Presynaptic Dopamine in Schizophrenia

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SUMMARY

Presynaptic dopamine (DA) transmission has been measured in schizophrenia using different paradigms aimed at providing estimates of the integrity or the activity of the presynaptic dopaminergic neuron. Researchers have measured: (1) DA synthesis capacity with [¹⁸F]DOPA, a measure of the activity of dopa decarboxylase, (2) DA release with studies measuring the impact of a DA releasing stimulant challenge on the binding of a D₂ receptor radiotracer, (3) D₂ baseline occupancy by DA, a measure of baseline intrasynaptic DA, assessed by the changes in binding of D₂ radiotracer induced by DA depletion, and (4) the DA and the vesicular monoamine transporters, to assess the integrity of presynaptic terminals. The relationship between DA release and D₂ receptor occupancy at baseline by DA has also been assessed in the same patients. Overall, these different imaging modalities have converged to show a dysregulation of presynaptic dopaminergic activity in schizophrenia, leading to excessive DA release in the striatum, particularly in the projection to the associative striatum, an area of integration between cognitive and limbic cortical inputs. Excessive striatal presynaptic DA is linked to the emergence of acute psychotic symptoms and to their response to treatment in schizophrenia. Understanding the etiology of this dysregulation and its consequences on the rest of the circuitry is important for future drug development.

Introduction

The dopamine (DA) hypothesis of schizophrenia was first formulated by Rossum et al. [1] based on the observation that antipsychotics may block DA receptors. It received support through the years from multiple lines of evidence. Initially, support derived from the findings that DA receptors are activated by psychostimulants, that non-reserpine neuroleptics are DA receptor antagonists and that DA plays an important role in the extrapyramidal motor system [2]. The correlation between clinical doses of antipsychotic drugs and their potency to block DA D₂ receptors [3,4], as well as the observations of psychotogenic effects of DA enhancing drugs [for review, see Refs. 5 and 6], provided additional support for the link between excessive dopamine activity and the psychotic symptoms of schizophrenia. Subsequently, a deficiency in mesocortical DA function was suggested as a possible integrative explanation for many clinical observations regarding negative symptoms and cognitive deficits, leading to a reformulation of this hypothesis [7] to incorporate an imbalance between subcortical excess and cortical deficit. Finally, with the advent of molecular imaging, various aspects of presynaptic DA transmission have been measured to test this hypothesis.

This review will focus on indices of presynaptic transmission, including studies of enzymatic activity within the dopaminergic terminals, transmitter release, and DA transporter (DAT) avail-

ability, after a brief review of the methodologies for the imaging paradigms used.

One index of presynaptic DA transmission is the activity of enzymes within the dopaminergic synthesis pathway. DA synthesis occurs within the DA neurons. Tyrosine is transported into the cell via amino acid carriers in the blood-brain barrier and cell membranes. Once in the intracellular space it is hydroxylated to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase (TH). L-DOPA is then decarboxylated by aromatic acid decarboxylase (AADC) to DA (Figure 1). The first positron emission tomography (PET) tracer developed for studies of DA synthesis and/or storage in the human brain was [¹⁸F]DOPA [8–10]. [¹⁸F]DOPA, a radioactive analogue of L-DOPA, the precursor of DA, is taken up by presynaptic monoaminergic neurons and is metabolized by AADC to ¹⁸F-Dopamine, which is trapped and stored within vesicles in the nerve terminals. [¹⁸F]DOPA uptake, quantified as the influx constant K_i, can be used as a measure of AADC activity and vesicular storage capacity [11]. High values for [¹⁸F]DOPA K_i are observed in areas of dense DA nerve terminal innervation (e.g., the striatum), [¹⁸F]DOPA has been extensively used to probe the functional integrity of striatal dopaminergic neurons, particularly in Parkinson's disease and other movement disorders [12–15] where [¹⁸F]DOPA uptake correlates with the number of surviving nigrostriatal cell numbers in both human studies and animal models [16,17]. Although AADC is not the rate-limiting step in

Figure 1 Summary of dopamine alterations in schizophrenia. Abbreviations: AADC, aromatic acid decarboxylase; AMPT, α -methyl-*para*-tyrosine; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; DOPA, 3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; VMAT, vesicular monoamine transporter.

the synthetic pathway for DA, it has been suggested that AADC activity may influence the rate of DA synthesis [18].

Acute treatment with D₂ receptor antagonists increases AADC activity in animal studies [19–21]. Conversely, acute treatment with the D₂ agonist apomorphine decreases ¹¹C-DOPA influx in monkeys [22]. This is consistent with the electrophysiological data showing that acute administration of antipsychotics increases DA neuron firing, whereas chronic administration decreases the number of spontaneously active DA neurons in the rat substantia nigra due to depolarization block [23]. These together suggest that [¹⁸F]DOPA imaging provides a measure of the activity of AADC in presynaptic DA terminals because the activity of the enzyme changes in a similar direction to the DA firing in response to pharmacological interventions.

Another index of presynaptic activity is transmitter release, which can be indirectly measured by assessing changes in binding of D₂ radiotracers after pharmacological manipulation with DA releasing or depleting agents. Administration of the DA releasing agent amphetamine produces a reduction in *in vivo* binding of D₂ radiotracers such as [¹¹C]raclopride and [¹²³I]IBZM; this reduction in binding is a well-validated measure of pharmacologically stimulated DA release. Conversely, administration of the dopamine depleting agent α -methyl-*para*-tyrosine (AMPT) unmasks D₂ receptors occupied by endogenous DA and results in a subsequent increase in *in vivo* binding of [¹¹C]raclopride or [¹²³I]IBZM (for review, see Ref. 24). The increased binding can be interpreted as measurement of baseline occupancy of D₂ receptors by DA.

Some studies have attempted to validate these imaging paradigms used to probe neurotransmitter levels and have suggested that the changes in *in vivo* binding associated with these paradigms reflect changes in synaptic DA levels rather than general extrasynaptic levels. This interpretation is based on the lack of correlation between the magnitude of DA increase measured with microdialysis and the magnitude of displacement of D₂ radiotracers across different challenge drugs [24]. Drugs that block the DAT, such as amphetamine and GBR12909, increase microdialysis-measured DA more than DA-releasing drugs that do not block the DAT, such as ketanserin and nicotine, yet the range of D₂ radiotracer displacement is similar for all, suggesting that this measure is affected only by changes in intrasynaptic DA. Thus, the imaging measures of DA in the stimulated (obtained with the amphetamine challenge) or baseline condition (obtained with the AMPT depletion paradigm) are assumed to reflect measures of synaptic release of DA. Furthermore, synaptic levels are also assumed to be mostly influenced by phasic release, related to burst activity. However, contribution by basal tonic release, driven by single spike activity, cannot be excluded. More definitive validation will derive from combining *in vivo* imaging with *ex vivo* measurements in rodent models of altered DA activity to clarify the exact molecular equivalence of the imaging measures.

Studies in Patients with Schizophrenia

Most of the information regarding presynaptic DA transmission in schizophrenia derives from imaging studies, although some post mortem work has also shed light on this topic. One post-mortem study of TH immunolabeling in patients with schizophrenia showed decreased TH labeled axons in layers 3 and 6 of the entorhinal cortex and in layer 6 of the prefrontal cortex [25,26], supporting the view that cortical DA is deficient in schizophrenia. This finding was unrelated to premortem neuroleptic exposure. On the other hand, Benes et al. (1997) observed no significant changes in TH positive varicosities in the dorsolateral prefrontal cortex (DLPFC). In the anterior cingulate region (layer 2), these authors observed a significant shift in the distribution of TH varicosities from large neurons to small neurons. Another presynaptic index, DAT density, has been examined in the striatum of patients with schizophrenia, and does not appear to differ from that of controls [27–32]. Postmortem studies of DA levels or DA metabolites have not yielded a conclusive set of findings.

Imaging DA Synthesis

Using PET and either [β -¹¹C]L-DOPA or [¹⁸F]DOPA, most studies examining this index of DA synthesis capacity have found increased striatal DOPA uptake in patients with schizophrenia compared to controls [33–40] (Figure 1). Of note, all investigations of patients experiencing an active psychotic episode at the time of scanning reported increased striatal DOPA uptake among patients [34–36]. Further, one study reported an association between positive symptoms and [¹⁸F]DOPA uptake in the putamen [35, for review and discussion, see Ref. 41]. Thus, overall this body of work provides evidence that as a group, individuals with schizophrenia are characterized by elevated presynaptic DA synthesis/storage,

and that this abnormality may be most evident in patients with active psychosis [see Ref. 41]. In addition, Meyer-Lindenberg et al. [39] found that reduced activation in the DLPFC during an executive functioning task, as measured by PET with [¹⁵O]H₂O, was associated with increased striatal DOPA uptake in patients but not controls, providing additional support for the relation between prefrontal dysfunction and potentiated striatal DA activity in the illness.

Howes et al. [37] recently reported that striatal [¹⁸F]DOPA uptake was significantly increased among individuals experiencing prodromal symptoms of schizophrenia compared to controls, and that DOPA uptake correlated significantly with severity of prodromal symptoms. Of note, these differences were observed in the associative, but not in the limbic or sensorimotor, striatum. Importantly, this study provides evidence that increased DA synthesis activity may occur before the full syndrome of schizophrenia emerges among those displaying prodromal symptoms of the illness. Furthermore, a recent study reported increased striatal [¹⁸F]DOPA uptake among nonpsychotic first-degree relatives of schizophrenia patients, suggesting that elevated presynaptic DA synthesis may be associated with the genetic vulnerability to the illness [42].

Imaging Stimulated DA Release

With imaging, synaptic DA release in the striatum, measured as the change in D₂ radiotracer binding potential after administration of the DA-releasing drug amphetamine, has been shown to be increased in schizophrenia [43–45] (Figure 1). Moreover, transient amphetamine-induced exacerbation of positive symptoms observed in a subgroup of schizophrenia patients was associated with the degree of amphetamine-induced reduction in striatal [¹²³I]IBZM binding potential. In addition, patients experiencing an acute phase of illness, including those at first episode who were antipsychotic naïve, had a significantly greater degree of amphetamine-induced striatal DA release compared to those in remission. The remitted group did not differ significantly from controls on this index of DA release, although they were numerically higher than controls [46]. The findings of these studies marked an important advance in schizophrenia research, as they more directly than any prior results supported the proposal that excessive DA transmission at striatal D₂ receptors is involved in the experiencing of psychotic symptoms, and highlighted a role for a dysregulated, hyperresponsive subcortical DA system that fluctuates in its degree of dysregulation during different phases of the illness. Since this time, Abi-Dargham and colleagues [47] have shown that as a group, patients with schizotypal personality disorder (SPD) are also characterized by a larger reduction in striatal [¹²³I]IBZM binding potential following amphetamine compared to controls. The degree of amphetamine-induced [¹²³I]IBZM displacement observed in SPD was similar to that previously observed in remitted patients with schizophrenia but significantly lower than that seen in acutely ill schizophrenia patients [47]. Taken together, these results suggest that a more modest increase in DA release may characterize individuals at risk for psychosis, and that a larger degree of DA dysregulation characterizes those reaching the threshold of active psychosis. This is consistent with the data in first degree

relatives showing elevation in DA synthesis capacity, [42], supporting the notion that dysregulation of striatal DA may have two components, a low-grade increase present in patients between episodes and in at risk states, such as spectrum disorders or relatives, and a higher level of dysregulation present in acute psychotic episodes, including first episode of the illness.

Baseline DA Release

This paradigm is based on acutely depleting synaptic DA by orally administering the TH inhibitor AMPT over 48 h [48]. Using this technique with single photon emission computed tomography (SPECT) and the D₂ radiotracer [¹²³I]IBZM, Abi-Dargham *et al.* [49] found that the increase in D₂ receptor availability after acute DA depletion was significantly larger in patients with schizophrenia compared to controls, indicating increased occupancy of striatal D₂ receptors by DA at baseline in schizophrenia. Of note, all of the patients of this study were experiencing an episode of illness exacerbation. It was further noted that AMPT exposure led to a significant reduction in severity of positive symptoms among patients, and that higher occupancy of striatal D₂ receptors by DA was significantly associated with a greater reduction in positive symptoms after 6 weeks of antipsychotic treatment [49]. These results provided evidence that schizophrenia is characterized by excessive striatal D₂ receptor stimulation by DA and that the degree of this dysregulation is associated with the degree of therapeutic response to antipsychotic medication observed in patients.

With the availability of high-resolution PET scanners and the development of methods to examine DA receptor parameters in the various subregions of the striatum, it became possible to probe aspects of DA transmission separately for the functional subdivisions of the striatum [50,51]. Using these methods with PET and [¹¹C]raclopride, patients with schizophrenia displayed a significantly larger increase in D₂ receptor availability after DA depletion compared to controls in the associative striatum (AST), but not in the limbic or sensorimotor striatal regions [52]. In particular, group differences were observed in the anterior (pre-commissural) dorsal caudate. This finding has challenged the notion that in schizophrenia, alterations in subcortical DA transmission are most prominently localized to the ventral, rather than dorsal, striatum and stimulated thinking regarding the potential role of the AST in the illness. This striatal region receives prominent input from the DLPFC, and is thought to play an important role in regulating the circuitry from various cortical regions [52].

Correlation of Stimulated and Baseline DA Release

One study involving antipsychotic-naïve patients with schizophrenia who participated in both the amphetamine-challenge and DA depletion paradigms indicated that indices of stimulated and baseline DA release are strongly associated in patients but not controls [53]. These results suggest that these measures are indexing the same pathological process in patients. They also highlight the variability in this DA transmission alteration across patients, which is an observation that informs our understanding of schizophrenia pathophysiology and may be important in the design of targeted treatment interventions [53].

Imaging DA Transporters

DAT are located on the presynaptic membrane of DA terminals and regulate phasic DA transmission at the synapse by rapidly removing DA from the synaptic cleft through reuptake [54]. Because striatal DAT are located exclusively on DA terminals, its measurement has been used to index the density of dopaminergic terminals or innervation into the striatum. Numerous studies have now examined striatal DAT density in antipsychotic-naïve or -free patients with schizophrenia using either PET or SPECT, and have failed to find significant differences between patients and controls [55–59]. These results suggest that the increased presynaptic striatal DA activity in schizophrenia indicated by other imaging parameters is not secondary to dysfunctional DAT or an elevation in the density of dopaminergic terminals. However, two studies using a dual-isotope SPECT technique with first-episode, antipsychotic-naïve patients have reported a positive association between DAT and D₂ receptor availability in patients but not controls [57,60]. Further, using [99mTc]TRODAT-1 and SPECT, researchers recently observed a significant increase in DAT availability in a subgroup of patients with predominantly positive symptoms compared to controls [60]. Pending further replication, most of the evidence at this point shows that the DAT is unaffected in schizophrenia. A similar picture has emerged for the vesicular monoamine transporter (VMAT) [61]. These together suggest integrity of striatal dopaminergic terminals.

Summary

Increased striatal DA function is one of the best established research findings in schizophrenia, observed with different imaging modalities and replicated by numerous independent labs. It seems most relevant to positive symptoms, as the severity of these correlates with magnitude of DA release [46,62], and their response to treatment is also a function of the degree of dysregulation of striatal DA function [49]. Indeed, the most relevant site of therapeutic efficacy of antipsychotics is striatal, as measured by the strength of relationship between D₂ occupancy in the striatum by antipsychotics and the response of positive symptoms [63,64]. On the other hand, response of negative symptoms is unrelated to striatal occupancy, and response of positive symptoms does not seem to be coupled to degree of extrastriatal occupancy. These observations suggest that striatal dopaminergic function determines severity and treatment response of psychosis.

Nonetheless, striatal dopaminergic dysfunction can be reciprocally linked to a cortical dopaminergic dysfunction. Studies have documented that cortical DA affects subcortical DA dynamics. More recently, however, the reciprocal effect has been shown in a mouse model of striatal D₂ overexpression that demonstrates cognitive impairment in tasks of working memory and behavioral flexibility, as well as altered prefrontal cortical DA levels, rates of DA turnover, and activation of prefrontal D₁ receptors [65]. The mechanism by which this may occur is yet to be determined, but this finding suggests that flow of information in cortico-striato-thalamo-cortical loops can be impaired at the striatal level, producing a bottom up impairment in cortical function.

The etiology of the striatal dopaminergic dysregulation is unknown, and most likely related to alterations in other systems that

regulate DA transmission. Thus, DA dysregulation may not be a primary dysfunction in schizophrenia, but rather may represent a final common pathway to psychosis. In addition, DA dysregulation itself may play a role in other pathogenic effects, as the striatum represents an essential integrative node, by receiving input from the hippocampus and the cortex, two areas of pathology in schizophrenia, by modulating DA midbrain neurons, and by projecting indirectly back to the cortex. Pathological changes in hippocampal activity lead to dopaminergic dysregulation in animal models. Hippocampal pathology is also present in patients with schizophrenia [66–68], suggesting that the hippocampus may play an essential role in the genesis of the dopaminergic pathology in schizophrenia. This could be mediated by a disinhibition of dopaminergic cells in the ventral tegmental area via the pallidal projection, leading to an increased sensitivity to excitatory inputs and an increase in phasic firing [69]. Testing in patients for an association between hippocampal hyperactivity and dopaminergic phasic dysregulation is needed to confirm the relevance of these preclinical observations to the pathophysiology of the disorder. The striatal DA dysregulation in turn may lead to an impairment of cortical inputs, imbalancing the cortico–limbic integration that takes place within the striatum and explaining the different domains of pathology that exist within the schizophrenia spectrum.

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Conclusion

Molecular imaging studies have provided robust support for the long-held hypothesis positing subcortical DA hyperactivity in schizophrenia. Importantly, these findings converge in pointing to a hyperresponsive subcortical DA system that fluctuates in its degree of dysregulation across phases of the illness; further, DA dysregulation appears to be present to some degree during the prodromal period of the illness, before threshold psychotic symptoms emerge. Increased presynaptic DA functioning may be particularly evident in the dorsal caudate of the anterior striatum. Finally, a more direct characterization of cortical DA as well as extrastriatal DA transmission in schizophrenia is needed, as the evidence for cortical deficit is largely by inference. These studies are now feasible with the development of high affinity benzamide radiotracers that allow visualization of D₂ receptors in low density areas of the brain and are sensitive to acute changes in DA tone.

Conflict of Interest

The authors have no conflict of interest.

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