A Critique of the Dopamine Hypothesis of Schizophrenia and Psychosis

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The dopamine hypothesis of schizophrenia and psychosis originated from observations of the dopamine-blocking actions of early neuroleptic drugs. These results support the dopamine hypothesis, however, only on the assumption that the drugs act by reversing an underlying disease mechanism (or part of it). An alternative explanation is that the drugs work by inducing a state of neurological suppression that reduces the intensity of symptoms. Although stimulant drugs are known to induce episodes of psychosis, the mechanism for stimulant-induced psychosis has not been clarified, and stimulants are known to affect many neurotransmitters other than dopamine. Recent imaging studies suggest that there may be increased dopamine release in response to amphetamine administration compared to controls. Some studies indicate increased uptake of L-dopa in parts of the striatum, but some do not. The potential confounding effects of factors associated with dopamine release—such as movement, arousal, attention, stress, and smoking—have rarely been examined, and prior medication use may also have influenced results in some studies. Comparable research on other psychiatric conditions associated with increased arousal, stress, and physical activity is sparse. Research on dopamine concentrations in postmortem brain tissue, on homovanillic acid concentrations, and on dopamine receptors has been negative or inconclusive. Therefore, the idea that the symptoms of psychosis or schizophrenia are caused by the overactivity of dopamine is not supported by current evidence. (HARV REV PSYCHIATRY 2009;17:214–225.)

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The dopamine hypothesis of schizophrenia and psychosis is currently popular again. In its original form the hypothesis suggested that schizophrenia might be due to increased activity of the neurotransmitter dopamine. More recently, it has been suggested that "dopaminergic dysregulation" is the final common pathway leading to the symptoms of acute psychosis, though not to schizophrenia per se.[1]

HISTORY OF THE DOPAMINE HYPOTHESIS

The dopamine hypothesis evolved from animal studies conducted in the 1960s showing that neuroleptic drugs blocked dopamine receptors in the brain.[2,3] An article by van Rossum[3] published in 1966 is often cited as the first expression of the dopamine theory of schizophrenia, but in fact, the article concerned only the mode of action of neuroleptic drugs. It stated: "The hypothesis is therefore put forward that dopamine receptor blockade is an important factor in the mode of action of neuroleptic drugs." In a book published the same year, van Rossum[4] remarked that this discovery may have "fargoing consequences for the pathophysiology of schizophrenia. Overstimulation of dopamine receptors could then be part of the aetiology."

By 1974, it appears that the dopamine hypothesis was already influential, being described as "shared by many

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investigators" and as exerting "a substantial influence on the design of experiments."[5] It was not clearly accepted or even formulated in the scientific literature, however, until the mid-1970s.[6–8] Indeed, for many researchers, the dopamine hypothesis remained a hypothesis about antipsychotic drug action rather than the etiology of schizophrenia.[9] As late as 1973, Steven Matthysse,[10] in one of the first reviews of research pertaining to a possible dopamine theory of schizophrenia, argued "this simple hypothesis is by no means the only possible interpretation (of some research data). It is not even the most plausible." A year later he was more confident, stating that "ideas connecting dopamine and schizophrenia have reached a certain maturity."[5] By 1976 a comprehensive review concluded that "the evidence for a role of dopamine in the pathophysiology of schizophrenia is compelling but not irrefutable."[11]

Among other things, the rediscovery of clozapine and observations that neuroleptic drugs did little, if anything, for negative manifestations of schizophrenia appeared to contradict the theory. Clozapine is a relatively unselective drug whose actions are not restricted to blockade of dopamine receptors, but include significant effects at numerous other neurotransmitters. The popularity of the hypothesis therefore waned during the 1980s and 1990s, and was consequently modified in an effort to accommodate these problems. In 1991 Davis[12] suggested that schizophrenia was caused by simultaneous dopamine overactivity in the subcortical area of the brain (giving rise to the "positive" symptoms) and underactivity in the frontal cortex (leading to "negative" symptoms). The idea that schizophrenia was due to a serotonin-dopamine imbalance was also proposed.[13] Recently, complex theories have been put forward—involving glutamate-dopamine system interaction and neuronal circuitry—that posit dopamine abnormality as part of a wider pathological process.[14,15] Kapur[1] recently proposed that dopamine is responsible for the "salience" of phenomena, the degree to which events are perceived as personally significant. He further suggested that psychosis is predominantly a condition of increased salience, in which neutral experiences are mistakenly endowed with personal meaning. This idea has been elaborated by Broome and colleagues.[16] The idea that schizophrenia involves a simultaneous overactivity of dopamine in the striatum and underactivity in the prefrontal cortex also remains influential.[17]

Therefore, although dopamine may no longer be regarded as the ultimate cause of schizophrenia or psychosis, many researchers continue to believe that dopamine function is abnormal in schizophrenia or psychosis and that this abnormality is involved in the production of symptoms. In particular, the claim is that psychotic symptoms are produced by abnormally high dopamine levels or activity. In the present article I critically examine the evidence for this view.

METHODS

Since the literature on dopamine in schizophrenia and psychosis is extensive, only the areas believed to represent the strongest evidence of an association were selected for detailed attention. Recent imaging studies of dopamine activity in people with psychosis were selected because these studies may present direct evidence of a dopamine abnormality. Indirect evidence such as the effects of antipsychotics and parallels with amphetamine-induced psychosis were also selected; they are longstanding pillars of the dopamine hypothesis and frequently quoted as supporting evidence. Research in other areas—such as dopamine receptor studies, where evidence is thought to be less compelling—is summarized briefly.

Recent imaging studies of dopamine activity were identified through Medline searches, citations of studies and other reviews, and contact with researchers in the field. Research on other aspects of the dopamine hypothesis were identified from citations in other review articles on the dopamine hypothesis and various related topics.

FUNCTIONS OF DOPAMINE

Although the numerous functions of dopamine have not yet been fully mapped out, especially in humans, it is important to understand what is already known. The reason for care here is that research on links between dopamine and psychosis—in particular, studies that compare dopamine activity between patients and controls—may be susceptible to confounding by associations between dopamine and other factors.

First, animal studies making use of lesioning techniques have established that dopamine is involved in motor activity, attention, executive function, and reaction times.[18] Studies with human subjects confirm that dopamine activity correlates with motor activity and attention.[19,20] Dopamine is also involved in the arousal induced by amphetamines.[21] Conversely, dopamine depletion, whether induced by experimental procedures or naturally occurring as in Parkinson's disease, is associated with reduced movement, tiredness, mental slowing or clouding, low mood, and loss of initiative or motivation.[22–24]

Second, dopamine release is associated with stress. Animals studies show dopamine release in the cortical and limbic areas of the brain in response to stress.[25] Studies of homovanillic acid levels in human subjects indicate increased dopamine turnover after stressors such as examination stress[26,27] and induction of hypoglycemia.[28] Two positron emission tomography (PET) studies in human volunteers suggested increased dopamine release after hypoglycemic stress[29] and after a stressful task involving mental

arithmetic,[30] but another study using a mental arithmetic task failed to replicate this finding.[31]

Third, it has been suggested that dopamine plays a role in pleasure- and reward-seeking behavior, including the effects of recreational drugs. The literature in this area is complex, however, and few findings are clear-cut.[32] The relationship between dopamine and nicotine is relevant here, given the prevalence of smoking among people with schizophrenia and psychosis. Some animal studies show an increase in dopamine release after nicotine administration,[33] but human studies have been mixed. A study of [^{11}C] raclopride binding did not find evidence of dopamine release after nicotine administration.[34] Some studies, however, show reduced dopamine transporter availability in smokers compared to nonsmokers, suggesting increased activity of the dopamine system.[35,36] One study found significantly higher levels of uptake of the radio-labeled dopamine precursor 6–^{18}F-fluoro-L-DOPA (F-dopa) in the basal ganglia of smokers compared to nonsmokers.[37] Studies of dopamine receptor availability are inconsistent.[35,38–40]

If patients with psychosis or schizophrenia have a particular susceptibility to any of the above factors that are potentially associated with dopamine activity, then research that looks for differences in dopamine activity between patients and controls, such as the imaging studies discussed later, may be confounded. For example, if patients are more aroused, more active, or more stressed, or if they smoke more than healthy controls, these factors may account for any observed differences in dopamine activity, and steps need to be taken in order to examine and control for their effects.

EVIDENCE FOR THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

Effects of Neuroleptics

The fact that all neuroleptic drugs block dopamine receptors, particularly the D2 receptor, is often held to be the strongest evidence that increased dopamine activity is involved in the pathogenesis of psychotic symptoms or acute schizophrenia. The underlying assumption here is that the drugs act on the pathophysiology responsible for generating the symptoms, but there is an alternative explanation for the drugs' therapeutic action.[41] Rather than reversing a pathological process, the benefits of neuroleptics may result from the characteristic neurological state that they induce. In normal volunteers, neuroleptics produce a state of physical and mental slowing, and emotional flattening or detachment.[42–44] These characteristic effects may account for their ability to reduce the impact of abnormal mental phenomena such as delusions and hallucinations.

In other publications I have referred to this view of how neuroleptic drugs work as the "drug-centered" model of drug action. This view is distinguished from the "disease-centered" model, which assumes that drugs act to reverse part of a disease process.[41] When neuroleptics were first introduced into psychiatry, they were regarded as acting in a drug-centered fashion, but a disease-centered view soon became dominant. Elsewhere I have documented the lack of evidence for this transformation; in particular, few studies have been designed to test whether neuroleptics are superior to drugs with similar qualities that do not act via dopamine.[45] Early studies suggested that neuroleptics are superior to barbiturates,[46,47] but studies of benzodiazepines are equivocal. A recent Cochrane review found significantly greater improvement in people taking benzodiazepines than in those taking placebo in short-term studies, but no difference in outcome in long-term studies.[48] Studies comparing benzodiazepines to neuroleptics found no differences on any measure of outcome that favored antipsychotics, although the authors noted the paucity of good quality studies in this area. In addition, another review found that in seven out of ten studies that specifically evaluated psychotic symptoms, benzodiazepines reduced these symptoms either more effectively than placebo or as well as antipsychotics.[49]

Although drugs such as benzodiazepines and barbiturates exert a sedative action, they do not produce the emotional flattening or indifference associated with neuroleptic drugs. Therefore, even if neuroleptics were superior to these other sedatives, this superiority may be due to the particular nature of their drug-induced effects rather than to any disease-specific action. The only randomized trial comparing a neuroleptic to another class of drug that produces a state of emotional detachment is an old study of chlorpromazine versus opium, which found the two drugs to be equally effective.[50]

Clinical trials do show that antipsychotic drugs are more effective than placebo, but they do not establish that this effect is achieved by reversing an underlying abnormality of dopamine. The alternative possibility that they work in a drug-centered fashion—in particular, by creating a drug-induced state that suppresses psychotic symptoms—has not been ruled out. It therefore cannot be assumed that psychosis is produced by the opposite biochemical state from the one used to treat it.[41]

The idea of reduced salience, introduced by Kapur and others, is a useful addition to the vocabulary used to describe the effects of dopamine-blocking drugs.[1,16] However, the relation between increased salience and psychosis is more speculative. First, the concept of salience is difficult to differentiate from motivation, attention, affect, and arousal, which appear to involve many neurotransmitter systems, not just dopamine. Second, although neuroleptics appear to reduce the intensity of psychotic symptoms, they often do not eliminate them completely, even in people who respond well[51]—which suggests that such symptoms are not entirely

attributable to increased salience. Finally, as demonstrated in volunteers, salience is not the only factor affected by neuroleptic drugs. Reduced salience can be viewed as one feature of the global reduction in physical and mental activity, emotion, and initiative that these drugs produce.

Although second-generation, or atypical, antipsychotics block D2 receptors, their propensity to do so is generally weaker than that of most older antipsychotics. Clozapine, in particular, appears to have relatively weak D2 blocking action relative to traditional neuroleptics despite its having equivalent, or some would say superior, efficacy against psychotic symptoms. One suggestion is that clozapine's effects on 5HT2A receptors add to, or interact with, its effects on the dopamine receptors to produce its clinical effects.[13] Recently, it has been hypothesized that clozapine and some other atypical antipsychotics bind to D2 receptors more loosely or reversibly than other neuroleptics and hence that they may exert their therapeutic activity primarily through D2 blockade, even though levels of D2 binding appear to be lower.[52] However, the fact that clozapine is less likely to cause extrapyramidal symptoms would seem to suggest that it has lower D2 blocking activity than other drugs at usual clinical doses and that its therapeutic effects must therefore occur at lower levels of D2 occupancy. If so, counteracting dopamine activity by blocking D2 receptors may not be the only mechanism for producing therapeutic effects in people with psychotic symptoms.

Stimulant-Induced Psychosis

The fact that the chronic ingestion of psychostimulant drugs such as amphetamine, cocaine, and L-dopa can lead to psychotic symptoms in some individuals without a previous psychiatric history has long been regarded as supporting the dopamine hypothesis. However, there are problems with this logic.

First, there is no reason to assume that the causes of chemically induced psychotic episodes are the same as for those that arise de novo. Some authors suggest there are clinical differences between stimulant-induced psychosis and idiopathic psychosis or schizophrenia, which might suggest they are distinct phenomena,[53] but others have highlighted the similarities. Characteristic schizophrenic symptoms such as "thought disorder," delusions of control, delusional perceptions, and inappropriate or flattened affect are rarely seen in stimulant psychoses. Likewise, in amphetamine psychosis, mood is usually one of extreme anxiety, sexual behavior is heightened, and visual hallucinations are more common than they are in idiopathic psychosis.[53] In animals, chronic stimulant use induces hyperactivity, and with increasing doses and prolonged use, it causes abnormal repetitive movements known as "stereotypies." Stimulants also cause hyperactivity in humans, and people with stimulant-induced psychosis sometimes show stereotypies.[54] Hyperactivity is not characteristic of idiopathic psychosis or schizophrenia. However, others have pointed out that stimulant-induced psychosis is rarely easy to differentiate from idiopathic psychosis, and that it may occasionally involve symptoms usually associated with schizophrenia, such as bizarre delusions, third-person hallucinations, and negative symptoms, including apathy and social withdrawal.[54,55] In addition, abnormal movements have been noted in untreated patients with schizophrenia.[56,57]

Overall, the evidence is not clear-cut, and it is possible to conclude that stimulant-induced psychosis is both somewhat distinctive and that it shares features with idiopathic psychotic disorders. Even if the distinctions are put aside, however, it remains possible that psychosis may result from different causal pathways in different situations.

Second, the actual cause of stimulant-induced psychosis in humans has not been established.[11] Based on animal research, dopamine is thought to be responsible for stimulant-induced hyperactivity and stereotypy,[58] though some research also shows an association between noradrenalin and locomotion.[59] Amphetamine strongly increases noradrenalin (and not just dopamine) availability; it affects the serotonin system; and as is the case for most drugs, prolonged use is likely to cause complex perturbations in different systems. Chronic cannabis use can also induce a psychotic episode, but cannabis has less obvious effects on the dopamine system and does not induce hyperactivity or stereotypies. LSD produces psychotic-like experiences without having pronounced dopaminergic effects.

Therefore, although there is evidence that biochemical mechanisms can induce episodes of psychosis, it has not been established that dopamine excess is the principal cause. Moreover, even if dopamine was the principal cause, it would not necessarily follow that other psychotic conditions must be caused by the same mechanism.

Imaging Studies of Amphetamine-Induced Dopamine Release

Table 1 lists the three studies and one meta-analysis that have investigated amphetamine-induced elevations of dopamine concentration in patients with schizophrenia, as measured by a reduction of post-amphetamine binding of a radio-labeled ligand, [^{123}I] iodobenzamide ([^{123}I] IBZM).[60–63] All three studies detected an enhanced release of dopamine in response to amphetamine challenge in people with schizophrenia compared to controls. The differences between patients and controls were small, however, with substantial overlap between results. In addition, although two of the three studies found a correlation between reduced ligand binding and increased positive symptoms,[60,62] one did not.[61]

TABLE 1. Amphetamine-Challenge Studies

Study	Number of subjects	Ligand used	Results
Laruelle et al. (1996)[60]	15 patients with schizophrenia, none neuroleptic naive 15 controls	[^{123}I] IBZM	Greater reduction in amphetamine-induced binding potential in patients (20%) vs. controls (8%) ($p = 0.01$)
Breier et al. (1997)[61]	11 patients with schizophrenia, 6 neuroleptic naive 12 controls	[^{11}C] raclopride	Greater reduction in binding potential in patients (22%) vs. controls (16%) ($p = 0.05$)
Abi-dargham et al. (1998)[62]	15 patients, 2 neuroleptic naive	[^{123}I] IBZM	Greater reduction in binding potential in patients (14%) vs. controls (7%) ($p < 0.05$)
	15 controls		No differences in amphetamine-induced reduction in plasma HVA levels or in post-amphetamine levels between patients & controls
Laruelle et al. (1999)[63]	Meta-analysis of data on 60 patients from previous studies plus 10 additional subjects; 7 neuroleptic-naive patients in total	[^{123}I] IBZM	Greater reduction in binding potential in patients (17%) vs. controls (8%) ($p < 0.001$) Significant difference between controls & neuroleptic-naive patients ($p < 0.003$) No difference between patients in remission & controls ($p = 0.3$)

[^{123}I] IBZM, [^{123}I]idodo-2-hydroxy-6-methoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide; HVA, homovanillic acid.

Research on the general functions of dopamine (described in the preceding section) indicates that dopamine is associated with numerous factors that may be differentially distributed among patients and controls—which may therefore confound the studies in question. First, the relation between dopamine and stress may be particularly relevant since patients are likely to be experiencing more stress than healthy controls. There are indications, for example, that psychotic patients who are acutely unwell have elevated hypothalamic-pituitary-adrenal axis function, indicating a physiological stress response.[64,65] Second, patients may be more aroused and show more movement than controls, which would increase dopamine levels. Third, smoking may play a role. Fourth, dopamine levels and dopamine receptors are known to decline with age,[66,67] and although most studies match patients and controls by age, some subgroup analyses may be affected by age discrepancies.

In addition, the use of neuroleptic drugs may confound studies since drug treatment is known to produce a compensatory increase in the density and sensitivity of D2 receptors. Animal research shows that these changes can occur after only a few days of the continuous administration of these drugs.[68] Clinical research with humans demonstrates that prior exposure to neuroleptics increases the dose at which extrapyramidal side effects are manifested, again suggesting that previous neuroleptic treatment affects dopamine function.[69]

Among the amphetamine-challenge studies, the meta-analysis was the only one to consider any possible confounders other than medication use.[63] It found significantly higher levels of anxiety in patients than controls, both before and during the procedure. Although the authors reported that there was no correlation between anxiety levels and IBZM displacement *within* the patient or control group when looked at separately, they did not report the correlation, if any, among all patients in both groups—which would be the usual way to investigate such an effect. The meta-analysis also suggested that increased dopamine release was more common in those people who were in an acute psychotic state than in those who were in remission.[63] This result may be evidence of a direct relationship between dopamine and psychotic symptoms, but it may also indicate that dopamine elevation is related to other features associated with an acute state, such as arousal, anxiety, or distress.

The authors of the meta-analysis conducted a careful examination of the effects of previous medication use. Twenty-seven subjects had long-term exposure to medication prior to being withdrawn from medication temporarily for the study, and only seven were drug naive. The amphetamine effect on the IZBM binding potential was found in both groups and was not lower in the drug-naive patients. The number of drug-naive patients was small, however, and they were younger than the control group by an average of over ten years. Although age was not statistically associated with reduced ligand binding in this sample, its known relation to dopamine levels means that it is difficult to discount an age effect entirely. The authors also assessed the impact of drug treatment by looking for associations between IZBM binding and both the length of the drug-free period prior to

the study and years of prior exposure to neuroleptic drugs. No correlations were detected.

Neuroleptic exposure has been found to result in a shift of dopamine receptors to a high-affinity state,[70] which could account for the greater reductions in IZBM binding seen in patients compared to controls.[17] Although the meta-analysis did not detect any associations with prior medication use, greater numbers of drug-naive patients would be needed to exclude this possibility.

None of the amphetamine-challenge studies considered possible confounding effects of smoking.

Even if the possible influence of confounders like previous medication and stress is ignored, the attribution of cause and effect on the basis of these studies is not straightforward. For example, it is possible that people who are psychotic have a stronger psychological reaction to the effects of amphetamine than those who are not, perhaps finding it more stressful and aversive when added to their preexisting psychotic state. Their stronger psychological response might provoke higher levels of dopamine release without there being any prior abnormality of the dopamine system. These studies cannot exclude such explanations.

Imaging Studies of Dopa Uptake

Seven studies, summarized in Table 2, have measured uptake of radio-labeled dopamine precursor molecules—and mainly, F-dopa.[71–77] Levels of re-uptake reflect the activity of the enzyme dopa decarboxylase, which is presumed to reflect the rate of dopamine synthesis. These studies included a total of 24 neuroleptic-naive patients. Several studies showed increased uptake in patients compared to controls, but the part of the striatum in which the effect was found varied across studies. The study finding the strongest effect was conducted exclusively with patients treated concurrently with neuroleptic drugs.[77] The largest study actually found a statistically significant decrease, rather than an increase, in dopa uptake in the ventral striatal area.[75] The inconsistency of the results may reflect numerous methodological differences, such as the type of reference tissue used, designation of the region of interest, and method for calculating uptake. It has also been suggested that the variation may reflect that the dopamine abnormality associated with psychosis may be located in a functional subregion of the striatum, known as the associative striatum, involving the

TABLE 2. DOPA Uptake Studies

Study	Number of subjects	Tracer used	Results
Reith et al. (1994)[71]	5 schizophrenia patients, 4 neuroleptic naive 9 controls	^{18}F-dopa	Statistically significant increase in F-dopa uptake in patients compared to controls in left ($p < 0.01$) & right caudate heads ($p < 0.02$), but not putamen
Hietala et al. (1999)[72]	10 patients, all neuroleptic naive 13 controls	^{18}F-dopa	Statistically significant increase in uptake of F-dopa in patients compared to controls in right & left putamen ($p = 0.02$), but not caudate
Dao-Castellano et al. (1997)[73]	6 patients, unspecified number neuroleptic naive 7 controls	^{18}F-dopa	No difference between groups ($p = 0.5$)
Lindstrom et al. (1999)[74]	12 patients, 10 neuroleptic naive 10 controls	^{11}C-L-dopa	Increased uptake in patients in caudate ($p = 0.001$), putamen ($p = 0.02$), & medial prefrontal cortex ($p = 0.03$); overall significant difference corrected for multiple comparisons ($p = 0.04$)
Elkashef et al. (2000)[75]	19 patients, none neuroleptic naive 13 controls	^{18}F-dopa	Decreased uptake in ventral striatum in drug-free patients vs. controls ($p = 0.04$) No differences in caudate & putamen Increased uptake in posterior cingulated gyrus ($p = 0.02$)
Meyer-Lindenberg et al. (2002)[76]	6 patients, none neuroleptic naive 6 controls	^{18}F-dopa	Increased uptake in striatum ($p < 0.02$)
Mcgowan et al. (2004)[77]	16 patients, all taking neuroleptics 12 controls	^{18}F-dopa	Increased uptake in striatum as a whole & ventral striatum ($p < 0.001$)

^{18}F-dopa, 6–^{18}F-fluoro-L-DOPA; ^{11}C-L-dopa, L-(β–^{11}C) DOPA.

dorsal part of the caudate and putamen.[78] This suggestion does not, however, explain away all the inconsistencies of the results.

Two studies examined the effects of smoking, and both found no difference in dopa uptake between smokers and nonsmokers. In both studies, however, the overall numbers and also the numbers of smokers were too small to detect anything but a large effect.[76,77]

None of these studies considered the potential influence of stress, movement, or arousal. A brief analysis of medication effects was performed only in the one study involving concurrently medicated patients. Although no correlation between current neuroleptic dose and uptake values was found, there was no analysis of duration of exposure, and the study could not compare patients on and off these drugs.[77] In one study all patients were noted to have "acute symptoms,"[74] and in another the patients, recruited from outpatient clinics, were described as "stable."[77] In others it is not clear whether the patients included were acutely psychotic or relatively stable. Where it was examined, no association was found between symptom severity and dopa uptake.[77]

Dopamine-Depletion Study

One study examined D2 receptor availability after acute dopamine depletion using the tyrosine hydroxylase inhibitor, α-methyl-para-tyrosine, in 18 patients. Eight were drug naive, and 10 were chronic patients who had stopped drug treatment an average of 139 days before. The level of increase in the radio-labeled dopamine receptor ligand-binding potential after dopamine depletion was taken to indicate occupancy levels of D2 receptors by dopamine prior to depletion.[79] The study reported that D2 receptor availability increased by 19% in patients and by 9% in controls, a difference that was statistically significant ($p < 0.01$). In addition, the α-methyl-para-tyrosine effect on D2 receptor binding potential correlated with subsequent response to antipsychotic treatment ($r = 0.58$, $p = 0.003$). No attempts were made, however, to control for any potential confounders, and there was evidence of increased D2 receptor density in previously treated patients, which correlated with the duration of the drug-free interval prior to the study ($r = 0.47$, $p = 0.03$). Although this last finding does not affect the overall results of the study since patients acted as their own controls, it does indicate that prior exposure to neuroleptic drugs had altered the dopamine system.

Evidence on Dopamine Activity in Other Disorders

If dopamine release is associated with "behavioral activation" or stress, then other psychiatric conditions associated with increased arousal, activity, anxiety, and behavioral problems might be expected to show similar results to those found in psychosis. Unfortunately, there are few such studies. One study found no difference in F-dopa uptake in the striatum as a whole between 13 drug-naive patients with "non psychotic" mania compared to controls.[80] Studies of depressed patients have found no overall difference in dopamine function as measured by amphetamine challenge and F-dopa uptake.[81,82] In one of these studies, patients were more anxious than controls, which might have been predicted to increase dopamine activity.[81] But the patients in this study also reported lower energy levels, and four out of nine had clinically recognizable psychomotor retardation, which might reduce dopamine activity and counteract any effect of anxiety. Where psychomotor retardation was investigated, it was associated with reduced dopamine uptake in part of the striatum.[82] In contrast, a recent study of patients with obsessive-compulsive disorder previously treated with a range of psychotropic drugs, including neuroleptics, found decreased D2 [^{123}I] IBZM binding in the left caudate, a possible indication of increased dopamine availability.[83] Two studies of children and adults with attention-deficit/hyperactivity disorder indicated increased F-dopa uptake in some brain areas but not the striatum.[84,85]

Other Studies

Total dopamine content of the brain can be measured directly only in a postmortem examination. Overall, such studies have not detected differences between people with schizophrenia and people without.[12,86] A meta-analysis of research on levels of the dopamine metabolite homovanillic acid in cerebrospinal fluid and urine found no abnormality compared to normal controls.[87] Imaging studies have not found any difference in the density of the dopamine transporter between patients and controls.[88,89]

Increased D2 receptor density in the brains of people diagnosed with schizophrenia was first reported from postmortem studies in the 1970s. The patients whose brains were examined had been taking neuroleptic drugs for long periods before they died, however, and subsequent postmortem studies that controlled for the effects of medication use found that abnormalities of dopamine receptors were attributable to the effects of drugs.[90–92] Animal research confirms that neuroleptic drugs increase the density of D2 receptors after a few days.[68,93] Although two early imaging studies of drug-free patients found a statistically significant increase in the density of D2 receptors in brains of patients with schizophrenia compared to controls,[94,95] numerous other studies have found no significant difference.[17] An updated meta-analysis of these studies revealed a small increase in D2 receptors compared to controls,[17] but the three

studies that included only drug-naive patients found no significant difference.[35,96,97]

Studies of D1 receptors postmortem have found no differences between people diagnosed with schizophrenia and controls.[17] Studies of D3 and D4 receptors have been inconsistent or negative.[17] PET studies of D1 receptors have shown no abnormality in the striatum, with inconsistent findings in the prefrontal cortex.[98–100]

DISCUSSION

The earliest support for the dopamine hypothesis of schizophrenia consisted of the observations that neuroleptic drugs affected dopamine transmission and that psychostimulants can cause psychosis. Recent studies that demonstrate increased dopamine release in response to amphetamine in acutely psychotic patients and increased uptake of a dopamine precursor, radio-labeled L-dopa, may provide more direct evidence of an abnormality of the dopamine system. Other indirect findings that may support the dopamine hypothesis (but that were beyond the reach of this review) include associations between schizophrenia and genes involved in dopamine regulation[101] and the incidence of abnormal movements in people with untreated psychosis. I have concentrated on evidence for an association between raised dopamine activity and symptoms of psychosis, and have not reviewed evidence either for an association between lowered cortical dopamine and negative symptoms or of interactions between dopamine and other systems.

Much research into dopamine levels, such as postmortem studies and studies of the dopamine metabolite homovanillic acid, has failed to disclose differences between patients and controls. Elevation of D2 receptors in patients, where it has been found, has been associated with prior drug treatment.

The evidence that is felt to be most supportive is also open to question. The action of neuroleptics supports a causal role for dopamine only on the assumption that these drugs counteract part of an underlying disease process that gives rise to psychotic symptoms. An alternative explanation, however, is equally plausible—namely, that the drugs induce a state of physical and mental suppression that reduces the impact of psychotic symptoms. It has not been established that dopamine dysfunction is the sole cause of stimulant-induced psychosis, and even if it was, one could not necessarily conclude that it was also the primary cause of idiopathic psychosis or schizophrenia. L-dopa uptake studies and studies of dopamine release in response to amphetamine have included only small numbers of drug-naive patients. In addition, there has been little attempt to control for factors, other than medication, known to increase dopamine release. Thus higher levels of stress, arousal, movement, and smoking, along with numerous other differences between being a psychiatric patient and being a control subject, may account for the results of these studies, apart from the specific diagnosis of psychosis.

Many factors need clarification to help us evaluate the strength of current evidence for the role of dopamine in psychosis or schizophrenia. We need to understand better the role of dopamine in people without psychiatric disorders—in particular, its role in arousal, stress, and motivation, in addition to its relation to other neurotransmitters involved in these states. This information would help to clarify whether or not these factors may act as confounders in direct studies of dopamine function (such as the amphetamine-challenge studies and studies of L-dopa uptake) in people with psychosis. Further research on the mechanism of stimulant-induced psychosis—specifically looking at the role of all the transmitters effected by these drugs—would be useful, as would comparison with the mechanism of action of cannabis. The mechanism by which drugs such as clozapine exert their sedative and antipsychotic effects also requires clarification, including further exploration of their known impact on other neurotransmitters systems.

Rather than focusing on psychiatric disorders or diagnoses, research on dopamine and other neurotransmitters should, in my judgment, focus on symptoms and behaviors that cut across diagnostic boundaries—like anxiety, arousal, agitation, and motivation. Moreover, concentrating on one or a few neurotransmitter systems may obscure the role of other brain chemicals and the interactions between them. There have been efforts to integrate the roles of glutamate and dopamine,[14] but neurotransmitters such as noradrenalin, acteyl choline, histamine, and others have received little attention.

Finally, the concept of cause and effect needs to be carefully explored. Abnormalities of neurotransmitters may be better understood as correlations of psychological states than as causes of them. For example, the surge of adrenalin that accompanies a frightening experience does not in itself produce fear. It is the physiological accompaniment to the emotional reaction. It may be difficult to clarify experimentally whether biochemical states qualify as causes of mental experiences or as symptoms. To establish causality, longitudinal studies in asymptomatic subjects would be needed to see if a biochemical abnormality, such as excess dopamine, preceded the onset of psychotic symptoms. Cohorts of high-risk and prodromal subjects recently identified for other research may provide such opportunities, but securing cooperation with repeated testing is likely to be difficult.

Overall, despite the resurgent popularity of the dopamine hypothesis of schizophrenia or psychosis, the evidence remains contradictory. The present state of research does not allow us to decide whether, independent of its other

functions, dopamine has a specific causal role in psychosis or schizophrenia.

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