Review

Biological Psychiatry

The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia

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ABSTRACT

The dopamine hypothesis is the longest standing pathoetiologic theory of schizophrenia. Because it was initially based on indirect evidence and findings in patients with established schizophrenia, it was unclear what role dopamine played in the onset of the disorder. However, recent studies in people at risk of schizophrenia have found elevated striatal dopamine synthesis capacity and increased dopamine release to stress. Furthermore, striatal dopamine changes have been linked to altered cortical function during cognitive tasks, in line with preclinical evidence that a circuit involving cortical projections to the striatum and midbrain may underlie the striatal dopamine changes. Other studies have shown that a number of environmental risk factors for schizophrenia, such as social isolation and childhood trauma, also affect presynaptic dopaminergic function. Advances in preclinical work and genetics have begun to unravel the molecular architecture linking dopamine, psychosis, and psychosocial stress. Included among the many genes associated with risk of schizophrenia are the gene encoding the dopamine D_2 receptor and those involved in the upstream regulation of dopaminergic synthesis, through glutamatergic and gamma-aminobutyric acidergic pathways. A number of these pathways are also linked to the stress response. We review these new lines of evidence and present a model of how genes and environmental factors may sensitize the dopamine system so that it is vulnerable to acute stress, leading to progressive dysregulation and the onset of psychosis. Finally, we consider the implications for rational drug development, in particular regionally selective dopaminergic modulation, and the potential of genetic factors to stratify patients.

Keywords: Dopamine, Etiology, Genetics, Neuroimaging, PET, Prodrome, Psychosis, Schizophrenia, Stress

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The dopamine hypothesis has been the leading pathoetiologic theory of schizophrenia for more than four decades (1–3). Our understanding of schizophrenia has progressed through advances in neuroimaging, epidemiology, and research into the prodromal phase that predates the onset of the disorder in many patients. Meanwhile, the role of genetic and environmental risk factors for schizophrenia has been clarified. Studies of how these risk factors affect the dopamine system, coupled with longitudinal studies during the prodrome, allow for a more refined understanding of what leads to the onset of psychosis. This review synthesizes the evidence on the nature of dopaminergic abnormalities in schizophrenia and its prodrome and how risk factors lead to illness, before considering the implications for treatment and prevention.

ORIGINS OF THE DOPAMINE HYPOTHESIS

The origins of the dopamine hypothesis lie in two lines of evidence. First, clinical studies established that dopaminergic agonists and stimulants could induce psychosis in healthy individuals and could worsen psychosis in patients with schizophrenia (4,5). Second was the discovery that antipsychotic drugs affect the dopamine system (6). Later, the potency of antipsychotic drugs was linked to their affinity for dopamine D_2 receptors, linking molecular action to clinical phenotype (7).

Postmortem studies provided the first direct evidence for dopaminergic dysfunction in the brain and its anatomical localization. These showed elevated levels of dopamine, its metabolites, and its receptors in the striata of people with schizophrenia (8,9). However, the studies were of patients who had received antipsychotic drugs. Consequently, it was not clear if the dysfunction was linked to onset or to an end-stage effect of the disorder or indeed was a consequence of antipsychotic drugs.

IN VIVO IMAGING OF DOPAMINE IN SCHIZOPHRENIA

The development of positron emission tomography (PET) and single photon computed tomography specific radiotracers enabled the dopamine system to be studied in vivo with high molecular specificity (10).

Studies of the dopamine transporter (3,11) and vesicular monoamine transporter (12,13) availability in the striatum show no abnormality either in patients with a chronic condition or in drug-naive first episode patients. Likewise, while meta-analysis has shown that there may be a small elevation in

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Table 1. PET Studies of the Dopaminergic System in Individuals at Increased Clinical Risk of Schizophrenia

Study	Population	Radiotracer	Study Type	Region Reported	Findings (Standard Effect Size)	Additional Findings
Bloemen *et al.*, 2013 (29)	14 CHR 15 HV	[^{123}I]IBZM	Dopamine depletion	Striatum	–	Positive correlation between D_2 and D_3 receptor occupancy by dopamine and positive CHR symptoms
Howes *et al.*, 2009 (30)	24 CHR 12 HV	[^{18}F]-DOPA	Dopamine synthesis capacity	Striatum	↑ (0.75)	
Howes *et al.*, 2011 (32)[a]	30 CHR 29 HV	[^{18}F]-DOPA	Dopamine synthesis capacity	Striatum	↑ (1.18)[a]	No change in CHR subjects who did not convert to psychosis
Egerton *et al.*, 2013 (31)	26 CHR 20 HV	[^{18}F]-DOPA	Dopamine synthesis capacity	Striatum	↑ (0.81)	
Mizrahi *et al.*, 2012 (28)	12 CHR 12 HV	[^{11}C]-+-PHNO	MIST-induced dopamine release	Striatum	↑ (0.98)	
Suridjan *et al.*, 2013 (27)	12 CHR 12 HV	[^{11}C]-+-PHNO	D_2^{high}/D_3 receptor availability	Striatum, thalamus, globus pallidus, substantia nigra	–	
Abi-Dargham *et al.*, 2004 (132)	13 Scztyp 13 HV	[^{123}I]IBZM	Amphetamine-induced dopamine release	Striatum	↑ (0.93)	
Soliman *et al.*, 2008 (133)[b]	16 Scztyp 10 HV	[^{11}C]raclopride	MIST-induced dopamine release	Ventral striatum	↑	

CHR, clinical high risk of psychosis; HV, healthy volunteer; MIST, Montreal Imaging Stress Task; PET, positron emission tomography; Scztyp, schizotypal; ↑, significantly higher in patient group; ↓, significantly lower level in patient group; –, no significant difference; [^{123}I]IBZM, [^{123}I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide; [^{11}C]-+-PHNO, [11C]-(+)-4-propyl-9-hydroxynaphthoxazine; [^{18}F]-DOPA, 6-[^{18}F]fluoro-L-dihydroxyphenylalanine.

[a]Synthesis capacity increased only in subgroup that transitioned to psychosis (n = 9).

[b]MIST leads to significant decrease in tracer binding in subgroup characterized as potential schizotype on the basis that subjects scored >1.95 SD on the negative subscale of Chapman schizotypy questionnaire.

dopamine $D_{2/3}$ receptor availability in schizophrenia, it is not reliably seen in patients naive for antipsychotic drugs (3).

Presynaptic dopaminergic function can be indexed either by using radiolabeled levo-dihydroxyphenylalanine or by measuring the change in radiotracer binding to $D_{2/3}$ receptors after a challenge designed to stimulate dopamine release. A significant elevation was reported in a meta-analysis of presynaptic dopaminergic function using these techniques (Cohen's d = 0.8) (3), and subsequent studies have reported even larger effect sizes (14–16). Furthermore, baseline occupancy of $D_{2/3}$ receptors by dopamine has also been found to be elevated, indicating higher synaptic dopamine levels at rest (17,18). Striatal dopamine release and baseline dopamine levels are closely correlated in schizophrenia (19), suggesting that the same abnormality underlies both.

While the striatum has received the greatest attention in PET studies, it has long been hypothesized that alterations in the dopamine system extend to additional brain regions (20). Dopaminergic hypofunction in the dorsolateral prefrontal cortex (DLPFC) has been proposed to account for negative and cognitive symptoms. Recently, people with schizophrenia have been found to show reduced dopamine release in the DLPFC after amphetamine challenge, and this release was shown to correlate with DLPFC activation during a working memory task (21). Meta-analysis of studies that have examined extrastriatal receptor densities indicate there are unlikely to be large differences in $D_{2/3}$ receptors and transporters in the regions studied, while the D_1 findings are inconsistent, potentially due to the effects of prior antipsychotic treatment (22).

IN VIVO IMAGING OF DOPAMINE IN PEOPLE AT CLINICAL HIGH RISK OF PSYCHOSIS

The use of structured clinical assessments has made it possible to identify cohorts with prodromal symptoms, in which the risk of transition to psychosis can be as high as 40%, although recent studies have reported lower rates (23). Various studies have suggested that dopaminergic abnormalities exist in people at clinical high risk (CHR) of psychosis. Antipsychotic treatment trials have demonstrated efficacy of dopamine blockade in reducing prodromal-type symptom severity (24,25), and elevations in peripheral dopamine metabolites have been observed in CHR cohorts (26). However, these findings cannot tell us directly about central dopaminergic dysfunction; in this respect imaging has been particularly useful.

Three studies have examined $D_{2/3}$ receptor density in CHR populations; all showed no differences between groups (Table 1) (27–29). In two studies this could conceivably have been due to increased synaptic dopamine masking a difference in receptor densities (27,28). One study, however, addressed this with a dopamine depletion paradigm and showed no significant differences (29).

Presynaptic Dopaminergic Function

Initial research showed that dopamine synthesis capacity was raised in CHR individuals (30) and was positively associated with the severity of prodromal-type symptoms (Table 1). This has subsequently been replicated (31) and found to be specific to prodromal individuals who progress to psychosis (32).