Dopamine Hypothesis of Schizophrenia: Making Sense of it All

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The dopamine (DA) hypothesis of schizophrenia has evolved over the last decade from the stage of circumstantial evidence related to clinical observations and empirical validation from antipsychotic treatment to finally reach more direct testing and validation from imaging studies. These have provided much information that allows us at this point to assemble all the pieces and attempt to synthesize them and integrate them with the other neurotransmitter alterations observed in this illness. Although clearly not sufficient to explain the complexity of this disorder, the DA dysregulation offers a direct relationship to symptoms and to their treatment. We will review here its history, validation, and implications for treatment.

Introduction

Hyperactivity of dopamine (DA) transmission was the first iteration of the DA hypothesis of schizophrenia [1], supported by the early observations that DA receptors are activated by psychostimulants and that nonreserpine neuroleptics are DA antagonists [2]. Furthermore, clinical doses of antipsychotic drugs blocked DA D_2 receptors [3,4], whereas DA-enhancing drugs were found to be psychotogenic (for review, see [5,6]). Given the predominant localization of DA terminals and D_2 receptors in subcortical regions such as the striatum and the nucleus accumbens, this hyperactivity focused on subcortical regions.

On the other hand, negative symptoms (flattening of affect, apathy, poverty of speech, anhedonia, and social withdrawal) and cognitive symptoms (deficits in attention, working memory, and executive functions) were resistant to D_2 receptor antagonism. Functional brain imaging studies suggested that these symptoms might arise from altered prefrontal cortex (PFC) functions (for reviews, see [7]). As preclinical studies stressed the importance of prefrontal DA transmission at D_1 receptors (the main DA receptor in the neocortex) for optimal PFC performance (for review, see [8]), the idea of a deficit in DA transmission at D_1 receptors underlying cognitive impairments and negative symptoms emerged [9,10], whereas the excess DA transmission became associated with "positive" symptoms (hallucinations, delusions).

As a result, an imbalance in DA with hyperactive subcortical mesolimbic projections (resulting in hyperstimulation of D_2 receptors and positive symptoms) and hypoactive mesocortical DA projections to the PFC (resulting in hypostimulation of D_1 receptors, negative symptoms, and cognitive impairment) became the predominant hypothesis. In addition, a relationship between these two was suggested by the initial observation of Pycock et al. [11]. Based on these observations, Weinberger [10] proposed that both arms of the DA imbalance model might be related inasmuch as a deficiency in mesocortical DA function might translate into disinhibition of mesolimbic DA activity.

Hyperstimulation of Striatal D_2: Clinical Evidence

Psychostimulant-induced paranoid psychosis

First mentioned in 1938 [12], amphetamine-induced psychosis was recognized as a possible consequence of chronic amphetamine use upon the publication a 42-case monograph by Connell [13].

In the early 1970s, several studies experimentally induced amphetamine psychosis in nonschizophrenic amphetamine abusers in order to better document the clinical pattern of this syndrome [14–16]. These experiments formally established that sustained psychostimulant exposure can produce paranoid psychosis in nonschizophrenic individuals in the context of a clear sensorium (sensory and perceptual abilities). Ellinwood et al. [17,18] described amphetamine-induced psychosis as a continuum that evolves from stimulation of interpretative mental activities to enhancement of perceptual acuity, reversal, and projection onto others (persecution), leading to paranoia and ideas of references. The "enhancement of sensitive acuity" develops into hallucinations, initially auditory, and then visual and tactile. The sensorium remains clear until toxic delirium is reached. Thought

disorders manifest toward the end of the continuum, near the toxic stage.

Low-dose psychostimulants that are not psychotogenic in healthy subjects are psychotogenic in patients with schizophrenia

A number of studies, reviewed by Lieberman et al. [19], showed that patients with schizophrenia, as a group, display increased sensitivity to the psychotogenic effects of acute psychostimulant administration. In other words, some, but not all, patients with schizophrenia present with emergence or worsening of psychotic symptoms after acute exposure to psychostimulants at doses that do not induce psychosis in healthy subjects. The psychotic response appears to be state dependent. First, patients who responded with a psychotic reaction to a psychostimulant challenge during an acute episode failed to show such a response when they were in remission. Second, the propensity to present a psychotic reaction to a psychostimulant challenge is predictive of relapse upon antipsychotic discontinuation. Thus, the clinical response to stimulants might "reveal" an active phase of the illness that is not readily identifiable by the clinical symptomatology in the absence of psychostimulant administration.

All antipsychotics bind to D_2 receptors

Since the discovery of the antipsychotic properties of chlorpromazine [20] in 1952, antipsychotic medications have fundamentally altered the course and the prognosis of schizophrenia by reducing severity of symptoms and preventing relapse. D_2 receptor antagonism is fundamental to their beneficial effects.

D_2 receptor occupancy by antipsychotic drugs has been confirmed by a large number of imaging studies (reviewed in [21]). Two studies performed with low doses of relatively selective D_2 receptor antagonists (haloperidol and raclopride) suggest that a minimum of 50% occupancy is required to observe a rapid clinical response [22,23]. Imaging studies have confirmed repeatedly the existence of a striatal D_2 receptor occupancy threshold (~ 80%) above which extrapyramidal symptoms are likely to occur [24]. Together, these data suggest the existence of a therapeutic window between 50% and 80% striatal D_2 receptor occupancy.

Hyperstimulation of striatal D_2: evidence from imaging studies

The development of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging techniques in the late 1980s made possible for the first time the examination of DA function in vivo in patients with schizophrenia.

Striatal D_2 and D_1 receptors

Striatal D_2 receptor density in schizophrenia has been extensively studied with PET and SPECT imaging. In a recent meta-analysis [25], 17 imaging studies comparing D_2 receptor parameters in patients with schizophrenia were analyzed (included a total of 245 patients and 231 control subjects), revealing a small (12%) but significant elevation of striatal D_2 receptors in untreated patients with schizophrenia. No clinical correlates of increased D_2 receptor binding parameters could be identified. Studies performed with butyrophenones (n = 7) show an effect size of 0.96 ± 1.05, significantly larger than the effect size observed with other ligands (benzamides and lisuride, n = 11, 0.19 ± 0.25, P = 0.02). This difference might be due to differences in vulnerability of the binding of these tracers to endogenous DA and elevation of endogenous DA in schizophrenia [26,27]. Interestingly, the fact that D_2 receptor levels are increased in healthy monozygotic twins compared with dizygotic twins of patients with schizophrenia has led to the conclusion that the caudate DA D_2 receptor up-regulation is related to genetic risk for schizophrenia [28]. Imaging studies of D_1 receptors have consistently failed to detect abnormalities of D_1 receptor availability in the striatum of patients with schizophrenia [29–31].

Striatal amphetamine-induced DA release

The decrease in [^{11}C]raclopride and [^{123}I]IBZM in vivo binding following acute amphetamine challenge has been well validated as a measure of the change in D_2 receptor stimulation by DA due to amphetamine-induced DA release [32–34] (Table 1).

Three studies [34–36] have shown that amphetamine-induced decrease in [^{11}C]raclopride or [^{123}I]IBZM binding is elevated in untreated patients with schizophrenia compared with well-matched controls. The clinical significance of this dysregulation [37] is summarized as follows: the increase in DA response is related to the transient induction or worsening of positive symptoms; it is observed in both first-episode/drug-naïve patients and previously treated patients; it is larger in patients experiencing an episode of illness exacerbation than in patients in remission at the time of the scan; and it does not appear to be a nonspecific effect of stress, as higher self-reports of anxiety before the experiments were not associated with larger effect of amphetamine on [^{123}I]IBZM binding. Furthermore, nonpsychotic subjects with unipolar depression, who reported levels of anxiety similar to those of the schizophrenic patients at the time of the scan, showed normal amphetamine-induced displacement of [^{123}I]IBZM [38].

These findings generally have been interpreted as reflecting an increase in synaptic DA following amphetamine challenge in the schizophrenic group. Another interpretation of these observations would be that schizophrenia is associated with increased affinity of D_2 receptors for DA.

DA transporters (DATs)

Three imaging studies (listed in Table 1) have confirmed the in vitro observation of normal striatal DAT density in

Table 1. Imaging studies of striatal presynaptic DA parameters in DN and DF patients with schizophrenia

Parameter	Study	Number of controls	Number of patients (DN/DF/T)	Radiotracer (/challenge)	Method	Outcome	*P*	Effect size*
DOPA accumulation	Reith et al. [58]	13	5 (4/0/1)	[^{18}F]DOPA	Kinetic	k3	< 0.05	0.91
	Hietala et al. [54]	7	7 (7/0/0)	[^{18}F]DOPA	Graphical	K_i	< 0.05	1.54
	Dao-Castellana et al. [51]	7	6 (2/4/0)	[^{18}F]DOPA	Graphical	K_i	NS	0.3
	Lindstrom et al. [55]	10	12 (10/2/0)	[^{11}C]DOPA	Graphical	K_i	< 0.05	0.77
	Hietala et al. [53]	13	10 (10/0/0)	[^{18}F]DOPA	Graphical	K_i	< 0.05	1.09
	Elkashef et al. [52]	13	19 (0/9/10)	[^{18}F]DOPA	Ratio	K_i	< 0.05	–0.65
	Meyer-Lindenberg et al. [57]	6	6 (0/6/0)	[^{18}F]DOPA	Graphical	K_i	< 0.02	1.96
	McGowan et al. [56•]	12	16 (0/0/16)	[^{18}F]DOPA	Graphical	K_i	0.001	1.6
Amphetamine-induced DA release	Laruelle et al. [35]	15	15 (2/13/0)	[^{123}I]IBZM/ amphetamine	Equilibrium	Delta BP	< 0.05	1.51
	Breier et al. [34]	18	18 (8/10/0)	[^{11}C]raclopride/ amphetamine	Equilibrium	Delta BP	< 0.05	1.73
	Abi-Dargham et al. [36]	16	21 (1/20/0)	[^{123}I]IBZM/ amphetamine	Equilibrium	Delta BP	< 0.05	1.07
Baseline DA concentration	Abi-Dargham et al. [44]	18	18 (8/10/0)	[^{123}I]IBZM/AMPT	Equilibrium	Delta BP	< 0.05	1.43
	Kegeles et al. [45•]	18		[^{11}C]raclopride/ AMPT	Equilibrium	Delta BP	< 0.05 in preDCA	
DAT density	Laakso et al. [40]	9	9 (9/0/0)	[^{18}F]CFT	Ratio	S/C	< 0.05	0.11
	Laruelle et al. [39]	22	22 (2/20/0)	[^{123}I]CIT	Equilibrium	BP	< 0.05	–0.43
	Hsiao et al. [96]	12	12 (12/0/0)	[^{99}mTc]TRODAT	Ratio	S/Occ	NS	0.22

*Effect size calculated as (mean patients – mean controls)/SD controls.
AMPT—α-methylparatyrosine; BP—binding potential; DA—dopamine; DAT—dopamine transporter; DF—drug-free; DN—drug-naïve; DOPA—dihydroxyphenylalanine; NS—not significant; preDCA—precommissural caudate; S/C—striatal over cerebellar; S/Occ—striatal over occipital; T—treated with antipsychotics.

schizophrenia [39,40]. In addition, no association between amphetamine-induced DA release and DAT density was found [39], suggesting that the increased presynaptic output revealed by the studies reviewed previously is not due to higher terminal density.

Vesicular monoamine transporter
Using the radiotracer [^{11}C]DTBZ, Taylor et al. [41] were not able to show any difference in vesicular monoamine transporter binding potential in patients with schizophrenia compared with healthy subjects.

Baseline occupancy of striatal D_2 receptors by DA
In rodents, acute depletion of synaptic DA is associated with an acute increase in the in vivo binding of [^{11}C]raclopride or [^{123}I]IBZM to D_2 receptors (for review, see [42]). The increased binding is observed in vivo but not in vitro, indicating that it is not due to receptor up-regulation [43], but rather to removal of endogenous DA and unmasking of D_2 receptors previously occupied by DA. A similar acute DA depletion technique paired with D_2 receptor imaging in humans using α-methylparatyrosine (α-MPT) has been developed to assess the degree of occupancy of D_2 receptors by DA [43]. In schizophrenia, there was a higher occupancy of D_2 receptors by DA in patients experiencing an episode of illness exacerbation compared with healthy controls [44] (Table 1). Again assuming normal affinity of D_2 receptors for DA, the data are consistent with higher DA synaptic levels in patients with schizophrenia. Higher synaptic DA levels in patients with schizophrenia were predictive of good therapeutic response of these symptoms following 6 weeks of treatment with atypical antipsychotic medications. This observation now has been replicated with PET and [^{11}C]raclopride in our lab. We observed that the increase at the level of the striatum observed initially is essentially accounted for by an increase in DA transmission at the level of the associative striatum, and in particular the precommissural caudate (preDCA) rather than the limbic or sensorimotor striatum [45•]. The preDCA is the area of the striatum that receives most of the cortico-striatal projections from the dorsolateral PFC (DLPFC) [46–50], the neocortical area most implicated in the pathophysiology of schizophrenia. The information is processed in the preDCA and sent back to the DLPFC via the globus pallidus (pars interna)/substantia nigra and ventral anterior thalamic nuclei. Thus, although subcortical DA dysregulation historically has been conceptualized as a possible consequence of DLPFC dysfunction, these findings suggest that in addition, alterations of subcortical DA transmission, if located in the preDCA, might in turn negatively impact on DLPFC function.

Striatal dihydroxyphenylalanine (DOPA) decarboxylase activity
Eight studies have reported rates of the DA-synthesizing enzyme DOPA decarboxylase (AADC) in patients with schizophrenia using [^{18}F]DOPA or [^{11}C]DOPA (Table 1). Six of eight studies reported increased accumulation of DOPA in the striatum of patients with schizophrenia [51–55,56•,57,58], one reported no change [51], and one study reported reduced [^{18}F]DOPA striatal uptake [52]. Three studies involved first-episode schizophrenia, and all three showed an increase of DOPA in the striatum [53–55]. Interestingly, a recent study observed a relationship between poor prefrontal activation during the Wisconsin Card Sorting task and elevated [^{18}F]DOPA accumulation in the striatum, suggesting a link between alteration of the DLPFC function and increased striatal DA activity in schizophrenia [57]. In rats as in anesthetized pigs, increases in AADC activity in vitro and in vivo have been reported following acute treatment with DA antagonists [59–61]. Conversely, acute treatment with the DA agonist apomorphine decreases ^{11}C-DOPA influx in monkeys [62]. However, evidence for such effects in humans is extremely limited. Thus, in the only comprehensive study to date, Grunder et al. [63] recently reported a decrease in [^{18}F]DOPA uptake in nine patients with schizophrenia following subchronic treatment with haloperidol [63], suggesting that chronic neuroleptic administration will tend to decrease AADC activity and, hence, DA synthesis. Interestingly, acute administration of antipsychotics increases DA neuron firing, whereas chronic administration decreases the number of spontaneously active DA neurons in the rat substantia nigra [64], suggesting that the different effects of antipsychotics on AADC activity in the living brain could reflect such phenomena.

Cortical DA Deficit

Indirect evidence supports the hypothesis that a deficit in prefrontal DA function might contribute to prefrontal impairment in schizophrenia. Preclinical studies have documented the importance of prefrontal DA function for cognition (for review, see [8,65]). This important role recently has been confirmed in humans by the repeated observation that carriers of the high-activity allele of catecol-O-methyltransferase, an enzyme involved in DA metabolism, display lower performance in various cognitive tasks compared with carriers of the allele that induce lower concentration of DA in PFC (for review, see [66•]). Clinical studies have suggested a relationship between low cerebrospinal fluid homovanillic acid, a measure reflecting low DA activity in the PFC, and poor performance in tasks involving working memory in schizophrenia [67,68]. Administration of DA agonists might have beneficial effects on the pattern of prefrontal activation measured by PET during these tasks [69,70]. Although these observations are consistent with the hypothesis of a hypodopaminergic state in the PFC of patients with schizophrenia, they do not constitute direct evidence.

Extrastriatal D_1 receptors

The main parameter of extrastriatal DA transmission that currently is quantifiable using noninvasive in vivo

studies is D_1 receptor availability. Three PET studies of prefrontal D_1 receptor availability in patients with schizophrenia recently have been published. Two studies were performed with the D_1 radiotracer [^{11}C]SCH 23390. The first reported decreased [^{11}C]SCH 23390 binding potential in the PFC [29], and the other reported no change [31]. One study was performed with [^{11}C]NNC 112 [30] and reported increased [^{11}C]NNC 112 binding potential in DLPFC and no change in other regions of the PFC such as the medial PFC or the orbitofrontal cortex. In patients with schizophrenia, increased [^{11}C]NNC 112 binding in the DLPFC was predictive of poor performance on a working memory task [30]. Many potential factors, including patient heterogeneity and differences in the boundaries of the sampled regions, might account for these discrepancies. However, severity of deficits at tasks involving working memory was reported to be associated with both decreased PFC [^{11}C]SCH 23390 binding potential in one study [29] and increased PFC [^{11}C]NNC 112 binding potential in another [30], suggesting that both alterations might reflect a common underlying deficit.

Because of the prevalent view that schizophrenia is associated with a deficit in prefrontal DA activity, the impact of acute and subchronic DA depletion on the in vivo binding of [^{11}C]SCH 23390 and [^{11}C]NNC 112 is highly relevant to the interpretation of these data [71]. Acute DA depletion does not affect the in vivo binding of [^{11}C]NNC 112 but results in decreased in vivo binding of [^{3}H]SCH 23390, a paradoxical response that might be related to DA depletion-induced translocation of D_1 receptors from the cytoplasmic to cell surface compartment [42,72,73]. In contrast, chronic DA depletion is associated with increased in vivo [^{11}C]NNC 112 binding, presumably reflecting a compensatory up-regulation of D_1 receptors. Interestingly, chronic DA depletion did not result in enhanced in vivo binding of [^{3}H]SCH 23390, possibly as a result of opposite effects of receptor up-regulation and externalization on the binding of these tracers.

A recent study showed an effect of genetic loading on cortical D_1 levels measured with [^{11}C]SCH 23390, with higher values associated with more loading; this study also showed lower cortical D_1 in medicated patients [74•]. A down-regulation of D_1 receptors by D_2 antagonists previously had been shown in the cortex of nonhuman primates [75]. This suggests that the discrepancies in findings with the two tracers may be related to differences in the patient populations rather than differences in the tracers' in vivo behavior.

In conclusion, studies with both radiotracers in the same patients are required to clarify this issue. In addition, more selective tracers are needed for future investigations, as we recently observed that 25% of the cortical binding of both tracers in monkeys is to the 5-HT_{2A} receptor [76]. This finding flags the need for better tracers going forward with investigations of cortical dopaminergic transmission in schizophrenia.

Extrastriatal D_2 receptors

The recent availability of high-affinity D_2 radiotracers allowed the study of D_2 receptors in low-density regions such as the substantia nigra, thalamus, and temporal cortex in patients with schizophrenia compared with controls. A first study found decreases in temporal cortex in both hemispheres in a very small group of patients compared with controls (seven patients and seven controls) [77]. A similarly small study found low thalamic binding that was later confirmed in a larger sample of drug-naïve patients [78•,79]. Suhara et al. [80] found decreased DA D_2 receptors in the anterior cingulate cortex and thalamic subregions in patients with schizophrenia, whereas Glenthoj et al. [81•] found a significant correlation between frontal D_2 receptor and positive symptoms in male schizophrenic patients. Clearly, more research is needed to reach conclusive evidence for alterations in D_2 transmission in extrastriatal regions, but the thalamic decreases seem to be a consistent observation thus far.

Occupancy of these receptors by antipsychotics also has been examined, with various results that are beyond the scope of this review; however, a recent study [82•] found no relationship with treatment response. If confirmed, this finding suggests that extrastriatal D_2 may not play an important role in the therapeutics of schizophrenia. Overall, this is an emerging field, and more research is needed to understand the role of extrastriatal D_2 transmission in schizophrenia.

Other DA Receptor Subtypes: D_3 and D_4

D_3 receptors

A significant increase in D_3 receptor number in the ventral striatum (VST) samples from patients with schizophrenia who were off neuroleptics at the time of death has been reported in one study [83]. In contrast, in patients who had been treated with neuroleptics up to the time of death, D_3 receptor levels did not differ significantly from those of controls [83]. These data were interpreted as indicating that antipsychotics down-regulate the D_3 receptor in schizophrenic patients who otherwise have a higher density of this receptor in the VST.

D_4 receptors

Based on ligand subtraction techniques, several studies have reported increased D_4-like receptors in schizophrenia [84–86]. These findings were not confirmed by other studies using the same technique [87,88] or by a study using [^{3}H]NGD 94-1, a selective D_4 ligand [89]. Moreover, the hypothesis that clozapine might act by blocking the D_4 receptor was not supported by clinical trials with D_4 antagonists [90].

Relationship of DA Alterations to Other Systems in Schizophrenia

Imaging studies have shown that N-methyl-D-aspartate (NMDA) hypofunction in nonschizophrenic subjects

can lead to DA alterations similar to those observed in schizophrenia, namely subcortical excess and cortical D_1 up-regulation [91•,92–94]. In addition, NMDA antagonists have been shown to engender some of the alterations in γ-aminobutyric acid (GABA) neurons in the DLPFC that have been described in schizophrenia [95•]. Such convergence suggests that the main neurochemical dysregulations described in schizophrenia are not mutually exclusive. Glutamatergic and GABAergic alterations in schizophrenia could be linked and could lead to or be associated with an inefficient control of cortical input onto subcortical striatal DA, as well as inefficient cortico-cortical connectivity and function. DA dysregulation may be the endpoint of a cascade of upstream events, an endpoint that is most directly associated with symptoms of the illness and their treatment.

Conclusions

The evidence for hyperactivity of subcortical transmission at D_2 receptors in schizophrenia is well established and has emerged as a phenotype of the illness. It is consistent with the known mode of action of current antipsychotic treatment (D_2 receptor blockade) and with the psychotogenic effects of sustained stimulation of DA function by psychostimulants. On the other hand, imaging and postmortem studies have suggested that hypodopaminergia in the DLPFC contributes to the pathophysiology of cognitive symptoms endured by patients with schizophrenia, although more conclusive evidence and better characterization of these deficits are needed. Finally, the DA alterations may be the endpoint or the result of a cascade of events involving other transmitters such as GABA and glutamate. However, DA alterations are the most clearly understood at this point and the most directly associated with the manifestations of the symptoms.

Knowledge of the pathophysiology has implications for treatment development. In light of the deficit of DA transmission in the cortex, D_1 agonists, as well as D_4 agonists may be useful drugs to test, at least for cognitive enhancement and treatment of negative symptoms. D_3 antagonists or partial agonists, if available, can be tested as antipsychotics that spare the nigrostriatal system, as these receptors are preferentially located in the VST. Finally, drugs that modulate DA release indirectly by acting on other transmitters that may affect DA tone are also possible therapeutic tools for future development.

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