The Dopamine Dysfunction in Schizophrenia Revisited: New Insights into Topography and Course

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Contents

Abstract Schizophrenia has long been associated with an imbalance in dopamine (DA) neurotransmission, and brain imaging has played an important role in advancing our knowledge and providing evidence for the dopaminergic abnormalities. This chapter reviews the evidence for DA dysfunction in different brain regions in schizophrenia, in particular striatal, extrastriatal, and prefrontal regions, with emphasis on recently published findings. As opposed to the traditional view that most striatal dopaminergic excess, associated with the positive symptoms of

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schizophrenia, involves the dopaminergic mesolimbic pathway, recent evidence points to the nigrostriatal pathway as the area of highest dysregulation. Furthermore, evidence from translational research suggests that dopaminergic excess may be present in the prodromal phase, and may by itself, as suggested by the phenotype observed in transgenic mice with developmental overexpression of dorso-striatal D_2 receptors, be an early pathogenic condition, leading to irreversible cortical dysfunction.

Keywords Schizophrenia • Psychosis • Dopamine dysfunction • Neurochemical imaging

1 Introduction

The psychotomimetic effects of stimulant drugs, in combination with the observed antipsychotic effects of D_2-blocking drugs, gave rise to the initial dopamine (DA) hypothesis of schizophrenia (Carlsson 1977, 1978; van Rossum 1966). Refined and modified in the intervening years, this theory to date remains central to the pathophysiology of schizophrenia (Howes and Kapur 2009; Laruelle et al. 2003; Lieberman et al. 1997).

Based on the observation that DA-enhancing drugs such as amphetamine show psychotomimetic properties while the effectiveness of classic antipsychotic medication, blocking DA D_2 receptors, had been shown to directly correlate with its affinity for the D_2 receptor (Creese et al. 1976), the dopamine hypothesis initially assumed a general dopaminergic hyperfunction (Carlsson 1977, 1978). However, subsequent findings, including reduced cerebral blood flow in the prefrontal cortex (PFC) of patients with schizophrenia and the observation that negative symptoms such as flattened affect, anhedonia, and compromised cognitive function did not respond to classic antipsychotic treatment targeting D_2 receptors, were incompatible with a generally overactive DA system. Accordingly, the dopamine hypothesis was reformulated as an imbalance in DA neurotransmission in different regions of the brain, characterized in particular by hyperactivity in the subcortical DA pathway and hypoactivity in the cortical DA system (Davis et al. 1991; Knable and Weinberger 1997; Weinberger 1987). It was also suggested that DA hyperactivity in subcortical brain regions, in particular striatal areas, accounted primarily for the positive symptoms of schizophrenia, while the negative symptoms were mostly associated with DA hypoactivity in cortical areas, particularly PFC (Abi-Dargham 2004).

In this chapter, we present the history as well as the latest research findings relating to dopamine dysfunction in schizophrenia. The two main new findings that will be emphasized here are the following: Unlike the traditional thinking that most dopaminergic excess causing positive symptoms involves the dopaminergic mesolimbic pathway, recent evidence points to the nigrostriatal pathway, projecting to the anterior caudate, part of the associative striatum, as the area of highest dysregulation. Furthermore, as opposed to the thinking that dopamine is a final

common pathway, recent evidence from studies in mice with a developmental overexpression of D_2 receptors (Kellendonk et al. 2006) and in patients at high risk for developing schizophrenia (Howes et al. 2009) suggests that dopamine dysregulation may be an early pathogenic mechanism that may lead to further dysregulation of brain function. We will review the evidence and outline future research needed to understand the molecular mechanisms and develop better therapeutic interventions.

2 Evidence for Dopamine (DA) Dysfunction in Schizophrenia

Direct empirical evidence for DA alterations in schizophrenia was initially elusive. Postmortem studies were difficult to interpret due to the possible confounding by prior antipsychotic exposure and the first imaging studies using Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) produced inconsistent findings. Advances in PET and SPECT imaging techniques, such as the development of new, high-affinity radiotracers, made it possible to study DA neurotransmission in several regions of the brain, including striatal, extrastriatal, and prefrontal cortical regions with more anatomical detail than previously possible.

2.1 Striatal DA Alterations

Using PET and SPECT imaging techniques, different paradigms have been employed in order to study aspects of presynaptic and postsynaptic striatal DA alterations in schizophrenia. These approaches include markers of DA synthesis, release and reuptake, as well as DA receptor availability and differences in receptor affinity states (Erritzoe et al. 2003; Laruelle 1998; Seeman et al. 2006).

2.1.1 Presynaptic DAergic Parameters

Dopamine Synthesis

DA is synthesized by hydroxylation of the precursor tyrosine to L-DOPA, which then is decarboxylated to DA by aromatic acid decarboxylase (AADC). Radioactive analogues of L-DOPA, such as [^{11}C]L-DOPA and [^{18}F]DOPA, have been used to estimate enzymatic activity of AADC, as an indicator of DA synthesis capacity (Brown et al. 1999; Cumming and Gjedde 1998; Garnett et al. 1978, 1983). However, this is overly simplified and other factors may affect the overall signal measured with [^{11}C]L-DOPA and [^{18}F]DOPA, including delivery of [^{11}C]L-DOPA and [^{18}F]DOPA to the brain, crossing the plasma membrane, storage in

presynaptic vesicles as a result of vesicular monoamine transporter (VMAT) activity, release of [^{11}C]L-DOPA and [^{18}F]DOPA, and degradation, all may play a role in addition to the activity of DOPA decarboxylase. Better knowledge of these mechanisms is needed to better understand the exact molecular processes underlying [^{11}C]L-DOPA and [^{18}F]DOPA uptake and their disturbance in schizophrenia.

Nevertheless, a number of studies have used radiolabeled L-DOPA, such as [^{11}C]L-DOPA or [^{18}F]DOPA, in schizophrenia. The first study, by Reith et al. (1994), revealed significantly elevated [^{18}F]DOPA uptake in drug-naïve patients compared to healthy controls. While the majority of the following studies using the same technique replicated this finding (Hietala et al. 1995, 1999; Howes et al. 2009; Lindstrom et al. 1999; McGowan et al. 2004; Meyer-Lindenberg et al. 2002; Nozaki et al. 2009), two studies failed to find markers of elevated DA synthesis capacity: One study reported a small but not significant increase in [^{18}F]DOPA uptake (Dao-Castellana et al. 1997), while another found decreased levels of [^{18}F]DOPA uptake (Elkashef et al. 2000). This discrepancy might be explained by differences in study population: Studies reporting positive findings were all conducted in acutely psychotic, mostly drug-naïve, patients (with the exception of McGowan and colleagues), while the two studies reporting negative or inverse findings were done in chronic, previously medicated, patients. Recently, DA synthesis capacity was investigated in twins discordant for schizophrenia. No elevation in striatal DA synthesis was observed in the unaffected twin, nor in the low-symptomatic medicated twin with chronic schizophrenia when compared to controls, suggesting that increased DA synthesis is not a genetic marker for schizophrenia (Shotbolt et al. 2011). Most recently, Howes et al. (2009) showed increases in [^{18}F]DOPA uptake in associative striatum in patients prodromal for schizophrenia, predicting conversion (Howes et al. 2011b) and progressing further on follow-up after 2 years to involve the sensorimotor striatal subregion (Howes et al. 2011a).

Dopamine Release

The next step in DA transmission is the release of DA from the presynaptic terminal. An estimation of DA release from striatal DA neuron terminals can be obtained by measuring changes in D_2 binding potential after pharmacologically induced DA release with SPECT and PET imaging techniques (Kegeles et al. 1999; Laruelle 2000; Laruelle et al. 1995). One of the first studies to investigate amphetamine-induced DA release in schizophrenia was conducted by Laruelle et al. (1996), using SPECT and the radiotracer [^{123}I]IBZM, an antagonist at $D_{2/3}$ receptors. Changes in $D_{2/3}$ binding potential as an estimation of amphetamine-induced DA release were measured in 15 medication-free patients with schizophrenia and 15 healthy control participants at the level of the striatum as a whole. The decrease in binding potential induced by amphetamine was significantly greater in patients with schizophrenia compared to controls. Furthermore, the amphetamine-induced decrease in $D_{2/3}$ binding potential was associated with the

transient increase in positive symptoms induced by amphetamine in the schizophrenia group (Laruelle et al. 1996). The results of a subsequent PET study using [^{11}C]raclopride as radiotracer were in line with these observations (Breier et al. 1997): The schizophrenia group showed greater amphetamine-induced decreases in [^{11}C]raclopride binding compared to controls, indicative of greater amphetamine-induced release of endogenous DA. Furthermore, the study did not find differences in amphetamine effects on [^{11}C]raclopride binding between medication-free ($N = 5$) and medication-naïve ($N = 6$) patients with schizophrenia, indicating that the effect occurs independent of earlier treatment with antipsychotics. Abi-Dargham et al. (1998) have since then replicated these findings. Furthermore, it was shown that changes in amphetamine-induced dopamine release in schizophrenia might be associated with illness phase, as amphetamine-induced transient worsening of psychotic symptoms correlated with changes in [^{11}C]raclopride binding in patients with schizophrenia and no difference in [^{11}C]raclopride binding was seen in patients in remission compared to controls (Laruelle et al. 1999).

The amphetamine paradigm shows stimulated release, as amphetamine increases dopamine levels by reversing DA transport. Another aspect of DA transmission is uncovered with depletion paradigms: The administration of alpha-methyl-para-tyrosine (αMPT), a reversible competitive inhibitor of tyrosine hydroxylase, causes acute depletion of endogenous DA and can be used as a method to assess the degree of baseline (nonstimulated) intrasynaptic DA concentration indirectly measured through $D_{2/3}$ occupancy (Laruelle et al. 1997), most likely reflecting basal release as a result of neuronal firing. Abi-Dargham et al. (2000) used this technique in combination with SPECT and [^{123}I]IBZM in 18 untreated patients with schizophrenia and 18 matched control participants before and after αMPT-induced DA depletion. Exposure to αMPT led to increased D_2 receptor availability in both patients with schizophrenia and healthy controls; however, the effect was larger in schizophrenia patients, indicative of higher baseline DA activity in this group. The magnitude of the effect did not differ between medication-naïve patients with schizophrenia and those previously treated with antipsychotics (Abi-Dargham et al. 2000). Similar results were recently obtained by Kegeles et al. (2010a), who employed the same depletion paradigm in combination with PET and [^{11}C]raclopride. Kegeles and colleagues furthermore showed that the largest effect of acute DA depletion on D_2 receptor binding was observed in the associative striatum and not in limbic striatum as was long hypothesized. Recently, it was shown that amphetamine-stimulated DA release and baseline DA activity are related in patients with schizophrenia but not in controls (Abi-Dargham et al. 2009). Pilot data from Canada furthermore suggest that DA release in patients with schizophrenia and individuals at high risk compared to healthy controls is also increased in response to psychosocial stress (Mizrahi 2010). Altogether, studies have consistently demonstrated increased amphetamine-stimulated DA release in schizophrenia. Depletion studies further suggest that schizophrenia is characterized by increased baseline DA activity.

Dopamine Reuptake

DA transmission in the striatum is regulated by DA transporters (DAT), which are located on the presynaptic membrane of DA terminals and rapidly remove DA from the synaptic cleft (Goto et al. 2007). Several studies have investigated DAT density in schizophrenia, using PET or SPECT, to obtain an index of density of DA terminals and striatal innervation (Hsiao et al. 2003; Laakso et al. 2000, 2001; Laruelle et al. 2000; Lavalaye et al. 2001; Mateos et al. 2005, 2007; Schmitt et al. 2005, 2006, 2008; Yang et al. 2004; Yoder et al. 2004). The majority of studies did not observe differences in DAT availability between antipsychotic-naïve patients with schizophrenia and controls (Hsiao et al. 2003; Laakso et al. 2000; Laruelle et al. 2000; Lavalaye et al. 2001; Schmitt et al. 2005, 2006; Yoder et al. 2004). Two studies reported reduced DAT binding in patients with schizophrenia compared to controls (Laakso et al. 2001; Mateos et al. 2005). However, since the patients were not medication-naïve, the researchers concluded that the observed reduction in DAT binding was secondary to prior treatment with antipsychotics. In order to clarify this issue, Mateos et al. (2007) repeated the experiment in a cohort of antipsychotic-naïve patients with schizophrenia and also found lower DAT density (Mateos et al. 2007). Still, this remains the only study, which reported decreased DAT binding in schizophrenia. So, taken together the evidence suggests that schizophrenia is not associated with changes in DAT density.

Recently, two dual-isotope SPECT studies used [^{99}mTc]TRODAT and [^{123}I]IBZM to simultaneously measure DAT and D_2 receptor availability in drug-naïve patients with schizophrenia and controls (Schmitt et al. 2008; Yang et al. 2004). In line with most of the previous findings, no overall differences in DAT or D_2 receptor availability were observed. However, in patients but not controls, DAT density correlated positively with D_2 receptor availability (Yang et al. 2004), which was most pronounced in patients presenting with predominantly positive symptoms (Schmitt et al. 2008).

2.1.2 Postsynaptic DAergic Parameters

DA Receptor Availability

The most extensively studied receptor in schizophrenia is the D_2 receptor, which is abundantly present in the human striatum. Numerous studies have measured the density of striatal D_2 receptors in schizophrenia, both in vivo and postmortem, and three meta-analyses have reviewed the strength and consistency of the reported findings (Kestler et al. 2001; Laruelle 1998; Zakzanis and Hansen 1998). We should note here that most of these studies refer to both D_2 and D_3 receptors, as the ligands are not specific to one subtype. Unless otherwise specified, when we mention the D_2 receptor in this review, we also refer to both subtypes. The first of these meta-analyses was conducted by Zakzanis and Hansen (1998) and included 17 studies of which 7 were postmortem. The results from 511 patients with schizophrenia and

534 controls suggested that, although D_2 receptor availability was elevated in approximately 70 % of the patients, increased receptor density failed to discriminate patients from controls and is therefore unlikely to represent a general marker of schizophrenia (Zakzanis and Hansen 1998). In line with this are the findings of the second meta-analysis, which included 15 in vivo studies on D_2 receptor density in schizophrenia, and concluded that there was small but significant elevation of receptor availability along with greater variability in schizophrenia patients compared to controls (Laruelle 1998). The more recent, comprehensive meta-analysis by Kestler et al. (2001) included 20 postmortem studies and 17 in vivo studies on D_2 receptor availability in schizophrenia and took into account differences in methodology such as in vivo versus postmortem measures as well as the possible influence of sample characteristics such as age, gender, or medication status. The authors concluded that the data were compatible with the idea of a subgroup of patients with schizophrenia being characterized by elevated D_2 density (Kestler et al. 2001). The results of a recent study using the high-affinity $D_{2/3}$ ligand [^{18}F]fallypride were also in line with this, showing selective alterations in D_2 density in schizophrenia patients (5 drug naïve, 16 drug free) (Kegeles et al. 2010b). Meta-analysis of D_2 receptor studies in schizophrenia has shown a modest increase in D_2 receptor density; however, the findings are likely to be confounded by prior treatment with antipsychotics. Chronic administration of antipsychotic medication has been shown to upregulate D_2 receptor density both in preclinical animal models and humans (Burt et al. 1977; Kashihara et al. 1986; Silvestri et al. 2000). A recent PET study in cats suggested that the magnitude of D_2 receptor upregulation depends on the percentage occupancy of D_2 receptor and the temporal pattern of the antipsychotic administration. A high dose (80 % occupancy of D_2 receptor) of haloperidol administered continuously by osmotic mini-pumps over 4 weeks produced a robust upregulation of D_2 receptor, still detectable 2 weeks after withdrawal. On the other hand, a lower dose (60 % occupancy D_2 receptor) or s.c administration once a day (transient 80 % occupancy for few hours) of haloperidol did not change D_2 receptor availability (Ginovart et al. 2009). For patients with schizophrenia, antipsychotics are prescribed both as oral and as depot medication and require occupancy between 60 and 80 % for therapeutic effect, beyond which the risk of side effects increases notably (Farde et al. 1992; Fitzgerald et al. 2000). The majority of studies of D_2 receptor availability in schizophrenia used mixed drug-free and drug-naïve patient groups; thus it is likely that increased D_2 receptor density may be, at least in part, related to prior exposure to antipsychotic rather than to the disease process per se.

Several lines of research indicate that, in addition to the D_2 receptor, the D_3 receptor might play an important role in the pathophysiology of schizophrenia (Griffon et al. 1995; Gurevich et al. 1997; Sokoloff et al. 2006). However, until recently it was not feasible to selectively target D_3 receptors with neurochemical imaging to obtain a direct measure of D_3 in schizophrenia, since the available radiotracers exhibited similar affinities for the D_2 and D_3 receptors and therefore could not distinguish between them. Using the $D_{2/3}$ agonist radiotracer [^{11}C]PHNO, which has higher affinity for D_3 than for D_2, a recent study did not reveal differences in receptor levels between patients with schizophrenia compared to

controls (Graff-Guerrero et al. 2009), although a more selective tracer would be needed to replicate this initial finding.

Several postmortem studies have used ligand subtraction methods to measure the distribution of striatal D_4 receptors in schizophrenia. However, these studies produced inconsistent results, some reporting increased availability of D_4 (Marzella et al. 1997; Murray et al. 1995; Seeman et al. 1993; Sumiyoshi et al. 1995), while others did not find differences in D_4 receptors between schizophrenia patients and controls (Lahti et al. 1996, 1998; Reynolds and Mason 1994). More selective tracers are needed to better characterize these receptors.

Most (postmortem) studies did not find altered levels of D_1 receptors in the striatum (Cross et al. 1981; Joyce et al. 1988; Knable et al. 1994; Pimoule et al. 1985; Reynolds and Czudek 1988; Seeman et al. 1987); one reported a slight decrease in D_1 density (Hess et al. 1987). The results of two in vivo studies of striatal D_1 density in schizophrenia are in line with the majority of postmortem findings and do not suggest alterations in striatal D_1 receptor levels in schizophrenia (Abi-Dargham et al. 2002; Okubo et al. 1997).

Taken together, it seems that a subgroup of schizophrenia patients is characterized by increased density of D_2-like (i.e., $D_{2/3}$) receptors, independent of age, gender, and prior antipsychotic exposure. The density of striatal D_1 receptors on the other hand seems to be unaltered. No conclusive data are available for D_4.

Balance in D_2 Receptor Affinity States

Being the primary target of antipsychotic medication, the D_2 receptor plays a major role in schizophrenia and psychosis (Kapur and Mamo 2003; Kapur and Remington 2001), although, as discussed earlier, its involvement in the pathophysiology of psychotic disorders remains unclear (Kestler et al. 2001; Laruelle 1998; Zakzanis and Hansen 1998). The D_2 receptor has been shown to exist in two different affinity states: a high-affinity, active state (D_2^{high}) and a low-affinity, inert state (D_2^{low}) (Sibley et al. 1982; Willeit et al. 2006). Preclinical work has shown that radiolabeled DA agonists such as (+)-PHNO, which selectively binds to $D_{2/3}$ receptors in the high-affinity state, in combination with PET can be used to study the distribution of D_2^{high} both in vitro (Nobrega and Seeman 1994) and in vivo (Galineau et al. 2006; Ginovart et al. 2006). The distribution of D_2^{high} using PET and [^{11}C](+)-PHNO was recently demonstrated also in human volunteers (Graff-Guerrero et al. 2008; Willeit et al. 2006).

For schizophrenia, it has been suggested that the observed supersensitivity to DA-enhancing drugs such as amphetamine is the result of an imbalance in D_2 affinity states, in particular elevated availability of D_2^{high} receptors (Seeman 2010; Seeman et al. 2005). However, evidence for this conclusions stems primarily from animal models of schizophrenia (for a review see Seeman 2010). Recently, the distribution of D_2^{high} was for the first time studied in patients with schizophrenia, and contrary to what could be expected from preclinical work, no elevation in D_2^{high} was observed in medication-free patients with schizophrenia compared to

controls (Graff-Guerrero et al. 2009). Although the authors acknowledge that differences in D_2^{high} between schizophrenia patients and controls could have been masked by endogenous DA, to date, there is no evidence for D_2^{high} dysregulation in schizophrenia.

2.2 Extrastriatal DA Alterations

Several studies have now used high-affinity radiotracers such as [^{18}F]fallypride, [^{11}C]FLB 457, and [^{123}I]epidepride to measure the distribution of D_2-type receptors in low-density brain regions such as the thalamus, anterior cingulate cortex, temporal cortex, or substantia nigra in unmedicated and medication-naïve patients with schizophrenia. Some studies found decreased D_2 receptor availability in the thalamus (Buchsbaum et al. 2006; Kessler et al. 2009; Talvik et al. 2003, 2006; Yasuno et al. 2004), anterior cingulate cortex (Buchsbaum et al. 2006; Suhara et al. 2002), temporal cortex (Buchsbaum et al. 2006; Tuppurainen et al. 2003), and midbrain (Tuppurainen et al. 2006), while some found no differences in the thalamus (Tuppurainen et al. 2006), anterior cingulate, and temporal cortex (Glenthoj et al. 2006; Kessler et al. 2009; Talvik et al. 2003), and one study found an increase in D_2 receptor availability in schizophrenia in the substantia nigra (Kessler et al. 2009). A large recent study did not confirm any of the above reported extrastriatal D_2 receptor alterations in schizophrenia (Kegeles et al. 2010b).

Another recent study has used the radiotracer [^{11}C]PE21 in combination with PET to visualize thalamic DAT in patients with schizophrenia, who were either medication-naïve or off medication for at least 6 months (Arakawa et al. 2009). In contrast to striatal brain regions, where DAT seems to be unaffected in schizophrenia, this study reported increased DAT binding in the thalamus of patients with schizophrenia compared to controls. Another study measured extrastriatal DA synthesis capacity using PET and [^{11}C]L-DOPA and found no differences between medication-naïve patients with schizophrenia and controls with regard to DA synthesis capacity in the thalamus or anterior cingulate and temporal cortex (Nozaki et al. 2009), although the ability of this tracer to measure extrastriatal dopamine synthesis is questionable (Cropley et al. 2008).

2.3 Prefrontal Cortical DA Alterations

While D_2 receptors are abundantly present in striatal regions of the brain, the predominant DA receptors in prefrontal cortical regions are of the D_1 type (Hall et al. 1994). The distribution of D_1 receptors in schizophrenia has been studied using the PET radiotracers [^{11}C]NNC 112 or [^{11}C]SCH 23390. However, the few studies that have been conducted produced conflicting results. While Okubo et al. (1997), using [^{11}C]SCH 23390, found a decrease in receptor binding in patients with schizophrenia compared to controls, the study by Karlsson et al. (2002), using the

same radiotracer, did not reveal any differences between groups (Karlsson et al. 2002; Okubo et al. 1997). However, patients in this latter study were all drug-naïve, while the former study also included drug-free patients. The more recent study by Hirvonen et al. (2006) reported decreased [^{11}C]SCH 23390 binding in fronto-temporal brain regions of previously medicated patients with schizophrenia compared to their unaffected co-twins and healthy comparison twins and higher doses of antipsychotics were associated with greater decreases in D_1 receptor binding. Interestingly, unaffected monozygotic co-twins displayed increased receptor binding compared to healthy comparison twins, and unaffected dizygotic co-twins showed intermediate levels. Two other studies used the radiotracer [^{11}C]NNC 112: One reported increased D_1 receptor binding in the schizophrenia group, which correlated with deficits in working memory performance (Abi-Dargham et al. 2002), and the second study found increases limited to the drug-naïve patients but not the previously treated ones (Abi-Dargham et al. in press). Studies of D_1 receptor availability in schizophrenia are summarized in Table 1.

While it is possible that the discrepancy in findings is due to the influence of antipsychotic medication, it might also be that differences in radioligand properties contributed to the diverging results, as shown by Guo et al. (2003): Using a DA depletion paradigm the researchers could demonstrate that the in vivo binding of the two radiotracers [^{11}C]SCH 23390 and [^{11}C]NNC 112 was affected differentially by changes in endogenous DA, indicating that the increased D_1 receptor availability observed in the studies by Abi-Dargham et al. (2002) using [^{11}C]NNC 112 might reflect an upregulation of D_1 receptors, secondary to chronically low DA levels. This interpretation would also be consistent with the observed correlation between increased D_1 receptor binding and deficits in working memory. However, since both radioligands also bind to the serotonergic 5-HT_{2A} receptor (Ekelund et al. 2007; Slifstein et al. 2007), selective tracers are needed to pursue these investigations of the role of cortical D_1 receptors in schizophrenia.

2.4 Dopamine in At-Risk and Prodromal States

The studies described earlier have revealed several aspects of DA dysfunction in patients with established schizophrenia. In order to extend these findings and shed light on the timing of DA dysfunction in schizophrenia, researchers have started recently to examine different aspects of DA transmission in individuals with prodromal signs of schizophrenia and individuals at genetic or psychometric risk for psychosis.

Three studies have investigated striatal DA synthesis capacity with PET and [^{18}F]DOPA. While Huttunen et al. (2008) observed increased [^{18}F]DOPA uptake in the caudate-putamen in low-symptomatic first-degree relatives of patients with schizophrenia compared to controls, the study by Shotbolt et al. (2011) did not reveal any changes in radiotracer uptake in unaffected and completely asymptomatic co-twins of schizophrenia patients compared to controls. Howes et al. (2009) found increased [^{18}F]-DOPA uptake in individuals with prodromal signs of

Table 1 PET studies on D_1 receptor availability in PFC in schizophrenia

Study	Ligand	*N*		Results
		Patients (drug-naïve/drug-free)	Controls	
Okubo et al. (1997)	[^{11}C]SCH23390	17 (10/7)	18	Decreased receptor binding in patients versus controls
Karlsson et al. (2002)	[^{11}C]SCH23390	10 (10/0)	10	No difference between patients and controls
Hirvonen et al. (2006)	[^{11}C]SCH23390	9 (0/9)	24	Decreased receptor binding in patients versus controls (i.e., their unaffected co-twins and healthy comparison twins), but increased receptor binding in unaffected co-twins versus healthy comparison twins
Abi-Dargham et al. (2002)	[^{11}C]NNC112	16 (9/7)	16	Increased receptor binding in patients versus controls
Abi-Dargham et al. (2011)	[^{11}C]NNC112	25 (12/13)	40	Increased receptor binding only in drug-naïve patients versus controls; no change in drug-free patients

schizophrenia compared to controls. Interestingly, this effect was most pronounced in the associative striatum and correlated positively with severity of prodromal symptoms. Moreover, in a subsequent study the authors could indicate that the increase in DA synthesis capacity observed in individuals in the prodromal phase of the illness progressed over time only in those individuals who later developed schizophrenia, but not in those who did not develop the disease (Howes et al. 2011a). However, in contrast to the findings in prodromal individuals, where the effect was most pronounced in associative striatum, the progression in DA synthesis alteration in those who developed the disease was only seen in sensorimotor striatum (Howes et al. 2011a).

Three other studies have examined stimulated DA release in individuals psychometrically at risk for schizophrenia (i.e., individuals with schizoptypal traits). Soliman et al. (2007) employed a psychosocial stress paradigm in combination with PET and [^{11}C]raclopride to study stress-induced DA release in psychometric

schizotypes compared to controls. No changes in DA release in response to stress were observed in normal controls, nor in the "positive" schizotypes (i.e., individuals with perceptual aberrations). Only the "negative" schizotypes (i.e., individuals with physical anhedonia) showed an increase in DA release in response to stress compared to baseline (Soliman et al. 2007). Abi-Dargham et al. (2004) as well as Woodward et al. (2010) studied amphetamine-induced DA release in individuals with schizotypal personality disorder (SPD) and individuals with schizotypal traits, respectively. In the SPD subjects of the first study, amphetamine caused a larger decrease in [^{123}I]IBZM binding compared to controls (Abi-Dargham et al. 2004). Similarly, amphetamine-induced DA release measured indirectly through D_2 occupancy with PET and [^{18}F]fallypride correlated positively with schizotypal traits in the second study (Woodward et al. 2010). In accordance with previous findings showing that DA dysregulation might be most pronounced in associative striatum as opposed to limbic or sensorimotor regions (Howes et al. 2009; Kegeles et al. 2010a), the correlation between stimulated DA release and schizotypal traits was strongest in associative striatum.

Finally, one study has investigated striatal D_2 receptor availability in six monozygotic and five dizygotic unaffected co-twins of patients with schizophrenia and compared them to control twins without a family history of psychosis. Elevated caudate D_2 receptor availability was observed only in the monozygotic co-twins of schizophrenia patients, compared to dizygotic co-twins and controls. No changes, however, were revealed in the dizygotic co-twins compared to controls (Hirvonen et al. 2005).

In summary, studies suggest an increase in DA in schizotypal states and in relation to schizotypal and prodromal symptoms, linking DA dysfunction to the expression of the schizophrenia phenotype. Combined with the findings of Shotbolt et al. (2011) who did not observe any changes in DA synthesis capacity in unaffected co-twins of patients with schizophrenia, this finding suggests that DA dysfunction does not relate to a general genetic vulnerability in the absence of behavioral manifestations but rather represents a biological marker for the very early expression of schizophrenia symptomatology.

2.5 Summary

The most consistently found dopaminergic alteration in schizophrenia is elevated presynaptic DA function in striatal brain regions (see Figs. 1 and 2 for an illustration), in particular associative striatum, as demonstrated by imaging studies showing (1) increased L-DOPA uptake as an index of increased DA synthesis capacity, (2) elevated amphetamine-induced DA release, and (3) elevated D_2 receptor occupancy by DA as revealed by the acute DA depletion. DAT seems to be unaffected in schizophrenia, and increased D_2 receptor availability was only found in a subgroup of patients. Although preclinical work suggests an imbalance in D_2 receptor affinity states being associated with psychosis, the only study in patients with schizophrenia did not find elevated D_2^{high}. The evidence concerning DA alterations in extrastriatal

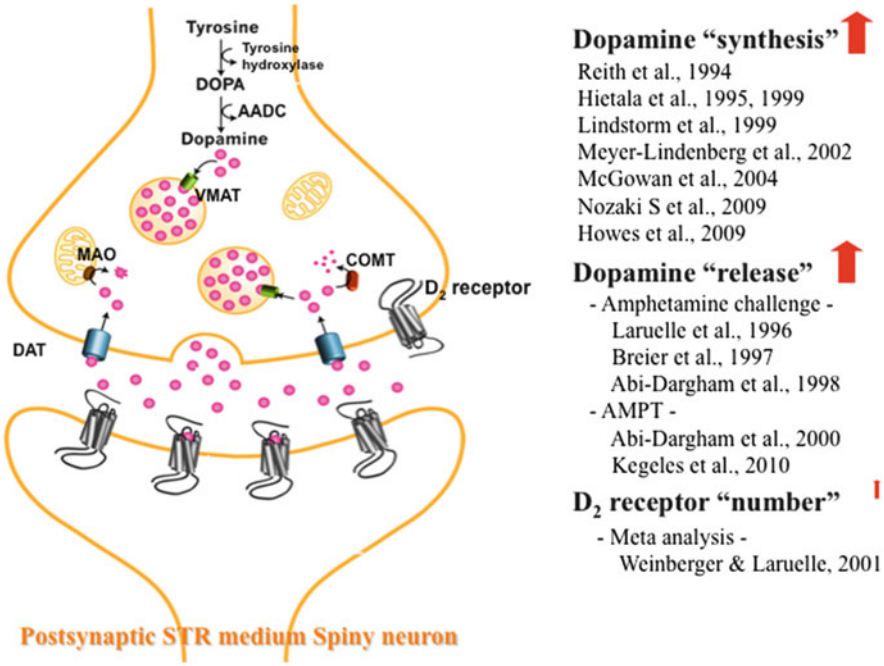

Fig. 1 *Dopaminergic* transmission at striatal (STR) medium spiny neurons. The most consistently found dysregulation in schizophrenia points to increased DA synthesis, increased stimulated DA release, and increased D_2 receptor binding after acute DA depletion

and prefrontal cortical brain areas in schizophrenia seems less consistent. While some studies found elevated levels of D_2 receptors in areas such as the thalamus, anterior cingulate, and temporal cortex or the midbrain and substantia nigra, others did not. The results of the few studies on D_1 receptor availability in prefrontal cortex in schizophrenia are also conflicting. Findings concerning the distribution of D_3 and D_4 remain understudied. To date, only one study used PET and the radiotracer [^{11}C] PHNO to investigate D_3 receptor in a small sample of patients with schizophrenia compared to controls and found no differences (Graff-Guerrero et al. 2009). Thus, while a lot of effort has been put into the investigation of striatal DA alterations in schizophrenia, research has been less successful with regard to extrastriatal and prefrontal cortical regions. More research is needed to resolve the inconsistencies in findings research has provided so far.

3 Functional and Clinical Implications

As defined in the current, fourth version of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000), schizophrenia is a highly heterogeneous disease, presenting with positive, negative, and cognitive

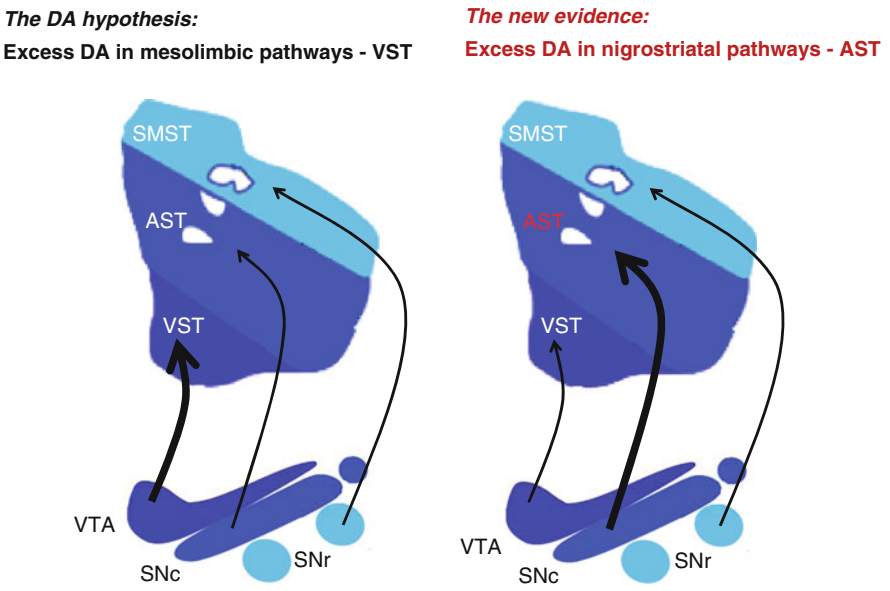

Fig. 2 New data bringing new evidence: The DA dysfunction in schizophrenia seems to be most pronounced in AST as opposed to VST as previously assumed. Adapted with permission from Simpson et al. (2010). SMST (sensorimotor striatum), AST (associative striatum), VST (ventral striatum), VTA (ventral tegmental area), SNc (substantia nigra pars compacta), SNr (substantia nigra pars reticulate)

symptoms. Positive symptoms include hallucinations and delusions, while negative symptoms refer to flattened affect, anhedonia, and loss of motivation. Cognitive disturbances are mostly seen in domains such as working memory, executive function, and aspects of social cognition. DA dysregulation plays a role within each of these dimensions. While positive symptoms seem to most directly relate to excessive striatal DA transmission, negative and cognitive symptoms have been associated with decreased DA function in PFC. The latter assumption was primarily based on the known and crucial involvement of the PFC in cognitive and emotional processes (Arnsten 2007, 2011; Goldman-Rakic and Selemon 1997). Still, after decades of research into DA and schizophrenia, it remains elusive how DA dysregulation actually translates into the complex and multifactorial symptoms that characterize the clinical picture of schizophrenia.

3.1 Relating DA Dysfunction to Positive Symptoms

Several of the imaging studies discussed in this chapter have reported associations between alterations in striatal DA function and symptomatology in patients with schizophrenia. Regarding DA synthesis, Hietala et al. (1999) found a negative correlation between striatal F-DOPA uptake and depressive symptoms and a

positive correlation with paranoid symptoms, although this was significant at trend level only. Howes et al. (2009) reported a positive correlation between severity of positive prodromal symptoms as well as neuropsychological impairment and increased DA synthesis capacity in associative striatum. However, this was not true for depressive symptoms. With regard to DA release, Laruelle et al. (1996) found that amphetamine-induced decrease in D_2 binding potential was associated with positive symptoms. In a subsequent study the authors could furthermore establish a relation between amphetamine-stimulated DA release and illness phase, as amphetamine-stimulated DA release was only increased in patients presenting with acute schizophrenia but not in patients in remission (Laruelle et al. 1999). Recently, Woodward et al. (2010) revealed a positive correlation between stimulated DA release and schizotypal personality traits in healthy individuals.

Assuming that striatal hyperdopaminergia plays a role in the emergence and experience of positive psychotic symptoms, the question arises as to how dopaminergic alterations in striatal brain regions ultimately give rise to the experience of hallucinations and delusions. Altered salience attribution has been suggested as a possible mechanism (Kapur et al. 2005). Burst firing of dopamine neurons in the ventral tegmental area markedly increases dopamine release in the striatum (Floresco et al. 2003) and is believed to mediate the perception of salience or reward associated with stimuli (Berridge and Robinson 1998; Schultz 1998; Stuber et al. 2008). The phasic bursts of dopamine release, which are highly dependent on glutamatergic excitatory afferents, have been shown to be regulated by constant low-frequency tonic firing of dopamine neurons (Goto et al. 2007). Tonic dopamine tone in turn is under control of GABAergic inhibition. Increased levels of tonic dopamine firing may result in decreased amplitude of phasic dopamine burst firing, thus dampening responsivity of this system. Decreased tonic dopamine levels, on the other hand, may result in a heightened responsivity of the phasic dopamine component (Bilder et al. 2004; Goto et al. 2007). Kapur has suggested that, in schizophrenia, dopamine dysregulation results in a psychological state of aberrant salience, in which mundane events and ideas may be attributed with undue significance (Kapur et al. 2005). Thus, a hyperdopaminergic state in striatal brain regions, which most likely reflects dysregulation of the phasic component of DA release (Grace 1991, 1995), is believed to create a condition in which logically unconnected ideas and associations are weaved together and elaborated upon, eventually leading to the emergence of a delusional system. The process of salience attribution has been related to associative and reinforcement learning, in which what is called "reward prediction error" plays a key role (Smith et al. 2006). It is hypothesized that previous reward outcomes are used to form a reward prediction, which is then compared to the actual current reward. The difference between reward prediction and actual outcome is referred to as the reward prediction error (Smith et al. 2006) and has been shown to be mediated, in animals as well as in humans, by dopamine activity in ventral midbrain and striatum (Abler et al. 2006; Bayer and Glimcher 2005; D'Ardenne et al. 2008; Pessiglione et al. 2006). Compared to healthy controls, patients with psychosis seem to exhibit aberrant reward prediction and reward-related learning, both at the behavioral and the neural level (Jensen et al. 2008; Juckel et al. 2006).

However, the relationship between dopamine dysfunction in these brain regions, alterations in reward processing, and symptomatology in schizophrenia has not directly been studied and remains speculative.

3.2 Relating DA Dysfunction to Negative and Cognitive Symptoms

As intact dopaminergic neurotransmission is critical for PFC functioning and cognition (Arnsten 2007; Goldman-Rakic 1999), the negative and cognitive symptoms of schizophrenia have been particularly associated with cortical hypodopaminergia (Abi-Dargham et al. 2002; Goldman-Rakic et al. 2004; Lynch 1992), although direct evidence for this association in schizophrenia is missing. The nature of dopamine dysfunction in the cortex remains unclear, although one study showing decreased tyrosine hydroxylase immunolabeling suggests decreased innervation (Akil et al. 2000). Recently, the group of Simpson et al. (2010) suggested a role for the striatum in the etiology of negative and cognitive symptoms of schizophrenia. Based on their preclinical work in D_2 overexpressing mice, the researchers demonstrated that striatal DA alterations in form of overexpression of D_2 receptors lead to changes in DA turnover and prefrontal D_1 receptor stimulation (Kellendonk et al. 2006). Behaviorally, this alteration was accompanied by deficits in working memory (Kellendonk et al. 2006) and operant performance, expressed in both reduced motivation and deficits in timing of the rewards (Drew et al. 2007). It was moreover shown that the deficits in cognitive performance were secondary to the motivational deficit directly resulting from the D_2 overexpression (Ward et al. 2009), and remained even after the D_2 receptor overexpression had been reversed (Drew et al. 2007). In line with these preclinical findings, studies in individuals with prodromal symptoms of schizophrenia have revealed an association between increased striatal DA synthesis capacity and altered activation in prefrontal cortical brain regions during cognitive engagement (Fusar-Poli et al. 2010, 2011). These studies highlight the concept of dopamine dysregulation occurring early on in the disease process and having pathogenic effects on the rest of the circuitry. It is likely that dopamine dysregulation early on may influence the development and function of other systems, as well as reciprocally, dopamine dysregulation itself may be a consequence of dysregulation in glutamatergic and GABAergic systems. We will discuss the interdependence of these alterations below.

3.3 Neural Circuitry; the Interdependence of Dopaminergic, Glutamatergic, and GABAergic Processes

We have outlined the dopaminergic alterations in schizophrenia in this chapter. There is also clear evidence for GABAergic abnormalities (Lewis and Gonzalez-Burgos

2000) and glutamatergic abnormalities. The hypothesis of a glutamatergic NMDA hypofunction initially derived from the observation that NMDA antagonists induce all three classes of symptoms (negative, cognitive, and positive) observed in schizophrenia and has received additional support from genetic, postmortem, and preclinical studies; for a review, see Moghaddam (2003). These alterations in GABA, dopamine, and glutamate can be interdependent. With imaging, we have observed that acute or chronic NMDA dysfunction can lead to striatal dopamine dysregulation (Kegeles et al. 2002) or to an increase in cortical D_1 receptors (Narendran et al. 2005), respectively. It is also believed that alterations in GABAergic interneurons in hippocampus (Zhang and Reynolds 2002) can lead to excess glutamate drive which in turn may lead to a dysregulation of midbrain dopamine activity. Preclinical studies have shown that the hippocampus is involved in the regulation of striatal dopamine by affecting firing patterns of midbrain dopamine cells (Grace 2012; Lodge and Grace 2008) and thus suggested that disinhibition due to NMDA receptor hypofunction on GABAergic interneurons in hippocampus may contribute to the hyperdopaminergic state in striatum (Lisman 2012). Recent work by Schobel and colleagues showed a significant increase in cerebral blood volume (CBV) in the hippocampus CA1 field in the prodromal stage predicting conversion to psychosis. CBV alterations were similar, although smaller in magnitude to those observed in patients with schizophrenia by Schobel et al. (2009), Harrison (2004), and Meyer-Lindenberg et al. (2005). Notably, the CA1 field is densely packed with pyramidal neurons and serves as the primary output area to the hippocampal-VTA loop. In the cortex, hypofunction of NMDA receptors on fast-spiking GABAergic interneurons leads to disinhibition of cortical excitatory neurons and impairment of synchronized oscillatory activity; for a review, see Lisman et al. (2008), which may relate to the cognitive deficits in schizophrenia as well as at least some of the negative symptoms that are less responsive to antipsychotics. In summary, the dopaminergic alterations have to be considered within the overall context of disordered circuitry and transmission in schizophrenia affecting multiple systems. Presynaptic dopamine alterations may be secondary to abnormal regulation by these systems. However, this suggestion does not necessarily mean that dopamine alterations cannot be in turn pathogenic, as observed in the D_2 overexpressing mouse model (Kellendonk et al. 2006). More work is needed to understand the sequence of alterations within patients' brains, but so far it is clear that both the hippocampal excess activity and the subcortical dopaminergic overactivity occur early on, could be related, and precede full onset of the disease.

4 Conclusions

This chapter reviewed evidence for DA dysfunction in schizophrenia. Most of this evidence stems from imaging studies applying PET and SPECT techniques. Due to advances in these imaging techniques it has become possible to study neurochemical alterations in the DA system in several regions of the brain. Accordingly, recent studies were able to examine DA neurotransmission in the different substructures of

the striatum and revealed that, in contrast to the prevailing idea of DA hyperactivity in the mesolimbic DA pathway, it is rather hyperactivity in associative striatum that is implicated in schizophrenia pathology, as illustrated in Fig. 2. It further seems that the dysfunction is predominantly presynaptic but also postsynaptic, characterized by increased DA synthesis capacity and increased phasic release to pharmacological and possibly also psychosocial challenges (see Fig. 1). Furthermore, this dysfunction occurs early in the disease and may represent an early pathogenic process leading to further dysregulation.

Despite recent advances in the study of DA dysregulation in schizophrenia, the etiology of DA imbalance remains unknown. It has been assumed that striatal DA hyperactivity results from decreased activity in PFC, due to its functional role in inhibiting subcortical DA transmission (Deutch 1992; Meyer-Lindenberg et al. 2002). Conversely, preclinical work has recently shown that striatal DA abnormalities result in altered PFC DA activity (Kellendonk et al. 2006). The striatum is a complex integrative structure, receiving among others input from the hippocampus, an area of pathology in schizophrenia (Harrison 2004; Meyer-Lindenberg et al. 2005), and in animal models changes in hippocampal activity lead to dysregulation of DA neuronal activity (Lodge and Grace 2008). Future research should combine imaging with translational models of the disease to understand the cellular mechanisms involved in the striatal and cortical dopamine dysfunction in schizophrenia.

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