Dopamine and Schizophrenia

By SOLOMON H. SNYDER, M.D.

When an author writes about the dopamine, serotonin, methylation, or any other hypothesis of a mental illness, the reader usually assumes that direct evidence implicates the cited chemical at the heart of the disease. In other words, the reader gets the impression that the particular chemical "causes" the illness. Unfortunately, to my awareness, one cannot make such an assertion about any chemical in any mental illness. Almost all the data relating neurotransmitters to emotional disturbance derive from the effects of drugs. Drugs may selectively alleviate or worsen symptoms. When pharmacologists determine that the drugs exert their clinical effects via a particular neurotransmitter, one draws the inference that the transmitter "has something to do with the disease." However, one cannot say whether what the transmitter "has to do" with the illness is causal or only peripheral. While the physician may titrate symptoms by altering a particular transmitter's synaptic activity, these manipulations may be several steps removed from the site of abnormality in the brain.

All these reservations apply to the dopamine hypothesis of schizophrenia. Nobody has found anything conclusively abnormal about dopamine in body fluids or brains of schizophrenics. One can, however, selectively exacerbate or relieve the symptoms of schizophrenia by the use of drugs. Moreover, pharmacologists can decipher reasonably well the neurochemical mechanisms whereby these drugs act — and all roads keep leading back to dopamine. Though we cannot directly relate dopamine to the pathophysiology of schizophrenia, describing the neurochemical mode of action of a psychotropic drug is itself no small accomplishment. There are very few drugs in all of clinical medicine whose mechanism of action is reliably understood. We do not know in molecular terms how aspirin relieves headaches, how cortisone ameliorates the symptoms of arthritis, or even how many antibiotics kill microorganisms. Despite the comparative youth of psychopharmacology as a branch of therapeutics, many advances have been made in explaining how psychotropic drugs act. This article will attempt...
to clarify what is known about how drugs affect schizophrenic symptoms.

**DOPAMINE**

Dopamine is one of the two principal catecholamines in the brain (Figure 1). "Catechol" refers to a benzene ring with two adjacent hydroxyl groups. In most areas of the brain, dopamine is merely the precursor of norepinephrine, to which it is transformed by the enzyme dopamine hydroxylase. However, some parts of the brain lack dopamine hydroxylase, and dopamine is the only catecholamine constituent of specific neuronal pathways, for which it is the presumed neurotransmitter and can be visualized by histochemical fluorescent techniques. The best known of these pathways has cell bodies in the substantia nigra of the brain stem, with nerve terminals in the corpus striatum, caudate nucleus, and putamen. This dopamine pathway is destroyed selectively in patients with idiopathic Parkinson’s disease. The result-ant dopamine depletion is causally related to the symptoms of the disease, because replacing the missing dopamine by treatment with its amino acid precursor, L-dopa, dramatically alleviates symptoms. Thus, in Parkinson’s disease, a “dopamine hypothesis” of causation has been translated into hard proof. A dopamine pathway with importance for endocrinologists has cell bodies in the arcuate nucleus of the hypothalamus and nerve terminals forming synapses upon the portal vessels in the median eminence. These vessels convey releasing factors from the hypothalamus to the pituitary gland. Dopamine in these neurons regulates releasing-factor activity and subsequent endocrine effects.

Other dopamine pathways may be more important to the symptoms of schizophrenia. Pathways with cell bodies close to the substan-

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**Figure 1.** Structures of amphetamine and the catecholamines dopamine and norepinephrine.
tia nigra project to the nucleus accumbens and olfactory tubercle, both components of the limbic system of the brain, which regulates emotional behavior. Recently described dopamine pathways with cell bodies in the same areas project to parts of the frontal, cingulate, and entorhinal cerebral cortex, phylogenetically older parts of the cerebral cortex linked in function to the limbic system.

**AMPHETAMINE ACTIONS**

In linking a drug to a particular illness, one may show that the drug can reproduce the symptoms of the disease. In this way, LSD psychosis was once heralded as a "model schizophrenia." However, psychiatrists argued that one cannot readily equate effects of psychedelic drugs such as LSD with schizophrenic symptoms. Psychedelic drugs produce perceptual changes in the visual sphere, while schizophrenic hallucinations are usually auditory. Under the influence of psychedelic drugs, people do not demonstrate classical schizophrenic disorders in affect or thought. Moreover, clinicians rarely mistake persons under the influence of psychedelic drugs for schizophrenics. By contrast, there are numerous reports in the literature in which nonschizophrenics suffering from amphetamine psychosis were misdiagnosed as acute paranoid schizophrenics until the history of drug ingestion was obtained. Some psychiatrists working with amphetamine psychotics have felt that their subjects manifested schizophrenic disorders of affect and thought, while others disagree.

Regardless of how well specific details of amphetamine psychosis match those of schizophrenia, the fact that amphetamine psychosis mimics schizophrenia well enough to deceive experienced psychiatrists indicates that it is probably the best-known drug model of schizophrenia.

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**Figure 2. Neuronal pathways of dopamine in rat brain.**
Amphetamine psychosis cannot simply represent precipitation of a latent schizophrenia or sleep deprivation psychosis, since in experimental studies psychosis has been produced by administration of amphetamine to persons found to have no history of schizoid disorders and the psychosis has occurred in some cases within 24 hours.  

Cocaine, like amphetamine, is a widely abused central nervous system stimulant. And like amphetamine, cocaine in high doses provokes a psychosis that is clinically indistinguishable from acute paranoid schizophrenia. Indeed, most of the symptoms of cocaine psychosis are essentially identical with those of amphetamine psychosis. How does cocaine act? An abundance of pharmacologic evidence indicates that cocaine’s behavioral effects are attributable to its facilitating catecholamine synaptic activities by blocking the reuptake inactivation of catecholamines. Unlike amphetamine, cocaine does not seem to cause a direct release of catecholamines.

In contrast to the very large doses of amphetamine (100-500 mg.) required to elicit amphetamine psychosis, amounts prescribed therapeutically for dieting or stimulant effects in schizophrenics can rapidly and reproducibly elicit a florid exacerbation of schizophrenic symptoms. Amphetamine and related drugs, such as methylphenidate (Ritalin®), do not produce a drug psychosis superimposed upon the schizophrenia, but they selectively worsen the patient’s symptoms. Amphetamines do not have this effect in depressed or manic patients. No other known drug can so selectively and dramatically exacerbate schizophrenic symptoms.

How do amphetamines act? Pharmacologists believe that behavioral effects of amphetamines, because of their close resemblance to brain catecholamines, are exerted via the catecholamines norepinephrine and dopamine, and they have confirmed these suspicions in a vast number of biochemical and pharmacologic studies. Amphetamines enhance the actions of catecholamines by directly releasing them into the synaptic cleft or by preventing their inactivation by reuptake into the nerve terminal that released them. Amphetamines do not affect other neurotransmitter or biochemical systems in the brain in so selective and potent a fashion. Though it is difficult to make a clear-cut distinction, the actions of amphetamines in exacerbating schizophrenic symptoms and eliciting amphetamine psychosis probably involve brain dopamine more than norepinephrine.

If amphetamines exacerbate schizophrenic symptoms by increasing synaptic dopamine, other pharmacologic maneuvers that produce the same biochemical end product should also worsen schizophrenic symptoms. The simplest technique would be to administer L-dopa, the precursor of dopamine. In the few studies in which L-dopa has been administered to schizophrenics, it does cause a marked exacerbation of behavioral abnormalities, much like that elicited by amphetamines.

PHENOTHIAZINES

It is now the general consensus of clinical psychopharmacologists that phenothiazines exert a specific antischizophrenic action. They appear to act primarily upon the fundamental symptoms of schizophrenia. Their effects are not merely sedative, since they activate withdrawn patients as well as calming hyperactive ones. Many other psychotropic drugs, including potent sedatives and anti-anxiety agents, have failed to provide selective benefit in schizophrenics at all comparable with the impressive actions of phenothiazines and related agents.

Clearly, understanding the mechanisms of action of phenothiazines would shed considerable light on brain mechanisms in schizophrenia. These drugs probably act by blocking postsynaptic receptor sites for the neurotransmitter actions of dopamine. This notion was first advanced by the Swedish pharmacologist Arvid continued
Carlsson on the basis of limited, indirect biochemical data.\textsuperscript{11} Carlsson presumed that if phenothiazines were to block dopamine receptors, this would produce a behavioral picture in animals resembling that induced by the dopamine depletion following treatment with such drugs as reserpine. Postsynaptic neurons would respond to the receptor blockade by sounding an alarm: "There is no more dopamine, turn on the dopamine machine!" By a feedback sys-

tem, dopamine cells would then fire more frequently and release more dopamine, providing an excess of dopamine metabolites or breakdown products. Carlsson did observe an increase in dopamine metabolites after phenothiazine administration and showed that these biochemical effects of phenothiazines were correlated with the clinical potency of the drugs. This is a crucial task in relating drug "effect" to "mechanism of clinical action."

Since phenothiazines are highly reactive chemicals, they produce many biochemical actions. Most of these do not correlate with clinical effects. Thus the phenothiazine promethazine (Phenergan\textsuperscript{®}) is a potent antihistamine, but it is totally inactive in treating schizophrenia. It exerts most phenothiazine-induced biochemical actions just as effectively as chlorpromazine. Carlsson showed that the increase in dopamine metabolites was produced by chlorpromazine and other phenothiazines in proportion to their milligram potency in treating schizophrenia, while promethazine was totally ineffective.

Subsequently, other pharmacologists found that the increased formation of dopamine metabolites elicited by phenothiazines derives from an increased synthesis and presumably release of dopamine.\textsuperscript{12,13} Only recently did Aghajanian and Bunney actually show that the dopamine neurons fire more frequently after phenothiazine administration, and finally they demonstrated that phenothiazines do block the neurophysiologic effects produced by the injection of minute amounts of dopamine onto postsynaptic cells possessing dopamine receptors.\textsuperscript{14} Thus, at a neurophysiologic level, one can now demonstrate the synaptic actions of dopamine (which appears to function as an inhibitory neurotransmitter) and the capacity of phenothiazines to block these effects in proportion to their clinical efficacy.

Neurophysiologic studies are quite difficult to perform, so only a limited number of drugs can be screened. Ideally, one would like to monitor dopamine receptor activity biochemically. This has been possible with two techniques, one indirect and a more recent, direct approach. Cyclic AMP is thought to be a second messenger mediating the actions of many hormones and neurotransmitters. Kebabian and his col-

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**TABLE 1**

PHENOTHIAZINE AND THIOXANTHENE DRUG EFFECTS ON SPECIFIC DOPAMINE RECEPTOR BINDING AND A DOPAMINE-SENSITIVE ADENYLAZE CYCLASE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Relative Potency in Competing for Dopamine Receptor Binding*</th>
<th>Relative Potency in Inhibiting Dopamine-Sensitive Adenylate Cyclase of Rat Corpus Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol\textsuperscript{®})</td>
<td>50 (Chlorpromazine = 100)</td>
<td>50</td>
</tr>
<tr>
<td>(+)-Butaclamol</td>
<td>1,200</td>
<td>728</td>
</tr>
<tr>
<td>α-Flupenthixol</td>
<td>625</td>
<td>4,545</td>
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<tr>
<td>Fluphenazine</td>
<td>465</td>
<td>1,087</td>
</tr>
<tr>
<td>(Prolin,\textsuperscript{®} Permitil\textsuperscript{®})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triluoperazine (Sielazine\textsuperscript{®})</td>
<td>181</td>
<td>250</td>
</tr>
<tr>
<td>Triluoperazine (Vesprin\textsuperscript{®})</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td>Perphenazine (Trilafon\textsuperscript{®})</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine\textsuperscript{®})</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Promazine (Sparine\textsuperscript{®})</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>(–)-Butaclamol</td>
<td>8</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Potency in competing for binding to the dopamine receptor is defined as the reciprocal of the nanomolar concentration to occupy 50 per cent of receptor binding sites $\times 1.5 \times 10^3$ in cell striatal membranes using the assay of Burt et al.\textsuperscript{15} Larger values indicate greater potency. Thus (+)-butaclamol inhibits binding 50 per cent at $1.25 \times 10^{-7}$ M concentration.

**Data are derived from the studies of Miller, Horn, and Iverson\textsuperscript{16} and Lippman et al.\textsuperscript{17} Clement-Corner et al.\textsuperscript{18} obtained similar results.
laborators showed that a cyclic AMP accumulating system, or adenylate cyclase, in areas of the brain rich in dopamine nerve terminals respond selectively to dopamine and is affected much less by other catecholamines10 (Table 1). This dopamine-sensitive adenylate cyclase is thus linked somehow to the dopamine receptor and provides an indirect reflection of dopamine receptor activity that can be readily monitored biochemically in vitro. Phenothiazines inhibit the effects of dopamine on the adenylate cyclase in proportion to their clinical potency16,17 (Table 1). Thus trifluoperazine (Stelazine®) and fluphenazine (Prolixin®, Permitil®), two very potent phenothiazines in clinical practice, are considerably more active on the dopamine-sensitive adenylate cyclase than is the clinically less potent chlorpromazine.

How might one directly measure the dopamine receptor biochemically? In our laboratory, we label neurotransmitter receptors in the brain by binding radioactive forms of the neurotransmitter or its antagonists to synaptic membranes in brain homogenates.18-20 Using such procedures, we have recently succeeded in biochemically identifying the dopamine receptor in the brain.21 Dopamine receptor binding displays all the characteristics one would expect of the dopamine receptor. Of the various catecholamines, dopamine has by far the greatest affinity, being almost 20 times more potent than norepinephrine and several thousand times more potent than isoproterenol, the catecholamine with the greatest affinity for beta-adrenergic receptors. The relative potencies of phenothiazines in competing for dopamine receptor binding closely parallel their clinical potency and their effects on the dopamine-sensitive adenylate cyclase. Optical and geometric isomers of phenothiazine-related drugs provide a uniquely powerful tool for studying receptor specificity. One would assume that the physical properties of the two isomers, especially optical isomers, are essentially the same, so any difference in pharmacologic potency must be related to specific aspects of the structure of the receptor sites. The isomeric specificity of the dopamine receptor binding sites for the isomers of butaclamol and flupenthixol parallels the influences of these isomers on the dopamine-sensitive adenylate cyclase and their pharmacologic potency in intact animals (Table 1).

Interestingly, one group of drugs does not "fit in" particularly well with either the dopamine-sensitive adenylate cyclase or the dopamine receptor binding labeled with radioactive dopamine. The butyrophenones, such as haloperidol (Haldol®), are considerably more potent on a milligram basis than phenothiazines in vivo, but they are not particularly potent in their influence on the radioactive dopamine binding in test tubes. In phar-

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"Of the various catecholamines, dopamine has by far the greatest affinity, being almost 20 times more potent than norepinephrine"

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macologic paradigms in intact animals, however, the potencies of butyrophenones in apparently blocking dopamine receptors correlate well with their clinical actions. Radioactive haloperidol labels dopamine receptors differently from labeled dopamine. Dopamine and haloperidol bind respectively to "agonist" and "antagonist" states of the receptors. Clinical potencies of butyrophenones are excellently predicted by their affinities for haloperidol "antagonist" sites.

How might phenothiazines be physically accommodated by the dopamine receptor? In what appears to be their optical shape or conformation, the side chain of phenothiazines tilts towards the A ring rather than being extended symmetrically between the A and C rings (Figure 3). Since the A and C rings are essentially identical except for the presence of a substituent at the 2 position on the A ring, it is likely that this substituent directs the side chain towards the A ring. In the conformation with the side chain approximating the A ring, the amino nitrogen of the side chain and the A ring correspond impressively to the amine and benzene rings of dopamine and indeed can be superimposed22-24 (Figure 3). One might predict

continued
that chemical factors stabilizing this dopaminelike conformation of phenothiazines might facilitate dopamine receptor blockade and enhance clinical potency. The most obvious chemical feature of importance for this conformation is the presence of the substituent at position #2 of ring A. A phenothiazine drug lacking such a substituent would possess symmetrical rings A and C, so the side chain would be fully extended in the midline and would not closely approximate the dopamine conformation. In accordance with this prediction, of all the widely used phenothiazines in clinical practice, the only two that are systematically inferior to all the others are promazine (Sparine®) and mepazine (Pacatal®). The sole chemical way in which these two drugs differ systematically from the other phenothiazines is in the absence of a substituent on ring A.

Of the phenothiazines that are clinically efficacious, what determines which will be the most potent on a milligram basis? One might presume a priori that differences in metabolism and ability to penetrate into the brain account for the large differences in potency, so that 5 mg. of fluphenazine would be equipotent to 400 mg. of chlorpromazine. Pharmacodynamic studies indicate, however, that such factors cannot account for the differences in clinical potency. Moreover, when assayed directly against dopamine receptors in binding studies or with the dopamine-sensitive adenylate cyclase, dif-

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**Figure 3.** Phenothiazines with the side chain "tilted" towards the A ring.
ferences in clinical potency are predicted by affinity for the dopamine receptor. One might therefore conclude that the more potent phenothiazines must be capable of assuming the dopaminelike conformation more frequently than less potent phenothiazines. Insofar as the A-ring substituent and the amine side chain are mutually attracted by chemical forces, the chemical variations that increase these attractive forces should stabilize the dopamine conformation of phenothiazines, producing more potent drugs. Thus, phenothiazines with a trifluoromethyl substituent in ring A are more potent than those with a chlorine. Molecular modeling (Figure 3) and computer calculations indicate that the trifluoromethyl group more closely approximates the amine side chain, providing for greater attractive forces than a chlorine substituent, so that drugs with trifluoromethyl groups should be more potent in binding to the dopamine receptor. Similarly, phenothiazines with piperazine side chains are more potent clinically than those with alkylamino side chains. Again, simple observations of space-filling molecular models indicate how the piperazine side chain would afford more points of attraction to the ring-A substituent than the alkylamino side chain. Drugs with hydroxyethyl-piperazine side chains, such as fluphenazine, are systematically more potent than those with simple piperazine rings, such as trifluoperazine. Again, drugs with hydroxyethyl-piperazine groups provide still more attractive possibilities than piperazines. Thus, simply by designing phenothiazine drugs that can ideally mimic the dopamine conformation, one can arrive at agents that are not only clinically efficacious but also considerably more potent than other drugs that mimic dopamine less faithfully.

CONCLUSIONS

Not only does blockade of dopamine receptors correlate with the antischizophrenic activity of phenothiazines, but more potent agents give the appearance of having been sculpted to plug into the dopamine receptor, though they were designed by chemists who had never heard of dopamine. The case that phenothiazines exert their clinical actions by blocking dopamine receptors is rather impressive. While blocking dopamine receptors relieves schizophrenic symptoms, flooding the receptors with more dopamine by using amphetamine exacerbates schizophrenic symptoms.

Psychopharmacologists can manipulate schizophrenic manifestations by titrating synaptic activities of dopamine, but this does not prove that dopamine is the causative "germ" of schizophrenia. Though genetic evidence is compelling that there must be some biologic abnormality in a substantial number of schizophrenics, this abnormality could be many steps removed from dopamine. No one has yet demonstrated a specific aberration in dopamine in the brains of schizophrenics. The closest is the finding of Wise and Stein that dopamine hydroxylase activity is lower in the brains of schizophrenics than in control subjects. One could argue that a deficiency of this enzyme would result in a build-up of dopamine that would be consistent with the effects of drugs on schizophrenic behavior. In one study attempting to confirm the abnormality of dopamine hydroxylase in the schizophrenic brain, it was found that while some schizophrenics had low dopamine hydroxylase levels, this seemed to relate primarily to how long the brain had been kept after death before assay. However, while it is still possible that there was a real decrement in dopamine hydroxylase in schizophrenic brains even in this study, definitive answers must await further attempts at replication.

Even the indirect evidence of the influence of drugs on schizophrenic behavior possesses certain flaws. While phenothiazines exert an antischizophrenic action, they do not really "cure" many schizophrenics. Psychiatrists are often impressed with the fact that schizophrenics in remission after phenothiazine treatment are still aberrant in their behavioral patterns. Of course,
it could be argued that one can hardly expect a
drug, even one that acts at the specific site of
abnormality in the brain, to completely reverse
events that have been going on for a lifetime.
Certainly, although appropriate antibiotics can
arrest an advanced case of tuberculosis, the pa-
tient will still be left with sequelae of the dis-
ease.

The use of amphetamine psychosis as a
model for schizophrenia has been attacked on
the grounds that the former disorder does not
display the abnormalities of thought and affect
that are classic in schizophrenia and that pa-
tients with amphetamine psychosis always ap-
pear paranoid, their disorder rarely resembling
other forms of schizophrenia. Some inves-
tigators have observed thought and affect dis-
orders in persons with amphetamine psychosis.4,5
It may be somewhat difficult to
recognize thought and affect abnormalities in
intelligent patients with well-organized
paranoid systems of ideation. Also, even if am-
phetamines cause changes in the brain similar
to those that occur in true schizophrenics, the
fact that the drug psychosis is taking place in a
nonschizophrenic person who "knows" that
the episode is likely to be short-lived makes for
major differences. By contrast, a schizophrenic
has been experiencing an abnormal mental state
for most of his life and has no hopes of any
major relief. The selective exacerbation of
schizophrenic symptoms by low doses of am-
phetamines is probably stronger evidence re-
garding the psychotogenic capabilities of these
drugs.

Despite these reservations, there is little
doubt that research prompted by the relation-
ship of drugs, dopamine, and schizophrenia
has greatly advanced our understanding of
psychotropic drug action. One hopes that it will
shed some light on schizophrenia.

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