Fyró et al. 1974; Sedvall et al. 1974). These patients had not received neuroleptics for at least 2 weeks.

Employing probenecid, two other laboratories also reported normal concentrations of CSF HVA in schizophrenics who were diagnosed according to Feighner's criteria (Post et al. 1975; Berger et al. 1980). Post et al. (1975) found no significant differences in baseline or postprobenecid CSF HVA levels between 25 drug-free acute schizophrenics and a control group consisting of normals and patients with neurological disorders or affective illness. In agreement with Bowers (1973), Post et al. reported that the schizophrenics with more first-rank symptoms had significantly lower postprobenecid HVA levels than a group of schizophrenics with few first-rank symptoms. HVA concentrations were not related to psycho-motor excitement in Post's study, but CSF probenecid levels were not measured. Berger et al. (1980) reported no significant differences between normals and schizophrenics in baseline or postprobenecid CSF HVA and DOPAC levels. These patients were kept neuroleptic-free for 2 weeks and the results were statistically corrected for measured CSF probenecid concentrations. The postprobenecid CSF HVA levels found in 33 acute schizophrenics by van Praag (1977) were similar to the levels reported in schizophrenics in the above studies.

Bowers (1974) determined CSF probenecid and HVA levels in 17 patients who received a clinical diagnosis of "schizophrenic reaction." Neuroleptic treatment was stopped 2 weeks before study. The schizophrenics had significantly lower postprobenecid CSF HVA levels compared to 11 patients with bipolar affective disorder, exhibiting primarily mania. When the schizophrenics were divided according to their scores on the rating scale of Stephens and Astrup (1963), the poor prognosis group had significantly lower HVA concentrations than the better prognosis group. It was noted that the "paranoid psychotics" studied by Rimon et al. (1971) might have fitted into Bowers' better prognosis group of schizophrenics. Thus, a relationship between good prognosis and high CSF HVA might explain the finding reported by Rimon et al. of significantly higher baseline CSF HVA levels in a group consisting of paranoid schizophrenics and "other paranoid psychoses" compared to a control group of neurotics and affectively ill patients. Bowers (1974) found no differences in CSF probenecid concentrations among his groups, so the observed changes were apparently not due to a differential probenecid effect. He speculated that the relationship between poor prognosis and low CSF HVA may be due to a post-synaptic supersensitivity or to a substance other than DA that stimulates postsynaptic receptors, leading to a feedback inhibition of DA-releasing neurons (Bowers 1974, 1978).

Subsequently, Bowers' laboratory compared postprobenecid HVA concentrations between 10 patients with depressive illness and a group of 10 patients which included acute and chronic schizophrenics meeting Feighner's criteria (Kirstein, Bowers, and Henninger 1976). The schizophrenics had significantly higher CSF HVA levels than the depressed patients. HVA concentrations were unrelated to CSF probenecid levels or body movement in both schizophrenics and depressed controls. Thus, Bowers (1976) reports an overall pattern in which chronic schizophrenics tend to have lower CSF HVA values than manics, and acute schizophrenics have higher CSF HVA levels than depressed patients.

Most recently, Bowers and his coworkers assayed HVA, 5-HIAA, and probenecid levels in CSF from 30 young schizophrenics (mean age in years ± SD: males, 23.1 ± 2.8; females, 24.3 ± 7.8), 41 patients with major affective disorders (bipolar I, $n = 11$; bipolar II, $n = 4$; unipolar, $n = 26$), and 31 schizoaffective patients (Leckman, Bowers, and Sturgess 1981). All of the subjects had been drug-free for 2 weeks and were diagnosed according to Research Diagnostic Criteria (Spitzer, Endicott, and Robins 1975). Ratings of premorbid sexual adjustment were completed for all subjects with an abbreviated form of the Phillips Rating Scale of Premorbid History (Harris 1975). Postprobenecid CSF HVA and 5-HIAA concentrations
did not differ among the diagnostic groups. Within the group of schizophrenics, but not in the other diagnostic groups, poor premorbid sexual adjustment was associated with significantly higher CSF HVA levels and a high ratio of HVA concentration to log pro-benecid concentration. At first glance, this finding seems inconsistent with the previously reported correlation between poor prognosis and low CSF HVA among schizophrenics (Bowers 1974). The authors indicated, however, that a direct comparison between the studies is problematic since the Stephens-Astrup prognosis scale employed earlier contains only one item (out of 11) that relates to sexual functioning.

Sedvall and Wode-Helgøt (1980) measured baseline CSF monoamine metabolite levels in 36 hospitalized schizophrenics. Their patients met Research Diagnostic Criteria and had not received psychoactive drugs for 1 month before study. Eleven (30 percent) of the schizophrenics had a sibling, parent, aunt, or uncle with a diagnosis of schizophrenia. This group of patients with a family history of schizophrenia had significantly higher mean CSF levels of HVA and 5-HIAA, but not 3-methoxy-4-hydroxyphenylglycol (MHPG), compared to the schizophrenics without such a family history. The authors tentatively concluded that there is one group of schizophrenic disorders that has a disturbance in central DA and serotonin metabolism and a family disposition that may be genetically determined; another group of schizophrenic disorders has a normal central monoamine metabolism and no or a weak hereditary disposition.

In summary, the studies reviewed above have not shown differences in CSF HVA concentrations between schizophrenics and normal or neurological controls. One laboratory has found that the CSF HVA values of schizophrenics tend to lie above the values of depressed patients and below those in patients exhibiting mania (Bowers 1976). Independent investigators have reported that, in schizophrenic subjects, low CSF HVA is associated with poor prognosis (Bowers 1974) and the presence of first-rank symptoms (Bowers 1973, Post et al. 1975), whereas high CSF HVA is significantly related to a positive family history of schizophrenia (Sedvall and Wode-Helgøt 1980) and poor premorbid sexual adjustment (Leckman, Bowers, and Sturges 1981).

### Enzyme Activities

**Dopamine-β-hydroxylase (DBH).** DBH activity in schizophrenics is of interest because it may relate to the DA hypothesis of schizophrenia as well as the hypothesis of Stein and Wise (1971) that noradrenergic "reward" pathways are damaged in schizophrenia. These investigators reported that their hypothesis was supported by a significantly decreased DBH activity in post-mortem specimens of hippocampus, diencephalon, and pons-medulla in 18 schizophrenics compared to 12 nonpsychiatric controls (Wise and Stein 1973; Wise, Baden, and Stein 1974). However, this finding has not been confirmed by later studies (Wyatt et al. 1975, 1978; Cross et al. 1978; Crow et al. 1979). Wyatt et al. (1975, 1978) found no significant differences in the DBH activities of post-mortem hypothalamus, hippocampus, and pons from nine chronic schizophrenics and nine nonpsychiatric controls. They suggested that negative correlations between enzyme activity and both morgue-to-autopsy time and neuroleptic dose will explain at least some of the differences between schizophrenics and controls reported by Wise and Stein, as they appear to do in our data. [Wyatt et al. 1975, p. 369]

Another laboratory demonstrated closely similar DBH activities in 12 schizophrenics and 12 general hospital controls in post-mortem samples of hippocampus, hypothalamus, and four cortical areas (Cross et al. 1978; Crow et al. 1979). Lerner et al. (1978) reported no significant differences in CSF DBH activities among four diagnostic groups: schizophrenia or schizoaffective disorder (n = 11), major depressive disorders (n = 16), alcoholism (n = 16), and personality disorders (n = 5).

Several studies indicate that plasma DBH activity is not significantly different in schizophrenics and normal controls (Shopsin et al. 1972; Wetterberg et al. 1972; Dunner et al. 1973; Lamprecht et al. 1973; Meltzer et al. 1976; Meltzer, Nasr, and Tong 1980; DeLisi et al. 1980, 1981a). Taken together, these investigations compile data on 333 schizophrenics and 423 normals. Two studies actually found tendencies toward higher mean DBH activities in schizophrenics compared to controls: Markianos, Mystrom, and Reichel (1976) and Lamprecht et al. (1973), respectively, reported 38-percent and 35-percent increases in schizophrenics. Okada et al. (1976) reported that the 24-hour rhythm of plasma DBH ac-
tivity in eight chronic schizophrenics was similar to that in normal subjects.

In contrast to the above findings, Fujita et al. (1978, 1979) reported a significant 59-percent decrease in plasma DBH activity in 159 schizophrenics compared to 153 normals. These patients met Schneider's (1959) diagnostic criteria and were receiving neuroleptics during the study. The report by DeLisi et al. (1981a) of a neuroleptic-induced 27-percent decrease in the plasma DBH activities in a group of schizophrenics suggests that at least some of the decrement observed by Fujita et al. (1978, 1979) may have been drug-induced. Alternatively, it has been speculated that the conflicting results of Fujita et al. (1978, 1979) may be due to differences in the presence and penetration of the DBH gene in the schizophrenic populations of different nationalities (Meltzer, Nasr, and Tong 1980).

Lamprecht et al. (1973) measured plasma DBH activity in 12 pairs of monozygotic twins discordant for schizophrenia. There was a highly significant correlation between enzyme activities in schizophrenic and nonschizophrenic cotwins, suggesting that plasma DBH activity is genetically determined. Baron, Levitt, and Perlman (1980) found that plasma DBH was significantly reduced in schizophrenics with a family history of schizophrenia spectrum disorders compared to a group of schizophrenics with unaffected relatives and a group of unrelated normal controls. Plasma DBH was also significantly lower in 9 schizophrenics compared to 26 of their normal relatives in an isolated Swedish pedigree (Boök, Wetterberg, and Modrzweska 1978; Wetterberg et al. 1979). However, DeLisi et al. (1980) reported that schizophrenic family members had higher plasma DBH activities than their healthy relatives in 9 of 13 American families (p < .01).

Again, the apparent disagreement between these results might be secondary to international differences in some characteristics of the DBH gene.

All of the above results were obtained when DBH activity was assayed in the presence of Cu²⁺ and/or N-ethylmaleimide in order to antagonize endogenous DBH inhibitors. Most of the studies have found no evidence of a significant decrease in brain, CSF, and plasma DBH activity in schizophrenics. Accordingly, Yu et al. (1980) recently reported that plasma DBH activity, assayed with Cu²⁺ and N-ethylmaleimide, was not significantly different in 24 chronic schizophrenics compared to 20 normal controls. When the assay was conducted without anti-inhibitors, though, the "apparent" DBH activities were considerably reduced in all cases, with the schizophrenic group becoming significantly lower than the control group. The plasma of four of the schizophrenics induced a 30- to 70-percent inhibition of purified bovine DBH activity in vitro. The authors hypothesized that some schizophrenics have unusually high endogenous DBH-inhibitory activity or a deficiency in the copper cofactor. In this regard, Wise and Stein (1973) reported that analysis of brain homogenates did not affect enzyme activity, suggesting that their finding of decreased brain DBH in schizophrenics was not due to an excess of endogenous dialyzable inhibitors. Wyatt et al. (1978) found no significant differences in DBH-inhibitory activity between chronic schizophrenics and controls in post-mortem hypothalamus and hippocampus. Furthermore, several studies indicate that schizophrenics actually have elevated plasma copper levels (reviewed by Baron et al. 1982). The novel results of Yu et al. (1980) require further clarification, including the assay of plasma DBH-inhibitory activity in schizophrenics and controls.

Monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). A lowered activity of a DA-degrading enzyme in schizophrenics would have obvious relevance to the DA hypothesis. In a recent review, Wyatt et al. (1980) reported that 22 out of 32 studies found significantly lower platelet MAO activity in chronic schizophrenics compared to controls. Acute schizophrenia generally is not associated with low platelet MAO activity (Wyatt et al. 1980). Some studies indicate that decreased platelet MAO activity may be especially prevalent among schizophrenics with auditory hallucinations and paranoid features (Wyatt et al. 1980; Jeste et al. 1982). The importance of endogenous MAO inhibitors in the plasma of chronic schizophrenics has not been settled (Vogel, Ladman, and Berrettini 1980; Demisch et al. 1981). Significantly reduced MAO activity was also found in the lymphocytes of chronic schizophrenics (Sullivan et al. 1978), and in skeletal muscle from acute and chronic schizophrenics (Meltzer, Jackman, and Arora 1980). Acute, but not chronic, schizophrenics were reported to have significantly decreased plasma amine oxidase activity (Meltzer et al. 1980a).
The MAO findings outlined above have an unclear etiological significance, especially since: neuroleptics can reduce platelet MAO activity in schizophrenics (Friedhoff, Miller, and Weisenfreund 1978; Jackman and Meltzer 1980; Chojnacki et al. 1981; DeLisi et al. 1981b; Sahai, Arora, and Meltzer 1981); low platelet MAO activity is also present in many normals (Buchsbaum, Coursey, and Murphy 1976; Murphy et al. 1977); the greatest group mean reduction of activity observed by any study was only 68 percent in schizophrenics compared to controls (Wyatt et al. 1980). Moreover, brain MAO activity apparently is not decreased in schizophrenics. Seven recent post-mortem studies found no differences between controls and schizophrenics in the MAO activities of up to 14 brain areas, using a wide range of MAO substrates (Meltzer, Jackman, and Arora 1980; Reveley et al. 1981). It is possible that a decreased peripheral MAO activity is only one factor, among other genetic and environmental factors, contributing to the etiology of schizophrenia (Wyatt et al. 1980).

Wise, Baden, and Stein (1974) measured post-mortem COMT activity in the brains of 18 schizophrenics and 12 controls. They reported a significantly decreased activity in the diencephalon of the schizophrenics, with no difference in the pons-medulla. The authors cautioned that this deficit must be regarded as provisional until verified in larger populations because individual values of COMT varied widely in the schizophrenics. More recently, two laboratories reported no differences in post-mortem COMT activity between schizophrenics and controls in up to 14 brain regions, including the hypothalamus and thalamus (Cross et al. 1978; Wyatt et al. 1978; Crow et al. 1979).

Poitou, Assicot, and Bohuon (1974) found that membrane-bound, but not soluble, erythrocyte COMT activity was significantly increased in schizophrenics compared with normal controls. Matthysses and Baldessarini (1972) reported a slightly greater (0.05 < p < 0.1) whole blood COMT activity in 20 chronic schizophrenics compared to 13 nonschizophrenic psychiatric patients. Three other groups found no differences between schizophrenics and controls in soluble erythrocyte COMT activity (Dunner et al. 1971; Briggs and Briggs 1973; Ebstein et al. 1976). Shospin et al. (1973) reported an increased K_m value for the soluble erythrocyte COMT in paranoid schizophrenics compared to either schizoaffective or chronic undifferentiated types.

Tyrosine hydroxylase (TOH) and dihydroxyphenylalanine decarboxylase (DD). Excessive DA synthesis conceivably could result from elevated activities of TOH and DD in dopaminergic neurons. One laboratory reported that the rate of decarboxylation of ^14C-labeled dl-dihydroxyphenylalanine (dl-DOPA) by erythrocytes was elevated in schizophrenics with hallucinations and thought disorder compared to normals and schizophrenics in remission (Tran, Laplante, and Lebel 1971; Tran-Manh et al. 1972). The authors concluded that this result may have been due to either an increased DD activity or an increased physical transport of DOPA across the cell membrane, or both. The functional importance of an elevated DD activity is uncertain since rat brain DD is normally present in great excess in comparison to TOH (Carlsson et al. 1972a). Thus, it seems improbable that an elevated DD activity alone could lead to excessive DA synthesis in schizophrenia. Moreover, post-mortem brain DD and TOH activities did not significantly differ between schizophrenics and controls in the putamen, caudate, substantia nigra, and globus pallidus (Wyatt et al. 1978). Crow et al. (1979) also found that post-mortem TOH activity was similar in schizophrenics and controls in the putamen, caudate, and nucleus accumbens.

Urinary Metabolites. Urine specimens have not been a primary source of information about central biogenic amine metabolism in schizophrenia because of the contamination by peripheral metabolites in the sample (Goodwin and Post 1975). However, the urine may contain abnormal metabolite levels if schizophrenics have a functional deficit in the peripheral metabolism of biogenic amines (i.e., a decreased peripheral MAO activity). Elevated unmetabolized biogenic amines could then cross the blood-brain barrier to cause behavioral symptoms. With this reasoning in mind, it is interesting that four out of six studies have found evidence of elevated phenylethylamine (PEA) levels in the urine of some schizophrenics (Wyatt et al. 1980; Jeste et al. 1981). PEA structurally resembles amphetamine and is known to induce a hyperactivity syndrome in animals which resembles the effects of dopaminergic drugs (Potkin et al. 1979). Potkin et al. (1979) recently measured the 24-hour excretion of PEA in 32...
normals and 31 chronic schizophrenics, 16 of whom had paranoid symptoms. The normals and nonparanoid patients did not differ in PEA excretion, but urinary PEA was significantly elevated in the paranoid group compared to controls. The paranoid and nonparanoid groups each had significantly decreased urinary phenylacetic acid (PAA) and elevated PEA/PAA ratios (Potkin, Wyatt, and Karoum 1980). These results suggest that some schizophrenics may have a functionally deficient activity of peripheral type B MAO, which converts PEA into its major metabolite, PAA (Domino 1980). It is noteworthy that PEA readily crosses the blood-brain barrier, and also has the highest affinity for type B MAO among the known endogenous substrates for the enzyme (Yang and Neff 1973; Domino 1980; Wyatt et al. 1980).

The existence of a type B MAO deficiency is also supported by the frequently observed peripheral MAO deficits in chronic schizophrenics (Wyatt et al. 1980). Peripheral MAO, such as in human platelets and skeletal muscle, is largely of the B type (Domino 1980). A functional type B deficiency might be expected to yield low levels of HVA in bodily fluids since DA is a mixed A and B MAO substrate that is largely converted to HVA (Goodall and Alton 1968; Domino 1980). However, Domino (1980) found no significant differences in urinary HVA levels between seven drug-free chronic schizophrenics and seven controls. Bowers (1976) suggested that a central type B MAO deficiency may be responsible for the low CSF HVA levels in chronic schizophrenics with poor prognoses. This hypothesis seems less likely in view of several recent reports that brain MAO activity is not reduced in schizophrenics (Meltzer, Jackman, and Arora 1980). Along this line, Reynolds et al. (1979) reported that CSF PAA levels were actually elevated in nine schizophrenics compared to controls. The latter finding casts further doubt on a central MAO deficiency and, instead, may reflect an abnormal elevation of PEA in schizophrenia.

Using the hypothesis that schizophrenics have a peripheral deficit in pure type B MAO, Domino (1980) predicted that the patients should have abnormal urinary levels of the substrates and products of type B, but not type A MAO. As expected, Domino (1980) found no evidence of a decreased type A MAO activity in chronic schizophrenics when he measured urinary levels of type A or mixed A and B MAO metabolites. It was proposed that a type B MAO functional deficiency could be tested for by examining the levels of type B substrates and their metabolites in the urine of schizophrenics under excess substrate conditions in vivo (Domino 1980).

DA Receptor Sensitivity

Post-mortem Brain Binding of DA Agonists and Antagonists. A recent theoretical trend has turned toward the consideration of postsynaptic receptor pathology since the majority of studies have not demonstrated an elevated DA turnover in schizophrenia (Bowers 1974; Snyder 1976). Four out of five laboratories have provided evidence for a postsynaptic dopaminergic supersensitivity in the post-mortem brains of schizophrenics (Lee et al. 1978; Owen et al. 1978; Mackay et al. 1980a, 1980b; Reisine et al. 1980a, 1980b; Reynolds et al. 1980, 1981).

Lee and Seeman (1980a, 1980b) have determined the specific binding of 3H-neuroleptics in the post-mortem brains of 59 neurologically normal controls and 50 schizophrenics who were diagnosed according to the presence of Schneider's first-rank symptoms. 3H-Haloperidol and 3H-spiroperidol binding was significantly elevated in the caudate and putamen of schizophrenics compared to controls, but 3H-apomorphine binding did not differ between the groups in the same regions (Lee et al. 1978; Lee and Seeman 1980a, 1980b; Seeman et al. 1980).

3H-Neuroleptic binding was also significantly increased in both the caudate and putamen of 11 schizophrenics who had no history of long-term neuroleptic treatment. Owen et al. (1978) obtained post-mortem brain samples from 19 general hospital controls and 19 schizophrenics who met Feighner's diagnostic criteria. Compared to controls, the schizophrenics had significantly elevated 3H-spiroperidol binding in the caudate, putamen, and nucleus accumbens. The binding of 3H-ADTN, a DA agonist, did not differ between the groups in the caudate and putamen (Cross, Crow, and Owen 1979; Crow et al. 1980). Scatchard analysis of the spiroperidol binding in the caudate revealed a significantly increased number of receptors and a decreased receptor affinity in the schizophrenics. On the basis of animal experiments, the apparently reduced affinity was attributed to the presence of residual neuroleptics in the brain samples. Maximum spiroperidol binding was sig-
significantly increased but affinity was unchanged in the caudates of five patients who had no neuroleptic treatment for at least 1 year before death. These findings were recently confirmed by the Scatchard analysis of $^3$H-flupenthixol binding in caudate samples from seven drug-free schizophrenics (Cross, Crow, and Owen 1981). The use of a selective DA D2 receptor antagonist indicated that only the D2, and not the D1, component of $^3$H-flupenthixol binding was elevated in drug-free patients. Thus, it is suggested that schizophrenia is associated with a supersensitivity of the D2 type of DA receptor which is not linked to an adenylate cyclase.

The binding of $^3$H-spiroperidol was determined by Reisine et al. (1980a, 1980b, 1980c) in the post-mortem brains of 11 nonneurological controls and 11 schizophrenics. In a comparison with controls, $^3$H-spiroperidol binding was significantly increased in both the caudate and putamen of the schizophrenics, but was unaltered in the frontal cortex. Significantly elevated caudate binding was also found in three schizophrenics who were not receiving neuroleptic therapy at the time of death. Mackay et al. (1978) reported a nonsignificant elevation of $^3$H-spiroperone binding in the nucleus accumbens of 26 schizophrenics compared to 17 controls. However, these investigators repeated the study and found that another group of schizophrenics had significantly increased numbers of receptors and a decreased receptor affinity in the caudate and nucleus accumbens (Mackay et al. 1980a, 1980b). In agreement with Owen et al. (1978), the authors felt that the decreased receptor affinity observed in schizophrenics was the result of competition for $^3$H-spiroperone binding by neuroleptic agents remaining in the brain after death. Mackay et al. (1980b) emphasized that the DA receptor alterations were not seen in a subgroup of schizophrenics who were free of neuroleptic drugs for 1 month or more before death. Compared to controls, both the receptor numbers and affinities were not significantly different in samples of caudate from seven drug-free patients and nucleus accumbens from four drug-free patients. This result differs from previous reports of elevated brain $^3$H-neuroleptic binding in drug-free schizophrenics by Lee and Seeman (1980a, 1980b; drug-free $n$ = 11); Cross, Crow, and Owen (1981; $n$ = 7); and Reisine et al. (1980a, 1980b; $n$ = 3).

In contrast to the results of the four laboratories reviewed above, Reynolds et al. (1980, 1981) found that the post-mortem putamen binding of $^3$H-spiroperone did not differ between 17 nonpsychiatric controls and 10 schizophrenics meeting Feighner's diagnostic criteria. The receptor numbers of four drug-free schizophrenics tended to lie within the control range (Reynolds et al. 1980). In accord with Owen et al. (1978) and Mackay et al. (1980b), receptor affinities were lower in neuroleptic-treated schizophrenics as compared to either the controls or drug-free patients (Reynolds et al. 1980).

More work is needed to determine whether the elevated brain binding of $^3$H-neuroleptics, reported by four out of five laboratories, is secondary to a drug effect or to the schizophrenic disease process. Animal investigations indicate that chronic neuroleptic treatment induces a postsynaptic DA receptor supersensitivity (Muller and Seeman 1978; Haracz and Tseng 1980). The schizophrenia binding studies have included only a small number of patients who were drug-free for 1 month or more before death. As pointed out above, there is conflicting evidence as to the presence of DA receptor abnormalities in drug-free schizophrenics.

Further clarification may be obtained by comparing the characteristics of DA receptors in brain samples from neuroleptic-treated animals and recently deceased schizophrenics. Already, Crow (1980) has underscored some differences in the animal and human data that may suggest that the schizophrenia binding results are not drug-related. Chronic neuroleptic administration to animals induced a smaller elevation in receptor number than that seen in many schizophrenics. Moreover, only the type of receptor labeled by DA antagonists is increased in schizophrenia, whereas receptors labeled by both antagonists and agonists are increased in animals after prolonged neuroleptic treatment.

Adenylate Cyclase Activity. Some postsynaptic DA receptors (D1-type) are thought to be associated with a DA-sensitive adenylate cyclase (Kebabian, Petzold, and Greengard 1972). Carelli et al. (1975) reported no significant differences between nine nonpsychiatric controls and seven chronic schizophrenics in the basal or DA-stimulated activity of adenylate cyclase (AC) in post-mortem caudate. This finding concurs with a recent report that the D1 compo-
nent of \(^3\)H-neuroleptic binding was not elevated in post-mortem caudate samples from schizophrenics (Cross, Crow, and Owen 1981). Pandey et al. (1977) found that platelet prostaglandin (PG) E\(_1\)-stimulated AC activity was significantly higher in five acute schizophrenics, but not four chronic patients, compared to 10 normals. On the other hand, Rotrosen et al. (1978, 1980) reported significantly lower PGE\(_1\)-stimulated activity of platelet AC in both acute (n = 7) and chronic (n = 32) schizophrenics compared to 29 normals. Kafka and van Kammen (1978) also found a reduced PGE\(_1\)-stimulated AC activity in the platelets of male schizophrenics compared to healthy males. Subsequent studies by Pandey's group apparently have not confirmed their initial finding of elevated platelet AC activity in acute schizophrenics (Rotrosen et al. 1978). It is not known if there is any relationship between the activities of brain and platelet AC.

Neuroendocrinology. The generality of the DA hypothesis of schizophrenia has been intensively studied with neuroendocrinologic methods. These studies examine dopaminergic activity in the hypothalamic-pituitary system in order to test for a generalized dopaminergic hyperactivity in the brains of schizophrenics. DA of hypothalamic origin appears to be physiologically involved in the stimulatory control of growth hormone (GH) secretion (Martin 1973) and the tonic inhibitory control of prolactin release (Meites and Clemens 1972; Gudelsky 1981).

Two approaches have been used in studies of the hypothalamic-pituitary DA system: (1) basal plasma hormone levels in schizophrenics and controls may reflect a presynaptic hyperactivity or a postsynaptic supersensitivity; (2) the effects of DA agonists on hormone levels might expose a postsynaptic DA receptor supersensitivity in schizophrenics. It should be cautioned that a demonstration of excessive hypothalamic-pituitary DA activity cannot necessarily be used as evidence for hyperactivity of the mesolimbic, mesocortical, and nigrostriatal DA systems (Meltzer et al. 1978).

In general, basal plasma prolactin levels have not differed in acute and chronic schizophrenics compared to controls or to a normal laboratory range (Meltzer, Sachar, and Frantz 1974a, 1974b; Brambilla et al. 1976; Ettigi et al. 1976; Meltzer and Fang 1976; Johnstone, Crow, and Mashiter 1977; Wode-Helgott et al. 1977; Cotes et al. 1978; Gruen et al. 1978; Rotrosen et al. 1979; Naber, Ackenheil, and Laakmann 1980). Brambilla et al. (1979a) reported "markedly low" basal prolactin levels in 6 of 10 chronic schizophrenics (p = 0.1). Most investigators also found that basal GH levels are within the normal range in schizophrenics (Schimmelbusch, Mueller, and Sheps 1971; Vigneri et al. 1974; Cotes et al. 1978; Brambilla et al. 1979a; Rotrosen et al. 1979; Meltzer et al. 1980b). In contrast, two studies have reported significantly elevated baseline GH in schizophrenics compared to controls (Ettigi et al. 1976; Janowsky et al. 1978). Ettigi et al. (1976) examined 17 chronic schizophrenics who had not received neuroleptics for at least 2 weeks, and Janowsky et al. (1978) studied a mixed group of 19 acute and chronic schizophrenics, most of whom were on neuroleptics. Thus, only 3 of 15 studies are consistent with a generalized DA hypothesis which would predict depressed basal prolactin and elevated basal GH levels in schizophrenics.

Rotrosen et al. (1979) recently reviewed several investigations of the effects of DA agonists on neuroendocrine function in schizophrenics. In their own experience, the plasma GH rise in response to apomorphine was reliable when measured on two or three occasions in the same subjects, whereas the prolactin depression was less reliable (Rotrosen et al. 1979). The authors concluded that prolactin suppression by DA agonists is a poor tool for quantitatively comparing individuals or groups. Studies of the endocrine responses to the indirect DA agonists, L-DOPA and amphetamine, produced highly variable results with no clear-cut differences between schizophrenics and controls (Rotrosen, Angrist, and Paquin 1978; Rotrosen et al. 1979). However, a more consistent pattern has emerged from studies of GH responses to apomorphine: significantly exaggerated GH responses were found in drug-free acute schizophrenics, and in those chronic schizophrenics with sporadic or little neuroleptic use (Pandey et al. 1977; Rotrosen et al. 1979). Chronic schizophrenics who had received prolonged neuroleptic treatment showed significantly blunted GH responses to apomorphine (Ettigi et al. 1976; Rotrosen et al. 1976; Tamminga et al. 1977). Similarly, Meltzer and coworkers reported a strong trend for schizophrenics ill less than 4 years to have a larger GH response than controls, whereas those ill 4 or more years tended to have a small-
er GH response than controls (Meltzer et al. 1980b; Meltzer, Busch, and Fang 1981).

The blunted GH responses in chronic schizophrenics did not seem to be due to residual neuroleptics since the patients in the above studies had been withdrawn from medication for periods ranging from 1 to 15 weeks. Instead, two independent studies found that the blunted responses were statistically related to the total years of previous neuroleptic treatment (Ettigi et al. 1976; Rotrosen et al. 1979). Along this line, Rotrosen et al. (1979) cited animal studies showing hypothalamic-pituitary subsensitivity induced by chronic neuroleptics. They concluded that a similar mechanism could result in the blunted responses to apomorphine in chronic schizophrenics. It was also suggested that the exaggerated GH responses in unmedicated acute and chronic schizophrenics may represent a DA receptor supersensitivity that is characteristic of the schizophrenic disease process. This hypothalamic-pituitary receptor supersensitivity may not be reflected in basal hormone levels due to other overriding neuroendocrine control mechanisms. Again, it is not clear if these results represent an isolated DA receptor supersensitivity in the hypothalamic-pituitary system, or if a generalized dopaminergic supersensitivity might exist.

**Clinical Effects of Drugs That Alter Dopaminergic Activity**

**DA Agonists.** Various drugs that increase or decrease dopaminergic activity have been given to schizophrenics in clinical tests of the DA hypothesis. Of these agents, DA agonists understandably have been the most intensively studied. The most forthright interpretation of the DA hypothesis would predict an exacerbation of schizophrenic symptomatology by DA agonists. The 24 studies outlined in table 2 appear to have yielded rather complex results, but some patterns in the data can be discerned.

Studies 1–7 (table 2) reported therapeutic improvements when l-DOPA or amphetamine was given to chronic schizophrenics in addition to, or instead of, the patients' usual maintenance neuroleptics. Descriptive information revealed that most of these patients had marked “negative” symptoms of withdrawal, motor retardation, and blunted affect. It has been suggested that these results are inconsistent with the DA hypothesis (Alpert and Friedhoff 1980), but the therapeutic improvement in each study largely consisted of a decrease in negative symptoms with little change in psychotic symptomatology. For example, Inanaga et al. (1975) reported that l-DOPA increased motivation, active contact, and activity while having little effect on hallucinations and delusions. Cesarec, Eberhard, and Nordgren (1974) found an improved initiative and interest in the surroundings when 15- to 20-mg daily oral doses of amphetamine were added to the neuroleptic regimen. Segal and Janowsky (1978) observed that those patients who improved following a methylphenidate infusion were often chronically deteriorated, chronically hospitalized schizophrenics. In contrast, a recent report indicated that d-amphetamine, 0.5 mg/kg orally, did not significantly improve the motor retardation and blunted affect in a group of acute and chronic schizophrenics (Angrist, Rotrosen, and Gershon 1980a). The latter patient group appeared to be more actively psychotic than the emotionally withdrawn patients predominating in studies 1–6 (table 2). Thus, the beneficial effect of DA agonists is most commonly seen in the chronically deteriorated patient whose clinical picture is dominated by negative symptoms.

There are at least two ways in which the improvement in negative symptoms can be explained in accord with the DA hypothesis: (1) Meltzer and Stahl (1976) suggested that low doses of DA agonists may counteract the neuroleptic-induced inhibition of dopaminergic activity in DA tracts (e.g., the nigrostriatal) that are not related to the pathogenesis of the psychosis; (2) Kety (1979) proposed that the negative symptoms of schizophrenia may result from a diminished noradrenergic activity. Although l-DOPA administration would elevate noradrenergic and dopaminergic activity, the DA effects would be blocked by the neuroleptics.

A clinical worsening was observed in studies 7–19 (table 2) when various DA agonists were given to schizophrenics orally or intravenously (i.v.). These studies included patients with prominent “positive” symptoms (i.e., hallucinations and delusions), unlike most of the patients in studies 1–6. Three groups explicitly described a DA agonist-induced worsening of preexisting positive symptoms (Yaryura-Tobias, Diamond, and Merlis 1970; Janowsky et al. 1973; Angrist and Gershon 1977). These
Table 2. Clinical effects of DA agonists in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n) and diagnostic criteria</th>
<th>DA agonist and neuroleptic treatment design</th>
<th>Research design</th>
<th>DA agonist effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarec, Ebertard, and Nordgren (1974)</td>
<td>9 chronic schizophrenics, clinical diagnoses</td>
<td>Amphetamine × 14 days, 15-20 mg/day, p.o. + NL</td>
<td>Open, uncontrolled</td>
<td>Clinical impression of negative symptoms: overall I (p &lt; .05), 5, 4 NC, 1 NC</td>
</tr>
<tr>
<td>Buchanan et al. (1975)</td>
<td>14 chronic schizophrenics, clinical diagnoses</td>
<td>L-DOPA × 8 weeks, maximum dose = 300-500 mg/day, p.o. + NL</td>
<td>Double blind, placebo control</td>
<td>RPRS, overall NS; clinical impression: 8, 5, 3 NC, 1 W</td>
</tr>
<tr>
<td>Gerlach and Luhdorf (1975)</td>
<td>13 simple schizophrenics, clinical diagnoses</td>
<td>L-DOPA × 12 weeks, maximum dose = 1,250 mg/day, + NL</td>
<td>Double blind, placebo control</td>
<td>Total BPRS: Overall I (p &lt; .05), 9, 1 NC, 1 NC, 1 W; YAWS: overall I activity (p &lt; .05)</td>
</tr>
<tr>
<td>Inanaga et al. (1975)</td>
<td>52 chronic schizophrenics, clinical diagnoses</td>
<td>L-DOPA × 6 weeks, maximum dose = 300-900 mg/day + benserazid 75-225 mg/day, p.o. + NL</td>
<td>Double blind, placebo control</td>
<td>&quot;Therapeutic response&quot;: overall I (p &lt; .05)</td>
</tr>
<tr>
<td>Ogura, Kishimoto, and Nakao (1976)</td>
<td>94 chronic schizophrenics, clinical diagnoses</td>
<td>L-DOPA × 4.6 months (average), maximum dose = 150-1,600 mg/day, + NL</td>
<td>Double blind, placebo control</td>
<td>Modified WRIS scores of affective disorder, active behavior, and maladjustment to reality: overall NS, 2, NC, 1 NC</td>
</tr>
<tr>
<td>Cali, Yesavage, and Hollister (1977)</td>
<td>38 chronic schizophrenics, 38 hebephrenic, 2 paranoid, 2 catatonic</td>
<td>L-DOPA x 6-8 weeks, maximum dose = 300-500 mg/day, p.o. + NL</td>
<td>Open, uncontrolled</td>
<td>&quot;Therapeutic effect&quot;: 21, 6, 9 NC, 1 W</td>
</tr>
<tr>
<td>Oguni, Yassen, and Nakao (199a)</td>
<td>6 chronic hebephrenic schizophrenics, WHO</td>
<td>L-DOPA × 30 days, maximum dose = 2 g/day, + carbidopa 200 mg/day, p.o. + NL</td>
<td>Double blind, placebo control</td>
<td>BPRS: 2, 1, NC, 1 W</td>
</tr>
<tr>
<td>Brambilla et al. (1979b)</td>
<td>6 chronic schizophrenics: 5 undifferentiated, 2 paranoid, DSM-III</td>
<td>L-DOPA × 8 weeks, maximum dose = 300-600 mg/day, p.o., + NL</td>
<td>Double blind, placebo control</td>
<td>&quot;Therapeutic effect&quot;: 3, 2, NC, 1 W</td>
</tr>
<tr>
<td>Cali, Yesavage, and Hollister (1977)</td>
<td>8 chronic schizophrenics: 7 undifferentiated, 1 RDC</td>
<td>L-DOPA × 24 days, maximum dose = 6 g/day, p.o.</td>
<td>Open, uncontrolled</td>
<td>BPRS: 2, 1, NC, 1 W</td>
</tr>
<tr>
<td>Yaqub and Gershon (1973)</td>
<td>9 chronic schizophrenics, clinical diagnoses</td>
<td>L-DOPA × 3 weeks, maximum dose = 3-9 g/day, + NL</td>
<td>Open, placebo control</td>
<td>Open, placebo control</td>
</tr>
<tr>
<td>Yaqub and Gershon (1973)</td>
<td>10 schizoaffective, clinical diagnoses</td>
<td>L-DOPA × 3 weeks, maximum dose = 3-9 g/day, + NL</td>
<td>Open, placebo control</td>
<td>BPRS, clinical impression: 7, I psychosis, 3 &quot;nonspecific stimulation&quot;</td>
</tr>
</tbody>
</table>

Clinical Impression of Negative Symptoms: overall I (p < .05), 5, 4 NC, 1 NC
RPRS: overall NS; clinical impression: 8, 5, 3 NC, 1 W
Total BPRS: Overall I (p < .05), 9, 1 NC, 1 NC, 1 W; YAWS: overall I activity (p < .05)
"Therapeutic response": overall I (p < .05)
Modified WRIS scores of affective disorder, active behavior, and maladjustment to reality: overall NS, 2, NC, 1 NC
"Therapeutic effect": 21, 6, 9 NC, 1 W
BPRS: 2, 1, NC, 1 W
"Therapeutic effect": 3, 2, NC, 1 W
BPRS: 2, 1, NC, 1 W
Clinical Impression: 4 hallucinations, 1 "diffuse toxic psychosis"
<table>
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<tr>
<th>Study</th>
<th>Patients (n) and diagnostic criteria</th>
<th>DA agonist and neuroleptic treatment</th>
<th>Research design</th>
<th>DA agonist effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Janowsky et al. (1973)</td>
<td>22 &quot;actively ill&quot; schizophrenics: 5 chronic undifferentiated, 4 acute, 5 schizoaffective, 7 paranoid, 1 catatonic, DSM–II</td>
<td>Methylphenidate, 0.5 mg/kg, i.v., + NL and − NL</td>
<td>Double blind, placebo control</td>
<td>Modified B-H; overall ↑ psychosis (p &lt; .00003) at + 15 minutes, results unaffected by NL</td>
</tr>
<tr>
<td>12. Angrist et al. (1975, 1977)</td>
<td>7 schizophrenics: 1 acute paranoid, 4 chronic undifferentiated, 2 schizoaffective, clinical diagnoses</td>
<td>ET-495 × 6–18 days, maximum dose = 80–320 mg/day, p.o., − NL</td>
<td>Open, uncontrolled</td>
<td>BPRS scores: overall NS; clinical impression: 4 ↑ psychosis, 2 NC, 1 ↓ psychosis</td>
</tr>
<tr>
<td>13. Davis and Janowsky (1973); Janowsky and Davis (1974, 1976)</td>
<td>16 &quot;actively ill&quot; schizophrenics, DSM–II</td>
<td>Single i.v. injections of 29 mg methylphenidate, 10–20 mg d-amphetamine, 28 mg l-amphetamine (no information on NL)</td>
<td>Double blind, placebo control, crossover</td>
<td>5-pt. scale: overall ↑ psychosis and activation scores (p &lt; .05) at + 10–20 minutes after all drugs</td>
</tr>
<tr>
<td>14. Janowsky et al. (1977); Janowsky, Huey, and Storms (1977)</td>
<td>16 &quot;actively psychotic&quot; schizophrenics, DSM–II</td>
<td>Methylphenidate, 0.5 mg/kg, i.v., + NL</td>
<td>Double blind, nonpsychotic in-patient control group</td>
<td>Schizophrenics: overall ↑ global psychosis ratings and pathologic responses in word association and ink blot tests (p &lt; .05) at + 15 minutes</td>
</tr>
<tr>
<td>15. Small et al. (1977)</td>
<td>5 chronic schizophrenics, RDC</td>
<td>Lergotrile × 3–14 days, maximum dose = 6–8 mg/day, + NL</td>
<td>Double blind, antiparkinsonism drug control</td>
<td>BPRS and clinical impression: 5 ↑ psychosis</td>
</tr>
<tr>
<td>16. Trabucchi et al. (1977)</td>
<td>12 patients with &quot;various psychotic syndromes, mostly schizophrenia,&quot; clinical diagnoses</td>
<td>Bromocriptine × 1 week, 15 or 37.5 mg/day, − NL</td>
<td>Open, uncontrolled</td>
<td>BPRS: overall NS. Tendency toward ↑ psychotic symptoms after the high dose</td>
</tr>
<tr>
<td>17. Tamminga and Schaffer (1979)</td>
<td>12 chronic schizophrenics including schizoaffective, undifferentiated, paranoid, RDC</td>
<td>Bromocriptine (10 mg/day) or CF 25–397 (60 mg/day) × 3 weeks, p.o., + NL and − NL</td>
<td>Double blind, placebo control, crossover</td>
<td>Modified NHSI: ↑ psychosis in 3 of 7 patients after bromocriptine, NC after CF 25–397, results were unaffected by NL</td>
</tr>
<tr>
<td>18. Angrist, Rotrosen, and Gershon (1980a, 1980b)</td>
<td>21 schizophrenics: 2 acute, 8 subacute, 4 subchronic, 7 chronic, RDC</td>
<td>d-Amphetamine, 0.5 mg/kg, p.o., − NL</td>
<td>Open, uncontrolled</td>
<td>Overall ↑ in total BPRS (p &lt; .01) and positive symptoms (p &lt; .001); total BPRS: 17 W, 3 I, 1 NC</td>
</tr>
<tr>
<td>19. van Kammen and Bunney (1979)</td>
<td>19 schizophrenics, 27 schizoaffective, RDC</td>
<td>d-Amphetamine, 20 mg, i.v., − NL</td>
<td>Double blind, placebo control</td>
<td>Modified B-H psychosis scores: overall NS, 18 W, 14 I, 14 NC</td>
</tr>
</tbody>
</table>
Table 2. Clinical effects of DA agonists in schizophrenia—Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n) and diagnostic criteria</th>
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<th>DA agonist effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. Corsini et al. (1977)</td>
<td>58 schizophrenics: 24 paranoid, 4 catatonic, 18 schizoaffective, 12 hebephrenic, clinical diagnoses</td>
<td>Apomorphine, 1 mg, i.m., − NL</td>
<td>Open, uncontrolled</td>
<td>Modified BPRS: 21 ↓ psychosis lasting 20-50 minutes</td>
</tr>
<tr>
<td>21. Smith, Tamminga, and Davis (1977)</td>
<td>4 chronic schizophrenics, RDC</td>
<td>Apomorphine, 1.5–6 mg, s.c. or p.o., + NL and − NL</td>
<td>Double blind, placebo control</td>
<td>NHSI: 3 ↓ psychosis and 1 slight worsening at + 20 and + 40 minutes, results were unaffected by NL</td>
</tr>
<tr>
<td>22. Tamminga et al. (1978)</td>
<td>18 chronic schizophrenics: 7 undifferentiated, 6 paranoid, 5 schizoaffective, RDC</td>
<td>Apomorphine, 3 mg, s.c., + NL</td>
<td>Double blind, placebo control</td>
<td>Modified NHSI: overall ↓ psychosis (p &lt; .02) at + 30 to + 60 minutes, 9 I, 4 NC, 5 slight W</td>
</tr>
<tr>
<td>23. Hollister, Davis, and Berger (1980)</td>
<td>11 schizophrenics, RDC</td>
<td>Apomorphine x 2 weeks, 20 mg/day, p.o., + NL</td>
<td>Blind, placebo control</td>
<td>BPRS: generally NC in psychosis</td>
</tr>
<tr>
<td>24. Kornetsky (1976)</td>
<td>25 chronic schizophrenics, clinical diagnoses</td>
<td>d-Amphetamine x 4–7 days, maximum dose = 20–40 mg/day, p.o., − NL</td>
<td>Double blind, placebo control</td>
<td>Clinical Impression: NC in psychosis</td>
</tr>
</tbody>
</table>

Abbreviations: WHO = World Health Organization (1977); DMS-II = Diagnostic and Statistical Manual of Mental Disorders-II (American Psychiatric Association 1968); RDC = Research Diagnostic Criteria (Spitzer, Endicott, and Robins 1975); WRS = Wittenborn Rating Scale (Brambilla et al. 1979b); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); RPRS = Rating Scale of Rockland and Pollin (1965); VAVS = Activity—Withdrawal Scale of Variables (1957), B-H = Bunney-Hamburg Scale of Psychiatric Symptoms (Bunney and Hamburg 1963); NHSI = New Haven Schizophrenia Index (Astrachan et al. 1972); +/- NL = patients were on or off neuroleptics during the study; p.o. = orally; l.v. = intravenously; l.m. = intramuscularly; s.c. = subcutaneously; I = improved; NC = no change, W = worsened; NS = nonsignificant.

An effort was made to identify unique subject groups.
The failure to find a universal biochemical defect among schizophrenics has contributed toward the consideration of multiple disease entities as a basis for the "schizophrenias" (Buchshein and Haier 1978; Hornykiewicz 1978; Meltzer 1979; Crow 1980; Berger 1981). With heterogeneity as a possibility, some researchers have begun attempts at identifying biologically homogeneous subgroups within the schizophrenic population (Wyatt et al. 1981; Jeste et al. 1992). Thus, among schizophrenic subjects, a positive family history of schizophrenia was significantly related to low plasma DBH activity (Baron, Levitt, and Perlman 1980) and high CSF HVA (Sedvall and Wode-Helgodt 1980). Elevated CSF HVA was also associated with poor premorbid sexual adjustment in a group of schizophrenics (Leckman, Bowers, and Sturges 1981). Low CSF HVA was correlated with poor prognosis (Bowers 1974) and the presence of first-rank symptoms (Bowers 1973; Post et al. 1975). The presence of auditory hallucinations and paranoid features may discriminate chronic schizophrenics with decreased platelet MAO activity (Wyatt et al. 1980; Jeste et al. 1982).

Based on clinical phenomenology, Crow (1980) has distinguished two syndromes among patients with diagnoses of schizophrenia:

The first (the type I syndrome, equivalent to "acute schizophrenia," and characterised by the positive symptoms—delusions, hallucinations, and thought disorder) is in some way associated with a change in dopaminergic transmission; the second process (the type II syndrome, equivalent to the "defect state," and characterised by the negative symptoms—afferent flattening and poverty of speech) is unrelated to dopaminergic transmission but may be associated with intellectual impairment and, perhaps, structural changes in the brain . . . [Type I symptoms] predict a potential response to neuroleptics; [type II symptoms] are more closely associated with a poor long-term outcome. Episodes of type I symptoms may be followed by development of the type II syndrome, and both may be present together. Type II symptoms . . . occasionally occur in the absence of the type I syndrome . . .

Crow's type I symptoms are similar to the first-rank symptomatology of Schneider, while the type II symptoms correspond to the fundamental schizophrenic symptoms of Kraepelin and Bleuler (Mackay and Crow 1980).

Crow's hypothetical subgroups are tentatively supported by pharmacological, neuroendocrinological, and neuroradiological evidence. On the basis of drug responses, the type I and type II syndromes resemble, respectively, the neuroleptic/AMPT-responsive and -resistant subgroups of Nasrallah et al. (1977, 1990). Nasrallah's subgroups were felt to be indistinguishable on standard diagnostic criteria, but it was noted that six of seven neuroleptic/AMPT-resistant patients had evidence of lateral cerebral ventricular enlargement on computerized tomographic scans (Nasrallah et al. 1980). Schizophrenics with normally sized cerebral ventricles are most apt to exhibit a correlation between psychosis scores and central dopaminergic activity as reflected in plasma prolactin levels (Kleinman et al. 1982). The increased ventricular size in patients with (1) negative symptoms (Johnstone et al. 1978b; Andreasen et al. 1982), (2) neuroleptic/AMPT resistance (Nasrallah et al. 1980), and (3) lack of a correlation be-
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Van Kammen and Bunney (1979) observed a differential response to d-amphetamine that appeared to be related to the initial clinical condition of the schizophrenics. A single i.v. injection produced a worsening in patients with relatively low initial psychosis scores, while severely psychotic patients actually improved (van Kammen et al. 1977). The authors suggested that the improvement in psychosis may be due to a feedback regulatory process affected by d-amphetamine.

Another explanation for the antipsychotic effect of d-amphetamine (van Kammen and Bunney 1979) could be a reduction in the sensitivity of postsynaptic DA receptors. We have shown that a single dose of d-amphetamine can reverse the neuroleptic-induced behavioral supersensitivity to apomorphine in rats (Haracz and Tseng 1980). Other animal studies also found that chronic l-DOPA treatment reduces the dopaminergic supersensitivity induced by neuroleptics (Friedhoff, Bonnet, and Rosengarten 1977; Ezrin-Waters and Seeman 1978; List and Seeman 1979). Alpert et al. (1978) gave l-DOPA therapy for several weeks to a group of schizophrenics with tardive dyskinesia. They reported an initial worsening of both “mental condition” and dyskinetic symptoms, followed by a habituation and reduction in dyskinetic symptoms, with the maximum response occurring after discontinuation of l-DOPA. The “chronic schizophrenic process” appeared to follow the same course as the dyskinesia in several patients. If this result represents a reduction in psychotic symptoms after l-DOPA, then it could provide evidence that a postsynaptic supersensitivity is an etiological agent in schizophrenia. However, Alpert et al. (1978) observed only a slight, nonsignificant improvement in the psychosis ratings of eight chronic schizophrenics at termination, and 4 days after termination, of chronic l-DOPA treatment. Furthermore, three other studies found only a return to baseline, without an improvement in schizophrenic psychosis, at 1 to 10 days after termination of DA agonist treatment (Yaryura-Tobias, Diamond, and Merlis 1970; Janowsky, Huey, and Storms 1977; Small et al. 1977). Thus, the effect of DA agonists on the sensitivity of postsynaptic DA receptors in schizophrenia requires further clarification.

Studies 19–22 (table 2) indicate that DA agonists can yield an improvement in schizophrenic psychosis under certain conditions. Neuroleptics did not appear to alter the antipsychotic effect of apomorphine (Smith, Tamminga, and Davis 1977; Tamminga et al. 1978). A potent apomorphine analog, N-α-propylnorapomorphine, also ameliorates psychotic symptoms (Tamminga et al. 1981).

The improvement after low-dose apomorphine has been explained (in line with the DA hypothesis) as resulting from a preferential stimulation of presynaptic DA receptors (Cutler et al. 1981). One group studied the clinical effect of two ergot derivatives, bromocriptine and CF 25–397, which are less active than apomorphine at the presynaptic DA receptor (Tammenga and Schaffer 1979; Tamminga et al. 1979). Low doses of these DA agonists had no antipsychotic effect; in fact three of seven schizophrenics worsened while receiving bromocriptine. Trabucchi et al. (1977) also found that bromocriptine tended to worsen psychotic symptoms. On the other hand, no antipsychotic effect was seen when apomorphine was given orally over a 2-week period (Hollister, Davis, and Berger 1980). The latter group found that high oral doses of apomorphine (up to 120 mg/day) actually aggravated the psychotic symptoms of two schiz-
ophrenics. Apparently, high-dose apomorphine has significant postsynaptic activity. Differences in doses and routes of administration may account for the variety of responses to apomorphine in studies 20–23 (table 2).

Finally, Kornetsky (1976; table 2) found that multiple oral doses of 3-aminophenyl ethylamine did not affect the psychotic symptomatology of 25 chronically hospitalized schizophrenics. Cesarec, Eberhard, and Nordgren (1974) similarly failed to find any worsening psychosis in nine chronic schizophrenics during a 14-day regimen of oral amphetamine. It seems that a particular population of chronic schizophrenics, possibly prevalent in chronic-care institutions, may be unresponsive to the psychotogenic effect of DA agonists.

**MAO Inhibitors.** Brenner and Shopsin (1980) pointed out that current biochemical constructs of schizophrenia would predict an aggravation of schizophrenic symptoms by the administration of an MAO inhibitor (MAOI). They recently reviewed 14 investigations in which 281 chronic schizophrenics were exclusively treated with MAOIs. Global treatment outcome was reported as unchanged in 71 percent of the patients, improved in 26 percent, and worsened in only 3 percent. A statistically significant tendency was found for patients to be rated as “improved” only when hallucinations and delusions were not evaluated in a given study. Thus, a reduction in negative symptoms accounted for most of the improvement, although some patients were described as showing improvement in hallucinations and delusions under open study conditions.

It is surprising, in terms of the DA hypothesis, that MAOIs failed to exacerbate psychotic symptoms in the vast majority of patients. The reviewers emphasized that, in comparison with the usual antidepressant MAOI regimens, the schizophrenic populations were generally treated with higher dosages of MAOIs for longer trial periods (Brenner and Shopsin 1980). However, none of the investigations included assays of MAO activity in the patients under treatment. Therefore, it is impossible to determine if the negative results were secondary to an incomplete MAO inhibition. Youdim (1979) reported that 85 percent of rat brain MAO activity must be inhibited before a hyperactivity syndrome occurs in response to L-DOPA or D-tryptophan treatment. Mendlewicz and Youdim (1978) measured the platelet MAO activities of 14 depressed patients who were undergoing a 40-day antidepressant regimen of 5-hydroxytryptophan plus deprenyl, an MAOI. A platelet MAO inhibition of less than 85 percent was found only in the four nonresponding patients, indicating that the level of MAO inhibition is a critical determinant of the observed psychological effects. The schizophrenia studies employed MAOIs other than deprenyl, so it would be difficult to use the depressed patients’ deprenyl dosage as a yardstick of adequate MAO inhibition. An 85 percent criterion of significant MAO inhibition also makes one wonder about the functional significance of the platelet MAO deficits in chronic schizophrenics, which were usually reported as less than 50 percent (Wyatt et al. 1980).

Aside from the question of adequate MAO inhibition, the DA hypothesis appears to be challenged by the improvement of psychosis in some schizophrenics. In defense of the DA hypothesis, it can be speculated that chronic MAOI treatment may reduce DA receptor sensitivity, as demonstrated in rats after chronic L-DOPA (Friedhoff, Bonnet, and Rosengarten 1977; Ezrin-Waters and Seeman 1978; List and Seeman 1979), thereby reducing psychotic symptoms. Alternatively, the clinical improvement after MAOIs and DA agonists (studies 1–7, table 2) may indicate that central dopaminergic transmission is either decreased or is not a primary etiologic factor in some chronic schizophrenics. A large proportion of the schizophrenics in the MAOI investigations were chronically hospitalized, as were the patients studied by Kornetsky (1976). Hence, more support is lent to the hypothesis that chronically deteriorated schizophrenics are hyperresponsive to the psychotogenic effects of elevated dopaminergic transmission.

**α-Methyl-p-Tyrosine (AMPT) and α-Methyldopa (AMD).** AMPT decreases catecholamine synthesis by inhibiting TOH, the rate-limiting enzyme of the synthetic pathway (Goodman and Gilman 1975). The catecholamine-depleting mechanism of AMD is not well established, although the inhibition of TOH may also be involved (Meltzer and Stahl 1976). The reduction of brain DA concentrations produced by these drugs should result in a favorable clinical outcome in schizophrenics according to the DA hypothesis.

Two early studies showed an overall lack of antipsychotic effect when AMPT was the only drug
administered to acute and chronic schizophrenics (Gershon et al. 1967; Charalampous and Brown 1967). Each study found decreases in urinary catecholamine metabolites that indicated some inhibition of TOH activity, but it is not known if central dopaminergic activity was significantly inhibited.

Carlsson's group reported that AMPT treatment allowed a 60- to 79-percent mean reduction in the neuroleptic dose required to control psychotic symptoms in eight chronic schizophrenics (Carlsson et al. 1972b, 1973; Walinder et al. 1976). This finding was replicated by Magelund, Gerlach, and Casey (1979), but not by Nasrallah et al. (1977) and Gillin et al. (1979). Magelund, Gerlach, and Casey (1979) studied 12 chronic schizophrenics whose psychotic symptoms had been exacerbated by a 67-percent mean reduction in their neuroleptic dosage. Compared to a placebo, AMPT significantly decreased the subjects' total Brief Psychiatric Rating Scale (BPRS) scores.

Nasrallah and colleagues obtained negative results when they studied 14 chronic schizophrenics (Nasrallah et al. 1977; Gillin et al. 1979). Each of these patients had a prolonged illness which was only moderately responsive to neuroleptic therapy. The addition of AMPT treatment did not affect the patients' BPRS psychosis scores, even though an inhibition of DA activity was suggested by the elevations in plasma prolactin levels. Nasrallah et al. (1980) proposed that the conflict with previous studies could be explained by the postulation of two subgroups of chronic schizophrenics: a neuroleptic/AMPT-resistant group, represented by their own patients who had shown little response to full maintenance dosages of neuroleptics; and a neuroleptic/AMPT-responsive group, such as the patients of Carlsson et al. (1972b, 1973). In agreement with this hypothesis, the AMPT-responding patients of Magelund, Gerlach, and Casey (1979) apparently were also responsive to their initial maintenance neuroleptic dosages.

AMPT, like AMPT, did not have a significant antipsychotic effect when administered alone to chronic schizophrenics (Herkert and Keup 1969; Pecknold et al. 1972). Neither of these studies included an assessment of the effect of AMD on the catecholamine metabolism in the patients. Chouinard et al. (1973) reported that AMD plus chlorpromazine significantly improved the psychopathology in 8 of 10 chronic schizophrenics who were unresponsive to their previous antipsychotic medication. Thus, it appears that both AMPT and AMD can potentiate the antipsychotic action of neuroleptics in at least a subgroup of chronic schizophrenics. These results offer additional indirect pharmacological support for the DA hypothesis.

**Summary and Conclusion**

The abundant generation of data indicates that the DA hypothesis of schizophrenia has been an extremely successful heuristic device. However, this research activity has not produced a solid body of confirmatory evidence for the hypothesis. Indirect pharmacological evidence still makes up the bulk of the support, despite the extensive study of tissue samples obtained from schizophrenics. Direct support is either uncompelling or has not been widely replicated. In post-mortem studies, for example, there are at least as many negative findings as there are positive reports of elevated brain DA levels in schizophrenics (table 1).

The most widely replicated biochemical finding in schizophrenia has been the low peripheral MAO activity in chronic schizophrenics (Buchsbaum, Coursey, and Murphy 1980). The elevated PEA found in the urine of chronic paranoid schizophrenics may reflect the functional significance of an MAO deficiency. Still, one might question the etiological significance of a deficient enzyme activity that is generally only 30-50 percent less than normal (Wyatt et al. 1980), is frequently found in normal subjects (Buchsbaum, Coursey, and Murphy 1976; Murphy et al. 1977), and is possibly associated with neuroleptic treatment (Chojnacki et al. 1981; DeLisi et al. 1981b; Sahai, Arora, and Meltzer 1981). Moreover, no behavioral improvements were produced by dietary and pharmacological methods that successfully decreased PEA in schizophrenics (Wyatt, Bigelow, and Gillin 1979).

The hypothesis that schizophrenics have supersensitive brain DA receptors receives some direct support and is also consistent with some indirect pharmacological evidence. Four out of five laboratories have reported elevated H-neuroleptic binding in the post-mortem brain samples of schizophrenics (Lee et al. 1978; Owen et al. 1978; Mackay et al. 1980a; Reisine et al. 1980b; Reynolds et al. 1981). Three of these laboratories (Owen et al. 1978; Lee and Seeman 1980b; Reisine et al. 1980b), but not the other two (Mackay et al. 1980b; Reynolds et al. 1981), also found
increased $^3$H-neuroleptic binding in specimens from a small number of drug-free patients. Exaggerated GH responses to apomorphine were observed in acute and chronic schizophrenics who had received little or no neuroleptic therapy (Rotrosen et al. 1979). Schizophrenics seem to be more sensitive than normals to the psychotogenic effect (Angrist and Gershon 1977), but not the emetic effect (Angrist, Rotrosen, and Gershon 1980), of DA agonists.

If the psychotogenic effect of DA agonists is related to the sensitivity of DA receptors, then neuroleptic withdrawal should heighten the sensitivity of schizophrenics to DA agonists (van Kammen et al. 1980). Evidence of DA receptor supersensitivity has been found in animals shortly after the cessation of chronic neuroleptic treatment (Muller and Seeman 1978; Haracz and Tseng 1980). However, a group of schizophrenics did not develop a supersensitivity to the psychosis-worsening effect of d-amphetamine after pimozide withdrawal (van Kammen and Bunney 1979; van Kammen et al. 1980). Thus, the hypothesized DA receptor supersensitivity in schizophrenia is challenged by some negative findings (Angrist, Rotrosen, and Gershon 1980b; van Kammen et al. 1980; Reynolds et al. 1981) and by the possibility that the elevated $^3$H-neuroleptic binding is drug-related (Mackay et al. 1980b; Snyder 1981).

The DA hypothesis of schizophrenia will require adjustment if compelling evidence for a gross disturbance in DA function is not forthcoming. Some modifications that stay consistent with the pharmacological foundations include: (1) an isolated dopaminergic abnormality in a discrete brain area; (2) a primary disturbance in another neurotransmitter system that interacts with a dopaminergic system; (3) relatively subtle abnormalities in several aspects of dopaminergic transmission (e.g., MAO deficiency, DA receptor supersensitivity) which synergistically yield a serious abnormality; (4) several 'schizophrenias,' each with a different dopaminergic dysfunction, so that a sample of the entire group does not show significant changes.

The failure to find a universal biochemical defect among schizophrenics has contributed toward the consideration of multiple disease entities as a basis for the 'schizophrenias' (Buchsbaum and Haier 1978; Hornykiewicz 1978; Meltzer 1979; Crow 1980; Berger 1981). With heterogeneity as a possibility, some researchers have begun attempts at identifying biologically homogeneous subgroups within the schizophrenic population (Wyatt et al. 1981; Jeste et al. 1982). Thus, among schizophrenic subjects, a positive family history of schizophrenia was significantly related to low plasma DBH activity (Baron, Levitt, and Perlman 1980) and high CSF HVA (Sedvall and Wode-Helgodt 1980). Elevated CSF HVA was also associated with poor premorbid sexual adjustment in a group of schizophrenics (Leckman, Bowers, and Sturges 1981). Low CSF HVA was correlated with poor prognosis (Bowers 1974) and the presence of first-rank symptoms (Bowers 1973; Post et al. 1975). The presence of auditory hallucinations and paranoid features may discriminate chronic schizophrenics with decreased platelet MAO activity (Wyatt et al. 1980; Jeste et al. 1982). Schizophrenics with a positive family history of schizophrenia did not differ in platelet MAO activity from schizophrenics with no such family history (Belmaker et al. 1978).

Based on clinical phenomenology, Crow (1980) has distinguished two syndromes among patients with diagnoses of schizophrenia:

The first (the type I syndrome, equivalent to 'acute schizophrenia,' and characterised by the positive symptoms—delusions, hallucinations, and thought disorder) is in some way associated with a change in dopaminergic transmission; the second process (the type II syndrome, equivalent to the 'defect state,' and characterised by the negative symptoms—affective flattening and poverty of speech) is unrelated to dopaminergic transmission but may be associated with intellectual impairment and, perhaps, structural changes in the brain. ... [Type I symptoms] predict a potential response to neuroleptics; [type II symptoms] are more closely associated with a poor long-term outcome. Episodes of type I symptoms may be followed by development of the type II syndrome, and both may be present together. Type II symptoms ... occasionally occur in the absence of the type I syndrome. ... [p. 68]

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In retrospect, it appears that two of the pharmacological cornerstones of the DA hypothesis actually apply only to a subgroup of schizophrenics. The presence of type I symptoms may be a necessary condition for a therapeutic response to neuroleptics and a psychosis-worsening response to DA agonists. For example, d-amphetamine, I-DOPA, and methylphenidate worsened pre-existing positive symptoms (Janowsky et al. 1973; Angrist and Gershon 1977), while patients in remission showed little response to methylphenidate (Janowsky et al. 1973). DA agonists rarely induced psychotic symptoms in patients whose clinical picture was dominated by negative symptoms (Cesarec, Eberhard, and Nordgren 1974; Gerlach and Luhdorf 1975; Inanaga et al. 1975; Brambilla et al. 1979b). An oft-repeated clinical observation has been the poor response of negative symptoms to neuroleptic therapy (Lemendia and Harris 1967; Johnstone et al. 1978a; Angrist, Rotrosen, and Gershon 1980a). To summarize, patients with active positive symptoms generally show a psychotogenic response to DA agonists and a therapeutic response to neuroleptics as predicted by the DA hypothesis. In opposition to the hypothesis, patients with mostly negative symptoms exhibit a beneficial activation in response to DA agonists and little or no clinical change after neuroleptic administration.

The divergent drug responses summarized above may hint at separate etiologies for positive and negative symptoms. Consistent with this notion, both cerebral ventricular size and regional cerebral blood flow appear to vary according to the presence of positive and negative symptoms in sub-chronic to chronic schizophrenia (Ingvar 1980; Andreasen et al. 1982). By applying the 133Xenon clearance technique to 40 chronic schizophrenics, Ingvar (1980) found that the more inactive, mute, and autistic the patients were, the lower was the cerebral blood flow in the frontal regions of their brains. Elevated flow in postcentral regions was significantly related to cognitive disturbance including hallucinatory activity. Since cerebral blood flow correlates with neuronal activity, it seems that positive and negative symptoms are associated with different regional patterns of neurobiological activity. In addition, Andreasen et al. (1982) reported that a subgroup of schizophrenics with large cerebral ventricles (more than one standard deviation above the control mean) had a preponderance of negative symptoms. The schizophrenics with the smallest cerebral ventricles (well within the control range) exhibited mainly positive symptoms.

The data reviewed above suggest that schizophrenics with predominantly positive (type I) or negative (type II) symptoms also tend to differ in their: (1) clinical
responses to DA agonists and antagonists, (2) regional cerebral blood flow patterns, and (3) cerebral ventricular size. Thus, Crow's type I/type II distinction could be a useful theoretical framework in the search for biologically homogeneous subgroups. Biological researchers should carefully characterize the positive and negative symptoms exhibited by their schizophrenic subjects since the two symptom types may result from different pathophysiological processes. Longitudinal studies which relate changes in symptoms to changes in the above pharmacological and neuroradiological parameters may be especially revealing.

The DA hypothesis not only appears to be limited in the range of patients to which it applies, but it is also restricted in theoretical scope. The hypothesis does not readily account for social aspects of schizophrenia (Wing 1978) or the biogenesis of specific schizophrenic symptoms. A full explanation of the disorder must deal with genetic data (Gottesman and Shields 1976) as well as environmental factors on the schizophrenic process (Wynne et al. 1977; Dohekenwend and Egri 1981). Kety (1972) and Bowers (1980) have pointed out that the DA hypothesis (or any other biological hypothesis of schizophrenia) must be related through some mechanism to the complex clinical phenomenology. In this regard, some authors have proposed that an attentional disorder in schizophrenia may be linked to a dopaminergic influence on the focus of attention (Matthysse 1977, 1978; Joseph, Frith, and Waddington 1979). No comprehensive biological scheme has yet been proposed to draw together the genetic, environmental, and clinical features of schizophrenia.

As in most medical research, relatively simple factors have initially been tested as possible causes of schizophrenia. A common early viewpoint was that one abnormal biological factor could produce psychopathology. In search of the abnormality, various authors proposed and tested at least 18 different catecholamine-related theories of schizophrenia (reviewed by Wyatt, Bigelow, and Gillin 1979). Research unrelated to catecholamines further multiplied the number of biological entities under examination. Although it is important to test a reasonable variety of potential markers, it may become necessary to contemplate more complex neurophysiological processes. If one considers the significance of environmental influences in schizophrenia (Kety 1978; Singer, Wynne, and Toohey 1978; Wing 1978), a fruitful research concern may be the adaptation of neuronal circuitry to environmental changes. Animal studies indicate that important behavioral effects can be generated by environmentally induced synaptic modifications (Rosenzweig 1971; Cragg 1975; van Hof-van Duin 1976; Cotman 1978; Hubel 1978; Schwartz and Rothblat 1980). Laboratory methods typically employed in schizophrenia research might not be sensitive to alterations in the function of certain key synapses. Attention to neurophysiological adaptations, perhaps in animal models of psychopathology, may lead to a more meaningful experimental design.

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