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