Evidence for Reduced and Dysregulated Turnover of Dopamine in Schizophrenia

by Andrew J. Heritch

Abstract

The dopamine (DA) hypothesis of schizophrenia proposes that schizophrenia is related to dopaminergic hyperactivity. To examine this hypothesis, this article reviews studies that have measured levels of DA and its metabolites in schizophrenic patients. From these studies, the following conclusions about schizophrenia emerge: (1) levels of DA and its metabolites can be highly variable; (2) DA turnover appears to be reduced in a subgroup of schizophrenic patients characterized as more chronic and treatment refractory, compared with normal controls; (3) DA turnover has been correlated positively with acute symptomatology and negatively with signs of chronic illness; and (4) central DA levels appear to be elevated. These conclusions support the author's hypothesis that DA turnover may be both reduced and dysregulated in schizophrenia. It is speculated that reduced turnover is primarily due to a deficiency in DA release and that dysregulation may result from the disruption of feedback mechanisms. Acute psychosis may be associated with a relative increase in the release of DA impinging on supersensitive postsynaptic receptors made so by chronic synaptic depletion of the transmitter.

A disorder of central dopaminergic systems is widely accepted as part of the pathology of schizophrenia. The dopamine (DA) hypothesis proposes that schizophrenia is related to dopaminergic hyperactivity (Meltzer and Stahl 1976). This hypothesis has rested on pharmacologic observations that dopaminomimetic drugs can be psychotogenic and that neuroleptics inhibit dopaminergic activity (Carlsson 1978). But these observations more specifically support increased DA-related activity in psychosis, which is only part of the schizophrenic syndrome. They also do not necessarily mean that neuronal release of DA is elevated above normal during schizophrenic psychosis since other mechanisms, particularly postsynaptic supersensitivity, can also result in DA-related hyperactivity.

Since the original DA hypothesis has not been completely supported by subsequent observations, several variations have been proposed. Post et al. (1975) and Chouinard and Jones (1979) have presented clinical and pharmacologic evidence of a DA deficiency in schizophrenia. Wyatt (1986) has presented a range of arguments from human and animal studies that could support dopaminergic hypoactivity. Weinberger (1987) has argued that the weight of current evidence suggests that mesocortical DA function is underactive and has also addressed the DA hypothesis from a developmental point of view. Csernansky et al. (1983) have argued for a dynamic model of schizophrenia in which variations in multiple transmitter systems occur over time. This model addresses the fluctuant course and biochemical heterogeneity seen in cross-sectional studies of schizophrenia. Expanding on the dynamic concept, Siever and Davis (1985) have proposed several criteria that may characterize dysregulated central neurotransmitter systems in psychiatric syndromes.

This article examines neurochemical studies of DA and its metabolites in schizophrenia. Over the past two decades, enough of these studies have been done to support the con

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clusion that DA turnover in schizophrenia may be reduced and hypervariable in the presence of elevated DA levels. Neurochemical evidence of reduced DA turnover in schizophrenic patients is both direct and inferential and includes studies of DA metabolite levels, DA levels, and postsynaptic receptors. Evidence for dysregulation comes primarily from studies correlating levels of DA and its metabolites with various indicators of acute and chronic illness. In the Discussion section, the speculation that the source of reduced and dysregulated turnover could be a DA release deficiency will be considered.

**Dopamine Metabolite Levels**

Listed in table 1 are studies that have examined DA metabolite levels in drug-free schizophrenic patients compared with those in normal controls or other patients, or that have correlated signs of schizophrenic illness with metabolite levels. Most of these studies measured cerebrospinal fluid (CSF) homovanillic acid (HVA), the major extraneuronal DA metabolite. Data obtained by Bowers (1972) indicated that CSF HVA levels represent processes of formation of the metabolite—that is, DA turnover—rather than removal of the metabolite. 3,4-Dihydroxyphenylacetic acid (DOPAC) is another DA metabolite that has been used to reflect intraneuronal DA metabolism (Van Kammen et al. 1986b). A wide variety of factors may affect CSF levels of DA and its metabolites and the measurement of those levels (Van Kammen et al. 1986a).

In the early studies of CSF HVA levels were at the lower limits of the detection methods. Probenecid inhibits the transport of HVA from CSF into the bloodstream, resulting in the accumulation of HVA in CSF and thereby amplifying values (Guldberg et al. 1966). This technique was therefore used in a number of studies. However, there were problems involving the variable and incomplete block of transport with probenecid (Bowers 1972).

Rimon et al. (1971) first reported that paranoia correlates positively with CSF HVA levels among psychiatric patients. This result was not specific for schizophrenia. Subsequent studies have demonstrated that CSF and plasma HVA levels correlate positively with acute psychotic symptomatology among schizophrenic patients (Davis et al. 1985, Lindström 1985, Van Kammen et al. 1986b; Davidson and Davis 1988). The only study that has not found a correlation is one that selected patients not considered to be in acute states or severely paranoid (Gerner et al. 1984). It has also been reported that agitation (Van Praag 1977) and hostility (Gattaz et al. 1982) correlate positively with CSF HVA levels in schizophrenic patients. CSF HVA levels were not correlated with increased motor activity (Kirstein et al. 1976). The increase in CSF HVA levels in acute schizophrenic patients does not exceed the levels of CSF HVA found in normal healthy individuals. Four studies (Bowers and Van Woert 1972; Post et al. 1975; Berger et al. 1980; Nybäck et al. 1983) reported that CSF HVA levels in acute schizophrenic patients were not significantly different from normal control levels, while one study (Lindström 1985) reported that acute schizophrenic patients had lower levels than normal controls.

Approaching acute schizophrenia from another angle, Post et al. (1975) reported that recovery from acute exacerbations was accompanied by a decrease in CSF HVA levels. This pattern was the same whether or not the patients received neuroleptics during their recovery. In a longitudinal study, Pickar et al. (1986) followed schizophrenic patients receiving neuroleptic treatment for several weeks. Reductions in acute symptomatology were associated with decreases in plasma HVA levels while return of psychosis during neuroleptic withdrawal was associated with increased levels. These studies appear to fulfill several of the criteria for dysregulation set forth by Siever and Davis (1985), including erratic basal output, slow return to baseline output following perturbation, and restored regulation with the addition of clinically efficacious pharmacologic agents.

Bowers (1974) first demonstrated that within a schizophrenic population, CSF HVA levels correlate negatively with severity and/or chronicity of illness. A poor prognosis group—distinguished by illness duration greater than 6 months, poor premorbid adjustment, schizoid personality, and emotional blunting—had lower CSF HVA levels than the good prognosis group. Three subsequent studies also reported negative correlations between CSF HVA levels and indicators of severity and/or chronicity of illness. These indicators included cortical atrophy on a computed tomography (CT) exam (Van Kammen et al. 1983, 1986b) and negative symptomatology (Lindström 1985). Van Kammen et al. (1986b) also found that three measures of DA utilization (see table 1 for definitions) correlated positively with premorbid function and negatively with age. Among patients without cortical atrophy, CSF HVA levels correlated negatively with scores on the withdrawal–retardation cluster of the Brief Psychiatric Rating Scale (Overall and Gorham 1962) while
### Table 1. Studies of dopamine metabolite levels in drug-free schizophrenic patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Compared with</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Berger et al. 1980</td>
<td>7 acute (all male), mean age 36.3</td>
<td>14 normal, 11 depressed</td>
<td>No difference in CSF HVA or DOPAC pre- or postprobenecid versus normals. Higher CSF HVA versus depressed</td>
</tr>
<tr>
<td>Bowers 1974</td>
<td>17 acute (7 male, 10 female), age 18-45, 7 previously hospitalized</td>
<td>11 affective</td>
<td>Lower postprobenecid CSF HVA in schizophrenic patients. CSF HVA correlated positively with prognosis</td>
</tr>
<tr>
<td>Bowers and Study 1979</td>
<td>8 acute, age 16-67</td>
<td>19 affective, 18 “other” psychosis</td>
<td>Higher postprobenecid CSF HVA in schizophrenic versus “other” psychotic patients</td>
</tr>
<tr>
<td>Bowers and Van Woert 1972</td>
<td>23 acute</td>
<td>15 inmates, 11 depressed, 10 Parkinsonian</td>
<td>No difference in postprobenecid CSF HVA except higher versus Parkinsonian</td>
</tr>
<tr>
<td>Davidson and Davis 1988</td>
<td>14 chronic, treatment-resistant (all male), mean age 33.6, mean length of illness 10 years</td>
<td>14 normal</td>
<td>Lower plasma HVA in schizophrenic patients. Plasma HVA correlated positively with CGI and BPRS scores</td>
</tr>
<tr>
<td>Davis et al. 1985</td>
<td>18 unspecified (all male), mean age 41</td>
<td>None</td>
<td>Plasma HVA correlated positively with CGI and BPRS scores</td>
</tr>
<tr>
<td>Gattaz et al. 1982</td>
<td>28 chronic paranoid, in relapse (all male)—mean age 31, mean duration of illness 10 years, mean number hospitalizations 11</td>
<td>16 neurologic</td>
<td>No difference in CSF HVA. CSF HVA correlated positively with hostility on BPRS</td>
</tr>
<tr>
<td>Gerner et al. 1984</td>
<td>20 chronic (16 male, 4 female), age 17-35 (mean 25), not acute or severely paranoid</td>
<td>38 normal, 41 depressed, 15 manic</td>
<td>No difference in CSF HVA for schizophrenic patients. No correlation between CSF HVA and psychosis rating</td>
</tr>
<tr>
<td>Gottfries et al. 1971</td>
<td>40 middle-aged (28 male, 12 female)</td>
<td>60 normal (divided into two age groups)</td>
<td>No differences in CSF HVA. CSF HVA increased with age in normals</td>
</tr>
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</table>
Table 1. Studies of dopamine metabolite levels in drug-free schizophrenic patients—Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Compared with</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Karoum et al. 1987</td>
<td>20 chronic, treatment-refractory (18 male, 2 female), mean age 30, mean duration of illness 5 years, mean duration of hospitalization 3 years</td>
<td>16 normal</td>
<td>Lower combined urinary excretion of HVA, DOPAC, and dopamine (sum DA). Lower sum DA/sum norepinephrine. No association with ventricular enlargement or cortical atrophy</td>
</tr>
<tr>
<td>Kirstein et al. 1976</td>
<td>9 acute, 1 residual, age 20–64, 5 previously hospitalized</td>
<td>10 affective</td>
<td>Higher postprobenecid CSF HVA in schizophrenic patients. No correlation between CSF HVA and behavioral rating or movement counts</td>
</tr>
<tr>
<td>Lindström 1985</td>
<td>40 acute (27 male, 13 female), age 20–41 (mean 27), 19 previously hospitalized, illness duration 1 month–14 years (median 2 years)</td>
<td>21 normal</td>
<td>Lower CSF HVA. No difference in CSF HVA between first admits and recurrent. Low CSF HVA correlated with lassitude and slowness of movement on CPRS. High CSF HVA correlated with social interaction and total positive scores on NOSIE–30</td>
</tr>
<tr>
<td>Nybäck et al. 1983</td>
<td>26 acutely psychotic (24 schizophrenic) (19 male, 11 female), age 17–44 (mean 28), 14 previously hospitalized</td>
<td>43 normal</td>
<td>No difference in CSF HVA. CSF HVA correlated negatively with size of lateral ventricle</td>
</tr>
<tr>
<td>Post et al. 1975</td>
<td>18 acute, age 16–54 (mean 25), with good prognosis</td>
<td>10 normal</td>
<td>No difference in pre- or postprobenecid CSF HVA versus normals. Lower CSF HVA in schizophrenic patients with more Schneiderian first-rank symptoms. Lower CSF HVA in Schneiderian-positive schizophrenic patients versus depressive controls. CSF HVA reduced in schizophrenic patients after recovery from acute episode</td>
</tr>
<tr>
<td>Rimon et al. 1971</td>
<td>31 acute (13 male, 18 female), mean age 29, all first admissions</td>
<td>27 psychiatric</td>
<td>No difference in CSF HVA. Higher CSF HVA in patients with paranoid psychoses (schizophrenic and nonschizophrenic) versus patients without paranoid psychoses</td>
</tr>
<tr>
<td>Sedvall et al. 1974</td>
<td>34 acute (11 male, 23 female), mean age 34</td>
<td>11 manic</td>
<td>Lower CSF HVA. CSF HVA higher in females versus males</td>
</tr>
</tbody>
</table>
Table 1. Studies of dopamine metabolite levels in drug-free schizophrenic patients—Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Compared with</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Kammen et al. 1983</td>
<td>33 unspecified, age 18–53 (mean 26)</td>
<td>None</td>
<td>CSF HVA correlated negatively with ventricle-brain ratio and cortical atrophy</td>
</tr>
<tr>
<td>Van Kammen et al. 1986b</td>
<td>53 unspecified (30 male, 23 female), age 18–53 (mean 26)</td>
<td>None</td>
<td>CSF HVA, DOPAC, and total DA metabolism correlated negatively with cortical atrophy. All three measures of DA utilization(^1) correlated positively with premorbid functioning and negatively with age. Among patients without atrophy, CSF HVA correlated positively with unusual thought content and negatively with withdrawal retardation (BPRS). DASO(_4) correlated negatively with unusual thought content and positively with duration of illness. Total DA utilization(^1) correlated negatively with duration of illness. Among patients without atrophy, CSF HVA correlated positively with unusual thought content and negatively with withdrawal retardation (BPRS). DASO(_4) correlated negatively with unusual thought content and positively with duration of illness. Total DA utilization(^1) correlated negatively with duration of illness. Higher CSF HVA among patients classified as most agitated and anxious.</td>
</tr>
<tr>
<td>Van Praag 1977</td>
<td>33 acute</td>
<td>None</td>
<td>Higher CSF HVA among patients classified as most agitated and anxious.</td>
</tr>
</tbody>
</table>

Note.—CSF = cerebrospinal fluid, HVA = homovanillic acid, DOPAC = dihydroxyphenylacetic acid, DA = dopamine, DASO\(_4\) = dopamine sulfate, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, NOSIE-30 = Nurses Observation Scale for Inpatient Evaluation, CPRS = Comprehensive Psychopathology Rating Scale.

\(^1\)DA utilization: Intraneuronal = DOPAC + conjugated DOPAC/DASO\(_4\); extraneuronal = HVA/DASO\(_4\); total = intraneuronal + extraneuronal.

Total DA utilization correlated negatively with duration of illness.

Bowers (1974) was also the first to report the possibility that DA metabolite levels may be reduced in a subgroup of schizophrenic patients compared with controls. His results are difficult to interpret, however, since he used patients with other psychiatric illnesses as a comparison group, and CSF HVA can vary in these illnesses as well (Papacchi and McClure 1971; Sjöström and Roos 1972). One study subsequently reported reduced DA metabolite levels in acute schizophrenic patients compared with levels in normal controls (Lindström 1985) while four studies reported no difference (Bowers and Van Woert 1972; Post et al. 1975; Berger et al. 1980; Nybäck et al. 1983). Two recent studies have been the first ones to compare peripheral DA metabolite levels in chronic, treatment-refractory schizophrenic patients versus normal controls, and both found significantly decreased levels in the schizophrenic patients (Karoum et al. 1987; Davidson and Davis 1988). Thus, a subgroup of schizophrenic patients appears to have lower DA metabolite levels compared with healthy individuals. Whether this subgroup represents a clinically distinct group, as argued by Goetz and Van Kammen (1986) based on CT findings of structural abnormalities, or the severe end of a continuous spectrum of illness will require further study to determine.

Results from these neurochemical studies have been consistent over time, with a few exceptions as noted, and have included methods with and without probenecid. Several conclusions emerge from these studies. DA turnover, as measured by HVA levels in CSF and plasma, can be highly variable in schizophrenia. Among schizophrenic patients, the degree of acute psychotic symptomatology correlates positively with HVA levels in CSF and plasma. CSF HVA and other measures of DA utilization seem to correlate negatively with signs of chronic illness. Schizophrenic patients who have more chronic and treatment-refractory symptomatology have been shown to have lower HVA in CSF and plasma than normal controls, while no study has found elevated metabolite levels in schizophrenic patients. It should be noted that most studies of DA metabolites in schizophrenia to date have been cross-sectional in nature and have used inpatients admitted for psychosis. Older, chronic patients...
tend to have fewer psychotic relapses. The reviewed studies indicate that DA metabolite levels may rise in acute psychosis and fall with resolution of psychosis and duration of illness. Consequently, many studies may have selected a skewed sample of patients with relatively higher metabolite levels because the patients were acutely psychotic. Most of these studies have also not been controlled for age or sex, both of which can influence DA metabolite levels (Gottfries et al. 1971; Bowers 1972; Sedvall et al. 1974). Other DA-related abnormalities in schizophrenia that may be interpreted as further support for reduced turnover of DA in schizophrenia will now be examined.

Dopamine Levels and Receptors

Table 2 lists postmortem studies that have measured DA levels in various brain sites in patients who have died with the diagnosis of schizophrenia. All studies except one, which had a small sample size and a significantly younger population of schizophrenic patients than of controls (Toru et al. 1982), demonstrated increased DA levels in at least one site compared with levels in normal individuals. The sites in which elevations were most frequently seen were the nucleus accumbens and the caudate nucleus. The location of these elevations has been somewhat variable among the reporting groups, perhaps due in part to differences in how the investigators defined anatomic areas (Bird et al. 1979). Unlike other postmortem changes in schizophrenia, such as those that occur in postsynaptic receptors, the increase in DA levels was not obviously related to use of neuroleptics, and increases were more pronounced in younger patients than in older ones (Mackay et al. 1982).

Investigators have recently begun to measure CSF conjugated DA (DA sulfate) in schizophrenic patients. Unconjugated DA is present in very small amounts in CSF (Van Kammen et al. 1986a). Van Kammen et al. (1986b) measured cortical atrophy on CT and found a positive trend with DA sulfate levels. Among patients without brain atrophy, DA sulfate levels correlated positively with duration of illness and negatively with unusual thought content. Thus, DA levels are also highly variable in schizophrenia. Furthermore, DA and DA metabolite levels appear to respond in opposite directions in schizophrenia relative to certain indicators of acute and chronic illness, such as psychotic thinking, brain atrophy, and duration of illness.

What does the relationship between DA levels and DA metabolite levels tell us about DA turnover? In pharmacological studies in animals, Neff and Costa (1968) demonstrated that DA levels and DA metabolite levels have a reciprocal relationship when turnover is varied. That is, reduced metabolism resulted in increased DA and decreased me-

Table 2. Postmortem dopamine levels in schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Amygdala</th>
<th>Anterior perforate</th>
<th>Caudate</th>
<th>Hypothalamus</th>
<th>Nucleus accumbens</th>
<th>Putamen</th>
<th>Septal nuclei</th>
<th>Thalamus</th>
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<tbody>
<tr>
<td>Bird et al. 1977</td>
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<td>NC</td>
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<td>Bird et al. 1979</td>
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<td>NC</td>
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<td>Bird et al. 1984</td>
<td>NC</td>
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<td>Bridge et al. 1985</td>
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<td>Crow et al. 1978</td>
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<td>NC</td>
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<tr>
<td>Crow et al. 1979</td>
<td>NC</td>
<td>t</td>
<td>NC</td>
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<tr>
<td>Mackay et al. 1982</td>
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<tr>
<td>Oke and Adams 1987</td>
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<td>Owen et al. 1978</td>
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<tr>
<td>Toru et al. 1982</td>
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</table>

Note.—t = increased; NC = no change.

1Demented schizophrenic patients.
regulated. DA receptor supersensitivity of DA receptors (Zelman et al. 1985). Thus, growth hormone response to apomorphine reflects release-induced activity of postsynaptic D₂ receptors (Zelman et al. 1985). Therefore, one possible implication is that all schizophrenia may be associated with reduced DA turnover, although turnover may reach normal levels during acute exacerbations and reductions may not be readily detectable in milder or less chronic cases. If this is indeed the case, studies of broader populations of schizophrenic subjects, controlled for age, sex, and state of illness, may better demonstrate the relationship of DA turnover to symptomatology.

Two obvious causes of reduced turnover in the presence of elevated DA levels are possible: reduced metabolism resulting in increased synaptic DA, and a release deficiency resulting in increased intraneuronal DA. Findings of reduced dopamine-beta-hydroxylase in schizophrenia (Wise and Stein 1973) lend credence to the former. However, since postsynaptic sensitivity correlates negatively with turnover (Zelman et al. 1985), reduced metabolism resulting in increased synaptic DA would not be expected to result in the supersensitivity that is observed. Oke and Adams (1987) have argued against generalized faulty metabolism on the basis of normal norepinephrine levels in their postmortem studies. Thus, the hypodopaminergic condition in schizophrenia appears more likely to be related to a release deficiency, although other mechanisms may also be involved either primarily or secondarily.

What are the possible sources for the pattern of dysregulation seen in schizophrenia? While no studies directly addressing this issue are available, it is recognized that DA release is regulated both locally and via multiple feedback mechanisms by other neurotransmitters that also show evidence of dysregulation in schizophrenia, including acetylcho-
line (Meltzer and Stahl 1976) and norepinephrine (Antelman and Caggiula 1977; Hornykiewicz 1982). There is also anatomical evidence that dopaminergic and serotonergic systems have reciprocal innervation (Oades and Halliday 1987) and that serotonin turnover varies with DA turnover relative to Schneiderian symptoms (Bowers 1974; Post et al. 1975). Thus, if DA release is reduced, it could disrupt the normal feedback mechanisms resulting in dysregulation of dopaminergic systems as well as those systems that DA helps to regulate. Animal models have demonstrated that lesions in a DA pathway can result in secondary changes in neurochemical levels and receptors in systems regulated by the lesioned pathway (Pycock et al. 1980).

The role of stress as a precipitant of acute schizophrenia has been widely studied (Meltzer and Stahl 1976). Stress is known to increase turnover selectively in mesocortical versus basal ganglionic dopaminergic pathways (Thierry et al. 1976; Deutch et al. 1985). Studies in normal individuals have demonstrated increased DA turnover in response to stress (Frankenhaeuser et al. 1986). It could be that stress is one factor that can cause a relative increase in DA release in schizophrenia.

The following scenario seems to emerge from the data presented here. Schizophrenia is associated with a reduction in DA release, which could cause postsynaptic supersensitivity. Stress or other factors may relatively raise the release rate in selected DA pathways, resulting in effective dopaminergic hyperactivity due to the supersensitive postsynaptic receptors and producing acute symptomatology. Thus, dopaminergic hyperactivity may occur despite the findings of normal or below-normal levels of DA metabolites compared with levels in normal individuals. This general scenario was proposed by Mackay (1980). Additionally, the increase in DA release may persist over a subacute period due to dysregulation. Furthermore, schizophrenic patients who progress to a predominantly chronic negative picture may have the lowest or a progressively reduced DA release. This scenario should, of course, be considered only a first approximation. Other factors such as kindling effects, co-transmitters, and the variety of presynaptic and postsynaptic receptors may also have roles. The effects on the rest of the brain obviously will be complex.

This review may help clarify the role of DA in schizophrenia. Further postmortem studies of dopaminergic neurons, as well as longitudinal and symptomatically broader-based studies of DA, DA metabolites, and DA receptors, might be particularly useful in clarifying the possible existence of reduced and dysregulated DA turnover in schizophrenia.

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Mackay, A.V.P.; Iversen, L.L.; Lanson, M.; Spokes, E.; Bird, E.; Arregui, A.; Creese, I.; and Snyder, S.

Meltzer, H.Y.; and Stahl, S.M.

Neff, N.H.; and Costa, E.

Nybäck, H.; Berggren, B.M.; Hindmarsh, T.; Sedvall, G.; and Wiesel, F.A.

Oades, R.D., and Halliday, G.M.


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